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# Interventions for renal vasculitis in adults (Review)

Walters GD, Willis NS, Cooper TE, Craig JC

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[Intervention Review]

# Interventions for renal vasculitis in adults

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## ABSTRACT

### Background

Renal vasculitis presents as rapidly progressive glomerulonephritis and comprises of a group of conditions characterised by acute kidney injury (AKI), haematuria and proteinuria. Treatment of these conditions involve the use of steroid and non-steroid agents in combination with plasma exchange. Although immunosuppression overall has been very successful in treatment of these conditions, many questions remain unanswered in terms of dose and duration of therapy, the use of plasma exchange and the role of new therapies. This 2019 publication is an update of a review first published in 2008 and updated in 2015.

### Objectives

To evaluate the benefits and harms of any intervention used for the treatment of renal vasculitis in adults.

### Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 21 November 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

Randomised controlled trials investigating any intervention for the treatment of renal vasculitis in adults.

### Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using a random effects model and results expressed as risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes or mean difference (MD) for continuous outcomes.

### Main results

Forty studies (3764 patients) were included. Studies conducted earlier tended to have a higher risk of bias due to poor (or poorly reported) study design, broad inclusion criteria, less well developed disease definitions and low patient numbers. Later studies tend to have improved in all areas of quality, aided by the development of large international study groups.

Induction therapy: Plasma exchange as adjunctive therapy may reduce the need for dialysis at three (2 studies: RR 0.43, 95% CI 0.23 to 0.78; $I^2$ = 0%) and 12 months (6 studies: RR 0.45, 95% CI 0.29 to 0.72; $I^2$ = 0%) (low certainty evidence). Plasma exchange may make little or no difference to death, serum creatinine (SCr), sustained remission or to serious or the total number of adverse events. Plasma exchange

may increase the number of serious infections (5 studies: RR 1.26, 95% CI 1.03 to 1.54; $I^2$ = 0%; low certainty evidence). Remission rates for pulse versus continuous cyclophosphamide (CPA) were equivalent but pulse treatment may increase the risk of relapse (4 studies: RR 1.79, 95% CI 1.11 to 2.87; $I^2$ = 0%) (low certainty evidence) compared with continuous cyclophosphamide. Pulse CPA may make little or no difference to death at final follow-up, or SCr at any time point. More patients required dialysis in the pulse CPA group. Leukopenia was less common with pulse treatment; however, nausea was more common. Rituximab compared to CPA probably makes little or no difference to death, remission, relapse, severe adverse events, serious infections, or severe adverse events. Kidney function and dialysis were not reported. A single study reported no difference in the number of deaths, need for dialysis, or adverse events between mycophenolate mofetil (MMF) and CPA. Remission was reported to improve with MMF however more patients relapsed. A lower dose of steroids was probably as effective as high dose and may be safer, causing fewer infections; kidney function and relapse were not reported. There was little of no difference in death or remission between six and 12 pulses of CPA. There is low certainty evidence that there were less relapses with 12 pulses (2 studies: RR 1.57, 95% CI 0.96 to 2.56; $I^2$ = 0%), but more infections (2 studies: RR 0.79, 95% CI 0.36 to 1.72; $I^2$ = 45%). One study reported severe adverse events were less in patients receiving six compared to 12 pulses of CPA. Kidney function and dialysis were not reported. There is limited evidence from single studies about the effectiveness of intravenous immunoglobulin, avacopan, methotrexate, immunoadsorption, lymphocytapheresis, or etanercept.

Maintenance therapy: Azathioprine (AZA) has equivalent efficacy as a maintenance agent to CPA with fewer episodes of leucopenia. MMF resulted in a higher relapse rate when tested against azathioprine in remission maintenance. Rituximab is an effective remission induction and maintenance agent. Oral co-trimoxazole did not reduce relapses in granulomatosis with polyangiitis. There were fewer relapses but more serious adverse events with leflunomide compared to methotrexate. There is limited evidence from single studies about the effectiveness of methotrexate versus CPA or AZA, cyclosporin versus CPA, extended versus standard AZA, and belimumab.

### Authors' conclusions

Plasma exchange was effective in patients with severe AKI secondary to vasculitis. Pulse cyclophosphamide may result in an increased risk of relapse when compared to continuous oral use but a reduced total dose. Whilst CPA is standard induction treatment, rituximab and MMF were also effective. AZA, methotrexate and leflunomide were effective as maintenance therapy. Further studies are required to more clearly delineate the appropriate place of newer agents within an evidence-based therapeutic strategy.

## PLAIN LANGUAGE SUMMARY

### Interventions for renal vasculitis in adults

#### What is the issue?

Renal vasculitis is a rapidly progressing form of kidney disease that causes damage to the small structures (glomeruli) inside the kidneys that help filter waste and fluids from blood to form urine. The disease means a rapid loss of kidney function. Steroids and cyclophosphamide are recommended to help suppress the immune system.

#### What did we do?

We searched the Cochrane Kidney and Transplant Register of Studies up to 21 November 2019 for randomised controlled trials investigating any intervention for the treatment of renal vasculitis in adults.

#### What did we find?

Forty studies (3764 patients) were identified. Plasma exchange reduces the risk of end-stage kidney disease in patients presenting with severe acute kidney failure (AKI). The use of pulse cyclophosphamide results in good remission rates but there was an increased risk of relapse. Other appropriate induction agents include rituximab and mycophenolate. Azathioprine is effective as maintenance therapy once remission has been achieved. A lower dose of steroids is just as effective as high dose and may be safer, causing fewer infections. One study shows that a new complement inhibitor can be used to replace steroids in the initial treatment of vasculitis. These are early data. The drug is likely to be very expensive so its place in treatment is not yet clearly defined. Mycophenolate mofetil has also been tested in maintenance treatment and was found to result in a higher rate of disease relapse, when compared to Azathioprine. Methotrexate and leflunomide are useful in maintenance therapy but their relative effectiveness are not clearly defined. Patients on immunosuppression for up to four years after diagnosis have a lowered relapse rate to those in whom treatment is ceased by three years.

#### Conclusions

Plasma exchange was effective in patients with severe AKI. Pulse cyclophosphamide may result in an increased risk of relapse when compared to continuous oral use but a reduced total dose. Whilst cyclophosphamide is used as standard induction treatment, rituximab and mycophenolate mofetil were also effective. Lower dose steroids can now be safely used in initial treatment protocols. Azathioprine, rituximab, mycophenolate, methotrexate and leflunomide are effective maintenance therapy. More trials are required to understand these drugs and new therapies for quickly treating renal vasculitis.

## Summary of findings for the main comparison. Plasma exchange as adjunctive therapy for renal vasculitis

**Plasma exchange as adjunctive therapy for renal vasculitis**

**Patient or population:** adults with renal vasculitis
**Settings:** inpatients then outpatients
**Intervention:** plasma exchange as adjunctive therapy

**Comparison**: standard therapy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Control | Plasma exchange | | | |
| **Death at one year** | **189 per 1000** | **197 per 1000** (108 to 364) | **RR 1.04** (0.57 to 1.92) | 267 (5) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serum creatinine at 1 year** | Mean serum creatinine in the plasma exchange group was 23.52 µmol/L higher (17.19 lower to 64.22 higher) than the control group | | -- | 156 (4) | ⊕⊕⊖⊖ **low**[1,3] |
| **Dialysis at one year** | **376 per 1000** | **169 per 1000** (109 to 271) | **RR 0.45** (0.29 to 0.72) | 235 (6) | ⊕⊕⊖⊖ **low**[1,2] |
| **Sustained remission** | **560 per 1000** | **571 per 1000** (498 to 649) | **RR 1.02** 0.89 to 1.16) | 704 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Relapse** | not reported | not reported | -- | -- | -- |
| **Total number of adverse events** | **577 per 1000** | **583 per 1000** (525 to 646) | **RR 1.01** (0.91 to 1.12) | 956 (5) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serious infections** | **253 per 1000** | **318 per 1000** (260 to 389) | **RR 1.26** (1.03 to 1.54) | 956 (5) | ⊕⊕⊖⊖ **low**[1,2] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Though some of the studies are of high quality, others have very significant problems (e.g. Mauri 1985; Pusey 1991)
[2] Event rate and sample size are small
[3] High heterogeneity across groups

**Summary of findings 2. Pulse cyclophosphamide versus continuous cyclophosphamide for remission induction**

**Pulse cyclophosphamide (CPA) versus continuous CPA for remission induction**

**Patient or population:** adults with renal vasculitis
**Settings:** inpatients then outpatients
**Intervention:** pulse CPA
**Comparison:** continuous CPA

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Continuous CPA | Pulse CPA | | | |
| **Death at final follow-up** | **206 per 1000** | **158 per 1000** (90 to 271) | **RR 0.77** (0.44 to 1.32) | 278 (4) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serum creatinine at 12 months** | Mean serum creatinine in the pulse CPA group was 9.78 µmol/L lower (53.16 lower to 33.61 higher) than the continuous CPA group | | -- | 52 (2) | ⊕⊕⊖⊖ **low**[2,3] |
| **Dialysis at end of study** | **74 per 1000** | **140 per 1000** (68 to 288) | **RR 1.90** (0.92 to 3.91) | 245 (4) | ⊕⊕⊖⊖ **low**[1,2] |
| **Remission at 6 months** | **880 to 1000** | **906 per 1000** (808 to 994) | **RR 1.03** (0.93 to 1.13) | 176 (2) | ⊕⊕⊖⊖ **low**[1,2] |
| **Relapse at the end of follow-up** | **181 per 1000** | **324 per 1000** (201 to 519) | **RR 1.79** (1.11 to 2.87) | 235 (4) | ⊕⊕⊖⊖ **low**[1,2] |

| | | | | | |
|---|---|---|---|---|---|
| **Adverse events - treatment failure** | **140 per 1000** | **190 per 1000** (21 to 1000) | **RR 1.36** (0.115 to 12.56) | 82 (2) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serious infections** | **348 per 1000** | **247 per 1000** (132 to 462) | **RR 0.71** (0.38 to 1.33) | 278 (4) | ⊕⊕⊖⊖ **low**[1,4] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Two of these studies had a high risk of bias.
[2] Sample size and/or event rate were low.
[3] Wide 95% CI
[4] Very different event rates across studies

### Summary of findings 3. Rituximab versus cyclophosphamide for renal vasculitis for remission induction

**Rituximab compared to cyclophosphamide (CPA) for remission induction**

**Patient or population:** adults with renal vasculitis
**Settings:** inpatients then outpatients
**Intervention:** rituximab
**Comparison:** CPA

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (studies)** | **Quality of the evidence (GRADE)** |
|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | |
| | **CPA** | **Rituximab** | | | |
| **Death at 6 months** | **28 per 1000** | **28 per 1000** (6 to 129) | **RR 1.00** (0.21 to 4.70) | 241 (2) | ⊕⊕⊕⊖ **moderate**[1] |
| **Kidney function** | not reported | not reported | -- | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| **Dialysis** | not reported | not reported | -- | -- | -- |
| **Remission at 6 months** | **661 per 1000** | **674 per 1000** (522 to 872) | **RR 1.02** (0.79 to 1.32) | 236 (2) | ⊕⊕⊕⊖ **moderate**[1] |
| **Relapse at 12 months** | **100 per 1000** | **143 per 1000** (18 to 1000) | **RR 1.43** (0.18 to 11.31) | 38 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serious adverse events** | **826 per 1000** | **971 per 1000** (594 to 1000) | **RR 1.11** (0.72 to 1.71) | 241 (2) | ⊕⊕⊕⊖ **moderate**[1] |
| **Serious Infections** | **92 per 1000** | **82 per 1000** (39 to 176) | **RR 0.89** (0.62 to 1.92) | 241 (2) | ⊕⊕⊕⊖ **moderate**[3] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Number of events overall is low
[2] One small study
[3] Different event rates in the 2 studies

### Summary of findings 4. Mycophenolate mofetil versus cyclophosphamide for remission induction

**Mycophenolate mofetil (MMF) versus cyclophosphamide (CPA) for remission induction**

**Patient or population:** adults with renal vasculitis
**Settings:** inpatients then outpatients
**Intervention:** MMF
**Comparison:** CPA

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (studies)** | **Quality of the evidence (GRADE)** |
|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | |

| | CPA | MMF | | | |
|---|---|---|---|---|---|
| **Death at 6 months** | **57 per 1000** | **71 per 1000** (20 to 255) | **RR 1.25** (0.35 to 4.46) | 140 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis** | **29 per 1000** | **29 per 1000** (4 to 197) | **RR 1.00** (0.14 to 6.90) | 140 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Relapse at any time point** | **203 per 1000** | **366 per 1000** (203 to 654) | **RR 1.80** (1.00 to 3.22) | 127 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Remission at 6 months** | **716 per 1000** | **837 per 1000** (723 to 966) | **RR 1.17** (1.01 to 1.35) | 216 (3) | ⊕⊕⊕⊖ **moderate**[3] |
| **Serious adverse events** | **400 per 1000** | **500 per 1000** (344 to 724) | **RR 1.25** (0.86 to 1.81 | 140 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Infection** | **183 per 1000** | **233 per 1000** (138 to 396) | **RR 1.27** (0.75 to 2.16) | 216 (3) | ⊕⊕⊕⊖ **moderate**[3] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study results
[2] Wide CI
[3] Some inconsistency in results between studies

## Summary of findings 5. Intravenous immunoglobulin versus placebo for renal vasculitis in adults

**Intravenous immunoglobulin (IVIg) compared to placebo for renal vasculitis in adults**

**Patient or population:** adults with renal vasculitis
**Settings:** inpatients then outpatients
**Intervention:** IVIg
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Placebo | IVIg | | | |
| **Death** | **118 per 1000** | **24 per 1000** (1 to 456) | **RR 0.20** (0.01 to 3.88) | 34 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis** | not reported | not reported | -- | -- | -- |
| **Response at 3 months** | **353 per 1000** | **822 per 1000** (416 to 1000) | **RR 2.33** (1.18 to 4.61) | 34 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Relapse at 3 months** | **267 per 1000** | **312 per 1000** (104 to 949) | **RR 1.17** (0.39 to 3.56) | 34 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Adverse events** | **235 per 1000** | **706 per 1000** (285 to 1000) | **RR 3.00** 1.21 to 7.45) | 34 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Serious infection** | not reported | not reported | -- | -- | -- |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Small sample size; single study results
[2] Wide CI

## Summary of findings 6. Azathioprine versus cyclophosphamide for maintenance therapy

**Azathioprine (AZA) versus cyclophosphamide (CPA) for maintenance therapy**

**Patient or population:** adults with renal vasculitis for maintenance therapy
**Settings:** inpatients then outpatients
**Intervention:** AZA
**Comparison:** CPA

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | CPA | AZA | | | |
| **Death (median follow-up time 8.5 years)** | **164 per 1000** | **127 per 1000 (58 to 283)** | **RR 0.77** (0.35 to 1.72) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis (median follow-up time 8.5 years)** | **110 per 1000** | **181 per 1000** | **RR 1.65** (0.57 to 4.79) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |
| **Relapse at 18 months** | **137 per 1000** | **155 per 1000** (70 to 342) | **RR 1.13** (0.51 to 2.50) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |
| **Relapse (median follow-up time 8.5 years)** | **356 per 1000** | **520 per 1000** (356 to 762) | **RR 1.46** (1.00 to 2.14) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |
| **Serious adverse events** | **96 per 1000** | **113 per 1000** (43 to 294) | **RR 1.18** (0.45 to 3.07) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |
| **Infections** | **178 per 1000** | **183 per 1000** (91 to 367) | **RR 1.03** (0.51 to 2.06) | 144 (1) | ⊕⊕⊕⊖ **moderate**[1] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study results
[2] Wide CI

## Summary of findings 7. Azathioprine versus methotrexate for maintenance therapy

**Azathioprine (AZA) versus methotrexate (MTX) for renal vasculitis for maintenance therapy**

**Patient or population:** adults with renal vasculitis for maintenance therapy
**Settings:** inpatients then outpatients
**Intervention:** AZA
**Comparison:** MTX

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | MTX | AZA | | | |
| **Death** | **16 per 1000** | **5 per 1000** (0 to 127) | **RR 0.33** (0.01 to 8.03 | 126 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis** | not reported | not reported | -- | -- | -- |
| **Relapse** | **333 per 1000** | **367 per 1000** (227 to 590) | **RR 1.10** (0.68 to 1.77) | 126 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Adverse events causing death or study drug discontinuation** | **190 per 1000** | **110 per 1000** (48 to 263) | **RR 0.58** (0.25 to 1.38) | 126 (1) | ⊕⊕⊖⊖ **low**[1,2] |
| **Severe adverse events** | **175 per 1000** | **79 per 1000** (30 to 215) | **RR 0.58** 0.25 to 1.38) | 126 (1) | ⊕⊕⊖⊖ **low**[1,2] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Single study results
[2] Wide CI

## Summary of findings 8. Antibiotics versus placebo for maintenance therapy

**Antibiotics versus placebo for maintenance therapy**

**Patient or population:** adults with renal vasculitis for maintenance therapy
**Settings:** inpatients then outpatients
**Intervention:** antibiotics

**Comparison**: placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Placebo | Antibiotics | | | |
| **Death at 6 months** | **25 per 1000** | **8 per 1000** (0 to 194) | **RR 0.33** (0.01 to 7.76) | 81 (1) | ⊕⊕⊖⊖ **low**[1] |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis** | not reported | not reported | -- | -- | -- |
| **Remission at one year** | **796 per 1000** | **908 per 1000** (780 to 1000) | **RR 1.14** (0.98 to 1.33) | 111 (2) | ⊕⊕⊖⊖ **low**[2,3] |
| **Relapse** | not reported | not reported | -- | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| **Adverse events causing study drug discontinuation** | **50 per 1000** | **195 per 1000** (44 to 863) | **RR 3.90** (0.88 to 17.26) | 81 (1) | ⊕⊕⊖⊖ **low**[1] |
| **Infection (urinary tract infection)** | **25 per 1000** | **8 per 1000** (0 to 194) | **RR 0.33** (0.01 to 7.76 | 81 (1) | ⊕⊕⊖⊖ **low**[1] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgrade 2 levels for study size and limitations with risk of bias assessment
[2] One study had multiple limitations in the reporting of the study design
[3] Two small studies

## Summary of findings 9. Leflunomide versus methotrexate for maintenance therapy

**Leflunomide compared to methotrexate (MTX) for maintenance therapy**

**Patient or population:** adults with renal vasculitis for maintenance therapy
**Settings:** inpatients then outpatients
**Intervention:** leflunomide
**Comparison:** MTX

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (studies)** | **Quality of the evidence (GRADE)** |
|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | |
| | **MTX** | **Leflunomide** | | | |
| **Death** | not reported | not reported | -- | -- | -- |
| **Kidney function** | not reported | not reported | -- | -- | -- |
| **Dialysis** | not reported | not reported | -- | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| **Relapse** | **464 per 1000** | **232 per 1000** (102 to 515) | **RR 0.50** (0.22 to 1.11) | 54 (1) | ⊕⊕⊖⊖ **low**[1] |
| **Serious adverse events*** | **no events** | **5/26*** | **RR 11.81** (0.69 to 203.68) | 54 (1) | ⊕⊕⊖⊖ **low**[1] |
| **Infection** | **429 per 1000** | **501 per 1000** (283 to 887) | **RR 1.17** (0.27 to 106.88) | 54 (1) | ⊕⊕⊖⊖ **low**[1] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgrade 2 levels for study size and limitations with risk of bias assessment
* 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

# BACKGROUND

## Description of the condition

Renal vasculitis presents as rapidly progressive glomerulonephritis (RPGN) which comprises of a group of conditions characterised by acute kidney injury (AKI), haematuria and proteinuria. Histological examination of the kidney reveals severe inflammation in the form of crescent formation, glomerular necrosis and vasculitis of small and medium sized vessels within the kidney. These conditions include the anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides, anti-glomerular basement membrane (anti-GBM) disease and idiopathic RPGN (Savage 1997). ANCA-associated vasculitides are generally small vessel vasculitides and include granulomatosis with polyangiitis (GPA; previously called Wegener's granulomatosis (WG)), microscopic polyangiitis (MPA) and renal-limited vasculitis (Seo 2004). GPA is characterised by granulomatous inflammation usually involving the sinuses, lungs and kidneys. It is usually associated with the detection of cytoplasmic-ANCA (c-ANCA) specific for proteinase-3 (PR3) in the serum of the patient (Jennette 2003). MPA is a small to medium vessel vasculitis in the presence of perinuclear-ANCA (p-ANCA) specific for myeloperoxidase (MPO). Studies often include GPA, MPA and renal-limited vasculitis together as ANCA-associated vasculitides though there is some evidence that they have distinct genetic backgrounds and therefore pathogenesis (Lyons 2012). Eosinophilic GPA is also classified as an ANCA-associated vasculitides (Jennette 2013), but is not specifically included in this review. In the majority of studies, it is excluded. It is a less well defined condition with overlap with other eosinophilic diseases. Evidence increasingly points to the pathogenicity of ANCA (Jennette 2008). Other conditions also cause vasculitis in the kidney such as Henoch Schonlein Purpura and cryoglobulinaemia resulting in immune deposits visible on electron microscopic examination of renal tissue. The treatment of Goodpasture's disease and other forms of RPGN with granular immune deposits (which have an entirely separate pathogenesis to the pauci-immune (no immune deposits) forms of the disease) has not been addressed in this review.

## Description of the intervention

Treatments for vasculitis involve suppression of the immune system and have been highly successful. Death of untreated vasculitis was 80% at one year (Phillip 2008). Recent figures suggest 80% five-year survival with modern immunosuppression (Harper 2011). Induction protocols have historically been based around the use of cyclophosphamide (CPA), either daily oral dosing or monthly intravenous (IV) pulses (Bolton 1989; Savage 1997). More recently anti-CD20 monoclonal antibody treatment has gained some popularity as a primary treatment, though supported by a considerably smaller body of evidence. In the presence of kidney failure, plasma exchange is often used as an adjunct to pharmacological treatment (Lockwood 1976; Pusey 1991; Rondeau 1989). Once remission of the disease is achieved, treatment is scaled back with lower doses of steroids and the induction agent is replaced by a less potent immunosuppressive, such as azathioprine (AZA). Co-trimoxazole has been used in GPA mainly to prevent the occurrence of pneumocystis infection, upper respiratory tract infection and subsequent relapse of disease. Various guidelines are available which summarise available treatment options and some of the evidence for their use (Lapraik 2007; Menahem 2008; Mukhtyar 2009).

## How the intervention might work

There are multiple interventions deployed in this condition. The majority of these interventions work by suppression of the immune system in various ways. Some of these are well defined whereas others are not. For instance, rituximab works by specifically binding to CD20 a molecule expressed on B cell subsets. It works to inhibit the actions of these cells and reduce levels of antibodies that are thought to be pathogenic in this disease. CPA also is directed against B cells. AZA is an anti-metabolite which inhibits cell proliferation and tends to inhibit lymphocytes, since they have a high rate of cell division. Steroids, also known as glucocorticoids, have a broad immunosuppressive effect via multiple cellular pathways.

## Why it is important to do this review

These treatments are well established but many questions remain unanswered. Though recent guidelines are comprehensive (KDIGO 2012), optimal agent, dose, duration, route and frequency of treatment are uncertain. CPA can be given as a daily oral dose or in intermittent oral or IV doses (Adu 1997). IV regimens tend to give a lower total dose and have fewer side effects, but give a higher rate of relapse (de Groot 2001; Harper 2011). Treatment may also include IV methylprednisolone or plasma exchange but their place in therapy is debated (Kerr 2001; Levey 1994). Other therapies including mycophenolate mofetil (MMF), anti-TNF alpha therapy, leflunomide, methotrexate (MTX), anti-adhesion molecule (CD52) therapy and IV immunoglobulin (IVIg) have been suggested (Jayne 2000a; Nowack 1997; Tervaert 2001) but the randomised controlled trial (RCT) data are limited.

Death from this condition remains significant with more than 10% of patients with severe ANCA-associated vasculitides dying in the first 12 months after diagnosis (Little 2010). Fifty percent of these are caused by treatment side effects.

# OBJECTIVES

To evaluate the benefits and harms of any intervention used for the treatment of renal vasculitis in adults.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All 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) looking at any intervention used for the treatment of renal vasculitis in adults.

### Types of participants

#### *Inclusion criteria*

All adult patients suffering from vasculitis with renal involvement. Renal involvement includes an episode of AKI, proteinuria and haematuria, or both, with a kidney biopsy showing severe acute glomerulonephritis with crescents, glomerular necrosis or other histological evidence of vasculitis or a positive test for ANCA antibodies. AKI was defined by the included studies.

***Exclusion criteria***

- RPGN with granular immune deposits such as systemic lupus erythematosus, cryoglobulinaemia, Henoch-Schonlein Purpura
- RPGN secondary to infections
- Polyarteritis nodosa (PAN)
- Eosinophilic GPA
- Goodpasture's disease (or anti-GBM antibody disease).

### Types of interventions

Any pharmacological intervention covering:

1. Corticosteroids versus placebo
2. Non-corticosteroid agents, including CPA, AZA, plasma exchange and immunoadsorption, with or without concurrent use of other immunosuppressive agents
3. Different doses and duration of corticosteroid treatment
4. Different doses, duration and route of administration of non-corticosteroid treatment
5. Any other agents evaluated in an RCT.

### Types of outcome measures

***Primary outcomes***

1. Death at 1, 2 and 5 years
2. Kidney function: serum creatinine (SCr), glomerular filtration rate (GFR) at 1, 2, 3, 6 and 12 months then annually
3. Need for kidney replacement therapy (KRT) at 1, 2, 3, 6 and 12 months then annually.

***Secondary outcomes***

1. Number of patients achieving remission
2. Number of patients relapsing (as defined by the study)
3. Adverse effects of each drug (e.g. nausea, leukopenia, infections)
4. Cumulative doses of steroid and other agents.

Relapse of disease was defined by the included studies, but typically included an increase in Birmingham Vasculitis Activity Score (BVAS) score or a recurrence of symptoms of vasculitis.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 21 November 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. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

## Data collection and analysis

### 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 two authors, who discarded studies that did not meet inclusion criteria although studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

### Data extraction and management

Data extraction was carried out by the same authors independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study exists, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions those data were used.

### Assessment of risk of bias in included studies

The following items were independently assessed 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

Dichotomous outcomes were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used.

The summary measure data were translated into number needed to treat (NNT) and number needed to harm (NNH) for the observed overall baseline risks. Adverse effects were tabulated and assessed with descriptive techniques. The risk differences with 95% CI were to be calculated for each adverse effect, either compared to no treatment or compared to another agent, unfortunately there were insufficient studies to do this.

#### Dealing with missing data

Any further information required from the original author was requested by written correspondence and any relevant data obtained in this manner were included in the review.

#### Assessment of heterogeneity

For this update 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 CI for $I^2$) (Higgins 2011).

#### Assessment of reporting biases

Although we planned to construct funnel plots to assess for the potential existence of small study bias, we did not identify sufficient studies to enable analysis (Higgins 2011).

#### Data synthesis

Data were pooled using the random effects model but the fixed effects model were also analysed to ensure robustness of the model chosen and susceptibility to outliers.

#### Subgroup analysis and investigation of heterogeneity

Because there were insufficient studies comparing the same pair of interventions we were unable to explore whether there were differences in the following study level characteristics; participants (age, gender and kidney function at presentation), treatments and study quality variability The review reports the therapeutic agent used, its dose and duration of therapy.

#### *'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 certainty 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 certainty 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). Two review authors independently rated the certainty of the evidence for each outcome. We used the GRADE system to rank the certainty of the evidence using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). See Appendix 3 for steps for assessing GRADE and reasons for upgrading or downgrading the certainty of the evidence. We presented the following outcomes in the 'Summary of findings' tables:

- Death (one year; end of study; end of follow-up)
- Kidney function (one year; end of study; end of follow-up)
- Dialysis (one year; end of study)
- Remission (induction only; six months; one year)
- Relapse (any time point)
- Serious adverse events (e.g. causing death or study drug discontinuation)
- Infections (serious; any).

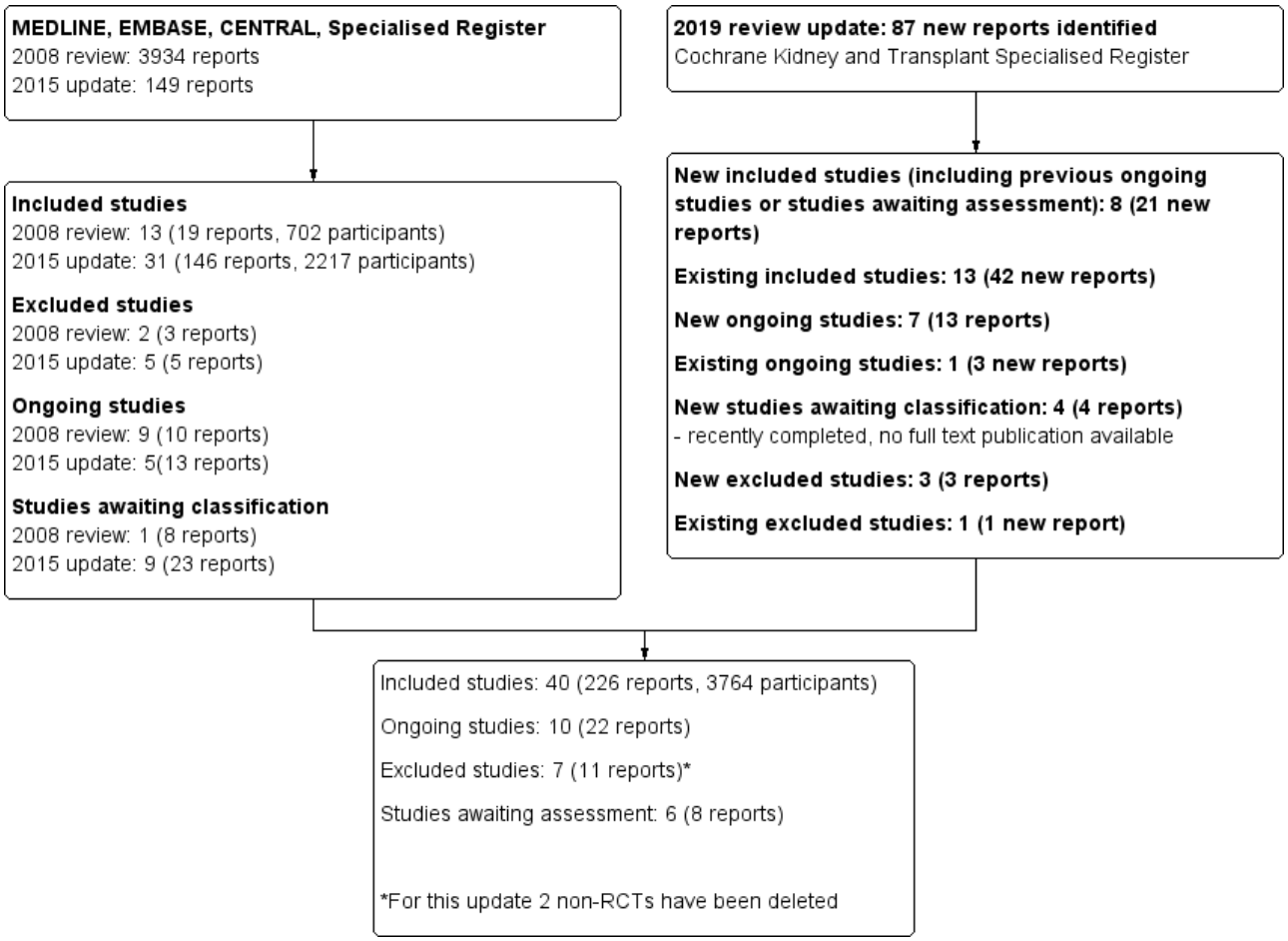
## RESULTS

### Description of studies

#### Results of the search

A PRISMA flow chart combining all searches and screening results is shown in Figure 1.

**Figure 1. Study flow diagram**




For this 2019 update, we searched the Cochrane Kidney and Transplant Specialised Register up to November 2019. Since 2008, inclusive of all updates of this review, we have identified a total of 4170 reports and examined 63 full-text studies (267 reports). We included 40 studies (226 reports) (see Included studies). We have excluded seven studies (11 reports) (Basu 2017; CHUSPAN 2 2017; De Vita 2012; Harper 2018; Imai 2006; Ribi 2010; Rifle 1990), six studies (eight reports) are awaiting classification (Chen 2011c; CLASSIC 2016; Henderson 2009; MAINTANCAVAS 2017; Pagnoux 2003; RATTRAP 2015), and ten studies (22 reports) are ongoing (ADVOCATE 2019; ALEVIATE 2018; CANVAS 2016; COMBIVAS 2019; MAINRITSAN 3 2015; MUPIBAC 2004; NCT03323476; RITAZAREM 2013; Tuin 2019).

### Included studies

Forty studies (3764 participants) were included in this review. See Characteristics of included studies. Nine new studies have been included since the 2015 update.

#### *Types of treatments for remission induction*

- Plasma exchange adjunctive therapy (Cole 1992; Glockner 1988; Mauri 1985; MEPEX 2007; PEXIVAS 2013; Pusey 1991; Rifle 1980; Szpirt 2011; Zauner 2002)
- Pulse versus continuous CPA treatment (Adu 1997; CYCLOPS 2004; Guillevin 1997; Haubitz 1998)
- Ten studies considered other potential treatments including: rituximab (RAVE 2010; RITUXVAS 2010), mycophenolate mofetil (Han 2011b; Hu 2008b; MYCYC 2012), methotrexate (NORAM 2005), avacopan (CLEAR 2013), intravenous immunoglobulin for refractory disease (Jayne 2000), immunoadsorption (Stegmayr 1999), lymphocytapheresis (Furuta 1998)
- Six to 12 pulses of CPA for vasculitis with poor prognostic factors (Guillevin 2003; CORTAGE 2015)
- Reduced dose to standard dose of steroids (PEXIVAS 2013)
- Etanercept and placebo (WGET 2002).

As the inclusion and exclusion criteria and treatment regimens varied so widely they have been listed in separate tables (see Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9).

#### *Types of maintenance therapies*

Maintenance treatment was considered by sixteen studies including comparisons of:

- Azathioprine after three months of remission induction with continued cyclophosphamide (CYCAZAREM 2003);
- Azathioprine and mycophenolate mofetil (IMPROVE 2003)
- Azathioprine and methotrexate (WEGENT 2008)
- Azathioprine and rituximab (MAINRITSAN 2014)

- Co-trimoxazole and placebo (Stegeman 1996; Zycinska 2009)
- Cyclosporin and cyclophosphamide (Szpirt 2011)
- Extended and standard azathioprine (AZA-ANCA 2016; REMAIN 2003)
- Methotrexate and leflunomide (Metzler 2007)
- Methotrexate and cyclophosphamide (Maritati 2017)
- Tailored and fixed rituximab (MAINRITSAN 2 2018)
- Pre-emptive therapy for relapse (Boomsma 2003; Tervaert 1990)
- Belimumab with placebo (BREVAS 2019).

As the inclusion and exclusion criteria and treatment regimens varied so widely they have been listed in separate tables (see Appendix 10; Appendix 11).

No quasi-RCTs were identified.

#### *Diagnoses*

The vast majority of the studies included patients now recognised as having ANCA-associated vasculitis in the forms of GPA, MPA and renal-limited vasculitis.

Other included diagnoses were mainly in earlier studies and included extracapillary and endo-extracapillary proliferative GN (Rifle 1980), Goodpasture's disease (Stegmayr 1999; only 6/52 patients had this diagnosis), lymphomatoid granulomatosis (Mauri 1985), necrotizing angiitis (Mauri 1985), post-infectious disease RPGN (Cole 1992), PAN (Adu 1997; Glockner 1988; Mauri 1985), scleroderma (Glockner 1988), and systemic lupus erythematous (Glockner 1988).

### Excluded studies

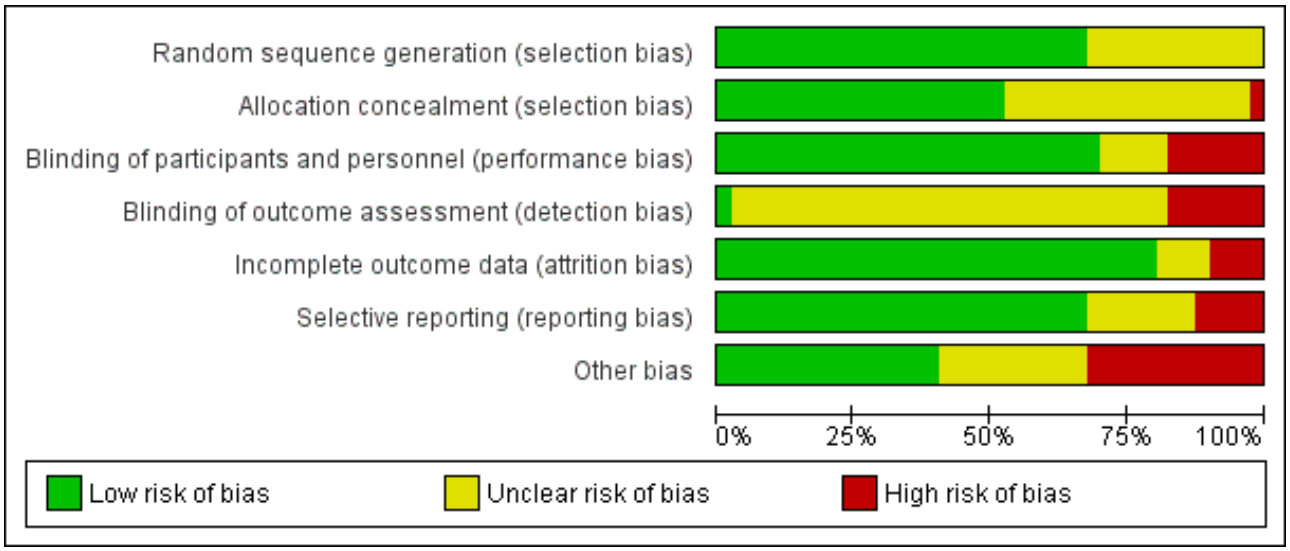
Seven studies have been excluded, five due to the wrong participant population to fit our criteria (CHUSPAN 2 2017; De Vita 2012; Imai 2006; Ribi 2010; Rifle 1990), and two studies were not induction or maintenance studies (Basu 2017; Harper 2018). See Characteristics of excluded studies.

Non-RCTs have been removed from this review update (Figure 1).

## Risk of bias in included studies

For a summary of the risk of bias assessments see Figure 2.

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




Studies conducted earlier tended to have a higher risk of bias due to poor (or poorly reported) study design, broad inclusion criteria, less well-developed disease definitions and low patient numbers. Later studies tend to have improved in all areas of quality, aided by the development of large transnational study groups.

### Allocation

#### *Random sequence generation*

Randomisation methods were not clearly reported in 13 studies (Boomsma 2003; Furuta 1998; Guillevin 1997; Haubitz 1998; Hu 2008b; Mauri 1985; Pusey 1991; Rifle 1980; Stegmayr 1999; Tervaert 1990; WGET 2002; Zauner 2002; Zycinska 2009).

Randomisation methods were adequately reported in the remaining 27 studies. Such methods included:

- Computer-generated random numbers and stratified for kidney function, urine volume, and by country and disease;
- Stratified for oliguria or dialysis;
- Stratified by disease severity and by recruiting centre;
- Telephone with a statistician;
- Stratified by hospital;
- Stratified for diagnosis; and centrally performed.

#### *Allocation concealment*

Allocation concealment was not performed in Maritati 2017, (high risk). Allocation concealment was unclear in 18 studies (Boomsma 2003; Cole 1992; CORTAGE 2015; Furuta 1998; Guillevin 1997; Guillevin 2003; Han 2011b; Haubitz 1998; Hu 2008b; Mauri 1985; Metzler 2007; Pusey 1991; REMAIN 2003; Rifle 1980; Stegmayr 1999; Tervaert 1990; Zauner 2002; Zycinska 2009), and at low risk of bias

for the remaining 21 studies (Adu 1997; AZA-ANCA 2016; BREVAS 2019; CLEAR 2013; CYCAZAREM 2003; CYCLOPS 2004; Glockner 1988; IMPROVE 2003; Jayne 2000; MAINRITSAN 2014; MAINRITSAN 2 2018; MEPEX 2007; MYCYC 2012; NORAM 2005; PEXIVAS 2013; RAVE 2010; RITUXVAS 2010; Stegeman 1996; Szpirt 2011; WEGENT 2008; WGET 2002).

### Blinding

#### *Performance bias*

Five studies provided adequate descriptions of blinding both the participants and study personnel (BREVAS 2019; CLEAR 2013; Jayne 2000; Stegeman 1996; WGET 2002) (low risk of performance bias). For 22 studies, blinding of participants or study personnel was not possible however the risk of bias was judged to be low as this was unlikely to affect the outcomes of the studies (Adu 1997; Boomsma 2003; CYCLOPS 2004; Glockner 1988; Guillevin 1997; Guillevin 2003; Han 2011b; Haubitz 1998; Hu 2008b; IMPROVE 2003; MEPEX 2007; Metzler 2007; MYCYC 2012; NORAM 2005; Pusey 1991; Rifle 1980; RITUXVAS 2010; Stegmayr 1999; Szpirt 2011; Tervaert 1990; WEGENT 2008; Zauner 2002). Cole 1992 blinded the participants and review of the initial biopsies (low risk).

Blinding or participants or investigators could not be determined in five studies and judged to be an unclear risk (CYCAZAREM 2003; Furuta 1998; Mauri 1985; RAVE 2010; Zycinska 2009).

Six studies were open-label and the methods used were judged to be high risk (AZA-ANCA 2016; CORTAGE 2015; MAINRITSAN 2014; MAINRITSAN 2 2018; Maritati 2017; PEXIVAS 2013; REMAIN 2003).

#### *Detection bias*

BREVAS 2019 was judged to be low risk for adequately blinding all outcome assessors.

In 32 studies there was a lack of information regarding blinding of the outcome assessors and judged to be unclear risk. Cole 1992 blinded the review of the final biopsies and Stegeman 1996 blinded the participant's physician. In CYCLOPS 2004 outcomes were classified by non-blinded investigators and validated by an independent observer. Two studies had centralised computer entry from data books (CYCAZAREM 2003; CYCLOPS 2004). For the rest of the studies no further information was reported.

Seven studies reported a clear indication that the outcome assessors were not blinded and judged to be high risk (AZA-ANCA 2016; CORTAGE 2015; MAINRITSAN 2014; MAINRITSAN 2 2018; Maritati 2017; MYCYC 2012; PEXIVAS 2013).

### Incomplete outcome data

The completeness of follow-up ranged from 82% to 100%. In most studies follow-up was generally good with few patients being lost to follow-up or being withdrawn from the studies.

Thirty-two studies were judged to be at low risk of attrition bias. Four studies were judged unclear risk due to insufficient details to judge (BREVAS 2019; MYCYC 2012; REMAIN 2003; Rifle 1980), and four studies were judged to be at high risk due to either high attrition rates, or too many missing participants who were not accounted for at the end of the trials (Haubitz 1998; Hu 2008b; Mauri 1985; Metzler 2007).

### Selective reporting

Selective reporting bias was generally not detected. These were mostly small studies with very limited reporting measures. The larger studies had very clearly defined outcomes which were clearly reported.

Twenty-seven studies were judged to be low risk of reporting bias. Eight studies were judged to be unclear risk (Cole 1992; CORTAGE 2015; Glockner 1988; Guillevin 2003; Maritati 2017; Pusey 1991; REMAIN 2003; Tervaert 1990), and five studies were judged to be at high risk of reporting bias (Boomsma 2003; Furuta 1998; Mauri 1985; Zauner 2002; Zycinska 2009).

### Other potential sources of bias

Sixteen studies were judged to be at low risk of other sources of bias.

Potential biases were unclear in 11 studies (Boomsma 2003; CORTAGE 2015; Furuta 1998; Hu 2008b; Mauri 1985; PEXIVAS 2013; REMAIN 2003; Rifle 1980; Stegmayr 1999; Szpirt 2011; Zauner 2002).

Thirteen studies were judged to be at high risk of other sources of bias:

- Groups appeared to be unbalanced (age, kidney function, BVAS score) (Adu 1997; BREVAS 2019; Guillevin 2003; Zycinska 2009).
- Studies were terminated early (interim analyses showed increased side effects; higher rate of relapses; significant differences between the groups) (AZA-ANCA 2016; BREVAS 2019; Guillevin 1997; Haubitz 1998; Metzler 2007).
- Funded by pharmaceutical industry (BREVAS 2019; CLEAR 2013; Jayne 2000; MAINRITSAN 2 2018).
- Patients crossed from one treatment arm to the other after four weeks of treatment (Glockner 1988)
- Time taken to complete the study (10 years) subject to biases involved in changing physician perceptions of the efficacy of treatment (Pusey 1991).

## Effects of interventions

See: **Summary of findings for the main comparison** Plasma exchange as adjunctive therapy for renal vasculitis; **Summary of findings 2** Pulse cyclophosphamide versus continuous cyclophosphamide for remission induction; **Summary of findings 3** Rituximab versus cyclophosphamide for renal vasculitis for remission induction; **Summary of findings 4** Mycophenolate mofetil versus cyclophosphamide for remission induction; **Summary of findings 5** Intravenous immunoglobulin versus placebo for renal vasculitis in adults; **Summary of findings 6** Azathioprine versus cyclophosphamide for maintenance therapy; **Summary of findings 7** Azathioprine versus methotrexate for maintenance therapy; **Summary of findings 8** Antibiotics versus placebo for maintenance therapy; **Summary of findings 9** Leflunomide versus methotrexate for maintenance therapy

### Remission induction studies

#### *1: Plasma exchange as adjunctive therapy*

Ten studies investigated plasma exchange as adjunctive therapy (Cole 1992; Glockner 1988; Mauri 1985; MEPEX 2007; PEXIVAS 2013; Pusey 1991; Rifle 1980; Stegmayr 1999; Szpirt 2011; Zauner 2002).

Zauner 2002 contained no extractable data and could not be included in the meta-analyses.

Plasma exchange may reduce the need for KRT at three months (Analysis 1.3.2 (2 studies, 147 participants): RR 0.43, 95% CI 0.23 to 0.78; $I^2$ = 0%; NNT = 5; low certainty evidence) and 12 months (Analysis 1.3.4 (6 studies, 235 participants): RR 0.45, 95% CI 0.29 to 0.72; $I^2$ = 0%; NNT = 5; low certainty evidence) post-treatment. The MEPEX 2007 included patients with SCr > 500 µM and reported a reduction in the need for dialysis at three and 12 months. A subgroup analysis included in Pusey 1991 showed that plasma exchange is effective in patients with severe AKI requiring dialysis. PEXIVAS 2013 reported no difference in the need for dialysis at any time point (Analysis 1.3.6). Currently there are no data available at specific time points for PEXIVAS 2013.

Plasma exchange may increase the number of serious infections compared to control (Analysis 1.5.1 (5 studies, 956 participants): RR 1.26, 95% CI 1.03 to 1.54; $I^2$ = 0%; low certainty evidence).

Plasma exchange may make little or no difference to death (Analysis 1.1), SCr (Analysis 1.2), sustained remission (Analysis 1.4), serious or total number of adverse events (Analysis 1.5.7; Analysis 1.5.8) (low certainty evidence).

***2: Pulse versus continuous cyclophosphamide***

Four studies (Adu 1997; Guillevin 1997; Haubitz 1998; CYCLOPS 2004) investigated the use of pulse and continuous administration of CPA for remission induction. Patients with systemic, rather than specifically renal, vasculitis were included in these studies. Raw data has been obtained from Adu 1997 and those patients with PAN have been excluded from these analyses.

Compared to continuous CPA, pulse CPA may make little or no difference to death at final follow-up (Analysis 2.1.5 (4 studies, 278 participants): RR 0.77, 95% CI 0.44 to 1.32; $I^2$ = 15%; low certainty evidence) or SCr at any time point (Analysis 2.2).

There were more patients requiring KRT at the end of the study period in the pulse CPA group than the continuous CPA group however further studies are required (Analysis 2.3.4 (4 studies, 245 participants): RR 1.90, 95% CI 0.92 to 3.91; $I^2$ = 0%; low certainty evidence).

Pulse CPA may make little or no difference to remission compared to continuous CPA (Analysis 2.4).

Pulse CPA may increase the risk of relapse compared to continuous CPA at the end of follow-up (Analysis 2.5.3 (4 studies, 235 participants): RR 1.79, 95% CI 1.11 to 2.87; $I^2$ = 0%; NNH = 5; low certainty evidence).

Leukopenia was less common with pulse treatment (Analysis 2.7.2 (4 studies, 278 participant): RR 0.53, 95% CI 0.36 to 0.77; $I^2$ = 0%; NNH = 5), however nausea was more common (Analysis 2.7.3 (2 studies, 97 participants): RR 2.51, 95% CI 1.07 to 5.89; $I^2$ = 0%; NNH = 7).

Pulse CPA compared to continuous CPA may make little or no difference to either treatment failure (Analysis 2.6) or serious infections (Analysis 2.7.1).

***3: Rituximab versus cyclophosphamide***

Two studies compared rituximab versus CPA for remission induction (RAVE 2010; RITUXVAS 2010).

Rituximab compared to CPA probably makes little or no difference to death (Analysis 3.1), remission (Analysis 3.2), relapse (Analysis 3.3), severe adverse events (Analysis 3.4.1), serious infections (Analysis 3.4.2), or severe adverse events (episodes/patient-months) (Analysis 3.5).

Kidney function and dialysis were not reported.

***4: Mycophenolate mofetil versus cyclophosphamide***

Three studies compared MMF and CPA for remission induction (Han 2011b; Hu 2008b; MYCYC 2012).

MYCYC 2012 reported 5/70 deaths in the MMF group and 4/70 in the CPA group (Analysis 4.1). Two patients in each group required dialysis at six months (Analysis 4.2).

MMF improved remission at six months compared to CPA (Analysis 4.3.1 (3 studies, 217 participants): RR 1.17, 95% CI 1.01 to 1.35; $I^2$ = 4%; high certainty evidence).

MYCYC 2012 reported more patients relapsed with MMF (21/63) than CPA (12/56) at 18 months (Analysis 4.4).

There were no differences in adverse events (GI symptoms, infections, leukopenia, serious adverse events) between the two groups (Analysis 4.5).

Kidney function was not reported.

***5: Methotrexate versus cyclophosphamide***

NORAM 2005 compared MTX with CPA.

There were no deaths in the MTX group at 6 months and 1/49 deaths in the CPA group. There were two deaths in each group at 18 months (Analysis 5.1)

Remission at 6 months was similar (MTX: 44/49; CPA: 43/46) (Analysis 5.2.1). The authors reported longer time to remission for MTX in patients with a higher disease activity index. Relapse post-remission rates were higher for the MTX group (32/46) than the CPA group (20/43) (Analysis 5.3). Relapse figures quoted here are end of study numbers, not a specific time point.

Adverse event rates were reported to be similar with leukopenia more frequent with CPA treatment (6 events in the CPA group and 0 events in the MTX group) and more liver dysfunction in MTX (7 events in the MTX group and 1 in the CPA group).

Kidney function and dialysis were not reported.

***6: Avacopan versus prednisolone***

CLEAR 2013 reported the mean eGFR at three months for patients receiving avacopan was 56.1 ± 5.2 mL/min/1.73 $m^2$ and 52.8 ± 3.6 mL/min/1.73 $m^2$ for those receiving prednisolone (Analysis 6.2). There were no deaths reported in either group (Analysis 6.1)

Remission (avacopan: 7/21; prednisolone: 8/20) (Analysis 6.3) and relapse (avacopan: 3/22; prednisolone: 2/23) (Analysis 6.4) were similar.

There were more serious adverse events in the avacopan group (avacopan: 8/22; prednisolone: 4/23) (Analysis 6.5).

Dialysis was not reported.

***7: Intravenous immunoglobulin use in persistent disease***

Jayne 2000 reported the use of IVIg demonstrated a therapeutic response in more patients at three months when compared with placebo. Response was defined as a reduction in BVAS of > 50% (IVIg: 14/17; control: 6/17) Analysis 7.2. Benefit was not demonstrated beyond three months. There were no deaths in the IVIg group and 2/17 deaths in the control group (Analysis 7.1). There were 5/16 relapses in the IVIg group and 4/15 in the control group (Analysis 7.3). There were more adverse events in the IVIg group (IVIg: 12/17; control: 4/17) (Analysis 7.4).

Kidney function and dialysis were not reported.

***8: Immunoadsorption versus plasma exchange***

Stegmayr 1999 reported 3/21 deaths in the immunoadsorption group and 2/23 deaths in the plasma exchange group (Analysis 8.1).

At six months SCr was 164.5 ± 94.1 µmol/L in the immunoadsorption group and 187.8 ± 61.2 µmol/L in the plasma exchange group (Analysis 8.2). Two of 18 needed dialysis in the immunoadsorption group and 3/21 in the plasma exchange group (Analysis 8.3).

Remission, relapse, and adverse events were not reported.

***9: Lymphocytapheresis***

Furuta 1998 reported a reduction in SCr with lymphocytapheresis (2.1 ± 0.3 mg/dL) compared to control (4.2 ± 0.9 mg/dL) at four weeks (Analysis 9.2). There were 2/12 deaths in the lymphocytapheresis group and 5/12 in the control group (Analysis 9.1). One of 12 patients required dialysis in the lymphocytapheresis group and 3/12 in the control group (Analysis 9.3).

Remission, relapse, and adverse events were not reported.

***10: Duration (6 versus 12 pulses) of cyclophosphamide induction***

Two studies compared six versus 12 pulses of cyclophosphamide for remission induction (CORTAGE 2015; Guillevin 2003).

Guillevin 2003 reported 6/19 deaths in the 6-pulse group compared to 6/28 in the 12-pulse group at the end of the study. CORTAGE 2015 reported 9/53 deaths in the 6-pulse group and 12/53 in the 12-pulse group at 3 years (Analysis 10.1).

There was little or no difference in remission between 6 and 12 pulses of CPA (Analysis 10.2 (2 studies, 151 participants): RR 0.99, 95% CI 0.85 to 1.15; $I^2$ = 11%; low certainty evidence). There is low certainty evidence that there were less relapses with 12 pulses (Analysis 10.3 (2 studies, 133 participants): RR 1.57, 95% CI 0.96 to 2.56; $I^2$ = 0%), but more infections (Analysis 10.4.1 (2 studies, 169 participants): RR 0.79, 95% CI 0.36 to 1.72; $I^2$ = 45%).

CORTAGE 2015 reported severe adverse events were less in patients receiving 6 (32/53) compared to 12 pulses (40/51) of CPA (Analysis 10.4.2).

Kidney function and dialysis were not reported.

***11: Reduced versus standard dose steroids***

PEXIVAS 2013 reported 46/353 death in the reduced dose group and 53/351 in the standard dose group (Analysis 11.1). There were 70/353 requiring dialysis in the reduced dose group and 68/351 in the standard dose group (Analysis 11.2).

In the reduce dose group 204/353 had sustained remission and there were 193/353 in the standard dose group (Analysis 11.3).

There were 231/353 severe adverse events and 96/353 serious infections in the reduced dose group and 218/351 and 116/351 in the standard dose group (Analysis 11.4.1) (Analysis 11.4.2).

Kidney function and relapse were not reported.

***12: Etanercept versus placebo***

WGET 2002 reported 4/89 deaths in the etanercept group and 2/85 in the placebo group (Analysis 12.1). There were 62/89 sustained remissions in the etanercept group and 64/85 in the placebo group (Analysis 12.2); 19/62 relapses in the etanercept group and 21/64 in the placebo group (Analysis 12.3). There were 44/89 infections and 6/89 cancers in the etanercept group and 42/85 and 0/85 in the placebo group (Analysis 12.4).

Kidney function and relapse were not reported.

**Maintenance therapy studies**

***13: Azathioprine versus cyclophosphamide***

CYCAZAREM 2003 reported there were 37/71 relapses after the introduction of AZA compared to 26/73 for the group who remained on CPA (Analysis 13.3). There were 35 episodes/1095 patient-months of leukopenia reported in patients treated with CPA and 22 episodes/1065 patient-months in the AZA group (Analysis 13.5.1).

Leukopenia was more frequent in the CPA group (35/73) compared to the AZA group (22/71) (Analysis 13.5) but no difference in infection (AZA: 13/71; CPA: 13/73) (Analysis 13.5.2) or serious adverse events (AZA: 8/71; CPA: 7/73) (Analysis 13.4.3).

Long-term follow-up (median time 8.5 years) showed no difference in death (AZA: 9/71; CPA: 12/73) (Analysis 13.1.1) or need for dialysis (AZA: 8/71; CPA: 5/73) Analysis 13.2).

Kidney function was not reported.

***14: Mycophenolate mofetil versus azathioprine***

IMPROVE 2003 reported no difference in death (Analysis 14.1) between MMF (1/76) and AZA (1/80). More patients were reported to relapse in the MMF group (42/76) compared to the AZA group (30/80) (Analysis 14.2.1). There were no differences between major (Analysis 14.2.2) and minor relapses (Analysis 14.2.3). In the MMF group there were 3/76 serious infections and 8/80 in the AZA group (Analysis 14.3.2). In the MMF group there 4/76 reports of leukopenia and 7/80 reports in the AZA group (Analysis 14.3.3).

Kidney function and dialysis were not reported.

***15: Azathioprine versus methotrexate***

WEGENT 2008 reported no differences between the treatments for death (AZA: 0/63; MTX: 1/63) (Analysis 15.1), relapse (AZA: 23/63;

MTX: 21/63) (Analysis 15.2), and event-free survival (AZA: 17/24; MTX: 15/25) (Analysis 15.4).

There were more patients with relapse-free survival at 18 (AZA: 30/43; MTX 40/43) and 24 months (AZA: 13/25; MTX: 22/30) in the MTX group (Analysis 15.3) but not at 36 months. There were more adverse events (AZA: 26/63; MTC: 35/63) (Analysis 15.5.1), severe adverse events (AZA: 5/63; MTX: 11/63) (Analysis 15.5.2), and adverse events causing death or study drug withdrawal (AZA: 7/63; MTTX: 12/63) (Analysis 15.5.2) in the MTX group.

Kidney function and dialysis were not reported.

***16: Rituximab versus azathioprine***

MAINRITSAN 2014 reported less major relapses in rituximab compared to azathioprine at one year (RTX: 1/57; AZA: 8/58) (Analysis 16.2.1), two years (RTX: 1/59; AZA: 10/58) (Analysis 16.2.2), and 28 months (RTX: 3/57; AZA: 17/58) (Analysis 16.2.3).

No differences were found between the two treatments for death (Analysis 16.1), minor relapse at 12, 24 and 28 months (Analysis 16.3), or serious infection (Analysis 16.4).

Kidney function and dialysis were not reported.

***17: Co-trimoxazole (antibiotics) versus placebo for relapse prevention***

Two studies investigated co-trimoxazole for relapse prevention (Stegeman 1996; Zycinska 2009). Stegeman 1996 reported death at six months and remission at 12 and 24 months; Zycinska 2009 reported remission at 12 and 18 months.

Stegeman 1996 reported no difference in death at six months (Analysis 17.1).

At 12 months antibiotics may make little or no difference to remission (Analysis 17.2.1 (2 studies, 111 participants): RR 1.14, 95% CI 0.98 to 1.33; $I^2$ = 0%; low certainty evidence).

Zycinska 2009 reported no improvement in remission at 18 months (antibiotics: 12/16; placebo: 8/15) (Analysis 17.2.2) and Stegeman 1996 reported no improvement at 24 months (antibiotics: 31/41; placebo: 23/39) (Analysis 17.2.3).

Stegeman 1996 reported more adverse events causing study drug discontinuation (antibiotics: 8/41; placebo: 2/40) (Analysis 17.3.6).

There were some significant difficulties with the reporting of Zycinska 2009 along with unbalanced groups at baseline which would bias in favour of the treatment being effective.

Kidney function and dialysis were not reported.

***18: Cyclosporin versus cyclophosphamide***

Szpirt 2011 reported no difference in the number of relapses with cyclosporin (10/16) compared to CPA (8/16) (Analysis 18.1).

Death, kidney function, dialysis, remission, adverse events, and infection were not reported.

***19: Extended versus standard azathioprine***

Two studies compared an extended azathioprine with a standard AZA treatment (AZA-ANCA 2016; REMAIN 2003). There were more relapses in the standard AZA group (Analysis 19.3 (2 studies, 162 participants): RR 0.41, CI 0.26 to 0.64).

No differences were found for death between the two groups (Analysis 19.1). REMAIN 2003 reported 0/61 in the extended AZA group and 4/56 in the standard AZA group needed dialysis (Analysis 19.2).

AZA-ANCA 2016 reported no differences in serious infections (Analysis 19.4.1) and leukopenia (Analysis 19.4.2) between the two treatments.

Kidney function was not reported.

***20: Leflunomide versus methotrexate***

Metzler 2007 reported more relapses in the MTX group (13/28) compared to the leflunomide group (6/26) (Analysis 20.1.1). More major relapses were also reported in the MTX group (7/28) compared to the leflunomide group (1/26) (Analysis 20.1.2). There were more severe adverse events in the leflunomide group (5/26) than the MTX group (0/28) (Analysis 20.2.1). There were no differences between the groups for infection (Analysis 20.2.2) or leukopenia (Analysis 20.2.3).

There were multiple methodological difficulties with this study addressed in the discussion section.

Death, kidney function, and dialysis were not reported.

***21: Methotrexate versus cyclophosphamide***

Maritati 2017 reported no differences in death (Analysis 21.1), relapse (Analysis 21.2.1), major relapse (Analysis 21.2.2), minor relapse (Analysis 21.2.3), or serious infection (Analysis 21.3.1) at 12 months. Leukopenia was more frequent in the CPA group (7/33) compared to the MTX group (3/38) (Analysis 21.3.2)

Kidney function and dialysis were not reported.

***22: Tailored versus fixed rituximab***

MAINRITSAN 2 2018 compared a tailored schedule of 500 mg rituximab infusion with a fixed schedule of 500 mg rituximab infusion and reported no differences for death (Analysis 22.1) and serious infection (Analysis 22.3.2) at 18 months. There were 6/81 major relapses in the tailored group and 3/81 in the fixed group (Analysis 22.2) and 26/81 serious adverse events in the tailored group and 31/81 in the fixed group (Analysis 22.3.1).

Kidney function and dialysis were not reported.

***23: Pre-emptive therapy for relapse***

Two studies investigated pre-emptive therapy for relapse (Boomsma 2003; Tervaert 1990).

For patients with a rising ANCA, fewer relapses occur for those randomised to increased immunosuppression in both studies (Analysis 23.1 (2 studies, 60 participants): RR 0.23, 95% CI 0.03 to 1.59; $I^2$ = 53%).

Death, kidney function, dialysis, adverse events, and infection were not reported.

#### *24: Belimumab versus placebo*

BREVAS 2019 compared belimumab to placebo and reported no difference to relapse (Analysis 24.1), any adverse event (Analysis 24.2.1) or infection (Analysis 24.2.2).

Death, kidney function, and dialysis were not reported.

## DISCUSSION

### Summary of main results

In this 2019 review update, an additional nine studies have been included since the 2015 update (a total of 40 studies, 3764 participants).

#### Remission induction

#### *Plasma exchange as adjunctive therapy*

This meta-analysis shows that plasma exchange confers a significant benefit to many patients with RPGN by reducing the risk of ESKD at both three and 12 months from diagnosis. Szpirt 2011 supports this effect and also suggests that the benefit may be present at five years follow-up. The 12-month RR of 0.45 suggests that the number of patients requiring dialysis may be halved by this intervention. Previous studies have shown an effect in the most severely ill patients. A subgroup analysis in Pusey 1991 showed a benefit for patients requiring dialysis at presentation. More recently, MEPEX 2007 has shown a benefit for patients with SCr > 500 µM with ANCA-associated vasculitis. The majority of patients included in these studies would meet the criteria for having severe AKI (SCr > 500 µM or dialysis required at presentation). It is therefore not clear whether plasma exchange has any impact in patients whose kidney failure is not severe. There was little statistical heterogeneity in all outcomes of these studies with the single exception of SCr at 12 months. Whilst the PEXIVAS results have been included in the review, they do not directly impact the outcomes at particular time points. At time of writing the final manuscript is not released and no data are available to the authors to enter data appropriately. The survival curves published suggest that there is an early effect of plasma exchange on the combined end point of death and dialysis but this has yet to be clarified by the research team. Currently the detailed evidence continues to suggest an effect of plasma exchange on reducing the requirement for dialysis treatment.

#### *Pulse versus continuous cyclophosphamide*

Pulse treatment with CPA was equivalent to continuous treatment for remission induction, but may increase the risk of relapse at the end of follow-up. None of the studies were powered to answer the question of relapse rate since this would require either much larger studies or significantly longer follow-up. We are therefore reliant on the results of meta-analysis to attempt to provide an answer. This answer is less than perfect since it is a meta-analysis of results at different times post treatment across studies with significantly different protocols. In spite of this, there is no evidence of heterogeneity in the outcome, suggesting that the final result is likely to be valid. This analysis is supported by the recent follow-up data from CYCLOPS 2004 showing that patients treated with pulse CPA suffered a 39.5% relapse rate as opposed to 19.8% for continuous daily treatment. Though the rates of relapse with pulse CPA treatment are perhaps discouraging, this does not invalidate this mode of treatment. Pulse therapy still delivers a significantly lower total dose of CPA. For those patients who remain in remission, they have likely benefited in terms of risk of long term side effects. The MAINRITSAN study has unexpectedly provided an interesting insight into the increased relapse rate with pulse therapy. This has been the only study to date that has utilised only pulse cyclophosphamide for induction treatment. Patients were then randomised to rituximab or azathioprine for maintenance, with the study showing an improved relapse rate on rituximab. However, the overall rate of relapse in the rituximab limb was similar to the rate in the azathioprine limb of the IMPROVE study. The IMPROVE study patients were treated with oral cyclophosphamide for induction. This shows that relapse rate is highly dependent on the induction treatment, as well as the maintenance therapy used.

There is a trend towards more patients requiring dialysis with the use of pulse CPA therapy. This is currently not statistically significant, but the fact remains that there were twice as many patients requiring dialysis after pulse therapy and that this effect is present in all studies. This effect was not confirmed in the long term follow-up of CYCLOPS 2004. CPA treatment was given for three months, approximately six months, one and two years in the four relevant studies. This difference may account for the significant level of statistical heterogeneity detected in death and the incidence of serious infections. Pulse therapy also caused significantly more nausea but less leukopenia and serious infections. In the light of data from CYCAZAREM 2003, it would seem reasonable to suggest that continuous oral CPA should be limited to three months treatment if the patient has achieved a sustained remission with a change to AZA for maintenance therapy. The optimal regimen for CPA administration for remission induction in ANCA-associated vasculitis remains unclear.

#### *Rituximab versus cyclophosphamide alone for remission induction*

RITUXVAS 2010 and RAVE 2010 are two well-designed studies showing that Rituximab is equivalent to CPA therapy for remission induction whilst side effects occur at a similar frequency, albeit possibly in a smaller number of patients with rituximab. The difference in remission rates of over 90% in RITUXVAS 2010 and 605 to 70% in RAVE 2010 at six months is of interest. The studies differed in their patient population (new versus new and relapsed), treatment protocols (rituximab with pulse CPA versus IV pulse CPA (RITUXVAS 2010) and rituximab alone against oral CPA (RAVE 2010)), and remission definitions. The patient populations differed in that all patients in RITUXVAS 2010 had kidney involvement as opposed to 52% in RAVE 2010. In a subgroup analysis of these patients in RAVE 2010, 61% of the rituximab group and 63% of the CPA group reached the primary endpoint. This does not account for the difference in remission rates between the studies. In RITUXVAS 2010, rituximab was given in conjunction with IV pulses of CPA whereas RAVE 2010 gave rituximab without concomitant CPA. CPA was given orally at 2 mg/kg/day in RAVE 2010 as opposed to the IV pulses in RITUXVAS 2010. There are no data to support a higher remission rate from pulse therapy per se. RITUXVAS 2010 defined remission as a BVAS of 0 for at least two months whereas RAVE 2010 defined remission as a BVAS of 0 and either no steroid treatment or less than 10 mg/day prednisolone. The latter figures from RAVE 2010 are included in this review. The inclusion of steroid doses in the definition of remission may be one of the main influences reducing the apparent remission rate in RAVE 2010.

### *Mycophenolate mofetil for remission induction*

The data currently available on this question have improved markedly with the publication of the initial results of MYCYC 2012. The data now suggests that MMF is an equivalent induction agent to CPA. The next question is the subsequent relapse rate and this has not so far been addressed. If the relapse rate is particularly high, MMF may simply turn out to be an expensive prelude to subsequent CPA. Data from MYCYC 2012 will be available later on the relapse rate in their population.

The populations of patients studied in Han 2011b and Hu 2008b are significantly different from those in other studies, most obviously in the proportion of patients with MPO-ANCA and MPA at 87%. This is significantly different from that reported from Europe where the majority of patients are PR3-ANCA positive. The remission rate is also lower than that achieved in similar studies from Europe with only 44% of patients achieving remission (CYCAZAREM 2003) as opposed to over 90% in MYCYC 2012. The external validity of these studies and wider applicability of their results have improved with MYCYC 2012 data showing very similar findings in terms of the comparison with CPA. The predominantly European cohort has again shown a higher level of remission induction on both agents.

Han 2011b is very similar to Hu 2008b. A very similar population of patients diagnosed with MPA were randomised who were almost exclusively MPO-ANCA positive. Hu 2008b excluded patients with severe and dialysis-dependent kidney failure whereas Han 2011b did not, though there were only nine patients in this subgroup. Both studies treated with CPA for six months regardless of time to remission and outcomes quoted are at six months only. MYCYC 2012 treated to remission with a minimum of three months CPA and a maximum of six.

### *Methotrexate for remission induction*

The single study (NORAM 2005) comparing the use of oral MTX with oral CPA showed that in patients with early disease and SCr < 150 µM, MTX is an effective induction agent. Time to remission may be a little longer with MTX though this was not conclusively shown. Side effects were similar on the two agents. The relapse rate in this study was high and the MTX group had a significantly higher rate than the CPA group. These data have been used to argue that 12 months of treatment is probably not adequate for patients with these diseases, especially for those with GPA who have a greater tendency to relapse. Considering the data on the utility of MTX as a maintenance agent, this study shows that MTX is a useful induction agent for patients with early systemic vasculitis. Longer term follow-up of these patients showed that those treated with MTX had longer periods of treatment with other agents than those initially treated with CPA.

### *Avacopan versus prednisolone for remission induction*

A single study (CLEAR 2013) comparing avacopan with prednisolone reported a higher mean eGFR (mL/min/1.73 $m^2$) at three months with avacopan, but no differences between the two treatments for remission. It is currently not clear how a complement inhibitor might fit into a treatment strategy for vasculitis or what the costs and benefits of such a treatment might be.

### *Intravenous immunoglobulin use for refractory vasculitis*

The single study in this area suggests a short-term benefit lasting no more than three months (Jayne 2000). The treatment can be viewed as a therapy available to help induce remission but has little bearing on the longer term problem of remission maintenance.

### *Lymphocytapheresis and immunoadsorption*

Lymphocytapheresis, described by Furuta 1998, gives some benefit when compared with three weeks of IV pulse methylprednisolone with a significantly lower SCr in treated patients. There was however no change in either the need for dialysis treatment or death at six months. Considering the lack of a comparison with plasma exchange and the recent data suggesting the use of plasma exchange is superior to pulse methylprednisolone, there is currently no compelling reason to consider using this therapy in these conditions. Immunoadsorption, similarly, appears to have no benefit over the use of plasma exchange.

### *Duration (6 versus 12) of cyclophosphamide induction for remission induction*

Two studies compared six pulses with 12 pulses of CPA and no significant differences were found between the two treatments in measuring death, remission, relapse, or infections (CORTAGE 2015; Guillevin 2003). CORTAGE 2015 reported less severe adverse events in patients receiving six pulses.

The numbers used in this review include only MPA patients whereas the original paper also included PAN. The relapse rate was high in the PAN patients treated with six pulses and this gave a significant result on survival analysis. Including all patients in our analysis still did not quite reach statistical significance. This study does not reflect current practice and has in some ways been superseded by CYCAZAREM 2003 which compared a short to a long course of CPA but also included maintenance therapy in the form of AZA. With the inclusion of patients with PAN, the absence of maintenance therapy and its inadequate size, this study is rather difficult to interpret.

### *Reduced dose versus standard dose steroids for remission induction*

PEXIVAS 2013 compared two different doses of steroid and found no differences between the two treatments in terms of remission induction, but did show a reduction in infections with the lower dose steroids. The lower dose of steroids therefore appears to be effective and safer.

### *Etanercept for remission induction*

The stated aim of the single study into the use of etanercept in systemic vasculitis was to demonstrate that the relapse rate would be reduced (WGET 2002). The study failed to show this and also suggested an increase in the incidence of malignancy in treated patients. There are currently no RCT data on the use of infliximab or other anti-TNF agents. There is some possibility that alternative agents may produce significantly different outcomes since their mechanism of action is distinct from that of etanercept. At this point in time there is no RCT data supporting their use.

**Maintenance therapy**

***Azathioprine versus cyclophosphamide for maintenance therapy***

The use of AZA as maintenance therapy after an initial three month treatment with CPA is strongly supported by the data from CYCAZAREM 2003. The number of relapses on AZA is similar to CPA with fewer episodes of leukopenia and similar numbers of infections. As well as the data on reduced leukopenia, the reduction in total dose of CPA is presumed to reduce longer term side effects from CPA such as infertility and neoplasia.

***Azathioprine versus mycophenolate mofetil for maintenance therapy***

IMPROVE 2003 was designed to test the hypothesis that MMF would be superior to AZA in remission maintenance but showed the opposite with an increased risk of relapse with MMF. Interestingly the separation of the groups started within the first 12 months of maintenance therapy when patients were treated at full dose of MMF. Major relapses appeared after the first year and could perhaps be due to a reduction in therapy. The study is clear, however, in rejecting MMF as a superior alternative to AZA for maintenance therapy.

***Azathioprine versus methotrexate for maintenance therapy***

WEGENT 2008 showed that the safety and efficacy profiles of MTX and AZA are comparable. The dosing regimen for MTX in this study was superior to that in the leflunomide/MTX study since the rate of rise in dose was faster and the final dose higher (Metzler 2007).

***Rituximab versus azathioprine for maintenance therapy***

MAINRITSAN 2014 found less major relapses when comparing rituximab to azathioprine, at one and two years and 28 months. There are, however some concerns with the data from this study. As mentioned above, this is one of the first studies where on pulse CPA was used for induction treatment, rather than a mix of oral and pulse CPA and rituximab. The relapse rate was high for the study with the relapse rate achieved with rituximab equivalent to that achieved with AZA in the IMPROVE study. The second problem is that the majority of relapses in this study were major relapses. This has not been reported previously. Whilst rituximab is clearly a superior agent compared to AZA, the final relapse rate achieved is a function of both the induction and maintenance regimens. The relapse rate achieved in the MAINRITSAN study is no better than that achieved previously with different induction regimens.

***Co-trimoxazole (antibiotics) versus placebo for maintenance of remission***

The use of co-trimoxazole to maintain remission was examined by Stegeman 1996. This study showed a benefit in reducing the risk of relapse but not on other outcomes. Analysis in the paper by life table analysis showed this result to be statistically significant. Our analysis found no difference (P = 0.12). Relapses detected in the study were mainly respiratory in nature but 11/23 patients with a relapse also had progressive glomerulonephritis. Zycinska 2009 adds some data to this but still does not clearly answer the question. There were some major limitations in the reporting of this study. Patients were said to be in remission at randomisation but the mean BVAS of the placebo group was 11 (remission is 0). There was no reporting of relapse, only numbers of patients in remission. A firm conclusion is not possible on the available data.

***Cyclosporin versus cyclophosphamide for maintenance therapy***

The limited data available suggest that there may be a higher relapse rate with the use of cyclosporin. The single trial was small. It is not possible to be conclusive.

***Extended versus standard length Azathioprine maintenance therapy***

The data strongly support continuation of immunosuppressive treatment with Azathioprine out to approximately 4 years from diagnosis. The REMAIN study was conducted in patients at fairly low risk of relapse. All patients had gone into remission with induction treatment and had no relapses by 18 months post diagnosis. When treatment was tapered, the relapse rate was high over the subsequent two years. This would suggest that patients are safer to continue immunosuppression for at least 4 years after diagnosis and possibly longer for patients at higher risk of relapse.

***Leflunomide versus methotrexate for maintenance therapy***

The single study of leflunomide suggests that this may be an appropriate treatment for patients who are intolerant of AZA (Metzler 2007). There are problems with interpretation and the external validity of this study. The dose of MTX was increased very slowly. Many commentators felt this to be an inadequate dose, potentially causing the higher relapse rate and inadequately reflecting the potential of MTX in this area. There were also a high number of adverse events in the leflunomide arm. The study does however give some data on the use of leflunomide and grounds for its clinical use. Final conclusions are difficult to draw. Further study of leflunomide is warranted as induction therapy and in comparison to AZA as maintenance therapy

***Methotrexate versus cyclophosphamide for maintenance therapy***

In a single study, no differences were found when comparing methotrexate with cyclophosphamide for the outcomes of death or relapse.

***Tailored versus fixed rituximab for maintenance therapy***

A single study compared a tailored schedule of 500mg rituximab infusion with a fixed schedule of 500mg rituximab infusion and reported no differences between treatment groups for death, major relapse, or serious infection at 18 months, but did find severe adverse events to be higher in the fixed schedule group. It is not easy to make clear conclusions from this study. The event rate was low, so the study was under-powered. There were numerically more relapses (both total and major) in the tailored therapy arm. Also 25% more of the patients were left ANCA positive at the end of treatment compared to the fixed schedule infusion group

***Pre-emptive therapy for relapse***

Two studies showed that patients will relapse less often on low level immunosuppression with either AZA or CPA plus prednisolone rather than no change in their treatment (Boomsma 2003; Tervaert 1990). It is difficult to interpret anything else from these studies. At the time they were undertaken, there was some suggestion that an asymptomatic rise in ANCA titre was likely to be a good predictor of imminent relapse. Current literature does not support that hypothesis. Boomsma 2003 was published as an abstract only. It would be interesting to know how many of the patients without an asymptomatic rise had a subsequent relapse. The abstract notes

that after immunosuppression, patients went on to have relapses. Those treated did not appear to benefit from a long term protection from relapse.

***Belimumab versus placebo for maintenance therapy***

BREVAS 2019 compared belimumab to placebo and reported no difference to relapse, any adverse event, or infection. There is currently no evidence for the use of belimumab in the treatment of vasculitis

## Overall completeness and applicability of evidence

The data on the treatment of vasculitis remain incomplete. However, this review summarises a significant body of research that represents some high quality data which clearly goes some way to giving guidance on treatment. The areas of the review with data from multiple studies are probably the most helpful and applicable. In these areas, the earlier studies carried multiple problems in disease ascertainment and methodology but their overall conclusions have generally been borne out by the later larger studies. This is reassuring on applicability. In some areas there are many further questions over how to deploy expensive and potentially harmful treatments. One example here is the data on the use of plasma exchange. This review suggests that it is a highly effective therapy when deployed in a particular group of patients, however this result rests on a relatively small number of outcomes. Questions remain as to whether it is a true effect and which patient groups will benefit. The PEXIVAS study should go some way to clarifying this. Data released so far are analyses over the whole seven-year course of the study and suggest that plasma exchange is not effective in the long term for reducing either death or dialysis. However, the published survival analyses suggest there may well be some effect within the first year on both death and the need for dialysis treatment. The majority of the data in this review is in patients with very poor kidney function. It may also work for patients with good kidney function. This hypothesis is still to be tested. For each of the areas of this review there are multiple such questions still to be answered.

## Quality of the evidence

The strength of this review rests on the breadth of the literature search which included non-English language studies. Unpublished individual patient data were obtained from Adu 1997. This is the first systematic review to cover all areas of renal vasculitis. The review is limited by the small number of available studies answering particular questions and some design features of the included studies. Several older studies included diagnoses other than renal vasculitis. Some date prior to the development of the ANCA assay. This will limit the validity of the data and diagnoses included in those studies. Other differences include those between interventions, notably the regimens of immunosuppressive drugs and the number and volume of plasma exchanges utilised. As noted above, some maintenance treatment studies appear to be influenced by the induction regimen dictated by the protocol, making relapse rates difficult to compare across studies. Some of these issues may have had a very significant impact on the outcomes of studies and may explain the level of heterogeneity in some of the results. Studies of renal vasculitis are notoriously difficult to carry out due to the low incidence of the disease and consequent need for broad collaboration to attain patient numbers for adequately powered studies.

The earlier studies included in this review suffered from some significant methodological problems and inclusion of a wide range of diagnoses which may not have been well validated. The more recent data are of much higher quality. These have generated a significant body of high quality data.

## Potential biases in the review process

We have attempted to avoid bias in our review process, including all studies that are available in the area. They have been examined with standard processes. For each update, we have followed our methods from the original protocol, or used revised methods as recommended by Cochrane (e.g. Risk of Bias and GRADE assessment).

## Agreements and disagreements with other studies or reviews

Three previous reviews have covered some of the subjects addressed in this review.

Bosch 2007 provides a broad review of the treatment of ANCA-associated vasculitis. This includes patients with localized disease and those without renal vasculitis. They include a large number of uncontrolled studies and there was no attempt at meta-analysis. In the area of severe vasculitis with kidney involvement, there is a brief summary of the RCT data as included in this review. Their conclusions are similar to ours.

de Groot 2001 is a review of the data relating to the use of pulse or continuous CPA for induction of remission of ANCA-associated vasculitis and includes a meta-analysis of the RCT data. As such, it performs a similar meta-analysis to ours in this area. There are, however, a number of differences. de Groot 2001 has utilised all the data from Adu 1997. We have extracted the data only for patients without PAN and with some evidence of glomerular involvement. This accounts for some of the differences but not all. de Groot 2001 reports that treatment failure is more likely with continuous treatment with CPA. This is based on 8/25 patients, in Adu 1997, failing treatment. Adu 1997 reports 4/30 patients failed remission induction. Of those, 1/20 suffered treatment failure in the data we have extracted. de Groot 2001 quotes 4/25 patients failing treatment on continuous treatment in Haubitz 1998. Our understanding of this paper suggests that of those four patients, three had in fact died, mostly of sepsis. This is not entirely clear from the paper and we have been so far unable to substantiate this further. Each of these changes contributes to the overall effect in de Groot 2001 showing an increased risk of treatment failure on continuous treatment. Currently we do not believe that a close inspection of the data bears this out. The difference in figures here is also reflected in the results for relapse rate. Our results show that continuous treatment is significantly better at preventing relapse. We have studied relapse as related to the initial number of patients whereas de Groot 2001 have recorded relapses as related to achieved remissions. With the higher treatment failure figures in the continuous arm, de Groot 2001 does not show a significant difference in the overall relapse rate.

Walsh 2011 performed a similar systematic review to ours in the area of plasma exchange and its effect on ESKD, death and a combined endpoint of both. They demonstrated similar results to ours with a profound reduction in the development of ESKD and no effect on death. They then combined those two endpoints to

argue that there was little conclusive evidence for the overall effect of plasma exchange on the "hard" endpoint of ESKD and death combined. It is currently our view that combining two outcomes with markedly different results does not serve to appropriately highlight the efficacy of plasma exchange. The current data suggests a striking reduction in the numbers of patients requiring KRT with no change in the risk of death.

## AUTHORS' CONCLUSIONS

### Implications for practice

Plasma exchange is effective in patients with severe AKI secondary to vasculitis. It is not yet clear whether the results of the PEXIVAS study alter this conclusion. On current data, the use of pulse CPA results in an increased risk of relapse when compared to continuous use but a reduced total CPA dose. Rituximab and MMF are comparable to CPA as induction agents. IVIg is useful but only as a short-term measure. The PEXIVAS protocol for lower dose glucocorticoid induction treatment appears to be safer than the higher dose with equivalent efficacy for remission induction.

AZA and MTX are effective as maintenance therapy once remission has been achieved. The use of MMF in remission maintenance should be third line after failure, or contraindication, of other agents such as AZA and MTX. Rituximab is a superior agent to AZA for maintenance treatment. The use of fixed interval dosing of rituximab may be more efficacious than tailored interval dosing but requires further study. Patients are likely to benefit from at least four years immunosuppression post diagnosis of renal vasculitis.

The use of co-trimoxazole is not supported for prevention of relapse of vasculitis. Etanercept and belimumab are not recommended for use in vasculitis. Leflunomide may be useful as maintenance therapy but requires further evaluation.

### Implications for research

The exact place of plasma exchange in the treatment of vasculitis requires further analysis of the huge dataset behind the PEXIVAS study. Clarity is required over the effect of treatments within the first 12 months of treatment. Whilst the "hard endpoints" at the end of the study are of great clinical and administrative concern, patients will find an extra 6 months alive and off dialysis of significant benefit. Also the use of plasma exchange in pulmonary haemorrhage has not been finally clarified.

The optimal dose of steroids to be used in induction treatment requires further study. Can the PEXIVAS study lower dose be halved without loss of efficacy? Should steroid treatment be more "front-loaded" with a higher percentage of the dose being given in the first 2 to 4 weeks of treatment with a more rapid dose reduction? Previously the currently side-lined MEPEX study clearly showed improved outcomes with plasma exchange rather than methylprednisolone. Should the first two weeks of prednisolone be replaced with alternate day plasma exchange with or without a complement inhibitor?

The data from the MAINRITSAN study seem to confirm previous findings that the use of pulse CPA induction therapy increase the risk of subsequent relapse. Whilst this was an appropriate strategy to increase the event rate in this study, it also gave a relapse rate that was no improvement upon the rate achieved in the IMPROVE study with induction using oral CPA and maintenance with AZA. The IMPROVE study regimen would then be the cheaper option for countries unable to access rituximab treatment. Studies are required that examine the long term effects of the main induction regimens (now oral and pulse CPA, rituximab and MMF) on both remission and relapse rate. One hypothesis would be that there are optimal induction/maintenance combinations that are likely to give equivalent outcomes over the longer term.

The use of AVACOPAN in treatment protocols needs further research. An initial study using the drug as steroid replacement has been successful, but this currently seems an unlikely clinical strategy in the short term due to clinicians' familiarity with steroids and their very low price. Equivalence with glucocorticoid seems unlikely to be an adequate reason for complement inhibitors to feature significantly in treatment protocols in vasculitis.

The AVACOPAN study does illustrate that the strategy of comparing gold standard treatment with a new treatment is potentially more likely to reveal new treatment modalities rather than the adjunctive treatment approach where gold standard therapy is given to both treatment arms and the new therapy is added. The etanercept and belimumab studies are "adjunctive therapy" approaches that have failed. The Avacopan study approach requires more courage, more complex ethical consideration and, potentially, a graded experimental design but may be more likely to be successful.

The studies in this review reflect the solid success of the collaborative efforts of the vasculitis networks which have culminated in the recent PEXIVAS study. Building on this success will hopefully continue to provide answers to the many questions remaining.

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* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

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

### Adu 1997

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: not reported<br>• Duration of follow-up (months): treatment group (0.7 to 63.6); control group (2.5 to 54.8) |
| Participants | • Country: UK<br>• Setting: single centre<br>• Inclusion criteria: 15 to 70 years with new-onset systemic necrotizing vasculitis. WG, classical PAN and MPA diagnosed by histological or radiological evidence<br>• Number: treatment group (24); control group (30)<br>• Median age, range (years): treatment group (47, 22 to 70); control group (62, 15 to 70)<br>• Sex (M/F): treatment group (17/7); control group (18/12)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• PCYP<br>  * Intermittent pulses of CPA and MP<br>  * CPA and MP were given IV at 0, 2 and 4 weeks<br>  * The same dose was then given as oral pulses over a 3-day period. The interval between pulses was gradually increased<br>Control group<br>• CCAZP<br>  * Continuous CPA, MP and AZA<br>  * Initial treatment: 0.85 mg/kg prednisolone then tapering according to a predefined schedule for 72 weeks<br>  * CPA given until a clinical decision that remission had been achieved at which point CPA was stopped and AZA commenced at 1.5 mg/kg/day<br>Other treatment<br>• Escalation of immunosuppression was allowed for severe or life-threatening disease. This included PE and IVIg<br>Duration of treatment: 72 weeks |

**Adu 1997** *(Continued)*

| | |
|---|---|
| Outcomes | • Complete and partial remission<br>  * Absence of clinical symptoms of vasculitis, resolution of pulmonary, renal or other organ changes or stable changes consistent with scarring and stabilization<br>  * Complete remission was defined as the absence of any active disease for at least one month<br>• Relapse<br>  * Re-emergence of new clinical symptoms attributable to vasculitis or worsening of original manifestations after 4 weeks of complete clinical remission had been achieved infection not included)<br>• Adverse events<br>  * Leukopenia, infective episodes, thrombocytopenia, steroid-induced diabetes, osteoporosis, basal-cell carcinoma, septicaemia, pancreatitis, bronchial neoplasm<br>• Treatment failure<br>  * Disease activity > 50%<br>• Chronic dialysis |
| Notes | • Follow-up<br>  * PCYP: median 35.1 months (range 0.7 to 63.3)<br>  * CCAZP: median 42.5 months (range 2.5 to 64.8)<br>  * CCAZP: median duration of CPA was 3 months (range 1.5 to 10)<br>• Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated random numbers, stratified for kidney function (< 250, 251 to 500, > 500 mmol/L) |
| Allocation concealment (selection bias) | Low risk | Sealed envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Study could not be blinded to investigators or participants; unlikely to affect results |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | All outcomes clearly stated |
| Other bias | High risk | Patients in PCYP had worse kidney function than the CCAZP group (median SCr 234, range 60 to1082 mmol/L vs 139, range 72 to 1255 mmol/L (P = 0.3)) |

**AZA-ANCA 2016**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: June 2003 to October 2014<br>• Duration of follow-up: 48 months |

**AZA-ANCA 2016** *(Continued)*

| | |
|---|---|
| Participants | • Country: Netherlands<br>• Setting: multicentre (12 sites)<br>• Inclusion criteria: > 18 years with newly diagnosed PR3 ANCA vasculitis recruited between diagnosis and remission. Those found to be ANCA positive at stable remission after 3 months were randomised. The other patients were treated with standard AZA treatment<br>• Number: treatment group (21); control group (24)<br>• Mean age, range (years): treatment group (56, 26 to 80); control group (53, 18 to 82)<br>• Sex (M/F): treatment group (12/9); control group (16/10)<br>• Exclusion criteria: intolerance for AZA or inability to give informed consent |
| Interventions | Treatment group<br>• Extended AZA therapy: 1.5 to 2.0 mg/kg/day until 4 years after diagnosis, then tapered by 25 mg every 3 months.<br>Control group<br>• Standard AZA therapy: 1.5 to 2.0 mg/kg/day until 12 months after diagnosis, then tapered by 25 mg every 3 months<br>Other treatment<br>• All patients received TMP/SMX 400/80 mg prophylaxis |
| Outcomes | • Relapse-free survival at 4 years<br>• Cumulative dosages of CPA, prednisolone and AZA<br>• Cumulative organ damage<br>• Side effects due to study medication and severity of relapses. |
| Notes | • Patients were withdrawn in the event of failure to control progressive disease using the induction protocol or for failure to achieve remission within 6 months after diagnosis<br>• Funding source: J.-S.F.S. was supported as a clinical research trainee by ZonMW (92003235). This work was supported by the Dutch Kidney Foundation (C02.2027) and the Dutch Arthritis Foundation (02-2-402) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed in blocks of four. Patients were stratified according to hospital, i.e. patients from the UMCG versus patients from other hospitals." |
| Allocation concealment (selection bias) | Low risk | Quote: "Closed envelopes with the randomised treatment duration were produced before inclusion of the first patient" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | open-label study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcomes assessed by unblinded observers by BVAS which is a subjective assessment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Outcomes appear to be comprehensively reported |

**AZA-ANCA 2016** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Organ damage was quoted in the secondary outcomes but no damage index was reported in the results. This is not a high risk for the overall study result |
| Other bias | High risk | Early termination of the study due to poor recruitment. Negative outcomes |

**Boomsma 2003**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: 1998 to 2001<br>• Duration of follow-up: to 2002 |
| Participants | • Country: Netherlands<br>• Setting: single centre<br>• Inclusion criteria: PR3 ANCA-associated vasculitis in remission on ≤ 50 mg daily CPA and ≤ 15 mg daily prednisolone; rise in ANCA titre of more than 75% from previous sample. 100 patients followed; 40 patients developed ANCA rise and were randomised<br>• Number: treatment group (20); control group (20)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• Pre-emptive therapy<br>  * AZA: 75 mg/day for 9 months<br>  * Prednisolone: 30 mg/day tapered over 4.5 months<br>Control group<br>• Follow-up only |
| Outcomes | • Relapse of vasculitis |
| Notes | • Abstract-only publication<br>• 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)<br>All outcomes | Low risk | Blinding not possible (pre-emptive versus follow-up treatment); unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |

**Boomsma 2003** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All 40 patients had outcomes reported |
| Selective reporting (reporting bias) | High risk | Abstract only with no protocol to detect reporting bias; no full-text publication identified 12 years after conference abstracts presented |
| Other bias | Unclear risk | Insufficient information to permit judgement |

**BREVAS 2019**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: first patient was enrolled on 20 March 20, 2013 and the last patient visit took place on 6 February 2017<br>• Duration of follow-up: Quote "the study was truncated after initiation, primarily due to a change in AAV standard of care that affected recruitment. Furthermore, the study design changed from “event driven” to “fixed completion” 12 months after the last patient was randomised, leading to variable durations of treatment. The sample size was reduced from ˜300 patients to ˜100 patients" |
| Participants | • Countries: 15<br>• Setting: multicentre (37 sites)<br>• Inclusion criteria: ≥ 18 years, clinical diagnosis of GPA or MPA, and tested positive (current or historical) for either PR3-ANCAs or MPO-ANCAs. Patients must have experienced either new-onset or relapsing GPA or MPA in the 26 weeks prior to day 0, that required treatment; patients had to be in remission on day 0 (with remission defined as a BVAS score of 0 and receiving glucocorticoids (presented as prednisone-equivalent doses) at ≤ 10 mg/day (on 2 consecutive measurements ≥ 14 days apart, and 6 to 26 weeks after the first dose of induction therapy)<br>• Number: treatment group (53); control group (52)<br>• Mean age ± SD (years): treatment group (56 ± 14); control group (54 ± 14)<br>• Sex (M/F): treatment group (27/26); control group (27/25)<br>• Exclusion criteria: coexistence of another autoimmune disease; any known intolerance or contraindications to AZA and MTX; receipt of any B cell–targeted therapy (excluding RTX) at any time, or any other investigational agent within 60 days of day 0 or 5 half-lives of the agent (whichever was longest); any acute or chronic infections requiring hospitalisation (within 60 days of day 0) and/or receipt of parenteral antibacterial drugs, antiviral drugs, antifungal drugs, or antiparasitic drugs (within 60 days of day 0); serologic evidence of infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus |
| Interventions | Treatment group<br>• Belimumab (IV): 10 mg/kg on days 0, 14, 28 and every 28 days until completion<br>Control group<br>• Placebo (IV)<br>Co-interventions<br>• AZA: 2 mg/kg/day<br>• Low-dose oral glucocorticoids: ≤10 mg/day |
| Outcomes | • Relapse: BVAS score ≥ 6<br>• Infection<br>• Adverse events |
| Notes | • Funded by GlaxoSmithKline |

**BREVAS 2019** *(Continued)*

- Sample size reduced for 300 to 100
- Imbalance in age between the 2 groups

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization schedule was produced by Human Genome Sciences (HGS)" |
| Allocation concealment (selection bias) | Low risk | Quote: " both the sites and study sponsor remained blinded with regard to treatment allocation at all times" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "both the sites and study sponsor remained blinded with regard to treatment allocation at all times" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcomes measured "Quote: "... at double-blind week 48 of year 1 and double-blind week 24 of year 2, as well as by visit"<br><br>Comment: outcome assessors appear to be blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | All patients had outcomes reported |
| Selective reporting (reporting bias) | Low risk | All outcomes clearly stated |
| Other bias | High risk | Funded by GlaxoSmithKline; study terminated early; imbalance across the age categories:<br><br>Quote: "the proportion of elderly patients (age ≥65 years) was higher in the belimumab group (18 [34.0%] of 53 patients) than in the placebo group (8 [15.4%] of 52 patients)." |

**CLEAR 2013**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: 12 October 2011 to 18 January 2016<br>• Duration of follow-up: 12 weeks |
| Participants | • Countries: Europe (11 countries)<br>• Setting: multicentre (32 sites)<br>• Inclusion criteria: ≥ 18 years with newly diagnosed or relapsing granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis according to the Chapel Hill Consensus Conference definitions 1) required CPA treatment (steps 1 and 2), CPA or RTX (step 3), were PR3 or MPO-ANCA positive or ANCA positive by indirect immunofluorescence, had an eGFR ≥ 20 mL/min/1.73 $m^2$, biopsy-proven renal vasculitis or haematuria (> 30 RBC/HPF or greater than 2+ by urine dipstick) plus albuminuria (at least 0.5 g/g creatinine) for steps 1 and 2, or had at least one major or three non-major items, or at least two renal items on the BVAS version 3 2 for step 3. Since the BVAS version 3 does not designate major items, these were selected to be consistent with the BVAS WG 3.<br>• Number: treatment group 1 (22); treatment group 2 (22); control group (23)<br>• Mean age ± SD (years): treatment group 1 (57.1 ± 14.2); treatment group 2 (57.4 ± 14.0); control group (59.1 ± 14.0) |

**CLEAR 2013** *(Continued)*

| | |
|---|---|
| | • Sex (M/F): treatment group 1 (14/8); treatment group 2 (16/6); control group (17/6)<br>• Exclusion criteria: severe disease (including RPGN, alveolar haemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system involvement); any other autoimmune disease, coagulopathy or bleeding disorder; received CPA within 12 weeks, RTX within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count > 0.01 x $10^9$/L); cumulative dose of IV glucocorticoids > 3 g within 12 weeks, or oral glucocorticoids > 10 mg/d prednisone equivalent for more than 6 weeks prior to screening |
| Interventions | Treatment group 1<br>• Avacopan: 40 mg/day<br>• Prednisone: 20 mg/day<br>Treatment group 2<br>• Avacopan: 30 mg/day<br>• Prednisone placebo<br>Control group<br>• Prednisone: 60 mg/day<br>• Avacopan placebo |
| Outcomes | • Proportion of patients with a treatment response at week 12 defined as a BVAS decrease from baseline of at least 50% plus no worsening in any body system<br>• Proportion of patients with a renal response, defined as an improvement in eGFR calculated using the MDRD equation, haematuria, and albuminuria at week 12<br>• Proportion of patients with disease remission (BVAS 0); and change from baseline in BVAS, eGFR, UACR, urinary RCC, urinary MCP-1-to-creatinine ratio, vasculitis damage index, SF-36 version 2, EQ-5D-5L, and rescue glucocorticoid use<br>• Death<br>• Adverse events |
| Notes | • Treatment group 1 was not used in the meta-analyses<br>• Funding source: ChemoCentryx, Inc., Mountain View, California |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomised, stratified by new or relapsing disease, PR3/MPO, induction therapy with cyclophosphamide or RTX. Stratification and randomisation were performed centrally via an interactive voice response system using a minimization algorithm to maintain balance among the treatment groups with respect to strata and study centre |
| Allocation concealment (selection bias) | Low risk | Randomisation performed centrally via interactive voice system. allocation was concealed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Patients and all study personnel were masked to treatment allocation. All study drugs had matching active and placebo capsules, and identical bottles and boxes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | BVAS is a subjective assessment |

**CLEAR 2013** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Stated outcomes reported |
| Other bias | High risk | Funded by ChemoCentryx, Inc., Mountain View, California; 4 authors are employees of the funder |

**Cole 1992**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: 1983 to 1989<br>• Duration of follow-up: 12 months |
| Participants | • Country: Canada<br>• Setting: multicentre, university hospitals<br>• Inclusion criteria: RPGN of undefined aetiology (idiopathic or postinfectious disease) with specific pathologic criteria; adults (16 to 75 years); normal sized kidneys SCr > 170 µmol/L, increasing by 44 µmol/week or both; no evidence of systemic disease or anti-GBM antibody-induced disease; renal biopsy within 5 days of study entry<br>• Number: treatment group (16); control group (16)<br>• Number of HD: treatment group (4); control group (7)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: cellular crescents in < 50% non-obsolescent glomeruli; evidence of serious infection or active ulcer disease |
| Interventions | Treatment group<br>• Immunosuppression: as for control group<br>• PE: at least 10 PE treatments within 16 days of study entry; 1 plasma volume with complete replacement using 5% albumin + crystalloid<br>Control group<br>• Immunosuppression<br>  * IV MP: 10 mg/kg/day for 3 days followed by prednisone 1.4 mg/kg/day for next 4 days and then tapered to 1 mg/kg/day over 2 weeks; 0.35 mg/kg/day at 1 month and 025 mg/kg/day at 2 months<br>  * AZA: 1.5 to 3.0 mg/kg/day with dose adjustment as necessary to ensure neutrophil count of ≥ 2.0 x $10^9$/L |
| Outcomes | • Kidney pathology<br>• Patients on dialysis at randomisation: dialysis at 1, 3, 6, 12 months<br>• Kidney function in patients not on dialysis: 1, 3, 6, 12 months<br>• Change in SCr<br>• Adverse events (serious infections, GI bleeding)<br>• Death |
| Notes | • Funding source: reported |
| ***Risk of bias*** | |

**Cole 1992** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated random numbers, stratified at entry with respect to urine volume, need for dialysis and > 50% glomeruli sclerosed |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | One patient randomised did not receive treatment due to GI bleed at time of randomisation |
| Selective reporting (reporting bias) | Unclear risk | Outcomes were not reported in the methods |
| Other bias | Low risk | "Supported by grants from Health & Welfare Canada and the Kidney Foundation of Canada, and the Metropolitan Toronto Community Foundation." |

**CORTAGE 2015**

| | |
|---|---|
| Methods | • Study design: parallel, open-label study<br>• Study duration: June 2005 to March 2008<br>• Duration of follow-up: 36 months |
| Participants | • Countries: Belgium, France<br>• Setting: multicentre (65 sites)<br>• Inclusion criteria: newly diagnosed PAN not related to hepatitis B virus infection, EGPA, GPA, or MPA; 2) to satisfy the 1990 American College of Rheumatology criteria and/or 1994 Chapel Hill nomenclature definitions (10 to 13); 3) to be in or after the year of their 65th birthday at the time of SNV diagnosis; and 4) to provide written informed consent. Patients could have started corticosteroids, but for no more than 1 month prior to enrolment, and could not have started CYC and/or received any other immunosuppressant before inclusion<br>• Number: treatment group (53); control group (51)<br>• Mean age ± SD (years): treatment group (75.1 ± 6.2); control group (75.3 ± 6.4)<br>• Sex (M/F): treatment group (27/26); control group (32/19)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• Corticosteroids: started at 1 mg/kg then progressively tapered after 3 weeks and stopped at 9 months<br>• CPA pulses: 500 mg every 2 weeks for first 3 pulses then every 3 weeks until remission<br>• Patients switched to MTX or AZA (or MMF for those with intolerance to MTX or AZA)<br>Control group<br>• Corticosteroids: started at 1 mg/kg the progressive tapered after 3 weeks until stopped at 26 months |

**CORTAGE 2015** *(Continued)*

| | |
|---|---|
| | • CPA pulses: 500 mg/m$^2$ for 6 doses with a further 3 doses for consolidation prior to maintenance therapy |
| Outcomes | • Occurrence of 1 or more serious adverse events defined as potentially life-threatening adverse events, requiring hospitalisation or its prolongation, causing significant disability, or resulting in death.<br>• Death<br>• Remission<br>• Relapse<br>• Serious adverse event-free survival<br>• Progression free survival |
| Notes | • Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was performed centrally. The randomisation list was computer generated, using random blocks of 6, with a between-arm randomisation ratio of 1:1 |
| Allocation concealment (selection bias) | Unclear risk | Sealed opaque envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Unclear risk | All outcomes reported |
| Other bias | Unclear risk | Study appears free of other biases |

**CYCAZAREM 2003**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 18 months |
| Participants | • Countries: 11 European countries<br>• Setting: multicentre (39 sites)<br>• Inclusion criteria: diagnosis of WG, MPA or kidney limited vasculitis. Renal involvement, other threatened loss of function of vital organ, or both. ANCA positivity. ANCA negative patients enrolled with biopsy evidence of vasculitis<br>• Number: treatment group (79); control group (76)<br>• Mean age, range (years): treatment group (59, 20 to 77); control group (57, 20 to 76) |

**CYCAZAREM 2003** *(Continued)*

- Sex (M/F): treatment group (33/46); control group (40/36)
- Exclusion criteria: cytotoxic drug in previous year; other multisystem autoimmune disease; hepatitis B e antigenaemia; hepatitis C; HIV infection; SCr > 500 µmol/L; cancer; pregnancy; aged < 18 years or >75 years

| | |
|---|---|
| Interventions | Treatment group<br>• CPA: 1.5 mg/kg/day from remission<br>• Switched to AZA (2 mg/kg/day) 12 months after study entry<br>Control group<br>• After remission induction<br>  * AZA: 2 mg/kg/day<br>  * Prednisolone: 10 mg/day<br>Co-interventions (both groups)<br>• Remission induction with oral CPA (2 mg/kg/day) and prednisolone (1 mg/kg/day) tapered to 0.25 mg/kg/day by 12 weeks<br>• From 12 months both groups received AZA (1.5 mg/kg/day) and prednisolone (7.5 mg/day) |
| Outcomes | • Relapse by 18 months<br>• Side effects including leukopenia and infections. |
| Notes | • Stopping point: 18 months after study entry<br>• Funding source: reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed centrally with the use of permuted blocks of four within each country, with stratification according to diagnosis." |
| Allocation concealment (selection bias) | Low risk | Not reported, however assumed to be performed centrally |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Other bias | Low risk | Supported by contracts (BMH1-CT93-1078, CIPD-CT94-0307, BMH4-CT97-2328, and IC20-CT97-0019) with the European Union |

**CYCLOPS 2004**

| | |
|---|---|
| Methods | • Study design: open-label, parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 18 months |
| Participants | • Country: 14 countries (Europe, Mexico)<br>• Setting: multicentre (42 sites)<br>• Inclusion criteria: newly diagnosed WG, MPA, or renal-limited MPA, renal involvement: at least one of: SCr > 150 µmol/L and < 500 µmol/L, biopsy evidence of necrotizing GN, erythrocyte casts, or haematuria and proteinuria, confirmatory histology or ANCA positivity<br>• Number: treatment group 1 (76); treatment group 2 (73)<br>• Mean age ± SD (years): treatment group 1 (56.6 ± 15.3); control group 2 (58.2 ± 13.7)<br>• Sex (M/F): treatment group 1 (41/35); treatment group 2 (47/26)<br>• Exclusion criteria: other multisystem autoimmune disease; hepatitis B or C virus or HIV infection/ SCr > 500 µmol/L; previous cancer; pregnancy; < 18 years or > 80 years |
| Interventions | Treatment group 1<br>• Pulse CPA<br>  * 3 IV pulses of CPA (15 mg/kg) 2 weeks apart followed by 3 weekly pulses (15 mg/kg (IV) or 5 mg/kg orally for 3 days) until remission then for another 3 months. Max dose 1.2 g. Reductions for age > 60 years and SCr > 300 µM and for previous low leukocyte nadir<br>Treatment group 2<br>• Continuous CPA<br>  * Oral CPA: 2 mg/kg/day to remission then 1.5 mg/kg for further 3 months. Max oral dose 200 mg Reductions for age > 60 years and leukopenia<br>Co-interventions (both groups)<br>• AZA: 2 mg/kg/day orally after induction therapy until month 18<br>• Prednisolone: 1 mg/kg orally tapered to 12.5 mg/day at the end of month 3 and 5 mg at end of study |
| Outcomes | • Primary outcome: time to remission defined as absence of new or worse signs of disease activity on the BVAS<br>• Proportion of patients who achieved remission at 6 and 9 months<br>• Proportion with major and minor relapses<br>• Death<br>• Change in kidney function<br>• Adverse events<br>• Cumulative dose of CPA and prednisolone calculated at 3, 6, 9, 12, 15 and 18 months |
| Notes | • Funding source: reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Random assignments were computer-generated and performed centrally by permuted blocks of 4, stratified by country and disease." randomised 1:1 to treatments. |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were enrolled by their treating physician and registered with the central trial coordinating office by fax submission of a form that contained information on centre, date of birth, sex, disease, and creatinine level." |

**CYCLOPS 2004** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Open-label study, unable to blind interventions; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Eleven patients were withdrawn before random assignment: 1 declined further participation, 8 were withdrawn by their physician, and 2 did not meet the entry criteria |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Other bias | Low risk | Quote: "This trial was funded by the European Union (European Community Systemic Vasculitis Trial project, contract BMH1-CT93-1078 and CIPD-CT94-0307, and Associated Vasculitis European Randomised Trial project, contract BMH4-CT97-2328 and IC20-CT97-0019)." |

**Furuta 1998**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 6 months |
| Participants | • Country: Japan<br>• Setting: single centre<br>• Inclusion criteria: biopsy-proven rapidly progressive GN<br>• Number: treatment group (12); control group (12)<br>• Mean age ± SD (years): treatment group (62 ± 3.0); control group (60 ± 3.2)<br>• Sex (M/F): treatment group (4/8); control group (8/4)<br>• Exclusion criteria**:** not reported |
| Interventions | Treatment group<br>• Lymphocytapheresis: 3 x 1 hour sessions on alternate days in each of 3 consecutive weeks<br>Control group<br>• IV MP: 1 g for 3 consecutive days in each of 3 consecutive weeks<br>Co-interventions (both groups)<br>• Prednisolone: 20 mg/day<br>• CPA: 50 mg/day |
| Outcomes | • SCr 4 weeks post treatment<br>• Death |
| Notes | • Stopping point: 4 weeks after therapy<br>• Research letter<br>• 50% of patients were diagnosed with IgA nephropathy<br>• Funding source: not reported |

**Furuta 1998** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Study described as randomised; method of randomisation not reported |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients randomised were analysed |
| Selective reporting (reporting bias) | High risk | Planned outcomes were not reported; our outcomes of need for KRT, relapse, adverse effects and cumulative dose were not reported |
| Other bias | Unclear risk | Funding not reported |

**Glockner 1988**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study:<br>• Duration of follow-up: 6 months |
| Participants | • Country: Germany<br>• Setting: multicentre<br>• Inclusion criteria: RPGN with > 70% crescents on kidney biopsy; CrCl < 50 mL/min; urine output >200 mL/24 hours<br>• Number: treatment group (16); control group (15)<br>• Mean age, range (years): treatment group (56.3, 38 to 75); control group (40.9, 18 to 66)<br>• Sex (M/F): treatment group (9/3); control group (8/6)<br>• Exclusion criteria: anti-GBM disease; life threatening conditions; contraindications to immunosuppression; previous treatment with AZA or CPA for > 14 d |
| Interventions | Treatment group<br>• PE: 9 x 50 mL/kg over 4 weeks replaced with 3% to 5% albumin solution<br>• Standard immunosuppression.<br>Control group<br>• Standard Immunosuppression.<br>Co-interventions (both groups) |

**Glockner 1988** *(Continued)*

| | |
|---|---|
| | • Standard immunosuppression<br>  * CPA (3 mg/kg/day) + AZA (1 mg/kg/day) for 1 week<br>  * AZA (2 mg/kg/day)<br>  * MP (1.5 mg/kg/day) for 14 days reducing in 4 mg/day steps to maintenance 8 mg/day<br>  * Patients with WG (2) did not receive AZA, only CPA (3 mg/kg/day) for entire study period |
| Outcomes | • Death at 6 months<br>• Dialysis at 6 months<br>• SCr at 4 weeks, 8 weeks and 6 months<br>• Adverse events including serious infections, GI haemorrhage and anaphylaxis |
| Notes | • Control patients not responding in the first 4 weeks were treated with PE in subsequent 4 weeks<br>• Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Telephone consultation with a statistician |
| Allocation concealment (selection bias) | Low risk | Telephone consultation with a statistician |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Three patients in Group A and 2 in Group B did not complete study (GI bleed, death, sepsis or anaphylactic reaction to PE) |
| Selective reporting (reporting bias) | Unclear risk | Outcomes were not clearly identified in the methods |
| Other bias | High risk | The study allowed cross-over from one treatment arm to another after four weeks of therapy |

**Guillevin 1997**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: October 1990 to December 1993<br>• Duration of follow-up (months): treatment group 1 (30.6 ± 16.7); treatment group 2 (24. ± 18.8) |
| Participants | • Country: France<br>• Setting: single centre<br>• Inclusion criteria: > 15 years; new diagnosis of systemic WG diagnosed clinically based on the presence of multiorgan involvement; monovisceral involvement representing a potential risk or severe morbidity of fatality; histopathologic characterization of necrotizing granulomatosis vasculitis or evidence of either granulomatous inflammation and vasculitis or segmental necrotizing GN |

**Guillevin 1997** *(Continued)*

- Number: treatment group 1 (27); treatment group 2 (23)
- Mean age ± SD (years): treatment group 1 (54 ± 13); treatment group 2 (53 ± 15)
- Sex (M/F): treatment group 1 (19/8); treatment group 2 (11/12)
- Exclusion criteria: not reported

| | |
|---|---|
| Interventions | Treatment group 1<br>• Initial regimen<br>• IV pulse CPA: mean dose 0.7 g/m$^2$ adjusted for neutrophil count and kidney function, administered every 3 weeks until complete remission and 1 year thereafter. Then every 4 weeks for 4 months, every 5 weeks for 4 months and every 6 weeks until discontinuation after 2 years if treatment. Adjusted up or down based on neutrophil count<br>Treatment group 2<br>• Initial regimen<br>• Oral CPA: 2 mg/kg/day on day 10 after initial CPA pulse, after neutrophil nadir had been reached. 1 year after complete remission, oral CPA was tapered by 25% every 4 months until discontinuation. Dose adjusted up or down based on neutrophil count<br>Initial regimen<br>• IV MP: 15 mg/kg/day for 3 days then oral prednisolone 1 mg/kg/day. One pulse of IV CPA was administered (0.7 g/m$^2$) the day after the last IV MP and concurrently with the 1st day of oral prednisolone. Oral prednisolone (1 mg/kg/day) for 6 weeks. If complete remission was achieved daily dose was tapered by 2.5 mg every 10 days until a level equivalent to half the original dose was reached. This was maintained for 3 weeks and then further decreased by 2.5 mg every 10 days to 20 mg/day. More gradual tapering for doses < 20 mg/day with decrease of 1mg/day every 2 weeks to 10 mg/day and then 1 mg/month until discontinuation<br>Co-interventions (both groups)<br>• Oral prednisone was prescribed at an initial dosage of 1 mg/kg/day for 6 weeks. For those patients in whom complete remission was achieved, the daily dosage was tapered gradually by 2.5 mg every 10 days until a level equivalent to half the initial dosage was reached. This dosage was maintained for 3 weeks, and was then further decreased by 2.5 mg every 10 days to 20 mg/day. A more gradual tapering schedule was then used for doses < 20 mg/day, with a decrease of the daily dosage by 1 mg every 2 weeks to 10 mg/day, then by 1 mg every month until discontinuation |
| Outcomes | • Treatment failure (no evidence of control of disease activity or when relapse occurred)<br>• Complete remission (general condition improved, no new manifestations and ESR rate returned to normal)<br>• Partial remission (clinical radiologic symptoms were stable or attenuated and lab abnormalities regressed or disappeared under constant treatment)<br>• Relapse (new major systemic manifestations affecting the same or a different organ, or worsening of initial symptoms of the disease<br>• Death<br>• Side effects (CPA-related, steroid-related, regimen-related, infections) |
| Notes | • Four excluded from Group B due to diagnosis of MPA<br>• Supported by grants from the Institut National pour la Sante et la Recherche Medicale (TNSERM), the Assistance Publique-Hopitaux de Paris (AP-HP), and the Association pour la Recherche sur les Angeites Necrosantes (ARAN). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Guillevin 1997** *(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)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Four patients were excluded post randomisation from oral CPA due to wrong initial diagnosis (MPA) |
| Selective reporting (reporting bias) | Low risk | All study and review outcomes were reported |
| Other bias | High risk | Recruitment was terminated early at 30 months due to an interim analysis suggesting higher incidence of side effects and relapse rate between the groups. |

**Guillevin 2003**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: January 1994 and April 2000<br>• Duration of follow-up: 36 months |
| Participants | • Country: France<br>• Setting: multicentre<br>• Inclusion criteria: new diagnosis of PAN or MPA with at least one of five factors: Cr > 1.58 mg/dL (140 µM), proteinuria > 1 g/day, severe GI involvement, cardiomyopathy, CNS involvement<br>• Number: treatment group 1 (31); treatment group 2 (34)<br>• Mean age ± SD (years): treatment group 1 (58 ± 16); treatment group 2 (53 ± 16)<br>• Sex (M/F): treatment group 1 (22/9); treatment group 2 (21/13)<br>• Exclusion criteria: not reported |
| Interventions | Initial regimen<br>• Tapering dose of steroids: 3 daily IV pulses of MP 15 mg/kg. Prednisolone (1 mg/kg/day) for 3 weeks, gradually tapered to stop<br>• CPA pulses given at 0, 2 and 4 weeks, then monthly<br>Treatment group 1<br>• CPA dose: 6 pulses<br>Treatment group 2<br>• CPA dose: 12 pulses |
| Outcomes | • Complete remission |

**Guillevin 2003** *(Continued)*

- Death
- Relapse

| | |
|---|---|
| Notes | • Supported by the Hospices Civils de Lyon, the Association pour la Recherche sur les Ange´ites Ne´crosantes (ARAN), and the UPRES EA-3409 Recherche clinique et the´rapeutique, Universite´ de Paris-Nord. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was centralized at the coordinating centre and made by phone, fax, or E-mail." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No major missing data |
| Selective reporting (reporting bias) | Unclear risk | The outcomes were not clearly defined in the methods. No kidney outcomes reported |
| Other bias | High risk | The groups did not appear well balanced at the start of the study, very different levels of renal involvement and Cr level though this was not assessed as statistically significant |

**Han 2011b**

| | |
|---|---|
| Methods | • Study design: open-label RCT<br>• Duration of study: January 2006 to December 2008<br>• Duration of follow-up: 6 months |
| Participants | • Country: China<br>• Setting: single centre<br>• Inclusion criteria: MPA with moderate to severe renal involvement (MPA by Chapel Hill Nomenclature)<br>• Number: treatment group 1 (19); treatment group 2 (22)<br>• Mean age ± SD (years): treatment group 1 (55.1 ± 11.5); treatment group 2 (57.3 ± 12.7)<br>• Sex (M/F): treatment group 1 (7/12); treatment group 2 (9/13)<br>• Exclusion criteria: severe lung haemorrhage (haemoptysis > 300 mL/24 h or hypoxaemia); CNS involvement; other life-threatening situations; cytotoxic drug in the previous 6 months; severe infection in the last month; active hepatitis or abnormal liver function; pregnancy; malignancies; > 70 years |
| Interventions | Treatment group 1 |

**Han 2011b** *(Continued)*

| | |
|---|---|
| | • MMF (oral): 1.0 g/day (1.5 g/day if weight > 70 kg)<br><br>Treatment group 2<br><br>• CPA (IV): 1.0 g/pulse (0.8G if body weight < 50 kg) monthly<br>• No switch to maintenance treatment indicated<br><br>Co-interventions (both groups)<br><br>• MP (IV): 360 to 500 mg/day for 3 days, then oral prednisone 0.6 to 0.8 mg/kg/day, gradually tapered |
| Outcomes | Primary outcome<br><br>• Remission at 6 months: remission defined as BVAS of 0 under low dose of prednisolone (< 7.5 mg)<br><br>Secondary outcomes<br><br>• Kidney function at 6 months<br>• Adverse events<br><br>Maintenance dialysis defined as HD or PD for at least 6 weeks without subsequent kidney recovery signs |
| Notes | • Treatment reduced for pulmonary infection with hypoxaemia, WCC < 3 x $10^9$/L or severe GI symptoms<br>• No plasmapheresis or immunoadsorption<br>• TMP/SMX recommended but not mandated<br>• Funding source: reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients entered into the study were divided into two groups randomly according to the randomised number table" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 5 patients lost to follow-up and presumed failed treatment, 3 in CPA and 2 in MMF groups |
| Selective reporting (reporting bias) | Low risk | All study and review outcomes were reported |
| Other bias | Low risk | Study was supported by grants from the National Natural Science Foundation of PR China (30801148) to Fei Han and the Key Projects in the National Science & Technology Pillar Program in the Eleventh Five-Year Plan Period (2008BAI60B04) to Jianghua Chen |

### Haubitz 1998

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: started June 1992<br>• Duration of follow-up: standardized follow-up ended 1 year after the end of CPA therapy |
| Participants | • Country: Germany<br>• Setting: multicentre (5 sites); initially inpatients and then seen as outpatients<br>• Inclusion criteria: new diagnoses of WG and MPA and kidney involvement; biopsy performed<br>• Number: treatment group 1 (22); treatment group 2 (25)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: < 18 years; pregnancy; HIV; malignancy; SCr > 200 µmol/L more than 1 year before presentation; cytotoxic drug therapy for > 1 week before start of study; HD for > 10 days before start of study |
| Interventions | Treatment group 1<br>• Steroid regime: same as for treatment group 2<br>• IV pulse CPA: 0.75 g/m$^2$ every 4th week. If CrCl < 30 mL/min, initial dosage was 0.5 g/m$^2$ and increased to 0.75 g/m$^2$ provided leucocyte counts remained > 3000/mL<br>  * CPA dose adjusted to the peripheral leucocyte count and dose reduced in increments of 0.125 g/m$^2$. If leucocyte count < 2500/mL dose was reduced by 0.25 g/m$^2$<br>• Antiemetic drugs were given immediately before and 8 h after treatment. At least 3 L of fluid was administered on day of CPA treatment<br>Treatment group 2<br>• Steroid regime: days 1 to 3: 0.5 g IV MP. Day 4 to 14: 1mg/kg/day oral prednisolone. Day 15 onwards tapering of steroids with a reduction of 10 mg/week. When a dosage or 30 mg/day was reached, tapering changed to 5 mg/week, at 15 mg/day tapering changed to 2.5 mg/week. This tapering protocol was not mandatory, however dosage had to be ≤ 12.5 mg/day at 6 months<br>• Oral daily CPA: 2 mg/kg/day. If CrCl < 30 mL/min, initial dosage started at 1.5 mg/kg/day and increase to 2 mg/kg/day after 2 weeks provided leucocyte counts were > 3000/mL<br>  * CPA dose reduced in steps of 0.5 mg/kg, unless leucocyte count was < 2500/mL then dose reduced by 50%, and if less than 1500/mL drug was withheld until increased to 2500/mL |
| Outcomes | • Complete remission (absence of symptoms or signs attributed to active vasculitis, with a BVAS of 0-1. Absence of kidney disease activity indicated by stable or falling Cr levels and absence of erythrocyte cell casts.)<br>• Partial remission (clear-cut suppression of the disease, with improvement and arrest of disease progression and stabilization of kidney function)<br>• Relapse (recurrence of first appearance of disease activity sufficient to warrant an increase in dosage<br>• Serious infection (diagnosed when hospitalisation and IV antibiotic or antiviral drug administration were required)<br>• ESR, CRP, ANCA, Hb, WBC. platelet count, SCr, urea, CrCl, quantitative proteinuria, urinary microscopy, alanine aminotransferase, aspartate aminotransferase, gonadal toxicity |
| Notes | • End points<br>  * Progression of disease in spite of immunosuppressive therapy<br>  * Lack of complete remission after 12 months of treatment<br>  * Relapse during or up to 1 year after end of CPA therapy after a complete remission had been achieved<br>  * Severe adverse effects of treatment leading to termination of the immunosuppressive treatment (severe opportunistic infections, intractable thrombocytopenia or leukopenia)<br>• Funding source: not reported |

**Haubitz 1998** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | The randomisation was stratified by the diagnosis, however the method was not reported |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | This is an "as treated" as opposed to an intention to treat analysis. 4 patients were excluded due to protocol violations with the interventions |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | High risk | The study was terminated when the analysis showed a difference. Quote: "The prospective, multicenter study was terminated in June 1997, since significant differences between the 2 treatment groups were found." p1836 |

**Hu 2008b**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: June 2003 to December 2004<br>• Duration of follow-up: 6 months |
| Participants | • Country: China<br>• Setting: single centre<br>• Inclusion criteria: newly diagnosed active ANCA-associated vasculitis; > 18 years with renal involvement with SCr < 500 µM; ANCA positive or ANCA negative with confirmatory kidney biopsy<br>• MMF group<br>• Number: treatment group 1 (18); treatment group 2 (17)<br>• Mean age ± SD (years): treatment group 1 (49.6 ± 10.6); treatment group 2 (47.9 ± 15.4)<br>• Sex (M/F): treatment group 1 (9/9); treatment group 2 (11/6)<br>• Exclusion criteria: cytotoxic drug treatment in 6 months prior; HBV, HCV, HIV or active CMV viral infection; acquired immune deficiency; severe kidney failure with Cr > 500 µM or on KRT; life-threatening organ manifestations (lung haemorrhage or CNS involvement); active TB; liver dysfunction; pregnancy or inadequate contraception if female; < 18 years or > 65 years |
| Interventions | Treatment group 1<br>• MMF: 2 g/day (1.5 g if weight < 50 kg) for 6 months<br>Treatment group 2 |

**Hu 2008b** *(Continued)*

| | |
|---|---|
| | • IV CPA: 0.75 to 1.0 g/m$^2$ for 6 months, modified depending on WCC nadir<br><br>Co-interventions (both groups)<br><br>• IV MP 0.5 g/day for 3 days followed by oral prednisolone at 0.6 to 0.8 mg/kg/day for 4 weeks tapered by 5 mg/week to 10 mg/day |
| Outcomes | Primary outcomes<br><br>• Remission rate at 6 months: defined as no clinical signs of vasculitis, improved or stable kidney function; no active urinary sediment and BVAS score 0<br><br>Secondary outcomes<br><br>• Changes in kidney function<br>• Side effects |
| Notes | • Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 4/17 patients on CPA were lost to follow-up at 3 months. The intention to treat analysis assumes that they did badly |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Unclear risk | Funding source not reported |

**IMPROVE 2003**

| | |
|---|---|
| Methods | • Study design: parallel, open-label RCT<br>• Duration of study: April 2002 to May 2004<br>• Duration of follow-up: 4 years |
| Participants | • Countries: 11<br>• Setting: multicentre (42)<br>• Inclusion criteria: newly diagnosed patients with WG, MPA or RLV; ANCA positivity. ANCA positivity requires PR3-ANCA or a typical c-ANCA pattern by IIF, preferably confirmed by anti-PR3 ELISA; MPO-AN- |

**IMPROVE 2003** *(Continued)*

| | |
|---|---|
| | CA determined by ELISA requires demonstration of p-ANCA, and p-ANCA by IIF requires confirmation by anti-MPO ELISA; optionally, central review of ANCA serology can be performed; 18 to 75 years<br>• Number: treatment group 1 (76): treatment group 2 (80)<br>• Mean age ± SD (years): treatment group 1 (54.2 ± 12.8): treatment group 2 (55.1 ± 15.2)<br>• Sex (M/F): treatment group 1 (46/30): treatment group 2 (58/22)<br>• Exclusion criteria: any cytotoxic drug within previous year, unless started within one months of entry and according to the protocol design; co-existence of another systemic autoimmune disease (e.g. SLE, Hepatitis B or HCV, HIV positivity); failure to achieve remission after 6 months of CPA therapy; failure to control progressive disease with induction protocol; malignancy (usually exclude unless agreed with trial coordinator); pregnancy or inadequate contraception; < 18 years and > 75 years; ESKD unless active extrarenal disease requires treatment (temporal dependency of HD is not an exclusion criterion); inability for informed consent |
| Interventions | Treatment group 1<br>• MMF: 2 g/day; reduced to 1500 mg/day after 12 months, 1000 mg/day after 18 months, and withdrawn after 42 months<br>* Complete blood cell count was taken weekly for the first month, biweekly for the second month, and then monthly for the first year, and then every 3 months<br>* MMF use was stopped for presence of leukopenia until recovery and reintroduced with the dose reduced by 500 mg/day. Patients intolerant of the initial dose were reduced to 1000 mg/day and increased monthly by 500 mg/day increments to the 2000 mg/day target or the highest tolerated dose. Dose reduction to 1000 mg/day was recommended for a GFR < 25 mL/min/kg<br>Treatment group 2<br>• AZA: 2 mg/kg/day (max 200 mg), rounded down to the nearest 25 mg increment. The dose was reduced to 1.5 mg/kg/day after 12 months, 1 mg/kg/day after 18 months, and withdrawn after 42 months<br>* Complete blood cell count and transaminases were measured weekly for 1month, bimonthly for the first year, and then every 3months<br>* AZA use was stopped for presence of leukopenia (4106/L) until recovery, and then reintroduced with the dose reduced by 25 mg/day. Patients with leukopenia were monitored weekly for a minimum of 4 weeks<br>Initial treatment (both groups)<br>• 1 mg/kg/day (maximum 80 mg) of oral prednisolone, which was reduced to 0.75 mg/kg/day after 1 week, 0.50 mg/kg/day after 2 weeks, 0.40 mg/kg/day after 4 weeks, 0.30 mg/kg/day after 7 weeks, 0.28 mg/kg/day after 10 weeks, and 0.25 mg/kg/day after 13 weeks; prednisolone was reduced to 15 mg/day at the start of the remission regimen, tapered to 5 mg/day after 12 months, and was withdrawn after 24 months |
| Outcomes | Primary outcome measure<br>• Time to first relapse<br>Secondary outcome measures<br>• Relapse rate<br>• Rate of side-effects and intolerance<br>• Proteinuria<br>• Cumulative doses (AZA, steroids, MMF)<br>• AUC for BVAS<br>• SF-36 or VDI<br>• Evolution of titres of ANCA and CRP |
| Notes | • Funding source: This trial received funding from the Cambridge Biomedical Research Centre, the Programme Hospitalier de Recherche Clinique Regionale 2001, and the French Ministry of Health. Hoffman-La Roche Ltd provided reimbursement for the study drugs to investigators in Germany, France, and Switzerland; for patients recruited in Belgium, France, and Switzerland; and for trial insurance in |

**IMPROVE 2003** *(Continued)*

| | |
|---|---|
| | Germany. Dr Hiemstra is supported by the Cambridge Biomedical Research Centre. Dr Walsh is supported by a randomised Controlled Trial Mentoring Award from the Canadian Institute for Health Research, a Clinical Scholar award from the Alberta Heritage Foundation for Medical Research, and a Krescent Postdoctoral Training Award |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "1:1 ratio with the use of a minimized central computerized randomisation procedure. Randomization was stratified for age, diagnosis (Wegener granulomatosis vs MPA), and route of cyclophosphamide administration (daily oral vs intravenous pulse)." |
| Allocation concealment (selection bias) | Low risk | Central allocation |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Reported planned outcomes |
| Other bias | Low risk | Funding source stated and had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript |

**Jayne 2000**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 12 months |
| Participants | • Country: UK<br>• Setting: multicentre (5)<br>• Inclusion criteria: prior diagnosis of WG or MPA; ANCA positivity at diagnosis; active vasculitis with a requirement for further therapy; at least 2 months treatment with prednisolone and CPA or AZA; ≥ 18 years<br>• Number: treatment group (17); control group (17)<br>• Mean age ± SD (years): treatment group (57.1 ± 10.5); control group (50.4 ± 19.9)<br>• Sex (M/F): treatment group (10/7); control group (9/8)<br>• Exclusion criteria: IVIg in previous 3 months; history of anaphylaxis to matched blood products; selective IgA deficiency; RPGN (20% rise in SCr in 2 weeks) or pulmonary haemorrhage |
| Interventions | Initial treatment (both groups) |

**Jayne 2000** *(Continued)*

| | |
|---|---|
| | • CPA and prednisolone for remission induction then AZA for maintenance then a 2-week observation period<br><br>Treatment group<br><br>• IVIg: 0.4 g/kg/day for 5 days<br><br>Control group<br><br>• Placebo (identical injections) for 5 days |
| Outcomes | Primary outcome<br><br>• Treatment response. BVAS reduction of 50% between entry and 3 months<br><br>Secondary outcomes<br><br>• Fall in BVAS, CRP and ANCA<br>• Relapse at 3 months<br>• Reduction in immunosuppressive drug doses<br>• Adverse effects |
| Notes | • Funding source: "This trial was supported by a grant and provision of trial medication from Novartis Pharmaceuticals UK." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Randomisation and distribution of trial medication was centrally controlled by Novartis UK" |
| Allocation concealment (selection bias) | Low risk | Medication distributed by Novartis UK |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "patients and physicians were blinded to the treatment limb" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | High risk | Funding source: Novartis |

**MAINRITSAN 2 2018**

| | |
|---|---|
| Methods | • Study design: parallel, open-label, pragmatic, multicentre, RCT<br>• Duration of study: enrolment November 2012 to November 2013 |

**MAINRITSAN 2 2018** *(Continued)*

| | |
|---|---|
| | • Duration of follow-up: 28 months |
| Participants | • Country: France<br>• Setting: multicentre (59 sites)<br>• Inclusion criteria: > 18 years; had newly diagnosed or relapsing GPA or MPA (defined by the Chapel Hill Consensus nomenclature); in complete remission after induction therapy, combining glucocorticoids and cyclophosphamide, RTX or methotrexate (as decided by each investigator), in accordance with French and international recommendations; BVAS of 0 (score range: 0–63, with higher scores indicating more active disease) defined complete remission.<br>• Number: treatment group 1 (81); treatment group 2 (81)<br>• Mean age ± SD (years): treatment group 1 (62 ± 14); treatment group (59 ± 13)<br>• Sex (M/F): treatment group 1 (31/50); treatment group (37/44)<br>• Exclusion criteria: another systemic vasculitis; induction with an agent not recommended; active disease; incapacity for informed consent; non-compliance; allergy to the study medication; pregnancy; breastfeeding; HIV, hepatitis B or C; severe infection declared during the 3 months before randomisation; cancer or malignant blood disease diagnosed during the 5 years preceding vasculitis diagnosis; participation in another clinical research protocol during the 4 weeks before inclusion; any clinical or psychiatric disorder that could expose the patient to a greater risk of an adverse event or could prevent treatment administration and patient follow-up according to the protocol; severe immunosuppression; administration of live vaccine during the 4 weeks before inclusion; severe chronic obstructive pulmonary diseases (maximum expiratory volume < 50% or dyspnoea grade III); chronic heart failure (dyspnoea NYHA III or IV); history of recent acute coronary syndrome unrelated to vasculitis; patients not enrolled in the French national health insurance |
| Interventions | Treatment group 1<br>• Tailored schedule: fixed 500 mg RTX infusions on day-0 post-randomisation, then every 3 months until month 18, when CD19 lymphocytes exceeded 0/mm$^3$ or ANCA status (reappearance)/titre (higher) differed from the previous determination<br>Treatment group 2<br>• Fixed schedule: 500 mg of RTX on days 0 and 14 post-randomisation, then 6, 12 and 18 months after the first infusion |
| Outcomes | • Major relapse<br>• Death<br>• Severe adverse events<br>• Serious infections |
| Notes | Quote: "2 new relapses occurred after the followup (month 28) and were censured from the main analysis". |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were randomised at a 1:1 ratio". "An independent statistician provided the computer-generated randomisation sequence, stratified by newly diagnosed or relapsing AAV" |
| Allocation concealment (selection bias) | Low risk | Quote: "An independent statistician provided the computer-generated randomisation sequence, stratified by newly diagnosed or relapsing AAV. Randomisation was centralised through electronic case-report forms (eCRF) to assure allocation concealment" |

**MAINRITSAN 2 2018** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study, no blinding of participants or clinicians |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcome assessors not blinded, open-label trial |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for and all outcome data complete |
| Selective reporting (reporting bias) | Low risk | Stated outcomes reported |
| Other bias | High risk | Pharmaceutical funding of study drug |

**MAINRITSAN 2014**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Study duration: October 2008 to June 2010<br>• Duration of follow-up 28 months |
| Participants | • Country: France<br>• Setting: multicentre (59 sites)<br>• Inclusion criteria: 18 to 75 years with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after combined treatment with glucocorticoids and pulse CPA; patients had to be ANCA-positive at diagnosis or during the course of their disease; have histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis; or both<br>• Number: treatment group (57); control group (58)<br>• Mean age ± SD (years): treatment group (54 ± 14); control group (56 ± 14)<br>• Sex (M/F): treatment group (37/20); control group (28/30)<br>• Exclusion criteria: other systemic vasculitis; secondary vasculitis (following neoplastic disease or an infection in particular); induction treatment with a regimen not corresponding to that recommended in France; patient who has not achieved remission; already received a treatment by biological agents (monoclonal antibody); incapacity or refusal to understand or sign the informed consent form; incapacity or refusal to adhere to treatment or perform the follow-up examinations required by the study; non-compliance; allergy, documented hypersensitivity or contraindication to the study medication (CPA, corticosteroids, AZA, RTX); history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies; patients receiving allopurinol cannot be included if the allopurinol must absolutely be maintained; pregnancy, breastfeeding; women of childbearing age must use a reliable method of contraception throughout the duration of immunosuppressive treatment up to 1 year after the last infusion of RTX; infection by HIV, HCV or HBV; progressive, uncontrolled infection requiring a prolonged treatment; severe infection declared during the 3 months before randomisation (CMV, HBV, HHV8, HCV, HIV, TB); progressive cancer or malignant blood disease diagnosed during the 5 years before the diagnosis of vasculitis; patients presenting a systemic disease receiving protocolized treatments (AZA, RTX) which could have unexpected and inappropriate side effects; participation in another clinical research protocol during the 4 weeks before inclusion; any medical or psychiatric disorder which, in the investigator's opinion, may prevent the administration of treatment and patient follow-up according to the protocol, and/or which may expose the patient to a too greater risk of an adverse effect; no social security; Churg and Strauss syndrome; viral, bacterial or fungal or mycobacterial infection uncontrolled in the 4 weeks before the inclusion; history of deep tissue infection (fasciitis, osteomyelitis, septic arthritis)in the first year before the inclusion; history of chronic and se- |

**MAINRITSAN 2014** *(Continued)*

| | |
|---|---|
| | vere or recurrent infection or history of pre-existing disease predisposing to severe infection; severe immunodepression; administration of live vaccine in the four weeks before inclusion; severe chronic obstructive pulmonary diseases (VEMS < 50 % or dyspnoea grade III); chronic heart failure stage III and IV (NYHA); history of recent acute coronary syndrome |
| Interventions | Initial regimen (both groups)<br>• Standard induction with prednisolone and IV CPA pulses. Prednisolone started at 1 mg/kg/day preceded by IV MP pulses of 500 to 1000 mg for 1 to 3 days. CPA pulses 0.6 g/m$^2$ day 0, 14 and 28 followed by 0.7 g/m$^2$ every 3 weeks for 3 to 6 pulses until remission. Patients were randomised after remission<br>Treatment group<br>• RTX: 500 mg day 0, 14 then at month 6, 12 and 18<br>Control group<br>• AZA: 2 mg/kg/day orally for 12 months, then 1.5 mg/kg/day for 6 months, then 1 mg/kg/day for 4 months before ceasing |
| Outcomes | • Major relapse<br>• Minor relapse<br>• Death<br>• Serious adverse event |
| Notes | • Funding source: Supported by a grant from the Programme Hospitalier de Recherche Clinique, French Ministry of Health (2008-002846-51) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated randomisation stratified according to disease flare category |
| Allocation concealment (selection bias) | Low risk | Centrally allocated |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcome assessors were unblinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Other bias | Low risk | Study appears free of other biases |

**Maritati 2017**

| | |
|---|---|
| Methods | • Study design: open label parallel RCT<br>• Duration of study: December 1997 to June 2011<br>• Duration of follow-up: 24 months |
| Participants | • Country: Italy<br>• Setting: single centre<br>• Inclusion criteria: diagnosis of clinically active systemic necrotizing vasculitis; aged 18 to 80 years; life-expectancy > 1 year; written informed consent; randomisation performed only if GFR > 30<br>• Number: treatment group 1 (38); treatment group 2 (33)<br>• Median age, IQR (years): treatment group 1 (52, 18 to 77); treatment group 2 (56, 36 to 71)<br>• Sex (M/F): treatment group 1 (19/19); treatment group 2 (17/16)<br>• Exclusion criteria: CrCl < 10 mL/min/1.73 $m^2$; aminotransferase levels more than twice the upper limit of the normal range; HBsAg positivity; anti-HCV Ig and HCV-RNA positivity; HIV positivity; active malignancies; coexistence of connective tissue disease; prednisolone, CPA or MTX hypersensitivity; pregnancy |
| Interventions | Treatment group 1<br>• MTX: 15 mg/week increased to 0.3 mg/kg/week<br>• Patients with eGFR of 30 to 50 mL/min/1.73 $m^2$ received 75% of the full CPA dose and half of the full MTX dose<br>Treatment group 2<br>• CPA: 1.5 mg/kg/day orally; treatment continued for 12 months<br>Co-interventions<br>• Both groups received induction therapy with 3 IV pulses of 500 mg MP followed by oral prednisone and CPA. Oral prednisolone starting at 1mg/kg/day, gradually tapered to 5 mg at month 6 and oral CP dose was 2mg/kg/day |
| Outcomes | • Relapse at 12 months, 18 and 24 months<br>• Major and minor relapses<br>• Change in eGFR<br>• Death<br>• Adverse events |
| Notes | • Funding source: "The author(s) received no specific funding for this work" |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer algorithm |
| Allocation concealment (selection bias) | High risk | Not performed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study |
| Blinding of outcome assessment (detection bias) | High risk | No blinding |

**Maritati 2017** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Unclear risk | All outcomes reported |
| Other bias | Low risk | Study appears free of other biases |

**Mauri 1985**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 12 months |
| Participants | • Country: Spain<br>• Setting: single centre<br>• Inclusion criteria: histologically proven crescentic GN and rapidly progressive kidney impairment<br>• Number: treatment group (12); control group (10)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: < 60% glomerular involvement, primary glomerulopathies, transplanted kidneys, SLE, HSP |
| Interventions | Treatment group<br>• CPA and prednisolone as for control group<br>• PE alternate days for 6 treatments<br>  * Exchanges of at least 3.5 L replaced with 3.5% albumin and 2 units FFP<br>Control group<br>• CPA: 2 mg/kg/day<br>  * Dose reduced to 0.5 mg/kg/day after 2 months then stopped after month 4<br>• Prednisolone: 1 mg/kg/day<br>  * Dose reduced to half after 8 weeks. Prednisolone dose tapered progressively |
| Outcomes | • Death during study<br>• Dialysis post treatment, at 3 months and 12 months after treatment<br>• SCr after treatment and 6 months later |
| Notes | • Funding source: not reported |

***Risk of bias***

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

**Mauri 1985** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 11/22 patients unaccounted for |
| Selective reporting (reporting bias) | High risk | Unlikely since outcomes are not clearly defined in the study |
| Other bias | Unclear risk | Funding not reported |

**MEPEX 2007**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: March 1995 to October 2002<br>• Duration of follow-up: 12 months |
| Participants | • Country: 9 European countries<br>• Setting: multicentre (28)<br>• Inclusion criteria: biopsy-proven ANCA-associated necrotizing GN with AKI (SCr > 500 µmol/L)<br>• Number: treatment group (70); control group (67)<br>• Median age, range (years): treatment group (67, 28 to 79); control group (66, 27 to 81)<br>• Sex (M/F): treatment group (38/29); control group (43/24)<br>• Exclusion criteria: aged < 18 years or > 80 years; inadequate contraception; pregnancy; previous malignancy; hepatitis B antigenaemia or hepatitis C antibody or HIV infection; other multisystem autoimmune disease; circulating anti-GBM antibody or linear staining of GBM on histology; life-threatening non-renal manifestations of vasculitis; dialysis for > 2 weeks before entry; Cr > 200 µM more than 1 year before entry; > 2 weeks treatment with CPA or AZA; > 500 mg of IV MP; PE within the preceding year; > 3 months treatment with oral prednisolone; allergy to study medications |
| Interventions | Treatment group<br>• Immunosuppression as for the control group<br>• PE: 7 x 60 mL/kg in first 2 weeks after diagnosis<br>Control group<br>• IV MP: 3 pulses of 1000 mg followed by oral CPA and a tapering regimen of prednisolone |
| Outcomes | • Death at 3 and 12 months<br>• Dialysis at 3 months and 12 months<br>• Total number of side effects<br>• Serious infections<br>• SCr at 12 months |
| Notes | • Stopping point: 12 months follow-up<br>• Funding source: reported |

**MEPEX 2007** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Central randomisation in permuted blocks of four stratified by country and oliguria or likely to require dialysis |
| Allocation concealment (selection bias) | Low risk | Performed centrally |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Low risk | Quote: "This trial was designed and launched as part of the European Community Systemic Vasculitis Trial project (contract nos. BMH1-CT93-1078 and CIPD-CT94-0307) and finished as part of the Associated Vasculitis European randomised Trial project (contract nos. BMH4-CT97-2328 and IC20-CT97-0019) funded by the European Union." |

**Metzler 2007**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: August 2001 to September 2003<br>• Duration of follow-up: 24 months |
| Participants | • Country: Germany<br>• Setting: multicentre (5)<br>• Inclusion criteria: aged 18 and 75 years with a diagnosis of generalized WG after successful induction therapy with prednisolone and CPA<br>• Number: treatment group 1 (26); treatment group 2 (28)<br>• Median age, range (years): treatment group 1 (55, 27 to 76); treatment group 2 (54, 25 to 67)<br>• Sex (M/F): treatment group 1 (16/10); treatment group 2 (16/12)<br>• Exclusion criteria: bone marrow insufficiency (leukopenia < 4000/µL, Hb < 10 g/dL, thrombocytopenia > 100,000/µL); SCr > 1.3 mg/dL (115 µM); malignancies; hepatitis B or C or HIV positivity; pregnancy or breast feeding; inadequate contraception; chronic liver disease or alcohol abuse; active gastric ulcer; lack of compliance; further coexisting autoimmune diseases or treatments interfering with the study medication |
| Interventions | Treatment group 1<br>• Leflunomide: loading dose of 100 mg/day for 3 days, followed by 20 mg/day from day 4 to end of week 4. Then increased to 30 mg/day thereafter |

**Metzler 2007** *(Continued)*

| | |
|---|---|
| | Treatment group 2<br>• MTX: 7.5 mg/week for weeks 1 to 4; 15 mg/week for weeks 5 to 8; 20 mg/week after week 8<br>Co-interventions<br>• Prednisolone allowed at a dose of 10 mg/day or less. In the absence of disease activity, the dose was tapered by 2.5 mg/month to 5 mg, then by 1 mg/month |
| Outcomes | Primary outcome<br>• Number of major and minor relapses<br>Secondary outcome measures<br>• DEI, BVAS, patient self-assessment of quality of life (SF-36), c-ANCA titre, ESR, CRP |
| Notes | • Though patients with significant kidney failure are excluded, they appear to have been assessed after induction therapy and may therefore have had significant renal failure prior to this. The study is therefore relevant for the treatment of patients with renal vasculitis if their renal function improves during induction therapy<br>• Funding source: "This study was supported by a grant from the Bundesministerium fur Bildung und Forschung (01GI9951) in co-operation with the German Network for Rheumatic Diseases (C 4.2) and by Sanofi Aventis and Wyeth companies." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed centrally (outside of all participating centres) with the use of permuted blocks of four." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Study terminated early |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | High risk | Study was terminated early due to a high rate of relapses in the MTX group |

**MYCYC 2012**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: 42 months (start date not reported) |

**MYCYC 2012** *(Continued)*

| | |
|---|---|
| | • Duration of follow-up: 18 months |
| Participants | • Country: 10 countries (UK and 9 others not stated in protocol)<br>• Setting: multicentre (20 sites)<br>• Inclusion criteria: new diagnosis of ANCA-associated systemic vasculitis (WG or MPA) (within the previous 6 months); active disease (defined by at least one major or three minor BVAS 2003 items); ANCA positivity (c-ANCA and PR3-ANCA or p-ANCA and MPO-ANCA) or histology confirming active vasculitis from any organ<br>• Number: treatment group (70); control group (70)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: previous treatment with MMF (more than two weeks ever), CPA (more than two weeks daily oral or more than 1 pulse of IV CPA 15 mg/kg), RTX or high dose IVIg within the last 12 months; active infection (including hepatitis B, C, HIV and TB); known hypersensitivity to MMF, AZA or CPA; cancer or an individual history of cancer (other than resected basal cell skin carcinoma); pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception; any condition judged by the investigator that would cause the study to be detrimental to the patient; any other multi-system autoimmune disease including Churg Strauss angiitis, SLE, anti GBM disease and cryoglobulinaemia; active serious digestive system disease (e.g. inflammatory bowel disease); imminently life threatening vasculitis (diffuse alveolar haemorrhage, intestinal perforation or major haemorrhage, cerebral vasculitis and cardiac vasculitis); RPGN and declining kidney function; eGFR fall > 20% in previous 2 weeks; GFR < 15 mL/min at entry or on dialysis |
| Interventions | Treatment group<br>• MMF: 2 g/day or maximum tolerated dose between 1 and 2 g/day, for 3 to 6 months until remission (BVAS = 0 for 2 consecutive study assessments), then switch to AZA maintenance regimen.<br>  * For those < 16 years 1200 mg/m$^2$/day, or maximum tolerated dose between 600 and 1200 mg/m$^2$/day<br>  * For persistent disease in adults at 4 weeks dose increase up to a maximum of 3 g/day allowed. Dose increase only permitted if 2 g/day is tolerated without moderate/severe side effects. Persistent disease is defined as persistence (NOT worsening) of major or minor BVAS items present at entry.<br>Control group<br>• CPA: 15 mg/kg at weeks 0, 2 and 4 then pulses every 3 weeks for 3 to 6 months (6 to 10 doses) until remission (BVAS = 0 for 2 consecutive study assessments), then switch to AZA maintenance regimen<br>Co-interventions (both groups)<br>• Planned additional therapies permitted before randomisation<br>  * IV MP: maximum 3 g<br>  * PE allowed according to local guidelines<br>  * Additional therapy will be included as minimization variables<br>• Prednisolone or prednisone: 1 mg/kg/day, tapered to 10 mg/day by week 13<br>• Prophylaxis<br>  * Mandatory<br>  ☐ TMP/SMX 480 mg (follow local protocol of either 3 times a week or daily) until week 26 for all patients unless allergic<br>  * Recommended but not mandatory<br>  ☐ Proton pump inhibitor, e.g. lansoprazole 30 mg/day or equivalent until prednisolone ≤ 10 mg/day<br>  ☐ Oral fungal prophylaxis, nystatin or amphotericin, until prednisolone < 20 mg/day according to local practice<br>  ☐ Calcium and vitamin D and/or oral bisphosphonate according to local practice |
| Outcomes | Primary outcome |

**MYCYC 2012** *(Continued)*

- Remission rates at 6 months
  * Remission defined as the absence of disease activity attributable to active vasculitis BVAS = 0 on 2 occasions at least 1 month apart and adherence to prednisolone taper. Patients in remission require low dose immunosuppression and oral prednisolone to continue in order to maintain remission

Secondary outcomes

- Time to remission (months)
- Adverse events: mild/moderate/severe and infections
- Relapse (relapse rates at 18 months and relapse free survival)
- Cumulative dose of corticosteroids
- Improvement in calculated GFR at 18months
- Cumulative vasculitis damage index (VDI) scores
- Change in SF-36 at 12 and 18 months
- BVAS (AUC) between entry and 18 months
- ANCA status at 6 months

Notes

- Study protocol and 1 abstract published to date
- Funding source: "This study has received financial support from Aspreva. It was initiated and designed by the EUVAS MYCYC steering committee. Funding provided by Aspreva covers, fees for registration and approval at ethics committees and regulatory agencies at least at each national coordinating centre according to a budget agreed on by the steering committee. Data will be collected, analysed and published independently from the source of funding."

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Minimisation algorithm utilised |
| Allocation concealment (selection bias) | Low risk | Faxed form returned in 24 hours |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Remission assessment performed by unblinded clinicians |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Study yet to be published in full |
| Selective reporting (reporting bias) | Low risk | All outcomes have been pre-stated |
| Other bias | Low risk | Funding source stated; "Data will be collected, analysed and published independently from the source of funding." |

**NORAM 2005**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: July 1995 to September 2000<br>• Duration of follow-up: 18 months |
| Participants | • Country: Europe (10 countries)<br>• Setting: multicentre (26)<br>• Inclusion criteria: new diagnosis of WG or MPA in 1 or more organ systems; elevated ESR or CRP or both or ANCA positivity, or a non-renal biopsy demonstrating small vessel vasculitis<br>• Number: treatment group (49); control group (46)<br>• Median age, range (years): treatment group (48.8, 18 to 72); control group (53.5, 22 to 78)<br>• Sex (M/F): treatment group (24/25); control group (20/36)<br>• Exclusion criteria: organ or life-threatening vasculitis (severe haemoptysis with bilateral pulmonary infiltrates, cerebral infarction due to vasculitis, rapidly progressive neuropathy, orbital pseudotumour, massive GI bleeding, heart failure due to pericarditis or myocarditis; Cr > 150 µM, urinary red cell casts or proteinuria >1 g/day; skin vasculitis only; another multisystem autoimmune disease; malignancy; hepatitis B or HIV infection; < 18 years or >75 years |
| Interventions | Treatment group<br>• MTX: 15 mg/week oral MTX increasing to 2 5mg/week at week 12, continued to month 10 then tapered to stop at month 12<br>Control group<br>• Oral CPA: group: 2 mg/kg/day (max 150 mg/day) until remission, minimum of 3 months, maximum of 6 months. At remission, dose reduced to 1.5 mg/kg/day continued to month 10 then tapered to stop at month 12. Dose adjusted for age and low WCC<br>Co-interventions (both groups)<br>• Oral prednisolone: 1 mg/kg/day tapered to 15 mg/day at 12 weeks and 7.5 mg/day by 6 months, stopped at 12 months |
| Outcomes | Primary endpoint<br>• Remission at 6 months<br>Secondary endpoints<br>• Disease relapse<br>• Adverse effects |
| Notes | • Funding: Supported by the European Community Systemic Vasculitis Trial project (grants BMH1-CT93-1078 and CIPD-CT94-0307) and the Associated Vasculitis European randomised Trial project (grants BMH4-CT97-2328 and IC20-CT97-0019), which was funded by the European Union. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Centrally in blocks of 4 by country and stratified by diagnosis |
| Allocation concealment (selection bias) | Low risk | Centrally performed |
| Blinding of participants and personnel (performance bias) | Low risk | States unblinded; unlikely to affect outcomes |

**NORAM 2005** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Follow-up losses all stated and counted as treatment failure |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Low risk | Funding source stated |

**PEXIVAS 2013**

| | |
|---|---|
| Methods | • Study design: parallel, open-label, 2 x 2 factorial RCT<br>• Duration of study: not reported<br>• Duration of follow-up: not reported |
| Participants | • Countries: USA, Australia, Europe<br>• Setting: multicentre (67 sites)<br>• New or previous clinical diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions AND positive test for proteinase 3-ANCA or myeloperoxidase-ANCA AND severe vasculitis defined by at least one of the following:<br>  * Renal involvement with both: renal biopsy demonstrating focal necrotizing glomerulonephritis or active urine sediment characterized by glomerular haematuria or red cell casts and proteinuria AND eGFR < 50 mL/min/1.73 $m^2$<br>  * Pulmonary haemorrhage due to active vasculitis defined by a compatible chest X-ray or CT scan (diffuse pulmonary infiltrates) AND the absence of an alternative explanation for all pulmonary infiltrates (e.g. volume overload or pulmonary infection)<br>  * AND At least one of the following: evidence of alveolar haemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage; observed haemoptysis; unexplained anaemia (< 10 g/dL) or documented drop in Hb >1 g/dL); increased diffusing capacity of carbon dioxide<br>• Number: treatment group 1 (352); treatment group 2 (352)<br>• Mean age ± SD (years): treatment group 1 (62.8 ± 14.4); treatment group 2 (63.5 ± 13.7)<br>• Sex (M/F): treatment group 1 (203/149); treatment group 2 (194/158)<br>• Exclusion criteria: diagnosis of vasculitis other than granulomatosis with polyangiitis or microscopic polyangiitis; positive anti-glomerular basement membrane antibody test or renal biopsy demonstrating linear glomerular immunoglobulin deposition; receipt of dialysis for > 21 days immediately prior to randomisation or prior renal transplant; aged < 15 years; pregnancy; inability or unwillingness to comply with birth control/abstinence; treatment with > 1 IV dose of CPA and/or > 14 days of oral CPA and/or > 14 days of prednisone/prednisolone (> 30 mg/day) and/or >1 dose of RTX within the 28 days immediately prior to randomisation; a comorbidity that, in the opinion of the investigator, precludes the use of CPA, glucocorticoids, or PE or absolutely mandates the use of PE |
| Interventions | Treatment group 1 (a, b)<br>• Adjunctive PE: 7 exchanges over 14 days 60 mL/kg<br>Treatment group 2 (a, b)<br>• No plasma exchange |

**PEXIVAS 2013** *(Continued)*

| | |
|---|---|
| | Treatment group 1a, 2a<br>• Reduced dose prednisolone<br>Treatment group 1b, 2b<br>• Full dose prednisolone |
| Outcomes | • Time to the composite of death from any cause and ESKD<br>• Death<br>• Dialysis<br>• Quality of life<br>• Serious infections<br>• Serious adverse events<br>• Sustained remission |
| Notes | • Funding source: Centre. CDP is supported by the Imperial Biomedical Research Centre. PEXIVAS is funded by the National Institutes of Health Research (UK), the Food and Drug Administration Office of Orphan Drugs Program (USA) (R01FD003516), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (USA) (U54AR057319), the Office of Rare Diseases Research (USA), the Canadian Institute of Health Research (Canada), the National Health and Medical Research Council (Australia), and Assistance Publique (France). The trial has received in-kind plasma exchange disposables from TerumoBCT, Fresenius Australia, and Gambro Australia. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Central web-based sequence generation with minimisation stratified by severity of renal disease, age, ANCA subtype, severity of pulmonary haemorrhage and induction therapy |
| Allocation concealment (selection bias) | Low risk | Central web-based system |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Other bias | Unclear risk | Study appears free of other biases |

**Pusey 1991**

| | |
|---|---|
| Methods | • Study design: parallel, open-label RCT |

**Pusey 1991** *(Continued)*

- Duration of study: not reported
- Duration of follow-up: to 8 years

| | |
|---|---|
| Participants | • Country: UK<br>• Setting/Design: single centre<br>• Inclusion criteria: focal necrotizing GN with crescents (WG, systemic vasculitis, polyarteritis, idiopathic RPGN)<br>• Number: treatment group (25); control group (23)<br>• Median age, range (years): treatment group (52, 18 to 76); control group (51, 14 to 69)<br>• Sex (M/F): treatment group (16/9); control group (14/9)<br>• Exclusion criteria: anti-GBM disease; SLE; HSP; chronic GN; previously treated with IV MP, oral CPA or PE |
| Interventions | Treatment group<br>• Induction/maintenance therapy: as for control group<br>• PE: 5 x 4 L exchanges of 5% albumin (plasma protein fraction) within first week. Two units of fresh frozen plasma were given at end of exchange. Total number of exchanges determined by clinical response<br>Control group<br>Induction therapy, 8 weeks of:<br>• 60 mg/day prednisolone, reducing by 15 mg at weekly intervals to 30 mg/day, then 5 mg at weekly intervals to 20 mg/day and then more slowly as clinically indicated<br>• CPA: 3 mg/kg/day or 2 mg/kg/day for those over 55 years<br>• AZA: 1 mg/kg/day or no AZA for those over 55 years<br>Maintenance therapy<br>• CPA stopped after 8 weeks in those with remission and AZA increased to 2-3 mg/kg/day, together with tapering doses of prednisolone<br>Study duration<br>• Treatment for 1 year after which attempts were made to discontinue |
| Outcomes | • Improvement (fall in SCr > 25% or rise in CrCl > 25%; recovery of kidney function in those initially on dialysis)<br>• SCr<br>• Dialysis<br>• Death<br>• Adverse events |
| Notes | • Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The randomisation procedure ensured that patients in different arms of the trial were equally distributed throughout its course" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |

**Pusey 1991** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to permit judgement |
| Other bias | High risk | This trial took 10 years to complete and is therefore subject to biases involved in changing physician perceptions of the efficacy of PE |

**RAVE 2010**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: 30 December 2004 to 30 June 2008<br>• Duration of follow-up: 18 months |
| Participants | • Country: USA<br>• Setting: multicentre (9)<br>• Inclusion criteria: weight ≥ 88 lbs (40 kg); diagnosis of WG or MPA; newly diagnosed patient of WG or MPA OR must be experiencing a disease flare characterized by: (a) active disease with a BVAS for WG of ≥ 3 that would normally require treatment with CPA; OR (b) disease severe enough to require treatment with CPA; OR (c) must be positive for either PR3-ANCA or MPO-ANCA at the screening; willing to use acceptable forms of contraception for the duration of the study and for up to 1 year after stopping study medications; willing to report pregnancies (female participants or male participants' partners) occurring at any time during the study and for up to 1 year after stopping study medications; parent or guardian willing to provide informed consent, if applicable<br>• Number: treatment group (99); control group (98)<br>• Mean aged ± SD (years): treatment group (54.0 ± 16.8); control group (51.5 ± 14.1)<br>• Sex (M/F): treatment group (46/54); control group (54/46)<br>• Exclusion criteria: diagnosis of Churg-Strauss Syndrome; limited disease that would not normally be treated with CPA; requires mechanical ventilation because of alveolar haemorrhage; history of severe allergic reactions to human or chimeric monoclonal antibodies; active systemic infection; deep-space infection, such as osteomyelitis, septic arthritis, or pneumonia complicated by pleural cavity or lung abscess, within 6 months prior to study entry; history of or current HBV or HCV; HIV; acute or chronic liver disease that, in the opinion of the investigator, may interfere with the study; history of or active cancer diagnosed within the last 5 years; history of anti-GBM disease; other uncontrolled disease, including drug and alcohol abuse; pregnancy or breastfeeding |
| Interventions | Treatment group<br>• RTX: 375 mg/m$^2$ infusions once/week for 4 weeks<br>• CPA placebo daily for 3 to 6 months<br>Control group<br>• RTX placebo: infusions once/week for 4 weeks<br>• CPA daily for 3 to 6 months |

**RAVE 2010** *(Continued)*

| | |
|---|---|
| | During the remission maintenance phase<br>• Participants in the treatment group will discontinue CPA placebo and start oral AZA placebo daily until month 18<br>• Participants in the control group will discontinue CPA and start AZA daily until month 18 |
| Outcomes | Primary outcome<br>• Complete remission during the first 6 months after randomisation. Defined as a BVAS for WG 0 and completion of the steroid taper to 0<br>Secondary outcome<br>• Rate of selected adverse events experienced by participants receiving RTX versus those receiving conventional therapy |
| Notes | • Funding source: "The site investigators gathered the data, and the data were analysed by the RAVE data committee, which consisted of the two coprincipal investigators and representatives of the Immune Tolerance Network, the National Institute of Allergy and Infectious Diseases, and the coordinating centre (Rho). The data committee did not include representatives of either Genentech or Biogen Idec, which provided funding and medications for the study. The manuscript was drafted and written by the first and last authors, with input as appropriate from members of the RAVE data committee and the clinical investigators. The RAVE data committee made the decision to submit the manuscript for publication, and the first and last authors vouch for the accuracy and completeness of the data and analyses." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Highly likely. stratified by clinical site and ANCA type. |
| Allocation concealment (selection bias) | Low risk | Centrally performed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients randomised were analysed |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Low risk | Funding source and study conduct disclosed |

**REMAIN 2003**

| | |
|---|---|
| Methods | • Study design: open label parallel RCT |

**REMAIN 2003** *(Continued)*

| | |
|---|---|
| | • Duration of study: enrolment from September 1998 to March 2010<br>• Duration of follow-up: 48 months |
| Participants | • Countries: Europe (11)<br>• Setting: multicentre (33 sites)<br>• Inclusion criteria: males or females > 18 years, and (1, 2 and 3 are required); (1) a diagnosis of MPA, GPA or renal-limited vasculitis; (2) renal involvement and/or other threatened loss of function of avital organ (lung, brain, eye, motor nerve or gut) and ANCA positivity, and ANCA-negative patients were eligible for enrolment in the study only when there was histological confirmation of pauci-immune vasculitis; (3) remission-induction therapy with CPA and prednisolone for at least 3 months, with or without PE; and (4) stable remission on AZA/prednisolone.<br>• Number (randomised/analysed): treatment group 1 (61/59); treatment group 2 (56/51)<br>• Mean age ± SD (years): treatment group 1 (57.7 ± 14.1); treatment group 2 (57.4 ± 14.3)<br>• Sex % (M/F): treatment group 1 (49/51); treatment group 2 (53/47)<br>• Exclusion criteria: < 18 years; pregnancy; previous malignancy; known HIV infection; previous life-threatening relapse; ESKD at inclusion; allergy to study medications |
| Interventions | Treatment group 1<br>• Continued limb: continues treatment at least until 30 months after start of REMAIN trial regimen European Vasculitis Study Group (EUVAS) AVERT project<br>Treatment group 2<br>• Withdrawal arm: discontinues all treatment 4 months after start of REMAIN trial regimen<br>Both groups<br>• AZA and prednisolone from cessation of CPA<br>• Relapse treated according to guidelines for treatment of relapse |
| Outcomes | • Relapse<br>• Major relapse<br>• Minor relapse<br>• Death<br>• Dialysis<br>• Severe adverse events<br>• Vasculitis Damage Index<br>• eGFR<br>• ANCA status |
| Notes | • Patients not in stable remission for at least 6 months at 18 months after commencement of therapy and patients who had discontinued AZA and/or prednisolone were excluded from the study<br>• Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation performed centrally with block randomisation per country (blocks of four) |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |

**REMAIN 2003** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open-label study |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>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 |

**Rifle 1980**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: October 1977 to March 1981<br>• Duration of follow-up: 4 to 45 months |
| Participants | • Country: France<br>• Setting: multicentre<br>• Inclusion criteria: new onset RPGN with > 50% glomerular crescents<br>• Number: treatment group (6); control group (8)<br>• Mean age, range (years): treatment group (40.7, 9 to 75); control group (52.1, 37 to 66)<br>• Sex (M/F): treatment group (3/3); control group (2/6)<br>• HD at start: treatment group (4/6); control group (7/8)<br>• Exclusion criteria: Goodpasture's syndrome; IgA nephropathies; SLE; systemic disease |
| Interventions | Treatment group<br>• Immunosuppression as per control group<br>• PE: 5 sessions during 5 successive days, then 3 sessions/week until 15 days after SCr reached a plateau<br>  * Treatment could not exceed 2 months<br>  * 150% plasma volume was exchanged for albumin and saline solution at each session<br>Control group<br>• Immunosuppression<br>  * IV pulse MP: 15 mg/kg/day for 3 days, tapered to 15 mg/day for 3 days, then 3 new pulses, then 15 mg/day for 7 weeks<br>• CPA: 2 to 3 mg/kg/day for 2 months<br>• Calcium heparinate 9 days after kidney biopsy for the duration of the study |
| Outcomes | • Dialysis: 2, 6 12, 24 months<br>• CrCl: 2, 6 and 12 months<br>• Recovery (off dialysis) according to initial SCr level<br>• Recovery (off dialysis) according to initial % of crescents<br>• Death<br>• Circulating immune complexes |

**Rifle 1980** *(Continued)*

| | |
|---|---|
| | • Pathology changes<br>• Adverse events (septicaemia) |
| Notes | • End point: treatment was stopped after 1 month in both groups if no improvement occurred<br>• Funding source: not reported |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "patients were divided into 2 groups" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unable to determine numbers randomised and if all were analysed |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Unclear risk | Funding source not reported |

**RITUXVAS 2010**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: June 2006 to June 2007<br>• Duration of follow-up: 2 years |
| Participants | • Countries: Australia, Czech Republic, Netherlands, Sweden, Switzerland, UK<br>• Setting: multicentre (14)<br>• Inclusion criteria: new diagnosis of ANCA-associated vasculitis, ANCA positivity, and renal involvement, as evidenced by necrotizing glomerulonephritis on biopsy or red-cell casts or haematuria (30 red cells per high-power field) on urinalysis<br>• Number: treatment group (33); control group (11)<br>• Median age, range (years): treatment group (68, 56 to 75); control group (67, 57 to 76)<br>• Sex (M/F): treatment group (17/16) control group (6/5)<br>• Exclusion criteria: previous CPA (> 2 weeks of an oral or IV pulse CPA regimen); co-existence of another multisystem autoimmune disease, e.g. SLE, Churg Strauss syndrome, HSP, rheumatoid vasculitis, essential mixed cryoglobulinaemia, anti-GBM antibody positivity; Hepatitis B antigen positive or hepatitis C antibody positive; known HIV positive; previous malignancy (usually exclude unless agreed with trial co-ordinator; pregnancy, breast feeding or inadequate contraception; allergy to a study medication; live vaccine within last four weeks |

**RITUXVAS 2010** *(Continued)*

| | |
|---|---|
| Interventions | Treatment group<br>• Immunosuppression as per control group<br>• IV RTX: 375 mg/m$^2$ IV once/week for 4 weeks<br>• CPA: 15 mg/kg 2 weeks apart given with the 1st and 3rd RTX dose<br>Control group<br>• Immunosuppression<br>  * IV MP: 1 g<br>  * Same oral glucocorticoid regimen (1 mg/kg/day initially, with a reduction to 5 mg/day at the end of 6 months<br>• Remission induction<br>  * IV CPA: 15 mg/kg for 3 to 6 months (6 to 10 doses total)<br>• Remission maintenance<br>  * AZA<br>Other interventions<br>• PE or IV MP will be allowed according to local practice for patients with organ threatening disease<br>Progressive disease treatment<br>• Within the first 6 months disease progression defined as a persistence of nephritic sediment or activity on a kidney biopsy and a failure to improve GFR 10 mL/min, if GFR at diagnosis is < 50 mL/min OR persistence or new occurrence of a major non-renal BVAS item at 6 weeks then additional treatment should occur:<br>  * Treatment group: 3rd dose of CPA (15 mg/kg)<br>  * Control group: PE or IV MP (according to local practice)<br>Relapse treatment<br>• Relapses will be categorised as major or minor<br>  * Treatment group: RTX with steroid will be used for major and minor relapse. Additional CPA may also be used for major relapse<br>  * Control group: Increased AZA and steroid for minor relapse and CPA and steroid for major relapse |
| Outcomes | Primary outcomes<br>• Sustained remission (BVAS = 0 at 6 months and sustained for 6 months)<br>• Severe adverse events at 12 months<br>Secondary outcomes<br>• Efficacy<br>  * Response rate at 6 weeks (BVAS < 50% baseline)<br>  * Remission at 6 months (BVAS = 0 for 2 months by 6 months)<br>  * Time to remission (BVAS = 0)<br>  * Relapses (all relapses and major/minor)<br>  * BVAS AUC<br>  * Change in GFR<br>  * Change in SF-36<br>  * Change in VDI<br>• Safety<br>  * Severe adverse events at 6 weeks and 6 months<br>  * All adverse events<br>  * Death<br>  * Prednisolone cumulative dose<br>  * CPA cumulative dose |

**RITUXVAS 2010** *(Continued)*

| | |
|---|---|
| | Tertiary outcomes<br>• Human anti-chimeric antibody testing<br>• Correlation of B cells with disease activity<br>• Change in ANCA and disease activity<br>• Histopathology predictors of outcome |
| Notes | • Quote: "The trial was sponsored by Cambridge University Hospitals National Health Service Foundation Trust. F. Hoffmann-La Roche provided the rituximab and a research grant that contributed to trial costs. The trial, which was designed by the first and last authors and the trial steering committee, received ethical approval from the ethics committee of each participating centre and was conducted according to the European Union Clinical Trials Directive (Directive 2001 EU/20/EC), (EudraCT number, 2005-003610-15). Regulatory approval was obtained from the national regulatory authorities in each country. The data were held by the investigators at Addenbrooke's Hospital. All of the authors decided to submit the manuscript for publication."<br>• Quote: "We are grateful to F Hoffman La Roche for the provision of a research grant and the rituximab to support the conduct of this trial." |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer minimization algorithm stratified by age diagnosis and renal function; 3:1 randomisation |
| Allocation concealment (selection bias) | Low risk | Quote: "maintained concealment of study group assignments for the investigators" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Open-label study; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients randomised were analysed |
| Selective reporting (reporting bias) | Low risk | All study and review outcomes were reported |
| Other bias | Low risk | Funding source and study conduct stated |

**Stegeman 1996**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: September 1990 to June 1993<br>• Duration of follow-up: to December 1994 |
| Participants | • Country: Netherlands<br>• Setting: multicentre (11 sites) |

**Stegeman 1996** *(Continued)*

- Inclusion criteria: 3 groups of patients
  - Group 1: necrotising GN and upper or lower airways disease consistent with WG
  - Group 2: biopsy-proven WG limited to the airways
  - Group 3: ANCA positive patients fulfilling American College of Rheumatologists criteria for WG but not for Groups 1 or 2
- Number: treatment group (41); control group (40)
- Median age, range (years): treatment group (56, 21 to 82); control group (57, 25 to 83)
- Sex (M/F): treatment group (30/11); control group (28/12)
- Exclusion criteria: allergy or adverse reactions to co-trimoxazole or one of its components; long term (> 6 weeks) antibiotic treatment; impaired kidney function (CrCl < 30 mL/min/24 hours)

| | |
|---|---|
| Interventions | Treatment group<br>• TMP/SMX: 160/800 mg twice daily for 24 months<br>Control group<br>• Placebo tablets for 24 months |
| Outcomes | • Death<br>• Remission at 24 months<br>• Infections/patient/years |
| Notes | • Compliance assessed by tablet counts<br>• Supported by a grant from the Dutch Kidney Foundation (89.0872)<br>• Roche Pharma Ltd., Reinach, Switzerland provided the TMP/SMX and matched placebo |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Stratified according to disease group. sequence generation not reported but all parties blinded |
| Allocation concealment (selection bias) | Low risk | Treatment assignment not known to investigators |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treatment assignment not known to investigators, patients or physicians |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Low risk | Funding source stated |

**Stegmayr 1999**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 6 months |
| Participants | • Country: Sweden<br>• Setting: multicentre (8 sites)<br>• Inclusion criteria: Goodpasture's disease*; ANCA positive vasculitis; idiopathic RPGN<br>• Number: treatment group (21); control group (23)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: HIV; hepatitis A, HBV, HCV, severe cardiac failure; malignancy; septicaemia<br><br>Only 6 patients had Goodpasture's disease; therefore we included this study |
| Interventions | Treatment group<br>• Immunoadsorption of at least 2 plasma volumes. Median of six sessions<br>Control group<br>• PE: 3 in first 5 days of at least 1 plasma volume, 4% albumin as replacement. Median of 6 sessions<br>Co-interventions (both groups)<br>• Immunosuppression with pulse MP and oral or IV CPA 2 mg/kg/day. CPA continued for 8 weeks or longer if ANCA positive |
| Outcomes | • Death at 6 months<br>• SCr at 3 and 6 months |
| Notes | • Quote: "We thank Gustav Samuelsson and Excorim AB for economical support and for access to the database." |

***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)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |

**Stegmayr 1999** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | Economical support stated |

**Szpirt 2011**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: 31 March 1990 to 16 December 1995<br>• Duration of follow-up: 5 years |
| Participants | • Country: Denmark<br>• Setting: single centre<br>• Inclusion criteria: new diagnosis of WG who were c-ANCA or PR3-ANCA positive; clinical manifestations as defined by Fauci 1973 from at least 2 organ systems, histology proven WG and positive ANCE by IIF and ELISA; all patients fulfilled the ACR 1990 classification for WG<br>• Number (first randomisation): treatment group (16); control group (16)<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): treatment group (12/4); control group (13/3)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• Immunosuppression as for control group<br>• PE: 6 sessions of 4L PE with 3% albumin in Ringer's Lactate Solution replacement on alternate days. Performed using Gambro F-1000 filters. If c-ANCA titres >320 or PR3-ANCA > 25U/mL on ELISA after 6 sessions the additional 3 to 6 sessions performed<br>Control group<br>• Prednisolone: 80 mg/day for 3 weeks tapered to 5 mg then stopped after 9 months<br>• CPA: 1.5 mg/kg/day for 3 months<br>After 3 months of induction treatment, all patients underwent a second randomisation to either continue CPA or to change to CSA for 9 months. Dose initiated 5 mg/kg/day with trough levels 150 to 200 µmol/L |
| Outcomes | Kidney outcomes<br>• Progression, remission and dialysis at 1, 3 and 12 months<br>  * Progression defined as unchanged Cr if initial Cr >300 µM or 15% increase if initial Cr < 300 µM<br>  * Remission defined as 15% fall in Cr from inclusion<br>• Relapse: clinical symptoms of active disease and at least 2 of: 2-fold increase in ANCA titre, 20% increase in Cr, increase in proteinuria and increase in ESR or CRP<br>• Kidney and patient survival to 5 years |
| Notes | • Gambro, Lund, Sweden provided the PE filters |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation by minimisation method stratified by sex, age, biopsy results, lung Infiltrates, c-ANCA level and kidney function<br>Second randomisation at 3 months to assign continued CPA or CSA |

**Szpirt 2011** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants or personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients randomised were analysed |
| Selective reporting (reporting bias) | Low risk | Study and review outcomes reported |
| Other bias | Unclear risk | Funding source not reported |

**Tervaert 1990**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: July 1987 to July 1989 |
| Participants | • Country: Netherlands<br>• Setting: single centre<br>• Inclusion criteria: ANCA-associated vasculitis in remission with a significant rise in ANCA titre<br>• Number: treatment group (9); control group (11)<br>• Mean age, range (years): treatment group (56.8, 41 to 67); control group (54.5, 40 to 74)<br>• Sex (M/F): treatment group (3/6); control group (6/5)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• CPA: 1 mg/kg/day tapered over 9 months<br>• Prednisolone: 30 mg/day tapered over 3 months<br>Control group<br>• No change to current treatment |
| Outcomes | • Relapse<br>• Cumulative dose<br>• Side effects: infection<br>• Death |
| Notes | • This study was supported by grants C. 84-514 and C. 85-552 from the Dutch kidney foundation. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Tervaert 1990** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "...block randomisation (block length four) was made after stratification for present treatment at the time of ANCA rise." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unable to blind participants and personnel; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients randomised were analysed |
| Selective reporting (reporting bias) | Unclear risk | Study and review outcomes reported |
| Other bias | Low risk | Funding source stated |

**WEGENT 2008**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: November 1998 to February 2005<br>• Duration of follow-up: 3 years |
| Participants | • Countries: France, Belgium<br>• Setting: multicentre<br>• Inclusion criteria: > 18 years; newly diagnosed WG and MPA<br>• Number: treatment group 1 (63); treatment group 2 (63)<br>• Mean age ± SD (years): treatment group 1 (56.3 ± 13.8); treatment group 2 (59.8 ± 11.9)<br>• Sex (M/F): treatment group 1 (36/27); treatment group 2 (25/38)<br>• Exclusion criteria: use of steroids for more than 1 months prior to CPA therapy; co-existence of another systemic disease; cancer (unless in remission for more than 3 years); HIV, HBV or HCV infection; contraindication to study drugs; pregnancy, absence of contraception in premenopausal women; mental or physical disabilities abrogating ability to consent; patients not entering remission were not randomised |
| Interventions | Initial treatment<br>• All patients received identical remission induction therapy<br>  * Pulse MP: 15 mg/kg for 3 days<br>  * Oral prednisolone: 1 mg/kg/day for 3 weeks, tapered to 12.5 mg at 6 months, 5 mg at 18 months, stopped at 24 months<br>  * Pulse CPA: 0.6 g/$m^2$, 3 doses at 2 week intervals then every 3 weeks until remission; 3 further consolidation doses at 3 week intervals; adjustments for age and CrCl<br>  * Patients also received mesna<br>  * TMP/SMX daily or aerosolized pentamidine, potassium supplements, calcium, vitamin D3 and oral bisphosphonates as indicated<br>Treatment group 1 |

**WEGENT 2008** *(Continued)*

| | |
|---|---|
| | • AZA: 2 mg/kg/day<br><br>Treatment group 2<br><br>• MTX: 0.3 mg/kg/week, increasing every week by 2.5 mg to 25 mg/week<br>• Folinic acid 25 mg or folic acid 5 mg given 48 hours after MTX<br><br>Maintenance therapy (both groups)<br><br>• Continued for 12 months then withdrawn over 3 months<br>• TMP/SMX 320/1600 daily recommended for WG patients for additional 2 years |
| Outcomes | Primary end point<br><br>• Adverse reaction causing death or leading to discontinuation of the study drug<br><br>Secondary end points<br><br>• Any adverse event<br>• Severe adverse event<br>• Relapse<br>• Relapse-free survival<br>• Event-free survival<br>• Quality of life<br><br>Remission defined as BVAS of 0, relapse required increased BVAS attributable to vasculitis<br><br>Follow-up to discontinuation of maintenance therapy on final patient |
| Notes | • Funding source: Supported by a contract with Hospices Civils de Lyon (Délégation àla Recherche Clinique, Lyon, France, trial no. 97.129) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Permuted blocks of six |
| Allocation concealment (selection bias) | Low risk | Central site |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Open-label study; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | Low risk | All outcomes reported |
| Other bias | Low risk | Funding source stated |

**WGET 2002**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: 9 June 2000 to 30 September 2002<br>• Duration of follow-up: median duration for treatment group was 25 months and 19 months for control group |
| Participants | • Country: USA<br>• Setting: multicentre (8)<br>• Inclusion criteria: at least 2 of 5 modified criteria of the American College of Rheumatology for classification of WG; either new or established disease; patients with BVAS/WG score of 3 or more; stratified to severe (life-threatening manifestations including RPGN, alveolar haemorrhage or neuropathy) or limited (skin, joints, sinus or mild renal abnormalities)<br>• Number: treatment group (89); control group (91)<br>• Mean age ± SD (years): treatment group (52.4 ± 13.9); control group (47.5 ± 16.5)<br>• Sex (M/F): treatment group (56/33); control group (52/39)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• Etanercept (SC): 25 mg twice/week<br>Control group<br>• Placebo: twice weekly injection<br>Co-interventions (both groups)<br>• Severe disease: CPA 2 mg/kg/day; replaced with MTX if in remission at 3 to 6 months<br>• Limited disease: MTX 0.25 mg/kg/week to maximum of 25 mg/week. 12 months after remission, MTX dose cut by 2.5 mg each month<br>• Prednisolone was given to patients with severe and limited disease starting at 0.5 to 1.0 mg/kg/day. Tapered to 0 mg at 6 months if no relapse<br>• Patients in remission with Cr > 2 mg/dL received AZA 2 mg/kg/day, decreased after 12 months in remission by 25 mg each month |
| Outcomes | Primary outcome<br>• Sustained remission: BVAS/WG score of 0 for at least 6 months<br>Secondary outcomes<br>• Number and rate of flares during treatment<br>• Percentage of patients with sustained low level of disease activity (BVAS/WG < 3 for at least 6 months)<br>• Percentage of patients with a remission<br>• Cumulative AUC for the BVAS/WG, adverse events, quality of life |
| Notes | • WGET 2002 is funded by NIAMS and the Food and Drug Administration/Office of Orphan Products Development (FDA/OPD). Etanercept and matching placebo are provided by Immunex Corporation (Seattle, WA). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Treatment assignments are generated in permuted blocks of varying lengths. Randomization is stratified by clinic and by disease severity (either |

**WGET 2002** *(Continued)*

| | | |
|---|---|---|
| | | severe or limited). The randomisation schedule is designed to yield an assignment ratio of 1:1" |
| Allocation concealment (selection bias) | Low risk | Performed centrally and stratified according to severity of disease and the centre |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Treatment assignment not known to investigators, patients or their physicians |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for; 7 excluded from control group (6 lost to follow-up, 1 wrong diagnosis) |
| Selective reporting (reporting bias) | Low risk | Protocol available; all outcomes reported |
| Other bias | Low risk | Funding source stated |

**Zauner 2002**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: commenced 1986<br>• Duration of follow-up: 10 years |
| Participants | • Country: Germany<br>• Setting: multicentre<br>• Inclusion criteria: clinical picture of biopsy-proven RPGN and Couser Type II or III (immune deposits or pauci-immune respectively)<br>• Number: treatment group (21); control group (18)<br>• Mean age: 52.3 years<br>• Sex (M/F): 25/14<br>• Exclusion criteria: Couser Type I GN (linear GBM Ab staining on biopsy); previous immunosuppression or PE |
| Interventions | Treatment group<br>• Immunosuppression as for control group<br>• PE: 40 mL/kg with FFP replacement daily for 3 exchanges, continued if no response to a maximum of 12 exchanges; mean number of PE = 6<br>Control group<br>• IV MP: 500 mg/day for 3 days. Prednisolone 80, 60 then 40 mg/day for a week each. Dose tapered by 5 mg/day each week to maintenance dose of 10 mg/day<br>• CPA: 2 mg/kg/day oral from day 1; dose reduced for side effects. Continued for 6 months after remission<br>Subsequent maintenance therapy is not mentioned |
| Outcomes | • Death |

**Zauner 2002** *(Continued)*

- ESKD
- SCr
- Adverse events

| | |
|---|---|
| Notes | • No results were extractable from the published paper<br>• 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)<br>All outcomes | Low risk | Open-label study, unable to blind interventions; unlikely to affect outcomes |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | High risk | Data could not be extracted for analysis |
| Other bias | Unclear risk | Funding source not reported |

**Zycinska 2009**

| | |
|---|---|
| Methods | • Study design: parallel RCT<br>• Duration of study: not reported<br>• Duration of follow-up: 1 months |
| Participants | • Country: Poland<br>• Setting: single centre<br>• Inclusion criteria: WG in remission after treatment with CPA and steroids<br>• Number: treatment group (16); control group (15)<br>• Median age, range (years): treatment group (46.1, 21,1 to 56.5); control group (51.4, 28.4 to 76.0)<br>• Sex (M/F): treatment group (8/8); control group (7/8)<br>• Exclusion criteria: not reported |
| Interventions | Treatment group<br>• TMP/SMX: 160/800 mg 3 times/week for 18 months<br>Control group |

**Zycinska 2009** *(Continued)*

| | |
|---|---|
| | • Placebo tablets: for 18 months |
| Outcomes | • Remission<br>• Relapse<br>• Infection<br>• Side effects |
| Notes | • Very brief report with few details in multiple areas. There is no date of the study. Disease definitions were stated. No randomisation method stated. Groups were unbalanced with older patients with more severe disease in the placebo group. BVAS for the placebo group 11 at baseline. Remission is 0. No deaths were mentioned. Remission and relapse criteria not published. Annual number of infections per patient stated as 0 for co-trimoxazole patients but three had herpes zoster<br>• 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)<br>All outcomes | Unclear risk | Placebo controlled, but blinding not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All patients accounted for |
| Selective reporting (reporting bias) | High risk | Results presented in a form that could not be meta-analysed |
| Other bias | High risk | The groups were not balanced. Patients in the placebo group were older, had worse kidney function and a higher mean BVAS score at baseline |

ACR - albumin-creatinine ratio; AKI - acute kidney injury; anti-GBM - antiglomerular basement membrane; ANCA - anti-neutrophil cytoplasmic antibody; AUC - area under the curve; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; c-ANCA - cytoplasmic-ANCA; CMV - cytomegalovirus; CPA - cyclophosphamide; Cr - creatinine; CrCl - creatinine clearance; CRP - C-reactive protein; CSA - cyclosporin A; DEI - Disease Extent Index; ELISA - Enzyme-Linked Immunosorbent Assay; ESKD - end-stage kidney disease; ESR - erythrocyte sedimentation rate; FFP - Fresh Frozen Plasma; GBM - glomerular basement membrane; GFR - glomerular filtration rate; GI - gastrointestinal; GN - glomerulonephritis; Hb - haemoglobin; HBV - hepatitis B virus; HCV - hepatitis C virus; HD - haemodialysis; HIV - human immunodeficiency virus; HSP - Henoch Schonlein Purpura; IIF - indirect immunofluorescence; IV - intravenous; IVIg - IV immunoglobulin; KRT - kidney replacement therapy; M/F - male/female; MMF - mycophenolate mofetil; MP - methylprednisolone; MPA - microscopic polyangiitis; MPO- myeloperoxidase; MTX - methotrexate; NYHA - New York Heart Association; PAN - polyarteritis nodosa; PD - peritoneal dialysis; PE- plasma exchange; p-ANCA - perinuclear-ANCA; PR3 - proteinase-3; RCT - randomised controlled trial; RLV - renal-limited vasculitis; RPGN - rapidly progressive glomerulonephritis; RTX - rituximab; SC - subcutaneous injection; SCr - serum creatinine; SLE - systemic lupus erythematosus; TB- tuberculosis; TMP/SMX - trimethoprim-sulphamethoxazole; VDI - Vasculitis Damage Index; WCC - white cell count; WG - Wegener's granulomatosis

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

| Study | Reason for exclusion |
|---|---|
| Basu 2017 | Not induction or maintenance therapy, treating fatigue |
| CHUSPAN 2 2017 | Mixed population: EGPA, MPA or PAN |
| De Vita 2012 | Wrong population: patients with cryoglobulinaemic vasculitis |
| Harper 2018 | Not induction or maintenance therapy, treating fatigue |
| Imai 2006 | Wrong patient population, mostly IgA; there were 5 patients with likely ANCA vasculitis in one group |
| Ribi 2010 | Excluded patients with kidney disease (raised Cr and proteinuria) and they were only randomised after a period of steroid treatment. It is a study of treatment failure and relapse treatment rather than induction or maintenance therapy |
| Rifle 1990 | Wrong diagnosis for most patients. Immunoglobulin deposits demonstrated in renal biopsies |

ANCA - anti-neutrophil cytoplasmic antibody; RCT - randomised controlled trial

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

**Chen 2011c**

| | |
|---|---|
| Methods | Parallel RCT |
| Participants | 19 patients with newly diagnosed ANCA-associated small vessel vasculitis |
| Interventions | MMF versus CPA for 6 months |
| Outcomes | BVAS, renal insufficiency, anaemia, pulmonary infection, severe infection |
| Notes | Abstract-only publication; data cannot be extracted/meta-analysed |

**CLASSIC 2016**

| | |
|---|---|
| Methods | Parallel RCT |
| Participants | Patients with relapsing AAV and PR3 or MPO ANCA |
| Interventions | Standard care + placebo (n = 13)<br>Standard care + 10 mg CCX168 twice daily (n = 13)<br>Standard care + 30 mg CCX168 twice daily (n = 16)<br>All patients received RTX or CPA |
| Outcomes | BVAS at 12 weeks<br>Serious adverse events: infection-related |
| Notes | Abstract-only publication; data cannot be extracted/meta-analysed |

**CLASSIC 2016** *(Continued)*

| | |
|---|---|
| | Completed but no results posted as of November 2019 |

**Henderson 2009**

| | |
|---|---|
| Methods | Pilot parallel RCT |
| Participants | Patients with AAC |
| Interventions | • Treatment group 1: CTLA4-Ig (n=6)<br>• Treatment group 2: placebo (n=1)<br><br>Additional therapies: all patients subsequently receiving a standard reducing regime of MTX and prednisolone |
| Outcomes | • Disease activity monitored<br>• ANCA titres<br>• Inflammatory markers<br>• Hepatic and renal function<br>• SF36 indices<br>• Adverse events |
| Notes | Abstract-only publication; data cannot be extracted/meta-analysed |

**MAINTANCAVAS 2017**

| | |
|---|---|
| Methods | Parallel, open-label RCT |
| Participants | ANCA vasculitis as defined by a positive MPO- and/or PR3-ANCA test together with clinical features characteristic of ANCA-positive diseases as detailed in the 2012 Chapel Hill Consensus Conference Definitions<br><br>eGFR > 30 mL/min/1.73 $m^2$; 18 to 82 years; treated with RTX-induced continuous B cell depletion and in remission (defined by a modified BVAS-WG=0 AND a prednisone dose ≤ 7.5 mg) for at least 24 months.<br><br>CD20 (B cells) undetectable at time of enrolment/randomisation; urine HCG negative for women of child bearing potential and not planning to become pregnant for at least 12 months from enrolment and at least 12 months after any study related RTX dose; judged to be otherwise healthy by the Investigator, based on medical history and physical examination (no known active disease process for which life expectancy is less than 36 months)<br><br>Exclusion criteria: secondary disease: disease suspected to be induced by levamisole-adulterated cocaine; all transplanted patients<br><br>Treatment: additional immunosuppressive agents other than RTX and/or total daily prednisone dose > 7.5 mg; hypogammaglobulinaemia: IgG level < 250 mg/dL; terminal cancer or other primary illness with life expectancy < 36 months; active anti-GBM disease and other known autoimmune disease for which the need for additional immunosuppression is likely; pregnancy or breastfeeding |
| Interventions | Treatment group 1<br><br>• IV RTX: 1g 2 to 3 weeks apart when B cells rise ≥10 cells/$mm^3$<br><br>Treatment group 2 |

**MAINTANCAVAS 2017** *(Continued)*

| | |
|---|---|
| | • IV RTX: 1 g 2 to 3 weeks apart when ANCA level rises above predetermined value (MPO 5-fold from baseline, 4 -old above normal range, PR3 4-fold from baseline, 2-fold from normal range) |
| Outcomes | • Number of disease relapses as defined by a (BVAS/WG) ≥ 2 (3 years)<br>• Number of serious adverse events (3 years)<br>• Composite of disease relapse (defined a BVAS/WG ≥ 2) and serious adverse events (3 years)<br>• Hypogammaglobulinaemia defined as an IgG < 400 mg/dL (3 years)<br>• Patient Survival (3 years)<br>• Health-related quality of life as assessed by the Short Form Health Survey (SF-36) score (3 years)<br>• RTX utilization measured in grams/patient (3 years)<br>• Organ damage as assessed by the Vasculitis Damage Index (VDI) (3 years)<br>• Number of major relapses defined as a BVAS/WG ≥ 3 (3 years)<br>• Number of infections defined as receiving oral or IV antibiotics (3 years) |
| Notes | • Abstract-only publication; data cannot be extracted/meta-analysed |

**Pagnoux 2003**

| | |
|---|---|
| Methods | Parallel, open-label RCT |
| Participants | Patients with newly diagnosed Churg Strauss Syndrome |
| Interventions | 6 versus 12 pulse CPA |
| Outcomes | Remission<br>Relapse<br>Death<br>Severe adverse effects |
| Notes | Abstract-only publication; data cannot be extracted/meta-analysed |

**RATTRAP 2015**

| | |
|---|---|
| Methods | Parallel RCT |
| Participants | 18 years and older |
| Interventions | Infliximab versus RTX |
| Outcomes | Primary outcome measures<br>Partial or complete remission of the vasculitides<br>Secondary outcome measures<br>To study the safety and adverse effects of both regimens MPA, WG, Churg-Strauss syndrome |
| Notes | Study completed, last updated 19 November 2017; no data available |

AAV - ANCA Associated Vasculitis; ANCA - anti-neutrophil cytoplasmic antibody; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; CPA - cyclophosphamide; CrCl - creatinine clearance; FFP - Fresh Frozen Plasma; GBM - glomerular basement membrane; GN - glomerulonephritis; HD - haemodialysis; HSP - Henoch Schonlein Purpura; IV - intravenous; IVIg - IV immunoglobulin; MP -

methylprednisolone; MPA - microscopic polyangiitis; RCT - randomised controlled trial; RPGN - rapidly progressive glomerulonephritis; SLE - systemic lupus erythematosus; WG - Wegener's Granulomatosis.

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

**ADVOCATE 2019**

| | |
|---|---|
| Trial name or title | A randomised phase 3 trial evaluating the safety and efficacy of avacopan in patients with new or relapsing ANCA-associated vasculitis |
| Methods | • Study design: parallel, double-blind RCT<br>• Study duration: 60 weeks<br>• Duration of follow-up: unclear |
| Participants | Inclusion criteria<br>• Clinical diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis<br>• Male and female subjects, aged at least 18 years, with newly-diagnosed or relapsed AAV where treatment with cyclophosphamide or RTX is needed; where approved by Regulatory Agencies, adolescents (12 to 17 years) may be enrolled<br>• Use of adequate contraception<br>• Positive test for anti-PR3 or anti-MPO<br>• At least 1 major item, or at least 3 non-major items, or at least the 2 renal items of proteinuria and haematuria on BVAS<br>• eGFR ≥15 mL/min/1.73 $m^2$ at screening<br>Exclusion criteria<br>• Pregnant or breast-feeding<br>• Alveolar haemorrhage requiring pulmonary ventilation support at screening<br>• Any other known multi-system autoimmune disease<br>• Required dialysis or plasma exchange within 12 weeks prior to screening<br>• Have a kidney transplant<br>• Received cyclophosphamide within 12 weeks prior to screening; if on azathioprine, mycophenolate mofetil or MTX at the time of screening, these drugs must be withdrawn prior to receiving the cyclophosphamide or RTX dose on Day 1<br>• Received intravenous glucocorticoids, > 3000 mg methylprednisolone equivalent, within 4 weeks prior to screening<br>• Have been taking an oral daily dose of a glucocorticoid of more than 10 mg prednisone-equivalent for more than 6 weeks continuously prior to screening<br>• Received RTX or other B-cell antibody within 52 weeks of screening or 26 weeks provided B cell reconstitution has occurred (i.e., CD19 count > 0.01 x $10^9$/L); received anti-TNF treatment, abatacept, alemtuzumab, IVIg, belimumab, tocilizumab, or eculizumab within 12 weeks prior to screening<br>• For patients scheduled to receive cyclophosphamide treatment, urinary outflow obstruction, active infection (especially varicella zoster infection), or platelet count <50,000/µL before start of dosing<br>• Participated previously in a CCX168 study |
| Interventions | • Experimental: CCX168 (avacopan)<br>• Intervention group: CCX168 in combination with RTX or in combination with CPA followed by AZA<br>• Active comparator: prednisone |
| Outcomes | Primary outcomes<br>• Remission (Time Frame: 26 weeks)<br>  * The proportion of patients achieving disease remission assessed by Birmingham Vasculitis Activity Score (BVAS) at Week 26 |

**ADVOCATE 2019** *(Continued)*

- Sustained remission (Time Frame: 52 weeks)
  - The proportion of patients achieving sustained disease remission assessed by BVAS at Week 52

Secondary

- Adverse events coded by MedDRA (Time Frame: 60 weeks)
  - Patient incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events
- Glucocorticoid-induced toxicity (Time Frame: 26 weeks)
  - Glucocorticoid-induced toxicity as measured by the Glucocorticoid Toxicity Index
- Response rapidity (Time Frame: 4 weeks)
  - Remission assessed by BVAS at week 4
- Health-related quality of life (Time Frame: 52 weeks)
  - Change in health-related quality-of-life based on the Short Form-36 version 2 component and domain scores and the EuroQOL-5D-5L visual analogue scale (in mm) and index
- Estimated glomerular filtration rate (eGFR) (Time Frame: 52 weeks)
  - Change from baseline in eGFR in mL/min/1.73^2
- Urinary albumin:creatinine ratio (UACR) (Time Frame: 52 weeks)
  - Change from baseline in UACR in mg/g creatinine
- Urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio (Time Frame: 52 weeks)
  - Change from baseline in urinary MCP-1:creatinine ratio in pg/mg creatinine
- Vasculitis Damage Index (Time Frame: 52 weeks)
  - Change from baseline in the Vasculitis Damage Index (VDI)

| | |
|---|---|
| Starting date | December 2016 |
| Contact information | Study Director: Cass Kelleher, MD. ChemoCentryx, Inc. |
| Notes | Abstract only publication. Recruitment status: Active, not recruiting. |

**ALEVIATE 2018**

| | |
|---|---|
| Trial name or title | Alemtuzumab for ANCA Associated Refractory Vasculitis (ALEVIATE) |
| Methods | • Study design: parallel, open-label RCT<br>• Study duration: 6 months<br>• Duration of follow-up: 12 months |
| Participants | Inclusion criteria<br>• Diagnosis of AAV, according to a standardized definition<br>• Active vasculitis with at least 1 severe or 3 non-severe items of BVAS/WG activity (equivalent to BVAS/WG > 3)<br>• Previous therapy with either CPA or MTX, in combination with prednisolone for at least 3 months.<br>Exclusion criteria<br>• Aged < 18 or > 60 years<br>• Creatinine > 150µmol/L (1.7 mg/dL)<br>• Total white count < 4 x $10^9$/L or lymphocyte count < 0.5 x $10^9$/L, or IgG < 5g/L, or neutrophil count < 1.5 x $10^9$/L<br>• Severe lung haemorrhage with hypoxia (< 85% on room air)<br>• Severe gastrointestinal, central nervous system or cardiac vasculitis<br>• Previous therapy with: Alemtuzumab at any time IVIg, infliximab, etanercept, adalimumab, abatacept, anti-thymocyte globulin or plasma exchange in past 3 months; RTX within the past 6 months |

**ALEVIATE 2018** *(Continued)*

| | |
|---|---|
| | • Intensive care unit requirement<br>• Active infection with HIV, hepatitis B or hepatitis C or other infection requiring parenteral or long-term oral antibiotics<br>• History of ITP or platelet count at screening below 50,000 x $10^6$/L<br>• Pregnancy or inadequate contraception in pre-menopausal women<br>• Breast feeding<br>• Any condition judged by the investigator that would cause the study to be detrimental to the patient.<br>• Any other multisystem autoimmune disease including Churg Strauss angiitis, systemic lupus erythematosus, anti-GBM disease and cryoglobulinaemia<br>• Any previous or current history of malignancy (other than resected basal cell carcinoma) |
| Interventions | Treatment group A<br>• Alemtuzumab: high dose (60 mg) 30 mg will be administered on Day 1 and Day 2 at 0 and 6 months<br>Treatment group B<br>• Alemtuzumab: low dose (30 mg) 15 mg will be administered on Day 1 and Day 2 at 0 and 6 months |
| Outcomes | Primary outcomes<br>• Proportion of patients with a vasculitis response at 6 months (Time Frame: 6 months)<br>  * Response includes patients in complete and partial remission. Complete remission (CR) is defined as a BVAS/WG of 0 for at least one month. Partial response (PR) is the absence of severe BVAS/WG items and at least 50% fall in BVAS/WG score from baseline.<br>• Proportion of patients with a severe adverse event (Time Frame: 6 months)<br>Secondary outcomes<br>• Proportion of patients with treatment failure (Time Frame: 12 months)<br>  * Treatment failure is defined as the failure to achieve a vasculitis response by six months or a vasculitis relapse between 6 and 12 months<br>• Combined damage assessment (CDA) scores (Time Frame: 12 months)<br>• Non severe adverse events (Time Frame: 12 months)<br>• Cumulative dose of corticosteroids (Time Frame: 12 months)<br>• Time to remission (Time Frame: 6 months)<br>  * Complete and partial<br>• Relapse (Time Frame: 12 months)<br>• Change in SF-36 (Time Frame: 12 months) |
| Starting date | February 2011 |
| Contact information | Dr David Jayne, Cambridge University Hospitals NHS Foundation Trust |
| Notes | Abstract only publication. Recruitment status: unknown last updated July 2011. |

**CANVAS 2016**

| | |
|---|---|
| Trial name or title | CMV Modulation of the Immune System in ANCA-associated Vasculitis (CANVAS) |
| Methods | • Study design: parallel, open-label RCT<br>• Study duration: not reported<br>• Duration of follow-up: 12 months |
| Participants | • Country: UK |

**CANVAS 2016** *(Continued)*

| | |
|---|---|
| | • Setting: single centre<br>• Patients with documented diagnosis of granulomatosis with polyangiitis (Wegener), microscopic polyangiitis or renal limited vasculitis according to Chapel Hill Consensus Conference Criteria; in stable remission (no documented clinical disease activity) for at least 6 months prior to study entry; on maintenance immunosuppression with prednisolone, MMF or AZA alone or in combination (maximum two agents); documented past evidence (any time point) of CMV infection (CMV-specific immunoglobulin G detected in peripheral blood); documentation that female patients of child-bearing potential are not pregnant and are using an appropriate form of contraception; written informed consent for study participation<br>• Number: 50<br>• Mean age ± SD (years): not reported<br>• Sex (M/F): not reported<br>• Exclusion criteria: stage 5 CKD (eGFR <1 5 mL/min/1.73 $m^2$); tests performed within 6 months of pre-baseline visit can be used for this assessment; other significant chronic infection (HIV, hepatitis B, hepatitis C or tuberculosis); B-cell depleting therapy within 12 months or T-cell depleting therapy within 6 months; treatment with anti-CMV therapies in the last month; underlying medical conditions, which in the opinion of the investigator place the patient at unacceptably high risk for participating in the study Inability to participate fully or appropriately in the study |
| Interventions | Treatment group<br>• Valaciclovir: 2 g, 4 times/day for 6 months. dose adjusted for kidney function<br>Control group<br>• No additional treatment |
| Outcomes | • Proportion of patients with CMV reactivation on quantitative PCR on blood and urine<br>• Change in proportion of CD4+CD28- cells<br>• Arterial stiffness, carotid to femoral pulse wave velocity<br>• Change in blood pressure<br>• Peripheral blood CD4+CD28- T cells analysed at baseline and 6 months<br>• IFN-a and TNF-a production with CMV lysate measured<br>• Persistence of effect of valaciclovir on T cells 6 months after treatment<br>• Change in the immune phenotype of CD4+ T cells<br>• Soluble markers on inflammation. Concentration of IL-2, tumour necrosis factor alpha (TNF-Î±), IFN-Î³, IL-6, IL-10, IL-17 and highly sensitive C-reactive protein (CRP) in peripheral blood soluble markers of endothelial damage.<br>• Concentration of fractalkine, IP-10, regulated on activation, normal T cell expressed and secreted (RANTES), P-selectin, E-selectin, monocytechemoattractant protein-1 (MCP-1), soluble vascular cell adhesion molecule 1 (sVCAM-1) and soluble intracellular cell adhesion molecule 1 (sICAM-1) in peripheral blood |
| Starting date | 4 July 2012 |
| Contact information | Professor Lorraine Harper, University of Birmingham |
| Notes | • Funding source: WT and Vasculitis UK<br>• Protocol and abstract-only publications |

**COMBIVAS 2019**

| | |
|---|---|
| Trial name or title | Rituximab and Belimumab Combination Therapy in PR3 COMBIVAS |
| Methods | • Study design: parallel, double-blind RCT |

**COMBIVAS 2019** *(Continued)*

| | |
|---|---|
| | • Study duration: 12 months<br>• Duration of follow-up: 2 years |
| Participants | Inclusion criteria<br>• Participants must be 18 of age<br>• Have a diagnosis of AAV (granulomatosis with polyangiitis or microscopic polyangiitis)<br>• Have PR3 ANCA positivity by ELISA at screening<br>• Have active disease defined by one major or three minor disease activity items on BVAS/WG<br>• Be capable of giving signed informed consent<br>Exclusion criteria<br>• MPO ANCA or anti-GBM antibody positivity by ELISA at screening<br>• Presence of pulmonary haemorrhage with hypoxia at screening<br>• eGFR < 30 mL/min/1.73 $m^2$ at screening<br>• Have an acute serious or chronic infection at screening<br>• Have received any B-cell targeted therapy within 364 days of Day 1<br>• Have received CPA within 180 days of Day 1<br>• Have received any steroid injection (e.g. intramuscular, intra-articular, or IV) within 60 days of Day 1 (unless given during or 14 days before screening period)<br>• Have received > 1.5 mg methylprednisolone (IV) between 14 days prior to screening and Day 1 (including Day 1)<br>• Have received oral prednisolone >10 mg/day (or equivalent) on average over the 30 days prior to screening<br>• Have undetectable peripheral blood B cells at screening<br>• Have IgG < 400 mg/dL at screening |
| Interventions | Treatment group<br>• Belimumab: weekly 200 mg SC injections of belimumab for 12 months<br>Control group<br>• Belimumab placebo: weekly SC injections of belimumab placebo for 12 months |
| Outcomes | Primary outcomes<br>• Time to PR3 ANCA negativity (Time Frame: Analysed at 24 months)<br>  * ELISA analysis at different time points to determine when PR3 ANCA can no longer be detected<br>Secondary outcomes<br>• Proportion of participants with PR3 ANCA negativity (Time Frame: 2 years)<br>  * Measured by ELISA at various time points<br>• Change from baseline of certain cell subsets (Time Frame: 2 years)<br>  * Measured by flow cytometry at various time points<br>• Time to clinical remission (Time Frame: 2 years)<br>  * Measured by BVAS/WG<br>• Incidence of serious adverse events (SAEs) (Time Frame: 2 years)<br>  * Hospitalisation or serious events |
| Starting date | February 2019 |
| Contact information | Rachel Jones, Cambridge University Hospitals NHS Foundation Trust |
| Notes | Recruiting. Estimated completion February 2022 |

**MAINRITSAN 3 2015**

| | |
|---|---|
| Trial name or title | Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab (MAINRITSAN3) |
| Methods | • Study design: parallel, double-blind RCT<br>• Study duration:<br>• Duration of follow-up: |
| Participants | Inclusion criteria<br>• First, patients must have been included in MAINRITSAN 2 and in addition to meeting the criteria for inclusion and non-inclusion.<br>MAINRITSAN 2 inclusion criteria<br>• Granulomatosis with Polyangiitis Or microscopic polyangiitis complying Or kidney-limited disease with or without detectable ANCA at the time of diagnosis or relapse, and at remission.<br>• Who have achieved remission using a treatment combining corticosteroids and an immunosuppressive agent, including corticosteroids, CPA IV or oral (the use of another immunosuppressant is allowed, according to the current French guidelines, as well as plasma exchanges and/or IV immunoglobulins, or RTX)<br>• Interval of 1 month between the end of the immunosuppressant treatment and the randomisation time if CPA or MTX were used, interval between 4 and 6 months if RTX was used<br>• Age > 18 years without age limit higher when the diagnosis is confirmed<br>• Informed and having signed the consent form to take part in the study<br>Patients must also meet all of the following criteria:<br>• In complete remission (BVAS 0) at 28 months of MAINRITSAN2 study<br>• Informed patient who accepted to participate in MAINRITSAN 2 and who signed the informed consent to this extension<br>• Randomised on the day of the evaluation of the primary endpoint of MAINRITSAN 2 during the visit M28 (last visit of the protocol)<br>Exclusion criteria:<br>• Eosinophilic granulomatosis with polyangiitis (EGPA)<br>• History of severe allergic manifestations or anaphylactic manifestations following humanized or murine monoclonal antibodies infusions<br>• Pregnant or breast feeding women. Contraception is required for women who could be pregnant during treatment follow up and during the year following the last infusion.<br>• Infection by HIV (positive serology), HCV (positive serology), or HBV (HBsAg positive or anti-HBc antibody positive with anti-HBs antibody negative)<br>• Uncontrolled infection at time of inclusion in the extended follow-up study<br>• Other severe bacterial, viral, mycobacterial or fungal infection(s), occurring within the last 3 months before of randomisation. A severe infection is defined by the hospitalisation, a life or organ threatening<br>• Severe chronic obstructive bronchopathy (FEV < 50% or dyspnoea stage III)<br>• Cardiac failure, stage IV according to the NYHA classification<br>• Recent history of coronary artery disease (< 1 month)<br>• Ongoing malignancy or hematologic disease within 5 years before inclusion<br>• Patient with severe immunodepression characterized by clinical manifestations<br>• Participation to another concomitant therapeutic study (except observational studies or studies without therapeutic intervention)<br>• Psychiatric disease that may interfere with the study<br>• Non affiliation to a health insurance |

**MAINRITSAN 3 2015** *(Continued)*

| | |
|---|---|
| | • Uncontrolled severe cardiac disease |
| Interventions | Treatment group<br>• 500 mg RTX infusion at the randomisation visit and every 6 months for 18 months<br>Control group<br>• Placebo infusion at the randomisation visit and every 6 months for 18 months |
| Outcomes | Primary outcomes<br>• Vasculitis score 2003 (BVAS 2003) (Time Frame: 28 months)<br>• Relapse free survival rates (BVAS > 0)<br>Secondary outcomes<br>• Number of adverse events, (Time Frame: 28 months) adverse events including infectious effects and their severity in each arm<br>• number of patients experiencing at least one adverse event in both arms (Time Frame: 28 months)<br>• correlation of ANCA level with the clinical events (Time Frame: 28 months)<br>• ANCA level during follow-up (Time Frame: 28 months)<br>• Correlation B-Lymphocytes CD-19 level with the clinical events (Time Frame: 28 months)<br>• B-Lymphocytes CD-19 level during follow-up (Time Frame: 28 months)<br>• number of B memory cells during follow-up in both arms (Time Frame: 28 months)<br>• Correlation number of B memory cells with the clinical events (Time Frame: 28 months)<br>• Number of patients with ANCA in each arm (Time Frame: 28 months)<br>• Time frame to death in both arms (Time Frame: 28 months)<br>• Time frame of first minor relapse (Time Frame: 28 months)<br>• Time frame of first major relapse (Time Frame: 28 months) "the reappearance of disease activity or worsening, with a Birmingham Vasculitis Activity Score >0, and involvement of one or more major organs, disease-related life-threatening events, or both"<br>• Cumulated dose of corticosteroid treatment (Time Frame: 28 months)<br>• Number and severity of damages (Time Frame: 28 months)<br>• Number of gammaglobulins (Time Frame: 28 months)<br>• Quality of life: SF36 (The Short Form (36) Health Survey) (Time Frame: 28 months)<br>• functional capacities: HAQ (Health Assessment Questionnaire) (Time Frame: 28 months) |
| Starting date | March 31, 2015 |
| Contact information | Study Chair: Loic GUILLEVIN, MD-PhD. Assistance Publique - Hôpitaux de Paris. |
| Notes | Ongoing. Recruitment finalised. Estimated completion September 2018. No outcome data published. |

**MUPIBAC 2004**

| | |
|---|---|
| Trial name or title | The prevention of relapses of Wegeners granulomatosis by the elimination of nasal S aureus carriage: a multicentre randomised study |
| Methods | RCT |
| Participants | Early systemic or generalized WG with GFR > 50 mL/min (in remission after 18 months) |
| Interventions | Mupirocin ointment vs placebo |

**MUPIBAC 2004** *(Continued)*

| | |
|---|---|
| Outcomes | Relapse and infection rates between 18-42 months |
| Starting date | |
| Contact information | www.bantao.org/2_2/2_2_1.pdf |
| Notes | Recruitment suspended due to problems with the supply of the trial ointment. The protocol is presently being redesigned |

**NCT03323476**

| | |
|---|---|
| Trial name or title | Maintaining or stopping immunosuppressive therapy in patients with ANCA vasculitis and end-stage renal disease: a prospective, multicenter, randomised, open-label, clinical trial |
| Methods | Parallel, open-label RCT |
| Participants | Inclusion criteria<br>• Age ≥ 18 years and ≤ 90 years<br>• Patients affected by a GPA or MPA AAV with a renal injury<br>• Patients with initial manifestation or relapse of AAV.<br>• Patients with ESRD, defined by a glomerular filtration rate estimated using the MDRD formula ≤15 mL/min or requirement for dialysis for more than 60 days<br>• Patients who gave written informed consent for participation in the study.<br>• Patients with affiliation to the French social security system.<br>Exclusion criteria<br>• Patients who experienced severe extra-renal disease due to AAV (intra-alveolar haemorrhage with blood oxygen saturation ≤ 85% on room air or ventilated, or central nervous system disease) in the last 12 months prior to inclusion<br>• Patients with AAV-associated renal involvement (with active inflammatory lesions in kidney biopsy) diagnosed less than three months and receiving induction treatment with CPA or RTX or diagnosed less than 45 days for patients who have received only treatment based on steroid infusion without CPA or RTX<br>• Patients who received maintenance immunosuppressive treatment for more than 6 months during the last 12 months<br>• Patient with a diagnosis of vasculitis other than GPA or MPA<br>• Patients with positive anti-glomerular basement membrane antibodies.<br>• Patients with another immunologic systemic disease (Lupus, sarcoidosis…) Patients with active HCV, HBV or HIV infection<br>• Patients with a history of serious viral infection (CMV, HHV8, etc.) in the 2 months prior to the inclusion, or severe uncontrolled chronic infection (e.g. tuberculosis)<br>• Patients with uncontrolled cancer or haemopathy<br>• Inability to understand and sign the informed consent<br>• Pregnant women<br>• Women of child-bearing age without effective method of contraception<br>• Age < 18 years or > 90 years.<br>• Patients under guardianship or trusteeship |
| Interventions | Treatment group 1<br>• Discontinuation (or not initiation) of immunosuppressive therapy<br>Treatment group 2 |

**NCT03323476** *(Continued)*

| | |
|---|---|
| | • Maintenance (or initiation) of immunosuppressive treatment: Imurel®, Mabthera®, Cellcept®, Cortancyl® |
| Outcomes | The primary end point will be the time between inclusion and the first severe prejudicial event (measured in days) during 24 months of follow-up (24 months)<br><br>Severe prejudicial event is defined by the occurrence of: severe infection, major AAV relapse, death |
| Starting date | 2 February 2018 |
| Contact information | Chloé MOREAU<br><br>chloe.moreau@chd-vendee.fr |
| Notes | |

**RITAZAREM 2013**

| | |
|---|---|
| Trial name or title | An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis |
| Methods | Parallel, open-label RCT |
| Participants | Patients with established ANCA vasculitis whose disease has come back 'relapsing vasculitis' |
| Interventions | Treatment group 1<br><br>• RTX IV infusion 1000 mg x 1 dose at months 4, 8, 12, 16 and 20 and glucocorticoids; 4 to 6-hour infusion. Treatment with RTX will cease at month 20<br><br>Treatment group 2<br><br>• Oral dosage form. Target dose is 2 mg/kg; maximum daily dose is 200 mg. This should be continued until month 24<br>• The dose should then by reduced by 50% and AZA completely withdrawn at month 27. The dose should be rounded down to the nearest 25 mg. The dose may vary on alternate days e.g. 100 mg one day, 150 mg the next for patients on an overall dose of 125 mg daily<br>• If patients are aged over 60 years, reduce the dose by 25%. If patients are aged over 75 years, reduce the dose by 50%. |
| Outcomes | • Time to disease relapse (either minor or major relapse) from randomisation<br>• Remission at 24 and 48 months. Proportion of patients who maintain remission at 24 and 48 months<br>• Combined damage assessment score at months 0, 4, 12, 24, 36. Cumulative accrual of damage as measured by the combined damage assessment score<br>• Health-related quality of life at months 0, 4, 12, 24, 36. Health-related quality of life as measured using SF-36<br>• Cumulative GC exposure up to 4 years. Cumulative glucocorticoid exposure during the trial<br>• Severe adverse event rate up to 4 years) Severe adverse event rate<br>• Infection rates up to 4 years. Infection (treated with intravenous or oral antibiotics) rates |
| Starting date | April 2013 |
| Contact information | David Jayne: Cambridge University Hospitals NHS Foundation Trust<br><br>Peter Merkel: University of Pennsylvania |

**RITAZAREM 2013** *(Continued)*

| | |
|---|---|
| Notes | Active, not recruiting |

**Tuin 2019**

| | |
|---|---|
| Trial name or title | Comparative study of the efficacy of induction therapy with cyclophosphamide or mycophenolate mofetil for non-life-threatening relapses of PR3- or MPO-ANCA associated vasculitis |
| Methods | Open RCT, safety and efficacy study |
| Participants | Males and females ≥ 18 years |
| Interventions | When relapses occur, patients will be randomised for either the standard therapy with CPA or for MMF |
| Outcomes | Primary outcome measures<br>• Remission induction rate<br>• Disease-free survival after 2 and 4 years<br>Secondary outcome measures<br>• Time to remission<br>• Cumulative organ damage<br>• Side-effects<br>• ANCA titres over time |
| Starting date | December 2004 |
| Contact information | Patricia M. Stassen, M.D.<br>+31503611295<br>p.m.stassen@int.umcg.nl |
| Notes | |

ANCA - anti-neutrophil cytoplasmic antibody; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; CPA - cyclophosphamide; eGFR - estimated glomerular filtration rate; IVIg - intravenous immunoglobulin; MMF - mycophenolate mofetil; MPO - myeloperoxidase; MTX - methotrexate; PR3 - proteinase-3; RCT - randomised controlled trial; rituximab - RTX; WG - Wegener's granulomatosis

## DATA AND ANALYSES

### Comparison 1. Plasma exchange as adjunctive therapy

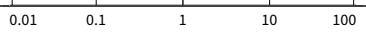
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Three months | 2 | 169 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.49, 2.15] |
| 1.2 Six months | 2 | 63 | Risk Ratio (M-H, Random, 95% CI) | 0.72 [0.08, 6.13] |
| 1.3 One year | 5 | 267 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.57, 1.92] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.4 Two years | 4 | 120 | Risk Ratio (M-H, Random, 95% CI) | 1.29 [0.49, 3.38] |
| 1.5 Five years | 3 | 80 | Risk Ratio (M-H, Random, 95% CI) | 1.21 [0.71, 2.04] |
| 1.6 Death at any time point | 6 | 957 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.72, 1.29] |
| 2 Kidney function: serum creatinine | 5 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.1 One month | 3 | 73 | Mean Difference (IV, Random, 95% CI) | -111.37 [-318.19, 95.45] |
| 2.2 Two months | 1 | 23 | Mean Difference (IV, Random, 95% CI) | -79.70 [-198.76, 39.36] |
| 2.3 Three months | 2 | 50 | Mean Difference (IV, Random, 95% CI) | 36.62 [-23.32, 96.57] |
| 2.4 Six months | 2 | 49 | Mean Difference (IV, Random, 95% CI) | 9.82 [-180.10, 199.74] |
| 2.5 Twelve months | 4 | 156 | Mean Difference (IV, Random, 95% CI) | 23.52 [-17.19, 64.22] |
| 3 Dialysis | 8 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 One month | 1 | 32 | Risk Ratio (M-H, Random, 95% CI) | 0.09 [0.01, 1.52] |
| 3.2 Three months | 2 | 147 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.23, 0.78] |
| 3.3 Six months | 4 | 104 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.13, 1.10] |
| 3.4 Twelve months | 6 | 235 | Risk Ratio (M-H, Random, 95% CI) | 0.45 [0.29, 0.72] |
| 3.5 Five years | 1 | 32 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.07, 14.64] |
| 3.6 At any time point | 1 | 704 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.70, 1.27] |
| 4 Sustained remission | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Adverse events | 5 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 Serious infections | 5 | 956 | Risk Ratio (M-H, Random, 95% CI) | 1.26 [1.03, 1.54] |
| 5.2 Myocardial infarction | 1 | 52 | Risk Ratio (M-H, Random, 95% CI) | 2.78 [0.31, 24.99] |
| 5.3 Lung haemorrhage | 1 | 52 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.11, 3.39] |
| 5.4 Subarachnoid haemorrhage | 1 | 52 | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.01, 7.26] |
| 5.5 Gastrointestinal haemorrhage | 2 | 63 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.08, 4.69] |
| 5.6 Anaphylaxis | 1 | 31 | Risk Ratio (M-H, Random, 95% CI) | 2.82 [0.12, 64.39] |

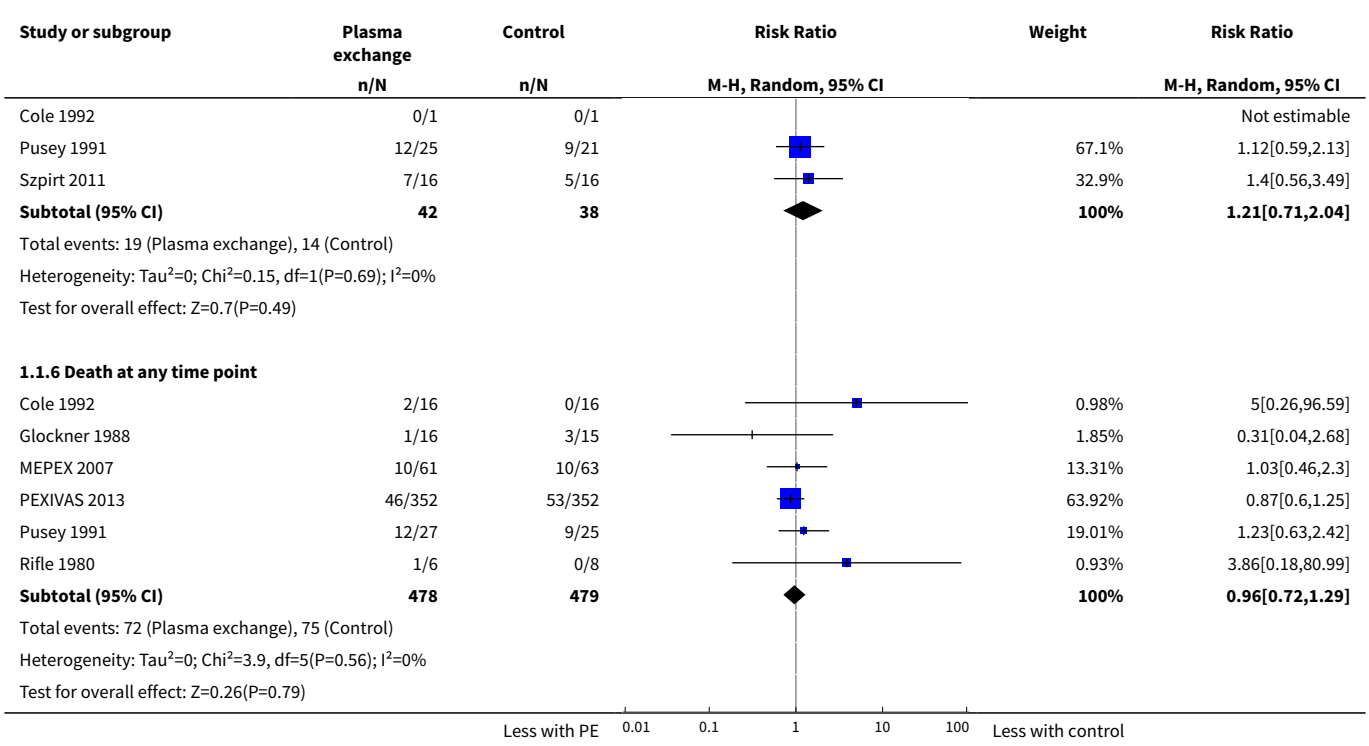
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.7 Serious adverse events | 1 | 704 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.89, 1.11] |
| 5.8 Total number of adverse events | 5 | 956 | Risk Ratio (M-H, Random, 95% CI) | 1.01 [0.91, 1.12] |

**Analysis 1.1. Comparison 1 Plasma exchange as adjunctive therapy, Outcome 1 Death.**

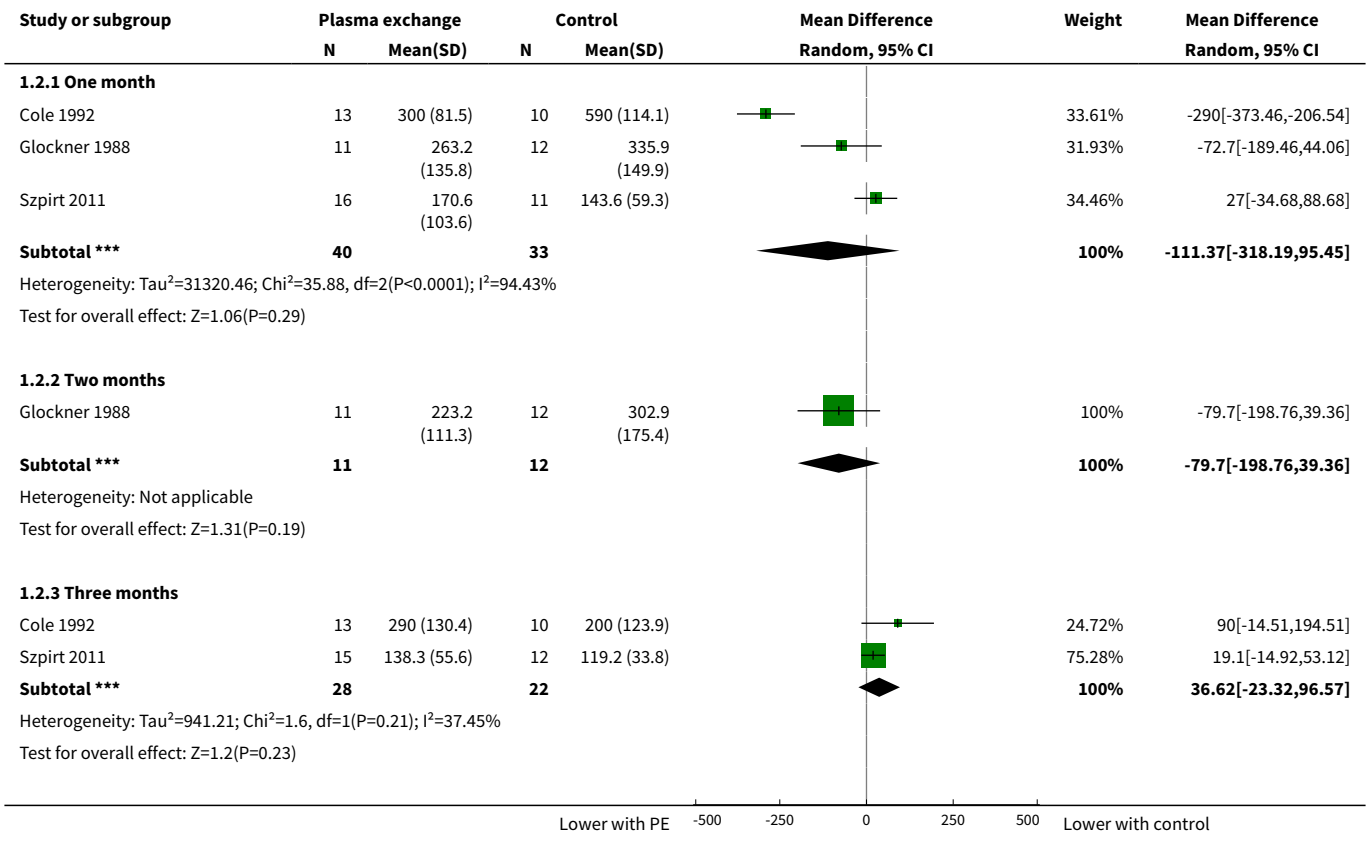
| Study or subgroup | Plasma exchange n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Three months** | | | | | |
| MEPEX 2007 | 11/70 | 11/67 | | 94.35% | 0.96[0.45,2.06] |
| Szpirt 2011 | 1/16 | 0/16 | | 5.65% | 3[0.13,68.57] |
| **Subtotal (95% CI)** | **86** | **83** | | **100%** | **1.02[0.49,2.15]** |
| Total events: 12 (Plasma exchange), 11 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.49, df=1(P=0.49); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.05(P=0.96) | | | | | |
| **1.1.2 Six months** | | | | | |
| Glockner 1988 | 1/16 | 3/15 | | 63.1% | 0.31[0.04,2.68] |
| Szpirt 2011 | 1/16 | 0/16 | | 36.9% | 3[0.13,68.57] |
| **Subtotal (95% CI)** | **32** | **31** | | **100%** | **0.72[0.08,6.13]** |
| Total events: 2 (Plasma exchange), 3 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.69; $Chi^2$=1.37, df=1(P=0.24); $I^2$=26.87% | | | | | |
| Test for overall effect: Z=0.3(P=0.76) | | | | | |
| **1.1.3 One year** | | | | | |
| Cole 1992 | 2/16 | 0/16 | | 4.09% | 5[0.26,96.59] |
| MEPEX 2007 | 19/70 | 16/67 | | 57.59% | 1.14[0.64,2.02] |
| Pusey 1991 | 6/27 | 9/25 | | 34.22% | 0.62[0.26,1.49] |
| Rifle 1980 | 0/6 | 0/8 | | | Not estimable |
| Szpirt 2011 | 2/16 | 0/16 | | 4.09% | 5[0.26,96.59] |
| **Subtotal (95% CI)** | **135** | **132** | | **100%** | **1.04[0.57,1.92]** |
| Total events: 29 (Plasma exchange), 25 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.08; $Chi^2$=3.68, df=3(P=0.3); $I^2$=18.55% | | | | | |
| Test for overall effect: Z=0.13(P=0.9) | | | | | |
| **1.1.4 Two years** | | | | | |
| Mauri 1985 | 1/12 | 0/10 | | 8.96% | 2.54[0.11,56.25] |
| Pusey 1991 | 7/27 | 9/25 | | 63.56% | 0.72[0.32,1.64] |
| Rifle 1980 | 1/6 | 0/8 | | 9.26% | 3.86[0.18,80.99] |
| Szpirt 2011 | 4/16 | 1/16 | | 18.22% | 4[0.5,31.98] |
| **Subtotal (95% CI)** | **61** | **59** | | **100%** | **1.29[0.49,3.38]** |
| Total events: 13 (Plasma exchange), 10 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.2; $Chi^2$=3.58, df=3(P=0.31); $I^2$=16.29% | | | | | |
| Test for overall effect: Z=0.51(P=0.61) | | | | | |
| **1.1.5 Five years** | | | | | |

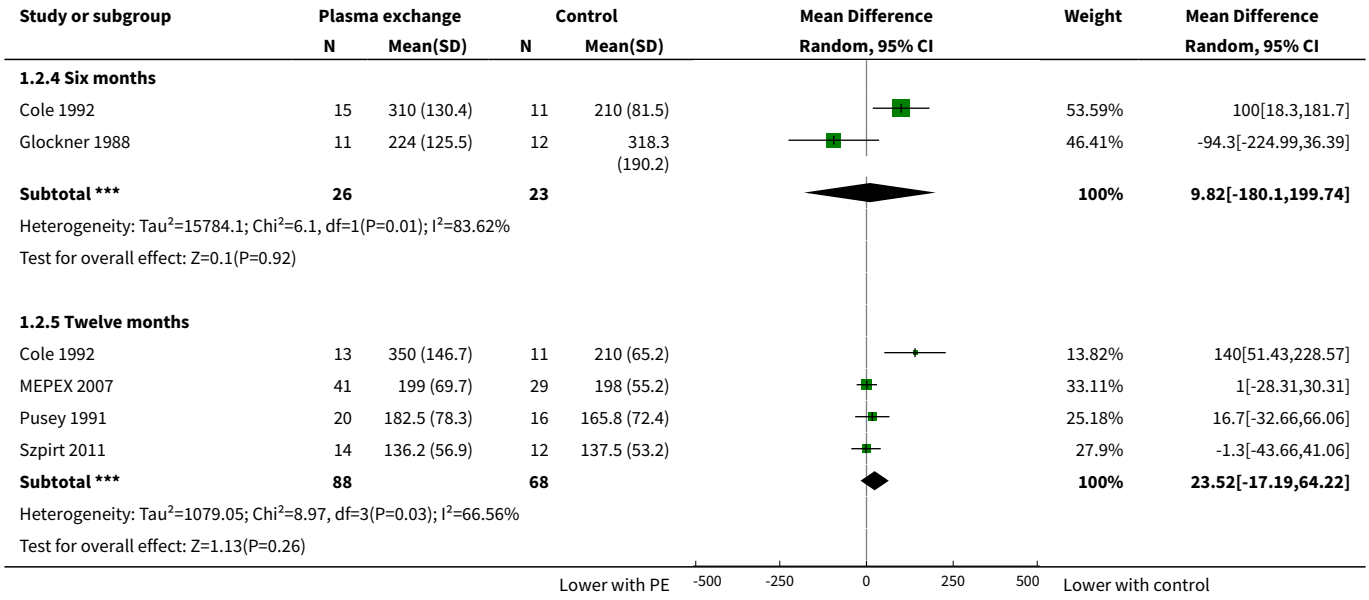



Less with PE — Less with control

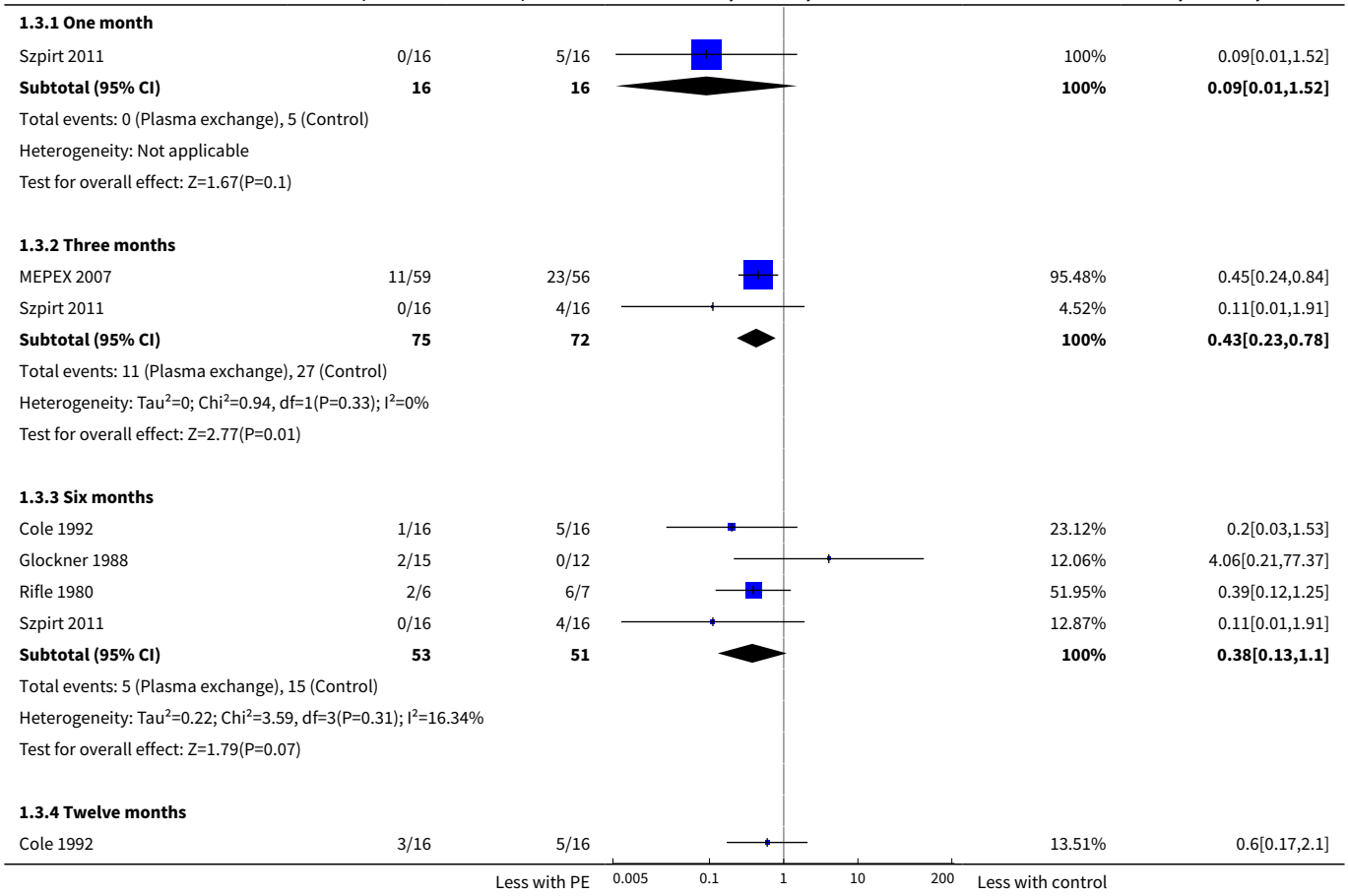


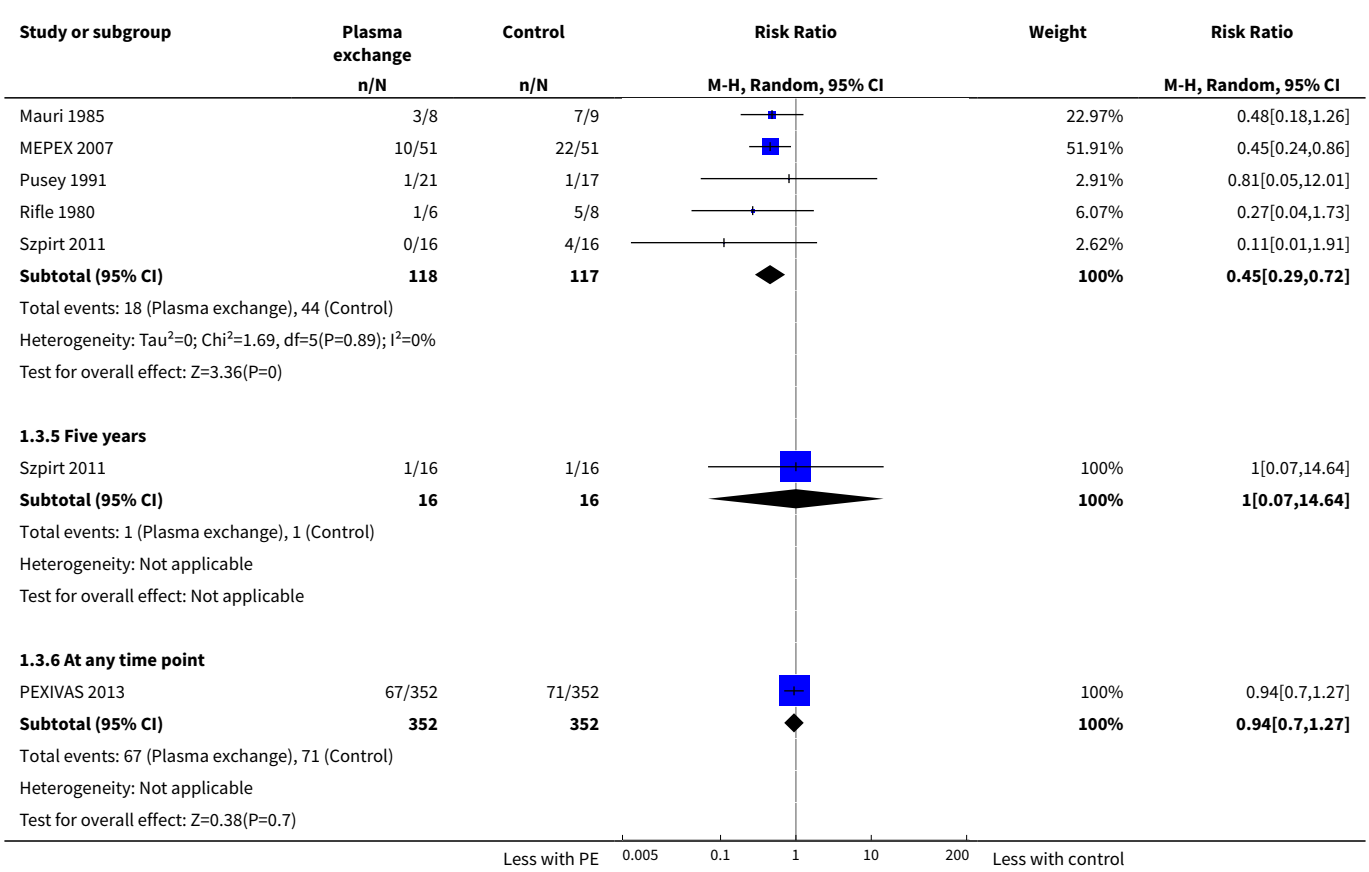

## Analysis 1.2. Comparison 1 Plasma exchange as adjunctive therapy, Outcome 2 Kidney function: serum creatinine.



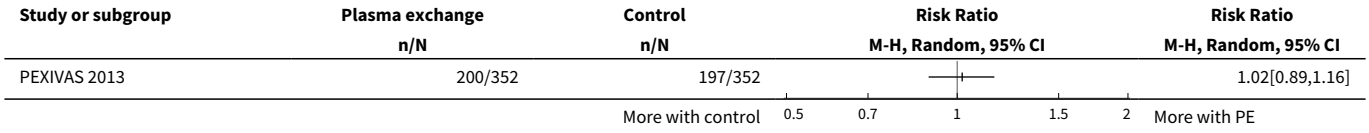



## Analysis 1.3. Comparison 1 Plasma exchange as adjunctive therapy, Outcome 3 Dialysis.

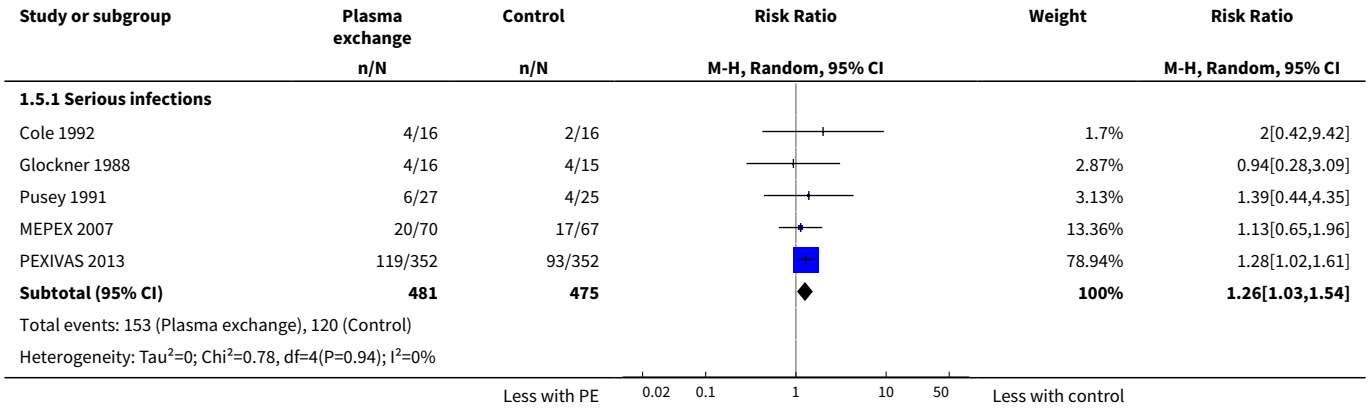


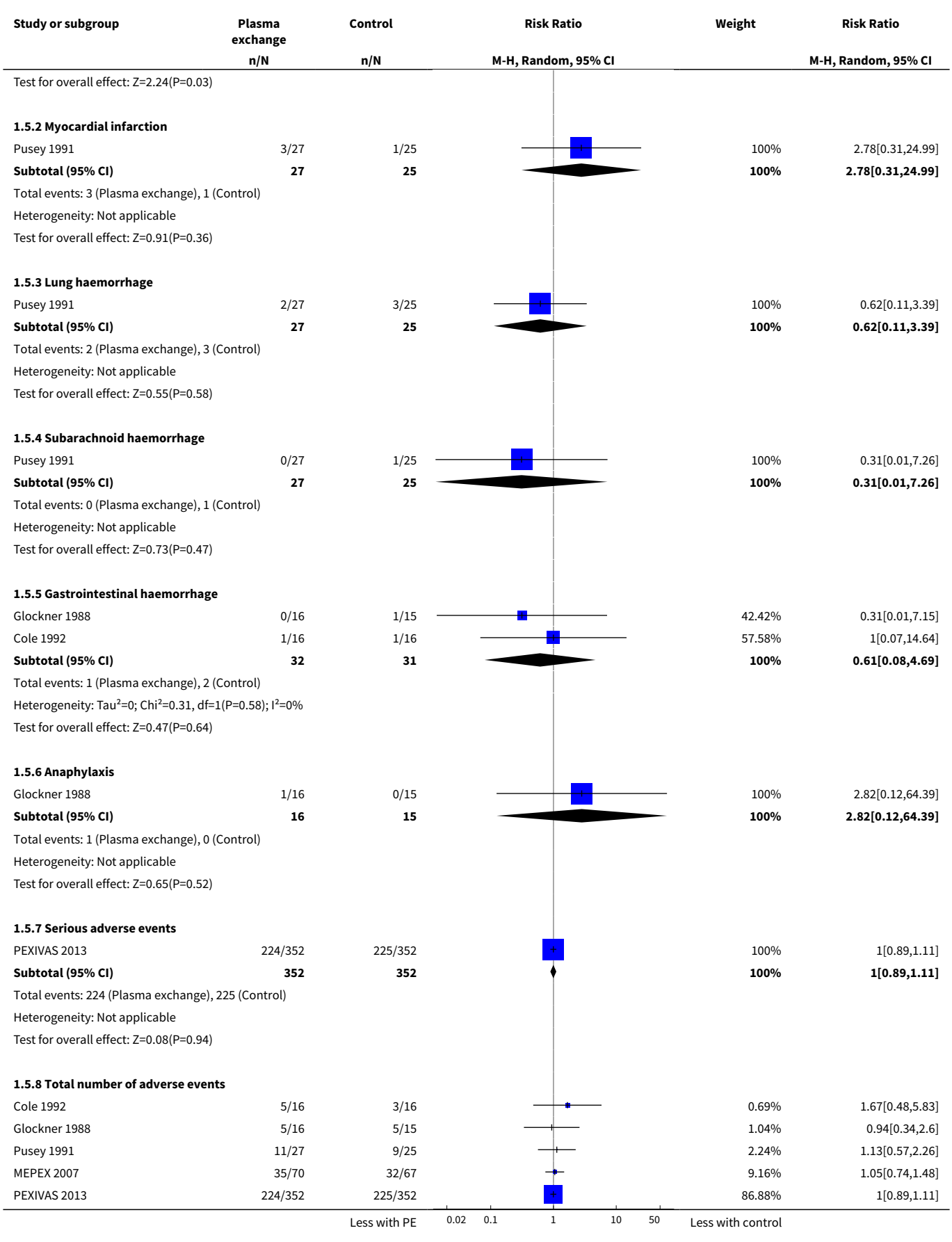


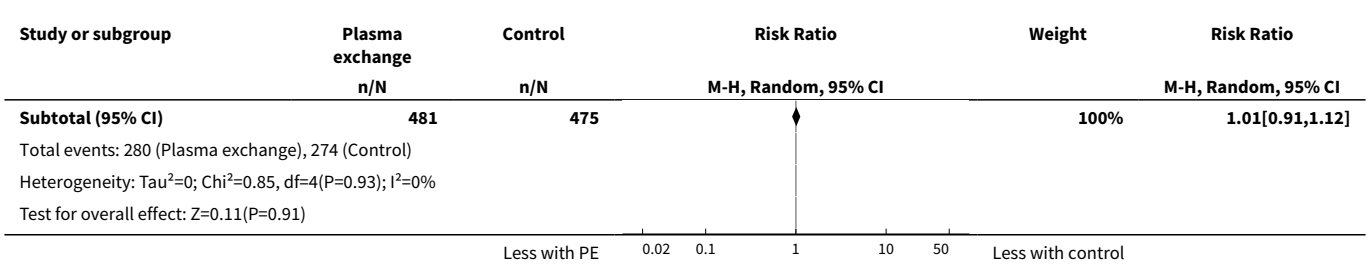

## Analysis 1.4. Comparison 1 Plasma exchange as adjunctive therapy, Outcome 4 Sustained remission.




## Analysis 1.5. Comparison 1 Plasma exchange as adjunctive therapy, Outcome 5 Adverse events.





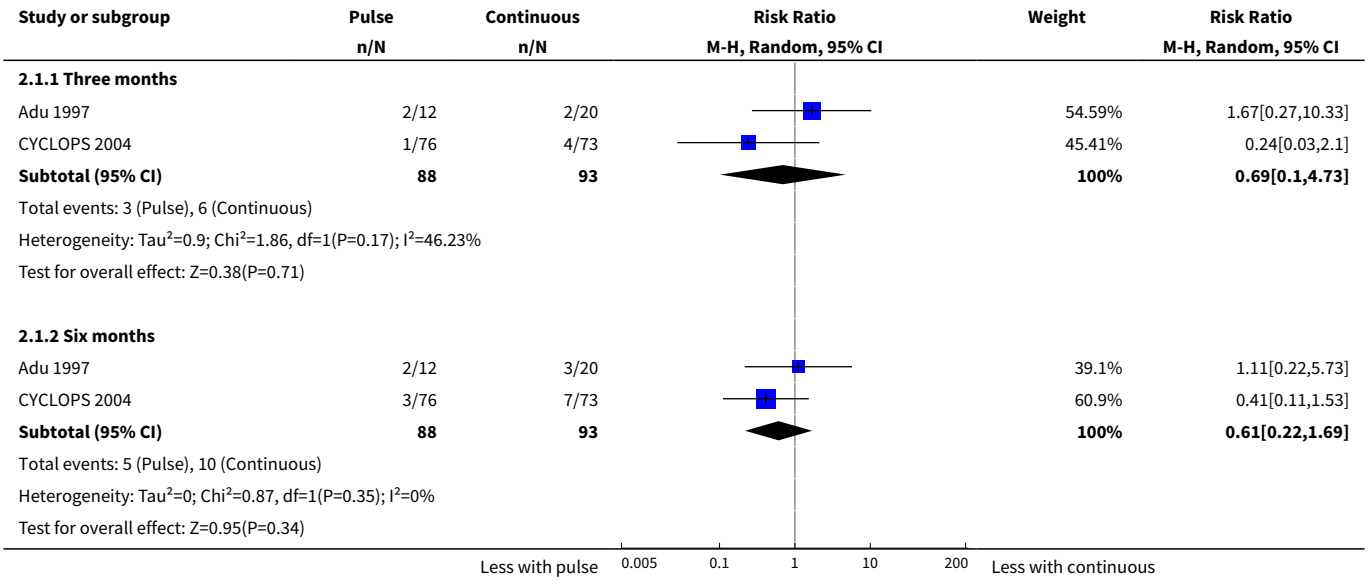


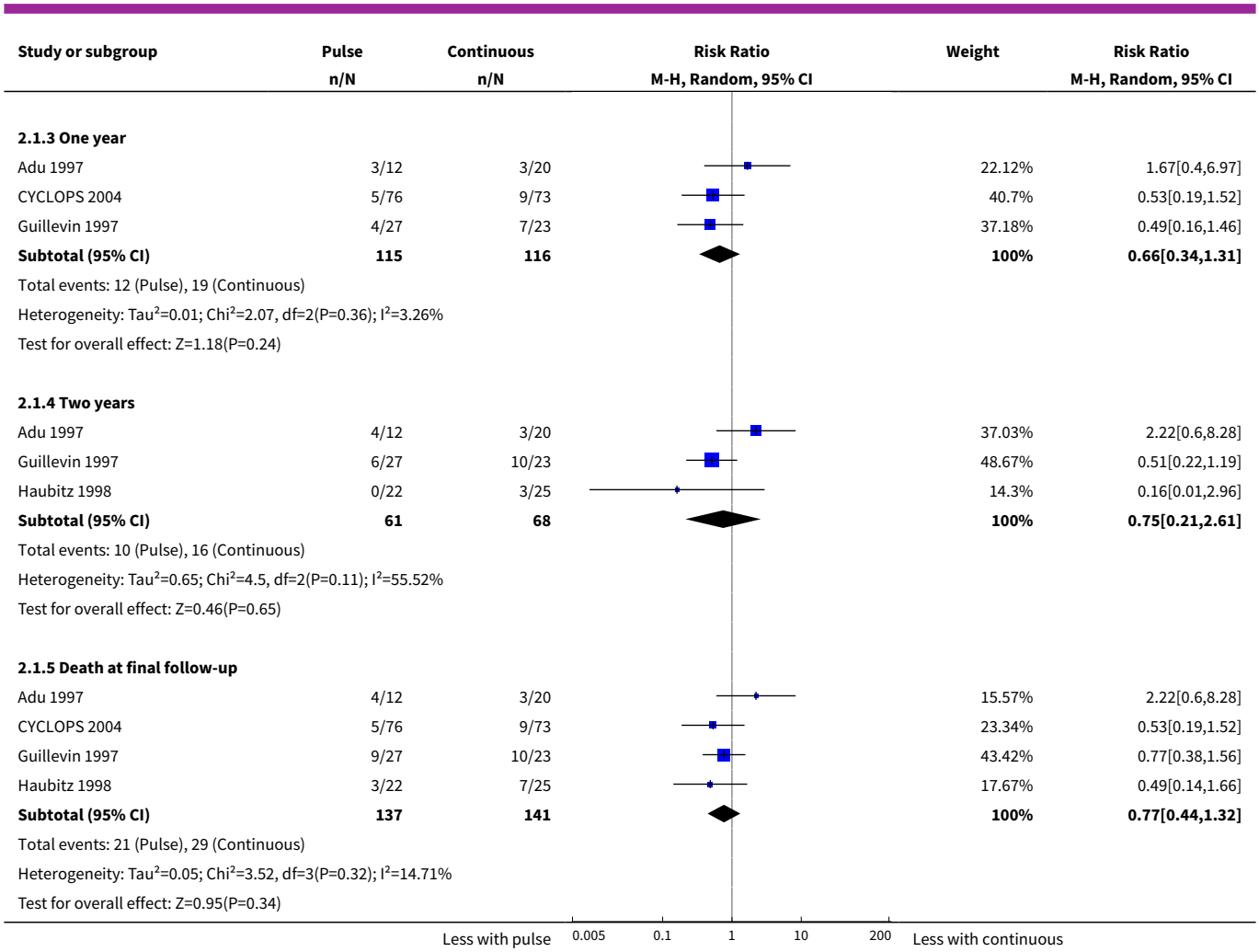

## Comparison 2. Pulse versus continuous cyclophosphamide

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Three months | 2 | 181 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.10, 4.73] |
| 1.2 Six months | 2 | 181 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.22, 1.69] |
| 1.3 One year | 3 | 231 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.34, 1.31] |
| 1.4 Two years | 3 | 129 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.21, 2.61] |
| 1.5 Death at final follow-up | 4 | 278 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.44, 1.32] |
| 2 Kidney function: serum creatinine | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2.1 One month | 0 | 0 | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Two months | 0 | 0 | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Three months | 1 | 28 | Mean Difference (IV, Random, 95% CI) | -4.58 [-97.77, 88.61] |
| 2.4 Six months | 1 | 27 | Mean Difference (IV, Random, 95% CI) | 51.69 [-81.03, 184.41] |
| 2.5 Twelve months | 2 | 52 | Mean Difference (IV, Random, 95% CI) | -9.78 [-53.16, 33.61] |
| 2.6 Two years | 2 | 51 | Mean Difference (IV, Random, 95% CI) | 4.46 [-67.90, 76.82] |
| 3 Dialysis | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 Three months | 1 | 137 | Risk Ratio (M-H, Random, 95% CI) | 2.71 [0.11, 65.43] |
| 3.2 Six months | 2 | 176 | Risk Ratio (M-H, Random, 95% CI) | 7.02 [0.90, 54.80] |
| 3.3 Twelve months | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 3.55 [0.41, 30.80] |
| 3.4 Dialysis end of study | 4 | 245 | Risk Ratio (M-H, Random, 95% CI) | 1.90 [0.92, 3.91] |
| 4 Remission | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |

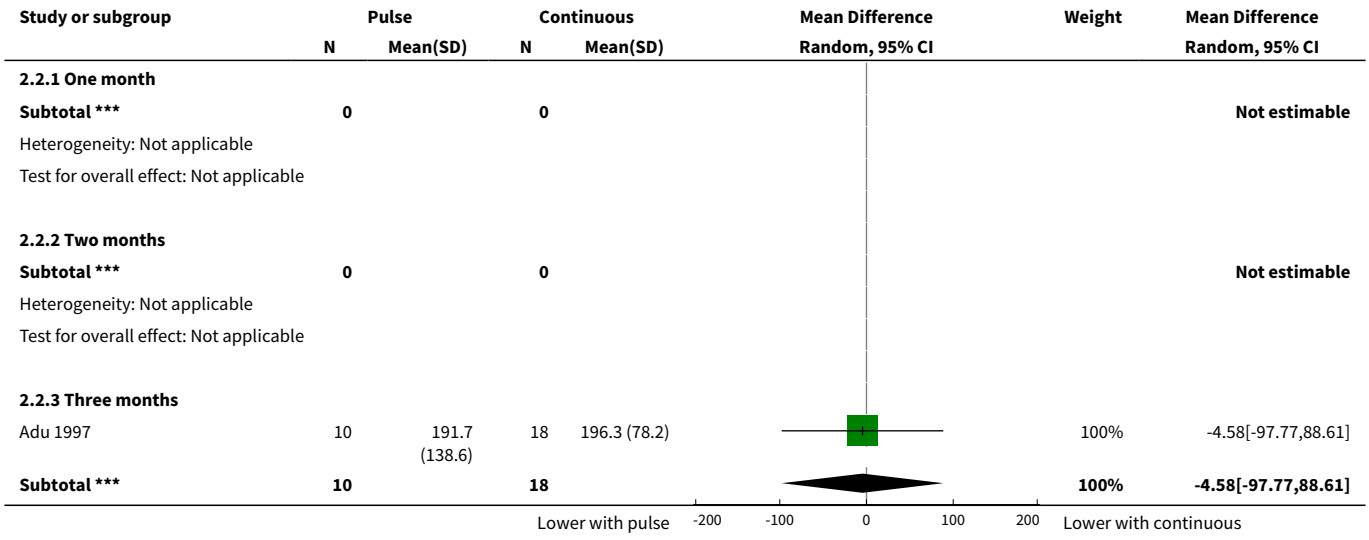
| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Three months | 1 | 137 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.81, 1.30] |
| 4.2 Six months | 2 | 176 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.93, 1.13] |
| 4.3 Nine months | 1 | 121 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.92, 1.02] |
| 4.4 Twelve months | 1 | 117 | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.94, 1.03] |
| 4.5 Eighteen months | 1 | 116 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.94, 1.03] |
| 4.6 Untimed | 1 | 47 | Risk Ratio (M-H, Random, 95% CI) | 1.18 [0.98, 1.42] |
| 5 Relapse | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 One year | 2 | 164 | Risk Ratio (M-H, Random, 95% CI) | 1.45 [0.57, 3.69] |
| 5.2 Two years | 1 | 47 | Risk Ratio (M-H, Random, 95% CI) | 1.89 [0.51, 7.03] |
| 5.3 Untimed | 4 | 235 | Risk Ratio (M-H, Random, 95% CI) | 1.79 [1.11, 2.87] |
| 6 Treatment failure | 2 | 82 | Risk Ratio (M-H, Random, 95% CI) | 1.36 [0.15, 12.56] |
| 7 Adverse events | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 7.1 Serious infections | 4 | 278 | Risk Ratio (M-H, Random, 95% CI) | 0.71 [0.38, 1.33] |
| 7.2 Leukopenia | 4 | 278 | Risk Ratio (M-H, Random, 95% CI) | 0.53 [0.36, 0.77] |
| 7.3 Nausea | 2 | 97 | Risk Ratio (M-H, Random, 95% CI) | 2.51 [1.07, 5.89] |

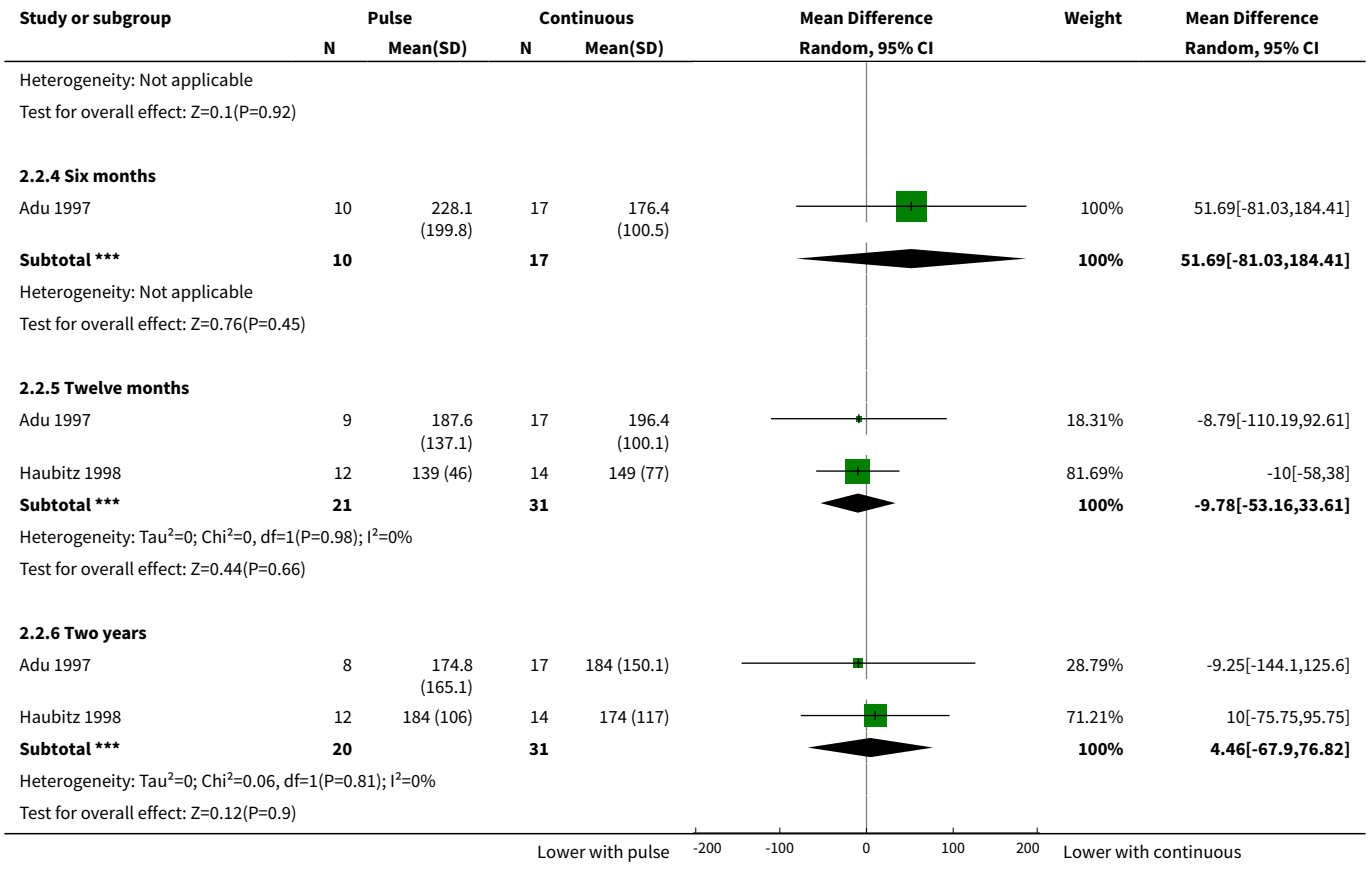
**Analysis 2.1. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 1 Death.**



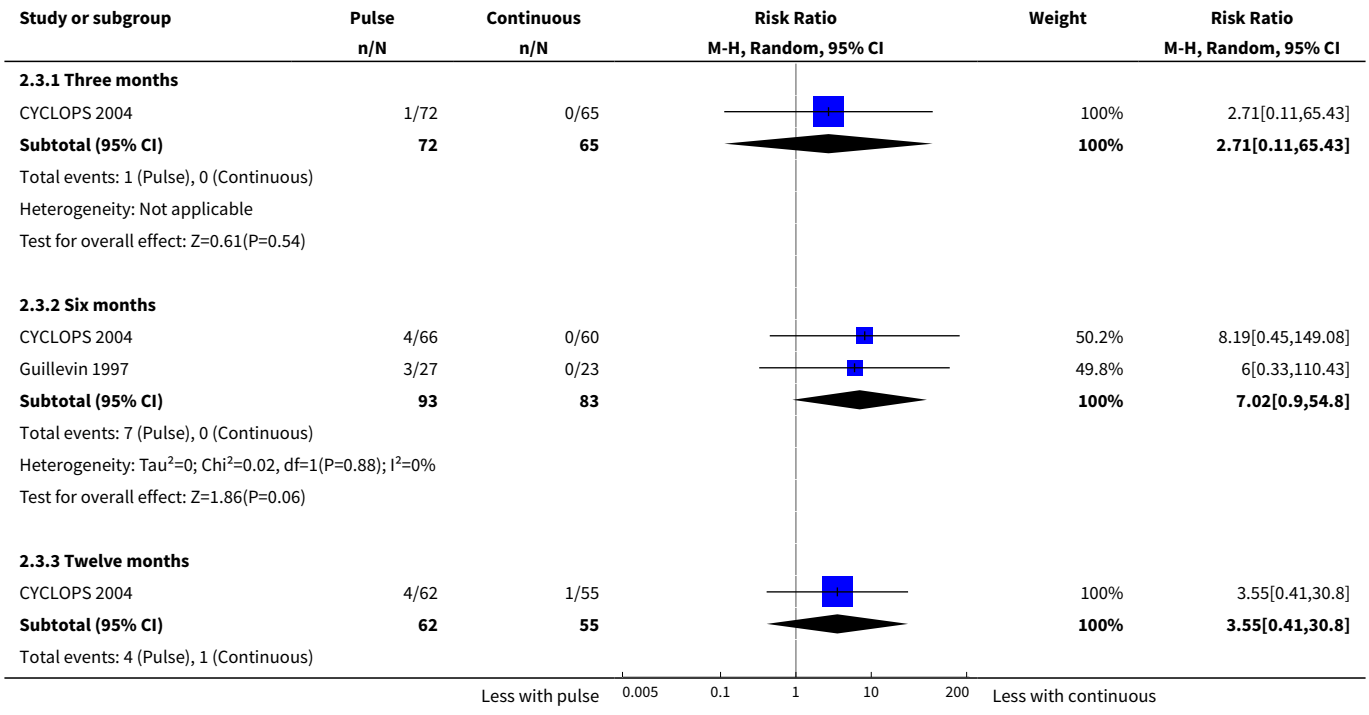


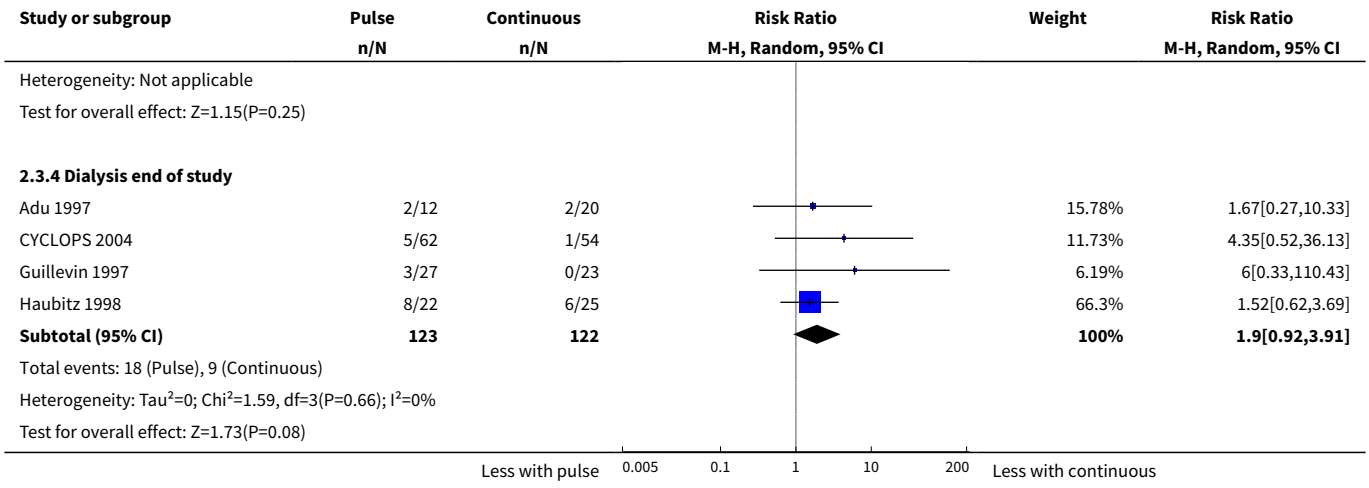

## Analysis 2.2. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 2 Kidney function: serum creatinine.



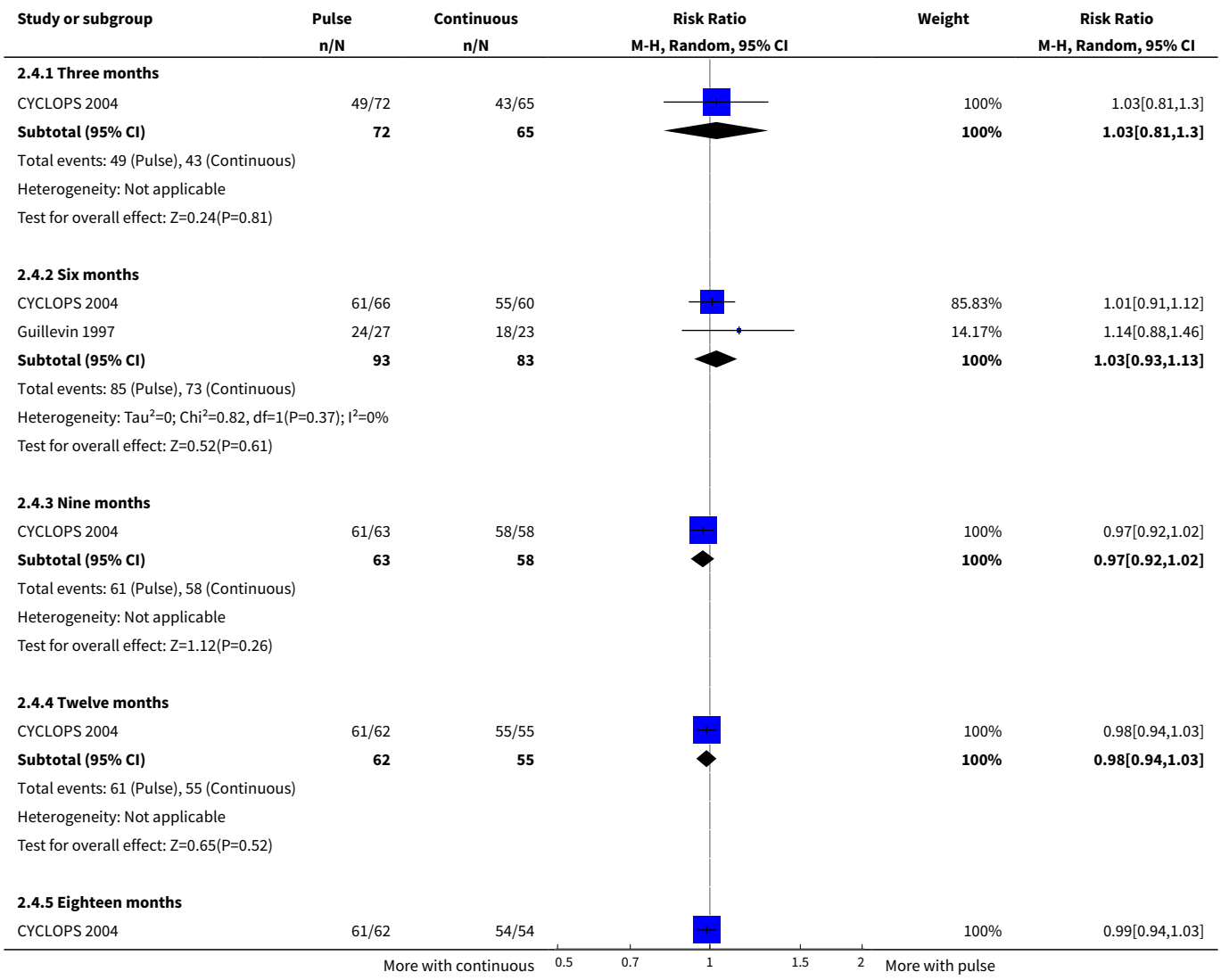


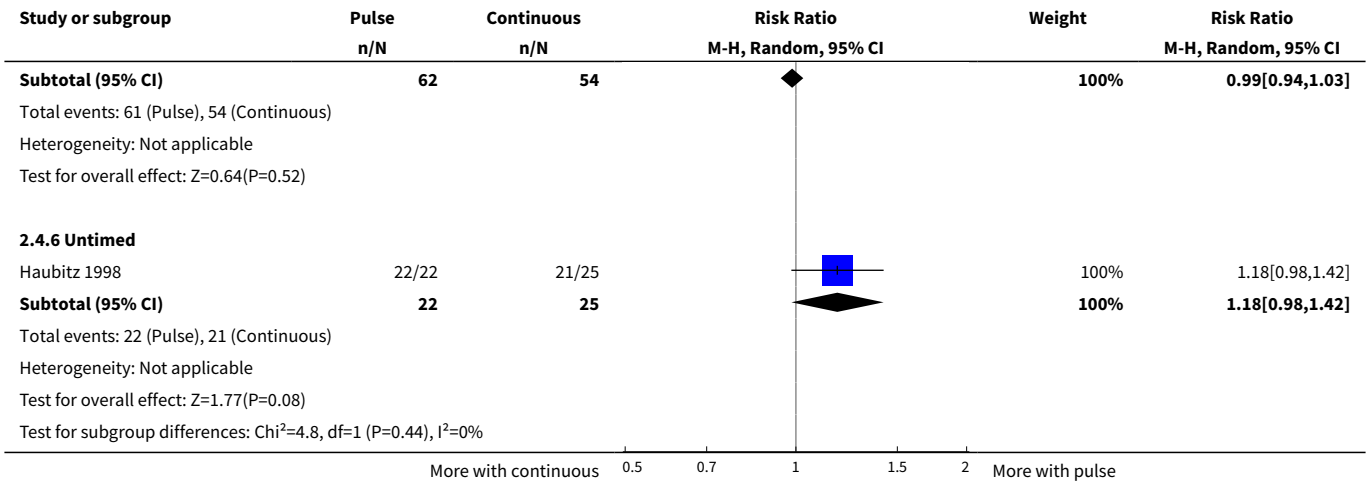

## Analysis 2.3. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 3 Dialysis.



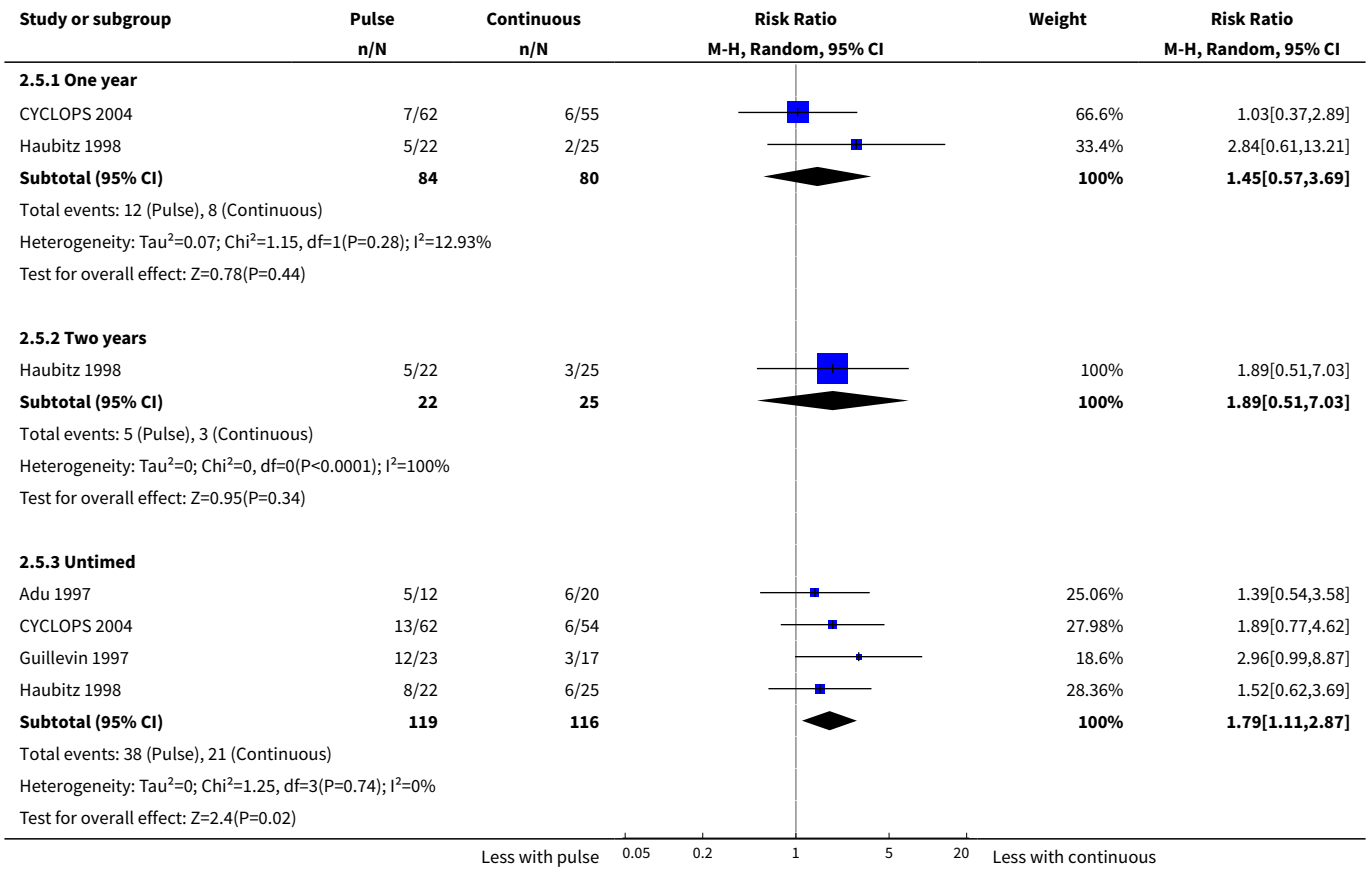



## Analysis 2.4. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 4 Remission.



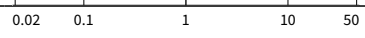



## Analysis 2.5. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 5 Relapse.



## Analysis 2.6. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 6 Treatment failure.

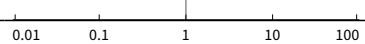
| Study or subgroup | Pulse n/N | Continuous n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Adu 1997 | 3/12 | 1/20 | | 42.89% | 5[0.58,42.8] |
| Guillevin 1997 | 3/27 | 5/23 | | 57.11% | 0.51[0.14,1.91] |
| **Total (95% CI)** | **39** | **43** | | **100%** | **1.36[0.15,12.56]** |
| Total events: 6 (Pulse), 6 (Continuous) | | | | | |
| Heterogeneity: $Tau^2$=1.8; $Chi^2$=3.18, df=1(P=0.07); $I^2$=68.55% | | | | | |
| Test for overall effect: Z=0.27(P=0.79) | | | | | |




Less with pulse — Less with continuous

## Analysis 2.7. Comparison 2 Pulse versus continuous cyclophosphamide, Outcome 7 Adverse events.

| Study or subgroup | Pulse n/N | Continuous n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **2.7.1 Serious infections** | | | | | |
| Adu 1997 | 10/12 | 13/20 | | 32.65% | 1.28[0.85,1.93] |
| CYCLOPS 2004 | 7/76 | 10/73 | | 21% | 0.67[0.27,1.67] |
| Guillevin 1997 | 11/27 | 16/23 | | 29.84% | 0.59[0.35,0.99] |
| Haubitz 1998 | 3/22 | 10/25 | | 16.5% | 0.34[0.11,1.08] |
| **Subtotal (95% CI)** | **137** | **141** | | **100%** | **0.71[0.38,1.33]** |
| Total events: 31 (Pulse), 49 (Continuous) | | | | | |
| Heterogeneity: $Tau^2$=0.27; $Chi^2$=10.3, df=3(P=0.02); $I^2$=70.88% | | | | | |
| Test for overall effect: Z=1.07(P=0.29) | | | | | |
| **2.7.2 Leukopenia** | | | | | |
| Adu 1997 | 3/12 | 9/20 | | 11.76% | 0.56[0.19,1.66] |
| CYCLOPS 2004 | 20/76 | 33/73 | | 68.44% | 0.58[0.37,0.92] |
| Guillevin 1997 | 2/27 | 2/23 | | 3.98% | 0.85[0.13,5.58] |
| Haubitz 1998 | 4/22 | 15/25 | | 15.82% | 0.3[0.12,0.78] |
| **Subtotal (95% CI)** | **137** | **141** | | **100%** | **0.53[0.36,0.77]** |
| Total events: 29 (Pulse), 59 (Continuous) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.78, df=3(P=0.62); $I^2$=0% | | | | | |
| Test for overall effect: Z=3.32(P=0) | | | | | |
| **2.7.3 Nausea** | | | | | |
| Guillevin 1997 | 1/27 | 0/23 | | 7.35% | 2.57[0.11,60.24] |
| Haubitz 1998 | 11/22 | 5/25 | | 92.65% | 2.5[1.03,6.08] |
| **Subtotal (95% CI)** | **49** | **48** | | **100%** | **2.51[1.07,5.89]** |
| Total events: 12 (Pulse), 5 (Continuous) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=0.99); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.1(P=0.04) | | | | | |

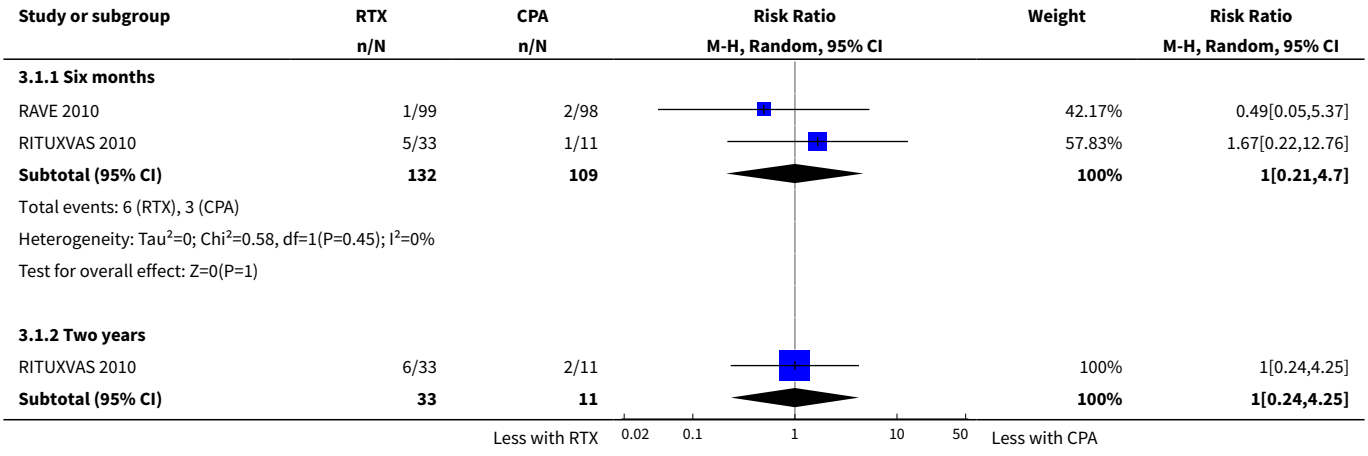


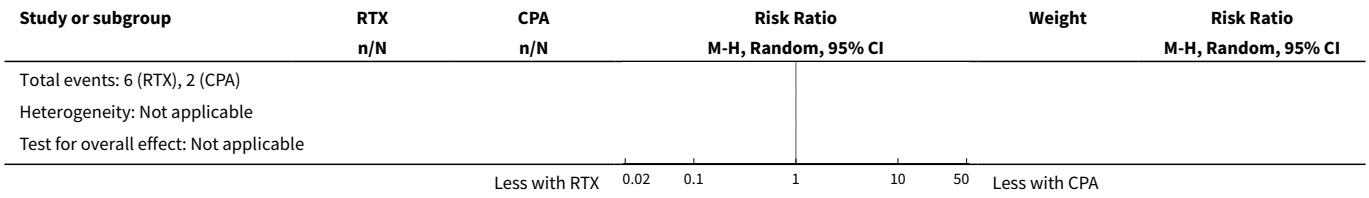

Less with pulse — Less with continuous

**Comparison 3. Rituximab versus cyclophosphamide**

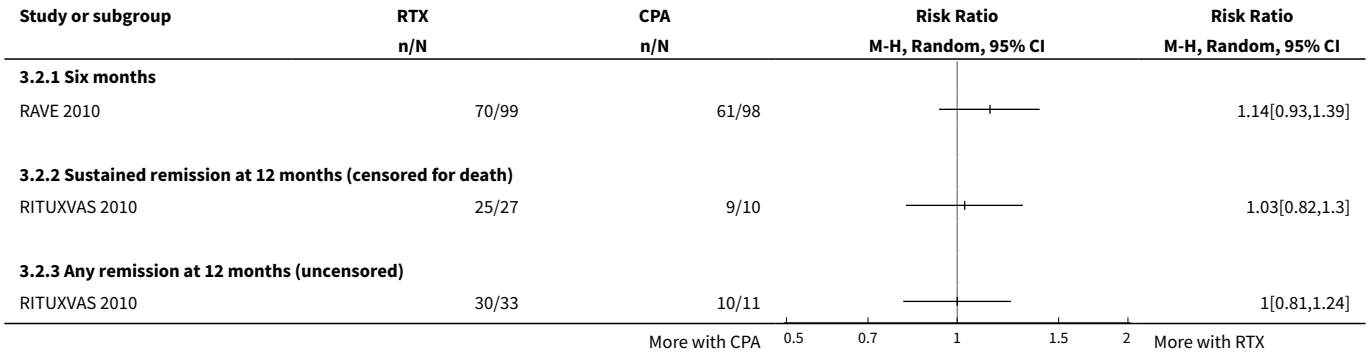
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Six months | 2 | 241 | Risk Ratio (M-H, Random, 95% CI) | 1.00 [0.21, 4.70] |
| 1.2 Two years | 1 | 44 | Risk Ratio (M-H, Random, 95% CI) | 1.0 [0.24, 4.25] |
| 2 Remission | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Sustained remission at 12 months (censored for death) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Any remission at 12 months (uncensored) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Twelve months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Adverse events | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 4.1 Serious adverse events | 2 | 241 | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.72, 1.71] |
| 4.2 Serious infections | 2 | 241 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.42, 1.92] |
| 5 Adverse events (episodes/patient-months) | 2 | 1710 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.62, 1.32] |

**Analysis 3.1. Comparison 3 Rituximab versus cyclophosphamide, Outcome 1 Death.**

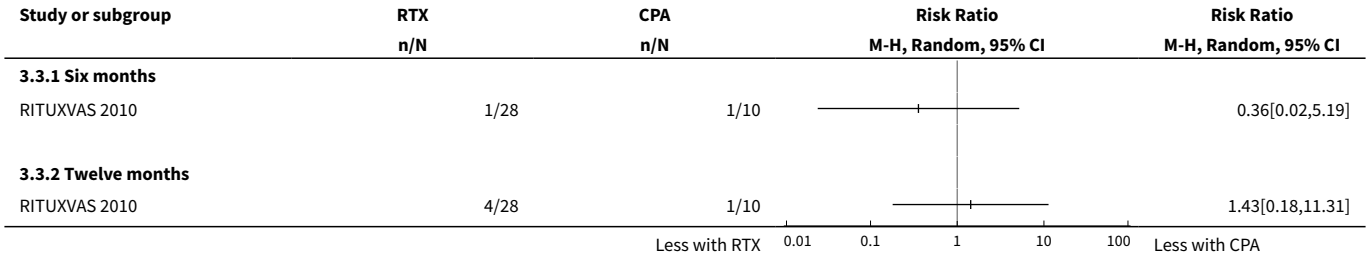




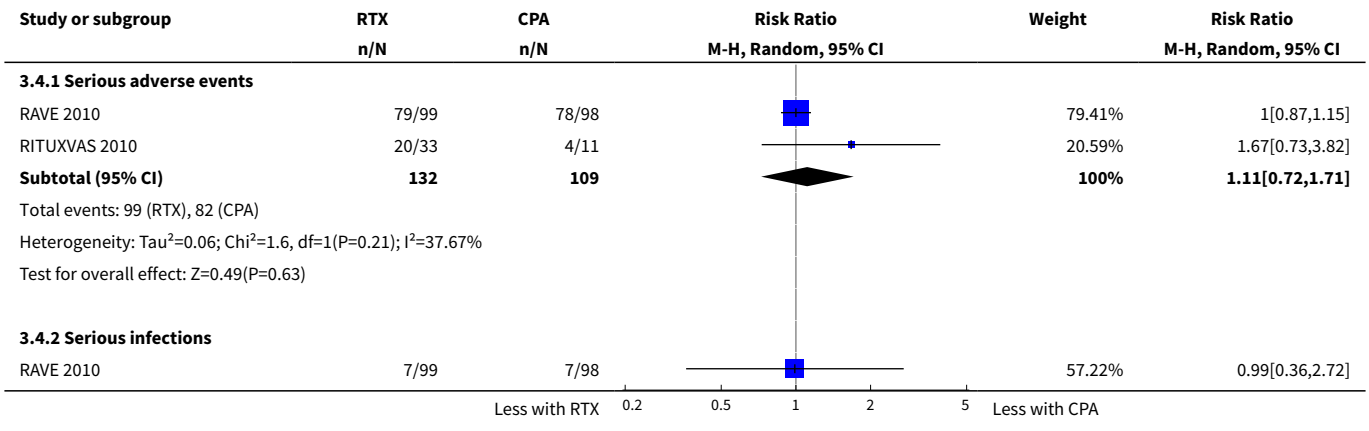

## Analysis 3.2. Comparison 3 Rituximab versus cyclophosphamide, Outcome 2 Remission.

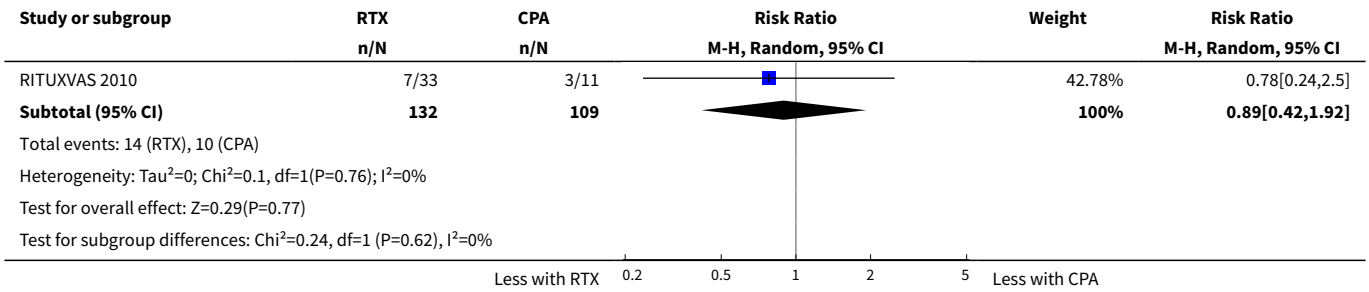



## Analysis 3.3. Comparison 3 Rituximab versus cyclophosphamide, Outcome 3 Relapse.

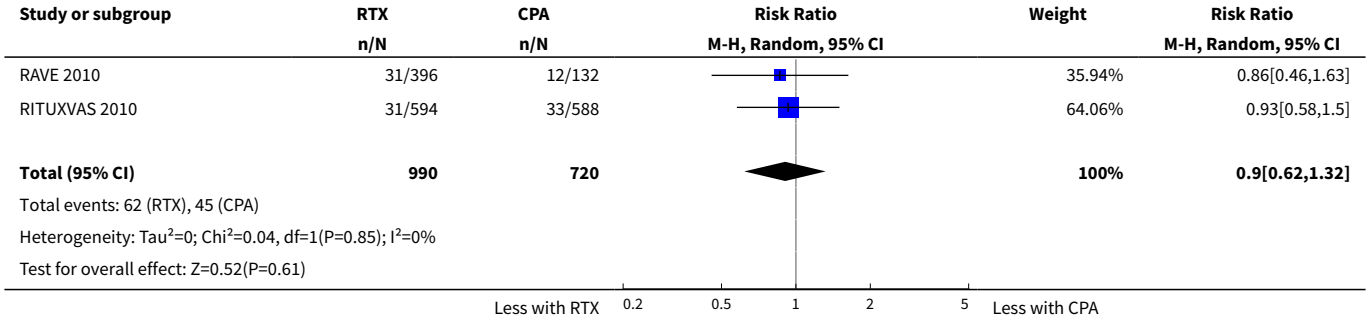



## Analysis 3.4. Comparison 3 Rituximab versus cyclophosphamide, Outcome 4 Adverse events.






### Analysis 3.5. Comparison 3 Rituximab versus cyclophosphamide, Outcome 5 Adverse events (episodes/patient-months).



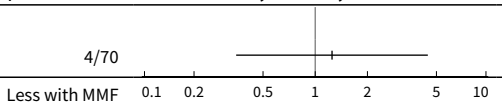

## Comparison 4. Mycophenolate mofetil versus cyclophosphamide

| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Remission | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 Six months | 3 | 216 | Risk Ratio (M-H, Random, 95% CI) | 1.17 [1.01, 1.35] |
| 3.2 Any time point | 1 | 140 | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.89, 1.09] |
| 4 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 18 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 At any time point | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 Minor relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.4 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 5 Adverse events | 3 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 5.1 Infections | 3 | 216 | Risk Ratio (M-H, Random, 95% CI) | 1.27 [0.75, 2.16] |
| 5.2 GI symptoms | 2 | 76 | Risk Ratio (M-H, Random, 95% CI) | 0.52 [0.17, 1.59] |
| 5.3 Leukopenia | 2 | 76 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.09, 5.15] |
| 5.4 Serious adverse events | 1 | 140 | Risk Ratio (M-H, Random, 95% CI) | 1.25 [0.86, 1.81] |

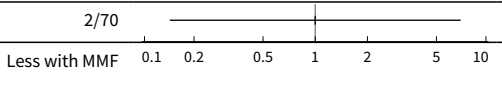
### Analysis 4.1. Comparison 4 Mycophenolate mofetil versus cyclophosphamide, Outcome 1 Death.

| Study or subgroup | MMF n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **4.1.1 Six months** | | | | |
| MYCYC 2012 | 5/70 | 4/70 | | 1.25[0.35,4.46] |



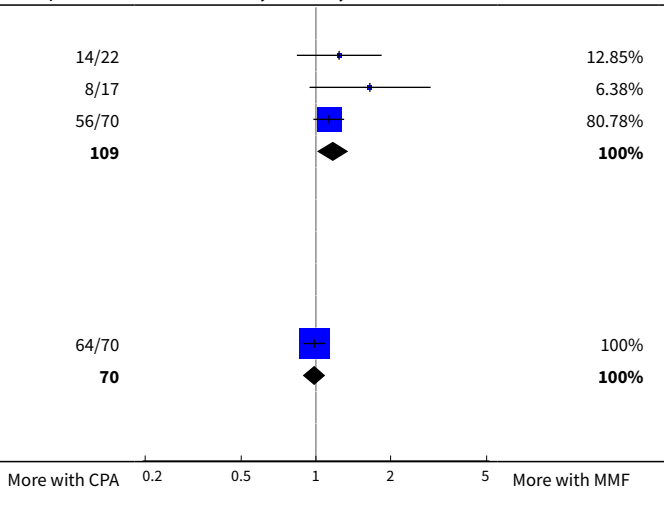

### Analysis 4.2. Comparison 4 Mycophenolate mofetil versus cyclophosphamide, Outcome 2 Dialysis.

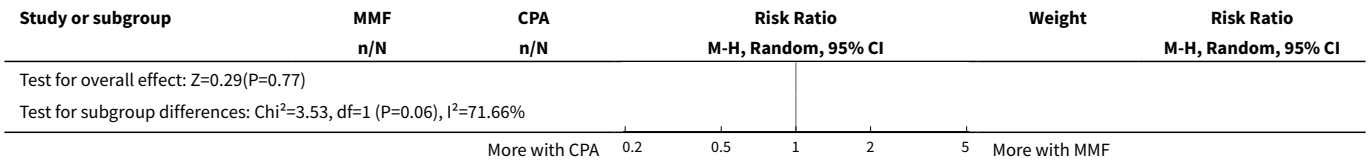
| Study or subgroup | MMF n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| MYCYC 2012 | 2/70 | 2/70 | | 1[0.14,6.9] |



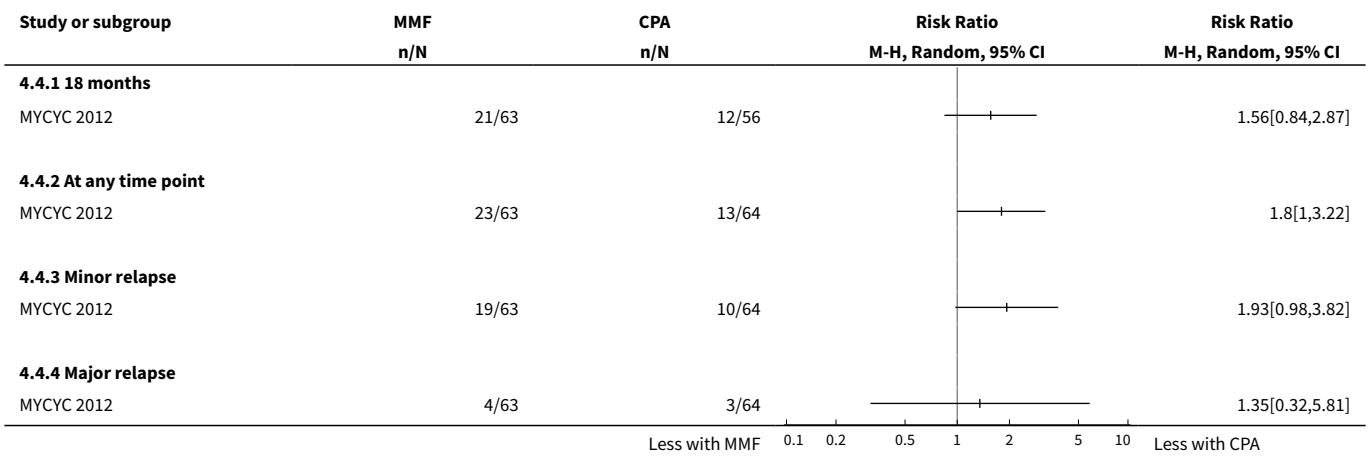

### Analysis 4.3. Comparison 4 Mycophenolate mofetil versus cyclophosphamide, Outcome 3 Remission.

| Study or subgroup | MMF n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **4.3.1 Six months** | | | | | |
| Han 2011b | 15/19 | 14/22 | | 12.85% | 1.24[0.84,1.84] |
| Hu 2008b | 14/18 | 8/17 | | 6.38% | 1.65[0.94,2.9] |
| MYCYC 2012 | 63/70 | 56/70 | | 80.78% | 1.13[0.98,1.3] |
| **Subtotal (95% CI)** | **107** | **109** | | **100%** | **1.17[1.01,1.35]** |
| Total events: 92 (MMF), 78 (CPA) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=2.09, df=2(P=0.35); $I^2$=4.45% | | | | | |
| Test for overall effect: Z=2.12(P=0.03) | | | | | |
| **4.3.2 Any time point** | | | | | |
| MYCYC 2012 | 63/70 | 64/70 | | 100% | 0.98[0.89,1.09] |
| **Subtotal (95% CI)** | **70** | **70** | | **100%** | **0.98[0.89,1.09]** |
| Total events: 63 (MMF), 64 (CPA) | | | | | |
| Heterogeneity: Not applicable | | | | | |

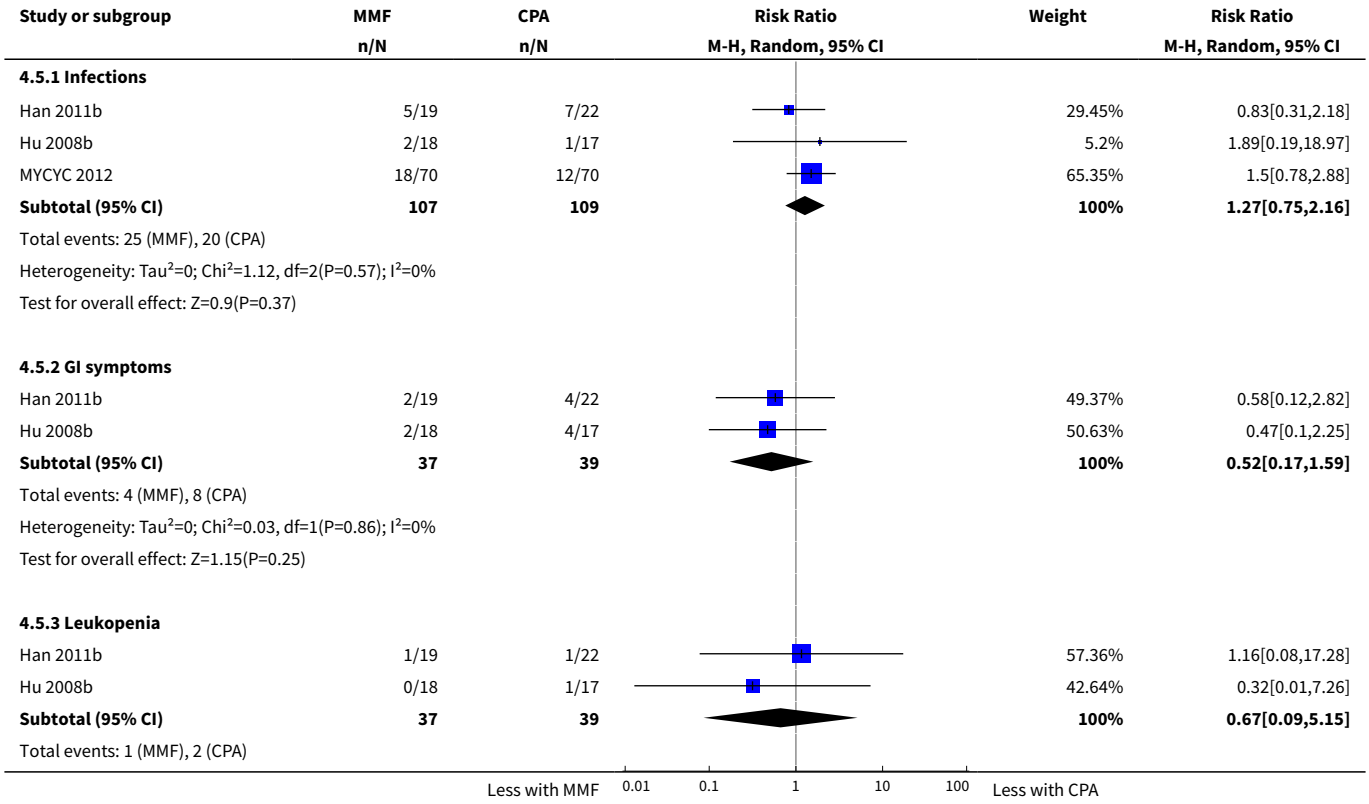


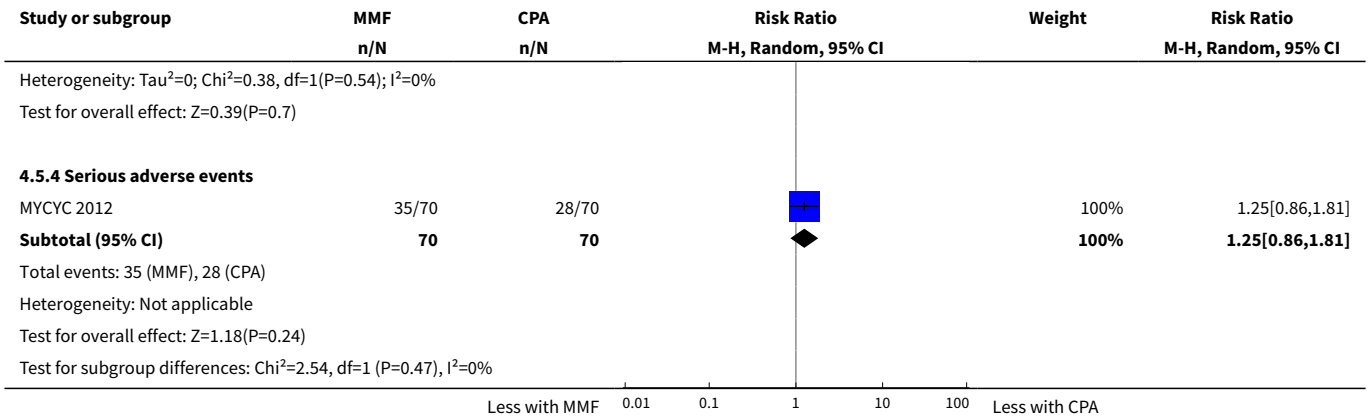



## Analysis 4.4. Comparison 4 Mycophenolate mofetil versus cyclophosphamide, Outcome 4 Relapse.




## Analysis 4.5. Comparison 4 Mycophenolate mofetil versus cyclophosphamide, Outcome 5 Adverse events.

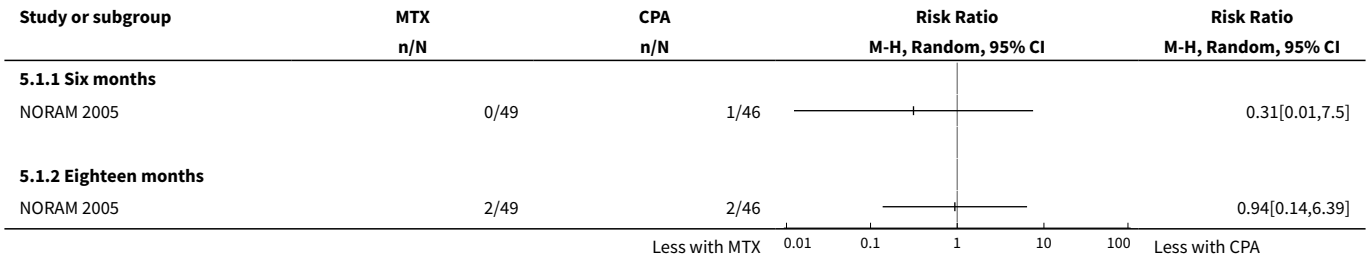





## Comparison 5. Methotrexate versus cyclophosphamide

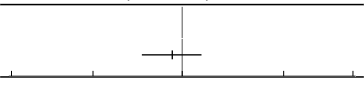
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Eighteen months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Remission | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Untimed | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 5.1. Comparison 5 Methotrexate versus cyclophosphamide, Outcome 1 Death.



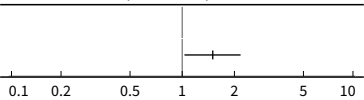
### Analysis 5.2. Comparison 5 Methotrexate versus cyclophosphamide, Outcome 2 Remission.

| Study or subgroup | MTX n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **5.2.1 Six months** | | | | |
| NORAM 2005 | 44/49 | 43/46 | | 0.96[0.85,1.08] |




### Analysis 5.3. Comparison 5 Methotrexate versus cyclophosphamide, Outcome 3 Relapse.

| Study or subgroup | MTX n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **5.3.1 Untimed** | | | | |
| NORAM 2005 | 32/46 | 20/43 | | 1.5[1.03,2.17] |

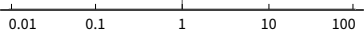



## Comparison 6. Avacopan versus prednisolone

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Kidney function: eGFR [mL/min/1.73 $m^2$] | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 3 Remission | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5.1 Any adverse event | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Serious infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Serious adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 6.1. Comparison 6 Avacopan versus prednisolone, Outcome 1 Death.

| Study or subgroup | Avacopan n/N | Prednisolone n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| CLEAR 2013 | 0/22 | 0/23 | | Not estimable |



### Analysis 6.2. Comparison 6 Avacopan versus prednisolone, Outcome 2 Kidney function: eGFR [mL/min/1.73 m$^2$].

| Study or subgroup | Avacopan N | Avacopan Mean(SD) | Prednisolone N | Prednisolone Mean(SD) | Mean Difference Random, 95% CI | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| CLEAR 2013 | 21 | 56.1 (5.2) | 20 | 52.8 (3.6) | | 3.3[0.57,6.03] |

Higher with prednisolone | -10 | -5 | 0 | 5 | 10 | Higher with avacopan

### Analysis 6.3. Comparison 6 Avacopan versus prednisolone, Outcome 3 Remission.

| Study or subgroup | Avacopan n/N | Prednisolone n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| CLEAR 2013 | 7/21 | 8/20 | | 0.83[0.37,1.87] |

More with prednisolone | 0.2 | 0.5 | 1 | 2 | 5 | More with avacopan

### Analysis 6.4. Comparison 6 Avacopan versus prednisolone, Outcome 4 Relapse.

| Study or subgroup | Avacopan n/N | Prednisolone n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| CLEAR 2013 | 3/22 | 2/23 | | 1.57[0.29,8.51] |

Less with avacopan | 0.01 | 0.1 | 1 | 10 | 100 | Less with prednisolone

### Analysis 6.5. Comparison 6 Avacopan versus prednisolone, Outcome 5 Adverse events.

| Study or subgroup | Avacopan n/N | Prednisolone n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **6.5.1 Any adverse event** | | | | |
| CLEAR 2013 | 21/22 | 21/23 | | 1.05[0.89,1.22] |
| **6.5.2 Serious infection** | | | | |
| CLEAR 2013 | 1/22 | 1/23 | | 1.05[0.07,15.7] |
| **6.5.3 Serious adverse events** | | | | |
| CLEAR 2013 | 8/22 | 4/23 | | 2.09[0.73,5.96] |

Less with avacopan | 0.01 | 0.1 | 1 | 10 | 100 | Less with prednisolone

## Comparison 7. Intravenous immunoglobulin versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Response | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Three months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Three months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 7.1. Comparison 7 Intravenous immunoglobulin versus placebo, Outcome 1 Death.

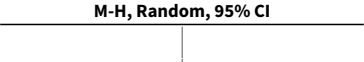
| Study or subgroup | IVIg n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| Jayne 2000 | 0/17 | 2/17 | | 0.2[0.01,3.88] |




Less with IVIg — Less with placebo

### Analysis 7.2. Comparison 7 Intravenous immunoglobulin versus placebo, Outcome 2 Response.

| Study or subgroup | IVIg n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **7.2.1 Three months** | | | | |
| Jayne 2000 | 14/17 | 6/17 | | 2.33[1.18,4.61] |




More with placebo — More with IVIg

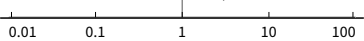
### Analysis 7.3. Comparison 7 Intravenous immunoglobulin versus placebo, Outcome 3 Relapse.

| Study or subgroup | IVIg n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **7.3.1 Three months** | | | | |
| Jayne 2000 | 5/16 | 4/15 | | 1.17[0.39,3.56] |


Less with IVIg — Less with placebo

### Analysis 7.4. Comparison 7 Intravenous immunoglobulin versus placebo, Outcome 4 Adverse events.

| Study or subgroup | IVIg n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| Jayne 2000 | 12/17 | 4/17 | | 3[1.21,7.45] |




Less with IVIg — Less with control

**Comparison 8. Plasma exchange versus immunoadsorption**

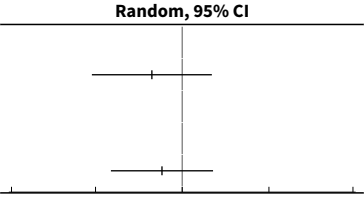
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Three months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Kidney function: serum creatinine | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 2.1 Three months | 1 | | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Six months | 1 | | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Three months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 8.1. Comparison 8 Plasma exchange versus immunoadsorption, Outcome 1 Death.**

| Study or subgroup | PE n/N | Immunoadsorption n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **8.1.1 Three months** | | | | |
| Stegmayr 1999 | 2/21 | 1/23 | | 2.19[0.21,22.43] |
| **8.1.2 Six months** | | | | |
| Stegmayr 1999 | 3/21 | 2/23 | | 1.64[0.3,8.89] |

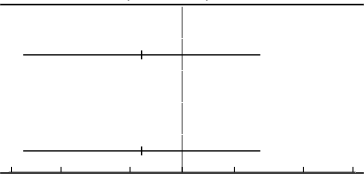

**Analysis 8.2. Comparison 8 Plasma exchange versus immunoadsorption, Outcome 2 Kidney function: serum creatinine.**

| Study or subgroup | PE N | PE Mean(SD) | Immunoadsorption N | Immunoadsorption Mean(SD) | Mean Difference Random, 95% CI | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **8.2.1 Three months** | | | | | | |
| Stegmayr 1999 | 18 | 177.2 (79.3) | 16 | 212.2 (119.8) | | -35.02[-104.2,34.16] |
| **8.2.2 Six months** | | | | | | |
| Stegmayr 1999 | 15 | 164.5 (94.2) | 12 | 187.8 (61.2) | | -23.36[-82.27,35.55] |



### Analysis 8.3. Comparison 8 Plasma exchange versus immunoadsorption, Outcome 3 Dialysis.

| Study or subgroup | PE n/N | Immunoadsorption n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **8.3.1 Three months** | | | | |
| Stegmayr 1999 | 2/18 | 4/21 | | 0.58[0.12,2.82] |
| **8.3.2 Six months** | | | | |
| Stegmayr 1999 | 2/18 | 4/21 | | 0.58[0.12,2.82] |




## Comparison 9. Lymphocytapheresis versus control

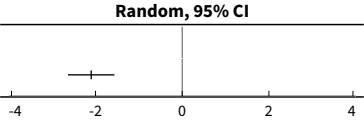
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Kidney function: serum creatinine | 1 | | Mean Difference (IV, Random, 95% CI) | Totals not selected |
| 2.1 One month | 1 | | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 9.1. Comparison 9 Lymphocytapheresis versus control, Outcome 1 Death.

| Study or subgroup | LCP n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **9.1.1 Six months** | | | | |
| Furuta 1998 | 2/12 | 5/12 | | 0.4[0.1,1.67] |

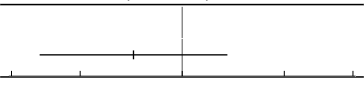

### Analysis 9.2. Comparison 9 Lymphocytapheresis versus control, Outcome 2 Kidney function: serum creatinine.

| Study or subgroup | LCP N | LCP Mean(SD) | Control N | Control Mean(SD) | Mean Difference Random, 95% CI | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|
| **9.2.1 One month** | | | | | | |
| Furuta 1998 | 12 | 2.1 (0.3) | 12 | 4.2 (0.9) | | -2.1[-2.64,-1.56] |



### Analysis 9.3. Comparison 9 Lymphocytapheresis versus control, Outcome 3 Dialysis.

| Study or subgroup | LCP n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **9.3.1 Six months** | | | | |
| Furuta 1998 | 1/12 | 3/12 | | 0.33[0.04,2.77] |

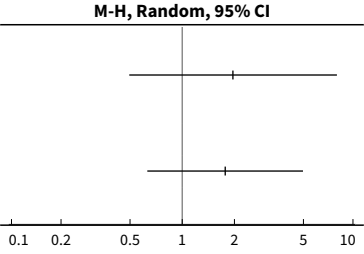


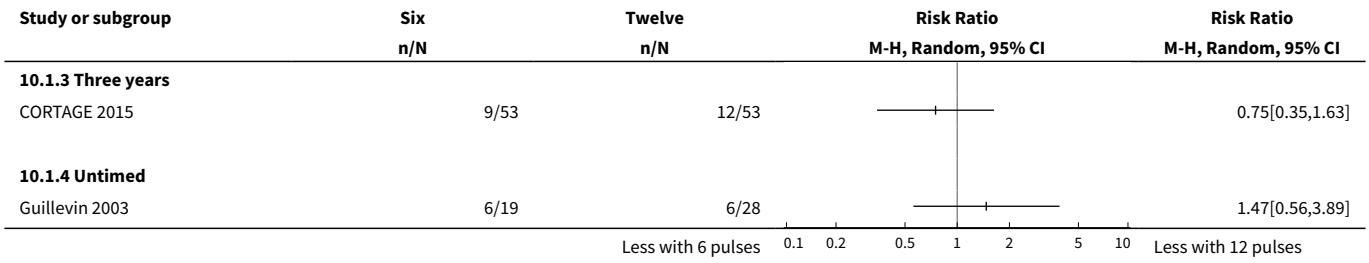

## Comparison 10. Six versus 12 cyclophosphamide pulses

| Outcome or sub-group title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 One year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.3 Three years | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.4 Untimed | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Remission | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 Untimed | 2 | 151 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.85, 1.15] |
| 3 Relapse | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 3.1 Untimed | 2 | 133 | Risk Ratio (M-H, Random, 95% CI) | 1.57 [0.96, 2.56] |
| 4 Adverse events | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 4.1 Infection | 2 | 169 | Risk Ratio (M-H, Random, 95% CI) | 0.79 [0.36, 1.72] |
| 4.2 Severe adverse events | 1 | 104 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.59, 1.00] |
| 4.3 Cytopenia | 1 | 104 | Risk Ratio (M-H, Random, 95% CI) | 0.36 [0.10, 1.28] |

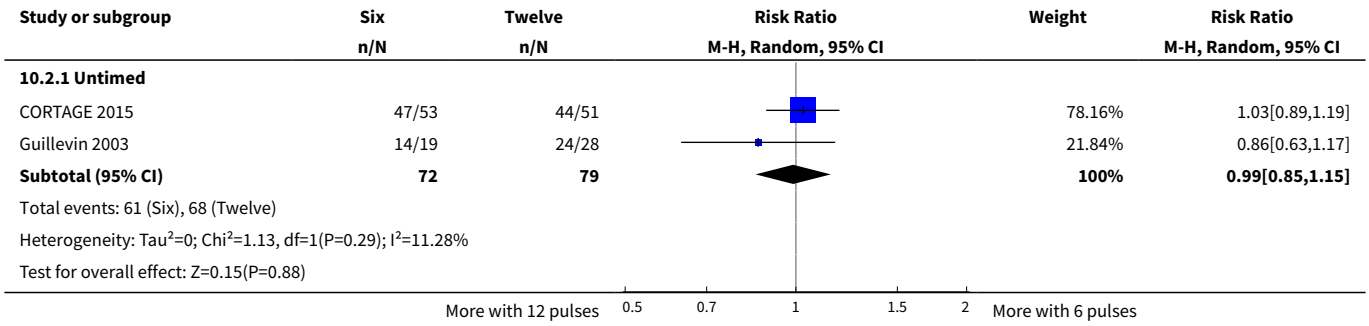
### Analysis 10.1. Comparison 10 Six versus 12 cyclophosphamide pulses, Outcome 1 Death.

| Study or subgroup | Six n/N | Twelve n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **10.1.1 Six months** | | | | |
| Guillevin 2003 | 4/19 | 3/28 | | 1.96[0.49,7.8] |
| **10.1.2 One year** | | | | |
| Guillevin 2003 | 6/19 | 5/28 | | 1.77[0.63,4.97] |

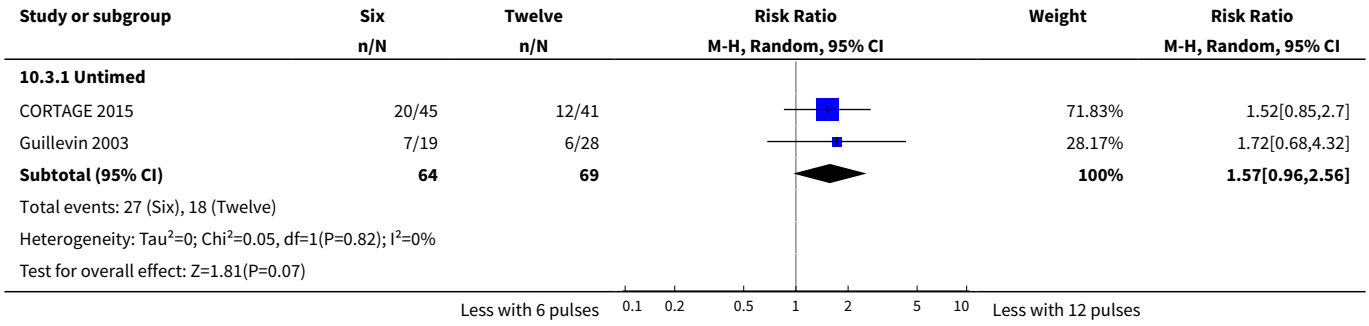




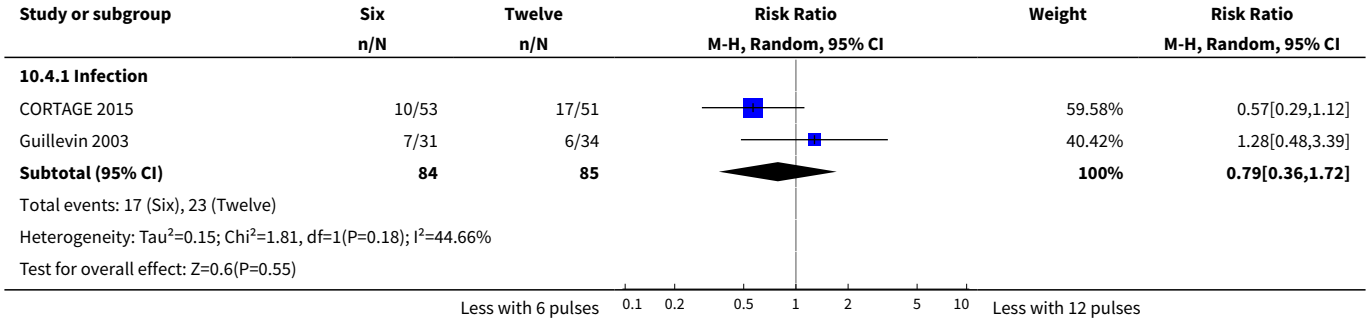

## Analysis 10.2. Comparison 10 Six versus 12 cyclophosphamide pulses, Outcome 2 Remission.

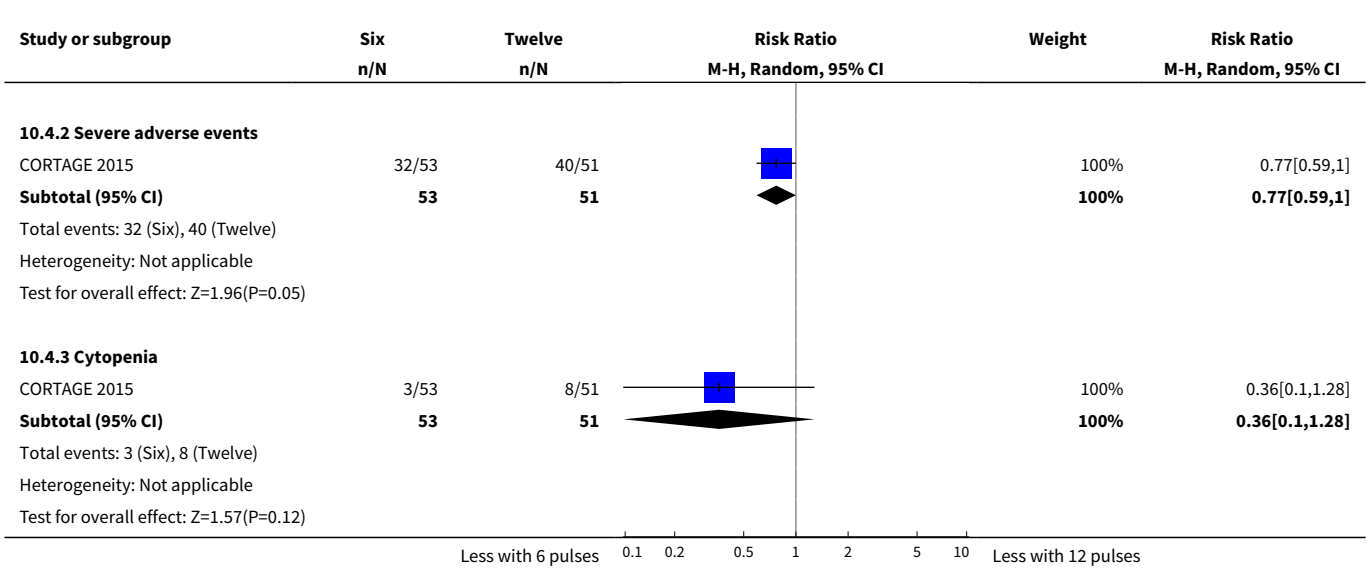



## Analysis 10.3. Comparison 10 Six versus 12 cyclophosphamide pulses, Outcome 3 Relapse.




## Analysis 10.4. Comparison 10 Six versus 12 cyclophosphamide pulses, Outcome 4 Adverse events.

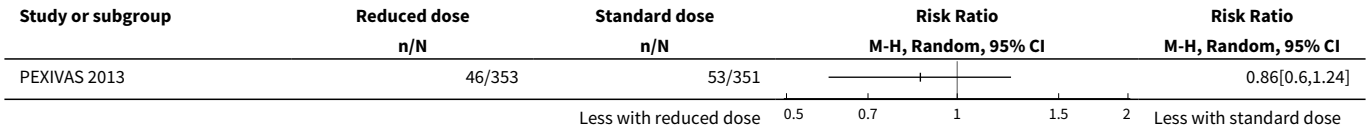





## Comparison 11. Reduced dose versus standard dose steroids

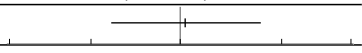
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Sustained remission | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Serious adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Serious infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 11.1. Comparison 11 Reduced dose versus standard dose steroids, Outcome 1 Death.



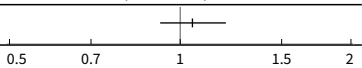
### Analysis 11.2. Comparison 11 Reduced dose versus standard dose steroids, Outcome 2 Dialysis.

| Study or subgroup | Reduced dose n/N | Standard dose n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| PEXIVAS 2013 | 70/353 | 68/351 | | 1.02[0.76,1.38] |



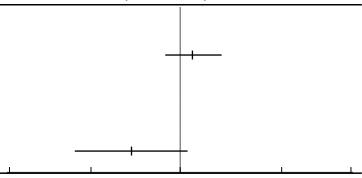

### Analysis 11.3. Comparison 11 Reduced dose versus standard dose steroids, Outcome 3 Sustained remission.

| Study or subgroup | Reduced dose n/N | Standard dose n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| PEXIVAS 2013 | 204/353 | 193/351 | | 1.05[0.92,1.2] |




### Analysis 11.4. Comparison 11 Reduced dose versus standard dose steroids, Outcome 4 Adverse events.

| Study or subgroup | Reduced dose n/N | Standard dose n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **11.4.1 Serious adverse events** | | | | |
| PEXIVAS 2013 | 231/353 | 218/351 | | 1.05[0.94,1.18] |
| **11.4.2 Serious infection** | | | | |
| PEXIVAS 2013 | 96/353 | 116/351 | | 0.82[0.66,1.03] |

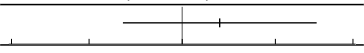



### Comparison 12. Etanercept versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Sustained remission | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Cancer | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

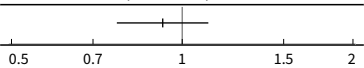
### Analysis 12.1. Comparison 12 Etanercept versus placebo, Outcome 1 Death.

| Study or subgroup | Etanercept n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| WGET 2002 | 4/89 | 2/85 | | 1.91[0.36,10.16] |



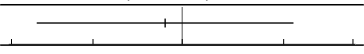

### Analysis 12.2. Comparison 12 Etanercept versus placebo, Outcome 2 Sustained remission.

| Study or subgroup | Etanercept n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| WGET 2002 | 62/89 | 64/85 | | 0.93[0.77,1.11] |



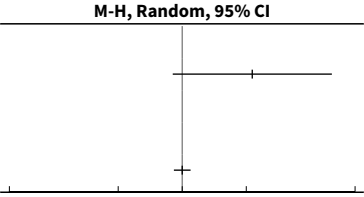

### Analysis 12.3. Comparison 12 Etanercept versus placebo, Outcome 3 Relapse.

| Study or subgroup | Etanercept n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| WGET 2002 | 19/62 | 21/64 | | 0.93[0.56,1.56] |




### Analysis 12.4. Comparison 12 Etanercept versus placebo, Outcome 4 Adverse events.

| Study or subgroup | Etanercept n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **12.4.1 Cancer** | | | | |
| WGET 2002 | 6/89 | 0/85 | | 12.42[0.71,217.18] |
| **12.4.2 Infection** | | | | |
| WGET 2002 | 44/89 | 42/85 | | 1[0.74,1.35] |



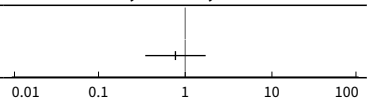

## Comparison 13. Maintenance therapy: azathioprine versus cyclophosphamide

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Long-term follow-up (median time 8.5 years) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Long-term follow-up (median time 8.5 years) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Eighteen months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Long-term follow-up (median time 8.5 years) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.3 Serious adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Adverse events (episodes/patient-months) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5.1 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 13.1. Comparison 13 Maintenance therapy: azathioprine versus cyclophosphamide, Outcome 1 Death.

| Study or subgroup | AZA n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **13.1.1 Long-term follow-up (median time 8.5 years)** | | | | |
| CYCAZAREM 2003 | 9/71 | 12/73 | | 0.77[0.35,1.72] |

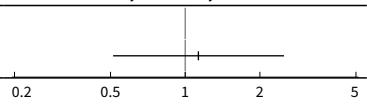


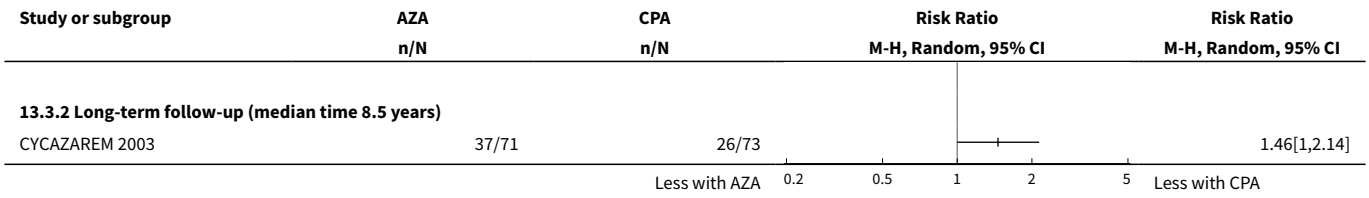

### Analysis 13.2. Comparison 13 Maintenance therapy: azathioprine versus cyclophosphamide, Outcome 2 Dialysis.

| Study or subgroup | AZA n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **13.2.1 Long-term follow-up (median time 8.5 years)** | | | | |
| CYCAZAREM 2003 | 8/71 | 5/73 | | 1.65[0.57,4.79] |

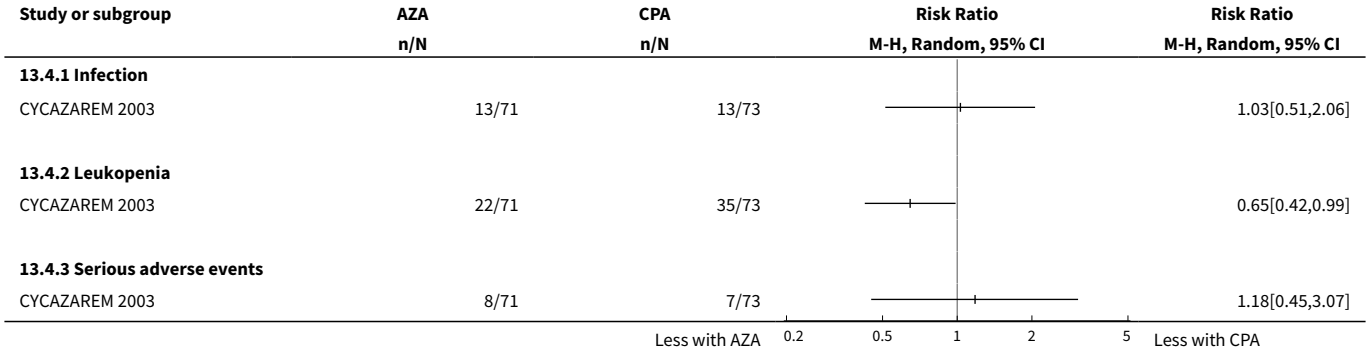

### Analysis 13.3. Comparison 13 Maintenance therapy: azathioprine versus cyclophosphamide, Outcome 3 Relapse.

| Study or subgroup | AZA n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **13.3.1 Eighteen months** | | | | |
| CYCAZAREM 2003 | 11/71 | 10/73 | | 1.13[0.51,2.5] |

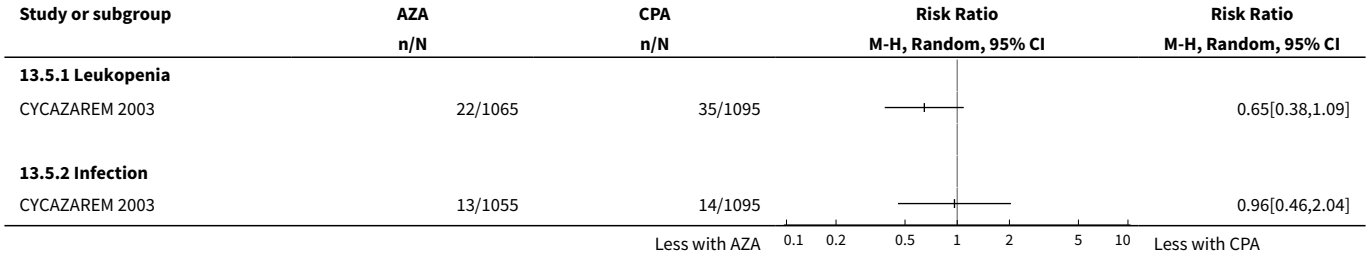





## Analysis 13.4. Comparison 13 Maintenance therapy: azathioprine versus cyclophosphamide, Outcome 4 Adverse events.




## Analysis 13.5. Comparison 13 Maintenance therapy: azathioprine versus cyclophosphamide, Outcome 5 Adverse events (episodes/patient-months).



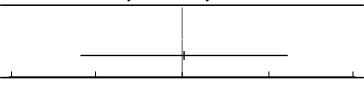

## Comparison 14. Maintenance therapy: mycophenolate mofetil versus azathioprine

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Untimed | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Any relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.3 Minor relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Any adverse event | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Serious infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 Serious adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

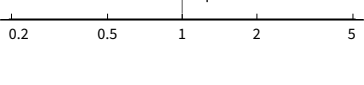
**Analysis 14.1. Comparison 14 Maintenance therapy: mycophenolate mofetil versus azathioprine, Outcome 1 Death.**

| Study or subgroup | MMF n/N | AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **14.1.1 Untimed** | | | | |
| IMPROVE 2003 | 1/76 | 1/80 | | 1.05[0.07,16.53] |



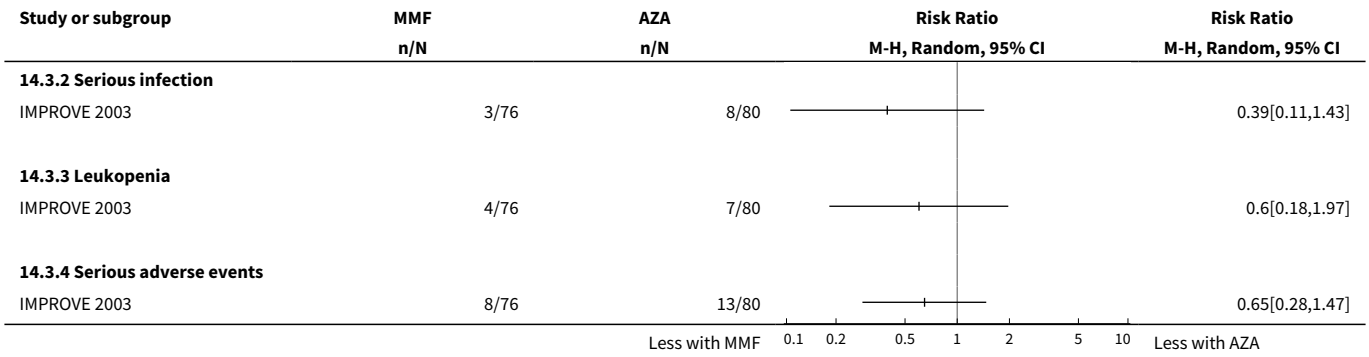

**Analysis 14.2. Comparison 14 Maintenance therapy: mycophenolate mofetil versus azathioprine, Outcome 2 Relapse.**

| Study or subgroup | MMF n/N | AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **14.2.1 Any relapse** | | | | |
| IMPROVE 2003 | 42/76 | 30/80 | | 1.47[1.04,2.09] |
| **14.2.2 Major relapse** | | | | |
| IMPROVE 2003 | 18/76 | 10/80 | | 1.89[0.93,3.84] |
| **14.2.3 Minor relapse** | | | | |
| IMPROVE 2003 | 24/76 | 20/80 | | 1.26[0.76,2.09] |




**Analysis 14.3. Comparison 14 Maintenance therapy: mycophenolate mofetil versus azathioprine, Outcome 3 Adverse events.**

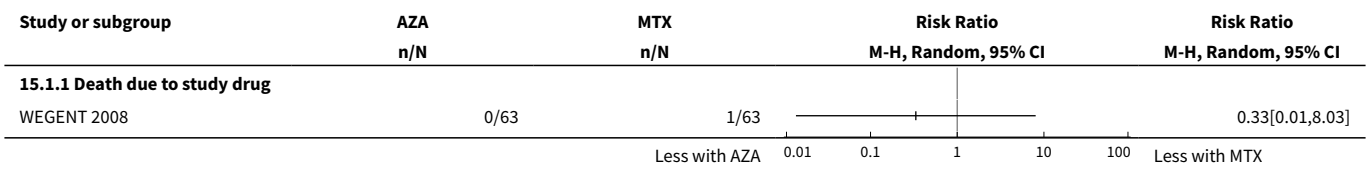
| Study or subgroup | MMF n/N | AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **14.3.1 Any adverse event** | | | | |
| IMPROVE 2003 | 22/76 | 28/80 | | 0.83[0.52,1.31] |




## Comparison 15. Maintenance therapy: azathioprine versus methotrexate

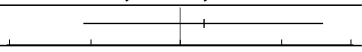
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Death due to study drug | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Relapse-free survival | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 18 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 24 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 36 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Event-free survival at 24 months | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5.1 Any adverse event | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Severe adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 Adverse event causing death or study drug discontinuation | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

### Analysis 15.1. Comparison 15 Maintenance therapy: azathioprine versus methotrexate, Outcome 1 Death.



### Analysis 15.2. Comparison 15 Maintenance therapy: azathioprine versus methotrexate, Outcome 2 Relapse.

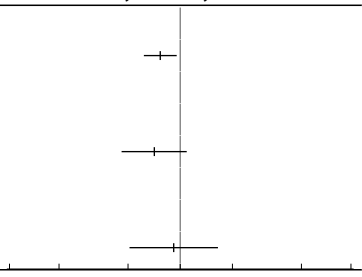
| Study or subgroup | AZA n/N | MTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| WEGENT 2008 | 23/63 | 21/63 | | 1.1[0.68,1.77] |




Less with AZA — Less with MTX

### Analysis 15.3. Comparison 15 Maintenance therapy: azathioprine versus methotrexate, Outcome 3 Relapse-free survival.

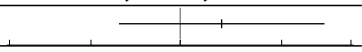
| Study or subgroup | AZA n/N | MTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **15.3.1 18 months** | | | | |
| WEGENT 2008 | 30/43 | 40/44 | | 0.77[0.62,0.95] |
| **15.3.2 24 months** | | | | |
| WEGENT 2008 | 13/25 | 22/30 | | 0.71[0.46,1.09] |
| **15.3.3 36 months** | | | | |
| WEGENT 2008 | 6/9 | 8/11 | | 0.92[0.51,1.65] |




More with MTX — More with AXA

### Analysis 15.4. Comparison 15 Maintenance therapy: azathioprine versus methotrexate, Outcome 4 Event-free survival at 24 months.

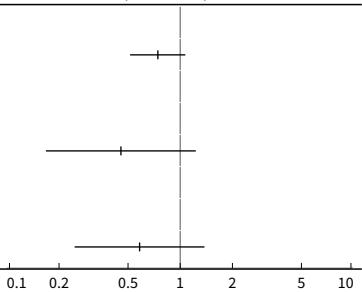
| Study or subgroup | AZA n/N | MTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| WEGENT 2008 | 17/24 | 15/25 | | 1.18[0.78,1.78] |




More with MTX — More with AZA

### Analysis 15.5. Comparison 15 Maintenance therapy: azathioprine versus methotrexate, Outcome 5 Adverse events.

| Study or subgroup | AZA n/N | MTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **15.5.1 Any adverse event** | | | | |
| WEGENT 2008 | 26/63 | 35/63 | | 0.74[0.51,1.07] |
| **15.5.2 Severe adverse events** | | | | |
| WEGENT 2008 | 5/63 | 11/63 | | 0.45[0.17,1.23] |
| **15.5.3 Adverse event causing death or study drug discontinuation** | | | | |
| WEGENT 2008 | 7/63 | 12/63 | | 0.58[0.25,1.38] |



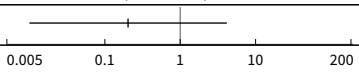

Less with AZA — Less with MTX

**Comparison 16. Maintenance therapy: rituximab versus azathioprine**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 One year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Two years | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 End of study (28 months) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Minor relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 One year | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Two years | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 End of study (28 months) | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Serious infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

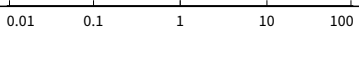
**Analysis 16.1. Comparison 16 Maintenance therapy: rituximab versus azathioprine, Outcome 1 Death.**

| Study or subgroup | RTX n/N | AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| MAINRITSAN 2014 | 0/57 | 2/58 | | 0.2[0.01,4.15] |

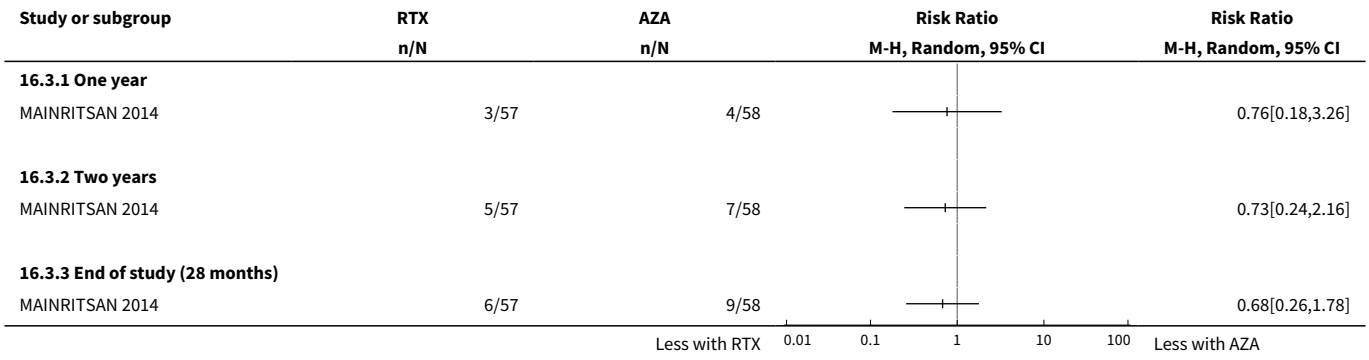



**Analysis 16.2. Comparison 16 Maintenance therapy: rituximab versus azathioprine, Outcome 2 Major relapse.**

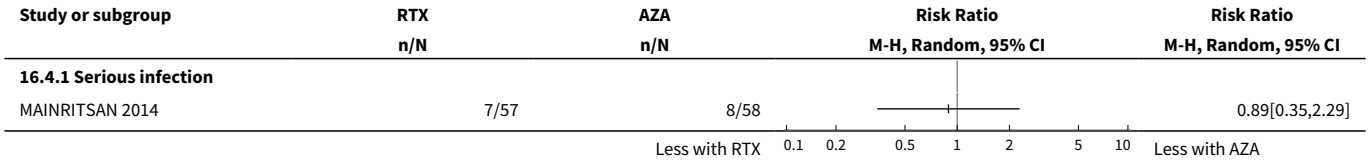
| Study or subgroup | RTX n/N | AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **16.2.1 One year** | | | | |
| MAINRITSAN 2014 | 1/57 | 8/58 | | 0.13[0.02,0.98] |
| **16.2.2 Two years** | | | | |
| MAINRITSAN 2014 | 1/57 | 10/58 | | 0.1[0.01,0.77] |
| **16.2.3 End of study (28 months)** | | | | |
| MAINRITSAN 2014 | 3/57 | 17/58 | | 0.18[0.06,0.58] |



### Analysis 16.3. Comparison 16 Maintenance therapy: rituximab versus azathioprine, Outcome 3 Minor relapse.




### Analysis 16.4. Comparison 16 Maintenance therapy: rituximab versus azathioprine, Outcome 4 Adverse events.



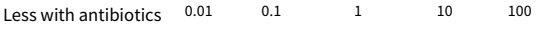

### Comparison 17. Maintenance therapy: co-trimoxazole (antibiotics) versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 Six months | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Remission | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2.1 One year | 2 | 111 | Risk Ratio (M-H, Random, 95% CI) | 1.14 [0.98, 1.33] |
| 2.2 18 months | 1 | 31 | Risk Ratio (M-H, Random, 95% CI) | 1.41 [0.81, 2.44] |
| 2.3 Two years | 1 | 80 | Risk Ratio (M-H, Random, 95% CI) | 1.28 [0.94, 1.76] |
| 3 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Anorexia and nausea | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Rash | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 Interstitial nephritis | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.4 Asymptomatic hepatotoxic effects | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.5 Recurrent urinary tract infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.6 Adverse events causing study drug discontinuation | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

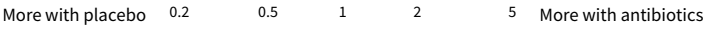
**Analysis 17.1. Comparison 17 Maintenance therapy: co-trimoxazole (antibiotics) versus placebo, Outcome 1 Death.**

| Study or subgroup | Antibiotics n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **17.1.1 Six months** | | | | |
| Stegeman 1996 | 0/41 | 1/40 | | 0.33[0.01,7.76] |



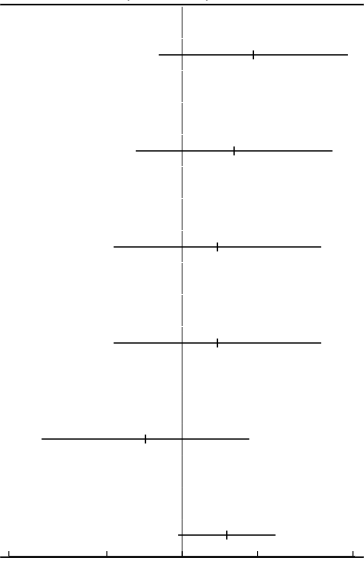

**Analysis 17.2. Comparison 17 Maintenance therapy: co-trimoxazole (antibiotics) versus placebo, Outcome 2 Remission.**

| Study or subgroup | Antibiotics n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **17.2.1 One year** | | | | | |
| Stegeman 1996 | 38/41 | 32/39 | | 81.49% | 1.13[0.95,1.34] |
| Zycinska 2009 | 14/16 | 11/15 | | 18.51% | 1.19[0.83,1.71] |
| **Subtotal (95% CI)** | **57** | **54** | | **100%** | **1.14[0.98,1.33]** |
| Total events: 52 (Antibiotics), 43 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.08, df=1(P=0.78); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.68(P=0.09) | | | | | |
| **17.2.2 18 months** | | | | | |
| Zycinska 2009 | 12/16 | 8/15 | | 100% | 1.41[0.81,2.44] |
| **Subtotal (95% CI)** | **16** | **15** | | **100%** | **1.41[0.81,2.44]** |
| Total events: 12 (Antibiotics), 8 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.21(P=0.23) | | | | | |
| **17.2.3 Two years** | | | | | |
| Stegeman 1996 | 31/41 | 23/39 | | 100% | 1.28[0.94,1.76] |
| **Subtotal (95% CI)** | **41** | **39** | | **100%** | **1.28[0.94,1.76]** |
| Total events: 31 (Antibiotics), 23 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.55(P=0.12) | | | | | |



### Analysis 17.3. Comparison 17 Maintenance therapy: co-trimoxazole (antibiotics) versus placebo, Outcome 3 Adverse events.

| Study or subgroup | Antibiotics n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **17.3.1 Anorexia and nausea** | | | | |
| Stegeman 1996 | 4/41 | 0/40 | | 8.79[0.49,158.07] |
| **17.3.2 Rash** | | | | |
| Stegeman 1996 | 2/41 | 0/40 | | 4.88[0.24,98.6] |
| **17.3.3 Interstitial nephritis** | | | | |
| Stegeman 1996 | 1/41 | 0/40 | | 2.93[0.12,69.83] |
| **17.3.4 Asymptomatic hepatotoxic effects** | | | | |
| Stegeman 1996 | 1/41 | 0/40 | | 2.93[0.12,69.83] |
| **17.3.5 Recurrent urinary tract infection** | | | | |
| Stegeman 1996 | 0/41 | 1/40 | | 0.33[0.01,7.76] |
| **17.3.6 Adverse events causing study drug discontinuation** | | | | |
| Stegeman 1996 | 8/41 | 2/40 | | 3.9[0.88,17.26] |

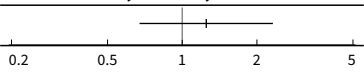



## Comparison 18. Maintenance therapy: cyclosporin versus cyclophosphamide

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

### Analysis 18.1. Comparison 18 Maintenance therapy: cyclosporin versus cyclophosphamide, Outcome 1 Relapse.

| Study or subgroup | CSA n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| Szpirt 2011 | 10/16 | 8/16 | | 1.25[0.67,2.32] |

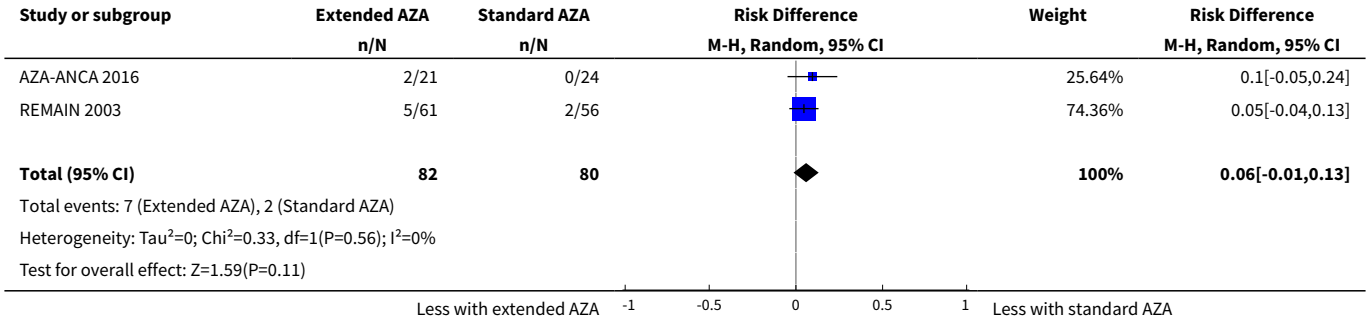



## Comparison 19. Maintenance therapy: extended versus standard azathioprine

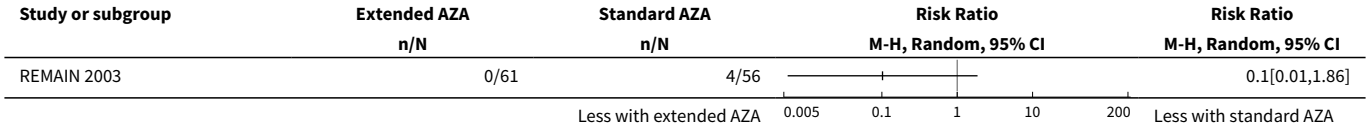
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 2 | 162 | Risk Difference (M-H, Random, 95% CI) | 0.06 [-0.01, 0.13] |
| 2 Dialysis | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Relapse | 2 | 162 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.26, 0.64] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 4.1 Serious infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Total side effects (episodes/patient-months) | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |

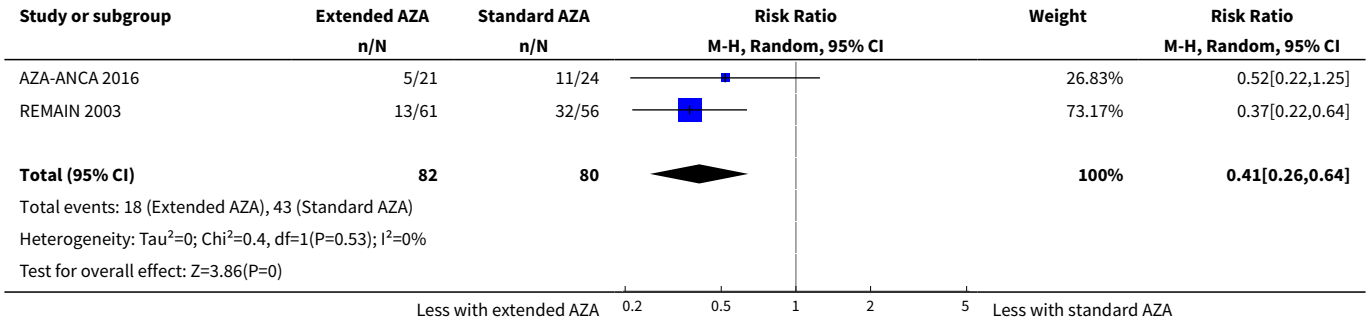
### Analysis 19.1. Comparison 19 Maintenance therapy: extended versus standard azathioprine, Outcome 1 Death.




### Analysis 19.2. Comparison 19 Maintenance therapy: extended versus standard azathioprine, Outcome 2 Dialysis.

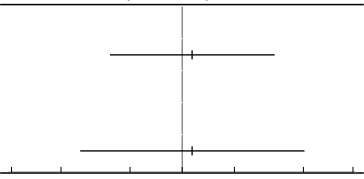



### Analysis 19.3. Comparison 19 Maintenance therapy: extended versus standard azathioprine, Outcome 3 Relapse.



### Analysis 19.4. Comparison 19 Maintenance therapy: extended versus standard azathioprine, Outcome 4 Adverse events.

| Study or subgroup | Extended AZA n/N | Standard AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **19.4.1 Serious infections** | | | | |
| AZA-ANCA 2016 | 5/21 | 5/24 | | 1.14[0.38,3.41] |
| **19.4.2 Leukopenia** | | | | |
| AZA-ANCA 2016 | 3/21 | 3/24 | | 1.14[0.26,5.07] |




### Analysis 19.5. Comparison 19 Maintenance therapy: extended versus standard azathioprine, Outcome 5 Total side effects (episodes/patient-months).

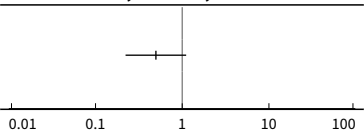
| Study or subgroup | Extended AZA n/N | Standard AZA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| AZA-ANCA 2016 | 27/1008 | 19/1152 | | 1.62[0.91,2.9] |

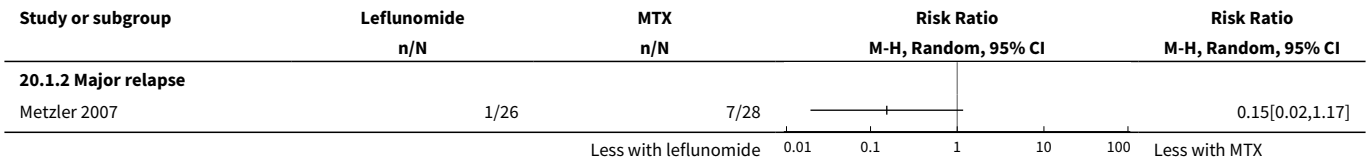

## Comparison 20. Maintenance therapy: leflunomide versus methotrexate

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 1.1 All relapses | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 1.2 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Severe adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

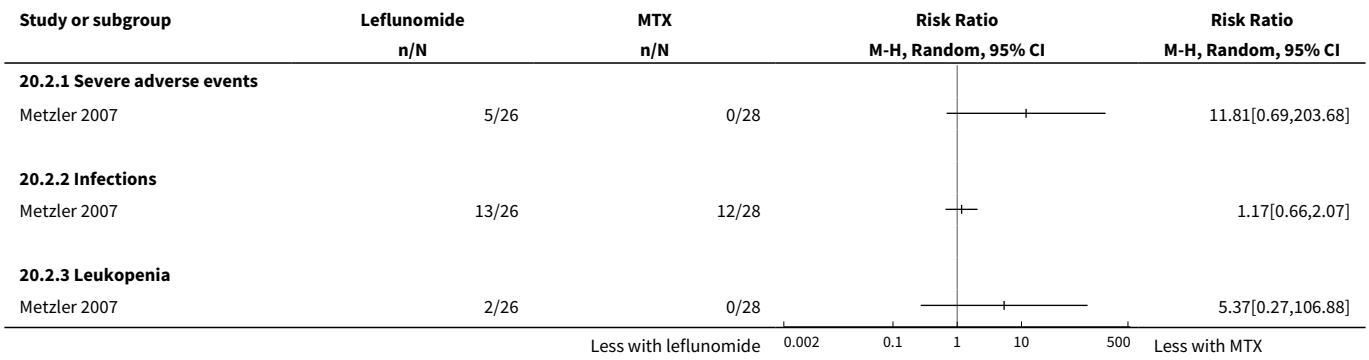
### Analysis 20.1. Comparison 20 Maintenance therapy: leflunomide versus methotrexate, Outcome 1 Relapse.

| Study or subgroup | Leflunomide n/N | MTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **20.1.1 All relapses** | | | | |
| Metzler 2007 | 6/26 | 13/28 | | 0.5[0.22,1.11] |





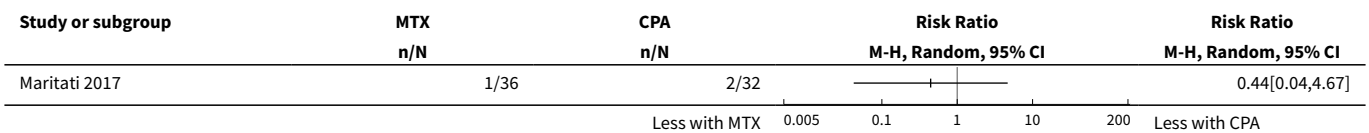

**Analysis 20.2. Comparison 20 Maintenance therapy: leflunomide versus methotrexate, Outcome 2 Adverse events.**




## Comparison 21. Maintenance therapy: methotrexate versus cyclophosphamide

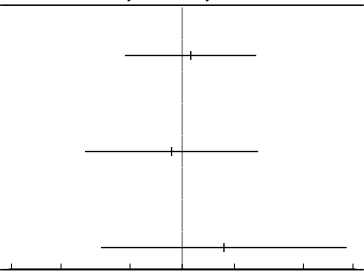
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 All relapses | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.3 Minor relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Serious infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Leukopenia | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

**Analysis 21.1. Comparison 21 Maintenance therapy: methotrexate versus cyclophosphamide, Outcome 1 Death.**



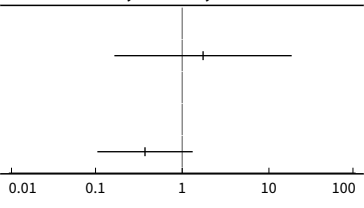
### Analysis 21.2. Comparison 21 Maintenance therapy: methotrexate versus cyclophosphamide, Outcome 2 Relapse.

| Study or subgroup | MTX n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **21.2.1 All relapses** | | | | |
| Maritati 2017 | 9/38 | 7/33 | | 1.12[0.47,2.67] |
| **21.2.2 Major relapse** | | | | |
| Maritati 2017 | 5/38 | 5/33 | | 0.87[0.28,2.74] |
| **21.2.3 Minor relapse** | | | | |
| Maritati 2017 | 4/38 | 2/33 | | 1.74[0.34,8.88] |




### Analysis 21.3. Comparison 21 Maintenance therapy: methotrexate versus cyclophosphamide, Outcome 3 Adverse events.

| Study or subgroup | MTX n/N | CPA n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **21.3.1 Serious infection** | | | | |
| Maritati 2017 | 2/38 | 1/33 | | 1.74[0.16,18.3] |
| **21.3.2 Leukopenia** | | | | |
| Maritati 2017 | 3/38 | 7/33 | | 0.37[0.1,1.32] |

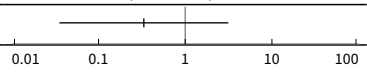



### Comparison 22. Maintenance therapy: tailored versus fixed rituximab

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Major relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3.1 Severe adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Serious infections | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

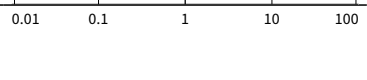
### Analysis 22.1. Comparison 22 Maintenance therapy: tailored versus fixed rituximab, Outcome 1 Death.

| Study or subgroup | Tailored RTX n/N | Fixed RTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| MAINRITSAN 2 2018 | 1/81 | 3/81 | | 0.33[0.04,3.14] |




### Analysis 22.2. Comparison 22 Maintenance therapy: tailored versus fixed rituximab, Outcome 2 Relapse.

| Study or subgroup | Tailored RTX n/N | Fixed RTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **22.2.1 Major relapse** | | | | |
| MAINRITSAN 2 2018 | 6/81 | 3/81 | | 2[0.52,7.72] |




### Analysis 22.3. Comparison 22 Maintenance therapy: tailored versus fixed rituximab, Outcome 3 Adverse events.

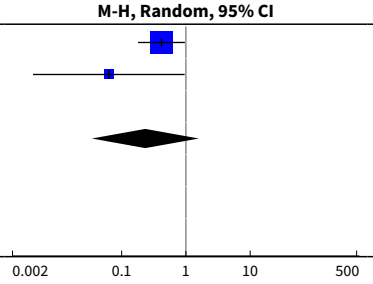
| Study or subgroup | Tailored RTX n/N | Fixed RTX n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **22.3.1 Severe adverse events** | | | | |
| MAINRITSAN 2 2018 | 26/81 | 31/81 | | 0.84[0.55,1.28] |
| **22.3.2 Serious infections** | | | | |
| MAINRITSAN 2 2018 | 18/81 | 18/81 | | 1[0.56,1.78] |


## Comparison 23. Maintenance therapy: pre-emptive therapy for relapse

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Relapse | 2 | 60 | Risk Ratio (M-H, Random, 95% CI) | 0.23 [0.03, 1.59] |

### Analysis 23.1. Comparison 23 Maintenance therapy: pre-emptive therapy for relapse, Outcome 1 Relapse.

| Study or subgroup | Pre-emptive n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Boomsma 2003 | 5/20 | 12/20 | | 69.29% | 0.42[0.18,0.96] |
| Tervaert 1990 | 0/9 | 9/11 | | 30.71% | 0.06[0,0.96] |
| **Total (95% CI)** | **29** | **31** | | **100%** | **0.23[0.03,1.59]** |
| Total events: 5 (Pre-emptive), 21 (Control) | | | | | |
| Heterogeneity: $Tau^2$=1.2; $Chi^2$=2.14, df=1(P=0.14); $I^2$=53.28% | | | | | |
| Test for overall effect: Z=1.49(P=0.14) | | | | | |

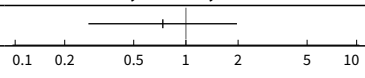


### Comparison 24. Maintenance therapy: belimumab versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Relapse | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 2 Adverse events | 1 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 2.1 Any adverse event | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Infection | 1 | | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

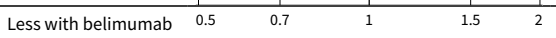
### Analysis 24.1. Comparison 24 Maintenance therapy: belimumab versus placebo, Outcome 1 Relapse.

| Study or subgroup | Belimumab n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| BREVAS 2019 | 6/53 | 8/52 | | 0% | 0.74[0.27,1.97] |




### Analysis 24.2. Comparison 24 Maintenance therapy: belimumab versus placebo, Outcome 2 Adverse events.

| Study or subgroup | Belimumab n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|
| **24.2.1 Any adverse event** | | | | |
| BREVAS 2019 | 49/53 | 43/52 | | 1.12[0.97,1.29] |
| **24.2.2 Infection** | | | | |
| BREVAS 2019 | 30/53 | 30/52 | | 0.98[0.7,1.37] |




## APPENDICES

### Appendix 1. Electronic search strategies

| Database | Search terms |
|---|---|
| CENTRAL | 1. wegener*<br>2. (systemic near/3 vasculitis):ti,ab,kw (Word variations have been searched)<br>3. ((renal or kidney*) and vasculitis):ti,ab,kw (Word variations have been searched)<br>4. rapidly progressive glomeruloneph*:ti,ab,kw (Word variations have been searched)<br>5. glomerular* and necrosis:ti,ab,kw (Word variations have been searched)<br>6. glomerular* and crescent*:ti,ab,kw (Word variations have been searched) |

*(Continued)*

| | |
|---|---|
| | 7. anti-neutrophil cytoplasmic antibod* or antineutrophil cytoplasmic antibod*:ti,ab,kw (Word variations have been searched)<br>8. anca associated vasculitis:ti,ab,kw (Word variations have been searched)<br>9. {or #1-#8} |
| MEDLINE | 1. exp Vasculitis/<br>2. Antibodies, Antineutrophil Cytoplasmic/<br>3. or/1-2<br>4. ((renal or kidney$) and vasculitis).tw.<br>5. rapidly progressive glomerulonephritis.tw.<br>6. glomerular necrosis.tw.<br>7. (crescent$ and glomerular$).tw.<br>8. (anti-neutrophil cytoplasmic antibod$ or antineutrophil cytoplasmic antibod$).tw.<br>9. anca associated vasculitis.tw.<br>10.granulomatosis with polyangiitis.tw.<br>11.(systemic adj3 vasculitis).tw.<br>12.or/4-10<br>13.3 and 13 |
| EMBASE | 1. wegener's granulomatosis/<br>2. Rapidly progressive glomerulonephritis/<br>3. neutrophil cytoplasmic antibody/<br>4. ANCA associated vasculitis/<br>5. wegener's granulomatosis.tw.<br>6. rapidly progressive glomerulonephritis.tw.<br>7. (anti-neutrophil cytoplasmic antibod$ or antineutrophil cytoplasmic antibod$).tw.<br>8. ((renal or kidney$) and vasculitis).tw.<br>9. glomerular necrosis.tw.<br>10.(crescent$ and glomerular$).tw.<br>11.(systemic adj3 vasculitis).tw.<br>12.anca associated vasculitis.tw.<br>13.or/1-12 |

## Appendix 2. Risk of bias assessment tool

| Potential source of bias | Assessment criteria |
|---|---|
| **Random sequence generation**<br><br>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** | *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; sequential- |

*(Continued)*

| | |
|---|---|
| Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment | ly 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**<br><br>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**<br><br>Detection bias due to knowledge of the allocated interventions by outcome assessors. | *Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |
| | *High risk of bias:* No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. |
| | *Unclear:* Insufficient information to permit judgement |
| **Incomplete outcome data**<br><br>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**<br><br>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 |

(Continued)

| | |
|---|---|
| | 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**<br><br>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. |

## Appendix 3. GRADE approach: rating the certainty of the evidence

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome (GRADE 2008; GRADE 2011; Higgins 2011). The GRADE system uses the following criteria for assigning the grade of evidence.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

Reasons for decreasing grade are due to:

- Serious (–1) or very serious (–2) limitation to study quality;
- Important inconsistency (–1);
- Some (–1) or major (–2) uncertainty about directness;
- Imprecise or sparse data (–1);
- High probability of reporting bias (–1).

## Appendix 4. Study criteria - plasma exchange

| Study ID | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Cole 1992 | RPGN of undefined aetiology (idiopathic or post-infectious disease) with specific pathologic criteria; adults (16 to 75 years); normal sized kidneys SCr > 170 µmol/L, increasing by 44 µmol/week or both; no evidence of systemic disease or anti-GBM antibody-induced disease; renal biopsy within 5 days of study entry | Cellular crescents in < 50% non-obsolescent glomeruli; evidence of serious infection or active ulcer disease |
| Glockner 1988 | RPGN with >70% crescents on kidney biopsy; CrCl < 50 mL/min; urine output >200 mL/24 h | Anti-GBM disease; life threatening conditions; contraindications to immunosuppression; previous treatment with AZA or CPA for > 14 days |
| Mauri 1985 | Histologically proven crescentic GN and rapidly progressive kidney impairment | < 60% glomerular involvement, primary glomerulopathies, transplanted kidneys, SLE, HSP |

(Continued)

| | | |
|---|---|---|
| MEPEX 2007 | Biopsy-proven ANCA-associated necrotizing GN with AKI (SCr > 500 µmol/L) | Aged < 18 years or > 80 years; inadequate contraception; pregnancy; previous malignancy; hepatitis B antigenaemia or hepatitis C antibody or HIV infection; other multisystem autoimmune disease; circulating anti-GBM antibody or linear staining of GBM on histology; life-threatening non-renal manifestations of vasculitis; dialysis for > 2 weeks before entry; Cr > 200 µM more than 1 year before entry; > 2 weeks treatment with CPA or AZA; > 500 mg of IV MP; PE within the preceding year; > 3 months treatment with oral prednisolone; allergy to study medications |
| PEXIVAS 2013 | New or previous clinical diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis consistent with the Chapel-Hill consensus definitions AND positive test for proteinase 3-ANCA or myeloperoxidase-ANCA AND severe vasculitis defined by at least one of the following:<br><br>Renal involvement with both: renal biopsy demonstrating focal necrotizing glomerulonephritis or active urine sediment characterized by glomerular haematuria or red cell casts and proteinuria AND eGFR <50 mL/min/1.73 $m^2$. Pulmonary haemorrhage due to active vasculitis defined by a compatible chest X-ray or CT scan (diffuse pulmonary infiltrates) AND the absence of an alternative explanation for all pulmonary infiltrates (e.g. volume overload or pulmonary infection) AND At least one of the following: evidence of alveolar haemorrhage on bronchoscopic examination or increasingly bloody returns with bronchoalveolar lavage; observed haemoptysis.<br><br>Unexplained anaemia (< 10 g/dL) or documented drop in Hb >1 g/dL); increased diffusing capacity of carbon dioxide | Diagnosis of vasculitis other than granulomatosis with polyangiitis or microscopic polyangiitis; positive anti-glomerular basement membrane antibody test or renal biopsy demonstrating linear glomerular immunoglobulin deposition; receipt of dialysis for > 21 days immediately prior to randomisation or prior renal transplant; aged < 15 years; pregnancy; inability or unwillingness to comply with birth control/abstinence; treatment with > 1 IV dose of CPA and/or > 14 days of oral CPA and/or > 14 days of prednisone/prednisolone (> 30 mg/day) and/or >1 dose of RTX within the 28 days immediately prior to randomisation; a comorbidity that, in the opinion of the investigator, precludes the use of CPA, glucocorticoids, or PE or absolutely mandates the use of PE |
| Pusey 1991 | Focal necrotizing GN with crescents (WG, systemic vasculitis, polyarteritis, idiopathic RPGN) | Anti-GBM disease; SLE; HSP; chronic GN; previously treated with IV MP, oral CPA or PE |
| Rifle 1980 | New onset RPGN with > 50% glomerular crescents | Goodpasture's syndrome; IgA nephropathies; SLE; systemic disease |
| Szpirt 2011 | All patients with a new diagnosis of WG who were c-ANCA or PR3-ANCA positive; clinical manifestations as defined by Fauci 1973 from at least 2 organ systems, histology proven WG and positive ANCE by IIF and ELISA; all patients fulfilled the ACR 1990 classification for WG | Not reported |
| Zauner 2002 | Patients with a clinical picture of RPGN and Couser Type II or III (immune deposits or pauci-immune respectively) | Couser Type I GN (linear GBM Ab staining on biopsy), previous immunosuppression or PE |

Footnotes: ACR - albumin creatinine ration; AKI - acute kidney injury; ANCA - anti-neutrophil cytoplasmic antibody; anti-GBM - anti-glomerular basement membrane; AZA - azathioprine; CPA - cyclophosphamide; Cr - creatinine; CrCl - creatinine clearance; GN - glomerulonephritis; HSP - Henoch-Schonlein Purpura; IV - intravenous; MP - methylprednisolone; PE - plasma exchange; PR3 -

proteinase-3; RPGN - rapidly progressive glomerulonephritis; SCr - serum creatinine; SLE - systemic lupus erythematosus; WG - Wegener's granulomatosis

## Appendix 5. Treatment regimens and study outcomes - plasma exchange

| Study ID | Treatment | Control | Study outcomes |
|---|---|---|---|
| Cole 1992 | Immunosuppression as for control group<br><br>PE: at least 10 PE treatments within 16 days of study entry; 1 plasma volume with complete replacement using 5% albumin + crystalloid | Immunosuppression<br><br>IV MP: 10 mg/kg/day for 3 days followed by prednisone 1.4 mg/kg/day for next 4 days and then tapered to 1 mg/kg/day over 2 weeks; 0.35 mg/kg/day at 1 month and 025 mg/kg/day at 2 months<br><br>AZA: 1.5 to 3.0 mg/kg/day with dose adjustment as necessary to ensure neutrophil count of ≥ 2.0 x $10^9$/L | Kidney pathology<br><br>Patients on dialysis at randomisation: dialysis at 1, 3, 6, 12 months<br><br>Kidney function in patients not on dialysis: 1, 3, 6, 12 months<br><br>Change in SCr<br><br>Adverse events (serious infections, gastrointestinal bleeding)<br><br>Death |
| Glockner 1988 | PE: 9 x 50 mL/kg over 4 weeks replaced with 3% to 5% albumin solution<br><br>Immunosuppression as for control group | Immunosuppression<br><br>• CPA (3 mg/kg/day) + AZA (1 mg/kg/day) for 1 week<br>• AZA (2 mg/kg/day)<br>• MP (1.5 mg/kg/day) for 14 days reducing in 4 mg/day steps to maintenance 8 mg/day<br>• Patients with WG (2) did not receive AZA, only CPA (3 mg/kg/day) for entire study period | Death at 6 months<br><br>Dialysis at 6 months<br>SCr at 4 weeks, 8 weeks and 6 months<br>Adverse events including serious infections, GI haemorrhage and anaphylaxis |
| Mauri 1985 | CPA and prednisolone as for control group<br><br>PE alternate days for 6 treatments<br><br>• Exchanges of at least 3.5 L replaced with 3.5% albumin and 2 units FFP | CPA: 2 mg/kg/day<br><br>• Dose reduced to 0.5 mg/kg/day after 2 months then stopped after month 4<br><br>Prednisolone: 1 mg/kg/day<br><br>• Dose reduced to half after 8 weeks; prednisolone dose tapered progressively | Death<br>Dialysis post treatment, at 3 months and 12 months after treatment<br>SCr after treatment and 6 months later |
| MEPEX 2007 | Immunosuppression as for the control group<br><br>PE: 7 x 60 mL/kg in first 2 weeks after diagnosis | Immunosuppression<br><br>• IV MP: 3 pulses of 1000 mg followed by oral CPA and a tapering regimen of prednisolone | Death at 3 and 12 months<br>Dialysis at 3 and 12 months<br>Side effects<br>SCr at 12 months |
| PEXIVAS 2013 | Treatment group 1 (a, b)<br>Adjunctive PE: 7 exchanges over 14 days 60 mL/kg<br><br>Treatment group 2 (a, b)<br>No plasma exchange | Treatment group 1a, 2a<br>Reduced dose prednisolone<br><br>Treatment group 1b, 2b<br>Full dose prednisolone | Time to the composite of death from any cause and ESKD<br><br>Death<br><br>Dialysis |

(Continued)

| | | | |
|---|---|---|---|
| | | | Quality of life<br>Serious infections<br>Serious adverse events<br>Sustained remission |
| Pusey 1991 | Induction/maintenance therapy as for control group<br>PE: 5 x 4 L exchanges of 5% albumin (plasma protein fraction) within first week. Two units of fresh frozen plasma were given at end of exchange. Total number of exchanges determined by clinical response | Induction therapy, 8 weeks of:<br>• 60 mg/day prednisolone, reducing by 15 mg at weekly intervals to 30 mg/day, then 5 mg at weekly intervals to 20 mg/day and then more slowly as clinically indicated<br>• CPA: 3 mg/kg/day or 2 mg/kg/day for those over 55 years<br>• AZA: 1 mg/kg/day or no AZA for those over 55 years<br>Maintenance therapy<br>• CPA stopped after 8 weeks in those with remission and AZA increased to 2-3 mg/kg/day, together with tapering doses of prednisolone | Improvement (fall in SCr > 25% or rise in CrCl > 25%; recovery of kidney function in those initially on dialysis)<br>SCr<br>Dialysis<br>Death<br>Adverse events |
| Rifle 1980 | Immunosuppression as per control group<br>PE: 5 sessions during 5 successive days, then 3 sessions/week until 15 days after SCr reached a plateau<br>• Treatment could not exceed 2 months<br>• 150% plasma volume was exchanged for albumin and saline solution at each session | Immunosuppression<br>• IV pulse MP: 15 mg/kg/day for 3 days, tapered to 15 mg/day for 3 days, then 3 new pulses, then 15 mg/day for 7 weeks<br>CPA: 2 to 3 mg/kg/day for 2 months<br>Calcium heparinate 9 days after kidney biopsy for the duration of the study | Dialysis: 2, 6 12, 24 months<br>CrCl: 2, 6 and 12 months.<br>Recovery (off dialysis) according to initial SCr level<br>Recovery (off dialysis) according to initial % of crescents<br>Death<br>Circulating immune complexes<br>Pathology changes<br>Adverse events (septicaemia) |
| Szpirt 2011 | Immunosuppression as for control group<br>PE: 6 sessions of 4L PE with 3% albumin in Ringer's lactate solution replacement on alternate days. Performed using Gambro F-1000 filters. If c-ANCA titres > 320 or PR3-ANCA > 25 U/mL on ELISA after 6 sessions the additional 3 to 6 sessions performed | Immunosuppression<br>• Prednisolone: 80 mg/day for 3 weeks tapered to 5 mg then stopped after 9 months<br>• CPA: 1.5 mg/kg/day for 3 months | Kidney outcomes: progression, remission and dialysis at 1, 3 and 12 months<br>• Progression defined as unchanged Cr if initial Cr > 300 µM or 15% increase if initial Cr < 300 µM.<br>• Remission defined as 15% fall in Cr from inclusion<br>Relapse: clinical symptoms of active disease and at least 2 of: a 2-fold increase in ANCA titre, 20% increase in Cr, increase in proteinuria and increase in ESR or CRP |

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| | | | Kidney and patient survival to 5 years |
| Zauner 2002 | Immunosuppression as for control group<br><br>PE: 40 mL/kg with FFP replacement daily for 3 exchanges, continued if no response to a maximum of 12 exchanges; mean number of PE = 6 | Immunosuppression<br>• IV MP: 500 mg/day for 3 days. Prednisolone 80, 60 then 40 mg/day for a week each. Dose tapered by 5 mg/day each week to maintenance dose of 10 mg/day<br>• CPA: 2 mg/kg/day oral from day 1; dose reduced for side effects. Continued for 6 months after remission | Death<br><br>ESKD<br><br>SCr<br><br>Adverse events |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; c-ANCA - cytoplasmic-ANCA; AZA - azathioprine; CPA - cyclophosphamide; Cr - creatinine; CrCl - creatinine clearance; CRP - C-reactive protein; ESKD - end-stage kidney disease; ESR - erythrocyte sedimentation rate; IV - intravenous; MP - methylprednisolone; PE - plasma exchange; PR3 - proteinase-3; SCr - serum creatinine; WG - Wegener's granulomatosis

## Appendix 6. Study criteria - pulse versus continuous cyclophosphamide

| Study ID | Inclusion criteria | Exclusion criteria |
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| Adu 1997 | Patients 15 to 70 years with new-onset systemic necrotizing vasculitis. WG, classical PAN and MPA diagnosed by histological or radiological evidence | Not reported |
| CYCLOPS 2004 | Newly diagnosed WG, MPA, or renal-limited MPA, kidney involvement: at least one of: SCr > 150 µmol/L and < 500 µmol/L, biopsy evidence of necrotizing GN, erythrocyte casts, or haematuria and proteinuria, confirmatory histology or ANCA positivity | Other multisystem autoimmune disease; hepatitis B or C virus or HIV infection/ SCr > 500 µmol/L; previous cancer; pregnancy; < 18 years or > 80 years |
| Guillevin 1997 | Aged > 15 years; new diagnosis of systemic WG diagnosed clinically based on the presence of multiorgan involvement; monovisceral involvement representing a potential risk or severe morbidity of fatality; histopathologic characterization of necrotizing granulomatosis vasculitis or evidence of either granulomatous inflammation and vasculitis or segmental necrotizing GN | Not reported |
| Haubitz 1998 | New diagnoses of WG and MPA and renal involvement; biopsy performed | < 18 years; pregnancy; HIV; malignancy; SCr > 200 µmol/L more than 1 year before presentation; cytotoxic drug therapy for > 1 week before start of study; HD for > 10 days before start of study |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; GN - glomerulonephritis; HD - haemodialysis; HIV - human immunodeficiency virus; MPA - microscopic polyangiitis; PAN - polyarteritis nodosa; SCr - serum creatinine; WG - Wegener's granulomatosis

## Appendix 7. Treatment regimens and study outcomes - pulse versus continuous cyclophosphamide

| Study ID | Treatment | Control | Study outcomes |
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| Adu 1997 | PCYP<br>• Intermittent pulses of CPA and<br>• CPA and prednisolone were given IV at 0, 2 and 4 weeks<br>• The same dose was then given as oral pulses over a 3-day period. The interval between pulses was gradually increased. | CCAZP<br>• Continuous CPA, prednisolone and AZA<br>• Initial treatment: 0.85 mg/kg prednisolone then tapering according to a predefined schedule for 72 weeks<br>• CPA given until a clinical decision that remission had been achieved at which point CPA was stopped and AZA commenced at 1.5 mg/kg/day | Complete and partial remission<br>Relapse<br>Adverse events<br>Treatment failure<br>Chronic dialysis |
| CYCLOPS 2004 | Immunosuppression as for control group<br>Pulse CPA<br>• 3 IV pulses of CPA (15 mg/kg) 2 weeks apart followed by 3 weekly pulses (15 mg/kg (IV) or 5 mg/kg orally for 3 days) until remission then for another 3 months. Max dose 1.2 g. Reductions for age > 60 years and SCr > 300 µM and for previous low leukocyte nadir | Immunosuppression<br>• AZA: 2 mg/kg/day orally after induction therapy until month 18<br>• Prednisolone: 1 mg/kg orally tapered to 12.5 mg/day at the end of month 3 and 5 mg at end of study<br>Continuous CPA<br>• Oral CPA: 2 mg/kg/day to remission then 1.5 mg/kg for further 3 months. Max oral dose 200 mg Reductions for age > 60 years and leukopenia | Time to remission<br>Proportion of patients who achieved remission at 6 and 9 months<br>Proportion with major and minor relapses<br>Death<br>Change in kidney function<br>Adverse events<br>Cumulative dose of CPA and prednisolone. calculated at 3, 6, 9, 12, 15 and 18 months |
| Guillevin 1997 | Initial regimen as for control group<br>IV pulse CPA<br>• Mean dose 0.7 g/m$^2$ adjusted for neutrophil count and kidney function, administered every 3 weeks until complete remission and 1 year thereafter. Then every 4 weeks for 4 months, every 5 weeks for 4 months and every 6 weeks until discontinuation after 2 years if treatment. Adjusted up or down based on neutrophil count | Initial regimen<br>• IV MP: 15 mg/kg/day for 3 days then oral prednisolone 1 mg/kg/day. One pulse of IV CPA was administered (0.7 g/m$^2$) the day after the last IV MP and concurrently with the 1st day of oral prednisolone. Oral prednisolone (1 mg/kg/day) for 6 weeks. If complete remission was achieved daily dose was tapered by 2.5 mg every 10 days until a level equivalent to half the original dose was reached. This was maintained for 3 weeks and then further decreased by 2.5 mg every 10 days to 20 mg/day. More gradual tapering for doses < 20 mg/day with decrease of 1mg/day every 2 weeks to 10 mg/day and then 1mg/month until discontinuation<br>Oral CPA<br>• 2 mg/kg/day on day 10 after initial CPA pulse, after neutrophil nadir had been reached. 1 year after complete remission, oral CPA was tapered by 25% every 4 months until discontinuation. Dose adjusted up or down based on neutrophil count | Treatment failure<br>Complete remission<br>Partial remission<br>Relapse<br>Death<br>Side effects |
| Haubitz 1998 | Steroid regime as for control group<br>IV pulse CPA | Steroid regime<br>• Days 1 to 3, 0.5 g IV MP. Day 4 to 14 1 mg/kg/day oral prednisolone. Day 15 onwards tapering of steroids with a reduction of 10 mg/week. When | Complete remission<br>Partial remission<br>Relapse<br>Serious infection |

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| | • 0.75 g/m$^2$ every 4th week. If CrCl < 30 mL/min, initial dosage was 0.5 g/m$^2$ and increased to 0.75 g/m$^2$ provided leucocyte counts remained > 3000/mL<br>* CPA dose adjusted to the peripheral leucocyte count and dose reduced in increments of 0.125 g/m$^2$. If leucocyte count < 2500/mL dose was reduced by 0.25 g/m$^2$<br><br>Antiemetic drugs were given immediately before and 8 h after treatment. At least 3 L of fluid was administered on day of CPA treatment | a dosage or 30 mg/day was reached, tapering changed to 5 mg/week, at 15 mg/day tapering changed to 2.5 mg/week. This tapering protocol was not mandatory, however dosage had to be ≤ 12.5 mg/day at 6 months<br><br>Oral daily CPA<br><br>• 2 mg/kg/day. If CrCl < 30 mL/min, initial dosage started at 1.5 mg/kg/day and increase to 2 mg/kg/day after 2 weeks provided leucocyte counts were > 3000/mL<br>* CPA dose reduced in step < 1500/mL drug was withheld until increased to 2500/mL | ESR, CRP, ANCA, Hb, WBC platelet count, SCr, urea, CrCl, quantitative proteinuria, urinary microscopy, alanine aminotransferase, aspartate aminotransferase, gonadal toxicity (FSH) |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; AZA - azathioprine; CCAZP - continuous CPA, then AZA and prednisolone; CPA - cyclophosphamide; Hb - haemoglobin; IV - intravenous; MP - methylprednisolone; PCYP - pulse cyclophosphamide and prednisolone; SCr - serum creatinine

## Appendix 8. Study criteria - other remission induction studies

| Study ID | Inclusion criteria | Exclusion criteria |
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| BREVAS 2019 | Eligible patients were ages ≥ 18 years, had a clinical diagnosis of GPA or MPA according to the 2012 Chapel Hill Consensus Conference definitions, and tested positive (current or historical) for either PR3-ANCAs or MPO-ANCAs. Patients must have experienced either new-onset or relapsing GPA or MPA in the 26 weeks prior to day 0, that required treatment under one of the following remission induction regimens: a single course of rituximab (375 mg/m$^2$ /week for 4 weeks) plus high-dose glucocorticoids; 2 doses of IV rituximab (1 gm), separated by a 2-week interval, plus high-dose glucocorticoids; oral cyclophosphamide (2 mg/kg/day); or pulses of IV cyclophosphamide (15 mg/kg), administered 2 weeks apart for 3 doses followed by further pulses every 3 weeks, plus high-dose glucocorticoids. Additionally, patients had to be in remission on day 0 (with remission defined as a BVAS score; of 0) and receiving glucocorticoids (presented as prednisone-equivalent doses) at ≤ 10 mg/day (on 2 consecutive measurements ≥ 14 days apart, and 6–26 weeks after the first dose of induction therapy) | Coexistence of another autoimmune disease; any known intolerance or contraindications to azathioprine and methotrexate; receipt of any B cell–targeted therapy (excluding rituximab) at any time, or any other investigational agent within 60 days of day 0 or 5 half-lives of the agent (whichever was longest); any acute or chronic infections requiring hospitalisation (within 60 days of day 0) and/or receipt of parenteral antibacterial drugs, antiviral drugs, antifungal drugs, or antiparasitic drugs (within 60 days of day 0); and serologic evidence of infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus |
| CLEAR 2013 | ≥ 18 years with newly diagnosed or relapsing granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis according to the | Severe disease (including RPGN, alveolar haemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system in- |

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| | Chapel Hill Consensus Conference definitions 1) required CPA treatment (steps 1 and 2), CPA or rituximab (step 3), were PR3 or MPO-ANCA positive or ANCA positive by indirect immunofluorescence, had an eGFR ≥ 20 mL/min/1.73 m2, biopsy-proven renal vasculitis or haematuria (> 30 RBC/HPF or greater than 2+ by urine dipstick) plus albuminuria (at least 0.5 g/g creatinine) for steps 1 and 2, or had at least one major or three non-major items, or at least two renal items on the BVAS version 3 2 for step 3. | volvement); any other autoimmune disease, coagulopathy or bleeding disorder; received CPA within 12 weeks, rituximab within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count > 0.01 x 109/L); cumulative dose of IV glucocorticoids > 3 g within 12 weeks, or oral glucocorticoids > 10 mg/day prednisone equivalent for more than 6 weeks prior to screening. |
| CORTAGE 2015 | Patients with newly diagnosed PAN not related to hepatitis B virus infection, EGPA, GPA, or MPA; 2) to satisfy the 1990 American College of Rheumatology criteria and/or 1994 Chapel Hill nomenclature definitions (10–13); 3) to be in or after the year of their 65th birthday at the time of SNV diagnosis; and 4) to provide written informed consent. Patients could have started corticosteroids, but for no more than 1 month prior to enrolment, and could not have started CYC and/or received any other immunosuppressant before inclusion | Not reported |
| Furuta 1998 | Biopsy-proven RPGN | Not reported |
| Guillevin 2003 | New diagnosis of PAN or MPA with at least one of five factors: Cr > 1.58 mg/dL (140 µM), proteinuria > 1 g/day, severe GI involvement, cardiomyopathy, CNS involvement | Not reported |
| Han 2011b | Patients with MPA with moderate to severe renal involvement (MPA by Chapel Hill Nomenclature) | Severe lung haemorrhage (haemoptysis > 300 mL/24 h or hypoxaemia); CNS involvement; other life-threatening situations; cytotoxic drug in the previous 6 months; severe infection in the last month; active hepatitis or abnormal liver function; pregnancy; malignancies; > 70 years |
| Hu 2008b | Newly diagnosed active ANCA-associated vasculitis; > 18 years of age with kidney involvement with SCr < 500 µM; ANCA positive or ANCA negative with confirmatory kidney biopsy | Cytotoxic drug treatment in 6 months prior; HBV, HCV, HIV or active CMV viral infection; acquired immune deficiency; severe kidney failure with Cr > 500 µM or on KRT; life-threatening organ manifestations (lung haemorrhage or CNS involvement); active TB; liver dysfunction; pregnancy or inadequate contraception if female; < 18 years or > 65 years |
| Jayne 2000 | Prior diagnosis of WG or MPA; ANCA positivity at diagnosis; active vasculitis with a requirement for further therapy; at least 2 months treatment with prednisolone and CPA or AZA; ≥ 18 years | IVIg in previous 3 months; history of anaphylaxis to matched blood products; selective IgA deficiency; RPGN (20% rise in SCr in 2 weeks) or pulmonary haemorrhage |
| MYCYC 2012 | New diagnosis of ANCA-associated systemic vasculitis (WG or MPA) (within the previous six months); active disease (defined by at least one major or three minor BVAS 2003 items); ANCA positivity (c-ANCA and PR3-ANCA or p-ANCA and MPO-ANCA) or histology confirming active vasculitis from any organ. | Previous treatment with MMF (more than two weeks ever), CPA (more than two weeks daily oral or more than 1 pulse of IV CPA 15 mg/kg), rituximab or high dose IVIg within the last 12 months; active infection (including HBV, HCV, HIV and TB); known hypersensitivity to MMF, AZA or CPA; cancer or an individual history of cancer (other than resected basal cell skin carcinoma); pregnant, breast feeding, or at risk of preg- |

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| | | nancy and not using a medically acceptable form of contraception; any condition judged by the investigator that would cause the study to be detrimental to the patient; any other multi-system autoimmune disease including Churg Strauss angiitis, SLE, anti-GBM disease and cryoglobulinaemia; active serious digestive system disease (e.g. inflammatory bowel disease); imminently life threatening vasculitis (diffuse alveolar haemorrhage, intestinal perforation or major haemorrhage, cerebral vasculitis and cardiac vasculitis); RPGN and declining kidney function; eGFR fall > 20% in previous 2 weeks; GFR < 15 mL/min at entry or on dialysis. |
| NORAM 2005 | New diagnosis of WG or MPA in 1 or more organ systems; elevated ESR or CRP or both or ANCA positivity, or a non-renal biopsy demonstrating small vessel vasculitis | Organ or life-threatening vasculitis (severe haemoptysis with bilateral pulmonary infiltrates, cerebral infarction due to vasculitis, rapidly progressive neuropathy, orbital pseudotumour, massive GI bleeding, heart failure due to pericarditis or myocarditis; Cr > 150 µM, urinary red cell casts or proteinuria >1 g/day; skin vasculitis only; another multisystem autoimmune disease; malignancy; hepatitis B or HIV infection; < 18 years or >75 years |
| RAVE 2010 | Weight ≥ 88 lbs (40 kg); diagnosis of WG or MPA; newly diagnosed patient of WG or MPA OR must be experiencing a disease flare characterized by: (a) active disease with a BVAS for WG of ≥ 3 that would normally require treatment with CPA; OR (b) disease severe enough to require treatment with CPA; OR (c) must be positive for either PR3-ANCA or MPO-ANCA at the screening; willing to use acceptable forms of contraception for the duration of the study and for up to 1 year after stopping study medications; willing to report pregnancies (female participants or male participants' partners) occurring at any time during the study and for up to 1 year after stopping study medications; parent or guardian willing to provide informed consent, if applicable | Diagnosis of Churg-Strauss Syndrome; limited disease that would not normally be treated with CPA; requires mechanical ventilation because of alveolar haemorrhage; history of severe allergic reactions to human or chimeric monoclonal antibodies; active systemic infection; deep-space infection, such as osteomyelitis, septic arthritis, or pneumonia complicated by pleural cavity or lung abscess, within 6 months prior to study entry; history of or current HBV or HCV; HIV; acute or chronic liver disease that, in the opinion of the investigator, may interfere with the study; history of or active cancer diagnosed within the last 5 years; history of anti-GBM disease; other uncontrolled disease, including drug and alcohol abuse; pregnancy or breastfeeding |
| RITUXVAS 2010 | New diagnosis of ANCA-associated vasculitis, ANCA positivity, and kidney involvement, as evidenced by necrotizing GN on biopsy or red-cell casts or haematuria (30 red cells per high-power field) on urinalysis | Previous CPA (> 2 weeks of an oral or IV pulse CPA regimen); co-existence of another multisystem autoimmune disease, e.g. SLE, Churg Strauss syndrome, HSP, rheumatoid vasculitis, essential mixed cryoglobulinaemia, anti-GBM antibody positivity; Hepatitis B antigen positive or hepatitis C antibody positive; known HIV positive; previous malignancy (usually exclude unless agreed with trial co-ordinator; pregnancy, breast feeding or inadequate contraception; allergy to a study medication; live vaccine within last four weeks |
| Stegmayr 1999 | Goodpasture's disease; ANCA positive vasculitis; idiopathic RPGN | HIV; hepatitis A, HBV, HCV, severe cardiac failure; malignancy; septicaemia |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; anti-GBM - anti-glomerular basement membrane; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; CMV - cytomegalovirus; CNS - central nervous system; CPA - cyclophosphamide; Cr - creatinine;

eGFR - estimated glomerular filtration rate; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HSP - Henoch-Schonlein Purpura; IV - intravenous; IVIg - IV immunoglobulin; KRT - kidney replacement therapy; MMF - mycophenolate mofetil; MPA - microscopic polyangiitis; MPO - myeloperoxidase; p-ANCA - perinuclear-ANCA; PR3 - proteinase-3; RPGN - rapidly progressive glomerulonephritis; SCr - serum creatinine; SLE - systemic lupus erythematosus; TB - tuberculosis; WG - Wegener's granulomatosis

## Appendix 9. Treatment regimens and study outcomes - other remission induction studies

| Study ID | Treatment | Control | Study Outcomes |
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| BREVAS 2019 | Belimumab (IV): 10 mg/kg<br><br>Co-interventions: azathioprine (2 mg/kg/day) and low-dose oral glucocorticoids (≤ 10 mg/day) | Placebo (IV)<br><br>Co-interventions: azathioprine (2 mg/kg/day) and low-dose oral glucocorticoids (≤ 10 mg/day) | Relapse (BVAR score)<br><br>Infection<br><br>Adverse events |
| CLEAR 2013 | Treatment group 1<br>Avacopan: 40 mg/day<br><br>Prednisone: 20 mg/day<br><br>Treatment group 2<br>Avacopan: 30 mg/day<br><br>Prednisone placebo | Prednisone: 60 mg/day<br><br>Avacopan placebo | Proportion of patients with a treatment response at week 12 defined as a BVAS decrease from baseline of at least 50% plus no worsening in any body system<br><br>Proportion of patients with a renal response, defined as an improvement in eGFR calculated using the MDRD equation, haematuria, and albuminuria at week 12<br><br>Proportion of patients with disease remission (BVAS 0); and change from baseline in BVAS, eGFR, UACR, urinary RCC, urinary MCP-1-to-creatinine ratio, vasculitis damage index, SF-36 version 2, EQ-5D-5L, and rescue glucocorticoid use |
| CORTAGE 2015 | Corticosteroids: started at 1 mg/kg then progressively tapered after 3 weeks and stopped at 9 months<br><br>CPA pulses: 500 mg every 2 weeks for first 3 pulses then every 3 weeks until remission<br><br>Patients switched to MTX or AZA (or MMF for those with intolerance to MTX or AZA) | Corticosteroids: started at 1 mg/kg the progressive tapered after 3 weeks until stopped at 26 months<br><br>CPA pulses: 500 mg/m2 for six doses with a further 3 doses for consolidation prior to maintenance therapy | Occurrence of 1 or more serious adverse events defined as potentially life-threatening adverse events, requiring hospitalisation or its prolongation, causing significant disability, or resulting in death.<br><br>Death<br><br>Remission<br><br>Relapse<br><br>Serious adverse event-free survival<br><br>Progression free survival |
| Furuta 1998 | Lymphocytapheresis: 3 x 1 hour sessions on alternate days in each of 3 consecutive weeks<br><br>Prednisolone: 20 mg/day | IV MP: 1 g for 3 consecutive days in each of 3 consecutive weeks<br><br>Prednisolone: 20 mg/day<br><br>CPA: 50 mg/day | SCr 4 weeks post treatment<br>Death |

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| | CPA: 50 mg/day | | |
| Guillevin 2003 | Initial regimen<br>Tapering dose of steroids: 3 daily IV pulses of MP 15 mg/kg. Prednisolone (1 mg/kg/day) for 3 weeks, gradually tapered to stop CPA pulses given at 0, 2 and 4 weeks, then monthly<br><br>Treatment group 1<br>CPA dose: 6 pulses | Treatment group 2<br>CPA dose: 12 pulses | Complete remission<br><br>Death<br><br>Relapse |
| Han 2011b | MMF (oral): 1.0 g/day (1.5 g/day if weight > 70 kg)<br><br>MP (IV): 360 to 500 mg/day for 3 days, then oral prednisone 0.6 to 0.8 mg/kg/day, gradually tapered | CPA (IV): 1.0 g/pulse (0.8G if body weight < 50 kg) monthly<br><br>MP (IV): 360 to 500 mg/day for 3 days, then oral prednisone 0.6 to 0.8 mg/kg/day, gradually tapered | Remission at 6 months<br><br>Kidney function at 6 months<br><br>Adverse events |
| Hu 2008b | IV MP 0.5 g daily for 3 days followed by oral prednisolone at 0.6 to 0.8 mg/kg/day for 4 weeks tapered by 5 mg/week to 10 mg/day<br><br>MMF: 2 g/day (1.5 g if weight < 50 kg) for 6 months | IV MP 0.5 g daily for 3 days followed by oral prednisolone at 0.6 to 0.8 mg/kg/day for 4 weeks tapered by 5 mg/week to 10 mg/day<br><br>IV CPA: 0.75 to 1.0 g/$m^2$ for 6 months, modified depending on WCC nadir | Remission rate at 6 months<br><br>Changes in kidney function<br><br>Side effects |
| Jayne 2000 | CPA and prednisolone for remission induction then AZA for maintenance<br>2 week observation period<br><br>IVIg: 0.4 g/kg/day for 5 days | CPA and prednisolone for remission induction then AZA for maintenance<br>2 week observation period<br><br>Placebo (identical injections) for 5 days | Treatment response<br><br>Fall in BVAS, CRP and ANCA<br><br>Relapse frequency between 3 and 12 months<br><br>Reduction in immunosuppressive drug doses<br><br>Adverse effects |
| MYCYC 2012 | MMF: 2 g/day or maximum tolerated dose between 1 and 2 g/day, for 3 to 6 months until remission (BVAS = 0 for 2 consecutive study assessments), then switch to AZA maintenance regimen<br><br>• For those < 16 years 1200 mg/$m^2$/day, or maximum tolerated dose between 600 and 1200 mg/$m^2$/day<br>• For persistent disease in adults at 4 weeks dose increase up to a maximum of 3 g/day allowed. Dose increase only permitted if 2 g/day is tolerated without moderate/severe side effects. Persistent disease is defined as persistence | CPA: 15 mg/kg at weeks 0, 2 and 4 then pulses every 3 weeks for 3 to 6 months (6 to 10 doses) until remission (BVAS = 0 for 2 consecutive study assessments), then switch to AZA maintenance regimen | Remission at 6 months<br><br>Time to remission (months)<br><br>Adverse events: mild/moderate/severe and infections<br><br>Relapse (relapse rates at 18 months and relapse free survival)<br><br>Cumulative dose of corticosteroids<br><br>Improvement in calculated GFR at 18months<br><br>Cumulative VDI scores<br><br>Change in SF-36 at 12 and 18 months |

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| | (NOT worsening) of major or minor BVAS items present at entry. | | BVAS (AUC) between entry and 18 months<br><br>ANCA status at 6 months |
| NORAM 2005 | MTX: 15 mg/week oral MTX increasing to 2 5mg/week at week 12, continued to month 10 then tapered to stop at month 12 | Oral CPA: group: 2 mg/kg/day (max 150 mg/day) until remission, minimum of 3 months, maximum of 6 months. At remission, dose reduced to 1.5 mg/kg/day continued to month 10 then tapered to stop at month 12. Dose adjusted for age and low white cell count<br><br>Co-interventions (both groups) Oral prednisolone: 1 mg/kg/day tapered to 15 mg/day at 12 weeks and 7.5 mg/day by 6 months, stopped at 12 months | Remission at 6 months<br>Disease relapse<br><br>Adverse effects |
| RAVE 2010 | Rituximab: 375 mg/m$^2$ infusions once weekly for 4 weeks<br><br>CPA placebo daily for 3 to 6 months<br><br>During the remission maintenance phase participants will discontinue CPA placebo and start oral AZA placebo daily until month 18 | Rituximab placebo: infusions once weekly for 4 weeks<br><br>CPA daily for 3 to 6 months<br><br>During the remission maintenance phase, participants will discontinue CPA and start AZA daily until month 18 | Complete remission during the first 6 months after randomisation<br><br>Rate of selected adverse events experienced by participants receiving rituximab versus those receiving conventional therapy |
| RITUXVAS 2010 | Immunosuppression as for control group<br><br>IV Rituximab: 375 mg/m$^2$ IV once a week for 4 weeks<br><br>CPA: 15 mg/kg 2 weeks apart given with the 1st and 3rd rituximab dose | Immunosuppression<br><br>• IV MP: 1 g<br>• Same oral glucocorticoid regimen (1 mg/kg/day initially, with a reduction to 5 mg/day at the end of 6 months<br><br>Remission induction<br><br>• IV CPA: 15 mg/kg for 3 to 6 months (6 to 10 doses total)<br><br>Remission maintenance<br><br>• AZA | Sustained remission<br><br>Severe adverse events<br><br>Response rate at 6 weeks<br><br>Remission at 6 months<br><br>Time to remission<br><br>Relapses (all relapses and major/minor)<br><br>BVAS AUC<br><br>Change in GFR<br><br>Change in SF-36<br><br>Change in VDI<br><br>Severe adverse events at 6 weeks and 6 months<br><br>All adverse events<br><br>Death<br><br>Prednisolone cumulative dose<br><br>CPA cumulative dose |

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| | | | Human anti-chimeric antibody testing<br>Correlation of B cells with disease activity<br>Change in ANCA and disease activity<br>Histopathology predictors of outcome |
| Stegmayr 1999 | Immunosuppression as for control group<br>Immunoadsorption of at least 2 plasma volumes. Median of six sessions | Immunosuppression<br>• Pulse MP and oral or IV CPA 2 mg/kg/day. CPA continued for 8 weeks or longer if ANCA positive<br>PE: 3 in first 5 days of at least 1 plasma volume, 4% albumin as replacement. Median of six sessions | Death at 6 months<br>SCr at 3 and 6 months |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; AUC - area under the curve; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; CPA - cyclophosphamide; CRP - C-reactive protein; GFR - glomerular filtration rate; IV - intravenous; IVIg - IV immunoglobulin; MMF - mycophenolate mofetil; MP - methylprednisolone; PE - plasma exchange; SCr - serum creatinine; VDI - vasculitis damage index; WCC - white cell count

## Appendix 10. Study criteria - maintenance treatment

| Study ID | Inclusion criteria | Exclusion criteria |
|---|---|---|
| AZA-ANCA 2016 | Patients > 18 years with newly diagnosed PR3 ANCA vasculitis recruited between diagnosis and remission. Those found to be cANCA positive at stable remission after 3 months were randomised. The other patients were treated with standard AZA treatment | Intolerance for AZA or inability to give informed consent |
| Boomsma 2003 | Patients with PR3 ANCA-associated vasculitis in remission on ≤ 50 mg daily CPA and ≤ 15 mg daily prednisolone; rise in ANCA titre of more than 75% from previous sample. 100 patients followed; 40 patients developed ANCA rise and were randomised | Not reported |
| CYCAZAREM 2003 | Diagnosis of WG, MPA or RLV. Kidney involvement, other threatened loss of function of vital organ, or both. ANCA positivity. ANCA negative patients enrolled with biopsy evidence of vasculitis | Cytotoxic drug in previous year; other multisystem autoimmune disease; hepatitis B e antigenaemia; hepatitis C; HIV infection; SCr > 500 µmol/L; cancer; pregnancy; aged < 18 years or > 75 years |
| IMPROVE 2003 | Newly diagnosed patients with WG, MPA or RLV; ANCA positivity. ANCA positivity | Any cytotoxic drug within previous year, unless started within one months of entry and according to the protocol design; |

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| | requires PR3-ANCA or a typical c-ANCA pattern by indirect immunofluorescence (IIF), preferably confirmed by anti-PR3 ELISA; MPO-ANCA determined by ELISA requires demonstration of p-ANCA, and p-ANCA by IIF requires confirmation by anti-MPO ELISA; optionally, central review of ANCA serology can be performed; 18 to 75 years | co-existence of another systemic autoimmune disease (e.g. SLE, HBV, HCV, HIV positivity); failure to achieve remission after 6 months of CPA therapy; failure to control progressive disease with induction protocol; malignancy (usually exclude unless agreed with trial co-ordinator); pregnancy or inadequate contraception; < 18y and > 75 years; ESKD unless active extrarenal disease requires treatment (temporal dependency of HD is not an exclusion criterion); inability for informed consent |
| MAINRITSAN 2 2018 | > 18 years old; had newly diagnosed or relapsing GPA or MPA (defined by the Chapel Hill Consensus nomenclature); in complete remission after induction therapy, combining glucocorticoids and cyclophosphamide, rituximab or methotrexate (as decided by each investigator), in accordance with French and international recommendations; Birmingham Vasculitis Activity Score V.3 (BVAS) of 0 (score range: 0–63, with higher scores indicating more active disease) defined complete remission. | Another systemic vasculitis; induction with an agent not recommended; active disease; incapacity for informed consent; non-compliance; allergy to the study medication; pregnancy; breastfeeding; HIV, hepatitis B or C; severe infection declared during the 3 months before randomisation; cancer or malignant blood disease diagnosed during the 5 years preceding vasculitis diagnosis; participation in another clinical research protocol during the 4 weeks before inclusion; any clinical or psychiatric disorder that could expose the patient to a greater risk of an adverse event (AE) or could prevent treatment administration and patient follow-up according to the protocol; severe immunosuppression; administration of live vaccine during the 4 weeks before inclusion; severe chronic obstructive pulmonary diseases (maximum expiratory volume <50% or dyspnoea grade III); chronic heart failure (dyspnoea NYHA III or IV); history of recent acute coronary syndrome unrelated to vasculitis; patients not enrolled in the French national health insurance. |
| MAINRITSAN 2014 | Patients aged 18 to 75 years of age with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after combined treatment with glucocorticoids and pulse CPA; patients had to be ANCA-positive at diagnosis or during the course of their disease; have histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited ANCA-associated vasculitis; or both | Other systemic vasculitis; secondary vasculitis (following neoplastic disease or an infection in particular); induction treatment with a regimen not corresponding to that recommended in France; patient who has not achieved remission; already received a treatment by biological agents (monoclonal antibody); incapacity or refusal to understand or sign the informed consent form; incapacity or refusal to adhere to treatment or perform the follow-up examinations required by the study; non-compliance; allergy, documented hypersensitivity or contraindication to the study medication (CPA, corticosteroids, AZA, RTX); history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies; patients receiving allopurinol cannot be included if the allopurinol must absolutely be maintained; pregnancy, breastfeeding; women of childbearing age must use a reliable method of contraception throughout the duration of immunosuppressive treatment up to 1 year after the last infusion of RTX; infection by HIV, HCV or HBV; progressive, uncontrolled infection requiring a prolonged treatment; severe infection declared during the 3 months before randomisation (CMV, HBV, HHV8, HCV, HIV, TB); progressive cancer or malignant blood disease diagnosed during the 5 years before the diagnosis of vasculitis; patients presenting a systemic disease receiving protocolized treatments (AZA, RTX) which could have unexpected and inappropriate side effects; participation in another clinical research protocol during the 4 weeks before inclusion; any medical or psychiatric disorder which, in the investigator's opinion, may prevent the administration of treatment and patient follow-up according to the protocol, and/or which may expose the patient to a too greater risk of an adverse effect; no social security; Churg |

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| | | and Strauss syndrome; viral, bacterial or fungic or mycobacterial infection uncontrolled in the 4 weeks before the inclusion; history of deep tissue infection (fasciitis, osteomyelitis, septic arthritis) in the first year before the inclusion; history of chronic and severe or recurrent infection or history of pre-existing disease predisposing to severe infection; severe immunodepression<br><br>Administration of live vaccine in the four weeks before inclusion; severe chronic obstructive pulmonary diseases (VEMS < 50 % or dyspnoea grade III); chronic heart failure stage III and IV (NYHA); history of recent acute coronary syndrome |
| Maritati 2017 | Diagnosis of clinically active SNV; aged 18 to 80 years; life-expectancy > 1 year; written informed consent; randomisation performed only if GFR > 30 | CrCl < 10 mL/min/1.73 $m^2$ |
| Metzler 2007 | Patients aged 18 and 75 years with a diagnosis of generalized WG after successful induction therapy with prednisolone and CPA | Bone marrow insufficiency (leukopenia <4000/µL, Hb < 10 g/dL, thrombocytopenia > 100,000/µL); SCr > 1.3 mg/dL (115 µM); malignancies; HBV, HCV or HIV positivity; pregnancy or breast feeding; inadequate contraception; chronic liver disease or alcohol abuse; active gastric ulcer; lack of compliance; further coexisting autoimmune diseases or treatments interfering with the study medication |
| REMAIN 2003 | Males or females > 18 years, and (1, 2 and 3 are required); (1) a diagnosis of MPA, GPA or renal-limited vasculitis; (2) renal involvement and/or other threatened loss of function of avital organ (lung, brain, eye, motor nerve or gut) and ANCA positivity, and ANCA-negative patients were eligible for enrolment in the study only when there was histological confirmation of pauci-immune vasculitis; (3) remission-induction therapy with CPA and prednisolone for at least 3 months, with or without PE; and (4) stable remission on AZA/prednisolone. | < 18 years; pregnancy; previous malignancy; known HIV infection; previous life-threatening relapse; ESKD at inclusion; allergy to study medications |
| Stegeman 1996 | Three groups of patients<br>• Group 1: necrotising GN and upper or lower airways disease consistent with WG<br>• Group 2: biopsy proven WG limited to the airways<br>• Group 3: ANCA positive patients fulfilling American College of Rheumatologists criteria for WG but not for groups 1 or 2 | Allergy or adverse reactions to co-trimoxazole or one of its components; long term (> 6 weeks) antibiotic treatment; impaired kidney function (CrCl < 30 mL/min/24 h) |
| Tervaert 1990 | Patients with ANCA-associated vasculitis in remission with a significant rise in ANCA titre | Not reported |
| WEGENT 2008 | Aged > 18 years; newly diagnosed WG and MPA | Use of steroids for more than 1 months prior to CPA therapy; co-existence of another systemic disease; cancer (unless in remission for more than 3 years); HIV, HBV or HCV infection; |

(Continued)

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| | | contraindication to study drugs; pregnancy, absence of contraception in premenopausal women; mental or physical disabilities abrogating ability to consent; patients not entering remission were not randomised |
| WGET 2002 | At least 2 of 5 modified criteria of the American College of Rheumatology for classification of WG; either new or established disease; patients with BVAS/WG score of 3 or more; stratified to severe (life-threatening manifestations including RPGN, alveolar haemorrhage or neuropathy) or limited (skin, joints, sinus or mild renal abnormalities) | Not reported |
| Zycinska 2009 | Patients with WG in remission after treatment with CPA and steroids | Not reported |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; BVAS - Birmingham Vasculitis Activity Score; CPA - cyclophosphamide; CrCl - creatinine clearance; ESKD - end-stage kidney disease; Hb - haemoglobin; HBV - hepatitis B virus; HCV - hepatitis C virus; HD - haemodialysis; HIV - human immunodeficiency virus; MPA - microscopic polyangiitis; MPO - myeloperoxidase; p-ANCA - perinuclear-ANCA; PR3 - proteinase-3; RLV - renal-limited vasculitis; RPGN - rapidly progressive glomerulonephritis; SCr - serum creatinine; SLE - systemic lupus erythematosus; WG - Wegener's granulomatosis

## Appendix 11. Treatment regimens and study outcomes - maintenance treatment

| Study ID | Treatment | Control | Study outcomes |
|---|---|---|---|
| AZA-ANCA 2016 | Extended AZA therapy: 1.5 to 2.0 mg/kg/day until 4 years after diagnosis, then tapered by 25 mg every 3 months. | Standard AZA therapy: 1.5 to 2.0 mg/kg/day until 12 months after diagnosis, then tapered by 25 mg every 3 months<br><br>Other treatment<br>All patients received TMP/SMX 400/80 mg prophylaxis | Relapse-free survival at 4 years<br><br>Cumulative dosages of CPA, prednisolone and AZA<br><br>Cumulative organ damage<br><br>Side effects due to study medication and severity of relapses. |
| Boomsma 2003 | Pre-emptive therapy<br><br>AZA: 75 mg/day for 9 months<br><br>Prednisolone: 30 mg/day tapered over 4.5 months | Follow-up only | Relapse of vasculitis |
| CYCAZAREM 2003 | Remission induction as for control group<br><br>After remission induction<br><br>• CPA: 1.5 mg/kg/day from remission | Remission induction<br><br>• Oral CPA (2 mg/kg/day) and prednisolone (1 mg/kg/day) tapered to 0.25 mg/kg/day by 12 weeks<br><br>After remission induction<br><br>• AZA: 2 mg/kg/day | Relapse by 18 months<br>Side effects including leukopenia and infections |

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| | Switched to AZA (2 mg/kg/day) and prednisolone (7.5 mg/day) 12 months after study entry | • Prednisolone: 10 mg/day<br>From 12 months received AZA (1.5 mg/kg/day) and prednisolone (7.5 mg/day) | |
| IMPROVE 2003 | Initial treatment as for control group<br>MMF: 2 g/day; reduced to 1500 mg/day after 12 months, 1000 mg/day after 18 months, and withdrawn after 42 months | Initial treatment<br>• 1 mg/kg/day (maximum 80 mg) of oral prednisolone, which was reduced to 0.75 mg/kg/day after 1 week, 0.50 mg/kg/day after 2 weeks, 0.40 mg/kg/day after 4 weeks, 0.30 mg/kg/day after 7 weeks, 0.28 mg/kg/day after 10 weeks, and 0.25 mg/kg/day after 13 weeks; prednisolone was reduced to 15 mg/day at the start of the remission regimen, tapered to 5 mg/day after 12 months, and was withdrawn after 24 months<br>AZA: 2 mg/kg/day (max 200 mg), rounded down to the nearest 25 mg increment. The dose was reduced to 1.5 mg/kg/day after 12 months, 1 mg/kg/day after 18 months, and withdrawn after 42 months | Time to first relapse<br>Relapse rate<br>Rate of side-effects and intolerance<br>Cumulative doses (AZA, steroids, MMF)<br>AUC for BVAS<br>SF-36 or VDI<br>Evolution of titres of ANCA and CRP |
| MAINRITSAN 2 2018 | Rituximab regimens: given according to ANCA status and/or circulating CD19 B-cell reconstitution vs systematically infused (controls).<br>'Tailored schedule' patients received fixed 500 mg RTX infusions on day 0 post-randomisation, then every 3 months until month 18, when CD19 lymphocytes exceeded 0/mm$^3$ or ANCA status (reappearance)/titre (higher) differed from the previous determination | 'Fixed schedule' controls received 500 mg of RTX on days 0 and 14 post-randomisation, then 6, 12 and 18 months after the first infusion. | Major relapse<br>Death<br>Severe adverse events<br>Serious infections |
| MAINRITSAN 2014 | Initial regimen (both groups)<br>Standard induction with prednisolone and IV CPA pulses. Prednisolone started at 1 mg/kg/day preceded by IV MP pulses of 500 to 1000 mg for 1 to 3 days. CPA pulses 0.6 g/m2 day 0, 14 and 28 followed by 0.7 g/m2 every 3 weeks for 3 to 6 pulses until remission. Patients were randomised after remission<br>Treatment group<br>RTX: 500 mg day 0, 14 then at month 6, 12 and 18 | Control group<br>AZA: 2 mg/kg/day orally for 12 months, then 1.5 mg/kg/day for 6 months, then 1 mg/kg/day for 4 months before ceasing | Major relapse<br>Minor relapse<br>Death<br>Serious adverse event |
| Maritati 2017 | MTX: 15 mg/week increased to 0.3 mg/kg/week<br>Patients with eGFR of 30 to 50 mL/min/1.73 m2 received 75% | CPA: 1.5 mg/kg/day orally; treatment continued for 12 months | Relapse at 12 months, 18 and 24 months<br>Major and minor relapses |

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| | of the full CPA dose and half of the full MTX dose | | Change in eGFR<br>Death<br>Adverse events |
| Metzler 2007 | Immunosuppression as for control group<br>PE: 7 x 60 mL/kg in first 2 weeks after diagnosis | Immunosuppression<br>• IV MP: 3 pulses of 1000 mg followed by oral CPA and a tapering regimen of prednisolone | Death at 3 and 12 months<br>Dialysis at 3 months and 12 months<br>Total number of side effect<br>Serious infections<br>SCr at 12 months |
| REMAIN 2003 | Continued limb: continues treatment at least until 30 months after start of REMAIN trial regimen European Vasculitis Study Group (EUVAS) AVERT project | Withdrawal arm: discontinues all treatment 4 months after start of REMAIN trial regimen<br>Both groups<br>AZA and prednisolone from cessation of CPA<br>Relapse treated according to guidelines for treatment of relapse | Relapse<br>Major relapse<br>Minor relapse<br>Death<br>Dialysis<br>Severe adverse events<br>Vasculitis Damage Index<br>eGFR<br>ANCA status |
| Stegeman 1996 | TMP/SMX: 160/800 mg twice/day for 24 months | Placebo tablets for 24 months | Death<br>Remission at 24 months<br>Number of infections/patient/years |
| Tervaert 1990 | CPA: 1 mg/kg/day tapered over 9 months<br>Prednisolone: 30 mg/day tapered over 3 months | No change to current treatment | Relapse<br>Cumulative dose<br>Side effects: infection<br>Death |
| WEGENT 2008 | Remission induction therapy as for control group<br>AZA: 2 mg/kg/day<br>Maintenance therapy as for control group | Remission induction therapy<br>• Pulse MP: 15 mg/kg for 3 days<br>• Oral prednisolone: 1 mg/kg/day for 3 weeks, tapered to 12.5 mg at 6 months, 5 mg at 18 months, stopped at 24 months<br>• Pulse CPA: 0.6 g/m$^2$, 3 doses at 2 week intervals then every 3 weeks until remission, 3 further consolidation doses at 3 week intervals. adjustments for age and CrCl.<br>• Patients also received mesna | Adverse reaction causing death or leading to discontinuation of the study drug<br>Any adverse event<br>Severe adverse event<br>Relapse<br>Relapse-free survival |

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| | | • SMX-TMP daily or aerosolized pentamidine, potassium supplements, calcium, vitamin D3 and oral bisphosphonates as indicated<br>MTX: 0.3 mg/kg/week, increasing every week by 2.5 mg to 25 mg/week<br>Folinic acid 25 mg or folic acid 5 mg given 48 hours after MTX<br>Maintenance therapy<br>• Continued for 12 months then withdrawn over 3 months<br>• TMP/SMX 320/1600 daily recommended for WG patients for additional 2 years | Event-free survival<br>Quality of life |
| WGET 2002 | SC etanercept: 25 mg twice weekly<br>Co-interventions as for control group | Twice weekly placebo injection<br>Co-interventions<br>• Severe disease: CPA 2 mg/kg/day; replaced with MTX if in remission at 3 to 6 months<br>• Limited disease: MTX 0.25 mg/kg/week to maximum of 25 mg/week. 12 months after remission, MTX dose cut by 2.5 mg each month<br>• Prednisolone was given to patients with severe and limited disease starting at 0.5 to 1.0 mg/kg/day. Tapered to 0 mg at 6 months if no relapse<br>• Patients in remission with Cr > 2 mg/dL received AZA 2 mg/kg/day, decreased after 12 months in remission by 25 mg each month | Sustained remission<br>Number and rate of flares during treatment<br>Percentage of patients with sustained low level of disease activity<br>Percentage of patients with a remission<br>Cumulative AUC for the BVAS/WG<br>Adverse events<br>Quality of life |
| Zycinska 2009 | TMP/SMX: 160/800 mg 3 times/week for 18 months | Placebo tablets for 18 months | Remission<br>Relapse<br>Infection<br>Side effects |

Footnotes: ANCA - anti-neutrophil cytoplasmic antibody; AUC - area under the curve; AZA - azathioprine; BVAS - Birmingham Vasculitis Activity Score; CPA - cyclophosphamide; Cr - creatinine; CRP - C-reactive protein; IV - intravenous; MMF - mycophenolate mofetil; MP - methylprednisolone; MTX - methotrexate; PE - plasma exchange; SC - subcutaneous; SCr - serum creatinine; TMP/SMX - trimethoprim-sulphamethoxazole; VDI - vasculitis disease index; WG - Wegener's granulomatosis

## Appendix 12. Patients randomised per study

| Study ID | Treatment | Control | Total |
|---|---|---|---|
| Adu 1997 | 24 | 30 | 54 |
| AZA-ANCA 2016 | 21 | 24 | 45 |
| Boomsma 2003 | 20 | 20 | 40 |

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|---|---|---|---|
| BREVAS 2019 | 81 | 81 | 81 |
| CLEAR 2013 | Group 1: 22<br>Group 2: 22 | 23 | 67 |
| Cole 1992 | 16 | 16 | 32 |
| CORTAGE 2015 | 53 | 51 | 104 |
| CYCAZAREM 2003 | 79 | 76 | 155 |
| CYCLOPS 2004 | 76 | 73 | 149 |
| Furuta 1998 | 12 | 12 | 24 |
| Glockner 1988 | 16 | 15 | 31 |
| Guillevin 1997 | 27 | 23 | 50 |
| Guillevin 2003 | 31 | 34 | 65 |
| Han 2011b | 19 | 22 | 41 |
| Haubitz 1998 | 22 | 25 | 47 |
| Hu 2008b | 18 | 17 | 35 |
| IMPROVE 2003 | 76 | 80 | 156 |
| Jayne 2000 | 17 | 17 | 34 |
| MAINRITSAN 2 2018 | 81 | 81 | 162 |
| MAINRITSAN 2014 | 57 | 58 | 115 |
| Maritati 2017 | 38 | 33 | 71 |
| Mauri 1985 | 12 | 10 | 22 |
| MEPEX 2007 | 70 | 67 | 137 |
| Metzler 2007 | 26 | 28 | 54 |
| MYCYC 2012 | 70 | 70 | 140 |
| NORAM 2005 | 49 | 46 | 95 |
| PEXIVAS 2013 | 352 | 352 | 704 |
| Pusey 1991 | 25 | 23 | 48 |
| RAVE 2010 | 99 | 98 | 197 |
| REMAIN 2003 | 61 | 56 | 117 |

(Continued)

| | | | |
|---|---|---|---|
| Rifle 1980 | 6 | 8 | 14 |
| RITUXVAS 2010 | 33 | 11 | 44 |
| Stegeman 1996 | 41 | 40 | 81 |
| Stegmayr 1999 | 21 | 23 | 44 |
| Szpirt 2011 | 16 | 16 | 32 |
| Tervaert 1990 | 9 | 11 | 20 |
| WEGENT 2008 | 63 | 63 | 126 |
| WGET 2002 | 89 | 91 | 180 |
| Zauner 2002 | 21 | 18 | 39 |
| Zycinska 2009 | 16 | 15 | 31 |
| **TOTAL** | **1907** | **1857** | **3764** |

Footnotes

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 19 December 2019 | New citation required and conclusions have changed | New interventions added |
| 19 December 2019 | New search has been performed | New studies added; SoF tables added |

## HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 3, 2008

| Date | Event | Description |
|---|---|---|
| 25 August 2015 | New citation required and conclusions have changed | New interventions included |
| 25 August 2015 | New search has been performed | Multiple new studies included; methodology updated |
| 20 March 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

- GW: study selection, quality assessment, data extraction, review writing

- NW: study selection, quality assessment, data extraction, review writing
- TC: quality assessment, data extraction, review writing
- JC: review writing, resolution of disagreements

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced quality assessment checklist (Walters 2001).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Kidney Injury [*therapy]; Azathioprine [therapeutic use]; Cyclophosphamide [therapeutic use]; Glomerulonephritis [complications]; Immunosuppressive Agents [therapeutic use]; Kidney [blood supply]; Kidney Diseases [*therapy]; Kidney Failure, Chronic [prevention & control]; Plasma Exchange; Randomized Controlled Trials as Topic; Vasculitis [*therapy]

### MeSH check words

Adult; Humans