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Immunosuppressive treatment for primary membranous nephropathy in adults with nephrotic syndrome (Review)

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[Intervention Review]

Immunosuppressive treatment for primary membranous nephropathy in adults with nephrotic syndrome

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ABSTRACT

Background

Primary membranous nephropathy (PMN) is a common cause of nephrotic syndrome in adults. Without treatment, approximately 30% of patients will experience spontaneous remission and one third will have persistent proteinuria. Approximately one-third of patients progress toward end-stage kidney disease (ESKD) within 10 years. Immunosuppressive treatment aims to protect kidney function and is recommended for patients who do not show improvement of proteinuria by supportive therapy, and for patients with severe nephrotic syndrome at presentation due to the high risk of developing ESKD. The efficacy and safety of different immunosuppressive regimens are unclear. This is an update of a Cochrane review, first published in 2004 and updated in 2013.

Objectives

The aim was to evaluate the safety and efficacy of different immunosuppressive treatments for adult patients with PMN and nephrotic syndrome.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 1 April 2021 with support from the Cochrane Kidney and Transplant Information Specialist using search terms relevant to this review. Studies in the Register were identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) investigating effects of immunosuppression in adults with PMN and nephrotic syndrome were included.

Data collection and analysis

Study selection, data extraction, quality assessment, and data synthesis were performed using Cochrane-recommended methods. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

Sixty-five studies (3807 patients) were included. Most studies exhibited a high risk of bias for the domains, blinding of study personnel, participants and outcome assessors, and most studies were judged unclear for randomisation sequence generation and allocation concealment.

Immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive treatment

In moderate certainty evidence, immunosuppressive treatment probably makes little or no difference to death, probably reduces the overall risk of ESKD (16 studies, 944 participants: RR 0.59, 95% CI 0.35 to 0.99; I^2 = 22%), probably increases total remission (complete and partial) (6 studies, 879 participants: RR 1.44, 95% CI 1.05 to 1.97; I^2 = 73%) and complete remission (16 studies, 879 participants: RR 1.70, 95% CI 1.05 to 2.75; I^2 = 43%), and probably decreases the number with doubling of serum creatinine (SCr) (9 studies, 447 participants: RR 0.46, 95% CI 0.26 to 0.80; I^2 = 21%). However, immunosuppressive treatment may increase the number of patients relapsing after complete or partial remission (3 studies, 148 participants): RR 1.73, 95% CI 1.05 to 2.86; I^2 = 0%) and may lead to a greater number experiencing temporary or permanent discontinuation/hospitalisation due to adverse events (18 studies, 927 participants: RR 5.33, 95% CI 2.19 to 12.98; I^2 = 0%). Immunosuppressive treatment has uncertain effects on infection and malignancy.

Oral alkylating agents with or without steroids versus placebo/no treatment/steroids

Oral alkylating agents with or without steroids had uncertain effects on death but may reduce the overall risk of ESKD (9 studies, 537 participants: RR 0.42, 95% CI 0.24 to 0.74; I^2 = 0%; low certainty evidence). Total (9 studies, 468 participants: RR 1.37, 95% CI 1.04 to 1.82; I^2 = 70%) and complete remission (8 studies, 432 participants: RR 2.12, 95% CI 1.33 to 3.38; I^2 = 37%) may increase, but had uncertain effects on the number of patients relapsing, and decreasing the number with doubling of SCr. Alkylating agents may be associated with a higher rate of adverse events leading to discontinuation or hospitalisation (8 studies 439 participants: RR 6.82, 95% CI 2.24 to 20.71; I^2 = 0%). Oral alkylating agents with or without steroids had uncertain effects on infection and malignancy.

Calcineurin inhibitors (CNI) with or without steroids versus placebo/no treatment/supportive therapy/steroids

We are uncertain whether CNI with or without steroids increased or decreased the risk of death or ESKD, increased or decreased total or complete remission, or reduced relapse after complete or partial remission (low to very low certainty evidence). CNI also had uncertain effects on decreasing the number with a doubling of SCr, temporary or permanent discontinuation or hospitalisation due to adverse events, infection, or malignancy.

Calcineurin inhibitors (CNI) with or without steroids versus alkylating agents with or without steroids

We are uncertain whether CNI with or without steroids increases or decreases the risk of death or ESKD. CNI with or without steroids may make little or no difference to total remission (10 studies, 538 participants: RR 1.01, 95% CI 0.89 to 1.15; I^2 = 53%; moderate certainty evidence) or complete remission (10 studies, 538 participants: RR 1.15, 95% CI 0.84 to 1.56; I^2 = 56%; low certainty evidence). CNI with or without steroids may increase relapse after complete or partial remission. CNI with or without steroids had uncertain effects on SCr increase, adverse events, infection, and malignancy.

Other immunosuppressive treatments

Other interventions included azathioprine, mizoribine, adrenocorticotropic hormone, traditional Chinese medicines, and monoclonal antibodies such as rituximab. There were insufficient data to draw conclusions on these treatments.

Authors' conclusions

This updated review strengthened the evidence that immunosuppressive therapy is probably superior to non-immunosuppressive therapy in inducing remission and reducing the number of patients that progress to ESKD. However, these benefits need to be balanced against the side effects of immunosuppressive drugs. The number of included studies with high-quality design was relatively small and most studies did not have adequate follow-up. Clinicians should inform their patients of the lack of high-quality evidence.

An alkylating agent (cyclophosphamide or chlorambucil) combined with a corticosteroid regimen had short- and long-term benefits, but this was associated with a higher rate of adverse events.

CNI (tacrolimus and cyclosporin) showed equivalency with alkylating agents however, the certainty of this evidence remains low.

Novel immunosuppressive treatments with the biologic rituximab or use of adrenocorticotropic hormone require further investigation and validation in large and high-quality RCTs.

PLAIN LANGUAGE SUMMARY

Immunosuppressive treatment for adults with idiopathic membranous nephropathy

What is the issue?

Primary membranous nephropathy (PMN) is an autoimmune disease, where the body's immune system attacks the kidneys. The term "primary" is used to describe membranous nephropathy that is not caused by another disease in the body. PMN is a leading cause of nephrotic syndrome in adults. Nephrotic syndrome is a condition, where the membrane of the kidney is damaged and becomes permeable for proteins. Primary membranous nephropathy is diagnosed through findings in a kidney biopsy and the presence of nephrotic syndrome.

PMN is not harmful in about one-third of patients, who will have a spontaneous "complete remission", which means that the disease will resolve by itself. However, about another one third will experience spontaneous remission but will have some protein in the urine that continues with normal kidney function. These patients usually only require supportive treatments that do not interact with the immune system. Without treatment, about 15% to 50% of patients progress to end-stage kidney disease (ESKD) within 10 years.

In some patients, PMN can be severe or continues to get worse even after using 6 months of supportive treatments. In these patients, extra treatment that dampens the activity of the immune system may be used to reduce damage to the kidney. It is not clear which of these treatment(s) is the most helpful and what side effects can occur. Therefore, the duration and intensity of immunosuppressive treatment need to be balanced against possible side effects. There are different classes of drugs used in immunosuppressive therapy. These drugs may or may not be combined with corticosteroids (drugs based on the body's stress response hormone cortisol).

What did we do?

We searched the Cochrane Kidney and Transplant specialised register up to 1 April 2021. We have combined studies to compare different treatment regimens with immunosuppressive therapy to assess which treatments help to treat patients with PMN and nephrotic syndrome with the least side effects.

What did we find?

This review identified sixty-five studies with 3807 patients. Different types of immunosuppressive treatment include alkylating agents (cyclophosphamide and chlorambucil), calcineurin inhibitors (tacrolimus and cyclosporine), antimetabolites (mycophenolate mofetil, azathioprine), biologicals (e.g. rituximab) and adrenocorticotropic hormone. These drugs may or may not be combined with corticosteroids (e.g. prednisone), which also suppresses the immune system. After combining the results of available studies together, we found that compared with no treatment, supportive treatment or steroids alone, the use of immunosuppressive treatment probably reduced the number of patients who progressed to ESKD by about 40% and increased the number of patients that achieved complete remission. However, immunosuppressive treatment may lead to more adverse events, which can cause treatment to be stopped or lead to the patients needing to go to hospital.

The different drugs that can be used in the immunosuppressive treatment were also examined in our review. We found that alkylating agents probably increases complete remission but may lead to more adverse events. We are uncertain whether alkylating agents increase infection or cancer. Based on the currently available evidence, the effectiveness of using calcineurin inhibitors is still unclear, but there is low certainty of the evidence, that CNI may lead to similar remission rates compared to alkylating agents.

Furthermore, other treatment options such as mycophenolate mofetil, adrenocorticotropic hormone, rituximab and others have only been examined in a few studies. There is not enough data to draw final conclusions on the use of these treatments in adults with PMN and nephrotic syndrome.

Conclusions

The treatment of patients with PMN and nephrotic syndrome with immunosuppressive therapy compared to no treatment or supportive therapy alone probably protects the kidney but may increase side effects. A combination of immunosuppressive therapy with steroids may decrease disease activity and the use of alkylating agent combined with steroids probably has the short-term and long-term benefits of limiting damage to the kidney. Other therapies such as calcineurin inhibitors, mycophenolate mofetil, rituximab and adrenocorticotropic hormone have less certainty regarding their safety and effectiveness from these studies.

SUMMARY OF FINDINGS

Summary of findings 1.   Immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive supportive treatment

Immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive supportive treatment for primary membranous nephropathy in adults with nephrotic syndrome

Patient or population: primary membranous nephropathy in adults with nephrotic syndrome
Setting: primary care
Intervention: immunosuppressive treatment
Comparison: control (placebo/no treatment/non-immunosuppressive supportive treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with immunosuppressive treatment			
Death at final follow-up (range: 9 months to 12 years)	40 per 1000	30 per 1000 (14 to 64)	RR 0.73 (0.34 to 1.59)	944 (16)	⊕⊕⊕⊖ Moderate [1]
End-stage kidney disease at final follow-up (range: 9 months to 12 years)	124 per 1000	73 per 1000 (43 to 123)	RR 0.59 (0.35 to 0.99)	944 (16)	⊕⊕⊕⊖ Moderate [1]
Total remission (complete or partial) at final follow-up (range: 6 months to 12 years)	337 per 1000	485 per 1000 (355 to 663)	RR 1.44 (1.05 to 1.97)	879 (16)	⊕⊕⊕⊖ Moderate [1]
Complete remission at final follow-up (range: 6 months to 12 years)	127 per 1000	216 per 1000 (133 to 349)	RR 1.70 (1.05 to 2.75)	879 (16)	⊕⊕⊕⊖ Moderate [1]
Recurrence of disease (relapse) at final follow-up (range: 21 months to 12 years)	114 per 1000	181 per 1000 (102 to 316)	RR 1.73 (1.05 to 2.86)	310 (3)	⊕⊕⊕⊖ Low [1,2]
100% increase in serum creatinine at final follow-up (range: 12 months to 12 years)	299 per 1000	138 per 1000 (78 to 240)	RR 0.46 (0.26 to 0.80)	447 (8)	⊕⊕⊕⊖ Moderate [1]
Adverse events: temporary/permanent discontinuation or hospitalisation at final follow-up (range: 6 months to 12 years)	2 per 1000	13 per 1000 (5 to 31)	RR 5.33 (2.19 to 12.98)	927 (16)	⊕⊕⊕⊖ Moderate [1]

Adverse events: infection at 3 years	54 per 1000	159 per 1000 (37 to 682)	RR 2.95 (0.69 to 12.61)	106 (1)	⊕⊖⊖⊖ **Very low** [1,3]
Adverse events: malignancy at final follow-up (range: 17 months to 3 years)	13 per 1000	14 per 1000 (2 to 120)	RR 1.03 (0.12 to 9.14)	182 (2)	⊕⊖⊖⊖ **Very Low** [1,3]

*****The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level: studies generally unclear or high risk of bias for many domains
[2] Downgraded one level: serious imprecision - due few events and participants in the included studies
[3] Downgraded two levels: very serious imprecision - only one study and very wide confidence intervals indicating appreciable benefit and harm
[4] Downgraded one level: serious imprecision - very wide confidence intervals indicating appreciable benefit and harm

Summary of findings 2.   Oral alkylating agents ± steroids versus placebo/no treatment/steroids

Oral alkylating agents ±steroids versus placebo/no treatment/steroids for primary membranous nephropathy in adults with nephrotic syndrome

Patient or population: primary membranous nephropathy in adults with nephrotic syndrome
Setting: primary care

Intervention: oral alkylating agents ± steroids
Comparison: control (placebo/no treatment/steroids)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with alkylating agents ± steroids			
Death at final follow-up (range: 9 months to 12 years	37 per 1000	28 per 1000 (9 to 84)	RR 0.76 (0.25 to 2.30)	440 (7)	⊕⊕⊖⊖ **Low** [1,2]

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	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
End-stage kidney disease at final follow-up (range: 9 months to 12 years)	146 per 1000	61 per 1000 (35 to 108)	RR 0.42 (0.24 to 0.74)	537 (9)	⊕⊕⊕⊖ Moderate [1]
Total remission (complete or partial) at final follow-up (range: 6 months to 12 years)	411 per 1000	604 per 1000 (459 to 803)	RR 1.37 (1.04 to 1.82)	468 (9)	⊕⊕⊕⊖ Moderate [1]
Complete remission at final follow-up (range: 9 months to 12 years)	171 per 1000	362 per 1000 (227 to 577)	RR 2.12 (1.33 to 3.38)	432 (8)	⊕⊕⊕⊖ Moderate [1]
Recurrence of disease (relapse) at final follow-up (range: 21 months to 12 years)	190 per 1000	152 per 1000 (76 to 307)	RR 0.80 (0.40 to 1.61)	161 (3)	⊕⊖⊖⊖ Very low [1,3]
100% increase in serum creatinine at final follow-up (range: 12 months to 12 years)	329 per 1000	194 per 1000 (99 to 382)	RR 0.59 (0.30 to 1.16)	332 (7)	⊕⊕⊕⊖ Moderate [1]
Adverse events - temporary/permanent discontinuation or hospitalisation at final follow-up (range: 9 months to 12 years)	5 per 1000	33 per 1000 (11 to 101)	RR 1.44 (0.96 to 2.15	184 (3)	⊕⊕⊖⊖ Low [1,4]
Adverse events - infection at 3 years	54 per 1000	91 per 1000 (16 to 511)	RR 1.68 (0.30 to 9.45)	70 (1)	⊕⊖⊖⊖ [1,3] Very low
Adverse events - malignancy at final follow-up (range: 3 to 4 years)	12 per 1000	19 per 1000 (2 to 146)	RR 1.63 (0.21 to 12.37)	199 (2)	⊕⊖⊖⊖ Very low [1,3]

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Study limitations: studies generally unclear or high risk of bias for many domains

2 Imprecision: estimate of effect includes negligible difference and considerable benefit and harm

3 Downgraded two levels: very serious imprecision - only one study and very wide confidence intervals indicating appreciable benefit and harm

4 Serious imprecision (few participants and few events)

Summary of findings 3.   Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids

Calcineurin inhibitors ± steroids versus to placebo/no treatment/supportive treatment/steroids for primary membranous nephropathy in adults with nephrotic syndrome

Patient or population: primary membranous nephropathy in adults with nephrotic syndrome
Setting: primary care

Intervention: calcineurin inhibitors ± steroids
Comparison: control (placebo/no treatment/supportive treatment/steroids)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with CNI			
Death at final follow-up (range: 9 to 60 months)	15 per 1000	25 per 1000 (7 to 92)	RR 1.69 (0.46 to 6.14)	296 (7)	⊕⊝⊝⊝ Very low [1,2,3]
End-stage kidney disease at final follow-up (range: 9 to 60 months)	82 per 1000	97 per 1000 (44 to 263)	RR 1.18 (0.54 to 2.60)	296 (7)	⊕⊝⊝⊝ Very low [1,3,4]
Total remission at final follow-up (range: 9 to 60 months)	416 per 1000	503 per 1000 (258 to 989)	RR 1.21 (0.62 to 2.38)	206 (5)	⊕⊕⊝⊝ Low [1,5]
Complete remission at final follow-up (range: 9 to 60 months)	146 per 1000	156 per 1000 (74 to 327)	RR 1.07 (0.51 to 2.24)	206 (5)	⊕⊕⊝⊝ Low [1,5]
Recurrence of disease (relapse) at final follow-up (range: 18 to 60 months)	259 per 1000	404 per 1000 (205 to 801)	RR 1.56 (0.79 to 3.09)	92 (2)	⊕⊝⊝⊝ Very Low [1,4]
100% increase in SCr at final follow-up (range: 18 to 60 months)	178 per 1000	149 per 1000 (66 to 331)	RR 0.84 (0.37 to 1.86)	117 (2)	⊕⊝⊝⊝ Very Low [1,4]
Adverse events - temporary or permanent discontin-uation/hospitalisation at final follow-up	0/63	2/98**	RR 5.45 (0.29 to 101.55)	156 (5)	⊕⊝⊝⊝ Very Low [1,4]

(range: 9 to 60 months)

Adverse events - infection at 36 months	54 per 1000	222 per 1000 (51 to 976)	RR 4.11 (0.94 to 18.06)	73 (1)	⊕⊖⊖⊖ **Very Low** [1,4]
Adverse events - malignancy at 36 months	0/38	2/69**	RR 2.79 (0.14 to 56.57)	107 (1)	⊕⊖⊖⊖ **Very Low** [1,2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Event rate derived from the raw data. A 'per thousand' rate is non-informative in view of the scarcity of evidence and zero events in the control group

CI: Confidence interval; **CNI:** calcineurin inhibitors; **RR:** Risk ratio

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GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Study limitations: studies generally unclear or high risk of bias for many domains
[2] Very serious imprecision (2 grades): few events, and estimate of effect includes negligible difference and considerable benefit and harm
[3] Serious Indirectness: insufficient follow-up for the outcome to occur ≤ 10 years
[4] Very serious imprecision: few events and estimate of effect includes negligible difference and considerable benefit and harm
[5] Serious imprecision: estimate of effect includes negligible difference and considerable benefit and harm
[6] Serious imprecision: only one study

Summary of findings 4. Calcineurin inhibitors ± steroids versus alkylating agents ± steroids

Calcineurin inhibitors ± steroids versus alkylating agents ± steroids for primary membranous nephropathy in adults with nephrotic syndrome

Patient or population: primary membranous nephropathy in adults with nephrotic syndrome
Setting: primary care

Intervention: calcineurin inhibitors ± steroids
Comparison: alkylating agents ± steroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)

	Risk with alky-lating agents ± steroids	Risk with CNI ± steroids			
Death at final follow-up (range: 9 to 60 months)	38 per 1000	34 per 1000 (13 to 89)	RR 0.90 (0.35 to 2.34)	394 (7)	⊕⊖⊖⊖ **Very low** [1,2,3]
End-stage kidney disease at final follow-up (range: 9 to 60 months)	15 per 1000	36 per 1000 (10 to 134)	RR 2.40 (0.64 to 9.01)	293 (5)	⊕⊖⊖⊖ **Very low** [1,2,3]
Total remission at final follow-up (range: 9 to 60 months)	784 per 1000	791 per 1000 (697 to 901)	RR 1.01 (0.89 to 1.15)	529 (10)	⊕⊕⊕⊖ **Moderate** [1]
Complete remission at final follow-up (range: 9 to 60 months)	429 per 1000	493 per 1000 (360 to 669)	RR 1.15 (0.84 to 1.56)	533 (10)	⊕⊕⊖⊖ **Low** [4,5]
Recurrence of disease (relapse) at final follow-up (range: 9 to 18 months)	61 per 1000	130 per 1000 (43 to 390)	RR 2.13 (0.71 to 6.37)	295 (6)	⊕⊕⊖⊖ **Low** [1,2]
100% increase in SCr at final follow-up (range: 9 to 60 months)	136 per 1000	95 per 1000 (41 to 226)	RR 0.70 (0.30 to 1.67)	132 (2)	⊕⊖⊖⊖ **Very low** [1,2,3]
Adverse events - temporary or permanent discontinuation/hospitalisation at final follow-up (range: 9 to 12 months)	42 per 1000	60 per 1000 (13 to 278)	RR 1.43 (0.31 to 6.67)	151 (3)	⊕⊖⊖⊖ **Very Low** [1,6]
Adverse events - infection (range: 9 to 30 months)	223 per 1000	191 per 1000 (96 to 381)	RR 0.86 (0.43 to 1.71)	552 (9)	⊕⊕⊖⊖ **Low** [1,2]
Adverse events - malignancy (range 30 to 36 months	33 per 1000	6 per 1000 (0 to 121)	RR 0.18 (0.01 to 3.69)	127 (2)	⊕⊖⊖⊖ **Very Low**[1,6]

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CNI:** calcineurin inhibitors; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] Study limitations (studies generally at unclear or high risk of bias for many domains)
[2] Serious imprecision: estimate of effect includes negligible difference and considerable benefit and harm
[3] Serious indirectness: Follow-up less than 10 years
[4] Serious study limitations: Unclear randomisation sequence generation and allocation concealment
[5] Serious inconsistency: point estimates vary widely, and the magnitude of statistical heterogeneity was high, with $I^2 = 53\%$
[6] Very serious imprecision (2 grades): few events, and estimate of effect includes negligible difference and considerable benefit and harm

BACKGROUND

Description of the condition

Membranous nephropathy is the most common cause of primary nephrotic syndrome in adults, and particularly affects elderly patients (Cameron 1996; Hofstra 2012; Vendemia 2001). Approximately 75% of membranous nephropathy cases are considered primary/idiopathic (Abe 1986) with the other 25% due to secondary causes, such as infections, autoimmune diseases, certain medications, or malignant diseases. Primary membranous nephropathy (PMN) shows a benign or indolent course in about one-third of patients, with a high rate of spontaneous remission in about 30% of patients (Polanco 2010). Approximately one third develops nephrotic syndrome but maintain normal kidney function. Despite this, 15% to 50% of patients who do not receive immunosuppressive treatment progress to end-stage kidney disease (ESKD) within 10 years (Deegens 2005; Ponticelli 2010; Waldman 2009). Recent findings of anti-phospholipase-A2-receptor-antibodies (anti-PLA2R) (Beck 2009) and anti-thrombospondin type-1 domain-containing protein 7A-antibodies (anti-THSD7A) (Tomas 2014) have improved understanding of the autoimmune pathophysiology of PMN. PMN is caused by the subepithelial formation of immune complex deposits in the kidney's glomerular basement membrane (GBM) (Lai 2015). The exact mechanisms behind this remain unclear, however, there are a number of presumptive hypotheses. Firstly, systemically pre-formed immune-complexes may deposit in the GBM, suggesting a similar pathophysiological mechanism as in lupus-associated nephritis (Lai 2015). Secondly, circulating antigens (such as during infection) might be targeted by antibodies, thus forming immune complexes that deposit in this site. this has especially been observed in infection-related (i.e. secondary) forms of membranous nephropathy, such as during infection with hepatitis B virus (Bhimma 2004; Lai 2000; Lai 2015). Thirdly, based on Heymann's model of nephritis (Heymann 1959), podocyte-antigens (such as megalin) may lead to binding of autoantibodies to the GBM's podocytes which cause the subepithelial deposits that are present in PMN (Tramontano 2006). However, thus far, this connection has not been clearly established through the extraction of anti-megalin-antibodies in PMN. Finally, the complement system and genetic factors might contribute to the autoimmune aetiology of PMN. So far, two associated genomic loci have been identified: chromosome 2q24 encodes for the anti-PLA2R-receptor auto-antibody and chromosome 6p21 encodes for HLADQA1, which might play pivotal roles in the pathogenesis of PMN (Bullich 2014; Stanescu 2011).

In a kidney biopsy, diagnosis of membranous nephropathy can be established by the presence of subepithelial immune deposits. In light-microscopy, a thickened, prominent GBM with "spikes" (local thickening of the membrane due to matrix reactions to the deposits) may indicate PMN, however electron microscopy and immunofluorescence are superior techniques in establishing the diagnosis of PMN. Immunofluorescence may show staining for PLA2R, complement (C3) and immunoglobulin (Fogo 2015; Lai 2015), whereas electron microscopy allows pathological staging of PMN into four stages according to the classification first suggested by Churg and Ehrenreich (Ehrenreich 1976). Electron microscopy may show "extensive foot process effacement and subepithelial deposits with increasing matrix spike reaction with advancing disease. As the disease progresses, an increase in matrix production can envelop these deposits and lead to a "laddering appearance" (Fogo 2015). The diagnosis of PMN is one of exclusion and secondary causes of membranous nephropathy must be ruled out.

Description of the intervention

Several immunosuppressive treatments have been used to treat patients with PMN and nephrotic syndrome, including corticosteroids, alkylating agents (chlorambucil and cyclophosphamide (CPA)), azathioprine (AZA), and mizoribine. More recently, other treatments such as calcineurin inhibitors (CNI) (cyclosporine (CSA) and tacrolimus (TAC)), mycophenolate mofetil (MMF), adrenocorticotropic hormone (ACTH), Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine), and therapeutic approaches such as biologics (rituximab and eculizumab) and high dose gamma-globulin have also been considered for PMN. However, due to the uncertain risk-benefit profile of immunosuppressive treatment and the lack of definite evidence on altering the long-term course of the disease, the most appropriate therapy remains unclear.

Currently, "Kidney Disease: Improving Global Outcomes" (KDIGO) guidelines suggest supportive therapy for all patients with PMN and immunosuppressive therapy should be considered only in patients with urinary protein exceeding 3.5 g/24 hours and eGFR ≤ 60 mL/min/1.73 m^2, or in patients with one risk for disease progression is present. Initial suggested therapy consists of a six-month course of alternating monthly cycles of oral and intravenous (IV) corticosteroids and CPA or TAC or rituximab as alternatives (KDIGO 2020).

How the intervention might work

Given the autoimmune aetiology of PMN, immunosuppressive treatment is used to decrease the overall activity of the immune system, leading to reduced damage to the kidneys. Most immunosuppressive drugs suppress the immune system more broadly, whereas some therapies such as rituximab aim to target specific parts of the immune system.

Why it is important to do this review

In the 2004 Cochrane review (Schieppati 2004), 19 studies with 1025 participants were included. This review found that immunosuppressive treatments could increase complete or partial remission. However, the long-term effects of immunosuppressive treatments on definite endpoints such as death (any cause) or the prevention of ESKD could not be demonstrated. Immunosuppressive treatments were found to lead to a significantly higher risk of severe adverse events.

In the 2014 update of the Cochrane review (Chen 2014), 39 studies with 1825 participants overall were included, which further strengthened the certainty of the evidence. New treatments have more recently been investigated in randomised controlled trials (RCTs) for the treatment of PMN, and studies have reported on the use of new therapies such as monoclonal antibodies in patients with PMN and traditional Chinese medicine (Shenqi particles) (Chen 2013e). Most notably, rituximab (GEMRITUX 2017; MENTOR 2015) have been tested in studies for PMN.

OBJECTIVES

Our objective was to assess the evidence and evaluate the safety and efficacy of immunosuppressive treatments for adult patients with PMN and nephrotic syndrome. The following questions relating to the management of PMN and nephrotic syndrome were addressed:

1. Is immunosuppressive therapy superior to non-immunosuppressive therapy?
2. If so, which immunosuppressive agent/s is the most effective and safe in treating patients with IMN and nephrotic syndrome?
3. What routes of administration and duration of therapy should be used?

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs that assessed the effects of immunosuppressive treatments in adult patients with IMN and nephrotic syndrome.

Types of participants

Inclusion criteria

- Adults (at least 18 years of age)
- Diagnosis of PMN, established by kidney biopsy (and possibly be further proven by detection of anti-PLA2R- or anti-THSD7-antibodies). Prior to 2009, membranous nephropathy was determined by kidney biopsy. Other underlying causes of membranous nephropathy were ruled out clinically to establish the diagnosis of primary membranous nephropathy
- Diagnosis of nephrotic syndrome as defined by the authors in each study. In studies that included > 50% non-nephrotic patients, analyses were restricted to nephrotic patients only. In the absence of an explicit definition of nephrotic syndrome, the cut-off value of proteinuria above 3.5 g/24 hours was used.

Exclusion criteria

Secondary forms of membranous nephropathy were excluded. We also excluded studies where it was impossible to identify how many adult PMN patients had nephrotic syndrome.

Types of interventions

We considered the following immunosuppressive treatments: corticosteroids, alkylating agents (chlorambucil and CPA), CNI (CSA and TAC), sirolimus, MMF, and synthetic ACTH. Other less commonly studied immunosuppressive regiments such as Tripterygium wilfordii (a traditional Chinese immunosuppressive medicine); Shenqi particles (a traditional Chinese immunosuppressive medicine), leflunomide, AZA, mizoribine, methotrexate, and levamisole were also investigated. Furthermore, high dose gamma-globulin and biologics (rituximab and eculizumab) were included in this review.

Non-immunosuppressive treatments were excluded: drugs aimed to reduce proteinuria through inhibition of the renin-angiotensin system (e.g. angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or aliskiren); drugs aimed to correct dyslipidaemia (e.g. statins); anti-aldosterone drugs (e.g. spironolactone); nonsteroidal anti-inflammatory drugs (e.g. indomethacin).

Types of outcome measures

Primary outcomes

- Death (any cause)
- ESKD (requiring kidney replacement therapy) at the last follow-up
- Complete or partial (total) remission, complete remission alone, and partial remission alone at different time points and at the last follow-up.

Complete and partial remission of nephrotic syndrome was assessed according to the definition provided in each study. In the absence of an explicit definition, complete remission was defined as proteinuria < 0.3 g/24 hours and with a normal or stable serum creatinine (SCr) (within 50% of baseline value). In the absence of an explicit definition, partial remission was defined as a reduction in proteinuria by at least 50% and remaining between 0.3 to 3.5 g/24 hours with a normal or stable SCr (within 50% of baseline value).

Secondary outcomes

- Relapse (recurrence of disease) after initial remission
- 100% increase (doubling) in SCr from baseline at different time points and at the last follow-up
- Quality of Life (as measured by study investigators).

The following side effects (toxicity) of treatments were considered.

- Adverse events (as defined by the study investigators)
  - Temporary or permanent discontinuation or hospitalisation due to adverse events
  - Infection
  - Malignancy.

The following continuous kidney function outcomes were analysed at the end of follow-up.

- SCr (µmol/L)
- Serum albumin (g/L)
- Glomerular filtration rate (GFR) (mL/min/1.73 m²)
- Proteinuria (g/24 hours)
- 50% increase in SCr from baseline at different time points and at the last follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 1 April 2021 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP

5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Handsearching proceedings of major rheumatology conferences.
3. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.

Data collection and analysis

Selection of studies

A search was performed to identify relevant studies. In this update, study selection was done by two authors (GW, TvG). The titles and abstracts of retrieved citations, and where necessary the full-text articles, were independently evaluated by two authors (GW, TvG). Disagreements were resolved by consulting a third author (DT). Where duplicated reports of the same study were confirmed, the initial first complete publication was selected (the index publication) and was the primary data source, but any other additional prior or subsequent reports were also included. These additional prior or subsequent reports containing supplementary outcome data (such as longer-term follow-up, or different outcomes) also contributed to the review and meta-analysis.

Data extraction and management

Data extraction was carried out independently by two authors (GW, TvG) using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. In case of duplicates, reports were grouped together and the publication with the most complete data was included. When relevant outcomes were only published in earlier versions, these data were used. Any differences between published versions were highlighted. A third author (DT) resolved these discrepancies. If needed, further details were requested by written correspondence to principal investigators and any relevant information obtained in this manner was included in this review. We also contacted principal investigators for missing data whenever necessary.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors (GW, TvG) using the risk of bias assessment tool (Higgins 2011) (see Appendix 2). Publication bias was especially investigated for the comparison of immunosuppressive treatments versus no immunosuppression.

- Was there adequate sequence generation (selection bias)?

- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

Dichotomous data

For dichotomous outcomes (death, ESKD, total remission, complete remission, partial remission, relapse, doubling of SCr, 50% increase in SCr, adverse events, infection, malignancy) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). RR was the selected effect measure because it describes the multiplication of risk and is relatively easy to understand, is a bounded measure of effect that provides a consistent estimate of effect.

Continuous data

When a continuous scale of measurement was used (eGFR, SCr, 24-hour proteinuria, quality of life), the mean difference (MD) with 95% CI was chosen or the standardised mean difference (SMD) was considered if a different scale was adopted or SMDs were reported in a publication.

Unit of analysis issues

In studies with multiple intervention arms we considered the following:

1. If different classes (for example, CPA, or MMF versus steroids), we included each treatment group in a separate meta-analysis, ensuring that we did not include outcome data for the control group participants more than once in a single meta-analysis
2. If interventions were the same therapy (for example Mizoribine 150 mg once/day versus Mizoribine 50 mg three times/day), we compared the two intervention arms with each other as in the study.

Dealing with missing data

Missing data were assessed for each included study. For missing participants due to drop-out, intention-to-treat analyses (ITT) were performed if the data were reported elsewhere or were provided by principal investigators in response to our requests for additional information. For missing statistics such as standard deviations, these studies were not considered in the meta-analysis unless the missing data could be appropriately imputed using methods recommended by the Cochrane Collaboration. We included missing participants in the analyses. Issues of missing data and imputation methods (for example last-observation-carried-forward) were critically appraised (Higgins 2011).

In one study that reported median and interquartile ranges (GEMRITUX 2017), we calculated mean and standard deviations, using the formula suggested by Hozo 2005 for larger sample sizes,

given the sample sizes of both groups in the study exceeded 25. We used the Vassarstats calculator (http://vassarstats.net/median_range.html), which is based on the Hozo formula.

We also contacted principal investigators to request missing data where possible.

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot, by examining the direction of the effect estimates and the overlap of confidence intervals. Heterogeneity was then further assessed by using the Chi² test, with a p-value less than 0.1 used to denote statistical significance, and with the I² statistic calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity rather than chance (Higgins 2011). A guide to the interpretation of I² values (Higgins 2003) is as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I² depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi² test, or a confidence interval for I²).

Assessment of reporting biases

We planned to assess for publication bias for the primary outcomes. We made every attempt to minimise publication bias by including unpublished studies (for example, including abstract-only publications and searching online trial registries). To assess publication bias we used funnel plots of the log odds ratio (OR) (effect versus standard error of the effect size) when a sufficient number of studies were available (10 studies or more) (Harbord 2009; Higgins 2011). For the analysis and interpretation of the funnel plots, other reasons for asymmetry besides publication bias were considered (differences in methodological quality and true heterogeneity in intervention effects). However, the limited amount of study data did not enable meaningful interpretation.

Data synthesis

Data were abstracted from individual studies and then pooled for summary estimates using a random-effects model. The random-effects model was chosen because it provides a more conservative estimate of effect in the presence of known or unknown potential heterogeneity (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are hypothesis-generating rather than hypothesis testing and should be treated with caution. Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants and interventions). Heterogeneity among participants could be related to age and disease severity. Heterogeneity in treatments could be related to the route, dose, and duration of therapies in the studies. Subgroup analysis was also performed to explore the following covariates: the language of publication, source of funding and sample size calculation as well as anti-PLA2R-

levels. However, there was limited data reported to undertake these subgroup analyses, in particular the reporting of anti-PLA2R-levels.

Sensitivity analysis

We considered the following sensitivity analyses in order to explore the influence of the following factors.

- Repeating the analysis excluding unpublished studies or low-quality studies based on the assessment of the risk of bias
- Repeating the analysis excluding studies that were of insufficient follow-up for the primary outcome
  - Death: 10-year follow-up
  - ESKD:10-year follow-up
  - Complete remission:2-year follow-up
- Repeating the analysis excluding any very long or very large study to determine the extent to which they unduly influenced the results.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as to the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Death
- ESKD
- Total remission (complete or partial)
- Complete remission
- Recurrence (relapse) of disease
- Doubling of SCr from baseline
- Adverse events
  - Temporary or permanent discontinuation or hospitalisation due to adverse events
  - Infection
  - Malignancy

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

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Results of the search

We searched the Cochrane Kidney and Transplant Register of Studies 1 April 2021 and identified 82 new reports. After full-text assessment, 57 new studies were identified; 24 new included studies (40 reports), 13 new studies (14 reports) were excluded, and 16 new ongoing studies were identified. Four new studies are awaiting assessment (recently completed but no data available). We also identified eight new reports of existing included and excluded studies.

In this update, we also reassessed the existing studies.

- Included studies: 1 study moved to excluded (not RCT)
- Excluded studies: 1 study moved to included; 10 studies deleted (not RCT, wrong population)
- Studies awaiting classification: 5 studies moved to included; 1 study deleted
- Ongoing studies: 8 studies moved to included studies; 3 studies move to awaiting classification.

A total of 65 studies (127 reports, 3807 randomised participants; Figure 1) were included, 25 excluded, 5 are awaiting assessment, and there are 20 ongoing studies.

Figure 1. 2021 review update: study selection flow diagram.
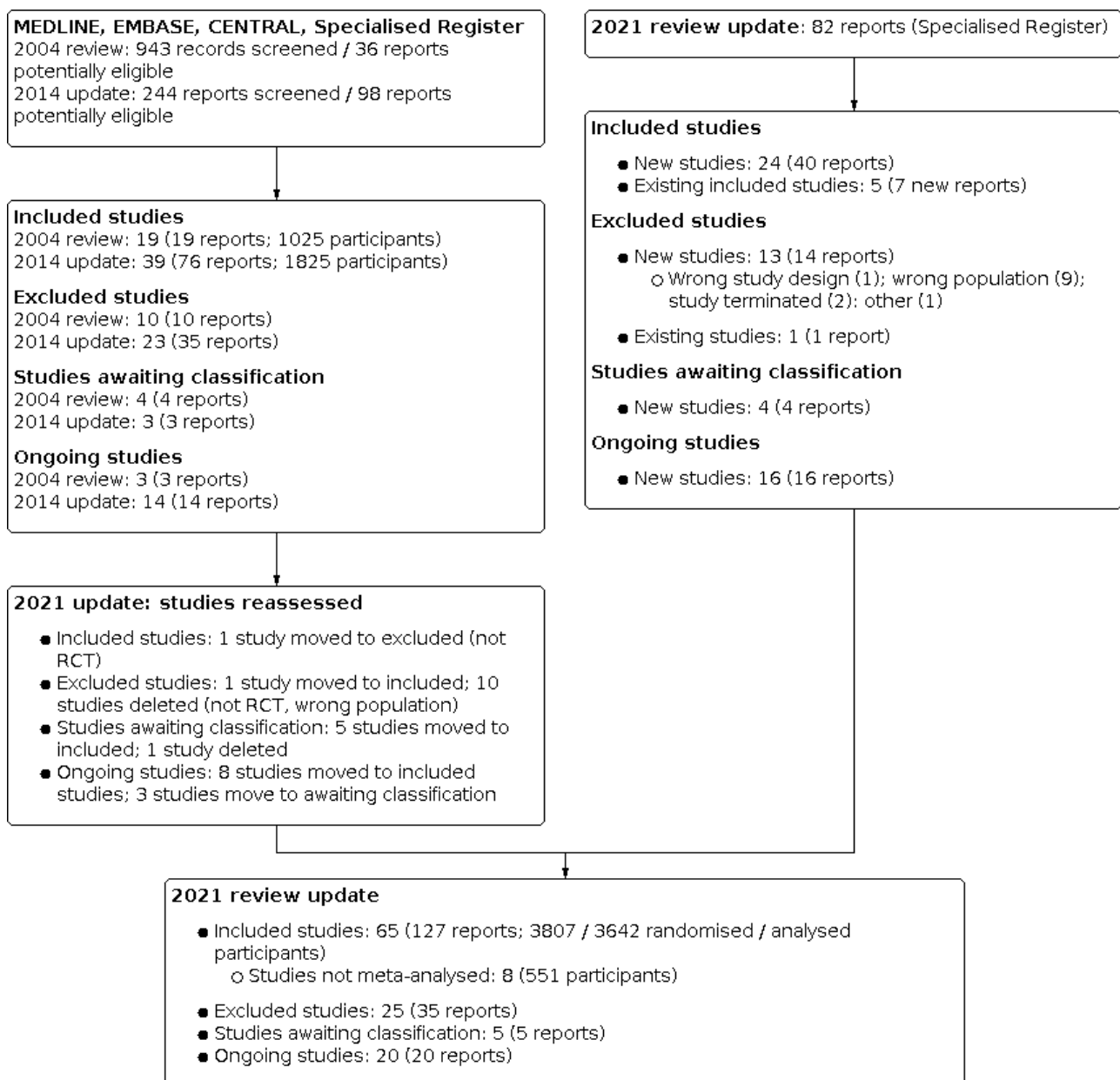
Included studies

A total of 65 studies (3807 randomised participants) investigating immunosuppressive therapy in adults with primary membranous nephropathy and nephrotic syndrome were included in this updated review (Figure 1). The median sample size was 57 (range 9 to 190) patients. The median follow-up time was 26 months

(range 6 months to 12 years). Unpublished data were provided by the authors of two studies (Braun 1995; CYCLOMEN 1994). Eight studies (Appel 2002; Austin 1996a; Dyadyk 2001a; Hladunewich 2014; Sahay 2002; Stegeman 1994; Sun 2014; Zhang 2015d) could not be included in the meta-analyses as we were unable to extract the necessary data. One study was prematurely terminated due to a low accrual rate (Stegeman 1994).

Four studies only investigated patients with deteriorating kidney function (Cattran 1995; CYCLOMEN 1994; Falk 1992; Reichert 1994). Some studies did not report whether or not they included patients with deteriorating kidney function.

Five studies involved patients who were resistant to corticosteroids monotherapy (Koshikawa 1993; Saito 2014; Shibasaki 2004) or corticosteroids plus alkylating agents (Cattran 2001; Naumovic 2011). Eleven studies included patients who had previously received immunosuppressive treatment before inclusion in the study or who had previously received immunosuppressive treatments if a defined wash-out period of not receiving any immunosuppressive treatment was completed (Cattran 1989; Chan 2007; Chen 2010a; Donadio 1974; Jha 2007; Liu 2009b; Murphy 1992; Praga 2007; Reichert 1994; Shibasaki 2004; Tiller 1981).

Studies were arranged into the following comparison groups.

1. Corticosteroids versus placebo/no treatment
2. Immunosuppressive treatments ± steroids versus placebo/no treatment/non-immunosuppressive treatments
3. Immunosuppressive treatments ± steroids versus steroids monotherapy
4. CPA + leflunomide + steroid versus CPA + steroid
5. Oral alkylating agents ± steroids versus placebo/no treatment/ supportive treatment/steroids
6. CPA + steroids versus chlorambucil + steroids
7. Early (immediate) CPA + steroids versus late (when SCr increased > 25%) CPA + steroids
8. CPA + leflunomide + steroids versus leflunomide + steroids
9. MMF + CNI versus CNI
10. CNI ± steroids versus placebo/no treatment/supportive treatment/steroids
11. CNI ± steroids versus alkylating agents ± steroids
12. Short-course tacrolimus + steroids short-course versus long-course tacrolimus + steroids
13. Cyclosporine + steroids versus steroids alone
14. Cyclosporine + steroids (3.0 mg/kg, once/day) versus cyclosporine + steroids (1.5 mg/kg, twice/day)
15. Cyclosporine + steroids versus tacrolimus + steroids
16. Cyclosporin versus AZA
17. AZA ± steroids versus no treatment
18. MMF versus no treatment/supportive therapy

19. MMF ± steroids versus alkylating agents ± steroids
20. MMF ± steroids versus CNI ± steroids
21. ACTH versus no treatment
22. ACTH versus alkylating agents + steroids
23. Mizoribine ± steroids versus placebo/no treatment/ corticosteroids
24. Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day)
25. Rituximab + supportive therapy versus supportive therapy alone
26. Rituximab versus cyclosporine
27. Traditional Chinese medicine versus immunosuppressive therapy (Shenqi particles; Tripterygium wilfordii)

The following comparisons were planned however no data were available.

1. Two non-steroid immunosuppressive agents versus one non-steroid immunosuppressive agent
2. CPA + leflunomide + steroid versus CPA + steroids
3. ACTH 40 IU versus ACTH 80 IU

Studies awaiting classification

Five studies are awaiting assessment (NCT00302523; NCT00518219; NCT01093157; NCT01386554; NCT01845688) and will be assessed in a future update when the methods and results become available.

Ongoing studies

We identified 20 ongoing studies which will be assessed in a future update (Chen 2020; ChiCTR-INR-15007440; ChiCTR-INR-17011400; ChiCTR-INR-17012070; ChiCTR-INR-17012212; ChiCTR-IPR-16008344; ChiCTR-IPR-16008527; ChiCTR-IPR-17011386; ChiCTR-IPR-17011702; ChiCTR-TRC-11001144; CTRI/2017/05/008648; EudraCT2007-005410-39; HIGHNESS 2011; ISRCTN17977921; ISRCTN70791258; MMF-STOP-IMN 2017; NCT02173106; RI-CYCLO 2020; STARMEN 2015; UMIN000001099).

Excluded studies

Twenty-five studies (35 records) were excluded. Reasons for exclusion were: wrong study design or conduct (Branten 1998; Michail 2004; Sharma 2009; Sun 2008); wrong or mixed population (Ambalavanan 1996; Badri 2013; Black 1970; ChiCTR-IPR-14005366; Edefonti 1988; Heimann 1987; Krasnova 1998; Lagrue 1975; Li 2012e; Liu 2016c; Majima 1990; MRCWP 1971; Nand 1997; Plavljanic 1998; Ponticelli 1993a; Sharpstone 1969; Xu 2011; Yang 2016a); study was terminated (EudraCT2011-000242-38; NCT01762852); and the status of one study is unknown 10 years after initial registration (ChiCTR-TRC-09000539).

Risk of bias in included studies

See Figure 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
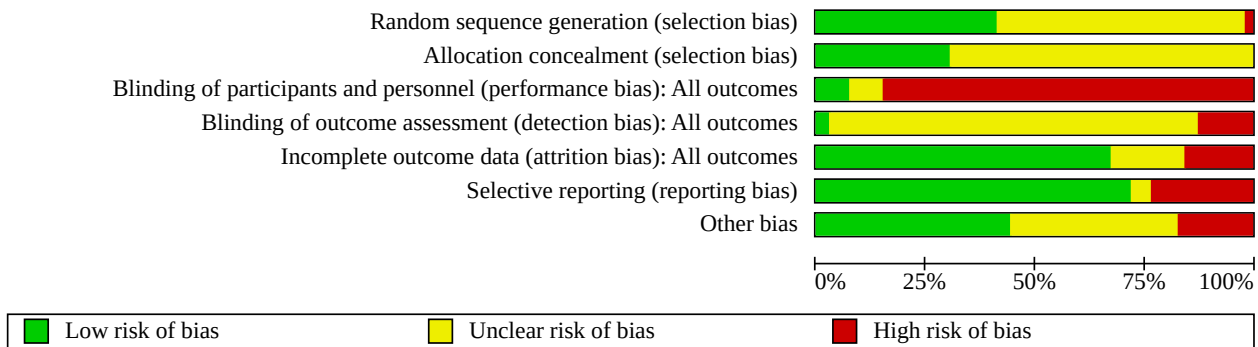
Allocation

Random sequence generation

Twenty-seven studies (48%) specified appropriate methods for random sequence generation and were considered to be at low risk of bias. Appropriate methods of randomisation were not reported in 39 studies (51%). These studies were thus considered to have an unclear risk of bias. One study (1%) was considered to have a high risk of bias for random sequence generation.

Allocation concealment

Twenty studies (31%) reported appropriate allocation concealment methods and were considered to be at low risk of bias, while the remaining45 studies (69%) did not provide details about allocation concealment and were considered to have an unclear risk of bias.

Blinding

Performance bias

Appropriate procedure relating to the blinding of participants was reported in five studies (8%) and were considered to be at low risk of bias. Five studies (5%) were considered to have an unclear risk of bias, and the remaining 55 studies (84%) did not perform adequate blinding of participants and were considered to be at high risk of bias.

Detection bias

Adequate blinding of personnel and outcome assessors was reported in four studies (6%) and were considered to be at low risk of bias. Fifty-five studies (85%) were considered to have an unclear risk of bias, and the remaining six studies (9%) did not perform adequate blinding of personnel and outcome assessors and were considered to be at high risk of bias.

Incomplete outcome data

Forty-four studies (68%) were considered to be at low risk of bias; 11 studies (17%) were considered to have an unclear risk of bias, and 10 studies (15%) were considered to be at high risk of bias.

Selective reporting

Forty-seven studies (72%) were considered to be at low risk of bias and, three studies (5%) were considered to have an unclear risk of bias. Fifteen studies (23%) were considered to be at high risk of bias.

Publication bias

It has been recommended that tests for publication bias should be used only when at least 10 studies are included in the meta-analysis (Harbord 2009). Given the wide variety of different treatments tested in studies, comparisons did not include more than 10 studies, so that publication bias could not be assessed properly (Figure 3).

Figure 3. Publication bias of comparison: 1 Immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive treatments, outcome: 1.1 death or risk of ESKD (Harbord test) (A); 1.6 complete or partial remission (Harbord test) (B); 1.1 death or risk of ESKD (funnel plot) (C); and 1.6 complete or partial remission (funnel plots) (D).
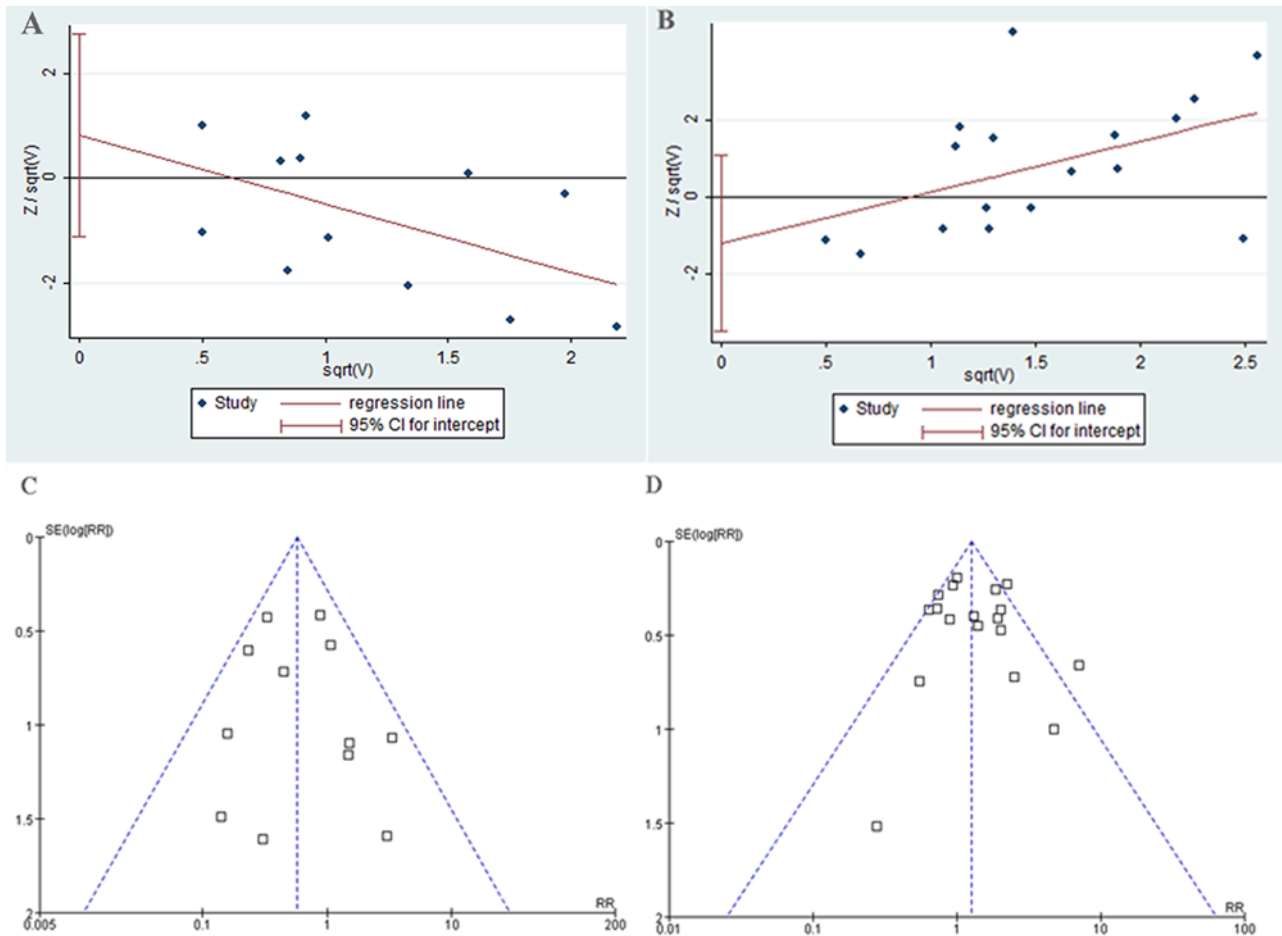
Other potential sources of bias

Twenty-nine studies (45%) were considered to be at low risk of bias; twenty-five studies (38%) were considered to have an unclear risk of bias. The remaining 11 studies (17%) were assessed as having a high risk of bias using GRADE in this section as there were concerns about potential financial interest or other significant conflicts of interest. Four studies were primarily funded and executed by private companies. These studies were evaluated to be at high risk of bias. Five studies received substantial financial and/or technical support or donated medicines from private companies. These studies were rated as low risk of bias if no employees of private companies were directly involved in the execution of the trial, data analysis and/or publication. Funding from foundations, not-for-profit and philanthropic organisations were not considered to increase the risk of bias. The underlying rationale has been detailed in the risk of bias tables in the Characteristics of included studies.

Effects of interventions

See: **Summary of findings 1** Immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive supportive treatment; **Summary of findings 2** Oral alkylating agents ± steroids versus placebo/no treatment/steroids; **Summary of findings 3** Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids; **Summary of findings 4** Calcineurin inhibitors ± steroids versus alkylating agents ± steroids

See Summary of findings tables for the main comparisons:

- Summary of findings 1: Immunosuppressive treatments versus placebo/no treatment/non-immunosuppressive treatments
- Summary of findings 2: Oral alkylating agent with or without steroids versus placebo/no treatment/steroids
- Summary of findings 3: CNI versus placebo/no treatment/supportive therapy/steroids
- Summary of findings 4: CNI with or without steroids versus alkylating agents with or without steroids.

1) Corticosteroids versus placebo or no treatment

Four studies (Cameron 1990; Cattran 1989; Coggins 1979; Donadio 1974) investigated monotherapy with corticosteroids versus placebo or no treatment.

Compared to placebo or no treatment, corticosteroids may make little or no difference to death (Analysis 1.1 (3 studies. 33 participants): RR 0.59, 95% CI 0.11 to 3.23, I² = 32%), ESKD (Analysis 1.2 (3 studies 333 participants): RR 0.83, 95% CI 0.35 to 1.98; I² = 17%), total (complete or partial) remission (Analysis 1.3 (3 studies, 295 participants): RR 1.15, 95% CI 0.58 to 2.27; I² = 69%), complete remission (Analysis 1.4 (2 studies, 192 participants): RR 0.64, 95% CI 0.29 to 1.42; I² = 0%), or partial remission (Analysis 1.5 (2 studies, 192 participants): RR 1.34, 95% CI 0.34 to 5.21; I² = 75%)

Compared to placebo or no treatment, corticosteroids may make little or no difference to the number with doubling of SCr (Analysis 1.6.1 (3 studies, 120 participants): RR 0.41, 95% CI 0.11 to 1.53; I² = 19%) or adverse events (Analysis 1.7 (2 studies, 175 participants): RR 1.04, 95% CI 0.11 to 9.82; I² = 0%).

It is unclear whether corticosteroids compared to placebo or no treatment improve kidney function (Analysis 1.8; Analysis 1.9; Analysis 1.10). The number relapsing after complete or partial remission was not reported.

2) Immunosuppressive treatment versus placebo, no treatment or non-immunosuppressive treatment

Eighteen studies investigated immunosuppressive treatment versus placebo/no treatment/non-immunosuppressive treatments (Arnadottir 2006; Badri 2013; Braun 1995; Cattran 1989; Coggins 1979; CYCLOMEN 1994; Donadio 1974; Dussol 2008; GEMRITUX 2017; Imbasciati 1980; Jha 2007; Koshikawa 1993; Kosmadakis 2010; Murphy 1992; Praga 2007; Sharma 2009; Shibasaki 2004; Silverberg 1976).

Compared to placebo/no treatment/non-immunosuppressive treatment, immunosuppressive treatment probably makes little or no difference to death (Analysis 2.1 (16 studies, 944 participants): RR 0.73, 95% CI 0.34 to 1.59; I² = 0%; moderate certainty evidence) but may reduce the overall risk of ESKD by 40% (Analysis 2.2 (16 studies, 944 participants): RR 0.59, 95% CI 0.35 to 0.99; I² = 22%; moderate certainty evidence) at final follow-up (9 months to 12 years), and in studies with follow-up of ≥ 10 years immunosuppressive treatment probably decreases ESKD by 71% (Analysis 2.2.2 (2 studies, 185 participants): RR 0.29, 95% CI 0.13 to 0.63; I² = 0%).

Compared to placebo/no treatment/non-immunosuppressive treatment, immunosuppressive treatment probably increases the number who achieve total remission (Analysis 2.3 (16 studies, 879 participants): RR 1.44, 95% CI 1.05 to 1.97; I² = 73%; moderate certainty evidence) and complete remission (Analysis 2.4 (16 studies, 879 participants): RR 1.70, 95% CI 1.05 to 2.75; I² = 43%; moderate certainty evidence), and may increase the number achieving partial remission (Analysis 2.5 (16 studies, 879 participants): RR 1.36, 95% CI 0.93 to 1.98; I² = 60%). The number relapsing after complete or partial remission may increase with immunosuppressive treatment (Analysis 2.6 (3 studies, 148 participants): RR 1.73, 95% CI 1.05 to 2.86; I² = 0%; low certainty evidence).

Immunosuppressive treatment probably decreases the number with doubling of SCr (Analysis 2.7 (9 studies, 447 participants): RR 0.46, 95% CI 0.26 to 0.80; I² = 21%; moderate certainty of the evidence), but may increase the number experiencing temporary or permanent discontinuation/hospitalisation due to adverse events

(Analysis 2.9 (18 studies, 927 participants): RR 5.33, 95% CI 2.19 to 12.98; I² = 0%; low certainty evidence). Immunosuppressive treatment has uncertain effects on infection and malignancy.

Immunosuppressive treatment may improve GFR (Analysis 2.14), proteinuria (Analysis 2.15), but not SCr (Analysis 2.13).

3) Immunosuppressive treatments with or without steroids versus steroids alone

Five studies (Ahmed 1994; Falk 1992; Hasegawa 2017; Pahari 1993; Ponticelli 1992) compared immunosuppressive treatment with steroids alone.

Immunosuppressive treatment may make little or no difference to death (Analysis 3.1) or ESKD (Analysis 3.2), but may increase the number achieving total remission (Analysis 3.3 (5 studies, 241 participants): (RR 1.47, 95% CI 1.19 to 1.82; I² = 0%) and complete remission (Analysis 3.4 (4 studies, 205 participants): RR 1.89, 95% CI 1.34 to 2.65; I² = 0%). There were no differences between studies that had a follow-up of less than 2 years and studies with 2 years or more of follow-up.

Immunosuppressive treatment had uncertain effects on doubling of SCr (Analysis 3.7 (3 studies, 97 participants): RR 1.19, 95% CI 0.52 to 2.71; I² = 0%), adverse events (Analysis 3.9; Analysis 3.8), and relapse after complete or partial remission (Analysis 3.6).

4) Cyclophosphamide plus leflunomide plus steroids versus cyclophosphamide plus steroids

Liu 2015e reported CPA plus leflunomide plus steroids may increase complete remission compared to leflunomide plus steroids (Analysis 4.1 (1 study. 48 participants): RR 1.50, 95% CI 1.04 to 2.17). No other outcomes were reported.

5) Oral alkylating agents with or without steroids versus placebo/no treatment/supportive treatment/steroids

Nine studies (Ahmed 1994; Braun 1995; Donadio 1974; Hasegawa 2017; Imbasciati 1980; Jha 2007; Kosmadakis 2010; Pahari 1993) investigated oral alkylating agents with or without steroids versus placebo/no treatment/supportive treatments/steroids only.

Oral alkylating agents may have little or no effects on death (Analysis 5.1 (7 studies, 440 participants): RR 0.76, 95% CI 0.25 to 2.30; I² = 0%; low certainty evidence) compared with no treatment/placebo/steroids alone but probably decreases ESKD at final follow-up (Analysis 5.2 (9 studies, 537 participants): RR 0.42, 95% CI 0.24 to 0.74; I² = 0%; moderate certainty evidence). In moderate certainty evidence, total and complete remission may increase using oral alkylating agents with or without steroids (Analysis 5.3 (9 studies, 468 participants): RR 1.37, 95% CI 1.04 to 1.82; I² = 70%; Analysis 5.4 (8 studies, 432 participants): RR 2.12, 95% CI 1.33 to 3.38; I² = 37%), but uncertain effects on partial remission (Analysis 5.5 (8 studies, 432 participants): RR 0.94, 95% CI 0.57 to 1.55; I² = 57%) and the number relapsing after complete or partial remission (Analysis 5.7). There was no evidence of difference for studies with < 10 years follow-up and the study with ≥ 10 years follow-up.

It is uncertain whether oral alkylating agents decrease the doubling of SCr (Analysis 5.6.1 (7 studies, 332 participants): RR 0.59, 95% CI 0.30 to 1.16; I² = 42%; low certainty evidence). Oral alkylating agents compared with placebo/no treatment/

steroids may increase temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 5.8 (8 studies 439 participants): RR 6.82, 95% CI 2.24 to 20.71; I² = 0%; low certainty evidence). Oral alkylating agents with or without steroids had uncertain effects on infection (Analysis 5.9.2), malignancy (Analysis 5.9.3) and final GFR (Analysis 5.10).

6) Cyclophosphamide plus steroids versus chlorambucil plus steroids

Two studies (Ponticelli 1998; Reichert 1994) investigated CPA plus steroids versus chlorambucil plus steroids.

There was only one death reported in the CPA group in Reichert 1994. We are uncertain whether CPA plus steroids increases the risk of ESKD (Analysis 6.2 (2 studies, 115 participants): RR 3.01, 95% CI 0.61 to 14.81; I² = 0%).

CPA plus steroids compared with chlorambucil plus steroids may increase total remission (Analysis 6.3 (2 studies, 115 participants): RR 1.23, 95% CI 1.01 to 1.50; I² = 0%; low certainty evidence), however, it had uncertain effects on complete (Analysis 6.4) and partial remission (Analysis 6.5) (low certainty evidence). Relapse after complete or partial remission was not reported.

It is uncertain whether CPA plus steroids decreases the number with doubling of SCr (Analysis 6.6), decreases temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 6.7), improves kidney function (Analysis 6.8), or decreases proteinuria (Analysis 6.9).

7) Early (immediate) cyclophosphamide versus late (serum creatinine increase > 25%) cyclophosphamide plus steroids

Hofstra 2010 investigated early (immediate) initiation of therapy with CPA versus late (SCr increase by > 25%) initiation of therapy with CPA and steroids. Participants were followed up for a mean period of 72 ± 22 months.

Hofstra 2010 reported one death in the initiation group (Analysis 7.1), and one patient reached ESKD in the early initiation group (Analysis 7.2).

We are uncertain whether early initiation of CPA improved total (Analysis 7.3), complete (Analysis 7.4) or partial remission (Analysis 7.5) due to very low certainty evidence. We are also uncertain whether early initiation of CPA improves temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 7.6), SCr (Analysis 7.7), eGFR (Analysis 7.8), or proteinuria (Analysis 7.9), because the certainty of the evidence is very low.

Relapse and other adverse events were not reported.

8) Cyclophosphamide plus leflunomide plus steroids versus leflunomide plus steroids

Liu 2015e reported CPA plus leflunomide plus steroids versus leflunomide plus steroids may make little or no difference to complete remission (Analysis 8.1 (1 study, 48 participants): RR 1.40, 95% CI 0.99 to 1.98) or malignancy (Analysis 8.2). No other outcomes were reported.

9) Mycophenolate mofetil plus calcineurin inhibitors versus calcineurin inhibitors alone

Jurubita 2012 investigated CSA plus MMF versus CSA alone and Nikolopoulou 2019 investigated TAC plus MMF versus TAC alone.

Nikolopoulou 2019 reported one patient in each group reached ESKD (Analysis 9.1). CNI plus MMF may increase both total remission (Analysis 9.2 (2 studies, 58 participants): RR 1.21, 95% CI 0.99 to 1.48; I² = 0%; low certainty of the evidence) and complete remission (Analysis 9.3 (2 studies, 58 participants): RR 1.18, 95% CI 0.93 to 1.51; I² = 0%), but not partial remission (Analysis 9.4). Nikolopoulou 2019 reported no difference in the number of relapses after complete or partial remission (Analysis 9.5) but more adverse events with MMF plus TAC (Analysis 9.6).

No other outcomes were reported.

10) Calcineurin inhibitors versus placebo/no treatment/ supportive treatment/steroids

Seven studies compared CNI with placebo/no treatment/ supportive treatments/steroids (Braun 1995; Cattran 1995; Cattran 2001; CYCLOMEN 1994; Howman 2013; Kosmadakis 2010; Praga 2007)

We are uncertain whether CNI increased or decreased the risk of death or ESKD because of very low certainty evidence. The certainty was downgraded because of few events reported in studies which resulted in wide CIs (Analysis 10.1; Analysis 10.2).

We are uncertain whether CNI increases or decreases total remission (Analysis 10.3 (5 studies, 206 participants): RR 1.21, 95% CI 0.62 to 2.38; I² = 77%), complete remission (Analysis 10.4 (5 studies, 206 participants): RR 1.07, 95% CI 0.51 to 2.24; I² = 15%), partial remission (Analysis 10.5 (5 studies. 206 participants): RR 1.08, 95% CI 0.53 to 2.22; I² = 65%), or relapse after complete or partial remission (Analysis 10.6).

CNI had uncertain effects on SCr increase (Analysis 10.7), temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 10.8), serious adverse events (Analysis 10.9.1), infection (Analysis 10.9.2), or malignancy (Analysis 10.9.3).

11) Calcineurin inhibitors with or without steroids versus alkylating agents with or without steroids

Eleven studies (Agarwal 2012a; Braun 1995; Chen 2010a; He 2013; Howman 2013; Kosmadakis 2010; Liang 2017; Peng 2016; Ramachandran 2016; Xu 2010; Xu 2013a) investigated CNI with or without steroids versus alkylating agents with or without steroids.

We are uncertain whether CNI with or without steroids increases or decreases the risk of death (Analysis 11.1) or ESKD (Analysis 11.2) because the certainty of the evidence is very low (due to serious risk of bias, imprecision, indirectness and insufficient follow-up).

CNI with or without steroids may make little or no difference to total remission (Analysis 11.3.1 (10 studies, 538 participants): RR 1.01, 95% CI 0.89 to 1.15; I² = 53%; moderate certainty evidence), complete remission (Analysis 11.4.1 (10 studies, 538 participants): RR 1.15, 95% CI 0.84 to 1.56; I² = 56%; low certainty evidence), or partial remission (Analysis 11.5.1 (10 studies, 528 participants): RR 0.82, 95% CI 0.58 to 1.18; I² = 48%) compared to alkylating agents

at final follow-up (9 to 60 months). For studies with a final follow-up of ≥ 2 years, there was little or no difference to total, complete or partial remission. CNI with or without steroids may increase relapse at final follow-up < 2 years (Analysis 11.6 (6 studies, 295 participants): RR 2.13, 95% CI 0.71 to 6.37; I² = 29%; low certainty of the evidence) and at ≥ 2 years (to 60 months) (Analysis 11.5).2 (3 studies, 169 participants): RR 0.34, 95% CI 0.09 to 1.32; I² = 67%).

CNI with or without steroids had uncertain effects on SCr increase (Analysis 11.7), adverse events (Analysis 11.8; Analysis 11.9), and kidney function (Analysis 11.10; Analysis 11.11; Analysis 11.12; Analysis 11.13; Analysis 11.14).

12) Short-course tacrolimus plus steroids versus long-course tacrolimus plus steroids

Two studies compared short- versus long-course TAC (Di 2018; Yuan 2013). Di 2018 compared 6 months of TAC (short course) plus steroids versus 12 months of TAC (long course) plus steroids, and Yuan 2013 compared 6 months TAC (short course) plus steroids with 24 months TAC (long course) plus steroids. Both studies had a follow-up period of 24 months.

Yuan 2013 reported no deaths in either group; neither study reported ESKD.

Short-course TAC plus steroids had uncertain effects on total remission (Analysis 12.2 (2 studies, 106 participant): RR 0.68, 95% CI 0.42 to 1.10; I² = 72%), complete remission (Analysis 12.3 (2 studies, 106 participants): RR 0.52, 95% CI 0.28 to 0.97; I² = 0%), partial remission (Analysis 12.4 (2 studies, 106 participants): RR 0.77, 95% CI 0.30 to 1.99; I² = 78%), and relapse after complete or partial remission (Analysis 12.5 (2 studies, 82 participants): RR 7.25, 95% CI 0.41 to 129.75; I² = 75%).

Short-course TAC plus steroids may make little or no difference to adverse events (Analysis 12.6.1) and infection (Analysis.12.6.2), SCr (Analysis 12.7), but may decrease final serum albumin (Analysis 12.8) and raise final proteinuria (Analysis 12.9).

13) Cyclosporine plus steroids versus cyclosporine alone

Two studies (CYPMEN 2006; Li 2015) compared CSA plus steroids versus CSA alone.

Li 2015 reported no deaths in either group; neither study reported ESKD.

CSA plus steroids had uncertain effects on total remission (Analysis 13.2) and partial remission (Analysis 13.4), but may increase complete remission (Analysis 13.3 (2 studies, 55 participants): RR 2.20, 95% CI 1.07 to 4.49; I² = 0%; low certainty evidence) compared to CSA alone.

CSA plus steroids had uncertain effects on SCr increase (Analysis 13.5) and infection (Analysis 13.6.2), but may reduce adverse events (Analysis 13.6.1 (1 study 27 participants): RR 2.37, 95% CI 1.13 to 4.97) compared to CSA alone.

14) Cyclosporine (3.0 mg/kg, once/day) plus steroids versus cyclosporine (1.5 mg/kg, twice/day) plus steroids

Saito 2014 compared CSA given twice/day at a dose of 1.5 mg/kg with CSA given once/day at a dose of 3.0 mg/kg. Both groups received additional therapy with steroids.

Once/day CSA plus steroids had uncertain effects on total remission (Analysis 14.1) complete remission (Analysis 14.2) or partial remission (Analysis 14.3). Relapse was not reported.

It is uncertain whether once/day CSA reduces the number of patients with doubling of SCr (Analysis 14.3), infection (Analysis 14.4.2), or malignancy (Analysis 14.4.3) compared to twice/day CSA.

15) Cyclosporine plus steroids versus tacrolimus plus steroids

Li 2017c and Omrani 2017 compared CSA plus steroids with TAC plus steroids however, Omrani 2017 only provided data for adverse events.

Li 2017c reported no difference between the groups for total (Analysis 15.1), complete (Analysis 15.2) and partial remission (Analysis 15.3). Omrani 2017 reported no difference between the two groups for serious adverse events (Analysis 15.4).

16) Cyclosporine versus azathioprine

Naumovic 2011 compared CSA with AZA in 23 participants.

No deaths occurred during the study period (Analysis 16.1). Naumovic 2011 reported no differences between the groups for ESKD (Analysis 16.2), total remission (Analysis 16.3), complete remission (Analysis 16.4), partial remission (Analysis 16.5, increase in SCr (Analysis 16.6), temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 16.7), final SCr (Analysis 16.8), final GFR (Analysis 16.9), and final proteinuria (Analysis 16.10).

17) Azathioprine with or without steroids versus no treatment/supportive treatment

Silverberg 1976 compared AZA with no treatment/supportive treatment.

Silverberg 1976 reported no differences between the groups for total remission (Analysis 17.3), complete remission (Analysis 17.4), increase in SCr (Analysis 17.6), final SCr (Analysis 17.8), final GFR (Analysis 17.9), or final proteinuria (Analysis 17.10).

There were no reported deaths, progression to ESKD, partial remissions, or temporary or permanent discontinuation of treatment or hospitalisation due to adverse events during the study period.

18) Mycophenolate mofetil versus no treatment/supportive therapy

Dussol 2008 compared MMF with no treatment.

There were no reported deaths, progression to ESKD, or increase in SCr during the study period.

Dussol 2008 reported no differences between the groups for total remission (Analysis 18.3), complete remission (Analysis 18.4), partial remission (Analysis 18.5), or final GFR (Analysis 18.8).

19) Mycophenolate mofetil with or without steroids versus alkylating agents with or without steroids

Four studies (Chan 2007; Fu 2012a; Peng 2016; Senthil Nayagam 2008) compared MMF with or without steroids versus alkylating agents with or without steroids. Fu 2012a followed-up patients over a period of 36 months.

There was only one death reported by one of the four studies (Peng 2016) in the MMF group, and there was no progression to ESKD reported by three studies (Chan 2007; Peng 2016; Senthil Nayagam 2008). Peng 2016 reported no increase in SCr.

MMF with or without steroids may make little or no difference to total remission (Analysis 19.3.1 (4 studies, 124 participants): RR 0.90, 95% CI 0.71 to 1.13; $I^2 = 0\%$); complete remission (Analysis 19.4.1 (4 studies, 124 participants): RR 1.01, 95% CI 0.58 to 1.73; $I^2 = 0\%$), partial remission (Analysis 19.5.1 (4 studies, 124 participants): RR 0.89, 95% CI 0.58 to 1.37; $I^2 = 0\%$) (low certainty of the evidence). This is consistent with findings from Fu 2012a which reported total remission (Analysis 19.3.2: RR 0.90 95% CI 0.71 to 1.13), complete remission (Analysis 19.4.2: RR 1.00, 95% CI 0.44 to 2.29) and partial remission (Analysis 19.5.2: RR 1.33, 95% CI 0.37 to 4.82) at 36 months in 24 participants.

It is uncertain whether MMF with or without steroids increases or decreases, temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 19.8), adverse events (Analysis 19.9), infection (Analysis 19.9.3) or kidney function measures (Analysis 19.10; Analysis 19.11; Analysis 19.12; Analysis 19.13).

20) Mycophenolate mofetil with or without steroids versus calcineurin inhibitors with or without steroids

Choi 2018 and Peng 2016 compared MMF with or without steroids versus CNI with or without steroids.

Peng 2016 reported one death in each group (Analysis 20.1), no progression to ESKD (Analysis 20.2), no increase in SCr (Analysis 20.7), and no temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 20.8).

MMF plus steroids may make little or no difference to total remission (Analysis 20.3 (2 studies, 97 participants): RR 0.94, 95% CI 0.70 to 1.27; $I^2 = 37\%$); complete remission (Analysis 20.4 (2 studies, 97 participants): RR 0.57, 95% CI 0.20 to 1.63; $I^2 = 48\%$), or partial remission (Analysis 20.5 (2 studies, 97 participants): RR 1.36, 95% CI 0.88 to 2.10; $I^2 = 0\%$) (low certainty of the evidence). Peng 2016 reported no difference in relapse between the two groups (Analysis 20.6).

MMF with or without steroids compared to CNI with or without steroids may make little or no difference to adverse events (Analysis 20.9), infection (Analysis 20.9.2), malignancy (Analysis 20.9.3), final serum albumin (Analysis 20.11), and final proteinuria (Analysis 20.13).

Choi 2018 reported no differences in final SCr (Analysis 20.11) and final GFR (Analysis 20.12) between the two groups.

21) Adrenocorticotropic hormone versus no treatment

Arnadottir 2006 compared ACTH with no treatment.

Arnadottir 2006 reported ACTH increased total remission (Analysis 21.1 (30 participants): RR 7.00, 95% CI 1.91 to 25.62), complete remission (Analysis 21.2 (30 participants): RR 11.00, 95% CI 1.62 to 74.88), but not partial remission (Analysis 21.3 (30 participants): RR 3.00, 95% CI 0.35 to 25.68).

No other outcomes were reported.

22) Adrenocorticotropic hormone versus alkylating agents plus steroids

Ponticelli 2006 compared ACTH with alkylating agents plus steroids.

Ponticelli 2006 reported no deaths, and one patient progressed to ESKD by the end of the study in the ACTH group.

There were no reported differences between the two groups for total remission (Analysis 22.3 (32 participants): RR 0.93, 95% CI 0.75 to 1.17); more patients achieved complete remission in the ACTH group (Analysis 22.4 (32 participants): RR 2.00, 95% CI 0.88 to 4.54); while more achieved partial remission in the alkylating agents plus steroids group (Analysis 22.5 (32 participants): RR 0.40, 95% CI 0.16 to 1.01).

There were no reported differences between the groups for increases in SCr (Analysis 22.6), temporary or permanent discontinuation or hospitalisation due to adverse events (Analysis 22.7), or final SCr (Analysis 22.8). Final proteinuria was reported to be lower in the ACTH group (Analysis 22.9).

23) Mizoribine with or without steroids versus placebo/no treatment/steroids

Three studies (Hasegawa 2017; Koshikawa 1993; Shibasaki 2004) compared mizoribine with or without steroids with placebo/no treatment/steroids only. Data from Hasegawa 2017 could not be extracted.

We are uncertain whether mizoribine with or without steroids increases or decreases total remission (Analysis 23.1), complete remission (Analysis 23.2), or partial remission (Analysis 23.3) because the certainty of the evidence is very low.

Koshikawa 1993 reported two patients discontinued treatment due to serious adverse events (Analysis 23.4).

No other outcomes were reported.

24) Mizoribine (150 mg) once a day versus mizoribine (50 mg) 3 times a day

Saito 2017 compared mizoribine (150 mg) once/day versus mizoribine (50 mg) 3 times/day.

Saito 2017 reported no differences between the groups for total remission (Analysis 24.1) complete remission (Analysis 24.2), or relapse after complete or partial remission (Analysis 24.4). More patients achieved partial remission with 50 mg 3 times/day (Analysis 24.3).

No adverse events or infections were reported in either group. Malignancy was reported in two patients in the once/day group (Analysis 24.5.3).

No other outcomes were reported.

25) Rituximab plus supportive therapy versus supportive therapy alone

GEMRITUX 2017 compared the biologic agent rituximab with supportive therapy (ACEi/ARB) versus supportive therapy alone (ACEi/ARB).

GEMRITUX 2017 reported rituximab plus supportive therapy may improve total remission at 6 months (Analysis 25.1.1 (75 participants): RR 2.21, 95% CI 1.37 to 3.57) and final follow-up (median 17 months) Analysis 25.1.2 (75 participants): RR 1.90, 95% CI 1.15 to 3.13) (low certainty of the evidence). More patients achieved complete remission (Analysis 25.2) and partial remission (Analysis 25.3) with rituximab.

There were no reported differences in adverse events between the two groups (Analysis 25.4.1), and malignancy was reported in one patient in the control group.

At the end of follow-up, GEMRITUX 2017 reported rituximab plus supportive therapy may improve serum albumin (Analysis 25.6 (75 participants): MD 5.70 g/L, 95% CI 4.59 to 6.81), protein-to-creatinine ratio (Analysis 25.8 (75 participants): MD -1348.50 mg/g, 95% CI -1993.39 to -703.61), and PLA2R antibody titre (Analysis 25.9 (75 participants): MD -81.80 RU/mL, 95% CI -105.38 to -58.22) compared to supportive therapy. However, rituximab with supportive therapy was reported to make little or no difference to SCr (Analysis 25.5 (75 participants): MD -0.40 µmol/L, 95% CI -5.44 to 4.64) or eGFR (Analysis 25.7 (75 participants): MD -4.00 mL/min/1.7 m², 95% CI -8.91 to 0.91) compared to supportive therapy (low certainty of the evidence).

No other outcomes were reported.

26) Rituximab versus cyclosporine

MENTOR 2015 compared rituximab plus supportive therapy with CSA plus supportive therapy.

MENTOR 2015 reported no deaths, and one patient progressed to ESKD in the CSA group by the end of the 24-month study period.

MENTOR 2015 reported rituximab may increase total remission (Analysis 26.3 (130 participants): RR 3.00, 95% CI 1.77 to 5.07) and complete remission (Analysis 26.4 (130 participants): RR 47.00, 95% CI 2.91 to 757.81) at 24 months but not partial remission (Analysis 26.5 (130 participants): RR 1.23, 95% CI 0.65 to 2.35) (low certainty of the evidence). The number relapsing after complete or partial remission was higher in the CSA group (Analysis 26.6 (73 participants): RR 0.10, 95% CI 0.02 to 0.39).

In patients with any form of remission (complete or partial), quality of life as measured by SF-12 scores (score range: 0-100 points) for physical health (Analysis 26.7.1) and mental health (Analysis 26.7.2) may be slightly lower in patients who receive rituximab compared with CSA. There were more reported serious adverse events in the CSA group (Analysis 26.8.1); the number of infections was similar (Analysis 26.8.2).

No other outcomes were reported.

27) Traditional Chinese medicine versus immunosuppressive therapy

Chen 2013e and Liu 2009b investigated the efficacy and safety of traditional Chinese medicine versus immunosuppressive therapy. Chen 2013e compared Shenqi particles with CPA plus steroids and Liu 2009b compared Tripterygium wilfordii plus steroids with Tripterygium wilfordii alone.

Chen 2013e reported three deaths with immunosuppressive therapy and none with Shenqi particles. Liu 2009b reported no

deaths in either group, and no patients progressed to ESKD (Analysis 27.1; Analysis 27.2).

Chen 2013e reported no difference in total, complete and partial remission between Shenqi particles and immunosuppressive therapy. Liu 2009b reported an increase in the number achieving total and complete remission with Tripterygium wilfordii plus steroids compared to Tripterygium wilfordii alone, but no difference in partial remission (Analysis 27.3; Analysis 27.4; Analysis 27.5).

Chen 2013e reported one case of doubling of SCr in the immunosuppressive therapy group and none in the Shenqi particle group; Liu 2009b reported no cases in either group.

Chen 2013e reported more severe adverse events in the immunosuppressive therapy (Analysis 27.7). The number of severe adverse events was similar in Liu 2009b.

Chen 2013e reported no differences between the groups for final serum albumin (Analysis 27.8) and proteinuria (Analysis 27.10); while final GFR was higher in the Shenqi particle group (Analysis 27.9).

Eculizumab 8 mg/kg every 2 weeks versus eculizumab 8 mg/kg every 4 weeks

Appel 2002 investigated IV eculizumab 8 mg/kg every two weeks versus IV eculizumab IV 8 mg/kg every four weeks. However, the only reports identified were a conference abstract and its associated press release; these reports did not contain any data that could be meta-analysed. The study enrolled 117 patients and reported no major hypersensitivity reactions and treatment with eculizumab was generally well tolerated. We could not identify published outcome data from this study.

Adrenocorticotropic hormone 40 IU versus adrenocorticotropic hormone 80 IU

Hladunewich 2014 investigated 40 IU ACTH versus 80 IU ACTH, however, we were not able to extract data because many patients switched treatment arms and results were not reported according to the two intervention groups as defined at the start of the study. We have provided a brief narrative summary of the main findings of this study.

The study was a phase Ib/II trial using ACTH in the form of H.P. Acthar® Gel (Questcor Pharmaceuticals, Inc.) in 20 adult patients with IMN with nephrotic syndrome. ACTH was generally well-tolerated and did not lead to any significant adverse events or discontinuation of treatment. By 12 months of follow-up, there was a significant improvement in proteinuria in the entire cohort, decreasing from baseline proteinuria of 9.07 ± 3.38 g/day to 3.87 ± 4.24 g/day (P < 0.001). Proteinuria decreased by more than 50% in 65% of the patients. A likely dose-response relationship was established during the trial period with better efficacy of the treatment in patients treated at higher doses than 40 IU.

DISCUSSION

Treatment of patients with PMN and nephrotic syndrome is complex and difficult to navigate because of multiple interventions and studies, which have compared numerous different treatment

regimens. As a result, the efficacy and safety of different immunosuppressive regimens remain unclear.

This original review (Schieppati 2004) included 19 RCTs with 1025 participants and found that immunosuppressive treatments, could increase the rates of complete or partial remission. However, the long-term effects of immunosuppressive treatments on definite endpoints such as death (any cause) or kidney survival rate could not be demonstrated. Immunosuppressive treatments also had a significantly higher risk of severe adverse events. The first update of this review (Chen 2014) included 39 studies with 1825 participants, which further strengthened the certainty of the evidence.

There was limited evidence available on other treatments such as MMF, AZA or traditional Chinese medicine and these studies did not show promising results in terms of superiority of these treatments over standard therapy.

The role of other therapies remains an ongoing topic of investigation and discussion.

Summary of main results

This review update included 65 studies that randomised 3807 participants and answered two aims of this systematic review.

1. Is immunosuppressive therapy superior to non-immunosuppressive therapy in treating patients with PMN and nephrotic syndrome?
2. If so, which immunosuppressive agent/s is most effective and safe in treating patients with PMN and nephrotic syndrome?

Immunosuppressive treatments compared with no treatment or non-immunosuppressive treatment probably provides a clinical benefit for the outcomes of reducing ESKD, doubling of SCr, and an increase in the rate of total remission and complete remission. However, the use of immunosuppressive treatments compared with no treatment/non-immunosuppressive treatments probably increased temporary or permanent discontinuation of treatment or hospitalisation due to adverse events of therapy.

This review firstly showed that immunosuppressive therapy with non-steroid immunosuppressive drugs with or without concomitant steroids may be superior in the induction of remission compared to immunosuppression with corticosteroids only.

Secondly, immunosuppressive therapy with oral alkylating agents with or without steroids compared to no treatment or supportive therapy or steroids alone probably increases remission rates but may lead to a decrease in rates of ESKD by up to 70%. However, there may be a three-fold increase in rates of serious adverse events. There was little difference in efficacy or safety when comparing alkylating agents CPA with steroids versus chlorambucil with steroids, except that CPA might increase rates of total remission. These findings may justify the use of CPA combined or alternated with steroids as first-line therapy for adults with PMN and nephrotic syndrome, who do not achieve remission within six months of supportive therapy, as recommended by KDIGO guidelines (KDIGO 2020).

Comparing CNI (CSA and TAC) with alkylating agents showed little or no difference in remission rates or improvement of other secondary outcomes, including adverse events. Due to the very low

certainty of the evidence, no conclusion can be made with regards to death or progression to ESKD.

The effectiveness and safety of many other interventions remain unclear, and the clinical use of these therapies, therefore, warrants caution. MMF showed similar effectiveness in inducing remission as alkylating agents or CNI, however, the certainty of the evidence is low, due to the small number of studies with a low number of events and insufficient length of follow-up to determine long-term efficacy and safety of this therapy in patents with PMN.

The combination of two non-steroidal immunosuppressive treatments (e.g. TAC with MMF) may improve rates of complete remission compared with one non-steroidal immunosuppressive treatment alone. Treatment regimens with two non-steroidal immunosuppressive drugs may be considered in patients with contraindications or severe side effects from treatment with steroids. However, this was only investigated in a small number of studies, therefore requiring further investigation. In our meta-analysis of this comparison, we included two studies that combined CSA with MMF and one study that combined CPA and leflunomide. It is noteworthy, that there was an unexpected lack of statistical heterogeneity.

Additionally, other studies examining mizoribine monotherapy, ACTH and rituximab have demonstrated some potential efficacy benefits, but the long-term efficacy and safety of these treatments are unknown and should be further examined in future RCTs.

Overall completeness and applicability of evidence

Our review was based on a standardised and highly sensitive electronic search of the Cochrane Kidney and Transplant Specialised Register, which includes a review of journal alerts and handsearching of all relevant conference proceedings. Many recent studies are registered with clinical trial registries such as clinicaltrials.gov, which leads to transparency and accountability and a smaller possibility of selective reporting. Furthermore, it is noteworthy that most recent studies report on remission rates as primary outcomes, which improves the consistency of reporting and comparability of results among different studies.

One major limitation was the relatively small numbers of included studies in some comparisons of immunosuppressive regimens, especially for the newer immunosuppressive treatments such as ACTH and rituximab. This issue is common in systematic reviews carried out in the field of glomerulonephritis (e.g. in lupus nephritis Tunnicliffe 2018 or IgA nephropathy Natale 2020). Another major concern is the relatively short follow-up period in most of the included studies (median follow-up of 24 months). It has been recognised that for long-term endpoints such as ESKD or death a follow-up period of at least seven to 10 years should be considered. For surrogate outcomes such as complete or partial remission, an adequate follow-up period should be of at least two to three years (du Buf-Vereijken 2005). This is especially important to monitor rates of relapse from remission as this is a frequent complication of membranous nephropathy, even under continued immunosuppressive treatment. Furthermore, most studies did not perform blinding of participants, personnel, and outcome assessors, leading to risk of bias. Finally, some of the investigated treatments, especially CNI, may have additional non-immunosuppressive actions that may positively or negatively

influence their efficiency in the treatment of PMN however lack of data has made it difficult to investigate this further.

Patient-reported outcomes, such as quality of life, are increasingly recognised as critical to healthcare decision making but these outcomes are often not measured nor reported in RCTs. A core outcome set that includes critically important outcomes from the perspective of patients, caregivers, researchers, and physicians alike, is vital to ensure that the evidence from RCTs is used to inform clinical decision making that is appropriate and valuable to all stakeholders. In addition, standardised measures of important efficacy outcomes such as remission would allow for ease of comparison across studies and help build the evidence for the treatment of patients with IMN and nephrotic syndrome. Such a set of core outcomes is currently under development by the SONG initiative (Standardised Outcomes in Nephrology), including a working group for glomerular disease.

Many recent studies have been conducted in Asian countries and it is unclear whether differences in response to treatment exist among patients of different ethnicity. Furthermore, other differences among patients with PMN require further investigation to assess whether certain patients may benefit from different therapeutic approaches such as whether the presence or level of certain antibodies influences treatment response.

Finally, current RCTs may not reflect the entire range of therapies that are used in clinical practice, such as biologic therapies which have been used increasingly and have been reported on in observational studies. However, given the greater potential for bias in observational studies, these treatments should be further investigated in RCTs.

Quality of the evidence

Certainty of the evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE 2011). In general, most studies did not perform blinding and had several study limitations (Begg 1996; Clarke 2000). Therefore, the risk of bias was high or moderate in most studies. The internal validity of the design, conduct and analysis of the included RCTs was difficult to assess in some studies because of the omission of important methodological details and not all trials had published trial protocols or registered their study with a clinical trial registry.

The generalisability of the evidence is limited by the small number of studies for many treatment options and the limited number of studies that examine differences between patient subgroups. For example, many studies did not report the number of patients with positive anti-PLA2R-antibodies or the histopathological stage of the kidney damage.

We were not able to assess for the presence of language bias through subgroup analysis, as only three studies were published in a language other than English. No studies were excluded on the basis of language. Sensitivity analysis could not be performed to explore the effect of dominating studies with very long follow-up or very large same size. Additionally, publication bias (the effect of small or unpublished studies on treatment effects) could often not be assessed given the small number of trials available. To reduce publication bias, new reports and existing reports from the hand-

searching of conference proceedings from the Cochrane Kidney and Transplants registry were included in this systematic review.

Potential biases in the review process

This systematic review update is reported using Cochrane methods and includes a comprehensive search of literature by the Cochrane Kidney and Transplant Information Specialist. As with any systematic review and meta-analysis, this review is limited to the outcomes reported in the included studies. For example, there was a lack of reporting of patient-reported outcomes in most RCTs. Many of the included studies were of insufficient follow-up to detect important clinical outcomes, such as death, ESKD, and complete remission. Subgroup analyses have been undertaken according to the duration of follow-up of studies to minimise indirectness. However, there were only a small number of studies, each with small numbers of participants, that were of sufficient follow-up and imprecision may be present in the overall effect estimate. Additionally, the small number of studies might have limited the power of statistical testing to detect important differences between studies. Heterogeneity was found to be substantial in certain comparisons. Study authors had no affiliation to any trial investigators. The review did not receive private industry funding.

Agreements and disagreements with other studies or reviews

Three systematic reviews were published before 1995 (Couchoud 1994; Hogan 1995; Imperiale 1995). Imperiale 1995 included five prospective studies, four RCTs and one non-RCT, in which alkylating agents were compared with corticosteroids, placebo or symptomatic treatments. They found a beneficial effect of alkylating agents on complete or partial remission in 228 patients. However, there was not enough evidence related to the effects of alkylating agents on the long-term endpoints. Hogan 1995 performed a pooled analysis of 35 retrospective and prospective studies in 1815 patients. Complete remission was more frequent with the use of alkylating agents compared with no treatment or corticosteroids. However, there was again insufficient evidence that corticosteroids or alkylating therapy could improve long-term kidney survival in patients with PMN and nephrotic syndrome.

Systematic reviews which included observational studies of rituximab treatment in PMN (Bomback 2009; Zou 2018) showed potential efficacy of rituximab in inducing remission in PMN with a generally good safety profile with mostly mild adverse reactions. The limited evidence available from RCTs that were included in our review showed a treatment effect in the same direction.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

In this review update, we found that immunosuppressive therapy compared to non-immunosuppressive therapy is probably beneficial for inducing remission and improving kidney survival in adult patients with PMN and nephrotic syndrome. The combination of an alkylating agent and corticosteroid regimen had short- and long-term benefits, including greater induction of remission and lower rates of ESKD. It should be emphasised that the number of included studies with high-quality design and appropriate blinding was relatively small and most of the included studies did not have

adequate follow-up or enough power to assess the prespecified definite endpoints, such as death and ESKD. Clinicians and patients should be aware of the low certainty of the evidence for these benefits as well as the well-recognised adverse events of therapy. Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function remains unclear.

An alkylating agent (CPA or chlorambucil) combined with a corticosteroid regimen may be beneficial for adult patients with PMN and nephrotic syndrome, however, this was associated with a higher rate of adverse events.

Therapy with a CNI such as TAC was recommended by the 2020 KDIGO Clinical Practice Guideline as a treatment regimen for adults with PMN and nephrotic syndrome (KDIGO 2020); however, it remains uncertain whether CNI could alter clinical outcomes such as death or ESKD. We found that treatment regimens of alkylating agents were equivalent to CNI with or without steroids on complete or total remission rates. Given the low certainty of the evidence, we cannot conclude that there is superiority over alkylating agents with the currently available evidence. Compared with no treatment or non-immunosuppressive supportive treatment, CNI showed little or no effect on complete and total remission rates; however, the certainty of this evidence is low because of study limitations and only a few RCTs with a small number of patients have been conducted.

There is low certainty of the evidence for the use of MMF in PMN. The number of corresponding studies for rituximab, ACTH, are still too sparse to draw firm conclusions for clinical practice. Observational trials may support the limited body of evidence from RCTs on both the use of rituximab (Fiorentino 2016; Ruggenenti 2006; Ruggenenti 2016) and ACTH (Berg 1999; Bomback 2011; Kittanamongkolchai 2016; Ponticelli 2006) until more high-quality RCTs become available.

Finally, the presence and the level of circulating antibodies, such as anti-PLA2R-, anti-THSD7A- or NELL1-antibodies may provide guidance in assessing immunological disease activity and response to treatment. This has been acknowledged in the scientific literature and recent updates to international treatment guidelines (KDIGO 2020). This review did not assess immunological disease activity based on antibody titres as only a few of the included studies have provided this data.

Implications for research

There is a need for more methodologically sound studies with an emphasis on adequate sample size and follow-up. This may require international multi-centre collaboration and the use of registry-based RCTs to clarify the risks and eventual benefits and harms of therapy, with the use of registry databases capturing important longer-term clinical outcomes. When possible, blinding of participants, clinicians and outcome assessors should be performed. Studies should also report the histopathological subclasses of PMN that are present at the initial biopsy. Furthermore, priority should be given to the use of definite rather than surrogate endpoints in studies. Moving forward, immunosuppressive treatments should be directly compared with alkylating agents and corticosteroids after the superiority of this treatment over no treatment, non-immunosuppressive treatment and corticosteroid-monotherapy has now been established in

patients with persistent nephrotic syndrome, deteriorating kidney function and those at high risk of developing ESKD.

The optimal dose/s, route/s of administration, and duration of therapies that are most beneficial and least harmful to patients of different ethnicity, ages, and clinical and pathological severity still need to be clarified. It is noteworthy that many of the recently published trials were conducted in China, and the generalisability of these findings to patients of other ethnicities is unclear. Therefore, a greater geographical and ethnic diversity of study participants may be beneficial in future studies. Standardised outcomes (as currently developed by the Standardised Outcomes in Nephrology (SONG-Glomerular Disease group) should be considered in the design of new studies to ensure better comparability of results between different trials and to ensure that both clinical outcomes and patient-reported outcomes are assessed and reported in studies.

Certainty of the evidence for CNI and MMF remains low and with an unclear profile of side effects. Therefore, further research into the efficacy and side effects of MMF and CNI treatment regimens with long-term follow-up is needed to better inform this evidence. As for tacrolimus, a shorter treatment period of six months compared to longer treatment periods demonstrated encouraging results in Yuan 2013 and Di 2018. Further studies of this treatment regimen would be helpful to further strengthen the evidence for this practice, which may be beneficial to patients.

A combination of two non-steroidal immunosuppressive treatments compared with one non-steroidal immunosuppressive treatment combined with steroids should be investigated further to evaluate whether steroid-free treatment regimens may be appropriate for the treatment of PMN with nephrotic syndrome. Future studies in this area should investigate and report adverse events so that the safety of dual treatment can be assessed.

Following up on the promising early results in observational or dose-finding studies, new therapies such as rituximab (Remuzzi 2002; Zou 2018) and ACTH (Hladunewich 2014) require further investigation with RCTs with more participants and longer follow-up to inform clinical practice.

Finally, there is growing insight into the role of anti-PLA2R antibodies (Beck 2009) and anti-THSD71 antibodies (Tomas 2014) both in research and the clinical management of PMN. Therefore, it would be helpful for future studies to include serial measurement of anti-PLA2R antibodies and anti-THSD7A antibodies to help guide immunosuppressive therapy in PMN and to improve the understanding of treatment effects.

Future studies should provide adequate follow-up of patients in order to better understand complications (such as adverse events, infections, development of malignancies) and the rates of relapse in patients that initially achieved remission.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2012a

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Follow-up period: primary endpoint at 6 months and secondary endpoint at 12 months
Participants	• Setting: single centre • Country: India • Inclusion criteria: IMN; nephrotic syndrome despite adequate treatment with telmisartan; eGFR > 30 mL/min • Baseline characteristics ○ Mean duration of oedema: 8 months

- ○ Pathological classification (I/II/III/IV): treatment group (0/18/2/0), control group (0/21/0/0)
- Number: treatment group (20), control group (21)
- Mean age: 38 years
- Sex (M/F): 34/7
- Exclusion criteria: not reported

Interventions	**Treatment group** • TAC (oral): 0.1 mg/kg/day for 6 months then tapered off over 6 months • Prednisolone: 0.5 mg/kg/day, until remission then tapered by 5 mg/week with a minimal maintenance dose **Control group** • Modified Ponticelli Regimen ○ CPA + prednisolone for 6 months
Outcomes	• Complete or partial remission at 6 months • Partial remission • Any remission • Kidney survival
Notes	• Abstract-only publication • Funding source: not reported • Declarations of Interests/disclosures: not reported • The author kindly provided further details (baseline characteristics and treatment arm sizes) upon request • Ethics: the protocol was ethically approved; an informed consent form was obtained from each participant • Trial registration or protocol registration or publication: Clinical Trial Registry of India (CTRI/2010/091/000231)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Primary and secondary endpoints comprehensively reported; trial registered at clinical trial registry

Agarwal 2012a *(Continued)*

Other bias	Unclear risk	Incomplete reporting. No financial disclosures provided

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Ahmed 1994

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: prior to 1994 • Follow-up period (months): treatment group 1 (14.6 ± 1.15); treatment group 2 (15.6 ± 2)

Participants	• Setting: single centre
	• Country: Bangladesh
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome; SCr < 1.7 mg/dL
	• Baseline characteristics
	  ○ Pathology stage: not reported
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (6.11 ± 1.86); treatment group 2 (7.61 ± 1.99)
	  ○ Hypertension: treatment group 1 (0/10); treatment group 2 (2/10)
	  ○ Mean SCr ± SD (mg/dL): treatment group 1 (1.35 ± 0.13); treatment group 2 (1.22 ± 0.16)
	  ○ Use of ACEi or ARB during follow-up: not reported
	  ○ Previous immunosuppressive treatment: none
	• Number: treatment group 1 (10); treatment group 2 (10)
	• Mean age ± SD (years): treatment group 1 (32 ± 7); treatment group 2 (38 ± 14)
	• Sex (M/F): treatment group 1 (8/2); treatment group 2 (8/2)
	• Exclusion criteria: not reported

Interventions	Treatment group 1 • Methylprednisolone (IV): 1 g/day for 3 consecutive days • Prednisolone: 0.5 mg/kg/day for 27 days • Chlorambucil: 0.2 mg/kg/day for 1 month for 3 cycles (6 months) Treatment group 2 • Prednisolone: 1.0 to 1.5 mg/kg/day for 8 weeks and then a tapering dose and finally withdrawal after 8 weeks
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: not reported • Confounding factors: one patient in the treatment group 1 developed hypertension at the end of follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Ahmed 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Not sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Appel 2002

Study characteristics	
Methods	- Study design: parallel, open-label RCT - Study duration: to be completed by August 2002 - Duration of follow-up: not reported
Participants	- Setting: multicentre (23 sites) - Country: not reported - Inclusion criteria: IMN - Baseline characteristics: not reported - Number: treatment group 1 (29); treatment group 2 (44); control group (44) - Mean age ± SD (years): not reported - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - Eculizumab: 8 mg/kg every 4 weeks for 4 months Treatment group 2 - Eculizumab: 8 mg/kg every 2 weeks for 4 months Control group - Placebo for 4 months
Outcomes	- Safety: frequency of adverse effects - Efficacy: 24-hour urinary protein

Appel 2002 *(Continued)*

Notes	• Funding Source: Alexion • No data reported, details from conference abstract and a press release of the conference presentation. Extension component of the trial continues 2-week treatment for 12 months in 72 patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No publication found 19 years after study ended
Other bias	Unclear risk	Insufficient information to permit judgement

Arnadottir 2006

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: before 2006 • Duration of follow-up: 21 months in each patient

Participants	• Countries: Iceland, Sweden
	• Setting: international multicentre
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	  ○ SCr (μmol/L): treatment group (107); control group (104)
	  ○ Use of ACEi or ARB during follow-up: yes
	• Number: treatment group (15); control group (15)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: not reported

Interventions	Treatment group • ACTH (SC): 1.0 mg once/week, 0.75 mg twice/week or 1.0 mg twice/week for 9 months

Arnadottir 2006 *(Continued)*

Control group

- No specific treatment

Outcomes	- Partial or complete remission - Proteinuria - GFR
Notes	- Abstract-only publication - Funding information: not reported - Baseline characteristics: comparable - Only remission data could be extracted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Only remission data could be extracted from the abstract
Other bias	Unclear risk	Insufficient information to permit judgement

Austin 1996a

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: not reported - Duration of follow-up: 1 year
Participants	- Setting: not reported - Country: USA - Inclusion criteria: IMN - Baseline characteristics ○ GFR: 24 to 156 mL/min - Number: treatment group (17); control group (14)

Austin 1996a *(Continued)*

- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group
	• CPA (IV): 0.5.0 g/m² every other month
	• Prednisone (oral): 40 mg/m² every other day for 2 months tapered to 10 mg/m²
	Control group
	• Prednisone (oral): 40 mg/m² every other day for 2 months tapered to 10 mg/m²
Outcomes	• Partial or complete remission
	• GFR
	• Proteinuria
Notes	• Abstract-only publication
	• Baseline characteristics: comparable
	• Funding information: not reported
	• Only abstract was available and data could not be used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data could not be extracted
Other bias	Unclear risk	Insufficient information to permit judgement

Braun 1995

Study characteristics

Methods	• Study design: parallel, open-label RCT

Braun 1995 *(Continued)*

	• Study duration: 1986 to 1996
	• Duration of follow-up: 68/97 patients completed the 5-year follow-up

Participants	• Setting: multicentre
	• Country: Germany
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	○ Pathology stage (I/II/III/IV): treatment group 1 (2/18/4/4); treatment group 2 (1/23/4/9); control group (1/11/2/4),
	○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (9.3 ± 6.3); treatment group 2 (7.2 ± 3.9); control group (6.5 ± 5.4)
	○ Hypertension: treatment group 1 (13/31); treatment group 2 (33/44); control group (9/22)
	○ Serum albumin (% of total protein): treatment group 1 (53 ± 12); treatment group 2 (52 ± 9); control group 3 (52 ± 9)
	○ Mean SCr ± SD (mg/dL): treatment group 1 (1.0 ± 0.3); treatment group 2 (1.2 ± 0.4); control group (1.0 ± 0.4)
	○ Mean GFR ± SD (mL/min): treatment group 1 (103 ± 31); treatment group 2 (102 ± 43); control group (107 ± 33)
	○ Baseline declining kidney function: no
	○ Use of ACEi or ARB during follow-up: yes; no confounding effect
	○ Previous immunosuppressive status: no
	• Number: treatment group 1 (31); treatment group 2 (44); control group (22)
	• Mean age ± SD (years): treatment group 1 (42.5 ± 13.9); treatment group 2 (43.0 ± 15.7); control group (46.9 ± 16.1)
	• Sex (M/F): treatment group 1 (25/6); treatment group 2 (21/23); control group (13/9)
	• Exclusion criteria: not reported

Interventions	Treatment group 1
	• Monthly cycles of steroids and chlorambucil
	○ Steroids: methylprednisolone (IV) 1g over 20 to 30 min for 3 consecutive days, followed by oral prednisone 0.5 mg/kg/day or methylprednisolone 0.4 mg/kg/day in months 1, 3 and 5
	○ Chlorambucil: 0.2 mg/kg/day, months 2, 4 and 6; the dose was lowered if the leukocyte count fell below 5000/mm^3
	Treatment group 2
	• CSA + steroids
	○ Oral CSA and prednisone for 6 months
	Control group
	• Symptomatic treatment as for the above two groups

Outcomes	• Death
	• ESKD
	• 50% or 100% SCr increase
	• Partial or complete remission
	• Side effects leading to patient withdrawal or hospitalisation

Notes	• Abstract-only publication
	• Baseline comparison: more patients in the two treatment groups had more severe nephrotic syndrome and aggressive IMN than the control group
	• Funding information: not reported
	• Only abstract was available and unpublished data were included

Braun 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The patients were randomised into one of the two treatment groups (1986 to 1990) using sealed envelopes that contained the treatment protocol and that were numbered according to a table of randomisation. The study group decided to change the randomisation protocol in 1990 by adding a control group to the two treatment arms. Patients were then randomised into one of the two treatment groups or the control group (1991 to 1996) using a computer based-randomisation table
Allocation concealment (selection bias)	Unclear risk	Randomisation method described could usually not allow investigators/participants to know or influence intervention group before eligible participant entered in the study. But the authors failed to clarify the randomisation was centrally performed and it was possible for investigators to open the sealed envelopes in advance
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 97/124 (78%) randomised patients were entered to the final analysis. Furthermore, of these 97 patients 18 were lost to follow-up and 11 did not complete the five-year follow-up. Eventually only 68/124 (55%) completed the five-year follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	Only abstract was available and unpublished data were included

Cameron 1990

Study characteristics

Methods	• Study design: parallel RCT • Study duration: November 1981 to February 1985 • Duration of follow-up: to 49 months

Participants	• Setting: multicentre
	• Country: UK
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	    ○ Pathology stage: 89/103 biopsies were reviewed and 70 were graded (4 as I, 32 as II, 26 as III, and 8 as IV)
	    ○ Mean proteinuria ± SD (g/24 hours): treatment group (10.8 ± 5.9); control group (10.4 ± 5.3)
	    ○ Hypertension: treatment group (9/52); control group (16/51)
	    ○ Mean serum albumin ± SD (g/L): treatment group (26 ± 6); group (25 ± 5)
	    ○ Mean SCr ± SD (µmol/L): treatment group (114 ± 42); control group (115 ± 43)

Cameron 1990 *(Continued)*

- ○ Mean GFR ± SD (mL/min): treatment group (87 ± 30); control group (89 ± 34)
- ○ Baseline declining kidney function: 13/103 patients with an initial SCr ≥ 150 μmol/L
- ○ Previous immunosuppressive status: no
- Number (randomised/analysed): treatment group (52/43); control group (51/43)
- Mean age ± SD (years): treatment group (45 ± 11.6); control group (44 ± 12.1)
- Sex (M/F): treatment group (43/9); control group (43/8)
- Exclusion criteria: aged > 65 years

Interventions	**Treatment group**
	- Prednisolone: 125 mg was given every alternate day for 8 weeks. Patients who weighed more than 80 kg received 150 mg on alternative days
	Control group
	- Placebo: identical tablets as prednisolone for 8 weeks
Outcomes	- Death - ESKD - 50% or 100% SCr increase - Final Cr - Final GFR - Partial or complete remission - Final proteinuria - Side effects leading to patient withdrawal or hospitalisation.
Notes	- Funding information: not reported - Confounding factors: at the last follow-up (49 months) a higher proportion of females were in remission or had stable function than corresponding males (P = 0.012)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was performed centrally, and coded tablets given locally from bottles supplied from the co-ordinator"
Allocation concealment (selection bias)	Low risk	Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical tablets were used, that contained either 5 mg of prednisolone or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients (8%) in the treatment group were lost at 4, 6, 21, and 24 months and 3 (6%) in the placebo group at 9, 18, and 21 months. Their data to the point of loss have been included in the analysis on an intention-to-treat basis. No patient lost was in remission or had a plasma Cr of over 400 μmol/L when lost. Thus, missing outcome data balanced in numbers across intervention groups and have been imputed using appropriate methods

Cameron 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Cattran 1989

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 1977 to 1985 • Duration of follow-up: 48 ± 3.2 months. 72% of the 158 patients were followed for 3 years or more

Participants	• Setting: single centre
	• Country: Canada
	• Inclusion criteria: biopsy-proven IMN; 120/158 patients with IMN had nephrotic-range proteinuria (64 in the prednisone group and 56 in the control group), while the remaining 38 patients did not have the diagnosis of nephrotic syndrome
	• Baseline characteristics
	   ○ Pathology stage (I/II/III/IV): treatment group (6/33/33/9); control group (7/35/28/7)
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group (6.9 ± 0.8); control group (5.2 ± 0.9)
	   ○ Hypertension: treatment group (28/81); control group (24/77)
	   ○ Mean serum albumin ± SD (g/L): treatment group (27 ± 1.3); control group (30 ± 1)
	   ○ Mean SCr ± SD (µmol/L): treatment group (120 ± 10); control group (103 ± 9)
	   ○ Mean GFR ± SD (mL/sec/1.73 m²): treatment group (1.3 ± 0.08); control group (1.5 ± 0.08)
	   ○ Baseline declining kidney function: a portion had declining kidney function
	   ○ Previous immunosuppressive status: the use of any immunosuppressive agent other than prednisone was not allowed in the 6 months before entry
	• Number (randomised/analysed): treatment group (81/65); control group (77/55)
	• Median age, range (years): treatment group (46, 18 to 77); control group (45, 16 to 83)
	• Sex (M/F): treatment group (61/20); control group (44/33)
	• Exclusion criteria: positive renal venogram for thrombosis

Interventions	Treatment group • Prednisone: 45 mg/m² in a single dose on alternate days for 6 months. The cumulative dose was 0.6 ± 0.05 mg/kg/day Control group • No specific treatment for 6 months
Outcomes	• Death • ESKD • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	• Baseline comparison: comparable • Funding information: supported by grants from the Kidney Foundation of Canada • Sample size calculation: the estimated total sample size was 150 patients; enrolled 158 • Confounding factors: no

Risk of bias

Cattran 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned by the study coordinator in Toronto Glomerulonephritis Registry according to a table of random numbers
Allocation concealment (selection bias)	Low risk	Central Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	27/158 (17%) patients were lost during follow-up of 48 months: 10/81 (12%) in the prednisolone group and 17/77 (22%) in the control group
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	158 patients were properly randomised, only 120 of them were diagnosed with nephrotic syndrome. The randomisation was not stratified according to nephrotic syndrome or non-nephrotic syndrome

Cattran 1995

Study characteristics

Methods	- Study design: parallel RCT - Study duration: before 1994 - Duration of follow-up: total observation was 21 months - Treatment group: 10.1 (4 to 13) months for the study and 20 (0 to 41) months for the extension observation - Control group: 8.9 (4 to 13) months for the study and 22 (6 to 56) months for the extension observation
Participants	- Setting: multicentre - Country: Canada - Inclusion criteria: biopsy-proven IMN with nephrotic-range proteinuria and progressive decline of kidney function (the decline of CrCl was ≥ 8 mL/min for 8 to 12 months before entry to the study) - Baseline characteristics - Mean proteinuria, range (g/24 hours): treatment group (11.5, 9 to 18); control group (12.8, 4 to 21) - Mean serum albumin ± SD (g/L): treatment group (29 ± 6.6); control group (30 ± 9.2) - Mean SCr ± SD (μmol/L): treatment group (186 ± 65); control group (204 ± 81) - Mean GFR ± SD (mL/min): treatment group (51 ± 20); control group (46 ± 16) - Baseline declining kidney function: yes - Use of ACEi or ARB during follow-up: yes, no confounding effect. No ACEi were allowed unless the patient had been on such therapy a minimum of 3 months prior to entry

Cattran 1995 *(Continued)*

- ○ Previous immunosuppressive status: no corticosteroids, immunosuppressive drugs or NSAIDs were allowed 8 to 12 months before entry to the study
- Number: treatment group (9); control group (8)
- Median age, range (years): treatment group (44, 22 to 59); control group (40, 20 to 61)
- Sex (M/F): treatment group (8/1); control group (6/2)
- Exclusion criteria: not reported

Interventions	Treatment group • CSA: 100 mg/mL, was initiated at 3.5 mg/kg/day taken in 2 divided doses, and periodic adjustments were made as necessary to achieve a 12-hour trough level of between 110 and 170 ng/mL. The mean dose of CSA was 3.8 mg/kg with a range between 2.5 and 4.9 Control group • Placebo: made of the identical carrier except CSA was excluded. It was initially prescribed at 0.035 mL/kg/day, taken in 2 divided quantities with periodic arbitrary adjustments in dose to match the CSA group
Outcomes	• Death • ESKD • Final GFR • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: grant support was in part by the Ontario Ministry of Health, Kidney Foundation of Canada, Metropolitan Toronto Community Foundation and Sandoz Canada Limited • Baseline comparison: comparable • An automatic dose reduction was reached because of a 30% rise in SCr in 10 patients (6 in the CSA group, 4 in the placebo group). With medication adjustment, this reversed in 5 in the CSA group but none in the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to either CSA or placebo in blocks stratified by centre
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	The patients were masked in regard to their assignment, but for safety reasons the physician in charge was not
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified

Cattran 1995 *(Continued)*

Other bias	Low risk	The study appeared to be free of other sources of bias

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Cattran 2001

Study characteristics

Methods	• Study design: parallel RCT • Study duration: before 2001 • Duration of follow-up: 18 months

Participants	• Setting: multi-centre (11 sites)
	• Countries: Canada, USA
	• Inclusion criteria: biopsy-proven steroid-resistant IMN and nephrotic-range proteinuria; all patients must have failed to achieve remission of their proteinuria after a minimum of 8 weeks of prednisone treatment at ≥ 1 mg/kg/day
	• Baseline characteristics
	   ○ Pathology stage (I-IV): treatment group 1 (2.2, 1-4); treatment group 2 (2.4, 1-4)
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (9.7 ± 5.3); treatment group 2 (8.8 ± 4.7)
	   ○ Mean serum albumin ± SD (g/L): treatment group 1 (28 ± 6); treatment group 2 (27 ± 6)
	   ○ Mean SCr ± SD (mg/dL): treatment group 1 (1.3 ± 0.5); treatment group 2 (1.1 ± 0.3)
	   ○ Mean GFR ± SD (mL/min/1.73 m²): treatment group 1 (95 ± 37); treatment group 2 (90 ± 27)
	   ○ Baseline declining kidney function: CrCl was ≥ 42 mL/min/1.73 m² in all included patients
	   ○ Use of ACEi or ARB during follow-up: yes, no confounding effect
	   ○ Previous immunosuppressive status: no immunosuppressive agents, plasma exchange therapy, or antilymphocyte products were allowed in the 6 months prior to entry to the study
	• Number: treatment group 1 (28); treatment group 2 (23)
	• Mean age ± SD (years): treatment group 1 (47 ± 11); treatment group 2 (49 ± 14)
	• Sex (M/F): treatment group 1 (26/2); treatment group 2 (16/7)
	• Exclusion criteria: women unwilling to take effective birth control; comorbid conditions with an expected survival of < 2 years; any serious systemic infection, DM; malignancy; conditions associated with secondary MGN; SLE; infection

Interventions	Treatment group 1
	
	• CSA + prednisone
	   ○ CSA: started at a dose of 3.5 mg/kg/day in 2 equal doses at 12-hour intervals. Adjustments in dosages were made to achieve a whole-blood 12-hour trough level measured by monoclonal assay between 125 and 225 mg/L. It was continued for 26 weeks and then tapered to zero over 4 weeks
	   ○ Prednisone: 0.15 mg/kg/day up to a maximum dose of 15 mg. This was reduced after 26 weeks by thirds at 4-week intervals and was stopped after 8 weeks
	• Early stop points included a confirmed ≥ 30% rise in baseline Cr. Confirmed meant that the Cr was not improved by two 25% reductions in the dose of the test medication spaced out over a four-week period. Other premature stop points included a doubling of baseline liver enzymes and intolerable side effects. The test medication was also stopped if a complete remission of proteinuria was achieved and persisted for 1 month or more. The mean CSA dose was 3.7 ± 2.0 mg/kg. The mean trough level at 26 weeks was 148 ± 29 ng/L. All patients completed the 6 months of the test medications except 1 case of complete remission, where the CSA was stopped at week 20 after 4 weeks with no proteinuria
	
	Treatment group 2
	
	• Placebo + prednisone
	   ○ Placebo: started at a dose of 0.035 mL/kg/day. A comparable number of adjustments were made in the placebo patient's medication volume to ensure that masking was maintained. It was continued for 26 weeks and then tapered to zero over 4 weeks

Cattran 2001 *(Continued)*

○ Prednisone: 0.15 mg/kg/day up to a maximum dose of 15 mg. This was reduced after 26 weeks by thirds at 4-week intervals and was stopped after 8 weeks

Outcomes	• Death • ESKD • 50% or 100% Cr increase • Final SCr • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: supported by the Kidney Foundation of Canada and Novartis Canada • Baseline comparison: comparable • Sample size calculation: the estimated total sample size was 50 patients. The number of finally included patients was similar to the estimate (51). • Confounding factors: no. At randomisation, 53% (27) of the patients were hypertensive (CSA (16), placebo (11)). Nineteen were on ACEi (CSA (11), placebo (8)), and 8 were on other antihypertensive medications. During the CS period, there was an increase in the number of patients in both groups that required antihypertensive medication, but more in the CSA than in the placebo group (8 versus 5). Despite this, no significant differences in supine, sitting, or mean arterial pressure measurements were noted during the active medication period or during the post-CSA period. Since ACEi could not be introduced in this period, these additional cases resulted in a decreased percentage of hypertensive patients within each group on this class of CSA. In the CSA group, this fell from 69% to 46% and in the placebo group from 73% to 50%. During the post-test medication period, neither the percentage of patients with hypertension nor the use of ACEi changed significantly. There was no difference in the CSA group between those on ACEi compared with those not on an ACEi in either baseline proteinuria or in the amount of protein reduction by week 26. The number, as well as the severity of hypertension, was greater in the CSA compared with the placebo group in the active treatment period. A new antihypertensive agent (8) or an increase in the dose of the antihypertensive drugs (2) was required in the CSA group versus a new agent (5) in the placebo group • The average per patient prednisone dose given prior to the 6-month run-in period was not different in the 2 groups. In the placebo group, the mean total dose was 92 mg/kg (range 65 to 120), and in the CSA group, it was 108 mg/kg (range 60 to 140). The mean duration of treatment was also similar at 12 weeks in the placebo patients (range 8 to 22) and 14 weeks in the CSA patients (range 8 to 28). In addition, in the prestudy period, 18 patients (placebo (10), CSA (8)) had failed a course of cytotoxic agents (CPA (9), chlorambucil (5), AZA (4)) for an average of 4 months (range 2 to 12)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by the clinical coordinating centre from a table of random numbers and was stratified by centre in blocks of two to ensure a balance between groups
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	The patients were masked in regard to CSA versus placebo assignment. Novartis Canada Ltd. (Whitby, Ontario, Canada) provided CSA in a drink solution (100 mg/mL) and an identical placebo made from the same carrier. The physicians were not masked in regard to CSA versus placebo assignment for safety reasons
Blinding of outcome assessment (detection bias)	Low risk	The end points were objective and measured centrally by a lab blinded to patient designation. No further information was provided

Cattran 2001 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients except 2 patients completed the study. The reasons were relocation outside of North America and noncompliance
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Chan 2007

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: before 2007 • Duration of follow-up: 15 to 24 months

Participants	• Setting: not reported
	• Country: China
	• Inclusion criteria: biopsy-proven IMN with proteinuria of ≥ 3 g/day
	• Baseline characteristics
	  ○ Pathology stage: not reported
	  ○ Mean proteinuria ± SD (g/24 hours): 5.7 ± 2.7
	  ○ Hypertension: 14/20
	  ○ Mean serum albumin ± SD (g/L): 26.5 ± 7.5
	  ○ Mean SCr ± SD (μmol/L): treatment group 1 (103.3 ± 48.7); treatment group 2 (85.7 ± 31.8)
	  ○ Mean GFR ± SD (mL/min): treatment group 1 (87.1 ± 38.5); treatment group 2 (101.8 ± 40.6)
	  ○ Baseline declining kidney function: initial Cr was < 300 μmol/L in all included patients 3/20 patients (2 in the MMF group and 2 in the control group) had abnormal SCr at baseline
	  ○ Use of ACEi or ARB during follow-up: in view of their confounding effects on proteinuria and kidney function, ACEi and ARB were not started during the study, and if a patient was already on either medication at the start of the study, the dose was kept unchanged. Only 1 patient was receiving ACEi prior to the study, and the dose was kept unchanged
	  ○ Previous immunosuppressive status: those who had received cytotoxic or CSA treatment within the previous 12 months, or who had received prednisolone at ≥ 20 mg/day for 4 weeks or more within the past 6 months, were excluded
	• Number: treatment group 1 (11); treatment group 2 (9)
	• Mean age ± SD (years): 49.5 ± 13.5
	• Sex (M/F): 13/7
	• Exclusion criteria: clinical evidence or suspicion of an underlying aetiology (such as infection, malignancy, systemic autoimmune disease); those who had received cytotoxic or cyclosporine treatment within the previous 12 months, or who had received prednisolone at 320 mg/day for 4 weeks or more within the past 6 months

Interventions	Treatment group 1 • MMF: 1 g twice/day was given for 6 months • Prednisolone (oral): started at 0.8 mg/kg/day, then tapered by 5 mg/day every fortnight until reaching 10 mg/day at around 4 months, then tapered by 2.5 mg/day every fortnight, till total withdrawal at around 6 months from baseline. The cumulative dose of prednisolone was 3.80 ± 0.28 g Treatment group 2

- Modified Ponticelli regimen
  - Methylprednisolone (IV): 1 g/day for 3 days, followed by oral prednisolone 0.4 mg/kg/day for 3 weeks, then 0.2 mg/kg/day till the end of the month, alternating with chlorambucil 0.2 mg/kg/day for 1 month, for a total duration of 6 months. The cumulative dose of prednisolone was 9.93 ± 0.25 g

Outcomes	- Death - ESKD - Final GFR - Partial or complete remission - Final proteinuria - Side effects leading to patient withdrawal or hospitalisation
Notes	- Funding information: the study received partial funding support from the Wai Hung Charity Foundation and Roche Pharmaceuticals (Hong Kong). The donors had no role in the study design and execution, data analysis and interpretation, or writing of the report - Sample size calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Patients who satisfied the selection criteria were randomised by drawing envelope into either one of two treatment groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Chen 2010a

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: July 2004 to August 2008 - Duration of follow-up: 12 months
Participants	- Country: China - Setting: multicentre

Chen 2010a *(Continued)*

- Inclusion criteria: biopsy-proven IMN and nephrotic syndrome
- Baseline characteristics
  - Pathology stage (I/II/III): treatment group 1 (16/21/2); treatment group 2 (16/17/1)
  - Mean proteinuria ± SD (g/24 hours): treatment group 1 (7.71 ± 3.93); treatment group 2 (7.28 ± 3.91)
  - Hypertension: not reported
  - Mean serum albumin ± SD (g/L): treatment group 1 (23.1 ± 4.25); treatment group 2 (23.1 ± 4.81)
  - Mean SCr ± SD (µmol/L): treatment group 1 (75.7 ± 22.4); treatment group 2 (85.0 ± 37.5)
  - Mean GFR ± SD (mL/min/1.73 m²): treatment group 1 (105.5 ± 28.7); treatment group 2 (97.0 ± 34.3)
  - Baseline declining kidney function: initial Cr was < 221 µmol/L in all included patients
  - Use of ACEi or ARB during follow-up: yes, no confounding effect. To exclude the interference of ACEi or ARB on the level of proteinuria, patients who were taking ACEi or ARB before initiation of immunosuppressive therapy were instructed to maintain the dose of ACEi or ARB; those not taking ACEi or ARB before initiation of immunosuppressive therapy were instructed not to take ACEi or ARB, and other antihypertensive drugs were prescribed in those patients who did not reach the above target values. There were no significant differences in both SBP and DBP between the two groups during follow-up. 12/39 patients in TAC group received ACEi or ARB; while 7/34 patients in the CPA group received ACEi or ARB (P = 0.32). Five new patients in the TAC group were diagnosed with hypertension and none in CPA were diagnosed (P = 0.09)
  - Previous immunosuppressive status: no immunosuppressive treatment was allowed within the previous 3 months before entry
- Number: treatment group 1 (39); treatment group 2 (34)
- Mean age ± SD (years): treatment group 1 (47.2 ± 11.9); treatment group 2 (48.6 ± 11.6)
- Sex (M/F): treatment group 1 (23/16); treatment group 2 (18/16)
- Exclusion criteria: coexistence of other severe kidney diseases; having life-threatening complications such as severe infections; hepatitis B or C virus-positive serology or serum amino-transferase exceeds 2-fold of the upper limit; malignancy, HIV infection, or other contraindications of corticosteroids and immunosuppressant; fasting blood glucose > 6.2 mmol/L; pregnant or lactating; hypertensive to macrolides medication; secondary diseased that cause membranous nephropathy such as SLE

Interventions	Treatment group 1

- TAC: started at a dose of 0.1 mg/kg/day, divided into 2 daily doses at a 12-hour interval. Later doses for the first 6 months were adjusted to achieve a whole blood 12 hours trough level between 5 and 10 ng/mL. Treatment was tapered for the next 3 months with a target trough level between 2 and 5 ng/mL. Doses were reduced by 25% every 2 weeks in the presence of a 50% SCr increase. If increasing of SCr persisted 50% of baseline values for 2 to 4 weeks after 75% reduction of TAC doses, the definition of endpoint was established. The daily dose was 4.43 ± 2.42 mg/day during the first 6 months
- Prednisone (oral): 1 mg/kg/day for 4 weeks, tapered gradually, and discontinued by 8 months

Treatment group 2

- CPA (oral): 100 mg/day for 4 months (accumulated dosage was 12 g). The dosage was reduced by 50 mg/day if the total white blood cell count fell below 4000/L (when it returns to the normal range, the dosage can be increased with careful monitoring).
- Prednisone (oral): 1 mg/kg/day for 4 weeks, tapered gradually, and discontinued by 8 months

Outcomes	

- Death
- ESKD
- 50% or 100% Cr increase
- Final GFR
- Partial or complete remission
- Final proteinuria
- Side effects leading to patient withdrawal or hospitalisation

Notes	

- Funding information: not reported
- Glucose intolerance was only noted in 11 patients in the TAC group (including 3 patients who developed diabetes mellitus) (P = 0.00). Infection and hypertension tended to be more common in the TAC

Chen 2010a *(Continued)*

group than in the CPA group although the P-value did not reach statistical significance (8 versus 1 with P = 0.55 for infection; 5 versus 1 with P = 0.09 for hypertension)

- Relapse occurred in 11 patients, 6 in the TAC group and 5 in the CPA group. All the patients experiencing relapse had partial remission to the initial treatment. All the relapses in the TAC group took place within 3 months after withdrawal of TAC. There was no significant difference of relapse rate between the 2 groups. For the 6 patients experiencing a relapse in the TAC group, 2 were retreated with TAC; 2 were retreated with CPA, and the other 2 received conservative therapies (ACEi and/or ARB). For the 5 patients experiencing a relapse in the CPA group, 2 received MMF, 1 received CSA, and the other 2 received conservative therapies (ACEi and/or ARB)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a clinical coordinating centre using a table of random numbers and was stratified by centres
Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque-closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 13/73 patients (18%) did not finish the 12-month follow-up. 6/39 patients (15%) withdrew in the TAC group (infection (3); severe gastrointestinal complaint (1); elevated aminotransferase (1); patient's intention (1)). In the CPA group 7/34 patients (21%) did not finish the follow-up: 3 patients withdrew (severe gastrointestinal complaint (1); elevated aminotransferase (1); patient's intention (1)) and 4 patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Chen 2013e

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: recruitment was from April 2008 to February 2011 - Duration of follow-up: 48 weeks
Participants	- Setting; multicentre (7 sites) - Country; China - Inclusion criteria: diagnosed with IMN by renal biopsy (stages I-IV); aged 18 to 75 years; eGFR > 30 mL/min, 24-hour urinary albumin ≥ 3.5 g - Baseline characteristics - Mean proteinuria ± SD (g/24 hours): treatment group (5.3 ± 2.7); control group (5.3 ± 2.4)

Chen 2013e *(Continued)*

- ○ Mean serum albumin ± SD (g/L): treatment group (25.0 ± 8.0); control group (24.6 ± 6.8)
- ○ Mean eGFR ± SD (mL/min/1.73 m²): treatment group (84.0 ± 27.4); control group (83.8± 24.9)
- ○ Mean triglyceride ± SD (mmol/L): treatment group (3.20 ± 2.30); control group (2.73 ± 1.56)
- ○ Mean SCr ± SD (μmol/L): treatment group (82.0 ± 41.5); control group (77.1 ± 23.6)
- ○ Mean BUN ± SD (mmol/L): treatment group (5.25 ± 1.75); control group (5.79 ± 2.14)
- ○ Mean serum cholesterol ± SD (mmol/L): treatment group (7.67 ± 2.20); control group (8.09 ± 2.50)
- Number: treatment group (95); control group (95)
- Mean age ± SD (years); treatment group (49 ± 14); control group (53 ± 12)
- Sex (M/F): treatment group (60/35); control group (65/30)
- Exclusion criteria: other 19 types of membranous nephropathy; rapid loss of kidney function > 50% decline in eGFR on 3 months; secondary membranous nephropathy; HbA1c > 6.2mmol/L; treatment with steroids in last 6 months with immunosuppressive medication for > 4 weeks; presence of infection or malignant disease; uncontrolled hypertension, BP > 130/80 mm Hg; alanine transferase level >40 U/L and aspartate aminotransferase level >38 U/L; treated with ACEi or ARB within last 2 weeks

Interventions	Treatment group

- Shenqi particles (TCM): 9.6 g, 3 times/day

Control group

- Prednisone (oral): 1 mg/day/kg, 12 weeks then tapered by 10 mg every 2 weeks to 30 mg/day, then tapered by 5 mg every 2 weeks to 20 mg/day and then 5 mg every 4 weeks to a maintenance dose of 10 mg/day
- CPA (IV): 0.8 to 1 g/m² body surface area once every month for 6 months and then once every 3 months for another 6 months with a total dose 9 to 12 g/m²

Duration of treatment

- 48 weeks

Outcomes	• Complete or partial remission

- ○ Complete remission: reduction in proteinuria to protein excretion≤ 0.3 g/day
- ○ Partial remission: reduction to > 0.3 g and < 3.5 g/day and a 50% reduction from peak value
- Serum albumin
- GFR (using MDRD)
- Doubling of SCr
- Initiation of KRT or transplantation (i.e. ESKD)
- Death
- Severe adverse effects

Notes	• Sample size, based on 20% difference in remission rate (80% to 60%)

- Analysed per protocol and Intention to treat
- Recruiting in December 2011
- No patient had haemodialysis or transplantation while on the trial
- Funded by National Science and Technology Support Project (2006BAI04A07-2), the Xing Lin Team of the Shanghai University of Traditional Chinese Medicine, and The Ministry of Science and Technology Twelve Five Plan Major Science and Technology Special Projects "Major New Drug Development"–Establishment of Clinical Evaluation Platform for New Traditional Chinese Herbal Drugs (Malignant tumour and other diseases) (project number: 2011ZX09302-006-04).

Risk of bias

Bias	Authors' judgement	Support for judgement

Chen 2013e *(Continued)*

Random sequence generation (selection bias)	Low risk	Allocation as per random sequence. SAS program PROC PLAN
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	High drop-out rate (58/190); main reasons were a) took other medication, b) missed follow-up visit
Selective reporting (reporting bias)	Low risk	Appropriate outcomes reported
Other bias	Low risk	Study appears free of other biases

Choi 2018

Study characteristics

Methods	• Study design: parallel RCT • Study duration: June 2013 to May 2016 • Duration of follow-up: 48 weeks

Participants	• Setting: multicentre
	• Country: Korea
	• Inclusion criteria: renal biopsy within last 12 months; ≥18 years; proteinuria > 8 g/day or proteinuria < 8 g/day and any 3 or more of the following:
	   ○ eGFR < 60 mL/min/1.73 m²
	   ○ Hypertension ≥140/90 mm Hg or ≥ 120/80 with antihypertensive drugs
	   ○ 24-hour urinary protein > 5.0 g/day or spot UPCR > 5 g/g
	   ○ Serum albumin < 3 g/dL
	   ○ Selectivity index > 0.2 (urine IgG x serum albumin/serum IgG x urine albumin
	• Baseline characteristics
	   ○ Mean SBP/DBP ± SD (mm Hg): 123.7 ± 17.2 / 76.5 ± 11.42
	   ○ Mean proteinuria ± SD: 8.7 ± 4.9 g/24 hours
	   ○ Mean serum albumin ± SD: 24 ± 6 g/L
	   ○ Mean GFR ± SD: 78.9 ± 28.7 mL/min/1.73 m²
	   ○ Mean SCr ± SD: 1.1 ± 0.4 mg/dL
	   ○ Mean serum cholesterol ± SD: 15.29 ± 3.86 mmol/L
	   ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: < 12 months
	   ○ Co-morbidities: DM (20.5%), hypertension (59.0%), microscopic haematuria (87.2%)
	• Number: treatment group (21); control group (18)
	• Mean age (years): treatment group (57.7), control group (52.7)
	• Sex (M/F): treatment group (16/5); control group (9/9)

Choi 2018 *(Continued)*

- Exclusion criteria: moderate to severe gastrointestinal disorder; history of allergy to MMF or CSA; acute or chronic allergy within 4 weeks; the presence of life-limiting comorbid disorders such as malignancy or uncontrollable active infection; drug or alcohol addiction within 6 months; uncontrolled hypertension > 160/100 mm Hg; eGFR ≤ 30 mL/min/1.73 m²; absolute neutrophil count < 1500/mm³ or WCC < 2500/mm³; platelets < 100,000/mm³; > 3 times the normal liver function test values; pregnancy or lactation; immunosuppressive agents within 6 months for secondary MN with a systemic disorder; life expectancy < 1 year

Interventions	Treatment group
	- MMF (oral)
	- Prednisolone (oral)
	Control group:
	- CSA (oral)
	- Prednisolone (oral)
	Duration
	- 46 weeks
	Co-medications
	- Most patients were treated with statins (94.9 %), ACEi/ARB (84.6%), proton pump inhibitor (48.7%)
Outcomes	- Complete remission: decrease in proteinuria to ≤ 200 mg/day and a sustained serum albumin level ≥ 3.5 g/dL
	- Partial remission: decrease in proteinuria to > 200 and < 3500 mg/day or a decrease > 50% compared to baseline
	- eGFR
	- Relapse
	- Improvement of hypoalbuminaemia and hypercholesterolaemia at 48 weeks
	- Proteinuria
	- Side effects
	- Relapse: proteinuria ≥ 3,500 mg/day after the achievement of partial or complete remission or an increase in proteinuria > 50% in patients in whom proteinuria had improved initially by > 50%
Notes	- Funding source: Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare, Republic of Korea (grant number HC15C1129, HI15C0001); drugs and placebo used in the study were provided by Hanmi Pharmaceutical, Co., Ltd. (Seoul, South Korea), which had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
	- Sample size; at least 28 patients in each group would be needed for 80% power assuming a 5% significance level. As a 10% screening failure and the dropout rate was estimated, 31 patients would finally need to be included in each group (does not state what % change in complete remission this is for)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation technique, using SAS randomisation program, managed by statisticians in external department
Allocation concealment (selection bias)	Low risk	Sealed sequential numbered opaque envelopes

Choi 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of any blinding, except that both drugs were provided as prepacked drugs in identical bottles
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	43 screened, 39 included, high drop-out (5/18 and 9/21) however all randomised patients were included in analysis (intention-to-treat)
Selective reporting (reporting bias)	Low risk	Complete and partial remission are appropriate outcomes. However, improvement in hypoalbuminaemia and hypercholesterolaemia were not reported as secondary outcomes on clinicaltrials.gov but were reported in the trial
Other bias	Low risk	Drugs were provided free of charge by pharmaceutical company that however was not involved in the study in any other way

Coggins 1979

Study characteristics

Methods	• Study design: parallel RCT • Study duration: before 1979 • Duration of follow-up: 23 ± 4.4 (4 to 52) months

Participants	• Setting: multicentre
	• Country: USA
	• Inclusion criteria: biopsy-proven IMN and nephrotic syndrome
	• Baseline characteristics
	  ○ Pathology stage (I/II/III-IV/Indeterminate): treatment group (5/18/9/2); control group (9/20/8/1)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group (9.4 ± 6); control group (8.3 ± 4)
	  ○ SCr (mg/dL): treatment group (1.1 ± 0.2); control group (1.0 ± 0.2)
	  ○ Mean GFR ± SD (mL/min/1.73 m²): > 60
	  ○ Baseline declining kidney function: no
	  ○ Use of ACEi or ARB during follow-up: not reported
	  ○ Previous immunosuppressive status: no patient received previous immunosuppressive treatment before entry
	• Number: treatment group (34); control group (38)
	• Mean age (range): 39 years (16 to 65)
	• Sex (M/F): treatment group (22/12); control group (20/18)
	• Exclusion criteria: secondary membranous nephropathy or treatment with other immunosuppressive therapies

Interventions	Treatment group
	
	• Prednisone
	  ○ Weight 45 to 80 kg: 125 mg, given as a single dose every other morning
	  ○ Weight < 45 kg: 100 mg every other day
	  ○ Weight > 80 kg: 150 mg, every other day
	• If no response at the end of 8 weeks, prednisone was tapered within an additional 4-week period. If a partial or complete response occurred, the drug was reduced by 25 mg/dose each week until a

Coggins 1979 *(Continued)*

dosage of 25 mg was reached and tapered 5 mg/dose/week thereafter. If a patient relapsed after a complete or partial remission, the dosage was returned to the original level, maintained at that level for 1 month, and tapered as before

Control group

- Placebo: identical placebo control tablets (supplied by Upjohn Company)
- If no response at the end of 8 weeks, the placebo was tapered within an additional 4-week period. If a partial or complete response occurred, the drug was reduced by 25 mg/dose each week until a dosage of 25 mg was reached and tapered 5 mg/dose/week thereafter. If a patient relapsed after a complete or partial remission, the dosage was returned to the original level, maintained at that level for 1 month, and tapered as before

Outcomes	
	- Death - ESKD - 50% or 100% Cr increase - Partial or complete remission - Side effects leading to patient withdrawal or hospitalisation

Notes	
	- Duration of follow-up: only 31/72 patients were followed for 24 months, and 21/72 were still under observation at 3 years - Funding information: The Collaborative Study, its members, and their institutions were supported by the following grants from the National Institutes of Health: AM15646, USPHS 5-M01-RR-00058, USPHS HL-05949, NIH 5 T32 AM 07241-02, 5K0 HL 4418, and USPHS RR-109

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Immediately after admission to the study, patients were randomly allocated to prednisone or placebo. Randomization was stratified according to initial histologic diagnosis with the light microscope (before review by the Central Pathology Board) in the participating hospital
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were assigned without the knowledge of either the patient or physician to prednisone therapy or identical placebo control tablets (supplied by the Upjohn Company)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

CYCLOMEN 1994

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: to 25 months

Participants	• Setting: multicentre
	• Country: Europe
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome and worsening kidney function
	• Baseline characteristics
	  ◦ Pathology stage: not reported
	  ◦ Mean proteinuria ± SD (g/24 hours): treatment group (6.8 ± 0.9); control group (4.0 ± 0.5)
	  ◦ Mean GFR ± SD (mL/min/1.73 m²): treatment group (49.3 ± 6.5); control group (47.8 ± 7.3)
	  ◦ Baseline declining kidney function: yes
	  ◦ Use of ACEi or ARB during follow-up: yes, no confounding effect
	  ◦ Previous immunosuppressive status: not reported
	• Number: treatment group (10); control group (11)
	• Mean age ± SD (years): not reported
	• Sex (M/F): treatment group (9/1); control group (8/3)
	• Exclusion criteria: not reported

Interventions	Treatment group • CSA: 5 mg/kg/day for 6 months Control group • Conservative therapy for 6 months
Outcomes	• Death • ESKD • Final SCr • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: not reported • Baseline comparison: the baseline proteinuria was not balanced (P < 0.05) • Sample size calculation: the estimated total sample size was 186 patients. This study was prematurely stopped and the number of finally included patients was far from the estimate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/22 (95%) randomised completed the treatment and were finally analysed
Selective reporting (reporting bias)	Low risk	The study protocol was available and it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

CYPMEN 2006

Study characteristics

Methods	• Design: parallel, open-label RCT • Study duration: from 1 June 2000 • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: biopsy-proven IMN; urinary protein excretion > 3.5 g/day; aged 16 to 80 years • Baseline characteristics: not reported • Number: treatment group 1 (14); control group (14) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: secondary forms of membranous nephropathy; CrCl < 70 mL/min; relapse or recurrence; treated with other immunosuppressants
Interventions	Treatment group 1 • CSA: 3 mg/kg/day • Prednisolone: 15 mg/day • Duration: 24 months Treatment group 2 • CSA: 3 mg/kg/day • Duration: 24 months
Outcomes	• Complete remission or partial remission • Relapse or recurrence by urinary examination until 24 months after the initiation of the treatment • Urinary protein excretion (g/day) • Serum protein and albumin (mg/dL) • CrCl (mL/min) • SCr (mg/dL)

CYPMEN 2006 *(Continued)*

	• Adverse effects until 24 months after the initiation of the treatment
Notes	• Completed before 18/11/2009 • Contact: Dr, Kouichi, Hirayama k-hira@tokyo-med.ac.jp and Dr, Akio, Koyama koyama@ipu.ac.jp. Emailed both on 11 July 2018. Replied with unpublished data 13 July 2018

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Di 2018

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: March 2012 to January 2016 • Duration of follow-up: 24 months for both groups
Participants	• Setting: multicentre • Country: China • Inclusion criteria: pathologically diagnosed with IMN at stage I-III based on the KDIGO Clinical Practice Guidelines; SCr < 221 µmol/L; pregnancy-bearing female patients with negative pregnancy test results, who agreed to take contraceptive measures • Baseline characteristics: not reported • Number (randomised/analysed): treatment group 1 (37/35); treatment group 2 (39/35) • Mean age ± SD (years): treatment group 1 (47.9 ± 17.1); treatment group 2 (46.9 ± 15.4) • Sex (M/F): treatment group 1 (22/13); treatment group 2 (20/15) • Exclusion criteria: infections; malignant tumours; tuberculosis or other serious kidney diseases; administered corticosteroids or other immunosuppressive agents within the last month; abnormal liver function, or type 1 or 2 DM; allergic to macrolide drugs

Di 2018 *(Continued)*

Interventions	Treatment group 1
	• TAC: 0.1 mg/kg/day for 12 months
	• Prednisone: 0.5 mg/kg/day for 12 months
	Treatment group 2
	• TAC: 0.1 mg/kg/day for 24 months
	• Prednisone: 0.5 mg/kg/day for 24 months
	Treatment details
	• Patients in both groups were administered low-dose prednisone (0.5 mg/kg/day) combined with TAC (0.1 mg/kg/day) orally for routine treatment. At 8 weeks following initial administration, the dose of prednisone was reduced by 5 mg every 4 weeks and then maintained at a total of 10 mg/day. The short-course treatment group received TAC (0.1 mg/kg/day) once every 12 h; patients were administered the drug orally when fasting (0.5 h prior to meals). Following 1 week of treatment, the plasma concentration of TAC was monitored and if the concentration was < 5 µg/L, the dosage of TAC was increased until the plasma concentration was maintained at 5 to 10 µg/L. This cut off value was based on a previous study. At 6 months of treatment, the plasma concentration of TAC was maintained at 2 to 4 µg/L and patients continued treatment until the 12-month period ended. The long-course group were administered the same treatment as the short-course group. At 6 months following treatment, TAC plasma concentration was maintained at 2 to 4 µg/L and patients continued to receive this dosage until the 24-month treatment period had ended
Outcomes	• Complete remission: urinary protein < 0.3 g, normal serum albumin levels and normal kidney function
	• Partial remission: urinary protein was 0.3 to 3.0 g, or when its basal value was reduced by > 50%. In addition, serum albumin had to be ≥ 30 g/L with stable kidney function
	• No remission: considered when the efficacy did not reach the criteria for partial remission
	• Recurrence was determined after the efficacy reached complete or partial remission, but symptoms in line with the diagnostic criteria for nephrotic syndrome recurred in the course of administration. The repeated occurrence occurred when the efficacy reached partial remission, but various incentives led to elevated levels of urinary protein, which did not meet the diagnostic criteria for nephrotic syndromes
Notes	• Funding: no funding was received
	• Ethics: The protocol was approved by the Ethics Committee of the First People's Hospital of Changzhou. Written, informed consent was obtained from all participants prior to enrolment
	• Declarations of Interests/disclosures: reported no conflict of Interest
	• Trial registration or Protocol registration or publication: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Di 2018 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete data. Comprehensive reporting. Low-drop-out rate (all due to severe adverse effects, which are reported)
Selective reporting (reporting bias)	High risk	No protocol reported, not all kidney outcomes reported
Other bias	Low risk	Conflict of Interest of authors not declared. Sources of Funding declared (public funding). No evidence of other bias

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Donadio 1974

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: May 1971 to June 1973 - Duration of follow-up: 19/22 patients were followed at least 12 months (treatment group (9); control group (10)); 17/22 patients were followed for an average of 1 year beyond the 1 year of treatment (treatment group (7); control group (8))
Participants	- Setting: single centre - Country: USA - Inclusion criteria: biopsy-proven IMN with nephrotic syndrome - Baseline characteristics - Pathology stage (I/II/III): treatment group (3/7/1); control group (2/8/1) - Mean proteinuria, range (g/24 hours): treatment group (7.8, 2 to 16.6); control group (7.6, 2 to 12.1) - Hypertension: treatment group (2/11); control group (2/11) - Mean serum albumin, range (g/L): treatment group (27, 19 to 34); control group (23, 16 to 37) - Mean SCr, range (mg/dL): treatment group (1.2, 0.8 to 1.9); control group (1.1, 0.8 to 2.2) - Mean GFR, range (mL/min/1.73 m^2): treatment group (75, 44 to 117); control group (80.6, 33 to 112) - Baseline declining kidney function: no - Use of ACEi or ARB during follow-up: not reported - Previous immunosuppressive status: no patients had received prior cytotoxic drug treatment; 3 patients in the treatment group (27%) and 4 in the control group (36%) had received or were currently receiving prednisone treatment; such treatment was tapered off and then stopped within 30 days - Number: treatment group (11); control group (11) - Mean age, range (years): treatment group (males: 41, 25 to 74; females: 48.5, 40 to 59); control group (males: 47.6, 34 to 69; females: 41, 26 to 65) - Sex (M/F): treatment group (9/2); control group (8/3) - Exclusion criteria: not reported
Interventions	Treatment group Oral CPA: 1.5 to 2.5 mg/kg/day (mean: 1.8) for 1 year. If the leukocyte count was < 3000/mmm^3 or if the platelet count was < 80000/mm^3 the drug was stopped for a minimum of 7 days. When the counts increased to above these limits, treatment was started again at one-half the previous dose and then increased to the initial dose level if possible. The cumulative dose was 538 ± 120 (310 to 665) mg/kg in the 9 patients who completed the 12-month treatment Control group

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Donadio 1974 *(Continued)*

	• No treatment

Outcomes	• Death • ESKD • 50% or 100% Cr increase • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: supported by a grant from the Mayo Foundation and by Public Health Service grant RR-585 from the National Institutes of Health Clinical Research Center • Nine patients in each group had nephrotic syndrome on initial evaluation. Two in each group presented with non-nephrotic proteinuria, but all had previously been documented to have the nephrotic syndrome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Only after a patient was deemed eligible was the treatment ascertained by referral to a list created from a table of random numbers (by WFT). The table was maintained by the renal pathologist (KEH) and was not seen by the clinicians (JVD and CFA)
Allocation concealment (selection bias)	Low risk	Neither patient nor clinician knew what treatment was going to be given before the patient agreed to enter study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/11 patients (18%) in the CPA group and 1/11 patients (9%) in the no-drug group did not complete the 12-month follow-up. In 2 patients in the CPA group, the drug was stopped after 8 months, on the advice of the clinicians, when data analysis to that point revealed no treatment benefit either to these patients or to the 19 patients who had completed the study. 1 patient in the no-drug group was dropped from the study because the patient was not considered to have purely IMN
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Dussol 2008

Study characteristics

Methods	• Study design: parallel, open-label RCT

Dussol 2008 *(Continued)*

- Study duration: January 2004 to January 2008
- Duration of follow-up: 12 months

Participants	• Setting: multicentre
	• Country: France
	• Inclusion criteria: biopsy-proven IMN and nephrotic syndrome
	• Baseline characteristics
	   ○ Pathology stage (I/II): treatment group (8/9); control group (13/6)
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group (6.2 ± 3.5); control group (9.5 ± 5.8)
	   ○ Mean serum albumin ± SD (g/L): treatment group (23.2 ± 7.3); control group (20.2 ± 6.0)
	   ○ Mean SCr ± SD (mg/dL): treatment group (1.01 ± 0.34); control group (1.09 ± 0.39)
	   ○ Mean GFR ± SD (mL/min/1.73 m^2): treatment group (92.1 ± 29.8); control group (80.7 ± 25.4)
	   ○ Baseline declining kidney function: initial Cr was < 200 µmol/L in all included patients
	   ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. In the control group, 14 patients received ACEi, 1 received ARB, and 2 received a combination of ACEi and ARB In the MMF group, 17 patients received ACEi, 1 received ARB, and 1 received a combination of ACEi and ARB
	   ○ Previous immunosuppressive status: no patient received previous immunosuppressive treatment before entry
	• Number (randomised/analysed): treatment group (19/15); control group (17/17)
	• Mean age ± SD (years): treatment group (47.8 ± 15.2); control group (55.9 ± 15.2)
	• Sex (M/F): treatment group (17/2); control group (15/2)
	• Exclusion criteria: secondary MGN regardless of the cause; diagnosis of MGN for more than 6 months; previously treated with an immunosuppressive agent

Interventions	Treatment group • MMF: 250 mg/day, progressively increased by 250 mg every other day to 2 g/day for 12 months. MMF therapy was then progressively stopped in 15 days. Mean dose of MMF was 1,850 mg. Sixteen patients could achieve the target dose of 2 g/day. Two patients were maintained on 1.5 g/day, and 1 was maintained on 1 g/day because of gastrointestinal symptoms • Conservative treatment (as per control) Control group • Conservative treatment ○ Renin-angiotensin blockers, statins, low-salt and low-protein diet, and diuretics in case of oedema
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final GFR • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: partial support for this study was provided by Roche through technical assistance and financing for the clinical research assistant. Roche did not intervene in the design or conduct of the study, analysis and interpretation of the data, or preparation of the article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was performed by each centre through a centralized Internet on-line application provided by the sponsor (minimization method). Randomization was stratified according to sex and centre"

Dussol 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Dyadyk 2001a

Study characteristics	
Methods	• Study design: RCT • Study duration: not reported • Duration of follow-up: 12 to 48 months
Participants	• Setting: not reported • Country: Ukraine • Inclusion criteria: IMN • Baseline characteristics: not reported • Number: treatment group 1 (16); treatment group 2 (16) • Mean age ± SD (years): not reported • Sex (M/F): treatment group 19/13 • Exclusion criteria: not reported
Interventions	Treatment group 1 • CPA: initial dose 1.5 to 3.5 mg/kg/day • Mean treatment duration: 5.8 months Treatment group 2 • AZA: initial dose 1.4 to 2.0 mg/kg/day • Mean treatment duration: 6.6 months
Outcomes	• Proteinuria • SCr
Notes	• Abstract-only publication, data could not be used • Funding source: not reported

Dyadyk 2001a *(Continued)*

- Baseline comparison: comparable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data could not be extracted for meta-analysis
Other bias	Unclear risk	Insufficient information to permit judgement

Falk 1992

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: March 1986 to November 1990 • Duration of follow-up: 29.2 ± 17.1 month

Participants	• Setting: multicentre
	• Country: USA
	• Inclusion criteria: biopsy-proven progressive IMN with either deteriorating kidney function or persistent proteinuria associated with morbid complications
	• Baseline characteristics
	    ○ Pathology stage: not reported
	    ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (12.4 ± 9.9); treatment group 2 (11.1 ± 6.7)
	    ○ Mean SCr ± SD (mg/dL): treatment group 1 (2.3 ± 1.0); treatment group 2 (2.7 ± 1.6)
	    ○ Baseline declining kidney function: yes
	    ○ Use of ACEi or ARB during follow-up: yes, no confounding effect
	    ○ Previous immunosuppressive status: all patients had received a course of corticosteroids therapy. All patients had received initial therapy with prednisone at a dose of 2.0 mg/kg body weight every other day (not exceeding a maximum single dose of 120 mg) for 8 weeks; the drug was then tapered by 25%/dose/week over 4 weeks. Patients were not eligible if they had previously been treated with CPA or chlorambucil
	• Number: treatment group 1 (13); treatment group 2 (13)
	• Mean age ± SD (years): treatment group 1 (43.3 ± 14.8); treatment group 2 (46.0 ± 13.7)

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Falk 1992 *(Continued)*

	• Sex (M/F): treatment group 1 (9/4); treatment group 2 (7/6)

Interventions	Treatment group 1
	• CPA + steroids: IV CPA in conjunction with a 3-day course of pulse methylprednisolone and alternate-day corticosteroids ○ Steroids: IV pulse methylprednisolone at a dose of 7 mg/kg (not exceeding a single maximum dose of 1000 mg) given on 3 consecutive days. Forty-eight hours after completing therapy with pulse methylprednisolone, patients began treatment with oral corticosteroids (prednisone, 1mg/kg every other day, not exceeding 80 mg/single dose) for 2 months; drug was tapered 25%/dose/week over the next 4 weeks ○ CPA (IV): monthly CPA was given at an initial dose of 0.5g/m². Leukocyte counts were monitored to maintain counts at levels no lower than 3×10^6/L If leukocyte nadir counts remained above 5×10^6/L after each treatment, the subsequent CPA dose was raised by 250 mg/m². The maximum single dose did not exceed 1000 mg/m². CPA was administered monthly for 6 months
	Treatment group 2
	• Prednisone: oral 2.0 mg/kg prednisone on alternate days for 8 weeks, and then tapered by 25%/dose/week over 4 weeks

Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation

Notes	• Funding information: in part by the Jessie Bell DuPont Religious, Charitable and Educational Fund, the Telephone Pioneers of North Carolina (Chapter 35, and the National Institutes of Health General Clinical Research Center) (grant RR00046) • To be included in the study, patients had to have either deteriorating kidney function or persistent proteinuria associated with morbid complications. Deterioration in kidney function was defined by a sustained doubling of the SCr over, at most, 2 years of follow-up or by a 50% fall in the GFR during the same interval. Additionally, patients were accepted into the protocol if they had a sustained SCr > 2.0 mg/dL (reciprocal value, 0.5) (two successive measurements at least 2 weeks apart). Patients were also eligible if they had an entry SCr < 2.0 mg/dL (reciprocal value, 0.5) but had persistent proteinuria with morbid complications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All patients were randomised under the same computer-generated randomisation table through the central Glomerular Disease Collaborative Network office. Patients were stratified on the basis of whether they had deterioration in kidney function or persistent proteinuria with morbid complications
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Falk 1992 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Two (one in each group) patients had less than 18 months of follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Fu 2012a

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: 36 months

Participants	• Setting: not reported
	• Country: China
	• Inclusion criteria: biopsy-proven IMN and nephritic syndrome; CD I & II; never had prednisolone or immunosuppression before
	• Baseline characteristics
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group (9.57 ± 8.94); control group (9.42 ± 2.86)
	   ○ Mean serum albumin ± SD (g/L): treatment group (23.4 ± 4.3); control group (23.5 ± 6.8)
	   ○ Mean eGFR ± SD (mL/min/1.73 m²): treatment group (95.7 ± 21.6); control group (96.1 ± 17.8)
	   ○ Mean SCr ± SD (µmol/L): treatment group (68.8 ± 20.2); control group (66.3 ± 15.7)
	   ○ Mean serum cholesterol ± SD (mmol/L): treatment group (8.47 ± 3.17); control group (8.38 ± 2.56)
	   ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	   ○ Pathological classification: not reported
	   ○ Co-morbidities: nephritic syndrome
	• Number: treatment group (13); control group (13)
	• Mean age ± SD (years): treatment group (43.1 ± 11.9); control group (42.7 ± 14.5)
	• Sex (M/F): treatment group (9/4); control group (8/5)
	• Exclusion criteria: secondary membranous nephropathy

Interventions	Treatment group
	
	• MMF + prednisone for 36 months
	   ○ MMF: 2 g/day split into 2 doses. After 6 months reduced to 1.5g/day; after 18 months 1g/day; after 30 months reduced to 0.5 g/day until gradually stopped
	   ○ Prednisone: initial dose 1 mg/kg/day in the morning, then gradually decreased for 6 weeks afterwards tapering 5 mg/weeks until 10 to 20 mg/week as maintenance treatment
	
	Control group
	
	• CPA + prednisone for 36 months
	   ○ CPA (IV): 1 g every month for 6 months, then every 3 months for 46 times
	   ○ Prednisone: initial dose 1 mg/kg/day in the morning, then gradually decreased
	
	Both groups
	
	• If worsening of IMN, then the maintenance of dose for 3 months before beginning the reduction. Initial dose of prednisone was 1 mg/kg/day in the morning and then gradually decreased in both groups

Fu 2012a *(Continued)*

	• Co-medications: not reported
Outcomes	• 24-hour urine protein excretion • Serum albumin • SCr • eGFR • WCC • Remission • Leucopenia • Abnormal liver enzymes Follow-up at 3, 12, 24 and 36 months
Notes	• Funding information/COI: authors reported no conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement. Groups are very similar in baseline characteristics, unlikely by chance. indicating some form of matching
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias. all patients completed course of the study
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. comprehensive reporting on all outcomes
Other bias	Low risk	No evidence of other bias. authors declare no conflict of interest

GEMRITUX 2017

Study characteristics

Methods	• Study design; parallel, open-label RCT • Study duration; 17 January 2012 to 3 July 2014 • Duration of follow-up: median time to follow-up was 17 months
Participants	• Setting: multicentre (31 sites) • Country: France • Inclusion criteria: ≥ 18 years; biopsy-proven diagnosis established, < 2 years before inclusion; urinary protein excretion ≥ 3.5 g/day or UPCR ≥ 3500 mg/g, and had serum albumin < 30 g/L for at least 6

GEMRITUX 2017 *(Continued)*

> months, despite maximal tolerated dose of NIAT (ACEi and/or ARB, diuretics, and statin); proteinuria was measured repeatedly before inclusion and treatment assignment to confirm the persistence of full-blown nephrotic syndrome; eGFR by MDRD formula had to be > 45 mL/min/1.73 m^2
>
> - Baseline characteristics: not reported
> - Number (randomised/analysed): treatment group (39/37); control group (38/38)
> - Median age, IQR (years): treatment group (53, 43 to 62); control group (58.5, 43.0 to 64)
> - Sex (M/F): treatment group (28/9); control group (24/14)
> - Exclusion criteria: secondary MN; pregnancy or breastfeeding; immunosuppressive treatment in the preceding 3 months, and active infectious disease; hepatitis B serology included Hbs antigen and Hbs and Hbc antibodies, active hepatitis B and those with past hepatitis B infection without anti-Hbs antibodies

Interventions	**Intervention group** - RTX (IV): 375 mg/m^2 on days 1 and 8 - NIAT: ACEi and/or ARB, diuretics, and statins **Control group** - NIAT alone: ACEi and/or ARB, diuretics, and statins

Outcomes	- Remission was defined according to 2012 KDIGO guidelines.
	  ○ Complete: urinary protein excretion < 500 mg/day or UPCR < 500 mg/g
	  ○ Partial: urinary protein excretion < 3.5 g/day or < 3500 mg/g Cr and ≥ 500 mg/g Cr with ≥ 50% reduction compared with baseline
	- Proteinuria
	- Serum albumin
	- SCr
	- PLA2RAb levels
	  ○ Antibody depletion was defined as the complete disappearance of antibodies in PLA2R-Ab–positive patients
	- Serious adverse events
	  ○ Adverse events and unexpected changes in clinical or laboratory parameters were reported in patient case report forms and monitored up to complete resolution
	- THSD7A-Abs
	- Composite endpoint defined as the reduction of proteinuria > 50% and increase of serum albumin level > 30% at month 6 of follow-up (post hoc)

Notes	- Funding source: "This study was funded by Programme Hospitalier de Recherche Clinique, French Ministry of Health grant AOM10089; European Research Council ERC-2012-ADG_20120314 grant agreement 322947; Agence Nationale pour la Recherche Programme Blanc SVSE1 (2012) Decision grant ANR-12-BSE1-0002-01; Fondation pour la Recherche Médicale Equipe FRM 2012 grant; and 7th Framework Programme of the European Community contract 2012- 305608 (European Consortium for High-Throughput Research in Rare Kidney Diseases). The sponsor of this study was Assistance Publique-Hôpitaux de Paris (Département de la Recherche Clinique et du Développement, Clinical Research and Development Department). Rituximab was given by Hoffmann-La Roche"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does say analysis was performed blind but not specifically outcome determination
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/77 (2.6%) excluded from analysis
Selective reporting (reporting bias)	Low risk	Most appropriate outcome, remission was reported
Other bias	Unclear risk	Insufficient information to permit judgement

Hasegawa 2017

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: 1 year after administration of medication

Participants	• Setting: multicentre (24 sites)
	• Country: Japan
	• Inclusion criteria: biopsy-proven IMN; > 65 years; preliminary obtained no therapy for IMN
	• Baseline characteristics
	  ○ Mean serum albumin ± SD (g/L): treatment group (20.5 ± 6.5); control group (20.3 ± 6.5)
	  ○ Mean eGFR ± SD (mL/min/1.73 m²): not reported
	  ○ Mean UPCR ± SD (g/g): treatment group (5.90 ± 3.47); control group (6.79 ± 3.51)
	  ○ Mean SCr ± SD (μmol/L): treatment group (80.44 ± 19.44); control group (82.21 ± 18.56)
	  ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	  ○ Pathological classification: not reported
	  ○ Co-morbidities: not reported
	• Number: treatment group (18); control group (18)
	• Mean age (years): treatment group (73.3); control group (72.8)
	• Sex (males): treatment group (66.7%); control group (72.2%)
	• Exclusion criteria: not reported

Interventions	Treatment group • Mizoribine: 150 mg • Prednisolone: 30 mg Control group • Prednisolone: 30 mg
Outcomes	• PLA2R titre • Complete remission: UPCR < 0.3 • Partial remission

Hasegawa 2017 *(Continued)*

- o Type 1: 0.3 < UPCR < 1.0
- o Type 2: 1.0 < UPCR < 3.5
- No response: UPCR ≥ 3.5 g/day
- UPCR at 3 and 12 months

Notes	• Abstract-only publication • PLA2R-levels were measured

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" and no further information provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Very limited information provided, much data not reported, including primary outcome on 3/4 of measurement-points
Other bias	Unclear risk	Insufficient information to permit judgement

He 2013

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: Jan 2008 to Feb 2010 • Duration of follow-up: 12 months

Participants	• Setting: single centre
	• Country: China
	• Inclusion criteria: IMN (stage I-IV) proven by renal biopsy; persistent nephrotic-range proteinuria (3.5 to 6 g/24 hours) accompanied by hypoalbuminaemia (serum albumin 20 to 25 g/L) after 3 months of corticosteroids monotherapy, serum albumin < 20 g/L and/or severe proteinuria (> 6 g/24 hours); aged 16 and 70 years; SCr < 133 μmol/L, with CrCl of > 60 mL/min/1.73 m²
	• Baseline characteristics
	  o Mean SBP/DBP ± SD (mm Hg): treatment group (124.7 ± 17.8 / 77.5 ± 12.9); control group (126.4 ± 19.5 / 80.6 ± 13.4)
	  o Mean proteinuria ± SD (g/24 hours): treatment group (6.76 ± 2.33); control group (6.38 ± 2.19)
	  o Mean serum albumin ± SD (g/L): treatment group (9.8 ± 5.8); control group (20.6 ± 5.6)

He 2013 *(Continued)*

- ○ Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (77.35 ± 28.28); control group (76.16 ± 25.24)
- ○ Mean triglyceride ± SD (mmol/L): treatment group (2.87 ± 1.74); control group (2.50 ± 1.48)
- ○ Mean SCr ± SD (μmol/L): treatment group (81.56 ± 27.22); control group (82.45 ± 26.36)
- ○ Mean serum cholesterol ± SD (mmol/L): treatment group (10.11 ± 3.67); control group (9.96 ± 3.13)
- ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
- ○ Pathological classification (stage I/II/III/IV): I: 25, II: 20, III: 8, IV: 3
- ○ Co-morbidities: hypertension (9 patients)
- Number: treatment group (28); control group (28)
- Mean age ± SD (years): treatment group (45.4 ± 11.5); control group (47.2 ± 13.4)
- Sex (M/F): treatment group (20/8); control group (19/9)
- Exclusion criteria: severe infection, hepatitis B or C virus-positive serology, liver function test abnormalities; abnormal glucose tolerance test; secondary diseases that cause membranous nephrology such as SLE; previous therapy with CPA, MMF and CSA

Interventions	**Treatment group**
	
	• TAC + low-dose prednisone
	  ○ TAC (oral) for 12 months: started with TAC at a dosage of 1 mg/day for 1 week. Later TAC was given by alternative dosage of 1 mg one day and 2 mg the other. The dosage of 2 mg of TAC was divided into 2 equal doses at 12-hour intervals. Dosage was adjusted according to the whole blood concentration, with a target of 2 to 4 ng/mL throughout the 12-month therapy period, and kept the maximum daily dose to no more than 6 mg.
	
	Control group
	
	• CPA + low-dose prednisone
	  ○ CPA (IV): 750 mg/m² once every 4 weeks for 24 weeks
	
	Both groups
	
	• Prednisone (oral): 1 mg/kg/day (max 60 mg/day) for 4 weeks; then gradually tapered by 5 mg/2 weeks down to a dosage of 30 mg/day; further tapered the dosage more slowly by 5 mg/month down to a dosage of 10 mg/day and maintain that dosage throughout the remainder of the 12-month therapy period
	• Co-medications: not reported

Outcomes	• Complete remission: decrease in daily urinary protein to ≤ 0.3 g, plus stable kidney function • Partial remission: decrease of at least 50% in daily proteinuria (i.e., < 3.5 g/day of urinary protein) with normal SCr • No response: decrease in daily proteinuria < 50% and/or > 3.5 g/day of urinary protein • Renal survival (doubling of SCr): 50% increase in baseline SCr • Adverse events: glucose intolerance, gastrointestinal syndrome, new hypertension, gouty arthritis, leukopenia, chest pain, UTI, herpes zoster hepatotoxicity • Albumin • Urinary protein excretion
Notes	• Funding source: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pre-printed randomisation table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

He 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Not sure how many were screened or whether more were randomised however outcomes are comprehensively and appropriately chosen and reported
Selective reporting (reporting bias)	Low risk	Outcomes reasonably complete and appropriate
Other bias	Low risk	No evidence of other bias; no evidence for conflict of interest

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Hladunewich 2014

Study characteristics

Methods	• Study design: parallel, open-label, dose-finding RCT • Study duration: recruitment period not reported; treatment for 12 weeks • Duration of follow up: 1 year

Participants	• Setting: multicentre (Mayo Clinic and University of Toronto)
	• Country: US & Canada
	• Inclusion criteria: IMN with diagnostic biopsy performed < 36 months from the time of dose randomisation and did not demonstrate in excess 30% glomerulosclerosis and/or interstitial fibrosis or tubular atrophy; > 18 years; at least 3 months of treatment with RAS blockade to lower BP to < 130/75 mm Hg in > 75% of the readings prior to the initiation of ACTH treatment; nephrotic range proteinuria as defined by UPCR ≥ 4.0 on a spot sample aliquot from a 24-h urine collection without significant renal insufficiency as defined by an eGFR ≥ 40 mL/min/ 1.73 m^2 while taking blockade of the RAS
	• Special cases that were included: partial response to other regimens or significant side effects were eligible. These study patients were required to be off glucocorticoid therapy, CNI or MMF for > 1 month, and alkylating agents for > 6 months
	• Baseline characteristics
	  ○ Mean SBP/DBP ± SD (mm Hg): 121 ± 16 / 72 ± 824
	  ○ Proteinuria (in gram/24h): 9.068 ± 3.384
	  ○ Mean serum albumin ± SD (g/L): 2.72 ± 0.83
	  ○ Mean eGFR ± SD (mL/min/1.73 m^2): 77 ± 30
	  ○ Mean triglyceride ± SD (mmol/L): 225 ± 190
	  ○ Mean serum cholesterol ± SD (mmol/L): 306 ± 133
	  ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: maximum 36 months
	  ○ Pathological classification: not reported
	  ○ Co-morbidities: not reported
	• Number: treatment group 1 (9); treatment group 2 (11)
	• Mean age ± SD: 51 ± 15 years
	• Sex (M/F): 13/7
	• Exclusion criteria: documented resistance to immunosuppressive routines used in IMN (e.g. CNI ± steroids or cytotoxic agents ± steroids); active infections; secondary causes of membranous nephropathy (e.g. hepatitis B, SLE, medications, malignancies); type 1 or 2 DM to exclude proteinuria secondary

Hladunewich 2014 *(Continued)*

to diabetic nephropathy; pregnancy or nursing women; documented acute thrombosis, requiring anticoagulation therapy

Interventions	**Treatment group 1** • ACTH(SC): 40 IU for up to 12 weeks. If at day 91 no response has been shown the option to increase the dose of ACTH to 80 units for up to an additional 120 days (5/9 had their dose increased to 80 IU after the trial, and followed up to 1 year) **Treatment group 2** • ACTH (SC): 80 IU for up to 12 weeks **Both groups** • The dose of ACTH was increased from one injection every other week to 2 injections/week. It was then continued at full dose, either 40 or 80 units twice/week, for 12 weeks. • The injections were given on the following days 　○ One injection/week: days 0, 14, 21, 28 　○ Two injections/week: days 31, 35, 38, 42, 45, 49, 52, 56, 59, 63, 66, 70, 73, 77,80, 84, 87 and 91 • Co-medications: antihypertensive therapy (most patients, ARB 1st choice, more medications added if needed to control BP) atorvastatin 10 mg (dose raised over time)
Outcomes	• Changes in the measures of nephrotic syndrome, including: 　○ Change in proteinuria 　○ Change in serum albumin 　○ Change in LDL cholesterol, HDL cholesterol, and triglycerides • Side effects/toxicity • Complete or partial remission, and the effect of maximizing angiotensin II blockade on proteinuria 　○ complete remission: proteinuria < 0.3 g/day 　○ partial remission: reduction in proteinuria by > 50% with a final urine protein < 3.5 g/day, but > 0.3 g/day 　○ No response: reduction in proteinuria by < 50% or worsening of proteinuria
Notes	• Funding source: Questor Pharmaceuticals • Not reported as a trial, doses changed after 12 weeks and outcomes reported for whole group, not randomised group. Not enough patients left in 40 IU treatment-arm for analysis • Anti-PLAR2-Ab levels were measured

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred in 1:1 ratio using a block randomisation technique
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome-assessors were blinded

Hladunewich 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Poor reporting of outcomes within the randomised groups. no intention-to-treat analysis. many patients switched treatment arms.
Selective reporting (reporting bias)	High risk	Outcomes not properly reported for randomised groups separately
Other bias	High risk	High number of patients that changed the treatment-arm during the study. SCr not reported in outcome measures. Industry-funded trial, however the pharmaceutical company had no role in the design and/or evaluation of the study, nor the writing of the manuscript

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Hofstra 2010

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: May 1998 to May 2005 • Duration of follow-up: 72 ± 22 months; treatment group 1 (73 ± 20); treatment group 2 (71 ± 2)

Participants	• Setting: multicentre
	• Country: Netherlands
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome and high risk for ESKD (urinary B_2 microglobulin > 0.5 µg/min and urinary IgG > 125 mg/24 hours)
	• Baseline characteristics
	  ◦ Pathology stage: not reported
	  ◦ Median proteinuria, range (g/10 mmol Cr): treatment group 1 (9.6, 5.9 to 14.4); treatment group 2 (12.0, 5.6 to 17.2)
	  ◦ Mean serum albumin ± SD (g/L): treatment group 1 (22.6 ± 4.8); treatment group 2 (22.3 ± 3.8)
	  ◦ Median SCr, range (µmol/L): treatment group 1 (94, 68 to 122); treatment group 2 (101, 75 to 126)
	  ◦ Mean GFR ± SD (mL/min/1.73 m²): treatment group 1 (81 ± 17); treatment group 2 (76 ± 13)
	  ◦ Baseline declining kidney function: no; SCr was < 135 µmol/L in all patients at randomisation
	• Number: treatment group 1 (14); treatment group 2 (12)
	• Mean age ± SD (years): treatment group 1 (48 ± 13); treatment group 2 (49 ± 10)
	• Sex (M/F): treatment group 1 (13/1); treatment group 2 (11/1)
	• Exclusion criteria: secondary cause of MN was suspected based on clinical or laboratory criteria; previously treated with immunosuppressive drugs; systemic diseases; pregnancy or inadequate contraception; active infection; unstable angina pectoris; DM, clinical evidence of renal vein thrombosis; liver function test abnormalities (> 2 times the upper limit of normal); use of NSAIDs; active peptic ulcer disease and gastrointestinal diseases that could impair the resorption of oral medication

Interventions	Treatment group 1
	
	• Early treatment: started immunosuppressive therapy immediately after randomisation
	  ◦ Oral CPA: 1.5 mg/kg/day for 12 months
	  ◦ IV methylprednisolone: 1 g on days 1, 2, 3, 60, 61, 62, 120, 121 and 122
	  ◦ Oral prednisone: 0.5 mg/kg/day for 6 months, and subsequently tapered by decreasing the dose by 5 mg/week
	  ◦ For prevention of gastric symptoms, famotidine 1 daily dose 20 mg was added.
	  ◦ From 1999 onwards, trimethoprim-sulfamethoxazole was added 480 mg/day in the first 4 to 6 months, to prevent *Pneumocystis jiroveci* pneumonia. In young fertile patients, the treatment regimen was modified because of the infertility risk associated with the use of CPA; in these patients, after 3 months of treatment CPA was replaced by AZA 1.5 mg/kg/day for the remaining 9 months. Three patients were treated according to the modified treatment scheme with AZA

Hofstra 2010 *(Continued)*

Treatment group 2

- Late treatment: started immunosuppressive treatment (as for early treatment) when kidney function deteriorated, defined as an increase of SCr with ≥ 25% reaching a level of ≥ 135 μmol/L or an increase of SCr with ≥ 50%
- Two patients received modified treatment with AZA after 3 months

Co-medication

- Use of ACEi or ARB during follow-up: all patients were aggressively treated to decrease BP (target value 130/80 mm Hg), primarily by using ACEi and/or ARB

Outcomes	
	- Death
	- ESKD
	- Partial or complete remission
	- Final proteinuria
	- Final SCr
	- Final GFR
	- Side effects leading to patient withdrawal or hospitalisation

Notes	
	- Funding information: supported by grants from the Dutch Kidney Foundation (NSN OW08 and NSN PC152)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	During the first year of the study, 3 patients were excluded because of the following reasons: discovery of a malignancy and withdrawal from the study within 3 months; protocol violation (start of prednisone by a physician in another hospital) and loss to follow-up due to emigration 7 months after randomisation. Thus, the final analysis included 26 patients
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Howman 2013

Study characteristics

Howman 2013 *(Continued)*

Methods	• Study design: parallel, open-label RCT • Study duration: 1 April 1998 to 31 March 2008 • Duration of follow-up: 3 years for a change in GFR
Participants	• Setting: multicentre, (37 sites) • Country: UK • Total number: 108 randomised, 106 analysed • Inclusion criteria: aged 18-75 years; biopsy-proven diagnosis of membranous nephropathy, regarded as idiopathic with no evidence of an underlying cause (such as drugs, infections, or tumours); SCr < 300 µmol/L; ≥ 20% decline in excretory kidney function (measured by CrCl or estimated with the Cockcroft-Gault calculation, and later by the MDRD formula that was based on at least three measurements over a period of 3 months or longer within the 2 years before study entry • Baseline characteristics ○ Mean SBP ± SD (mm Hg): treatment group 1 (141 ± 16); treatment group 2 (143 ± 21); control group (138 ± 19) ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (10.1 ± 5.3); treatment group 2 (6.8 ± 4.7); control group (9.1 ± 5.3) ○ Mean CrCl ± SD (mL/min): treatment group 1 (50 ± 16); treatment group 2 (49 ± 18); control group (50 ± 20) ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported ○ Pathological classification: not reported ○ Co-morbidities: not reported • Number (randomised/analysed): treatment group 1 (33/33); treatment group 2 (37/36); control group (38/37) • Mean age ± SD (years): treatment group 1 (58 ± 12); treatment group 2 (58 ± 11); control group (56 ± 16) • Sex (M/F): not reported • Exclusion criteria: secondary causes (defined according to usual clinical practice); known infection with hepatitis B or C virus or HIV; known malignant disease; positive antibodies to double-stranded DNA; current treatment with gold, penicillamine, NSAIDs, cytotoxic drugs, or CSA; > 3 months' treatment with corticosteroids in the preceding 2 years; pregnancy or unreliable contraception; previous adverse reaction to prednisolone, methylprednisolone, chlorambucil or CSA
Interventions	**Treatment group 1** • Methylprednisolone (IV): 1 g/day for 3 consecutive days then oral prednisolone 0·5 mg/kg/day for 28 days during months 1, 3, and 5. IV prednisolone was administered in hospital • Chlorambucil (oral): during months 2, 4, and 6, starting dose of 0·15 mg/kg/day • Supportive care (see control group) • Duration: 6 months **Treatment group 2** • CSA: starting dose of 5 mg/kg/day, adjusted according to trough blood concentration to achieve 100 to 200 µg/L, dose reduced if toxicity was evident • Supportive care (see control group) • Duration: 12 months **Control group** • All patients received supportive therapy, including RAS blockade, statins, and anticoagulants as indicated Co-medications: not reported
Outcomes	• Change in GFR, 20% decline from baseline. Cockcroft-Gault equation • Proteinuria: measured with 24-h urinary collections or estimated UPCR by multiplying the ratio (in mg/mmol) by 10 (means and mean differences of each group not reported)

Howman 2013 *(Continued)*

- Severe adverse events at 12 months and later. Primary investigator identified which adverse events were serious and categorised them according to the most affected body system
- Death
- Malignant disease (only reported in treatment group 1)
- ESKD

Notes	• Funding source: UK Medical Research Council (MRC; grant reference G9721265). sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Before MRC funding was obtained, a small unrestricted grant from Novartis supported the purchase of trial record books and some other trial materials. Additional contributions to continuation funding came from Kidney Research UK and the Renal Association • Completed 31/03/2009. Added 23/09/09: Closed to recruitment, 108 recruited, in follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table had been prepared to allocate patients to one of three groups. Patients were randomly assigned by a member of staff in the clinical trials office at the Glasgow Royal Infirmary, Glasgow, UK, who was not otherwise involved in the trial
Allocation concealment (selection bias)	Low risk	Allocation was not influenced by patient characteristics, random allocation by a non-otherwise involved person at the clinical trials office at the Glasgow Royal Infirmary
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. "Treatment allocation was communicated by fax to the clinician entering the patient into the trial. We did not attempt to mask patients or investigators."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/108 (1.9%) excluded post randomisation; no evidence for missing data
Selective reporting (reporting bias)	Low risk	Outcomes appropriate and reasonably extensive; registered trial including outcomes
Other bias	Low risk	Methods, details and results well reported; no evidence of other risk of bias; no evidence for Conflict of Interest

Imbasciati 1980

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 1976 to 1985 • Duration of follow-up: median 5 years (2 to 11) in the first report and 10 years in the second report
Participants	• setting: multicentre • country: Italy

Imbasciati 1980 *(Continued)*

- Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
- Baseline characteristics
  - Pathology stage (I/II/III/IV): treatment group (11/21/8/2); control group (7/23/7/2)
  - Mean proteinuria ± SD (g/24 hours): treatment group (6.18 ± 2.98); control group (5.30 ± 2.84)
  - Hypertension: treatment group (8/42); control group (12/39)
  - Mean SCr ± SD (µmol/L): treatment group (93.8 ± 21.5); control group (93.1 ± 25.3)
  - Baseline declining kidney function: no
  - Use of ACEi or ARB during follow-up: yes; 2 (1 per group) were recorded to receive captopril during the 5-year follow-up
  - Previous immunosuppressive status: patients who had previously received steroids or cytotoxic therapy were excluded
- Number: treatment group (42); control group (39)
- Mean age, range (years): treatment group (43.5, 15 to 70); control group (42, 16 to 74)
- Sex (M/F): treatment group (34/8); control group (29/10)
- Exclusion criteria: < 16 years; SCr > 150 µmol/L; previous steroid or cytotoxic therapy; clinical or biological evidence of SLE, DM, drug reaction, viral hepatitis, or other infection

Interventions	Treatment group

	- Chlorambucil + steroids
	  a. Methylprednisolone (IV): 1g was given for 20 to 30 minutes on 3 consecutive days
	  b. Cycle A: on day 4, oral methylprednisolone (0.4 mg/kg/day) or prednisone (0.5 mg/kg/day) was given in a single morning dose for 27 days. At the end of the first month, the steroid was discontinued
	  c. Cycle B: chlorambucil (0.2 mg/kg/day) for 1 month; the dose was lowered if the leukocyte count fell below 5.0x10^9/L. After 1 month the chlorambucil was discontinued
	  d. Cycle A
	  e. Cycle B
	  f. Cycle A
	  g. Cycle B
	- The entire duration of the treatment period was 6 months. During the study, it was decided that clinicians would be free to treat the patients again, but not until 2 years after the first 6-month course of therapy. No patient relapsed within the first 2 years
	
	Control group
	
	- No specific therapy
	
	Co-interventions
	
	- Both the treatment and control groups received low salt diets and were given a diuretic and antihypertensive agents as needed

Outcomes	- Death - ESKD - 50% or 100% SCr increase - Final SCr - Partial or complete remission - Final proteinuria - Side effects leading to patient withdrawal or hospitalisation
Notes	- Funding information: supported in part by a grant (82.01308.04) from the Consiglio Nazionale delle Rice

Risk of bias

Bias	Authors' judgement	Support for judgement

Imbasciati 1980 *(Continued)*

Random sequence generation (selection bias)	Low risk	For all patients, the indications for therapy were contained in sealed, completely opaque envelopes numbered in sequence according to a table of random numbers
Allocation concealment (selection bias)	Low risk	Randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four patients in the treatment group did not complete the 6-month therapy, these patients were continued to be followed up because of side effects. They were considered to be treated patients in the data analysis, according to the intention-to-treat principle. In the case of patients who died, data obtained before the time of death were included. 3/81 patients (3%) were lost to 5-year follow-up: two controls and one treated patient were lost to follow-up 22, 28, and 24 months after randomisation, respectively. At the second analysis, 9/42 (21%) treated patients and 10/39 (26%) controls were lost to follow-up from 12 to 96 months after randomisation. These 3 patients were also considered in the analyses
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Jha 2007

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: March 1993 to February 1995 • Duration of follow-up: median 11 years (10.5 to 12)

Participants	• Setting: not reported
	• Country: India
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	  ◦ Pathology stage: the majority of the patients had stage II IMN with minimal interstitial scaring
	  ◦ Mean proteinuria ± SD (g/24 hours): treatment group (6.11 ± 2.5); control group (5.91 ± 2.2)
	  ◦ Hypertension: treatment group (5/47); control group (7/46)
	  ◦ Mean serum albumin ± SD (g/L): treatment group (23.4 ± 5.8); control group (24.2 ± 8.1)
	  ◦ Mean SCr ± SD (mg/dL): treatment group (1.21 ± 0.31); control group (1.17 ± 0.22)
	  ◦ Mean GFR ± SD (mL/min): treatment group (89 ± 26); control group (84 ± 22)
	  ◦ Baseline declining kidney function: a portion had declining kidney function
	  ◦ Previous immunosuppressive status: patients who had received steroids or immunosuppressive drugs for ≥ 2 months were excluded

Jha 2007 *(Continued)*

- Number (randomised/analysed): treatment group (51/47); control group (53/46)
- Mean age ± SD (years): treatment group (38.0 ± 13.6); control group (37.2 ± 12.4)
- Sex (M/F): treatment group (30/17); control group (27/19)
- Exclusion criteria: systemic illness; malignancy; DM; hepatitis B surface antigen positivity; renal vein thrombosis; received steroids or immunosuppressive drugs for ≥ 2 months

Interventions	**Treatment group** • Methylprednisolone (IV): 1 g/day for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days in the first, third, and fifth months • CPA (oral): 2 mg/kg/day in the second, fourth, and sixth months. It was withheld temporarily when the counts fell to 3500/mm³ until recovery to 4000/mm³. Treatment was halted when a patient exhibited any evidence of active ulcer disease, neoplasm, diabetes, and/or life-threatening infection **Control group** • Supportive therapy that consisted of dietary sodium restriction, diuretics, and antihypertensive agents **Co-interventions** • Use of ACEi or ARB during follow-up: ACEi and ARB were withheld for at least 1 year after randomisation. During follow-up, more control group patients developed hypertension that required drugs for control (16/47 versus 7/35 at the 10-year follow-up, P < 0.01). Treatment group patients exhibited a significantly lower prevalence of ACEi/ARB use at various time points (13/47 versus 32/46 at the 10-year follow-up, P < 0.01). The actual mean BP values were not different between the two groups either at baseline or during follow-up
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Jha 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	11/104 (11%) patients were lost to follow-up, 4/51 (8%) in treatment group and 7/53 (13%) in control group, between 18 to 48 month of randomisation and excluded from analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	Study appears free of other biases

Jurubita 2012

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: before 2012 • Duration of follow-up: 12 months

Participants	• Setting: single centre
	• country: Romania
	• Inclusion criteria: biopsy-proven IMN with persistent heavy proteinuria (> 8 g/day, minimum 6 months)
	• Baseline characteristics
	  o Pathology stage: not reported
	  o Mean proteinuria, range (g/24 hours): treatment group 1 (10.4, 8.4 to 14.9); treatment group 2 (10.26, 8 to 14.1)
	  o GFR (mL/min/1.73 m²): > 60
	  o Baseline declining kidney function: not reported
	  o Previous immunosuppressive status: not reported
	• Number: treatment group 1 (9); treatment group 2 (9)
	• Mean age ± SD (years): not reported
	• Sex: not reported
	• Exclusion criteria: not reported

Interventions	Treatment group 1 • MMF: 1 g/day • CSA: 2 mg/kg/day, but not exceeding 150 mg/day • Prednisolone: 0.15 mg/kg/day • Duration: 12 months Treatment group 2 • CSA: 5 mg/kg/day, but not exceeding 150 mg/day • Prednisolone: 0.15 mg/kg/day Co-interventions • Use of ACEi or ARB during follow-up: not reported
Outcomes	• Partial or complete remission
Notes	• Funding information: not reported • Only abstract was available and unpublished data were not used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient was lost to follow-up, and an intention-to-treat analysis was used
Selective reporting (reporting bias)	High risk	Only remission data were provided in the abstract
Other bias	Unclear risk	Only abstract was available and unpublished data were not used

Koshikawa 1993

Study characteristics

Methods	- Study design: parallel RCT - Study duration: April 1989 to June 1992 - Duration of follow-up: 24 weeks
Participants	- Setting: not reported - Country: Japan - Inclusion criteria: biopsy-proven IMN with steroid-resistant nephrotic syndrome - Baseline characteristics - Pathology stage: not reported - GFR: ≥ 50 mL/min - Baseline declining kidney function: not reported - Previous immunosuppressive status: receiving a daily maintenance dose of 20 mg prednisolone-equivalent a day (including zero dosage) before entry was allowed. Other immunosuppressant medication should be stopped at the start of the study - Number: treatment group (48); control group (41) - Age: > 15 years - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group Mizoribine: 50 mg 3 times/day after meals for 24 weeks Control group

Koshikawa 1993 *(Continued)*

	• Placebo
	Co-interventions
	• Use of ACEi or ARB during follow-up: not reported

Outcomes	• 50% or 100% SCr increase • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation

Notes	• Funding information: not reported • Published in Japanese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; no information on blinding of outcome-assessors provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2/48 patients in the treatment group did not complete 24-week follow-up
Selective reporting (reporting bias)	High risk	The primary outcome such as death and ESKD were not reported
Other bias	High risk	The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant primary nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation was not stratified according to the pathologic diagnosis

Kosmadakis 2010

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: before 2010 • Duration of follow-up: at least 9 months

Participants	• Setting: single centre • country: Greece • Inclusion criteria: biopsy-proven IMN with nephrotic syndrome

Kosmadakis 2010 *(Continued)*

- Baseline characteristics
  - Pathology stage: not reported
  - Mean proteinuria ± SE (g/24 hours): treatment group 1 (6.6 ± 1.0); treatment group 2 (7.0 ± 0.7); control group (5.2 ± 0.8)
  - Hypertension: patients with prior history of essential hypertension were excluded
  - Mean serum albumin ± SE (g/L): treatment group 1 (27 ± 7); treatment group 2 (28 ± 2); control group (22 ± 1.4)
  - Mean GFR ± SE (mL/min/1.73 m^2): treatment group 1 (81.6 ± 8); treatment group 2 (51.5 ± 7); control group (65.7 ± 5.6)
  - Baseline declining kidney function: a portion had declining function
  - Previous immunosuppressive status: not reported
- Number: treatment group 1 (10); treatment group 2 (8); control group (10)
- Mean age ± SE (years): treatment group 1 (50.5 ± 4.9); treatment group 2 (55.4 ± 2.8); control group (51.8 ± 5.4)
- Sex (M/F): treatment group 1 (8/2); treatment group 2 (4/4); control group (5/5)
- Exclusion criteria: prior essential hypertension

Interventions	Treatment group 1

Treatment group 1

- CSA (oral): 3 to 3.5 mg/kg/day
- Methylprednisolone (oral): 12.5 mg/day
- Duration: 9 months

Treatment group 2

- CPA (oral): 2 mg/kg/24 hours
- Methylprednisolone (oral): 1.5 mg/kg/48 hours
- Duration: 9 months

Control group (supportive therapy only)

- Lisinopril for 9 months

Co-interventions

- Use of ACEi or ARB during follow-up: used only in the control group

Outcomes	

- Death
- ESKD
- Final GFR
- Partial or complete remission
- Final proteinuria
- Side effects leading to patient withdrawal or hospitalisation

Notes	

- Funding information: not reported
- Baseline comparison: GFR was worse in the CPA group than the other 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Kosmadakis 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	There was a significant difference in the baseline GFR (P = 0.021). The sample size was also small for a 3-arm study

Li 2015

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: January 2008 to January 2013 • Duration of follow-up: 6 to 48 months; mean duration was 13.5 ± 6.2 months

Participants	• Setting: single centre
	• Country: China
	• Age: 65-81 years
	• Sex: 15 men, 12 women
	• Inclusion criteria: IMN confirmed by biopsy examined using light microscopy, immunofluorescence, and electron microscopy, and the condition of the patients was pathologically diagnosed as IMN stage I and II; 24-hour protein levels > 4 g; > 65 years
	• Baseline characteristics
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group (7.5 ± 3.8); control group (7.2 ± 3.4)
	   ○ Mean eGFR ± SD (mL/min/1.73 m²): treatment group (70.9 ± 11.9); control group (69.6 ± 10.3)
	   ○ Mean triglyceride ± SD (mmol/L): not reported
	   ○ SCr (μmol/L): treatment group (91.6 ± 20.9); control group (98.8 ± 15.1)
	   ○ Mean serum cholesterol ± SD (mmol/L): not reported
	   ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	   ○ Pathological classification: stage I or stage 2
	   ○ Co-morbidities: not reported
	   ○ Co-medications: all patients received lipid-lowering drugs and anti-platelet adhesion drugs. BP was controlled to target < 140/90 mm Hg
	• Number: treatment group (13); control group (14)
	• Mean age (years): treatment group (74.8): control group (75.1)
	• Sex (M/F) 15/12: treatment group (10/3); control group (10/4)
	• Exclusion criteria: secondary membranous nephropathy induced by secondary factors such as autoimmune diseases, cancer, infections and drugs, or atypical membranous nephropathy; HIV infection; diagnosed with malignant tumour infection; active hepatitis B or C or with positive replication indexes

Li 2015 *(Continued)*

Interventions	**Treatment group**
	• CSA (oral) initial dose was 2 mg/kg/day and the treatment duration was not less than 6 months
	• Methylprednisolone (oral): initial dose was 0.4 mg/kg/day which gradually decreased after 8 to 12 weeks administration; the total duration of treatment was 6 to 12 months
	Control group
	• Low-dose CSA

Outcomes	• Clinical remission rate: complete + partial remission / total number of patients x 100%
	• Complete remission: defined as urinary protein level ≤ 0.3 g/day, serum albumin level > 35 g/L, stable kidney function (increase in the SCr < 15% of the baseline value)
	• Partial remission: defined as the decrease in urinary protein level by more than 50% of the baseline value, urinary protein level ≤ 3.5 g/day, stable kidney function
	• No remission: defined as the decrease in the urinary protein level less than 50% of the baseline value, or the urinary protein level was > 3.5 g/day or the SCr > 50% of the baseline value
	• Safety
	◦ Adverse reactions observed during the treatment were infection, osteonecrosis, steroid glycosuria, and hepatonephritic toxicity, and patients discontinued treatment
	◦ Complications were steroid diabetes
	◦ Hypertension (uncontrollable)
	◦ Infection
	◦ SCr increase > 50%
	◦ Recurrence rate after drug withdrawal

Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasonable and comprehensive outcome reporting. Unable to determine if more were randomised than reported
Selective reporting (reporting bias)	Low risk	Reports on remissions, most appropriate outcome. All outcomes were reported
Other bias	Low risk	No evidence for other bias. no evidence for conflict of interest, however, no trial protocol published

Li 2017c *(Continued)*

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: September 2015 to March 2016 - Duration of follow-up: 6 months
Participants	- Setting: single centre - Country: China - Inclusion criteria: aged 18 to 60 years; IMN (stage I-IV) proven by renal biopsy and laboratory examination; persistent proteinuria > 8 g/day; met diagnostic criteria for nephritic syndrome; SCr < 133 µmol/L - Baseline characteristics - Pathology stage (I/II/III/IV): treatment group 1 (1/11/4/0); treatment group 2 (3/11/1/0) - Hypertension: treatment group 1(3/16); treatment group 2 (4/15) - Mean SBP/DBP ± SD (mm Hg): treatment group 1 (133.1 ± 15.0 / 87.1 ± 9.2); treatment group 2 (125.2 ± 13.8 / 83.4 ± 8.2) - Mean proteinuria ± SD (g/24 hours): treatment group 1 (9.5 ± 1.9); treatment group 2 (9.7 ± 2.5) - Mean serum albumin ± SD (g/L): treatment group 1 (22.8 ± 3.8); treatment group 2 (23.2 ± 5.8) - Mean total cholesterol ± SD (mmol/L): treatment group 1 8.0 ± 3.2); treatment group 2 (9.1 ± 3.1) - Mean triglycerides ± SD (mmol/L): treatment group 13.1 ± 2.2); treatment group 2 (2.3 ± 1.3) - Mean SCr ± SD (µmol/L): treatment group 1 71.8 ± 17.4); treatment group 2 73.3 ± 16.5) - Number: treatment group 1 (16); treatment group 2 (15) - Mean age (years): treatment group 1 (39.4); treatment group 2 (42.8) - Sex (M/F): treatment group 1 (12/4); treatment group 2 (13/2) - Exclusion criteria: serious complications such as thromboembolism, kidney failure or infection; serious diseases companied such as HIV, cardiac dysfunction, hepatitis B, hepatitis C or liver function test abnormalities, DM, and other kidney diseases; received any cytotoxic drugs and immunosuppressant treatment in the past; pregnant or lactating women; poor adherence to the drug
Interventions	Treatment group 1 - TAC: 0.05 to 0.1 mg/kg/day divided into 2 equal doses at 12-hour intervals. The drug concentration was first checked after 1 week and dosage according to the whole blood concentration, with a target of 5 to 10 ng/mL Treatment group 2 - CSA: 3 to 5 mg/kg/day divided into 2 equal doses at 12-hour intervals. The dose was adjusted to achieve a blood trough concentration of 100 to 200 ng/mL. Lower blood trough concentration levels of TAC or CSA were accepted if patients were in remission Co-interventions - Both groups received oral prednisone at a dose of 0.5 mg/kg/day. This dose was tapered by 5 mg/month down to 10 mg/day and maintained that dosage throughout the remainder of the 6-month therapy period - Antihypertensive agents were administered to achieve a target BP (SBP < 125 mm Hg and DBP < 75 mm Hg). ARB or ACEI and other antihypertensive drugs were prescribed in those patients who did not reach the above target values - Participants with serum cholesterol > 5.6 mmol/L were treated with rosuvastatin - Anticoagulant drugs, calcium carbonate and vitamin D were also prescribed to all the patients
Outcomes	- Complete remission: daily proteinuria < 0.3 g, normal serum albumin (≥ 35 g/L), and stable kidney function - Partial remission: proteinuria of 0.3 to 3.5 g/day that had declined to ≤ 50% of the baseline value with a serum albumin concentration of at least 30 g/L and a stable kidney function

Li 2017c *(Continued)*

- No response: proteinuria ≥ 3.5 g/day and decease < 50% of the baseline value
- Adverse events

Notes	• Funding source
	  ○ National Natural Science Foundation of China (81300605)
	  ○ Major Medical Science and Technology Program Plan of Henan Province (201501010)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to a randomisation list generated from the table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	Low risk	All outcomes appear to be reported
Other bias	Low risk	Study appears free of other biases

Liang 2017

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: January 2013 to April 2016 • Duration of follow-up: median observation period was 12 months (6 to 30 months)

Participants	• Setting: single centre
	• Country: China
	• Inclusion criteria: aged 18 to 75 years; confirmed as the onset IMN by kidney biopsy in our centre; nephrotic syndrome, which was defined as urinary protein excretion of 3.5 g/24 hours, and serum albumin of 30 g/L; initial SCr level of < 133 μmol/L; no immunosuppressive agents used in the previous 6 months
	• Baseline characteristics
	  ○ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (124.3 ± 16.0 / 76.4 ± 11.9); treatment group 2 (129.9 ± 16.3 / 81.9 ± 13.2)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (5.9 ± 2.7); treatment group 2 (6.9 ± 2.2)
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (26.5 ± 6.2); treatment group 2 (24.1 ± 6.2)
	  ○ Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (93.6 ± 21.7); treatment group 2 (87.9 ± 24.9)

Liang 2017 *(Continued)*

- ○ Mean triglyceride ± SD (mmol/L): treatment group 1 (2.7 ± 1.8); treatment group 2 (3.1 ± 2.3)
- ○ Mean SCr ± SD (μmol/L): treatment group 1 (70.7 ± 17.5); treatment group 2 (81.0 ± 22.5)
- ○ Mean serum cholesterol ± SD (mmol/L): treatment group 1 (7.5 ± 2.0); treatment group 2 (8.8 ± 3.0)
- ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
- ○ Pathological classification
  - ■ Treatment group 1: stage 1 (20/30); stage 2 (9/30); stage 3 (1/30); stage 4 (0/30)
  - ■ Treatment group 2: stage 1 (19/28); stage 2 (9/28); stage 3 (1/28); stage 4 (0/28)
- ○ Co-morbidities: not reported
- • Number: treatment group 1(30); treatment group 2 (28)
- • Mean age ± SD (years): treatment group 1 (48.2 ± 13.5); treatment group 2 (53.9 ± 10.4)
- • Sex (M/F): treatment group 1(16/14); treatment group 1 (9/19)
- • Exclusion criteria: secondary membranous nephropathy, such as SLE; malignant tumour; infection, such as hepatitis B or C virus infection, tuberculosis, and syphilis; fasting blood glucose > 6.2 mmol/L; pregnancy or lactating; coexistence of life-threatening complications, such as heart failure or active gastrointestinal bleeding

Interventions	Treatment group 1 • TAC: initial dose of 0.05 to 0.1 mg/kg/day divided into two doses at intervals of 12 hours without corticosteroids. The dose was adjusted according to the target trough blood concentration of 5 to 10 ng/mL for the first 6 months and reduced to 4 to 6 ng/mL for the subsequent 3 months. The dose was tapered gradually and discontinued at the end of 12 months. TAC dosage was to be reduced by 30% when a 30% increase in SCr is noted compared with the baseline value, and TAC was withdrawn if the kidney function was not improved after 2 weeks Treatment group 2 • CPA (IV): 0.5 to 0.75 g/m² once in every month for the initial 6 months and once in every 2 to 3 months for the later period. The accumulated dosage was 150 mg/kg • Prednisone (oral): 1 mg/kg/day for 4 weeks and tapered by 5 mg every 2 weeks to 30 mg/day and then reduced by 5 mg every 4 weeks until complete withdrawal at the end of 12 months Co-medications • Calcium-channel blockers (5/58), beta-receptor blockers (3/58) and diuretics (3/58) were prescribed in those patients who did not meet the target BP (< 125/75 mm Hg) • ACEi and ARB were not initiated during immunosuppressive therapy but were continued in patients who already received ACEi or ARB before recruitment (16/58) • Altiazem was used to elevate the concentration of TAC in blood • Anticoagulant drugs and statins were prescribed to all the patients
Outcomes	• Complete remission: defined as a daily proteinuria level < 0.5 g with stable kidney function • Partial remission: defined as proteinuria of 0.5 to 3.5 g/day that was reduced no less than 50% of baseline levels with well-preserved kidney function • Total remission: defined as either complete or partial remission • No remission: was defined as patients who did not achieve complete or partial remission criteria after 6 months of initial treatment • Relapse: defined as proteinuria >3.5 g/day in two consecutive urinalyses or a persistent severe hypoproteinaemia in patients who had achieved complete or partial remission • Changes in proteinuria • Changes in serum albumin • Changes in eGFR • Side effects
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	High risk	Not reported how random allocation was performed. Patients were able to switch their randomised intervention group after randomisation based on per-sonal preferences, which some patients did
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (perfor-mance bias) All outcomes	High risk	Open-label study
Blinding of outcome as-sessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported whether more were screened or allocated than were reported in the analysis however outcomes reported comprehensively
Selective reporting (re-porting bias)	Low risk	Outcomes of interest reported
Other bias	Low risk	No evidence for other bias; no evidence for financial conflict of interest

Liu 2009b

Study characteristics

Methods	- Study design: parallel, open-label RCT - Study duration: January 2006 to December 2007 - Duration of follow-up: 12 months
Participants	- Setting: not reported - Country: China - Inclusion criteria: biopsy-proven IMN with nephrotic syndrome - Baseline characteristics - Pathology stage: not reported - Mean proteinuria ± SD (g/24 hours): treatment group 1 (6.04 ± 2.52); treatment group 2 (5.66 ± 2.28) - Hypertension: treatment group 1 (10/43); treatment group 2 (11/41) - Mean serum albumin ± SD (g/L): treatment group 1 (24.1 ± 3.66); treatment group 2 (27.3 ± 4.96) - Mean SCr ± SD (mg/dL): treatment group 1 (0.79 ± 0.31); treatment group 2 (0.88 ± 0.38) - Baseline declining kidney function: 9/84 patients with an initial SCr of between 1.25 and 1.5 mg/dL (treatment group 1 (4); treatment group 2 (5)). No patients had SCr > 1.5 mg/dL - Use of ACEi or ARB before the end of the study/during follow-up: treatment group 1 (15/14); treat-ment group 2 (14/12) - Previous immunosuppressive status: no differences in the number of patients that had been pre-viously treated with steroids alone or in combination with cytotoxics. Previous treatment with steroids/steroids plus cytotoxics: treatment group 1 (13/4); treatment group 2 (14/3) - Number: treatment group 1 (43); treatment group 2 (41)

Liu 2009b *(Continued)*

- Mean age ± SD (years): treatment group 1 (40.5 ± 12.0); treatment group 2 (48.6 ± 10.3)
- Sex (M/F): treatment group 1 (31/12); treatment group 2 (30/11)
- Exclusion criteria: treated with steroids or immunosuppressive therapy within the 3-month period before screening

Interventions	**Treatment group 1** • Tripterygium wilfordii: 120 mg/day for 3 months. If the patients had complete remission, then gradually reduced to 60 mg/day for the remaining 9 months. If the patients did not reach complete remission, then continued the 120 mg dosage to a maximum of 6 months and then gradually reduced to 60 mg/day for the remission 6 months • Prednisone: 30 mg/day for 8 weeks, and gradually reduced by 5 mg every 2 weeks and then maintained at 10 mg every 2 days **Treatment group 2** • Tripterygium wilfordii: 120 mg/day for 3 months. If the patients had complete remission, then gradually reduced to 60 mg/day for the remaining 9 months. If the patients did not reach complete remission, then continued the 120 mg dosage to a maximum of 6 months and then gradually reduced to 60 mg/day for the remission 6 months
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding information: supported by Chinese grants (06G040, BK2007718, and 06Z025) • Published in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3/84 patients (all in treatment group 2) lost to 12-month follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Published in Chinese

Liu 2015e

Study characteristics

Methods	- Study design: parallel, 3-arm RCT - Study duration: treatment duration not reported - Duration of follow-up: 1 year
Participants	- Setting: single centre - Country: China - Inclusion criteria: IMN nephrotic syndrome - Baseline characteristics: not reported - Number: treatment group 1 (24); treatment group 2 (24); treatment group 3 (24) - Mean age ± SD (years): not reported - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - Glucocorticoid + CPA: dosage, route of administration not reported Treatment group 2 - Glucocorticoid + leflunomide: dosage, route of administration not reported Treatment group 3 - Glucocorticoid +CPA + leflunomide: dosage, route of administration not reported
Outcomes	- Urine protein - Safety - Complete remission - Serum albumin - Serum total cholesterol - SCr
Notes	- Abstract-only publication - Funding source: not reported - Insufficient detail in results for outcomes other than complete remission

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly divided into three groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Liu 2015e *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Many outcomes not reported; abstract-only publication
Other bias	Unclear risk	No information on potential conflict of interests and funding sources

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MENTOR 2015

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: March 2012 to September 2015 • Duration of follow-up: 2 years

Participants	• Setting: multicentre (22 sites)
	• Country: USA
	• Inclusion criteria: IMN diagnosed by renal biopsy; aged 18 to 80 years; If female must be post-menopausal, surgically sterile or practising a medically approved method of contraception; must be off prednisone or MMF for > 1 month and alkylating agents for > 6 months; treatment with an ACEi and/or ARB, for ≥ 3 months prior to randomisation and adequate BP control or if the patient is intolerant to even a very low dose of either ACEi or ARB therapy; proteinuria ≥ 5 g/24 hours using the average from two 24-hour urine collections collected within 14 days of each other despite ACEI or ARB for ≥ 3 months as described; eGFR ≥ 40 mL/min/1.73 m² while taking ACEi/ARB therapy or quantified endogenous CrCl ≥ 40 mL/min based on a 24-hour urine collection
	• Baseline characteristics
	  ◦ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (125.7 ± 14.8 / 74.7 ± 10.1); treatment group 2 (123.3 ± 13.4 / 76.5 ± 9.8)
	  ◦ Mean SCr ± SD (mg/dL): treatment group 1 (1.3 ± 0.4); treatment group 2 (1.3 ± 0.4)
	  ◦ Serum albumin (median, IQR; g/dL): treatment group 1 (2.5, 2.1 to 2.9); treatment group 2 (2.5, 2.1 to 2.9)
	  ◦ Proteinuria (median, IQR; g/24 hours): treatment group 1 (8.9, 6.8 to 12.3); treatment group 2 (8.9, 6.7 to 12.9)
	  ◦ Mean CrCl ± SD (mL/min/1.73 m²): treatment group 1 (84.9 ± 29.8); treatment group 2 (87.4 ± 34.4)
	  ◦ History of immunosuppressive therapy: treatment group 1 (19/65); treatment group 2 (20/65)
	• Number; treatment group 1 (65); treatment group 2 (65)
	• Mean age ± SD (years): treatment group 1 (51.9 ± 12.6); treatment group 2 (52.2 ± 12.4)
	• Sex (M/F): treatment group 1 (47/18); treatment group 2 (52/12)
	• Exclusion criteria: presence of active infection or a secondary cause of IMN (e.g. hepatitis B, SLE, medications, malignancies); type 1 or 2 DM: to exclude proteinuria secondary to diabetic nephropathy; recent history of steroid-induced diabetes but no evidence on renal biopsy performed within 6 months of entry into the study are potentially eligible for enrolment; pregnancy or breastfeeding; history of resistance to CSA or other CNI, RTX or alkylating agents

Interventions	Treatment group 1 • RTX (IV): 1000 mg (2 infusions, days 1 and 15) ◦ If proteinuria was reduced from baseline by at least 25% at 6 months but there was not complete remission, a second course of rituximab was administered regardless of the CD19+ B-cell count. If complete remission was observed at 6 months, no second course was given. If proteinuria was

MENTOR 2015 *(Continued)*

reduced by < 25% by 6 months, the patient was considered to have treatment failure and no further rituximab was administered

Treatment group 2

- CSA (oral): 3.5 to 5 mg/kg/day for 6 months divided into 2 equal doses given at 12 h intervals (continued for another 6 months if a substantial reduction in proteinuria (equal to or > 25%) is seen at 6 months. Target trough CSA blood levels 125 to 175 ng/mL.
  - For patients who achieve complete remission at 6 months, CSA will be tapered by approximately 1/3 of the maintenance dose monthly and hence discontinued after two months. If there has been at least an equal to or >25% reduction compared to their central laboratory baseline (Time 0) proteinuria, CSA will be continued for an additional 6 months. A persistent and otherwise unexplained increase in SCr >30% will prompt an approximate 25% dose reduction of CSA, aiming for a corresponding 25% reduction in the CSA trough level. If with this dose reduction the SCr does not return to within 30% of baseline levels within 3 weeks, then a second dose reduction of approximately 25% with a similar reduction in CSA trough level will be implemented. If the SCr does not fall to within 30% of baseline values with this second dose reduction, the drug will be discontinued. If after 6 months the reduction in proteinuria is < 25% compared to baseline, the drug will be discontinued, and the patient will exit from the study and will be considered a failure of therapy. At the end of 12 months, CSA will be tapered by 1/3 of the maintenance dose monthly and hence discontinued at the end of 2 months. The use of corticosteroids is not allowed

Co-intervention (both groups)

- Common run-in phase for both groups with conservative therapy for 3 months. If proteinuria can be brought below 5 g/24 hours, patients will not be eligible for the study. Target RR < 130/80 mm Hg in > 75% of readings with SBP ≤ 100 mm Hg. ACEi will be used and up-dosed every 2 weeks until max tolerated dose or FDA-approved dose. ARB will be added if RR target not met
- Atorvastatin 10mg/day until maximum 40 mg/day
- Low salt-diet
- Dietary protein target intake of 0.8 to 1.0 g/kg ideal body weight
- Patients with proteinuria >10g/24h and serum albumin < 2 g/dL will be considered for anticoagulation.

Outcomes	- Remission at 24 months post-randomisation - Complete remission: proteinuria ≤ 0.3 g/24 hours and serum albumin ≥ 3.5 g/dL - Partial remission: reduction in baseline proteinuria ≥ 50% plus final proteinuria ≤ 3.5 g/24 hours but > 0.3 g/24 hours - No response: reduction in baseline proteinuria < 25% (includes an increase in proteinuria) after 6 months of immunosuppression - Relapse: development of nephrotic range proteinuria following complete or partial remission (> 3.5 g/24 hours) - Relapse rate at 24 months - Autoantibodies to the M type phospholipase A2 receptor (PLA2R) levels - Quality of life as measured by modified KDQOL - Adverse events - ESKD - Relapse status at 6, 12, 18 and 2 months post-randomisation - Time to complete or partial relapse - The effect of treatment on kidney function, as assessed by slope of CrCl from baseline to 24 months
Notes	- Funding source: Fulk Foundation and Genentech, Incorporated - PLA2R-Ab-levels were measured

Risk of bias

Bias	Authors' judgement	Support for judgement

MENTOR 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The randomization schedule was computer-generated, stratified according to site, blocked with randomly varied block sizes of two and four, and concealed with the use of a Web-based, locked central randomization system"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization schedule was computer-generated, stratified according to site, blocked with randomly varied block sizes of two and four, and concealed with the use of a Web-based, locked central randomization system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label study; many outcomes are based on laboratory results, however not stated how these results are interpreted
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients have been accounted for
Selective reporting (reporting bias)	Low risk	All outcomes of relevant to this review have been reported
Other bias	High risk	Industry-funded. Genentech provides its own drug free of charge for evaluation in this trial. Study PIs have a conflict of interest as they received funding from Genentech.

Murphy 1992

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 1978 to 1986 • Duration of follow-up: 24 months

Participants	• Setting: multicentre (2)
	• Country: Australia
	• Inclusion criteria: biopsy-proven IMN
	• Baseline characteristics:
	  ○ Pathology stage (I/II/III): treatment group (4/14/1); control group (5/15/1)
	  ○ Mean proteinuria, range (g/24 hours): treatment group (5.0, 0.9 to 13); control group (3.9, 0.5 to 12)
	  ○ Hypertension: treatment group (6/19); control group (6/21)
	  ○ Mean serum albumin, range (g/L): treatment group (28, 16 to 42); control group (30, 19 to 41)
	  ○ Mean SCr, range (μmol/L): treatment group (110, 50 to 280); control group (90, 50 to 200)
	  ○ Baseline declining kidney function: 2 patients had the SCr > 200 μmol/L (one in each group)
	  ○ Use of ACEi or ARB during follow-up: not reported
	  ○ Previous immunosuppressive status: patients who had received any immunosuppressive therapy within 12 months prior to consideration of study entry were excluded
	• Number (randomised/analysed): treatment group (19/13); control group (21/13)
	• Mean age, range (years): treatment group (47, 26 to 66); control group (40, 18 to 65)
	• Sex (M/F): treatment group (12/7); control group (14/7)
	• Exclusion criteria: secondary MGN; renal vein thrombosis

Murphy 1992 *(Continued)*

Interventions	**Treatment group** • Oral CPA: a maximum dose of 1.5 mg/kg/day for 6 mouths • Dipyridamole and sodium warfarin therapy were continued for 2 years • Symptomatic treatment **Control group** • Symptomatic treatment only
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Insufficient information about the sequence generation process to permit judgement. However, it could be done
Allocation concealment (selection bias)	Low risk	After consent was obtained from patient, randomisation was performed by opening sealed envelops
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All except 1 patient completed the 2 years of follow-up. One treatment group patient died 8 months after study entry, 2 months after cessation of CPA. As this patient had a severe nephrotic syndrome and was the only patient with progressive deterioration in kidney function, his death and consequent removal from the remainder of the study could have biased data at time points after 6 months in favour of a benefit of therapy. Accordingly, it was decided to enter dummy values for SCr and proteinuria. These dummy values were chosen to be higher (900 μmol/L for SCr and 30g/24 h for proteinuria) than all the other patients at that time point, in order to ensure that any bias introduced due to the death of this patient would be against an effect of treatment
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	40 patients were properly randomised, only 26 were diagnosed with nephrotic syndrome, 13 in each group. The randomisation was not stratified according to nephrotic syndrome or non-nephrotic syndrome

Naumovic 2011

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 1995 to 2002 • Duration of follow-up: at least 36 months

Participants	• Setting: single centre
	• Country: Serbia
	• Inclusion criteria: biopsy-proven high-risk IMN; all had nephrotic syndrome with average proteinuria of 9 g/day
	• Baseline characteristics
	  ○ Pathology stage (I/II/III/IV): treatment group 1 (mean 2.2); treatment group 2 (mean 2.08)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (11.6 ± 4.7); treatment group 2 (7.0 ± 2.7)
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (22.9 ± 4.8); treatment group 2 (28.3 ± 6.4)
	  ○ Mean SCr ± SD (μmol/L): treatment group 1 (124.5 ± 75.9); treatment group 2 (120.5 ± 46.5)
	  ○ Mean GFR ± SD (mL/min): treatment group 1 (80.7±27.5); treatment group 2 (76.2 ± 31.3)
	  ○ Baseline declining kidney function: 22% of the patients exhibited elevated SCr values, and nearly 40% had lower CrCl
	  ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. ACEi were also given to all patients either in doses needed for adequate regulation of arterial hypertension or in normotensive patients in smaller amounts to achieve an antiproteinuric effect. During the 3-year follow-up, newly diagnosed hypertension was recorded in two patients in the CSA group that required an increased dose of ACEi or addition of another antihypertensive. Hypertension developed in three new patients of AZA was successfully regulated by ACEi and calcium channel antagonists
	  ○ Previous immunosuppressive status: all the patients previously received chlorambucil and corticosteroids for 6 months. The lead-time between the end of this treatment and the beginning of the new treatment was at least 1 year: treatment group 1 (17.9 ± 4.9 months); treatment group 2 (19.5 ± 8.1 months)
	• Number: treatment group 1 (10); treatment group 2 (13)
	• Mean age ± SD (years): treatment group 1 (39.2 ± 13.1); treatment group 2 (47.5 ± 8.2)
	• Sex (M/F): treatment group 1 (9/1); treatment group 2 (10/3)
	• Exclusion criteria: not reported

Interventions	Treatment group 1 • CSA: 3 mg/kg/day. During follow-up, the CSA dose was adjusted to achieve 12-hour trough levels of 80 to 100 ng/mL • Prednisone: 0.5 mg/kg/day for 8 weeks. The dose was gradually reduced to 5 to 10 mg/day and remained unchanged until the end of the treatment. • CSA and prednisone were slowly discontinued over 2 weeks at the end of the 24-month period Treatment group 2 • AZA: 1.5 to 2 mg/kg for 6 months, and afterwards 50 mg/day. AZA was temporarily withdrawn, or the dose was reduced if the WCC fell below 4 x 10^9/L • Prednisone: 0.5 mg/kg/day for 8 weeks. The dose was gradually reduced to 5 to 10 mg/day and remained unchanged until the end of the treatment • AZA and prednisone were slowly discontinued over 2 weeks at the end of the 24-month period
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Final GFR • Partial or complete remission

Naumovic 2011 *(Continued)*

- Final proteinuria
- Side effects leading to patient withdrawal or hospitalisation

Notes	• Funding information: funded by the Ministry of Science and Technology of the Republic of Serbia (project number 145043)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	This study was not fully randomised

Nikolopoulou 2019

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: March 2009 to December 2014 • Duration of follow-up: minimum 3-year follow-up after treatment

Participants	• Setting: single centre
	• Country: UK
	• Inclusion criteria: biopsy-proven IMN and nephrotic syndrome or patients who had biopsy within' 12 months prior to recruitment with worsening of proteinuria and exhibited deteriorating kidney function
	• Baseline characteristics
	   ○ Pathology stage (I/II/III/IV): treatment group 1 (3/12/3/5); treatment group 2 (4/12/3/3)
	   ○ Median SCr, range (mg/dL): treatment group 1 (0.8, 0.5 to 1.2); treatment group 2 (0.8, 0.5 to 1.4)
	   ○ Median SBP, range (mm Hg): treatment group 1 (131, 110 to 179); treatment group 2 (119, 101 to 155)
	   ○ Median DBP, range (mm Hg): treatment group 1 (81, 66 to 119); treatment group 2 (77.5, 101 to 155)
	   ○ Median UPCR, range (mg/mmol): treatment group 1 (756, 123 to 1784); treatment group 2 (704, 203 to 2159)

Nikolopoulou 2019 *(Continued)*

- ○ Median eGFR, range (mL/min/1.73 m²): treatment group 1 (121, 63 to 201); treatment group 2 (109, 44 to 142)
- ○ Median serum albumin, range (g/L): treatment group 1 (18, 11 to 27); treatment group 2 (17, 8 to 30)
- ○ Use of ACEI or ARB: treatment group 1 (17/20); treatment group 2 (20/20)
- ○ Previous treatment with immunosuppressive agent: treatment group 1 (0/20); treatment group 2 (1/20)
- Number: treatment group 1 (20); treatment group 2 (20)
- Median age, range (years): treatment group 1 (48, 28 to 66); treatment group 2 (55, 24 to 68)
- Sex (M/F): treatment group 1 (13/20); treatment group 2 (11/20)
- Exclusion criteria: secondary membranous nephropathy; positivity for Hepatitis B, C or HIV; malignancy; untreated infection. We also excluded pregnant or breastfeeding females and those planning a pregnancy or using unreliable contraception

Interventions	**Treatment group 1** • TAC: initial dose of 2 mg twice daily titrated to achieve whole blood levels of 5 to 12 ng/mL • MMF: 500 mg twice daily titrated to achieve blood MPA levels of 1.5 to 3.0 mg/L • Treatment for one year • When patients were in remission for 12 months, MMF was stopped and TAC tapered over 6 months. Follow-up for at least 3 years **Treatment group 2** • TAC monotherapy: initial dose of 2 mg twice daily titrated to achieve whole blood levels of 5 to 12 ng/mL. • Treatment for one year • When patients were in remission for 12 months TAC tapered over 6 months. Follow-up for at least 3 years
Outcomes	• Efficacy of MMF in preventing relapse of nephrotic syndrome secondary to membranous glomerulonephritis on withdrawal of TAC therapy. This will be initially measured at 6 months post-withdrawal of TAC therapy • Time to obtain remission from proteinuria • Complete or partial remission • The rate of decline of kidney function measured by the MDRD equation for GFR
Notes	• Funding source: "sponsored by the Imperial College Healthcare NHS Trust and supported by the NIHR Imperial Biomedical Research Centre providing the infrastructure for conducting the trial but had no involvement in trial design or the collection, analysis and interpretation of data" • Estimated primary completion date: February 2014 (final data collection date for primary outcome measure)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Nikolopoulou 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up (2 in each group); major deviations from protocol (2 in MMF/TAC group); ITT analysis performed
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported and could be meta-analysed
Other bias	Low risk	Study appears free of other potential biases

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Omrani 2017

Study characteristics

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 6 months

Participants	• Setting: single centre
	• Country: Iran
	• Inclusion criteria: aged 15 to 70 years; primary biopsy-proven diagnosis of IMN
	• Baseline characteristics
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (391.8 ± 149.9): treatment group 2 (389.9 ± 110.2)
	  ○ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (128.5 ± 18.8 / 81.3 ± 7.3): treatment group 2 (126.2 ± 16.1 / 81.3 ± 4.8)
	  ○ Mean SCr ± SD (mg/dL): treatment group 1 (1.3 ± 0.8): treatment group 2 (1.3 ± 0.7)
	  ○ Mean CrCl ± SD (%): treatment group 1 (73.2 ± 33.3): treatment group 2 (77.2 ± 21.8)
	  ○ Use of ACEi/ARB during follow-up: not reported
	  ○ Previous immunosuppressive treatment: not reported
	• Number: treatment group 1 (34); treatment group 2 (34)
	• Mean age ± SD (years): treatment group 1 (); treatment group 2 ()
	• Sex (M/F): treatment group 1 (16/18); treatment group 2 (13/21)
	• Exclusion criteria: secondary membranous nephropathy such as hepatitis B, hepatitis C and SLE

Interventions	Treatment group 1 • CSA: 3 to 6 mg/kg/day and a low dose of prednisolone for 6 months Treatment group 2 • TAC: 0.05 mg/kg/day and a low dose of prednisolone for 6 months
Outcomes	• Complete or partial remission: defined as 24-hour urinary protein excretion < 0.3 or 3.0 g (with at least 50% reduction compared with baseline), respectively, in at least two consecutive visits • SCr at 3 and 6 months • 24-hour urine protein at 3 and 6 months • CrCl at 3 and 6 months • SBP at 3 and 6 months • DBP at 3 and 6 months

Omrani 2017 *(Continued)*

	• Side effects, at 3 and 6 months
Notes	• Funding source: not reported • No data could be analysed because SDs were not given. Only patients with side effects were included in the analysis • Complete and partial remission was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study design
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to ascertain, only provides final numbers in analysed group
Selective reporting (reporting bias)	High risk	Primary outcome was not reported; SDs not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Pahari 1993

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: before 1993 • Duration of follow-up: 46 ± 10.2 months

Participants	• Setting: not reported
	• Country: India
	• Patients with biopsy-proven IMN and > 2.0 g/24 hours proteinuria
	• Baseline characteristics
	  ◦ Proteinuria (g/24 hours): ≥ 2
	  ◦ SCr (mg/dL): ≤ 2
	  ◦ Baseline declining kidney function: no
	• Number (randomised/analysed): treatment group 1 (42/36); treatment group 2 (48/35)
	• Mean age ± SD (years): treatment group 1 (35 ± 16); treatment group 2 (32 ± 20)
	• Sex (M/F): treatment group 1 (25/11); treatment group 2 (24/11)

Pahari 1993 *(Continued)*

Interventions	**Treatment group 1**
	• Prednisolone (oral): 4 mg/kg/day from 1 to 3 days followed by oral prednisolone 0.5 mg/kg/day from 4 to 30 days (Injection dexamethasone 1 mg/kg/day from 1 to 3 days in cases who are intolerant to high dose oral prednisolone)
	• CPA (oral): 2 mg/kg/day from 1 to 30 days of next months (oral chlorambucil was used in patients intolerant to oral CPA). The treatment was continued for 1 year
	Treatment group 2
	• Prednisolone (oral): 60 mg/day was given for 12 weeks
Outcomes	• Death
	• ESKD
	• 50% or 100% SCr increase
	• Partial or complete remission
	• Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: not reported
	• Drop-out rate: treatment group 1 (6/42); treatment group 2 (13/48)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	90 patients were randomised, only 71/90 (79%) were finally analysed. The missing outcome data were not balanced in numbers across intervention groups: 6/42 (14%) in CPA group and 13/48 (27%) in prednisolone group
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	The inclusion criteria of proteinuria was 2 g/24 hours rather than 3.5 g/24 hours

Peng 2016

Study characteristics

Methods	• Study design; 3-arm, parallel, open-label RCT

Peng 2016 *(Continued)*

- Study duration; January 2009 to May 2013
- Duration of follow-up: 9 months

Participants	- Setting: single centre - Country: China - Inclusion criteria: 18 to 75 years; diagnosis of IMN by renal biopsy and laboratory examination; persistent proteinuria (> 8 g/day) after observation for at least 1 month; nephrotic syndrome; not previously received any immunosuppressive treatment - Baseline characteristics - Mean SBP/DBP ± SD (mm Hg): treatment group 1 (122.3 ± 16.1 / 78.5 ± 10.5); treatment group 2 1(23.3 ± 14.0 / 77.7 ± 8.5); treatment group 3 (122.1 ± 12.6 / 80.2 ± 10.4) - Mean proteinuria ± SD (g/24 hours): treatment group 1 (11.7 ± 3.2); treatment group 2 (11.9 ± 1.5); treatment group 3 (12.1 ± 3.7) - Mean serum albumin ± SD (g/L): treatment group 1 (20.5 ± 3.4); treatment group 2 (19.8 ± 3.8); treatment group 3 (21.9 ± 4.9) - Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (87.9 ± 16.5); treatment group 2 (97.3 ± 23.0); treatment group 3 (95.8 ± 24.9) - Mean triglyceride ± SD (mmol/L): treatment group 1 (3.3 ± 2.0); treatment group 2 (2.8 ± 1.2); treatment group 3 (2.9 ± 1.2) - Mean SCr ± SD (μmol/L): treatment group 1 (82.4 ± 13.6); treatment group 2 (78.4 ± 13.8); treatment group 3 (78.7 ± 13.8) - Mean serum cholesterol ± SD (mmol/L): treatment group 1 (10.4 ± 3.2); treatment group 2 (10.1 ± 2.6); treatment group 3 (9.8 ± 3.1) - Disease-course (time since diagnosis) at immunosuppressive Tx initiation: not reported - Pathological stage: (I/II/III/IV): treatment group 1 (10/15/5/0); treatment group 2 (10/13/7/0); treatment group 3 (12/13/5/0) - Hypertension: treatment group 1 (8); treatment group 2 (7); treatment group 3 (5) - Antihypertensive agents were administered to achieve a target BP (systolic < 130 mm Hg and diastolic < 80 mm Hg) were not initiated during follow-up, but were continued in patients who were already on such treatment prior to recruitment - Number (randomised/analysed): treatment group 1 (30/29); treatment group 2 (20/28); treatment group 3 (30/29) - Mean age ± SD (years): treatment group 1 (43.9 ± 13.2); treatment group 2 (40.8 ± 13.3); treatment group 3 (39.9 ± 14.3) - Sex (M/F): treatment group (17/13); treatment group 2 (16/14); treatment group 3 (14/16) - Exclusion criteria; SCr > 133 mmol/L; active infection; DM; autoimmune disease; tumours; liver function test abnormalities; active peptic ulcer disease
Interventions	Treatment group 1 - TAC (oral): 0.05 mg/kg/day divided into two doses at intervals of 12 hours initially. The dose was adjusted to achieve a blood trough concentration of 4 to 8 ng/mL for 6 months and then reduced to 2 to 4 ng/mL in the subsequent 3 months - Corticosteroid (oral): 0.5 mg/kg/day Treatment group 2 - CPA (IV): 750 mg/m^2 once a month for 6 months, which was then reduced to 750 mg/m^2 every 3 months - Corticosteroid (oral): 1 mg/kg/day for 2 months, which was reduced by 5 mg/day every 2 weeks to 20 mg/day. At that point, corticosteroid was tapered to zero according to the condition of the patient Treatment group 3 - MMF (oral): 1.5 to 2.0 g/day in 2 doses - Corticosteroid (oral): 1 mg/kg/day for 2 months, which was reduced by 5 mg/day every 2 weeks to 20 mg/day. At that point, corticosteroid was tapered to zero according to the condition of the patient Duration of treatment

Peng 2016 *(Continued)*

- Nine months

Co-interventions

- Anticoagulant drugs and simvastatin were prescribed to all patients
- ACEi/ARB: treatment group 1 (8); treatment group 2 (7); treatment group 3 (5) administered to achieve a target BP (SBP < 130 mm Hg and DBP < 80 mm Hg)

Outcomes	- Remission
	  ○ Complete remission: daily proteinuria < 0.3 g, normal serum albumin ≥ 35 g/L), and stable kidney function
	  ○ Partial remission: proteinuria 0.3 to 3.5 g/day that had declined to 50% of the baseline value, serum albumin concentration of at least 30 g/L, and a stable kidney function
	  ○ No response: proteinuria > 3.5 g/day or a value of 0.3 to 3.5 g/d, but with serum albumin < 30 g/L or an increase in the SCr greater than 50% above the baseline value
	  ○ Relapse: proteinuria > 3.5 g/day in two consecutive measurements in patients with complete or partial remission, and not recovering within 2 weeks
	- Death
	- Relapse after partial response
	- Time to remission
	- Proteinuria
	- Serum albumin
	- SCr
	- > 30% increase in SCr
	- Adverse events

Notes	- Funding sources:
	  ○ National Basic Research Program of China
	  ○ National Natural Science Foundation of China
	  ○ Doctoral Program of Ministry of Education of China
	  ○ Special Grade of China Postdoctoral Science Foundation
	  ○ Heilongjiang Postdoctoral Science Research Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 lost to follow-up, 2 died, 1 ceased due to leucopenia

Peng 2016 *(Continued)*

Selective reporting (re-porting bias)	Low risk	Data on primary outcome comprehensive, all outcomes reported data. intention-to-treat analysis was performed
Other bias	Low risk	No evidence for other sources of bias. no evidence for potential conflict of interest however, no study protocol was published beforehand

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Ponticelli 1992

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: before December 1989 • Duration of follow-up: 4 years*

Participants	• Setting: multicentre (Italian Idiopathic Membranous Nephropathy Treatment Study Group)
	• Country: Italy
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	  ○ Pathology stage (I-II/III-IV): treatment group 1 (27/18); treatment group 2 (29/18)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (7.6 ± 4.2); treatment group 2 (7.0 ± 4.1)
	  ○ Hypertension: treatment group 1 (15/45); treatment group 2 (14/47)
	  ○ SCr (mg/dL): treatment group 1 (1.0 ± 0.3); treatment group 2 (1.0 ± 0.3)
	  ○ Baseline declining kidney function: no, patients with SCr > 1.7 mg/dL (150 µmol/L) were excluded
	  ○ Use of ACEi or ARB during follow-up: not reported
	  ○ Previous immunosuppressive status: patients with previous treatment with corticosteroids or cytotoxic agents were excluded
	• Number: treatment group 1 (45); treatment group 2 (47)
	• Mean age, range (years): treatment group 1 (46, 14-65); treatment group 2 (47, 14-64)
	• Sex (M/F): treatment group 1 (32/13); treatment group 2 (27/20)
	• Exclusion criteria: aged < 14 and > 65 years; SCr > 1.7 mg/dL; previous treatment with corticosteroids or cytotoxic agents; positive for anti-DNA antibodies, hepatitis B antigen or Venereal Disease Research Laboratory test; low C3 or C4; DM; infection; exposure to drugs that could induce IMN

Interventions	Treatment group 1 • Methylprednisolone: 3 cycles (IV) of 1 g on 3 consecutive days and then 0.4 mg/kg/day given orally for 27 days, in a single morning dose • Chlorambucil (oral): 0.2 mg/kg/day Treatment group 2 • Methylprednisolone (IV): 1 g on 3 consecutive days at the beginning of treatment and again 2 and 4 months • Methylprednisolone (oral): 0.4 mg/kg every other day, except during the period of IV administration, for six months
Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Remission (complete and partial) • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation

Ponticelli 1992 *(Continued)*

	• Follow-up time points: 1, 2, 3, and 4 years

| Notes | • Funding source: not reported
• *Duration of follow-up treatment group 1 (54 ± 16 months); treatment group 2 (54 ± 17 months). 63/92 (68%) patients completed the 48-month follow-up and were analysed for the outcomes of partial or complete remission (treatment group 1 (32/45, 71%), treatment group 2 (31/47, 66%). 50/92 (54%) patients had data for final proteinuria at 48 months (treatment group 1 (26/45, 58%); treatment group 2 24/47 (51%)) |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The coordinating centre assigned the patients consecutively to one of the two treatment regimens in random order
Allocation concealment (selection bias)	Low risk	Central randomisation method described could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients who could not complete treatment were included in the analysis according to the intention-to-treat principle. For the two patients who died and the one who was lost to follow-up, data obtained at the last observation were considered
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Ponticelli 1998

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Duration of follow-up: treatment group 1 (36, 12 to 78 months); treatment group 2 (42, 12 to 72 months)

Participants	• Setting: multicentre
	• Country: Italy
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	   ○ Pathology stage (I-II/III-IV): treatment group 1 (32/18); treatment group 2 (27/18)
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (7.96 ± 5.19); treatment group 2 (6.85 ± 3.51)
	   ○ Hypertension: treatment group 1 (15/50); treatment group 2 (14/45)
	   ○ SCr (mg/dL): treatment group 1 (1.06 ± 0.27); treatment group 2 (1.04 ± 0.27)

Ponticelli 1998 *(Continued)*

- ○ Baseline declining kidney function: patients with SCr > 1.7 mg/dL were excluded
- ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. The use of ACEi was discouraged but not prohibited
- ○ Previous immunosuppressive status: patients who had previously received corticosteroids, immunosuppressive drugs, or CSA were excluded
- Number: treatment group 1 (50); control group 2 (45)
- Mean age, range (years): treatment group 1 (50, 18-65); control group 2 (48, 17-55)
- Sex (M/F): treatment group 1 (37/13); control group 2 (29/16)
- Exclusion criteria: SCr > 1.7 mg/dL; previous treatment with corticosteroids immunosuppressive drugs or CSA; positive for anti-DNA antibodies, hepatitis B antigen, hepatitis C virus antibodies, or Venereal Disease Research Laboratory test; low C3 or C4; DM; infection; malignancy; SLE; exposure to drugs that could induce IMN

Interventions	**Treatment group 1** - Methylprednisolone: 1 g IV on 3 consecutive days and then 0.4 mg/kg/day given orally for 27 days, in a single morning dose - Chlorambucil (oral): 0.2 mg/kg/day for 1 month. The total duration of treatment, therefore, was 6 months for both groups; 3 months with the same doses of methylprednisolone and 3 months with either of the two cytotoxic drugs. Steroids were completely stopped at the end of the study period. Two relapse patients were retreated with steroids and chlorambucil. One did not respond, and the other attained partial remission **Treatment group 2** - Methylprednisolone: 1 g IV on 3 consecutive days and then 0.4 mg/kg/day given orally for 27 days, in a single morning dose - CPA (oral): 2.5 mg/kg/day. Two relapse patients were retreated. One patient was retreated with steroids and CPA and had complete remission. Another patient was treated with steroids and chlorambucil and had partial remission
Outcomes	- Death - ESKD - 50% or 100% SCr increase - Final SCr - Partial or complete remission - Final proteinuria - Side effects leading to patient withdrawal or hospitalisation
Notes	- Funding information: supported in part by a grant from Ospedale Maggiore di Milan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At the coordinating centre, patients were assigned consecutively to one of the two treatment regimens, according to a centre-stratified random order
Allocation concealment (selection bias)	Low risk	Central randomisation method described above could not allow investigators/participants to know or influence intervention group before eligible participant entered in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Ponticelli 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 8/95 (8%) patients did not complete the 6-month regimen and then excluded in some final analyses: treatment group 1 (6/50), treatment group 2 (2/45). Two patients did not present at the follow-up visit and a 51-yr-old woman died because of a deep-vein thrombosis with acute kidney failure and cardiac shock 3 months after the diagnosis of membranous nephropathy, before treatment was started. Four patients in treatment group 1 and one in treatment group 2, who completed the treatment, did not present at the follow-up visit and were considered lost to follow-up after the sixth month
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appears to be free of other sources of bias

Ponticelli 2006

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: September 2001 to December 2003 • Duration of follow-up (months): treatment group 1 (21.8 ± 7.5); treatment group 2 (21.8 ± 7.6)
Participants	• Setting: multicentre • Country: Italy • Inclusion criteria: biopsy-proven IMN with nephrotic syndrome • Baseline characteristics ○ Pathology stage (I-II/III-IV): treatment group 1 (12/4); treatment group 2 (14/2) ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (5.5 ± 2.0); treatment group 2 (6.7 ± 2.8) ○ Hypertension: treatment group 1 (9/16); treatment group 2 (9/16) ○ SCr (mg/dL): treatment group 1 (0.9 ± 0.17); treatment group 2 (1.0 ± 0.36) ○ Baseline declining kidney function: no; patients with SCr concentrations > 1.9 mg/dL (168 mol/L) were excluded ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. Eleven patients in treatment group 2 and 12 patients in treatment group 1 were treated with ACEi and/or ARB during the study. There was no significant difference between the 2 groups in the probability of remission between patients administered ACEi and/or ARB or statins and those not administered either of these drugs ○ Previous immunosuppressive status: patients who previously received treatment with corticosteroids or cytotoxic agents were excluded • Number: treatment group 1 (16); treatment group 2 (16) • Mean age ± SD (years): treatment group 1 (51.4 ± 9.5); treatment group 2 (48 ± 12.9) • Sex (M/F): treatment group 1 (7/9); treatment group 2 (12/4) • Exclusion criteria: < 16 years; SCr > 1.9 mg/dL; previously received treatment with corticosteroids or cytotoxic agents; conditions associated with secondary MN
Interventions	Treatment group 1 • Methylprednisolone: 1 g (IV) on 3 consecutive days, and then 0.4 mg/kg/day (oral) for 27 days, administered in a single morning dose • Oral chlorambucil (0.2 mg/kg/day orally) or oral CPA (2.5 mg/kg/day) for 1 month

Treatment group 2

- Synthetic ACTH (tetracosactide): 1 mg (IM) between 7:00 and 9:00 AM. Administration of ACTH was increased from 1 injection every other week to 2 injections/week for a total treatment period of 1 year

Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: "Project Glomerulonephritis" grant. The corresponding author was an external consultant to Novartis, which produces tetracosactide used in this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The coordinating centre assigned patients consecutively by telephone to 1 of the 2 treatment regimens in a centralized randomised order, with assignation produced by a table from a statistical textbook
Allocation concealment (selection bias)	Low risk	The sequence was concealed until intervention was assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Praga 2007

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: January 2003 to September 2006 • Duration of follow-up: 30 months
Participants	• Setting: multicentre • Country: Spain

Praga 2007 *(Continued)*

- Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
- Baseline characteristics
  - Pathology stage (I/II/III/IV): treatment group (4/15/3/0); control group (4/18/1/0)
  - Mean proteinuria ± SD (g/24 hours): treatment group (7.2 ± 3.3); control group (8.4 ± 5.4)
  - Mean serum albumin ± SD (g/L): treatment group (27 ± 8); control group (29 ± 8)
  - SCr (mg/dL): treatment group (0.98 ± 0.2); control group (1.1 ± 0.3)
  - Mean GFR ± SD (mL/min/1.73 m²): treatment group (104 ± 26); control group (107 ± 63)
  - Baseline declining kidney function: no; GFR by Cockroft-Gault formula was ≥ 50 mL/min/1.73 m² in all included patients
  - Use of ACEi or ARB during follow-up: yes, no confounding effect. Included patients who also had to be treated with an ACEi or an ARB at their maximal tolerated doses for at least 2 months before screening. All the patients were instructed to maintain the same doses of ACEi or ARB that they were taking at randomisation until the end of the study
  - Previous immunosuppressive status: patients treated with steroids or immunosuppressive therapy within the 6-month period before screening were excluded. There were no differences in the number of patients that had been previously treated with steroids alone or in combination with cytotoxics (previous treatment with steroids/steroids plus cytotoxics: treatment group (5/4); control group (6/4)
- Number: treatment group (25); control group (23)
- Mean age ± SD (years): treatment group (3.7 ± 12.1); control group (50.1 ± 12.2)
- Sex (M/F): treatment group (20/5); control group (20/3)
- Exclusion criteria: DM; malignancy; SLE; any other systemic disease known to be associated with secondary MGN; infections (including a positive test for hepatitis C and B virus and HIV); treated with steroids or immunosuppressive therapy within the 6-month period before screening

Interventions	**Treatment group** - TAC: 0.05 mg/kg/day, divided into two daily doses at 12-hour intervals. Later doses were adjusted to achieve a whole blood 12-hour trough level between 3 and 5 ng/mL. When a remission was not obtained after the first 2 months of treatment, doses were increased to achieve levels between 5 and 8 ng/mL. TAC treatment was continued for 12 months and then gradually tapered off for the next 6 months; a 25% TAC dose reduction was indicated at months 12, 14, and 16 and treatment was withdrawn by month 18. TAC doses were reduced by 25% every 2 weeks in the presence of a 50% SCr increase. If SCr persisted > 50% of baseline values 2 to 4 weeks after > 75% reduction of TAC doses, the definition of endpoint was established **Control group** - No specific immunosuppressive treatment
Outcomes	- Death - ESKD - 50% or 100% SCr increase - Partial or complete remission - Final proteinuria - Side effects leading to patient withdrawal or hospitalisation
Notes	- Funding source: partially supported by Astellas Pharmaceuticals. Astellas did not intervene in the design or conduct of the study, analysis, and interpretation of the data or preparation of this paper - Baseline comparison: comparable except that DBP was significantly higher in the control group than in the TAC group at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement

Praga 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was performed by the clinical coordinating centre using a table of random numbers and was stratified by centres
Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque-closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 8/48 (17%) randomised patients did not complete the 18-month regimen. Two patients of the treated group (personal decision because lack of response after 6 months of treatment and a partial seizure in a patient with history of epilepsy) and one of the control group (severe oedema six months after randomisation and deafness attributed to high-dose diuretics) withdrew from the study. Five patients (three in the control group and two in the treatment group) were lost to follow-up between 3 and 18 months after randomisation. But they were all included in the final analyses according to the intention-to-treat basis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Ramachandran 2016

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration; enrolled September 2011 to December 2013 • Duration of follow-up: continued to December 2014

Participants	• Setting: single centre
	• Country: India
	• Inclusion criteria: aged 18 to 60 years; biopsy-proven IMN based on light microscopy and immunofluorescence; persistent nephrotic syndrome despite 6 months of treatment with either ACEi or ARB; deep vein thrombosis (DVT) (no 6 months of ACEi/ARB tried)
	• Baseline characteristics
	  ○ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (126.3 ± 16.34 / 79.77±8.11); treatment group 2 (130.0 ± 19.79 / 80.11 ± 10.71)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (6.76 ± 3.59); treatment group 2 (5.44 ± 2.66)
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (22.0 ± 6.7); treatment group 2 (22.3 ± 5.5)
	  ○ Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (96.72 ± 27.13); treatment group 2 (89.04 ± 27.63)
	  ○ Mean SCr ± SD (μmol/L): treatment group 1 (0.9 ± 0.27); treatment group 2 (0.91 ± 0.26)
	  ○ Disease-course (time since diagnosis) at immunosuppressive Tx initiation (months): 10.87 ± 4.01 (10.31 ± 4.77 in TAC vs. 11.43 ± 3.47 in MP regimen)
	  ○ Pathological classification: not reported

Ramachandran 2016 *(Continued)*

- ○ Co-morbidities: not reported
- Number: treatment group 1 (35); treatment group 2 (35)
- Mean age ± SD (years): treatment group 1 (38.66 ± 1.91); treatment group 2 (40.80 ± 10.64)
- Sex (M/F): treatment group 1 (27/08); treatment group 2 (20/15)
- Exclusion criteria: SCr >2.5 mg/dL; prior, active infection including hepatitis B/C and HIV infection; positive for anti-nuclear factor, monoclonal proteins in serum/urine; any suggestion of malignancy on ultrasonography; hypocomplementaemia; presence of tubular atrophy and interstitial fibrosis in > 1/3 biopsy area; pre-existing DM; abnormal liver function tests; secondary MN

Interventions	Treatment group 1 • TAC (oral): 0.1 mg/kg/day was given in 2 divided doses for 1 year to keep trough levels at 5 to 10 ng/mL in 1st 6 months and 4 to 8 ng/mL in the next 6 months • Prednisolone (oral): 0.5 mg/kg/day for 6 months and was then tapered and stopped Treatment group 2 • Methylprednisolone 1 g/day (IV) in 100 mL normal saline was administered over 60 min on 3 consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days in the first, third, and fifth month • CPA (oral): 2 mg/kg/day in the second, fourth, and sixth month Co-medications • Maximum tolerable dose of ACEi or ARB • Statins in all patients

Outcomes	• Percentage of patients achieving complete remission and partial remission at 6 and 12 months
	• eGFR as measured by MDRD equation
	• Adverse events
	• Definitions
	  ○ Nephrotic syndrome: proteinuria > 4 g/day or ≥ 2.0 g/day along with serum albumin < 2.5 g/dL
	  ○ Complete remission: proteinuria < 500 mg/day with normal serum albumin (≥ 3.5 g/dL) and normal SCr
	  ○ Partial Remission: proteinuria ≥ 500 mg/day, but < 2 g/day or < 50% of baseline with normal serum albumin (≥ 3.5 g/dL) and normal SCr
	  ○ Nephrotoxicity: rise in SCr by 2 times the baseline

Notes	• Funding source: Indian Society of Nephrology • PLA2R-Ab-levels were measured at baseline and at months 6 and 12 of therapy • TAC-group started off with lower APLA2R-AB levels (about 50%) and better SCr, indicating a potentially different severity of disease in this population

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based random numbers. Random sequence generation was performed by an author, who was not otherwise involved in the enrolment and allocation of treatment of the participants
Allocation concealment (selection bias)	Low risk	Labelled sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Ramachandran 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 eligible and randomised, all are included in outcome analyses
Selective reporting (reporting bias)	Low risk	Remission most relevant and is reported. Generally comprehensive reporting of outcome data
Other bias	Low risk	No evidence of other sources of bias. No evidence for conflict of interest or financial interests

Reichert 1994

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: June 1989 to November 1992 • Duration of follow-up (months): treatment group 1 (26 ± 12); treatment group 2 (13 ± 5.8)

Participants	• Setting: multicentre
	• Country: Netherlands
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome and deteriorating kidney function
	• Baseline characteristics
	  ○ Pathology stage (I-II/III/unavailable): treatment group 1 (6/2/1); treatment group 2 (6/3/0)
	  ○ Proteinuria (g/10 mmol of Cr): treatment group 1 (8.5 ± 2.5); treatment group 2 (9.8 ± 4.8)
	  ○ Hypertension: treatment group 1 (7/9); treatment group 2 (5/9)
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (22.9 ± 6.4); treatment group 2 (25.9 ± 9.7)
	  ○ Mean SCr ± SD (µmol/L): treatment group 1 (260 ± 112); treatment group 2 (218 ± 85)
	  ○ Baseline declining kidney function: yes
	  ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. Three patients in treatment group 1 and 5 patients in treatment group 2 received ACEi
	  ○ Previous immunosuppressive status: six patients in treatment group 1 and 5 patients in treatment group 2 had been treated previously with short-term, high-dose prednisone according to Coggins 1979
	• Number: treatment group 1 (9); treatment group 2 (9)
	• Mean age, range (years): treatment group 1 (45, 31-65); treatment group 2 (49, 24-65)
	• Sex (M/F): treatment group 1 (9/0); treatment group 2 (8/1)
	• Exclusion criteria: < 18 years; SCr < 150 µmol/L, evidence of secondary types of membranous nephropathy (malignancy, hepatitis infection, positive anti-DNA antibodies, drugs use that may induce membranous nephropathy); planned pregnancy; DM; clinical evidence of renal vein thrombosis

Interventions	Treatment group 1 • Chlorambucil (oral): 0.15 mg/kg/day in months 2, 4, and 6 • Prednisone: 3 IV pulses of 1 g of methylprednisolone followed by oral prednisone at 0.5 mg/kg/day in months 1, 3, and 5 ○ Three patients were retreated with new immunosuppressive therapy Treatment group 2 • CPA (IV): 750 mg/m² once every month for 6 months

Reichert 1994 *(Continued)*

- Methylprednisolone: 3 IV 1 g pulses in months 1, 3, and 5
  - One patient was retreated with new immunosuppressive therapy

Outcomes	
	• Death
	• ESKD
	• 50% or 100% SCr increase
	• Final SCr
	• Partial or complete remission
	• Side effects leading to patient withdrawal or hospitalisation

Notes	
	• Funding source: NWO grant 900/716-111 from the Netherlands Foundation of Scientific Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/20 patients completed the study. 2 (1 from each treatment group) immediately withdrew after assignment: one had to receive regular dialysis before treatment with methylprednisolone and CPA had begun, and the other became psychotic 2 weeks after starting prednisone treatment. Because these 2 patients received neither chlorambucil nor CPA, their data are not used for analysis
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Sahay 2002

Study characteristics

Methods	
	• Study design: parallel, open-label, 3-arm study
	• Study duration: conducted over 8 years
	• Duration of follow-up: minimum follow-up of 2 years

Participants	
	• Setting: single centre
	• Country: India
	• Inclusion criteria: IMN
	• Baseline characteristics:

Sahay 2002 *(Continued)*

- ○ Mean proteinuria ± SD (g/day): treatment group 1 (3.2 ± 0.6); treatment group 2 (3.8 ± 0.6); treatment group 3 (3.6 ± 0.7)
- ○ Mean SCr ± SD (mg/dL): treatment group 1 (1.36 ± 0.1); treatment group 2 (1.40); treatment group 3 (1.43 ± 0.3)
- Number: 60 total, number per group not clearly specified but implies 20 per group
- Mean age ± SD: 32 ± 12 years
- Sex (M/F): 32/28
- Exclusion criteria: not reported

Interventions	Treatment group 1 • ACEi Treatment group 2 • Oral steroids Treatment group 2 • Ponticelli regime
Outcomes	• Complete remission • Partial remission • Proteinuria • Kidney function • Adverse effects
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Reports 12/20 in the Ponticelli regime completed the study and were analysed; no other data provided
Selective reporting (reporting bias)	High risk	Data could not be meta-analysed (percentages reported and unsure of numbers per group)
Other bias	Unclear risk	Insufficient information to permit judgement

Saito 2014 *(Continued)*

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: 2004 to 2007 • Duration of follow-up: 48 weeks

Participants	• Setting: multicentre
	• Country: Japan
	• Inclusion criteria: 16 to 75 years; biopsy-proven IMN with steroid-resistance; nephrotic syndrome with at least proteinuria of > 3.5 g/day and serum albumin < 3.0 g/dL or serum total protein < 6.0 g/dL; prednisolone-alone treatment for > 4 weeks did not decrease urinary protein into < 1 g/day; no history of treatment with CyA-MPEC
	• Baseline characteristics (median, IQR)
	  ○ Mean proteinuria, range (g/24 hours): treatment group 1 (3.5,1.8 to 10); treatment group 2 (3.8, 1.0 to 6.5)
	  ○ Mean serum albumin, range (g/L): treatment group 1 (27, 22 to 35); treatment group 2 (26, 15 to 33)
	  ○ Mean SCr, range (µmol/L): treatment group 1 (70.72, 44.2 to 106.08); treatment group 2 (70.72; 53.04 to 141.44)
	  ○ Mean BUN, range (mmol/L): treatment group (5.0, 2.9 to 8.6); treatment group 2 (5.35, 3.2 to 11.8)
	  ○ Mean serum cholesterol, range (mmol/L): treatment group 1 (112.10, 81.75 to 220.27); treatment group 2 (106.39, 76.04 to 304.52)
	  ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	  ○ Previous immunosuppressive status: steroids
	  ○ Pathological classification: not reported
	  ○ Co-morbidities: not reported
	• Number (randomised/analysed: treatment group 1 (25/18); treatment group 2 (25/21)
	• Median age, IQR (years): treatment group 1 (56, 19 to 70); treatment group 2 (57, 39 to 70)
	• Sex (M/F): treatment group 1 (16/7); treatment group 2 (17/8)
	• Exclusion criteria: secondary MN; CrCl < 50 mL/min or SCr > 2 mg/dL; received other immunosuppressants within one month prior to the study; treated with nephrotoxic or hyperkalaemic agents during the study; hypertension that cannot be controlled with drugs; malabsorption syndrome, cerebral dysfunction, epilepsy; severe cardiac, hepatic or pancreatic disease; severe hyperkalaemia or hyperuricaemia; pregnancy, nursing or suspected to be pregnant; infectious complication and not eligible for immunosuppressive treatment; history of hypersensitivity to CSA-MEPC; determined inappropriate to study by the investigator

Interventions	Treatment group 1 • CSA: 1.5 mg/kg twice a day for 48 weeks • Prednisolone: initially prescribed at 40 mg/day and tapered Treatment group 2 • CSA: 3 mg/kg once a day before breakfast for 48 weeks • Prednisolone: initially prescribed at 40 mg/day and tapered Co-medications • Antihypertensive, lipid therapy and anticoagulant drugs allowed

Outcomes	• Complete remission: proteinuria < 0.3 g/dL
	• Partial (incomplete) remission: resolution of nephrotic syndrome but with continuing overt proteinuria, divided into 2 grades
	  ○ ICR1: proteinuria 0.3 to 1.0 g/day
	  ○ ICR2: > 1.0 to 3.5 g/day

Saito 2014 *(Continued)*

- No response: persistence of nephrotic syndrome
- Kidney function in 3 categories
  - Normal SCr concentration < 1.5 mg/dL
  - Renal insufficiency SCr >1.5 mg/dL
  - ESKD SCr > 3.0 mg/dL
- Secondary outcomes: not clearly reported

Notes	• Funding sources
	  ○ The Kidney Foundation Japan
	  ○ Ministry of Health, Labour and Welfare (Japan)
	• Declarations of Interests/Disclosures: 3 of the authors have received lecturing fees from Novartis. Two of the authors have received research grants from Novartis
	• Trial registration or protocol registration or publication: University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) no. UMIN C000000369

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	Comprehensive reporting of primary outcomes
Other bias	Low risk	Industry co-funded trial. Otherwise, no evidence for other sources of bias

Saito 2017

Study characteristics

Methods	• Study design; parallel, open-label RCT • Study duration: enrolled April 2004 to December 2007, treated for 2 years • Duration of follow-up: 24 months
Participants	• Setting: multicentre (23 sites) • Country: Japan • Inclusion criteria: biopsy-proven IMN with primary steroid-resistant nephrotic syndrome; 16 to 75 years; proteinuria ≥ 3.5 g/day and serum albumin level ≤ 3.0 g/dL; prednisolone treatment alone for

Saito 2017 *(Continued)*

> 4 weeks did not decrease proteinuria to < 1 g/day; no history of treatment with mizoribine before registration; informed consent form signed voluntarily by the participant

- Baseline characteristics (median, IQR)
  - Proteinuria (g/day): treatment group 1 (3.7, 1.0 to 7.5); treatment group 2 (3.3, 1.3 to 7.1)
  - BUN (mg/dL): treatment group 1 (14.5, 7.0 to 23.7); treatment group 2 (15.1, 7.0 to 29.0)
  - SCr (mg/dL): treatment group 1 (0.8, 0.5 to 1.3); treatment group 2 (0.9, 0.6 to 1.4)
  - Serum albumin (g/dL): treatment group 1 (2.5, 1.8 to 3.4); treatment group 2 (2.6, 1.0 to 3.9)
- Number (randomised/analysed): treatment group 1 (26/19); treatment group 2 (25/18)
- Median age, range (years): treatment group 1 (60, 35 to 70); treatment group 2 (60, 43 to 74)
- Sex (M/F): treatment group 1 (15/4); treatment group 2 (14/4)
- Exclusion criteria: membranous nephropathy secondary to systemic diseases, e.g., diabetic nephropathy and collagen diseases; CrCl < 50 mL/min or SCr > 2 mg/dL; history of severe hypersensitive reaction to Mizoribine; previously treated with Mizoribine; WCC < 3000/mm³ in peripheral blood; currently pregnant, suspected to be pregnant, or nursing; any severe complication; any severe bacterial, fungal, or viral infection; determined to be inappropriate for participation in the study by an investigator

Interventions	**Treatment group 1** • Mizoribine (oral): 150 mg once/day after breakfast for 2 years **Treatment group 2** • Mizoribine (oral): 50 mg 3 times/day after meals for 2 years

Outcomes	• Urine protein excretion (g/day)
	• Remission status of nephrotic syndrome
	• Kidney function (CrCl)
	• Serum total protein and albumin levels
	• Complete or partial (incomplete) remission
	• Definitions
	  ○ Nephrotic syndrome: defined according to the standard criteria used in Japan
	    ■ Urinary protein excretion > 3.5 g/day
	    ■ Serum albumin < 3.0 g/dL or serum total protein < 6.0 g/dL
	    ■ Presence of oedema
	    ■ Total cholesterol > 250 mg/dL
	  ○ Complete remission: urine protein < 0.3 g/day
	  ○ Partial (incomplete) remission: resolution of nephrotic syndrome but with continuing overt proteinuria, and was divided into 2 grades
	    ■ ICR1: urinary protein excretion: 0.3 to 0.99 g/day
	    ■ ICR2: urinary protein excretion: 1.0 to 3.5 g/day
	  ○ Kidney function
	    ■ Normal kidney function: SCr < 1.5 mg/dL
	    ■ Renal insufficiency:1.5 to 3.0 mg/dL
	    ■ ESKD: SCr > 3.0 mg/dL

Notes	• Funding source: "supported by a grant for Progressive Renal Disease Research Projects from the Ministry of Health, Labor and Welfare, Japan, and by a grant from the Japan Kidney Foundation" • Author declarations: "T Saito and N Yorioka have received research funds from Asahi Kasei Pharma. T Mitarai has received lecturer's fee from Asahi Kasei Pharma"

Risk of bias

Bias	Authors' judgement	Support for judgement

Saito 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	51 randomised, 37 reported in outcomes data
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Senthil Nayagam 2008

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: before 2008 • Duration of follow-up (months): treatment group 1 (18.2, 14.6 to 20.8); treatment group 2 (16.1, 13.1 to 18.8)

Participants	• Setting: single centre
	• Country: India
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome and FSGS
	• Baseline characteristics
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (27 ± 7); treatment group 2 (27 ± 4)
	  ○ Mean GFR ± SD (mL/min): treatment group 1 (85 ± 10.8); treatment group 2 (80 ± 13.4)
	  ○ Baseline declining kidney function: a small number had declining kidney function
	  ○ Use of ACEi or ARB during follow-up: yes, no confounding effect. All patients with GFR of > 60 mL/min were started on escalating doses of ACEi and/or ARB before entry and during the study
	  ○ Previous immunosuppressive status: patients who had received steroids or immunosuppressive drugs previously were excluded
	• Number (whole study/IMN): treatment group 1 (28/11); treatment group 2 (26/10)
	• Mean age ± SD of whole study (years): treatment group 1 (30.2 ± 12.6); treatment group 2 (33.1 ± 12.4)
	• Sex of whole study (M/F): treatment group 1 (21/7); treatment group (18/8)
	• Exclusion criteria: systemic illness; malignancy; DM; hepatitis virus positivity, renal vein thrombosis; pregnant women; received steroids or immunosuppressive drugs

Interventions	Treatment group 1 • MMF: 2 g/day in 2 divided doses for 6 months. MMF dose was decreased by 25% to 33% for persistent gastrointestinal symptoms, discontinued temporarily if the WCC decreased to < 4000 µL, platelets be-

Senthil Nayagam 2008 *(Continued)*

low 100,000 µL or if the patient developed severe infections or unacceptable gastrointestinal symptoms. It was permanently discontinued if there was any evidence of the development of malignancy

- Prednisolone: 0.5 mg/kg/day for 8 to 12 weeks. The cumulative dose was 1.8 ± 0.3 g

Treatment group 2

- Methylprednisolone (IV): 1 g/day for 3 consecutive days followed by oral prednisolone 0.5 mg/kg/day for 27 days; 3 cycles for 6 months. The cumulative prednisolone dose was 2 ± 0.4 g
- CPA (oral): 2 mg/kg/day for 30 days

Outcomes	• Death • ESKD • Final GFR • Partial or complete remission • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: supported by a grant from M/s Panacea Biotec Ltd, New Delhi, India • Results for IMN and FSGS reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation was based on minimization, using the following parameters: (MN or FSGS), sex and GFR. Minimization is a valid alternative to randomisation, and ensures uniformity between the two groups with respect to the characteristics used in the allocation process
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/11 patients in MMF group was lost to follow-up after 1.5 months and was included in the non-responder category
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Low risk	The study appeared to be free of other sources of bias

Shibasaki 2004

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: April 1996 to June 2001

Shibasaki 2004 *(Continued)*

	• Duration of follow-up: 2 years

Participants	• Setting: multicentre
	• Country: Japan
	• Inclusion criteria: biopsy-proven IMN with steroid-resistant nephrotic syndrome. Steroid resistance was defined as the absence of a satisfactory response to corticosteroid therapy for 3 months
	• Baseline characteristics
	○ SCr (mg/dL): < 2.0
	○ GFR (mL/min): ≥ 40
	○ Baseline declining kidney function: not reported
	○ Use of ACEi or ARB during follow-up: yes, no confounding effect. Concomitant use of ACEi, antiplatelet agents, and anticoagulants was allowed, and the same method of administration of these drugs was followed during the study period as is usual for these drugs.
	○ Previous immunosuppressive status: receiving a daily maintenance dose of 20 mg prednisolone-equivalent a day (including zero dosage) before entry was allowed. Other immunosuppressant medication should be stopped at the start of the study
	• Number: treatment group (14); control group (11)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: CrCl < 40mL/min or SCr ≥ 2.0mg/dL; WCC ≤ 3000/mm^3; pregnant or nursing women, or women keenly desirous of becoming pregnant during the study period; presence of serious infections or other complications; on immunosuppressant medication at the start of the study; frequently recurrent nephrotic syndrome; secondary nephrotic syndrome; ≤ 14 years

Interventions	Treatment group
	• Mizoribine: 50 mg, 3 times/day after meals
	• No particular restriction was placed on the use of corticosteroids during the study period
	Control group
	• Conservative therapy
	• No particular restriction was placed on the use of corticosteroids during the study period

Outcomes	• Partial or complete remission

Notes	• Funding source: not reported
	• Duration of follow-up: 2 years
	• Other: The data were abstracted from an RCT aiming to investigate the effect of mizoribine on steroid-resistant nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation was not stratified according to the pathologic diagnosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Shibasaki 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement, likely no blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Approximate 32% (8/25) of patients were lost in the two-year follow-up: 21% (3/14) in the mizoribine group and 45% (5/11) in the control group. The proportion of loses in the follow-up could have a substantial influence on the results. The reason for missing data were not specified and the missing data were not imputed using appropriate methods
Selective reporting (reporting bias)	High risk	Only complete or partial remission were reported. The primary outcome such as death and ESKD were not stated; side effects leading to patient withdrawal were not recorded
Other bias	High risk	The data were abstracted from a RCT aiming to investigate the effect of mizoribine on steroid-resistant nephrotic syndrome. This study included all different pathologic variants of nephrotic syndrome. The randomisation was not stratified according to the pathologic diagnosis

Silverberg 1976

Study characteristics	
Methods	• Study design: parallel RCT • Study duration: before 1976 • Duration of follow-up: 12 months

Participants	• Setting: multicentre (4 sites)
	• Country: Canada
	• Inclusion criteria: patients with biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	  ○ Pathology stage (I/II/III): treatment group (0/4/1); control group (1/3/0)
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group (12.2 ± 4.9); control group (9.1 ± 5.9)
	  ○ Hypertension: treatment group (2/5); control group (1/4)
	  ○ Mean serum albumin ± SD (g/L): treatment group (24 ± 5); control group (25 ± 3)
	  ○ SCr (mg/dL): treatment group (1.1 ± 0.4); control group (1.5 ± 0.5)
	  ○ Mean GFR ± SD (mL/min/1.73 m²): treatment group (95 ± 37); control group (74 ± 22)
	  ○ Baseline declining kidney function: CrCl > 50 mL/min/1.73 m² in all included patients
	  ○ Use of ACEi or ARB during follow-up: not reported
	  ○ Previous immunosuppressive status: patients were required to have received no AZA, CPA, or nitrogen mustard for at least 1 year before entry into the study, and no steroids for at least 4 months
	• Number: treatment group (5); control group (4)
	• Mean age ± SD (years): treatment group (41 ± 15); control group (45 ± 18)
	• Sex (M/F): treatment group (3/2); control group (3/1)
	• Exclusion criteria: not reported

Interventions	Treatment group • AZA: 2.5 mg/kg/day (in 50 mg tablets) once/day for 1 year Control group • Placebo: similar number of placebo tablets as AZA

Silverberg 1976 *(Continued)*

Outcomes	• Death • ESKD • 50% or 100% SCr increase • Final SCr • Final GFR • Partial or complete remission • Final proteinuria • Side effects leading to patient withdrawal or hospitalisation
Notes	• Funding source: supported by the Medical Research Council of Canada, grant MA 4718, and by Burroughs-Wellcome Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Low risk	Closed-envelope technique
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Only the pharmacist knew which tablets were AZA and which were placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study and there were no losses to follow-up
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Insufficient information to permit judgement

Stegeman 1994

Study characteristics

Methods	• Study design: parallel, open-label RCT • Study duration: January 1994 to January 1996 • Duration of follow-up: 60 months

Participants	• Setting: multicentre
	• Country: Europe (8 countries)
	• Inclusion criteria: biopsy-proven IMN with nephrotic syndrome
	• Baseline characteristics
	  ○ Pathology stages: 1-IV
	  ○ Proteinuria: ≥ 3 g/day

Stegeman 1994 *(Continued)*

- ○ CrCl: > 60 mL/min/1.73 m²
- ○ Baseline declining kidney function: not reported
- ○ Use of ACEi or ARB during follow-up: no
- ○ Previous immunosuppressive status: no previous antiproteinuric treatments with cytotoxic drugs and/or steroids
- Number: treatment group 1 (50); treatment group 2 (50); control group (50)
- Age range: 18 to 65 years
- Sex (M/F): not reported
- Exclusion criteria: secondary cause of membranous nephropathy; CrCl < 60 mL/min/1.73 m², clinical suspicion of renal vein thrombosis; contraindication for steroids; need for NSAIDs or dipyridamole; ACEI contraindicated; persistent oedema; pregnant or nursing women or those of childbearing age not following a medically-accepted method of contraception; MI in last 6 months or unstable angina pectoris; haemodynamically significant valvular heart disease, serum potassium > 5.5 mmol/L on more than 1 occasion during pre-inclusion phase

Interventions	Treatment group 1
	- ACEi: 10 mg/day for the study period
	Treatment group 2
	- Prednisolone: 6 months treatment, dose adjusted for body weight at the start of the study and tapered from 8 weeks
	Control group
	- No specific treatment: continuation of salt restriction and diuretics as needed
Outcomes	- Partial or complete remission - Relapse after complete or partial remission
Notes	- Funding source: not reported - This study was terminated due to poor accrual rate - Data presented here is from the published study protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified centrally according to the clinical characteristics during the pre-treatment phase
Allocation concealment (selection bias)	Low risk	Central trial coordinator will randomly allocate eligible patients after stratification
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated due to poor accrual rate

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Stegeman 1994 *(Continued)*

Selective reporting (reporting bias)	High risk	Study terminated due to poor accrual rate
Other bias	High risk	Study terminated due to poor accrual rate

Sun 2014

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: recruited May 2011 to May 2012 • Duration of follow-up: > 6 months

Participants	• Setting: single centre
	• Country: China
	• Inclusion criteria: biopsy-proven IMN (stages II–IV); TAC < 4 ng/mL after taking TAC and corticosteroids for 3 days
	• Baseline characteristics
	  ○ Pathological classification (I/II/III/IV): 0/8/13/9
	  ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (11.32 ± 3.68); treatment group 2 (11.74 ± 2.98)
	  ○ Mean serum albumin ± SD (g/L): treatment group 1 (18.48 ± 3.52); treatment group 2 (18.62 ± 4.01)
	  ○ Mean SCr ± SD (µmol/L): treatment group 1 (86.90 ± 19.80); treatment group 2 (88.25 ± 22.57)
	  ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: treatment group 1 (12.5 ± 5.0); treatment group 2 (11.0 ± 4.5)
	  ○ Co-morbidities: not reported
	• Number: treatment group 1 (30); treatment group 2 (30)
	• Mean age ± SD (years): treatment group 1 (40.15 ± 10.05); treatment group 2 (39.37 ± 11.73)
	• Sex (M/F): treatment group 1 (17/13); treatment group 2 (19/11)
	• Exclusion criteria: no history of the use of corticosteroids or immunosuppressants; taking antibiotics, antifungal agents, potassium-sparing diuretics, rilonacept, or calcium blockers (i.e., agents that could affect the blood concentration of TAC during the study)

Interventions	Treatment group 1 • TAC: 0.5 mg/kg/day • Wuzhi capsules: initial dose of 1 capsule, 3 times/day. This dose was maintained or increased (one capsule at a time) 3 times/day according to the blood concentration of TAC until it reached a trough value of 4 to 8 ng/mL, with a maximum dose of three WZCs 3 times/day for each patient. If 3 WZCs 3 times/day were not sufficient to reach that trough value, the TAC dose was increased gradually until the blood concentration was 4 to 8 ng/mL. Three months after the trough value had been reached, the TAC dose was reduced and readjusted until the end of the experimental period • Prednisone: initial dose of 30 mg/day. After 8 weeks, the prednisone dose was reduced by 5 mg every 4 weeks until the dose was 10 mg/day and was maintained at that level • Duration of treatment: > 6 months Treatment group 2 • TAC: 0.5 mg/kg/day. TAC dose was increased routinely according to the blood concentration of TAC until it reached a trough value of 4 to 8 ng/mL. The TAC dose was maintained at that level for 3 months. Then, it was reduced and adjusted routinely according to the practice guidelines for glomerulonephritis set by the Kidney Disease Improving Global Outcomes until the entire period of therapy was completed

Sun 2014 *(Continued)*

- Prednisone: initial dose of 30 mg/day. After 8 weeks, the prednisone dose was reduced by 5 mg every 4 weeks until the dose was 10 mg/day and was maintained at that level
- Duration of treatment: > 6 months

Outcomes	• Complete or partial remission
	○ Complete remission: 24-hour proteinuria < 0.3 g, and serum albumin and SCr were normal
	○ Partial remission: stable kidney function as serum albumin > 30 g/L, a decrease in 24-hour proteinuria > 50%, but complete remission was not achieved
	○ Therapy was considered to be ''ineffective'' if the decrease in 24-hour proteinuria was < 50%
	• Albumin
	• Alanine transferase
	• Aspartate aminotransferase
	• Triglycerides
	• Low-density lipoprotein cholesterol
	• Proteinuria
	• Blood sugar
	• SCr
	• Side effects
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported, says only patients were divided randomly equally into the groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients reported as included are in the primary outcome analysis
Selective reporting (reporting bias)	Unclear risk	Secondary outcomes not clearly defined. No pre-published trial protocol available
Other bias	Low risk	No evidence of other sources of bias. No evidence of conflicts of interest

Tiller 1981

Study characteristics

Methods	• Study design: parallel, open-label RCT

Tiller 1981 *(Continued)*

- Study duration: May 1974 to November 1980
- Duration of follow-up: 36 months

Participants	- Setting: multicentre
	- Country: Australia
	- Inclusion criteria: biopsy-proven IMN
	- Baseline characteristics
	    ○ Pathology stage: not reported
	    ○ SCr: patients with SCr < 350 µmol/L
	    ○ GFR: patients with GFR ≥ 0.33 mL/sec/1.73 m² (20 mL/min/1.73 m²)
	    ○ Baseline declining kidney function: no
	    ○ Use of ACEi or ARB during follow-up: not reported
	    ○ Previous immunosuppressive status: previous treatment did not preclude patients from the study, provided that they had been on no "specific" treatment for a period of 6 months before entering the study
	- Number: treatment group (27); control group (27)
	- Mean age ± SD (years): not reported
	- Sex (M/F): not reported
	- Exclusion criteria: not reported

Interventions	Treatment group - CPA: 1.5 mg/kg/day for 6 mouths - Dipyridamole and sodium warfarin therapy were prescribed - Symptomatic treatment Control group - Symptomatic treatment
Outcomes	- Death - ESKD - Side effects leading to patient withdrawal or hospitalisation
Notes	- Funding source: supported by a grant from the National Health and Medical Research Council of Australia - The full text was published at a conference

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Tiller 1981 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	29/54 patients (54%) completed the 36-month follow-up: 14/27 (52%) in the treatment group and 15/27 (56%) in the control group. The missing numbers of patients were balanced and the missing reason was specified in each patient. The rate of loss to follow-up was high (54%), intention-to-treat principle was used to deal with these data to avoid potential bias
Selective reporting (reporting bias)	Low risk	The primary outcomes and key adverse effects were detailed in the publication, although other outcomes were not available to be included in this meta-analysis
Other bias	Unclear risk	Insufficient information to permit judgement

Xu 2010

Study characteristics

Methods	• Study design: parallel RCT • Study duration: November 2006 to January 2008 • Duration of follow-up: 2 years
Participants	• Setting: not reported • Country: China • Inclusion criteria: biopsy-proven IMN with severe nephrotic syndrome (urinary protein excretion > 5 g/24 hours or albumin < 25 g/L) or kidney dysfunction • Baseline characteristics: not reported • Number: treatment group 1 (11); treatment group 2 (12) • Mean age ± SD (years): treatment group 1 (55.0 ± 13.5); treatment group 2 (54.6 ± 13.5) • Sex (M/F): treatment group 1 (6/5); treatment group 2 (9/4) • Exclusion criteria: not reported
Interventions	Treatment group 1 • TAC • Steroids Treatment group 2 • CPA • Steroids
Outcomes	• Final proteinuria • Complete or partial remission • Adverse events • Serum albumin
Notes	• Funding source: not reported • Abstract-only publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement

Xu 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No sufficient detail about concealment of the random allocation sequence before or during enrolment of participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was claimed that double-blind was performed, however no further details were provided because it was only published in the conference abstract
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 of 24 randomised patients completed the study. Only 2 patients in FK506 group dropped out at 2 years
Selective reporting (reporting bias)	Unclear risk	No pre-published protocol was available. Outcomes are randomly described at different time points and not all measured time points are reported. Reason for drop-out of patients in intervention-group not reported.
Other bias	Unclear risk	Only abstract was available. Financial disclosure was not provided.

Xu 2013a

Study characteristics	
Methods	• Study design: parallel, open-label RCT
	• Study duration/recruitment period: June 2007 to October 2012
	• Duration of follow-up: > 18 months
Participants	• Setting: single centre
	• Country: China
	• Inclusion criteria: biopsy-proven IMN with severe nephrotic syndrome or kidney dysfunction with moderate proteinuria or severe oedema (severe nephrotic syndrome; 24-hour urinary protein excretion ≥ 5 g or albumin ≤ 25 g/L on admission; eGFR 15 to 60 mL/min; aged 18 to 80 years; no immunosuppressive agent in previous 6 months
	• Baseline characteristics
	○ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (132 ± 20 / 80 ± 11); treatment group 2 (132 ± 21 / 81 ± 11)
	○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (5.10 ± 2.20); treatment group 2 (5.39 ± 2.51)
	○ Mean serum albumin ± SD (g/L): treatment group 1 (19.3 ± 3.7); treatment group 2 (18.4 ± 5.1)
	○ Mean eGFR ± SD (mL/min/1.73 m²): treatment group 1 (90.0 ± 35.8); treatment group 2 (94.4 ± 24.6)
	○ Mean triglyceride ± SD (mmol/L): treatment group 1 (2.66 ± 1.43); treatment group 2 (2.78 ± 1.37)
	○ Mean SCr ± SD (µmol/L): treatment group 1 (87.7 ± 46.8); treatment group 2 (77.5 ± 22.7)
	○ Mean serum cholesterol ± SD (mmol/L): treatment group 1 (7.77 ± 1.75); treatment group 2 (8.05 ± 2.51)
	○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	○ Pathological classification (I/II/III/IV): treatment group 1 (5/35/11/1); treatment group 2 (9/31/7/1)
	○ Co-morbidities: not reported
	• Number: treatment group 1 (52); treatment group 2 (48)
	• Mean age ± SD (years): treatment group 1 (57.8 ± 14.8); treatment group 2 (56.3 ± 13.2)
	• Sex (M:F): treatment group 1 (1.36:1); treatment group 2 (1.82:1)

Xu 2013a *(Continued)*

- Exclusion criteria: systemic disease such as lupus rheumatoid arthritis, Sjogren's syndrome, hyperthyroidism or other autoimmune disease; malignancy; infection (hepatitis B or C, tuberculosis, syphilis); drugs or toxicants (e.g. gold mercury penicillamine); history of diabetes; CKD stage 4; alanine aminotransferase and or aspartate aminotransferase levels twice normal range; pregnancy or inadequate contraception; life-threatening complications of nephrotic syndrome (e.g. severe infection or heart failure)

Interventions	Treatment group 1 • CPA: 0.5 to 0.75 g/m²/month, maximum dose 1.0 g/month for 9 months. Pulsed IV CTX once a month for 6 months then once every 2 to 3 months • Prednisone: 1 mg/kg/day (max 70 mg/day) if < 65 years, 0.5 mg/kg/day if > 65 years Treatment group 2 • TAC: 0.1 mg/kg/day initially, then adjusted according to measured serum concentration • Prednisone: 0.5mg/kg/day, slowly tapered Duration of treatments and follow up details • 9 months treatment and at least 18 months follow-up period Co-medications • Some patients were treated with ACEi and/or ARB

Outcomes	• Remission: complete and partial (remission rates of the two groups were compared at 1, 2, 3, 6, 12, and 18 months)
	  ○ Complete remission: proteinuria < 0.5 g/day with normal kidney function
	  ○ Partial remission: proteinuria 0.5 to 3.5g/day declined to ≤ 50% of baseline value with stable kidney function
	  ○ Relapse: after complete or partial remission and 24-hour urine protein > 3.5 g in 2 measurements or serum albumin < 25 g/L
	  ○ No response; neither complete nor partial remission
	• Estimated kidney survival: defined as a 50% increase in the baseline SCr concentration
	• SCr
	• eGFR
	• 24-hour urine protein
	• serum albumin
	• Serum triglycerides
	• Serum cholesterol
	• Uric acid

Notes	• Funding source: This work was supported by grants from the National Basic Research Program of China 973, grant No. 2012CB517600 (grant No. 2012CB517604), the Research on Hypertensive Nephropathy and Ischemic Kidney Diseases National Key Technology R&D Program (12-5), grant No. 2011BAI10B00 (Grant No. 2011BAI10B06), and the National Natural Science Foundation of China (Grant No. 30871001)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, no other details reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Xu 2013a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Uncertain if total number included
Selective reporting (reporting bias)	Low risk	No evidence for missing data; outcomes comprehensively reported
Other bias	Low risk	No evidence of other sources of bias; no evidence for Conflict of Interest

Yuan 2013

Study characteristics	
Methods	• Study design: parallel, open-label RCT • Study duration: enrolled March 2004 to August 2009 • Duration of follow-up: 18 months

Participants	• Setting: single centre
	• Country: China
	• Inclusion criteria: 16 to 69 years; biopsy-proven IMN, class I-III; primary nephrotic syndrome; no other immunosuppressive or NSAIDs prior to study
	• Baseline characteristics
	   ○ Mean SBP/DBP ± SD (mm Hg): treatment group 1 (113 ± 17 / 64 ± 11); treatment group 2 (119 ± 18 / 67 ± 15)
	   ○ Mean proteinuria ± SD (g/24 hours): treatment group 1 (9.07 ± 2.73); treatment group 2 (8.15 ± 2.62)
	   ○ Mean serum albumin ± SD (g/L): treatment group 1 (16.1 ± 5.8); treatment group 2 (17.0 ± 6.6)
	   ○ Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (95.2 ± 17.8); treatment group 2 (94.4 ± 16.4)
	   ○ Mean triglyceride ± SD (mmol/L): treatment group 1 (2.96 ± 1.18); treatment group 2 (3.19 ± 1.50)
	   ○ Mean SCr ± SD (µmol/L): treatment group 1 (72.6 ± 15.8); treatment group 2 (76.7 ± 14.9)
	   ○ Mean serum cholesterol ± SD (mmol/L): treatment group 1 (6.76 ± 1.41); treatment group 2 (7.13 ± 0.79)
	   ○ Disease-course (time since diagnosis) at immunosuppressive treatment initiation: not reported
	   ○ Pathological classification: not reported
	   ○ Co-morbidities: not reported
	• Number (randomised/analysed): treatment group 1 (20/18); treatment group 2 (22/18)
	• Mean age ± SD (years): treatment group 1 (55.4 ± 13.7); treatment group 2 (47.2 ± 15.8)
	• Sex (M/F): treatment group1 (13/7); treatment group 2 (16/6)
	• Exclusion criteria: pregnancy; serious complications such as severe infection, malignancy, HIV infection or active HBV infection; SCr > 221 µmol/L; secondary causes of nephrotic syndrome including diabetic nephropathy, systemic disease such as lupus nephritis or drug-associated nephropathy; known allergy to CNI

Interventions	Treatment group 1 • TAC + prednisone for 6 months

Yuan 2013 *(Continued)*

Treatment group 2

- TAC + prednisone for 24 months

TAC dose

- 0.05 to 0.08 mg/kg/day orally in 2 divided doses in fasting patients

Prednisone dose

- 30 mg/day, single dose in the morning for 8 weeks, after that tapered by 5 mg every 4 weeks until a dose of 10 mg/day was reached and maintained throughout the study

Co-medications

- Use of NSARs, ACEi, ARBs were prohibited during the study period. Patients with ACEi or ARBs 4 weeks prior to the study were allowed to keep drug

Outcomes	- Complete and partial remission
	  ○ Complete remission: proteinuria < 0.4 g/day
	  ○ Partial remission: urine protein excretion 0.4 to 2.9 g/day and decline in proteinuria > 50% to basal level with serum albumin ≥ 30 g/L
	  ○ No response: proteinuria > 3 g/day or serum albumin < 30 g/dL
	- Relapse: patients who had attained complete or partial remission expressing severe nephrotic syndrome and not recovering within 2 weeks

Notes	- Funding source: This work was supported by grants from the Jilin Provincial Science and Technology Department - Trial registration or Protocol registration or publication: Chinese Clinical Trial Registry ChiC-TR-TRC-09000539

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pre-printed randomisation table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No suggestion of missing data. However, not certain of total number analysed
Selective reporting (reporting bias)	Low risk	Comprehensive reporting of all outcomes. no evidence of selective reporting
Other bias	Unclear risk	Poorly reported methods. Conflict of interest of authors not declared. Sources of funding declared and no suggestion for bias

Zhang 2015d

Study characteristics

Methods	- Study design: parallel RCT - Study duration: not reported - Duration of follow-up: 24 months
Participants	- Setting: not reported - Country: China - Inclusion criteria: IMN with nephrotic syndrome - Baseline characteristics: not reported - Number: treatment group 1 (41); treatment group 2 (40) - Mean age ± SD (years): not reported - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group 1 - TAC + corticosteroids: no further information provided Group 2 - CPA+ corticosteroids: no further information provided
Outcomes	- Urinary protein excretion - Albumin - Remission - Relapse - Abnormal glucose metabolism
Notes	- Abstract-only publication - No patient numbers for results reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Selective reporting (reporting bias)	High risk	Very limited reporting. no pre-published protocol available. primary/secondary outcomes not clearly defined. selective outcome reporting. outcomes not reported in absolute numbers
Other bias	Unclear risk	Insufficient information to permit judgement

ACTH - adrenocorticotropic hormone; AZA - azathioprine, BP - blood pressure; BP - blood pressure; BUN - blood urea nitrogen; ACEi - angiotensin converting enzyme inhibitors; ARB - angiotensin receptor blockers; Cr - creatinine; CrCl - creatinine clearance; CPA - cyclophosphamide; CSA - cyclosporine; DBP - diastolic blood pressure; DM - diabetes mellitus; ESKD - end-stage kidney disease; (e)GFR - (estimated) glomerular filtration rate; HIV - human immunodeficiency virus; IM - intramuscular; IMN - idiopathic membranous nephropathy; IQR - interquartile range; ITT - intention-to-treat; IU - international units; IV - intravenous; KRT - kidney replacement therapy; MDRD - modified Diet in Renal Disease; MGN - membranous glomerular nephritis; MMF - mycophenolate mofetil; NIAT - non-immunosuppressive antiproteinuric treatment; NSAID - nonsteroidal anti-inflammatory drugs; PLA2R - anti-phospholipase A2 receptor; RAS - renin angiotensin system; RCT - randomised controlled trial; RTX - rituximab; SBP - systolic blood pressure; SC - subcutaneous; SCr - serum creatinine; SLE - systemic lupus erythematosus; TAC - tacrolimus; TCM - traditional Chinese medicine; UACR - urinary albumin:creatinine ratio; UPCR - urinary protein:creatinine ratio; WCC - white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambalavanan 1996	Mixed population / wrong intervention duration: cross-over design compared the efficacy of CSA versus ACEi in the treatment of adult PMN and secondary MN. We could not determine the number of patients with IMN in each intervention group. The first period of the cross-over was only 3 months (< 6 months)
Badri 2013	Wrong population: not PMN
Black 1970	Mixed population: RCT compared prednisone and supportive treatment in patients with nephrotic syndrome; we could not determine the number of patients diagnosed with PMN and nephrotic syndrome in each intervention group
Branten 1998	Wrong study design: study details a combination of RCT and observational data after the RCT were stopped
ChiCTR-IPR-14005366	Wrong population: atypical MN
ChiCTR-TRC-09000539	Unknown review status: RCT over 10 years old and no published data
Edefonti 1988	Wrong population: 35/66 patients received renal biopsy and all patients were diagnosed with MCN and FSGS; no PMN were included
EudraCT2011-000242-38	Study terminated: ended prematurely without results being reported
Heimann 1987	Wrong population: not PMN
Krasnova 1998	Mixed population: MN (12), MSGN (16), MSGN (3) We could not determine the number of patients with PMN and nephrotic syndrome in each intervention group
Lagrue 1975	Mixed population: we could not determine the number of patients diagnosed with PMN and nephrotic syndrome in each intervention group
Li 2012e	Wrong population: secondary MN
Liu 2016c	Wrong population: refractory nephrotic syndrome, not PMN

Study	Reason for exclusion
Majima 1990	Mixed population: we could not determine whether all included patients had the diagnosis of nephrotic syndrome. The age of included patients was not available for us to make sure they were all adults
Michail 2004	Wrong study design: unclear whether randomisation was used
MRCWP 1971	Mixed population: we could not determine the number of patients with PMN and nephrotic syndrome in each intervention group
Nand 1997	Mixed population: we could not determine the number of patients with PMN and nephrotic syndrome in each intervention group
NCT01762852	Study terminated: study was withdrawn due to poor recruitment
Plavljanic 1998	Wrong population: patients with MN; it was uncertain that MN were primary or secondary; the clinical diagnosis of nephrotic syndrome was unclear
Ponticelli 1993a	Wrong population: all patients were diagnosed with MCN and FSGS. No PMN were included
Sharma 2009	Wrong study design: not RCT; patients divided into 2 groups - control group included only those cases of GN who dropped out of the study or refused their inclusion
Sharpstone 1969	Wrong population: proliferative glomerulonephritis
Sun 2008	Study design/conduct: RCT compared 24-month TAC plus steroids with 6-month TAC plus steroids in 20 adults diagnosed as PMN and nephrotic syndrome. The recruiting of patients was from March 2004 to August 2007; the publication of this study was submitted to that journal on February 2008. Thus, we concluded that some of randomised patients did not complete the 24-month treatment of TAC plus steroids
Xu 2011	Wrong population: Hepatitis B virus MN (secondary MN)
Yang 2016a	Wrong population: Hepatitis B virus MN (secondary MN)

ACEi - angiotensin-converting enzyme inhibitors; AZA - azathioprine; CPA - cyclophosphamide; CKD - chronic kidney disease; CSA - cyclosporine; FSGS - focal segmental glomerulosclerosis; I/PMN - idiopathic/primary membranous nephropathy; MCGN - mesangiocapillary glomerulonephropathy; MCN - minimal change nephropathy; MN - membranous nephropathy; MSGN - mesangial proliferative glomerulonephropathy; RCT - randomised controlled trial; TAC - tacrolimus

Characteristics of studies awaiting classification [ordered by study ID]

NCT00302523

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 18 months
Participants	• Setting: not reported • Country: China • Inclusion criteria: biopsy-proven IMN; nephrotic syndrome with proteinuria (> 4 g/day) and serum albumin < 30 g/dL; informed consent • Number (planned/actual enrolment): 40/16 • Age: 18 to 60 years • Sex (M/F): both

NCT00302523 *(Continued)*

- Exclusion criteria: abnormal liver function tests; prior therapy with sirolimus, CSA, MMF, or AZA, cytoxan, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 90 days; active/serious infection, hepatitis B surface antigen or hepatitis C antibody positive; DM; allergic or intolerant to macrolide antibiotics or TAC

Interventions	Treatment group 1 - TAC Treatment group 2 - IV CPA pulse
Outcomes	- Proteinuria - Kidney function - Adverse effects
Notes	- Funding source: not reported - Primary completion date: December 2008 (final data collection date for primary outcome measure) - Last verified: February 2010; study completed however no published data has been identified

NCT00518219

Methods	- Study design: parallel, open-label RCT - Study duration: 12 months - Duration of follow-up: 12 months
Participants	- Setting: single centre - Country: China - Inclusion criteria: biopsy-proven PMN nephrotic syndrome with proteinuria (> 4 g/day) and serum albumin < 30 g/dL - Number: 68 - Age: > 18 years (with informed consent) - Sex: both - Exclusion criteria: abnormal liver function tests; prior therapy with sirolimus, CSA, MMF, TAC or AZA, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 90 days; active/serious infection; hepatitis B surface antigen or hepatitis C antibody positive
Interventions	Group 1 - Tripterygium wilfordii: 120 mg/day Group 2 - Valsartan: 160 mg/day
Outcomes	- Efficacy of treating heavy proteinuria
Notes	- Primary completion date: March 2009 (Final data collection date for primary outcome measure) - Unable to find trial data (July 2018) - Emailed investigator 11 Jul 2018, liuzhihong@nju.edu.cn

NCT01093157

Methods	• Study design: parallel, open-label RCT • Study duration: 3 months • Duration of follow-up: 3 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: biopsy-proven IMN with adequately controlled BP (< 130/75 mm Hg in > 75% of readings), proteinuria (UPCR > 4.0 mg/g on a spot sample aliquot from a 24-hour urine collection), and eGFR ≥ 40 mL/min/1.73 m² while taking ACEi/ARB therapy • Number: 68 • Age: 18 to 65 years • Sex (M/F): both • Exclusion criteria: abnormal liver function tests; prior therapy with sirolimus, CSA, MMF, TAC or AZA, chlorambucil, levamisole, methotrexate, or nitrogen mustard in the last 90 days; active/serious infection; hepatitis B surface antigen or hepatitis C antibody positive
Interventions	Group 1 • ACTH (HP Acthar gel): 40 units Group 2 • ACTH (HP Acthar gel): 80 units Both therapies will be administered subcutaneously and given in a dose escalating frequency beginning at once every 2 weeks escalating to a maximum of twice/week over a total of 3 months exposed
Outcomes	• Change in proteinuria (3 months) • Complete or partial remission at 3 months • Adverse effects
Notes	• Recruitment status: completed (4 May 2017 last updated); no results posted on clinicaltrials.gov • Duration of study: 3 months • No contact details on trial registry site, no publication when searched in Google Scholar

NCT01386554

Methods	• Study design: parallel RCT • Study duration: August 2011 to May 2017 • Duration of follow-up: 24 weeks
Participants	• Setting: multicentre • Country: USA • Inclusion criteria: history of nephrotic syndrome due to PMN as confirmed by documented results from a kidney biopsy performed within 4 years prior to screening • Number: 60 • Age: > 18 years • Sex (M/F): both • Exclusion criteria: history of previous use of Acthar for treatment of nephrotic syndrome; prior sensitivity to Acthar or other porcine protein products or planned treatment with live or live attenuated vaccines once enrolled in the study; contraindication to Acthar per prescribing Information (scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of peptic ulcer, congestive heart failure, uncontrolled hyper-

NCT01386554 *(Continued)*

tension, primary adrenocortical insufficiency, or adrenocortical hyperfunction; known diabetic nephropathy or nephrotic syndrome due to a disease or process other than idiopathic membranous nephropathy; requiring diagnostic or interventional procedure requiring a contrast agent must delay screening/randomisation for at least 7 days; history of SLE; type 1 or Type 2 DM; history of deep vein thrombosis ≤ 6 months prior to screening visit; history of or active congestive heart failure (NYHA Class II to IV); history of known dilated cardiomyopathy with left ventricular ejection fraction ≤ 40%; occurrence of unstable angina, MI or coronary artery bypass graft or percutaneous transluminal coronary angioplasty; Transient ischaemic attack or cerebrovascular disease or unstable arrhythmia in last 3 months

Interventions	Group 1 • Acthar (Repository Corticotropin injection): 80 U (1.0 mL) twice/week Group 2 • Acthar (Repository Corticotropin injection): 40 U (1.0 mL) twice/week Group 3 • Placebo
Outcomes	• Complete or partial remission in proteinuria • Proportion of subjects that have sustained complete or partial remission
Notes	• Estimated primary completion date: March 2013 • Recruitment status; completed • No contact details on trial registry site, no publication when searched in Google Scholar

NCT01845688

Methods	• Study design: parallel RCT • Study duration; started November 2011 • Duration of follow-up: 24 weeks
Participants	• Setting: single centre • Country: China • Inclusion criteria: clinically biopsy-proven PMN; 6.0 g ≥ 24-hour urinary protein ≥ 1.0g; serum albumin ≥ 26g/L; eGFR > 30 mL/min/1.73 m² ; willing to participate in the trial and signed an informed consent • Number: 72 • Age: 18 to 70 years • Sex (M/F): both • Exclusion criteria secondary MN; malignant tumours or malignancy, HIV infection, a history of mental illness, any serious systemic infection, serious gastrointestinal diseases, circulating hepatitis B surface antigens positive or persistent abnormal serum transaminase, abnormal glucose metabolism or DM; pregnant and lactating women; undergoing other clinical trials
Interventions	Group 1 • Losartan tablets + qingReMoShen granule Group 2 • Losartan tablet + placebo granule
Outcomes	• 24-hour urine protein

NCT01845688 *(Continued)*

- Serum albumin
- eGFR
- Alanine transaminase
- T-cell classification

Notes	• Study Director: Lin Wang, Shanghai University of Traditional Chinese medicine
	• Data from registry site only
	• Status; active, not recruiting
	• No contact details on registry site; no publication was found through Google scholar 11 July 2018

ACEi - angiotensin converting enzyme inhibitors; ACTH - adrenocorticotropic hormone; ARB - angiotensin receptor blockers; AZA - azathioprine; BP - blood pressure; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporine; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; I/PMN - idiopathic/primary membranous nephropathy; MMF - mycophenolate mofetil; NYHA - New York Heart Association; MN - membranous nephropathy; RCT - randomised controlled trial; SCr - serum creatinine; SLE - systemic lupus erythematosus; TAC - tacrolimus; UPCR - urinary protein:creatinine ratio

Characteristics of ongoing studies *[ordered by study ID]*

Chen 2020

Study name	Comparison of the efficacy and safety of tacrolimus monotherapy and cyclophosphamide combined with glucocorticoid in the treatment of adult primary membranous nephropathy: protocol of a multicenter, randomised, controlled, open study
Methods	• Study design: parallel, open-label RCT
	• Study duration: commenced 1 December 2018
	• Duration of follow-up: 24 months
Participants	• Setting: multicentre
	• Country: China
	• Inclusion criteria: written and informed consent will be obtained; 18 to 65 years; urinary protein excretion persistently > 3.5 g/day, serum albumin < 30 g/L after 6 months of antiproteinuric therapy with ACEi/ARB; biopsy-proven IMN; SCr < 133 µmol/L; no immunosuppressive treatment in previous 6 months
	• Number (planned): 90
	• Age range: 18 to 65 years
	• Sex (M/F): both
	• Exclusion criteria: secondary MN (e.g., hepatitis B, SLE, medications, malignancies); positive HBV serological indexes (HBsAg or/and HBeAg or HBcAb), positive HCV or patients with abnormal liver function (ALT, AST, or bilirubin show an increase > 2 times the upper limit of normal range for more than 2 weeks); DM; history of peptic ulcer and/or gastrointestinal bleeding within the preceding 6 months; congenital or acquired immunodeficiency, or with infections such as active tuberculosis and active CMV, or with severe infections requiring IV antibiotic therapy; serious physical or mental illness; congenital heart disease, arrhythmia, heart failure and other serious cardiovascular diseases; pregnancy or inadequate contraception; participated in other clinical trials within three months prior to enrolment
Interventions	Treatment group 1
	• TAC (oral): starting dose of 0.05 to 0.1 mg/kg/day divided into two equal doses given at 12-hour intervals. The dose is adjusted according to the target trough blood concentration of 5 to 7 ng/mL. TAC dosage should be reduced by 30% when a 30% increase in SCr is noted compared with the baseline value, and TAC is withdrawn if the kidney function is not improved after 2 weeks. This treatment period is for at least 12 weeks.
	Treatment group 2

Chen 2020 *(Continued)*

	• CPA (IV): 750 mg/m²/2 weeks for 8 weeks and then every 4 weeks for the next 16 weeks (8 pulses in total)
	• Prednisone (oral): 1 mg/kg/day for 4 weeks, tapering to 5 mg every 2 weeks to 30 mg/day and then being reduced by 5 mg every 4 weeks until complete withdrawal at the end of 12 months
Outcomes	• Complete or partial remission • Relapse • Withdrawal due to adverse drug reactions • Types of adverse drug reactions • Proportion whose treatment is ineffective or discontinue • Number converted to other immunosuppressants • Kidney function • Proteinuria • Time to remission • Serum albumin • SCr increases of > 40% • Death or ESKD • Serum anti-PLA2R
Starting date	• Registered 12 June 2017 • Recruitment start date: 1 December 2018
Contact information	Daqing Hong: Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Medical School of University of Electronic Science and Technology of China, Chengdu, 610072, China
Notes	• Funding source: not reported • Expected recruited completion date: 31 June 2021

ChiCTR-INR-15007440

Study name	Multitarget therapy for treatment of refractory idiopathic membranous nephropathy
Methods	• Study design: parallel RCT • Study duration: 1 October 2012 to 30 October 2015 • Sample size: not reported
Participants	• Setting: single centre • Country: China • Inclusion criteria: clinical pathology diagnosis of IMN; 18 to 65 years; 24-hour urinary protein quantity of at least 3.5 g with eGFR > 60 mL/min/1.73 m²; treatment with corticosteroids plus immunosuppressive agents MMF, CA CNI for 23 months without remission • Exclusion criteria: clinical pathology diagnosis of secondary membranous nephropathy; IV antibiotics should be used for severe infections within the 2 weeks before randomisation; treatment with immunosuppressive agents, such as CSA, and Tripterygium glycosides, were more than one week within 1 month before enrolment; treatment with TAC (except for topical use), MMF or CPA within 1 month before enrolment; treatment with IV methylprednisolone pulse therapy within 1 month before enrolment; history of allergy to MMF, TAC, CPA or methylprednisolone; eGFR < 60 mL/min/1.73 m², or SCr > 260 µmol/L (or 3 mg/dL); hepatic dysfunction; HBV or HCV Infection; active tuberculosis; severe immunodeficiency disease; a history of gastrointestinal bleeding within 3 months before enrolment; congenital heart diseases, arrhythmia, heart failure and other serious cardiovascular disease; resistant hypertension; pregnant, nursing or unwilling to take contraceptive measures; recurrence of tumour patients within 5 years; participated in other clinical trials

within 3 months before enrolment; condition of patient not suitable for this experiment by the research physician judgment

Interventions	Group 1
	• Prednisolone (oral): 1 mg/kg
	• MMF (oral): 0.5 every 12 hours
	• FK506 (oral): 2 mg every 12 hours
	Group 2
	• Prednisolone (oral): 1 mg/kg
	• FK506 (oral): 2mg every 12 hours
	Group 3
	• Prednisolone (oral): 1 mg/kg
	• CPA: 50 mg twice/day
Outcomes	• 24-hour urine protein
	• Albumin
	• SCr
Starting date	• 1 October 2012
Contact information	• Dongwei Liu; liu-dongwei@126.com
	• Zhangsuo Liu; zhangsuoliu@sina.com
Notes	• Funding: Scientific research fund and pharmaceutical company fund
	• Emailed study author 23 May 2018

ChiCTR-INR-17011400

Study name	The effect of the treatment of idiopathic membranous nephropathy was observed in the treatment of idiopathic membranous nephropathy, and the effect of the treatment on Th17 / Treg
Methods	• Study design; parallel, open-label RCT
	• Study duration: from May 2017
	• Duration of follow-up: not reported
Participants	• Setting: single centre
	• Country: China
	• Number: group 1 (40); group 2 (40)
	• Sex (M/F): both
	• Inclusion criteria: 18 to 70 years; 24-hour urine protein is ≥ 3.5 g; SCr < 442 µmol/L; renal biopsy pathology of Sanjia hospital proved to be membranous nephropathy; a combination of the hormone combined immunosuppressant therapy for 3 months was invalid
	• Exclusion criteria: secondary membranous nephropathy; acute and chronic infectious diseases; malignant tumour; severe diabetes, hypertension, and liver dysfunction; pregnancy; mental illness
Interventions	Group 1
	• Glucocorticoid + tacmox + Chinese medicine
	Group 2

ChiCTR-INR-17011400 *(Continued)*

	• Glucocorticoid + tacosa treatment
Outcomes	• 24 hours of urine protein quantification
Starting date	• Registration site date last refreshed 14 May 2017
Contact information	• liuyongzhidaifu@163.com
Notes	• Not yet recruiting

ChiCTR-INR-17012070

Study name	Yongquan acupoint Shenque moxibustion curative effect of traditional Chinese medicine in the treatment of membranous nephropathy
Methods	• Study design; parallel, open-label RCT • Study duration: from July 2017 • Sample size: 150 planned
Participants	• Setting: single centre • Country: China • Inclusion criteria: 18 to 75 years; the pathological examination of renal biopsy confirmed membranous nephropathy stage I and II, and the exclusion of secondary membranous nephropathy; 24-hour urinary protein quantitative 1 to 4 g, GFR > 30 mL/min can enter the screening phase • Exclusion criteria: rapidly progressive membranous nephropathy; membranous nephropathy with IgA nephropathy; merge life-threatening complications, such as severe infections; HBV serological markers were positive except for HbsAb and those with persistent hepatic dysfunction were detected with abnormal aminotransferase; malignant tumours or with a history of malignancy, HIV infection history, psychiatric history, acute central nervous system diseases, severe gastrointestinal; diseases, immunosuppressive agents; combined with other organs, serious diseases and dysfunction; severe hypoproteinaemia, plasma albumin less than 25 g
Interventions	Group 1 • Yongquan Shenque paste of Chinese medicine with mild moxibustion Group 2 • Valsartan Tablets
Outcomes	• Urine protein
Starting date	Registration site updated; 20 July 2017
Contact information	Shi Wei 593224713@qq.com
Notes	States not yet recruiting (20/7/2017)

ChiCTR-INR-17012212

Study name	Use of sirolimus in patients with primary idiopathic membranous nephropathy: a prospective randomised control trial
Methods	• Study design: RCT

ChiCTR-INR-17012212 *(Continued)*

- Study duration: planned 28 July 2017 to 31 May 2019
- Sample size: 70 planned

Participants	- Setting: single centre - Country: China - Inclusion criteria: 18 to 70 years; diagnosed as primary membranous nephropathy by renal biopsy and exclusion of secondary causes; corticosteroids and immunosuppressive agents not in the recent 3 months; BP < 140/90 mm Hg; proteinuria ≥ 3.5 g/day and eGFR ≥ 45mL/min/1.73 m²; with at least 3-month treatment of maximum tolerance dosage of ACEi/ARB; SCr ≤ 133 µmol/L; agree to sign informed consent - Exclusion criteria: any type of secondary membranous nephropathy by renal biopsy; any other type of kidney disease; uncontrolled infection; Interstitial pneumonia; new onset of cardiovascular disease in recent 3 months; severe liver disease, liver enzyme elevation is not higher than 3 times; uncontrolled severe hypertension; A new or recurring malignancy within 8.5 years; peptic ulcer or active digestive tract bleeding; severe autoimmune disease; pregnancy, lactation or scheduled pregnancy; expected survival was less than December; other clinical studies are currently in progress; do not agree to sign informed consent; the researchers found other conditions unsuitable for the study
Interventions	Group 1 - CSA Group 2 - CSA + sirolimus
Outcomes	Proteinuria
Starting date	28 July 2017
Contact information	Fang Wang, wangfang@bjmu.edu.cn
Notes	Sponsor: Huabei Pharmaceutical Company Status: recruiting (refreshed 1 Aug 2017)

ChiCTR-IPR-16008344

Study name	A study for comparing alternating glucocorticoid and cyclophosphamide versus glucocorticoid plus tacrolimus in idiopathic membranous nephropathy
Methods	- Study design: parallel RCT - Study duration: 19 April 2016 to 19 April 2017 - Sample size: 60 planned
Participants	- Setting: single centre - Country: China - Inclusion criteria: clinical pathology diagnosis of membranous nephropathy and all patients were screened for secondary membranous nephropathy; 24-hour urine protein > 6 g, or 3.5 to 6 g, but nephrotic syndrome is obvious; normal SCr; voluntary and signed informed consent. - Number - planned sample size: treatment group (30); control group (30) - Exclusion criteria: secondary membranous nephropathy; patients with serious complications, malignancy, pregnant, severe liver damage and other drug contraindications; patients who rejected this regimen or could not follow up were excluded; treatment with glucocorticoid or other immunosuppressive agents within 1 month before enrolment; known allergy to the CNI

ChiCTR-IPR-16008344 *(Continued)*

Interventions	Group 1 • CPA Group 2 • TAC
Outcomes	• 24-hour urine protein • Albumin • SCr • Adverse event rate
Starting date	
Contact information	
Notes	• Funding source: self-financed • Emailed author for publication 23 May 2018 www.chictr.org.cn/showproj.aspx?proj=14061 • Date of registration 22 April 2016

ChiCTR-IPR-16008527

Study name	Rituximab in the treatment of refractory membranous nephropathy: a multicenter, randomised, controlled clinical study
Methods	• Study design: parallel RCT • Study duration: July 2016 to December 2020 (inclusive) • Sample size: 120 planned
Participants	• Setting: single centre • Country: China • Inclusion criteria: 18 to 70 years, male or female; membranous nephropathy proved by renal pathology; eliminate secondary membranous nephropathy (HBV, HCV, malignant tumour, SLE, autoimmune disease or drug-associated MN); EPI-GFR ≥ 30 mL/min; sign informed consent; recurrent or no remission after at least 6 months of glucocorticoid plus immunosuppressant therapy; 24-hour proteinuria ≥4g/day and serum albumin < 30 g/L • Number: treatment group (60); control group (60) • Exclusion criteria: already used RTX; allergic to investigational drug; recent operation plan; severe acute or chronic infection (sepsis, respiratory/urinary/digestive infection), or patients receiving antibiotic treatment; severe cardiac lesion, NYHA III-IV; WBC < 4 x 10^9/L, Hb < 10 g/dL, PLT < 100 x 10^9/L; pregnancy or lactation; uncontrolled diabetes; severe hepatic lesion (GPT or GOT > 2 times of normal range); or HBV-DNA positive; newly diagnosed malignant tumour or patients receiving radiotherapy/chemotherapy; severe oedema; condition unstable to receive the treatment; refuse to participate
Interventions	Treatment group • RTX (IV) Control group • CSA (oral) • glucocorticosteroid
Outcomes	• Complete remission

ChiCTR-IPR-16008527 *(Continued)*

- Partial remission
- Relapse
- eGFR
- Death
- Thrombosis/embolism complication

Starting date	
Contact information	
Notes	• Contacts: Study leader CHEN Nan, cnrj100@126.com, Registration applicant; GAO Chenni gaochenni77@126.com. Emailed 23 May 2018 • Date of study registration; 24 May 2016

ChiCTR-IPR-17011386

Study name	Study on the effect and mechanism of interleukin-2 in the treatment of idiopathic membranous nephropathy
Methods	• Study design: parallel RCT • Study duration: 1 June 2017 to 1 June 2018 • Sample size: 100 planned
Participants	• Setting: single centre • Country; China • Inclusion criteria: 18 to 70 years, male or female; membranous nephropathy proved by renal pathology and clinical 2 times the usual dose of ACEI/ARB treatment for 3 months or more, 24-hour proteinuria ≥ 4 g/day and serum albumin < 30 g/L; nearly 1 month without the use of hormones and immunosuppressive therapy; BP < 140/90 mm Hg; EPI-GFR ≥ 30 mL/min • Exclusion criteria: secondary membranous nephropathy: secondary to hepatitis B or hepatitis C virus, systemic lupus erythematosus, malignant tumours, heavy metal poisoning caused by membranous nephropathy; diabetic patients; active ulcer or gastrointestinal bleeding; combined with other types of kidney disease; uncontrolled infection; uncontrolled high BP; combined with autoimmune diseases; active malignancy; pregnancy or breastfeeding; combined with chronic liver disease, or liver enzyme > 2 times the normal upper limit
Interventions	Group 1 • CSA • Glucocorticosteroid • Interleukin 2 Group 2 • CSA • glucocorticosteroid
Outcomes	• 24-hour urinary protein quantity • Regulatory T cells • eGFR • Anti-PLA2R
Starting date	1 June 2017

ChiCTR-IPR-17011386 *(Continued)*

Contact information	Yinghui Jiang, 176305893@qq.com
Notes	http://www.chictr.org.cn/showprojen.aspx?proj=19215

ChiCTR-IPR-17011702

Study name	Compare of the treatment of membranous nephropathy with mizoribine and steroid or cyclophosphamide and steroid
Methods	• Study design: parallel RCT • Study duration: 1 July 2017 to 3 June 2019 • Sample size: 100 planned
Participants	• Setting: single centre • Country: China • Inclusion criteria: pathological diagnosis of membranous nephropathy; 24-hour urinary protein excretion > 3.5 g; normal kidney function; ≥ 55 years; no previous use of immunosuppressants (except mizoribine and CPA); informed consent • Exclusion criteria: secondary nephritic syndrome; leukocyte reduction; pregnancy; serious haematuria; serious heart or liver disease; poor compliance
Interventions	Group 1 • Mizoribine • Steroid Group 2 • CPA • Steroid
Outcomes	• Total remission rate: complete + partial remission rate • Complete remission rate • Partial remission rate • Changes of leukocyte, haemoglobin, liver function, blood electrolyte, blood glucose, serum albumin, SCr, eGFR, cholesterol, triglyceride, uric acid, urine routine examination • Adverse events • Incidence of abnormal clinical examination
Starting date	1 July 2017
Contact information	Wang Xichao ctxichao@outlook.com and Tu Yangke tuyangke@aliyun.com
Notes	States pending recruitment

ChiCTR-TRC-11001144

Study name	A prospective randomised study on the efficacy of steroid combined with CTX or tacrolimus in IMN patients with NS
Methods	• Study design: parallel RCT • Study duration: 19 April 2016 to 19 April 2017

ChiCTR-TRC-11001144 *(Continued)*

	• sample size: 60 planned
Participants	• Setting: single centre • Country: China • Inclusion criteria: PMN patients proven by biopsy within 24 weeks and exclusion of secondary causes; 24-hour urinary protein excretion at admission ≥ 5 g or serum albumin < 25 g/L; renal insufficiency defined as CKD 2-3 stage with moderate proteinuria or severe nephrotic syndrome with pleural effusion, ascites, renal venous thrombosis; nephrotic syndrome patients without severe oedema, follow-up 3 months, 24-hour urinary protein excretion > 5 g or serum albumin < 25 g/L; written informed consent • Exclusion criteria: secondary membranous nephropathy; serious complications, malignancy, pregnant, severe liver damage and other drug contraindications; rejected this regimen or could not follow up were excluded; treatment with glucocorticoid or other immunosuppressive agents within 1 month before enrolment; known allergy to the CNI
Interventions	Group 1 • CPA • Prednisone Group 2 • TAC • Prednisone
Outcomes	• 24-hour urinary protein excretion • SCr • Serum albumin
Starting date	2008/01/01
Contact information	Chen Nan, Zhang Wen, Tel: +86 021 64370045, Fax: +86 021 64456419, chen-nan@medmail.com.cn, zhangwen255@163.com, nephrology department, Shanghai Jiaotong university affiliated Ruijin hospital, No.197, Ruijin NO.2 Road, Luwan District, Shanghai, 200025, China
Notes	Recruiting in December 2011

CTRI/2017/05/008648

Study name	Randomised controlled trial of aPLA2R-targeted therapy versus standard treatment in PLA2R related membranous nephropathy
Methods	• Study design: parallel RCT • Study duration: 1 June 2017 to December 2020 • Sample size: 60 planned
Participants	• Setting: single centre • Country: India • Inclusion criteria: 18 to 75 years; biopsy-proven PMN, have a urinary protein excretion of > 3.5 g/day or a UPCR > 3500 mg/g, and have serum albumin of ≤ 3.0 g/L, despite maximally tolerated dose of NIAT for 6 months or those with complications of nephrotic syndrome; vascular thrombosis; respiratory tract infections requiring hospitalisation or severe anasarca despite a maximal tolerable dose of diuretics

- Exclusion criteria: secondary MN; eGFR < 45 mL/min 1.73 m²; pregnancy, breastfeeding; immuno-suppressive treatment in the 3 preceding months; hepatitis B surface antigen /anti-HCV positive; other active infectious disease

Interventions	Group 1
	- Cyclical CPA
	- Steroid therapy
	- Anti-PLA2R Targeted therapy
	Group 2
	- Cyclical CPA
	- Steroids
Outcomes	- Remission of nephrotic syndrome (both complete and partial)
	- Adverse events
	- Anti-PLA2R levels
	- Decline in eGFR
Starting date	1 June 2017
Contact information	Raja Ramachandran drraja_1980@yahoo.co.in
Notes	

EudraCT2007-005410-39

Study name	Estudio piloto aleatorizado comparativo de tacrolimus vs ciclofosfamida-prednisona en la nefropatía membranosa idiopática - MEMTAC
Methods	- Study design: parallel RCT
	- Study duration: not reported
	- Duration of follow-up: 18 months
	- Sample size: 40 planned
Participants	- Country: Spain
	- Setting: not reported
	- Inclusion criteria: PMN; both sexes; ≥ 18 years; diagnosed by renal biopsy, of IMN proteinuria in the nephrotic range (> 3.5 g/24 hours) with hypoalbuminaemia (serum albumin ≤ 25 to 30 g/dL) sustained for at least 6 months; kidney function with SCr <1.3 mg/dL and CrCl > 60 mL/min according to the Cockroft-Gault formula; taking ACEi and/or ARA II for at least 6 months before the start of the study; written informed consent
	- Exclusion criteria: pregnant or breast-feeding or of childbearing age who do not use medically suitable methods of contraception (barrier methods) and who do not have a negative pregnancy test; diabetic; secondary glomerulonephritis (drugs, systemic diseases, tumours); received previous treatments with immunosuppressants in the previous 6 months; neoplasia or history of cancer; serious systemic infection; histologically proven liver cirrhosis or significant elevation of liver enzymes; HIV or for the surface antigen of hepatitis B or for the antibodies of the Hepatitis C virus; addiction or abuse of drugs, medications or alcohol; psychiatric alterations or condition that could invalidate the communication between the researcher and the patient; life expectancy diminished for any reason, so that they cannot complete the study
Interventions	Group1
	- TAC

EudraCT2007-005410-39 *(Continued)*

Group 2

- CPA
- Steroid

Outcomes	• Complete and partial remission • Complete remission: proteinuria < 0.3 g/day, with GFR > 60 mL/min/1.73 m² and albuminaemia ≤ 30 g/L • Partial remission: reduction > 50% of basal proteinuria, the last being < 3.5 g/day; with GFR > 60 mL/min/1.73 m² and albuminaemia ≤ 30 g/L • Kidney function: SCr and CrCl at 6, 12 and 18 months • Nephrotic time: time to complete remission/partial remission • Recurrence: in the subpopulation of patients who have reached a remission of the disease, it will be determined until the end of the study in each patient whether or not they have a nephrotic proteinuria
Starting date	11/06/2008
Contact information	Spain
Notes	None

HIGHNESS 2011

Study name	High-dose gamma-globulin therapy for nephrotic membranous nephropathy patients
Methods	• Study design: parallel, open-label RCT • Study duration: not reported • Sample size: not reported
Participants	• Setting: not reported • Country: Japan • Inclusion criteria: MN with nephrotic syndrome • Age: 30 to 90 years • Sex (M/F): both • Exclusion criteria: Secondary MN; DM; recent cardiovascular accidents within 6 months; malignancy; liver diseases; treated with immunosuppressive therapy
Interventions	Group 1 • Immunoglobulin Group 2 • ARB or ACEi with or without statin
Outcomes	• Remission rate • Alteration of proteinuria or kidney function • Complication of infectious diseases or cardiovascular diseases
Starting date	2012/02/01
Contact information	Hitoshi Yokoyama, Kanazawa Medical University Hospital Nephrology, 1-1 Daigaku, Uchinada, Ishikawa, Japan, Telephone: 076-286-2211(3401), Email: h-yoko@kanazawa-med.ac.jp

HIGHNESS 2011 *(Continued)*

Notes	• Not yet recruiting in May 2012 • Recruitment status: terminated

ISRCTN17977921

Study name	A randomised controlled study of tacrolimus for the treatment of idiopathic membranous nephropathy
Methods	• Study design: parallel RCT • Study duration: June 2016 to June 2017 • Sample size: target 120
Participants	• Setting: multicentre • Country: China • Inclusion criteria: IMN confirmed by renal biopsy (light microscopy + SEM); clinical manifestations of nephrotic syndrome: persistent SCr < 115 mmol/L or the reference value of SCr; any age group, male or female • Exclusion criteria: secondary MN with hepatitis or malignant tumour; use of steroids, cytotoxic drugs, or immunosuppressants within 3 months of this study; other severe organ diseases; fasting blood glucose > 6.2 mmol/L or confirmed diabetes; pregnant or nursing women
Interventions	Group 1 • Prednisone: 0.5 mg/kg/day (maximum dose: 30 mg/day); the dose will be tapered 2 weeks after the patient has achieved clinical remission, at a rate of 5 mg/day every 2 weeks; once the dose has been reduced to 10 mg/day, the dose will be tapered at a rate of 2.5 mg/day every two weeks until withdrawal; for patients who fail to achieve clinical remission within 4 weeks, the dose will be tapered as described above Group 2 • TAC: 0.05 mg/kg/day (2 doses/day, morning and night) 1 hour before or 2 hours after meals. The TAC dose will be adjusted based on its plasma concentration, and the goal is to maintain the plasma concentration in the range of 5 to 10 ng/mL. To reduce the TAC dose, for both groups, TAC will be reduced by 30% at 2 months after complete or partial clinical remission. The plasma concentration of TAC will be maintained at 3 to 6 ng/mL
Outcomes	• Change in 24-hour urine protein from baseline and per cent change • Change in serum albumin from baseline and per cent change • Changes in SCr and eGFR from baseline and per cent changes • Change in serum PLA2R antibodies from baseline • Measured at baseline, 2, 4, 8, 12, 24 weeks
Starting date	
Contact information	
Notes	Funding source: The First Affiliated Hospital of Zhengzhou University (China) Data from trial registration site only (June 2018). Contact; Zhanzheng Zhao 13938525666@139.com. Emailed 11 July 2018

ISRCTN70791258

Study name	Treatment with adrenocorticotropic hormone in idiopathic membranous nephropathy
Methods	• Study design: parallel, open-label RCT • Study duration: 6 July 1999 to 31 January 2005 • Sample size: target 30
Participants	• Setting: not reported • Country: Sweden • Inclusion criteria: males and females, aged 18 to 90 years; membranous nephropathy according to kidney biopsy; proteinuria of the nephrotic range for at least 6 months; treatment with a statin and an ACEi for at least 3 months; urinary albumin excretion > 3000 mg/24 hours; serum albumin concentration < 26 g/L • Exclusion criteria: moderate or heavy tubulointerstitial changes in the kidney biopsy; recognisable cause of the nephrotic syndrome; previous immunosuppressive treatment for the membranous nephropathy; allergy to Synacthen Depot; severe psychiatric disease; pregnancy; history of noncompliance

Interventions	Group 1
	
	• Depot preparation of a synthetic fragment of ACTH versus no specific treatment. The dosage scheme of Synacthen Depot given subcutaneously was as follows:
	  ○ Month one: 1.0 mg once/week
	  ○ Month two: 0.75 mg twice/week
	  ○ Months three to six: 1.0 mg twice/week
	  ○ Month seven: 0.75 mg twice/week
	  ○ Month eight: 1.0 mg once/week
	  ○ Month nine: 0.5 mg once/week
	
	Control group
	
	• Supportive therapy

Outcomes	• Complete remission, at 9 and 21 months • Complete and partial remission at the end of the treatment period (9 months after study start) and at the end of the follow-up period (21 months after study start) • Serum albumin • SCr • Apolipoprotein A1 • Apolipoprotein B • Lipoprotein(a) • Urinary excretion/24 hours of albumin • Immunoglobulin G • Protein HC • GFR • Mean arterial pressure
Starting date	
Contact information	
Notes	Funding source: Department of Nephrology, University Hospital in Lund (Sweden) Information from trial registration site only (June 2018), emailed Ann-lena.berg@njur.lu.se and sponsor kerstin.wihlborg@med.lu.se on 13 Jun 2018

MMF-STOP-IMN 2017

Study name	Mycophenolate mofetil plus steroid in the treatment of patients with progressive idiopathic membranous nephropathy (MMF-STOP-IMN)
Methods	• Study design: parallel RCT • Study duration: start date 1 June 2018, planned completion 31 December 2020 • Sample size: 128 planned
Participants	• Setting: not reported • Country: China • Inclusion criteria: provided informed consent; diagnosed as membranous nephropathy by renal biopsy and other secondary factors are excluded; ≥ 18 years, male or female; 24-hour urine protein or spot UPCR > 8.0 g/day at least twice confirmed; satisfy more than three of following items are included even if proteinuria is < 8 g/day • Exclusion criteria: severe infective disease; allergy history to clinical trial medication and acute or chronic allergy for 4 weeks recently; clinical history of treatment with other immunosuppressive medication; probability of pregnancy, breastfeeding woman; uncontrolled hypertension (> 160/100 mm Hg); eGFR < 30 mL/min/1.73 m^2; abnormal liver function test (more than 3 times above compared with normal value); absolute neutrophil count < 1500/mm^3 or leukocyte < 2,500/mm^3 or platelets < 100,000/mm^3; secondary membranous nephropathy; expected life expectancy < 1 year; the researchers evaluated that the patient's compliance was not appropriate for the trial; previous or present history of cancer and have the risk of recurrence or metastasis
Interventions	Group 1 • Steroid: 1 mg/kg/day • MMF: 500 mg twice/day Group 2 • Steroid: 0.15 mg/kg/day • CSA: 3 to 5 mg/kg/day

Outcomes	• Complete remission
	  ◦ Urinary protein excretion < 0.3 g/day (UPCR < 300 mg/g or < 30 mg/mmol) confirmed by two values at least 1 week apart
	  ◦ Normal serum albumin
	  ◦ Normal SCr

Starting date	1 June 2018
Contact information	Contact: Xinling Liang, MD, PhD 86-13808819770 xinlingliang_ggh@163.com
Notes	Details obtained from trial registration site 11 July 2018

NCT02173106

Study name	A controlled study of steroids plus cyclosporin therapy for patients of idiopathic membranous nephropathy
Methods	• Study design: parallel RCT • Study duration: start June 2014, planned completion December 2016 • Sample size: 180 planned

NCT02173106 *(Continued)*

Participants	• Setting: single centre • Country: China • Inclusion criteria: 14 to 75 years, regardless of gender without secondary reason, primary membranous nephropathy by renal biopsy; average urinary protein excretion of ≥ 3.5 g/24 hours on 2 successive examinations or plasma albumin < 30 g/L; eGFR ≥ 40 mL/min/1.73 m²; willingness to sign an informed consent • Exclusion criteria: secondary membranous nephropathy such as SLE, hepatitis B-associated nephritis; current or recent (within 30 days) exposure to high-dose of steroids or immunosuppressive therapy (CPA, MMF, CSA, TCA); cirrhosis, chronic active liver disease; history of significant gastrointestinal disorders (e.g. severe chronic diarrhoea or active peptic ulcer disease); any active systemic infection or history of serious infection within one month; other major organ system disease (e.g. serious cardiovascular diseases including congestive heart failure, chronic obstructive pulmonary disease, asthma requiring oral steroid treatment or central nervous system diseases); active tuberculosis; known allergy, contraindication or intolerance to the steroids; pregnancy or breastfeeding at the time of entry or unwillingness to comply with measures for contraception; malignant tumours; excessive drinking or drug abuse; mental aberrations; current or recent (within 30 days) exposure to any other investigational drugs
Interventions	Group 1 • CSA • Prednisolone Group 2 • CSA alone
Outcomes	• Remission of proteinuria (complete or partial) • Deterioration of kidney function (50% rise from baseline SCr levels, or a 25% decline from baseline eGFR levels, or onset of ESKD or dialysis treatment, or kidney transplantation
Starting date	
Contact information	
Notes	Data from trial registry site only Status; Unknown, no update since Jul 2014 Investigator Yanhong Deng, at Sun Yat-sen University. Contact; jx.home@medmail.com.cn. Emailed 11 Jul 2018

RI-CYCLO 2020

Study name	Rituximab versus steroids and cyclophosphamide in the treatment of idiopathic membranous nephropathy (RI-CYCLO)
Methods	• Study design: parallel RCT • Study duration: start January 2012, planned completion December 2018 • Sample size: 70 planned • Duration of follow-up: 36 months
Participants	• Setting: unknown • Country: Italy • Inclusion criteria: biopsy-proven diagnosis of primary MN performed within the past 24 months; proteinuria > 3.5 g/24 hours on 3 24-hour urine collection (once a week for 3 weeks); eGFR ≥ 30 mL/

RI-CYCLO 2020 *(Continued)*

min/1.73 m² under ACEi/ARB therapy; post-menopausal females, or females surgically sterile or practising a medically approved method of contraception (no birth-control pill); 3 months of ACEi and/or ARB therapy before treatment; BP < 130/80 mm Hg; HMG-CoA reductase inhibitor therapy; proteinuria > 3.5 g/24 hours after 3 months of ACEi and/or ARB therapy and BP < 130/80 mm Hg may be randomised to RTX/cyclical corticosteroid/alkylating-agent therapy without the need of the run-in/conservative phase of the study

- Exclusion criteria: SCr >2.5 mg/dL; eGFR < 30 mL/min/1.73 m²; previous treatment with RTX, steroids, alkylating agents, CNI, synthetic ACTH, MMF, AZA; the presence of active infection; secondary cause of MN (e.g. hepatitis B, SLE, medications, malignancies); testing for HIV, hepatitis B and C should have occurred < 6 months prior to enrolment into the study; type 1 or 2 DM; pregnancy or nursing for safety reasons; renal vein thrombosis documented prior to entry by renal US or CT scan

Interventions	Group 1 - RTX Group 2 - CPA - Steroids
Outcomes	- Change in probability of complete remission (proteinuria < 0.3 g/day) - Change from baseline in proteinuria
Starting date	January 2012 Status: recruiting
Contact information	Contacts: pravani@ucalgary.ca and ceccoscolari@gmail.com
Notes	Details from trial registration site

STARMEN 2015

Study name	Sequential therapy with tacrolimus and rituximab in primary membranous nephropathy (STARMEN)
Methods	- Study design: parallel, open-label RCT - Study duration: January 2014 to December 2018, Completion date April 2019 - Sample size: planned 106 - Duration of follow-up: 24 months
Participants	- Setting: unknown - Country: Spain - Inclusion criteria: > 18 years that provide written informed consent; biopsy-proven primary MN within 2 years of enrolment; patients with nephrotic syndrome relapse after remission (either spontaneous or induced by immunosuppression) can be included without a new renal biopsy if they meet all the other inclusion/exclusion criteria; eGFR ≥ 45 mL/min/1.73 m² in at least 2 measurements performed within the 2 weeks prior to randomisation; nephrotic-range proteinuria (> 4 g/day and remaining > 50% of the baseline value) plus hypoalbuminaemia (< 3 g/dL) during at least a 3-month period before screening. These values must be met in at least two measurements performed within the 2 weeks prior to randomizations. Patients showing severe or disabling symptoms related to the nephrotic syndrome or severe hypoalbuminaemia (< 2 g/dL) can be included before the completion of this 6-month observation period, at the investigator's discretion; treatment with an ACEi or ARB for at least 2 months before screening unless intolerance to ACEi/ARB, contraindications to their use or a low BP that could induce side effects, at the in-

STARMEN 2015 *(Continued)*

vestigator's discretion, with a controlled BP for at least last 3 months (target < 140/90 mm Hg); negative urine pregnancy test for potentially fertile females

- Exclusion criteria: diagnosis of secondary causes of MN: diagnosis of type 1 or 2 DM, cancer, systemic infections, systemic autoimmune diseases (e.g. SLE), amyloidosis, or any other acute or chronic inflammatory disease; moderate or severe liver disease (aspartate amino-transferase and alanine amino-transferase > 2.5 times upper range limit and total bilirubin > 1.5 times upper range limit); patients who are taking part in any other investigational study and/or are receiving or have received treatment with another investigational drug or intervention (within 1 month prior to the study); suspected or known hypersensitivity, allergy and/or immunogenic reaction history of any interventional drug or any of their ingredients (including excipients); previous treatment with corticosteroids or any other immunosuppressive agent in the 6-month period before screening; previous treatment with RTX or any other biological agent in the 2-year period before screening; patients who were non-responders to previous immunosuppressant drugs; women showing a positive pregnancy test or during lactation period or plans to become pregnant; inability or unwillingness of individual or legal guardian/ representative to give written informed consent; any other medical unstable, uncontrolled or severe condition or any other relevant laboratory test finding which, at the investigator's own discretion, could increase the associated risk of the patient's participation in the study; current drug or alcohol use or dependence that would interfere with adherence to study requirements

Interventions	Group 1
	- TAC: initial dose of 0.05 mg/kg/day oral, adjusted to achieve blood trough levels of 5 to 7 ng/mL for 6 months. Starting at the end of month 6, TAC dosage will be reduced by 25%/month, resulting in a complete withdrawal at the end of month 9
	- RTX: single dose of 1 g IV will be given at day 180, before the onset of TAC dose reduction
	Group 2
	- Steroids: months 1, 3 and 5: 1 g IV methylprednisolone daily (days 1 to 3) then oral methylprednisolone (0.5 mg/kg/day) for 27 days (days 4 to 30)
	- CPA (oral): months 2, 4 and 6 2.0 mg/kg/day for 30 days

Outcomes	
	- Proportion of patients reaching either complete or partial remission at 24 months of study treatment
	- the number of patients with an increase of SCr ≥ 50% at the end of follow-up (renal survival)
	- The proportion of patients with relapsing nephrotic syndrome among patients who previously underwent partial remission or complete remission
	- The time to nephrotic syndrome relapse
	- The number of patients with limited response at 12, 18 and 24 months of study treatment
	- The percentage of patients with preserved renal function (eGFR ≥ 45 mL/min/1.73 m^2) at the end of follow-up
	- Serum anti-PLA2R levels before treatment and at 12 and 24 months post-therapy
	- The number of immune cells (CD4+ and CD8+ T cells, and CD19+ B cells) before treatment and at 12 and 24 months post-therapy
	- Proportion of patients with drug-related adverse events during the study

Starting date	January 2014

Contact information	MANUEL PRAGA, mpragat@senefro.org and Jorge Rojas jerori2003@yahoo.com

Notes	
	- Complete remission: reduction of proteinuria to ≤ 0.3 g/24 hours plus stable renal function (eGFR ≥ 45 mL/min/1.73 m^2)
	- Partial remission: reduction of proteinuria to 0.3 to 3.5 g/24 hours and 50% lower than baseline with stable renal function (eGFR ≥ 45 mL/min/1.73 m^2)
	- Limited response: proteinuria is reduced from baseline level > 50% but remains > 3.5 g/24 hours
	- Non-response: reduction of proteinuria < 50% from baseline level

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STARMEN 2015 *(Continued)*

- Kidney survival: at the end of the follow-up, SCr does not increase ≥ 50% of baseline SCr concentrations
- Relapse: reappearance of proteinuria > 3.5 g/24 hours and at least 50% higher than the lowest post-treatment value in at least 3 consecutive visits in those who previously presented a partial or complete remission.
- Kidney function: this will be evaluated by means of SCr values and eGFR, calculated by the MDRD-4
- Protocol paper: Rojas-Rivera 2015

UMIN000001099

Study name	Optimal use of cyclosporine in idiopathic membranous nephropathy associated with nephrotic syndrome
Methods	• Study design: parallel, open-label RCT • Study duration: • Sample size: 50
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: IMN associated with nephrotic syndrome • Age: > 16 years • Sex (M/F): both • Exclusion criteria: CSA therapy for nephrotic syndrome; doctor's decision
Interventions	Group 1 • Steroid • CSA Group 2 • Steroid
Outcomes	• Quantity of urinary protein, frequency of relapse, kidney function (SCr, eGFR), time to remission, total dose of steroid (until remission) • Adverse effects of steroid and CSA, total dose of steroid (in all treatment period), duration of hospitalisation, serum albumin, serum total protein, serum total cholesterol, degree of oedema
Starting date	July 2007
Contact information	Masaaki Izumi, Hyogo College of Medicine, Division of Kidney and Dialysis, Department of Internal Medicine, 1-1, Mukogawa, NIshinomiya, Hyogo, Japan, TEL +81-798-45-6521, Email izumi@hyo-med.ac.jp
Notes	Last follow-up date: 2010/07

ACEi - angiotensin converting enzyme inhibitors; ACTH - adrenocorticotropic hormone; ARB - angiotensin receptor blockers; CKD - chronic kidney disease; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporine; ECG - electrocardiogram, eGFR - estimated glomerular filtration rate; GFR - glomerular filtration rate; IMN/PMN - idiopathic/primary membranous nephropathy; MN - membranous nephropathy; RCT - randomised controlled trial; RTX- rituximab; SCr - serum creatinine; TCM - traditional Chinese medicine; UPCR - urinary protein/creatinine ratio

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	3	333	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.11, 3.23]
1.2 ESKD (dialysis/transplantation)	3	333	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.35, 1.98]
1.3 Complete or partial remission	3	295	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.58, 2.27]
1.4 Complete remission	2	192	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.28]
1.5 Partial remission	2	192	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.34, 5.21]
1.6 Increase in serum creatinine	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 100% increase in serum creatinine	3	120	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.11, 1.53]
1.6.2 50% increase in serum creatinine	1	103	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.34, 0.94]
1.7 Adverse events	2	175	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.11, 9.82]
1.8 Final serum creatinine	1	87	Mean Difference (IV, Random, 95% CI)	48.00 [-21.30, 117.30]
1.9 Final CrCl	1	86	Mean Difference (IV, Random, 95% CI)	8.00 [-9.88, 25.88]
1.10 Final proteinuria	1	86	Mean Difference (IV, Random, 95% CI)	0.00 [-1.99, 1.99]

Analysis 1.1. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 1: Death

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1979	0	34	2	38	24.4%	0.22 [0.01 , 4.48]	
Cattran 1989	3	81	1	77	36.9%	2.85 [0.30 , 26.83]	
Cameron 1990	1	52	4	51	38.7%	0.25 [0.03 , 2.12]	
Total (95% CI)		**167**		**166**	**100.0%**	**0.59 [0.11 , 3.23]**	
Total events:	4		7				

Heterogeneity: Tau² = 0.72; Chi² = 2.94, df = 2 (P = 0.23); I² = 32%

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

```
         0.01   0.1    1    10    100
      Less with steroids   Less with control
```

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Analysis 1.2. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1979	1	34	5	38	15.8%	0.22 [0.03 , 1.82]	
Cattran 1989	3	81	4	77	29.6%	0.71 [0.16 , 3.08]	
Cameron 1990	8	52	6	51	54.6%	1.31 [0.49 , 3.50]	
Total (95% CI)		**167**		**166**	**100.0%**	**0.83 [0.35 , 1.98]**	
Total events:	12		15				

Heterogeneity: Tau² = 0.11; Chi² = 2.40, df = 2 (P = 0.30); I² = 17%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with steroids   Less with control

Analysis 1.3. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 3: Complete or partial remission

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cameron 1990	10	52	7	51	26.9%	1.40 [0.58 , 3.40]	
Coggins 1979	12	34	7	38	29.0%	1.92 [0.85 , 4.30]	
Cattran 1989	30	65	35	55	44.1%	0.73 [0.52 , 1.01]	
Total (95% CI)		**151**		**144**	**100.0%**	**1.15 [0.58 , 2.27]**	
Total events:	52		49				

Heterogeneity: Tau² = 0.25; Chi² = 6.37, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with control   More with steroids

Analysis 1.4. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 4: Complete remission

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1979	4	34	4	38	15.5%	1.12 [0.30 , 4.13]	
Cattran 1989	16	65	19	55	84.5%	0.71 [0.41 , 1.25]	
Total (95% CI)		**99**		**93**	**100.0%**	**0.76 [0.46 , 1.28]**	
Total events:	20		23				

Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.31)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with control   More with steroids

Analysis 1.5. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 5: Partial remission

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Coggins 1979	8	34	3	38	42.4%	2.98 [0.86 , 10.34]	
Cattran 1989	14	65	16	55	57.6%	0.74 [0.40 , 1.38]	
Total (95% CI)		**99**		**93**	**100.0%**	**1.34 [0.34 , 5.21]**	
Total events:	22		19				

Heterogeneity: Tau² = 0.74; Chi² = 3.93, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable

0.05 0.2 1 5 20
More with control — More with steroids

Analysis 1.6. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 6: Increase in serum creatinine

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.6.1 100% increase in serum creatinine							
Murphy 1992	1	13	0	13	16.3%	3.00 [0.13 , 67.51]	
Donadio 1974	1	11	2	11	28.4%	0.50 [0.05 , 4.75]	
Coggins 1979	2	34	11	38	55.3%	0.20 [0.05 , 0.85]	
Subtotal (95% CI)		**58**		**62**	**100.0%**	**0.41 [0.11 , 1.53]**	
Total events:	4		13				

Heterogeneity: Tau² = 0.29; Chi² = 2.47, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.33 (P = 0.18)

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.6.2 50% increase in serum creatinine							
Cameron 1990	15	52	26	51	100.0%	0.57 [0.34 , 0.94]	
Subtotal (95% CI)		**52**		**51**	**100.0%**	**0.57 [0.34 , 0.94]**	
Total events:	15		26				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)

0.01 0.1 1 10 100
Less with steroids — Less with control

Analysis 1.7. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 7: Adverse events

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cameron 1990	1	52	0	51	49.8%	2.94 [0.12 , 70.61]	
Coggins 1979	0	34	1	38	50.2%	0.37 [0.02 , 8.82]	
Total (95% CI)		**86**		**89**	**100.0%**	**1.04 [0.11 , 9.82]**	
Total events:	1		1				

Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

0.005 0.1 1 10 200
Less with steroids — Less with control

Analysis 1.8. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 8: Final serum creatinine

Study or Subgroup	Steroids Mean [μmol/L]	SD [μmol/L]	Total	Control Mean [μmol/L]	SD [μmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [μmol/L]	Mean Difference IV, Random, 95% CI [μmol/L]
Cameron 1990	251	165.8312	44	203	163.936	43	100.0%	48.00 [-21.30 , 117.30]	
Total (95% CI)			**44**			**43**	**100.0%**	**48.00 [-21.30 , 117.30]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)
Test for subgroup differences: Not applicable

-200 -100 0 100 200
Lower with steroids   Lower with control
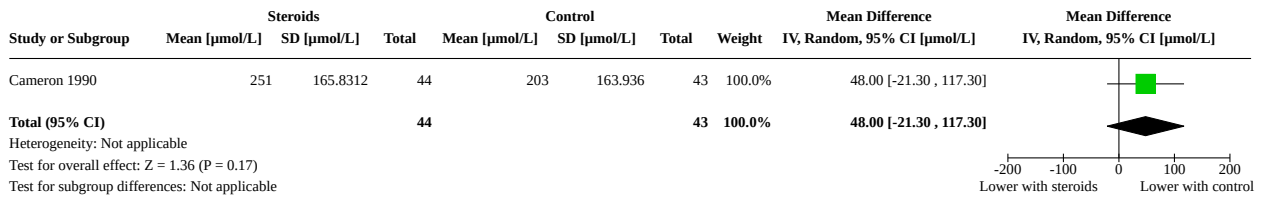
Analysis 1.9. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 9: Final CrCl

Study or Subgroup	Steroids Mean [mL/min]	SD [mL/min]	Total	Control Mean [mL/min]	SD [mL/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/min]	Mean Difference IV, Random, 95% CI [mL/min]
Cameron 1990	75	41.3119	43	67	43.2791	43	100.0%	8.00 [-9.88 , 25.88]	
Total (95% CI)			**43**			**43**	**100.0%**	**8.00 [-9.88 , 25.88]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
Higher with control   Higher with steroids

Analysis 1.10. Comparison 1: Corticosteroids versus placebo/no treatment, Outcome 10: Final proteinuria
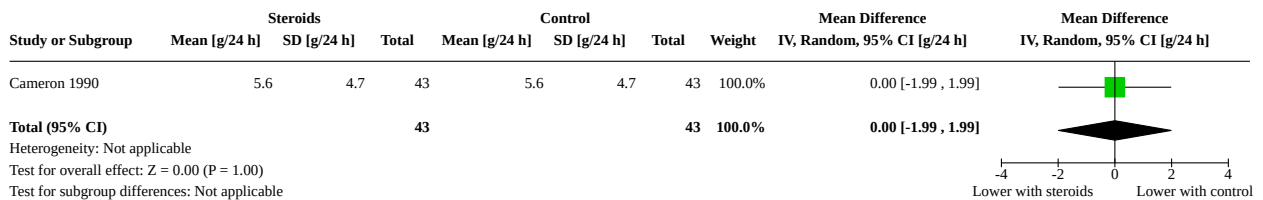
Study or Subgroup	Steroids Mean [g/24 h]	SD [g/24 h]	Total	Control Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Cameron 1990	5.6	4.7	43	5.6	4.7	43	100.0%	0.00 [-1.99 , 1.99]	
Total (95% CI)			**43**			**43**	**100.0%**	**0.00 [-1.99 , 1.99]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

-4 -2 0 2 4
Lower with steroids   Lower with control

Comparison 2. Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Death	16	944	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.34, 1.59]
2.1.1 Final follow-up < 10 years	15	840	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.36, 1.85]
2.1.2 Final follow-up ≥ 10 years	1	104	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.22]
2.2 ESKD (dialysis/transplantation)	16	944	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 0.99]
2.2.1 Final follow-up < 10 years	14	759	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.49, 1.44]
2.2.2 Final follow-up ≥ 10 years	2	185	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.63]
2.3 Complete or partial remission	16	879	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.05, 1.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.1 Final follow-up < 2 years	11	524	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.91, 2.14]
2.3.2 Final follow-up ≥ 2 years	5	355	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.90, 2.65]
2.4 Complete remission	16	879	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.05, 2.75]
2.4.1 Final follow-up < 2 years	12	605	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.84, 2.95]
2.4.2 Final follow-up ≥ 2 years	4	274	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.87, 4.54]
2.5 Partial remission	16	879	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.93, 1.98]
2.5.1 Final follow-up < 2 years	11	524	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.87, 2.53]
2.5.2 Final follow-up ≥ 2 years	5	355	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.65, 2.16]
2.6 Relapse after complete or partial remission	3	148	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.05, 2.86]
2.6.1 Final follow-up (≥ 2 years)	3	148	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.05, 2.86]
2.7 100% increase in serum creatinine	8	447	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.26, 0.80]
2.7.1 Steroids versus placebo/no treatment at 24 months	1	72	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.85]
2.7.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (≤ 2 years)	3	129	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.05, 2.94]
2.7.3 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (> 2 years)	2	146	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.20]
2.7.4 Calcineurin inhibitors + steroids versus placebo/no treatment (60 months)	1	55	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.21, 2.11]
2.7.5 MMF versus placebo/no treatment at final follow-up (12 months)	1	36	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.7.6 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.07, 9.18]
2.8 50% increase in serum creatinine	8	410	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.8.1 Steroids versus placebo/no treatment at 36 months	1	103	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.34, 0.94]
2.8.2 Alkylating agents versus placebo/no treatment at final follow-up (≤ 2 years)	2	48	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.20, 4.91]
2.8.3 Alkylating agents ± steroids versus placebo/no treatment at final follow-up (> 2 years)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.68]
2.8.4 Calcineurin inhibitors versus placebo/no treatment (30 months)	1	48	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.18]
2.8.5 MMF versus placebo/no treatment (12 months)	1	32	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.8.6 Azathioprine versus placebo/no treatment (12 months)	1	9	Risk Ratio (M-H, Random, 95% CI)	4.17 [0.25, 68.16]
2.8.7 Mizoribine versus placebo/no treatment (6 months)	1	89	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.23, 2.16]
2.9 Temporary or permanent discontinuation/hospitalisation due to adverse events	16	927	Risk Ratio (M-H, Random, 95% CI)	5.33 [2.19, 12.98]
2.9.1 Steroids versus placebo/no treatment	3	295	Risk Ratio (M-H, Random, 95% CI)	2.20 [0.37, 12.96]
2.9.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy	7	342	Risk Ratio (M-H, Random, 95% CI)	8.14 [2.22, 29.82]
2.9.3 Calcineurin inhibitors versus placebo/no treatment/supportive therapy	5	156	Risk Ratio (M-H, Random, 95% CI)	5.45 [0.29, 101.55]
2.9.4 MMF versus placebo/no treatment	1	36	Risk Ratio (M-H, Random, 95% CI)	8.10 [0.47, 140.24]
2.9.5 Azathioprine versus placebo/no treatment	1	9	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.9.6 Mizoribine versus placebo/no treatment	1	89	Risk Ratio (M-H, Random, 95% CI)	4.29 [0.21, 86.80]
2.10 Adverse events	2	181	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.85, 1.89]
2.10.1 Alkylating agents + steroids versus supportive therapy	1	106	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.83, 1.95]
2.10.2 Rituximab versus supportive therapy	1	75	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.41, 3.69]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11 Infection	1	106	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.69, 12.61]
2.12 Malignancy	2	182	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.12, 9.14]
2.13 Final serum creatinine	5	198	Mean Difference (IV, Random, 95% CI)	25.43 [10.09, 40.78]
2.13.1 Steroids versus placebo/no treatment at final follow-up (36 months)	1	87	Mean Difference (IV, Random, 95% CI)	48.00 [-42.71, 138.71]
2.13.2 Alkylating agents ± steroids versus placebo/no treatment at final follow-up (24 to 120 months)	2	81	Mean Difference (IV, Random, 95% CI)	26.41 [10.24, 42.58]
2.13.3 Calcineurin inhibitors versus placebo/no treatment at final follow-up (12 months)	1	21	Mean Difference (IV, Random, 95% CI)	11.50 [-50.19, 73.19]
2.13.4 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	-53.10 [-219.98, 113.78]
2.14 Final GFR [mL/min/1.73 m²]	8	296	Mean Difference (IV, Random, 95% CI)	9.59 [3.84, 15.33]
2.14.1 Steroids versus placebo/no treatment at final follow-up (36 months)	1	86	Mean Difference (IV, Random, 95% CI)	8.00 [-11.49, 27.49]
2.14.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (9 to 120 months)	3	125	Mean Difference (IV, Random, 95% CI)	6.06 [-6.74, 18.87]
2.14.3 Calcineurin inhibitors versus placebo/no treatment/supportive therapy at final follow-up (9 to 24 months)	3	44	Mean Difference (IV, Random, 95% CI)	4.20 [-10.65, 19.05]
2.14.4 MMF versus placebo/no treatment at final follow-up (12 months)	1	32	Mean Difference (IV, Random, 95% CI)	12.37 [-4.93, 29.67]
2.14.5 Azathioprine versus placebo/no treatment at final follow-up (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	33.00 [-19.01, 85.01]
2.15 Final proteinuria	9	402	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.75, -0.08]
2.15.1 Steroids versus placebo/no treatment (36 months)	1	86	Mean Difference (IV, Random, 95% CI)	0.00 [-1.99, 1.99]
2.15.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy (12 months)	2	32	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.85, -0.07]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.15.3 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (24 to 120 months)	2	174	Mean Difference (IV, Random, 95% CI)	-2.06 [-3.69, -0.44]
2.15.4 Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive therapy (24 months)	2	69	Mean Difference (IV, Random, 95% CI)	1.30 [-4.53, 7.13]
2.15.5 Calcineurin inhibitors + steroids versus supportive therapy at final follow-up (9 to 21 months)	2	32	Mean Difference (IV, Random, 95% CI)	-1.70 [-6.62, 3.22]
2.15.6 Azathioprine versus placebo/no treatment (12 months)	1	9	Mean Difference (IV, Random, 95% CI)	1.10 [-2.79, 4.99]

Analysis 2.1. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/ no treatment/non-immunosuppressive supportive treatment, Outcome 1: Death

Study or Subgroup	Immunosuppressive Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.1.1 Final follow-up < 10 years							
Silverberg 1976	0	5	0	4		Not estimable	
Dussol 2008	0	19	0	17		Not estimable	
Donadio 1974	0	11	0	11		Not estimable	
CYCLOMEN 1994	0	10	0	11		Not estimable	
Kosmadakis 2010	0	18	0	10		Not estimable	
Praga 2007	0	25	1	23	6.0%	0.31 [0.01 , 7.20]	
Murphy 1992	1	13	0	13	6.1%	3.00 [0.13 , 67.51]	
Cattran 1995	1	9	0	8	6.3%	2.70 [0.13 , 58.24]	
Coggins 1979	0	34	2	38	6.6%	0.22 [0.01 , 4.48]	
Tiller 1981	0	27	2	27	6.6%	0.20 [0.01 , 3.98]	
Braun 1995	4	75	0	22	7.1%	2.72 [0.15 , 48.73]	
Cattran 1989	3	64	1	56	11.9%	2.63 [0.28 , 24.52]	
Imbasciati 1980	1	42	3	39	12.0%	0.31 [0.03 , 2.85]	
Cameron 1990	1	52	4	51	12.7%	0.25 [0.03 , 2.12]	
Howman 2013	4	69	1	37	12.8%	2.14 [0.25 , 18.50]	
Subtotal (95% CI)		**473**		**367**	**88.1%**	**0.81 [0.36 , 1.85]**	
Total events:	15		14				
Heterogeneity: Tau² = 0.00; Chi² = 7.61, df = 9 (P = 0.57); I² = 0%							
Test for overall effect: Z = 0.50 (P = 0.62)							
2.1.2 Final follow-up ≥ 10 years							
Jha 2007	1	51	3	53	11.9%	0.35 [0.04 , 3.22]	
Subtotal (95% CI)		**51**		**53**	**11.9%**	**0.35 [0.04 , 3.22]**	
Total events:	1		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.93 (P = 0.35)							
Total (95% CI)		**524**		**420**	**100.0%**	**0.73 [0.34 , 1.59]**	
Total events:	16		17				
Heterogeneity: Tau² = 0.00; Chi² = 8.10, df = 10 (P = 0.62); I² = 0%							
Test for overall effect: Z = 0.79 (P = 0.43)							
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%							

0.01 0.1 1 10 100
Less with immunosuppressive Less with control

Analysis 2.2. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/ non-immunosuppressive supportive treatment, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.2.1 Final follow-up < 10 years							
Donadio 1974	0	11	0	11		Not estimable	
Murphy 1992	0	13	0	13		Not estimable	
Kosmadakis 2010	0	18	0	10		Not estimable	
Silverberg 1976	0	5	0	4		Not estimable	
Praga 2007	0	25	0	23		Not estimable	
Dussol 2008	0	19	0	17		Not estimable	
Tiller 1981	0	27	1	27	2.6%	0.33 [0.01 , 7.84]	
Coggins 1979	1	34	5	38	5.5%	0.22 [0.03 , 1.82]	
CYCLOMEN 1994	3	10	1	11	5.5%	3.30 [0.41 , 26.81]	
Cattran 1995	1	9	4	8	6.1%	0.22 [0.03 , 1.60]	
Braun 1995	6	75	2	22	9.4%	0.88 [0.19 , 4.06]	
Cattran 1989	3	65	4	55	10.1%	0.63 [0.15 , 2.71]	
Howman 2013	7	69	4	37	14.2%	0.94 [0.29 , 3.00]	
Cameron 1990	8	52	6	51	17.7%	1.31 [0.49 , 3.50]	
Subtotal (95% CI)		**432**		**327**	**71.0%**	**0.84 [0.49 , 1.44]**	
Total events:	29		27				
Heterogeneity: Tau² = 0.00; Chi² = 6.24, df = 7 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.64 (P = 0.52)							
2.2.2 Final follow-up ≥ 10 years							
Imbasciati 1980	2	42	9	39	10.0%	0.21 [0.05 , 0.90]	
Jha 2007	5	51	16	53	19.0%	0.32 [0.13 , 0.82]	
Subtotal (95% CI)		**93**		**92**	**29.0%**	**0.29 [0.13 , 0.63]**	
Total events:	7		25				
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%							
Test for overall effect: Z = 3.13 (P = 0.002)							
Total (95% CI)		**525**		**419**	**100.0%**	**0.59 [0.35 , 0.99]**	
Total events:	36		52				
Heterogeneity: Tau² = 0.15; Chi² = 11.50, df = 9 (P = 0.24); I² = 22%							
Test for overall effect: Z = 1.98 (P = 0.05)							
Test for subgroup differences: Chi² = 4.97, df = 1 (P = 0.03), I² = 79.9%							

0.002 0.1 1 10 500
Less with immunosuppressive   Less with control

Analysis 2.3. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/ non-immunosuppressive supportive treatment, Outcome 3: Complete or partial remission

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.3.1 Final follow-up < 2 years							
Silverberg 1976	0	5	1	4	1.0%	0.28 [0.01 , 5.43]	
Donadio 1974	4	11	2	11	3.2%	2.00 [0.46 , 8.76]	
CYCLOMEN 1994	2	10	4	11	3.3%	0.55 [0.13 , 2.38]	
Arnadottir 2006	14	15	2	15	3.8%	7.00 [1.91 , 25.62]	
Murphy 1992	8	13	4	13	5.6%	2.00 [0.80 , 5.03]	
Coggins 1979	12	34	7	38	6.3%	1.92 [0.85 , 4.30]	
Dussol 2008	7	15	7	17	6.5%	1.13 [0.52 , 2.48]	
Koshikawa 1993	19	48	8	41	7.0%	2.03 [0.99 , 4.14]	
Cattran 1989	16	65	19	55	8.1%	0.71 [0.41 , 1.25]	
GEMRITUX 2017	24	37	13	38	8.5%	1.90 [1.15 , 3.13]	
Kosmadakis 2010	14	18	10	10	10.0%	0.80 [0.60 , 1.06]	
Subtotal (95% CI)		**271**		**253**	**63.4%**	**1.40 [0.91 , 2.14]**	
Total events:	120		77				
Heterogeneity: Tau² = 0.30; Chi² = 33.94, df = 10 (P = 0.0002); I² = 71%							
Test for overall effect: Z = 1.53 (P = 0.13)							
2.3.2 Final follow-up ≥ 2 years							
Shibasaki 2004	6	14	1	11	2.1%	4.71 [0.66 , 33.61]	
Praga 2007	10	25	7	23	6.5%	1.31 [0.60 , 2.87]	
Imbasciati 1980	35	42	15	39	9.1%	2.17 [1.42 , 3.30]	
Jha 2007	34	51	19	53	9.2%	1.86 [1.24 , 2.80]	
Braun 1995	44	75	16	22	9.8%	0.81 [0.59 , 1.11]	
Subtotal (95% CI)		**207**		**148**	**36.6%**	**1.54 [0.90 , 2.65]**	
Total events:	129		58				
Heterogeneity: Tau² = 0.26; Chi² = 20.45, df = 4 (P = 0.0004); I² = 80%							
Test for overall effect: Z = 1.56 (P = 0.12)							
Total (95% CI)		**478**		**401**	**100.0%**	**1.44 [1.05 , 1.97]**	
Total events:	249		135				
Heterogeneity: Tau² = 0.24; Chi² = 55.51, df = 15 (P < 0.00001); I² = 73%							
Test for overall effect: Z = 2.25 (P = 0.02)							
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%							

0.002   0.1   1   10   500
More with control   More with immunosuppressive

Analysis 2.4.   Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 4: Complete remission

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Final follow-up < 2 years						
Donadio 1974	0	11	0	11		Not estimable
CYCLOMEN 1994	0	10	1	11	2.1%	0.36 [0.02 , 8.03]
Silverberg 1976	0	5	1	4	2.3%	0.28 [0.01 , 5.43]
Kosmadakis 2010	5	18	0	10	2.6%	6.37 [0.39 , 104.54]
Dussol 2008	1	15	2	17	3.6%	0.57 [0.06 , 5.64]
Murphy 1992	2	13	1	13	3.6%	2.00 [0.21 , 19.44]
Koshikawa 1993	4	48	1	41	4.0%	3.42 [0.40 , 29.37]
Arnadottir 2006	11	15	1	15	4.7%	11.00 [1.62 , 74.88]
Coggins 1979	4	34	4	38	7.9%	1.12 [0.30 , 4.13]
Cattran 1989	6	64	11	56	11.0%	0.48 [0.19 , 1.21]
GEMRITUX 2017	13	37	8	38	12.8%	1.67 [0.78 , 3.55]
Imbasciati 1980	24	42	7	39	13.2%	3.18 [1.55 , 6.54]
Subtotal (95% CI)		**312**		**293**	**67.7%**	**1.57 [0.84 , 2.95]**
Total events:	70		37			

Heterogeneity: Tau² = 0.43; Chi² = 18.78, df = 10 (P = 0.04); I² = 47%
Test for overall effect: Z = 1.42 (P = 0.16)

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.2 Final follow-up ≥ 2 years						
Shibasaki 2004	3	14	0	11	2.5%	5.60 [0.32 , 98.21]
Praga 2007	3	25	5	23	7.8%	0.55 [0.15 , 2.06]
Jha 2007	15	51	5	53	10.9%	3.12 [1.22 , 7.95]
Braun 1995	34	75	4	22	11.1%	2.49 [0.99 , 6.26]
Subtotal (95% CI)		**165**		**109**	**32.3%**	**1.99 [0.87 , 4.54]**
Total events:	55		14			

Heterogeneity: Tau² = 0.29; Chi² = 5.25, df = 3 (P = 0.15); I² = 43%
Test for overall effect: Z = 1.63 (P = 0.10)

Total (95% CI)		**477**		**402**	**100.0%**	**1.70 [1.05 , 2.75]**
Total events:	125		51			

Heterogeneity: Tau² = 0.32; Chi² = 24.53, df = 14 (P = 0.04); I² = 43%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%

0.005   0.1   1   10   200
More with control   More with immunosuppressive

Analysis 2.5. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/ no treatment/non-immunosuppressive supportive treatment, Outcome 5: Partial remission

Study or Subgroup	Immunosuppressive Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.5.1 Final follow-up < 2 years							
Silverberg 1976	0	5	0	4		Not estimable	
Arnadottir 2006	3	15	1	15	2.5%	3.00 [0.35 , 25.68]	
CYCLOMEN 1994	2	10	3	11	4.0%	0.73 [0.15 , 3.53]	
Donadio 1974	4	11	2	11	4.4%	2.00 [0.46 , 8.76]	
Coggins 1979	8	34	3	38	5.4%	2.98 [0.86 , 10.34]	
Murphy 1992	6	13	3	13	5.9%	2.00 [0.63 , 6.34]	
Dussol 2008	6	15	5	17	7.1%	1.36 [0.52 , 3.56]	
GEMRITUX 2017	15	37	5	38	7.5%	3.08 [1.25 , 7.62]	
Cattran 1989	10	64	8	56	7.8%	1.09 [0.46 , 2.58]	
Koshikawa 1993	15	48	7	41	8.3%	1.83 [0.83 , 4.05]	
Kosmadakis 2010	9	18	10	10	10.9%	0.52 [0.33 , 0.84]	
Subtotal (95% CI)		**270**		**254**	**64.0%**	**1.49 [0.87 , 2.53]**	
Total events:	78		47				
Heterogeneity: Tau² = 0.42; Chi² = 25.13, df = 9 (P = 0.003); I² = 64%							
Test for overall effect: Z = 1.46 (P = 0.15)							
2.5.2 Final follow-up ≥ 2 years							
Shibasaki 2004	3	14	1	11	2.6%	2.36 [0.28 , 19.66]	
Praga 2007	7	25	2	23	4.4%	3.22 [0.74 , 13.95]	
Imbasciati 1980	9	42	11	39	8.5%	0.76 [0.35 , 1.63]	
Jha 2007	19	51	11	53	9.6%	1.80 [0.95 , 3.39]	
Braun 1995	28	75	12	22	10.8%	0.68 [0.42 , 1.11]	
Subtotal (95% CI)		**207**		**148**	**36.0%**	**1.18 [0.65 , 2.16]**	
Total events:	66		37				
Heterogeneity: Tau² = 0.24; Chi² = 9.73, df = 4 (P = 0.05); I² = 59%							
Test for overall effect: Z = 0.55 (P = 0.58)							
Total (95% CI)		**477**		**402**	**100.0%**	**1.36 [0.93 , 1.98]**	
Total events:	144		84				
Heterogeneity: Tau² = 0.29; Chi² = 34.62, df = 14 (P = 0.002); I² = 60%							
Test for overall effect: Z = 1.57 (P = 0.12)							
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%							

0.002   0.1   1   10   500
More with control   More with immunosuppressive

Analysis 2.6. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/ non-immunosuppressive supportive treatment, Outcome 6: Relapse after complete or partial remission

Study or Subgroup	Immunosuppressive Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.6.1 Final follow-up (≥ 2 years)							
Jha 2007	8	34	4	19	22.5%	1.12 [0.39 , 3.23]	
Cattran 1989	10	16	5	19	35.7%	2.38 [1.02 , 5.52]	
Braun 1995	23	44	5	16	41.7%	1.67 [0.77 , 3.65]	
Subtotal (95% CI)		**94**		**54**	**100.0%**	**1.73 [1.05 , 2.86]**	
Total events:	41		14				
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.55); I² = 0%							
Test for overall effect: Z = 2.14 (P = 0.03)							
Total (95% CI)		**94**		**54**	**100.0%**	**1.73 [1.05 , 2.86]**	
Total events:	41		14				
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.55); I² = 0%							
Test for overall effect: Z = 2.14 (P = 0.03)							
Test for subgroup differences: Not applicable							

0.002   0.1   1   10   500
More with control   More with immunosuppressive

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Analysis 2.7. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/ non-immunosuppressive supportive treatment, Outcome 7: 100% increase in serum creatinine

	Immunosuppressive		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
2.7.1 Steroids versus placebo/no treatment at 24 months							
Coggins 1979	2	34	11	38	11.9%	0.20 [0.05 , 0.85]	
Subtotal (95% CI)		**34**		**38**	**11.9%**	**0.20 [0.05 , 0.85]**	
Total events:	2		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.18 (P = 0.03)							
2.7.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (≤ 2 years)							
Murphy 1992	1	13	0	13	3.0%	3.00 [0.13 , 67.51]	
Donadio 1974	1	11	2	11	5.4%	0.50 [0.05 , 4.75]	
Imbasciati 1980	1	42	13	39	6.8%	0.07 [0.01 , 0.52]	
Subtotal (95% CI)		**66**		**63**	**15.2%**	**0.37 [0.05 , 2.94]**	
Total events:	3		15				
Heterogeneity: Tau² = 1.84; Chi² = 4.47, df = 2 (P = 0.11); I² = 55%							
Test for overall effect: Z = 0.94 (P = 0.35)							
2.7.3 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (> 2 years)							
Braun 1995	8	31	3	11	17.0%	0.95 [0.30 , 2.94]	
Jha 2007	10	51	26	53	34.5%	0.40 [0.22 , 0.74]	
Subtotal (95% CI)		**82**		**64**	**51.5%**	**0.54 [0.24 , 1.20]**	
Total events:	18		29				
Heterogeneity: Tau² = 0.15; Chi² = 1.71, df = 1 (P = 0.19); I² = 41%							
Test for overall effect: Z = 1.52 (P = 0.13)							
2.7.4 Calcineurin inhibitors + steroids versus placebo/no treatment (60 months)							
Braun 1995	8	44	3	11	16.7%	0.67 [0.21 , 2.11]	
Subtotal (95% CI)		**44**		**11**	**16.7%**	**0.67 [0.21 , 2.11]**	
Total events:	8		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
2.7.5 MMF versus placebo/no treatment at final follow-up (12 months)							
Dussol 2008	0	19	0	17		Not estimable	
Subtotal (95% CI)		**19**		**17**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.7.6 Azathioprine versus placebo/no treatment at final follow-up (12 months)							
Silverberg 1976	1	5	1	4	4.7%	0.80 [0.07 , 9.18]	
Subtotal (95% CI)		**5**		**4**	**4.7%**	**0.80 [0.07 , 9.18]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.18 (P = 0.86)							
Total (95% CI)		**250**		**197**	**100.0%**	**0.46 [0.26 , 0.80]**	
Total events:	32		59				
Heterogeneity: Tau² = 0.13; Chi² = 8.87, df = 7 (P = 0.26); I² = 21%							
Test for overall effect: Z = 2.77 (P = 0.006)							
Test for subgroup differences: Chi² = 2.00, df = 4 (P = 0.74), I² = 0%							

0.005 0.1 1 10 200
Less with immunosuppressive   Less with control

Analysis 2.8. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 8: 50% increase in serum creatinine

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.8.1 Steroids versus placebo/no treatment at 36 months							
Cameron 1990	15	52	26	51	45.2%	0.57 [0.34 , 0.94]	
Subtotal (95% CI)		**52**		**51**	**45.2%**	**0.57 [0.34 , 0.94]**	
Total events:	15		26				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.21 (P = 0.03)							
2.8.2 Alkylating agents versus placebo/no treatment at final follow-up (≤ 2 years)							
Donadio 1974	1	11	2	11	3.7%	0.50 [0.05 , 4.75]	
Murphy 1992	2	13	1	13	3.6%	2.00 [0.21 , 19.44]	
Subtotal (95% CI)		**24**		**24**	**7.3%**	**0.99 [0.20 , 4.91]**	
Total events:	3		3				
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%							
Test for overall effect: Z = 0.01 (P = 0.99)							
2.8.3 Alkylating agents ± steroids versus placebo/no treatment at final follow-up (> 2 years)							
Imbasciati 1980	7	42	20	39	26.8%	0.33 [0.15 , 0.68]	
Subtotal (95% CI)		**42**		**39**	**26.8%**	**0.33 [0.15 , 0.68]**	
Total events:	7		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.97 (P = 0.003)							
2.8.4 Calcineurin inhibitors versus placebo/no treatment (30 months)							
Praga 2007	1	25	6	23	4.5%	0.15 [0.02 , 1.18]	
Subtotal (95% CI)		**25**		**23**	**4.5%**	**0.15 [0.02 , 1.18]**	
Total events:	1		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.80 (P = 0.07)							
2.8.5 MMF versus placebo/no treatment (12 months)							
Dussol 2008	0	15	0	17		Not estimable	
Subtotal (95% CI)		**15**		**17**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.8.6 Azathioprine versus placebo/no treatment (12 months)							
Silverberg 1976	2	5	0	4	2.4%	4.17 [0.25 , 68.16]	
Subtotal (95% CI)		**5**		**4**	**2.4%**	**4.17 [0.25 , 68.16]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.00 (P = 0.32)							
2.8.7 Mizoribine versus placebo/no treatment (6 months)							
Koshikawa 1993	5	48	6	41	13.8%	0.71 [0.23 , 2.16]	
Subtotal (95% CI)		**48**		**41**	**13.8%**	**0.71 [0.23 , 2.16]**	
Total events:	5		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
Total (95% CI)		**211**		**199**	**100.0%**	**0.52 [0.33 , 0.81]**	
Total events:	33		61				
Heterogeneity: Tau² = 0.05; Chi² = 6.81, df = 6 (P = 0.34); I² = 12%							
Test for overall effect: Z = 2.91 (P = 0.004)							
Test for subgroup differences: Chi² = 6.09, df = 5 (P = 0.30), I² = 17.9%							

0.005   0.1   1   10   200
Less with immunosuppressive   Less with control

Analysis 2.8. (Continued)

Test for overall effect: Z = 2.91 (P = 0.004)

Less with immunosuppressive   Less with control

Test for subgroup differences: Chi² = 6.09, df = 5 (P = 0.30), I² = 17.9%

Analysis 2.9. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 9: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.9.1 Steroids versus placebo/no treatment							
Cameron 1990	1	52	0	51	7.9%	2.94 [0.12 , 70.61]	
Coggins 1979	0	34	1	38	7.9%	0.37 [0.02 , 8.82]	
Cattran 1989	4	65	0	55	9.4%	7.64 [0.42 , 138.78]	
Subtotal (95% CI)		**151**		**144**	**25.2%**	**2.20 [0.37 , 12.96]**	
Total events:	5		1				
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%							
Test for overall effect: Z = 0.87 (P = 0.38)							
2.9.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy							
Braun 1995	0	31	0	11		Not estimable	
Kosmadakis 2010	0	8	0	5		Not estimable	
Murphy 1992	1	13	0	13	8.2%	3.00 [0.13 , 67.51]	
Imbasciati 1980	4	42	0	39	9.5%	8.37 [0.47 , 150.62]	
Jha 2007	5	51	0	53	9.6%	11.42 [0.65 , 201.45]	
Donadio 1974	3	11	0	11	9.7%	7.00 [0.40 , 121.39]	
Tiller 1981	7	27	0	27	10.0%	15.00 [0.90 , 250.24]	
Subtotal (95% CI)		**183**		**159**	**47.0%**	**8.14 [2.22 , 29.82]**	
Total events:	20		0				
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 4 (P = 0.96); I² = 0%							
Test for overall effect: Z = 3.17 (P = 0.002)							
2.9.3 Calcineurin inhibitors versus placebo/no treatment/supportive therapy							
Praga 2007	0	25	0	23		Not estimable	
Braun 1995	0	44	0	11		Not estimable	
Cattran 1995	0	9	0	8		Not estimable	
Kosmadakis 2010	0	10	0	5		Not estimable	
CYCLOMEN 1994	2	10	0	11	9.3%	5.45 [0.29 , 101.55]	
Subtotal (95% CI)		**98**		**58**	**9.3%**	**5.45 [0.29 , 101.55]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.14 (P = 0.26)							
2.9.4 MMF versus placebo/no treatment							
Dussol 2008	4	19	0	17	9.7%	8.10 [0.47 , 140.24]	
Subtotal (95% CI)		**19**		**17**	**9.7%**	**8.10 [0.47 , 140.24]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
2.9.5 Azathioprine versus placebo/no treatment							
Silverberg 1976	0	5	0	4		Not estimable	
Subtotal (95% CI)		**5**		**4**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.9.6 Mizoribine versus placebo/no treatment							
Koshikawa 1993	2	48	0	41	8.8%	4.29 [0.21 , 86.80]	
Subtotal (95% CI)		**48**		**41**	**8.8%**	**4.29 [0.21 , 86.80]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.95 (P = 0.34)							
Total (95% CI)		**504**		**423**	**100.0%**	**5.33 [2.19 , 12.98]**	

Analysis 2.9. (Continued)

Total (95% CI)		504		423	100.0%	5.33 [2.19 , 12.98]		
Total events:	33		1					

Heterogeneity: Tau² = 0.00; Chi² = 4.10, df = 10 (P = 0.94); I² = 0%

Test for overall effect: Z = 3.68 (P = 0.0002)

Test for subgroup differences: Chi² = 1.47, df = 4 (P = 0.83), I² = 0%

0.002   0.1   1   10   500
Less with immunosuppressive   Less with control
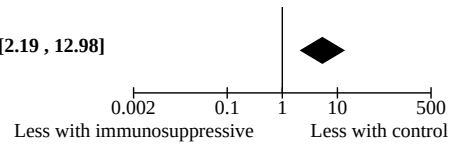
Analysis 2.10. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 10: Adverse events

	Immunosuppressive		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.10.1 Alkylating agents + steroids versus supportive therapy							
Howman 2013	38	69	16	37	86.9%	1.27 [0.83 , 1.95]	
Subtotal (95% CI)		**69**		**37**	**86.9%**	**1.27 [0.83 , 1.95]**	
Total events:	38		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
2.10.2 Rituximab versus supportive therapy							
GEMRITUX 2017	6	37	5	38	13.1%	1.23 [0.41 , 3.69]	
Subtotal (95% CI)		**37**		**38**	**13.1%**	**1.23 [0.41 , 3.69]**	
Total events:	6		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
Total (95% CI)		**106**		**75**	**100.0%**	**1.27 [0.85 , 1.89]**	
Total events:	44		21				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

0.1   0.2   0.5   1   2   5   10
Less with immunosuppressive   Less with control
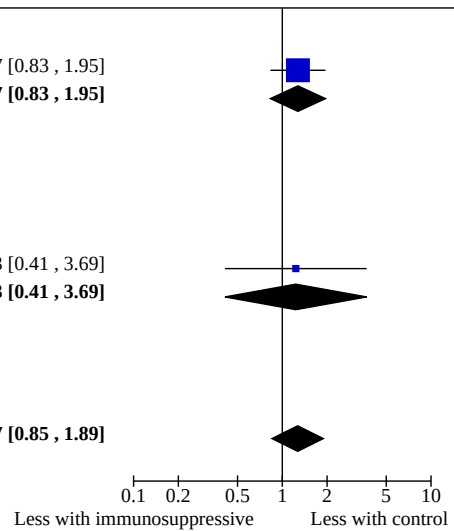
Analysis 2.11. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 11: Infection

	Immunosuppressive		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Howman 2013	11	69	2	37	100.0%	2.95 [0.69 , 12.61]	
Total (95% CI)		**69**		**37**	**100.0%**	**2.95 [0.69 , 12.61]**	
Total events:	11		2				

Heterogeneity: Not applicable

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable
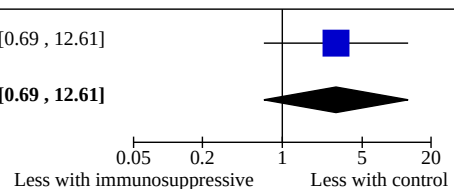
0.05   0.2   1   5   20
Less with immunosuppressive   Less with control

Analysis 2.12. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 12: Malignancy

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
GEMRITUX 2017	0	37	1	38	47.4%	0.34 [0.01 , 8.14]	
Howman 2013	2	69	0	38	52.6%	2.79 [0.14 , 56.57]	
Total (95% CI)		**106**		**76**	**100.0%**	**1.03 [0.12 , 9.14]**	
Total events:	2		1				

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

Less with immunosuppressive   Less with control

Analysis 2.13. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 13: Final serum creatinine

Study or Subgroup	Immunosuppressive Mean [µmol/L]	Immunosuppressive SD [µmol/L]	Total	Control Mean [µmol/L]	Control SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
2.13.1 Steroids versus placebo/no treatment at final follow-up (36 months)									
Cameron 1990	251	257	44	203	166	43	2.9%	48.00 [-42.71 , 138.71]	
Subtotal (95% CI)			**44**			**43**	**2.9%**	**48.00 [-42.71 , 138.71]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.04 (P = 0.30)									
2.13.2 Alkylating agents ± steroids versus placebo/no treatment at final follow-up (24 to 120 months)									
Murphy 1992	127.67	104.95	12	107.69	40.65	13	5.9%	19.98 [-43.38 , 83.34]	
Imbasciati 1980	73.71	32.71	31	46.85	30.94	25	84.2%	26.86 [10.14 , 43.58]	
Subtotal (95% CI)			**43**			**38**	**90.1%**	**26.41 [10.24 , 42.58]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%									
Test for overall effect: Z = 3.20 (P = 0.001)									
2.13.3 Calcineurin inhibitors versus placebo/no treatment at final follow-up (12 months)									
CYCLOMEN 1994	189.2	65.4	10	177.7	78.7	11	6.2%	11.50 [-50.19 , 73.19]	
Subtotal (95% CI)			**10**			**11**	**6.2%**	**11.50 [-50.19 , 73.19]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
2.13.4 Azathioprine versus placebo/no treatment at final follow-up (12 months)									
Silverberg 1976	159.1	106.1	5	212.2	141.4	4	0.8%	-53.10 [-219.98 , 113.78]	
Subtotal (95% CI)			**5**			**4**	**0.8%**	**-53.10 [-219.98 , 113.78]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.62 (P = 0.53)									
Total (95% CI)			**102**			**96**	**100.0%**	**25.43 [10.09 , 40.78]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 4 (P = 0.85); I² = 0%
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Chi² = 1.30, df = 3 (P = 0.73), I² = 0%

Lower with immunosuppressive   Lower with control

Analysis 2.14. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/no treatment/non-immunosuppressive supportive treatment, Outcome 14: Final GFR [mL/min/1.73 m²]

Study or Subgroup	Immunosuppressive			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
2.14.1 Steroids versus placebo/no treatment at final follow-up (36 months)									
Cameron 1990	75	49	43	67	43	43	8.7%	8.00 [-11.49 , 27.49]	
Subtotal (95% CI)			**43**			**43**	**8.7%**	**8.00 [-11.49 , 27.49]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.80 (P = 0.42)									
2.14.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (9 to 120 months)									
Donadio 1974	76.67	18.76	9	82	27.77	10	7.4%	-5.33 [-26.46 , 15.80]	
Kosmadakis 2010	62	17	8	62.1	19.9	5	7.4%	-0.10 [-21.15 , 20.95]	
Jha 2007	64	18	47	50	22	46	49.3%	14.00 [5.82 , 22.18]	
Subtotal (95% CI)			**64**			**61**	**64.1%**	**6.06 [-6.74 , 18.87]**	
Heterogeneity: Tau² = 63.87; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%									
Test for overall effect: Z = 0.93 (P = 0.35)									
2.14.3 Calcineurin inhibitors versus placebo/no treatment/supportive therapy at final follow-up (9 to 24 months)									
Cattran 1995	43.24	16.12	5	35.43	28.46	3	2.7%	7.81 [-27.36 , 42.98]	
Kosmadakis 2010	71.3	25.3	10	62.1	19.9	5	6.0%	9.20 [-14.26 , 32.66]	
CYCLOMEN 1994	44.1	27.2	10	46.2	26.2	11	6.3%	-2.10 [-24.99 , 20.79]	
Subtotal (95% CI)			**25**			**19**	**15.0%**	**4.20 [-10.65 , 19.05]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%									
Test for overall effect: Z = 0.55 (P = 0.58)									
2.14.4 MMF versus placebo/no treatment at final follow-up (12 months)									
Dussol 2008	86.6	27.84	15	74.23	21.13	17	11.0%	12.37 [-4.93 , 29.67]	
Subtotal (95% CI)			**15**			**17**	**11.0%**	**12.37 [-4.93 , 29.67]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.40 (P = 0.16)									
2.14.5 Azathioprine versus placebo/no treatment at final follow-up (12 months)									
Silverberg 1976	87	54	5	54	22	4	1.2%	33.00 [-19.01 , 85.01]	
Subtotal (95% CI)			**5**			**4**	**1.2%**	**33.00 [-19.01 , 85.01]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.24 (P = 0.21)									
Total (95% CI)			**152**			**144**	**100.0%**	**9.59 [3.84 , 15.33]**	
Heterogeneity: Tau² = 0.00; Chi² = 5.76, df = 8 (P = 0.67); I² = 0%									
Test for overall effect: Z = 3.27 (P = 0.001)									
Test for subgroup differences: Chi² = 1.47, df = 4 (P = 0.83), I² = 0%									

-100 -50 0 50 100
Higher with control   Higher with immunosuppressive

Analysis 2.15. Comparison 2: Immunosuppressive treatment ± steroids versus placebo/ no treatment/non-immunosuppressive supportive treatment, Outcome 15: Final proteinuria

Study or Subgroup	Immunosuppressive Mean [g/24 h]	SD [g/24 h]	Total	Control Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
2.15.1 Steroids versus placebo/no treatment (36 months)									
Cameron 1990	5.6	4.7	43	5.6	4.7	43	9.8%	0.00 [-1.99 , 1.99]	
Subtotal (95% CI)			43			43	9.8%	0.00 [-1.99 , 1.99]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
2.15.2 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy (12 months)									
Donadio 1974	4.2	3.15	9	4.69	3.76	10	5.4%	-0.49 [-3.60 , 2.62]	
Kosmadakis 2010	1	1.1	8	2	0.6	5	17.5%	-1.00 [-1.93 , -0.07]	
Subtotal (95% CI)			17			15	22.9%	-0.96 [-1.85 , -0.07]	
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%									
Test for overall effect: Z = 2.12 (P = 0.03)									
2.15.3 Alkylating agents ± steroids versus placebo/no treatment/supportive therapy at final follow-up (24 to 120 months)									
Imbasciati 1980	2.1	2.4	42	5.2	4.5	39	12.3%	-3.10 [-4.69 , -1.51]	
Jha 2007	1.1	0.2	47	2.5	0.8	46	21.9%	-1.40 [-1.64 , -1.16]	
Subtotal (95% CI)			89			85	34.2%	-2.06 [-3.69 , -0.44]	
Heterogeneity: Tau² = 1.11; Chi² = 4.31, df = 1 (P = 0.04); I² = 77%									
Test for overall effect: Z = 2.49 (P = 0.01)									
2.15.4 Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive therapy (24 months)									
CYCLOMEN 1994	7.5	7.6	10	2.8	2.5	11	2.5%	4.70 [-0.24 , 9.64]	
Praga 2007	1.9	4	25	3.2	4.62	23	7.6%	-1.30 [-3.75 , 1.15]	
Subtotal (95% CI)			35			34	10.1%	1.30 [-4.53 , 7.13]	
Heterogeneity: Tau² = 14.04; Chi² = 4.55, df = 1 (P = 0.03); I² = 78%									
Test for overall effect: Z = 0.44 (P = 0.66)									
2.15.5 Calcineurin inhibitors + steroids versus supportive therapy at final follow-up (9 to 21 months)									
Cattran 1995	4.5	4	9	9.2	5	8	3.2%	-4.70 [-9.04 , -0.36]	
Kosmadakis 2010	2.4	1.6	10	2	0.6	5	15.9%	0.40 [-0.72 , 1.52]	
Subtotal (95% CI)			19			13	19.0%	-1.70 [-6.62 , 3.22]	
Heterogeneity: Tau² = 10.39; Chi² = 4.97, df = 1 (P = 0.03); I² = 80%									
Test for overall effect: Z = 0.68 (P = 0.50)									
2.15.6 Azathioprine versus placebo/no treatment (12 months)									
Silverberg 1976	5.2	2.9	5	4.1	3	4	3.8%	1.10 [-2.79 , 4.99]	
Subtotal (95% CI)			5			4	3.8%	1.10 [-2.79 , 4.99]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.55 (P = 0.58)									
Total (95% CI)			208			194	100.0%	-0.91 [-1.75 , -0.08]	
Heterogeneity: Tau² = 0.81; Chi² = 26.23, df = 9 (P = 0.002); I² = 66%									
Test for overall effect: Z = 2.15 (P = 0.03)									
Test for subgroup differences: Chi² = 4.41, df = 5 (P = 0.49), I² = 0%									

-20 -10 0 10 20
Lower with immunosuppressive   Lower with control

Comparison 3. Immunosuppressive treatment ± steroids versus steroids

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 Follow-up < 10 years	2	143	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.19, 12.01]
3.2 ESKD (dialysis/transplantation)	3	148	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.36, 2.58]
3.3 Complete or partial remission	5	241	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.19, 1.82]
3.3.1 Complete or partial remission (< 2 years)	3	107	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.93, 2.37]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.3.2 Complete or partial remission at final follow-up (≥ 2 years)	2	134	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.15, 1.86]
3.4 Complete remission	4	205	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.34, 2.65]
3.4.1 Complete remission at final follow-up (< 2 years)	2	71	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.60, 4.60]
3.4.2 Complete remission at final follow-up (≥ 2 years)	2	134	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.93, 3.22]
3.5 Partial remission	4	205	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.42, 3.97]
3.5.1 Partial remission at final follow-up (< 2 years)	2	71	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.50, 6.98]
3.5.2 Partial remission at final follow-up (≥ 2 years)	2	134	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.01, 18.32]
3.6 Relapse after complete or partial remission	2	81	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.33, 2.28]
3.7 Increase in serum creatinine	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 100% increase in serum creatinine	3	97	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.52, 2.71]
3.7.2 50% increase in serum creatinine	3	189	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.34, 1.59]
3.8 Temporary or permanent dis-continuation/hospitalisation due to adverse events	1	92	Risk Ratio (M-H, Random, 95% CI)	4.18 [0.49, 35.97]
3.9 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.9.1 Adverse events	1	92	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.55, 3.30]
3.9.2 Malignancy	1	92	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.07, 16.20]

Analysis 3.1. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 1: Death

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 Follow-up < 10 years							
Cattran 2001	1	28	0	23	43.0%	2.48 [0.11 , 58.20]	
Ponticelli 1992	1	45	1	47	57.0%	1.04 [0.07 , 16.20]	
Subtotal (95% CI)		73		70	100.0%	1.52 [0.19 , 12.01]	
Total events:	2		1				

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with immunosuppressives — Less with steroids

Analysis 3.2. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cattran 2001	1	28	0	23	9.7%	2.48 [0.11 , 58.20]	
Pahari 1993	1	36	2	35	17.5%	0.49 [0.05 , 5.12]	
Falk 1992	4	13	4	13	72.8%	1.00 [0.32 , 3.17]	
Total (95% CI)		77		71	100.0%	0.96 [0.36 , 2.58]	
Total events:	6		6				

Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with immunosuppressive — Less with steroids

Analysis 3.3. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 3: Complete or partial remission

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 Complete or partial remission (< 2 years)							
Cattran 2001	11	28	3	23	3.4%	3.01 [0.95 , 9.52]	
Hasegawa 2017	6	18	5	18	4.6%	1.20 [0.45 , 3.23]	
Ahmed 1994	8	10	6	10	12.8%	1.33 [0.74 , 2.41]	
Subtotal (95% CI)		56		51	20.8%	1.49 [0.93 , 2.37]	
Total events:	25		14				

Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)

3.3.2 Complete or partial remission at final follow-up (≥ 2 years)							
Ponticelli 1992	20	32	13	31	18.5%	1.49 [0.91 , 2.44]	
Pahari 1993	33	36	22	35	60.6%	1.46 [1.11 , 1.92]	
Subtotal (95% CI)		68		66	79.2%	1.47 [1.15 , 1.86]	
Total events:	53		35				

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)

Total (95% CI)		124		117	100.0%	1.47 [1.19 , 1.82]	
Total events:	78		49				

Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 4 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%

0.1 0.2 0.5 1 2 5 10
More with steroids — More with immunosuppressive

Analysis 3.4. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 4: Complete remission

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Steroids Events	Steroids Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.4.1 Complete remission at final follow-up (< 2 years)							
Cattran 2001	2	28	1	23	2.1%	1.64 [0.16 , 16.99]	
Ahmed 1994	5	10	3	10	9.0%	1.67 [0.54 , 5.17]	
Subtotal (95% CI)		38		33	11.2%	1.66 [0.60 , 4.60]	
Total events:	7		4				
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.98 (P = 0.33)							
3.4.2 Complete remission at final follow-up (≥ 2 years)							
Ponticelli 1992	8	32	7	31	14.7%	1.11 [0.46 , 2.69]	
Pahari 1993	33	36	15	35	74.1%	2.14 [1.44 , 3.18]	
Subtotal (95% CI)		68		66	88.8%	1.73 [0.93 , 3.22]	
Total events:	41		22				
Heterogeneity: Tau² = 0.11; Chi² = 1.87, df = 1 (P = 0.17); I² = 46%							
Test for overall effect: Z = 1.74 (P = 0.08)							
Total (95% CI)		106		99	100.0%	1.89 [1.34 , 2.65]	
Total events:	48		26				
Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 3 (P = 0.59); I² = 0%							
Test for overall effect: Z = 3.66 (P = 0.0003)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%							

0.01 0.1 1 10 100
More with steroids More with immunosuppressive

Analysis 3.5. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 5: Partial remission

Study or Subgroup	Immunosuppressive Events	Immunosuppressive Total	Steroids Events	Steroids Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.5.1 Partial remission at final follow-up (< 2 years)							
Cattran 2001	9	28	2	23	25.8%	3.70 [0.89 , 15.44]	
Ahmed 1994	3	10	3	10	27.2%	1.00 [0.26 , 3.81]	
Subtotal (95% CI)		38		33	53.0%	1.88 [0.50 , 6.98]	
Total events:	12		5				
Heterogeneity: Tau² = 0.40; Chi² = 1.80, df = 1 (P = 0.18); I² = 44%							
Test for overall effect: Z = 0.94 (P = 0.35)							
3.5.2 Partial remission at final follow-up (≥ 2 years)							
Pahari 1993	0	36	7	35	11.7%	0.06 [0.00 , 1.09]	
Ponticelli 1992	12	32	6	31	35.3%	1.94 [0.83 , 4.52]	
Subtotal (95% CI)		68		66	47.0%	0.44 [0.01 , 18.32]	
Total events:	12		13				
Heterogeneity: Tau² = 6.22; Chi² = 6.49, df = 1 (P = 0.01); I² = 85%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Total (95% CI)		106		99	100.0%	1.28 [0.42 , 3.97]	
Total events:	24		18				
Heterogeneity: Tau² = 0.75; Chi² = 7.60, df = 3 (P = 0.06); I² = 61%							
Test for overall effect: Z = 0.43 (P = 0.66)							
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%							

0.002 0.1 1 10 500
More with steroids More with immunosuppressive

Analysis 3.6. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 6: Relapse after complete or partial remission

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pahari 1993	2	33	3	22	31.7%	0.44 [0.08 , 2.45]	
Cattran 2001	10	21	2	5	68.3%	1.19 [0.37 , 3.81]	
Total (95% CI)		**54**		**27**	**100.0%**	**0.87 [0.33 , 2.28]**	
Total events:	12		5				

Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with immunosuppressive   Less with steroids

Analysis 3.7. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 7: Increase in serum creatinine

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.7.1 100% increase in serum creatinine							
Ahmed 1994	1	10	2	10	13.6%	0.50 [0.05 , 4.67]	
Cattran 2001	4	28	2	23	26.4%	1.64 [0.33 , 8.18]	
Falk 1992	5	13	4	13	59.9%	1.25 [0.43 , 3.63]	
Subtotal (95% CI)		**51**		**46**	**100.0%**	**1.19 [0.52 , 2.71]**	
Total events:	10		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%							
Test for overall effect: Z = 0.40 (P = 0.69)							
3.7.2 50% increase in serum creatinine							
Pahari 1993	1	36	5	35	11.8%	0.19 [0.02 , 1.58]	
Falk 1992	6	13	5	13	42.6%	1.20 [0.49 , 2.96]	
Ponticelli 1992	7	45	11	47	45.5%	0.66 [0.28 , 1.56]	
Subtotal (95% CI)		**94**		**95**	**100.0%**	**0.74 [0.34 , 1.59]**	
Total events:	14		21				

Heterogeneity: Tau² = 0.15; Chi² = 2.89, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 0.77 (P = 0.44)

0.02 0.1 1 10 50
Less with immunosuppressive   Less with steroids

Analysis 3.8. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 1992	4	45	1	47	100.0%	4.18 [0.49 , 35.97]	
Total (95% CI)		**45**		**47**	**100.0%**	**4.18 [0.49 , 35.97]**	
Total events:	4		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with immunosuppressive   Less with steroids

Analysis 3.9. Comparison 3: Immunosuppressive treatment ± steroids versus steroids, Outcome 9: Adverse events

Study or Subgroup	Immunosuppressive Events	Total	Steroids Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.9.1 Adverse events							
Ponticelli 1992	9	45	7	47	100.0%	1.34 [0.55 , 3.30]	
Subtotal (95% CI)		45		47	100.0%	**1.34 [0.55 , 3.30]**	
Total events:	9		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
3.9.2 Malignancy							
Ponticelli 1992	1	45	1	47	100.0%	1.04 [0.07 , 16.20]	
Subtotal (95% CI)		45		47	100.0%	**1.04 [0.07 , 16.20]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							

Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%

0.01 0.1 1 10 100
Less with immunosuppressive   Less with steroids
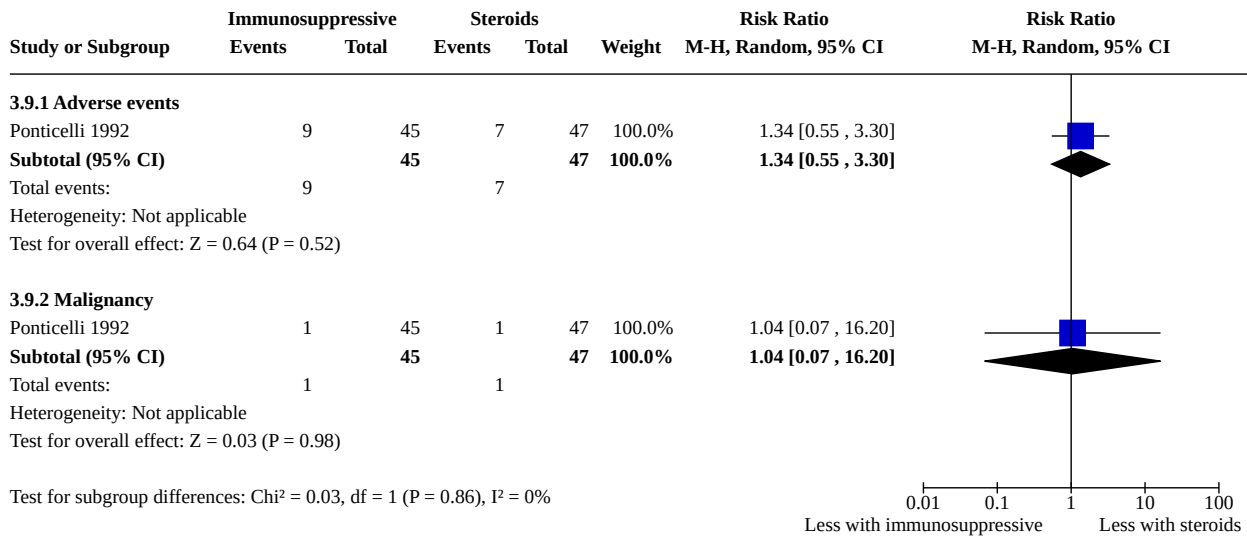
Comparison 4. Cyclophosphamide + leflunomide + steroid versus cyclophosphamide + steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Complete remission	1	48	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.04, 2.17]

Analysis 4.1. Comparison 4: Cyclophosphamide + leflunomide + steroid versus cyclophosphamide + steroid, Outcome 1: Complete remission

Study or Subgroup	CPA+leflunomide Events	Total	CPA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Liu 2015e	21	24	14	24	100.0%	1.50 [1.04 , 2.17]	
Total (95% CI)		24		24	100.0%	**1.50 [1.04 , 2.17]**	
Total events:	21		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.15 (P = 0.03)							
Test for subgroup differences: Not applicable							

0.2 0.5 1 2 5
More with CPA   More with CPA+leflunomide
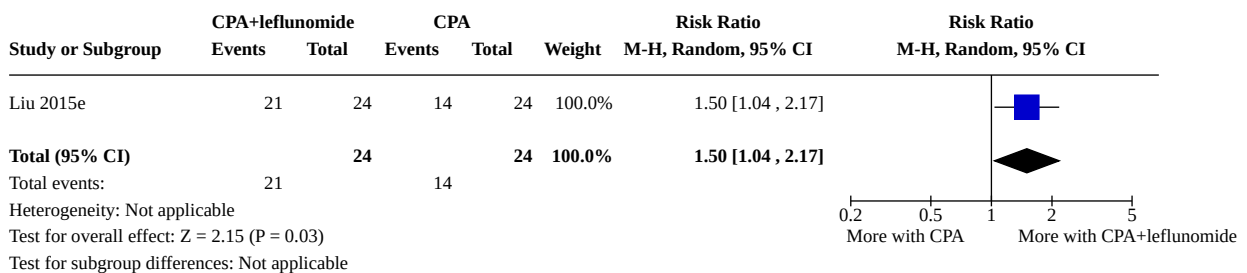
Comparison 5. Oral alkylating agents ± steroids versus placebo/no treatment/steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Death	7	440	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.25, 2.30]
5.1.1 Follow-up < 10 years	5	255	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.37, 8.22]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1.2 Follow-up ≥ 10 years	2	185	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.58]
5.2 ESKD (dialysis/transplantation)	9	537	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.74]
5.2.1 Final follow-up < 10 years	7	352	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.29, 1.44]
5.2.2 Final follow-up ≥ 10 years	2	185	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.63]
5.3 Complete or partial remission	9	468	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.04, 1.82]
5.3.1 Complete or partial remission at final follow-up (< 2 years)	4	96	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.76, 2.09]
5.3.2 Complete or partial remission at final follow-up (≥ 2 years)	5	372	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.04, 2.04]
5.4 Complete remission	8	432	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.33, 3.38]
5.4.1 Complete remission at final follow-up (< 2 years)	3	60	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.46, 18.52]
5.4.2 Complete remission at final follow-up (≥ 2 years)	5	372	Risk Ratio (M-H, Random, 95% CI)	2.10 [1.22, 3.60]
5.5 Partial remission	8	432	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.55]
5.5.1 Partial remission at final fol-low-up (< 2 years)	3	60	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.37, 1.87]
5.5.2 Partial remission at final fol-low-up (≥ 2 years)	5	372	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.48, 1.91]
5.6 Increase in serum creatinine	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.6.1 100% increase in serum crea-tinine	7	332	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.16]
5.6.2 50% increase in serum creati-nine	6	318	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.08]
5.7 Relapse after complete or par-tial remission	3	161	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.40, 1.61]
5.8 Temporary or permanent dis-continuation/hospitalisation due to adverse events	8	439	Risk Ratio (M-H, Random, 95% CI)	6.82 [2.24, 20.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.9 Adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.9.1 Adverse events	3	184	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.96, 2.15]
5.9.2 Infection	1	70	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.30, 9.45]
5.9.3 Malignancy	2	199	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.21, 12.37]
5.10 Final GFR [mL/min/1.73 m²]	1	19	Mean Difference (IV, Random, 95% CI)	-5.33 [-26.46, 15.80]

Analysis 5.1. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 1: Death

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.1.1 Follow-up < 10 years							
Kosmadakis 2010	0	8	0	10		Not estimable	
Donadio 1974	0	11	0	11		Not estimable	
Braun 1995	1	31	0	22	12.3%	2.16 [0.09 , 50.59]	
Ponticelli 1992	1	45	1	47	16.3%	1.04 [0.07 , 16.20]	
Howman 2013	2	33	1	37	22.1%	2.24 [0.21 , 23.61]	
Subtotal (95% CI)		**128**		**127**	**50.6%**	**1.74 [0.37 , 8.22]**	
Total events:	4		2				

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.49)

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.1.2 Follow-up ≥ 10 years							
Jha 2007	1	51	3	53	24.6%	0.35 [0.04 , 3.22]	
Imbasciati 1980	1	42	3	39	24.8%	0.31 [0.03 , 2.85]	
Subtotal (95% CI)		**93**		**92**	**49.4%**	**0.33 [0.07 , 1.58]**	
Total events:	2		6				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)

Total (95% CI)		**221**		**219**	**100.0%**	**0.76 [0.25 , 2.30]**	
Total events:	6		8				

Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Chi² = 2.19, df = 1 (P = 0.14), I² = 54.3%

Less with alkylating agents — Less with control

Analysis 5.2.   Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Alkylating agents		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
5.2.1 Final follow-up < 10 years							
Donadio 1974	0	11	0	11		Not estimable	
Kosmadakis 2010	0	8	0	10		Not estimable	
Ponticelli 1992	0	45	2	47	3.5%	0.21 [0.01 , 4.23]	
Pahari 1993	1	36	2	35	5.7%	0.49 [0.05 , 5.12]	
Howman 2013	1	33	4	37	6.9%	0.28 [0.03 , 2.38]	
Braun 1995	2	31	2	22	8.9%	0.71 [0.11 , 4.66]	
Falk 1992	4	13	4	13	23.7%	1.00 [0.32 , 3.17]	
Subtotal (95% CI)		**177**		**175**	**48.7%**	**0.64 [0.29 , 1.44]**	
Total events:	8		14				
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 4 (P = 0.76); I² = 0%							
Test for overall effect: Z = 1.07 (P = 0.29)							
5.2.2 Final follow-up ≥ 10 years							
Imbasciati 1980	2	42	9	39	14.6%	0.21 [0.05 , 0.90]	
Jha 2007	5	51	16	53	36.7%	0.32 [0.13 , 0.82]	
Subtotal (95% CI)		**93**		**92**	**51.3%**	**0.29 [0.13 , 0.63]**	
Total events:	7		25				
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%							
Test for overall effect: Z = 3.13 (P = 0.002)							
Total (95% CI)		**270**		**267**	**100.0%**	**0.42 [0.24 , 0.74]**	
Total events:	15		39				
Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 6 (P = 0.66); I² = 0%							
Test for overall effect: Z = 2.99 (P = 0.003)							
Test for subgroup differences: Chi² = 2.02, df = 1 (P = 0.16), I² = 50.5%							

0.01   0.1   1   10   100
Less with alkylating agents   Less with control

Analysis 5.3. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 3: Complete or partial remission

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 Complete or partial remission at final follow-up (< 2 years)							
Donadio 1974	4	11	2	11	3.0%	2.00 [0.46 , 8.76]	
Hasegawa 2017	8	18	5	18	6.3%	1.60 [0.65 , 3.96]	
Ahmed 1994	8	10	6	10	10.1%	1.33 [0.74 , 2.41]	
Kosmadakis 2010	8	8	10	10	17.0%	1.00 [0.82 , 1.23]	
Subtotal (95% CI)		**47**		**49**	**36.4%**	**1.26 [0.76 , 2.09]**	
Total events:	28		23				
Heterogeneity: Tau² = 0.14; Chi² = 7.28, df = 3 (P = 0.06); I² = 59%							
Test for overall effect: Z = 0.91 (P = 0.36)							
5.3.2 Complete or partial remission at final follow-up (≥ 2 years)							
Imbasciati 1980	26	42	13	39	11.6%	1.86 [1.12 , 3.07]	
Braun 1995	14	31	14	22	11.7%	0.71 [0.43 , 1.17]	
Ponticelli 1992	20	32	13	31	11.8%	1.49 [0.91 , 2.44]	
Jha 2007	34	51	16	53	12.5%	2.21 [1.40 , 3.47]	
Pahari 1993	33	36	22	35	15.9%	1.46 [1.11 , 1.92]	
Subtotal (95% CI)		**192**		**180**	**63.6%**	**1.46 [1.04 , 2.04]**	
Total events:	127		78				
Heterogeneity: Tau² = 0.10; Chi² = 12.24, df = 4 (P = 0.02); I² = 67%							
Test for overall effect: Z = 2.18 (P = 0.03)							
Total (95% CI)		**239**		**229**	**100.0%**	**1.37 [1.04 , 1.82]**	
Total events:	155		101				
Heterogeneity: Tau² = 0.11; Chi² = 26.43, df = 8 (P = 0.0009); I² = 70%							
Test for overall effect: Z = 2.24 (P = 0.03)							
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%							

0.02   0.1   1   10   50
More with control   More with alkylating agents

Analysis 5.4. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 4: Complete remission

Study or Subgroup	Alkylating agents		Control		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
5.4.1 Complete remission at final follow-up (< 2 years)							
Donadio 1974	0	11	0	11		Not estimable	
Kosmadakis 2010	4	8	0	10	2.6%	11.00 [0.68 , 178.34]	
Ahmed 1994	5	10	3	10	12.1%	1.67 [0.54 , 5.17]	
Subtotal (95% CI)		29		31	14.7%	2.93 [0.46 , 18.52]	
Total events:	9		3				
Heterogeneity: Tau² = 0.93; Chi² = 1.79, df = 1 (P = 0.18); I² = 44%							
Test for overall effect: Z = 1.14 (P = 0.25)							
5.4.2 Complete remission at final follow-up (≥ 2 years)							
Imbasciati 1980	17	42	2	39	8.7%	7.89 [1.95 , 31.97]	
Braun 1995	6	31	4	22	11.9%	1.06 [0.34 , 3.33]	
Jha 2007	15	51	5	53	15.6%	3.12 [1.22 , 7.95]	
Ponticelli 1992	8	32	7	31	16.7%	1.11 [0.46 , 2.69]	
Pahari 1993	33	36	15	35	32.4%	2.14 [1.44 , 3.18]	
Subtotal (95% CI)		192		180	85.3%	2.10 [1.22 , 3.60]	
Total events:	79		33				
Heterogeneity: Tau² = 0.17; Chi² = 7.78, df = 4 (P = 0.10); I² = 49%							
Test for overall effect: Z = 2.69 (P = 0.007)							
Total (95% CI)		221		211	100.0%	2.12 [1.33 , 3.38]	
Total events:	88		36				
Heterogeneity: Tau² = 0.13; Chi² = 9.50, df = 6 (P = 0.15); I² = 37%							
Test for overall effect: Z = 3.18 (P = 0.001)							
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%							

0.005 0.1 1 10 200
More with control   More with alkylating agents

Analysis 5.5. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 5: Partial remission

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.5.1 Partial remission at final follow-up (< 2 years)							
Donadio 1974	4	11	2	11	7.9%	2.00 [0.46 , 8.76]	
Ahmed 1994	3	10	3	10	8.9%	1.00 [0.26 , 3.81]	
Kosmadakis 2010	4	8	10	10	17.1%	0.52 [0.27 , 1.02]	
Subtotal (95% CI)		**29**		**31**	**33.9%**	**0.83 [0.37 , 1.87]**	
Total events:	11		15				
Heterogeneity: Tau² = 0.21; Chi² = 3.26, df = 2 (P = 0.20); I² = 39%							
Test for overall effect: Z = 0.45 (P = 0.65)							
5.5.2 Partial remission at final follow-up (≥ 2 years)							
Pahari 1993	0	36	7	35	2.8%	0.06 [0.00 , 1.09]	
Ponticelli 1992	12	32	6	31	14.4%	1.94 [0.83 , 4.52]	
Imbasciati 1980	9	42	11	39	15.6%	0.76 [0.35 , 1.63]	
Braun 1995	8	31	10	22	15.8%	0.57 [0.27 , 1.20]	
Jha 2007	19	51	11	53	17.6%	1.80 [0.95 , 3.39]	
Subtotal (95% CI)		**192**		**180**	**66.1%**	**0.96 [0.48 , 1.91]**	
Total events:	48		45				
Heterogeneity: Tau² = 0.37; Chi² = 11.93, df = 4 (P = 0.02); I² = 66%							
Test for overall effect: Z = 0.11 (P = 0.91)							
Total (95% CI)		**221**		**211**	**100.0%**	**0.94 [0.57 , 1.55]**	
Total events:	59		60				
Heterogeneity: Tau² = 0.27; Chi² = 16.22, df = 7 (P = 0.02); I² = 57%							
Test for overall effect: Z = 0.26 (P = 0.79)							
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%							

0.002   0.1   1   10   500
More with control   More with alkylating agents

Analysis 5.6. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 6: Increase in serum creatinine

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.6.1 100% increase in serum creatinine							
Murphy 1992	1	13	0	13	4.2%	3.00 [0.13 , 67.51]	
Donadio 1974	1	11	2	11	7.3%	0.50 [0.05 , 4.75]	
Ahmed 1994	1	10	2	10	7.4%	0.50 [0.05 , 4.67]	
Imbasciati 1980	1	42	13	39	8.9%	0.07 [0.01 , 0.52]	
Falk 1992	5	13	4	13	19.8%	1.25 [0.43 , 3.63]	
Braun 1995	8	31	6	22	22.9%	0.95 [0.38 , 2.34]	
Jha 2007	10	51	26	53	29.4%	0.40 [0.22 , 0.74]	
Subtotal (95% CI)		**171**		**161**	**100.0%**	**0.59 [0.30 , 1.16]**	
Total events:	27		53				

Heterogeneity: Tau² = 0.30; Chi² = 10.41, df = 6 (P = 0.11); I² = 42%
Test for overall effect: Z = 1.54 (P = 0.12)

Study or Subgroup	Events	Total	Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	
5.6.2 50% increase in serum creatinine							
Murphy 1992	2	13	1	13	6.0%	2.00 [0.21 , 19.44]	
Donadio 1974	1	11	2	11	6.2%	0.50 [0.05 , 4.75]	
Pahari 1993	1	36	5	35	7.0%	0.19 [0.02 , 1.58]	
Falk 1992	6	13	5	13	24.5%	1.20 [0.49 , 2.96]	
Ponticelli 1992	7	45	11	47	26.1%	0.66 [0.28 , 1.56]	
Imbasciati 1980	7	42	20	39	30.2%	0.33 [0.15 , 0.68]	
Subtotal (95% CI)		**160**		**158**	**100.0%**	**0.60 [0.33 , 1.08]**	
Total events:	24		44				

Heterogeneity: Tau² = 0.16; Chi² = 7.23, df = 5 (P = 0.20); I² = 31%
Test for overall effect: Z = 1.71 (P = 0.09)

0.005   0.1   1   10   200
Less with alkylating agents   Less with control

Analysis 5.7. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 7: Relapse after complete or partial remission

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pahari 1993	2	33	3	22	16.8%	0.44 [0.08 , 2.45]	
Braun 1995	5	31	5	22	39.6%	0.71 [0.23 , 2.16]	
Jha 2007	8	34	4	19	43.6%	1.12 [0.39 , 3.23]	
Total (95% CI)		**98**		**63**	**100.0%**	**0.80 [0.40 , 1.61]**	
Total events:	15		12				

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

0.002   0.1   1   10   500
More with control   More with immunosuppressive

Analysis 5.8. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Braun 1995	0	31	0	11		Not estimable	
Kosmadakis 2010	0	8	0	10		Not estimable	
Murphy 1992	1	13	0	13	12.7%	3.00 [0.13 , 67.51]	
Imbasciati 1980	4	42	0	39	14.8%	8.37 [0.47 , 150.62]	
Jha 2007	5	51	0	53	15.0%	11.42 [0.65 , 201.45]	
Donadio 1974	3	11	0	11	15.2%	7.00 [0.40 , 121.39]	
Tiller 1981	7	27	0	27	15.6%	15.00 [0.90 , 250.24]	
Ponticelli 1992	4	45	1	47	26.7%	4.18 [0.49 , 35.97]	
Total (95% CI)		**228**		**211**	**100.0%**	**6.82 [2.24 , 20.71]**	
Total events:	24		1				

Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)
Test for subgroup differences: Not applicable

0.002   0.1   1   10   500
Less with alkylating agents   Less with control

Analysis 5.9. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 9: Adverse events

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.9.1 Adverse events							
Donadio 1974	3	11	0	11	2.0%	7.00 [0.40 , 121.39]	
Ponticelli 1992	9	45	7	47	20.3%	1.34 [0.55 , 3.30]	
Howman 2013	20	33	16	37	77.6%	1.40 [0.88 , 2.22]	
Subtotal (95% CI)		**89**		**95**	**100.0%**	**1.44 [0.96 , 2.15]**	
Total events:	32		23				
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 1.75 (P = 0.08)							
5.9.2 Infection							
Howman 2013	3	33	2	37	100.0%	1.68 [0.30 , 9.45]	
Subtotal (95% CI)		**33**		**37**	**100.0%**	**1.68 [0.30 , 9.45]**	
Total events:	3		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.59 (P = 0.56)							
5.9.3 Malignancy							
Howman 2013	2	69	0	38	45.3%	2.79 [0.14 , 56.57]	
Ponticelli 1992	1	45	1	47	54.7%	1.04 [0.07 , 16.20]	
Subtotal (95% CI)		**114**		**85**	**100.0%**	**1.63 [0.21 , 12.37]**	
Total events:	3		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%							
Test for overall effect: Z = 0.47 (P = 0.64)							

Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² = 0%

0.005   0.1   1   10   200
Less with alkylating agents   Less with control

Analysis 5.10. Comparison 5: Oral alkylating agents ± steroids versus placebo/no treatment/steroids, Outcome 10: Final GFR [mL/min/1.73 m²]

Study or Subgroup	Alkylating agents			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Donadio 1974	76.67	18.76	9	82	27.77	10	100.0%	-5.33 [-26.46 , 15.80]	
Total (95% CI)			**9**			**10**	**100.0%**	**-5.33 [-26.46 , 15.80]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable

-50   -25   0   25   50
Higher with control   Higher with alkylating agents

Comparison 6. Cyclophosphamide + steroids versus chlorambucil + steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Death	2	115	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
6.2 ESKD (dialysis/transplantation)	2	115	Risk Ratio (M-H, Random, 95% CI)	3.01 [0.61, 14.81]
6.3 Complete or partial remission	2	115	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.01, 1.50]
6.4 Complete remission	2	115	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.84, 2.90]
6.5 Partial remission	2	115	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.41, 2.15]
6.6 Increase in serum creatinine	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.6.1 100% increase in serum creatinine (15 months)	1	20	Risk Ratio (M-H, Random, 95% CI)	6.00 [0.87, 41.21]
6.6.2 50% increase in serum creatinine (15 to 39 months)	2	115	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.93, 4.39]
6.7 Temporary or permanent discontinuation/hospitalisation due to adverse events	2	115	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.13, 1.82]
6.8 Final serum creatinine	2	101	Mean Difference (IV, Random, 95% CI)	28.25 [-73.04, 129.54]
6.9 Final proteinuria	1	87	Mean Difference (IV, Random, 95% CI)	-0.42 [-1.53, 0.69]

Analysis 6.1. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 1: Death

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 1998	0	45	0	50		Not estimable	
Reichert 1994	1	10	0	10	100.0%	3.00 [0.14 , 65.90]	
Total (95% CI)		**55**		**60**	**100.0%**	**3.00 [0.14 , 65.90]**	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable

Less with CPA   Less with chlorambucil
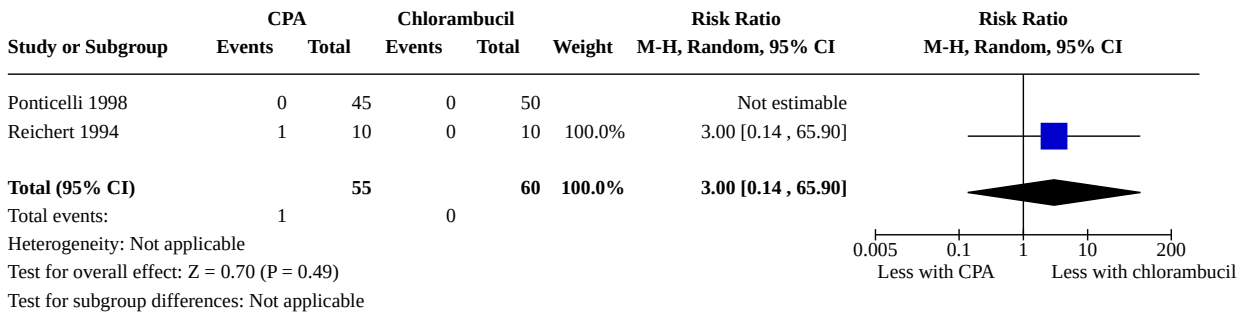
Analysis 6.2. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 1998	1	45	1	50	33.8%	1.11 [0.07 , 17.25]	
Reichert 1994	5	10	1	10	66.2%	5.00 [0.70 , 35.50]	
Total (95% CI)		**55**		**60**	**100.0%**	**3.01 [0.61 , 14.81]**	
Total events:	6		2				

Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

Less with CPA   Less with chlorambucil
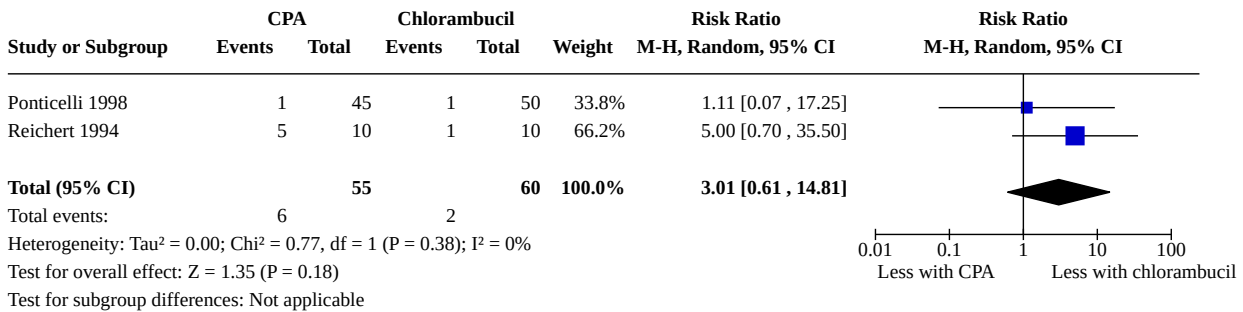
Analysis 6.3. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 3: Complete or partial remission

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Reichert 1994	3	10	3	10	2.2%	1.00 [0.26 , 3.81]	
Ponticelli 1998	40	45	36	50	97.8%	1.23 [1.01 , 1.51]	
Total (95% CI)		**55**		**60**	**100.0%**	**1.23 [1.01 , 1.50]**	
Total events:	43		39				

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable

More with chlorambucil   More with CPA
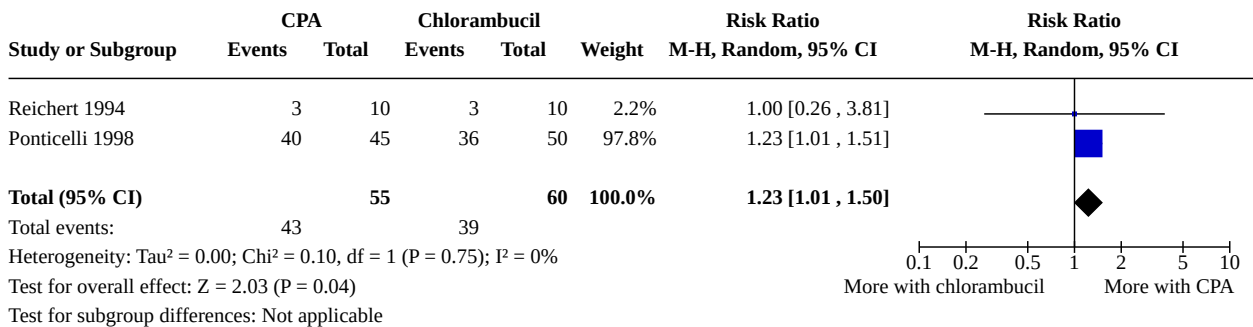
Analysis 6.4. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 4: Complete remission

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI
Reichert 1994	2	10	0	10	4.5%	5.00 [0.27 , 92.62]
Ponticelli 1998	16	45	12	50	95.5%	1.48 [0.79 , 2.78]
Total (95% CI)		**55**		**60**	**100.0%**	**1.56 [0.84 , 2.90]**
Total events:	18		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
More with chlorambucil   More with CPA
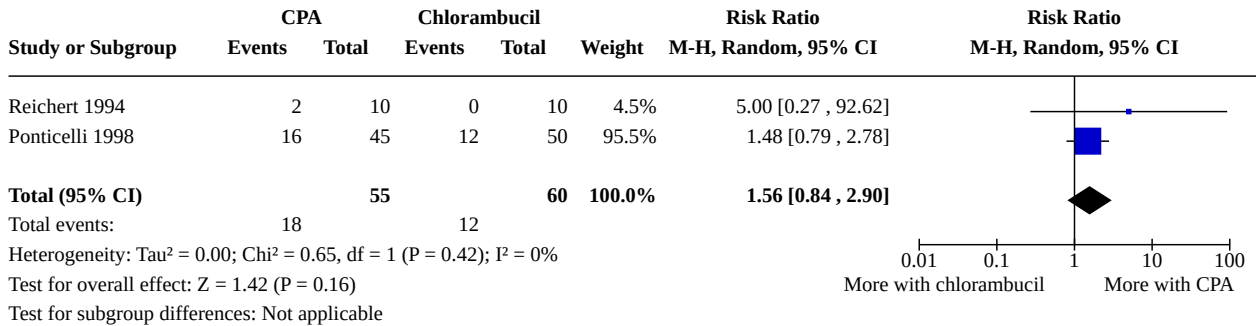
Analysis 6.5. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 5: Partial remission

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI
Reichert 1994	1	10	3	10	13.7%	0.33 [0.04 , 2.69]
Ponticelli 1998	24	45	24	50	86.3%	1.11 [0.75 , 1.65]
Total (95% CI)		**55**		**60**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	25		27			

Heterogeneity: Tau² = 0.16; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI
0.02 0.1 1 10 50
More with chlorambucil   More with CPA

Analysis 6.6. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 6: Increase in serum creatinine

Study or Subgroup	CPA Events	CPA Total	Chlorambucil Events	Chlorambucil Total	Weight	Risk Ratio M-H, Random, 95% CI
6.6.1 100% increase in serum creatinine (15 months)						
Reichert 1994	6	10	1	10	100.0%	6.00 [0.87 , 41.21]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**6.00 [0.87 , 41.21]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
6.6.2 50% increase in serum creatinine (15 to 39 months)						
Ponticelli 1998	2	45	1	50	10.7%	2.22 [0.21 , 23.69]
Reichert 1994	8	10	4	10	89.3%	2.00 [0.88 , 4.54]
Subtotal (95% CI)		**55**		**60**	**100.0%**	**2.02 [0.93 , 4.39]**
Total events:	10		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)

Risk Ratio M-H, Random, 95% CI
0.02 0.1 1 10 50
Less with CPA   Less with chlorambucil

Analysis 6.7. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 7: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	CPA Events	Total	Chlorambucil Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Reichert 1994	1	10	1	10	25.8%	1.00 [0.07 , 13.87]	
Ponticelli 1998	2	45	6	50	74.2%	0.37 [0.08 , 1.74]	
Total (95% CI)		**55**		**60**	**100.0%**	**0.48 [0.13 , 1.82]**	
Total events:	3		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with CPA   Less with chlorambucil

Analysis 6.8. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 8: Final serum creatinine

Study or Subgroup	CPA Mean [µmol/L]	SD [µmol/L]	Total	Chlorambucil Mean [µmol/L]	SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
Reichert 1994	371.8	265.73	5	222.44	91.44	9	15.4%	149.36 [-91.10 , 389.82]	
Ponticelli 1998	116.7	152	43	110.5	121.1	44	84.6%	6.20 [-51.63 , 64.03]	
Total (95% CI)			**48**			**53**	**100.0%**	**28.25 [-73.04 , 129.54]**	

Heterogeneity: Tau² = 2286.33; Chi² = 1.29, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

-500 -250 0 250 500
Lower with CPA   Lower with chlorambucil

Analysis 6.9. Comparison 6: Cyclophosphamide + steroids versus chlorambucil + steroids, Outcome 9: Final proteinuria

Study or Subgroup	CPA Mean [g/24 h]	SD [g/24 h]	Total	Chlorambucil Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Ponticelli 1998	1.69	2.36	43	2.11	2.89	44	100.0%	-0.42 [-1.53 , 0.69]	
Total (95% CI)			**43**			**44**	**100.0%**	**-0.42 [-1.53 , 0.69]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

-2 -1 0 1 2
Lower with CPA   Lower with chlorambucil

Comparison 7. Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Death	1	26	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.50]
7.2 ESKD (dialysis/transplantation)	1	26	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.12, 58.48]
7.3 Complete or partial remission	1	26	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.77, 1.69]
7.4 Complete remission	1	26	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.45]
7.5 Partial remission	1	26	Risk Ratio (M-H, Random, 95% CI)	4.29 [0.58, 31.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.6 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	26	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.16]
7.7 Final serum creatinine	1	26	Mean Difference (IV, Random, 95% CI)	-12.00 [-73.26, 49.26]
7.8 Final GFR [mL/min/1.73 m²]	1	26	Mean Difference (IV, Random, 95% CI)	8.00 [-8.59, 24.59]
7.9 Final proteinuria	1	26	Mean Difference (IV, Random, 95% CI)	0.59 [-0.64, 1.82]

Analysis 7.1. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 1: Death

Study or Subgroup	Early CPA Events	Total	Late CPA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	0	14	1	12	100.0%	0.29 [0.01 , 6.50]	
Total (95% CI)		14		12	100.0%	0.29 [0.01 , 6.50]	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with early CPA   Less with late CPA
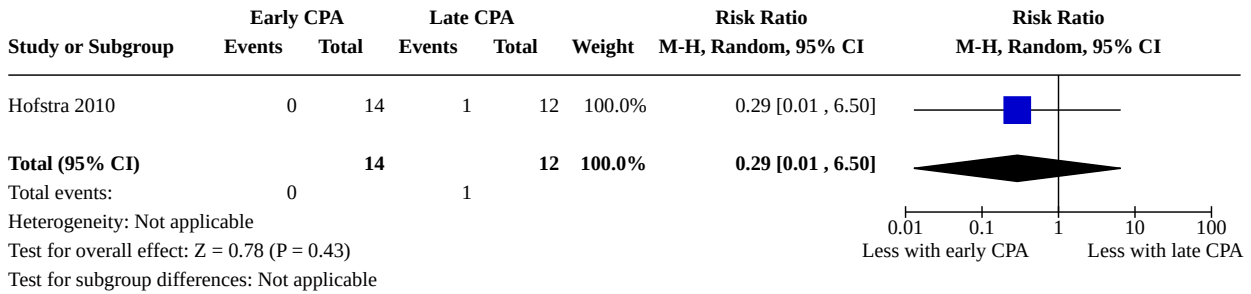
Analysis 7.2. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Early CPA Events	Total	Late CPA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	1	14	0	12	100.0%	2.60 [0.12 , 58.48]	
Total (95% CI)		14		12	100.0%	2.60 [0.12 , 58.48]	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with early CPA   Less with late CPA
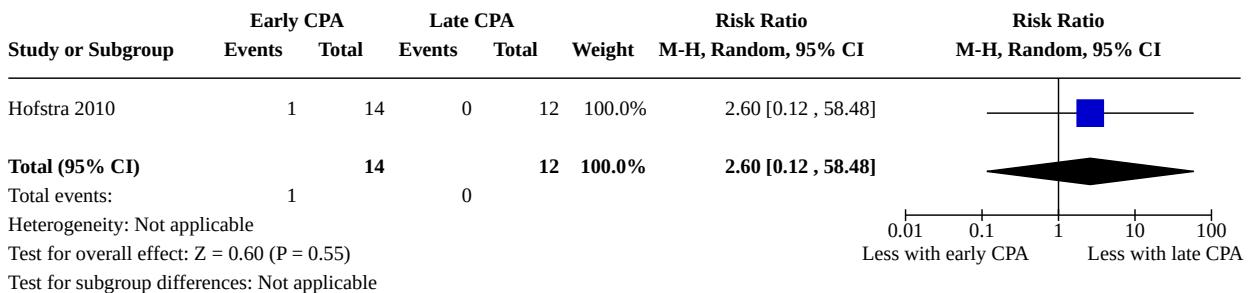
Analysis 7.3. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 3: Complete or partial remission

Study or Subgroup	Early CPA Events	Early CPA Total	Late CPA Events	Late CPA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	12	14	9	12	100.0%	1.14 [0.77 , 1.69]	
Total (95% CI)		14		12	100.0%	**1.14 [0.77 , 1.69]**	
Total events:	12		9				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable

0.5 0.7 1 1.5 2
More with late CPA   More with early CPA
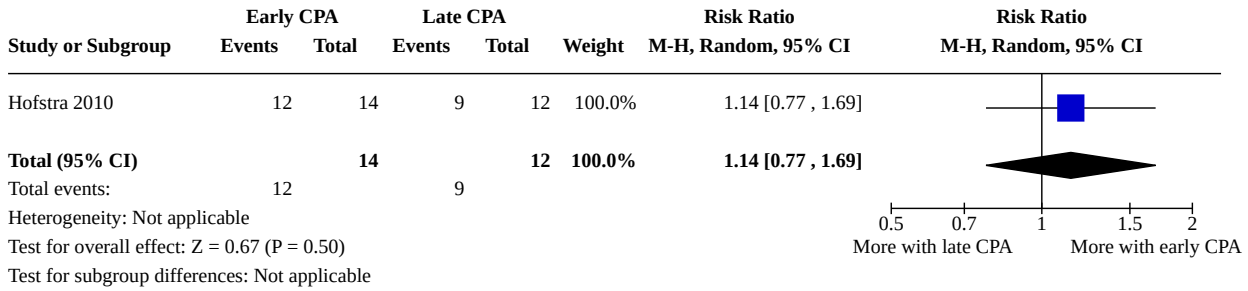
Analysis 7.4. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 4: Complete remission

Study or Subgroup	Early CPA Events	Early CPA Total	Late CPA Events	Late CPA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	7	14	8	12	100.0%	0.75 [0.39 , 1.45]	
Total (95% CI)		14		12	100.0%	**0.75 [0.39 , 1.45]**	
Total events:	7		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with late CPA   More with early CPA
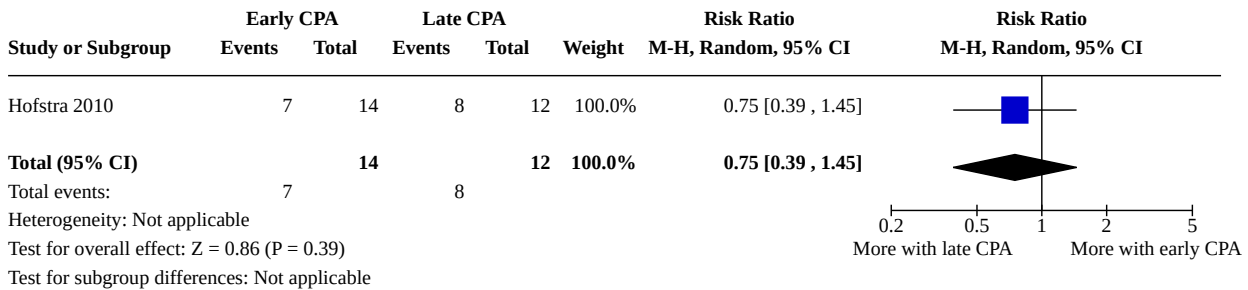
Analysis 7.5. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 5: Partial remission

Study or Subgroup	Early CPA Events	Early CPA Total	Late CPA Events	Late CPA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	5	14	1	12	100.0%	4.29 [0.58 , 31.79]	
Total (95% CI)		14		12	100.0%	**4.29 [0.58 , 31.79]**	
Total events:	5		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with late   More with early
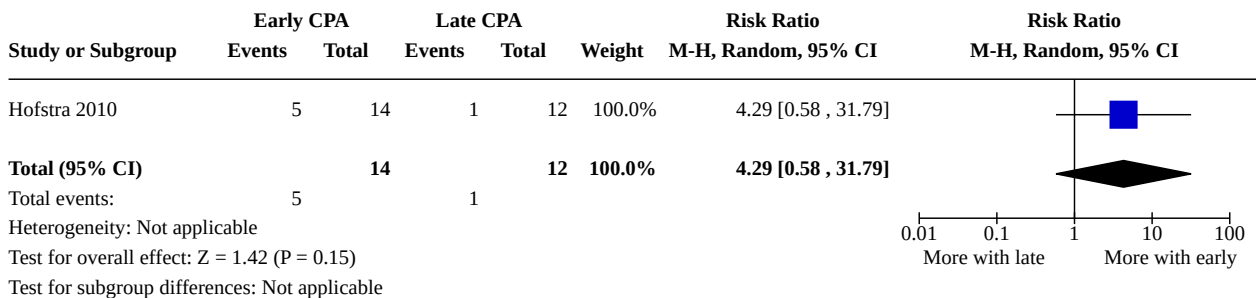
Analysis 7.6. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 6: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	Early CPA Events	Total	Late CPA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hofstra 2010	2	14	6	12	100.0%	0.29 [0.07 , 1.16]	
Total (95% CI)		**14**		**12**	**100.0%**	**0.29 [0.07 , 1.16]**	
Total events:	2		6				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable

0.05 0.2 1 5 20
Less with early CPA   Less with late CPA
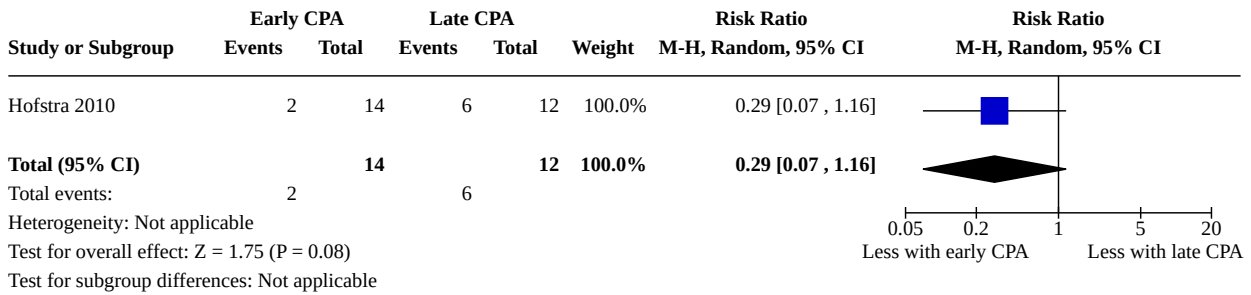
Analysis 7.7. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 7: Final serum creatinine

Study or Subgroup	Early CPA Mean [μmol/L]	SD [μmol/L]	Total	Late CPA Mean [μmol/L]	SD [μmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [μmol/L]	Mean Difference IV, Random, 95% CI [μmol/L]
Hofstra 2010	93	105.75	14	105	46.25	12	100.0%	-12.00 [-73.26 , 49.26]	
Total (95% CI)			**14**			**12**	**100.0%**	**-12.00 [-73.26 , 49.26]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Lower with early CPA   Lower with late CPA
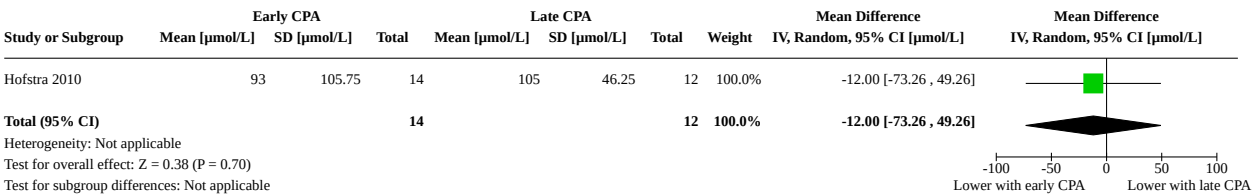
Analysis 7.8. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 8: Final GFR [mL/min/1.73 m²]

Study or Subgroup	Early CPA Mean	SD	Total	Late CPA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Hofstra 2010	76	25	14	68	18	12	100.0%	8.00 [-8.59 , 24.59]	
Total (95% CI)			**14**			**12**	**100.0%**	**8.00 [-8.59 , 24.59]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
Higher with late CPA   Higher with early CPA
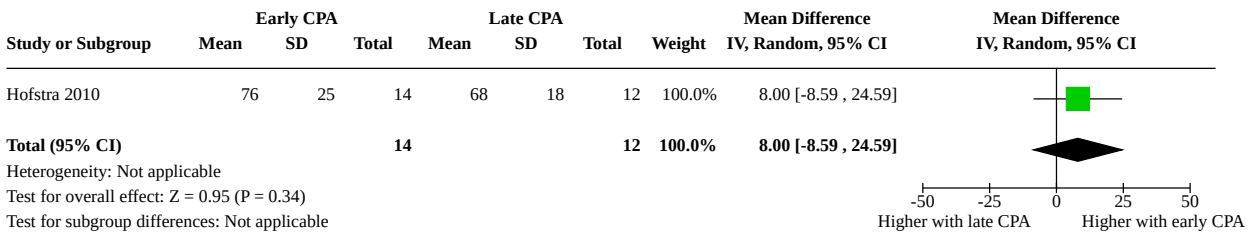
Analysis 7.9. Comparison 7: Early (immediate) cyclophosphamide + steroids versus late (when SCr increase > 25%) cyclophosphamide + steroids, Outcome 9: Final proteinuria

Study or Subgroup	Early CPA Mean [g/24 h]	SD [g/24 h]	Total	Late CPA Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Hofstra 2010	0.77	1.3325	14	0.18	1.78	12	100.0%	0.59 [-0.64 , 1.82]	
Total (95% CI)			**14**			**12**	**100.0%**	**0.59 [-0.64 , 1.82]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable

-2 -1 0 1 2
Lower with early CPA   Lower with late CPA
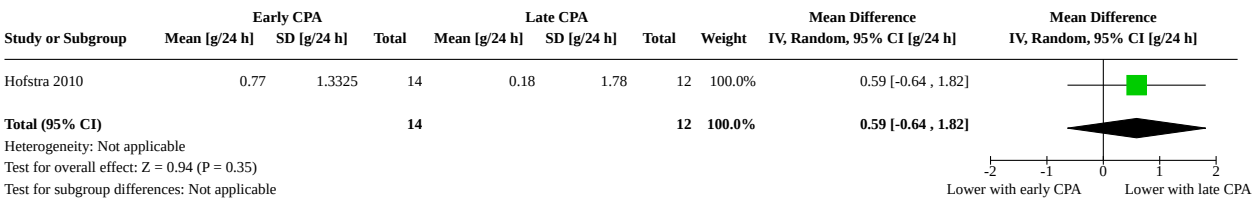
Comparison 8.   Cyclophosphamide + leflunomide + steroid versus leflunomide + steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Complete remission	1	48	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.99, 1.98]
8.2 Malignancy	1	70	Risk Ratio (M-H, Random, 95% CI)	5.59 [0.28, 112.34]

Analysis 8.1.   Comparison 8: Cyclophosphamide + leflunomide + steroid versus leflunomide + steroid, Outcome 1: Complete remission

Study or Subgroup	CPA+leflunomide Events	Total	Leflunomide Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Liu 2015e	21	24	15	24	100.0%	1.40 [0.99 , 1.98]	
Total (95% CI)		24		24	100.0%	**1.40 [0.99 , 1.98]**	
Total events:	21		15				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with leflunomide   More with CPA+leflunomide

Analysis 8.2.   Comparison 8: Cyclophosphamide + leflunomide + steroid versus leflunomide + steroid, Outcome 2: Malignancy

Study or Subgroup	Alkylating agents Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Howman 2013	2	33	0	37	100.0%	5.59 [0.28 , 112.34]	
Total (95% CI)		33		37	100.0%	**5.59 [0.28 , 112.34]**	
Total events:	2		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

0.005 0.1 1 10 200
Less with alkylating agents   Less with control

Comparison 9.   Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 ESKD (dialysis/transplantation)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1.1 MMF + TAC versus TAC alone	1	40	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 14.90]
9.2 Complete or partial remission	2	58	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.99, 1.48]
9.3 Complete remission	2	58	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.93, 1.51]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
9.3.1 MMF + CSA versus CSA alone	1	18	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.86, 1.86]
9.3.2 MMF + TAC versus TAC alone	1	40	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.55]
9.4 Partial remission	2	58	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.56, 3.18]
9.5 Relapse after complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.5.1 MMF + TAC versus TAC alone	1	35	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.73]
9.6 Severe adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.6.1 MMF + TAC versus TAC alone	1	40	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.70, 7.76]

Analysis 9.1. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 1: ESKD (dialysis/transplantation)

	MMF+CNI		CNI			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
9.1.1 MMF + TAC versus TAC alone							
Nikolopoulou 2019	1	20	1	20	100.0%	1.00 [0.07 , 14.90]	
Subtotal (95% CI)		20		20	100.0%	1.00 [0.07 , 14.90]	
Total events:	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

0.02 0.1 1 10 50
Less with MMF+CNI   Less with CNI alone

Analysis 9.2. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 2: Complete or partial remission

	MMF+CNI		CNI			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jurubita 2012	9	9	7	9	28.2%	1.27 [0.86 , 1.86]	
Nikolopoulou 2019	19	20	16	20	71.8%	1.19 [0.93 , 1.51]	
Total (95% CI)		29		29	100.0%	1.21 [0.99 , 1.48]	
Total events:	28		23				

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with CNI alone   More with MMF+CNI

Analysis 9.3. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 3: Complete remission

Study or Subgroup	MMF+CNI Events	Total	CNI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.3.1 MMF + CSA versus CSA alone							
Jurubita 2012	9	9	7	9	39.8%	1.27 [0.86 , 1.86]	
Subtotal (95% CI)		**9**		**9**	**39.8%**	**1.27 [0.86 , 1.86]**	
Total events:	9		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.20 (P = 0.23)							
9.3.2 MMF + TAC versus TAC alone							
Nikolopoulou 2019	17	20	15	20	60.2%	1.13 [0.83 , 1.55]	
Subtotal (95% CI)		**20**		**20**	**60.2%**	**1.13 [0.83 , 1.55]**	
Total events:	17		15				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.78 (P = 0.43)							
Total (95% CI)		**29**		**29**	**100.0%**	**1.18 [0.93 , 1.51]**	
Total events:	26		22				
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%							
Test for overall effect: Z = 1.37 (P = 0.17)							
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%							

0.5 0.7 1 1.5 2
More with CNI alone   More with MMF+CNI

Analysis 9.4. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 4: Partial remission

Study or Subgroup	MMF+CNI Events	Total	CNI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Nikolopoulou 2019	2	20	1	20	14.0%	2.00 [0.20 , 20.33]	
Jurubita 2012	5	9	4	9	86.0%	1.25 [0.49 , 3.19]	
Total (95% CI)		**29**		**29**	**100.0%**	**1.33 [0.56 , 3.18]**	
Total events:	7		5				
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.51)							
Test for subgroup differences: Not applicable							

0.01 0.1 1 10 100
More with CNI alone   More with MMF+CNI

Analysis 9.5. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 5: Relapse after complete or partial remission

Study or Subgroup	MMF+CNI Events	Total	CNI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.5.1 MMF + TAC versus TAC alone							
Nikolopoulou 2019	8	19	8	16	100.0%	0.84 [0.41 , 1.73]	
Subtotal (95% CI)		**19**		**16**	**100.0%**	**0.84 [0.41 , 1.73]**	
Total events:	8		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							

0.1 0.2 0.5 1 2 5 10
Less with MMF+CNI   Less with CNI alone
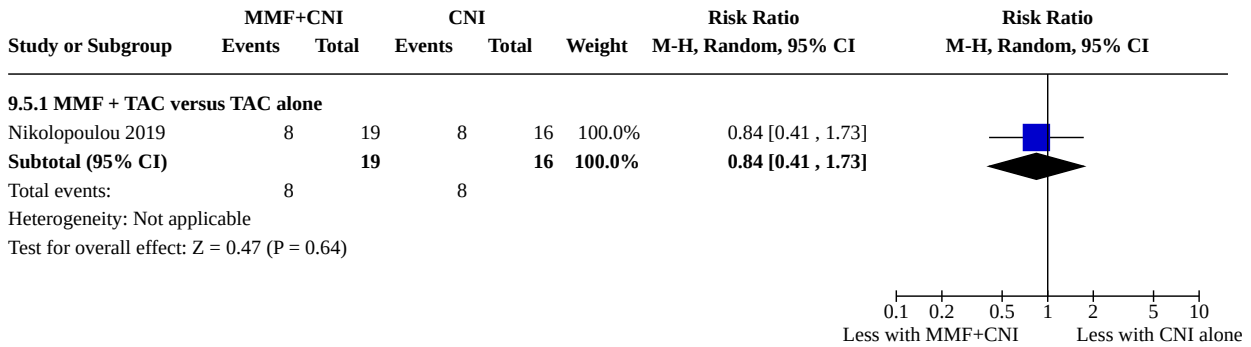
Analysis 9.6. Comparison 9: Mycophenolate mofetil + calcineurin inhibitors versus calcineurin inhibitors, Outcome 6: Severe adverse events
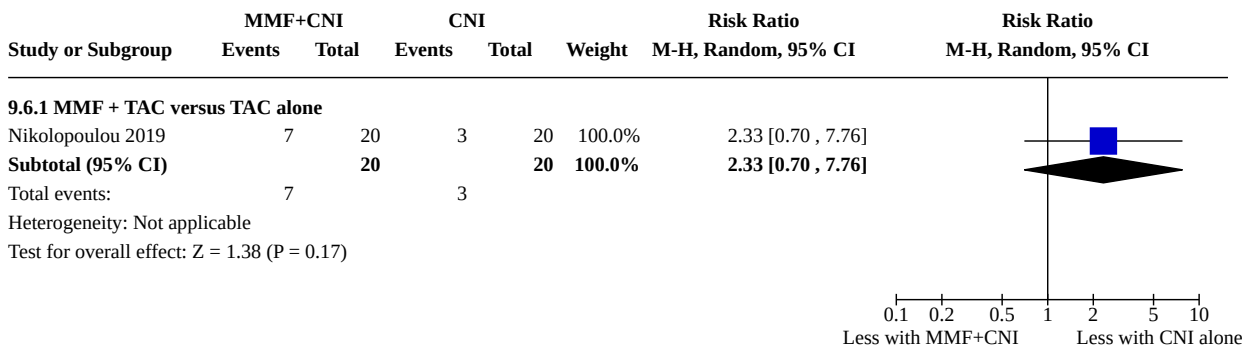
Study or Subgroup	MMF+CNI Events	Total	CNI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.6.1 MMF + TAC versus TAC alone							
Nikolopoulou 2019	7	20	3	20	100.0%	2.33 [0.70 , 7.76]	
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.33 [0.70 , 7.76]**	
Total events:	7		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							

0.1 0.2 0.5 1 2 5 10
Less with MMF+CNI   Less with CNI alone

Comparison 10. Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Death	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1.1 Death (any cause)	7	296	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.46, 6.14]
10.1.2 Death due to deteriorating kidney function	3	111	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.35, 14.75]
10.2 ESKD (dialysis/transplantation)	7	296	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.54, 2.60]
10.3 Complete or partial remission	5	206	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.62, 2.38]
10.3.1 Complete or partial remission (< 2 years)	3	92	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.30, 3.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3.2 Complete or partial remission (≥ 2 years)	2	114	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.39, 7.28]
10.4 Complete remission	5	206	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.51, 2.24]
10.4.1 Patients with normal kidney function	4	185	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.51, 2.92]
10.4.2 Patients with deteriorating kidney function	1	21	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.03]
10.5 Partial remission	5	206	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.53, 2.22]
10.5.1 Patients with normal kidney function	4	185	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.51, 2.78]
10.5.2 Patients with deteriorating kidney function	1	21	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.15, 3.53]
10.6 Relapse after complete or partial remission	2	92	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.79, 3.09]
10.7 Increase in serum creatinine	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.7.1 100% increase in serum creatinine	2	117	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.37, 1.86]
10.7.2 50% increase in serum creatinine	2	99	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.05, 5.75]
10.8 Temporary or permanent discontinuation/hospitalisation due to adverse events	5	161	Risk Ratio (M-H, Random, 95% CI)	5.45 [0.29, 101.55]
10.9 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.9.1 Serious adverse events	1	75	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.70, 1.90]
10.9.2 Infection	1	73	Risk Ratio (M-H, Random, 95% CI)	4.11 [0.94, 18.06]
10.9.3 Malignancy	1	107	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.14, 56.57]

Analysis 10.1. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids, Outcome 1: Death

Study or Subgroup	CNI Events	CNI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.1.1 Death (any cause)							
Kosmadakis 2010	0	10	0	10		Not estimable	
CYCLOMEN 1994	0	10	0	11		Not estimable	
Cattran 2001	1	28	0	23	16.8%	2.48 [0.11 , 58.20]	
Praga 2007	0	25	1	23	16.8%	0.31 [0.01 , 7.20]	
Cattran 1995	1	9	0	8	17.7%	2.70 [0.13 , 58.24]	
Braun 1995	2	44	0	22	18.6%	2.56 [0.13 , 51.05]	
Howman 2013	2	36	1	37	30.1%	2.06 [0.19 , 21.69]	
Subtotal (95% CI)		**162**		**134**	**100.0%**	**1.69 [0.46 , 6.14]**	
Total events:	6		2				
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 4 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.79 (P = 0.43)							
10.1.2 Death due to deteriorating kidney function							
CYCLOMEN 1994	0	10	0	11		Not estimable	
Cattran 1995	1	9	0	8	37.0%	2.70 [0.13 , 58.24]	
Howman 2013	2	36	1	37	63.0%	2.06 [0.19 , 21.69]	
Subtotal (95% CI)		**55**		**56**	**100.0%**	**2.27 [0.35 , 14.75]**	
Total events:	3		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%							
Test for overall effect: Z = 0.86 (P = 0.39)							
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%							

0.01   0.1   1   10   100
Less with CNI   Less with control

Analysis 10.2. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	CNI Events	CNI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kosmadakis 2010	0	10	0	10		Not estimable	
Praga 2007	0	25	0	23		Not estimable	
Cattran 2001	1	28	0	23	6.2%	2.48 [0.11 , 58.20]	
CYCLOMEN 1994	3	10	1	11	13.9%	3.30 [0.41 , 26.81]	
Cattran 1995	1	9	4	8	15.6%	0.22 [0.03 , 1.60]	
Braun 1995	4	44	2	22	22.8%	1.00 [0.20 , 5.04]	
Howman 2013	6	36	4	37	41.6%	1.54 [0.47 , 5.01]	
Total (95% CI)		**162**		**134**	**100.0%**	**1.18 [0.54 , 2.60]**	
Total events:	15		11				
Heterogeneity: Tau² = 0.03; Chi² = 4.13, df = 4 (P = 0.39); I² = 3%							
Test for overall effect: Z = 0.42 (P = 0.68)							
Test for subgroup differences: Not applicable							

0.01   0.1   1   10   100
Less with CNI   Less with control

Analysis 10.3. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids, Outcome 3: Complete or partial remission

	CNI		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
10.3.1 Complete or partial remission (< 2 years)							
CYCLOMEN 1994	2	10	4	11	12.4%	0.55 [0.13 , 2.38]	
Cattran 2001	11	28	3	23	15.9%	3.01 [0.95 , 9.52]	
Kosmadakis 2010	6	10	10	10	25.3%	0.62 [0.37 , 1.03]	
Subtotal (95% CI)		**48**		**44**	**53.6%**	**0.99 [0.30 , 3.22]**	
Total events:	19		17				
Heterogeneity: Tau² = 0.80; Chi² = 8.14, df = 2 (P = 0.02); I² = 75%							
Test for overall effect: Z = 0.02 (P = 0.99)							
10.3.2 Complete or partial remission (≥ 2 years)							
Praga 2007	15	25	4	23	18.7%	3.45 [1.34 , 8.89]	
Braun 1995	30	44	16	22	27.7%	0.94 [0.68 , 1.30]	
Subtotal (95% CI)		**69**		**45**	**46.4%**	**1.69 [0.39 , 7.28]**	
Total events:	45		20				
Heterogeneity: Tau² = 0.99; Chi² = 8.56, df = 1 (P = 0.003); I² = 88%							
Test for overall effect: Z = 0.71 (P = 0.48)							
Total (95% CI)		**117**		**89**	**100.0%**	**1.21 [0.62 , 2.38]**	
Total events:	64		37				
Heterogeneity: Tau² = 0.40; Chi² = 17.65, df = 4 (P = 0.001); I² = 77%							
Test for overall effect: Z = 0.56 (P = 0.57)							
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%							

0.05 0.2 1 5 20
More with control   More with CNI

Analysis 10.4. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/ no treatment/supportive treatment/steroids, Outcome 4: Complete remission

	CNI		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
10.4.1 Patients with normal kidney function							
Kosmadakis 2010	1	10	0	10	5.5%	3.00 [0.14 , 65.90]	
Cattran 2001	2	28	1	23	9.2%	1.64 [0.16 , 16.99]	
Praga 2007	8	25	3	23	28.7%	2.45 [0.74 , 8.15]	
Braun 1995	10	44	8	22	51.2%	0.63 [0.29 , 1.36]	
Subtotal (95% CI)		**107**		**78**	**94.6%**	**1.22 [0.51 , 2.92]**	
Total events:	21		12				
Heterogeneity: Tau² = 0.25; Chi² = 4.35, df = 3 (P = 0.23); I² = 31%							
Test for overall effect: Z = 0.44 (P = 0.66)							
10.4.2 Patients with deteriorating kidney function							
CYCLOMEN 1994	0	10	1	11	5.4%	0.36 [0.02 , 8.03]	
Subtotal (95% CI)		**10**		**11**	**5.4%**	**0.36 [0.02 , 8.03]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		**117**		**89**	**100.0%**	**1.07 [0.51 , 2.24]**	
Total events:	21		13				
Heterogeneity: Tau² = 0.12; Chi² = 4.72, df = 4 (P = 0.32); I² = 15%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%							

0.01 0.1 1 10 100
More with control   More with CNI

Analysis 10.5. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/ no treatment/supportive treatment/steroids, Outcome 5: Partial remission

Study or Subgroup	CNI Events	CNI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.5.1 Patients with normal kidney function							
Praga 2007	7	25	2	23	14.2%	3.22 [0.74 , 13.95]	
Cattran 2001	9	28	2	23	14.7%	3.70 [0.89 , 15.44]	
Kosmadakis 2010	5	10	10	10	28.1%	0.52 [0.29 , 0.96]	
Braun 1995	20	44	12	22	30.0%	0.83 [0.51 , 1.37]	
Subtotal (95% CI)		**107**		**78**	**86.9%**	**1.19 [0.51 , 2.78]**	
Total events:	41		26				
Heterogeneity: Tau² = 0.49; Chi² = 11.70, df = 3 (P = 0.009); I² = 74%							
Test for overall effect: Z = 0.41 (P = 0.68)							
10.5.2 Patients with deteriorating kidney function							
CYCLOMEN 1994	2	10	3	11	13.1%	0.73 [0.15 , 3.53]	
Subtotal (95% CI)		**10**		**11**	**13.1%**	**0.73 [0.15 , 3.53]**	
Total events:	2		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.39 (P = 0.70)							
Total (95% CI)		**117**		**89**	**100.0%**	**1.08 [0.53 , 2.22]**	
Total events:	43		29				
Heterogeneity: Tau² = 0.38; Chi² = 11.50, df = 4 (P = 0.02); I² = 65%							
Test for overall effect: Z = 0.22 (P = 0.82)							
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%							

0.05 0.2 1 5 20
More with control   More with CNI

Analysis 10.6. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/ supportive treatment/steroids, Outcome 6: Relapse after complete or partial remission

Study or Subgroup	CNI Events	CNI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cattran 2001	10	21	2	5	34.7%	1.19 [0.37 , 3.81]	
Braun 1995	18	44	5	22	65.3%	1.80 [0.77 , 4.20]	
Total (95% CI)		**65**		**27**	**100.0%**	**1.56 [0.79 , 3.09]**	
Total events:	28		7				
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%							
Test for overall effect: Z = 1.27 (P = 0.20)							
Test for subgroup differences: Not applicable							

0.01 0.1 1 10 100
More with control   More with CNI

Analysis 10.7. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids, Outcome 7: Increase in serum creatinine

	CNI		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
10.7.1 100% increase in serum creatinine							
Cattran 2001	4	28	2	23	25.0%	1.64 [0.33 , 8.18]	
Braun 1995	8	44	6	22	75.0%	0.67 [0.26 , 1.68]	
Subtotal (95% CI)		**72**		**45**	**100.0%**	**0.84 [0.37 , 1.86]**	
Total events:	12		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
10.7.2 50% increase in serum creatinine							
Praga 2007	1	25	6	23	46.4%	0.15 [0.02 , 1.18]	
Cattran 2001	4	28	2	23	53.6%	1.64 [0.33 , 8.18]	
Subtotal (95% CI)		**53**		**46**	**100.0%**	**0.55 [0.05 , 5.75]**	
Total events:	5		8				
Heterogeneity: Tau² = 2.02; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%							
Test for overall effect: Z = 0.50 (P = 0.61)							
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%							

0.01   0.1   1   10   100
Less with CNI   Less with control

Analysis 10.8. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/no treatment/supportive treatment/steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

	CNI		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Kosmadakis 2010	0	10	0	10		Not estimable	
Praga 2007	0	25	0	23		Not estimable	
Braun 1995	0	44	0	11		Not estimable	
Cattran 1995	0	9	0	8		Not estimable	
CYCLOMEN 1994	2	10	0	11	100.0%	5.45 [0.29 , 101.55]	
Total (95% CI)		**98**		**63**	**100.0%**	**5.45 [0.29 , 101.55]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.14 (P = 0.26)							
Test for subgroup differences: Not applicable							

0.002   0.1   1   10   500
Less with CNI   Less with control
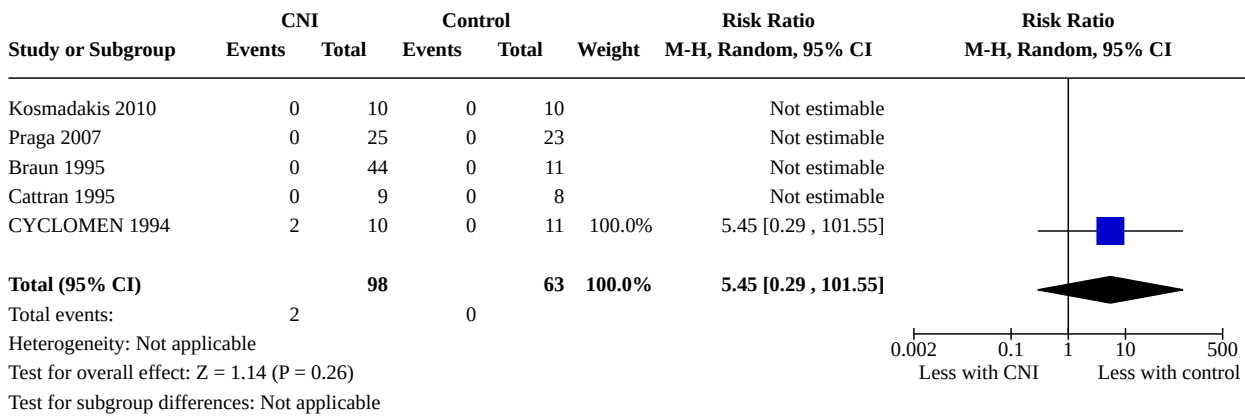
Analysis 10.9. Comparison 10: Calcineurin inhibitors ± steroids versus placebo/ no treatment/supportive treatment/steroids, Outcome 9: Adverse events

Study or Subgroup	CNI Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.9.1 Serious adverse events							
Howman 2013	18	37	16	38	100.0%	1.16 [0.70 , 1.90]	
Subtotal (95% CI)		**37**		**38**	**100.0%**	**1.16 [0.70 , 1.90]**	
Total events:	18		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
10.9.2 Infection							
Howman 2013	8	36	2	37	100.0%	4.11 [0.94 , 18.06]	
Subtotal (95% CI)		**36**		**37**	**100.0%**	**4.11 [0.94 , 18.06]**	
Total events:	8		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.87 (P = 0.06)							
10.9.3 Malignancy							
Howman 2013	2	69	0	38	100.0%	2.79 [0.14 , 56.57]	
Subtotal (95% CI)		**69**		**38**	**100.0%**	**2.79 [0.14 , 56.57]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							

Test for subgroup differences: Chi² = 2.77, df = 2 (P = 0.25), I² = 27.8%

0.01 0.1 1 10 100
Less with CNI   Less with control

Comparison 11. Calcineurin inhibitors ± steroids versus alkylating agents ± steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Death	7	394	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.35, 2.34]
11.2 ESKD (dialysis/transplantation)	5	293	Risk Ratio (M-H, Random, 95% CI)	2.40 [0.64, 9.01]
11.3 Complete or partial remission	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.3.1 Complete or partial remission at final follow-up	10	538	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.15]
11.3.2 Complete or partial remission at final follow-up (≥ 2 years)	3	169	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.66, 1.35]
11.4 Complete remission	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.4.1 Complete remission at final follow-up	10	538	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.84, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.4.2 Complete remission at final follow-up (≥ 2 years)	3	169	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.47, 2.18]
11.5 Partial remission	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.5.1 Partial remission at final follow-up	10	538	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.18]
11.5.2 Partial remission at final follow-up (≥ 2 years)	3	169	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.09, 1.32]
11.6 Relapse after complete or partial remission	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.6.1 Relapse after complete or partial remission (< 2 years)	6	295	Risk Ratio (M-H, Random, 95% CI)	2.13 [0.71, 6.37]
11.6.2 Relapse after complete or partial remission (≥ 2 years)	2	88	Risk Ratio (M-H, Random, 95% CI)	3.78 [1.01, 14.18]
11.7 Increase in serum creatinine	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.7.1 100% increase in serum creatinine	2	132	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.30, 1.67]
11.7.2 50% increase in serum creatinine	4	286	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.8 Temporary or permanent discontinuation/hospitalisation due to adverse events	3	151	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.31, 6.67]
11.9 Adverse events	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.9.1 Serious adverse events	10	567	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.64, 1.20]
11.9.2 Infection	9	552	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.43, 1.71]
11.9.3 Malignancy	2	127	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.69]
11.10 Final serum creatinine	1	70	Mean Difference (IV, Random, 95% CI)	0.06 [-0.04, 0.16]
11.11 Final serum albumin	5	227	Mean Difference (IV, Random, 95% CI)	1.34 [-1.82, 4.49]
11.12 Final GFR [mL/min/1.73 m^2]	4	206	Mean Difference (IV, Random, 95% CI)	-0.52 [-6.94, 5.90]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.13 Loss of GFR > 20%	1	69	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.00, 1.95]
11.14 Final proteinuria	8	443	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.66, 0.26]

Analysis 11.1. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 1: Death

	CNI		Alkylating agents			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chen 2010a	0	39	0	34		Not estimable	
Kosmadakis 2010	0	10	0	8		Not estimable	
Liang 2017	0	30	0	28		Not estimable	
Peng 2016	1	30	0	30	9.1%	3.00 [0.13 , 70.83]	
Agarwal 2012a	1	20	1	21	12.5%	1.05 [0.07 , 15.68]	
Howman 2013	2	36	2	33	25.2%	0.92 [0.14 , 6.14]	
Braun 1995	4	44	4	31	53.3%	0.70 [0.19 , 2.60]	
Total (95% CI)		**209**		**185**	**100.0%**	**0.90 [0.35 , 2.34]**	
Total events:	8		7				

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable

0.005 0.1 1 10 200
Less with CNI   Less with alkylating agents

Analysis 11.2. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 2: ESKD (dialysis/transplantation)

	CNI		Alkylating agents			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chen 2010a	0	39	0	34		Not estimable	
Kosmadakis 2010	0	10	0	8		Not estimable	
Liang 2017	0	30	0	28		Not estimable	
Howman 2013	6	36	1	33	39.2%	5.50 [0.70 , 43.31]	
Braun 1995	4	44	2	31	60.8%	1.41 [0.27 , 7.22]	
Total (95% CI)		**159**		**134**	**100.0%**	**2.40 [0.64 , 9.01]**	
Total events:	10		3				

Heterogeneity: Tau² = 0.05; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with CNI   Less with alkylating agents

Analysis 11.3. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 3: Complete or partial remission

Study or Subgroup	CNI Events	Total	Alkylating agent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.3.1 Complete or partial remission at final follow-up							
Kosmadakis 2010	6	10	8	8	4.5%	0.63 [0.37 , 1.05]	
Braun 1995	32	44	16	31	6.8%	1.41 [0.96 , 2.07]	
He 2013	23	28	18	28	8.4%	1.28 [0.92 , 1.77]	
Chen 2010a	33	39	22	34	9.8%	1.31 [0.99 , 1.73]	
Ramachandran 2016	23	35	31	35	10.3%	0.74 [0.57 , 0.97]	
Liang 2017	24	30	23	28	11.1%	0.97 [0.76 , 1.25]	
Peng 2016	25	29	22	28	11.3%	1.10 [0.86 , 1.40]	
Xu 2010	10	11	13	13	11.5%	0.91 [0.72 , 1.15]	
Agarwal 2012a	18	20	18	21	11.9%	1.05 [0.84 , 1.32]	
Xu 2013a (1)	21	24	39	42	14.3%	0.94 [0.79 , 1.12]	
Subtotal (95% CI)		**270**		**268**	**100.0%**	**1.01 [0.89 , 1.15]**	
Total events:	215		210				
Heterogeneity: Tau² = 0.02; Chi² = 19.26, df = 9 (P = 0.02); I² = 53%							
Test for overall effect: Z = 0.19 (P = 0.85)							
11.3.2 Complete or partial remission at final follow-up (≥ 2 years)							
Braun 1995	32	44	16	31	29.2%	1.41 [0.96 , 2.07]	
Ramachandran 2016	21	35	30	35	33.6%	0.70 [0.52 , 0.95]	
Xu 2010	10	11	13	13	37.2%	0.91 [0.72 , 1.15]	
Subtotal (95% CI)		**90**		**79**	**100.0%**	**0.95 [0.66 , 1.35]**	
Total events:	63		59				
Heterogeneity: Tau² = 0.07; Chi² = 8.20, df = 2 (P = 0.02); I² = 76%							
Test for overall effect: Z = 0.31 (P = 0.76)							

Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

0.2　0.5　1　2　5
More with alkylating agents　　More with CNI

Footnotes
(1) Data at 18 months

Analysis 11.4. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 4: Complete remission

Study or Subgroup	CNI Events	CNI Total	Alkylating agent Events	Alkylating agent Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.4.1 Complete remission at final follow-up							
Kosmadakis 2010	1	10	4	8	2.1%	0.20 [0.03 , 1.45]	
Braun 1995	10	44	8	31	8.3%	0.88 [0.39 , 1.98]	
Chen 2010a	11	39	9	34	9.0%	1.07 [0.50 , 2.26]	
Xu 2010	9	11	5	13	9.1%	2.13 [1.01 , 4.47]	
Peng 2016	16	29	8	28	10.0%	1.93 [0.99 , 3.78]	
He 2013	18	28	8	28	10.4%	2.25 [1.18 , 4.30]	
Liang 2017	15	30	12	28	11.8%	1.17 [0.67 , 2.04]	
Agarwal 2012a	13	20	11	21	12.4%	1.24 [0.74 , 2.09]	
Ramachandran 2016	15	35	20	35	13.1%	0.75 [0.46 , 1.21]	
Xu 2013a (1)	12	24	30	42	13.8%	0.70 [0.45 , 1.09]	
Subtotal (95% CI)		**270**		**268**	**100.0%**	**1.15 [0.84 , 1.56]**	
Total events:	120		115				

Heterogeneity: Tau² = 0.13; Chi² = 20.27, df = 9 (P = 0.02); I² = 56%
Test for overall effect: Z = 0.88 (P = 0.38)

Study or Subgroup	CNI Events	CNI Total	Alkylating agent Events	Alkylating agent Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.4.2 Complete remission at final follow-up (≥ 2 years)							
Braun 1995	10	44	8	31	30.4%	0.88 [0.39 , 1.98]	
Xu 2010	9	11	5	13	32.1%	2.13 [1.01 , 4.47]	
Ramachandran 2016	12	35	20	35	37.4%	0.60 [0.35 , 1.03]	
Subtotal (95% CI)		**90**		**79**	**100.0%**	**1.01 [0.47 , 2.18]**	
Total events:	31		33				

Heterogeneity: Tau² = 0.33; Chi² = 7.35, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 0.03 (P = 0.97)

Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%

0.02 0.1 1 10 50
More with alkylating agents   More with CNI

Footnotes
(1) Data at 18 months

Analysis 11.5. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 5: Partial remission

Study or Subgroup	CNI Events	Total	Alkylating agent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.5.1 Partial remission at final follow-up							
Xu 2010	1	11	8	13	3.1%	0.15 [0.02 , 1.01]	
Braun 1995	2	44	8	31	4.7%	0.18 [0.04 , 0.77]	
Kosmadakis 2010	5	10	4	8	9.0%	1.00 [0.39 , 2.53]	
He 2013	7	28	10	28	10.5%	0.70 [0.31 , 1.58]	
Agarwal 2012a	7	20	8	21	10.5%	0.92 [0.41 , 2.06]	
Ramachandran 2016	8	35	11	35	10.9%	0.73 [0.33 , 1.59]	
Xu 2013a (1)	9	24	9	42	11.0%	1.75 [0.81 , 3.80]	
Liang 2017	9	30	11	28	11.9%	0.76 [0.37 , 1.56]	
Peng 2016	9	29	14	28	12.9%	0.62 [0.32 , 1.20]	
Chen 2010a	22	39	13	34	15.5%	1.48 [0.89 , 2.45]	
Subtotal (95% CI)		**270**		**268**	**100.0%**	**0.82 [0.58 , 1.18]**	
Total events:	79		96				

Heterogeneity: Tau² = 0.15; Chi² = 17.21, df = 9 (P = 0.05); I² = 48%
Test for overall effect: Z = 1.05 (P = 0.29)

Study or Subgroup	CNI Events	Total	Alkylating agent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.5.2 Partial remission at final follow-up (≥ 2 years)							
Xu 2010	1	11	8	13	25.1%	0.15 [0.02 , 1.01]	
Braun 1995	2	44	8	31	31.5%	0.18 [0.04 , 0.77]	
Ramachandran 2016	9	35	10	35	43.5%	0.90 [0.42 , 1.94]	
Subtotal (95% CI)		**90**		**79**	**100.0%**	**0.34 [0.09 , 1.32]**	
Total events:	12		26				

Heterogeneity: Tau² = 0.94; Chi² = 6.05, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.1%

0.02   0.1   1   10   50
More with alkylating agents   More with CNI

Footnotes
(1) Data at 18 months

Analysis 11.6. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 6: Relapse after complete or partial remission

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.6.1 Relapse after complete or partial remission (< 2 years)							
He 2013	0	23	0	18		Not estimable	
Liang 2017	2	15	0	12	11.5%	4.06 [0.21 , 77.37]	
Ramachandran 2016	5	23	0	31	12.2%	14.67 [0.85 , 252.61]	
Peng 2016	2	25	1	22	16.7%	1.76 [0.17 , 18.11]	
Xu 2013a (1)	3	29	1	42	18.0%	4.34 [0.48 , 39.73]	
Chen 2010a	6	33	5	22	41.6%	0.80 [0.28 , 2.30]	
Subtotal (95% CI)		**148**		**147**	**100.0%**	**2.13 [0.71 , 6.37]**	
Total events:	18		7				
Heterogeneity: Tau² = 0.46; Chi² = 5.65, df = 4 (P = 0.23); I² = 29%							
Test for overall effect: Z = 1.35 (P = 0.18)							
11.6.2 Relapse after complete or partial remission (≥ 2 years)							
Liang 2017	3	15	0	12	21.2%	5.69 [0.32 , 100.45]	
Ramachandran 2016	7	31	2	30	78.8%	3.39 [0.76 , 15.02]	
Subtotal (95% CI)		**46**		**42**	**100.0%**	**3.78 [1.01 , 14.18]**	
Total events:	10		2				
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%							
Test for overall effect: Z = 1.97 (P = 0.05)							

Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%

0.002   0.1   1   10   500
Less with CNI   Less with alkylating agents

Footnotes
(1) Data at 12 months

Analysis 11.7. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 7: Increase in serum creatinine

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.7.1 100% increase in serum creatinine							
Peng 2016	0	29	0	28		Not estimable	
Braun 1995	8	44	8	31	100.0%	0.70 [0.30 , 1.67]	
Subtotal (95% CI)		**73**		**59**	**100.0%**	**0.70 [0.30 , 1.67]**	
Total events:	8		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
11.7.2 50% increase in serum creatinine							
Peng 2016	0	29	0	28		Not estimable	
Xu 2013a	0	48	0	52		Not estimable	
Chen 2010a	0	39	0	34		Not estimable	
He 2013	0	28	0	28		Not estimable	
Subtotal (95% CI)		**144**		**142**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10
Less with CNI   Less with alkylating agents

Analysis 11.8. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kosmadakis 2010	0	10	0	8		Not estimable	
Peng 2016	0	30	1	30	22.4%	0.33 [0.01 , 7.87]	
Chen 2010a	5	39	2	34	77.6%	2.18 [0.45 , 10.52]	
Total (95% CI)		**79**		**72**	**100.0%**	**1.43 [0.31 , 6.67]**	
Total events:	5		3				

Heterogeneity: Tau² = 0.15; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with CNI — Less with alkylating agents

Analysis 11.9. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 9: Adverse events

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.9.1 Serious adverse events							
Kosmadakis 2010	0	10	0	8		Not estimable	
Liang 2017	0	30	0	28		Not estimable	
Braun 1995	0	22	0	16		Not estimable	
Peng 2016	2	30	1	30	1.7%	2.00 [0.19 , 20.90]	
Chen 2010a	6	39	2	34	3.7%	2.62 [0.56 , 12.11]	
Xu 2010	3	11	4	13	5.3%	0.89 [0.25 , 3.14]	
Xu 2013a	11	48	21	52	15.2%	0.57 [0.31 , 1.05]	
Howman 2013	18	37	20	33	21.8%	0.80 [0.52 , 1.23]	
He 2013	15	28	22	28	23.3%	0.68 [0.46 , 1.01]	
Ramachandran 2016	29	35	24	35	29.0%	1.21 [0.92 , 1.58]	
Subtotal (95% CI)		**290**		**277**	**100.0%**	**0.88 [0.64 , 1.20]**	
Total events:	84		94				

Heterogeneity: Tau² = 0.07; Chi² = 11.37, df = 6 (P = 0.08); I² = 47%

Test for overall effect: Z = 0.80 (P = 0.43)

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.9.2 Infection							
Xu 2010	0	11	5	13	4.8%	0.11 [0.01 , 1.73]	
Liang 2017	1	30	1	28	4.9%	0.93 [0.06 , 14.22]	
Agarwal 2012a	1	20	1	21	5.0%	1.05 [0.07 , 15.68]	
Chen 2010a	8	39	1	34	7.5%	6.97 [0.92 , 52.96]	
He 2013	3	28	6	28	12.4%	0.50 [0.14 , 1.80]	
Howman 2013	8	37	3	33	12.8%	2.38 [0.69 , 8.23]	
Peng 2016	6	30	7	30	15.3%	0.86 [0.33 , 2.25]	
Xu 2013a	8	48	31	52	18.1%	0.28 [0.14 , 0.55]	
Ramachandran 2016	16	35	13	35	19.1%	1.23 [0.70 , 2.16]	
Subtotal (95% CI)		**278**		**274**	**100.0%**	**0.86 [0.43 , 1.71]**	
Total events:	51		68				

Heterogeneity: Tau² = 0.56; Chi² = 21.66, df = 8 (P = 0.006); I² = 63%

Test for overall effect: Z = 0.43 (P = 0.67)

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.9.3 Malignancy							
Liang 2017	0	30	0	28		Not estimable	
Howman 2013	0	36	2	33	100.0%	0.18 [0.01 , 3.69]	
Subtotal (95% CI)		**66**		**61**	**100.0%**	**0.18 [0.01 , 3.69]**	
Total events:	0		2				

Heterogeneity: Not applicable

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Chi² = 1.04, df = 2 (P = 0.60), I² = 0%

0.002 0.1 1 10 500
Less with CNI   Less with alkylating agents

Analysis 11.10. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 10: Final serum creatinine

Study or Subgroup	CNI Mean [mg/dL]	CNI SD [mg/dL]	Total	Alkylating agents Mean [mg/dL]	Alkylating agents SD [mg/dL]	Total	Weight	Mean Difference IV, Random, 95% CI [mg/dL]	Mean Difference IV, Random, 95% CI [mg/dL]
Ramachandran 2016	0.98	0.25	35	0.92	0.18	35	100.0%	0.06 [-0.04 , 0.16]	
Total (95% CI)			**35**			**35**	**100.0%**	**0.06 [-0.04 , 0.16]**	

Heterogeneity: Not applicable

Test for overall effect: Z = 1.15 (P = 0.25)

Test for subgroup differences: Not applicable

-0.5 -0.25 0 0.25 0.5
Lower with CNI   Lower with alkylating agents

Analysis 11.11. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 11: Final serum albumin

Study or Subgroup	CNI Mean [g/L]	CNI SD [g/L]	CNI Total	Alkylating agents Mean [g/L]	Alkylating agents SD [g/L]	Alkylating agents Total	Weight	Mean Difference IV, Random, 95% CI [g/L]
Xu 2010	31.4	5.9	11	26	6	13	17.0%	5.40 [0.63 , 10.17]
Liang 2017	36.9	8.2	30	32.4	9	28	18.0%	4.50 [0.06 , 8.94]
Ramachandran 2016	35.7	8.9	35	40	6.2	35	20.5%	-4.30 [-7.89 , -0.71]
Kosmadakis 2010	42	5	10	42	2	8	21.1%	0.00 [-3.39 , 3.39]
Peng 2016	38.7	4.3	29	36.6	5.6	28	23.5%	2.10 [-0.50 , 4.70]
Total (95% CI)			**115**			**112**	**100.0%**	**1.34 [-1.82 , 4.49]**

Heterogeneity: Tau² = 9.29; Chi² = 15.01, df = 4 (P = 0.005); I² = 73%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Mean Difference IV, Random, 95% CI [g/L]
-20 -10 0 10 20
Lower with CNI   Lower with alkylating agents

Analysis 11.12. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 12: Final GFR [mL/min/1.73 m²]

Study or Subgroup	CNI Mean	CNI SD	CNI Total	Alkylating agents Mean	Alkylating agents SD	Alkylating agents Total	Weight	Mean Difference IV, Random, 95% CI
Kosmadakis 2010	71.3	25.3	10	62	17	8	10.7%	9.30 [-10.31 , 28.91]
Chen 2010a	108.5	30.8	33	104.3	20.6	27	24.1%	4.20 [-8.87 , 17.27]
Liang 2017	90.6	26.7	30	91.7	23.8	28	24.4%	-1.10 [-14.10 , 11.90]
Ramachandran 2016	80.92	22.17	35	86.45	20.65	35	40.9%	-5.53 [-15.57 , 4.51]
Total (95% CI)			**108**			**98**	**100.0%**	**-0.52 [-6.94 , 5.90]**

Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable

Mean Difference IV, Random, 95% CI
-50 -25 0 25 50
Higher with alkylating agents   Higher with CNI

Analysis 11.13. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 13: Loss of GFR > 20%

Study or Subgroup	CNI Events	CNI Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI
Howman 2013	29	36	19	33	100.0%	1.40 [1.00 , 1.95]
Total (95% CI)		**36**		**33**	**100.0%**	**1.40 [1.00 , 1.95]**
Total events:	29		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI
0.2 0.5 1 2 5
More with alkylating agents   More wit CNI

Analysis 11.14. Comparison 11: Calcineurin inhibitors ± steroids versus alkylating agents ± steroids, Outcome 14: Final proteinuria

Study or Subgroup	CNI Mean	CNI SD	CNI Total	Alkylating agents Mean	Alkylating agents SD	Alkylating agents Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
Kosmadakis 2010	2.4	1.6	10	1	1.1	8	9.2%	0.95 [-0.04 , 1.94]	
Xu 2010	0.3	0.29	11	1.5	1.2	13	10.0%	-1.28 [-2.17 , -0.38]	
He 2013	0.72	0.43	28	2.18	1.37	28	12.7%	-1.42 [-2.01 , -0.83]	
Peng 2016	1.4	1.7	29	2.1	2	28	13.3%	-0.37 [-0.90 , 0.15]	
Liang 2017	2.2	2.9	30	1.5	2.1	28	13.3%	0.27 [-0.25 , 0.79]	
Chen 2010a	1.96	2.98	33	2.32	2.71	27	13.4%	-0.12 [-0.63 , 0.38]	
Ramachandran 2016	2.4	3.51	35	1.27	1.67	35	13.7%	0.41 [-0.07 , 0.88]	
Xu 2013a	3.1	2.46	48	3.13	2.31	52	14.4%	-0.01 [-0.40 , 0.38]	
Total (95% CI)			**224**			**219**	**100.0%**	**-0.20 [-0.66 , 0.26]**	

Heterogeneity: Tau² = 0.34; Chi² = 37.52, df = 7 (P < 0.00001); I² = 81%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable

-4 -2 0 2 4
Lower with CNI   Lower with alkylating agents

Comparison 12. Short-course tacrolimus + steroids versus long-course tacrolimus + steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.2 Complete or partial remission	2	106	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.42, 1.10]
12.2.1 6 months versus 12 months TAC	1	36	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.33, 0.81]
12.2.2 12 months versus 24 months TAC	1	70	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.65, 1.07]
12.3 Complete remission	2	106	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.97]
12.3.1 6 months versus 24 months TAC	1	36	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.17, 2.14]
12.3.2 12 months versus 24 months TAC	1	70	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.25, 1.01]
12.4 Partial remission	2	106	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.30, 1.99]
12.4.1 6 months versus 24 months TAC	1	36	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.23, 0.94]
12.4.2 12 months versus 24 months TAC	1	70	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.71, 2.06]
12.5 Relapse after complete or partial remission	2	82	Risk Ratio (M-H, Random, 95% CI)	7.25 [0.41, 129.75]
12.6 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.6.1 Adverse events	1	36	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.35, 2.87]
12.6.2 Infection	1	36	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.20, 2.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.7 Final serum creatinine	2	107	Mean Difference (IV, Random, 95% CI)	-1.65 [-10.98, 7.69]
12.7.1 6 months versus 24 months TAC	1	36	Mean Difference (IV, Random, 95% CI)	-2.30 [-18.10, 13.50]
12.7.2 12 months versus 24 months TAC	1	71	Mean Difference (IV, Random, 95% CI)	-1.30 [-12.87, 10.27]
12.8 Final serum albumin	1	71	Mean Difference (IV, Random, 95% CI)	-6.40 [-8.75, -4.05]
12.9 Final proteinuria	1	71	Mean Difference (IV, Random, 95% CI)	1.70 [1.34, 2.06]

Analysis 12.1. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 1: Death

Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Yuan 2013	0	20	0	22	Not estimable	

0.01   0.1   1   10   100
Less with 6 months   Less with 24 months

Analysis 12.2. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 2: Complete or partial remission

Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.2.1 6 months versus 12 months TAC							
Yuan 2013	9	18	18	18	42.3%	0.51 [0.33 , 0.81]	
Subtotal (95% CI)		**18**		**18**	**42.3%**	**0.51 [0.33 , 0.81]**	
Total events:	9		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.87 (P = 0.004)							
12.2.2 12 months versus 24 months TAC							
Di 2018	25	35	30	35	57.7%	0.83 [0.65 , 1.07]	
Subtotal (95% CI)		**35**		**35**	**57.7%**	**0.83 [0.65 , 1.07]**	
Total events:	25		30				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.43 (P = 0.15)							
Total (95% CI)		**53**		**53**	**100.0%**	**0.68 [0.42 , 1.10]**	
Total events:	34		48				

Heterogeneity: Tau² = 0.09; Chi² = 3.51, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Chi² = 3.34, df = 1 (P = 0.07), I² = 70.0%

0.2   0.5   1   2   5
More with short course   More with long course

Analysis 12.3. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 3: Complete remission

Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.3.1 6 months versus 24 months TAC							
Yuan 2013	3	18	5	18	23.6%	0.60 [0.17 , 2.14]	
Subtotal (95% CI)		**18**		**18**	**23.6%**	**0.60 [0.17 , 2.14]**	
Total events:	3		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
12.3.2 12 months versus 24 months TAC							
Di 2018	8	35	16	35	76.4%	0.50 [0.25 , 1.01]	
Subtotal (95% CI)		**35**		**35**	**76.4%**	**0.50 [0.25 , 1.01]**	
Total events:	8		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.92 (P = 0.05)							
Total (95% CI)		**53**		**53**	**100.0%**	**0.52 [0.28 , 0.97]**	
Total events:	11		21				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%							
Test for overall effect: Z = 2.06 (P = 0.04)							
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%							

0.1 0.2 0.5 1 2 5 10
More with long course — More with short course

Analysis 12.4. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 4: Partial remission

| Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.4.1 6 months versus 24 months TAC							
Yuan 2013	6	18	13	18	46.8%	0.46 [0.23 , 0.94]	
Subtotal (95% CI)		**18**		**18**	**46.8%**	**0.46 [0.23 , 0.94]**	
Total events:	6		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.12 (P = 0.03)							
12.4.2 12 months versus 24 months TAC							
Di 2018	17	35	14	35	53.2%	1.21 [0.71 , 2.06]	
Subtotal (95% CI)		**35**		**35**	**53.2%**	**1.21 [0.71 , 2.06]**	
Total events:	17		14				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
Total (95% CI)		**53**		**53**	**100.0%**	**0.77 [0.30 , 1.99]**	
Total events:	23		27				
Heterogeneity: Tau² = 0.37; Chi² = 4.55, df = 1 (P = 0.03); I² = 78%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi² = 4.55, df = 1 (P = 0.03), I² = 78.0%							

0.1 0.2 0.5 1 2 5 10
More with long course — More with short course

Analysis 12.5. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 5: Relapse after complete or partial remission

Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Yuan 2013	9	9	0	18	40.8%	36.10 [2.33 , 558.40]	
Di 2018	8	25	4	30	59.2%	2.40 [0.82 , 7.04]	
Total (95% CI)		**34**		**48**	**100.0%**	**7.25 [0.41 , 129.75]**	
Total events:	17		4				

Heterogeneity: Tau² = 3.36; Chi² = 3.98, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
Less with short course   Less with long course

Analysis 12.6. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 6: Adverse events

Study or Subgroup	Short-course TAC Events	Total	Long-course TAC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.6.1 Adverse events							
Yuan 2013	5	18	5	18	100.0%	1.00 [0.35 , 2.87]	
Subtotal (95% CI)		**18**		**18**	**100.0%**	**1.00 [0.35 , 2.87]**	
Total events:	5		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

12.6.2 Infection							
Yuan 2013	3	18	4	18	100.0%	0.75 [0.20 , 2.88]	
Subtotal (95% CI)		**18**		**18**	**100.0%**	**0.75 [0.20 , 2.88]**	
Total events:	3		4				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%

0.1 0.2 0.5 1 2 5 10
Less with short course   Less with long course

Analysis 12.7. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 7: Final serum creatinine

Study or Subgroup	Short-course TAC Mean [µmol/L]	SD [µmol/L]	Total	Long-course TAC Mean [µmol/L]	SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
12.7.1 6 months versus 24 months TAC									
Yuan 2013	73.8	17.8	18	76.1	29.2	18	34.9%	-2.30 [-18.10 , 13.50]	
Subtotal (95% CI)			**18**			**18**	**34.9%**	**-2.30 [-18.10 , 13.50]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.29 (P = 0.78)									
12.7.2 12 months versus 24 months TAC									
Di 2018	92	25.6	35	93.3	24.1	36	65.1%	-1.30 [-12.87 , 10.27]	
Subtotal (95% CI)			**35**			**36**	**65.1%**	**-1.30 [-12.87 , 10.27]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.22 (P = 0.83)									
Total (95% CI)			**53**			**54**	**100.0%**	**-1.65 [-10.98 , 7.69]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%

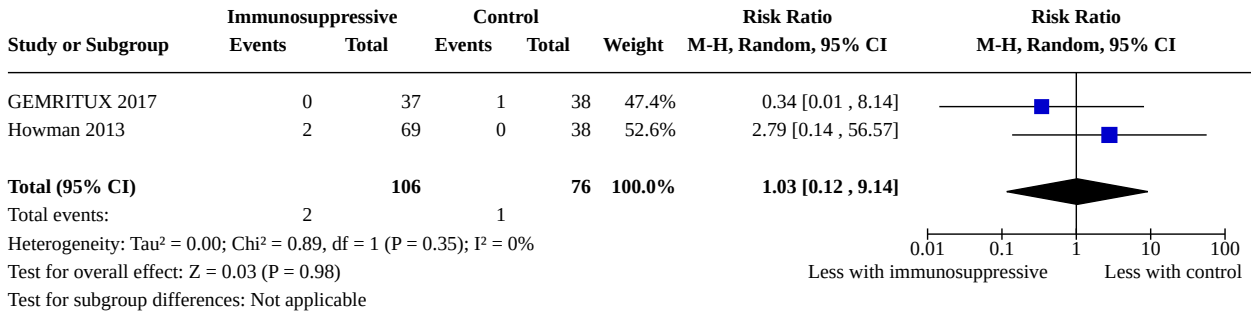-20 -10 0 10 20
Favours short course   Favours long course

Analysis 12.8. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 8: Final serum albumin

Study or Subgroup	Short-course TAC			Long-course TAC			Weight	Mean Difference IV, Random, 95% CI [g/L]	Mean Difference IV, Random, 95% CI [g/L]
	Mean [g/L]	SD [g/L]	Total	Mean [g/L]	SD [g/L]	Total			
Di 2018	32.2	4.8	35	38.6	5.3	36	100.0%	-6.40 [-8.75 , -4.05]	
Total (95% CI)			**35**			**36**	**100.0%**	**-6.40 [-8.75 , -4.05]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 5.34 (P < 0.00001)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Lower with short course   Lower with long course
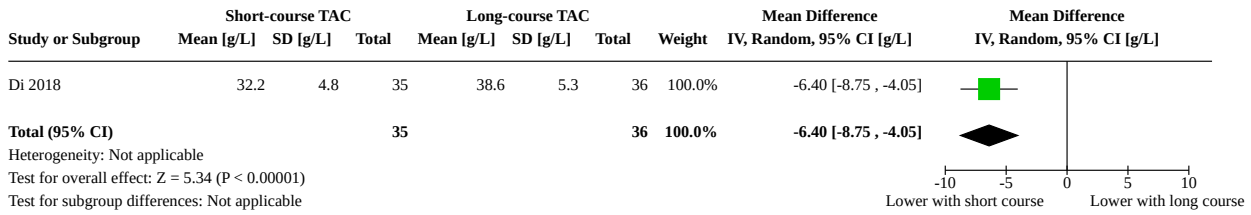
Analysis 12.9. Comparison 12: Short-course tacrolimus + steroids versus long-course tacrolimus + steroids, Outcome 9: Final proteinuria

Study or Subgroup	Short-course TAC			Long-course TAC			Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
	Mean [g/24 h]	SD [g/24 h]	Total	Mean [g/24 h]	SD [g/24 h]	Total			
Di 2018	2.8	1	35	1.1	0.4	36	100.0%	1.70 [1.34 , 2.06]	
Total (95% CI)			**35**			**36**	**100.0%**	**1.70 [1.34 , 2.06]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 9.36 (P < 0.00001)
Test for subgroup differences: Not applicable

-4 -2 0 2 4
Lower with short course   Lower with long course

Comparison 13. Cyclosporine + steroids versus cyclosporine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.2 Complete or partial remission	2	55	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.77, 1.33]
13.3 Complete remission	2	55	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.07, 4.49]
13.4 Partial remission	2	55	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.06, 3.17]
13.5 50% increase in serum creatinine	1	27	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.39, 5.23]
13.6 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.6.1 Adverse events	1	27	Risk Ratio (M-H, Random, 95% CI)	2.37 [1.13, 4.97]
13.6.2 Infection	1	27	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.22, 21.03]

Analysis 13.1. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 1: Death

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2015	0	13	0	14	Not estimable	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with CSA+steroids   Less with CSA alone
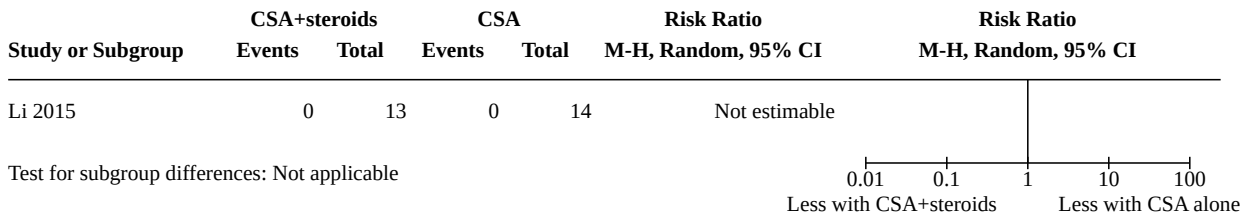
Analysis 13.2. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 2: Complete or partial remission

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2015	8	13	8	14	19.0%	1.08 [0.58 , 2.01]	
CYPMEN 2006	12	14	12	14	81.0%	1.00 [0.74 , 1.35]	
Total (95% CI)		27		28	100.0%	1.01 [0.77 , 1.33]	
Total events:	20		20				

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with CSA alone   More with CSA+steroids

Analysis 13.3. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 3: Complete remission

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2015	2	13	1	14	9.9%	2.15 [0.22 , 21.03]	
CYPMEN 2006	11	14	5	14	90.1%	2.20 [1.03 , 4.68]	
Total (95% CI)		27		28	100.0%	2.20 [1.07 , 4.49]	
Total events:	13		6				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
More with CSA alone   More with CSA+steroids

Analysis 13.4. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 4: Partial remission

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
CYPMEN 2006	1	14	7	14	40.1%	0.14 [0.02 , 1.01]	
Li 2015	6	13	7	14	59.9%	0.92 [0.42 , 2.03]	
Total (95% CI)		27		28	100.0%	0.44 [0.06 , 3.17]	
Total events:	7		14				

Heterogeneity: Tau² = 1.55; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with CSA alone   More with CSA+steroids

Analysis 13.5. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 5: 50% increase in serum creatinine

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2015	4	13	3	14	100.0%	1.44 [0.39 , 5.23]	
Total (95% CI)		13		14	100.0%	**1.44 [0.39 , 5.23]**	
Total events:	4		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Less with CSA+steroids   Less with CSA alone
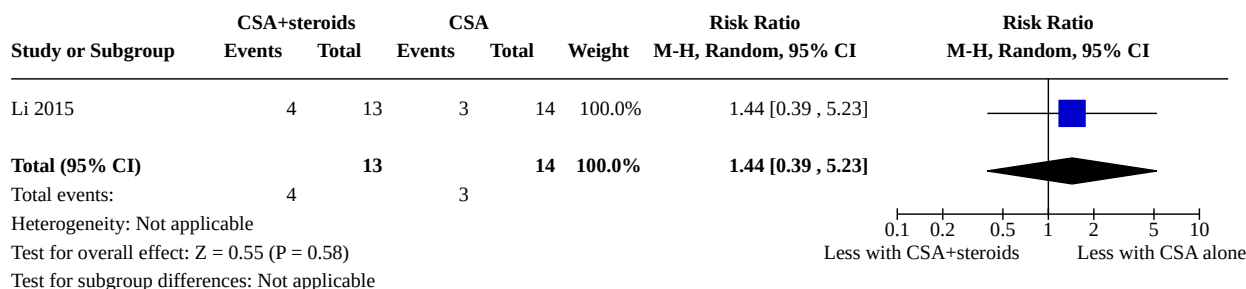
Analysis 13.6. Comparison 13: Cyclosporine + steroids versus cyclosporine alone, Outcome 6: Adverse events

Study or Subgroup	CSA+steroids Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
13.6.1 Adverse events							
Li 2015	11	13	5	14	100.0%	2.37 [1.13 , 4.97]	
Subtotal (95% CI)		13		14	100.0%	**2.37 [1.13 , 4.97]**	
Total events:	11		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)

13.6.2 Infection							
Li 2015	2	13	1	14	100.0%	2.15 [0.22 , 21.03]	
Subtotal (95% CI)		13		14	100.0%	**2.15 [0.22 , 21.03]**	
Total events:	2		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%

0.01 0.1 1 10 100
Less with CSA+steroids   Less CSA alone

Comparison 14. Cyclosporine (3.0 mg/kg, once/day) + steroids versus cyclosporine (1.5 mg/kg, twice/day) + steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Complete or partial remission	1	48	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.65, 1.18]
14.2 Complete remission	1	48	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.73, 2.27]
14.3 Doubling of serum creatinine	1	48	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.17, 7.10]
14.4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.4.1 Adverse events	1	48	Risk Ratio (M-H, Random, 95% CI)	Not estimable
14.4.2 Infection	1	48	Risk Ratio (M-H, Random, 95% CI)	3.25 [0.14, 76.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.4.3 Malignancy	1	48	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.45]

Analysis 14.1. Comparison 14: Cyclosporine (3.0 mg/kg, once/day) + steroids versus cyclosporine (1.5 mg/kg, twice/day) + steroids, Outcome 1: Complete or partial remission

Study or Subgroup	CSA once/day Events	Total	CSA twice/day Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2014	17	23	21	25	100.0%	0.88 [0.65 , 1.18]	
Total (95% CI)		23		25	100.0%	**0.88 [0.65 , 1.18]**	
Total events:	17		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable

More with twice/day — More with once/day
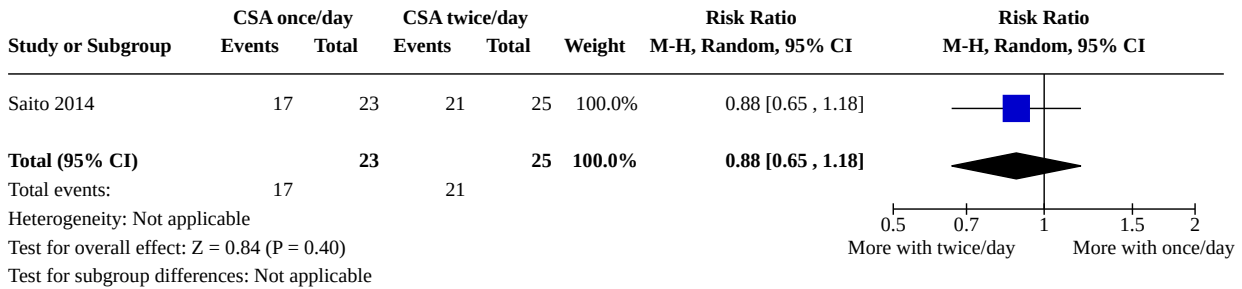
Analysis 14.2. Comparison 14: Cyclosporine (3.0 mg/kg, once/day) + steroids versus cyclosporine (1.5 mg/kg, twice/day) + steroids, Outcome 2: Complete remission

Study or Subgroup	CSA once/day Events	Total	CSA twice/day Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2014	13	23	11	25	100.0%	1.28 [0.73 , 2.27]	
Total (95% CI)		23		25	100.0%	**1.28 [0.73 , 2.27]**	
Total events:	13		11				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

More with twice/day — More with once/day
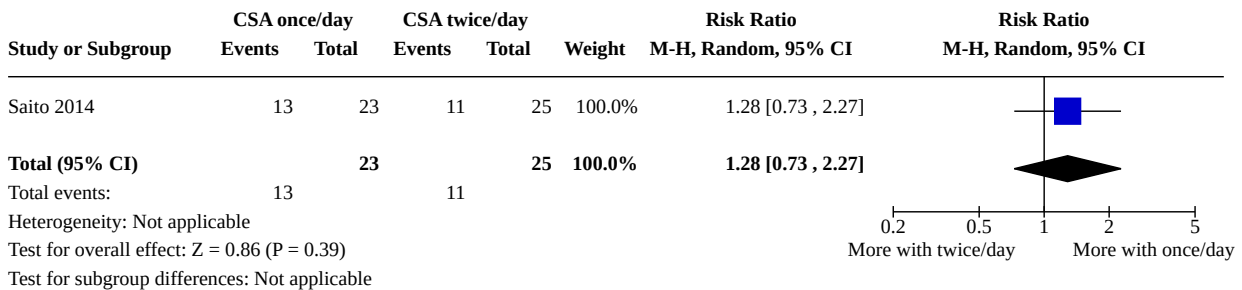
Analysis 14.3. Comparison 14: Cyclosporine (3.0 mg/kg, once/day) + steroids versus cyclosporine (1.5 mg/kg, twice/day) + steroids, Outcome 3: Doubling of serum creatinine

Study or Subgroup	CSA once/day Events	Total	CSA twice/day Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2014	2	23	2	25	100.0%	1.09 [0.17 , 7.10]	
Total (95% CI)		23		25	100.0%	**1.09 [0.17 , 7.10]**	
Total events:	2		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

Less with once/day — Less with twice/day
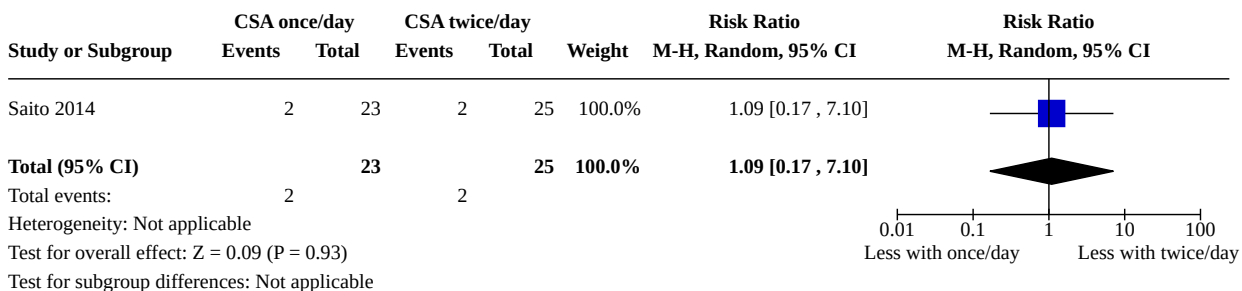
Analysis 14.4. Comparison 14: Cyclosporine (3.0 mg/kg, once/day) + steroids versus cyclosporine (1.5 mg/kg, twice/day) + steroids, Outcome 4: Adverse events

Study or Subgroup	CSA once/day Events	Total	CSA twice/day Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
14.4.1 Adverse events							
Saito 2014	0	23	0	25		Not estimable	
Subtotal (95% CI)		**23**		**25**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
14.4.2 Infection							
Saito 2014	1	23	0	25	100.0%	3.25 [0.14 , 76.01]	
Subtotal (95% CI)		**23**		**25**	**100.0%**	**3.25 [0.14 , 76.01]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.73 (P = 0.46)							
14.4.3 Malignancy							
Saito 2014	0	23	1	25	100.0%	0.36 [0.02 , 8.45]	
Subtotal (95% CI)		**23**		**25**	**100.0%**	**0.36 [0.02 , 8.45]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							

0.01 0.1 1 10 100
Less with once/day   Less with twice/day

Comparison 15. Cyclosporine + steroids versus tacrolimus + steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Complete or partial remission	1	31	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
15.2 Complete remission	1	31	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.31, 1.89]
15.3 Partial remission	1	31	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.40, 2.10]
15.4 Serious adverse events	1	68	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.19]

Analysis 15.1. Comparison 15: Cyclosporine + steroids versus tacrolimus + steroids, Outcome 1: Complete or partial remission

Study or Subgroup	CSA Events	CSA Total	TAC Events	TAC Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2017c	11	15	14	16	100.0%	0.84 [0.59 , 1.20]	
Total (95% CI)		**15**		**16**	**100.0%**	**0.84 [0.59 , 1.20]**	
Total events:	11		14				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable

0.5 0.7 1 1.5 2
More with TAC   More with CSA
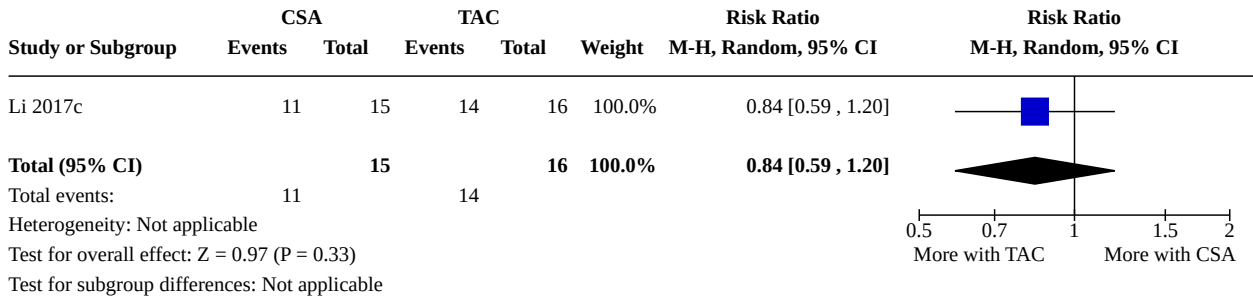
Analysis 15.2. Comparison 15: Cyclosporine + steroids versus tacrolimus + steroids, Outcome 2: Complete remission

Study or Subgroup	CSA Events	CSA Total	TAC Events	TAC Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2017c	5	15	7	16	100.0%	0.76 [0.31 , 1.89]	
Total (95% CI)		**15**		**16**	**100.0%**	**0.76 [0.31 , 1.89]**	
Total events:	5		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with TAC   More with CSA
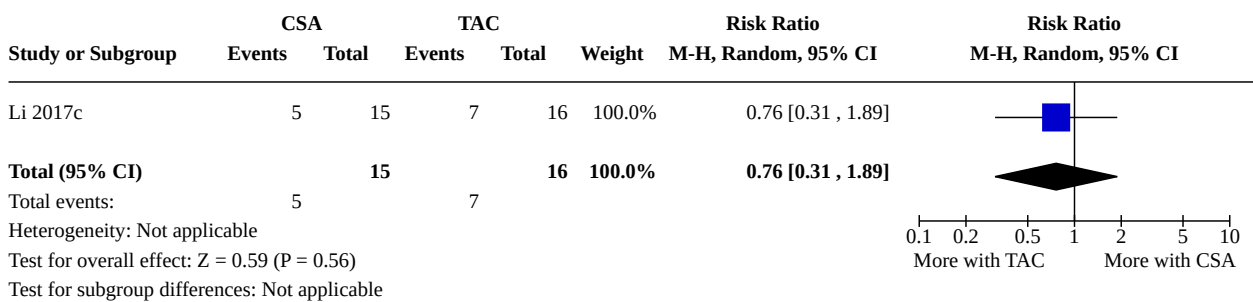
Analysis 15.3. Comparison 15: Cyclosporine + steroids versus tacrolimus + steroids, Outcome 3: Partial remission

Study or Subgroup	CSA Events	CSA Total	TAC Events	TAC Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2017c	6	15	7	16	100.0%	0.91 [0.40 , 2.10]	
Total (95% CI)		**15**		**16**	**100.0%**	**0.91 [0.40 , 2.10]**	
Total events:	6		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with TAC   More with CSA
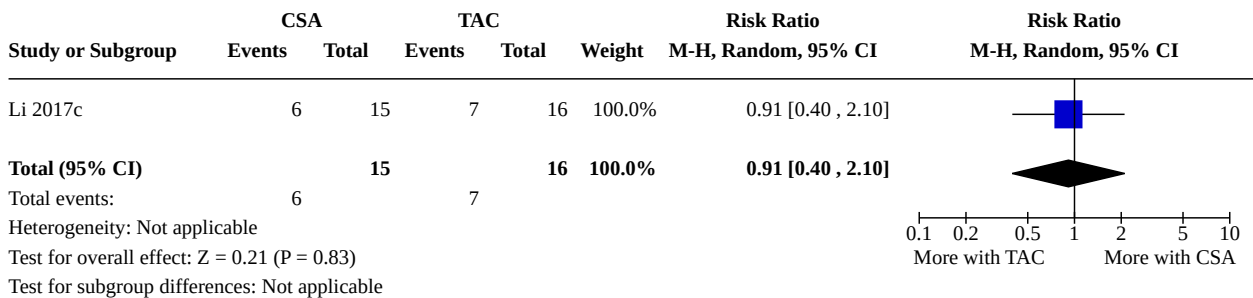
Analysis 15.4. Comparison 15: Cyclosporine + steroids versus tacrolimus + steroids, Outcome 4: Serious adverse events

Study or Subgroup	CSA Events	CSA Total	TAC Events	TAC Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Omrani 2017	16	34	21	34	100.0%	0.76 [0.49 , 1.19]	
Total (95% CI)		**34**		**34**	**100.0%**	**0.76 [0.49 , 1.19]**	
Total events:	16		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Less with CSA   Less with TAC
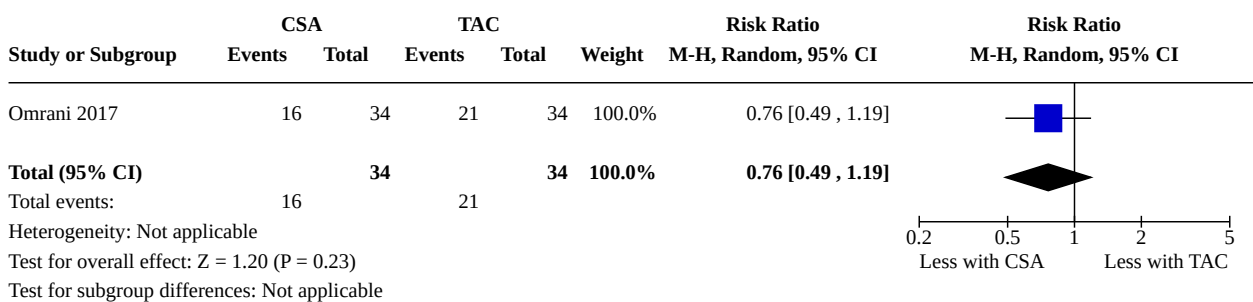
Comparison 16. Cyclosporine versus azathioprine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.2 ESKD (dialysis/transplantation)	1	23	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.02, 9.43]
16.3 Complete or partial remission	1	23	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.68, 2.48]
16.4 Complete remission	1	23	Risk Ratio (M-H, Random, 95% CI)	1.95 [0.40, 9.54]
16.5 Partial remission	1	23	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.37, 2.90]
16.6 Increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.6.1 50% increase in serum creatinine	1	23	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.87]
16.7 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	23	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 4.78]
16.8 Final serum creatinine	1	23	Mean Difference (IV, Random, 95% CI)	-102.50 [-280.28, 75.28]
16.9 Final GFR [mL/min/1.73 m^2]	1	23	Mean Difference (IV, Random, 95% CI)	23.20 [-1.98, 48.38]
16.10 Final proteinuria	1	23	Mean Difference (IV, Random, 95% CI)	1.00 [-2.02, 4.02]

Analysis 16.1. Comparison 16: Cyclosporine versus azathioprine, Outcome 1: Death

	CSA		AZA		Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Naumovic 2011	0	10	0	13	Not estimable	

0.01 0.1 1 10 100
Less with CSA   Less with AZA

Analysis 16.2. Comparison 16: Cyclosporine versus azathioprine, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Naumovic 2011	0	10	1	13	100.0%	0.42 [0.02 , 9.43]	
Total (95% CI)		**10**		**13**	**100.0%**	**0.42 [0.02 , 9.43]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with CSA   Less with AZA
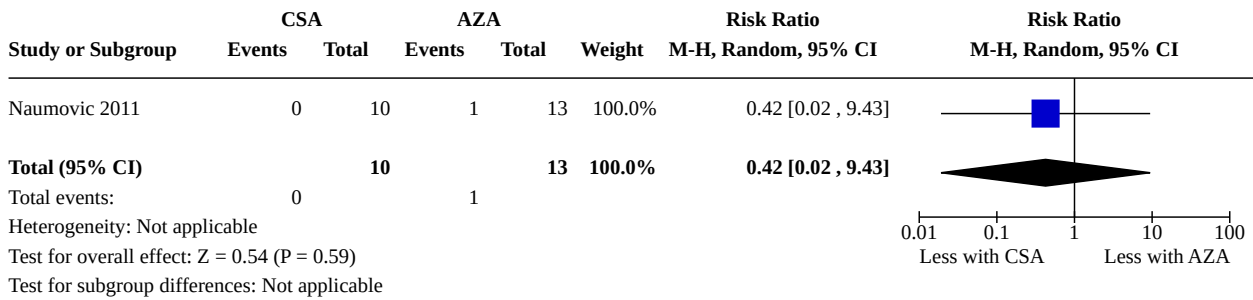
Analysis 16.3. Comparison 16: Cyclosporine versus azathioprine, Outcome 3: Complete or partial remission

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Naumovic 2011	7	10	7	13	100.0%	1.30 [0.68 , 2.48]	
Total (95% CI)		**10**		**13**	**100.0%**	**1.30 [0.68 , 2.48]**	
Total events:	7		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with AZA   More with CSA
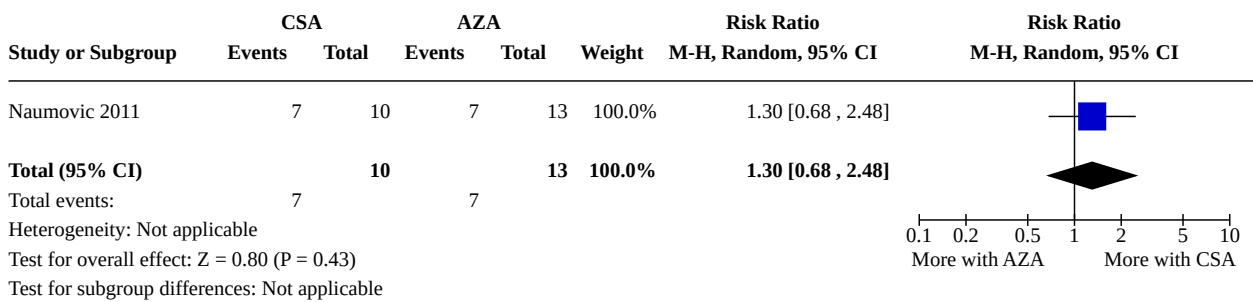
Analysis 16.4. Comparison 16: Cyclosporine versus azathioprine, Outcome 4: Complete remission

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Naumovic 2011	3	10	2	13	100.0%	1.95 [0.40 , 9.54]	
Total (95% CI)		**10**		**13**	**100.0%**	**1.95 [0.40 , 9.54]**	
Total events:	3		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
More with AZA   More with CSA
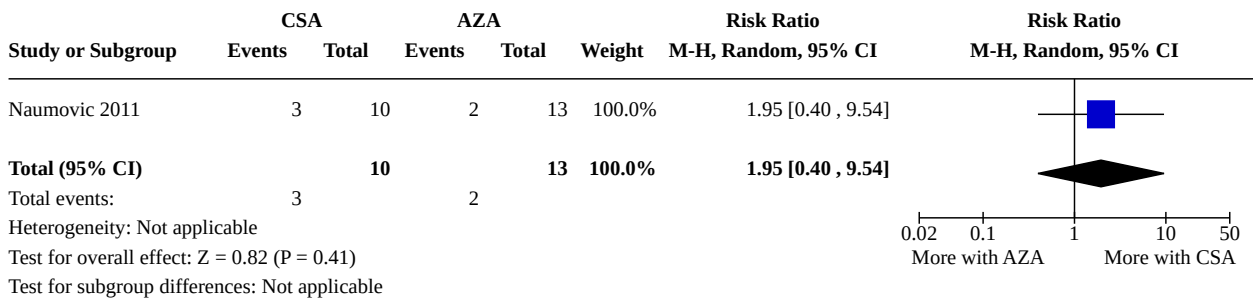
Analysis 16.5. Comparison 16: Cyclosporine versus azathioprine, Outcome 5: Partial remission

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Naumovic 2011	4	10	5	13	100.0%	1.04 [0.37 , 2.90]	
Total (95% CI)		**10**		**13**	**100.0%**	**1.04 [0.37 , 2.90]**	
Total events:	4		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with AZA   More with CSA
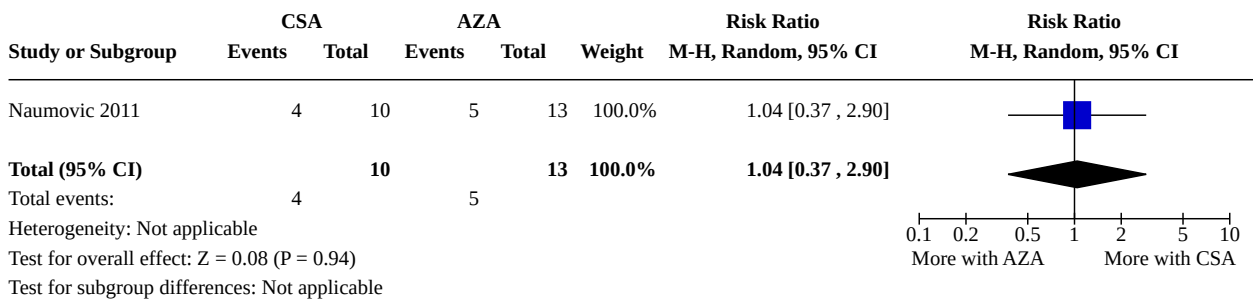
Analysis 16.6.   Comparison 16: Cyclosporine versus azathioprine, Outcome 6: Increase in serum creatinine

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
16.6.1 50% increase in serum creatinine							
Naumovic 2011	2	10	4	13	100.0%	0.65 [0.15 , 2.87]	
Subtotal (95% CI)		**10**		**13**	**100.0%**	**0.65 [0.15 , 2.87]**	
Total events:	2		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							

0.1 0.2 0.5 1 2 5 10
Less with CSA   Less with AZA
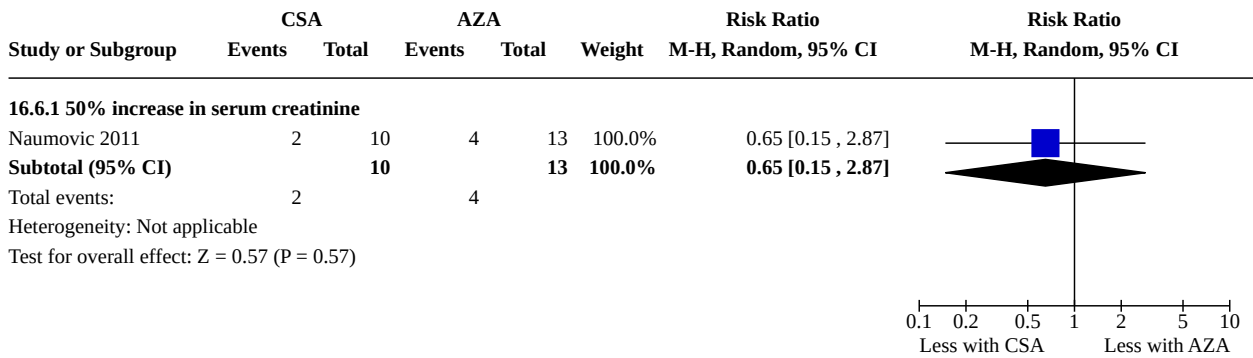
Analysis 16.7.   Comparison 16: Cyclosporine versus azathioprine, Outcome 7: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	CSA Events	CSA Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Naumovic 2011	0	10	2	13	100.0%	0.25 [0.01 , 4.78]	
Total (95% CI)		**10**		**13**	**100.0%**	**0.25 [0.01 , 4.78]**	
Total events:	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							
Test for subgroup differences: Not applicable							

0.005 0.1 1 10 200
Less with CSA   Less with AZA
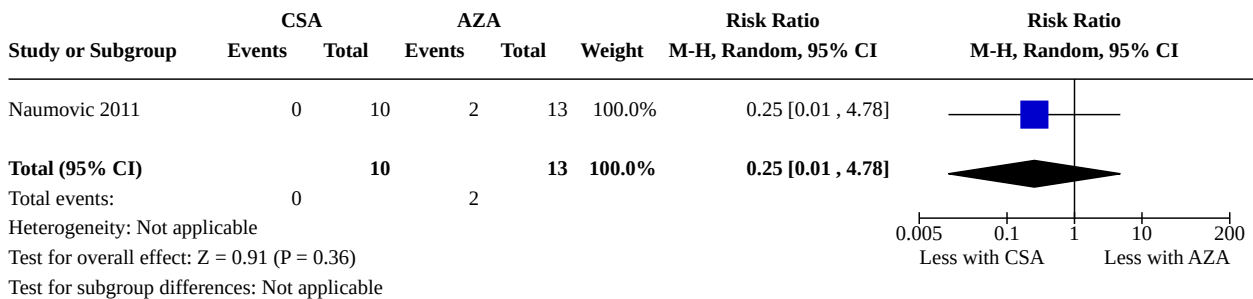
Analysis 16.8.   Comparison 16: Cyclosporine versus azathioprine, Outcome 8: Final serum creatinine

Study or Subgroup	CSA Mean [µmol/L]	CSA SD [µmol/L]	Total	AZA Mean [µmol/L]	AZA SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
Naumovic 2011	167.3	146.3	10	269.8	281.3	13	100.0%	-102.50 [-280.28 , 75.28]	
Total (95% CI)			**10**			**13**	**100.0%**	**-102.50 [-280.28 , 75.28]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.13 (P = 0.26)									
Test for subgroup differences: Not applicable									

-500 -250 0 250 500
Lower with CSA   Lower with AZA

Analysis 16.9.   Comparison 16: Cyclosporine versus azathioprine, Outcome 9: Final GFR [mL/min/1.73 m²]

Study or Subgroup	CSA Mean	CSA SD	Total	AZA Mean	AZA SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Naumovic 2011	77.9	29.3	10	54.7	32.1	13	100.0%	23.20 [-1.98 , 48.38]	
Total (95% CI)			**10**			**13**	**100.0%**	**23.20 [-1.98 , 48.38]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.81 (P = 0.07)									
Test for subgroup differences: Not applicable									

-50 -25 0 25 50
Higher with AZA   Higher with CSA
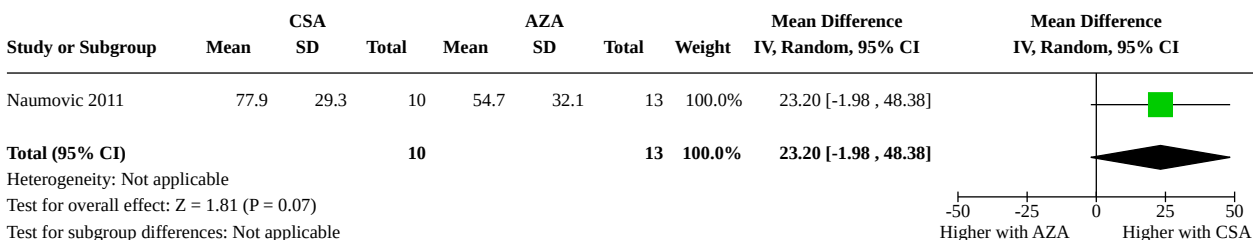
Analysis 16.10. Comparison 16: Cyclosporine versus azathioprine, Outcome 10: Final proteinuria

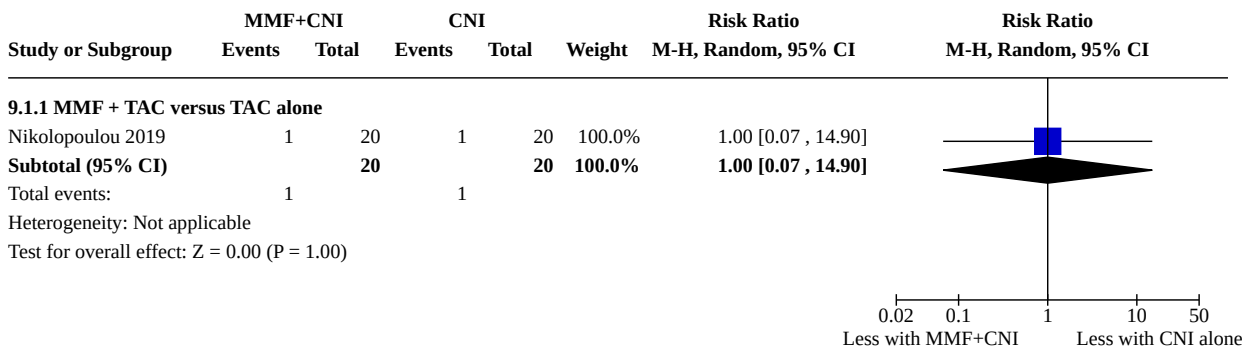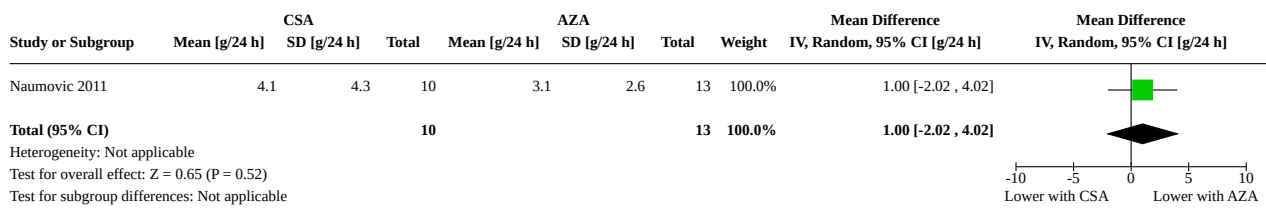| Study or Subgroup	CSA Mean [g/24 h]	SD [g/24 h]	Total	AZA Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Naumovic 2011	4.1	4.3	10	3.1	2.6	13	100.0%	1.00 [-2.02 , 4.02]	
Total (95% CI)			10			13	100.0%	1.00 [-2.02 , 4.02]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable

```
        -10   -5    0    5    10
        Lower with CSA   Lower with AZA
```

Comparison 17. Azathioprine ± steroids versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.2 ESKD (dialysis/transplantation)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.3 Complete or partial remission	1	9	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 5.43]
17.4 Complete remission	1	9	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 5.43]
17.5 Partial remission	1	9	Risk Ratio (M-H, Random, 95% CI)	Not estimable
17.6 Increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.6.1 100% increase in serum creatinine	1	9	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.07, 9.18]
17.6.2 50% increase in serum creatinine	1	9	Risk Ratio (M-H, Random, 95% CI)	4.17 [0.25, 68.16]
17.7 Temporary or permanent discontinuation/hospitalisation due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.8 Final serum creatinine	1	9	Mean Difference (IV, Random, 95% CI)	-53.10 [-219.98, 113.78]
17.9 Final GFR [mL/min/1.73 m^2]	1	9	Mean Difference (IV, Random, 95% CI)	33.00 [-19.01, 85.01]
17.10 Final proteinuria	1	9	Mean Difference (IV, Random, 95% CI)	1.10 [-2.79, 4.99]

Analysis 17.1. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 1: Death

Study or Subgroup	AZA+steroids		Control		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Silverberg 1976	0	5	0	4	Not estimable	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with AZA+steroids   Less with control

Analysis 17.2. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	AZA+steroids		Control		Risk Ratio	Risk Ratio
	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Silverberg 1976	0	5	0	4	Not estimable	

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with AZA+steroids   Less with control

Analysis 17.3. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 3: Complete or partial remission

Study or Subgroup	AZA+steroids		Control		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Silverberg 1976	0	5	1	4	100.0%	0.28 [0.01 , 5.43]	
Total (95% CI)		**5**		**4**	**100.0%**	**0.28 [0.01 , 5.43]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
More with control   More with AZA+steroids

Analysis 17.4. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 4: Complete remission

Study or Subgroup	AZA+steroids		Control		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Silverberg 1976	0	5	1	4	100.0%	0.28 [0.01 , 5.43]	
Total (95% CI)		**5**		**4**	**100.0%**	**0.28 [0.01 , 5.43]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
More with control   More with AZA+control

Analysis 17.5. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 5: Partial remission

Study or Subgroup	AZA+steroids Events	AZA+steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Silverberg 1976	0	5	0	4		Not estimable	
Total (95% CI)		**5**		**4**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

0.001 0.1 1 10 1000
More with control   More with AZA+steroids
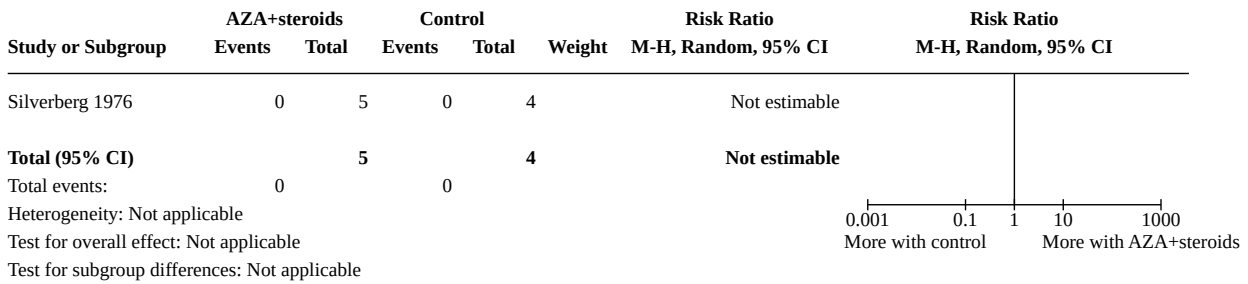
Analysis 17.6. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 6: Increase in serum creatinine

Study or Subgroup	AZA+steroids Events	AZA+steroids Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
17.6.1 100% increase in serum creatinine							
Silverberg 1976	1	5	1	4	100.0%	0.80 [0.07 , 9.18]	
Subtotal (95% CI)		**5**		**4**	**100.0%**	**0.80 [0.07 , 9.18]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.18 (P = 0.86)							
17.6.2 50% increase in serum creatinine							
Silverberg 1976	2	5	0	4	100.0%	4.17 [0.25 , 68.16]	
Subtotal (95% CI)		**5**		**4**	**100.0%**	**4.17 [0.25 , 68.16]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.00 (P = 0.32)							

0.01 0.1 1 10 100
More with control   More with AZA+steroids

Analysis 17.7. Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 7: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	AZA+steroids Events	AZA+steroids Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Silverberg 1976	0	5	0	4	Not estimable	
Test for subgroup differences: Not applicable						

0.01 0.1 1 10 100
Less with AZA+steroids   Less with control

Analysis 17.8.   Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 8: Final serum creatinine

Study or Subgroup	AZA+steroids			Control			Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
	Mean [µmol/L]	SD [µmol/L]	Total	Mean [µmol/L]	SD [µmol/L]	Total			
Silverberg 1976	159.1	106.1	5	212.2	141.4	4	100.0%	-53.10 [-219.98 , 113.78]	
Total (95% CI)			**5**			**4**	**100.0%**	**-53.10 [-219.98 , 113.78]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable

-500 -250 0 250 500
Lower with AZA+steroids   Lower with control

Analysis 17.9.   Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 9: Final GFR [mL/min/1.73 m²]

Study or Subgroup	AZA+steroids			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Silverberg 1976	87	54	5	54	22	4	100.0%	33.00 [-19.01 , 85.01]	
Total (95% CI)			**5**			**4**	**100.0%**	**33.00 [-19.01 , 85.01]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.21)
Test for subgroup differences: Not applicable

-100 -50 0 50 100
Higher with control   Higher with AZA+steroids

Analysis 17.10.   Comparison 17: Azathioprine ± steroids versus no treatment, Outcome 10: Final proteinuria
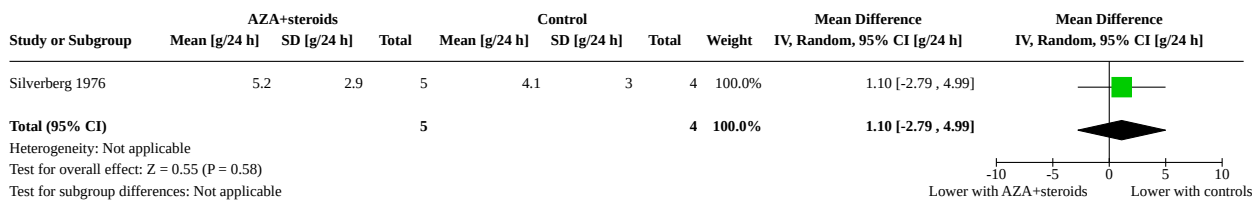
Study or Subgroup	AZA+steroids			Control			Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
	Mean [g/24 h]	SD [g/24 h]	Total	Mean [g/24 h]	SD [g/24 h]	Total			
Silverberg 1976	5.2	2.9	5	4.1	3	4	100.0%	1.10 [-2.79 , 4.99]	
Total (95% CI)			**5**			**4**	**100.0%**	**1.10 [-2.79 , 4.99]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Lower with AZA+steroids   Lower with controls

Comparison 18.   Mycophenolate mofetil versus no treatment/supportive therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.2 ESKD (dialysis/transplantation)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.3 Complete or partial remission	1	32	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.52, 2.48]
18.4 Complete remission	1	32	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.64]
18.5 Partial remission	1	32	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.52, 3.56]
18.6 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	36	Risk Ratio (M-H, Random, 95% CI)	8.10 [0.47, 140.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.7 Increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.7.1 100% increase in serum creatinine	1	32	Risk Ratio (M-H, Random, 95% CI)	Not estimable
18.7.2 50% increase in serum creatinine	1	32	Risk Ratio (M-H, Random, 95% CI)	Not estimable
18.8 Final GFR [mL/min/1.73 m²]	1	32	Mean Difference (IV, Random, 95% CI)	12.37 [-4.93, 29.67]

Analysis 18.1. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 1: Death

	MMF		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Dussol 2008	0	19	0	17	Not estimable	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Less with MMF Less with control

Analysis 18.2. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 2: ESKD (dialysis/transplantation)

	MMF		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Dussol 2008	0	19	0	17	Not estimable	

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Less with MMF Less with control

Analysis 18.3. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 3: Complete or partial remission

	MMF		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Dussol 2008	7	15	7	17	100.0%	1.13 [0.52 , 2.48]	
Total (95% CI)		15		17	100.0%	**1.13 [0.52 , 2.48]**	
Total events:	7		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with control More with MMF

Analysis 18.4. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 4: Complete remission

Study or Subgroup	MMF Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dussol 2008	1	15	2	17	100.0%	0.57 [0.06 , 5.64]	
Total (95% CI)		**15**		**17**	**100.0%**	**0.57 [0.06 , 5.64]**	
Total events:	1		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with control   More with MMF
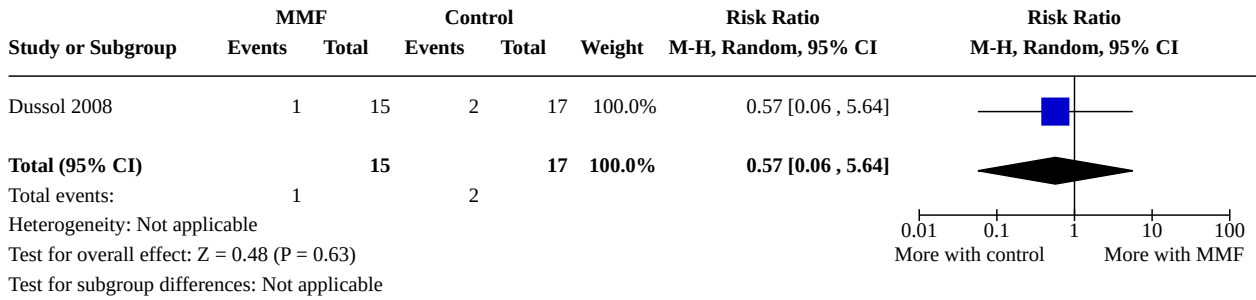
Analysis 18.5. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 5: Partial remission

Study or Subgroup	MMF Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dussol 2008	6	15	5	17	100.0%	1.36 [0.52 , 3.56]	
Total (95% CI)		**15**		**17**	**100.0%**	**1.36 [0.52 , 3.56]**	
Total events:	6		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with control   More with MMF
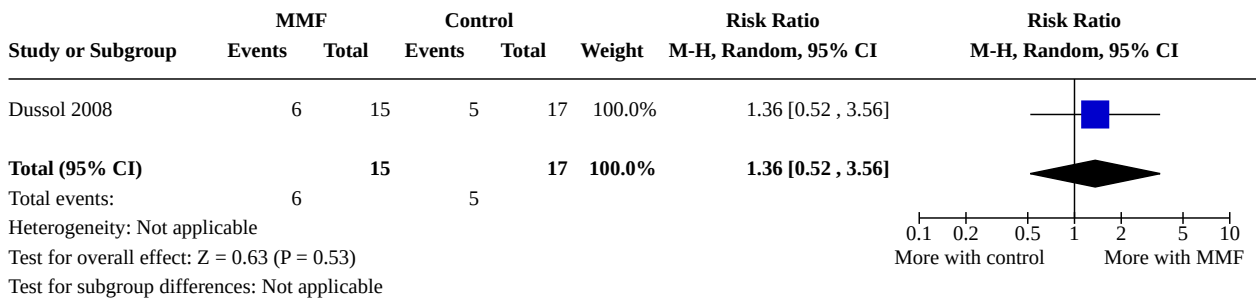
Analysis 18.6. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 6: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	MMF Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Dussol 2008	4	19	0	17	100.0%	8.10 [0.47 , 140.24]	
Total (95% CI)		**19**		**17**	**100.0%**	**8.10 [0.47 , 140.24]**	
Total events:	4		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable

0.002 0.1 1 10 500
Less with MMF   Less with control
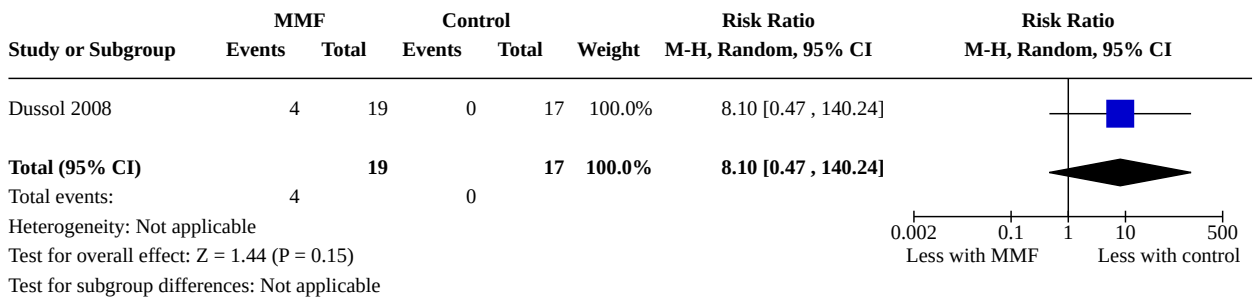
Analysis 18.7. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 7: Increase in serum creatinine

Study or Subgroup	MMF Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
18.7.1 100% increase in serum creatinine							
Dussol 2008	0	15	0	17		Not estimable	
Subtotal (95% CI)		**15**		**17**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
18.7.2 50% increase in serum creatinine							
Dussol 2008	0	15	0	17		Not estimable	
Subtotal (95% CI)		**15**		**17**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

0.1 0.2 0.5 1 2 5 10
Less with MMF   Less with control

Analysis 18.8. Comparison 18: Mycophenolate mofetil versus no treatment/supportive therapy, Outcome 8: Final GFR [mL/min/1.73 m²]

Study or Subgroup	MMF Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Dussol 2008	86.6	27.84	15	74.23	21.13	17	100.0%	12.37 [-4.93 , 29.67]	
Total (95% CI)			**15**			**17**	**100.0%**	**12.37 [-4.93 , 29.67]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.40 (P = 0.16)									
Test for subgroup differences: Not applicable									

-50 -25 0 25 50
Higher with control   Higher with MMF

Comparison 19. Mycophenolate mofetil ± steroids versus alkylating agents ± steroids

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
19.1 Death	4	127	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 70.83]
19.2 ESKD (dialysis/transplantation)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.3 Complete or partial remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.3.1 Complete or partial remission at final follow-up)	4	124	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.13]
19.3.2 Complete or partial remission at follow-up (≥ 2 years)	1	26	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.56, 1.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.4 Complete remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.4.1 Complete remission at final follow-up	4	124	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.58, 1.73]
19.4.2 Complete remission at follow-up (≥ 2 years)	1	26	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.44, 2.29]
19.5 Partial remission	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.5.1 Partial remission at final follow-up	4	124	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.37]
19.5.2 Partial remission at follow-up (≥ 2 years)	1	26	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.37, 4.82]
19.6 Relapse after complete or partial remission	3	71	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.33, 5.43]
19.7 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.8 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
19.9 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.9.1 Severe adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]
19.9.2 Infection	2	86	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.49, 2.60]
19.10 Final serum creatinine	1	26	Mean Difference (IV, Random, 95% CI)	-1.60 [-18.14, 14.94]
19.11 Final serum albumin	1	57	Mean Difference (IV, Random, 95% CI)	0.90 [-1.63, 3.43]
19.12 Final GFR [mL/min/1.73 m²]	2	45	Mean Difference (IV, Random, 95% CI)	3.75 [-6.12, 13.62]
19.13 Final proteinuria	1	57	Mean Difference (IV, Random, 95% CI)	0.10 [-0.89, 1.09]

Analysis 19.1. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 1: Death

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Senthil Nayagam 2008	0	11	0	10		Not estimable	
Fu 2012a	0	13	0	13		Not estimable	
Chan 2007	0	11	0	9		Not estimable	
Peng 2016	1	30	0	30	100.0%	3.00 [0.13 , 70.83]	
Total (95% CI)		65		62	100.0%	3.00 [0.13 , 70.83]	
Total events:	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with alkylating agents

Analysis 19.2. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Senthil Nayagam 2008	0	11	0	10	Not estimable	
Peng 2016	0	30	0	30	Not estimable	
Chan 2007	0	11	0	9	Not estimable	

0.01 0.1 1 10 100
Less with MMF   Less with alkylating agents

Analysis 19.3. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 3: Complete or partial remission

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.3.1 Complete or partial remission at final follow-up)							
Fu 2012a	6	13	7	13	8.9%	0.86 [0.40 , 1.86]	
Chan 2007	7	11	6	9	12.8%	0.95 [0.50 , 1.82]	
Senthil Nayagam 2008	7	11	8	10	17.9%	0.80 [0.46 , 1.37]	
Peng 2016	21	29	22	28	60.3%	0.92 [0.69 , 1.24]	
Subtotal (95% CI)		64		60	100.0%	0.90 [0.71 , 1.13]	
Total events:	41		43				

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

19.3.2 Complete or partial remission at follow-up (≥ 2 years)							
Fu 2012a	9	13	10	13	100.0%	0.90 [0.56 , 1.44]	
Subtotal (95% CI)		13		13	100.0%	0.90 [0.56 , 1.44]	
Total events:	9		10				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%

0.1 0.2 0.5 1 2 5 10
More with alkylating agents   More with MMF

Analysis 19.4. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 4: Complete remission

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.4.1 Complete remission at final follow-up							
Chan 2007	3	11	3	9	16.6%	0.82 [0.22 , 3.11]	
Senthil Nayagam 2008	5	11	3	10	22.5%	1.52 [0.48 , 4.77]	
Fu 2012a	5	13	4	13	26.0%	1.25 [0.43 , 3.63]	
Peng 2016	6	29	8	28	34.8%	0.72 [0.29 , 1.82]	
Subtotal (95% CI)		**64**		**60**	**100.0%**	**1.01 [0.58 , 1.73]**	
Total events:	19		18				
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 3 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.02 (P = 0.98)							
19.4.2 Complete remission at follow-up (≥ 2 years)							
Fu 2012a	6	13	6	13	100.0%	1.00 [0.44 , 2.29]	
Subtotal (95% CI)		**13**		**13**	**100.0%**	**1.00 [0.44 , 2.29]**	
Total events:	6		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%							0.05 0.2 1 5 20

More with alkylating agents ← → More with MMF

Analysis 19.5. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 5: Partial remission

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.5.1 Partial remission at final follow-up							
Fu 2012a	2	13	4	13	8.0%	0.50 [0.11 , 2.27]	
Senthil Nayagam 2008	2	11	5	10	9.4%	0.36 [0.09 , 1.47]	
Chan 2007	4	11	3	9	12.5%	1.09 [0.33 , 3.66]	
Peng 2016	15	29	14	28	70.2%	1.03 [0.62 , 1.72]	
Subtotal (95% CI)		**64**		**60**	**100.0%**	**0.89 [0.58 , 1.37]**	
Total events:	23		26				
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%							
Test for overall effect: Z = 0.53 (P = 0.60)							
19.5.2 Partial remission at follow-up (≥ 2 years)							
Fu 2012a	4	13	3	13	100.0%	1.33 [0.37 , 4.82]	
Subtotal (95% CI)		**13**		**13**	**100.0%**	**1.33 [0.37 , 4.82]**	
Total events:	4		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.44 (P = 0.66)							
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%							0.05 0.2 1 5 20

More with alkylating agents ← → More with MMF

Analysis 19.6. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 6: Relapse after complete or partial remission

	MMF		Alkylating agents			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chan 2007	2	7	1	6	42.8%	1.71 [0.20 , 14.55]	
Peng 2016	2	21	1	22	36.2%	2.10 [0.20 , 21.42]	
Senthil Nayagam 2008	0	7	1	8	21.0%	0.38 [0.02 , 7.96]	
Total (95% CI)		35		36	100.0%	1.34 [0.33 , 5.43]	
Total events:	4		3				

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with alkylating agents
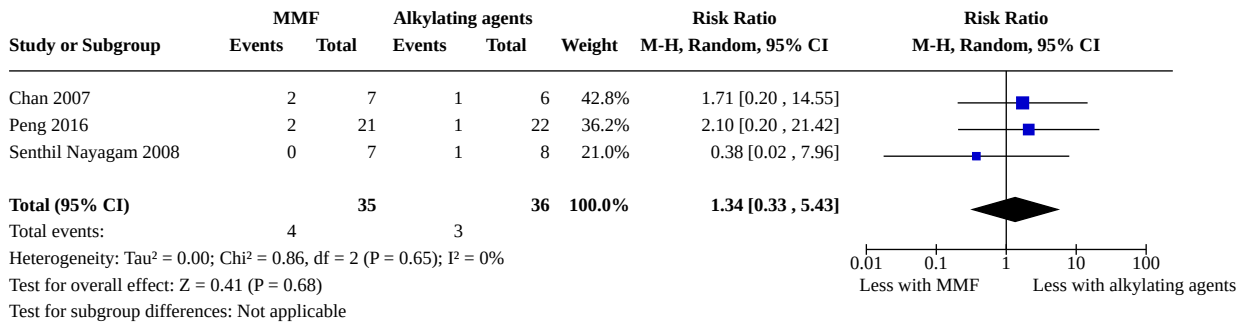
Analysis 19.7. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 7: Doubling of serum creatinine

	MMF		Alkylating agents		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Peng 2016	0	29	0	28	Not estimable	

0.01 0.1 1 10 100
Less with MMF   Less with alkylating agents
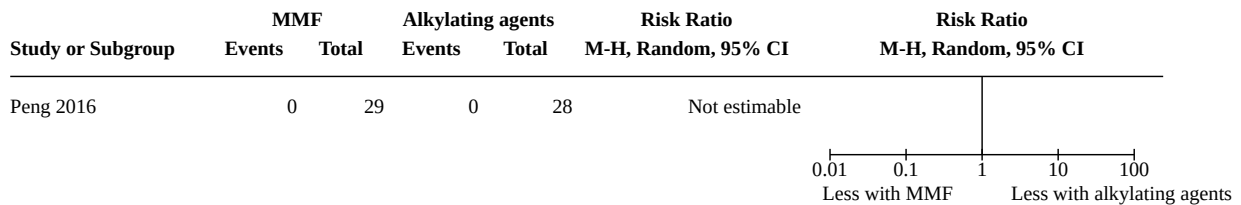
Analysis 19.8. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

	MMF		Alkylating agents			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Peng 2016	0	30	1	30	100.0%	0.33 [0.01 , 7.87]	
Total (95% CI)		30		30	100.0%	0.33 [0.01 , 7.87]	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with alkylating agents
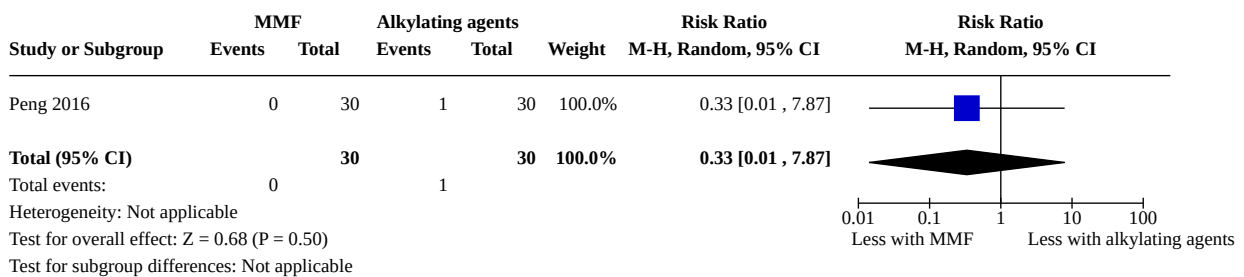
Analysis 19.9. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 9: Adverse events

Study or Subgroup	MMF Events	MMF Total	Alkylating agents Events	Alkylating agents Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.9.1 Severe adverse events							
Peng 2016	0	30	1	30	100.0%	0.33 [0.01 , 7.87]	
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.50)							
19.9.2 Infection							
Fu 2012a	1	13	1	13	9.8%	1.00 [0.07 , 14.34]	
Peng 2016	8	30	7	30	90.2%	1.14 [0.47 , 2.75]	
Subtotal (95% CI)		**43**		**43**	**100.0%**	**1.13 [0.49 , 2.60]**	
Total events:	9		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%							
Test for overall effect: Z = 0.28 (P = 0.78)							
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.46), I² = 0%							

0.01 0.1 1 10 100
Lower with MMF   Lower with alkylating agents

Analysis 19.10. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 10: Final serum creatinine

Study or Subgroup	MMF Mean [μmol/L]	MMF SD [μmol/L]	Total	Alkylating agents Mean [μmol/L]	Alkylating agents SD [μmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [μmol/L]	Mean Difference IV, Random, 95% CI [μmol/L]
Fu 2012a	70.5	19.2	13	72.1	23.6	13	100.0%	-1.60 [-18.14 , 14.94]	
Total (95% CI)			**13**			**13**	**100.0%**	**-1.60 [-18.14 , 14.94]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.19 (P = 0.85)									
Test for subgroup differences: Not applicable									

-20 -10 0 10 20
Lower with MMF   Lower with alkylating agents
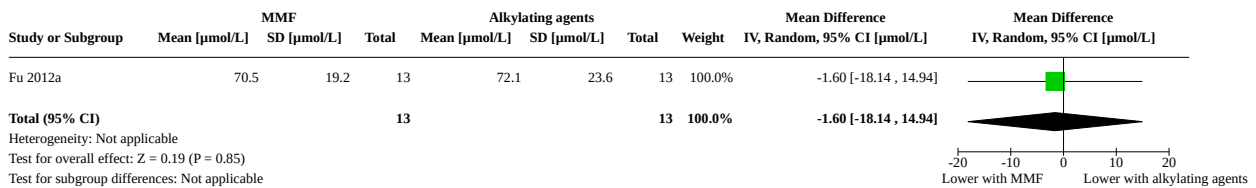
Analysis 19.11. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 11: Final serum albumin

Study or Subgroup	MMF Mean [g/L]	MMF SD [g/L]	Total	Alkylating agents Mean [g/L]	Alkylating agents SD [g/L]	Total	Weight	Mean Difference IV, Random, 95% CI [g/L]	Mean Difference IV, Random, 95% CI [g/L]
Peng 2016	37.5	4	29	36.6	5.6	28	100.0%	0.90 [-1.63 , 3.43]	
Total (95% CI)			**29**			**28**	**100.0%**	**0.90 [-1.63 , 3.43]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.70 (P = 0.49)									
Test for subgroup differences: Not applicable									

-4 -2 0 2 4
Lower with MMF   Lower with alkylating agents
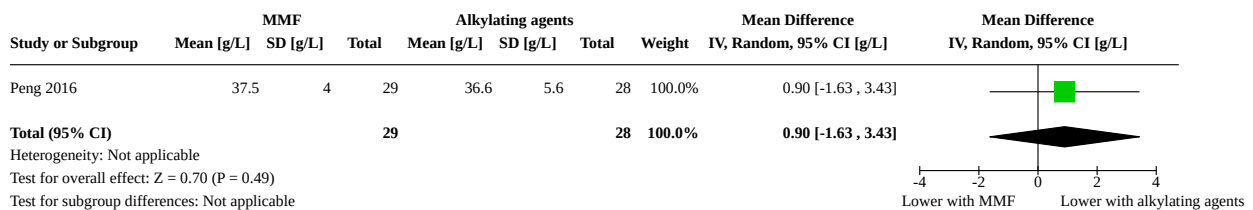
Analysis 19.12. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 12: Final GFR [mL/min/1.73 m²]

Study or Subgroup	MMF Mean	SD	Total	Alkylating agents Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Fu 2012a	90.9	35.7	13	92.3	20.4	13	19.5%	-1.40 [-23.75 , 20.95]	
Senthil Nayagam 2008	81	12.5	9	76	11.9	10	80.5%	5.00 [-6.00 , 16.00]	
Total (95% CI)			**22**			**23**	**100.0%**	**3.75 [-6.12 , 13.62]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
Higher with alkylating agents   Higher with MMF
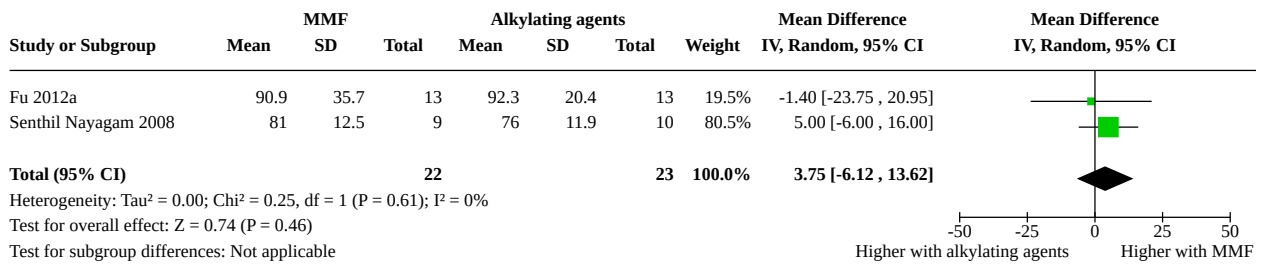
Analysis 19.13. Comparison 19: Mycophenolate mofetil ± steroids versus alkylating agents ± steroids, Outcome 13: Final proteinuria

Study or Subgroup	MMF Mean [g/24 h]	SD [g/24 h]	Total	Alkylating agents Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Peng 2016	2.2	1.8	29	2.1	2	28	100.0%	0.10 [-0.89 , 1.09]	
Total (95% CI)			**29**			**28**	**100.0%**	**0.10 [-0.89 , 1.09]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable

-2 -1 0 1 2
Lower with MMF   Lower with alkylating agents
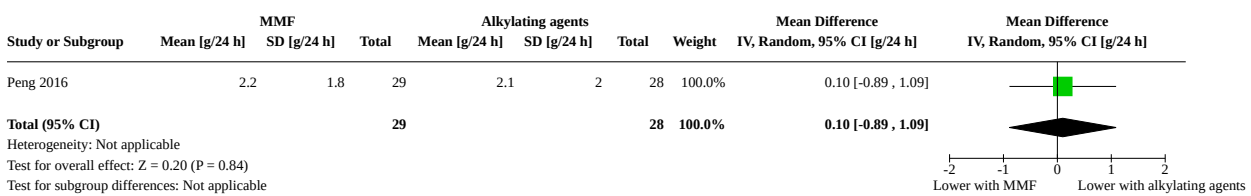
Comparison 20. Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Death	1	60	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 15.26]
20.2 ESKD (dialysis/transplantation)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.3 Complete or partial remission	2	97	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.27]
20.4 Complete remission	2	97	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.20, 1.63]
20.5 Partial remission	2	97	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.88, 2.10]
20.6 Relapse after complete remission	1	46	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.18, 7.74]
20.7 Increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.7.1 50% increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20.8 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable
20.9 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.9.1 Adverse events	1	39	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.63, 2.07]
20.9.2 Infection	2	99	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.80, 3.12]
20.9.3 Malignancy	1	39	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.06, 12.75]
20.10 Final serum creatinine	1	39	Mean Difference (IV, Random, 95% CI)	0.10 [-0.12, 0.32]
20.11 Final serum albumin	2	97	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.28, 0.10]
20.12 Final GFR [mL/min/1.73 m²]	1	39	Mean Difference (IV, Random, 95% CI)	-13.90 [-31.05, 3.25]
20.13 Final proteinuria	2	97	Mean Difference (IV, Random, 95% CI)	0.31 [-0.45, 1.07]

Analysis 20.1. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 1: Death

	MMF		CNI			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Peng 2016	1	30	1	30	100.0%	1.00 [0.07 , 15.26]	
Total (95% CI)		30		30	100.0%	**1.00 [0.07 , 15.26]**	
Total events:	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with CNI

Analysis 20.2. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 2: ESKD (dialysis/transplantation)

	MMF		CNI		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Peng 2016	0	30	0	30	Not estimable	

0.01 0.1 1 10 100
Less with MMF   Less with CNI

Analysis 20.3. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 3: Complete or partial remission

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Choi 2018	16	21	12	18	37.6%	1.14 [0.76 , 1.71]	
Peng 2016	21	29	25	29	62.4%	0.84 [0.64 , 1.10]	
Total (95% CI)		**50**		**47**	**100.0%**	**0.94 [0.70 , 1.27]**	
Total events:	37		37				

Heterogeneity: Tau² = 0.02; Chi² = 1.58, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with CNI   More with MMF
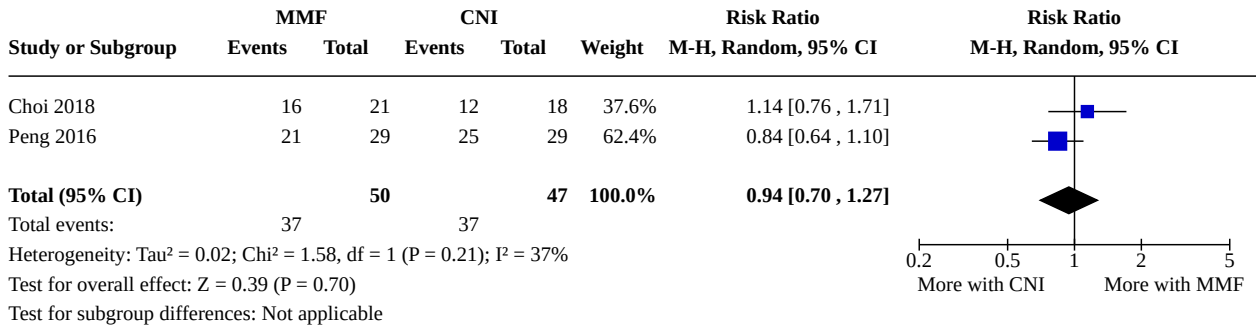
Analysis 20.4. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 4: Complete remission

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Choi 2018	4	21	3	18	37.1%	1.14 [0.29 , 4.44]	
Peng 2016	6	29	16	29	62.9%	0.38 [0.17 , 0.82]	
Total (95% CI)		**50**		**47**	**100.0%**	**0.57 [0.20 , 1.63]**	
Total events:	10		19				

Heterogeneity: Tau² = 0.30; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with CNI   More with MMF
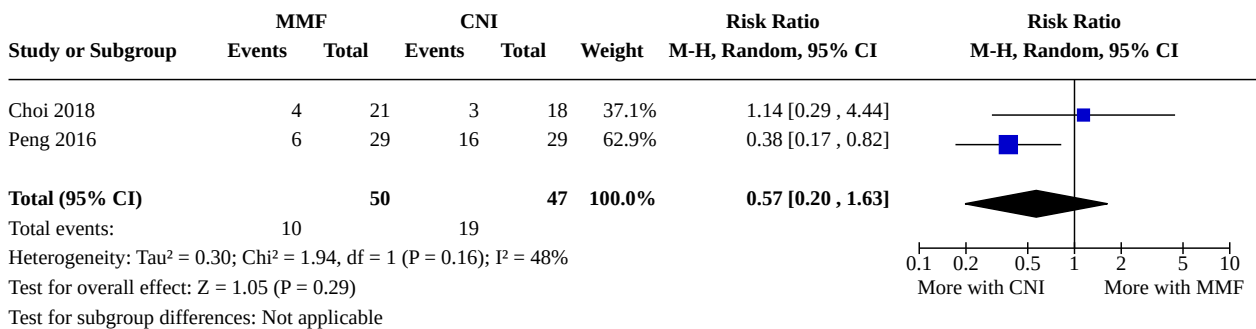
Analysis 20.5. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 5: Partial remission

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Peng 2016	15	29	9	29	45.6%	1.67 [0.87 , 3.18]	
Choi 2018	12	21	9	18	54.4%	1.14 [0.63 , 2.07]	
Total (95% CI)		**50**		**47**	**100.0%**	**1.36 [0.88 , 2.10]**	
Total events:	27		18				

Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with CNI   More with MMF
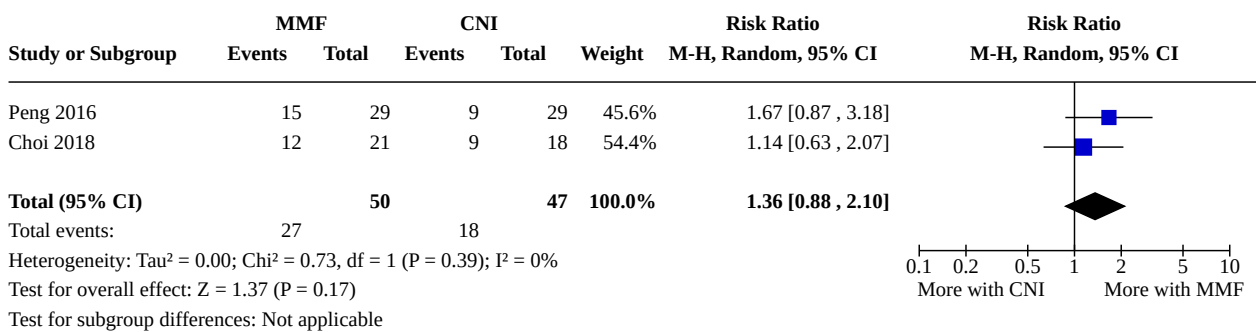
Analysis 20.6. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 6: Relapse after complete remission

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Peng 2016	2	21	2	25	100.0%	1.19 [0.18 , 7.74]	
Total (95% CI)		**21**		**25**	**100.0%**	**1.19 [0.18 , 7.74]**	
Total events:	2		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with CNI
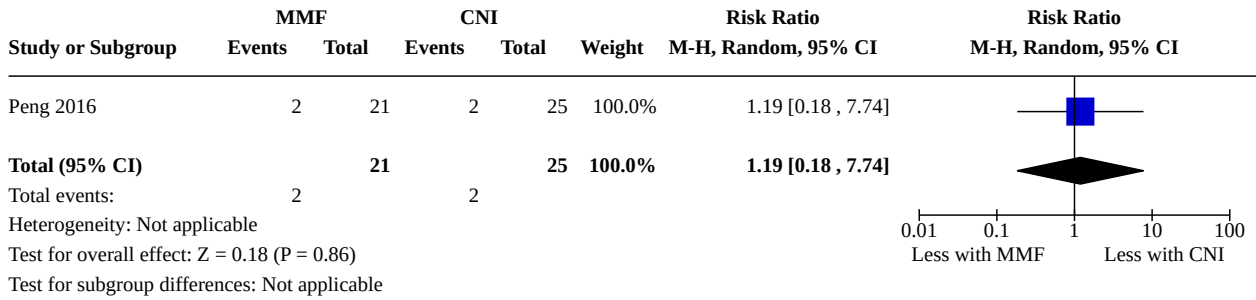
Analysis 20.7. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 7: Increase in serum creatinine

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.7.1 50% increase in serum creatinine						
Peng 2016	0	30	0	30	Not estimable	

0.01 0.1 1 10 100
Less with MMF   Less with CNI
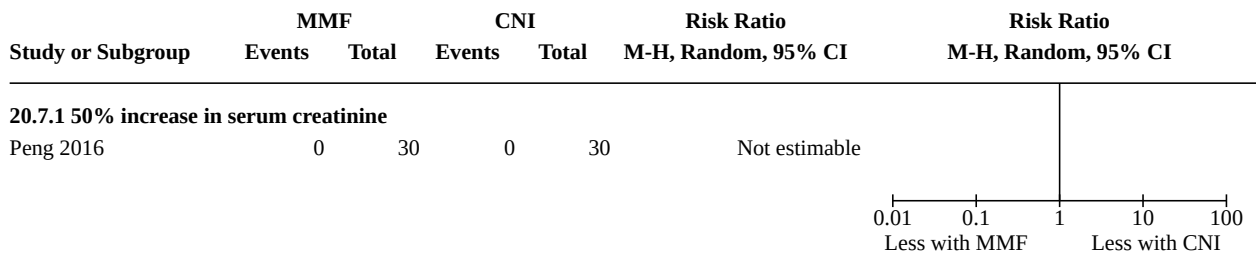
Analysis 20.8. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 8: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	MMF Events	MMF Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Peng 2016	0	30	0	30		Not estimable	
Total (95% CI)		**30**		**30**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with MMF   Less with CNI
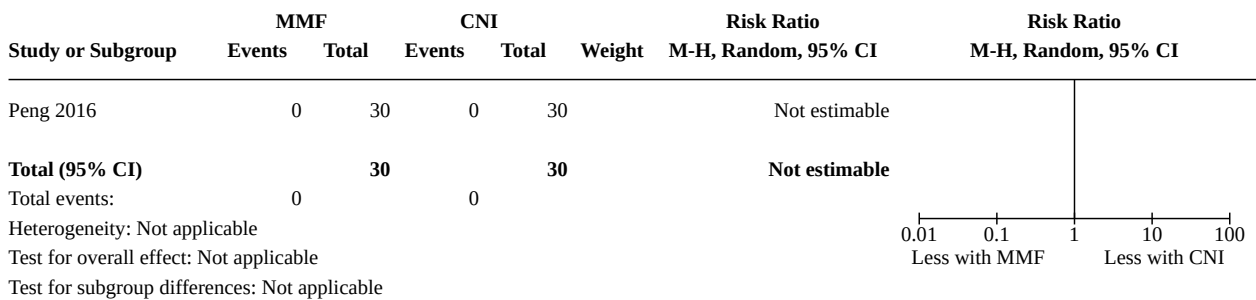
Analysis 20.9. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 9: Adverse events

Study or Subgroup	MMF Events	Total	CNI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.9.1 Adverse events							
Choi 2018	12	21	9	18	100.0%	1.14 [0.63 , 2.07]	
Subtotal (95% CI)		**21**		**18**	**100.0%**	**1.14 [0.63 , 2.07]**	
Total events:	12		9				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.44 (P = 0.66)							
20.9.2 Infection							
Choi 2018	9	21	4	18	46.6%	1.93 [0.71 , 5.22]	
Peng 2016	8	30	6	30	53.4%	1.33 [0.53 , 3.38]	
Subtotal (95% CI)		**51**		**48**	**100.0%**	**1.58 [0.80 , 3.12]**	
Total events:	17		10				
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%							
Test for overall effect: Z = 1.33 (P = 0.18)							
20.9.3 Malignancy							
Choi 2018	1	21	1	18	100.0%	0.86 [0.06 , 12.75]	
Subtotal (95% CI)		**21**		**18**	**100.0%**	**0.86 [0.06 , 12.75]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.11 (P = 0.91)							

Test for subgroup differences: Chi² = 0.60, df = 2 (P = 0.74), I² = 0%

0.01 0.1 1 10 100
Lower with MMF   Lower with CNI

Analysis 20.10. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 10: Final serum creatinine

Study or Subgroup	MMF Mean [mg/dL]	SD [mg/dL]	Total	CNI Mean [mg/dL]	SD [mg/dL]	Total	Weight	Mean Difference IV, Random, 95% CI [mg/dL]	Mean Difference IV, Random, 95% CI [mg/dL]
Choi 2018	1.1	0.3	21	1	0.4	18	100.0%	0.10 [-0.12 , 0.32]	
Total (95% CI)			**21**			**18**	**100.0%**	**0.10 [-0.12 , 0.32]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.87 (P = 0.38)									
Test for subgroup differences: Not applicable									

-1 -0.5 0 0.5 1
Lower with MMF   Lower with CNI
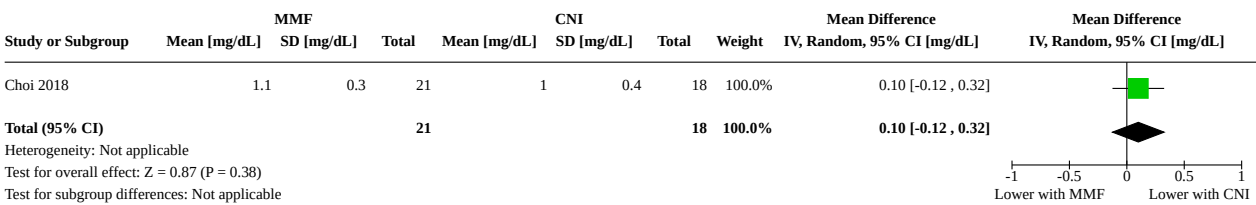
Analysis 20.11. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 11: Final serum albumin

Study or Subgroup	MMF Mean [g/dL]	SD [g/dL]	Total	CNI Mean [g/dL]	SD [g/dL]	Total	Weight	Mean Difference IV, Random, 95% CI [g/dL]	Mean Difference IV, Random, 95% CI [g/dL]
Choi 2018	3.6	0.9	21	3.6	0.7	18	14.4%	0.00 [-0.50 , 0.50]	
Peng 2016	3.8	0.4	29	3.9	0.4	29	85.6%	-0.10 [-0.31 , 0.11]	
Total (95% CI)			**50**			**47**	**100.0%**	**-0.09 [-0.28 , 0.10]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%									
Test for overall effect: Z = 0.88 (P = 0.38)									
Test for subgroup differences: Not applicable									

-1 -0.5 0 0.5 1
Lower with MMF   Lower with CNI
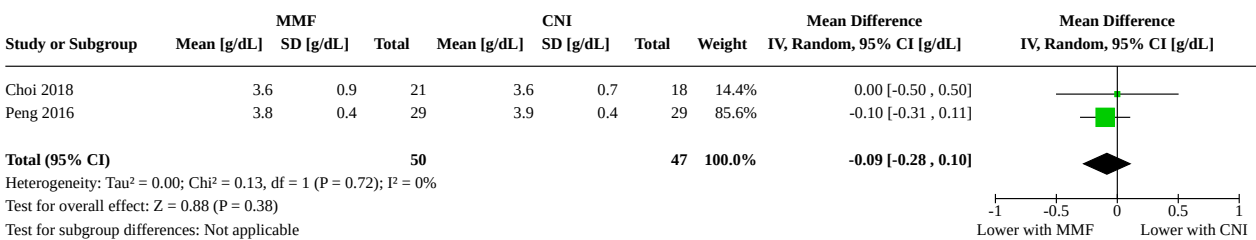
Analysis 20.12. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 12: Final GFR [mL/min/1.73 m²]

Study or Subgroup	MMF Mean	SD	Total	CNI Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Choi 2018	70.1	19.2	21	84	32.6	18	100.0%	-13.90 [-31.05 , 3.25]	
Total (95% CI)			21			18	100.0%	-13.90 [-31.05 , 3.25]	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
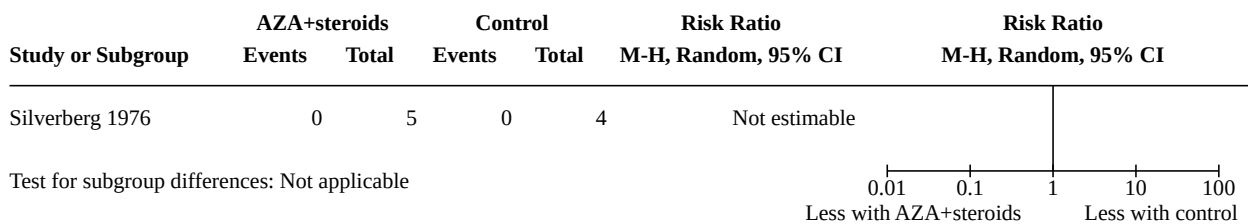Higher with CNI   Higher with MMF
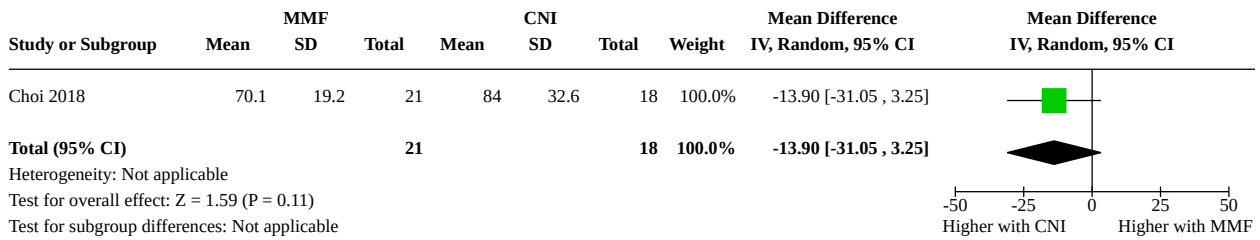
Analysis 20.13. Comparison 20: Mycophenolate mofetil ± steroids versus calcineurin inhibitors ± steroids, Outcome 13: Final proteinuria

Study or Subgroup	MMF Mean [g/L]	SD [g/L]	Total	CNI Mean [g/L]	SD [g/L]	Total	Weight	Mean Difference IV, Random, 95% CI [g/L]	Mean Difference IV, Random, 95% CI [g/L]
Peng 2016	2.2	1.8	29	1.4	1.7	29	38.6%	0.80 [-0.10 , 1.70]	
Choi 2018	3.6	0.9	21	3.6	0.7	18	61.4%	0.00 [-0.50 , 0.50]	
Total (95% CI)			50			47	100.0%	0.31 [-0.45 , 1.07]	

Heterogeneity: Tau² = 0.18; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

-2 -1 0 1 2
Lower with MMF   Lower with CNI
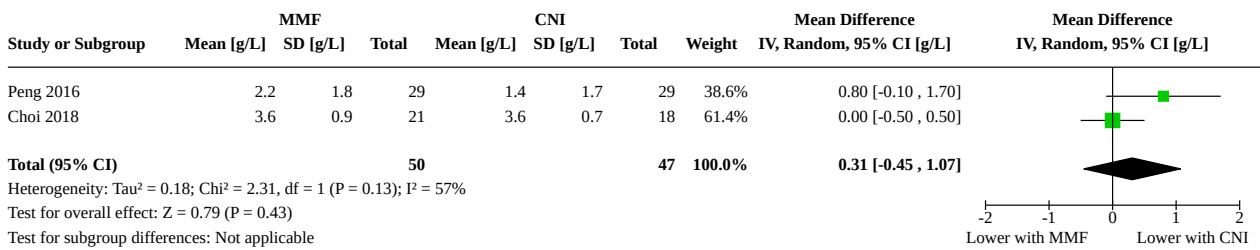
Comparison 21. Adrenocorticotropic hormone versus no treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
21.1 Complete or partial remission	1	30	Risk Ratio (M-H, Random, 95% CI)	7.00 [1.91, 25.62]
21.2 Complete remission	1	30	Risk Ratio (M-H, Random, 95% CI)	11.00 [1.62, 74.88]
21.3 Partial remission	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.35, 25.68]

Analysis 21.1. Comparison 21: Adrenocorticotropic hormone versus no treatment, Outcome 1: Complete or partial remission

Study or Subgroup	ACTH Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arnadottir 2006	14	15	2	15	100.0%	7.00 [1.91 , 25.62]	
Total (95% CI)		15		15	100.0%	7.00 [1.91 , 25.62]	
Total events:	14		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Not applicable

0.02 0.1 1 10 50
More with control   More with ACTH
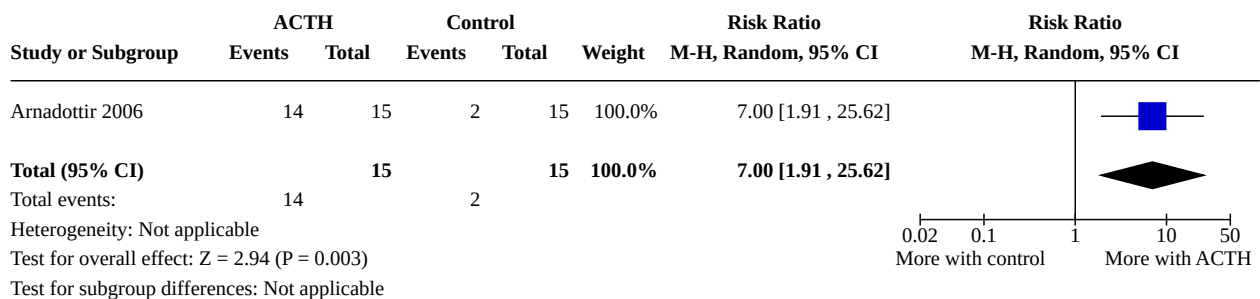
Analysis 21.2. Comparison 21: Adrenocorticotropic hormone versus no treatment, Outcome 2: Complete remission

Study or Subgroup	ACTH Events	ACTH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arnadottir 2006	11	15	1	15	100.0%	11.00 [1.62 , 74.88]	
Total (95% CI)		**15**		**15**	**100.0%**	**11.00 [1.62 , 74.88]**	
Total events:	11		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with control   More with ACTH
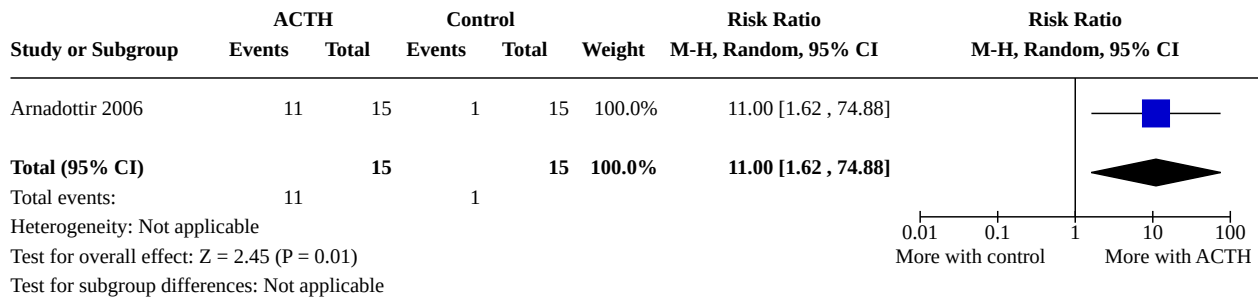
Analysis 21.3. Comparison 21: Adrenocorticotropic hormone versus no treatment, Outcome 3: Partial remission
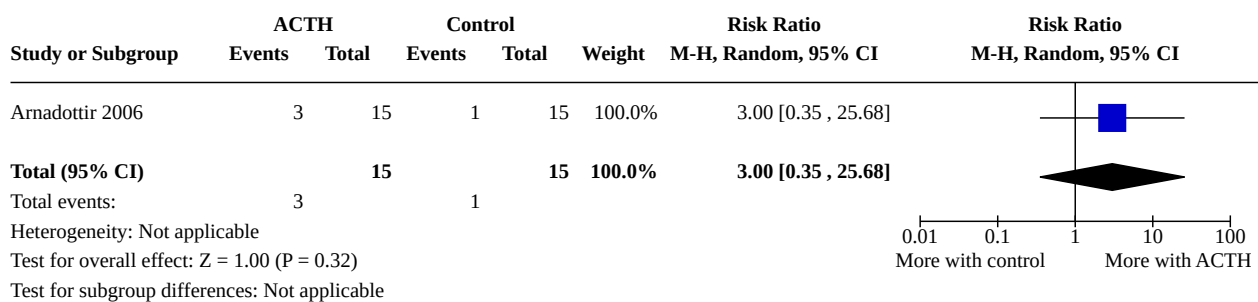
Study or Subgroup	ACTH Events	ACTH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Arnadottir 2006	3	15	1	15	100.0%	3.00 [0.35 , 25.68]	
Total (95% CI)		**15**		**15**	**100.0%**	**3.00 [0.35 , 25.68]**	
Total events:	3		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with control   More with ACTH

Comparison 22. Adrenocorticotropic hormone versus alkylating agents + steroids

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
22.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.2 ESKD (dialysis/transplanta-tion)	1	32	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.57]
22.3 Complete or partial remission	1	32	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.17]
22.4 Complete remission	1	32	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.88, 4.54]
22.5 Partial remission	1	32	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.16, 1.01]
22.6 Increase in serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.6.1 100% increase in serum cre-atinine	1	32	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.57]
22.6.2 50% increase in serum crea-tinine	1	32	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.7 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	32	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.16, 6.25]
22.8 Final serum creatinine	1	31	Mean Difference (IV, Random, 95% CI)	-1.00 [-19.07, 17.07]
22.9 Final proteinuria	1	31	Mean Difference (IV, Random, 95% CI)	-1.80 [-3.19, -0.41]

Analysis 22.1. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 1: Death
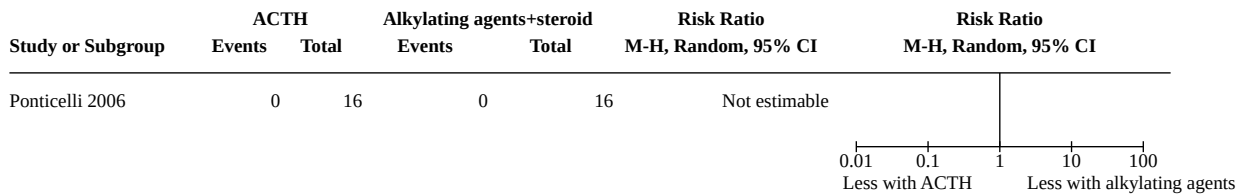
Analysis 22.2. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 2: ESKD (dialysis/transplantation)
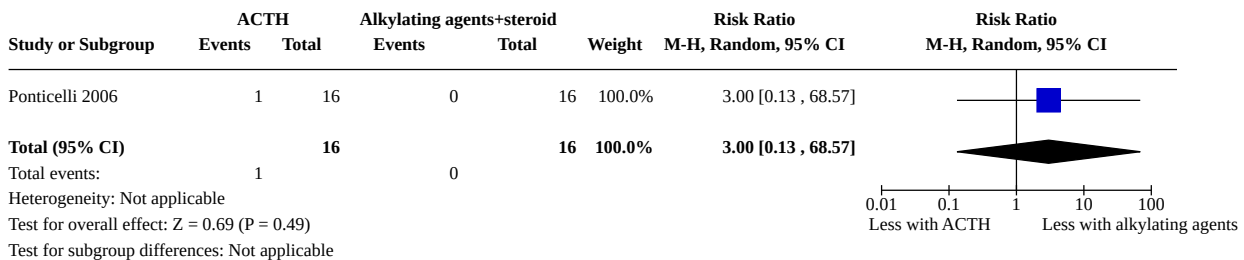
Analysis 22.3. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 3: Complete or partial remission

Analysis 22.4. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 4: Complete remission

Study or Subgroup	ACTH		Alkylating agents+steroid		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Ponticelli 2006	10	16	5	16	100.0%	2.00 [0.88 , 4.54]	
Total (95% CI)		16		16	100.0%	2.00 [0.88 , 4.54]	
Total events:	10		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.66 (P = 0.10)							
Test for subgroup differences: Not applicable							

0.1 0.2 0.5 1 2 5 10
More with alkylating agents   More with ACTH
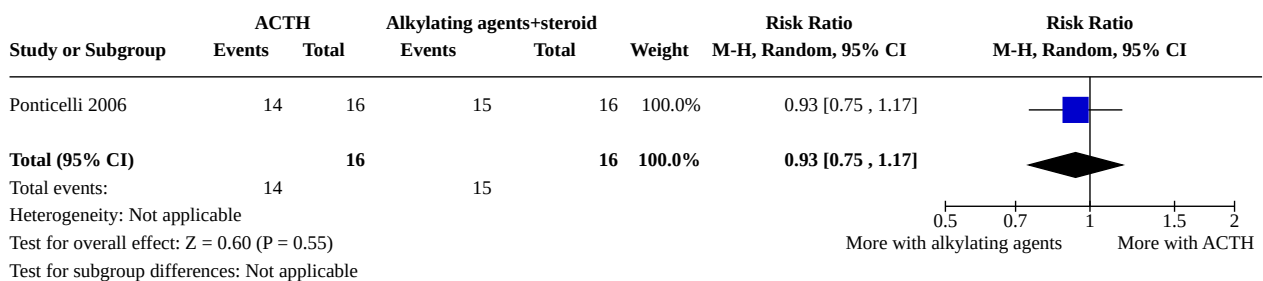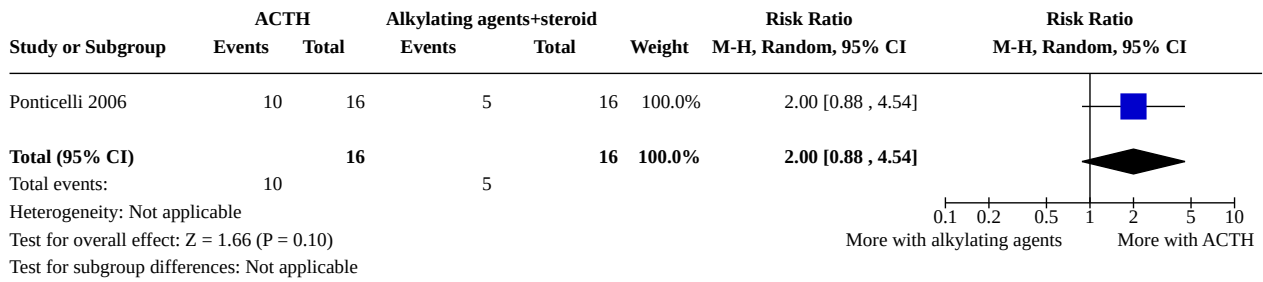
Analysis 22.5. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 5: Partial remission

Study or Subgroup	ACTH		Alkylating agents+steroid		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Ponticelli 2006	4	16	10	16	100.0%	0.40 [0.16 , 1.01]	
Total (95% CI)		16		16	100.0%	0.40 [0.16 , 1.01]	
Total events:	4		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.93 (P = 0.05)							
Test for subgroup differences: Not applicable							

0.1 0.2 0.5 1 2 5 10
More with alkylating agents   More with ACTH
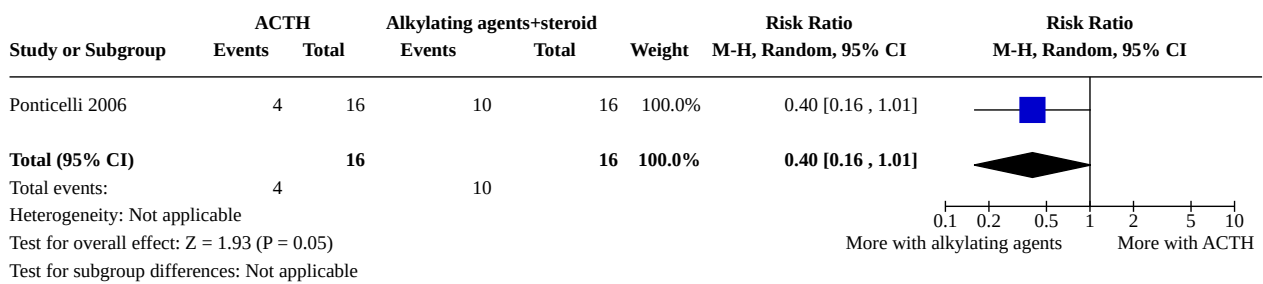
Analysis 22.6. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 6: Increase in serum creatinine

Study or Subgroup	ACTH		Alkylating agents+steroid		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
22.6.1 100% increase in serum creatinine							
Ponticelli 2006	1	16	0	16	100.0%	3.00 [0.13 , 68.57]	
Subtotal (95% CI)		16		16	100.0%	3.00 [0.13 , 68.57]	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
22.6.2 50% increase in serum creatinine							
Ponticelli 2006	1	16	0	16	100.0%	3.00 [0.13 , 68.57]	
Subtotal (95% CI)		16		16	100.0%	3.00 [0.13 , 68.57]	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%

0.002 0.1 1 10 500
Less with ACTH   Less with alkylating agents

Analysis 22.7. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 7: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	ACTH Events	ACTH Total	Alkylating agents+steroid Events	Alkylating agents+steroid Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ponticelli 2006	2	16	2	16	100.0%	1.00 [0.16 , 6.25]	
Total (95% CI)		16		16	100.0%	1.00 [0.16 , 6.25]	
Total events:	2		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Less with ACTH   Less with alkylating agents
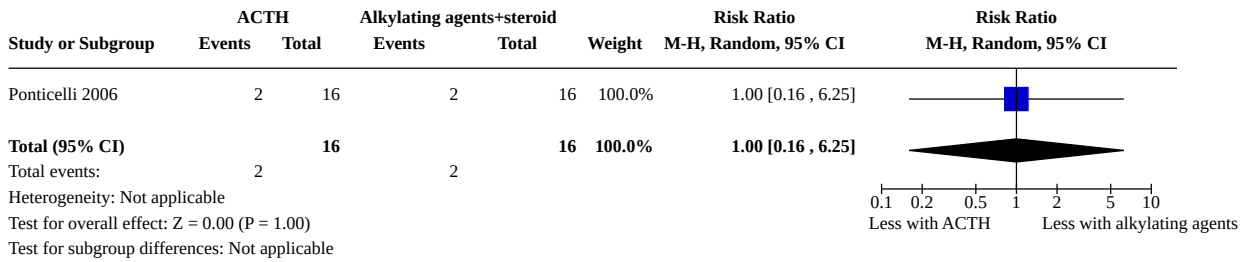
Analysis 22.8. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 8: Final serum creatinine

Study or Subgroup	ACTH Mean [µmol/L]	ACTH SD [µmol/L]	Total	Alkylating agents+steroid Mean [µmol/L]	SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
Ponticelli 2006	79	33.3	15	80	13.3	16	100.0%	-1.00 [-19.07 , 17.07]	
Total (95% CI)			15			16	100.0%	-1.00 [-19.07 , 17.07]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable

-50 -25 0 25 50
Lower with ACTH   Lower with alkylating agents
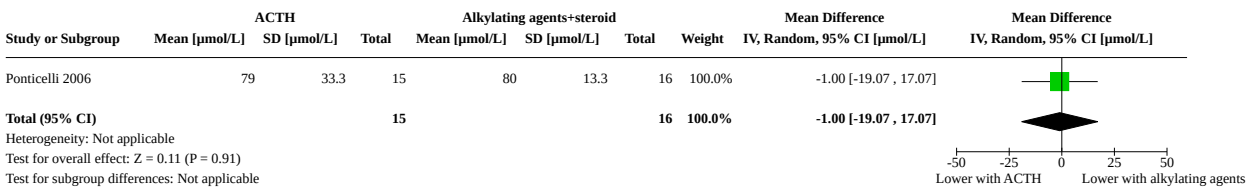
Analysis 22.9. Comparison 22: Adrenocorticotropic hormone versus alkylating agents + steroids, Outcome 9: Final proteinuria

Study or Subgroup	ACTH Mean [g/24 h]	ACTH SD [g/24 h]	Total	Alkylating agents+steroid Mean [g/24 h]	SD [g/24 h]	Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
Ponticelli 2006	0.3	1.26	15	2.1	2.52	16	100.0%	-1.80 [-3.19 , -0.41]	
Total (95% CI)			15			16	100.0%	-1.80 [-3.19 , -0.41]	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable

-4 -2 0 2 4
Lower with ACTH   Lower with alkylating agents
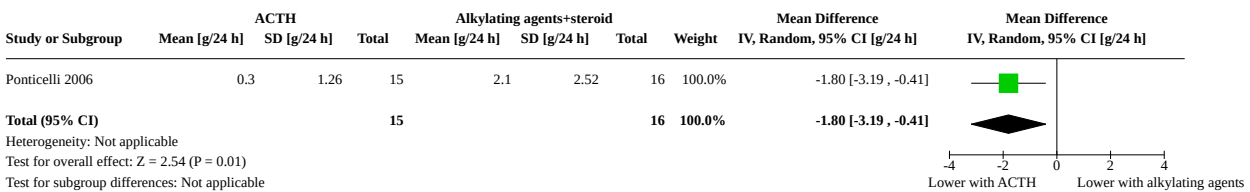
Comparison 23. Mizoribine ± steroids versus placebo/no treatment/corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Complete or partial remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1.1 Complete or partial remission at final follow-up	2	114	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.14, 4.38]
23.1.2 Complete or partial remission at final follow-up (≥ 2 years)	1	25	Risk Ratio (M-H, Random, 95% CI)	4.71 [0.66, 33.61]
23.2 Complete remission	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.2.1 Complete remission at final follow-up	3	150	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.69, 3.84]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
23.2.2 Complete remission at final follow-up (> 2 years)	1	25	Risk Ratio (M-H, Random, 95% CI)	5.60 [0.32, 98.21]
23.3 Partial remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.3.1 Partial remission at final follow-up	2	114	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.90, 3.97]
23.3.2 Partial remission at final follow-up (≥ 2 years)	1	25	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.28, 19.66]
23.4 Temporary or permanent discontinuation/hospitalisation due to adverse events	1	89	Risk Ratio (M-H, Random, 95% CI)	4.29 [0.21, 86.80]

**Analysis 23.1. Comparison 23: Mizoribine ± steroids versus placebo/
no treatment/corticosteroids, Outcome 1: Complete or partial remission**
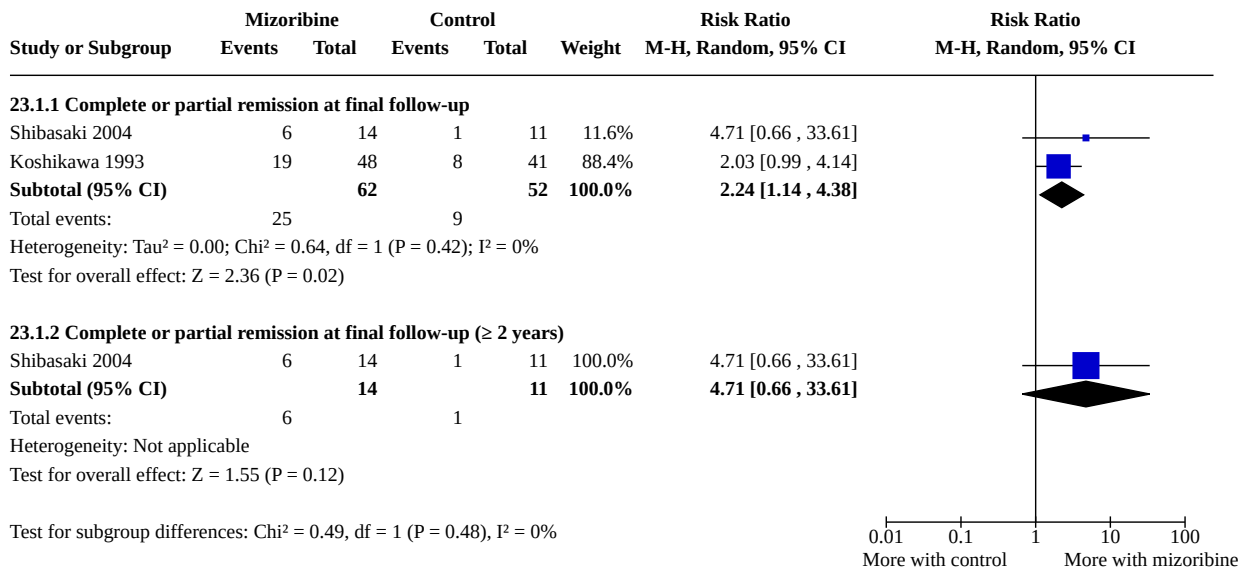
Analysis 23.2. Comparison 23: Mizoribine ± steroids versus placebo/ no treatment/corticosteroids, Outcome 2: Complete remission

Study or Subgroup	Mizoribine Events	Mizoribine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
23.2.1 Complete remission at final follow-up							
Shibasaki 2004	3	14	0	11	9.0%	5.60 [0.32 , 98.21]	
Koshikawa 1993	4	48	1	41	15.9%	3.42 [0.40 , 29.37]	
Hasegawa 2017	6	18	5	18	75.1%	1.20 [0.45 , 3.23]	
Subtotal (95% CI)		**80**		**70**	**100.0%**	**1.63 [0.69 , 3.84]**	
Total events:	13		6				
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%							
Test for overall effect: Z = 1.11 (P = 0.27)							
23.2.2 Complete remission at final follow-up (> 2 years)							
Shibasaki 2004	3	14	0	11	100.0%	5.60 [0.32 , 98.21]	
Subtotal (95% CI)		**14**		**11**	**100.0%**	**5.60 [0.32 , 98.21]**	
Total events:	3		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							

Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%

0.002   0.1   1   10   500
More with control   More with mizoribine

Analysis 23.3. Comparison 23: Mizoribine ± steroids versus placebo/ no treatment/corticosteroids, Outcome 3: Partial remission

Study or Subgroup	Mizoribine Events	Mizoribine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
23.3.1 Partial remission at final follow-up							
Shibasaki 2004	3	14	1	11	12.3%	2.36 [0.28 , 19.66]	
Koshikawa 1993	15	48	7	41	87.7%	1.83 [0.83 , 4.05]	
Subtotal (95% CI)		**62**		**52**	**100.0%**	**1.89 [0.90 , 3.97]**	
Total events:	18		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%							
Test for overall effect: Z = 1.67 (P = 0.09)							
23.3.2 Partial remission at final follow-up (≥ 2 years)							
Shibasaki 2004	3	14	1	11	100.0%	2.36 [0.28 , 19.66]	
Subtotal (95% CI)		**14**		**11**	**100.0%**	**2.36 [0.28 , 19.66]**	
Total events:	3		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							

Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%

0.01   0.1   1   10   100
More with mizoribine   More with control

Analysis 23.4. Comparison 23: Mizoribine ± steroids versus placebo/no treatment/corticosteroids, Outcome 4: Temporary or permanent discontinuation/hospitalisation due to adverse events

Study or Subgroup	Mizoribine Events	Mizoribine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Koshikawa 1993	2	48	0	41	100.0%	4.29 [0.21 , 86.80]	
Total (95% CI)		48		41	100.0%	**4.29 [0.21 , 86.80]**	
Total events:	2		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with mizoribine   Less with control

Comparison 24. Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Complete or partial remission	1	37	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.13]
24.2 Complete remission	1	37	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.66, 2.78]
24.3 Partial remission	1	37	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.06, 0.97]
24.4 Relapse after complete or partial remission	1	27	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.05, 3.51]
24.5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.5.1 Adverse events	1	37	Risk Ratio (M-H, Random, 95% CI)	Not estimable
24.5.2 Infection	1	37	Risk Ratio (M-H, Random, 95% CI)	Not estimable
24.5.3 Malignancy	1	37	Risk Ratio (M-H, Random, 95% CI)	4.75 [0.24, 92.65]

Analysis 24.1. Comparison 24: Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day), Outcome 1: Complete or partial remission

Study or Subgroup	Once/day Events	Once/day Total	3 times/day Events	3 times/day Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2017	12	19	15	18	100.0%	0.76 [0.51 , 1.13]	
Total (95% CI)		19		18	100.0%	**0.76 [0.51 , 1.13]**	
Total events:	12		15				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.18)
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
More with 3 times/day   More with once/day
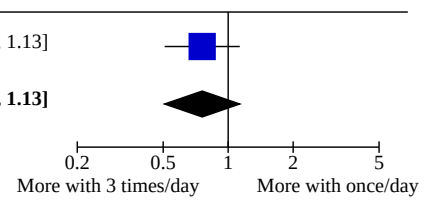
Analysis 24.2. Comparison 24: Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day), Outcome 2: Complete remission

Study or Subgroup	Once/day Events	Once/day Total	3 times/day Events	3 times/day Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2017	10	19	7	18	100.0%	1.35 [0.66 , 2.78]	
Total (95% CI)		19		18	100.0%	**1.35 [0.66 , 2.78]**	
Total events:	10		7				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with 3 times/day   More with once/day

Analysis 24.3. Comparison 24: Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day), Outcome 3: Partial remission

Study or Subgroup	Once/day Events	Once/day Total	3 times/day Events	3 times/day Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2017	2	19	8	18	100.0%	0.24 [0.06 , 0.97]	
Total (95% CI)		19		18	100.0%	**0.24 [0.06 , 0.97]**	
Total events:	2		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More with 3 times/day   More with once/day

Analysis 24.4. Comparison 24: Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day), Outcome 4: Relapse after complete or partial remission

Study or Subgroup	Once/day Events	Once/day Total	3 times/day Events	3 times/day Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Saito 2017	1	12	3	15	100.0%	0.42 [0.05 , 3.51]	
Total (95% CI)		12		15	100.0%	**0.42 [0.05 , 3.51]**	
Total events:	1		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with once/daily   Less with 3/day

Analysis 24.5. Comparison 24: Mizoribine: 150 mg (once/day) versus 50 mg (3 times/day), Outcome 5: Adverse events

Study or Subgroup	Once/day		3 times/day		Weight	Risk Ratio	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
24.5.1 Adverse events							
Saito 2017	0	19	0	18		Not estimable	
Subtotal (95% CI)		**19**		**18**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
24.5.2 Infection							
Saito 2017	0	19	0	18		Not estimable	
Subtotal (95% CI)		**19**		**18**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
24.5.3 Malignancy							
Saito 2017	2	19	0	18	100.0%	4.75 [0.24 , 92.65]	
Subtotal (95% CI)		**19**		**18**	**100.0%**	**4.75 [0.24 , 92.65]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.03 (P = 0.30)							

```
0.01   0.1    1    10   100
Less with once/day    Less with 3 times/day
```

Comparison 25. Rituximab + supportive therapy versus supportive therapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1.1 Complete or partial remission (6 months)	1	75	Risk Ratio (M-H, Random, 95% CI)	2.21 [1.37, 3.57]
25.1.2 Complete or partial remission (median 17 months)	1	75	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.15, 3.13]
25.2 Complete remission	1	75	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.78, 3.55]
25.3 Partial remission	1	75	Risk Ratio (M-H, Random, 95% CI)	3.08 [1.25, 7.62]
25.4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.4.1 Serious adverse events	1	75	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.41, 3.69]
25.4.2 Malignancy	1	75	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.14]
25.5 Final serum creatinine	1	75	Mean Difference (IV, Random, 95% CI)	-0.40 [-5.44, 4.64]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
25.6 Final serum albumin	1	75	Mean Difference (IV, Random, 95% CI)	5.70 [4.59, 6.81]
25.7 Final GFR [mL/min/1.73 m²]	1	75	Mean Difference (IV, Random, 95% CI)	-4.00 [-8.91, 0.91]
25.8 Final protein:creatinine ratio	1	75	Mean Difference (IV, Random, 95% CI)	-1.35 [-1.99, -0.70]
25.9 Final PLA2R-Ab titre	1	75	Mean Difference (IV, Random, 95% CI)	-81.80 [-105.38, -58.22]

Analysis 25.1. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 1: Complete or partial remission

Study or Subgroup	Rituximab Events	Rituximab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
25.1.1 Complete or partial remission (6 months)							
GEMRITUX 2017	28	37	13	38	100.0%	2.21 [1.37 , 3.57]	
Subtotal (95% CI)		37		38	100.0%	**2.21 [1.37 , 3.57]**	
Total events:	28		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.26 (P = 0.001)							
25.1.2 Complete or partial remission (median 17 months)							
GEMRITUX 2017	24	37	13	38	100.0%	1.90 [1.15 , 3.13]	
Subtotal (95% CI)		37		38	100.0%	**1.90 [1.15 , 3.13]**	
Total events:	24		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.50 (P = 0.01)							

Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%

0.1 0.2 0.5 1 2 5 10
More with control   More with rituximab

Analysis 25.2. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 2: Complete remission

Study or Subgroup	Rituximab Events	Rituximab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
GEMRITUX 2017	13	37	8	38	100.0%	1.67 [0.78 , 3.55]	
Total (95% CI)		37		38	100.0%	**1.67 [0.78 , 3.55]**	
Total events:	13		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.33 (P = 0.18)							
Test for subgroup differences: Not applicable							

0.1 0.2 0.5 1 2 5 10
More with control   More with rituximab

Analysis 25.3. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 3: Partial remission

Study or Subgroup	Rituximab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
GEMRITUX 2017	15	37	5	38	100.0%	3.08 [1.25 , 7.62]	
Total (95% CI)		37		38	100.0%	**3.08 [1.25 , 7.62]**	
Total events:	15		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Not applicable

0.05 0.2 1 5 20
More with control   More with rituximab
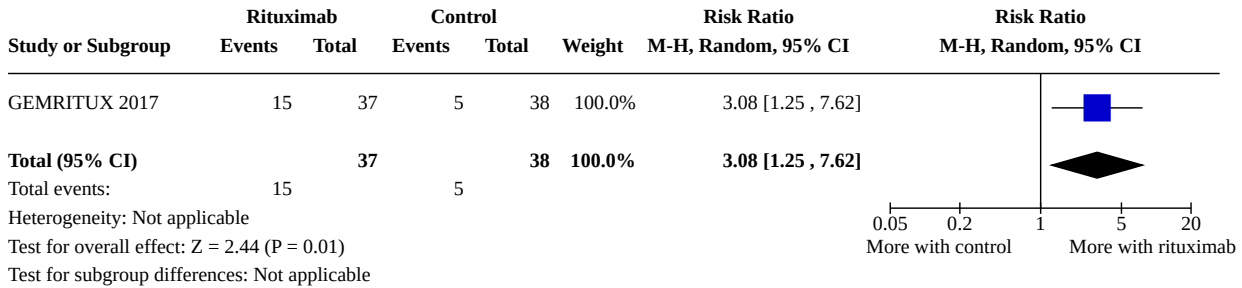
Analysis 25.4. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 4: Adverse events

Study or Subgroup	Rituximab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
25.4.1 Serious adverse events							
GEMRITUX 2017	6	37	5	38	100.0%	1.23 [0.41 , 3.69]	
Subtotal (95% CI)		37		38	100.0%	**1.23 [0.41 , 3.69]**	
Total events:	6		5				
25.4.2 Malignancy							
GEMRITUX 2017	0	37	1	38	100.0%	0.34 [0.01 , 8.14]	
Subtotal (95% CI)		37		38	100.0%	**0.34 [0.01 , 8.14]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%

0.01 0.1 1 10 100
Less with rituximab   Less with control

Analysis 25.5. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 5: Final serum creatinine

Study or Subgroup	Rituximab Mean [µmol/L]	SD [µmol/L]	Total	Control Mean [µmol/L]	SD [µmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [µmol/L]	Mean Difference IV, Random, 95% CI [µmol/L]
GEMRITUX 2017	98.8	6.09	37	99.2	14.6	38	100.0%	-0.40 [-5.44 , 4.64]	
Total (95% CI)			37			38	100.0%	**-0.40 [-5.44 , 4.64]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Lower with rituximab   Lower with control

Analysis 25.6. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 6: Final serum albumin

Study or Subgroup	Rituximab Mean [g/L]	SD [g/L]	Total	Control Mean [g/L]	SD [g/L]	Total	Weight	Mean Difference IV, Random, 95% CI [g/L]	Mean Difference IV, Random, 95% CI [g/L]
GEMRITUX 2017	30	2.3	37	24.3	2.6	38	100.0%	5.70 [4.59 , 6.81]	
Total (95% CI)			37			38	100.0%	**5.70 [4.59 , 6.81]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 10.06 (P < 0.00001)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Lower with rituximab   Lower with control

Analysis 25.7. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 7: Final GFR [mL/min/1.73 m²]

Study or Subgroup	Rituximab Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
GEMRITUX 2017	67.8	10.9	37	71.8	10.8	38	100.0%	-4.00 [-8.91 , 0.91]	
Total (95% CI)			37			38	100.0%	**-4.00 [-8.91 , 0.91]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable

-20 -10 0 10 20
Higher with control   Higher with rituximab

Analysis 25.8. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 8: Final protein:creatinine ratio

Study or Subgroup	Rituximab Mean [g/g]	SD [g/g]	Total	Control Mean [g/g]	SD [g/g]	Total	Weight	Mean Difference IV, Random, 95% CI [g/g]	Mean Difference IV, Random, 95% CI [g/g]
GEMRITUX 2017	3.832	1.348	37	5.18	1.498	38	100.0%	-1.35 [-1.99 , -0.70]	
Total (95% CI)			37			38	100.0%	**-1.35 [-1.99 , -0.70]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 4.10 (P < 0.0001)
Test for subgroup differences: Not applicable

-4 -2 0 2 4
Lower with rituximab   Lower with control

Analysis 25.9. Comparison 25: Rituximab + supportive therapy versus supportive therapy alone, Outcome 9: Final PLA2R-Ab titre

Study or Subgroup	Rituximab Mean [RU/mL]	SD [RU/mL]	Total	Control Mean [RU/mL]	SD [RU/mL]	Total	Weight	Mean Difference IV, Random, 95% CI [RU/mL]	Mean Difference IV, Random, 95% CI [RU/mL]
GEMRITUX 2017	8.5	9.8	37	90.3	73.5	38	100.0%	-81.80 [-105.38 , -58.22]	
Total (95% CI)			37			38	100.0%	**-81.80 [-105.38 , -58.22]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 6.80 (P < 0.00001)
Test for subgroup differences: Not applicable

-200 -100 0 100 200
Lower with rituximab   Lower with control

Comparison 26. Rituximab versus cyclosporine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 ESKD (dialysis/transplantation)	1	130	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.03]
26.3 Complete or partial remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.3.1 Complete or partial remission at end of therapy (12 months)	1	130	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.85, 1.56]
26.3.2 Complete or partial remission at final follow-up (2 years)	1	130	Risk Ratio (M-H, Random, 95% CI)	3.00 [1.77, 5.07]
26.4 Complete remission	1	130	Risk Ratio (M-H, Random, 95% CI)	47.00 [2.91, 757.81]
26.5 Partial remission	1	130	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.65, 2.35]
26.6 Relapse after complete or partial remission	1	73	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.02, 0.39]
26.7 Quality of Life in patients with any remission	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
26.7.1 SF-12 Score Physical Health	1	130	Mean Difference (IV, Random, 95% CI)	-2.10 [-5.03, 0.83]
26.7.2 SF-12 Score Mental Health	1	130	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.56, 0.36]
26.8 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.8.1 Serious adverse events	1	130	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.29, 1.05]
26.8.2 Infection	1	130	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.63]

Analysis 26.1. Comparison 26: Rituximab versus cyclosporine, Outcome 1: Death

	Rituximab		CSA		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
MENTOR 2015	0	65	0	65	Not estimable	

0.01   0.1   1   10   100
Less with rituximab   Less with CSA

Analysis 26.2. Comparison 26: Rituximab versus cyclosporine, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	Rituximab Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
MENTOR 2015	0	65	1	65	100.0%	0.33 [0.01 , 8.03]	
Total (95% CI)		**65**		**65**	**100.0%**	**0.33 [0.01 , 8.03]**	
Total events:	0		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable

0.002 0.1 1 10 500
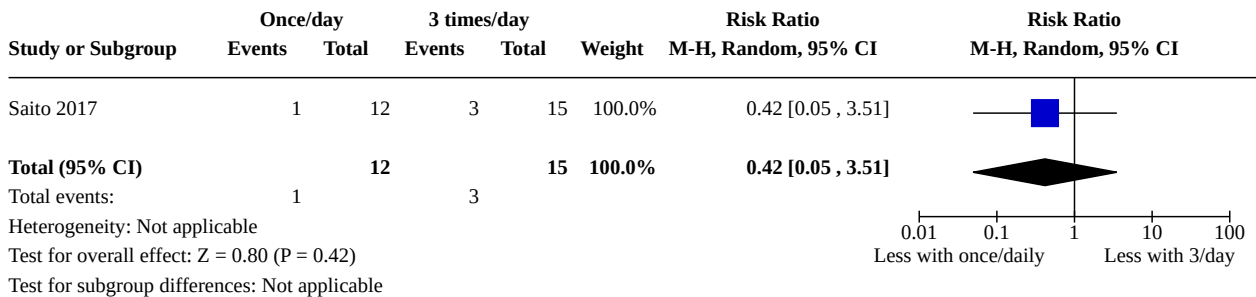Less with rituximab   Less with CSA

Analysis 26.3. Comparison 26: Rituximab versus cyclosporine, Outcome 3: Complete or partial remission

Study or Subgroup	Rituximab Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.3.1 Complete or partial remission at end of therapy (12 months)							
MENTOR 2015	39	65	34	65	100.0%	1.15 [0.85 , 1.56]	
Subtotal (95% CI)		**65**		**65**	**100.0%**	**1.15 [0.85 , 1.56]**	
Total events:	39		34				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.88 (P = 0.38)							
26.3.2 Complete or partial remission at final follow-up (2 years)							
MENTOR 2015	39	65	13	65	100.0%	3.00 [1.77 , 5.07]	
Subtotal (95% CI)		**65**		**65**	**100.0%**	**3.00 [1.77 , 5.07]**	
Total events:	39		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.10 (P < 0.0001)							

Test for subgroup differences: Chi² = 9.62, df = 1 (P = 0.002), I² = 89.6%

0.1 0.2 0.5 1 2 5 10
More with CSA   More with rituximab

Analysis 26.4. Comparison 26: Rituximab versus cyclosporine, Outcome 4: Complete remission

Study or Subgroup	Rituximab Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
MENTOR 2015	23	65	0	65	100.0%	47.00 [2.91 , 757.81]	
Total (95% CI)		**65**		**65**	**100.0%**	**47.00 [2.91 , 757.81]**	
Total events:	23		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable

0.001 0.1 1 10 1000
More with CSA   More with rituximab
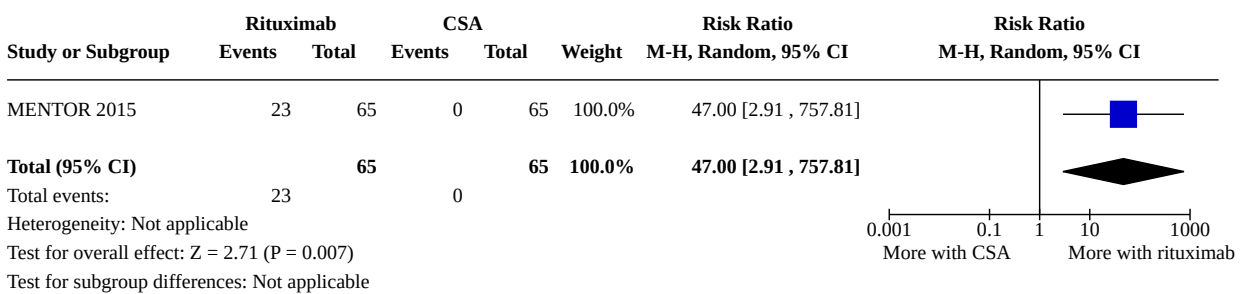
Analysis 26.5. Comparison 26: Rituximab versus cyclosporine, Outcome 5: Partial remission

Study or Subgroup	Rituximab Events	Rituximab Total	CSA Events	CSA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
MENTOR 2015	16	65	13	65	100.0%	1.23 [0.65 , 2.35]	
Total (95% CI)		**65**		**65**	**100.0%**	**1.23 [0.65 , 2.35]**	
Total events:	16		13				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
More with CSA   More with rituximab
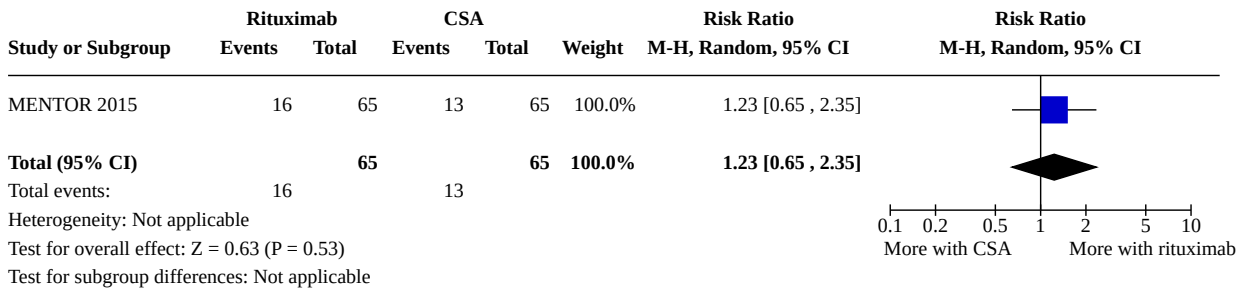
Analysis 26.6. Comparison 26: Rituximab versus cyclosporine, Outcome 6: Relapse after complete or partial remission

Study or Subgroup	Rituximab Events	Rituximab Total	CSA Events	CSA Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
MENTOR 2015	2	39	18	34	100.0%	0.10 [0.02 , 0.39]	
Total (95% CI)		**39**		**34**	**100.0%**	**0.10 [0.02 , 0.39]**	
Total events:	2		18				

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Less with rituximab   Less with CSA
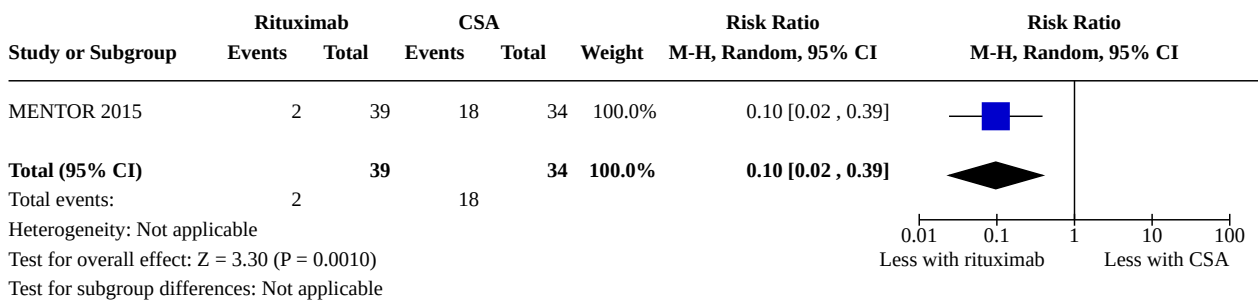
Analysis 26.7. Comparison 26: Rituximab versus cyclosporine, Outcome 7: Quality of Life in patients with any remission

Study or Subgroup	Rituximab Mean	Rituximab SD	Rituximab Total	CSA Mean	CSA SD	CSA Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
26.7.1 SF-12 Score Physical Health									
MENTOR 2015	47.8	8	65	49.9	9	65	100.0%	-2.10 [-5.03 , 0.83]	
Subtotal (95% CI)			**65**			**65**	**100.0%**	**-2.10 [-5.03 , 0.83]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.41 (P = 0.16)									
26.7.2 SF-12 Score Mental Health									
MENTOR 2015	53.4	7	65	55	4	65	100.0%	-1.60 [-3.56 , 0.36]	
Subtotal (95% CI)			**65**			**65**	**100.0%**	**-1.60 [-3.56 , 0.36]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.60 (P = 0.11)									

Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%

-10 -5 0 5 10
Better with CSA   Better with rituximab

Analysis 26.8. Comparison 26: Rituximab versus cyclosporine, Outcome 8: Adverse events

Study or Subgroup	Rituximab Events	Total	CSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.8.1 Serious adverse events							
MENTOR 2015	11	65	20	65	100.0%	0.55 [0.29 , 1.05]	
Subtotal (95% CI)		**65**		**65**	**100.0%**	**0.55 [0.29 , 1.05]**	
Total events:	11		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.80 (P = 0.07)							
26.8.2 Infection							
MENTOR 2015	18	65	19	65	100.0%	0.95 [0.55 , 1.63]	
Subtotal (95% CI)		**65**		**65**	**100.0%**	**0.95 [0.55 , 1.63]**	
Total events:	18		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.19 (P = 0.85)							

Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.21), I² = 36.6%

```
0.1   0.2    0.5    1    2    5    10
   Less with rituximab    Less with CSA
```

Comparison 27. Traditional Chinese medicine versus immunosuppressive therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1.1 Shenqi particle versus CPA +steroids	1	190	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.73]
27.1.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	Not estimable
27.2 ESKD (dialysis/transplantation)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
27.2.1 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
27.3 Complete or partial remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.3.1 Shenqi particle versus CPA +steroids	1	132	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.13]
27.3.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.32, 0.76]
27.4 Complete remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.4.1 Shenqi particle versus CPA +steroids	1	132	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.31, 1.16]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
27.4.2 Triptergyium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.03, 0.54]
27.5 Partial remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.5.1 Shenqi particle versus CPA +steroids	1	132	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.81, 1.56]
27.5.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.47, 1.54]
27.6 Doubling of serum creatinine	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.6.1 Shenqi particle versus CPA +steroids	1	132	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.79]
27.6.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	Not estimable
27.7 Severe adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.7.1 Shenqi particle versus CPA +steroids	1	190	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.77]
27.7.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids	1	84	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.33, 5.87]
27.8 Final serum albumin	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.8.1 Shenqi particle versus CPA +steroids	1	132	Mean Difference (IV, Random, 95% CI)	-0.47 [-3.40, 2.46]
27.9 Final GFR [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.9.1 Shenqi particle versus CPA +steroids	1	132	Mean Difference (IV, Random, 95% CI)	19.00 [7.85, 30.15]
27.10 Final proteinuria	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.10.1 Shenqi particle versus CPA +steroids	1	132	Mean Difference (IV, Random, 95% CI)	0.16 [-0.69, 1.01]

Analysis 27.1. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 1: Death

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.1.1 Shenqi particle versus CPA+steroids							
Chen 2013e	0	95	3	95	100.0%	0.14 [0.01 , 2.73]	
Subtotal (95% CI)		**95**		**95**	**100.0%**	**0.14 [0.01 , 2.73]**	
Total events:	0		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.29 (P = 0.20)							
27.1.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	0	41	0	43		Not estimable	
Subtotal (95% CI)		**41**		**43**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

0.001 0.1 1 10 1000
Less with TCM   Less with immunosuppressive

Analysis 27.2. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 2: ESKD (dialysis/transplantation)

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
27.2.1 Tripterygium wilfordii versus Tripterygium wilfordii+steroids						
Liu 2009b	0	43	0	41	Not estimable	

0.01 0.1 1 10 100
Less with TCM   Less with immunosuppressive

Analysis 27.3. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 3: Complete or partial remission

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.3.1 Shenqi particle versus CPA+steroids							
Chen 2013e	46	63	54	69	100.0%	0.93 [0.77 , 1.13]	
Subtotal (95% CI)		**63**		**69**	**100.0%**	**0.93 [0.77 , 1.13]**	
Total events:	46		54				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.70 (P = 0.49)							
27.3.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	15	41	32	43	100.0%	0.49 [0.32 , 0.76]	
Subtotal (95% CI)		**41**		**43**	**100.0%**	**0.49 [0.32 , 0.76]**	
Total events:	15		32				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.17 (P = 0.002)							
Test for subgroup differences: Chi² = 6.82, df = 1 (P = 0.009), I² = 85.3%							

0.1 0.2 0.5 1 2 5 10
More with immunosuppressive   More with TCM

Analysis 27.4. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 4: Complete remission

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.4.1 Shenqi particle versus CPA+steroids							
Chen 2013e	11	63	20	69	100.0%	0.60 [0.31 , 1.16]	
Subtotal (95% CI)		**63**		**69**	**100.0%**	**0.60 [0.31 , 1.16]**	
Total events:	11		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
27.4.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	2	41	16	43	100.0%	0.13 [0.03 , 0.54]	
Subtotal (95% CI)		**41**		**43**	**100.0%**	**0.13 [0.03 , 0.54]**	
Total events:	2		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.83 (P = 0.005)							

Test for subgroup differences: Chi² = 3.72, df = 1 (P = 0.05), I² = 73.1%

0.01 0.1 1 10 100
More with immunosuppressive   More with TCM

Analysis 27.5. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 5: Partial remission

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.5.1 Shenqi particle versus CPA+steroids							
Chen 2013e	35	63	34	69	100.0%	1.13 [0.81 , 1.56]	
Subtotal (95% CI)		**63**		**69**	**100.0%**	**1.13 [0.81 , 1.56]**	
Total events:	35		34				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
27.5.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	13	41	16	43	100.0%	0.85 [0.47 , 1.54]	
Subtotal (95% CI)		**41**		**43**	**100.0%**	**0.85 [0.47 , 1.54]**	
Total events:	13		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.53 (P = 0.60)							

Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%

0.1 0.2 0.5 1 2 5 10
More with immunosuppressive   More with TCM

Analysis 27.6. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 6: Doubling of serum creatinine

Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.6.1 Shenqi particle versus CPA+steroids							
Chen 2013e	0	63	1	69	100.0%	0.36 [0.02 , 8.79]	
Subtotal (95% CI)		**63**		**69**	**100.0%**	**0.36 [0.02 , 8.79]**	
Total events:	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
27.6.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	0	41	0	43		Not estimable	
Subtotal (95% CI)		**41**		**43**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

0.001   0.1   1   10   1000
Less with TCM   Less with immunosuppressive

Analysis 27.7. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 7: Severe adverse events

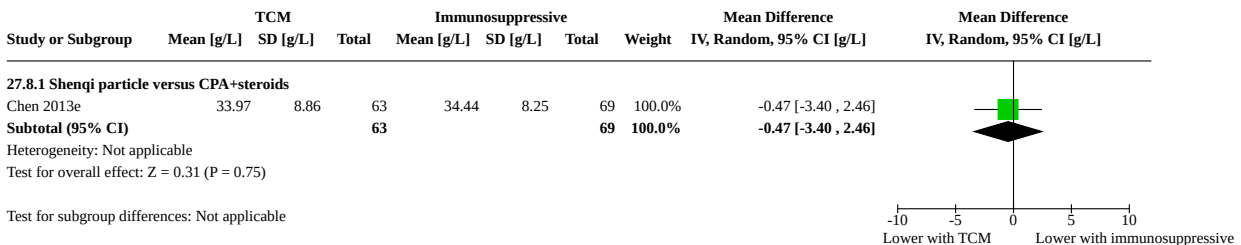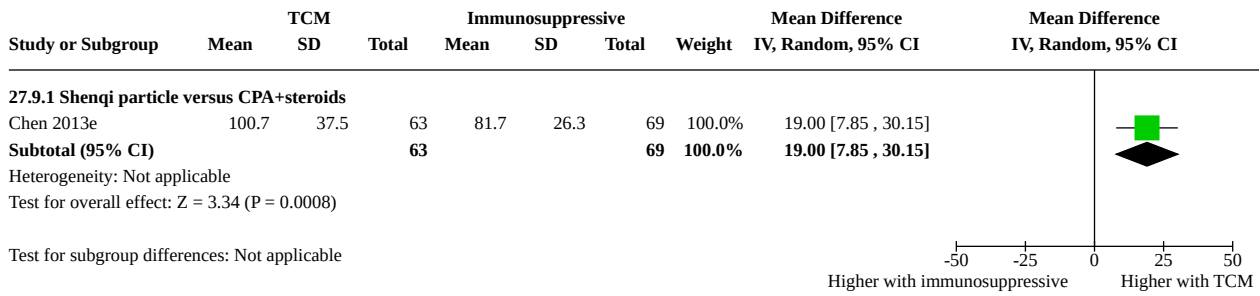| Study or Subgroup	TCM Events	TCM Total	Immunosuppressive Events	Immunosuppressive Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.7.1 Shenqi particle versus CPA+steroids							
Chen 2013e	1	95	10	95	100.0%	0.10 [0.01 , 0.77]	
Subtotal (95% CI)		**95**		**95**	**100.0%**	**0.10 [0.01 , 0.77]**	
Total events:	1		10				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.22 (P = 0.03)							
27.7.2 Tripterygium wilfordii versus Tripterygium wilfordii+steroids							
Liu 2009b	4	41	3	43	100.0%	1.40 [0.33 , 5.87]	
Subtotal (95% CI)		**41**		**43**	**100.0%**	**1.40 [0.33 , 5.87]**	
Total events:	4		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
Test for subgroup differences: Chi² = 4.31, df = 1 (P = 0.04), I² = 76.8%							

0.01   0.1   1   10   100
Less with TCM   Less with immunosuppressive

Analysis 27.8. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 8: Final serum albumin

Study or Subgroup	TCM Mean [g/L]	TCM SD [g/L]	Total	Immunosuppressive Mean [g/L]	SD [g/L]	Total	Weight	Mean Difference IV, Random, 95% CI [g/L]	Mean Difference IV, Random, 95% CI [g/L]
27.8.1 Shenqi particle versus CPA+steroids									
Chen 2013e	33.97	8.86	63	34.44	8.25	69	100.0%	-0.47 [-3.40 , 2.46]	
Subtotal (95% CI)			**63**			**69**	**100.0%**	**-0.47 [-3.40 , 2.46]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.31 (P = 0.75)									
Test for subgroup differences: Not applicable									

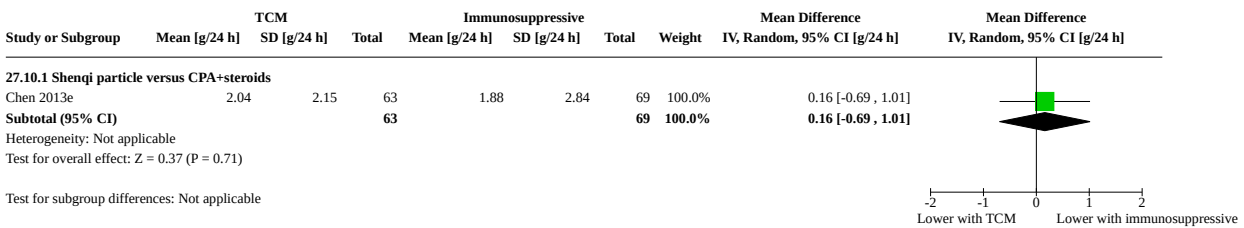-10   -5   0   5   10
Lower with TCM   Lower with immunosuppressive

Analysis 27.9. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 9: Final GFR [mL/min/1.73 m²]

Study or Subgroup	TCM Mean	TCM SD	TCM Total	Immunosuppressive Mean	Immunosuppressive SD	Immunosuppressive Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
27.9.1 Shenqi particle versus CPA+steroids									
Chen 2013e	100.7	37.5	63	81.7	26.3	69	100.0%	19.00 [7.85 , 30.15]	
Subtotal (95% CI)			**63**			**69**	**100.0%**	**19.00 [7.85 , 30.15]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.34 (P = 0.0008)									
Test for subgroup differences: Not applicable									

-50 -25 0 25 50
Higher with immunosuppressive   Higher with TCM

Analysis 27.10. Comparison 27: Traditional Chinese medicine versus immunosuppressive therapy, Outcome 10: Final proteinuria

Study or Subgroup	TCM Mean [g/24 h]	TCM SD [g/24 h]	TCM Total	Immunosuppressive Mean [g/24 h]	Immunosuppressive SD [g/24 h]	Immunosuppressive Total	Weight	Mean Difference IV, Random, 95% CI [g/24 h]	Mean Difference IV, Random, 95% CI [g/24 h]
27.10.1 Shenqi particle versus CPA+steroids									
Chen 2013e	2.04	2.15	63	1.88	2.84	69	100.0%	0.16 [-0.69 , 1.01]	
Subtotal (95% CI)			**63**			**69**	**100.0%**	**0.16 [-0.69 , 1.01]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Test for subgroup differences: Not applicable									

-2 -1 0 1 2
Lower with TCM   Lower with immunosuppressive

A P P E N D I C E S

Appendix 1. Electronic search strategies

Databases	Search terms
CENTRAL	1. MeSH descriptor Glomerulonephritis, Membranous, this term only in MeSH products 2. membranous nephropathy:ti,ab,kw 3. (membranous glomerulo*):ti,ab,kw 4. (extramembranous next glomerulo*):ti,ab,kw 5. mgn:ti,ab,kw 6. (#1 OR #2 OR #3 OR #4 OR #5)
MEDLINE	1. Glomerulonephritis, Membranous/ 2. membranous nephroapthy.tw 3. (membranous glomerulo$).tw 4. extramembranous glomerulopathy.tw. 5. imn.tw. 6. or/1-5
EMBASE	1. Membranous Glomerulonephritis/ 2. membranous nephroapthy.tw 3. (membranous glomerulo$).tw. 4. extramembranous glomerulopathy.tw. 5. imn.tw.

(Continued)

	6. or/1-5

NOTE: Search strategies used in the original review can be found in Schieppati 2004

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.	groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
8 November 2021	New citation required and conclusions have changed	New comparisons in this review for included studies that investigated novel treatments (rituximab, ACTH, traditional Chinese medicine, mizoribine)
8 November 2021	New search has been performed	Search strategy update; recently published studies included in this review for already existing comparisons

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 4, 2004

Date	Event	Description
19 November 2014	Amended	Minor edit to study names and number of reports of studies excluded and awaiting classification
30 June 2014	New citation required and conclusions have changed	The conclusion has been changed in this update
30 June 2014	New search has been performed	New search undertaken, new studies identified and included
9 October 2008	Amended	Converted to new review format.
30 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- Study selection: TvG, GW, DJT
- Quality assessment: TvG, GW, DJT
- Data extraction and data entry: TvG, GW, DJT
- Resolution of disagreements: DJT
- Manuscript draft: TvG, DJT
- Manuscript review: GW, EA, AM, YC, EH

DECLARATIONS OF INTEREST

- Thilo C von Groote has declared that they have no conflict of interest
- Gabrielle Williams has declared that they have no conflict of interest
- Eric H Au has declared that they have no conflict of interest
- Yizhi Chen has declared that they have no conflict of interest
- Anna T Mathew has declared that they have no conflict of interest
- Elisabeth M Hodson has declared that they have no conflict of interest
- David J Tunnicliffe has declared that they have no conflict of interest

SOURCES OF SUPPORT

Internal sources

- Division of Nephrology, State Key Discipline and State Key Laboratory of Kidney Diseases (2011DAV00088), Chinese People's Liberation Army (PLA) General Hospital (301 Hospital), Chinese PLA Medical Academy, Fuxing Road 28, Haidian District, Beijing 100853, China

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review update includes several differences from the previous Cochrane review update (Chen 2013)

- The updated Cochrane risk of bias tool has replaced the previous Risk of bias tool
- Further sensitivity analysis of follow-up (death and ESKD ≥ 10 years; remission ≥ 2 years) has been included in this review update
- We referred to the disease as "primary" membranous nephropathy as opposed to "idiopathic" membranous nephropathy because this terminology is now more commonly used and easier to understand

- Performing subgroup-analysis for levels of anti-PLA2R was not possible due to only few studies reporting this outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Azathioprine; Cyclosporine; *Glomerulonephritis, Membranous [complications] [drug therapy]; Immunosuppressive Agents [adverse effects]; *Nephrotic Syndrome [complications] [drug therapy]

MeSH check words

Humans