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Immunosuppressive agents for treating IgA nephropathy (Review)

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Immunosuppressive agents for treating IgA nephropathy.
Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD003965.
DOI: 10.1002/14651858.CD003965.pub3.

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TABLE OF CONTENTS

[Intervention Review]

Immunosuppressive agents for treating IgA nephropathy

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Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2020.

Citation: Natale P, Palmer SC, Ruospo M, Saglimbene VM, Craig JC, Vecchio M, Samuels JA, Molony DA, Schena FP, Strippoli GFM. Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database of Systematic Reviews* 2020, Issue 3. Art. No.: CD003965. DOI: 10.1002/14651858.CD003965.pub3.

ABSTRACT

Background

IgA nephropathy is the most common glomerulonephritis world-wide. IgA nephropathy causes end-stage kidney disease (ESKD) in 15% to 20% of affected patients within 10 years and in 30% to 40% of patients within 20 years from the onset of disease. This is an update of a Cochrane review first published in 2003 and updated in 2015.

Objectives

To determine the benefits and harms of immunosuppression strategies for the treatment of IgA nephropathy.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 9 September 2019 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs of treatment for IgA nephropathy in adults and children and that compared immunosuppressive agents with placebo, no treatment, or other immunosuppressive or non-immunosuppressive agents.

Data collection and analysis

Two authors independently assessed study risk of bias and extracted data. Estimates of treatment effect were summarised using random effects meta-analysis. Treatment effects were expressed as relative risk (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes and mean difference (MD) and 95% CI for continuous outcomes. Risks of bias were assessed using the Cochrane tool. Evidence certainty was evaluated using GRADE methodology.

Main results

Fifty-eight studies involving 3933 randomised participants were included. Six studies involving children were eligible. Disease characteristics (kidney function and level of proteinuria) were heterogeneous across studies. Studies evaluating steroid therapy generally included patients with protein excretion of 1 g/day or more. Risk of bias within the included studies was generally high or unclear for many of the assessed methodological domains.

In patients with IgA nephropathy and proteinuria > 1 g/day, steroid therapy given for generally two to four months with a tapering course probably prevents the progression to ESKD compared to placebo or standard care (8 studies; 741 participants: RR 0.39, 95% CI 0.23 to 0.65; *moderate certainty evidence*). Steroid therapy may induce complete remission (4 studies, 305 participants: RR 1.76, 95% CI 1.03 to 3.01; *low certainty evidence*), prevent doubling of serum creatinine (SCr) (7 studies, 404 participants: RR 0.43, 95% CI 0.29 to 0.65; *low certainty evidence*), and may lower urinary protein excretion (10 studies, 705 participants: MD -0.58 g/24 h, 95% CI -0.84 to -0.33;*low certainty evidence*). Steroid therapy had uncertain effects on glomerular filtration rate (GFR), death, infection and malignancy. The risk of adverse events with steroid therapy was uncertain due to heterogeneity in the type of steroid treatment used and the rarity of events.

Cytotoxic agents (azathioprine (AZA) or cyclophosphamide (CPA) alone or with concomitant steroid therapy had uncertain effects on ESKD (7 studies, 463 participants: RR 0.63, 95% CI 0.33 to 1.20; *low certainty evidence*), complete remission (5 studies; 381 participants: RR 1.47, 95% CI 0.94 to 2.30; very low certainty evidence), GFR (any measure), and protein excretion. Doubling of serum creatinine was not reported.

Mycophenolate mofetil (MMF) had uncertain effects on the progression to ESKD, complete remission, doubling of SCr, GFR, protein excretion, infection, and malignancy. Death was not reported.

Calcineurin inhibitors compared with placebo or standard care had uncertain effects on complete remission, SCr, GFR, protein excretion, infection, and malignancy. ESKD and death were not reported.

Mizoribine administered with renin-angiotensin system inhibitor treatment had uncertain effects on progression to ESKD, complete remission, GFR, protein excretion, infection, and malignancy. Death and SCr were not reported.

Leflunomide followed by a tapering course with oral prednisone compared to prednisone had uncertain effects on the progression to ESKD, complete remission, doubling of SCr, GFR, protein excretion, and infection. Death and malignancy were not reported.

Effects of other immunosuppressive regimens (including steroid plus non-immunosuppressive agents or mTOR inhibitors) were inconclusive primarily due to insufficient data from the individual studies in low or very low certainty evidence. The effects of treatments on death, malignancy, reduction in GFR at least of 25% and adverse events were very uncertain. Subgroup analyses to determine the impact of specific patient characteristics such as ethnicity or disease severity on treatment effectiveness were not possible.

Authors' conclusions

In moderate certainty evidence, corticosteroid therapy probably prevents decline in GFR or doubling of SCr in adults and children with IgA nephropathy and proteinuria. Evidence for treatment effects of immunosuppressive agents on death, infection, and malignancy is generally sparse or low-quality. Steroid therapy has uncertain adverse effects due to a paucity of studies. Available studies are few, small, have high risk of bias and generally do not systematically identify treatment-related harms. Subgroup analyses to identify specific patient characteristics that might predict better response to therapy were not possible due to a lack of studies. There is no evidence that other immunosuppressive agents including CPA, AZA, or MMF improve clinical outcomes in IgA nephropathy.

PLAIN LANGUAGE SUMMARY

Immunosuppressive agents for treating IgA nephropathy

What is the issue?
IgA nephropathy is a common kidney disease that often leads to decreased kidney function and may result ultimately in kidney failure for one-third of affected people. The cause of IgA nephropathy is not known, although most people with the disease have abnormalities in their immune system.

What did we do?
We searched for all the research trials that assessed the effect of immunosuppressive therapy in people with IgA nephropathy in September 2019. We measured the certainty we could have about the treatments using a system called "GRADE".

What did we find?
We found 58 studies involving 3933 adults and children who were treated with immunosuppressive therapy. Patients in the studies were given either steroids or other forms of therapy to reduce the actions of their immune system. The treatment they got was decided by random chance. Steroid therapy taken for 2 to 4 months appeared to slow damage to the kidney and probably prevents patients from developing kidney failure. It is really uncertain whether steroids cause side effects such as serious infection. One study was stopped early because patients who received steroid therapy had more infections than those patients who were given placebo. Other medications like cyclophosphamide, azathioprine, and mycophenolate mofetil did not clearly protect kidney function in people with IgA nephropathy.

Conclusions

Steroid therapy may prevent kidney failure in IgA nephropathy but the risks of serious infections are uncertain with treatment.

Summary of findings for the main comparison. Systemic corticosteroid versus no corticosteroid regimen for IgA nephropathy

Systemic corticosteroid versus no corticosteroid regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Setting: Australia, China, Europe, Japan, USA

Intervention: corticosteroid regimen (includes steroids alone or with RAS inhibitors)

Comparison: no corticosteroid regimen

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with no steroids	Risk with steroids			
End-stage kidney disease Follow-up: 2 to 10 years	141 per 1000	55 per 1000 (32 to 92)	RR 0.39 (0.23 to 0.65)	741 (8)	⊕⊕⊕⊖ moderate [1]
Complete remission Follow-up: 2 to 5 years	364 per 1000	641 per 1000 (375 to 1000)	RR 1.76 (1.03 to 3.01)	305 (4)	⊕⊕⊖⊖ low [1,3]
GFR loss ≥ 50% Follow-up: 2 to 2.1 years	96 per 1000	54 per 1000 (24 to 119)	RR 0.56 (0.25 to 1.24)	326 (2)	⊕⊕⊖⊖ low [1,2]
Annual GFR loss (mL/min/1.73 m^2) Follow-up: 2.1 to 5 years	The mean annual GFR loss ranged across control groups from 6.17 to 6.95 mL/min/1.73 m^2	The mean annual GFR loss in the intervention group was -5.40 mL/min/1.73 m^2 less than the control group (95% CI -8.55 less to -2.25 less)	--	359 (2)	⊕⊕⊕⊖ moderate [1]
Death (any cause) Median follow-up: 2.1 years	8 per 1000	15 per 1000 (1 to 162)	RR 1.85 (0.17 to 20.19)	262 (1)	⊕⊖⊖⊖ very low [1,4]
Infection Median follow-up: 2.1 years	No events	11/136**	RR 21.32 (1.27, 358.10)	262 (1)	⊕⊖⊖⊖ very low [1,2,3]
Malignancy	23 per 1000	23 per 1000	RR 1.00	86 (1)	⊕⊖⊖⊖ very low [1,2,4]

Follow-up: 6 years		(1 to 356)	(0.06 to 15.48)

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). The **corresponding risk** (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; **RR:** Risk Ratio

** 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

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 due to study limitations including lack of allocation concealment and lack of blinding
[2] Downgraded due to imprecision in treatment estimate (consistent with appreciable benefit or harm)
[3] Downgraded due to evidence of important statistical heterogeneity
[4] Downgraded two levels due to severe imprecision in treatment estimate (consistent with appreciable benefit or harm)

Summary of findings 2. Cytotoxic regimen versus no cytotoxic regimen for IgA nephropathy

Cytotoxic regimen versus no cytotoxic regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Settings: Australia, China, Europe, Japan

Intervention: cytotoxic therapy (including combinations of cyclophosphamide or azathioprine with steroid therapy)

Comparison: no cytotoxic therapy

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with no cytotoxic therapy	Risk with cytotoxic therapy			
End-stage kidney disease Follow-up: 1 to 7 years	166 per 1000	105 per 1000 (55 to 199)	RR 0.63 (0.33 to 1.20)	463 (7)	⊕⊕⊖⊖ low [1,3]

Complete remission Follow-up: 0.5 to 5 years	337 per 1000	495 per 1000 (317 to 775)	RR 1.47 (0.94 to 2.30)	381 (5)	⊕⊖⊖⊖ very low [1,3,4]
GFR loss ≥ 50%	No data observations	Not estimable	No studies	No studies	Not estimable
Annual GFR loss (mL/min/1.73 m^2) Follow-up: 3 years	The mean GFR loss was 0.01 mL/min/1.73 m^2 in the control group	The mean GFR loss in the intervention group was 0.01 mL/min/1.73 m^2 lower than the control group (95% CI -0.03 to 0.01)	--	162 (1)	⊕⊕⊖⊖ low [1,3]
Death (any cause) Follow-up: 3 years	13 per 1000	13 per 1000 (1 to 199)	RR 0.98 (0.06 to 15.33)	162 (1)	⊕⊖⊖⊖ very low [1,2]
Infection Follow-up: 1 to 7 years	22 per 1000	37 per 1000 (10 to 149)	RR 1.70 (0.43 to. 6.76)	268 (4)	⊕⊖⊖⊖ very low [1,2]
Malignancy Follow-up: 3 years	No events	2/82**	RR 4.88 (0.24 to 100.08)	162 (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). The **corresponding risk** (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; **RR:** Risk Ratio

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2 Downgraded two levels due to severe imprecision in treatment estimate (consistent with appreciable benefit or harm)
3 Downgraded due to imprecision in treatment estimate (consistent with appreciable benefit or harm)
4 Downgraded due to evidence of important statistical heterogeneity

Summary of findings 3. MMF regimen versus no MMF regimen for IgA nephropathy

MMF regimen versus no MMF regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Settings: Australia, China, Europe

Intervention: MMF regimen (includes MMF alone, or in combination with RAS inhibitors or steroids)

Comparison: mo MMF regimen

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk without MMF	Risk with MMF			
End-stage kidney disease Follow-up: 1 to 3 years	96 per 1000	70 per 1000 (15 to 310)	RR 0.73 (0.16 to 3.23)	280 (4)	⊕⊖⊖⊖ very low [1,2,3]
Complete remission Follow-up: 1 to 2 years	267 per 1000	280 per 1000 (195 to 406)	RR 1.05 (0.73 to 1.52)	271 (4)	⊕⊖⊖⊖ very low [1,2]
GFR loss ≥ 50% Follow-up: 2 years	133 per 1000	294 per 1000 (67 to 1000)	RR 2.21 (0.50 to 9.74)	32 (1)	⊕⊖⊖⊖ very low [1,2]
Annual GFR loss (mL/min/1.73 m^2) Follow-up: 1 year	The mean GFR loss was 10.6 mL/min/1.73 m^2 in the control group	The mean GFR loss in the intervention group was 2.00 mL/min/1.73 m^2 lower than the control group (95% CI -25.15 to 29.15)	--	28 (1)	⊕⊖⊖⊖ very low [1,2]
Death (any cause)	No data observations	Not estimable	No studies	No studies	Not estimable
Infection Follow-up: 1 to 3 years	169 per 1000	230 per 1000 (147 to 358)	RR 1.36 (0.87 to 2.12)	301 (4)	⊕⊖⊖⊖ very low [1,2]
Malignancy Follow-up: 1 to 3 years	50 per 1000	14 per 1000 (2 to 127)	RR 0.28 (0.03 to 2.54)	86 (2)	⊕⊖⊖⊖ 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). The **corresponding risk** (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; **RR:** Risk Ratio.

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[3] Downgraded due to evidence of important statistical heterogeneity

Summary of findings 4. Calcineurin inhibitor regimen versus no calcineurin inhibitor regimen for IgA nephropathy

Calcineurin inhibitor regimen versus no calcineurin inhibitor regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Settings: China

Intervention: calcineurin inhibitor regimen (includes calcineurin inhibitor alone or in combination with steroids)

Comparison: no calcineurin inhibitor regimen

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk without calcineurin inhibitor	Risk with calcineurin inhibitor			
End-stage kidney disease	No data observations	Not estimable	No studies	No studies	Not estimable
Complete remission Follow-up: 0.5 to 1 year	541 per 1000	492 per 1000 (325 to 752)	RR 0.91 (0.60 to 1.39)	72 (2)	⊕⊖⊖⊖ very low [1,2]
GFR loss ≥ 50%	No data observations	Not estimable	No studies	No studies	Not estimable

Annual GFR loss (mL/min/ 1.73 m^2)	No data observations	Not estimable	No studies	No studies	Not estimable
Death (any cause)	No data observations	Not estimable	No studies	No studies	Not estimable
Infection Follow-up: 1 year	130 per 1000	40 per 1000 (4 to 356)	RR 0.31 (0.03 to 2.74)	48 (1)	⊕⊖⊖⊖ very low [1,2]
Malignancy Follow-up: 1 year	40 per 1000	14 per 1000 (1 to 338)	RR 0.36 (0.02 to 8.45)	48 (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). The **corresponding risk** (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; **RR:** Risk Ratio.

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Summary of findings 5. Mizoribine regimen versus no mizoribine regimen for IgA nephropathy

Mizoribine regimen compared with no mizoribine regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Settings: Japan

Intervention: mizoribine regimen (includes mizoribine alone or with RAS inhibitors)

Comparison: no mizoribine regimen

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk without mizoribine	Risk with mizoribine			
End-stage kidney disease Follow-up: 3 years	48 per 1000	48 per 1000 (3 to 718)	RR 1.00 (0.07 to 14.95)	42 (1)	⊕⊖⊖⊖ very low [1,2]
Complete remission Follow-up: 3 years	467 per 1000	887 per 1000 (495 to 1000)	RR 1.90 (1.06 to 3.43)	24 (1)	⊕⊖⊖⊖ very low [1,2]
GFR loss ≥ 50%	No data observations	Not estimable	No studies	No studies	Not estimable
Annual GFR loss **(mL/min/1.73 m^2)**	No data observations	Not estimable	No studies	No studies	Not estimable
Death (any cause)	No data observations	Not estimable	No studies	No studies	Not estimable
Infection Follow-up: 1 to 2.1 years	60 per 1000	91 per 1000 (8 to 969)	RR 1.52 (0.14 to 16.15)	104 (2)	⊕⊖⊖⊖ very low [1,2,3]
Malignancy Follow-up: 3 years	No events	1/21**	RR 3.00 (0.13 to 69.70)	42 (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). The **corresponding risk** (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; **RR:** Risk Ratio.

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[3] Downgraded due to evidence of important statistical heterogeneity

Summary of findings 6. Leflunomide regimen versus no leflunomide regimen for IgA nephropathy

Leflunomide regimen compared with no leflunomide regimen for IgA nephropathy

Patient or population: adults and children who have IgA nephropathy proven on renal biopsy

Settings: China

Intervention: leflunomide regimen (includes leflunomide alone or with steroids or RAS inhibitor)

Comparison: no leflunomide regimen

Outcomes	Anticipated absolute benefits* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk without leflunomide	Risk with leflunomide			
End-stage kidney disease Follow-up: 7.3 years	111 per 1000	76 per 1000 (19 to 294)	RR 0.68 (0.17 to 2.65)	85 (1)	⊕⊖⊖⊖ very low [1,2]
Complete remission Follow-up: 0.25 to 7.3 years	357 per 1000	386 per 1000 (286 to 521)	RR 1.08 (0.80 to 1.46)	282 (4)	⊕⊖⊖⊖ very low [1,2]
GFR loss ≥ 50%	No data observations	Not estimable	No studies	No studies	Not estimable
Annual GFR loss **(mL/min/1.73 m²)**	No data observations	Not estimable	No studies	No studies	Not estimable
Death (any cause)	No data observations	Not estimable	No studies	No studies	Not estimable
Infection Follow-up: 0.5 to 7.3 years	56 per 1000	54 per 1000 (25 to 117)	RR 0.97 (0.45 to 2.09)	387 (3)	⊕⊖⊖⊖ very low [1,2]
Malignancy	No data observations	Not estimable	No studies	No studies	Not estimable

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). The **corresponding risk** (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; **RR:** Risk Ratio.

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BACKGROUND

Description of the condition

IgA nephropathy was first described in 1968 by Dr J. Berger. Characterised by prominent mesangial IgA deposits seen diffusely on immunofluorescence microscopy, the condition was initially thought to be a rare and benign cause of recurrent haematuria (Berger 1968). It has since become apparent, however, that IgA nephropathy is neither rare nor benign. Although biopsy practices differ from region to region, thus affecting the frequency of diagnosis of IgA nephropathy, it has been demonstrated that IgA nephropathy is the most common glomerular disease world-wide (D'Amico 1987; Han 2010) with a variable prevalence ranging from 5% to more than 40% (Schena 2009).

The natural history of IgA nephropathy is now known to be highly heterogeneous and far from benign in many patients. While up to 50% of patients experience lasting remission (Kim 2016; Nolin 1999), 40% can develop end-stage kidney disease (ESKD) within 20 years (Manno 2007), while another 30% to 40% experience decreased kidney function (Inagaki 2017; Rekola 1991). Overall, as many as 15% to 50% of those affected develop chronic kidney disease (CKD) and eventually ESKD (Rostoker 1995; Schena 2001). Studies have demonstrated that risk factors associated with disease progression include evidence of proteinuria, especially in people with proteinuria < 1 g/day (Reich 2007), hypertension (Liu 2019) or elevated serum creatinine (SCr) at the time of kidney biopsy, microhematuria at diagnosis (Gallo 1988; Manno 2007; Neelakantappa 1988), and specific histological lesions (as reported in the Oxford classification) (Cattran 2009; Haas 2017; Trimarchi 2017). These prognostic data may help stratify those patients at highest need for effective therapy.

Evidence suggests that IgA nephropathy is a consequence of abnormal glycosylation of O-linked glycans in the hinge region of IgA1, resulting in increased circulation of galactose-deficient IgA1 (Gd-IgA1) (Gale 2017; Mestecky 1993). Most patients have some abnormalities of the immune system some time in their disease course, including increased circulating IgA or some other humoral or cellular abnormality. It has been shown that the IgA molecules deposited in the glomerular mesangium have the same abnormalities of glycosylation (Hiki 2001). Altered IgA glycosylation may enhance mesangial deposition due to the formation of pathogenic immune complexes or by promoting IgA molecular interactions with kidney matrix proteins and/or mesangial cell immune receptors.

Complement system activation occurs in IgA nephropathy through the alternative and lectin pathways, with complement components identified in pathogenic mesangial deposits (Maillard 2015), Evidence for complement activity in the progression of IgA nephropathy glomerular injury has led to the development of short interfering RNA molecules (siRNA) against complement component 5 (C5) which is undergoing evaluation in a phase 2 randomised controlled trial (RCT) (NCT03841448).

Description of the intervention

Despite better understanding of the pathogenic mechanisms causing IgA nephropathy, there is no established disease-targeted treatment for IgA nephropathy and various treatments have been applied, including corticosteroid, azathioprine (AZA), calcineurin inhibitors (CNIs), cyclophosphamide (CPA), mycophenolate mofetil (MMF), rituximab and leflunomide (Hou 2017; Lafayette 2017; Locatelli 1999; Pozzi 2010; Song 2017).

IgA nephropathy has been identified as having an inflammatory basis leading to the biological rationale of corticosteroid therapy (Coppo 2018). Over the last decades, some studies have reported that intravenous steroid pulse therapy in combination with oral prednisolone are effective for reducing proteinuria and preventing ESKD, as well as increasing 10-year survival (Pozzi 1999). Evidence from observational studies (Tesar 2015) and RCTs (TESTING 2017) showed potential benefits of corticosteroid treatment in patients with proteinuric IgA nephropathy, although severe infectious complications and a higher mortality risk has suggested the need to evaluate intervention strategies that have lower toxicity.

Tonsillectomy combined with steroid pulse therapy has been shown to induce had a significant impact on clinical remission of IgA proteinuria and may be beneficial for long-term kidney survival (Hotta 2001). In Asian countries, tonsillectomy is performed in at least 50% of adults with IgA nephropathy, however genetic variation may impact on IgA susceptibility and therapeutic response to this intervention strategy (Hirano 2019). By contrast, some studies have shown no therapeutic effect of corticosteroid (Lai 1986) and tonsillectomy (Piccoli 2010) in patients with IgA nephropathy leading to therapeutic uncertainty.

The recent focus on the role of gut–kidney axis in IgA nephropathy has led to development of selective corticosteroid formulations targeting the intestinal mucosal immune system, aiming to reduce proteinuria and stabilise kidney function with fewer systemic adverse events from steroid therapy (NEFIGAN 2017).

Patients may not always respond to corticosteroid therapy leading to consideration of additive immunosuppressive therapies to obtain a synergistic effect. Although IgA nephropathy is likely an autoimmune kidney disease, there is uncertainty about whether some immunosuppressive agents such as AZA or CPA suppress disease activity, reduce proteinuria or protect kidney function particularly in the absence of rapidly progressive glomerulonephritis (Locatelli 1999; Walker 1990a). The supportive versus immunosuppressive therapy for the treatment of progressive IgA nephropathy (STOP-IgAN 2008) RCT showed that combined corticosteroid and immunosuppressive therapy may be superior to supportive care alone.

CNIs possess potent immunosuppressive properties, suppressing the activation and proliferation of T cells to inhibit synthesis of interleukin (IL)-2. This suppresses secondary synthesis of various cytokines, including IL-4 and tumour necrosis factor-alpha. Despite these immunomodulating effects, there are limited data for protection of kidney function and evidence of increased side effects with CNIs (Song 2017).

MMF selectively inhibits the proliferation of T and B lymphocytes, antibody production, generation of cytotoxic T cells and the recruitment of leukocytes to sites of inflammation. However, experimental evidence has not clearly shown that the anti-inflammatory properties of MMF, by attenuating glomerular and interstitial injury, are beneficial in the treatment of progressive IgA nephropathies with an acceptable safety profile (Maes 2004).

Few RCTs have evaluated the efficacy of leflunomide in the treatment of IgA nephropathy to demonstrate reduction in proteinuria and protection of kidney function (Cheng 2015). Leflunomide, generally evaluated in China, has very limited efficacy data (Lou 2006).

There has been limited stratification by risk of ESKD or disease severity in studies evaluating IgA nephropathy management. Substantial disease heterogeneity suggests a validated tool for IgA nephropathy could support accurate prediction of disease progression and enrich trial populations with patients at highest risk of ESKD (Barbour 2019). Although clinical evidence suggests that treatment of IgA nephropathy with either single and combined treatments regimen can lead to partial or complete remission and prevent loss of kidney function, some patients still experience progressive kidney injury (Moriyama 2019). The protective role of immunosuppressive therapy has been uncertain in part due to the small sample sizes and short duration therapy and follow-up in available studies. In addition, global heterogeneity in disease activity and susceptibility based on ethnicity may impact on interpretation of treatment efficacy in different ethnicity groups and international regions (Kiryluk 2012). As a consequence of fewer data and heterogeneous disease activity in existing studies, the longer term effects of immunosuppression have been uncertain.

How the intervention might work

IgA nephropathy often progresses very slowly, taking decades to reach the clinical outcomes usually studied in clinical studies (death and need for dialysis or kidney transplantation). It has thus been difficult to establish the most effective treatment regimen for IgA nephropathy. Reviews have examined the evidence for treatment of both adults (Nolin 1999) and children (Wyatt 2001) with IgA nephropathy to find optimal regimens. These analyses included studies of varying methodological quality, and are mostly case series and other forms of non-randomised evaluation. These data have resulted in conflicting information regarding the optimal therapy. The most commonly used regimens include immunosuppressive agents such as glucocorticoids (steroids), cyclosporin A (CSA), or CPA. Additionally, non-immunosuppressive medications including fish oils, anticoagulants, antihypertensive agents and surgical tonsillectomy with and without immunosuppression have been tested in a variety of studies including RCTs.

Why it is important to do this review

Given the burden of disease and the known risks of progression, as well as the lack of an accepted effective therapy, a systematic review of these treatments was necessary to aid healthcare providers in managing this condition. The present review focuses on the benefits and harms of immunosuppressive treatment for IgA nephropathy. The initial review was published in 2003 (Samuels 2003b; Samuels 2004) and was updated in 2015 (Vecchio 2015).

A separate review summarises the benefits and harms of non-immunosuppressive treatments for IgA nephropathy (Reid 2011).

OBJECTIVES

To determine the benefits and harms of immunosuppression for the treatment of IgA nephropathy.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) that compared immunosuppressive therapy (corticosteroids, cytotoxic agents, MMF, leflunomide, or other) with other immunosuppressive agents, non-immunosuppressive treatment (including antihypertensive agents and anticoagulants), or placebo or no treatment/standard care for the treatment of IgA nephropathy were included.

Types of participants

Adult and children with biopsy-proven IgA nephropathy.

Types of interventions

- Immunosuppressive agent versus placebo, no treatment/ standard care, or other non-immunosuppressive agent (including renin-angiotensin system (RAS) inhibitors)
- Head to head comparisons between immunosuppressive agents.

Types of outcome measures

Primary outcomes

- ESKD requiring kidney replacement therapy (KRT) (dialysis or kidney transplantation)
- Complete remission: defined by a reduction in urinary protein excretion to less than 1 g/24 hours in three consecutive daily samples or as defined by the investigators
- Doubling of SCr
- SCr (µmol/L)
- Estimated or measured glomerular filtration rate (GFR) (either creatinine clearance (CrCl) (mL/min) or Cockcroft clearance (mL/min/1.73 m^2)
- Urinary protein excretion (g/24 hours)

Secondary outcomes

- Death
- Infection
- Malignancy

Where possible, time to reach the above end-points in each treatment arm was included in the analysis.

Adverse effects

- Dropout rate due to treatment-related adverse events
- Bone density, fracture or shorter stature

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 9 September 2019 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. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were searched.

Data collection and analysis

The initial review was undertaken by five authors (JAS, GFMS, JCC, FPS, DAM) and was updated by 10 authors (PN, SCP, MR, VS, JCC, MV, JAS, DAM, FPS, GFMS).

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by at least two authors, who discarded studies that were not applicable; however, studies and reviews that may have included relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, where necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by at least two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports be grouped together and the publication with the most complete data was used in the analyses. When relevant outcomes were only published in earlier versions these data were used. Any discrepancies between published versions were to highlighted.

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2011) (*see* Appendix 2).

- 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 a risk of bias?

Measures of treatment effect

For dichotomous outcomes (mortality, infection, ESKD, doubling of SCr, malignancy, reduction in GFR at least 25 or 50%, complete remission, adverse events) results were expressed as relative risk (RR) with 95% confidence intervals (CI) for individual studies. When continuous scales of measurement were used, we assessed the effects of treatment (SCr, CrCl, annual GFR loss and urinary protein excretion), using the mean difference (MD), or the standardised mean difference (SMD) if different scales had been used. Adverse events were summarised descriptively. As measures of proteinuria and albuminuria were reported using various measures, including relative to urinary creatinine, we have harmonised all endpoints to a single measure of milligrams per day or excretion. We followed the methods reported by Lambers Heerspink 2015 to convert the albumin excretion rate per day to protein excretion rate by dividing the albumin excretion by 0.6, recognising that a total daily protein excretion of 500 mg/day is approximately equal to 300 mg/day of albumin.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing or writing to corresponding author) and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was 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 I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

It was planned that if sufficient RCTs were identified, an attempt would be made to assess for publication bias using a funnel

plot (Egger 1997). However, insufficient data precluded subgroup analyses in this review update.

Data synthesis

Treatment effects were summarised using a random effects model. For each analysis, the fixed effects model was also evaluated to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore how possible sources of heterogeneity (paediatric versus adult population, stage of renal biopsy, race of participants) might have influenced the treatment effects observed. However, due to the small number of studies, subgroup analyses to determine the impact of patient characteristics on treatment effectiveness were not possible.

Post hoc subgroup analysis

We performed a post hoc subgroup analysis to assess the effect of the background of treatments with and without RAS blockade and blood pressure (BP) control (ACE inhibitor and/or ARB) on risks of ESKD.

'Summary of findings' tables

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 include 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 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 within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

We presented the following outcomes in the 'Summary of findings' table:

- ESKD
- Complete remission
- ≥ 50% GFR loss
- Annual GFR loss (mL/min/1.73 m^2)
- Death (any cause)
- Infection
- Malignancy

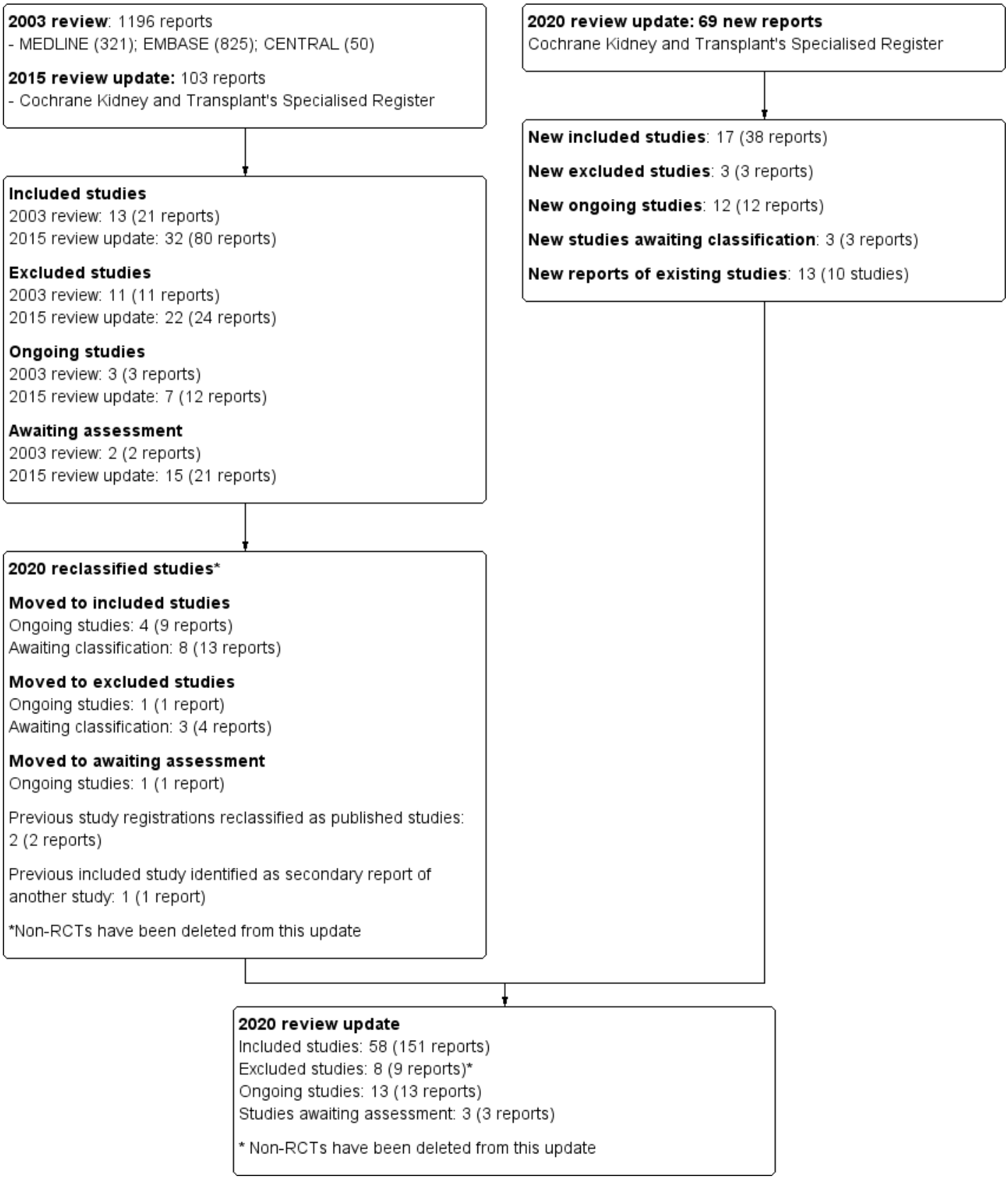
RESULTS

Description of studies

Results of the search

Search results are shown in Figure 1. For this 2020 review update, we identified 69 new reports. There were 36 new studies (56 reports) and 13 new reports of 10 existing studies. Seventeen new studies (38 reports) were eligible (BRIGHT-SC 2016; CAST-IgA 2015; Cheung 2018; Hirai 2017; Hou 2017; Koitabashi 1996; Lee 2003; Masutani 2016; Min 2017; NEFIGAN 2017; Shen 2013; Shi 2012a; Shima 2018; STOP-IgAN 2008; TESTING 2017; Wu 2016; Yamauchi 2001) and three studies (three reports) were excluded (GloMY 2010; Imai 2006; Yonemura 2000b).

Figure 1. Study flow diagram.



There are 13 ongoing studies (AIGA 2016; ARTEMIS-IgAN 2018; ChiCTR1800014442; MAIN 2013; NCT00657059; NCT02808429; NCT03468972; NEFIGARD 2018; PIRAT 2015; SIGN 2014; TIGER 2017; TOPplus-IgAN 2013; UMIN000032031) that have not yet been completed according to details held within the www.ClinicalTrials.gov registry, www.chictr.org.cn and https://upload.umin.ac.jp/; and three studies are awaiting classification while we try to determine if they meet our inclusion criteria (NCT00301600; NCT02160132; NCT02571842). These 16 studies will be assessed in a future update of this review.

In addition, four previous ongoing studies (2nd NA IgAN 2004; Hou 2017; Lafayette 2017; STOP-IgAN 2008) and eight studies awaiting assessment (Chen 2002; Cruzado 2011; Kawamura 2014; Kim 2013b; Liu 2010a; Liu 2014; Stangou 2011; Xie 2011) have been reclassified as included. One ongoing study (Dal Canton 2005) and three studies awaiting classification have been reclassified as excluded (Chen 2009b; Czock 2007; Shen 2009).

For this 2020 update there are 58 included studies, 13 ongoing studies, 3 studies awaiting assessment and 8 excluded studies. Non-RCTs have been removed from this update.

Included studies

The characteristics of the participants and the interventions in included studies are detailed in the Characteristics of included studies. Overall, 58 studies (151 publications) enrolling a total of 3933 patients, were included in this review update (2nd NA IgAN 2004; Ballardie 2002; BRIGHT-SC 2016; Cao 2008; CAST-IgA 2015; Chen 2002; Cheung 2018; Cruzado 2011; Frisch 2005; Harmankaya 2002; Hirai 2017; Horita 2007; Hou 2017; Julian 1993; Kanno 2003; Katafuchi 2003; Kawamura 2014; Kim 2013b; Kobayashi 1996; Koike 2008; Koitabashi 1996; Lafayette 2017; Lai 1986; Lai 1987; Lee 2003; Liu 2010a; Liu 2014; Locatelli 1999; Lou 2006; Lv 2009; Maes 2004; Manno 2001; Masutani 2016; Min 2017; NA IgAN 1995; NEFIGAN 2017; Ni 2005; Nuzzi 2009; Pozzi 1999; Segarra 2006; Shen 2013; Shi 2012a; Shima 2018; Shoji 2000; Stangou 2011; STOP-IgAN 2008; Takeda 1999; Tang 2005; TESTING 2017; Walker 1990a; Welch 1992; Woo 1987; Wu 2016; Xie 2011; Yamauchi 2001; Yoshikawa 1999; Yoshikawa 2006; Zhang 2004). Ten authors were contacted for clarifications relating to their publications and to request additional unpublished information. Four authors replied to our request.

Six studies included paediatric participants (Kobayashi 1996; Nuzzi 2009; Shima 2018; Welch 1992; Yoshikawa 1999; Yoshikawa 2006). Twenty-six studies included people with daily protein excretion > 1 g/24 hours (Cao 2008; Chen 2002; Cruzado 2011; Frisch 2005; Horita 2007; Hou 2017; Kawamura 2014; Lee 2003; Kobayashi 1996; Lai 1987; Liu 2014; Locatelli 1999; Lou 2006; Lv 2009; Maes 2004; Manno 2001; Min 2017; Ni 2005; Pozzi 1999; Segarra 2006; Shen 2013; Shi 2012a; Stangou 2011; Tang 2005; TESTING 2017; Walker 1990a). Thirteen studies (BRIGHT-SC 2016; Chen 2002; Cheung 2018; Kawamura 2014; Koitabashi 1996; Lafayette 2017; Nuzzi 2009; Segarra 2006; Shi 2012a; Shima 2018; Takeda 1999; Welch 1992; Yamauchi 2001) did not report data in an extractable format that could be included in our meta-analysis.

We identified five study of head-to-head comparisons between different immunosuppressive agents (Chen 2002; Hou 2017; Liu 2010a; Shen 2013; Wu 2016) and there were no studies that compared different doses of the same immunosuppressive agents.

See Characteristics of included studies.

Excluded studies

We excluded eight studies (nine reports) as they did not include all participants with IgA nephropathy (Imai 2006; Sulimani 2001; Yonemura 2000b), did not evaluate a immunosuppressive agent intervention (Chen 2009b; Czock 2007; Shen 2009), or did not complete the participant recruitment (Dal Canton 2005; GloMY 2010). See Characteristics of excluded studies.

Risk of bias in included studies

The risks of bias in the included studies are summarised in Figure 2. Risks of bias in individual studies are shown in Figure 3 and described in the Characteristics of included studies.

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

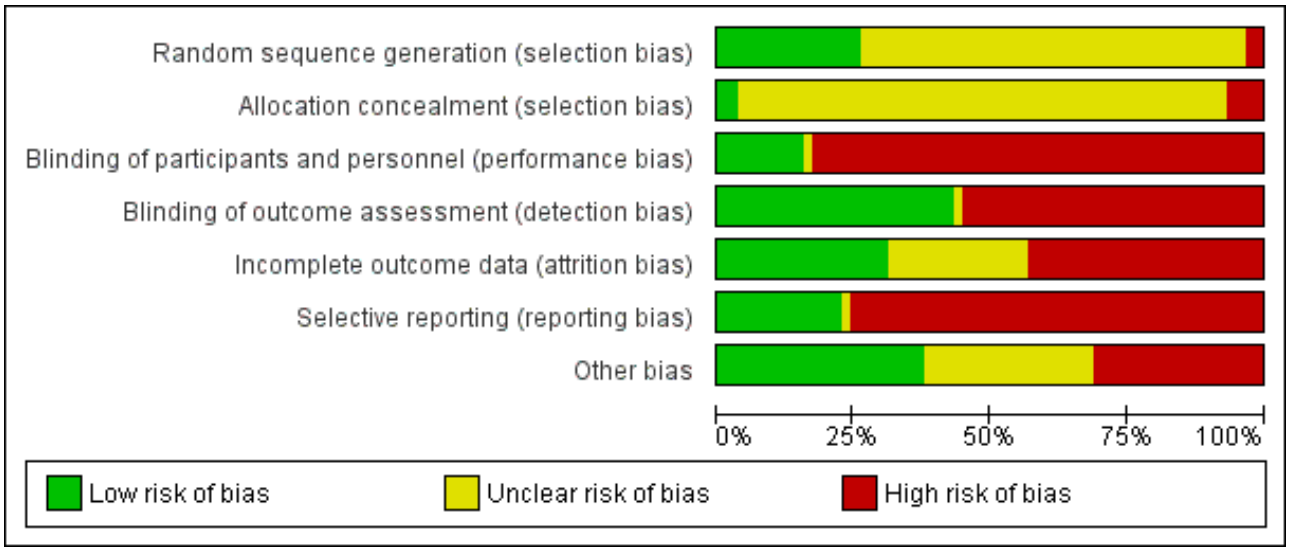


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

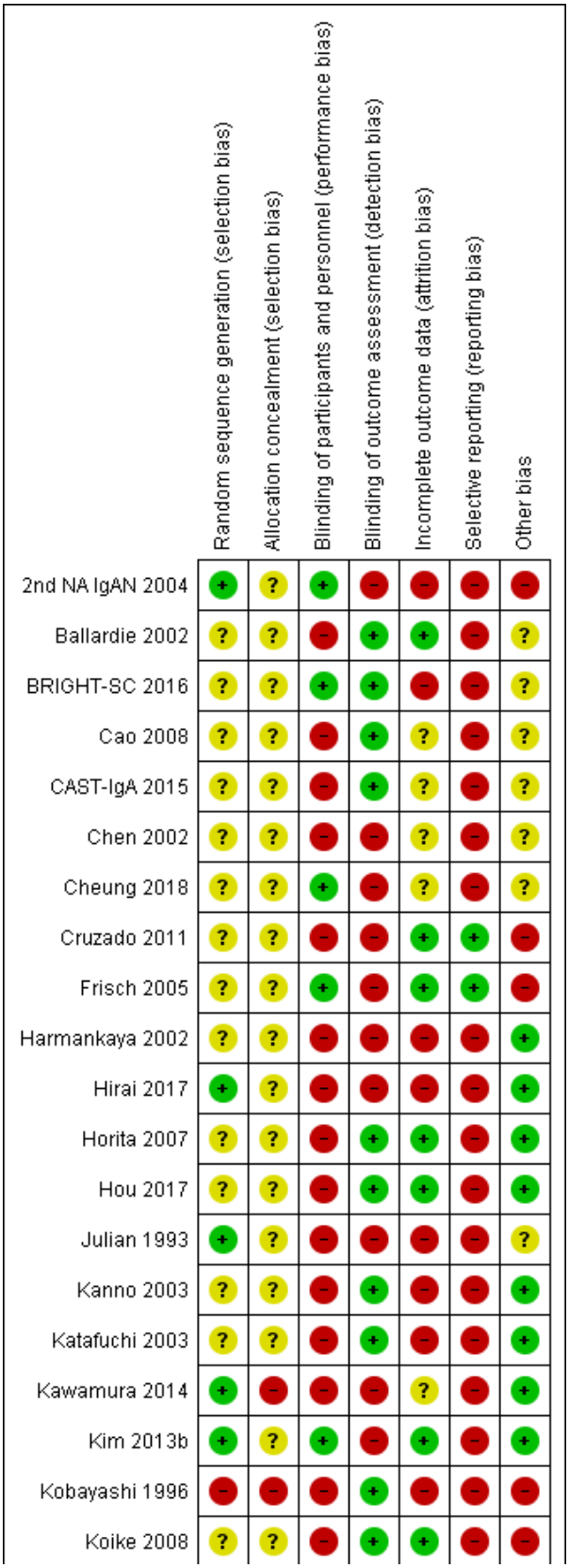


Figure 3. (Continued)

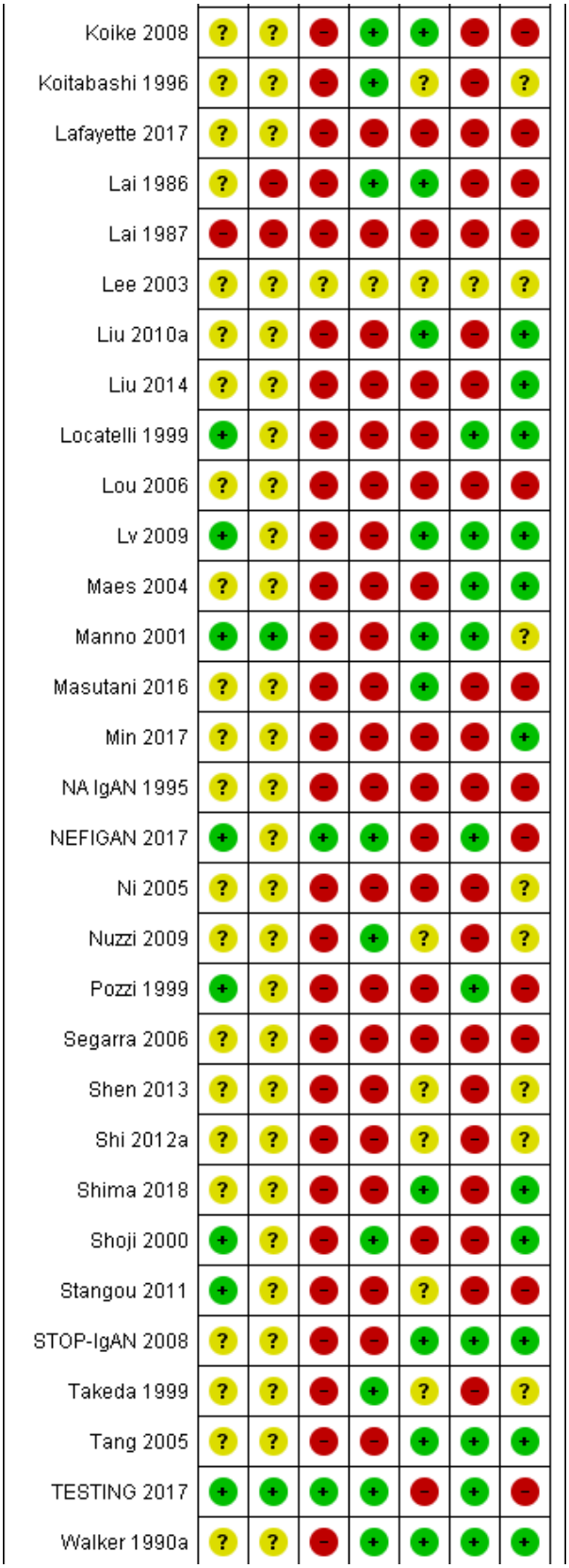
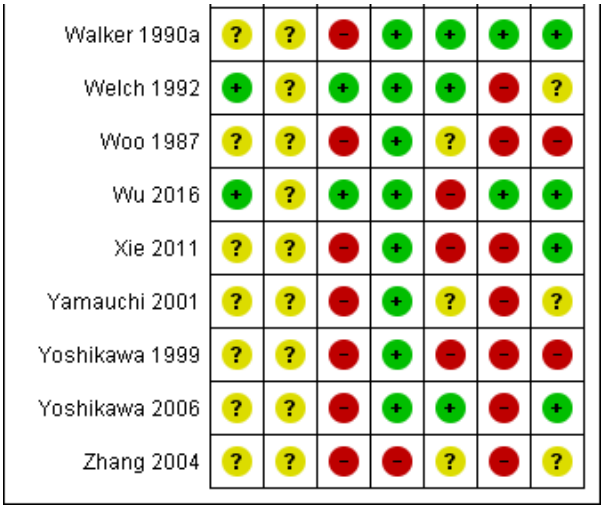


Figure 3. (Continued)



Allocation

Random sequence generation was considered at low risk of bias in 15 studies (2nd NA IgAN 2004; Hirai 2017; Julian 1993; Kawamura 2014; Kim 2013b; Locatelli 1999; Lv 2009; Manno 2001; NEFIGAN 2017; Pozzi 1999; Shoji 2000; Stangou 2011; TESTING 2017; Welch 1992; Wu 2016), at high risk in two studies (Kobayashi 1996; Lai 1987), and unclear in the remaining 41 studies.

Allocation concealment was adjudicated as low risk of bias in two studies (Manno 2001; TESTING 2017), at high risk in four studies (Kawamura 2014; Kobayashi 1996; Lai 1986; Lai 1987); and unclear in the remaining 52 studies.

Blinding

Nine studies (2nd NA IgAN 2004; BRIGHT-SC 2016; Cheung 2018; Frisch 2005; Kim 2013b; NEFIGAN 2017; TESTING 2017; Welch 1992; Wu 2016) were blinded and considered to be at low risk of bias and one study (Lee 2003) was assessed as unclear risk of performance bias. The remaining 48 studies were not blinded and were considered at high risk of performance bias.

Outcome assessment was considered to be at low risk of detection bias in 25 studies (Ballardie 2002; BRIGHT-SC 2016; Cao 2008; CAST-IgA 2015; Horita 2007; Hou 2017; Kanno 2003; Katafuchi 2003; Kobayashi 1996; Koike 2008; Koitabashi 1996; Lai 1986; NEFIGAN 2017; Nuzzi 2009; Shoji 2000; Takeda 1999; TESTING 2017; Walker 1990a; Welch 1992; Woo 1987; Wu 2016; Xie 2011; Yamauchi 2001; Yoshikawa 1999; Yoshikawa 2006), unclear in one study (Lee 2003), and high risk the remaining 32 studies.

Incomplete outcome data

Eighteen studies were judged to be a low risk of attrition bias (Ballardie 2002; Cruzado 2011; Frisch 2005; Horita 2007; Hou 2017; Kim 2013b; Koike 2008; Lai 1986; Liu 2010a; Lv 2009; Manno 2001; Masutani 2016; Shima 2018; STOP-IgAN 2008; Tang 2005; Walker 1990a; Welch 1992; Yoshikawa 2006), 25 studies were at high risk of attrition bias (2nd NA IgAN 2004; BRIGHT-SC 2016; Harmankaya 2002; Hirai 2017; Julian 1993; Kanno 2003; Katafuchi 2003; Kobayashi 1996; Lafayette 2017; Lai 1987; Liu 2014; Locatelli 1999; Lou 2006; Maes 2004; Min 2017; NA IgAN 1995; NEFIGAN 2017; Ni 2005; Pozzi 1999; Segarra 2006; Shoji 2000; TESTING 2017; Wu 2016; Xie 2011; Yoshikawa 1999), and the remaining 15 studies were unclear.

Selective reporting

Thirteen studies were judged to be at low risk of reporting bias (Cruzado 2011; Frisch 2005; Locatelli 1999; Lv 2009; Maes 2004; Manno 2001; NEFIGAN 2017; Pozzi 1999; STOP-IgAN 2008; Tang 2005; TESTING 2017; Walker 1990a; Wu 2016), one study was unclear (Lee 2003), and 44 were at high risk of reporting bias.

Other potential sources of bias

We adjudicated 22 studies as low risk of bias from other potential sources (Harmankaya 2002; Hirai 2017; Horita 2007; Hou 2017; Kanno 2003; Katafuchi 2003; Kawamura 2014; Kim 2013b; Liu 2010a; Liu 2014; Locatelli 1999; Lv 2009; Maes 2004; Min 2017; Shima 2018; Shoji 2000; STOP-IgAN 2008; Tang 2005; Walker 1990a; Wu 2016; Xie 2011; Yoshikawa 2006) considering balance of participant characteristics and co-interventions, governmental or academic sources of funding and balanced timing of outcome assessment for all treatment groups. Eighteen studies (2nd NA IgAN 2004; Cruzado 2011; Frisch 2005; Kobayashi 1996; Koike 2008; Lafayette 2017; Lai 1986; Lai 1987; Lou 2006; Masutani 2016; NA IgAN 1995; NEFIGAN 2017; Pozzi 1999; Segarra 2006; Stangou 2011; TESTING 2017; Woo 1987; Yoshikawa 1999) was assessed as high risk of bias. Risk of bias was unclear in the remaining 18 studies.

Effects of interventions

See: **Summary of findings for the main comparison** Systemic corticosteroid versus no corticosteroid regimen for IgA nephropathy; **Summary of findings 2** Cytotoxic regimen versus no cytotoxic regimen for IgA nephropathy; **Summary of findings 3** MMF regimen versus no MMF regimen for IgA nephropathy; **Summary of findings 4** Calcineurin inhibitor regimen versus no calcineurin inhibitor regimen for IgA nephropathy; **Summary of findings 5** Mizoribine regimen versus no mizoribine regimen for IgA

nephropathy; **Summary of findings 6** Leflunomide regimen versus no leflunomide regimen for IgA nephropathy

See: Summary of findings for the main comparison: Steroid regimen versus no steroid regimen for treating IgA nephropathy; Summary of findings 2: Cytotoxic regimen versus no cytotoxic regiment for treating IgA nephropathy; Summary of findings 3: MMF regimen versus no MMF regimen for IgA nephropathy; Summary of findings 4: CNI regimen versus no CNI regimen for IgA nephropathy; Summary of findings 5: Mizoribine regimen versus no mizoribine regimen for IgA nephropathy; Summary of findings 6: Leflunomide regimen versus no leflunomide regimen for IgA nephropathy.

We grouped the included studies into nine treatment comparisons.

1. Systemic corticosteroid versus no corticosteroid regimen (Julian 1993; Kanno 2003; Katafuchi 2003; Lee 2003; Kobayashi 1996; Koike 2008; Lai 1986; Lv 2009; Manno 2001; NA IgAN 1995; Nuzzi 2009; Pozzi 1999; Shoji 2000; Takeda 1999; TESTING 2017; Welch 1992; Yamauchi 2001)
2. Locally-acting steroid versus no locally-acting steroid (NEFIGAN 2017)
3. Cytotoxic (CPA, AZA or belimumab) versus no cytotoxic regimen (Ballardie 2002; BRIGHT-SC 2016; Cheung 2018: Harmankaya 2002; Koitabashi 1996; Lafayette 2017; Locatelli 1999; Stangou 2011; STOP-IgAN 2008; Yoshikawa 1999; Yoshikawa 2006; Walker 1990a; Woo 1987)
4. MMF versus no MMF regimen (2nd NA IgAN 2004; Chen 2002; Frisch 2005; Hou 2017; Maes 2004; Tang 2005)
5. CNI versus no CNI regimen (Kim 2013b; Lai 1987; Liu 2014; Shen 2013)
6. Mizoribine versus no mizoribine regimen (Hirai 2017; Masutani 2016; Shima 2018; Xie 2011)
7. Leflunomide versus no leflunomide regimen (Cao 2008; Liu 2010a; Lou 2006; Min 2017; Ni 2005; Shi 2012a; Wu 2016; Zhang 2004)
8. Steroid plus non-immunosuppressive agents versus steroid alone (CAST-IgA 2015; Horita 2007; Kawamura 2014; Segarra 2006)
9. mTOR inhibitor versus no mTOR inhibitor regimen (Cruzado 2011).

End-stage kidney disease requiring kidney replacement therapy

In patients mostly with mild to moderate kidney disease and protein excretion of over 1 g/24 hours, steroid treatment was administered generally as oral prednisolone 0.6 to 1 mg/kg during 2 to 4 months of therapy followed by a tapering course for a median follow-up of 54 months (between 24 and 120 months). Participant follow-up for occurrence of ESKD was generally between 2 and 10 years. In eight studies, steroid therapy probably reduces the absolute risk of reaching ESKD compared with standard care without steroid therapy or placebo (Analysis 1.1 (8 studies, 741 participants): RR 0.39, 95% CI 0.23 to 0.65; I^2 = 0%; *moderate certainty evidence*). There was moderate statistical heterogeneity in the treatment effects between the studies.

CPA or AZA alone or with concomitant steroid treatment for 3 to 6 months had uncertain effects on ESKD over 2 to 7 years of follow-up (Analysis 3.1 (7 studies; 463 participants): RR 0.63, 95% CI 0.33 to 1.20; I^2 = 34%; *low certainty evidence*) compared to standard care or placebo without steroid therapy.

MMF (1.5 to 2 g/day) with or without steroid therapy administered for between 24 weeks and 3 years had uncertain effects on progression to ESKD when compared with placebo, standard care or steroid alone (Analysis 4.1 (4 studies; 280 participants): RR 0.73, 95% CI 0.16 to 3.23; I^2 = 54%; *very low certainty evidence*). There was moderate statistical heterogeneity in the treatment effects between the studies.

Mizoribine administered at 150 mg/day for 12 months had uncertain effects within a single study in which two ESKD events (one in each group) occurred over 36 months (Analysis 6.1 (42 participants): RR 1.00, 95% CI 0.07 to 14.95; *very low certainty evidence*).

Leflunomide (20 mg/day) for 12 months in conjunction with oral prednisone (0.8 mg/day) for 4 to 6 weeks versus prednisone (1.0 mg/day) for 8 to 12 weeks had uncertain effects on ESKD in a single study (Analysis 7.1 (85 participants): RR 0.68, 95% CI 0.17 to 2.65; *very low certainty evidence*).

There was no evidence for the effects of CNIs, steroids combined with non-immunosuppressive agents, or mTOR inhibitors on ESKD.

Complete remission

Prednisone (0.8 to 1 mg/kg/d or 40 to 60 mg/day), methylprednisolone (0.6 to 0.8 mg/kg/day), or prednisolone (40 to 60 mg/day) were administered during 10 weeks to 8 months of therapy followed by a tapering course. Steroid therapy may incur complete remission compared with placebo, standard care or RAS inhibitor therapy during 2 to 5 years follow-up (Analysis 1.2 (4 studies, 305 participants): RR 1.76, 95% CI 1.03 to 3.01; I^2 = 69%; *low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

CPA or AZA with concomitant steroid treatment given for 4 months to 2 years had uncertain effects on complete remission compared to steroid alone, standard care or anticoagulant/antiplatelet during 6 months to 5 years follow-up (Analysis 3.2 (5 studies, 381 participants): RR 1.47, 95% CI 0.94 to 2.30; I^2 = 72%; *very low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

MMF (1.5 to 2 g/day) with or without steroid therapy administered given for 6 months to 1 year had uncertain effects on complete remission when compared with placebo, standard care or steroid alone (Analysis 4.2 (4 studies, 271 participants): RR 1.05, 95% CI 0.73 to 1.52; I^2 = 0%; *very low certainty evidence*).

CNIs (CSA 3 mg/day or tacrolimus 0.05 to 0.1 mg/kg/day) were administered during 6 months to 1 year with concomitant steroid treatment had uncertain effects on complete remission (Analysis 5.1 (2 studies, 72 participants): RR 0.91, 95% CI 0.60 to 1.39; I^2 = 0%; *very low certainty evidence*).

Mizoribine administered at 150 mg/day for 12 months had uncertain effects within a single study in which 15 complete remissions occurred during 36 months follow-up (Analysis 6.2 (24 participants): RR 1.90, 95% CI 1.06 to 3.43; *very low certainty evidence*).

Leflunomide (10 to 60 mg/day) for 3 to 12 months with or without oral prednisone had uncertain effects on complete remission over 3 to 88 months follow-up (Analysis 7.2 (4 studies, 282 participants): RR 1.08, 95% CI 0.80 to 1.46; I^2 = 0%; *very low certainty evidence*) compared to prednisone alone or RAS inhibitor.

Steroid (steroid pulse followed by prednisolone or prednisolone alone 30 mg followed by a tapering course) for 6 to 24 months with RAS inhibitor or ARB had uncertain effects on complete remission for 24 months follow-up (Analysis 8.1 (2 studies, 115 participants): RR 1.05, 95% CI 0.83 to 1.31; I^2 = 0%; *low certainty evidence*) compared to prednisolone with or without steroid pulse and tonsillectomy.

There was no evidence for the effects of mTOR inhibitors on complete remission.

Doubling of serum creatinine

Prednisone (0.5 to 1 mg/kg/day or 40 to 60 mg/day) and prednisolone (0.8 mg/kg/day or 20 to 60 mg/day) with or without methylprednisolone (1 g IV) were administered during 10 weeks to 2 years of therapy followed by a tapering course. Steroid therapy may prevent the doubling of SCr compared with standard care or RAS inhibitor therapy during 1 to 10 years follow-up (Analysis 1.3 (7 studies, 404 participants): RR 0.43, 95% CI 0.29 to 0.65; I^2 = 0%; *low certainty evidence*).

MMF (2 g/day) for up to 3 years had uncertain effects on occurrence of doubling of SCr when compared with placebo or standard care (Analysis 4.3 (2 studies, 74 participants): RR 2.01, 95% CI 0.28 to 14.44; I^2 = 0%; *low certainty evidence*).

Leflunomide (40 mg/day) for 12 months with oral prednisone had uncertain effects on occurrence of doubling of SCr over 88 months follow-up in a single study (Analysis 7.3 (85 participants): RR 0.50, 95% CI 0.17 to 1.50; *low certainty evidence*) compared to prednisone alone.

There was no evidence for the effects of cytotoxic agents, CNIs, mizoribine, steroids combined with non-immunosuppressive agents or of mTOR inhibitors on doubling of SCr.

Serum creatinine

Prednisone (0.5 to 1 mg/kg/day or 40 to 60 mg/day) and prednisolone (0.5 to 0.8 mg/kg/day or 20 to 60 mg/day) with or without methylprednisolone (1 g IV) were administered during 4 to 36 months of therapy followed by a tapering course. Steroid therapy had uncertain effects on SCr compared with standard care or other non-immunosuppressive treatment during 1 to 6 years follow-up (Analysis 1.4 (7 studies, 211 participants) MD -21.07 µmol/L, 95% CI -44.12 to 1.99; I^2 = 78%; *very low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

MMF (1.5 g/day) with steroid therapy administered for 6 months of therapy followed by a tapering course had uncertain effects on SCr when compared with steroid combined with leflunomide in a single study (Analysis 4.4 (40 participants): MD -1.58 µmol/L, 95% CI -19.29 to 16.13; *low certainty evidence*).

CSA (5 mg/kg/day) or tacrolimus (0.1 mg/kg/day) administered for 3 to 4 months followed by a tapering course had uncertain effects on SCr when compared with placebo during 4 to 6 months follow-up (Analysis 5.2 (2 studies, 62 participants): MD 7.75 µmol/L, 95% CI -6.76 to 22.27; I^2 = 0%; *low certainty evidence*).

Leflunomide (40 to 50 mg/day) for 6 to 12 months followed by a tapering course with oral prednisone had uncertain effects on SCr over 6 to 88 months follow-up (Analysis 7.4 (2 studies, 125 participants): MD -4.29 µmol/L, 95% CI -15.81 to 7.24; I^2 = 0%; *low certainty evidence*) compared to prednisone with or without MMF.

There was no evidence for the effects of cytotoxic agents, mizoribine, steroids combined with non-immunosuppressive agents or of mTOR inhibitors on SCr.

Glomerular filtration rate

Reduction in glomerular filtration rate (at least 50%)

In the two studies evaluating steroid treatment and reporting this outcome, steroids were administered as prednisone (initially 60 mg/m^2) on alternate days or methylprednisolone (0.6 to 0.8 mg/kg/day) were administered during 6 to 24 months of therapy. Participant follow-up for reduction in GFR of at least 50% was generally over two years. Steroid therapy had uncertain effects on risks of a ≥ 50% reduction compared to fish oil or placebo (Analysis 1.5 (2 studies; 326 participants): RR 0.56, 95% CI 0.25 to 1.24; I^2 = 0%; *low certainty evidence*).

MMF administered at 2000 mg for 52 weeks had uncertain effects on the risk of GFR reduction ≥ 50% at 2 years of follow-up in a single study (Analysis 4.5 (32 participants) RR 2.21, 95% CI 0.50 to 9.74; *very low certainty evidence*).

Risks of reduction in GFR of at least 50% was not reported for cytotoxic agents, CNIs, mizoribine, leflunomide, steroids combined with non-immunosuppressive agents, or mTOR inhibitors.

Reduction glomerular filtration rate (at least 25%)

MMF (2 g/day) had uncertain effects on the risk of GFR reduction ≥ 35% over 3 years in a single study (Analysis 4.6 (34 participants): RR 2.17, 95% CI 0.53 to 8.88; *low certainty evidence*).

Risks of reduction in GFR of at least 25% was not reported for steroids, cytotoxic agents, CNIs, mizoribine, leflunomide, steroids combined with non-immunosuppressive agents, or mTOR inhibitors.

Annual glomerular filtration loss

Prednisone (1 mg/kg/day) or methylprednisolone (0.6 to 0.8 mg/kg/d were administered during 6 to 8 months of therapy followed by a tapering course. Steroid therapy probably prevents annual GFR loss compared with placebo or RAS inhibitors during 2.1 to 5 years follow-up (Analysis 1.6 (2 studies, 359 participants): MD -5.40 mL/min/1.73 m^2, 95% CI -8.55 to -2.25; I^2 = 0%; *moderate certainty evidence*).

CPA followed by AZA with concomitant steroid treatment given for 6 months had uncertain effects on annual GFR loss compared to standard care during 3 years follow-up in a single study (Analysis 3.3 (162 participants): MD -0.01 mL/min/1.73 m^2, 95% CI -0.03 to 0.01; *low certainty evidence*).

MMF (2 g/day) had uncertain effects on annual GFR loss compared to placebo during 12 months follow-up in a single study (Analysis 4.7 (28 participants): MD 2.0 mL/min/1.73 m^2, 95% CI -25.15 to 29.15; *very low certainty evidence*).

There was no evidence for the effects of CNIs, mizoribine, leflunomide, steroids combined with non-immunosuppressive agents, or mTOR inhibitors on annual GFR loss.

Glomerular filtration rate (any measure)

Prednisolone (0.8 mg/kg/day or 40 to 60 mg/day) and prednisone (0.5 mg/kg/day or 40 to 60 mg/day) with or without methylprednisolone (1 g IV) were administered during 4 to 18 months of therapy followed by a tapering course. Steroid therapy had uncertain effects on GFR compared with standard care or other non-immunosuppressive treatment during 1 to 10 years follow-up (Analysis 1.7 (4 studies, 138 participants): MD 17.87 mL/min/1.73 m^2, 95% CI 4.93 to 30.82; I^2 = 53%; *very low certainty evidence*). There was moderate heterogeneity in treatment effects observed between the studies.

AZA (1 to 2 mg/kg/day) with concomitant steroid treatment given for 1 to 2 years had uncertain effects on GFR compared to steroid alone or anticoagulant/antiplatelet therapy (Analysis 3.4 (3 studies, 174 participants): MD 3.07 mL/min/1.73 m^2, 95% CI -6.57 to 12.72; I^2 = 0%; *low certainty evidence*).

MMF (2 g/day) administered for 12 months had uncertain effects on GFR when compared with placebo in a single study (Analysis 4.8 (28 participants): MD -2.50 mL/min/1.73 m^2, 95% CI -30.79 to 25.79; *low certainty evidence*).

CSA (3 to 5 mg/day) with or without concomitant steroid treatment and tacrolimus (0.1 mg/kg/day) for 3 to 12 months had uncertain effects on GFR during 4 to 60 months follow-up (Analysis 5.3 (3 studies, 110 participants): MD -0.18 mL/min/1.73 m^2, 95% CI -7.42 to 7.07; I^2 = 0%; *low certainty evidence*).

Mizoribine (150 to 250 mg/day) with RAS inhibitor treatment had uncertain effects on GFR when compared with RAS inhibitor alone in a single study (Analysis 6.3 (65 participants): MD 2.05 mL/min/1.73 m^2, 95% CI -10.16 to 14.26; *low certainty evidence*).

Leflunomide (40 to 60 mg/day) for 6 to 12 months with or without oral prednisone had uncertain effects on GFR over 6 to 88 months follow-up (Analysis 7.5 (2 studies, 131 participants): MD 11.11 mL/min/1.73 m^2, 95% CI -3.32 to 25.55; I^2 = 62%; *very low certainty evidence*) compared to prednisone alone or RAS inhibitor. There was substantial heterogeneity in treatment effects observed between the studies.

Prednisolone (30 mg) followed by a tapering course for 24 months combined with ARB had uncertain effects on GFR in a single study (Analysis 8.2 (38 participants): MD 16.00 mL/min/1.73 m^2, 95% CI -6.89 to 38.89; *low certainty evidence*) compared to prednisolone alone.

There was no evidence for the effects of mTOR inhibitors on GFR.

Urinary protein excretion

Methylprednisolone (0.6 to 0.8 mg/kg/day), prednisolone (0.4 to 0.8 mg/kg/day or 20 to 60 mg/day) and prednisone (0.5 mg/kg/day or 40 to 60 mg/day) with or without methylprednisolone (1 g IV) were administered during 4 to 24 months of therapy followed by a tapering course. Steroid therapy may lower urinary protein excretion compared with placebo, standard care or other non-immunosuppressive treatment during 1 to 10 years follow-up (Analysis 1.8 (10 studies, 705 participants): MD -0.58 g/24 h, 95% CI -0.84 to -0.33; I^2 = 60%;*low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

CPA and/or AZA with concomitant steroid treatment given for 3 to 24 months had uncertain effects on urinary protein excretion compared to standard care, steroid alone or other non-immunosuppressive treatment (Analysis 3.5 (5 studies, 255 participants): MD -0.77 g/24 h, 95% CI -1.80 to 0.26; I^2 = 98%; *very low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

MMF (1.5 to 2 g/day) with or without steroid therapy administered for up to 3 years had uncertain effects on urinary protein excretion when compared with placebo, standard care or steroid with leflunomide over 6 months to 3 years follow-up (Analysis 4.9 (5 studies, 172 participants): MD -0.06 g/24 h, 95% CI -0.92 to 0.81; I^2 = 96%; *very low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

CSA (3 to 5 mg/day) with or without concomitant steroid treatment or tacrolimus (0.1 mg/kg/day) for 3 to 12 months had uncertain effects on urinary protein excretion during 4 to 60 months follow-up (Analysis 5.4 (3 studies, 110 participants): MD -0.50 g/24 h, 95% CI -1.12 to 0.12; I^2 = 82%; *very low certainty evidence*). There was substantial heterogeneity in treatment effects observed between the studies.

Mizoribine (150 to 250 mg/day) with RAS inhibitor or steroid treatment had uncertain effect on reduction of urinary protein excretion when compared with RAS inhibitor or steroid alone (Analysis 6.4 (2 studies, 105 participants): MD -0.04 g/24 h, 95% CI -0.30 to 0.22; *low certainty evidence*).

Leflunomide (20 to 50 mg/day) with or without oral prednisone had uncertain effects on urinary protein excretion over 3 to 6 months follow-up (Analysis 7.6 (3 studies, 125 participants): MD 0.20 g/24 h, 95% CI -0.60 to 1.00; I^2 = 69%; *very low certainty evidence*) compared to steroid with or without MMF. There was substantial heterogeneity in treatment effects observed between the studies.

Prednisolone (30 mg) followed by a tapering course for 24 months combined with ARB had uncertain effect on reduction of urinary protein excretion in a single study (Analysis 8.3 (38 participants): MD -0.20 g/24 h, 95% CI -0.26 to -0.14; *low certainty evidence*) compared to prednisolone alone.

Sirolimus (1 mg/day) had uncertain effect on reduction of urinary protein excretion during 12 months follow-up compared with no mTOR inhibitors in a single study (Analysis 9.1 (23 participants): MD -0.80 g/24 h, 95% CI -1.83 to 0.23; *low certainty evidence*).

Death (any cause)

Due to the rarity of death during follow-up with this condition, the effects of all treatment strategies on the outcome of total death were either imprecisely known or not reported.

One parallel-group study measured the effects of steroid versus placebo on the risks of death (any cause). During a median of 25 months, 3 deaths among 262 participants were reported. The comparative effects of treatment on death (any cause) was uncertain with an imprecise treatment effect (Analysis 1.9: RR 1.85, 95% CI 0.17 to 20.19; *very low certainty evidence*). Similarly, in a parallel-group study evaluating CPA followed by AZA plus steroid versus steroid alone for 36 months, two deaths (one in each group) were recorded and treatment effects were uncertain (Analysis 3.6 (162 participants): RR 0.98, 95% CI 0.06 to 15.33; *very low certainty evidence*).

Death (any cause) was not reported for other treatment regimens including MMF, CNIs, mizoribine, leflunomide, steroid therapy combined with non-immunosuppressive agents and mTOR inhibitors.

Infection

Methylprednisolone (0.6 to 0.8 mg/kg/day) was administered during 6 months of therapy followed by a tapering course. Corticosteroid therapy had uncertain effects on infection compared with placebo during 2 years follow-up with very low imprecision in the estimated effect in a single study (Analysis 1.10 (262 participants): RR 21.32, 95% CI 1.27 to 358.10; *very low certainty evidence*). TESTING 2017 study was terminated early on the recommendation of the Data Safety Monitoring Committee due to an excess of serious adverse events in the corticosteroid group (mainly infections).

NEFIGAN 2017, a novel targeted release formulation of budesonide, a glucocorticoid which is released in the distal ileum, with low systemic availability, had very uncertain effects on increasing infection adverse events during 12 months (Analysis 2.1 (150 participants): RR 0.83, 95% CI 0.21 to 3.35; *very low certainty evidence*). Budesonide (8 to 16 mg/day) was administered during 9 months of therapy.

CPA or AZA with concomitant steroid treatment given for 3 to 12 months had uncertain effects on infection compared to placebo or standard care (Analysis 3.7 (4 studies, 268 participants): RR 1.70, 95% CI 0.43 to 6.76; I^2 = 0%; *very low certainty evidence*).

MMF (1.5 to 2 g/day) with or without steroid therapy administered for up to 3 years had uncertain effects on occurrence of infection when compared with placebo, standard care or steroid alone (Analysis 4.10 (4 studies, 301 participants): RR 1.36, 95% CI 0.87 to 2.12; I^2 = 0%; *very low certainty evidence*).

CSA (3 mg/day) with concomitant steroid treatment for 12 months had uncertain effects in a single study in which four infections occurred during 60 months follow-up (Analysis 5.5 (48 participants): RR 0.31, 95% CI 0.03 to 2.74; *very low certainty evidence*).

Mizoribine (150 to 250 mg/day) with concomitant steroid or RAS inhibitor treatment had uncertain effects on occurrence of infection when compared with steroid or RAS inhibitor alone (Analysis 6.5 (2 studies, 104 participants): RR 1.52, 95% CI 0.14 to 16.15; I^2 = 52%; *very low certainty evidence*). There was moderate statistical heterogeneity in the treatment effects between the studies

Leflunomide (20 to 40 mg/day) for 6 to 12 months with or without oral prednisone had uncertain effects on occurrence of infection over 6 to 24 months follow-up (Analysis 7.7 (3 studies, 387 participants): RR 0.97, 95% CI 0.45 to 2.09; I^2 = 0%; *very low certainty evidence*) compared to prednisone alone or placebo.

There was no evidence for the effects of steroids combined with non-immunosuppressive agents or of mTOR inhibitors on infection.

Malignancy

Prednisone (0.5 mg/kg/day) for 6 months and methylprednisolone (1g IV) had uncertain effects in a single study in which 2 malignancies (1 in each group) occurred during 6 years follow-up (Analysis 1.11 (86 participants): RR 1.00, 95% CI 0.06 to 15.48; *very low certainty evidence*).

CPA followed by AZA with concomitant steroid treatment given for 6 months had uncertain effects on malignancy compared to standard care during 3 years follow-up in a single study (Analysis 3.8 (162 participants): RR 4.88, 95% CI 0.24 to 100.08; *very low certainty evidence*).

MMF (2 g/day) administered for up to 3 years had uncertain effects on occurrence of malignancies when compared with placebo (Analysis 4.11 (2 studies, 86 participants): RR 0.28, 95% CI 0.03 to 2.54; I^2 = 0%; *very low certainty evidence*).

CSA (3 mg/day) with concomitant steroid treatment for 12 months had uncertain effects in a single study in which one malignancy occurred (Analysis 5.6 (48 participants): RR 0.36, 95% CI 0.02 to 8.45; *very low certainty evidence*).

Mizoribine (150 mg/day) for 12 months had uncertain effects on occurrence of malignancy when compared with standard care in a single study (Analysis 6.6 (42 participants): RR 3.00, 95% CI 0.13 to 69.70; *very low certainty evidence*). There was no evidence for the effects of leflunomide, steroids combined with non-immunosuppressive agents or of mTOR inhibitors on malignancy.

Adverse events

Table 1 details the adverse events in studies when they were described.

Publication bias

Due to the insufficient number of studies in each meta-analysis, we were not able to assess for evidence of missing data due to small study effects or publication bias.

Subgroup analysis

We planned subgroup analysis assessing the treatment effects in studies involving various ethnicities, but due to limitations in the number of available studies, a subgroup analysis based on ethnicity was not possible

Post hoc subgroup analysis

There was no evidence that treatment effects of steroid therapy on risk of ESKD was different among participants receiving concomitant RAS blockade and BP control (ACEi and/or ARB) and those participants in whom additional background therapy was not specifically prescribed.

DISCUSSION

The aim of this Cochrane review was to evaluate the effectiveness and safety of immunosuppression for treatment of IgA nephropathy to prevent progression to ESKD needing dialysis or kidney transplantation. In addition to the clinical endpoint of ESKD, we also examined the effects of various immunosuppression strategies on intermediate kidney endpoints including at least 50% reduction in eGFR, annual GFR loss, SCr, urinary protein excretion, and IgA nephropathy disease remission. Potential harms of treatment were evaluated including infection and malignancy. This is an update of a Cochrane review first published in 2003 and updated in early 2015 (which included 32 studies involving 1781 participants).

Summary of main results

In this substantive review update, 58 studies involving 3933 randomised participants were included. The major Immunosuppressive strategies were systemic corticosteroids and local corticosteroids (including budesonide), were frequently heterogeneous, and were allocated to nine intervention-containing regimens:

- Systemic corticosteroids
- Locally-acting steroid
- Cytotoxic therapy (CPA or AZA)
- MMF
- CNI (CSA or tacrolimus)
- Mizoribine
- Leflunomide
- Steroid plus non-immunosuppressive agents
- mTOR inhibitor (sirolimus).

Systemic corticosteroid therapy given for two to four months followed by a tapering dose has beneficial effects on a range of clinical and intermediate renal outcomes in people with IgA nephropathy and proteinuria. In people with generally moderate to severe proteinuria > 1 g/24 hours and mild to moderate CKD, corticosteroid treatment probably prevents ESKD requiring dialysis or transplantation (moderate certainty evidence); reduces annual loss of GFR for two to five years; incurs complete disease remission; and may reduce protein excretion by 0.5 g/24 hours. The effects of steroid therapy on preventing 50% loss in eGFR, infection, death (any cause), and malignancy were uncertain as there were few studies that reported these outcomes.

The effects of all other immunosuppressive regimens on clinical outcomes of IgA nephropathy (locally-acting steroid, cytotoxic agents, MMF, CNIs, mizoribine, leflunomide, and mTOR inhibitors alone or with steroids) was uncertain. In general data were sparse due to few studies or intervention effects did not reach clinical or statistical significance. The various immunosuppression strategies had uncertain treatment effects on risks of ESKD, infection, complete remission, malignancy, GFR, SCr or doubling of SCr and urinary protein excretion. Steroids given together with non-immunosuppressive agents similarly had uncertain effects on complete remission, GFR and urinary protein excretion compared to steroids administered alone.

There was no evidence that treatment effects of steroid therapy on risk of ESKD was different among participants receiving concomitant RAS blockade and BP control (ACE inhibitor and/or ARB) and those participants in whom additional background therapy was not specifically prescribed.

Overall completeness and applicability of evidence

In this substantive update, we were able to include an additional 26 studies with almost 2000 additional participants to the previous Cochrane review. Despite this now larger number of studies, limitations in the existing available studies include the rarity of many clinical events such as death and malignancy, precluding certainty of the impact of treatment on these clinical outcomes. Although ESKD tends to be a relatively rare outcome, studies evaluating steroid therapy tended to include participants with moderate or severe levels of proteinuria who are at higher risk for kidney failure. Intermediate kidney outcomes including change in eGFR, complete clinical disease remission, and reduction in protein excretion rate were improved with steroid therapy. Concordance between effects on clinical (ESKD) and surrogate outcomes (doubling SCr, reduction in proteinuria) strengthens the findings of the contributing studies. Studies measured effects of treatment on ESKD for between two and 10 years. providing sufficient statistical power to evaluate a hard renal endpoint. The findings of the review may not apply to those patients with milder clinical presentations with lower levels of proteinuria (< 1 gram) at the time of diagnosis. The benefits and risks of treatment in patients with marked impairment of kidney disease (GFR category 4) may be less certain. The treatment estimates are provided by evidence of moderate certainty. Due to disease heterogeneity in contributing studies and a lack of capacity to conduct subgroup analyses by subgroups of disease severity and ethnicity, knowledge of treatment efficacy based on specific patient characteristics is limited. It is unclear whether the findings of steroid effectiveness are applicable to patients with crescentic or rapidly progressive IgA nephropathy who are underrepresented in the available studies, and who may warrant a more aggressive treatment strategy. It was not possible to estimate whether treatment strategies had different effects based on age, ethnicity, or other clinical factors. We planned subgroup analysis assessing the treatment effects in studies involving various ethnicities, but due to limitations in the number of available studies, a subgroup analysis based on ethnicity was not possible.

We have included in the systemic corticosteroid meta-analysis, only participants in STOP-IgAN 2008 that received systemic corticosteroids alone. We analysed participants receiving combined systemic corticosteroids with additional cytotoxic agents in a separate relevant meta-analysis.

Quality of the evidence

Due to the heterogeneity of participants, interventions and comparators, we have attempted to reduce complexity by categorising therapeutic strategies into specific groups. This may have over-simplified the treatment interventions used and drawn differing treatment approaches into a single analysis, when important therapeutic effects might have existed. Despite combining treatment groups into overarching categories, we did not observe substantial statistical heterogeneity in the analyses, with the key finding of steroid effects on risk of ESKD having moderate certainty. There has been limited stratification by risk of ESKD in people with IgA nephropathy. Substantial disease heterogeneity suggests a validated tool for IgA nephropathy could

predict the disease progression and enrich trial populations with patients at highest risk of ESKD.

The majority of studies in this review were at unclear risk of bias for many of the risk of bias domains, lowering certainty in the results due to study limitations. It was likely that most studies were not blinded, which may have impacted on treatment adherence and outcome assessment. For assessment of steroid therapy, GRADE assessment of outcomes led to trials being downgraded due to study limitations, while imprecision was present in some estimates due to a small number of studies or the rarity of clinical endpoints.

Potential biases in the review process

The evidence for this review is derived from a systematic search of the Cochrane Kidney and Transplant's specialised register, which provides literature from grey sources including conference proceedings and handsearched journals. This approach may help to minimise omission of potentially relevant trials. We additionally requested data from authors. The literature search was screened independently by two review authors who were involved in the process of the whole review, to limit errors in data management and analysis, and determining the risks of bias in contributing studies.

There was a high degree of heterogeneity between the available trials in the study interventions, clinical presentation and severity of IgA nephropathy, follow-up duration, and measurement of outcome data. Despite this, we were able to summarise treatment effects across many trials with limited evidence of statistical heterogeneity. We have made generalisations about the dose and duration of corticosteroid therapy in the interests of assisting in clinical application of the findings of this review, that contained an element of subjectivity.

Agreements and disagreements with other studies or reviews

The findings in this review are consistent with a recently published systematic review with network meta-analysis that identified treatment with steroid therapy plus RAS inhibition was the most effective treatment to prevent ESKD among patients with proteinuria more than 1 gram per day (Yang 2018). Similarly, the finding in this study that MMF has uncertain effects on renal outcomes in IgA nephropathy is consistent with a recently updated meta-analysis of RCTs (Zheng 2018) and a second meta-analysis which found that MMF did not reduce proteinuria significantly in patients with IgA nephropathy and persistent proteinuria after RAS blockade (Hogg 2015).

The findings of this systematic review are consistent with global guideline recommendations for the management of IgA nephropathy (KDIGO 2012). These guidelines suggest:

- Patients with IgA nephropathy who have persistent proteinuria above 1 g/day despite three to six months of conservative management and who have an estimated GFR above 50 mL/min might receive benefit from steroid therapy (six months) based on low-quality evidence
- Patients with IgA nephropathy do not receive combined corticosteroid and CPA or AZA treatment unless there is crescentic IgA nephropathy with deteriorating kidney function
- Not using MMF in the treatment of IgA nephropathy.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review are consistent with global guidelines and existing systematic reviews.

In adults and children with biopsy-proven IgA nephropathy, proteinuria of 1 g/day or higher and mild to moderate kidney disease, steroid therapy given for 2 to 4 months with a tapering course probably prevents ESKD (moderate certainty) and slows annual progression of kidney failure (moderate certainty), while corticosteroids may decrease proteinuria (low certainty). Caution with corticosteroid therapy is needed due to the potential for serious infections, and at present evidence certainty about risks of adverse infection events in available trials is very low.

Other immunosuppression strategies do not appear to have detectable benefits on kidney function among adults and children with IgA nephropathy. Specifically, treatment with CPA, AZA, or MMF do not appear to be indicated to treat IgA nephropathy.

Treatment strategies for aggressive forms of IgA nephropathy have limited evidence, and the findings in this review may not be generalisable to patients with mild disease.

Implications for research

While available data suggest steroid therapy might be effective to reduce ESKD and improve complete remission, additional specific data would be informative.

Due to the wide heterogeneity of disease in IgA nephropathy, stratification of study populations using risk stratification scoring may assist to improve precision in treatment estimates and identify populations with specific disease risks or severity that are most responsive to evaluated treatments.

Based on available data, and the promising utility of steroid therapy in IgA nephropathy, a larger study comparing targeted release formulation of budesonide against placebo and prednisone and sufficiently powered to evaluate infection-related adverse events would help to inform clinical practice. The absence of studies among patients with lower GFR suggests additional studies that include patients with rapidly progressive disease and with lower GFRs may be informative.

In addition, studies of steroid treatment with evaluation of patient-relevant endpoints that focus on the following questions would be helpful.

- Effect of baseline proteinuria level on treatment effectiveness (appropriate threshold for initiating therapy)
- Duration of treatment
- Effects of ethnicity on treatment effectiveness.

A trials network that provides a multinational multicentre approach (as is utilised in research of rare glomerulonephritides) may increase the feasibility of studies in this clinical setting that are powered to evaluate treatment effects on patient-relevant outcomes.

Based on this evidence synthesis showing potential harm from steroid therapy, further evaluation of newer targeted therapies

such as budesonide and eculizumab and other complement-targeted therapies is warranted.

ACKNOWLEDGEMENTS

The authors are grateful to the following peer reviewers for their time and comments: Ainslie M. Hildebrand MD MSc, Professor Jonathan Barratt PhD FRCP (The Mayer Professor of Renal Medicine, Department of Cardiovascular Sciences, University of Leicester; Honorary Consultant Nephrologist, John Walls Renal Unit, Leicester General Hospital, UK), Richard J. Glassock MD (Emeritus Professor, Geffen School of Medicine at UCLA, Los Angeles, CA, USA).

The authors are particularly indebted to Drs C Pozzi, RG Walker, R Katafuchi, and O Harmankaya for providing additional data relating to their studies upon request.

We also thank Professor Vlado Perkovic for providing additional data for the TESTING 2017 study in the 2020 update.

Bibiana Bonerba was an author on the 2015 update.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

2nd NA IgAN 2004

Methods	• Study design: parallel, 2-arm RCT
	• Time frame
	  * Study start date: January 2002
	  * Primary completion date: March 2008
	  * Actual completion date: March 2010
	• Duration of follow-up: 12 months

Participants	• Setting: multicentre (30 sites) • Country: USA and Canada

2nd NA IgAN 2004 *(Continued)*

- Inclusion criteria: aged 7 to 70 years, kidney biopsy diagnostic for IgAN based on mesangial immunofluorescence staining for IgA ≥ IgG and IgM, UPCR 0.6 ≥ g/g (males) or ≥ 0.8 g/g (females), and eGFR ≥ 50 mL/min/1.73 m^2 (or ≥ 40 mL/min/1.73 m^2 in those already receiving an ACEi or ARB)
- Number (analysed/randomised): treatment group (13/25); treatment group (15/27)
- Mean age ± SD (years): treatment group (31.8 ± 11.7); control group (32.2 ± 13.2)
- Sex (M/F): treatment group (14/11); control group (18/9)
- Exclusion criteria: SLE; HSP; chronic liver disease or hepatitis; history of significant gastrointestinal disorder; HIV infection; any systemic infection; absolute neutrophil count < 2000/µL; HCT < 28%; known contraindication to MMF, highly purified omega-3 fatty acid, or lisinopril (or losartan if used instead of lisinopril); other major organ system disease or malignancy; current or prior treatment with MMF or AZA; pregnancy or breast-feeding at time of entry or unwillingness to comply with measures for contraception; and current or recent exposure to any investigational drug

Interventions	Treatment group • MMF: maximum 1 g twice/day. Initial dose for the first 2 weeks of therapy was approximately one-half to two-thirds of the full dose. The target dose was 25 to 36 mg/kg/day for 12 months. The dose was reduced if a person developed gastrointestinal toxicity, HCT < 25%, or absolute neutrophil count was 1000 to 1500/µL. The study drugs were discontinued if these problems persisted or in the event of pregnancy, refusal to maintain contraception, non adherence to the protocol, or decrease in eGFR ≥ 40% from study entry Control group • Placebo Co-interventions • Lisinopril (or losartan) plus a highly purified omega-3 fatty acid
Outcomes	• eGFR < 60% of the baseline level (estimated with the Schwartz (age < 18 years) or Cockcroft-Gault (age ≥ 18 years) formula) • Annual change in eGFR • UPCR • Malignancy • Complete remission (UPCR < 0.3 g/g) • Partial remission (UPCR decreased ≥ 50%) • Adverse events • Serious adverse events
Notes	• This study was supported by an unrestricted grant from Roche Laboratories Inc • Trials registration identification number: NCT00318474 • The trial was conducted under an investigator-initiated Investigational New Drug application (Funding Opportunity Announcement number 48,977) in US centres, and with the approval of Health Canada (Bureau of Pharmaceutical Assessment [BPA] control number 076948) in Canadian sites

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised scheme that was constructed with a computer-based pseudo-random number generator
Allocation concealment (selection bias)	Unclear risk	The biostatistician determined the treatment group assignment for all eligible patients

2nd NA IgAN 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	12/25 participants assigned to MMF (fall in GFR (2); patient choice (2); prolonged hospitalisation (1); non-adherence (1); trial termination (6)) and 12/27 participants assigned to placebo (loss-to-follow up (1); patient choice (4); malignant melanoma (1); pregnancy (1); trial terminated (5)) did not complete study at 12 months
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause) and ESKD) were not reported
Other bias	High risk	An independent Data and Safety Monitoring Committee met in person or by teleconference at least annually. In year 5 of the trial (2007), following careful consideration of the unblinded trial data, the committee concluded that it was extremely unlikely that any efficacy could be demonstrated from the limited additional enrolment and follow-up that was going to be possible. The committee therefore recommended termination of the trial. There were no safety issues leading to this decision. Baseline characteristics were balanced across treatment groups

Ballardie 2002

Methods	• Study design: parallel, 2-arm RCT • Time frame: 1991 to 1996 • Duration of follow-up: 2 to 6 years or until ESKD
Participants	• Setting: Renal units in the northwest UK • Country: UK • Inclusion criteria: impaired (SCr < 130 µmol/L) or declining kidney function as a result of persisting immune-mediated glomerular disease; controlled hypertension during the preceding 12 months, age from 18 to 54 years. Patients were selected for moderately rapidly progressive disease, defined by a 15% increase in SCr in the year before study entry • Number (analysed/randomised): Immunosuppression group (19/19); control group (19/19) • Age range: 18 to 54 years • Sex (M/F): 34/4 • Exclusion criteria: not known cardiac, liver, or other system pathology, secondary forms of IgA nephropathy, previous accelerated hypertension, related systemic disease (vasculitis), arteriopathic disease, DM, women of reproductive age, patients who had received immunosuppressive or corticosteroid treatment
Interventions	Treatment group • Prednisolone: 40 mg/d tapered to 10 mg/d by 2 years, continued for 6 years • CPA: 1.5 mg/kg/d for 3 months • AZA: 1.5 mg/kg/d from 3 months to 2 to 6 years Control group

Ballardie 2002 *(Continued)*

	• No treatment Co-interventions • BP control; first-line therapy calcium antagonists and beta-blockers
Outcomes	• ESKD • Infection • Decline in GFR • Urinary protein excretion • Renal histology
Notes	• Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants remained in study and were included in analysis for ESKD at 24 months
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), infection)
Other bias	Unclear risk	Not reported in sufficient detail to perform adjudication. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

BRIGHT-SC 2016

Methods	• Study design: parallel, 2-arm RCT
	• Time frame
	  * Study start date: June 2013
	  * Study primary completion date: March 2017
	  * Actual study completion date: 30 June 2017
	• Duration of follow-up: 6 months

BRIGHT-SC 2016 *(Continued)*

Participants	• Setting: multicentre (number of sites not reported) • Country: Czech Republic, Germany, Hong Kong, Republic of Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, UK • Inclusion criteria: biopsy-proven IgAN; UPCR 1 to 6 g/g; eGFR > 30 mL/min/1.73 m^2, on renin-angiotensin blockade • Number (analysed/randomised): 47/57 • Mean age ± SD (years): not reported • Sex (M/F): 45% men • Exclusion criteria: clinical or histologic evidence of non-IgA-related GN; IgA nephropathy > 50% glomerulosclerosis or cortical scarring; meets eGFR criteria; history of treatment with oral or parenteral corticosteroids within 3 months or immunosuppressants within 6 months; malignancy within past 5 years; known to be positive for HIV and/or positive at the screening visit for hepatitis B, or hepatitis C; liver disease; neutropenia; active infection requiring hospitalisation or treatment with parenteral antibiotics within the past 60 days or history of repeated herpetic viral infections; history of active tuberculosis or a history of tuberculosis infection; pregnant or nursing
Interventions	Treatment group • Blisibimod: 100 mg 3 times/week for 8 weeks, then 200 mg/week Control group • Placebo Co-interventions • Not reported
Outcomes	• ESKD • eGFR • UPCR • Serum immunoglobulins IgA, IgG and IgM • Plasma cells and B-cell subsets • Complement C3 and C4 • Requiring addition of corticosteroid therapy
Notes	• Conference abstract • Responsible party: Anthera Pharmaceuticals. Results submitted to trial registry; currently in quality control • Funding: Anthera Pharmaceuticals

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

BRIGHT-SC 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was not reported. However, the study outcomes of interest were objectively measured, therefore this was adjudicated as low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	10/57 participants did not complete 6 months of study follow-up and were not included in analysis. It was not clear whether there was differential loss in the treatment groups and the reasons for dropout were not provided
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

Cao 2008

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: progressive IgAN (renal biopsy proven newly with proteinuria > 1.0 g/d, plus Lee SMK grade II-V and/or SCr between 178 and 250 µmol/L) • Number (analysed/randomised): treatment group (not reported/18); control group (not reported/18) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Leflunomide: 40 mg/day for 3 days followed by 20 mg/d for 6 months • Prednisone: 0.8 mg/kg/day tapered to10 mg/d for 6 months Control group • Prednisone: 1 mg/kg/day tapered to 10 mg/day for 6 months Co-interventions • Not reported
Outcomes	• Proteinuria • SCr • Urinary V-CAM-1
Notes	• Conference abstract • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Cao 2008 *(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	There was no report of blinding. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was not reported. However, the study outcomes of interest were objectively measured, therefore this was adjudicated as low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

CAST-IgA 2015

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: patients with IgAN • Number (analysed/randomised): treatment group (not reported/40); control group (not reported/37) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Steroid pulse followed by oral prednisolone for 6 months, tonsillectomy, and ARB (candesartan) for 6 months Control group • Steroid pulse followed by oral prednisolone for 6 months and tonsillectomy Co-intervention • Among all patients in both groups who did not achieve remission of proteinuria at 12 months, candesartan was initiated and titrated until the 24 month visit
Outcomes	• Remission of proteinuria (<0.2 g/g Cr)

CAST-IgA 2015 *(Continued)*

	• Remission of haematuria
Notes	• Conference abstract • 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	Low risk	Outcome assessment was not reported. However, the study outcomes of interest were objectively measured, therefore this was adjudicated as low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

Chen 2002

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 18 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: severe IgAN, Lee SMK grade IV-V, with urinary protein >2.0 g/d, SCr < 355.2 µmol/L • Number (analysed/randomised): treatment group (not reported/31); control group (not reported/31) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • MMF 1.0 g/d (body weight <50 kg) or 1.5 g/d (body weight >50 kg), reduced to 0.75 to 1.00 g/d after 6 months, and maintained at 0.5 to 0.75 g/d after 12 months of treatment Control group

Chen 2002 *(Continued)*

	• Prednisone: 0.8 mg/kg/day Co-interventions • Not reported
Outcomes	• Proteinuria • Plasma albumin, serum cholesterol and triglycerides • Adverse events
Notes	• Conference abstract • Trials registration identification number: not reported • 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

Cheung 2018

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: intervention administered for 52 weeks; subjects will be followed for a further 12 months
Participants	• Setting: multicentre • Country: The UK • Inclusion criteria: biopsy-proven IgAN with persistent proteinuria (24 h urine protein excretion > 0.5 g) despite best supportive measures are at increased risk of progression to ESKD

Cheung 2018 *(Continued)*

- Number (analysed/randomised): not reported/21
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: Subjects with severely reduced kidney function

Interventions	Treatment group • Belimumab (Benlysta - IgG1 monoclonal antibody) given fortnightly then monthly by IV infusion at a dose of 10 mg/kg Control group • Placebo Co-interventions • ACEi or ARB
Outcomes	• Percent change from baseline in UPCR at week 52 • Change from baseline in eGFR at week 52 • Levels of poorly glycosylates IgA1, IgA1 immune complexes, pharmacodynamic biomarker • QoL
Notes	• Conference abstract • Trials registration identification number: not reported • Funding: 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
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Interpretation of subjective outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), infection, malignancy, ESKD, doubling of SCr, complete remission, SCr)
Other bias	Unclear risk	Insufficient information to permit judgement

Cruzado 2011

Methods	• Study design: parallel, 2-arm RCT • Time frame: July 2006 to August 2009 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (3 sites) • Country: Spain • Inclusion criteria: biopsy proven IgAN diagnosed in the previous 3 months; age 18- to 70-years old; absence of known hepatic, cardiac, pulmonary or intestinal disease; GFR estimated by Cockcroft-Gault formula within 30 to 60 mL/min/1.73 m^2; proteinuria >1 g/day; hypertension defined as SBP >140 mmHg or DBP >90 mmHg associated with proteinuria between 0.3 to 1 g/day • Number (analysed/randomised): treatment group (14/14); control group (9/9) • Mean age ± SD (years): treatment group (42 ± 11); control group (50 ± 9) • Sex (M/F): treatment group (12/2); control group (7/2) • Exclusion criteria: positive serology for HIV or hepatitis B virus infection or hepatitis C virus infection; treatment with steroids or any other immunosuppressant in the 2 previous years; evidence of active infection; pregnancy at the time of inclusion in the study; GFR < 30 mL/min/1.73 m^2; serum bilirubin > 2 mg/dL; ALT and AST 2 times higher than the normal upper limit; DM; poor controlled hypertension or evidence or suspicion of renovascular disease; thrombocytopenia < 100,000/mm^3 or total neutrophil counts < 2000/mm^3; triglycerides > 4.6 mmol/L; cholesterol > 7.8 mmol/L; LDL > 5.2 mmol/L; systemic IgAN forms, i.e. HSP, IgAN secondary forms; cases presented in the form of rapidly progressive kidney failure; extra capillary proliferation > 50% at renal biopsy; use of any other medication under research; cancer diagnosis in the 5 previous years, except suitably removed skin basal cell carcinoma; known intolerance to sirolimus or macrolides
Interventions	Treatment group • Sirolimus: initially 1 mg/day. Blood concentrations were monitored and the dose adjusted to be within 4 to 8 ng/mL Control group • Usual care Co-interventions • Enalapril (and other antihypertensive medications) to lower BP < 130/80 mmHg • Atorvastatin to lower total cholesterol levels < 4.2 mmol/L
Outcomes	• Variation of haematuria • Proteinuria • Change in the GFR • BP • Renal histology • Adverse events • ESKD ("dialysis-free")
Notes	• This research was performed in the context of The Red de Investigacio´n Renal (REDinREN, ISCIII 06/0016) • The study was approved by The Spanish Drug Agency

Risk of bias

Bias	Authors' judgement	Support for judgement

Cruzado 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Permuted-block randomisation with a block size of six and an allocation ratio of 1:1
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were available
Selective reporting (reporting bias)	Low risk	All relevant outcomes, except death, were reported
Other bias	High risk	Recruitment terminated early due to lack of recruitment (achieved recruitment of 23 out of 30 planned participants). Participants in control group were older (imbalance of baseline characteristics)

Frisch 2005

Methods	• Study design: parallel, 2-arm RCT • Time frame: recruitment between August 2000 and May 2003; follow-up stopped July 2003 • Duration of follow-up: 1 year treatment completion, total follow-up was 2 years
Participants	• Setting: single centre • Country: USA • Inclusion criteria: biopsy-proven IgAN; proteinuria >1 g/day plus at least two of the following risk factors: male sex, hypertension > 150/90 mmHg, CrCl < 80 mL/min, severe lesions on biopsy • Number (analysed/randomised): treatment group (17/17); control group (15/15) • Mean age, range (years): treatment group (39, 19 to 72); control group (37, 22 to 59) • Sex (M/F): treatment group (16/1); control group (11/4) • Exclusion criteria: aged < 18 or > 76 years; pregnant females and females unwilling to use contraception; presence of malignancy, infection, liver disease or SLE, HSP or other serious systemic disease; CrCl ≤ 20 mL/min; presence of other diagnosis on renal biopsy; received corticosteroids or other immunosuppressive agents < 6 months prior to randomisation; > 50% active crescents on biopsy
Interventions	Treatment group • MMF: 1000 mg twice/day for 52 weeks Control group • Placebo for 52 weeks Co-interventions

Frisch 2005 *(Continued)*

	• All patients received an ACEI or an ARB, or both at study entry and other antihypertensives were included as needed to maintain BP at optimal levels (target 130/80 mmHg). Due to their uncertain efficacy but lack of toxicity, patients were allowed to take fish oils at their own or at their physician's discretion
Outcomes	• ESKD requiring KRT • 50% increase in SCr • SCr decrease 0.5 mg/dL • Adherence • Remission of proteinuria • death (any cause) • Serious infection • Adverse events
Notes	• Study terminated after second scheduled interim analysis • Funding: "This study was supported in part by Roche Pharmaceuticals and the Glomerular Center at Columbia University as an investigator-initiated study (J.L. and G.A.), the NKF of NY/NJ under the Fred C. Trump Fellowship (J.L.), a KUFA fellowship (J.R.) and the Kidney Foundation of Canada (G.F.)." • Trials registration identification number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised using permuted blocks of four. Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Known only to the research pharmacy. Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and physicians were blinded to the therapy by use of identical capsules. Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Key outcomes were objective laboratory measures or clinical events and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were available
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	High risk	The study was terminated early after the second scheduled interim analysis done by the independent study monitor revealed a trend towards a worse outcome in the MMF group that would have made it highly unlikely to show a benefit for MMF given our rate of recruitment and our target sample size. Follow-up stopped in July 2003

Harmankaya 2002

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: median 60 months (range 12 to 120 months)
Participants	• Setting: single centre • Country: Turkey • Inclusion criteria: biopsy-proven IgAN and isolated haematuria and well-reserved kidney function (mean CrCl 89.2 ± 10.2 mL/min) • Number (analysed/randomised): treatment group (21/21); control group (22/22) • Mean age, range (years): treatment group (25, 13 to 42); control group (27, 17 to 63) • Sex (M/F): treatment group (15/6); control group (14/8) • Exclusion criteria: secondary causes of IgAN (SLE, HSP); hepatic disease
Interventions	Treatment group • Prednisolone: 40 mg/d for 2 months, reduced to 20 mg/d and then slowly tapered over 2 months • AZA: 100 mg/d for 4 months Control group • No treatment Co-interventions • Not reported
Outcomes	• ESKD • Renal histology • Adverse events
Notes	• Funding: not reported • Trials registration identification number: not applicable

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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all participant data were reported

Harmankaya 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Low risk	The study appears to be free of other sources of bias

Hirai 2017

Methods	• Study design: parallel, 2-arm RCT • Time frame: April 2009 to March 2016 (enrolment April 1, 2009 to March 31, 2013) • Duration of follow-up: 36 months
Participants	• Setting: multicentre (Saitama Medical Center, Jichi Medical University, Saiseikai Kawaguchi General Hospital, Saitama Social Insurance Hospital, and Dokkyo University Koshigaya Medicak Center, in Saitama, Japan) • Country: Japan • Inclusion criteria: biopsy-proven IgAN; urinary protein excretion > 0.5 g/day; age > 16 years • Number (analysed/randomised): treatment group (9/21); control group (15/21) • Mean age ± SD (years): treatment group (41.6 ± 14.7); control group (43.2 ± 19.4) • Sex (M/F): treatment group (13/8); control group (13/8) • Exclusion criteria: mizoribine hypersensitivity; leukocyte count < 3000/mm^3; pregnant patients or patients desiring to be pregnant; patients receiving KRT; and use of other immunosuppressants
Interventions	Treatment group • Mizoribine: 150 mg once/day for 12 months Control group • Usual care Co-interventions • Not reported
Outcomes	• Percentage reduction in urinary protein excretion • Haematuria • Disappearance of proteinuria • Clinical remission rate • Absolute changes in eGFR from baseline • Change in daily dose of prednisolone • Initiation of KRT • Malignancy
Notes	• Funding: not reported • Trials registration identification number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done at the registration centre of Jichi Medical University using a computer-based allocation program

Hirai 2017 *(Continued)*

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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	12/21 participants lost to follow up in mizoribine group (including for adverse events); 6/21 participants lost to follow up in control group. Imbalance in discontinuation between groups
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), ESKD, GFR loss, infection)
Other bias	Low risk	The study appears to be free of other sources of bias

Horita 2007

Methods	• Study design: parallel, 2-arm RCT • Time frame: 2000 to 2003 • Duration of follow-up: 24 months
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: normal BP of < 140/90 mmHg; MAP < 107 mmHg; persistent to moderate proteinuria (1.6 ± 0.5 g/d); normal or mild to moderately reduced but stable kidney function (CrCl > 50 mL/min/1.73 m^2); renal glomerular score 4 to 7 according to Katafuchi's scale • Number (analysed/randomised): treatment group (20/20); control group (18/20) • Mean age ± SD (years): treatment group (34 ± 12); control group (32 ± 10) • Sex (M/F): treatment group (12/8); control group (8/10) • Exclusion criteria: systemic diseases (DM); SLE; chronic liver disease; kidney allograft; HSP
Interventions	Treatment group • Prednisolone: 30 mg/dL for 2 months, 25 mg/dL for 2 months, 15 mg/dL for 6 months, 10 mg/dL for 12 months, 5 mg dL for 1 month • Losartan: 50 mg/d for 24 months Control group • Prednisolone: 30 mg/dL for 2 months, 25 mg/dL for 2 months, 15 mg/dL for 6 months, 10 mg/dL for 12 months, 5 mg dL for 1 month Co-intervention • Dipyridamole
Outcomes	• Complete remission • Urinary protein excretion

Horita 2007 *(Continued)*

	• CrCl • SCr • BP
Notes	• Funding: not reported • Trials registration identification number: 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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/22 patients dropped out of the prednisolone group due to postural hypotension
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), ESKD, GFR loss, infection)
Other bias	Low risk	The study appears to be free of other sources of bias

Hou 2017

Methods	• Study design: parallel, 2-arm RCT • Time frame: December 2010 to April 2013 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (5 sites) • Country: China • Inclusion criteria: biopsy-proven IgAN, with active proliferative lesions (cellular and fibrocellular crescents, endocapillary hypercellularity, or necrosis), proteinuria with protein excretion ≥ 1.0 g/24 hours, and eGFR > 30 mL/min/1.73 m^2 • Number (analysed/enrolled): treatment group (86/87); control group (88/89) • Mean age, range (years): treatment group (30.5, 25 to 37); control group (32.5, 25 to 43) • Sex (M/F): treatment group (39/47); control group (38/50) • Exclusion criteria: IgAN from a secondary cause and with eGFR < 30 mL/min/1.73 m^2
Interventions	Treatment group • MMF: 1.5 g/day for 6 months

Hou 2017 *(Continued)*

	Control group • Prednisone: 0.8 to 1 mg/kg/day for 2 months and then tapered by 20% each month for the next 4 months Co-interventions • Prednisone (0.4 to 0.6 mg/kg/day) for 2 months and then tapered by 20% each month for the next 4 months and stopped at 6 months
Outcomes	• Complete remission (proteinuria becoming undetectable, with a stable SCr level (defined as not > 25% above the baseline) • Partial remission (protein excretion > 0.4 to < 1.0 g/24 hours, serum albumin level ≥ 35 g/L, and stable SCr level (defined as not > 25% above baseline) • Relapse (remission (complete or partial) followed by proteinuria with protein excretion > 1.0 g/24 hours on 2 consecutive measurements)
Notes	• The trial was funded by the National Key Technology R&D Program (2013BAI09B04, 2015BAI12B05) • Trials registration identification number: nCT01269021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Hangzhou Tigermed Consulting Co Ltd created the randomisation list
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered concealed envelopes containing group assignments were provided to investigators. Not stated if envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes were adjudicated by an independent Clinical End Points Committee, blinded to the treatment regimen
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/87 in treatment group not included in primary analysis. 1/89 in control group not included in primary analysis
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), ESKD, GFR loss, infection)
Other bias	Low risk	The study appears to be free of other sources of bias

Julian 1993

Methods	• Study design: parallel, 2-arm RCT • Time frame: started March 1990 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (6 sites)

Julian 1993 *(Continued)*

- Country: USA
- Inclusion criteria: IgAN; CrCl > 25 mL /min/1.73 m^2
- Number (analysed/randomised): not reported/35
- Mean age ± SD (years): women (34 ± 3); men (39 ± 3)
- Sex (M/F): 26/9
- Exclusion criteria: IgA disease secondary to other causes (HSP, SLE, celiac disease, liver disease); DM; cataracts; osteonecrosis; active peptic ulcer disease; pregnancy

Interventions	Treatment group • Alternate-day prednisone: 60 mg for 3 months, 40 mg for 3 months, 30 mg for 6 months, 25 mg for 3 months, 20 mg for 3 months, 15 mg for 3 months, 10 mg for 3 months Control group • No treatment Co-interventions • Not reported
Outcomes	• Change in kidney function (reciprocal of SCr) • SCr • Urinary protein excretion • Adverse events • Kidney failure
Notes	• Preliminary findings only reported • Funding: "This work was supported in part by the National Institute of Health, grant number AI-1875 and DK 40177." • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	This is a preliminary report - only 3 patients had completed the full 2 year study; 24 remain in the study and 21 of these have completed at least 6 months and 16 have completed 12 months

Julian 1993 *(Continued)*

Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection)
Other bias	Unclear risk	Insufficient information to permit judgement. Methods of randomisation, baseline characteristics were not reported to assess quality of randomisation

Kanno 2003

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 3 years
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: biopsy-proven IgAN, aged 12 to 65 years • Number (analysed/randomised): treatment group (6/8); control group (4/7) • Mean age ± SD (years): treatment group (30 ± 5); control group (37 ± 5) • Sex (M/F): treatment group (7/1); control group (5/2) • Exclusion criteria: not reported
Interventions	Treatment group • Prednisolone 0.5 mg/kg/day for approximately 1 month, when a 10% taper was instituted until the dose reached 0.12 mg/kg/day; for 36 months Control group • Warfarin: 5 mg given for the first 2 days with further doses adjusted according to the value of the thrombotest, targeting around 30% Co-interventions • Not reported
Outcomes	• Urinary protein excretion • SCr
Notes	• Funding: not reported • Trials registration identification number: not applicable

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

Kanno 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	5/15 patients did not complete study (2 in the treatment group and 3 in the control group)
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection)
Other bias	Low risk	The study appears to be free of other sources of bias

Katafuchi 2003

Methods	• Study design: parallel, 2-arm RCT • Time frame: July 1991 to September 1995 • Duration of follow-up: 60 months
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: biopsy-proven IgAN; aged < 60 years; SCr ≤ 1.5 mg/dL • Number (analysed/randomised): treatment group (43/49); control group (47/54) • Mean age ± SD (years): treatment group (33.6 ± 13.4); control group (32.5 ± 10.8) • Sex (M/F): treatment group (15/28); control group (22/25) • Exclusion criteria: previous treatment with steroids; pregnancy; HPS; SLE; DM; neoplasia; active peptic ulcer disease; viral hepatitis; other infection
Interventions	Treatment group • Prednisolone: 20 mg/day for 1 month, 15 mg/day for 1 month, 10 mg/day for 1 month, 7.5 mg/day for 3 months, 5 mg/day for 18 months • Dipyridamole: 150 or 300 mg/day Control group • Dipyridamole: 150 or 300 mg/day Co-interventions • Not reported
Outcomes	• ESKD • Urinary protein excretion • SCr • CrCl
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement

Katafuchi 2003 *(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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	6/49 participants lost to follow up in intervention group; 7/54 participants lost to follow up in control group
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), malignancy, infection)
Other bias	Low risk	The study appears to be free of other sources of bias

Kawamura 2014

Methods	• Study design: parallel, 2-arm RCT • Time frame: April 2005 to March 2010 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (18 sites) • Country: Japan • Inclusion criteria: biopsy-proven IgAN; aged 10 to 69 years; urinary protein excretion 1.0 to 3.5 g/day; SCr ≤ 1.5 mg/dL; a histological grade diagnosed as a relatively good prognosis, a relatively poor prognosis, or a poor prognosis in the classification proposed in 2004, and SBP < 140 mmHg and DBP < 90 mmHg • Number (analysed/randomised): treatment group (33/40); control group (39/40) • Mean age ± SD (years): treatment group (36 ± 13); control group (40 ± 13) • Sex (M/F): treatment group (17/16); control group (18/21) • Exclusion criteria: nephrotic syndrome; SCr of > 1.5 mg/dL, recent treatment with corticosteroids and/or immunosuppressive agents, and contraindications for general anaesthesia and/or tonsillectomy as assessed by otolaryngologists
Interventions	Treatment group • Patients underwent tonsillectomy and subsequently received 0.5 g/day of IV methylprednisolone for 3 consecutive days at 1 to 3 weeks later and then at 2 and 4 months later Control group • Steroid pulse therapy only Co-interventions • Oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months

Kawamura 2014 *(Continued)*

Outcomes	• Percentage decrease in urinary protein excretion from baseline • Frequency of the disappearance of proteinuria and/or haematuria 12 months after the initial treatment • Change in GFR • Doubling of SCr from baseline • 50% decrease in eGFR from baseline • KRT • Adverse effects
Notes	• The study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research (Research on Intractable Disease) from the Ministry of Health, Labour and Welfare of Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by a technical assistant in the registration centre using a computer-based allocation program with a minimisation method, which was developed by an outside company
Allocation concealment (selection bias)	High risk	Allocation was based on the presence or absence of tonsillectomy
Blinding of participants and personnel (performance bias) All outcomes	High risk	Since the allocation was based on the presence or absence of tonsillectomy, neither the patients nor the physicians were blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although those assessing the outcomes were not blinded, they assessed the data regarding the pre-defined outcomes using pre-specified statistical analyses. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), infection) were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Kim 2013b

Methods	• Study design: parallel, 2-arm RCT • Time frame: November 2010 to June 2011 • Duration of follow-up: 4 months
Participants	• Setting: single centre • Country: Korea • Inclusion criteria: biopsy-proven IgAN; aged ≥ 18 and < 70 years; SCr ≤1.5 mg/dL or eGFR ≥ 45 mL/min/1.73 m^2, UACR ≥ 0.3 and < 3.0 g/g creatinine, and BP < 130/80 mmHg during the 3-month period before randomisation

Kim 2013b *(Continued)*

- Number (analysed/randomised): treatment group (20/20); control group (20/20)
- Mean age ± SD (years): treatment group (36.9 ± 11.4); control group (40.1 ± 12.8)
- Sex (M/F): treatment group (6/14); control group (6/20)
- Exclusion criteria: ≥ 20% variations of BP, urinary albumin, SCr during 3 months before randomisation, or with potassium sparing diuretics, corticosteroid, immunosuppressive medication, omega-3 fatty acid, or two or more medications of renin angiotensin system blocker (RAS blocker), pregnancy, secondary IgAN

Interventions	Treatment group • Tacrolimus: 0.1 mg/kg/day administered in two divided doses and titrated to maintain trough concentrations at 5 to 10 ng/mL. If concentration ≥ 15 ng/mL the tacrolimus was stopped for 2 weeks. After 8 weeks of randomisation, the dose of tacrolimus was reduced to 0.05 mg/kg/day or to half of the decided dose to maintain the trough level in 5 to 10 ng/mL at the 8-week visit and continued this up to 16 weeks after randomisation Control group • Placebo Co-interventions • Not reported
Outcomes	• Percentage change (from the trial phase to the observational phase) of time-averaged proteinuria (TA-proteinuria; g/g creatinine) • eGFR • Complete remission • Doubling of SCr • Adverse events
Notes	• Trials registration identification number: NCT01224028 • This study was designed and supported by Astellas Pharma Korea

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Conducted by the independent statistical committee (independent from the researcher (doctors, nurses, and pharmacists related to this study) and patients))
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/20 participants assigned to tacrolimus did not complete study. 1/20 participants assigned to control did not complete study

Kim 2013b *(Continued)*

Selective reporting (reporting bias)	High risk	The reported study outcomes matched the outcomes reported in the published study protocol (published with the study). Key outcomes expected for this type of study (death (any cause), ESKD, change in GFR, infection) were not reported
Other bias	Low risk	The study appeared to be free from other sources of bias

Kobayashi 1996

Methods	• Study design: parallel, 2-arm quasi-RCT • Time frame: April 1972 to December 1983 (patient diagnosis) • Duration of follow-up: 10 years
Participants	• Setting: single renal unit • Country: Japan • Inclusion criteria: primary diagnosis of IgAN, proteinuria between 1 to 2 g/d; CrCl ≥ 70 mL/min; histological severity score ≥ 7 • Number (analysed/randomised): treatment group (20/31); control group (26/59) • Mean age ± SD (years): treatment group (30 ± 7); control group (33 ± 10) • Sex (M/F): treatment group (12/8); control group (12/14) • Exclusion criteria: not reported
Interventions	Treatment group • Prednisolone: 40 mg/d for 3 weeks, 30, 25 and then 20 mg/d for 8 weeks; maintained at 15 mg/d for 6 months and then further tapered (most of the patients received steroid therapy for 18 months) • Antithrombocyte drugs were prescribed after discontinuation of steroid therapy until final observation Control group • Antithrombocyte drugs until final observation Co-interventions • Not reported
Outcomes	• ESKD • CrCl • Urinary protein excretion
Notes	• Funding: supported by grants from the Ministry of Health and Welfare, Japan • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospectively divided into two groups according to the order of renal biopsy
Allocation concealment (selection bias)	High risk	Prospectively divided into two groups according to the order of renal biopsy. This is a quasi-randomised study design

Kobayashi 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	11/31 patients in the treatment group and 33/59 patients from the control group were excluded from the analyses
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), malignancy, infection) were not reported
Other bias	High risk	The participants received differential prescribing of anti-thrombotic drugs during follow-up. There was imbalance in sex and history of hypertension at baseline

Koike 2008

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: IgAN on renal biopsy (mild inflammatory activities, presence of cellular and/or fibrocellular crescents, mesangial interposition with mononuclear cell infiltration and interstitial inflammatory cell infiltration) • Number analysed/randomised: treatment group (24/24); control group (24/24) • Mean age ± SD (years): treatment group (37.9 ± 10.1); control group (38.3 ± 12.7) • Sex (M/F): treatment group (6/18); control group (5/19) • Exclusion criteria: systemic diseases, such as DM, collagen disease, abnormal hyper gamma globulinaemia and chronic liver disease
Interventions	Treatment group • Prednisolone: 0.4 mg/kg/d for 4 weeks, and the dose was gradually reduced to 10 to 20 mg on alternate days for the next 12 months, and then 5 to 10 mg on alternate days for a subsequent year. When the treatment was effective, alternate-day prednisolone 5 to 10 mg administration was continued during the next follow-up period. When the treatment was not effective, the dose was further reduced to discontinuation • Dipyridamole or dilazep hydrochloride: 150 or 300 mg/d for 24 months Control group • Dipyridamole or dilazep hydrochloride: 150 or 300 mg/d for 24 months Co-interventions • ACEi
Outcomes	• Urinary protein excretion • SCr

Koike 2008 *(Continued)*

	• Haematuria • BP
Notes	• Funding: not reported • Trials registration identification number: 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	Quote: "Two doctors who did not know the histological scores randomly assigned the patients to either the steroid or control group. The doctors used two envelopes consisting of A (steroid group) or B (control group) and containing study instructions"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind due to the tapering of the prednisolone
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in study follow-up
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), malignancy, infection) were not reported
Other bias	High risk	Co-intervention with antihypertensive therapy was imbalanced between groups (administered to intervention group participants only). There was imbalance in kidney function between groups (the control group participants had a higher mean SCr)

Koitabashi 1996

Methods	• Study design: parallel, 4-arm RCT • Time frame: November 2010 to June 2011 • Duration of follow-up: 4 months
Participants	• Setting: multicentre (40 sites) • Country: Japan • Inclusion criteria: IgAN; aged < 15 years; no administration of steroids nor immunosuppressive drugs; no functionally disordered; diffuse proliferative GN • Number (analysed/randomised): 115/not reported • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1

Koitabashi 1996 *(Continued)*

	• Chinese medicine (Saireito) in children with minor renal histology abnormalities or focal and segmental proliferative GN Treatment group 2 • No treatment in children with minor renal histology abnormalities or focal and segmental proliferative GN Treatment group 3 • Prednisolone + AZA + anticoagulants + dipyridamole in children with diffuse proliferative GN Control group • Anticoagulants + dipyridamole in children with diffuse proliferative GN Co-intervention: not reported
Outcomes	• Proteinuria • Haematuria • Kidney function • Renal histopathological findings
Notes	• Conference abstract • Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement

Lafayette 2017

Methods	• Study design: parallel, 2-arm RCT • Time frame: February 2009 to September 2015 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (number of sites not reported) • Country: USA • Inclusion criteria: aged 18 to 70 years old, with biopsy-proven IgAN shown within 2 years of enrolment • Number (analysed/randomised): treatment group (14/17); control group (15/17) • Mean age, range (years): treatment group (43, 29 to 63); control group (33, 21 to 59) • Sex (M/F): treatment group (10/7); control group (15/2) • Exclusion criteria: biopsy showed > 50% glomerular sclerosis or interstitial fibrosis or > 10% glomerular crescents; patients with secondary forms of IgAN, such as cirrhosis; previously received rituximab, were receiving other immunosuppressive therapy, or had ever received > 6 months of prednisone or other systemic corticosteroid therapy in the past
Interventions	Treatment group • Rituximab: 1 g infusion followed by an identical dose 2 weeks later. They received an identical 2 g course of rituximab 6 months later Control group • Usual care Co-interventions • Fish oil supplements were required at a minimal dose of 3 g/day plus acetaminophen (1 g) and diphenhydramine HCl (50 mg) by mouth from 30 to 60 minutes before the start of an infusion. Premedication with corticosteroids (10 mg IV dexamethasone) was also given 30 minutes before the first infusion of each series of rituximab
Outcomes	• Change in proteinuria and eGFR at 12 months • Adverse events • Infusion-related reactions • Hypogammaglobulinaemia • Infections
Notes	• This study was sponsored by Genentech/Roche, Inc. and the Fulk Family Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Central randomisation
Allocation concealment (selection bias)	Unclear risk	Random assignment by prefilled envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. As the treatment assignment was unblinded and the outcomes included adverse events and re-

Lafayette 2017 *(Continued)*

		actions to the infusions, it is possible that outcome assessment was influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	2/17 drop-out in control group; 2/17 drop-out in rituximab group + 1 patient randomised but treatment not given
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	High risk	Different use of co-interventions (acetaminophen and diphenhydramine plus dexamethasone with rituximab infusion). There was imbalance in age, race, SCr, eGFR, and proteinuria between treatment groups

Lai 1986

Methods	• Study design: parallel, 2-arm quasi-RCT • Time frame: July 1977 to December 1984 • Duration of follow-up: the mean study period was 38 months (12 to 106)
Participants	• Setting: single centre • Country: Hong Kong • Inclusion criteria: Chinese nephrotic patients with biopsy-proven IgAN • Number analysed/randomised: treatment group (17/17); control group (17/17) • Mean age ± SD (years): treatment group (28.9 ± 7.9); control group (26.9 ± 8.6) • Sex (M/F): treatment group (10/7); control group (7/10) • Exclusion criteria: Systemic lupus nephritis; Henoch Schonlein Purpura; hepatic disease
Interventions	Treatment group • Prednisolone/prednisone: 40 to 60 mg/d for 2 months, then 1/2 dose for 2 months Control group • No treatment Co-interventions • Not reported
Outcomes	• SCr • CrCl • Urinary protein excretion
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

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

Lai 1986 *(Continued)*

Allocation concealment (selection bias)	High risk	The patients were divided into two groups according to the treatment regime
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were available
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	High risk	Imbalance between groups at baseline (SCr higher in control group, CrCl lower in control group, urinary protein excretion lower in control group)

Lai 1987

Methods	• Study design: parallel, 2-arm quasi-RCT • Time frame: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Hong Kong • Inclusion criteria: 16 to 60 years, IgAN for 12 months or more diagnosed on renal biopsy; proteinuria ≥ 1.5 g/day • Number analysed/randomised: treatment group (9/11); placebo group (10/11) • Mean age ± SEM (years): treatment group (33.1 ± 1.4); placebo group (38.7 ± 4.1) • Sex (M/F): treatment group (4/5); placebo group (6/4) • Exclusion criteria: CrCl < 50 mL/min/1.73 m^2; previous therapy with cytostatic agents such as anti-lymphocyte globulin; corticosteroid therapy within four weeks prior to the study; thrombo-embolic diseases; active infection; malignancy; uncontrolled hypertension; impaired liver function; history of epilepsy; concomitant treatment with nephrotoxic drugs
Interventions	Treatment group • Cyclosporin: 5 mg/kg/day in 2 equal doses for 12 weeks. Titrated to whole blood concentrations and dose adjusted if changes in SCr Control group • Placebo: matched; 0.05 mL/kg/d Co-interventions • Nadolol to maintain BP < 150/90 mmHg
Outcomes	• Urinary protein excretion • CrCl

Lai 1987 *(Continued)*

	• SCr
Notes	• Funding: "...supported by a grant from the Croucher Foundation. We thank Dr B von Graffenreid, immunology department, Sandoz Pharmaceuticals, Basle, Switzerland, for giving us the placebo." • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Computer generated. However, "All patients were given a number in the trial based on their order of entry"
Allocation concealment (selection bias)	High risk	All patients were given a number in the trial based on their order of entry, which determined their allocation to the treatment or placebo group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Initially blinded however "We decided to reduce the dose of cyclosporin by 20% if plasma creatinine concentration exceeded 25% of the baseline value or the plasma cyclosporin trough concentration (concentration measured 12 hours after administration) reached 150 µg/l (evaluated by radioimmunoassay with a Sandoz kit). Similarly we decided to increase the dose of cyclosporin by 20% if the plasma cyclosporin trough concentration fell below 45 µg/l."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The patients were interviewed by telephone weekly about any side effects. Interpretation of subjective outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcomes were reported for 9 participants in cyclosporin group and 10 participants in placebo group. However, in a secondary publication, there were 11 participants allocated to each treatment group
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	High risk	Imbalance in baseline characteristics (age, plasma creatinine, urinary protein)

Lee 2003

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: combination group was followed up for 28 months, ARB group was followed up for 30 months
Participants	• Setting: not reported • Country: Korea • Inclusion criteria: IgAN and proteinuria ≥ 1.0 g/d and SCr (SCr) ≤ 1.3 mg/dL • Number (analysed/randomised): treatment group (not reported/12); control group (not reported/11) • Mean age ± SD (years): treatment group (32.3 ± 8.4); control group (33.7 ± 10.4) • Sex (M/F): treatment group (5/7); control group (5/6) • Exclusion criteria: not reported
Interventions	Treatment group: • Combination therapy of steroid: daily high-dose for 6 months

Lee 2003 *(Continued)*

	• ARB Control group: • ARB alone therapy Co-interventions • Not reported
Outcomes	• 24h proteinuria • Complete remission • Decline of renal function
Notes	• Korean paper; abstract in English • Trials registration identification number: 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	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)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Liu 2010a

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: adults with biopsy-proven IgAN manifesting with nephrotic syndrome • Number analysed/randomised: treatment group (20/20); control group (20/20) • Mean age ± SD (years): treatment group (30.4 ± 16.2); control group (32.1 ± 14.6)

Liu 2010a *(Continued)*

- Sex (M/F): treatment group (10/10); control group (11/9)
- Exclusion criteria: SCr > 442 µmol/L; abnormal liver function or severe infection; poor compliance; pregnancy or lactation

Interventions	Treatment group • Prednisone: 0.8 mg/kg/day • Leflunomide: 50 mg/day for the first 3 days and then 20 mg/day Control group • Prednisone: 0.8 mg/kg/day • MMF: 1.5 g/d for the first 3 months and then 1 g/day Co-interventions • Not reported
Outcomes	• Urinary protein excretion • Creatinine • Cholesterol • Adverse events
Notes	• Funding: not reported • Trials registration identification number: 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drug withdrawal or termination occurred in any of the patients in the two groups
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), infection, ESKD) were not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Liu 2014

Methods	• Study design: parallel, 2-arm RCT • Time frame: January 2008 to November 2010 • Duration of follow-up: at least 12 months (12-60 months)
Participants	• Setting: single centre • Country: China • Inclusion criteria: adults with biopsy-proven IgAN; aged 18 to 69 years; urinary protein excretion > 1.0 g/24 hours; eGFR > 30 mL/min/1.73 m^2 • Number analysed/randomised: treatment group (25/26); control group (23/25) • Mean age ± SD (years): treatment group (36.84 ± 8.06); control group (42.39 ± 13.10) • Sex (M/F): treatment group (12/13); control group (10/13) • Exclusion criteria: IgAN with severe chronic tubulointerstitial damage or crescentics formation of 50% of the glomeruli; IgAN with minimal change syndrome; secondary IgAN, such as that due to lupus nephritis, Henoch-Schonlein purpura or hepatitis B virus (HBV)-associated glomerulonephritis; consecutive treatment for more than three months with corticosteroids or immunosuppressive drugs within the previous one year; DM; severe uncontrolled hypertension (a diastolic BP of 120 mmHg); severe liver disease; pregnancy or lactation; and an known allergy or intolerance to the study medication
Interventions	Treatment group • Cyclosporin A: 12 month course of cyclosporin A began with a dose of 3 mg/kg/day (before meals, the highest dose was 200 mg/d). The dose was reduced by 25% when the SCr level increased by more than 25% of the baseline value. Twelve weeks later, the dose was gradually reduced by 50 mg every month then maintained at a maintenance dose of 25 mg/d. • Methylprednisolone: at the same time, the patients were given a medium dose of methylprednisolone of 0.4 mg/kg/d (the highest dose was 36 mg/d) orally for 8 weeks, after which the dose was tapered by 4 to 8 mg every 2 weeks to a maintenance dose of 4 mg/d or 4 mg every other day Control group • Methylprednisolone alone: 0.8 mg/kg/d, the highest dose was 48 mg/d) orally for 8 weeks. The dose was then reduced by 4 to 8 mg every 2 weeks until reaching a maintenance dose of 4 mg/d or 4 mg every other day Co-interventions (both groups) • Losartan: 50 mg/day • Dipyridamole: 50 mg/day
Outcomes	• Complete remission • Decrease in eGFR • Relapse in proteinuria • Severe adverse effects
Notes	• This study was funded by the Ministry of Science and Technology of the People's Republic of China (2011BAJ18B03) • Trials registration identification number: 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

Liu 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Three patients were lost to follow-up (one from the steroid group, two from the combination group), and two patients in the combination group discontinued cyclosporin A after three months of treatment due to severe pulmonary infections. After six months of treatment, one patient in the steroid group without a response to treatment was converted to cyclosporin A
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), infection, ESKD) were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Locatelli 1999

Methods	• Study design: parallel, 2-arm RCT • Time frame: May 1998 to January 2005 (enrolment December 1999 to November 2005) • Duration of follow-up: 7 years
Participants	• Setting: multicentre (27 sites) • Country: Italy, Switzerland • Inclusion criteria: IgAN; CrCl ≤ 2.0 mg/dL and proteinuria ≥1.0 g/d for at least 3 months • Number (analysed/randomised): treatment group (13/20); control group (22/26) • Mean age, range (years): treatment group (43.0, 32.6 to 52.4); control group (37.3, 32.7 to 52.3) • Sex (M/F): treatment group (17/3); control group (20/6) • Exclusion criteria: steroid or cytotoxic drug treatment during the previous 3 years; contraindications to steroids or AZA; evidence of systemic disease; diabetes; severe hypertension; extra capillary proliferation > 20%

Interventions	Treatment group
	• AZA: 1.5 mg/kg/day
	• Corticosteroids
	  * Methylprednisolone: 1 g IV for 3 consecutive days in months 1, 3, 5
	  * Prednisone: 0.5 mg/kg/d every other day
	Control group
	• Corticosteroids
	  * Methylprednisolone: 1 g IV for 3 consecutive days in months 1, 3, 5
	  * Prednisone: 0.5 mg/kg/d every other day
	Co-interventions
	• Not reported

Outcomes	• ESKD • Renal survival (time to 50% increase in SCr)

Locatelli 1999 *(Continued)*

	• Proteinuria • Adverse events
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Two centralised, computer-generated randomisation lists (1 for each stratum)
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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	7/20 participants allocated to steroids and AZA did not complete follow up (6 due to side effects); 4/26 participants allocated to steroids only did not complete follow up (4 due to side effects)
Selective reporting (reporting bias)	Low risk	All relevant outcomes, except mortality, were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lou 2006

Methods	• Study design: parallel, 2-arm RCT • Time frame: November 2001 to November 2003 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: 18 to 65 years with biopsy-proven IgAN; proteinuria > 1.0 g/day and < 3.0 g/day; SCr < 354 µmol/L • Number (analysed/randomised): treatment group (23/25); control group (23/24) • Mean age ± SD (years): treatment group (29 ± 11); control group (34 ± 11) • Sex (M/F): treatment group (8/16); control group (10/12) • Exclusion criteria: acute GN; secondary IgAN (e.g. HSP); obvious liver dysfunction; pregnancy; use of other immunosuppressive agent; renal artery stenosis; hyperkalaemia
Interventions	Treatment group • Leflunomide: loading dose of 60 mg/day for 3 days then 20 mg/day for 6 months. If complete remission occurred, the dose could be reduced to 10 mg/day

Lou 2006 *(Continued)*

	Control group • Fosinopril: Dose not reported Co-interventionS • BP lowering to maintain BP < 125/75 mmHg (calcium channel blocker, beta-blocker)
Outcomes	• Complete remission: 24-hour proteinuria < 0.3 g, serum albumin increased to normal levels (> 35 g/L) and kidney function remained normal) • Partial remission: 24-hour proteinuria decreased more than 50% and kidney function improved • Effective: decline of 24-hour proteinuria by more than 25%, but less than 50%, and improvement in kidney function • Deterioration: kidney function declined more than 30% and proteinuria increased more than 30% from basal levels • eGFR • Adverse events
Notes	• Funding: not reported • Trials registration identification number: 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients were lost to follow up (one was from experimental group, one from control group), one withdrew from study because of side-effects."
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), infection, ESKD) were not reported
Other bias	High risk	Imbalance in baseline characteristics suggesting problems with randomisation. Control treatment and balance of co-interventions not reported adequately

Lv 2009

Methods	• Study design: parallel, 2-arm RCT • Duration of study: January 2004 to September 2006

Lv 2009 *(Continued)*

	• Duration of follow-up: 48 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: biopsy-proven IgAN aged 18 to 65 years; proteinuria 1 to 5 g/d on 3 consecutive measurements 4 to 6 weeks apart; eGFR > 30 mL/min/1.73 m^2 • Number (analysed/randomised): treatment group (31/33); control group (29/30) • Mean age ± SD (years): treatment group (27.8 ± 8.9); control group (30.43 ± 8.8) • Sex (M/F): treatment group (20/13); control group (19/11) • Exclusion criteria: treatment with steroids or cytotoxic drugs during the previous year; pregnancy or planning pregnancy; HSP; DM; neoplasia; active peptic ulcer disease; viral hepatitis; infection
Interventions	Treatment group • Prednisone: 0.8 to 1.0 mg/kg/day, for 8 weeks, then the dose was tapered by 5 to 10 mg every 2 weeks • Cilazapril: 5 mg/day for 24 months Control group • Cilazapril: 5 mg/day for 24 months Co-interventions • Not reported
Outcomes	• ESKD (CKD stage 5) • Remission of proteinuria • 25% decrease in eGFR • 50% increase in SCr • Mean arterial pressure • Urine protein excretion • 50% decrease in protein excretion • Major adverse events • Serious infections
Notes	• Funding: "This work was funded by the National Natural Science Foundation of China (Grant No. 30670981), the Foundation of Ministry of Education (985-2-2007-113), and National Key Technology R & D Progression (2007 BAI04B10), People's Republic of China." • Trials registration identification number: NCT00378443

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation code
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)	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowl-

Lv 2009 *(Continued)*

All outcomes		edge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/33 participants withdrawn from combination group and 1/30 withdrawn from control group
Selective reporting (reporting bias)	Low risk	All relevant outcomes that would be expected in a study of this type, except mortality, were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Maes 2004

Methods	• Study design: parallel, 2-arm RCT • Time frame: October 1997 to December 1999 • Duration of follow-up: 3 years
Participants	• Setting: single centre • Country: Belgium • Inclusion criteria: aged >18 years; biopsy-proven IgAN in conjunction with decreased kidney function at diagnosis and/or proteinuria > 1 g/d/1.73 m^2, and/or arterial hypertension, and/or prognostic unfavourable criteria • Number (analysed/randomised): treatment group (18/21); placebo group (11/13) • Mean age ± SD (years): treatment group (39 ± 11); placebo group (43 ± 15) • Sex (M/F): not reported • Exclusion criteria: rapidly progressive IgAN; other kidney diseases; systemic diseases (SLE, Goodpasture syndrome, vasculitis); intake of other immunosuppressive drugs or any study drug during the last 6 months; pregnant or lactating women or women with childbearing potential using no effective contraceptives; malignancy, active central nervous/hepatic/metabolic/cardiovascular/gastrointestinal diseases; psychiatric antecedents; ongoing or latent infections; leucopenia (< 3000/mm^3) or thrombocytopenia (< 75,000/mm^3) or a contraindication for the use of ACEi
Interventions	Treatment group • MMF 2 g/day for 3 years (decreased doses if intolerance or leucopenia/thrombocytopaenia) Control group • Placebo: identical lactose-containing capsule Co-interventions • Not reported
Outcomes	• ESKD • 25% reduction in measured GFR • SCr increase by 50% or more • Urinary protein excretion • Death • Adverse effects • Measured GFR (inulin clearance) • SCr • Haematuria • SBP/DBP

Maes 2004 *(Continued)*

	• Adherence • Adverse effects (infection/gastrointestinal/leucopenia/cancer)
Notes	• Funding: "B. Maes is the holder of the Janssen-Cilag Chair for Nephrology at the University of Leuven. The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland." • Trials registration identification number: not applicable

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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Several dropouts and exclusions: treatment group (ESKD (2), adverse events (1), emigration (2)); control group (death (1), adverse events (1))
Selective reporting (reporting bias)	Low risk	All relevant outcomes expected for this type of study were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Manno 2001

Methods	• Study design: parallel, 2-arm RCT • Time frame: June 2000 to June 2004 • Duration of follow-up: At least 3 years (median 5 years)
Participants	• Setting: multicentre (14) • Country: Italy • Inclusion criteria: biopsy-proven IgAN aged 16 to 70 years; proteinuria ≥ 1.0 g/ay for at least 2 months; eGFR ≥ 50 mL/min/1.73 m^2 • Number (analysed/randomised): treatment group (45/48); control group (46/49) • Mean age ± SD (years): treatment group (31.8 ± 11.3); control group (34.9 ± 11.2) • Sex (M/F): treatment group (33/15); control group (35/14) • Exclusion criteria: treatment with corticosteroids or immunosuppressive drugs in the previous 2 years; acute myocardial infarction or stroke in the previous 6 months; severe uncontrolled hypertension; evidence or suspicion of renovascular disease, insulin-dependent DM; infections; severe liver diseases; malignancies; active peptic-ulcer disease; secondary IgAN or relapse in kidney transplant; pregnancy;

Manno 2001 *(Continued)*

	other contraindications to corticosteroids or ACEi; alcohol abuse; patients with fibrinoid necrosis lesions at biopsy
Interventions	Treatment group • Prednisone: 1.0 mg/kg/d for 2 months and then the dose was tapered by 0.2 mg/kg/day every month for a total of 6 months of therapy • Ramipril: started at a dose of 2.5 mg/day and was then increased by 1.25 mg/day every month to achieve and maintain a SBP and DBP < 120/80 mmHg and to reduce 24-hour proteinuria to ≤ 1.0 g for 24 months Control group • Ramipril: started at a dose of 2.5 mg/day and was then increased by 1.25 mg/day every month to achieve and maintain a SBP and DBP < 120/80 mm Hg and to reduce 24-hour proteinuria to ≤ 1.0 g for 24 months Co-intervention • If necessary, some patients received diuretics, antihypertensives, antacids and anti ulcer medication, and antidiabetic drugs. No antiplatelet, antiinflammatory and other immunosuppressive drugs were administered. The patients were advised to limit their daily sodium intake and to eat no more than 1.0 g of protein/kg/day. Dietary adherence was assessed by measuring 24-hour urinary sodium and urea excretion
Outcomes	• ESKD • Doubling of baseline SCr • Rate of kidney function decline/year • BP • Remission of proteinuria (< 1 g/day) • Adverse effects
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An allocation assignment sequence was generated at the coordinating centre by random number tables; a list divided into blocks of 10 was adequately concealed to prevent attempts to subvert randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "Central telephone randomisation for every eligible patient was performed by the Scientific Secretariat."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed for the primary outcome

Manno 2001 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes, except death (any cause), was reported
Other bias	Unclear risk	The study appeared to be free of other sources of bias. Non-random block allocation may have led to prediction of treatment within centres

Masutani 2016

Methods	• Study design: parallel, 2-arm RCT • Time frame: November 2006 to April 2010 • Duration of follow-up: 25 months
Participants	• Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: biopsy-proven primary IgAN, aged 15–59 years, and with a previously reported glomerular score of 5 or higher determined by scoring method • Number (analysed/randomised): treatment group (20/20); control group (20/20) • Mean age ± SD (years): treatment group (43.8 ± 10.8); control group (36.4 ± 12.9) • Sex (M/F): treatment group (11/9); control group (11/9) • Exclusion criteria: secondary IgAN caused by lupus nephritis, purpura nephritis (IgA vasculitis), rheumatoid arthritis, viral hepatitis, or liver cirrhosis; previous treatment with corticosteroids, mizoribine or other immunosuppressants; DM; viral hepatitis; malignant tumour; pregnancy; active infectious disease; white blood cell count < 3000/μL; and known allergy to the study medication
Interventions	Treatment group • Prednisolone: 500 mg IV methylprednisolone for 3 days in weeks 1 and 2, followed by 30 mg/day oral prednisolone for 2 weeks. The prednisolone dose was then reduced by 2.5 to 5.0 mg for 12 months until 5 mg/day which was the maintenance dose for 13 months • Mizoribine: started at 150 mg/day when the daily dose of prednisolone was 20 mg, and continued for 24 month. Blood levels of mizoribine were measured at 2 or 4 weeks after initial administration, and the concentration level after 3 h (C3 level) confirmed was within the range of 1.0 to 5.0 μg/mL Control group • Prednisolone: 500 mg IV methylprednisolone for 3 days in weeks 1 and 2, followed by 30 mg/day oral prednisolone for 2 weeks. The prednisolone dose was then reduced by 2.5 to 5.0 mg for 12 months until 5 mg/day which was the maintenance dose for 13 months Co-interventions • RAS inhibitors were used when BP > 130/80 mmHg • Tonsillectomy offered as optional treatment
Outcomes	• Reduction of urinary protein defined as ≥ 50% decrease • Doubling of SCr or 50% decline in eGFR • BP • Adverse events
Notes	• This study was funded by The Kidney Foundation, Japan

Risk of bias

Bias	Authors' judgement	Support for judgement

Masutani 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Patients were allocated using a minimisation method in which stratifying factors were UPCR ≥ 2.0 g/g Cr), serum Cr levels (≥ 1.2 mg/dL for males and ≥ 1.0 mg/dL for females), and adding tonsillectomy
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/20 participants allocated to mizoribine and prednisolone did not complete follow-up; 2/20 participants allocated to prednisolone did not complete follow up. However, "Although 5 patients did not complete study medication because of the side effects, retracted consent or deviation from the tapering schedule, no patient was lost to follow-up, and we could perform ITT analyses."
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), infection, ESKD) were not reported
Other bias	High risk	Imbalance at baseline in age, BP, and eGFR

Min 2017

Methods	• Study design: parallel, 2-arm RCT • Time frame: June 2004 to June 2010 • Duration of follow-up: 12 months of treatment and an average follow-up of 88 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: biopsy-proven primary IgAN; aged 18 to 65 years; proteinuria ≥ 1.0 g/24 hours and an eGFR ≥ 30 mL/1.73 m^2 • Number (analysed/randomised): treatment group (40/44); control group (45/46) • Mean age ± SD (years): treatment group (36.90 ± 10.49); control group (36.60 ± 11.53) • Sex (M/F): treatment group (14/26); control group (22/23) • Exclusion criteria: rapidly progressive IgAN (rapid decline in renal function characterized histologically by necrotising capillaritis or > 50% active crescents on biopsy); secondary IgAN due to systemic diseases such as HSP nephritis, hepatitis-associated nephritis, lupus nephritis, etc; use of corticosteroid or other immunosuppressive agents within 6 months prior to randomisation; SCr > 250 µmol/L; severe infections; hepatitis B virus carriers and other chronic liver diseases; presence of malignancy, HIV infection, or acute central nervous system diseases; abnormal glucose metabolism; pregnancy or lactation; poor compliance or allergy to study drugs
Interventions	Treatment group • Leflunomide: 40 mg/day for 3 days, after which the dose was reduced to 20 mg/day and administered for 12 months • Prednisone (oral): 0.8 mg/kg/day for 4-6 weeks. The maximum daily dose of prednisone was 40 mg. Then, prednisone was gradually tapered by 10, 5, and 2.5 mg to a maintenance dose of 5 mg/day

Min 2017 *(Continued)*

	Control group • Full-dose prednisone: 1.0 mg/kg/day for 8 to 12 weeks, with a maximum daily dose of 60 mg. Then, the daily dose was tapered by 5 and 2.5 mg to a maintenance dose of 10 mg/day Co-interventions • Not reported
Outcomes	• ESKD • 50% increase in baseline SCr • Complete remission (urine protein excretion < 0.3 g/d with stable SCr (defined as a change in SCr of ≤ 15% above baseline values) • Partial remission (at least a 50% reduction in urine protein excretion compared with baseline or urine protein excretion 0.3 to 3.5 g/day with stable SCr • No response was defined as urine protein excretion > 3.5 g/day or a < 50% reduction in urine protein excretion with or without kidney deterioration • Relapse: reappearance of significant proteinuria, defined as > 1.0 g/d and as a urine protein excretion increase of > 50% from the lowest level of proteinuria after remission • Adverse events
Notes	• This study was supported by the National Natural Science Foundation of China (81370794 and 81570604) as well as by a program from the Shanghai Health Bureau (No. ZHYY-ZXYJHZX-1-02) • Trials registration identification number: 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	37/44 participants assigned to leflunomide completed the study follow-up. 43/46 patients assigned to steroid therapy completed study follow-up
Selective reporting (reporting bias)	High risk	All relevant outcomes, except death (any cause), were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

NA IgAN 1995

Methods	• Study design: parallel, 3-arm RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Setting: multicentre (37 centres; 44 centres were described in study protocol) • Country: USA • Inclusion criteria: < 40 years, able to swallow 500 mg placebo tablet; eGFR ≥ 50 mL/min/1.73 m^2; persistent severe proteinuria; biopsy-proven IgAN within 3 years of entry • Number (analysed/randomised): treatment group (not reported/33); control group 1 (not reported/32); control group 2 (not reported/31) • Mean age ± SD (years): treatment group (24 ± 10); control group 1 (20 ± 10); control group 2 (21 ± 10) • Sex (M): treatment group (70%); control group 1 (66%); control group 2 (65%) • Exclusion criteria: SLE; HSP nephritis; abnormal liver function; pregnancy or unwilling to use appropriate contraception; diabetes; cataracts; aseptic necrosis of any bone; use of study agents in the 3 months prior to entry
Interventions	Treatment group • Prednisone: 60 mg/m^2 on alternate days for 3 months, 40 mg/m^2 on alternate days for 9 months, 30 mg/m^2 on alternate days for 12 months Control group 1 • Fish oil: up to 4 g/d for 2 years Control group 2 • Placebo: half received fish oil placebo and half received prednisone placebo Co-interventions • Not reported
Outcomes	• Time to kidney failure (decrease in CrCl ≤ 60% baseline value) • Adverse events
Notes	• Funding: "Supported by National Institute of Diabetes and Digestive and Kidney Diseases grant R01 DK49368. Medications that were used in this trial were generously donated by Merck and Co. Inc. (enalapril), Pharmacia and Upjohn (prednisone [Deltasone] and matching placebo), and Pronova Biocare (Omacor and matching placebo)." • Trials registration identification number: not applicable

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

NA IgAN 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "72 completed 2 years of trial drugs and 18 patients exited prematurely. Six patients dropped out of the trial after randomisation but before the start of study drugs."
Selective reporting (reporting bias)	High risk	The primary outcome was changed between the protocol (CrCl < 70% of baseline value) and the final study publication (CrCl <of 60% of baseline value)
Other bias	High risk	Interim analyses were planned but not clearly reported. The methods for interim analyses were different in the protocol and the final study publication. Imbalance at baseline for level of proteinuria between study groups

NEFIGAN 2017

Methods	• Study design: parallel, 3-arm RCT • Time frame: December 2012 to June 2015 • Duration of follow-up: 12 months
Participants	• Setting: 62 sites • Country: 10; Belgium, Czech Republic, Denmark, Finland, Germany, Italy, Spain, Sweden, the Netherlands, UK • Inclusion criteria: men or women aged at least 18 years with biopsy-confirmed primary IgAN and overt proteinuria for the run-in phase; eGFR of at least 45 mL/min/1.73 m^2 and a UPCR of more than 0.5 g/g or urinary total protein of at least 0.75 g/day • Number (analysed/randomised): treatment group 1 (51/51); treatment group 2 (48/51); control group (50/51) • Mean age ± SD (years): treatment group 1 (40.6 ± 13.0); treatment group 2 (37.5 ± 11.9); control group (38.9 ± 12.0) • Sex (M/F): treatment group 1 (37/14); treatment group 2(33/15); control group (35/15) • Exclusion criteria: unacceptable BP defined as a SBP > 160 mmHg or DBP > 100 mmHg; eGFR (CKD-EPI) loss > 30% over the entire duration of the Run-in Phase; for women only; pregnant or breast feeding or unwilling to use adequate contraception during the trial
Interventions	Treatment group 1 • TRF-budesonide: 8 mg/day; 2 active + 2 placebo capsules daily for 9 months Treatment group 2 • TRF-budesonide: 16 mg/day; 4 active capsules daily for 9 months Control group • Placebo: 4 placebo capsules daily for 9 months Co-interventions • Not reported
Outcomes	• Change in UPCR at 9 months • Change in UPCR, eGFR, UACR, urine albumin excretion at 12 months • Presence or absence of microhaematuria

NEFIGAN 2017 *(Continued)*

	• Adverse events • Decline in kidney function • death (any cause) • ESKD
Notes	• The study was funded by Pharmalink AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to treatment groups using a computer algorithm method of permuted blocks
Allocation concealment (selection bias)	Unclear risk	Treatment code envelopes were provided for each randomised patient. In case of emergency, the code envelope could be opened. Any unmasked patient had to be withdrawn from the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation; however participants were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	46/51 patients completed treatment and follow-up in placebo group; 40/51 and 34/51 completed treatment and follow-up in TRF-budesonide 8 mg and 16 mg group, respectively. There was differential loss to follow up due to severe adverse events which were higher in the higher dose budesonide group
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	High risk	Imbalance between groups in eGFR, weight, and time from diagnosis at baseline

Ni 2005

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Setting: multicentre (number of sites not reported) • Country: China • Inclusion criteria: progressive biopsy-proven IgAN; proteinuria > 1.0 g/day or SCr > 178 μmol/L and < 250 μmol/L • Number (analysed/randomised): treatment group (unclear/53); control group (unclear/49) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Ni 2005 *(Continued)*

Interventions	Treatment group • Leflunomide: 40 mg/day for 3 days followed by 20 mg/d for 12 months • Prednisone: 0.8 mg/kg tapered to 10 mg/kg for 12 months Control group • Prednisone: 1 mg/kg/day tapered to 10 mg/day for 12 months Co-interventions • not reported
Outcomes	• Remission of proteinuria • SCr • GFR • Adverse events
Notes	• Abstract-only publication • Funding: not reported • Trials registration identification number: 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Preliminary reports, unsure of final number enrolled. 73/102 participants completed 12 months, 28/102 completed 24 months
Selective reporting (reporting bias)	High risk	Data for outcomes such as ESKD, death (any cause), and malignancy were not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Nuzzi 2009

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported

Nuzzi 2009 *(Continued)*

	• Duration of follow-up: treatment group (mean 26.8 months); control group (mean 29.8 months)
Participants	• Setting: single centre • Country: Italy • Inclusion criteria: children with biopsy-proven IgAN; normal kidney function; normal arterial pressure; proteinuria estimated during microscopic haematuria • Number (analysed/randomised): treatment group (not reported/15); control group (not reported/12) • Mean age (years): treatment group (10.1; SD not reported); control group (11.3; SD not reported) • Sex (M/F): treatment group (9/5); control group (9/3) • Exclusion criteria: not reported
Interventions	Treatment group • Methylprednisolone: 1 g/body surface area 1.73 m^2 for 3 consecutive days • Oral prednisone: 0.5 mg/kg/day for a month, then same dose but on alternate days for the following 5 months Control group • No treatment Co-interventions • Not reported
Outcomes	• Urinary protein excretion • Microscopic haematuria
Notes	• Abstract only publication • Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data for outcomes such as ESKD, death (any cause), and malignancy were not reported

Nuzzi 2009 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Pozzi 1999

Methods	• Study design: parallel, 2-arm RCT • Duration of study: July 1987 to September 1995 • Duration of follow-up: 6 years
Participants	• Setting: multicentre (7) • Country: Italy • Inclusion criteria: aged 15 to 69 years; biopsy-proven IgAN; proteinuria 1.0 to 3.5 g/day for at least 3 months, and SCr ≤ 133 mol/L • Number (analysed/randomised): treatment group (not reported/43); control group (not reported/43) • Mean age, range (years): treatment group (38, 26 to 45); control group (40, 29 to 51) • Sex (M/F): not reported • Exclusion criteria: treatment with steroids or cytotoxic drugs during the previous 3 years; pregnancy; HSP nephritis; systemic lupus nephritis; diabetes; neoplasia; active peptic-ulcer disease, viral hepatitis; other infections
Interventions	Treatment group • Methylprednisolone: 1g IV for 3 days, repeated at 2 and 4 months • Prednisone 0.5 mg/kg/day on alternating days for 6 months Control group • No treatment Co-interventions • Both groups of patients were administered diuretics, antihypertensive drugs and antiplatelet agents as needed. ACEi were allowed for the treatment of hypertension
Outcomes	• ESKD • SCr • CrCl • Urinary protein excretion • Adverse events
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

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

Pozzi 1999 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients in the steroid group completed the 6 months of therapy; high dropout in both groups after this period
Selective reporting (reporting bias)	Low risk	Data for outcomes such as death (any cause), and infection were not reported. All other outcomes that would be expected for this type of study were reported
Other bias	High risk	Four patients in the control group received steroids as rescue therapy

Segarra 2006

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 24 months
Participants	• Setting: multicentre (number of sites not reported) • Country: Spain • Inclusion criteria: IgAN; persistent proteinuria >2.5 g/day; GFR > 30 mL/min; BP < 130/80 mmHg • Number (analysed/randomised): treatment group (19/not reported); steroid group (17/not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Immunoglobulin: 0.4 g/kg/day administered during 4 consecutive days every month • Steroid: 1 mg/kg/d for 4 weeks and then reduced at a rate of 5 mg/day every week until suppression Control group • Steroid: 1 mg/kg/d for 4 weeks and then reduced at a rate of 5 mg/day every week until suppression Co-intervention: not reported
Outcomes	• Remission of proteinuria (< 1 g/day) • SCr • GFR • 24 hour proteinuria • Serum IgA • Complement • Secretory IgA • IL-6. IL-8, MCP-1, TGF beta • Adverse events
Notes	• Abstract-only publication • Funding: not reported • Trials registration identification number: not reported

Segarra 2006 *(Continued)*

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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study were not reported
Other bias	High risk	Insufficient information to permit judgement

Shen 2013

Methods	• Study design: parallel, 3-arm RCT • Time frame: 2010 to 2011 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: China • Inclusion criteria: primary IgAN; 30 mL/min GFR < 90 mL/min and urinary protein excretion > 1.0 g/24 hours (with or without hypertension) • Number analysed/randomised: treatment group 1 (12/not reported); treatment group 2 (12/not reported); control group (12/not reported) • Mean age ± SD (all participants): 37.53 ± 11.35 years • Sex (M/F) (all participants): 26/10 • Exclusion criteria: not reported
Interventions	Treatment group 1 • Corticosteroid: initial dosage was 0.5 to 0.8 mg/kg/day, decreasing the dosage gradually after 8 weeks then 10 to 15 mg/day for 24 weeks • CPA: 0.5 to 0.75 g/m^2/month; maintenance period was 24 weeks of CPA 0.5 to 0.75 g/m^2 every 8 weeks Treatment group 2 • Corticosteroid: initial dosage was 0.5 to 0.8 mg/kg/day, decreasing the dosage gradually after 8 weeks then 10 to 15 mg/day for 24 weeks

Shen 2013 *(Continued)*

	• Tacrolimus 0.1 mg/kg/day (effective serum drug concentration 6 to 10 ng/mL; maintenance period was 24 weeks of tacrolimus 0.05 mg/day Control group • Corticosteroid: initial dosage was 0.5 to 0.8 mg/kg/day, decreasing the dosage gradually after 8 weeks then 10 to 15 mg/day for 24 weeks Co-interventions • Not reported
Outcomes	• Remarkable effect: 24-hour urinary protein excretion < 0.3 g/24 hours, SCr decreased > 10% than baseline • Effect: 24-hour urinary protein excretion decreased over 50% than pre-treatment and SCr was stable • Non-effect: 24-hour urinary protein excretion did not meet the above criteria, or SCr increased > 8%/year • Adverse events
Notes	• Abstract-only publication • Funding: not reported • Trials registration identification number: 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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study were not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Shi 2012a

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported

Shi 2012a *(Continued)*

	• Duration of follow-up: 24 months
Participants	• Setting: multicentre (number of sites not reported) • Country: China • Inclusion criteria: progressive biopsy-proven IgAN; Lee SMK grade II-IV, proteinuria >1.0 g/day and/or eGFR 29-60 mL/min/1.73 m^2 • Number (analysed/randomised): treatment group (not reported/38); prednisone group (not reported/47) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Leflunomide: 40 mg/day for 3 days followed by 20 mg/day for 12 months • Prednisone: 0.8 mg/kg tapered to 10 mg/kg for 12 months Control group • Prednisone: 1 mg/kg/day tapered to 10 mg/day for 12 months Co-interventions • All participants received ACEi or ARB
Outcomes	• Safety • MBl gene polymorphism in peripheral blood DNA and histological tubular-intestinal damage • Adverse events • Remission of proteinuria • Serum albumin • SCr • Uric acid level
Notes	• Abstract-only publication • Funding: Government support - Non-US • Trials registration identification number: 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	There was no report of blinding. As the treatments were physically different, it was likely that participants and/or investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation

Shi 2012a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Data for outcomes such as ESKD, death (any cause), malignancy, and infections were not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Shima 2018

Methods	• Study design: parallel, 2-arm RCT • Time frame: August 2001 to March 2009 • Duration of follow-up: 24 months
Participants	• Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: children with new diagnosed severe IgAN with diffuse mesangial proliferation by renal biopsy; 2 to 18 years; sufficient renal biopsy specimens available for pathological evaluation (minimum of 10 glomeruli); heavy proteinuria > 0.3 g/dL and hypoproteinaemia (serum total protein ≤ 6.0 g/dL) on at least one occasion between onset and entry to the study due the Japanese health insurance system regulation the use of mizoribine • Number (analysed/randomised): treatment group (34/35); control group (36/36) • Median age, IQR (years): treatment group (11.7, 9.6 to 13.3); control group (10.7, 7.4 to 12.8) • Sex (M/F): treatment group (10/24); control group (24/12) • Exclusion criteria: secondary IgAN such as IgA vasculitis, systemic lupus erythematosus, accompanied by liver disease; previous treatment with corticosteroids or immunosuppressive drugs
Interventions	Treatment group • Prednisolone: 2 mg/kg/day in 3 divided doses for a total dose of not more than 80 mg/day for 4 weeks. This was followed by 2 mg/kg every 2 days, given as a single dose in the morning every other day for 4 weeks, 1.5 mg/kg per 2 days for 4 weeks, and 1 mg/kg day per 2 days for 21 months • Mizoribine: 4 mg/kg/day in two divided doses for a total dose of no more than 150 mg/day for 24 months • Warfarin: single morning dose to maintain thrombotest at 20% to 50% for 24 months • Dipyridamole (oral): 6 mg/kg/day in 3ree divided doses for a total dose of up to 300 mg/day for 24 months Control group • Prednisolone: 2 mg/kg/day in 3 divided doses for a total dose of not more than 80 mg/day for 4 weeks. This was followed by 2 mg/kg every 2 days, given as a single dose in the morning every other day for 4 weeks, 1.5 mg/kg per 2 days for 4 weeks, and 1 mg/kg day per 2 days for 21 months • Mizoribine: 4 mg/kg/day in 2 divided doses for a total dose of no more than 150 mg/day for 24 months Co-interventions • Not reported
Outcomes	• Efficacy • Blood counts (including haemoglobin, white blood cells, and platelets) • Adverse events • Remission of proteinuria • Thrombotest

Shima 2018 *(Continued)*

- SCr
- BUN
- Serum IgA concentration
- Urinary protein excretions
- Hemostix test
- BP
- Body weight

Notes	• Funding: Health and Labor Sciences Research Grant from the Japanese Ministry of Health Labor and Welfare

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	Sealed envelopes. Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. However, reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient in the treatment group withdrew consent after allocation. all other patients completed the study
Selective reporting (reporting bias)	High risk	Data for outcomes such as ESKD, death (any cause), malignancy, and infections were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Shoji 2000

Methods	• Study design: parallel, 2-arm RCT • Time frame: January 1994 to December 1997 • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Japan • Inclusion criteria: aged 15 to 55 years with biopsy-proven IgAN; known duration of abnormal urinalysis results < 36 months; proteinuria < 1.5 g/d of protein; SCr < 1.5 mg/dL; mesangial cell proliferation or matrix accumulation involving more than 50% of glomeruli; no previous treatment • Number (analysed/randomised): treatment group (11/11); control group (8/10) • Mean age ± SD (years): treatment group (28.7 ± 11.2); control group (33.3 ± 11.9) • Sex (M/F): treatment group (5/6); control group (1/7)

Shoji 2000 *(Continued)*

	• Exclusion criteria: cellular crescents involving more than 20% of glomeruli; arterial BP > 150/90 mmHg; DM; chronic liver disease; autoimmune disease
Interventions	Treatment group • Prednisolone: daily dose 0.8 mg/kg/d gradually reduced to 0.4 g/kg/d during the first month, then tapered to 10 mg every other day for the remainder of 1 year of therapy Control group • Dipyridamole: 300 mg/day for 1 year Co-interventions • Not reported
Outcomes	• SCr • CrCl • Urinary protein excretion • Serum IgA • BP • Renal biopsy
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	2/10 patients from the control group withdrew - refused repeat biopsy
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Stangou 2011

Methods	• Study design: parallel, 2-arm RCT

Stangou 2011 *(Continued)*

	• Time frame: not reported • Duration of follow-up: 12 months
Participants	• Setting: single centre • Country: Greece • Inclusion criteria: primary IgAN; urine protein ≥ 1 g/24 hours and eGFR ≥ 30 mL/min/1.73 m^2; previous treatment with ACEi and/or ARB and polyunsaturated fatty acids for at least 6 months in all patients; maintenance of BP at levels < 130/80 mmHg • Number (analysed/randomised): treatment group (not reported/12); control group (not reported/10) • Mean age ± SD (years): treatment group (46.6 ± 12.1); control group (51.3 ± 9.1) • Sex (M/F): treatment group (8/4); control group (6/4) • Exclusion criteria: hepatitis; hepatic cirrhosis; SLE; rheumatoid arthritis; psoriasis; DM
Interventions	Treatment group • AZA: 1 mg/kg/day for a total of 12 months • Methylprednisolone: 0.6 mg/kg/day (equivalent to prednisolone 0.75 mg/kg), in two equal doses, and progressively reduced by 4 mg every 15 days until the dose of 8 mg. This dose remained stable until it was tapered and stopped at the end of the 2-month period. Total dosage of methylprednisolone was approximately estimated to 90 mg/kg, equivalent to 112.5 mg/kg prednisolone Control group • Methylprednisolone: 0.6 mg/kg daily (equivalent to prednisolone 0.75 mg/kg), in two equal doses, and progressively reduced by 4 mg every 15 days until the dose of 8 mg. This dose remained stable until it was tapered and stopped at the end of the 2-month period. Total dosage of methylprednisolone was approximately estimated to 90 mg/kg, equivalent to 112.5 mg/kg prednisolone Co-interventions • Not reported
Outcomes	• Complete remission (reduction in urine protein ≥ 50%) • Partial remission (reduction in urine protein 10% to 50%) • Relapse in proteinuria (≥ 50% increase in proteinuria and levels ≥ 1 g/24 hours in patients with complete or partial remission) • Infection • Adverse events
Notes	• Funding: not reported • Trials registration identification number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
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

Stangou 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), ESKD) were not reported
Other bias	High risk	Imbalance at baseline in eGFR and time since diagnosis

STOP-IgAN 2008

Methods	• Study design: 2-group, parallel, group-sequential RCT • Time frame: February 2008 to February 2015 • Duration of follow-up: 36 months
Participants	• Setting: multicentre (32 sites) • Country: Germany • Inclusion criteria: primary IgAN confirmed on biopsy; 18 to 70 years; proteinuria level > 0.75 g/day of urinary protein excretion plus arterial hypertension (defined by the use of antihypertensive medication or by an ambulatory BP ≥ 140/90 mmHg), impaired kidney function (defined as an eGFR < 90 mL/min/1.73 m^2), or both • Number (analysed/randomised): treatment group (80/80); control group (82/82) • Mean age ± SD (years): treatment group (45.8 ± 12.5); control group (42.8 ± 13.1) • Sex (M/F): treatment group (61/19); control group (56/24) • Exclusion criteria: eGFR < 30 mLmin/1.73 m^2; secondary and rapidly progressive, crescentics IgAN; other CKDs; any prior immunosuppressive therapy

Interventions	Treatment group
	• Patients with GFR of at least 60 mL/min/1.73 m^2
	  * Methylprednisolone (IV): 1 g/ day for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg/kg per 48 hours on the other day
	• Patients with an eGFR between 30 and 59 mL/min/1.73 m^2
	  * CPA: 1.5 mg/kg/day for 3 months, followed by AZA at a dose of 1.5 mg/kg/day during months 4 through 36
	  * Prednisolone (oral): 40 mg/day, tapered to 10 mg/day, over the first 3 months of the study, 10 mg/day during months 4 through 6, and 7.5 mg/day during months 7 through 36 months
	Control group
	• No treatment
	Co-interventions
	• Comprehensive supportive care that included blockers of the RAS to lower BP to a target below 125/75 mm Hg. If proteinuria remained above the target of 0.75 g/day of urinary protein excretion despite blood-pressure control, the dose of RAS blocker was increased to the maximum approved daily dose or to the highest dose at which the patient did not have unacceptable side effects. Patients received dietary counselling and were advised to quit smoking and to avoid nonsteroidal antiinflammatory

STOP-IgAN 2008 *(Continued)*

	drugs and other nephrotoxins. Total cholesterol levels were lowered to < 200 mg/dL (5.2 mmol/L) with the use of statins, if necessary
Outcomes	• Complete remission: defined as proteinuria with a UPCR of < 0.2 and stable kidney function with a decrease in GFR of < 5 mL/min/1.73 m^2 from the baseline eGFR at the end of the 3-year trial phase • GFR loss of 15 mL/min or higher from baseline GFR • GFR loss ≥ 30 mL/min from baseline • Annual change in slope of the reciprocal of SCr • Proteinuria • Disappearance of microhaematuria • ESKD • death (any cause) • Adverse events including malignancy/infection
Notes	The study was funded through German Federal Ministry of Education and Research grant GFVT01044604

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	Randomisation codes that were used to assign patients in a 1:1 ratio were generated by means of covariate adaptive randomisation with respect to factors that had the potential to modify the treatment effect (i.e., eGFR and proteinuria). Telephone randomisation by the study secretary. After the investigator establishes the eligibility of the patient to participant in the study, the study centre sends a fax to the Trial Office. The Trial Office assigned a treatment to the patient after being sent the following information: initials, gender, age, Cr-Cl, degree of proteinuria
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/82 assigned to immunosuppression were lost to follow up. 4/80 assigned to supportive care were lost to follow up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Takeda 1999

Methods	• Study design: parallel, 2-arm RCT

Takeda 1999 *(Continued)*

	• Time frame: not reported • Duration of follow-up: 2 years
Participants	• Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: IgAN with 10% to 30% of cellular crescents; CrCl ≥ 50 mL/min • Number (analysed/randomised): treatment group (not reported/13); control group (not reported/12) • Mean age ± SD (years): not reported • Sex (M/F): treatment group (8/5); control group (7/5) • Exclusion criteria: not reported
Interventions	Treatment group • Prednisolone: 40mg/day for 1 month tapered during lasting 2 years • Dilazep dihydrochloride: dose not reported Control group • Dilazep dihydrochloride: dose not reported Co-interventions • Not reported
Outcomes	• Urinary protein excretion • Haematuria • CrCl • DBP • Serum albumin • Renal histology
Notes	• Abstract-only publication; numeric data not available • Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Takeda 1999 *(Continued)*

Selective reporting (reporting bias)	High risk	No numeric data were available
Other bias	Unclear risk	Insufficient information to permit judgement

Tang 2005

Methods	• Study design: parallel, 2-arm RCT • Time frame: July 2001 to December 2003 • Duration of follow-up: 72 weeks
Participants	• Setting: multicentre (2 sites) • Country: Hong Kong • Inclusion criteria: IgAN and clinically significant proteinuria > 1 g/d on 3 or more consecutive measurements 4 to 6 weeks apart • Number (analysed/randomised): treatment group (20/20); control group (20/20) • Mean age ± SD (years): treatment group (42 ± 2.6); control group (43.3 ± 2.8) • Sex (M/F): treatment group (6/14); control group (8/12) • Exclusion criteria: glomerulopathies other than IgAN; SCr > 300 µmol/L; systemic infection or malignancy; and women of child-bearing age who were pregnant, lactating, or unwilling to practice reliable contraception
Interventions	Treatment group • MMF: 2 g/d for 24 weeks Control group • No treatment Co-interventions • ACEi or ARB: titrated to reach the target BP of < 125/85 mm Hg for 24 weeks
Outcomes	• Complete remission (< 0.3 g/24 hours) • Partial remission (≥ 50% decline in proteinuria over baseline) • Urinary protein excretion • ESKD • Blood count • BP • Urine sodium excretion • Adverse events
Notes	• Funding: "This work was supported in part by the Hong Kong Society of Nephrology Research Grant 2002, and a grant from the Research Grant Council (grant number HKU 7452/04M). Roche Pharmaceuticals supplied the MMF used in this study." • Trials registration identification number: not reported

Risk of bias

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

Tang 2005 *(Continued)*

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	High risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were reported
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

TESTING 2017

Methods	• Study design: parallel, 2-arm RCT • Time frame: April 2012 to November 2015 • Duration of follow-up: median 25 months (estimated 5 years)
Participants	• Setting: multicentre (was to be up to 100 sites) • Countries: Australia, China • Inclusion criteria: primary IgAN proven on kidney biopsy' eGFR between 20 and 120 mL/min/1.73 m^2; urinary protein excretion > 1 g/day • Number (analysed/randomised): treatment group (134/136); placebo group (126/126) • Mean age ± SD (years): treatment group (38.6 ± 11.5); placebo group (38.6 ± 10.7) • Sex (M/F): treatment group (86/50); placebo group (80/46) • Exclusion criteria: strong indication, or contraindication, for corticosteroid therapy, based on the judgement of the treating physician (patients were included if the patient and physician had clinical equipoise regarding the use of the treatment), or the use of systemic immunosuppressive therapy in the previous year
Interventions	Treatment group • Methylprednisolone: 0.6 to 0.8 mg/kg/day; maximum, 48 mg/day, for 2 months, then tapered by 8 mg/day each month, with a total treatment period of 6 to 8 months Control group • Matching placebo Co-interventions • Treatment adjusted to maximum labelled or tolerated dose of RAS blockade along with optimised BP control according to guidelines
Outcomes	• 50% decrease in eGFR • ESKD

TESTING 2017 *(Continued)*

	• Death due to kidney disease • Composite of ESKD, 40% decrease in eGFR, and death (any cause); the composite of ESKD, 50% decrease in eGFR, and death (any cause); and each of ESKD, death due to kidney disease, and death (any cause). The secondary end points also included proteinuria reduction • Serious adverse events and adverse events • Annual decrease in GFR
Notes	• Trial terminated because of excess serious adverse events • This study was supported by the National Health and Medical Research Council of Australia, the Peking University Health Central Clinical Research Project, and the Canadian Institutes of Health Research. Study drug was provided by Pfizer Pharmaceuticals • Trials registration identification number: NCT01560052

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a minimization algorithm based on the stratification variables; the algorithm was centrally generated and used by all centres to minimize any imbalances in key variables
Allocation concealment (selection bias)	Low risk	Randomly assigned 1:1 via a password-protected encrypted web site interface
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation; however participants were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	There were only 2/136 lost to follow up in methylprednisolone group. Imbalance in discontinuation between groups
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	High risk	Trial terminated early because of excess serious adverse events

Walker 1990a

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: treatment group (6 to 24 months, mean 22.6 months); control group (18 to 24 months; mean 23.3 months)
Participants	• Setting: single centre • Country: Australia • Inclusion criteria: IgAN and one of the following: 1) urinary red cell count >200,000/mL on 2 occasions; 2) proteinuria > 1.0 g/day on 2 occasions; 3) SCr > 0.12 mmol/L and ≤ 0.20 mmol/L; 4) > 10% crescents

Walker 1990a *(Continued)*

- Number (analysed/randomised): treatment group (25/25); control group (27/27)
- Mean age ± SEM (years): treatment group (34.3 ± 2.4); control group (34.4 ± 1.9)
- Sex (M/F): treatment group (18/7); control group (16/11)
- Exclusion criteria: SLE; HSP; clinical evidence of vasculitis

Interventions	Treatment group • CPA: 1 to 2 mg/kg/day for 6 months • Dipyridamole: 400 mg/day for 2 years • Warfarin: adjusted to a thrombotest (%) in the anticoagulant range for 2 years Control group • No treatment Co-interventions • Not reported
Outcomes	• SCr • Urinary protein excretion • BP • ESKD
Notes	• Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data were reported
Selective reporting (reporting bias)	Low risk	Adverse events and death (any cause) were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Welch 1992

Methods	• Study design: cross-over, 2-arm RCT • Time frame: 1983 to 1989 • Duration of follow-up: 24 weeks
Participants	• Setting: single centre • Country: USA • Inclusion criteria: children with IgAN • Number (analysed/randomised): 20/20 • Mean age: 13 years (SD not reported) • Sex (M/F): 15/5 • Exclusion criteria: SCr ≥140 µmol/L; hypertension (BP consistently 99th percentile for age and gender)
Interventions	Two, 3-month courses of therapy separated by a 3-month rest period Treatment group • Prednisolone: 2 mg/kg/day for 2 weeks, then every other day for 10 weeks Control group • Placebo: 2 mg/kg/day for 2 weeks, then every other day for 10 weeks Co-interventions • Not reported
Outcomes	• Urinary protein excretion • SCr
Notes	• Funding: not reported • Trials registration identification number: not applicable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The first course for each patient was assigned by a random-numbers table."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drugs were dispensed by the Children's Hospital Medical Center pharmacy with a coded label, so that neither patients nor investigators were aware of the identity of the medication."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in analyses
Selective reporting (reporting bias)	High risk	Relevant numeric data were not available. Patient-centred outcomes of relevance were not reported

Welch 1992 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Woo 1987

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 36 months
Participants	• Setting: single centre • Country: Singapore • Inclusion criteria: IgAN aged 17 to 35 years • Number (analysed/randomised): treatment group (27/not reported); control group (21/not reported) • Mean age ± SD (years): treatment group (25 ± 6); control group (26 ± 9) • Sex (M/F): treatment group (18/9); control group (16/5) • Exclusion criteria: systemic lupus; liver disease; HSP
Interventions	Treatment group • CPA: 1.5 mg/kg/day for 6 months • Dipyridamole: 300 mg/day for 36 months • Warfarin: to maintain thrombotest between 30% and 50% Control group • No treatment Co-interventions • Not reported
Outcomes	• SCr • CrCl • Urinary protein excretion • ESKD • Adverse events
Notes	• Funding: not reported • Trials registration identification number: not applicable

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

Woo 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Outcomes relevant to study design were not reported such as death (any cause) and infection/malignancy
Other bias	High risk	Imbalance in duration of follow up and proteinuria between treatment groups

Wu 2016

Methods	• Study design: parallel, 4-arm RCT • Time frame: June 2009 to June 2012 • Duration of follow-up: 6 months
Participants	• Setting: multicentre (13 sites) • Country: China • Inclusion criteria: 18 to 55 years; biopsy confirmed (within the past year) IgAN of Lee's grade II–IV, proteinuria of 0.5 to 3.5 g/day, SCr < 265 µmol/L, and BP between 90/60 and 130/80 mmHg with or without antihypertensive treatments • Number (analysed/randomised): treatment group 1 (100/100); treatment group 2 (100/100); treatment group 3 (100/100); treatment group 4 (99/99) • Mean age ± SD (years): treatment group 1 (39.01 ± 9.78); treatment group 2 (36.52 ± 9.59); treatment group 3 (38.12 ± 10.62); treatment group 4 (37.06 ± 10.46) • Sex (M/F): treatment group 1 (54/46); treatment group 2 (61/39); treatment group 3 (54/46); treatment group 4 (62/37) • Exclusion criteria: IgAN secondary to other diseases; previous adverse reaction to telmisartan, clopidogrel, or leflunomide; DM; pregnancy or unreliable contraception; and use of corticosteroids or other immunosuppressive agents (including leflunomide) in the preceding 3 months
Interventions	Treatment group 1 • Telmisartan: 80 mg/day • Clopidogrel placebo • Leflunomide placebo Treatment group 2 • Telmisartan: 80 mg/day • Clopidogrel: 50 mg/day • Leflunomide placebo Treatment group 3 • Telmisartan: 80 mg/day • Clopidogrel placebo • Leflunomide: 20 mg/day Treatment group 4 • Telmisartan: 80 mg/day

Wu 2016 *(Continued)*

	• Clopidogrel: 50 mg/day • Leflunomide: 20 mg/day Co-interventions • Not reported
Outcomes	• Change in the 24-hour urinary protein excretion at 24 weeks • Changes in the SCr and eGFR
Notes	• This work is supported by the grants from National Key Technology Research and Development Program (No. 2011BAI10B00); from National High Technology Research and Development Program of China (863 Program No. 2012AA02A512); two grants from National Clinical Research Center for Kidney Disease (No. 2013BAI09B05 and No. 2015BAI12B06), and from the Science and Technology Project of Beijing, China (No. D09050704310904, No. D131100004713003)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list was produced by a staff member at the Peking University Clinical Research Institute (Beijing, China) who was not otherwise involved in the study
Allocation concealment (selection bias)	Unclear risk	Detailed blind coding was recorded and covertly preserved in the coordinating centre. Each study centre was randomly stratified according to the enrolment order
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	In total, 25/400 patients were lost to follow-up. However the proportion was low, the proportion of loss to follow-up was different for each treatment group
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Xie 2011

Methods	• Study design: parallel, 3-arm RCT • Time frame: June 2009 to June 2012 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (8 sites) • Country: China • Inclusion criteria: pathologically diagnosed primary IgAN by renal biopsy; mean urinary protein excretion on 2 measurements within 1 week of 0.5 to 3.5 g/24 hours; mean SCr level on 2 measurements

Xie 2011 *(Continued)*

	within 1 week of 353.6 mol/L; age of 14 to 70 years regardless of sex; and lack of use of steroids, immunosuppressants, ACEi and ARB drug within the 3-month period preceding the study • Number (analysed/randomised): treatment group 1 (25/30); treatment group 2 (29/35); control group (30/34) • Mean age ± SD (years): treatment group 1 (33.67 ± 11.62); treatment group 2 (33.63 ± 11.71); control group (33.68 ± 10.29) • Sex (M/F): treatment group 1 (14/16); treatment group 2 (14/21); control group (14/20) • Exclusion criteria: sensitivity to mizoribine or losartan; leukocyte count 3000/mm^3; pregnant or desiring to be pregnant; and secondary IgAN (SLE, hypersensitive purpura, type B hepatitis, cirrhosis, etc)
Interventions	Treatment group 1 • Different doses of mizoribine were administered orally according to body weight and SCr level * Body weight < 50 kg: 200 mg/day (100 mg in the morning and 100 mg in the afternoon) * Body weight ≥ 50 kg: 250 mg/day (150 mg in the morning and 100 mg in the afternoon) * SCr > 176.8 mol/L, 150 mg/day (100 mg in the morning and 50 mg in the afternoon) Treatment group 2 • Losartan (oral): administered every morning as losartan potassium (100 mg/day) Control group • In the combination group, the doses and timing of administration were the same as in the losartan and mizoribine groups Co-interventions • Calcium antagonists, beta-receptor blockers or alfa-receptor blockers could be used for patients with hypertension in the losartan group and the combination group whose BP was higher than 130/80 mmHg despite oral administration of losartan 100 mg; in addition, the same drugs could be used for patients with hypertension in the mizoribine group. The target BP was 130/80 mmHg. The use of steroids, immunosuppressants other than mizoribine, ACEi and ARB other than losartan was excluded
Outcomes	• 24-hour urinary protein excretion • SCr • eGFR • Serum uric acid • BP • Adverse events
Notes	• The protocol was registered with the Cochrane Renal Prospective Trial Registry in 2006 and also with the Australian and New Zealand Clinical Trial Registration Centre in 2009 • This study was supported by the Key Program of the National Natural Science Foundation of China (Grant No.30630033), National Key Technologies R&D Program of China (Grant No. 2007BAI04B10) and Science and Technology Project of Beijing, China (Grant No. D09050704310904)

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

Xie 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	6/35 participants in mizoribine group did not complete study. 4/34 participants in combination group did not complete study. 5/30 participants in the losartan group did not complete study
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause), ESKD) were not reported
Other bias	Low risk	The study appeared to be free of other source of bias

Yamauchi 2001

Methods	• Study design: RCT • Time frame: September 1990 to December 1997 • Duration of follow-up: mean 41 months
Participants	• Setting: not reported • Country: Japan • Inclusion criteria: patients diagnosed as primary IgA nephropathy. They had a histological diagnosis of IgA nephropathy with immunofluorescence showing mesangial IgA deposits • Number (analysed/randomised): overall (not reported/37); treatment group (not reported/17); control group (not reported/20) • Mean age ± SD (years): overall (not reported); treatment group (not reported); control group (not reported) • Sex (M/F): overall (13/24); treatment group (not reported); control group (not reported) • Exclusion criteria: not reported
Interventions	Treatment group • IV methylprednisolone: 1g daily for 3 consecutive days • Oral prednisolone: for 12 months Control group • No steroid treatment Co-interventions • Not reported
Outcomes	• ESKD • Renal survival (doubling of SCr) • Urinary protein excretion • Mesangial cell proliferation • Mesangial matrix • Cellular crescents

Yamauchi 2001 *(Continued)*

Notes	• Conference abstract • Funding: not reported • Trials registration identification number: not applicable

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	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	There was no pre-specified protocol identified for this study. The study did not report extractable data for the key outcomes that would be expected for a study of this type (e.g., death (any cause), GFR loss, infection, malignancy)
Other bias	Unclear risk	Insufficient information to permit judgement

Yoshikawa 1999

Methods	• Study design: parallel, 2-arm RCT • Time frame: January 1990 to December 1993 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (20 sites) • Country: Japan • Inclusion criteria: children with IgAN aged < 15 years at study entry; no previous treatment with corticosteroids or immunosuppressive drugs; sufficient renal biopsy tissue available for histologic evaluation (minimum of 10 glomeruli) • Number (analysed/randomised): treatment group (40/40); control group (34/38) • Mean age ± SD (years): treatment group (12.2 ± 3.0); control group (11.6 ± 2.3) • Sex (M/F): treatment group (22/18); control group (29/9) • Exclusion criteria: not reported
Interventions	Treatment group • Prednisone: 2 mg/kg/day in 3 divided doses for 4 weeks, then single dose of 2 mg/kg on alternate days for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks; 1 mg/kg on alternate days for 21 months • AZA: 2 mg/kg/day for 2 years

Yoshikawa 1999 *(Continued)*

- Heparin: continuous IV infusion in sufficient doses to keep the partial thromboplastin time at 60 sec for 28 days. This was followed by oral warfarin given in a single morning dose to maintain the thrombotest at 30% to 50% for 23 months
- Dipyridamole: 5 mg/kg/day in 3 divided doses for a total dose of not more than 400 mg/day for 24 months

Control group

- Heparin: continuous IV infusion in sufficient doses to keep the partial thromboplastin time at 60 sec for 28 days. This was followed by oral warfarin given in a single morning dose to maintain the thrombotest at 30% to 50% for 23 months
- Dipyridamole: 5 mg/kg/day in 3 divided doses for a total dose of not more than 400 mg/day for 24 months

Co-interventions

- Not reported

Outcomes	• CrCl • Urinary protein excretion • Serum IgA • BP • Renal histology • Adverse effects • Height • Obesity
Notes	• Funding: "This study was supported in part by a grant from Tsumura Co. Ltd (Tokyo, Japan)." • Trials registration identification number: not applicable

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	Quote: "Sealed envelope technique in blocks of four."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not specifically reported. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	4/38 participants allocated to control group did not complete trial. 0/40 participants allocated to immunosuppression completed trial. Imbalance in discontinuation between groups
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause) and ESKD) were not reported
Other bias	High risk	Imbalance in urine protein excretion at baseline

Yoshikawa 2006

Methods	• Study design: parallel, 2-arm RCT • Time frame: January 1994 to December 1998 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (20 sites) • Country: Japan • Inclusion criteria: aged ≤ 15 years with IgAN; no previous treatment with corticosteroids or immunosuppressive drugs; sufficient renal biopsy tissue available for histologic evaluation (minimum of 10 glomeruli) • Number (analysed/randomised): treatment group (39/40); control group (39/40) • Mean age ± SD (years): treatment group (11.5 ± 3.2); control group (11.1 ± 2.8) • Sex (M/F): treatment group (22/18); control group (21/19) • Exclusion criteria: not reported
Interventions	Treatment group • Prednisone: 2 mg/kg/day in 3 divided doses for 4 weeks, then single dose of 2 mg/kg on alternate days for 4 weeks, 1.5 mg/kg on alternate days for 4 weeks; 1 mg/kg on alternate days for 21 months • AZA: 2 mg/kg/day for 2 years • Oral warfarin: single morning dose to maintain the thrombotest at 30% to 50% for 23 months • Dipyridamole: 5 mg/kg/d 3 divided doses for a total dose of not more than 400 mg/day for 24 months Control group • Prednisone alone Co-interventions • Not reported
Outcomes	• Remission of proteinuria (urinary protein excretion < 0.1 g/m^2/day) • Urinary protein excretion • Urine Hb • Serum IgA • BP • CrCl
Notes	• Funding: "This study was supported in part by Health and Labor Sciences Research Grants (Research on Children and Families) by Japanese Ministry of Health Labor and Welfare." • Trials registration identification number: 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	"Sealed envelope technique in blocks of four."
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Yoshikawa 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Two independent investigators who were blinded to the treatment status reviewed the second biopsies. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/40 participants did not complete study from each treatment group
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause) and ESKD) were not reported
Other bias	Low risk	The study appeared to be free of other sources of bias

Zhang 2004

Methods	• Study design: parallel, 2-arm RCT • Time frame: not reported • Duration of follow-up: 12 weeks
Participants	• Setting: multicentre (number of sites not reported) • Country: China • Inclusion criteria: IgAN • Number (analysed/randomised): treatment group (27/not reported); control group (22/not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Leflunomide: 20 mg/day for 3 months Control group • Methylprednisolone: 0.5 g/day for 3 days • Prednisolone: 0.5 mg/kg every day or every other day 3 months Co-interventions • Not reported
Outcomes	• Complete remission: 24-hour urinary protein < 0.2 g with normal kidney function • Partial remission: 24-hour urinary protein decrease > 50% with normal kidney function • Urinary protein excretion • SCr • Adverse events
Notes	• Abstract-only publication; numeric data not available • Funding: not reported • Trials registration identification number: not applicable
Risk of bias	

Zhang 2004 *(Continued)*

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	High risk	Two independent investigators who were blinded to the treatment status reviewed the second biopsies. Key outcomes were objective laboratory measures and were unlikely to be affected by any knowledge of treatment allocation. Reporting of adverse events may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Key outcomes expected for this type of study (death (any cause) and ESKD) were not reported
Other bias	Unclear risk	Insufficient information to permit judgement

ACEi - angiotensin-converting enzyme inhibitor/s; ALT - alanine aminotransferase; ARB - angiotensin receptor blockers; ASP - aspartate aminotransferase; AZA - azathioprine; BP - blood pressure; BUN - blood urea nitrogen; CKD - chronic kidney disease; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; DBP - diastolic blood pressure; DM - diabetes mellitus; ESKD - end-stage kidney disease; (e)GFR - (estimated) glomerular filtration rate; GN - glomerulonephritis; HCT - haematocrit; HIV - human immunodeficiency virus; HSP - Henoch-Schönlein Purpura; IgAN - IgA nephropathy; IQR - interquartile range; IV - intravenous; KRT - kidney replacement therapy; LDL - low density lipoprotein; M/F - male/female; MAP - mean arterial pressure; MMF - mycophenolate mofetil; QoL - quality of life; RAS - renin-angiotensin system; RCT - randomised controlled trial; SBP - systolic blood pressure; SCr - serum creatinine; SD - standard deviation; SEM - standard error of the mean; SLE - systemic lupus erythematosus; UACR - urinary albumin:creatinine ratio; UPCR - urinary protein:creatinine ratio

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

Study	Reason for exclusion
Chen 2009b	Wrong intervention: not immunosuppressive agent intervention; the study evaluated Tripterygium wilfordii Hook F. This treatment was adjudicated as not immunosuppression
Czock 2007	Wrong intervention: not immunosuppressive agent intervention; the study evaluated the pharmacokinetics of two different mycophenolic acid formulations. As the study did not compare two different immunosuppression agents, this study was adjudicated as not fulfilling the eligibility criteria on the basis of intervention
Dal Canton 2005	This study was abandoned without completing participant recruitment.
GloMY 2010	This study was adjudicated as not completing recruitment target. The study authors let us know that the trial was closed to recruitment on 21 August 2012 with 3 patients with IgAN randomised. The trial was intended as a pilot for feasibility for a larger trial.

Study	Reason for exclusion
Imai 2006	Wrong population: not all participants with biopsy-proven IgAN; the study included participants with a range of crescentics glomerulopathies. Data for those participants with IgAN were not available separately.
Shen 2009	Wrong intervention: not immunosuppressive agent intervention; the study compared combined regime of Tripterygium glycosides and benazepril. These treatments were adjudicated as not immunosuppression.
Sulimani 2001	Wrong population: not all patients had IgAN; data for those participants with IgAN were not available separately.
Yonemura 2000b	Wrong population: not all participants had IgAN; the study included participants with minimal change disease.

IgAN - IgA nephropathy

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00301600

Methods	Single centre parallel RCT
Participants	40 patients with crescentics IgAN
Interventions	Pulse IV CPA or oral MMF
Outcomes	Efficacy, safety, tolerability and relapse of MMF
Notes	Study completed in 2006. Written to investigators to request update/data. As study is completed >10 years previously, trial data are unlikely to be available or obtained.

NCT02160132

Methods	Parallel RCT
Participants	• Setting: multicentre • Country: China • Patients with age 14 to 65 years, regardless of gender; clinical evaluation and renal biopsy diagnostic for IgAN, presenting with active pathological changes,including cellular crescents,necrosis and microthrombus; average urinary protein excretion of 0.5 to 3.5 g/24 hours on two successive examinations; eGFR ≥ 50 mL/min/1.73 m^2 • Number: 180 participants planned • Mean age ± SD (years): not available • Sex (M/F): not available • Exclusion criteria: Secondary IgAN such as SLE, HSP; nephritis and hepatitis B -associated nephritis; rapidly progressive nephritic syndrome (crescent formation ≥ 50%); AKI, including rapidly progressive IgAN; current or recent (within 30 days) exposure to high-dose of steroids or immunosuppressive therapy (CPA, MMF, CSA, FK506); date of renal biopsy exceeds more than 30 days; 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; malignant hyperten-

NCT02160132 *(Continued)*

	sion that is difficult to be controlled by oral drugs; known allergy, contraindication or intolerance to the steroids; pregnancy or breast feeding 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	Treatment group 1 • IV methylprednisolone 0.5 g/day for 3 consecutive days in the 1st, 2nd and 3rd month, and then oral methylprednisolone 0.4 mg/kg/day on consecutive days for 6 months Treatment group 2 • IV Methylprednisolone 0.5 g/day for 3 consecutive days in the 1st, 3rd and 5th month, and then oral methylprednisolone 0.4 mg/kg/day on consecutive days for 6 months
Outcomes	• Remission of proteinuria (complete or partial) • Deterioration of kidney function • Longitudinal decline of kidney function (eGFR)
Notes	Study completed on December 2016 Emailed investigators on 21.5.2018 to request update on trial status, but not answer was provided Clinicaltrials.gov identifier: NCT02160132 No study results available

NCT02571842

Methods	Parallel RCT
Participants	• Setting: single centre • Country: Thailand • Any kidney transplant recipients between the age of 18 and 70 years of age and able to give informed consent; GFR by 24-hour CrCl > 30 mL/min/1.73 m^2; biopsy-proven recurrent IgAN with endocapillary proliferation pattern • Number: 30 participants planned • Mean age ± SD (years): not available • Sex (M/F): not available • Exclusion criteria: clinical and histologic evidence of IgA combination with other forms of GN; clinical evidence of cirrhosis, chronic active liver disease or known infection with hepatitis B, C or HIV; 24-hour CrCl < 30 mL/min/1.73 m^2 at the time of screening; active systemic infection or history of serious infection within one month of entry; positive pregnancy test or breast feeding at time of study entry; patients receiving > 6 months therapy with oral prednisone > 5 mg/day or glucocorticoid equivalent; live vaccine within 28 days of study enrolment
Interventions	Treatment group 1 • Rituximab: 375 mg/m^2 on treatment month 1, 2, 3, 4 Treatment group 2 • An ACEI and/or ARB will be used to achieve proteinuria reduction and a BP goal of < 130/80 mmHg. Patients not attaining the target BP with an ACEI or ARB alone should be treated with the combination of ACEI + ARB • Corticosteroids will be used as prednisolone 0.5 mg/kg/day with gradually taper off in 6 to 8 weeks to 5 mg/day daily

NCT02571842 *(Continued)*

Outcomes	• Remission rate • Incidence of all adverse events
Notes	Study completed on December 2016 Email investigators to request update on trial status, but not answer was provided Clinicaltrials.gov identifier: NCT02571842 No study results available

ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BP - blood pressure; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin A; (e)GFR - (estimated) glomerular filtration rate; GN - glomerulonephritis; HIV - human immunodeficiency virus; HSP - Henoch-Schönlein Purpura; IgAN - IgA nephropathy; IV - intravenous; MMF - mycophenolate mofetil; RCT - randomised controlled study; SLE - systemic lupus erythematosus; UACR - urine albumin creatinine ratio

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

AIGA 2016

Trial name or title	Efficacy and safety of a combination of mycophenolate mofetil and corticosteroid in advanced IgA nephropathy (AIGA)
Methods	Parallel RCT

Participants	• Setting: multicentre
	• Country: Korea
	• Inclusion criteria
	  * Patients aged 19 to 65 years old
	  * Diagnosed with IgAN
	  * Confirmed with proteinuria more than 1.0 g/day at least twice within 6 months from the time of screening
	  * If eGFR (by MDRD) is < 50 mL/min/1.73 m^2, ≥15 mL/min/1.73 m^2; ACE inhibitor or ARB for at least 3 months
	  * Willing and able to provide written informed consent
	• Number: 100 participants planned
	• Mean age ± SD (years): not yet available
	• Sex (M/F): not yet available
	• Exclusion criteria
	  * If eGFR (by MDRD) is < 15 mL/min/1.73 m^2
	  * BP is SBP >160 mmHg or DBP >100 mmHg
	  * Systemic infection or have been diagnosed with cancer within the last 5 years (excluding treatment squamous cell or basal cell carcinoma skin cancer)serious digestive disorder; WBC < 3000/mm^3
	  * Acute (within 4 weeks) or chronic(need to treatments) allergic/hypersensitivity reaction in the history of Investigational drugs
	  * Administration of other Investigational drugs within 28 days before screening period
	  * Administration of Investigator drug or other immunosuppressants within 84 days before screening period
	  * Women in pregnant or breast-feeding or don't using adequate contraception
	  * Patient has conversation impairment because alcohol or drugs addiction history within 6 months or mental illness In investigator's judgment

Interventions	Treatment group 1

AIGA 2016 *(Continued)*

	• MMF and corticosteroid: MMF less than 80 kg: 1500 mg/day, 80 kg or more: 2000 mg/day divided twice a day and administered orally Treatment group 2 • Conservative treatment (ACEi or ARB)
Outcomes	• Remission rate (complete/partial) • eGFR • The incidence of KRT • The average time to occurrence of KRT
Starting date	June 2016
Contact information	Eunju Jung oakly74@nate.com; Jonghyuk Lee leejongh@ckdpharm.com
Notes	Study completion date: October 2018 No study results available

ARTEMIS-IgAN 2018

Trial name or title	Study of the safety and efficacy of OMS721 in patients with immunoglobulin A (IgA) nephropathy
Methods	Parallel RCT
Participants	• Setting: not yet available • Country: USA • Patients aged 18 years and above with a biopsy-confirmed diagnosis of IgAN within 10 years, with 24-hour urinary protein excretion that is > 1 g/day at baseline, eGFR of ≥ 30 and ≤9 0 mL/min/1.73 m^2, currently on physician-directed, stable treatment with RAS blockade (ACEI, ARB, direct renin inhibitors) and have a systolic BP of <150 mmHg and a diastolic BP of <100 mmHg at rest • Number: approximately 430 patients are to enrolled in two groups of 215 patients per arm • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: Treatment with immunosuppressants (e.g., AZA or CPA), cytotoxic drugs, or eculizumab within 24 weeks prior to screening; unwilling or unable to discontinue systemic corticosteroids 12 weeks prior to randomisation; female patients who are pregnant, breast feeding, or planning to become pregnant up through 12 weeks after the last dose of study drug, including possible re treatments; clinical or biological evidence of DM, systemic lupus erythematosus, IgA vasculitis (HSP), secondary IgAN, or other renal disease; history of renal transplantation; have a known hypersensitivity to any constituent of the investigational product; rapidly progressive GN; significant abnormalities in clinical laboratory values; BMI ≥ 35 kg/m^2, history of HIV (HIV), hepatitis B infection and hepatitis C infection; diagnosis of a malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or other cancer from which the patient has been disease-free for ≥ 5 years; have received any other investigational drug or device or experimental procedures within 30 days of the screening visit
Interventions	Treatment group 1 • OMS721

ARTEMIS-IgAN 2018 *(Continued)*

	Treatment group 2 • Placebo (5% dextrose in water or normal saline solution)
Outcomes	• Change from baseline in 24-hour urine protein excretion in g/day at 24 weeks from beginning of treatment • Number of patients with treatment related adverse events as assessed by CTCAE v 4.0 • Change from baseline in kidney function as determined by the rate of change in eGFR up to 144 weeks from beginning of treatment • Change from baseline in 24-hour urine protein excretion in g/day at 24 weeks from beginning of treatment in the subset of patients with baseline high proteinuria (defined as 24-hour urinary protein excretion ≥ 2 g/day) • Time-averaged change in UPCR through 24 weeks
Starting date	February 2018
Contact information	Laura Haas (206) 676-0886 lhaas@omeros.com Fay Wang (206) 676-0863 fwang@omeros.com
Notes	Estimated study completion date: April 2023 No study results available

ChiCTR1800014442

Trial name or title	Prospective study of the efficacy and safety of improved Italy scheme therapy for IgA nephropathy
Methods	Not reported
Participants	• Setting: not yet available • Country: China • Patients with IgAN; histological diagnosis of IgA; nephropathy with immunofluorescence showing mesangial IgA deposits; age between 15 and 75 years; urinary protein excretion of 0.5 to 3.5 g/day; SCr ≤ 171 mol/L (2 mg/dL) • Number: not yet available • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: not yet available
Interventions	Treatment group 1 • Methylprednisolone Treatment group 2 • Methylprednisolone with low dose oral glucocorticoids
Outcomes	• 24 hours urinary protein

ChiCTR1800014442 *(Continued)*

- eGFR
- Clearance creatinine
- Albumin
- Triglycerides and cholesterol
- Fasting plasma glucose
- Uric acid; blood routine test
- Routine urine

Starting date	Not reported
Contact information	Li Y: Telephon number and email were not reported
Notes	Estimated study completion date: not reported No study results available

MAIN 2013

Trial name or title	The Effects of mycophenolate mofetil (MMF) on renal outcomes in advanced immunoglobulin A (IgA) nephropathy patients (MAIN)
Methods	Parallel RCT
Participants	• Setting: multicentre • Country: China • Patients with biopsy-proven primary IgAN with urinary proteinuria excretion over 1g/24 hour, subjects must meet 2 of the following criteria: global glomerular sclerosis plus focal segmental glomerular sclerosis ratio ≥ 50%; eGFR 30 to 60 mL/min; hypertension (BP over 140/90 mmHg or taking antihypertensive drugs) • Number: 232 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: secondary IgAN; familial IgAN; concomitant disease: cancer, infection, DM, connective tissue disease, abnormal liver function; pregnancy or breasting; inability to comply with study and follow-up procedures
Interventions	Treatment group 1 • MMF: 1.5 g/day and maximum tolerated labelled dose of losartan Treatment group 2 • Losartan: maximum tolerated labelled dose
Outcomes	• Time to the first occurrence of a component of the composite renal endpoint: doubling of SCr or the onset of ESKD • A decrease in eGFR of 30% or ≥ 60 mL/min at the exit visit if the baseline eGFR ≥ 60 mL/min • Or a decrease in eGFR ≥ 50% at the exit visit if the baseline eGFR < 60 mL/min
Starting date	June 2013
Contact information	Fan Fan Hou 0086-20-61641591

MAIN 2013 *(Continued)*

	ffhouguangzhou@163.com
Notes	Estimated study completion date: June 2018 No study results available

NCT00657059

Trial name or title	Mycophenolate mofetil (MMF) in patients With IgA nephropathy
Methods	Parallel RCT
Participants	• Setting: multicentre • Country: China • Aged 14 to 60 years, regardless of gender; clinical evaluation and renal biopsy diagnostic for IgAN, excluded secondary IgAN. Renal histological criteria should be defined by Lee's glomerular grading system;1 g/day ≤ proteinuria < 3.5 g/day, or UPCR ≥ 0.6 (male) or ≥ 0.8 (female) when taking ARB; eGFR ≥ 40 mL/min/1.73 m^2 • Number: 151 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: inability or unwillingness to sign the informed consent; inability or unwillingness to meet the scheme demands raised by the investigators; rapidly progressive nephritic syndrome and AKI, including rapidly progressive IgAN (IgAN with rapid decline in kidney function characterized histologically by necrotizing vasculitis and crescent formation ≥ 30%) necessitating the use of other immunosuppressive agents; secondary IgAN such as SLE, HSP nephritis and hepatitis B -associated nephritis; eGFR < 40 mL/min/1.73m^2; malignant hypertension that is difficult to be controlled by oral drugs; 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 of entry or known infection with HIV, hepatitis B, or hepatitis C; 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); malignant tumours (except fully cured basal cell carcinoma); absolute neutrophil count < 1500/mm^3, absolute platelet count < 75,000/mm^3 or HCT < 28% (anaemic subjects may be reevaluated after the anaemia has been treated); known allergy, contraindication or intolerance to the MMF, corticosteroids or ACEI/ARB; pregnancy or breast feeding at the time of entry or unwillingness to comply with measures for contraception; current exposure to MMF or AZA. In case of current treatment with oral steroid or ACEI/ARB, entry is permitted after corticosteroids or ACEI/ARB are stopped for 2 weeks; current or recent (within 30 days) exposure to any other investigational drugs
Interventions	Treatment group 1 • Prednisone: IV methylprednisolone at a dose of 0.5 g/day for 3 days at the start of months 1, 3, and 5; then take oral prednisone (0.5 mg/kg/day) on alternate days. Prednisone will be tapered 5 mg/month from the 7th to the 12th month Treatment group 2 • MMF. 1.0 g twice/day (weight ≥ 50 kg) or 0.75 g twice/day (weight < 50 kg) for the first 6 months of drug treatment phase, then 0.5 g twice/day for the remaining 6 months Treatment group 3 • Prednisone: IV methylprednisolone at a dose of 0.5 g/day for 3 days at the start of months 1, 3, and 5; then take oral prednisone (0.5 mg/kg/day) on alternate days. Prednisone will be tapered 5 mg per month from the seventh month to the 12th month.

NCT00657059 *(Continued)*

	• MMF: 1.0 g twice/day (weight ≥ 50 kg) or 0.75 g twice/day (weight < 50 kg) for the first 6 months of drug treatment phase, then 0.5 g twice/day for the remaining 6 months Co-interventions • Irbesartan. In the ARB lead-in phase, each subject will be on a strict sodium-restricted diet (< 5 g NaCl/day), and then given a stable dose (150 mg to 300 mg/day) of irbesartan (Aprovel) for 3 months until reaching the target BP level of ≤ 125/75 mmHg. Patients will continue ARB treatment in the drug treatment phase and at least 3 years in the follow-up phase
Outcomes	• Complete remission • Deterioration of kidney function
Starting date	September 2007
Contact information	Xueqing Yu 8620-87766335 yuxq@mail.sysu.edu.cn Qiongqiong Yan 8620-87755766 ext 8843 qqyzzm@yahoo.com.cn
Notes	Estimated study completion date: April 2019 No study results available

NCT02808429

Trial name or title	Efficacy and safety of atacicept in IgA nephropathy
Methods	Parallel RCT
Participants	• Setting: multinational • Country: USA, Japan, UK • Greater than or equal to 18 years of age; biopsy-provenIgAN; UPCR ≥ 0.75 and ≤ 6 mg/mg during screening; stable and optimal dose of ACEi and/or ARB at least 8 weeks prior to screening • Number: 30 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: concomitant significant kidney disease other than IgAN; IgAN with significant glomerulosclerosis or cortical scarring; diagnosis of HSP; failure to meet eGFR and biopsy requirement criteria; serum IgG below 6 g/L; use of CPA ever or use of other immunosuppressants or systemic corticosteroids within 4 months; active infection requiring hospitalisation or treatment with parenteral anti-infective within 4 weeks; history, or current diagnosis, of active TB, or untreated latent TB infection; history of or positive HIV and/or positive for hepatitis B or hepatitis C at screening; history of malignancy; nursing or pregnancy; any condition, including any uncontrolled disease state other than IgAN
Interventions	Treatment group 1 • Atacicept (SC): 25 mg once/week for 156 weeks Treatment group 2

NCT02808429 *(Continued)*

	• Atacicept (SC): 75 mg once/week for 156 weeks Treatment group 2 • Atacicept (SC) 150 mg once/week for 156 weeks Control group • Placebo (SC): once/week for 156 weeks
Outcomes	• Proportion of subjects with adverse events, adverse events of special interest, serious adverse events, adverse events leading to discontinuation, and adverse events leading to death • Percent change from baseline in proteinuria • Change from baseline in kidney function
Starting date	January 2017
Contact information	Study Director: EMD Serono Research & Development Institute, Inc., a subsidiary of Merck KGaA, Darmstadt, Germany US Medical Information 888-275-7376 service@emdgroup.com Merck KGaA Communication Center 49 6151 72 5200 service@merckgroup.com
Notes	Estimated completion date: July 2020 No study results available

NCT03468972

Trial name or title	Effect of immunosuppression in IgA nephropathy
Methods	Parallel RCT
Participants	• Setting: multicentre (19 hospitals) • Country: Korea • Patients with biopsy-proven IgAN within 5 years; persistent proteinuria who have preserved eGFR of ≥ 30 mL/min/1.73 m^2; proteinuria < 1.0 g/g creatinine; 19 to 75 years, baseline eGFR ≥ 30 mL/min/1.73 m^2 assessed by CKD-EPI equation • Number: estimated 87 subjects (a total of 174) would be required for each group • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: nephrotic syndrome, atypical IgAN; crescents ≥ 25%; overt pulmonary tuberculosis; malignancy within 5 years of enrolment; pregnancy or breast feeding; active hepatitis, chronic hepatitis, liver cirrhosis, HIV; kidney transplant; current use of immunosuppressive treatment or prior use of immunosuppressive drugs within 1 year of enrolment; uncontrolled hypertension (> 160/100 mmHg); aged < 19 years; secondary IgAN such as lupus nephritis, chronic liver disease, or HSP; involvement of other clinical trials within 3 months of enrolment
Interventions	Treatment group 1

NCT03468972 *(Continued)*

	• Corticosteroid Treatment group 2 • Supportive care: including the use of RAS blockers, BP control with a target of < 130/80 mmHg, and protein restriction diet
Outcomes	• Development of a ≥ 30% decline in eGFR • Onset of ESKD • Changes in urinary protein excretion and haematuria
Starting date	Estimated March 2019
Contact information	Seung Hyeok Han 82-2-2228-1984 hansh@yuks.ac
Notes	Estimated study completion date: May 2023 No study results available

NEFIGARD 2018

Trial name or title	Efficacy and safety of nefecon in patients with primary IgA (immunoglobulin A) nephropathy (NEFIGARD)
Methods	Parallel RCT
Participants	• Setting: multicentre • Country: multinational • Adult patients with primary biopsy-proven IgAN at risk of progressing to ESKD; stable dose of RAS inhibitor therapy (ACEi and/or ARB) at the maximum allowed dose or maximum tolerated dose according to the 2012 KDIGO guidelines; UPCR ≥ 1 g/24 hours; eGFR ≥ 45 mL/min/1.73 m^2 and ≤ 90 mL/min/1.73 m^2 using CKD-EPI formula; willing and able to give informed consent • Number: estimated 450 participants • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: systemic diseases that may cause mesangial IgA deposition; patients who have undergone a kidney transplant; patients with acute or chronic infectious disease including hepatitis, TB, HIV, and chronic urinary tract infections; patients with liver cirrhosis, as assessed by the Investigator; patients with a diagnosis of type 1 or type 2 DM which is poorly controlled; patients with history of unstable angina, class III or IV congestive heart failure, and/or clinically significant arrhythmia, as judged by the Investigator; patients with unacceptable BP control defined as a BP consistently above national guidelines for proteinurics renal disease, as assessed by the Investigator; patients with diagnosed malignancy within the past 5 years
Interventions	Treatment group 1 • Nefecon (oral): 16 mg/month (Budosenide modified released capsule) for 9 months Treatment group 2 • Placebo capsules (oral): daily administration for 9 months
Outcomes	• Change in proteinuria, measured as UPCR

NEFIGARD 2018 *(Continued)*

	• Events based on renal function measured as eGFR, calculated using the CKD-EPI formula • The incidence of treatment-emergent adverse events • Renal function measured as eGFR using the CKD-EPI formula
Starting date	August 2018
Contact information	Medpace Research, Inc +1 800 730 5779 info@medpace.com
Notes	Estimated study completion date: December 2024 No study results available

PIRAT 2015

Trial name or title	Prevention in recipients with Primary IgA Nephropathy of Recurrence After Kidney Transplantation: ATG-F versus basiliximab as induction immunosuppressive treatment (PIRAT)
Methods	Parallel RCT
Participants	• Setting: multicentre • Country: France • Patients 18 to 75 years with diagnosis of native kidney primary IgA GN biopsy-proven; first kidney transplantation (one kidney) • Number: 115 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: PRA (PRA global or class I or class II PRA) over 50% on a serum before transplantation; multi-organ graft; transplants using donor limits or sub-optimal: donor age ≥ 70 years, donors in the study BIGRAS or taken heart beating donors (tested on computer infusion) or other restriction factors; IgA GN secondary to HSP or SLE or alcoholic cirrhosis; history of cancer older than 5 years or with advanced cancer, but except for non-recurrent skin cancers; infectious diseases scalable: TB, HIV, Hepatitis B virus or Hepatitis C virus infection with viral replication and/or chronic hepatitis; allergy to rabbit proteins; severe thrombocytopenia (< 50,000 platelets/µL); bacterial infection, viral and fungal uncontrolled therapeutically; pregnancy or lactation
Interventions	Treatment group 1 • Rabbit immunoglobulin antilymphocyte human T (ATG-Fresenius®): administered by slow infusion over 4 hours after antihistamine (2 bulbs Polaramine® IV) and IV methylprednisolone (minimum 30 mg); it is started on day 0 prior to surgery at doses of 4 mg/kg, and then continued to day 1, day 2 to 4 mg/kg, then day 3, day 4 at the dose of 3 mg/kg Treatment group 2 • The anti CD25 (basiliximab, Simulect®): IV administered before surgery of kidney transplantation (day 0 and day + 4) (1 ampoule of 20 mg x 2 times)
Outcomes	• Clinical recurrence • Histological recurrence defined by the presence of mesangial deposits of IgA (at least 1+) by immunofluorescence on a biopsy of the graft
Starting date	January 2011

PIRAT 2015 *(Continued)*

Contact information	Principal Investigator: Francois Berthoux
Notes	Estimated study completion date: December 2019 No study results available Sponsor: Centre Hospitalier Universitaire de Saint Etienne

SIGN 2014

Trial name or title	Safety and efficacy study of fostamatinib to treat immunoglobulin A (IgA) nephropathy
Methods	Parallel RCT
Participants	• Setting: multinational • Country: USA, Austria, Germany, Hong Kong, Taiwan, UK • Patients 18 to 70 years with biopsy-proven IgAN; treatment with ACEi or ARB for at least 90 days; proteinuria > 1 g/day at diagnosis or > 0.5 g/day at second screening visit; BP ≤ 130/80 mmHg with angiotensin blockade with or without other anti-hypertensive treatments • Number: 75 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: recent use of CPA, MMF, AZA, or rituximab; use of prednisone > 15 mg/day or other corticosteroid equivalent
Interventions	Treatment group 1 • Fostamatinib (oral): 150 mg twice/day Treatment group 2 • Fostamatinib (oral): 100 mg twice/day Control group • Placebo (oral): twice/da Co-interventions • Treatment with an ACEi and/or an ARB for at least 90 days at the maximum approved (or tolerated) dose
Outcomes	• Mean change of proteinuria as measured by spot UPCR
Starting date	October 2014
Contact information	Study director: Rigel Pharmaceuticals Inc (no other specific information available)
Notes	Estimated study completion date: November 2018 No study results available Responsible party: Rigel Pharmaceuticals

TIGER 2017

Trial name or title	Treatment of IgA Nephropathy According to Renal Lesions (TIGER)
Methods	Parallel RCT
Participants	• Setting: multicentre • Country: France • Age >18 years; IgAN diagnosed on renal biopsy < 45 days; UPCR > 0.75 g/g (within 15 days before or after the renal biopsy); renal biopsy with at least 8 glomeruli • Number: 122 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: > 30% increase of SCr within 15 days after starting RAS blockade therapy; > 50% cellular/fibrocellular crescents, or > 50% tubulointerstitial fibrosis or > 50% globally sclerotic glomeruli; > 50% SCr increase within the last 3 months before the renal biopsy; nephrotic syndrome with minimal change disease and IgA deposits; GFR < 20 mL/min/1.73 m^2 (CKD-EPI formula) within 15 days before or after the renal biopsy; uncontrolled BP (SBP > 180 mmHg or DBP > 110 mmHg); previous corticosteroids treatment (> 20 mg/day during more than 15 days, within the last 3 months before the renal biopsy); pregnancy or breast feeding or women without sufficient contraception; secondary known forms of IgAN; HSP; additional other CKD; contraindication for immunosuppressive therapy, including active intestinal bleeding, active gastric or duodenal ulcer; active infection; any malignancy in a last years before the inclusion; severe psychiatric disease; living vaccines; anti-inflammatory dosages of acetylsalicylic acid; contraindication for RAS blockade therapy; known allergy or intolerance to corticoids or lactose; organ transplant patient
Interventions	Treatment group • Corticotherapy: 3 IV pulses steroids followed by oral steroids for 4 months • RAS blockade treatment (oral) Control group • RAS blockade treatment (oral)
Outcomes	• Failure at 24 months • GFR • Proteinuria • SF36 scale
Starting date	February 2018
Contact information	Dominique Joly +33 1 44 49 54 12 dominique.joly@nck.aphp.fr Sandra Colas 01 71 19 64 32 sandra.colas@aphp.fr
Notes	Estimated study completion: June 2019 No study results available

TOPplus-IgAN 2013

Trial name or title	Treatment of Prednisone Plus Cyclophosphamide in Patients With Advanced-stage IgA Nephropathy (TOPplus-IgAN)
Methods	Parallel RCT
Participants	• Setting: single centre • Country: China • Biopsy-proven primary IgAN; aged 18 to 70 years; elevated SCr and < 3.0 mg/dL • Number: 122 participants planned • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: DM; contraindications for the treatment of prednisone and/or CPA, any treatment with steroids or immunosuppressive drugs prior to this study, acute deterioration of renal function(including those of glomerular origin)
Interventions	Treatment group 1 • Prednisone: 0.5 mg/kg/day for 6 months • CPA (IV): 1 g/ month for 6 months Treatment group 2 • Prednisone: 0.5 mg/kg/day for 6 months Co-interventions • Supportive care, including ACEi or ARB and BP control
Outcomes	• Changes of kidney function or death • Changes of proteinuria
Starting date	December 2012
Contact information	Principal Investigator: Wei Shi. Guangdong General Hospital
Notes	Study completion: December 2019 No study results available

UMIN000032031

Trial name or title	The steroid internal use method for patients with IgA nephropathy
Methods	Parallel RCT
Participants	• Setting: not yet available • Country: Japan • Patients with biopsy-proven IgAN (at least 20 years old) and with indication with steroid therapy • Number: estimated 100 participants • Mean age ± SD (years): not yet available • Sex (M/F): not yet available • Exclusion criteria: patients decided by the doctor to be unsuitable to use the study other than above
Interventions	Treatment group 1

UMIN000032031 *(Continued)*	• Prednisolone: 0.5 mg/kg/day Treatment group 2 • Prednisolone: 0.25 mg/kg/day
Outcomes	• Safety • Efficacy • Adverse events
Starting date	April 2018
Contact information	Hitoshi Suzuki 03-5802-1065 shitoshi@juntendo.ac.jp
Notes	Estimated study completion date: not yet available No study results available

ACEi - angiotensin-converting enzyme inhibitor; AKI - acute kidney injury; ARB - angiotensin receptor blocker; AZA - azathioprine; BMI - body mass index; BP - blood pressure; CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration; CPA - cyclophosphamide; CrCl - creatinine clearance; CSA - cyclosporin; DBP - diastolic blood pressure; DM - diabetes mellitus; ESKD - end-stage kidney disease; (e)GFR - (estimated) glomerular filtration rate; GN - glomerulonephritis; HCT - hematocrit; HIV - human immunodeficiency virus; HSP - Henoch-Schönlein purpura; IgAN - IgA nephropathy; KRT - kidney replacement therapy; M/F - male/female; MDRD - Modified Diet in Renal Disease; MMF - mycophenolate mofetil; PRA - panel reactive antibody; RAS - renin-angiotensin system; RCT - randomised controlled trial; SBP - systemic blood pressure; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; SLE - systemic lupus erythematosus; TB - tuberculosis; WBC - white blood cell count; UPCR - urinary protein:creatinine ratio

DATA AND ANALYSES

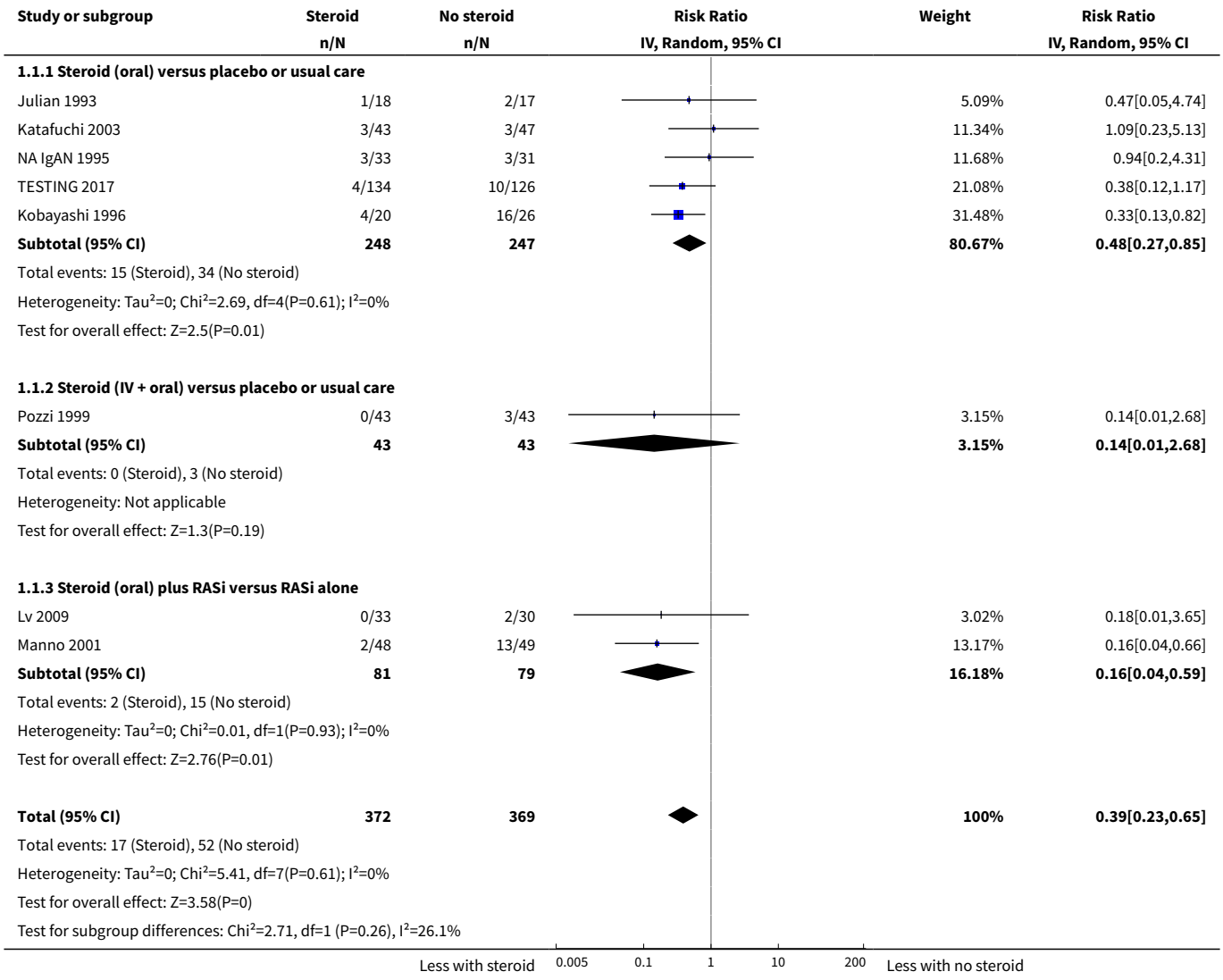
Comparison 1. Systemic corticosteroid versus no corticosteroid regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	8	741	Risk Ratio (IV, Random, 95% CI)	0.39 [0.23, 0.65]
1.1 Steroid (oral) versus placebo or usual care	5	495	Risk Ratio (IV, Random, 95% CI)	0.48 [0.27, 0.85]
1.2 Steroid (IV + oral) versus placebo or usual care	1	86	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.68]
1.3 Steroid (oral) plus RASi versus RASi alone	2	160	Risk Ratio (IV, Random, 95% CI)	0.16 [0.04, 0.59]
2 Complete remission	4	305	Risk Ratio (IV, Random, 95% CI)	1.76 [1.03, 3.01]
2.1 Steroid (oral) versus placebo or usual care	2	145	Risk Ratio (IV, Random, 95% CI)	3.47 [0.71, 17.08]

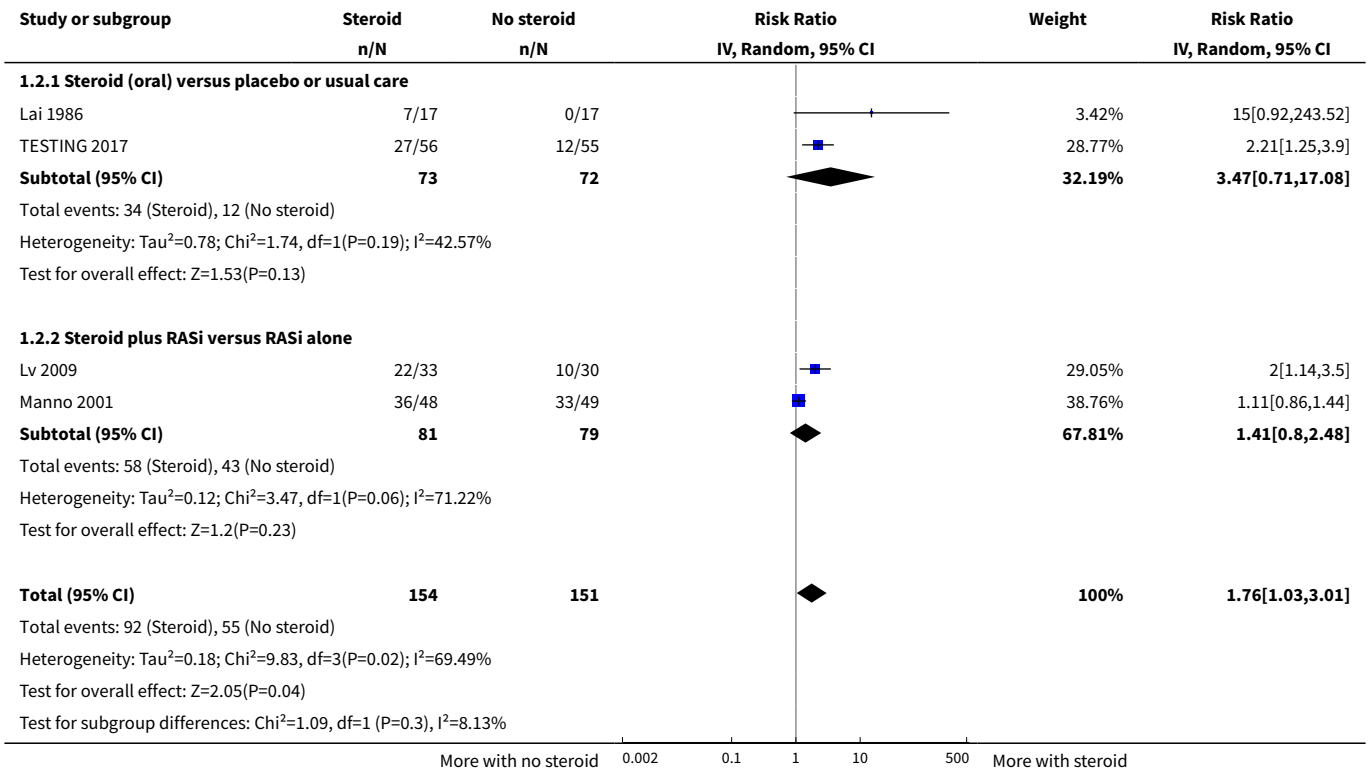
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Steroid plus RASi versus RASi alone	2	160	Risk Ratio (IV, Random, 95% CI)	1.41 [0.80, 2.48]
3 Doubling of serum creatinine	7	404	Risk Ratio (IV, Random, 95% CI)	0.43 [0.29, 0.65]
3.1 Steroid (oral) versus placebo or usual care	6	341	Risk Ratio (IV, Random, 95% CI)	0.45 [0.29, 0.69]
3.2 Steroid (oral) plus RASi versus RASi alone	1	63	Risk Ratio (IV, Random, 95% CI)	0.26 [0.06, 1.15]
4 Serum creatinine	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	7	211	Mean Difference (IV, Random, 95% CI)	-21.07 [-44.12, 1.99]
5 GFR loss: ≥ 50%	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Steroid (oral) versus placebo or usual care	2	326	Risk Ratio (IV, Random, 95% CI)	0.56 [0.25, 1.24]
6 Annual GFR loss [mL/min/1.73 m^2]	2	359	Mean Difference (IV, Random, 95% CI)	-5.40 [-8.55, -2.25]
6.1 Steroid (oral) versus placebo or usual care	1	262	Mean Difference (IV, Random, 95% CI)	-5.16 [-9.79, -0.53]
6.2 Steroid (oral) plus RASi versus RASi alone	1	97	Mean Difference (IV, Random, 95% CI)	-5.61 [-9.91, -1.31]
7 GFR (any measure)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	4	138	Mean Difference (IV, Random, 95% CI)	17.87 [4.93, 30.82]
8 Urinary protein excretion	10	705	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.84, -0.33]
8.1 Steroid plus dipyridamole versus dipyridamole alone	1	48	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.78, 0.04]
8.2 Steroid versus no treatment or placebo or other non-immunosuppressive treatment	9	657	Mean Difference (IV, Random, 95% CI)	-0.63 [-0.92, -0.33]
9 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
9.1 Steroid (oral) versus placebo or usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Infection	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10.1 Steroid (oral) versus placebo or usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
11.1 Steroid (IV + oral) versus placebo or usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

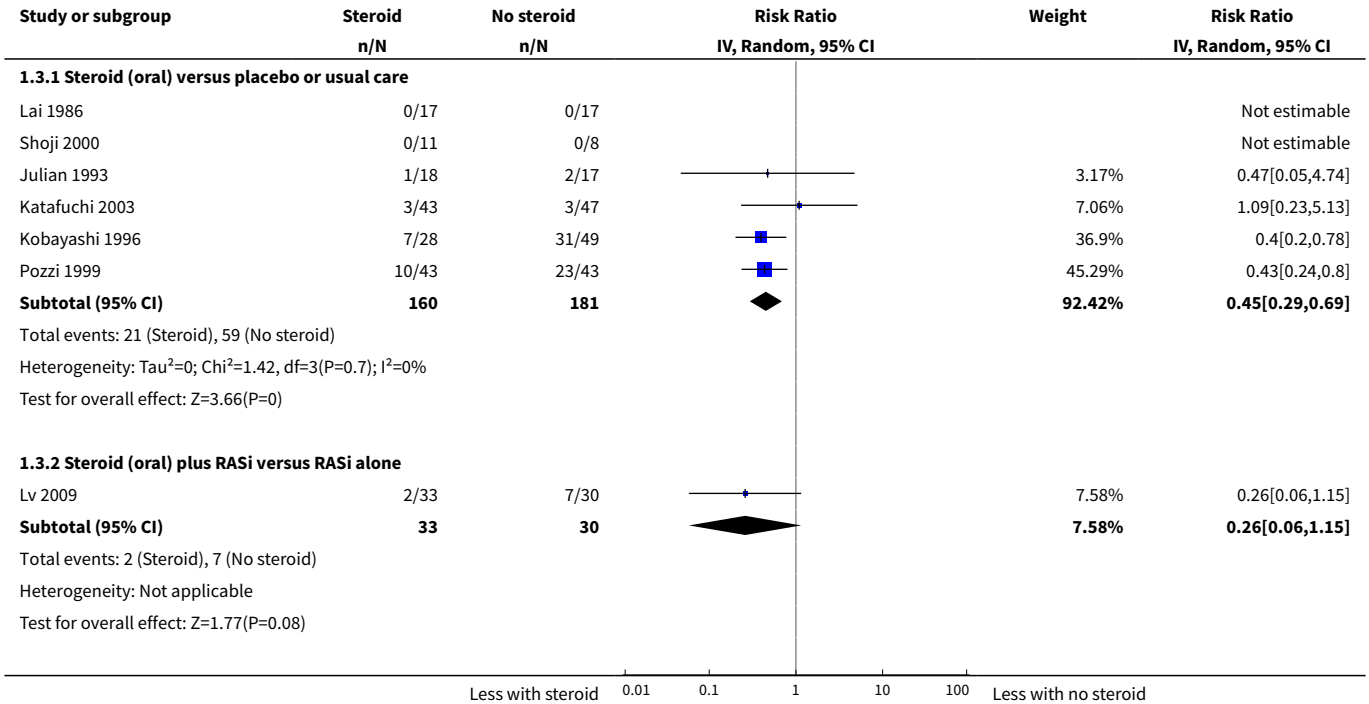
Analysis 1.1. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 1 ESKD.

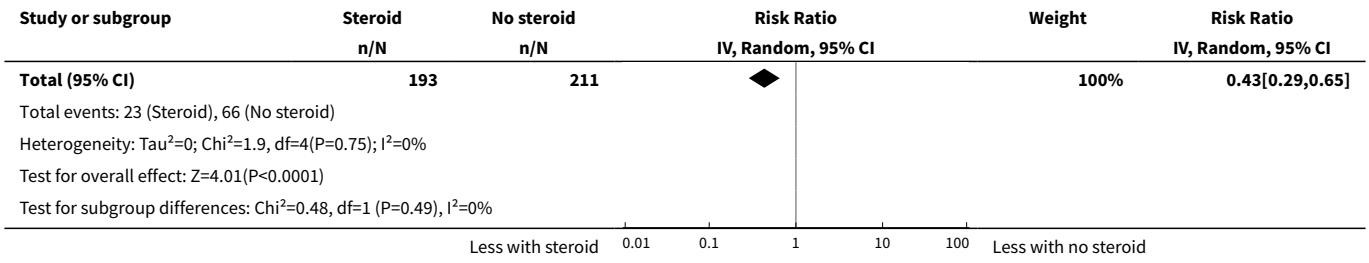


Analysis 1.2. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 2 Complete remission.

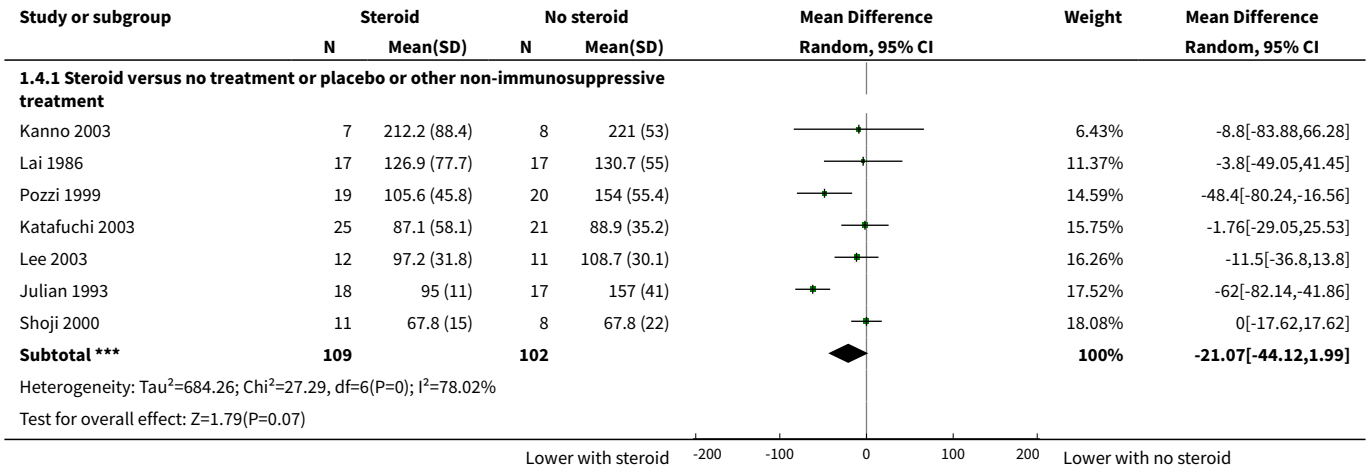


Analysis 1.3. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 3 Doubling of serum creatinine.

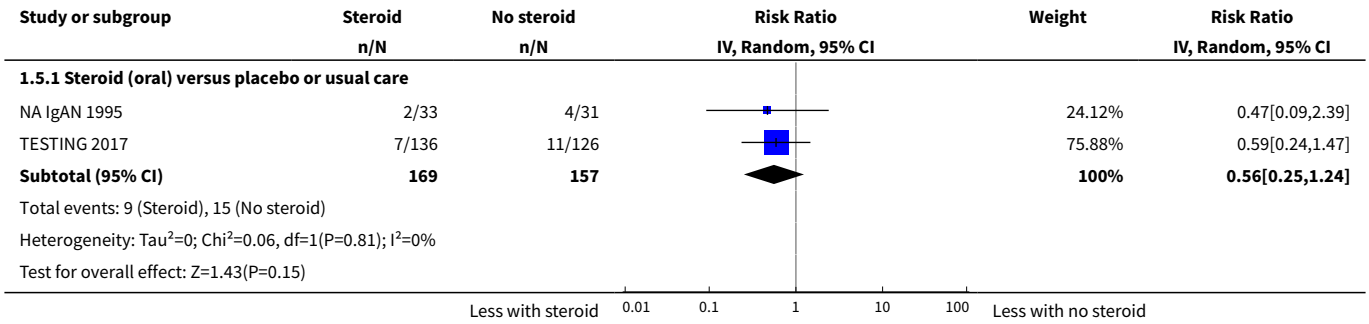




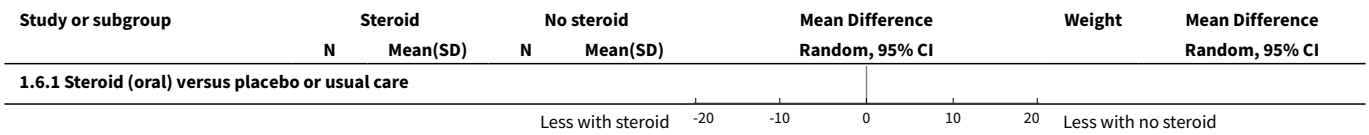
Analysis 1.4. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 4 Serum creatinine.

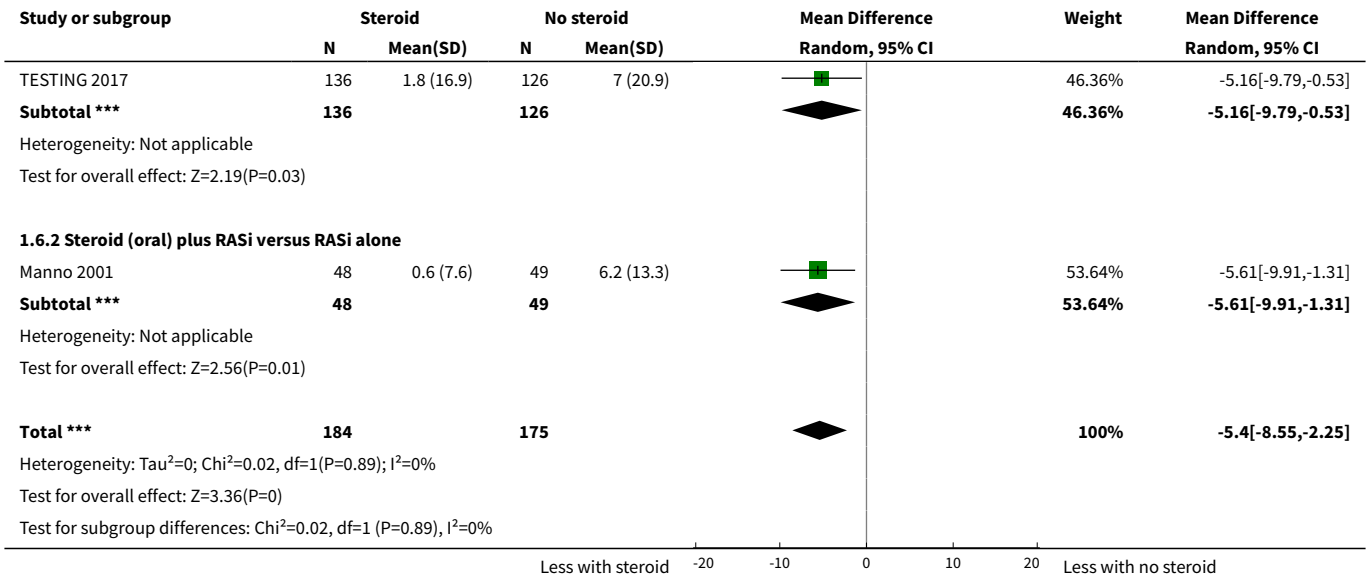


Analysis 1.5. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 5 GFR loss: ≥ 50%.

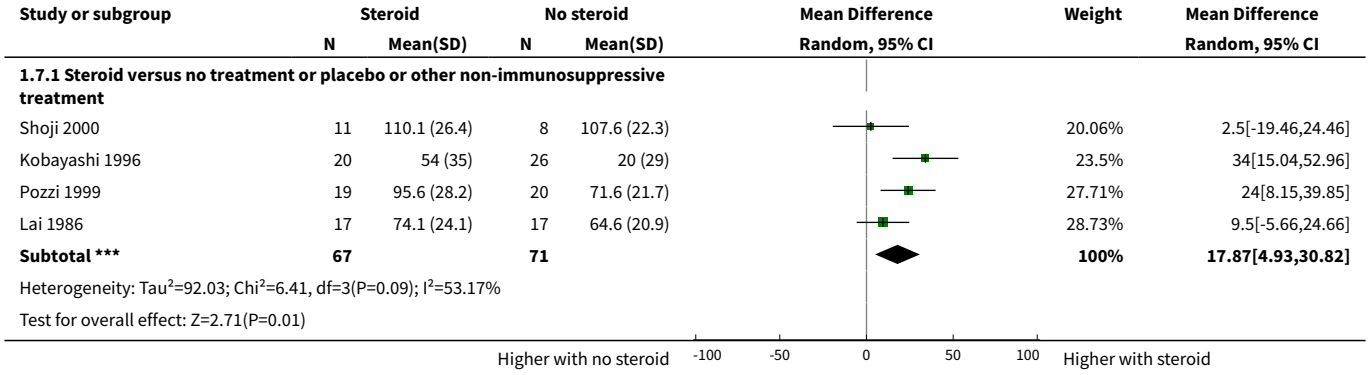


Analysis 1.6. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 6 Annual GFR loss [mL/min/1.73 m^2].

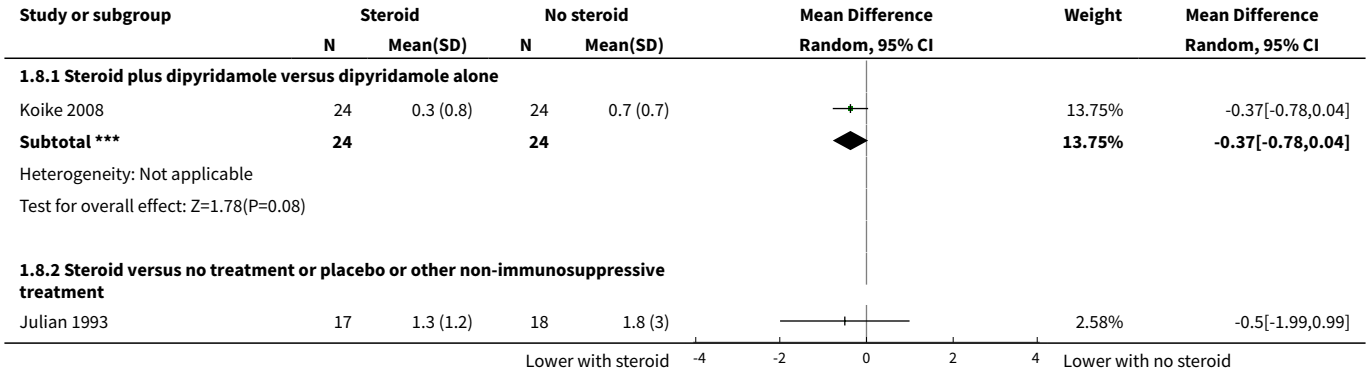




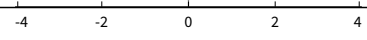
Analysis 1.7. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 7 GFR (any measure).



Analysis 1.8. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 8 Urinary protein excretion.

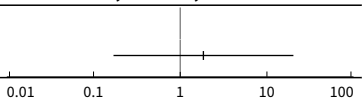


Study or subgroup	Steroid N	Steroid Mean(SD)	No steroid N	No steroid Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lai 1986	17	2.3 (2.2)	17	3.3 (2.1)		2.73%	-1[-2.45,0.45]
Pozzi 1999	19	0.7 (0.5)	20	1.8 (2.3)		4.74%	-1.1[-2.14,-0.06]
Lee 2003	12	0.5 (0.5)	11	1.9 (1.2)		7.37%	-1.35[-2.11,-0.59]
Katafuchi 2003	43	1.3 (1.4)	47	1.4 (2)		8.22%	-0.08[-0.78,0.62]
Kobayashi 1996	20	0.8 (0.5)	26	1.5 (1.3)		10.78%	-0.7[-1.25,-0.15]
TESTING 2017	136	1.4 (1.1)	126	2.4 (1.7)		15.3%	-0.98[-1.32,-0.64]
Shoji 2000	11	0.3 (0.2)	8	0.7 (0.4)		16.3%	-0.42[-0.72,-0.12]
STOP-IgAN 2008	55	0.6 (0.5)	54	0.8 (0.6)		18.24%	-0.23[-0.45,-0.01]
Subtotal * **	**330**		**327**			**86.25%**	**-0.63[-0.92,-0.33]**
Heterogeneity: Tau^2=0.1; Chi^2=21.96, df=8(P=0); I^2=63.57%							
Test for overall effect: Z=4.17(P<0.0001)							
Total * **	**354**		**351**			**100%**	**-0.58[-0.84,-0.33]**
Heterogeneity: Tau^2=0.08; Chi^2=22.28, df=9(P=0.01); I^2=59.6%							
Test for overall effect: Z=4.48(P<0.0001)							
Test for subgroup differences: Chi^2=1.01, df=1 (P=0.32), I^2=0.84%							



Analysis 1.9. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 9 Death (any cause).

Study or subgroup	Steroid n/N	No steroid n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
1.9.1 Steroid (oral) versus placebo or usual care				
TESTING 2017	2/136	1/126		1.85[0.17,20.19]



Analysis 1.10. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 10 Infection.

Study or subgroup	Steroid n/N	No steroid n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
1.10.1 Steroid (oral) versus placebo or usual care				
TESTING 2017	11/136	0/126		21.32[1.27,358.1]

Analysis 1.11. Comparison 1 Systemic corticosteroid versus no corticosteroid regimen, Outcome 11 Malignancy.

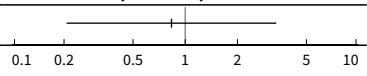
Study or subgroup	Steroid n/N	No steroid n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
1.11.1 Steroid (IV + oral) versus placebo or usual care				
Pozzi 1999	1/43	1/43		1[0.06,15.48]

Comparison 2. Locally-acting steroid versus no locally-acting steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Locally-acting steroid versus no locally-acting steroid, Outcome 1 Infection.

Study or subgroup	Budesonide n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
NEFIGAN 2017	5/100	3/50		0.83[0.21,3.35]



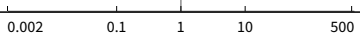
Comparison 3. Cytotoxic versus no cytotoxic regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	7	463	Risk Ratio (IV, Random, 95% CI)	0.63 [0.33, 1.20]
1.1 Cyclophosphamide then azathioprine plus steroid versus usual care	2	200	Risk Ratio (IV, Random, 95% CI)	0.49 [0.14, 1.75]
1.2 Cyclophosphamide plus antiplatelet/anticoagulant versus usual care	2	100	Risk Ratio (IV, Random, 95% CI)	0.31 [0.03, 2.85]
1.3 Azathioprine plus steroid versus placebo/usual care	1	43	Risk Ratio (IV, Random, 95% CI)	3.14 [0.13, 72.96]
1.4 Azathioprine plus steroid versus steroid alone	1	46	Risk Ratio (IV, Random, 95% CI)	1.17 [0.59, 2.32]
1.5 Azathioprine plus steroid plus anticoagulant/antiplatelet versus anticoagulant/antiplatelet	1	74	Risk Ratio (IV, Random, 95% CI)	0.34 [0.07, 1.64]
2 Complete remission	5	381	Risk Ratio (IV, Random, 95% CI)	1.47 [0.94, 2.30]
2.1 Cyclophosphamide then azathioprine plus steroid versus usual care	1	162	Risk Ratio (IV, Random, 95% CI)	3.41 [1.17, 9.93]
2.2 Cyclophosphamide plus steroid versus steroid	1	24	Risk Ratio (IV, Random, 95% CI)	0.78 [0.44, 1.39]
2.3 Azathioprine plus steroids versus placebo/usual care	1	43	Risk Ratio (IV, Random, 95% CI)	5.94 [2.03, 17.34]
2.4 Azathioprine plus steroids plus anticoagulants versus steroids alone	1	78	Risk Ratio (IV, Random, 95% CI)	1.24 [1.01, 1.52]

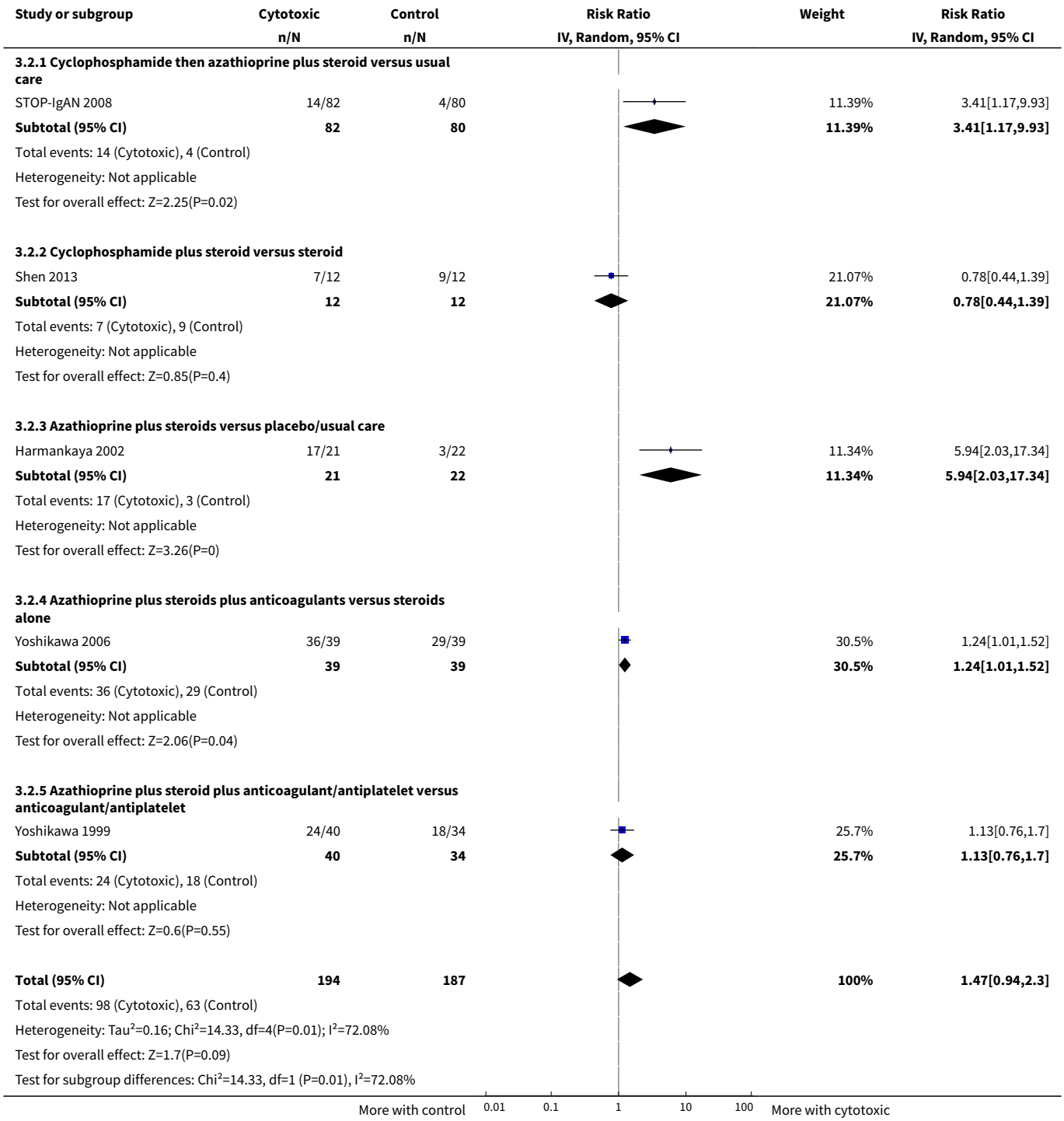
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Azathioprine plus steroid plus anticoagulant/antiplatelet versus anticoagulant/antiplatelet	1	74	Risk Ratio (IV, Random, 95% CI)	1.13 [0.76, 1.70]
3 Annual GFR loss [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Cyclophosphamide then azathioprine plus steroid versus usual care	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 GFR (any measure) [mL/min/1.73 m^2]	3	174	Mean Difference (IV, Random, 95% CI)	3.07 [-6.57, 12.72]
4.1 Azathioprine plus steroid plus anticoagulant/antiplatelet versus anticoagulant/antiplatelet	1	74	Mean Difference (IV, Random, 95% CI)	2.0 [-15.98, 19.98]
4.2 Azathioprine plus steroids plus anticoagulants versus steroids alone	2	100	Mean Difference (IV, Random, 95% CI)	3.51 [-7.92, 14.94]
5 Urinary protein excretion	5	255	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.80, 0.26]
5.1 Cytotoxic agents plus steroids versus placebo, no treatment or anticoagulant/antiplatelet	3	155	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.71, 0.21]
5.2 Cytotoxic agents plus steroids plus anticoagulants versus steroids alone	2	100	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.09, 0.05]
6 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 Cyclophosphamide then azathioprine plus steroid versus steroid	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Infection	4	268	Risk Ratio (IV, Random, 95% CI)	1.70 [0.43, 6.76]
7.1 Cyclophosphamide then azathioprine plus steroid versus usual care	2	200	Risk Ratio (IV, Random, 95% CI)	4.65 [0.54, 39.85]
7.2 Azathioprine plus steroid versus steroid alone	2	68	Risk Ratio (IV, Random, 95% CI)	0.85 [0.14, 5.10]
8 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Cyclophosphamide then azathioprine plus steroid versus usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 1 ESKD.

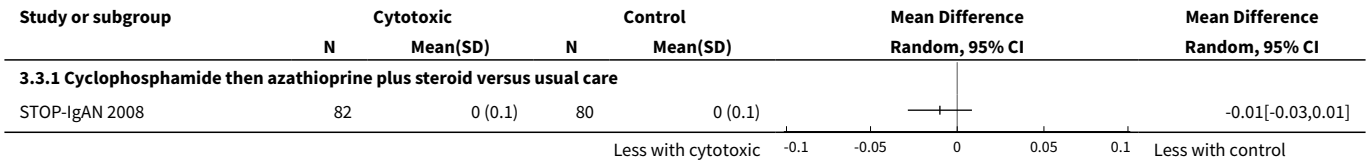
Study or subgroup	Cytotoxic n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Cyclophosphamide then azathioprine plus steroid versus usual care					
STOP-IgAN 2008	6/82	6/80		20.27%	0.98[0.33,2.9]
Ballardie 2002	4/19	15/19		24.7%	0.27[0.11,0.66]
Subtotal (95% CI)	**101**	**99**		**44.96%**	**0.49[0.14,1.75]**
Total events: 10 (Cytotoxic), 21 (Control)					
Heterogeneity: Tau^2=0.58; Chi^2=3.24, df=1(P=0.07); I^2=69.09%					
Test for overall effect: Z=1.1(P=0.27)					
3.1.2 Cyclophosphamide plus antiplatelet/anticoagulant versus usual care					
Walker 1990a	0/25	1/27		3.89%	0.36[0.02,8.43]
Woo 1987	0/27	1/21		3.9%	0.26[0.01,6.12]
Subtotal (95% CI)	**52**	**48**		**7.78%**	**0.31[0.03,2.85]**
Total events: 0 (Cytotoxic), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					
3.1.3 Azathioprine plus steroid versus placebo/usual care					
Harmankaya 2002	1/21	0/22		3.91%	3.14[0.13,72.96]
Subtotal (95% CI)	**21**	**22**		**3.91%**	**3.14[0.13,72.96]**
Total events: 1 (Cytotoxic), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
3.1.4 Azathioprine plus steroid versus steroid alone					
Locatelli 1999	9/20	10/26		30.85%	1.17[0.59,2.32]
Subtotal (95% CI)	**20**	**26**		**30.85%**	**1.17[0.59,2.32]**
Total events: 9 (Cytotoxic), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
3.1.5 Azathioprine plus steroid plus anticoagulant/antiplatelet versus anticoagulant/antiplatelet					
Yoshikawa 1999	2/40	5/34		12.5%	0.34[0.07,1.64]
Subtotal (95% CI)	**40**	**34**		**12.5%**	**0.34[0.07,1.64]**
Total events: 2 (Cytotoxic), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
Total (95% CI)	**234**	**229**		**100%**	**0.63[0.33,1.2]**
Total events: 22 (Cytotoxic), 38 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=9.13, df=6(P=0.17); I^2=34.27%					
Test for overall effect: Z=1.4(P=0.16)					
Test for subgroup differences: Chi^2=4.3, df=1 (P=0.37), I^2=7.02%					



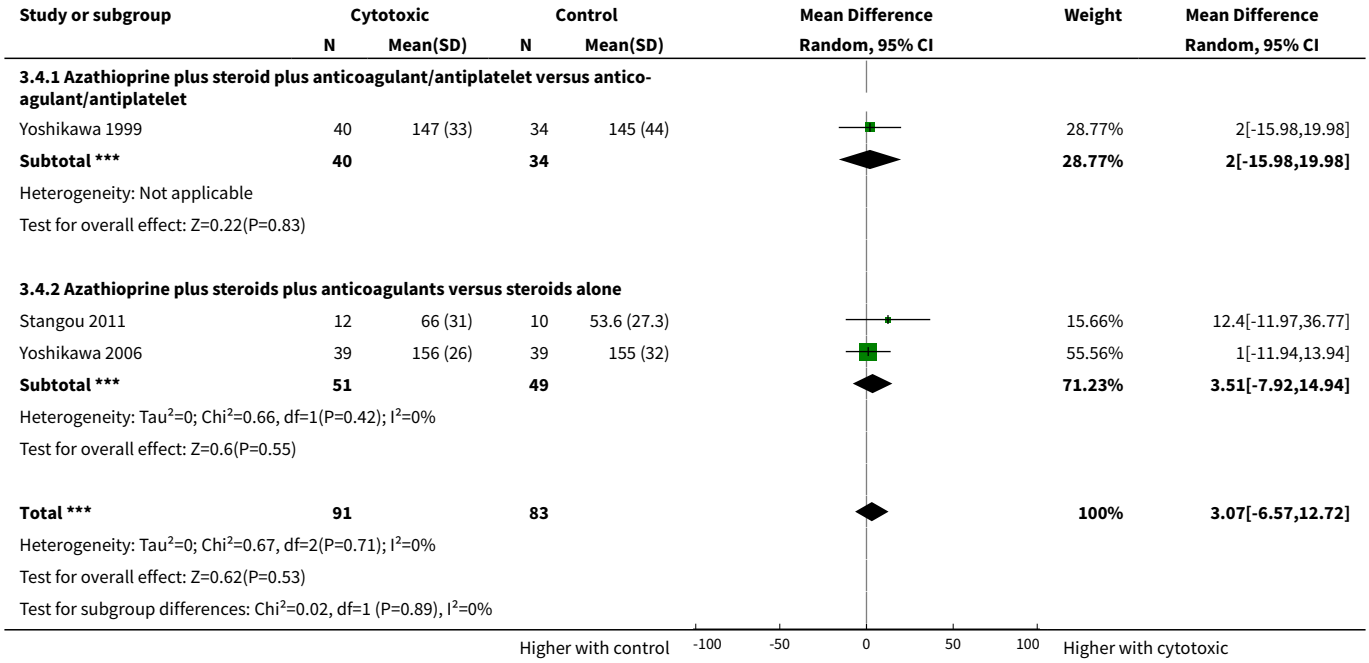
Analysis 3.2. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 2 Complete remission.



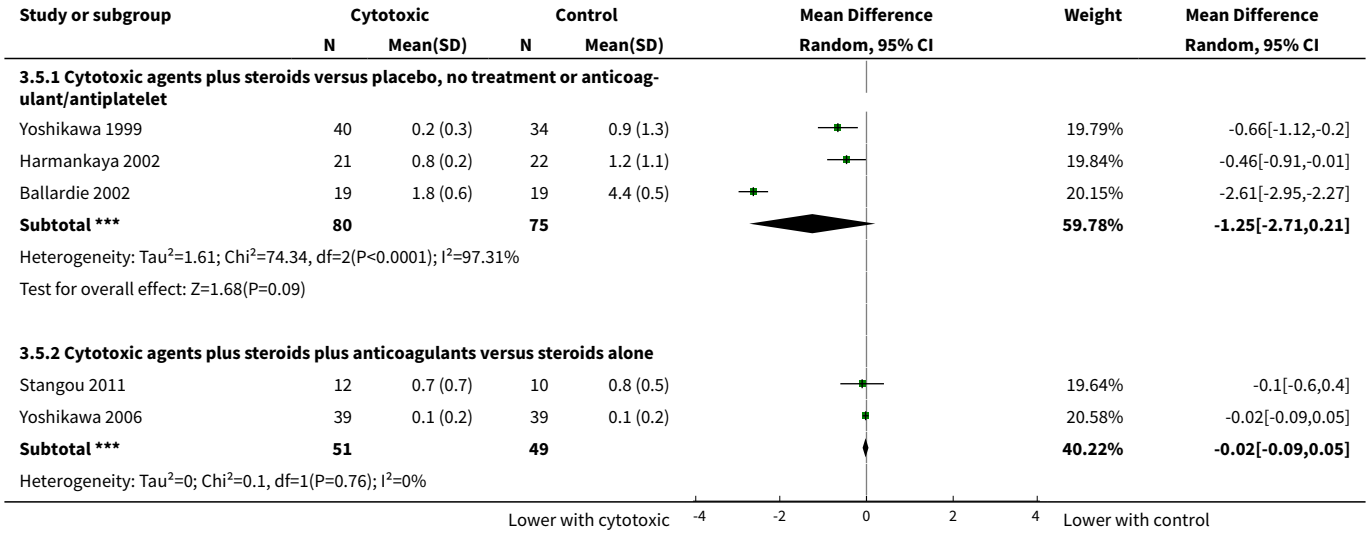
Analysis 3.3. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 3 Annual GFR loss [mL/min/1.73 m^2].

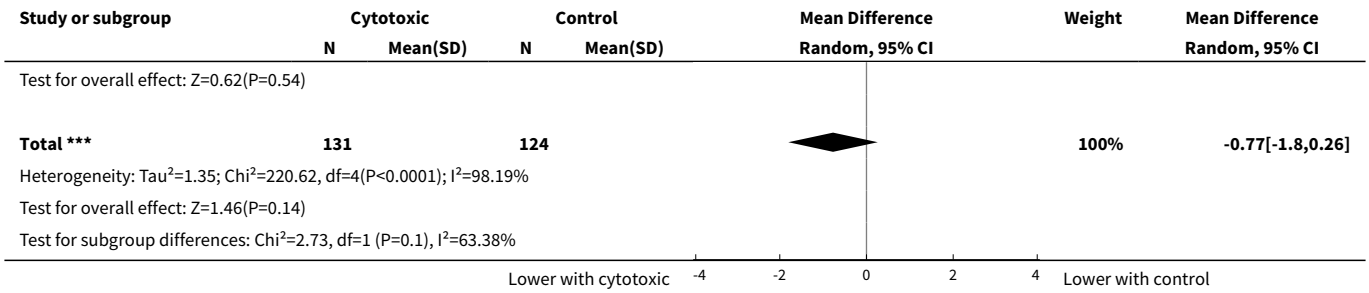


Analysis 3.4. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 4 GFR (any measure) [mL/min/1.73 m^2].

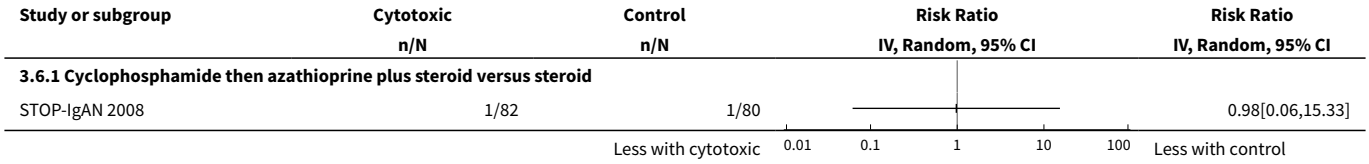


Analysis 3.5. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 5 Urinary protein excretion.

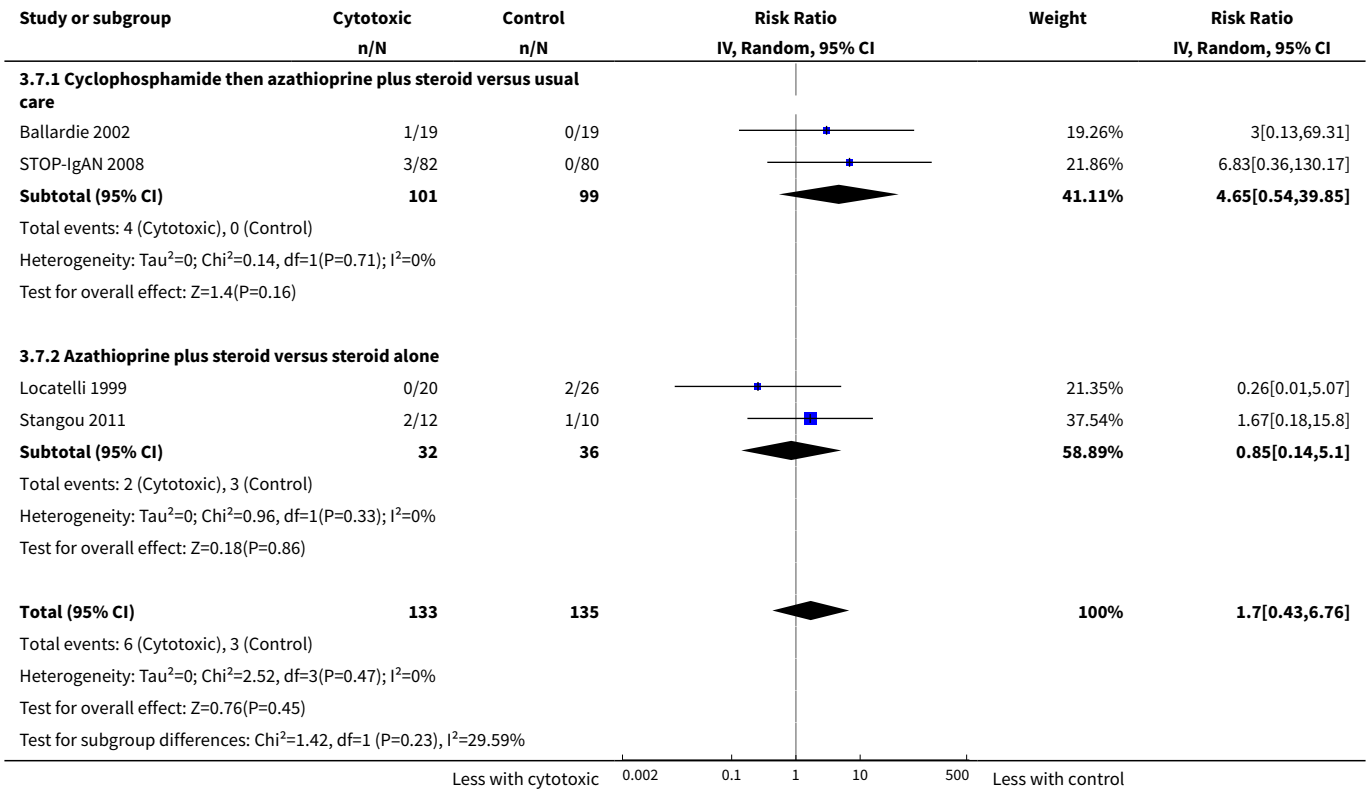




Analysis 3.6. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 6 Death (any cause).

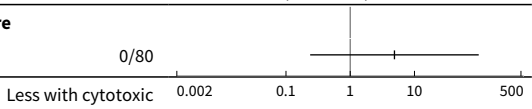


Analysis 3.7. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 7 Infection.



Analysis 3.8. Comparison 3 Cytotoxic versus no cytotoxic regimen, Outcome 8 Malignancy.

Study or subgroup	Cytotoxic n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
3.8.1 Cyclophosphamide then azathioprine plus steroid versus usual care				
STOP-IgAN 2008	2/82	0/80		4.88[0.24,100.08]

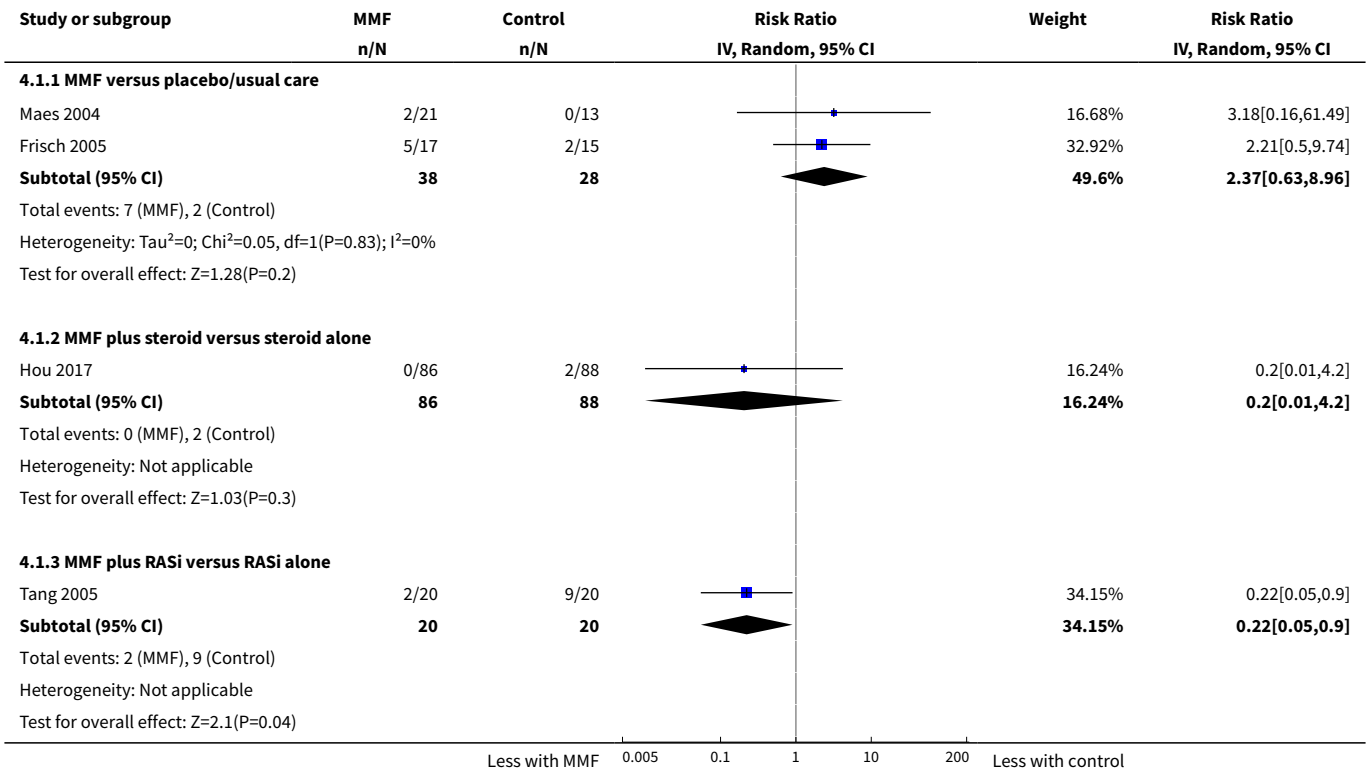


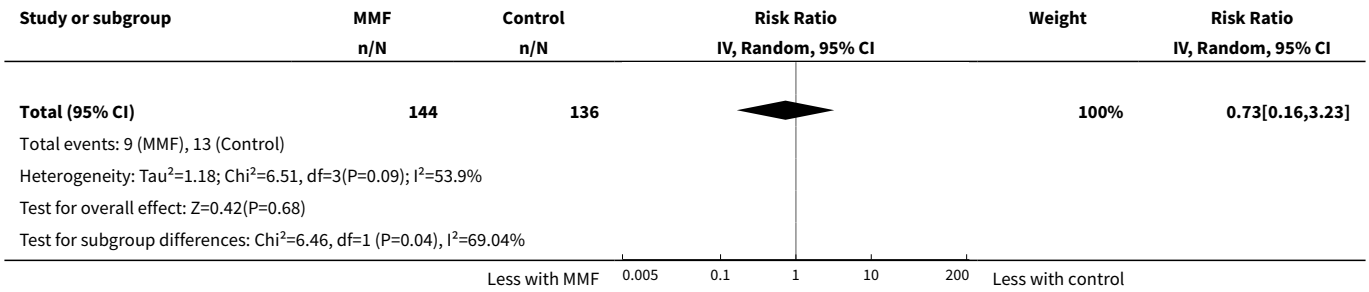
Comparison 4. MMF versus no MMF regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	4	280	Risk Ratio (IV, Random, 95% CI)	0.73 [0.16, 3.23]
1.1 MMF versus placebo/usual care	2	66	Risk Ratio (IV, Random, 95% CI)	2.37 [0.63, 8.96]
1.2 MMF plus steroid versus steroid alone	1	174	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 4.20]
1.3 MMF plus RASi versus RASi alone	1	40	Risk Ratio (IV, Random, 95% CI)	0.22 [0.05, 0.90]
2 Complete remission	4	271	Risk Ratio (IV, Random, 95% CI)	1.05 [0.73, 1.52]
2.1 MMF versus placebo/usual care	3	97	Risk Ratio (IV, Random, 95% CI)	2.02 [0.55, 7.38]
2.2 MMF plus steroid versus steroid alone	1	174	Risk Ratio (IV, Random, 95% CI)	0.99 [0.68, 1.46]
3 Doubling of serum creatinine	2	74	Risk Ratio (IV, Random, 95% CI)	2.01 [0.28, 14.44]
3.1 MMF versus placebo/usual care	1	34	Risk Ratio (IV, Random, 95% CI)	4.45 [0.25, 79.87]
3.2 MMF plus RASi versus RASi alone	1	40	Risk Ratio (IV, Random, 95% CI)	1.0 [0.07, 14.90]
4 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 GFR loss: ≥ 50%	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 MMF versus placebo/usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 GFR loss: ≥ 25%	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 MMF versus placebo/usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Annual GFR loss [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 MMF versus placebo/usual care	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 GFR (any measure) [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

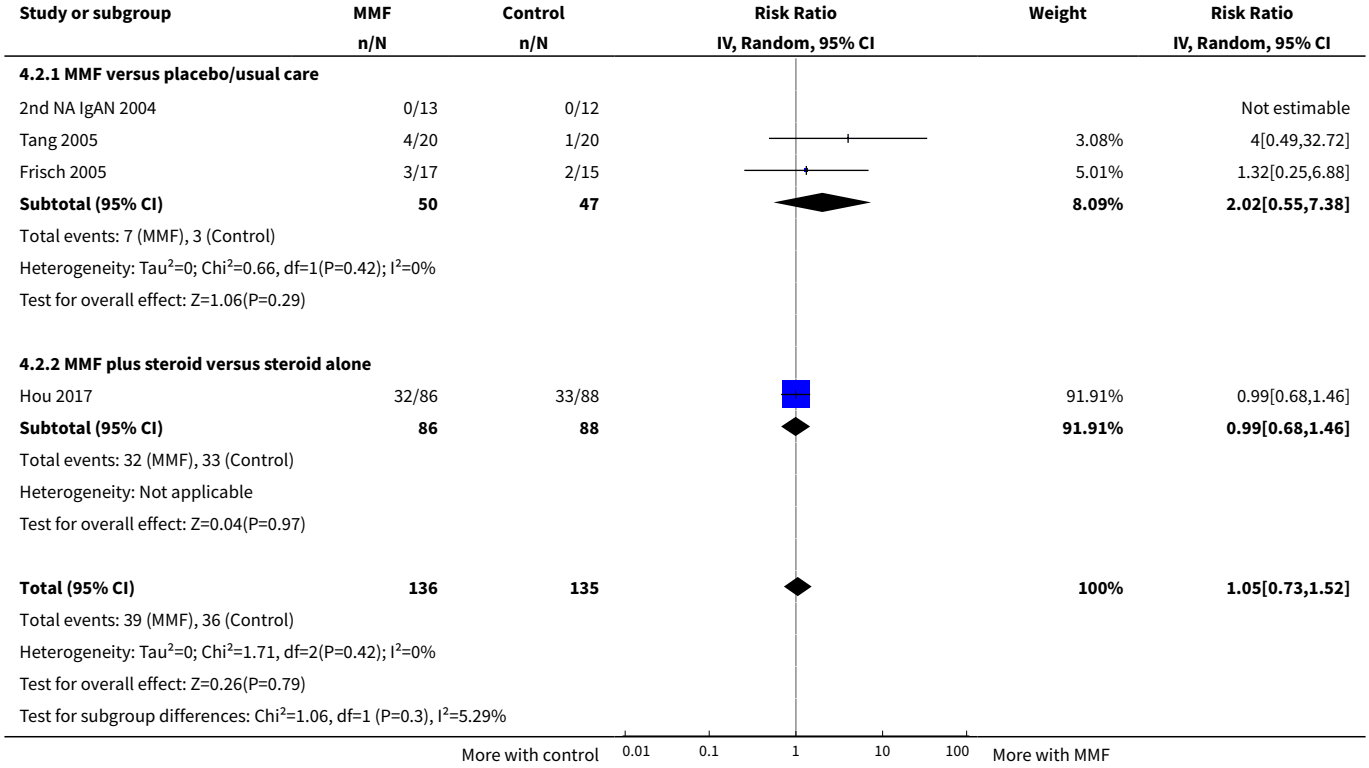
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9 Urinary protein excretion	5	172	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.92, 0.81]
9.1 MMF versus placebo	3	92	Mean Difference (IV, Random, 95% CI)	0.59 [0.20, 0.98]
9.2 MMF plus RASi versus RASi alone	1	40	Mean Difference (IV, Random, 95% CI)	-1.26 [-1.46, -1.06]
9.3 MMF versus leflunomide	1	40	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.20, 0.16]
10 Infection	4	301	Risk Ratio (IV, Random, 95% CI)	1.36 [0.87, 2.12]
10.1 MMF versus placebo/usual care	3	126	Risk Ratio (IV, Random, 95% CI)	1.35 [0.50, 3.64]
10.2 MMF plus steroid versus steroid alone	1	175	Risk Ratio (IV, Random, 95% CI)	1.37 [0.83, 2.24]
11 Malignancy	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
11.1 MMF versus placebo/usual care	2	86	Risk Ratio (IV, Random, 95% CI)	0.28 [0.03, 2.54]

Analysis 4.1. Comparison 4 MMF versus no MMF regimen, Outcome 1 ESKD.

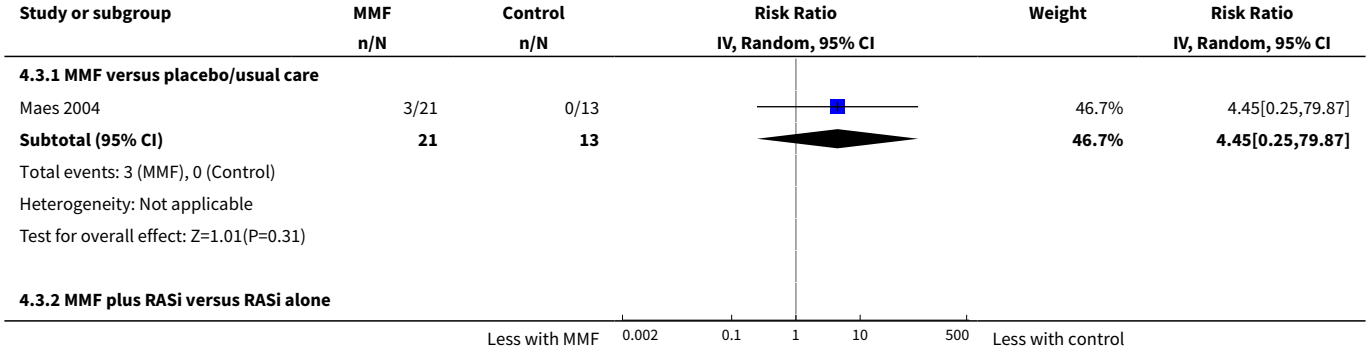


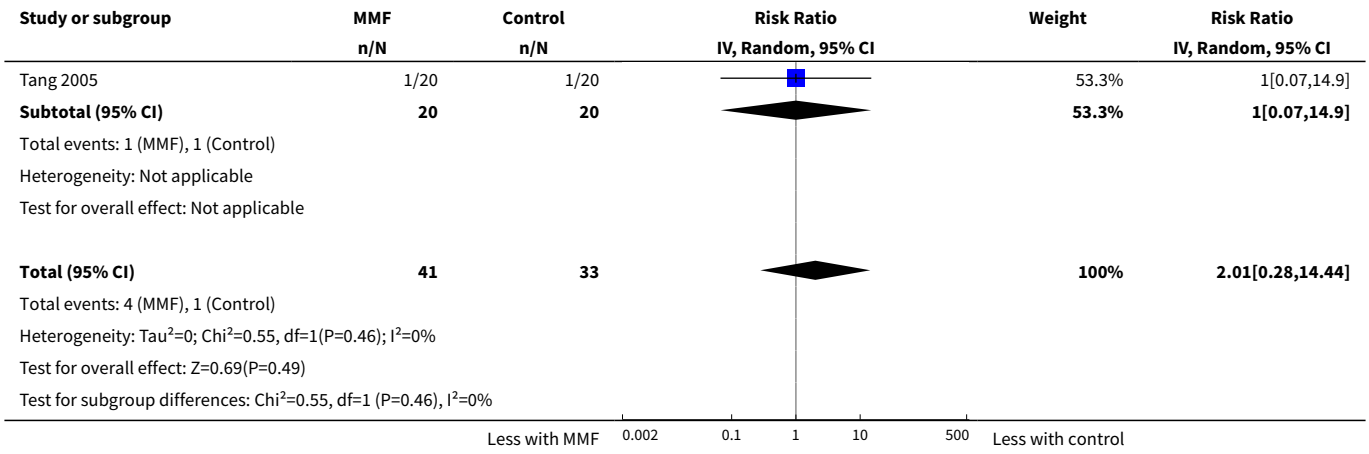


Analysis 4.2. Comparison 4 MMF versus no MMF regimen, Outcome 2 Complete remission.

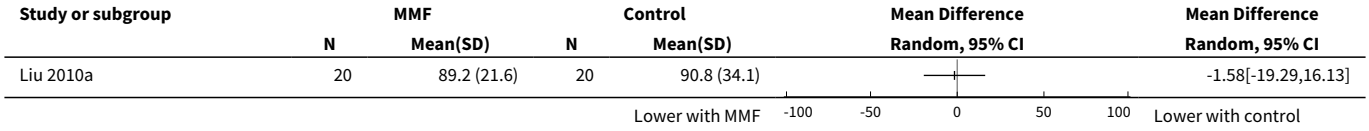


Analysis 4.3. Comparison 4 MMF versus no MMF regimen, Outcome 3 Doubling of serum creatinine.

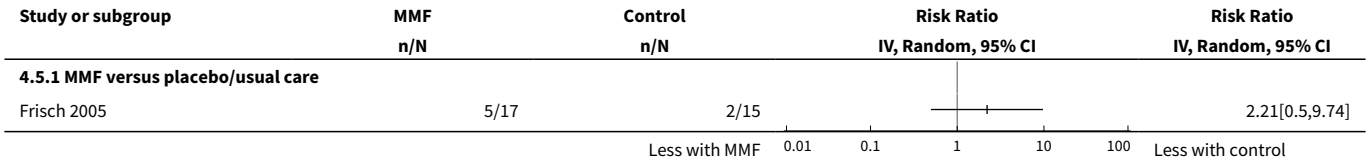




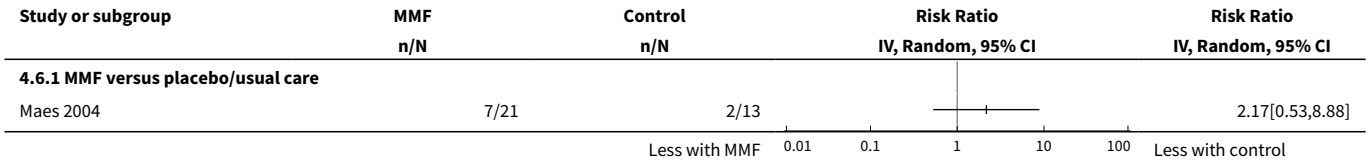
Analysis 4.4. Comparison 4 MMF versus no MMF regimen, Outcome 4 Serum creatinine.



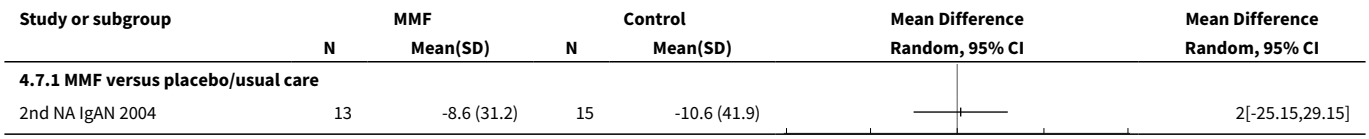
Analysis 4.5. Comparison 4 MMF versus no MMF regimen, Outcome 5 GFR loss: ≥ 50%.



Analysis 4.6. Comparison 4 MMF versus no MMF regimen, Outcome 6 GFR loss: ≥ 25%.



Analysis 4.7. Comparison 4 MMF versus no MMF regimen, Outcome 7 Annual GFR loss [mL/min/1.73 m^2].



Analysis 4.8. Comparison 4 MMF versus no MMF regimen, Outcome 8 GFR (any measure) [mL/min/1.73 m²].

Study or subgroup	MMF N	MMF Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2nd NA IgAN 2004	13	92.6 (33.6)	15	95.1 (42.7)		-2.5[-30.79,25.79]

Higher with control -100 -50 0 50 100 Higher with MMF

Analysis 4.9. Comparison 4 MMF versus no MMF regimen, Outcome 9 Urinary protein excretion.

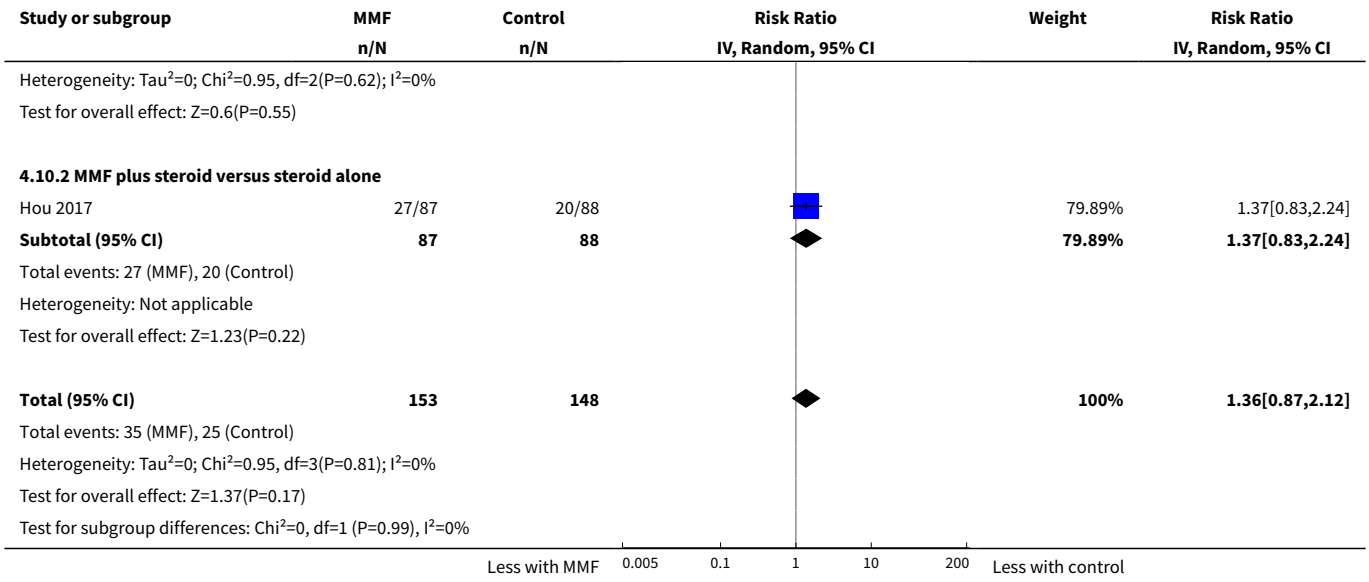
Study or subgroup	MMF N	MMF Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.9.1 MMF versus placebo							
2nd NA IgAN 2004	13	1.5 (2.2)	15	1.5 (2.9)		11.65%	0.01[-1.85,1.87]
Frisch 2005	16	3.2 (2.3)	14	2.4 (1.7)		14.85%	0.8[-0.64,2.24]
Maes 2004	21	1.6 (0.6)	13	1 (0.6)		23.79%	0.6[0.18,1.02]
Subtotal ***	**50**		**42**			**50.29%**	**0.59[0.2,0.98]**
Heterogeneity: Tau²=0; Chi²=0.46, df=2(P=0.79); I²=0%							
Test for overall effect: Z=2.96(P=0)							
4.9.2 MMF plus RASi versus RASi alone							
Tang 2005	20	1.1 (0.2)	20	2.4 (0.4)		24.82%	-1.26[-1.46,-1.06]
Subtotal ***	**20**		**20**			**24.82%**	**-1.26[-1.46,-1.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=12.21(P<0.0001)							
4.9.3 MMF versus leflunomide							
Liu 2010a	20	1 (0.3)	20	1.1 (0.3)		24.88%	-0.02[-0.2,0.16]
Subtotal ***	**20**		**20**			**24.88%**	**-0.02[-0.2,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.83)							
Total ***	**90**		**82**			**100%**	**-0.06[-0.92,0.81]**
Heterogeneity: Tau²=0.77; Chi²=110.56, df=4(P<0.0001); I²=96.38%							
Test for overall effect: Z=0.12(P=0.9)							
Test for subgroup differences: Chi²=110.1, df=1 (P<0.0001), I²=98.18%							

Lower with MMF -4 -2 0 2 4 Lower with control

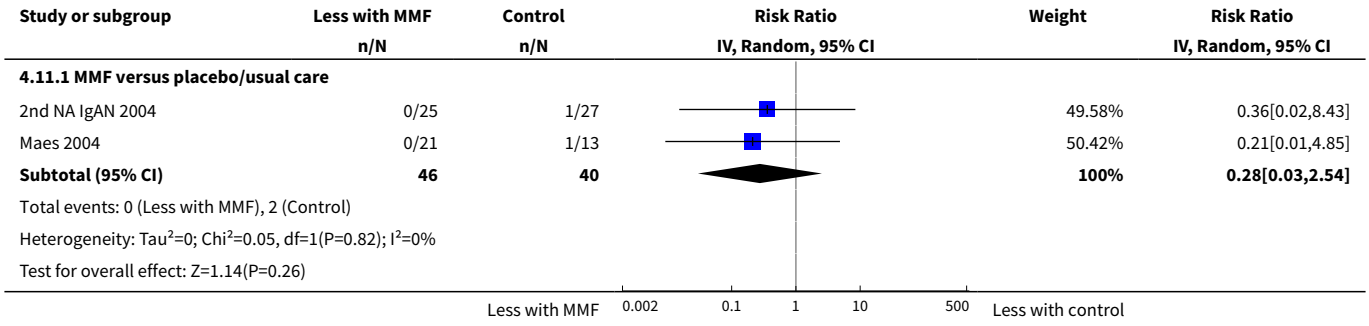
Analysis 4.10. Comparison 4 MMF versus no MMF regimen, Outcome 10 Infection.

Study or subgroup	MMF n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.10.1 MMF versus placebo/usual care					
Maes 2004	1/21	0/13		2.01%	1.91[0.08,43.65]
Tang 2005	2/20	0/20		2.22%	5[0.26,98]
2nd NA IgAN 2004	5/25	5/27		15.88%	1.08[0.35,3.29]
Subtotal (95% CI)	**66**	**60**		**20.11%**	**1.35[0.5,3.64]**
Total events: 8 (MMF), 5 (Control)					

Less with MMF 0.005 0.1 1 10 200 Less with control



Analysis 4.11. Comparison 4 MMF versus no MMF regimen, Outcome 11 Malignancy.



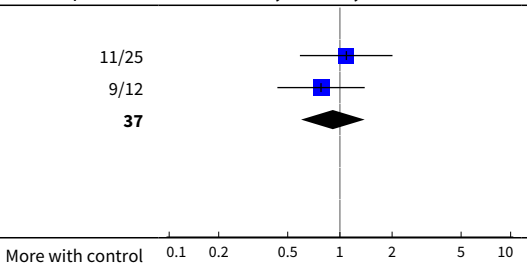
Comparison 5. Calcineurin inhibitor (CNI) versus no CNI regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 CNI plus steroid versus steroid	2	72	Risk Ratio (IV, Random, 95% CI)	0.91 [0.60, 1.39]
2 Serum creatinine	2	62	Mean Difference (IV, Random, 95% CI)	7.75 [-6.76, 22.27]
2.1 Cyclosporin versus placebo or usual care	1	22	Mean Difference (IV, Random, 95% CI)	0.0 [-32.39, 32.39]
2.2 Tacrolimus versus placebo	1	40	Mean Difference (IV, Random, 95% CI)	9.70 [-6.53, 25.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 GFR (any measure)	3	110	Mean Difference (IV, Random, 95% CI)	-0.18 [-7.42, 7.07]
3.1 Cyclosporin versus placebo or no treatment [mL/min/1.73 m^2]	1	22	Mean Difference (IV, Random, 95% CI)	4.5 [-7.36, 16.36]
3.2 Tacrolimus versus placebo	1	40	Mean Difference (IV, Random, 95% CI)	-5.70 [-20.27, 8.87]
3.3 CNI plus steroid versus steroid	1	48	Mean Difference (IV, Random, 95% CI)	-1.17 [-12.92, 10.58]
4 Urinary protein excretion	3	110	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.12, 0.12]
4.1 Cyclosporin versus placebo or no treatment	1	22	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.43, -0.77]
4.2 Tacrolimus versus placebo	1	40	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.52, 0.30]
4.3 CNI plus steroid versus steroid	1	48	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.46, 0.12]
5 Infection	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5.1 CNI plus steroid versus steroid	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 CNI plus steroid versus steroid	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

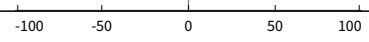
Analysis 5.1. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 1 Complete remission.

Study or subgroup	CNI n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 CNI plus steroid versus steroid					
Liu 2014	11/23	11/25		47.03%	1.09[0.59,2.01]
Shen 2013	7/12	9/12		52.97%	0.78[0.44,1.39]
Subtotal (95% CI)	**35**	**37**		**100%**	**0.91[0.6,1.39]**
Total events: 18 (CNI), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					



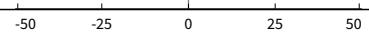
Analysis 5.2. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 2 Serum creatinine.

Study or subgroup	CNI N	CNI Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.2.1 Cyclosporin versus placebo or usual care							
Lai 1987	11	115.3 (40.5)	11	115.3 (37)		20.07%	0[-32.39,32.39]
Subtotal ***	**11**		**11**			**20.07%**	**0[-32.39,32.39]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.2.2 Tacrolimus versus placebo							
Kim 2013b	20	97.2 (28.3)	20	87.5 (23.9)		79.93%	9.7[-6.53,25.93]
Subtotal ***	**20**		**20**			**79.93%**	**9.7[-6.53,25.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.17(P=0.24)							
Total ***	**31**		**31**			**100%**	**7.75[-6.76,22.27]**
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=1.05(P=0.3)							
Test for subgroup differences: Chi^2=0.28, df=1 (P=0.6), I^2=0%							

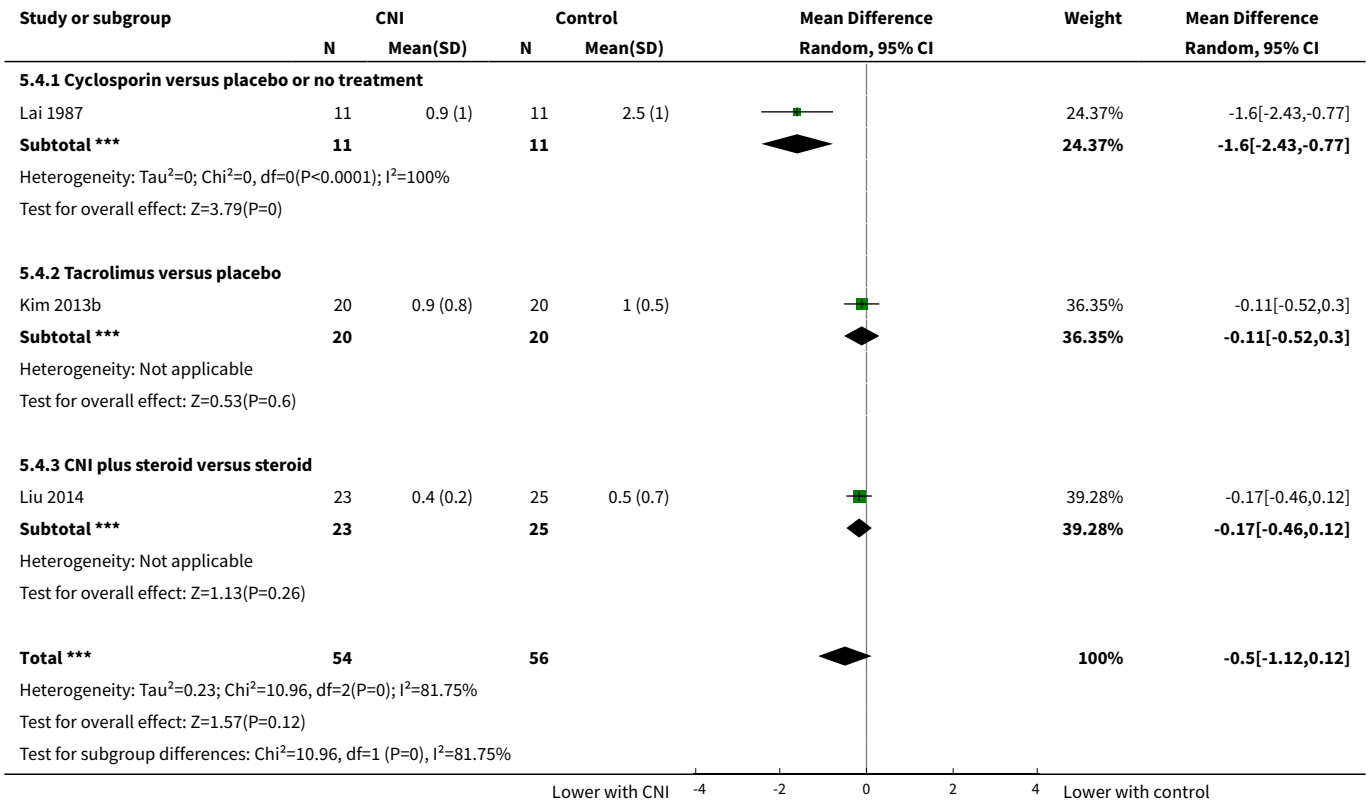


Analysis 5.3. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 3 GFR (any measure).

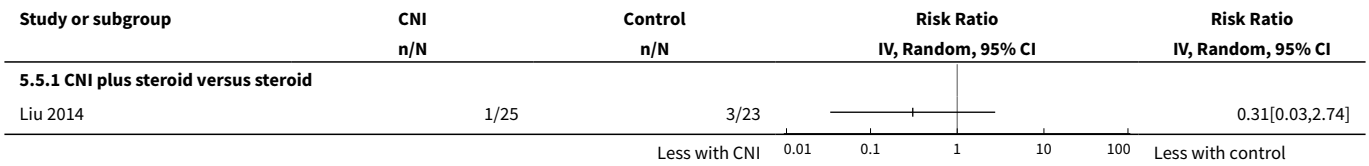
Study or subgroup	CNI N	CNI Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.3.1 Cyclosporin versus placebo or no treatment [mL/min/1.73 m2]							
Lai 1987	11	71.2 (17.2)	11	66.7 (10.3)		37.29%	4.5[-7.36,16.36]
Subtotal ***	**11**		**11**			**37.29%**	**4.5[-7.36,16.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
5.3.2 Tacrolimus versus placebo							
Kim 2013b	20	77.4 (22.9)	20	83.1 (24.1)		24.72%	-5.7[-20.27,8.87]
Subtotal ***	**20**		**20**			**24.72%**	**-5.7[-20.27,8.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.77(P=0.44)							
5.3.3 CNI plus steroid versus steroid							
Liu 2014	23	80.5 (22.7)	25	81.6 (18.4)		38%	-1.17[-12.92,10.58]
Subtotal ***	**23**		**25**			**38%**	**-1.17[-12.92,10.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.85)							
Total ***	**54**		**56**			**100%**	**-0.18[-7.42,7.07]**
Heterogeneity: Tau^2=0; Chi^2=1.18, df=2(P=0.56); I^2=0%							
Test for overall effect: Z=0.05(P=0.96)							
Test for subgroup differences: Chi^2=1.18, df=1 (P=0.56), I^2=0%							



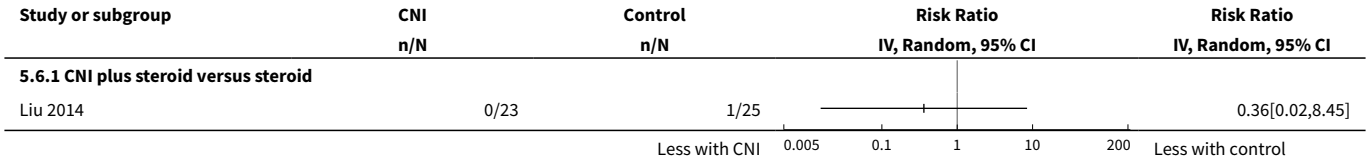
Analysis 5.4. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 4 Urinary protein excretion.



Analysis 5.5. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 5 Infection.



Analysis 5.6. Comparison 5 Calcineurin inhibitor (CNI) versus no CNI regimen, Outcome 6 Malignancy.

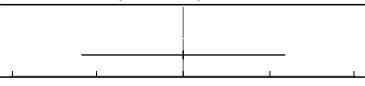


Comparison 6. Mizoribine versus no mizoribine regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Mizoribine versus placebo/usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete remission	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Mizoribine versus placebo/usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 GFR (any measure)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Urinary protein excretion	2	105	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.30, 0.22]
4.1 Mizoribine versus ACEi	1	65	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.39, 0.05]
4.2 Mizoribine plus steroid versus steroid alone	1	40	Mean Difference (IV, Random, 95% CI)	0.10 [-0.15, 0.35]
5 Infection	2	104	Risk Ratio (IV, Random, 95% CI)	1.52 [0.14, 16.15]
5.1 Mizoribine plus steroid (IV + oral) versus steroid alone	1	40	Risk Ratio (IV, Random, 95% CI)	7.0 [0.38, 127.32]
5.2 Mizoribine plus RASi versus RASi	1	64	Risk Ratio (IV, Random, 95% CI)	0.59 [0.11, 3.29]
6 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.1 Mizoribine versus placebo/usual care	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

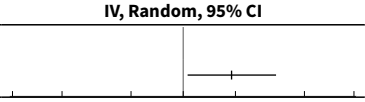
Analysis 6.1. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 1 ESKD.

Study or subgroup	Mizoribine n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
6.1.1 Mizoribine versus placebo/usual care				
Hirai 2017	1/21	1/21		1[0.07,14.95]

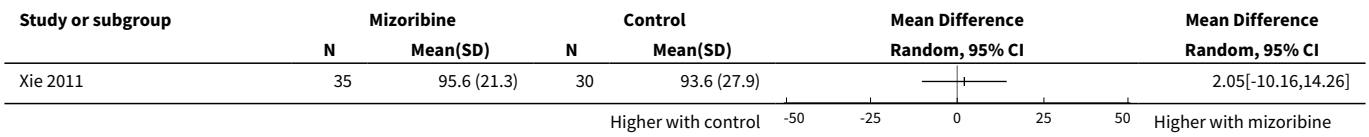


Analysis 6.2. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 2 Complete remission.

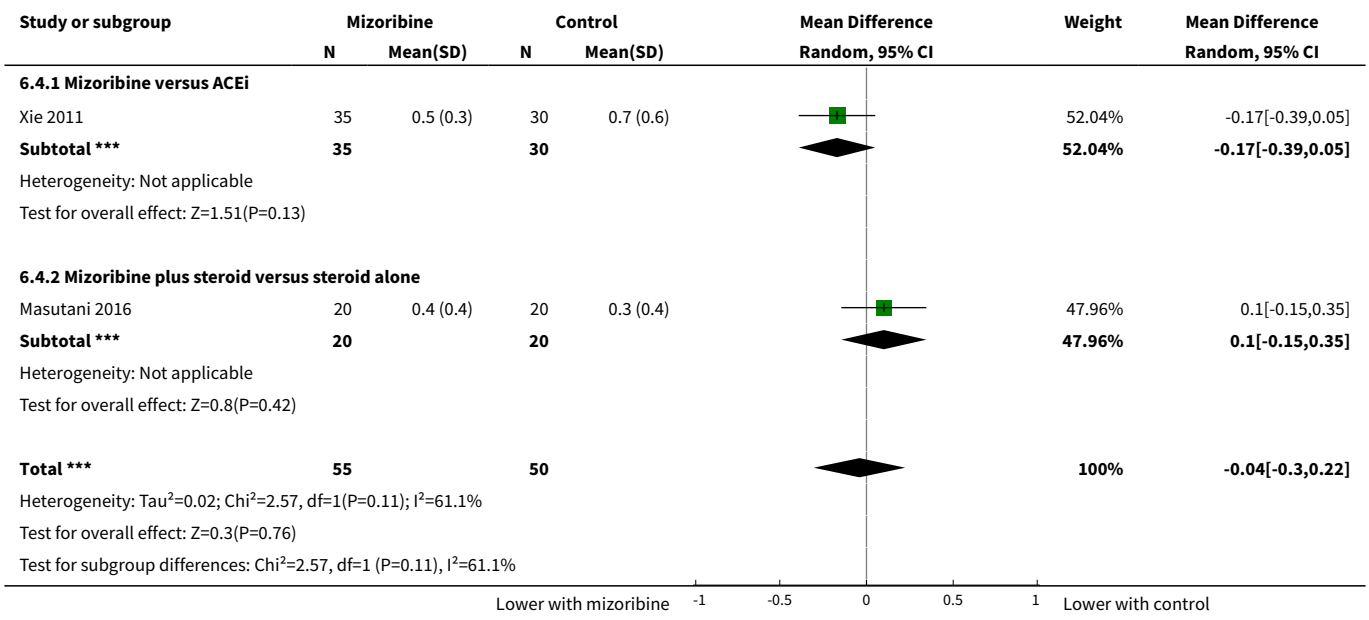
Study or subgroup	Mizoribine n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
6.2.1 Mizoribine versus placebo/usual care				
Hirai 2017	8/9	7/15		1.9[1.06,3.43]



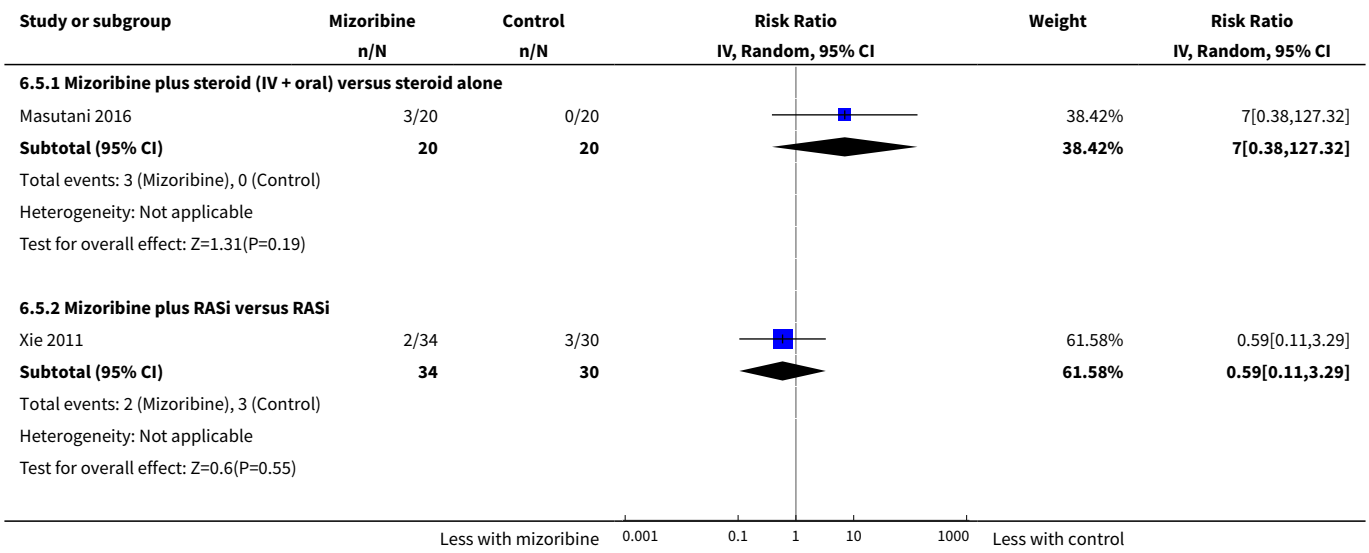
Analysis 6.3. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 3 GFR (any measure).

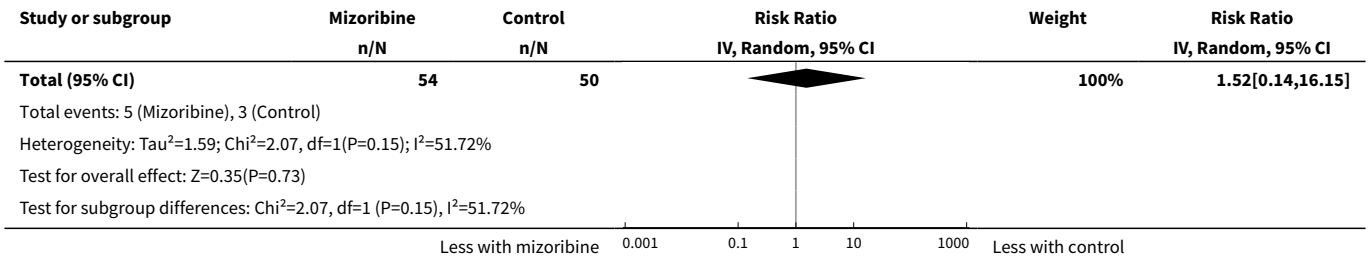


Analysis 6.4. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 4 Urinary protein excretion.

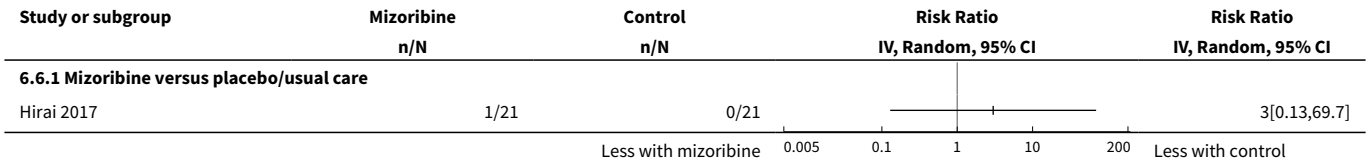


Analysis 6.5. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 5 Infection.





Analysis 6.6. Comparison 6 Mizoribine versus no mizoribine regimen, Outcome 6 Malignancy.

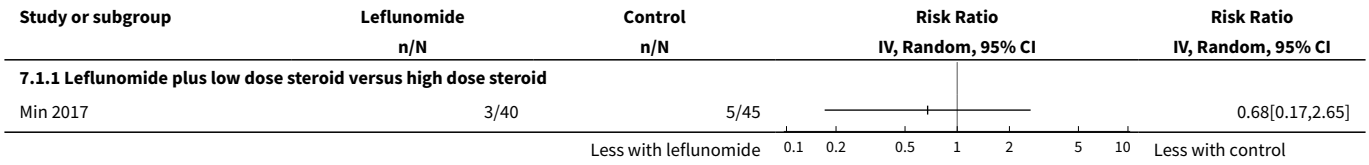


Comparison 7. Leflunomide versus no leflunomide regimen

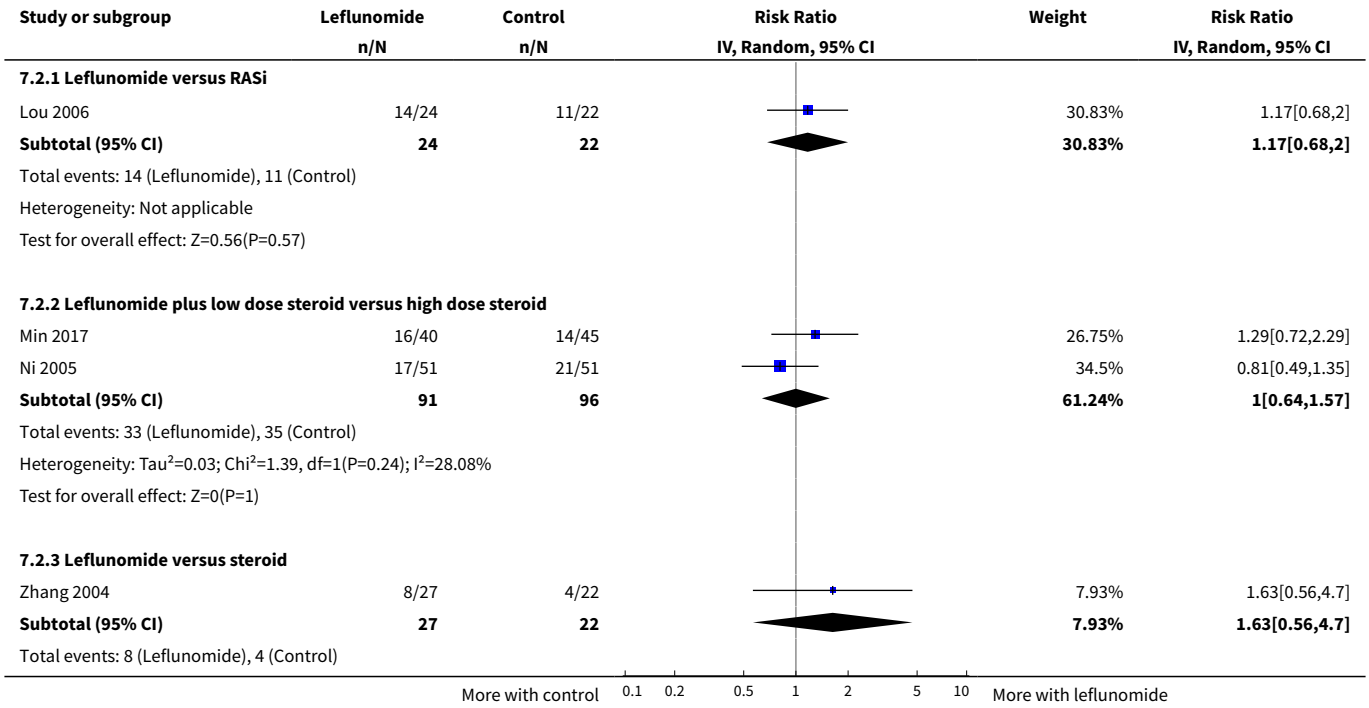
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 ESKD	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Leflunomide plus low dose steroid versus high dose steroid	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete remission	4	282	Risk Ratio (IV, Random, 95% CI)	1.08 [0.80, 1.46]
2.1 Leflunomide versus RASi	1	46	Risk Ratio (IV, Random, 95% CI)	1.17 [0.68, 2.00]
2.2 Leflunomide plus low dose steroid versus high dose steroid	2	187	Risk Ratio (IV, Random, 95% CI)	1.00 [0.64, 1.57]
2.3 Leflunomide versus steroid	1	49	Risk Ratio (IV, Random, 95% CI)	1.63 [0.56, 4.70]
3 Doubling of serum creatinine	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.1 Leflunomide plus low dose steroid versus high dose steroid	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Serum creatinine	2	125	Mean Difference (IV, Random, 95% CI)	-4.29 [-15.81, 7.24]
5 GFR (any measure)	2	131	Mean Difference (IV, Random, 95% CI)	11.11 [-3.32, 25.55]
5.1 Leflunomide plus low dose steroid versus high dose steroid	1	85	Mean Difference (IV, Random, 95% CI)	3.77 [-8.82, 16.36]
5.2 Leflunomide versus RASi	1	46	Mean Difference (IV, Random, 95% CI)	18.5 [5.81, 31.19]

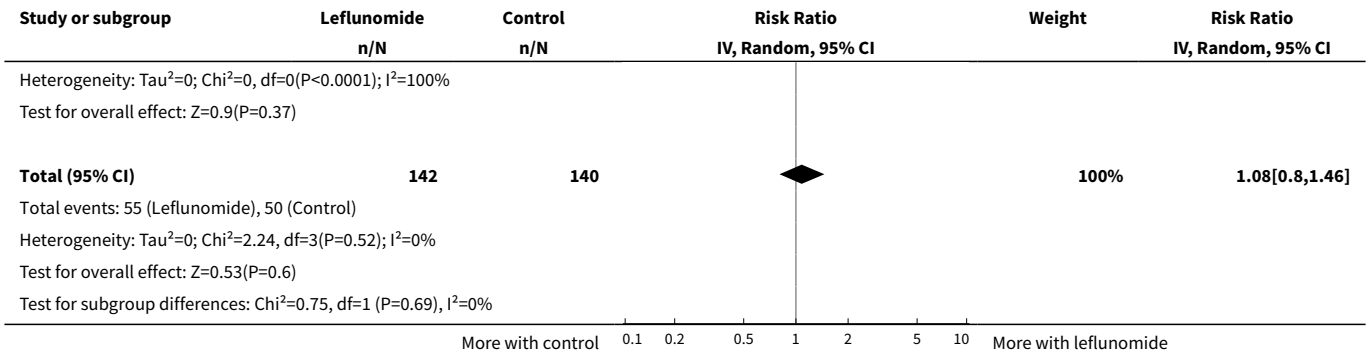
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Urinary protein excretion	3	125	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.25]
6.1 Leflunomide plus steroid versus steroid alone	2	85	Mean Difference (IV, Random, 95% CI)	0.03 [-0.66, 0.72]
6.2 Leflunomide vs MMF	1	40	Mean Difference (IV, Random, 95% CI)	0.02 [-0.16, 0.20]
7 Infection	3	387	Risk Ratio (IV, Random, 95% CI)	0.97 [0.45, 2.09]
7.1 Leflunomide plus low dose steroid versus high dose steroid	2	187	Risk Ratio (IV, Random, 95% CI)	0.90 [0.41, 1.99]
7.2 Leflunomide versus placebo	1	200	Risk Ratio (IV, Random, 95% CI)	3.0 [0.12, 72.77]

Analysis 7.1. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 1 ESKD.

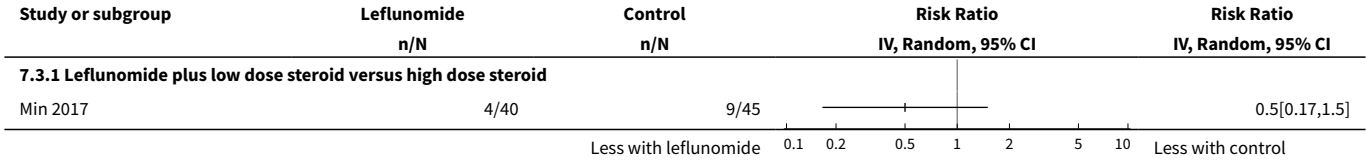


Analysis 7.2. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 2 Complete remission.

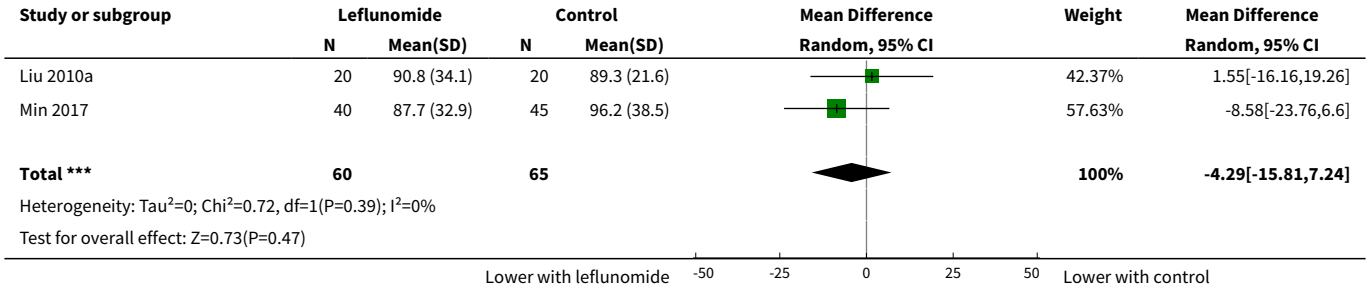




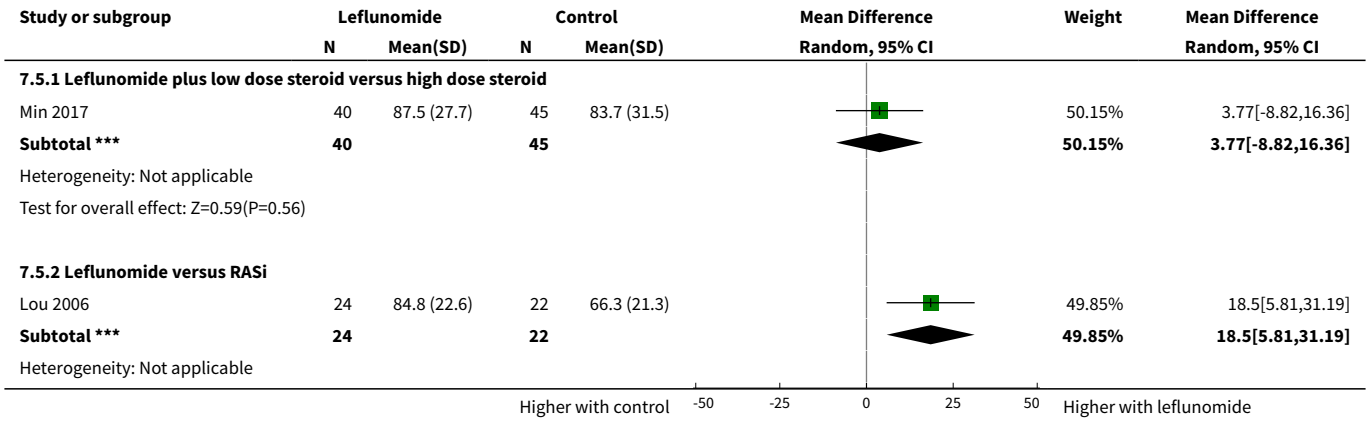
Analysis 7.3. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 3 Doubling of serum creatinine.

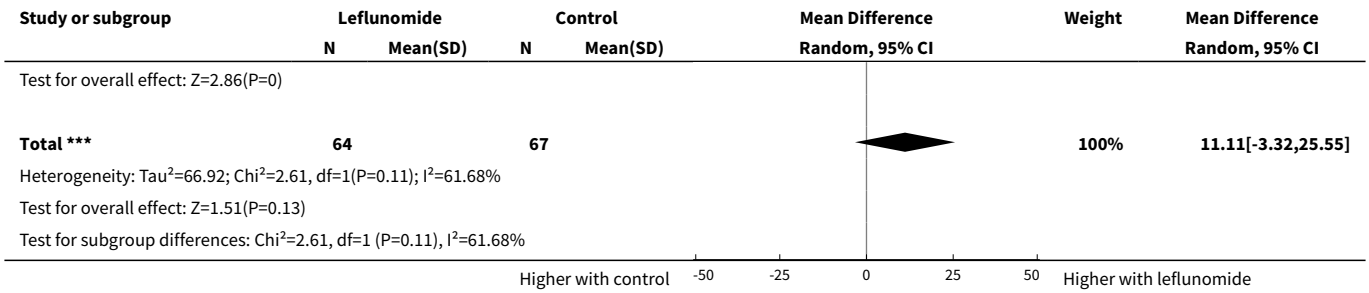


Analysis 7.4. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 4 Serum creatinine.

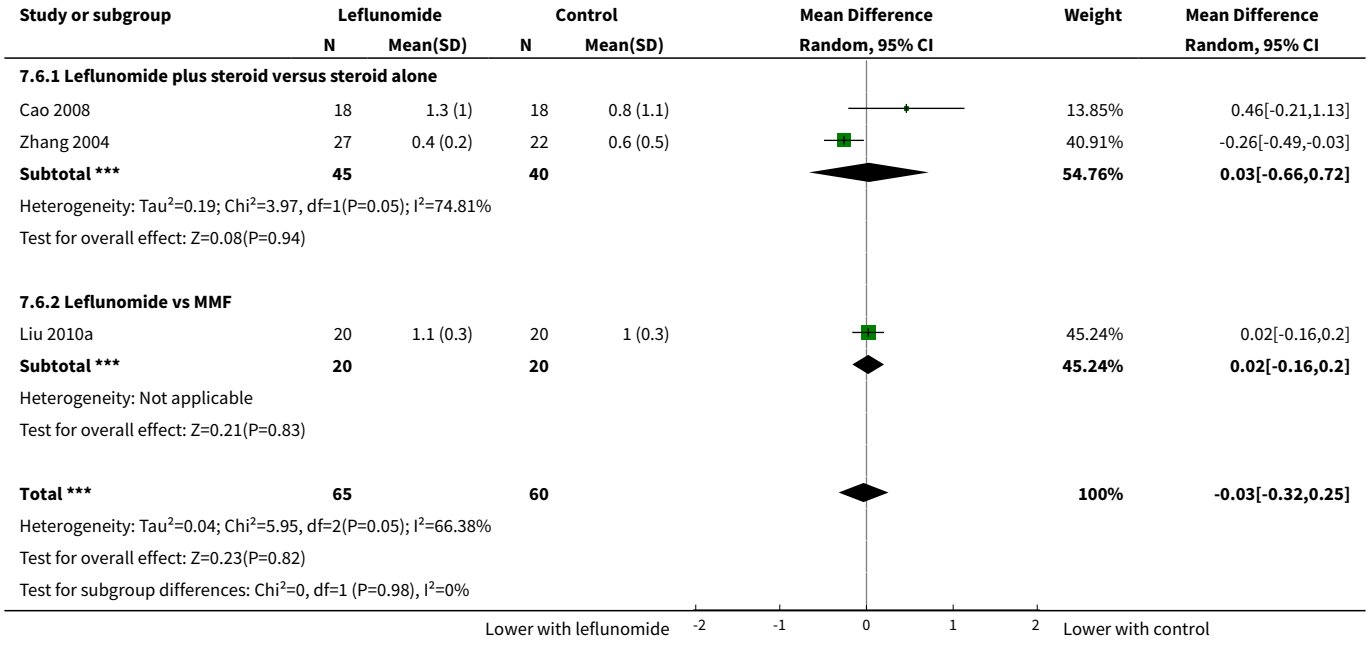


Analysis 7.5. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 5 GFR (any measure).

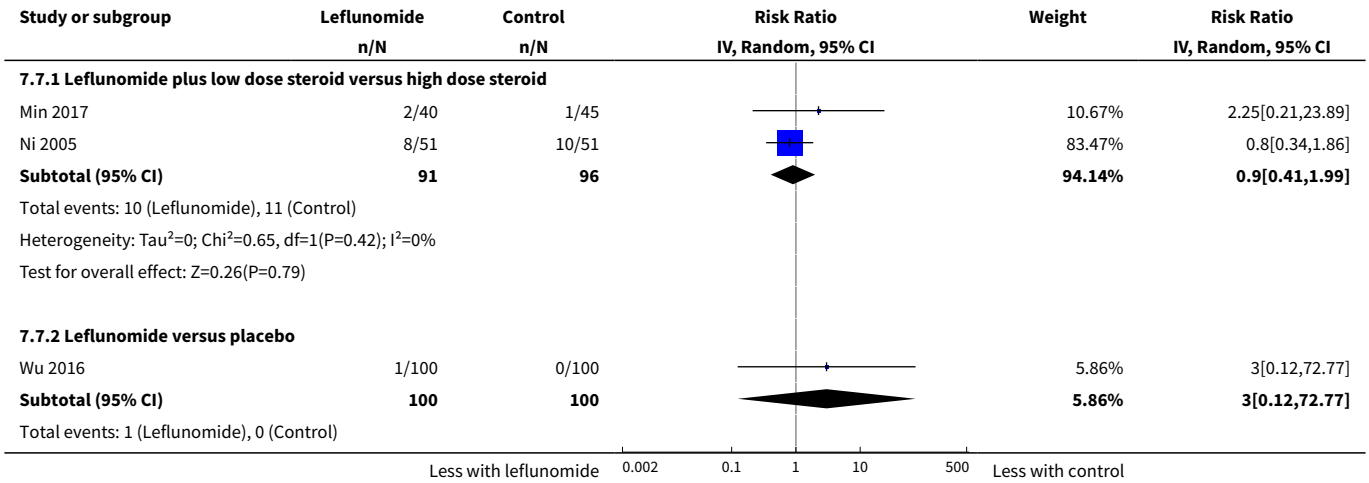


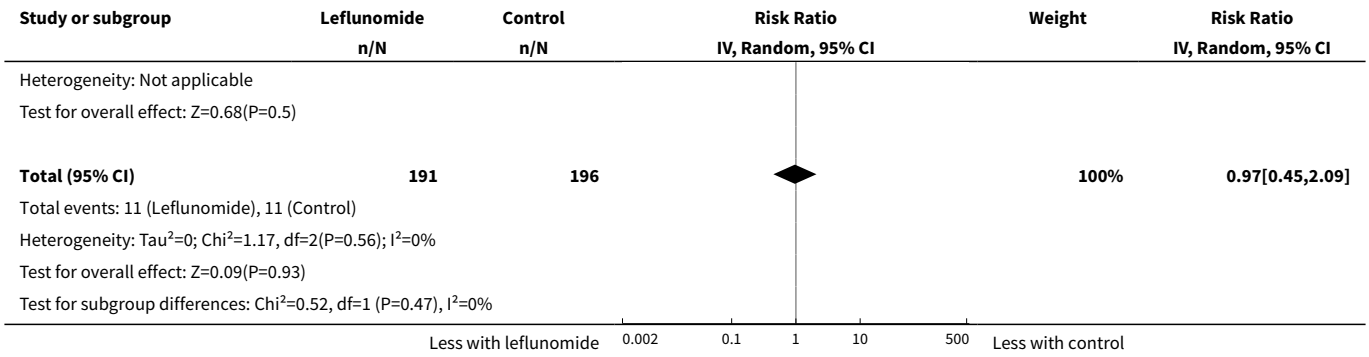


Analysis 7.6. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 6 Urinary protein excretion.



Analysis 7.7. Comparison 7 Leflunomide versus no leflunomide regimen, Outcome 7 Infection.

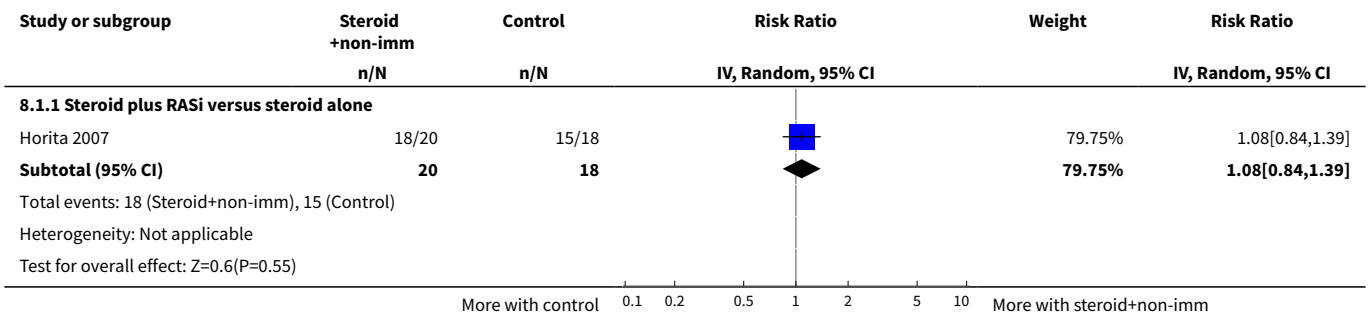


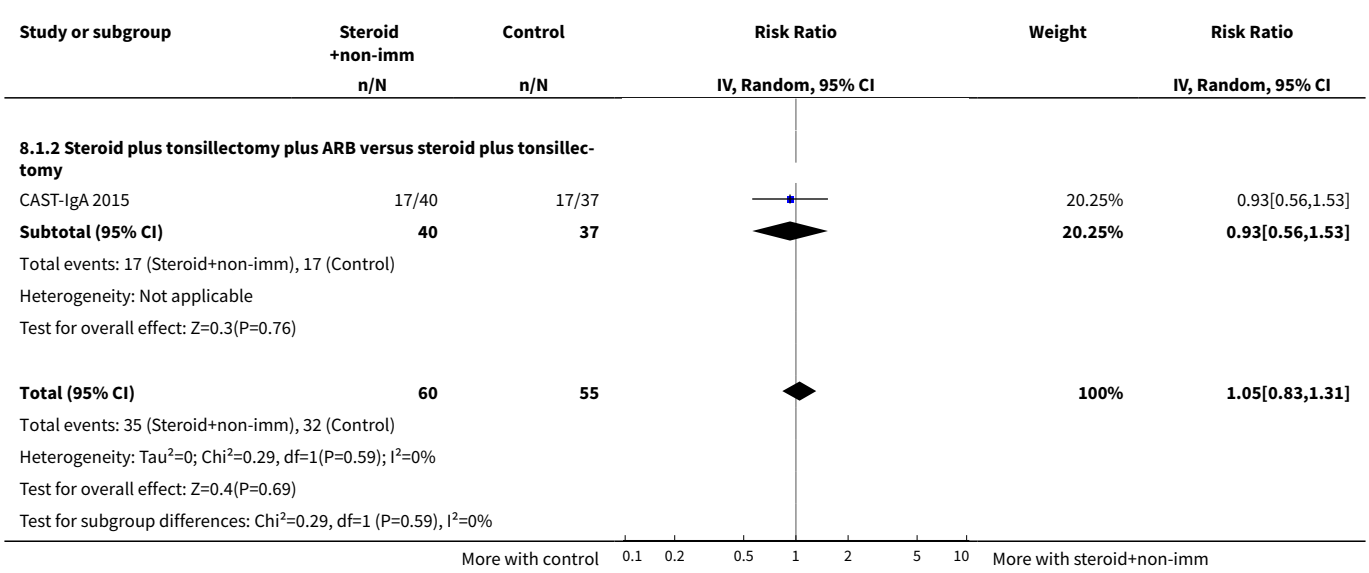


Comparison 8. Steroid plus non-immunosuppressive agents versus steroid alone

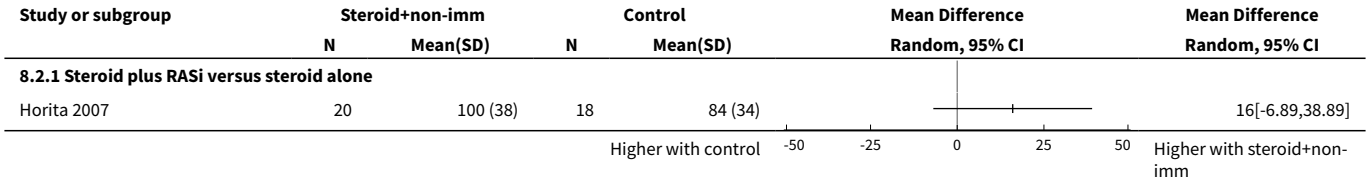
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete remission	2	115	Risk Ratio (IV, Random, 95% CI)	1.05 [0.83, 1.31]
1.1 Steroid plus RASi versus steroid alone	1	38	Risk Ratio (IV, Random, 95% CI)	1.08 [0.84, 1.39]
1.2 Steroid plus tonsillectomy plus ARB versus steroid plus tonsillectomy	1	77	Risk Ratio (IV, Random, 95% CI)	0.93 [0.56, 1.53]
2 GFR (any measure) [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Steroid plus RASi versus steroid alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Urinary protein excretion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Steroid plus RASi versus steroid alone	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Steroid plus non-immunosuppressive agents versus steroid alone, Outcome 1 Complete remission.

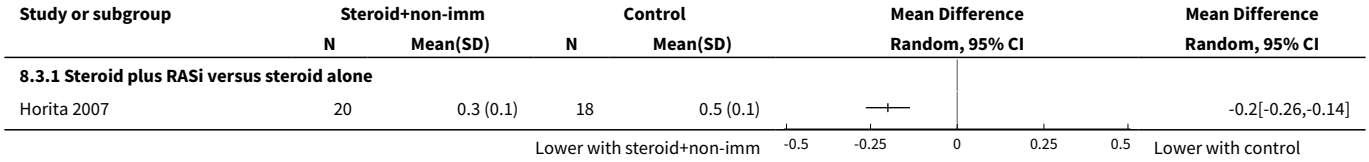




Analysis 8.2. Comparison 8 Steroid plus non-immunosuppressive agents versus steroid alone, Outcome 2 GFR (any measure) [mL/min/1.73 m²].



Analysis 8.3. Comparison 8 Steroid plus non-immunosuppressive agents versus steroid alone, Outcome 3 Urinary protein excretion.

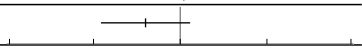


Comparison 9. mTORi versus no mTORi regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary protein excretion	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 mTORi versus no mTORi regimen, Outcome 1 Urinary protein excretion.

Study or subgroup	mTORi N	mTORi Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cruzado 2011	14	2 (0.9)	9	2.8 (1.4)		-0.8[-1.83,0.23]

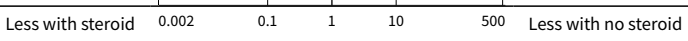


Comparison 10. Subgroup analysis for ESKD: steroid versus no steroid regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ESKD	8	741	Risk Ratio (IV, Random, 95% CI)	0.39 [0.23, 0.65]
1.1 Baseline ACEi/ARB	4	484	Risk Ratio (IV, Random, 95% CI)	0.35 [0.17, 0.75]
1.2 No baseline ACEi/ARB	4	257	Risk Ratio (IV, Random, 95% CI)	0.42 [0.20, 0.87]

Analysis 10.1. Comparison 10 Subgroup analysis for ESKD: steroid versus no steroid regimen, Outcome 1 ESKD.

Study or subgroup	Steroid n/N	No steroid n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
10.1.1 Baseline ACEi/ARB					
Lv 2009	0/33	2/30		3.02%	0.18[0.01,3.65]
NA IgAN 1995	3/33	3/31		11.68%	0.94[0.2,4.31]
Manno 2001	2/48	13/49		13.17%	0.16[0.04,0.66]
TESTING 2017	4/134	10/126		21.08%	0.38[0.12,1.17]
Subtotal (95% CI)	**248**	**236**		**48.94%**	**0.35[0.17,0.75]**
Total events: 9 (Steroid), 28 (No steroid)					
Heterogeneity: Tau^2=0; Chi^2=3.01, df=3(P=0.39); I^2=0.29%					
Test for overall effect: Z=2.73(P=0.01)					
10.1.2 No baseline ACEi/ARB					
Pozzi 1999	0/43	3/43		3.15%	0.14[0.01,2.68]
Julian 1993	1/18	2/17		5.09%	0.47[0.05,4.74]
Katafuchi 2003	3/43	3/47		11.34%	1.09[0.23,5.13]
Kobayashi 1996	4/20	16/26		31.48%	0.33[0.13,0.82]
Subtotal (95% CI)	**124**	**133**		**51.06%**	**0.42[0.2,0.87]**
Total events: 8 (Steroid), 24 (No steroid)					
Heterogeneity: Tau^2=0; Chi^2=2.29, df=3(P=0.51); I^2=0%					
Test for overall effect: Z=2.34(P=0.02)					
Total (95% CI)	**372**	**369**		**100%**	**0.39[0.23,0.65]**
Total events: 17 (Steroid), 52 (No steroid)					
Heterogeneity: Tau^2=0; Chi^2=5.41, df=7(P=0.61); I^2=0%					
Test for overall effect: Z=3.58(P=0)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.75), I^2=0%					



ADDITIONAL TABLES

Table 1. Reports of adverse events in individual studies

Study ID	Intervention	Reported side effect	Number of events in treatment group (N)	Number of events in control group (N)
2nd NA IgAN 2004	MMF versus placebo	Malignant melanoma, multiple intra-abdominal injuries	0+1 (13)	1+0 (15)
Ballardie 2002	Steroids + CPA versus no treatment	Pulmonary TB, overt diabetes, bone marrow toxicity, gastrointestinal toxicity	1+1+1+1 (19)	0+0+0+0 (19)
BRIGHT-SC 2016	Carboxylic acids (Blisibimod) versus placebo	Not reported	Not reported	Not reported
Cao 2008	Steroids + leflunomide versus steroids	None reported	0 (18)	0 (18)
CAST-IgA 2015	Steroid + prednisolone + tonsillectomy + ARB versus steroid + prednisolone	Not reported	Not reported	Not reported
Chen 2002	MMF versus prednisone	Diarrhoea, herpes zoster, nausea	% participants reported diarrhoea, herpes zoster, nausea (31)	Not reported
Cheung 2018	Belimumab versus placebo	Not reported	Not reported	Not reported
Cruzado 2011	Macrolide lactams (sirolimus) versus usual care	Fever, reversible hyperkalaemia, prostatic syndrome, unspecific acute gastritis, cholesterol increase, anaemia, oedema, mild facial rash	0+1+1+1+2+1+2 (14)	1+2+1+0+0+0+0+0+0 (9)
Frisch 2005	MMF versus placebo	Gastrointestinal effects, deep vein thrombosis	2+0 (17)	2+1 (15)
Harmankaya 2002	Steroids + AZA versus no treatment	Increased transaminase levels, minor cushingoid features, gastric pain	1+2+1 (21)	0 (22)
Hirai 2017	Mizoribine versus usual care	Hepatotoxicity, low-grade fever, malignant lymphoma	1+1+1 (21)	0+0+0 (21)
Horita 2007	Steroids + RAS inhibitors versus steroids	Hypotension	2 (20)	0 (20)
Hou 2017	MMF versus prednisone	Pneumonia, acute kidney injuries, ophthalmos-neuritis, osteonecrosis of the femoral head, ESKD, gastric perforation, newly diagnosed diabetes, impaired glucose tolerance, infections, hepatic dysfunction,	3+1+1+0+0+0+ (87)	1+1+0+2+1+1+1+1+1+2+2+5+2 (88)

Table 1. Reports of adverse events in individual studies *(Continued)*

		gastrointestinal symptoms, cushing syndrome, acne, cramps, insomnia, alopecia, tremors		
Julian 1993	Steroids versus no treatment	Overt diabetes, insomnia, acne	2+2+3 (18)	1 (17)
Kanno 2003	Steroids versus warfarin	None reported	0 (6)	0 (4)
Katafuchi 2003	Steroids + dipyridamole versus dipyridamole (in an abstract (Katafuchi 1997) that reported steroids versus antiplatelet agent in 80 participants, no adverse events were reported)	Palpitations/insomnia	3 (43)	1 (47)
Kawamura 2014	Methylprednisolone + tonsillectomy versus steroid	None reported	0 (33)	0 (39)
Lee 2003	Steroids + ARB versus ARB	Not reported	Not reported	Not reported
Kim 2013b	Tacrolimus versus placebo	Cardiovascular, gastrointestinal, genitourinary, hematologic, musculoskeletal, neurologic, respiratory, dermatologic	2+21+4+1+3+12 (20)	1+4+2+0+3+1+5+1 (20)
Kobayashi 1996	Steroids versus no treatment	None reported	0 (20)	0 (26)
Koike 2008	Prednisolone + dipyridamole versus dipyridamole	None reported	0 (24)	0 (24)
Koitabashi 1996	Chinese medicine (Saireito) versus no treatment versus prednisolone + AZA + anticoagulants + dipyridamole versus anticoagulants + dipyridamole	Not reported	Not reported	Not reported
Lafayette 2017	Rituximab versus usual care	Cough, fever, flu, gastrointestinal symptoms, embolism, infections, rush, nasal congestion, eye problems, wart left 5th digit, right flank tenderness, headache, haemorrhage, pruritus, confusion, fatigue, muscle problems, back pain, dyspnoea, heartburn and cardiac problems, anorexia, sore throat, flushing, hypertension, photosensitivity, vaginal bleeding, left hand numbness	Not reported (17)	Not reported (17)
Lai 1986	Steroids versus no treatment	Gastritis, hypertension	1+3 (17)	0+0 (17)
Lai 1987	CSA versus placebo	Dyspepsia, headache, hypertension, hirsutism	6+7+1+3+7 (12)	0+0+0+0+1 (12)
Liu 2010a	Prednisone + leflunomide versus prednisone + MMF	Not reported	Not reported	Not reported
Liu 2014	Methylprednisolone + CSA versus methylprednisolone	Severe pneumonia, recurrent urinary tract infection, elevated blood sugar,	3+2+2+5 (23)	1+3+2+9 (25)

Table 1. Reports of adverse events in individual studies *(Continued)*

		eyesight degradation		
Locatelli 1999	Steroids + AZA versus steroids	Hepatotoxicity, leukopenia, GI symptoms, bacterial Infections, viral Infections, Pneumocystis carinii infection, type 2 diabetes, hypertension	5+3+3+3+1+1+1+0+0 (101)	0+0+0+2+1+0+2+1 (106)
Lou 2006	Leflunomide versus RAS inhibitors	Serum transaminases, mild alopecia, severe diarrhoea, cough	2+1+1+0 (24)	0+0+0+2 (22)
Lv 2009	Steroids + RAS inhibitors versus RAS inhibitors	Cough, hyperkalaemia, palpitation, arthralgia	2+0+1+1 (33)	1+0+0+0 (30)
Maes 2004	MMF versus placebo	Reactivation of pulmonary TB, gastrointestinal complaints, leukopenia, rectal carcinoma	1+2+1+0 (21)	0+0+0+1 (19)
Manno 2001	Steroids + RAS inhibitors versus RAS inhibitors	Striae, glucidic intolerance, cough	3+1+0 (48)	0+0+2 (49)
Masutani 2016	Prednisolone followed by mizoribine versus prednisolone	Pneumonia, herpes zoster, severe drug allergy	2+0+0 (20)	0+1+1 (20)
Min 2017	Leflunomide + prednisone versus full dose prednisone	Hepatotoxicity, upper respiratory infection, pulmonary infection, diarrhoea, herpes-zoster virus infection, pruritus, insomnia, alopecia, abnormal glucose metabolism	3+4+2+1+0+1+0+2+1+0 (40)	2+4+1+0+2+0+2+0+2 (45)
NA IgAN 1995	Steroids versus placebo	Heartburn, increased appetite, weight gain	15+24+22 (33)	5+10+13 (31)
NEFIGAN 2017	Low dose TRF-budesonide versus high dose TRF-budesonide versus placebo	Nasopharyngitis, acne, joint swelling, cushingoid, insomnia, diarrhoea, dyspepsia, headache, alopecia, back pain, mood swings, oedema peripheral, blood creatine phosphokinase increased, hirsutism, hypertension, muscle spasms, abdominal pain, nausea, upper respiratory tract infection	Treatment group 1 8+8+8+5+6+1+2+3+4+6+3+2+3+3+3+5+4 (51) Treatment group 2 10+9+9+8+8+5+7+6+4+3+5+6+3+5+5+2 (49)	10+3+2+3+2+7+4+3+2+1 (50)
Ni 2005	Steroids + leflunomide versus steroids	Elevated liver enzyme, infection, diarrhoea, nausea, rash, insomnia, blood glucose increase	4+8+2+1+1+0+0 (51)	4+10+0+0+1+1+1 (51)
Nuzzi 2009	Steroids versus no treatment	None reported	0 (15)	0 (12)
Pozzi 1999	Steroids versus no treatment	None reported	0 (43)	0 (43)
Segarra 2006	Immunoglobulin + steroids versus steroids	Cutaneous rush, DM	1+0 (19)	0+1 (17)
Shen 2013	Corticosteroid + CPA versus corticosteroid + tacrolimus versus corticosteroid	Not reported	Not reported	Not reported
Shi 2012a	Steroids + leflunomide versus steroids	Adverse events were assessed but not clearly reported	Not reported	Not reported

Table 1. Reports of adverse events in individual studies *(Continued)*

Shima 2018	Prednisolone + mizoribine + warfarin + dipyridamole versus prednisolone + mizoribine	Obesity, hyperuricaemia, hypertension, headache, steroid-induced gastric ulcer, glaucoma, steroid acne, stretch marks, bleeding, decreased bone mineral density, cataract, elevation of serum bilirubin, psychosis	6+2+1+6+2+2+2	7+15+2+0+0+2+2+1+0+1+
Shoji 2000	Steroids versus dipyridamole	Headache	0 (11)	1 (8)
Stangou 2011	AZA + methylprednisolone versus methylprednisolone	Not reported	Not reported	Not reported
STOP-IgAN 2008	Methylprednisolone versus no treatment	Diverticulitis or appendicitis, pneumonia or respiratory tract infection, viral exanthema, knee empyema, death, malignant neoplasm, impaired glucose tolerance or DM, gastrointestinal bleeding, fracture, osteonecrosis, weight gain	3+3+1+1+1+2+9 (82)	1+0+1+1+0+1+4+0+1+0+0+0+ (80)
Takeda 1999	Steroids + antiplatelet agent versus antiplatelet agent	None reported	0 (13)	0 (12)
Tang 2005	MMF + RAS inhibitors versus RAS inhibitors	Fall in haemoglobin level, diarrhoea, upper gastrointestinal upset, infective episodes	3+1+1+3 (20)	None reported (20)
TESTING 2017	Methylprednisolone versus placebo	Respiratory infection, pneumocystis pneumonia, cryptococcal meningitis, nocardia infection of skin and knee joint, perianal abscess, urinary tract infection, fever, duodenal ulcer, gastrointestinal bleeding, gastric perforation, vascular necrosis, osteochondroma, pulmonary embolism, deep vein thrombosis, hepatotoxicity, haemoptysis, acute right upper quadrant pain, arthralgia, symptomatic incarcerated paraumbilical hernia, uremia, soft tissue injury, new-onset DM, vascular necrosis, fracture	4+3+1+1+1+1+1 1+2+1+1 (136)	0+0+2+0+2+0+0+2+0+0+1+ 0+3+0+0 (126)
Walker 1990a	CPA + dipyridamole + warfarin versus no treatment	Gonadal toxicity, headache	2+1 (25)	0+0 (27)
Welch 1992	Steroids versus placebo	None reported	0 (20)	0 (20)
Woo 1987	CPA + dipyridamole + warfarin versus no treatment	Gum bleeding	2 (27)	0 (21)
Wu 2016	Telmisartan + clopidogrel placebo + leflunomide placebo versus telmisartan + clopidogrel + leflunomide placebo versus telmisartan + clopidogrel placebo + leflunomide versus telmisartan + clopidogrel + leflunomide	Death, abnormal liver function, hypotension, hyperkalaemia, neutropenia, rash, skin purpura, upper gastrointestinal bleeding, herpes zoster, urinary tract infection, upper respiratory tract infection	Treatment group 1 0+0+0+1+1+0+0+0+1+0+1 (100) Treatment group 2 0+3+1+2+0+0+0+0+1+0 (100) Treatment group 3	0+3+0+0+2+2+1+1+0+0+ (99)

Table 1. Reports of adverse events in individual studies *(Continued)*

			0+1+2+1+0+0+0+0+0+0 (100)	
Xie 2011	Mizoribine versus losartan versus combination group	Serious adverse events, hyperuricaemia, upper respiratory tract infection, herpes zoster, leukopenia, elevation of transaminases, vertigo, alopecia	Treatment group 1 0+3+2+1+0+0+1+1 (34) 0+3+1+0+1+1+0+0 (35) Treatment group 2 0+1+3+0+1+1+1+0 (30)	
Yoshikawa 1999	Steroids + AZA + dipyridamole versus dipyridamole	Alopecia, anaemia, leukopenia, cataract, ulcer, depression	1+0+3+1+1+1 (40)	0+1+0+0+0+0 (38)
Yoshikawa 2006	Steroids + dipyridamole + AZA + warfarin versus steroids	Hypertension, glucosuria, aseptic necrosis of femur, glaucoma, cataract, headache, leukopenia, bleeding, anaemia, elevated transaminase concentration	0+0+1+2+0+3+3+1+2 (40)	3+3+1+2+2+0+0+0+0+1 (40)
Zhang 2004	Leflunomide versus steroids	Elevate liver enzyme, nausea, lose hair, leukopenia	3+1+1+1 (27)	None reported (22)

ARB - angiotensin receptor blocker; AZA - azathioprine; CPA - cyclophosphamide; CSA - cyclosporin A; DM - diabetes mellitus; MMF - mycophenolate mofetil; RAS - renin-angiotensin system; TB - tuberculosis; TRF-budesonide - targeted-release formulation of budesonide

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Glomerulonephritis, IGA explode all trees in MeSH products 2. iga next glomeruloneph* in Clinical Trials 3. iga next nephropath* in Clinical Trials 4. IgAGN in Clinical Trials 5. ("iga-n" or "igan") in Clinical Trials 6. berger* next disease* in Clinical Trials 7. ("immunoglobulin a" next nephropath*) in Clinical Trials 8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
MEDLINE	1. Glomerulonephritis, IGA/ 2. iga glomerulonephritis.tw. 3. iga nephropath$.tw. 4. IgAGN.tw. 5. igA-N.tw. 6. berger$ disease.tw. 7. immunoglobulin a nephropathy.tw. 8. or/1-7

(Continued)

EMBASE	1. Immunoglobulin a Nephropathy/ 2. iga nephropathy.tw. 3. iga glomerulonephritis.tw. 4. berger$ disease.tw. 5. IgAGN.tw. 6. igA-N.tw. 7. immunoglobulin a nephropathy.tw. 8. or/1-7

Appendix 2. Assessment of source of bias

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.

(Continued)

	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 Attrition bias due to amount, nature or handling of 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 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
18 March 2020	Amended	Risk of bias judgements added for Yamauchi 2001

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 4, 2003

Date	Event	Description
9 September 2019	New search has been performed	Search update and update of included studies and outcome data
9 September 2019	New citation required and conclusions have changed	New studies and interventions added
15 July 2015	New search has been performed	Review updated
15 July 2015	New citation required and conclusions have changed	New interventions identified
22 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

2003 review

- This review is the product of an equal contribution from Joshua Samuels and Giovanni FM Strippoli, who conceived it, developed the protocol, designed and conducted the review, performed the data extraction, data analysis and wrote the final review
- Jonathan C Craig was involved in the conduct, data-analysis and writing of the review
- Donald Molony reviewed the final draft
- Francesco P Schena reviewed the final draft

2015 review update

- This review is the product of an equal contribution from Joshua Samuels and Giovanni FM Strippoli, who conceived it, developed the protocol, designed and conducted the review, performed the data extraction, data analysis and wrote the final review
- Mariacristina Vecchio data extraction, data analysis and wrote the final review
- Bibiana Bonerba data extraction, data analysis and wrote the final review
- Marinella Ruospo data extraction, data analysis and wrote the final review
- Jonathan C Craig reviewed and commented on the final draft
- Donald Molony reviewed and commented on the final draft.
- Francesco P Schena reviewed and commented on the final draft

2020 review update

- The update of the review was conducted by Patrizia Natale and Marinella Ruospo, who performed the data extraction, data analysis and wrote the final review
- Suetonia C Palmer provided intellectual input throughout the review update process
- Giovanni FM Strippoli reviewed and commented on the final draft
- Valeria Saglimbene reviewed and commented on the final draft
- Mariacristina Vecchio reviewed and commented on the final draft
- Joshua A Samuels reviewed and commented on the final draft
- Jonathan C Craig reviewed and commented on the final draft
- Donald Molony reviewed and commented on the final draft.
- Francesco P Schena reviewed and commented on the final draft

DECLARATIONS OF INTEREST

No author has a vested interest in any of the products or procedures included in the analysis.

SOURCES OF SUPPORT

Internal sources

- Cochrane Renal Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2015 review update: Risk of bias assessment has replaced the quality checklist.

2020 review update: We have added additional outcomes including annual change in eGFR and malignancy.

NOTES

Risk of bias judgements added for Yamauchi 2001.

INDEX TERMS

Medical Subject Headings (MeSH)

Creatinine [blood]; Drug Therapy, Combination; Glomerulonephritis, IGA [*drug therapy]; Immunosuppressive Agents [*therapeutic use]; Kidney Failure, Chronic [prevention & control] [therapy]; Proteinuria [drug therapy]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Humans