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Anti-cytokine targeted therapies for ANCA-associated vasculitis (Review)

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[Intervention Review]

Anti-cytokine targeted therapies for ANCA-associated vasculitis

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ABSTRACT

Background

Anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) are a group of rare auto-inflammatory diseases that affects mainly small vessels. AAV includes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Anti-cytokine targeted therapy uses biological agents capable of specifically targeting and neutralising cytokine mediators of the inflammatory response.

Objectives

To assess the benefits and harms of anti-cytokine targeted therapy for adults with AAV.

Search methods

We searched the Cochrane Central Register of Controlled Trials (2019, Issue 7), MEDLINE and Embase up to 16 August 2019. We also examined reference lists of articles, clinical trial registries, websites of regulatory agencies and contacted manufacturers.

Selection criteria

Randomised controlled trials (RCTs) or controlled clinical trials of targeted anti-cytokine therapy in adults (18 years or older) with AAV compared with placebo, standard therapy or another modality and anti-cytokine therapy of different type or dose.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included four RCTs with a total of 440 participants (mean age 48 to 56 years). We analysed the studies in three groups: 1) mepolizumab (300 mg; three separate injections every four weeks for 52 weeks) versus placebo in participants with relapsing or refractory EGPA; 2) belimumab (10 mg/kg on days 0, 14, 28 and every 28 days thereafter until 12 months after the last participant was randomised) or etanercept (25 mg twice a week) with standard therapy (median 25 months) versus placebo with standard therapy (median 19 months) in participants with GPA/MPA; and 3) infliximab (3 mg/kg on days 1 and 14, before the response assessment on day 42) versus rituximab (0.375g/m^2 on days 1, 8, 15 and 22) in participants with refractory GPA for up to 12 months. None of the studies were assessed as low risk

of bias in all domains: one study did not report randomisation or blinding methods clearly. Three studies were at high risk and one study was at unclear risk of bias for selective outcome reporting.

One trial with 136 participants with relapsing or refractory EGPA compared mepolizumab with placebo during 52 weeks of follow-up and observed one death in the mepolizumab group (1/68, 1.5%) and none in the placebo group (0/68, 0%) (Peto odds ratio (OR) 7.39, 95% confidence interval (CI) 0.15 to 372.38; low-certainty evidence). Low-certainty evidence suggests that more participants in the mepolizumab group had ≥ 24 weeks of accrued remission over 52 weeks compared to placebo (27.9% versus 2.9%; risk ratio (RR) 9.5, 95% CI 2.30 to 39.21), and durable remission within the first 24 weeks sustained until week 52 (19.1% mepolizumab versus 1.5% placebo; RR 13.0, 95% CI 1.75 to 96.63; number needed to treat for an additional beneficial outcome (NNTB) 6, 95% Cl 4 to 13). Mepolizumab probably decreases risk of relapse (55.8% versus 82.4%; RR 0.68, 95% CI 0.53 to 0.86; NNTB 4, 95% CI 3 to 9; moderate-certainty evidence). There was low-certainty evidence regarding similar frequency of adverse events (AEs): total AEs (96.9% versus 94.1%; RR 1.03, 95% CI 0.96 to 1.11), serious AEs (17.7% versus 26.5%; RR 0.67, 95% CI 0.35 to 1.28) and withdrawals due to AEs (2.9% versus 1.5%; RR 2.00, 95% CI 0.19 to 21.54). Disease flares were not measured.

Based on two trials with different follow-up periods (mean of 27 months for etanercept study; up to four years for belimumab study) including people with GPA (n = 263) and a small group of participants with MPA (n = 22) analysed together, we found low-certainty evidence suggesting that adding an active drug (etanercept or belimumab) to standard therapy does not increase or reduce mortality (3.4% versus 1.4%; Peto OR 2.45, 95% CI 0.55 to 10.97). Etanercept may have little or no effect on remission (92.3% versus 89.5%; RR 0.97, 95% CI 0.89 to 1.07), durable remission (70% versus 75.3%; RR 0.93, 95% CI 0.77 to 1.11; low-certainty evidence) and disease flares (56% versus 57.1%; RR 0.98, 95% CI 0.76 to 1.27; moderate-certainty evidence). Low-certainty evidence suggests that belimumab does not increase or reduce major relapse (1.9% versus 0%; RR 2.94, 95% CI 0.12 to 70.67) or any AE (92.5% versus 82.7%; RR 1.12, 95% CI 0.97 to 1.29). Low-certainty evidence suggests a similar frequency of serious or severe AEs (47.6% versus 47.6%; RR 1.00, 95% CI 0.80 to 1.27), but more frequent withdrawals due to AEs in the active drug group (11.2%) compared to the placebo group (4.2%), RR 2.66, 95% CI 1.07 to 6.59).

One trial involving 17 participants with refractory GPA compared infliximab versus rituximab added to steroids and cytotoxic agents for 12 months. One participant died in each group (Peto OR 0.88, 95% CI, 0.05 to 15.51; 11% versus 12.5%). We have very low-certainty evidence for remission (22% versus 50%, RR 0.44, 95% Cl 0.11 to 1.81) and durable remission (11% versus 50%, RR 0.22, 95% CI 0.03 to 1.60), any severe AE (22.3% versus 12.5%; RR 1.78, 95% CI 0.2 to 16.1) and withdrawals due to AEs (0% versus 0%; RR 2.70, 95% CI 0.13 to 58.24). Disease flare/relapse and the frequency of any AE were not reported.

Authors' conclusions

We found four studies but concerns about risk of bias and small sample sizes preclude firm conclusions.

We found moderate-certainty evidence that in patients with relapsing or refractory EGPA, mepolizumab compared to placebo probably decreases disease relapse and low-certainty evidence that mepolizumab may increase the probability of accruing at least 24 weeks of disease remission. There were similar frequencies of total and serious AEs in both groups, but the study was too small to reliably assess these outcomes. Mepolizumab may result in little to no difference in mortality. However, there were very few events.

In participants with GPA (and a small subgroup of participants with MPA), etanercept or belimumab may increase the probability of withdrawal due to AEs and may have little to no impact on serious AEs. Etanercept may have little or no impact on durable remission and probably does not reduce disease flare.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of anti-cytokine medicines for ANCA-associated vasculitis?

Why this question is important

The body’s defence (immune) system fights injury or infection by sending white blood cells to surround and protect the affected area. This causes redness and swelling, called inflammation.

Vasculitis is an inflammation of the blood vessels. In vasculitis, instead of reacting to harm, the immune system attacks healthy blood vessels. The reason for this reaction is often unknown.

One rare type of vasculitis is antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). AAV covers three different conditions that are grouped together because they all affect small blood vessels:

- MPA: microscopic polyangiitis;

- GPA: granulomatosis with polyangiitis; and

- EPGA: eosinophilic granulomatosis with polyangiitis.

The areas of the body most commonly affected are kidneys, lungs, joints, ears, nose and nerves. It is important to treat AAV early, to prevent serious damage to these organs.

Currently, the recommended treatment for AAV is to use medicines that control the immune system and medicines against inflammation (steroids). However, this treatment causes serious unwanted effects. Medicines that target cytokines (small molecules that influence the immune system's reactions) are an alternative option. To evaluate the benefits and risks of anti-cytokine medicines, we reviewed the evidence from research studies.

How we identified and assessed the evidence

First, we searched for all relevant studies in the medical literature. We then compared the results, and summarised the evidence from all the studies. Finally, we assessed how certain the evidence was. We considered factors such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorized the evidence as being of very low, low, moderate or high certainty.

What we found

We found four studies on a total of 440 adults from the USA and Europe. The average age of people ranged between 48 and 56 years. They received treatment for between 2 and 25 months, and were then followed for between 8 weeks and four years. Three studies compared anti-cytokine medicines (mepolizumab, belimumab and etanercept) to a placebo (fake medicine) and one study compared two different anti-cytokine medicines (rituximab versus infliximab). Three studies received at least partial funding from pharmaceutical companies.

Mepolizumab versus placebo in people with EGPA that returned after, or did not respond to, initial treatment

Moderate-certainty evidence indicates that mepolizumab probably reduces the likelihood of the disease returning within a year of treatment.

Low-certainty evidence suggests that mepolizumab:

- may make little or no difference to mortality;

- may increase the likelihood of the disease partially or fully disappearing for at least 24 weeks, and may increase the chances of this disappearance lasting for another six months at least;

- may make little or no difference to unwanted events, serious unwanted events or withdrawal from studies due to unwanted events.

The impact of mepolizumab on disease flare (worsening) is unknown, as this was not measured.

Etanercept or belimumab versus placebo in GPA and MPA

Moderate-certainty evidence indicates that etanercept probably makes little or no difference to disease flare.

Low-certainty evidence suggests that etanercept or belimumab may make little or no difference to:

- mortality;

- the disease fully disappearing for at least 24 weeks, or disappearance lasting at least another six months after that;

- the disease returning strongly;

- unwanted events or severe/serious unwanted events

Evidence of low certainty suggests that etanercept or belimumab may slightly increase chances of people withdrawing from studies due to unwanted events.

Infliximab versus rituximab, plus steroids and cytotoxic agents (substances that kill cells), in people with GPA that did not respond to other treatments

The one study we found was too small to assess the differences between treatments (very low-certainty evidence).

What this means

Mepolizumab probably reduces the likelihood of the disease returning within a year of treatment, and etanercept probably makes little or no difference to disease flare. We are less certain of the other potential benefits or risks of anti-cytokine medicines because the evidence is of low or very low certainty. Further research is likely to change the findings of this review.

How-up-to date is this review?

The evidence in this Cochrane Review is current to August 2019.

Summary of findings 1. Mepolizumab compared to placebo for adults with EGPA ANCA-associated vasculitis

Mepolizumab compared to placebo for adults with EGPA ANCA-associated vasculitis

Patient or population: adults (age 18 years and older) with EGPA ANCA-associated vasculitis
Setting: clinical centres
Intervention: mepolizumab (300 mg; 3 separate injections every 4 weeks)
Comparison: placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		With placebo	With mepolizumab	Difference		
Mortality follow-up: 52 weeks Number of participants: 136 (1 RCT)	Peto OR 7.39 (0.15 to 372.38)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW [1]	During 52 weeks follow-up, one death was reported in the mepolizumab group and no deaths in placebo group. The low-certainty evidence suggests that mepolizumab results in little to no difference in mortality.
Remission for at least 24 weeks assessed with: BVAS v.3 of 0 (on a scale from 0 to 63) follow-up: 52 weeks Number of participants: 136 (1 RCT)	RR 9.50 (2.30 to 39.21)	2.9%	27.9% (6.8 to 100)	25.0% more (3.8 more to 112.4 more)	⊕⊕⊖⊖ LOW [1]	The low-certainty evidence suggests mepolizumab results in a large increase of the probability of accruing at least 24 weeks of remission over a 52-week period. NNTB 4, 95% CI 3 to 8
Durable remission within the first 24 weeks sustained until week 52 assessed with: BVAS v.3 of 0 (on a scale from 0 to 63) follow-up: 52 weeks Number of participants: 136 (1 RCT)	RR 13.00 (1.75 to 96.33)	1.5%	19.1% (2.6 to 100)	17.6% more (1.1 more to 140.2 more)	⊕⊕⊖⊖ LOW [1]	The low-certainty evidence suggests that mepolizumab results in a large increase of the probability of durable remission within the first 24 weeks, sustained until week 52. NNTB 6 95% CI 4 to 13
Disease relapse follow-up: 52 weeks Number of participants: 136	RR 0.68 (0.53 to 0.86)	82.4%	56.0% (43.6 to 70.8)	26.4% fewer (38.7 fewer to 11.5 fewer)	⊕⊕⊕⊖ MODERATE [2]	Mepolizumab probably results in a reduction in disease relapse. NNTB 4, 95% CI 3 to 9

(1 RCT)						
Disease flares	Not measured					
Any adverse event follow-up: 52 weeks Number of participants: 136 (1 RCT)	RR 1.03 (0.96 to 1.11)	94.1%	96.9% (90.4 to 100)	2.8% more (3.8 fewer to 10.4 more)	⊕⊕⊖⊖ LOW [1]	The low-certainty evidence suggests that mepolizumab does not increase any adverse event. Number of participants reporting similar rates of any AEs in mepolizumab and placebo group (97% vs 94%).
Any serious adverse event follow-up: 52 weeks Number of participants: 136 (1 RCT)	RR 0.67 (0.35 to 1.28)	26.5%	17.7% (9.3 to 33.9)	8.7% fewer (17.2 fewer to 7.4 more)	⊕⊕⊖⊖ LOW [1]	The low-certainty evidence suggests that mepolizumab results in little to no difference in any serious adverse event.
Any withdrawals due to AEs follow-up: 52 weeks Number of participants: 136 (1 RCT)	RR 2.00 (0.19 to 21.54)	1.5%	2.9% (0.3 to 31.7)	1.5% more (1.2 fewer to 30.2 more)	⊕⊕⊖⊖ LOW [1]	The low-certainty evidence suggests that mepolizumab does not increase any withdrawals due to AEs. The study reported similar number of patients withdrawn from mepolizumab and placebo groups due to AEs.

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

ANCA: anti-neutrophilic cytoplasmic antibodies; **CI:** Confidence interval; **BVAS:** Birmingham Vasculitis Activity Score; **EGPA:** eosinophilic granulomatosis with polyangiitis; **RR:** Risk ratio; **OR:** Odds ratio;

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

[1]Downgraded by two levels for imprecision: CIs are wide and the number of events was too low to reliably assess optimal information size (OIS); or OIS not met
[2]Downgraded by one level for imprecision: the number of events was lower than indicated in GRADE guidance
AE - adverse event
ANCA – antineutrophil cytoplasmic antibody
BVAS – Birmingham Vasculitis Activity Score
EGPA – eosinophilic granulomatosis with polyangiitis
NNTB - number needed to treat for an additional beneficial outcome
OR - odds ratio
RCT - randomized controlled trial

RR - relative risk

Summary of findings 2. Active drug (etanercept or belimumab) with standard therapy compared to standard therapy with placebo for adults with GPA ANCA-associated vasculitis

Active drug (etanercept or belimumab) with standard therapy compared to standard therapy with placebo for adults with GPA ANCA-associated vasculitis

Patient or population: adults (age 18 years and older) with GPA ANCA-associated vasculitis or microscopic polyangiitis (only a subset of patients in one study, i.e. 7.7% of total population and not analysed separately)
Setting: clinical centres in etanercept study and not reported in belimumab study
Intervention: active drug (etanercept: 25 mg twice a week for a median of 25 months or belimumab: 10 mg/kg on days 0, 14, 28 and every 28 days thereafter until 12 months after the last participant was randomised) with standard therapy
Comparison: standard therapy with placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		With standard therapy and placebo	With active drug (etanercept or belimumab) with standard therapy	Difference		
Mortality Number of participants: 285 (2 RCTs) WGET 2005 follow-up: 27 months; BREVAS 2018 follow-up: approximately up to 4 years	Peto OR 2.45 (0.55 to 10.97)	1.4%	3.4% (0.8 to 15.3)	2.0% more (0.6 fewer to 13.9 more)	⊕⊕⊖⊖ LOW [1]	Five deaths was reported in active drug (etanercept or belimumab) with standard therapy group and two deaths in standard therapy with placebo group. Low-certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy when compared with standard therapy does not increase/reduce mortality.
Remission (number of patients with remission) assessed with: BVAS/WG = 0 WGET 2005 follow-up: 27 months Number of participants: 180 (1 RCT)	RR 0.97 (0.89 to 1.07)	92.3%	89.5% (82.2 to 98.8)	2.8% fewer (10.2 fewer to 6.5 more)	⊕⊕⊖⊖ LOW [2, 3]	Low-certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy when compared with standard therapy with placebo may have little or no effect on remission. However, any effect is likely to be small.
Durable remission	RR 0.93 (0.77 to 1.11)	75.3%	70.0% (58 to 83.6)	5.3% fewer	⊕⊕⊖⊖ LOW [1]	Low-certainty evidence suggests that etanercept added to standard therapy

assessed with: BVAS/WG = 0 for ≥ 6 months follow-up: 27 months Number of participants: 174 (1 RCT)				(17.3 fewer to 8.3 more)		when compared with standard therapy and placebo may have little or no effect on durable remission.
Major relapse assessed with: BVAS (experiencing at least 1 major BVAS item) follow-up: year 2 week 28 Number of participants: 105 (1 RCT)	RR 2.94 (0.12 to 70.67)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW [1]	Low-certainty evidence suggests that belimumab added to standard therapy when compared with standard therapy and placebo does not increase/reduce major relapse.
Disease flare assessed with: BVAS/WG - increase of at least one point in scale follow-up: 27 months Number of participants: 180 (1 RCT)	RR 0.98 (0.76 to 1.27)	57.1%	56.0% (43.4 to 72.6)	1.1% fewer (13.7 fewer to 15.4 more)	⊕⊕⊕⊖ MODERATE [3]	Etanercept added to standard therapy when compared with standard therapy with placebo probably does not reduce disease flare.
Any adverse event follow-up: approximately up to 4 years Number of participants: 105 (1 RCT)	RR 1.12 (0.97 to 1.29)	82.7%	92.5% (2.5 to 24)	9.9% more (2,5 fewer to 24 more)	⊕⊕⊖⊖ LOW[1]	The low-certainty evidence suggests that belimumab added to standard therapy when compared with standard therapy with placebo may result in little or no difference in any AE.
Any severe or serious AE (grade 3, 4 or 5) assessed with: the National Cancer Institute Toxicity Grading Scale WGET 2005 follow-up: 27 months; BREVAS 2018 follow-up: approximately up to 4 years Number of participants: 285 (2 RCTs)	RR 1.00 (0.80 to 1.27)	47.6%	47.6% (38 to 60.4)	0.0% fewer (9.5 fewer to 12.8 more)	⊕⊕⊖⊖ LOW [2, 3]	The low certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy when compared with standard therapy with placebo may result in little or no difference in severe or serious AE (grade 3, 4 or 5).
Any withdrawals due to AE assessed with the National Cancer Institute Toxicity Grading Scale	RR 2.66 (1.07 to 6.59)	4.2%	11.2% (4.5 to 27.7)	7.0% more (0.3 more to 23.5 more)	⊕⊕⊖⊖ LOW [2, 3]	The low-certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy when compared with standard therapy with placebo results in a slight increase in any withdrawals due to AE.

	WGET 2005 follow-up: 27 months; BREVAS 2018 follow-up: approximately up to 4 years Number of participants: 285 (2 RCTs)			NNTH 15, 95% CI 8 to 100

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

ANCA: anti-neutrophilic cytoplasmic antibodies; **CI:** Confidence interval;**BVAS/WG:** Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; **GPA:** granulomatosis with polyangiitis; **RR:** Risk ratio; **OR:** Odds ratio

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

[1]Downgraded by two levels for imprecision: optimal information size (OIS) not achieved; low number of events; confidence intervals very wide or indicating both harm and benefit
[2]Downgraded by one level due to high risk of selective outcome reporting bias in both studies
[3]Downgraded by one level for imprecision: OIS criteria are met, but the CIs are very wide; or OIS not achieved, and confidence interval indicates both harm and benefit
AE - adverse event
ANCA – antineutrophil cytoplasmic antibody
BREVAS - Belimumab in Remission of VAScultis
BVAS – Birmingham Vasculitis Activity Score
BVAS/WG – Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis
GPA – granulomatosis with polyangiitis
NNTH - number needed to treat for an additional harmful effect
OR - odds ratio
RCT - randomized controlled trial
RR - relative risk
WGET - Wegener's Granulomatosis Etanercept Trial

Summary of findings 3. Infliximab compared to rituximab for adults with refractory GPA ANCA-associated vasculitis

Infliximab compared to rituximab for adults with refractory GPA ANCA-associated vasculitis
Patient or population: adults (age 18 years and older) with refractory GPA ANCA-associated vasculitis **Setting:** hospitals **Intervention:** infliximab (3 mg/kg on days 1 and 14, before the response assessment on day 42; further treatment depending on the response) **Comparison:** rituximab (0.375g/m^2 on days 1, 8, 15 and 22 before the response assessment at month 2; further treatment depending on the response)

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		With rituximab	With infliximab	Difference		
Mortality follow-up: 12 months Number of participants: 17 (1 RCT)	Peto OR 0.88 (0.05 to 15.51)	12.5%	11.0% (0.6 to 193.9)	1.5% fewer (11.9 fewer to 181.4 more)	⊕⊖⊖⊖ VERY LOW [1,2]	One death was reported in each group. The evidence is very uncertain about the effect of infliximab when compared to rituximab on mortality.
Remission assessed with: BVAS=0 follow-up: 12 months Number of participants: 17 (1 RCT)	RR 0.44 (0.11 to 1.81)	50.0%	22.0% (5.5 to 90.5)	28.0% fewer (44.5 fewer to 40.5 more)	⊕⊖⊖⊖ VERY LOW [1,2]	The evidence is very uncertain about the effect of infliximab when compared with rituximab on remission at month 12.
Durable remission during additional follow-up beyond 12 months follow-up: mean 30.6 months Number of participants: 17 (1 RCT)	RR 0.22 (0.03 to 1.60)	50.0%	11.0% (1.5 to 80)	39.0% fewer (48.5 fewer to 30 more)	⊕⊖⊖⊖ VERY LOW [1,2]	The evidence is very uncertain about the effect of infliximab when compared with rituximab on durable remission during additional follow-up beyond 12 months.
Disease flare/relapse	This outcome was not reported in included trial.					
Any adverse event	The total number of any AEs was not reported in the study.					
Any severe AEs assessed with: the World Health Organization classification (2003) follow-up: 12 months Number of participants: 17 (1 RCT)	RR 1.78 (0.20 to 16.10)	12.5%	22.3% (2.5 to 100)	9.8% more (10 fewer to 188.8 more)	⊕⊖⊖⊖ VERY LOW [1,2]	The evidence is very uncertain about the effect of infliximab when compared with rituximab on any severe AEs.
Any withdrawals due to AEs assessed with: the World Health Organization classification (2003) follow-up: 12 months Number of participants: 17 (1 RCT)	RR 2.70 (0.13 to 58.24)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW [1,2]	The evidence is very uncertain about the effect of infliximab when compared with rituximab on any withdrawals due to AEs.

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

CI: Confidence interval; **GPA:** granulomatosis with polyangiitis; **RR:** Risk ratio; **OR:** Odds ratio;

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

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[1]Downgraded by one level due to risk of bias – unclear randomisation and concealment, no blinding and unclear selective outcome reporting
[2]Downgraded by two levels for imprecision: optimal information size (OIS) not met and CI indicates both harm and benefit; and/or low number of events
AE - adverse event
ANCA – antineutrophil cytoplasmic antibody
BVAS – Birmingham Vasculitis Activity Score
GPA – granulomatosis with polyangiitis
OR - odds ratio
RCT - randomized controlled trial
RR - relative risk

BACKGROUND

Description of the condition

Vasculitides are a heterogenous group of rare diseases characterised by inflammation of the vessel wall. Infectious, environmental (e.g. drugs), genetic and other factors are probably involved in the pathogenesis of vasculitis (McKinney 2014). The underlying pathology is complex and characteristically involves immune-mediated inflammation of blood vessel walls, resulting in ischaemic and localised inflammatory injury to tissues in the territory of the affected vessels (Gonzalez-Gay 2002). Disease subtypes follow the Chapel Hill Consensus Conference (CHCC) nomenclature system, which has been in use since 1994. This document categorises vasculitides on the basis of several aetiological and clinical features, including the diameter of the affected vessels (large, medium, small vessel vasculitis). Major advances in our understanding of the vasculitis pathology, including the importance of ANCA status, were among the main reasons for the CHCC 2012 revision. Additionally, disease eponym names were replaced with descriptive names (e.g. granulomatosis with polyangiitis, instead of Wegener's granulomatosis) (Jeanette 2013).

According to this nomenclature, ANCA-associated vasculitis (AAV) predominantly affects small vessels and consists of three entities: granulomatosis with polyangiitis (GPA; Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss vasculitis) (Merkel 2015). AAV entities are rare diseases with combined prevalence estimated at between 90 and 144 per million, and with annual incidence of around 20 per million (Cotch 1996; Gibson 2006; Mahr 2004; Watts 2000).

The frequency of ANCA-associated vasculitis seems to be geographically determined. For example, increased incidence of GPA occurs in northern Europe, whereas greater MPA incidence has been reported in southern Europe (Katsuyama 2014). Some evidence indicates that the incidence is increasing (Watts 2000). Not all AAV conditions have positive ANCA status; this status differs by entity. Approximately 85% to 90% of patients with GPA, 70% of those with MPA and approximately 30% to 40% of patients with EGPA are ANCA-positive (Mahr 2014; Merkel 2015).

If ANCAs are present in AAV, they are most commonly directed against myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) (Harper 2001) and can help in establishing the diagnosis. Increasing evidence suggests that ANCA status determines the disease course and clinical manifestations (Cottin 2017).

Description of the intervention

Treatment recommended for AAV depends on disease severity; induction therapy based on glucocorticosteroids and cyclophosphamide or rituximab is indicated for patients with organ-threatening disease, particularly of the lungs, kidneys and the nervous system; and glucocorticosteroids and methotrexate or mycophenolate mofetil for those with non-organ-threatening AAV (Yates 2016). Cyclophosphamide, which was introduced in the 1970s by Hoffman and Fauci (Kamesh 2002), is a potent, cytotoxic immunosuppressive agent that has dramatically improved survival among patients with some forms of vasculitides. The combination of cyclophosphamide and prednisolone has become the gold standard for treatment of patients with active systemic vasculitis but it is associated with serious adverse effects, including neutropenia, opportunistic infection, premature menopause and increased rates of cancer, most notably, cancer of the bladder (Fauci 1983; Kamesh 2002). Prolonged follow-up of patients who have received cyclophosphamide reveals increasing over time dose-dependent rates of bladder cancer (Knight 2004). To overcome these treatment-related toxicities, strategies for introducing less toxic immunosuppressive agents (e.g. methotrexate or azathioprine after induction therapy with a series of cyclophosphamide infusions) have been used with moderate success (Jayne 2003). However, there remains an unmet need for more effective and less toxic treatments for patients in induction and remission phases of vasculitides. Recently, biological immunotherapies capable of specifically targeting and neutralising cytokine mediators of the inflammatory response have entered clinical practice for a variety of immune-mediated inflammatory diseases. Among biological therapies, treatment options include anti-tumour necrosis factor (TNF) agents (infliximab, etanercept, adalimumab) or rituximab, which belongs to the group of anti-CD20 monoclonal antibodies (Kamesh 2002, Silva-Fernández 2014). Another Cochrane Review, now in development, is assessing the benefit of rituximab (Riminton 2008). Molecules other than anti-TNF agents and rituximab, such as abatacept, mepolizumab (an anti-IL5 antibody) and alemtuzumab (a humanised monoclonal anti-CD52 antibody) have been used in refractory cases of AAV. These agents hold promise for safer, more effective targeted intervention, and studies in ANCA-associated vasculitis have commenced. Mepolizumab has been used in a pilot study on EGPA to allow decreasing steroid doses (Kim 2010) and has been fully assessed in a randomised trial called MIRRA (Wechsler 2017).

How the intervention might work

Consideration of the mechanisms underlying chronic inflammatory disease such as vasculitis has revealed a primary, pivotal role of cytokines. Cytokines comprise a diverse family of small molecule mediators of intercellular communication that have essential roles in mobilisation of the inflammatory response. Tumour necrosis factor-alpha (TNF-alpha), as one example, has a central role in the downstream production of both pro-inflammatory and anti-inflammatory cytokines, which appear to be maintained at a dysfunctional equilibrium in chronic inflammatory disease. TNF-alpha is among the first of the cytokines to rise in response to bacterial infection (Feldmann 2006). Studies have shown that TNF-alpha plays a central role in mouse models of renal vasculitis, and the treatment of the affected mice with anti-TNF-alpha has improved their outcomes (Feldmann 2006). In another chronic immune-mediated inflammatory disease, rheumatoid arthritis (RA), the inhibition of TNF-alpha activity by both monoclonal antibodies and a soluble receptor decoy has been shown to be effective in the management of signs, symptoms and radiographic progression (Chen 2006). Another anti-cytokine therapy, namely, interleukin-1 receptor antagonist (IL-1RA; anakinra), has been shown to provide benefit for patients with RA (Cohen 2002). Future directions and potential therapeutic options include interleukin (IL)-6 antagonist (B-cell stimulatory factor-2; BSF-2). Several studies have reported that tocilizumab (anti-interleukin-6 agent) was successfully used for some systemic diseases such as RA, and its benefit in RA is well established (Berli 2015). Inhibition of pro-inflammatory cytokines has therefore emerged as an attractive prospect for the management of ANCA-associated vasculitis.

Why it is important to do this review

ANCA-associated vasculitis comprises a group of rare systemic diseases. Effective treatment is important because progression of these diseases may be dramatic. Physicians who are responsible for the care of these patients are confronted with an important dilemma: whether to employ conventional cytotoxic immunosuppressive strategies with unsatisfactory primary resistance, relapse and drug-induced adverse events (AEs); or whether to employ novel biological anti-cytokine therapies with the potential for greater benefit and tolerability. Further uncertainty is raised by the use of combinations of conventional and novel therapies, and by a rapidly evolving evidence base. Anti-cytokine therapies represent another treatment option. Systematic reviews can provide some answers.

Use of anti-cytokine therapy has been reported in patients with ANCA-associated vasculitides (e.g. Al-Bishri 2005; Lamprecht 2002; WGET 2005), but no Cochrane systematic review has focused on this type of treatment in this group of patients.

We conducted this review according to the guidelines provided by the Cochrane Musculoskeletal Group Editorial Board (Ghogomu 2014).

OBJECTIVES

To assess the benefits and harms of anti-cytokine targeted therapy for adults with ANCA-associated vasculitis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) and controlled clinical trials (CCTs) for inclusion in this review. We planned to include studies reported as abstracts without data in the 'Studies awaiting assessment' category and to contact study authors for additional detailed data, but we have not come across such a study. However, we came across several studies that were registered and completed but did not report their results. In such cases, we attempted to contact the authors for additional information. We applied no restrictions on length of follow-up or language.

Types of participants

We restricted inclusion in this review to trials that met the following criteria.

- All studies primarily concerning ANCA-associated vasculitis in adult populations (18 years of age or older).
- Specific confirmed diagnoses of participants including GPA, EGPA and MPA) .

We excluded patients with other types of vasculitides.

Types of interventions

We considered all randomised controlled comparisons of specifically targeted anti-cytokine therapy versus placebo, standard therapy or another modality. We considered various types and dosages of anti-cytokine therapy.

We considered all available anti-cytokine therapies, such as TNF-alpha inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), inhibitors of soluble B-lymphocyte stimulator (BLyS) cytokine (belimumab), interleukin receptor antagonists and interleukin inhibitors (anakinra, basiliximab, benralizumab, brodalumab, canakinumab, clazakizumab, daclizumab, dupilumab, ixekizumab, lebrikizumab, mepolizumab, olokizumab, pitrakinra, reslizumab, rilonacept, sarilumab, secukinumab, siltuximab, sirukumab, tocilizumab, tralokinumab, ustekinumab), as well as anti-cytokine therapies that will be developed in the future. We did not include interventions that were not specifically directed at cytokines but that may nevertheless alter cytokine expression or function (e.g. corticosteroids).

Types of outcome measures

Major outcomes

Major benefit outcomes included:

- mortality;
- remission (as defined by study authors, typically as complete absence of disease activity (Merkel 2011) measured by Birmingham Vasculitis Activity Score (BVAS), BVAS/ WG (for GPA) or BVAS v3);
- durable remission (defined according to BVAS, BVAS WG or BVAS v3 for at least six months) (WGET 2005); and
- disease flare/relapse (as defined by study authors, typically as increased disease activity from a previous low or absent state) (Merkel 2011).

Major harms outcomes included:

- total AEs;
- serious AEs; and
- withdrawals due to AEs.

Minor outcomes

Minor outcomes included:

- treatment response (defined as quantifiable improvement in disease activity (Merkel 2011) as assessed by BVAS, BVAS WG or BVAS v3 with cut-off point as defined by study authors);
- health-related quality of life (as assessed by Short Form (SF)-36 or other health-related quality of life measures, including those specific to AAV);
- control of asthma/sinonasal disease (as defined by study authors); and
- disease damage according to the Vasculitis Damage Index (VDI), the AAV Index of Damage (AVID) or other validated disease damage scores accepted by Outcome Measures in Rheumatology (OMERACT).

Time points

We planned to collect data reported at six months,12 months and more than 12 months, as well as during active treatment and after treatment cessation. Ultimately, we included all time points reported in the studies.

Search methods for identification of studies

We searched all databases from their inception to the 16 August 2019, and we imposed no restriction on language and date of publication.

Electronic searches

We searched the following electronic databases and sources to identify studies (all searches performed on 16 August 2019).

- Cochrane Central Register of Controlled Trials (2019, Issue 7).
- MEDLINE (OVID).
- Embase (OVID).

We searched the following ongoing trial registries (all searches performed on 28 August 2019).

- ClinicalTrials.gov (www.ClinicalTrials.gov).
- European Trials Register (www.clinicaltrialsregister.eu).
- ISRCTN (International Standard Randomised Controlled Trial Number Registry; www.isrctn.com).
- WHO (World Health Organization) trials portal (www.who.int/ictrp/en).

For the assessments of AEs, we searched the web sites of regulatory agencies (all searches performed on 3 September 2019), such as the US Food and Drug Administration-MedWatch (www.fda.gov/Safety/MedWatch/default.htm), the European Medicines Evaluation Agency (www.emea.europa.eu), the Australian Adverse Drug Reactions Bulletin (www.tga.gov.au/adr/aadrb.htm) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) for pharmacovigilance and drug safety updates (www.mhra.gov.uk). We searched each database using basic terms, e.g. ANCA vasculitis, etanercept, mepolizumab, infliximab and belimumab.

See Appendix 1 for the MEDLINE search strategy, Embase search strategy and CENTRAL search strategy.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' web sites for trial information. When we identified unpublished trials, we sought contact with relevant authors for further information. We checked www.clinicaltrialresults.org and the web sites of regulatory agencies such as the US Food and Drug Administration-MedWatch (www.fda.gov) and the European Medicines Evaluation Agency (www.emea.europa.eu) for unpublished data.

We searched for errata and retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and planned to report in the review the date this was done, but no such cases occurred.

Data collection and analysis

Selection of studies

For study selection, we used Covidence (www.covidence.org), a new tool recommended by Cochrane to facilitate production of systematic reviews. Two review authors (JZ, MK, TMM, MMB, JJ or WS) independently screened titles and abstracts of articles identified by the search to determine their potential for inclusion in the review and coded them as 'yes/maybe' (eligible or potentially eligible/unclear) or 'no.' We retrieved full-text study reports/publications, and two review authors (JZ, MK, TMM, MMB, JJ or WS) independently screened full texts to identify studies for inclusion and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion, or, if required, we consulted a third review author (WS or MMB). We identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (PRISMA Group) (Moher 2009) and 'Characteristics of excluded studies' tables.

Data extraction and management

If Covidence allowed for adjustment of data extraction forms, we planned to use this tool for data extraction; otherwise, we planned to prepare a data extraction form in Microsoft Excel. Ultimately, we extracted the data to the forms prepared in Microsoft Excel. We recorded study characteristics and outcome data on a data collection form that was piloted on at least one study in the review. We planned that the extraction process would be carried out by one review author and spot-checked by another one, but to improve the quality of our review we decided to proceed with independent extraction by two review authors (JZ, JJ or MK). We extracted the following study characteristics from the included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals, date of study.
- Participants: number of participants included in the study and number of participants in each group, number of participants who completed follow-up, mean age, age range, sex, disease duration, severity of condition, diagnostic criteria, important ANCA vasculitides-specific baseline data such as prior treatment, presence of comorbidity.
- Interventions: intervention, comparison, dosing regimen, route of administration, concomitant use of steroids, excluded medications, duration of treatment.
- Outcomes: major and minor outcomes specified and collected, time points reported.
- Characteristics of trial design as outlined in the 'Assessment of risk of bias in included trials' section.
- Notes: funding for trial, notable declarations of interest of trial authors.

Each extraction was checked for accuracy against the trial report by an additional review author (MMB, TMM or WS).

Two review authors (JZ, JJ or MK) independently extracted outcome data from the included studies. We extracted numbers of events and participants per treatment group for dichotomous outcomes; and means, standard deviations and numbers of participants per treatment group for continuous outcomes. If reported, we extracted confidence intervals and P values. We planned to note in the 'Characteristics of included studies' table if outcome data were not reported in a useable way and if data were transformed or estimated from a graph. We resolved disagreements by reaching consensus or by involving a third review author (MMB, TMM or WS). One review author (MK, JZ or JJ) transferred data

into the Review Manager (RevMan 2014) file. We double-checked whether that data were entered correctly by comparing data presented in the systematic review with the study reports.

We used results from an intention-to-treat analysis, if possible. If a study reported multiple time point measurements, we extracted all time point values and used final values data for analysis. For continuous outcomes, if both final values and change from baseline values were reported for the same outcome, we planned to extract both values and use change values for primary analysis. If investigators reported both adjusted and unadjusted values for the same outcome, we planned to extract both estimates and use adjusted values with the maximum number of covariates.

Assessment of risk of bias in included studies

Two pairs of review authors (JZ, MK, JJ, MMB, TMM or WS) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved disagreements by discussion or by consultation with another review author (WS or MMB). We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias (such as bias related to issues of study design, baseline imbalance, stopping early for benefit, influence of interim results on study conduct, inappropriate administration of co-interventions and selective reporting of subgroups).

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements per outcomes within a study and per outcomes across studies.

When we obtained information on risk of bias related to unpublished data or correspondence with a trialist, we planned to note this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to that outcome.

We presented figures generated by the 'risk of bias' tool to provide summary assessments of the risk of bias.

We considered a study to have low risk of bias if we judged it to be at low risk in all domains for each outcome; otherwise, we considered the study to have a high risk of bias.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) or Peto odds ratios (OR) when the outcome was a rare event (approximately < 10%) and used 95% confidence intervals (CIs). We planned to analyse continuous data as mean differences (MDs) or standardised mean differences (SMDs), depending on whether the same scale was used to measure the outcome, and 95% CIs. We planned to enter data presented as a scale with a consistent direction of effect across studies.

We planned to back-translate SMD to a typical scale (e.g. BVAS) by multiplying the SMD by a typical among-person standard deviation (e.g. standard deviation of the control group at baseline from the most representative trial) (as per Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011b)).

If results were reported only as mean differences with standard errors (SEs) or 95% CIs, we planned to pool them using the generic inverse variance method available in RevMan5.

We planned to analyse time-to-event data as hazard ratios (HR).

In the 'Effects of intervention' section under 'Results' and in the 'Comments' column of the 'Summary of findings' table, we planned to provide the absolute percentage difference, the relative percentage change from baseline and the number needed to treat for an additional beneficial outcome (NNTB). We provided the NNTB only when the outcome showed a statistically significant difference.

For dichotomous outcomes, such as serious AEs, we planned to calculate the NNTB/number needed to treat for an additional harmful effect (NNTH) from the control group event rate and the risk difference (RD) using the Visual Rx NNT calculator (Cates 2008). When this was not possible, we used RD and 95% CI calculated in RevMan to calculate NNTB with 100/RD formula. We planned to calculate the NNTB/NNTH for continuous measures using the Wells calculator (available at the CMSG Editorial Office; musculoskeletal.cochrane.org).

For dichotomous outcomes, we calculated the absolute RD using the RD statistic in RevMan (RevMan 2014) and expressed the result as a percentage. For continuous outcomes, we planned to calculate the absolute benefit as improvement in the intervention group minus improvement in the control group, in original units, and express this as a percentage.

We calculated the relative percentage change for dichotomous data as the risk ratio - 1 and expressed this as a percentage. For continuous outcomes, we planned to calculate the relative difference in change from baseline as the absolute benefit divided by the baseline mean of the control group.

Unit of analysis issues

When multiple trial arms were reported in a single trial, we planned to include only relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we planned to halve the control group to avoid double-counting.

We did not expect to find cross over studies or cluster RCTs but had we done so, we would have followed the guidance in chapter 16 of the Cochrane Handbook (Higgins 2011b).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only, or when data were not available for all participants). When this was not possible, and missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis. We planned to clearly describe assumptions and imputations required to handle missing data and explore the effect of imputation by performing sensitivity analyses. In all analyses, we included the numbers of participants reported by the authors for particular outcome and we performed sensitivity analyses in the case of studies with missing data.

For dichotomous outcomes (e.g. number of withdrawals due to AEs), we planned to calculate the withdrawal rate by using the number of participants randomised in the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we planned to calculate the mean MD or the SMD by using the number of participants analysed at that time point. If the number of participants analysed was not presented for each time point, we planned to use the number of randomised participants in each group at baseline.

Where possible, we planned to compute missing SDs from other statistics such as SEs, CIs or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If standard deviations could not be calculated, we planned to impute them (e.g. from other studies in the meta-analysis) following the advice of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Assessment of heterogeneity

We assessed the clinical and methodological diversity of the included studies, in terms of participants, interventions, outcomes and study characteristics, to determine whether meta-analyses were appropriate. We planned to do this by observing data derived from data extraction tables. We planned to assess statistical heterogeneity by visually inspecting forest plots to look for obvious differences in results among studies, and by using I^2 and Chi^2 statistical tests.

The *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011) advises that an I^2 value from 0% to 40% might not represent important heterogeneity; a value from 30% to 60% may represent 'moderate' heterogeneity; a value from 50% to 90% may represent 'substantial' heterogeneity; and a value from 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions*, we kept in mind that the importance of I^2 depends on the magnitude and direction of effects, and on strength of the evidence for heterogeneity.

We interpreted the Chi^2 test with a P value ≤ 0.10 as evidence of statistical heterogeneity.

If we identified substantial heterogeneity, we planned to report this and investigate possible causes by following the recommendations provided in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Assessment of reporting biases

If possible, we planned to create and examine a funnel plot to explore possible small study biases. In interpreting funnel plots, we planned to examine different possible reasons for funnel plot asymmetry, as outlined in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* and planned to relate this to review results. If we were able to pool more than 10 trials, we planned to undertake formal statistical tests to investigate funnel plot asymmetry in accordance with the recommendations provided in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

To assess outcome reporting bias, we checked trial protocols against published reports. For studies published after 1 July 2005, we searched the International Clinical Trials Registry Platform of the World Health Organization (apps.who.int/trialssearch) for the *a priori* trial protocol. We compared the available protocols with the final results to evaluate whether selective reporting of outcomes occurred.

Data synthesis

We planned to undertake meta-analysis only when this is meaningful (i.e. when treatments, participants and the underlying clinical question are similar enough for pooling to make sense). For the main analyses, we planned to pool results for the longest follow-up point available.

We planned to use a random-effects model and planned to perform a sensitivity analysis based on the fixed-effect model. However, our analyses included either single studies presented on the forest plots, or there was no statistical heterogeneity. Therefore, sensitivity analysis with a fixed-effect model would not have been meaningful.

We planned to restrict the primary analysis of self-reported outcomes in this review to trials at low risk of detection and selection bias. However, there was only one such trial.

'Summary of findings' table

We created a 'Summary of findings' (SoF) table using the following outcomes: mortality, remission, durable remission, disease flare/relapse, total AEs, serious AEs and withdrawals due to AEs. The first SoF table presents the comparison of mepolizumab to placebo for adult patients with EGPA ANCA-associated vasculitis, followed by the SoF table with comparison of active drug (etanercept or belimumab) and standard therapy with standard therapy and placebo in adult patients with GPA ANCA-associated vasculitis and SoF table with comparison of infliximab with rituximab in adult patients with refractory GPA ANCA-associated vasculitis.

Two review authors (JJ and MK) independently assessed the certainty of the evidence. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it relates to studies that contribute data to meta-analyses for prespecified outcomes. We used methods and recommendations described in Sections 8.5 and 8.7, in Chapter 11 and in Chapter

13, Section 13.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; Schünemann 2011a; Schünemann 2011b). We used GRADEpro software to prepare SoF tables (GRADEpro GDT 2015). We justified all decisions to downgrade or upgrade the certainty of studies by using footnotes, and we provided comments to aid the reader's understanding of the review when necessary.

In the 'What happens' column of the SoF table, we provided the absolute percentage difference, the relative percentage change from baseline and the NNTB or the NNTH (but only when the outcome showed a statistically significant difference).

Subgroup analysis and investigation of heterogeneity

If possible, we planned to carry out the following subgroup analyses.

- Newly diagnosed or relapsing - as treatment effects may differ in participants receiving treatment for the first time and those receiving repeated treatment.
- Different dosage regimens - different doses may show different treatment effects.
- Duration of treatment - duration of treatment may also influence the results.
- Type of AAV.
- ANCA status.

We planned to use the following outcomes in subgroup analyses.

- Remission.
- Total AEs.

We planned to use the formal test for subgroup interactions in Review Manager (RevMan 2014) and apply caution in interpreting subgroup analyses, as advised in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We planned to compare the magnitude of effects between subgroups by assessing the overlap of confidence intervals of the summary as estimated. Non-overlap of confidence intervals indicates statistical significance.

Since the included studies recruited participants with GPA/MPA only or with EGPA only (relapsing or refractory) we decided to summarise the results separately in the population groups (GPA and EGPA) due to their clinical heterogeneity, as combining them would not be clinically meaningful. We did not have enough studies to carry out other subgroup analyses, therefore, we provided the results in subgroups presented by the authors of the analysed studies, if there was stratification for that characteristic at randomisation.

Sensitivity analysis

We planned to carry out the following sensitivity analyses.

- Effect of assessing study risk of bias - as adequate allocation concealment and outcome assessor blinding.
- Effect of imputing missing data.
- Effect of including different types of data (i.e. instead of change value, final value for continuous outcomes; instead of adjusted value, unadjusted value).

However, only one study reported excluding participants from analysis (WGET 2005) and only in the control group. We repeated the analyses that included this study in the scope of the outcomes for the excluded participants, with the assumption that the participants missing in the control group had the best possible outcome.

Since we had planned to perform analyses across all AAV and based on clinical heterogeneity, we decided to pool the data separately for each type of AAV. We performed sensitivity analysis by pooling the different AAV types together for the outcomes for which we had data from more than one study.

Interpreting results and reaching conclusions

We followed the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (see Chapter 12) (Schünemann 2011b) when interpreting results, and we were aware of distinguishing the lack of evidence of effect from the lack of effect. We based our conclusions only on findings from the quantitative or narrative synthesis of the studies included in the studies used in this review. We avoided making recommendations for practice, and our implications for research suggest priorities for future studies while outlining the remaining uncertainties in this area.

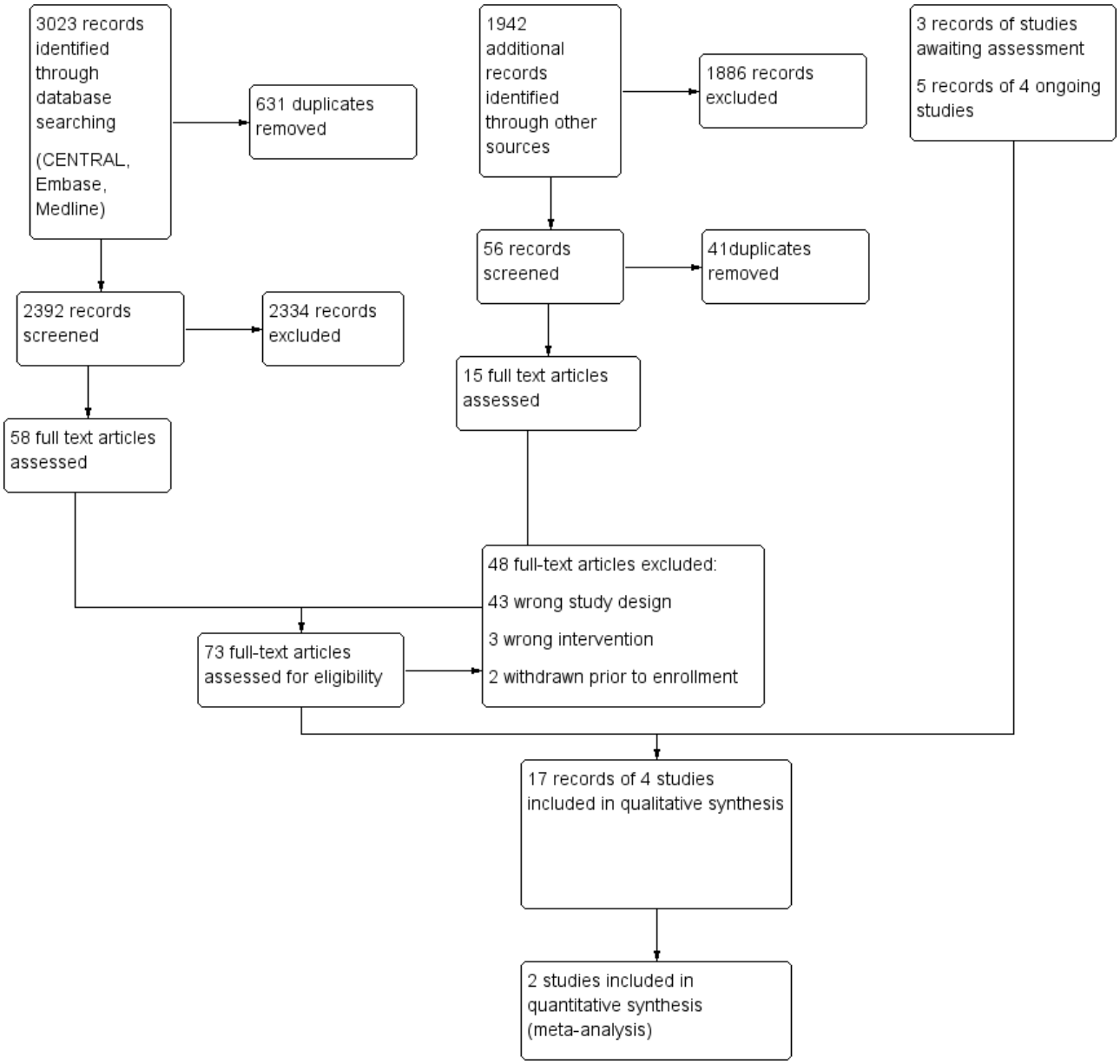
RESULTS

Description of studies

Results of the search

We performed our final searches on 16 August 2019. After removing duplicates, we identified 3023 records. We searched trial registries on 28 August 2019 and found 1835 additional records (Figure 1). Of those records, we retrieved 73 and reviewed them in full text. We excluded papers due to wrong study design (43 papers) or wrong intervention (three papers). We excluded two studies that were withdrawn and stopped by the sponsor because they did not enrol any participants (BIANCA-SC, Eculizumab 2011) and thus published no results. We identified three studies that still await assessment, as there was insufficient information in the databases. Two of them were closed without being completed (NIAID 1999, NIAID 2002); one was terminated due to slow recruitment, and posted no results (ABAVAS 2008).

Figure 1. Study flow diagram.



Searching trials registries, we identified four ongoing studies (ABROGATE; ALEVIATE; AAVTCZ; COMBIVAS). The ABROGATE (NCT02108860) and COMBIVAS (NCT03967925) trials are ongoing and are currently recruiting participants. ALEVIATE trial (NCT01405807) has completed recruitment but follow-up is ongoing. In AAVTCZ trial (JPRN-UMIN000024574) first enrolment was planned on 1st May 2017.

Searching the databases reporting on AEs, we identified no relevant studies.

Reasons for study exclusions are reported in Characteristics of excluded studies.

We included four studies fulfilling criteria of our review (de Menthon 2011; Wechsler 2017; WGET 2005; BREVAS 2018). These studies were reported in 17 references.

Included studies

The four included studies were described as RCTs. Three were described as double blind (BREVAS 2018; Wechsler 2017; WGET 2005. One study provided no information about blinding (de Menthon 2011). All records were available in English. We extracted data from full-text publications for all of them, and supplemented these, when available, with data posted in clinicaltrials.gov and clinicaltrialsregister.eu (BREVAS 2018).

We presented details of the methods, participants, interventions and outcome measures in each study in Characteristics of included studies.

Funding

One study was funded from a commercial source (BREVAS 2018). One study was funded from a hospital research program (de

Menthon 2011). Two studies had mixed funding from public and commercial sources (Wechsler 2017; WGET 2005).

Participants

The included studies enrolled a total of 440 participants with ANCA vasculitis. The number of participants ranged from 17 (de Menthon 2011) to 181 (WGET 2005). All trials enrolled adult participants (18 years of older). Participants with GPA were included in three studies (de Menthon 2011; WGET 2005; BREVAS 2018). One of those studies also included participants with MPA (BREVAS 2018), but the results of MPA participants were added to the GPA participant analysis. The fourth study focused on participants with relapsing or refractory EGPA (Wechsler 2017). Participants in de Menthon 2011 had refractory disease and failed previous standard treatment.

The mean age of participants was between 48 years (control group of Wechsler 2017) and 56 years (SD 14) (belimumab group of BREVAS 2018). The proportion of females varied between 37% in etanercept group (WGET 2005) to 62% in mepolizumab group (Wechsler 2017). The proportion differed more in de Menthon 2011 study, where there were 12.5% of females in rituximab group and 89% in infliximab group.

Study duration

All studies lasted at least one year. The treatment was maintained up to12 months (de Menthon 2011), 52 weeks (Wechsler 2017), 12 months after the last participant was randomised (BREVAS 2018), and a median of 25 months in etanercept and 19 months in placebo group in WGET 2005 . BREVAS 2018 did not report on mean or median treatment duration. Reported follow-up differed among the studies: Wechsler 2017 followed participants for 8 weeks, while in de Menthon 2011 study the average follow-up reached 30.6 months. In WGET 2005 the mean follow-up for the overall cohort was 27 months, and in BREVAS 2018 study follow-up was approximately four years.

Location

One study was carried out in the USA (WGET 2005). One was conducted in several French hospitals (de Menthon 2011). Two trials were conducted by international groups in the USA and Europe (BREVAS 2018; Wechsler 2017).

Setting

Two trials were conducted in clinical centres (Wechsler 2017; WGET 2005) and one in hospitals (de Menthon 2011). The setting for one study was not reported (BREVAS 2018).

Interventions

One study compared two pharmacological treatments: rituximab at a dose of 0.375 g/m^2 versus infliximab at a dose of 3 mg/kg (de Menthon 2011). Three studies compared active drugs with placebo: belimumab at a dose of 10 mg/kg (BREVAS 2018), mepolizumab 300 mg (Wechsler 2017) and etanercept 25 mg twice a week (WGET 2005).

Major outcome measures

All studies reported mortality as the number of deaths (BREVAS 2018; de Menthon 2011; Wechsler 2017; WGET 2005). Remission was reported in three studies (de Menthon 2011; Wechsler 2017; WGET 2005). One study assessed complete and partial remission, defined as the absence of active vasculitis manifestation (BVAS = 0) and partial regression of the clinical manifestations and a decrease in BVAS by > 50%, respectively (de Menthon 2011). The second study reported remission as the proportion of participants who had remission (BVAS = 0 and the receipt of prednisone at a dose of ≤ 4.0 mg/d over 52 weeks) for a certain period of time (in five categories of remission accrual; however, we described only remission for at least one week and remission for at least 24 weeks); and at weeks 36 and 48 of the study treatment period (Wechsler 2017). The third trial assessed disease remission defined as a BVAS/WG of 0 (WGET 2005).

Three studies also reported durable or sustained remission (de Menthon 2011; Wechsler 2017; WGET 2005), defined as remission for at least six months (WGET 2005); remission achieved within 24 weeks and sustained until week 52 (Wechsler 2017); or persistent remission, defined as remission during a long-term follow-up (de Menthon 2011). In BREVAS 2018, all participants were in remission at the beginning of the study. The study authors looked at the maintained remission at one and two years (BVAS = 0).

Minor outcome measures

All trials published data regarding number of participants with confirmed disease relapse/flares (BREVAS 2018; de Menthon 2011; Wechsler 2017; WGET 2005). BREVAS 2018 assessed time to first relapse, which was defined more broadly than vasculitis relapse, i.e. at least one major BVAS item or a minimum total BVAS score of 6 or receiving prohibited medications for any reason, which resulted in treatment failure. The study also reported sensitivity analysis using vasculitis only relapse defined as a minimum total BVAS score of 6, at least one pre-defined major BVAS item or receiving prohibited medications for vasculitis (BREVAS 2018). The study reported on major relapse, defined as number of participants who experienced at least 1 major BVAS item (BREVAS 2018). Only one study assessed health-related quality of life change, using scores for the physical and mental health aspects of the SF-36 (WGET 2005). One study reported the mean score for the VDI at the end of the trial (WGET 2005). Two trials published data regarding disease damage.

AEs were reported in all studies (BREVAS 2018; de Menthon 2011; Wechsler 2017; WGET 2005).

Excluded studies

The most common reason for exclusion (n = 43) was the wrong study design. In three trials, the intervention was inappropriate. Two studies were withdrawn prior to enrolment. Reasons for exclusion are provided in Characteristics of excluded studies.

Risk of bias in included studies

Details for each study are presented in Characteristics of included studies. Figure 2 shows the overall risk of bias in each domain for studies included in this review. The risk of bias by trial can be seen in Figure 3.

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

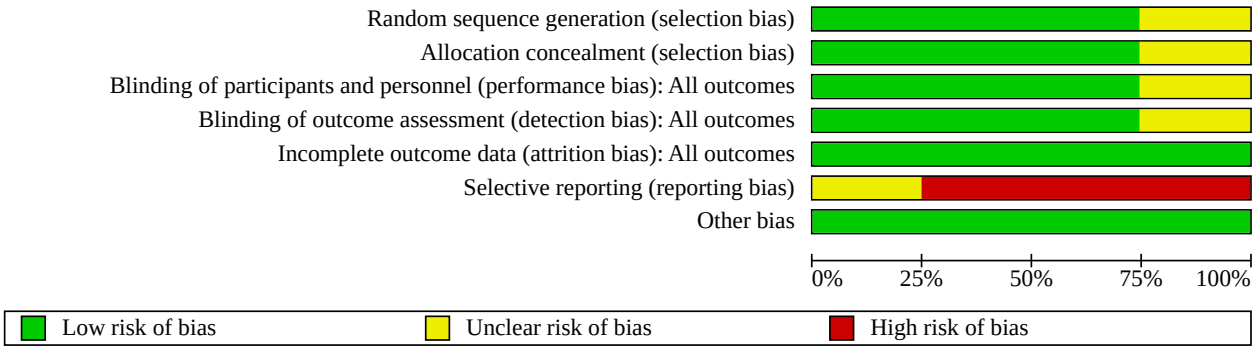
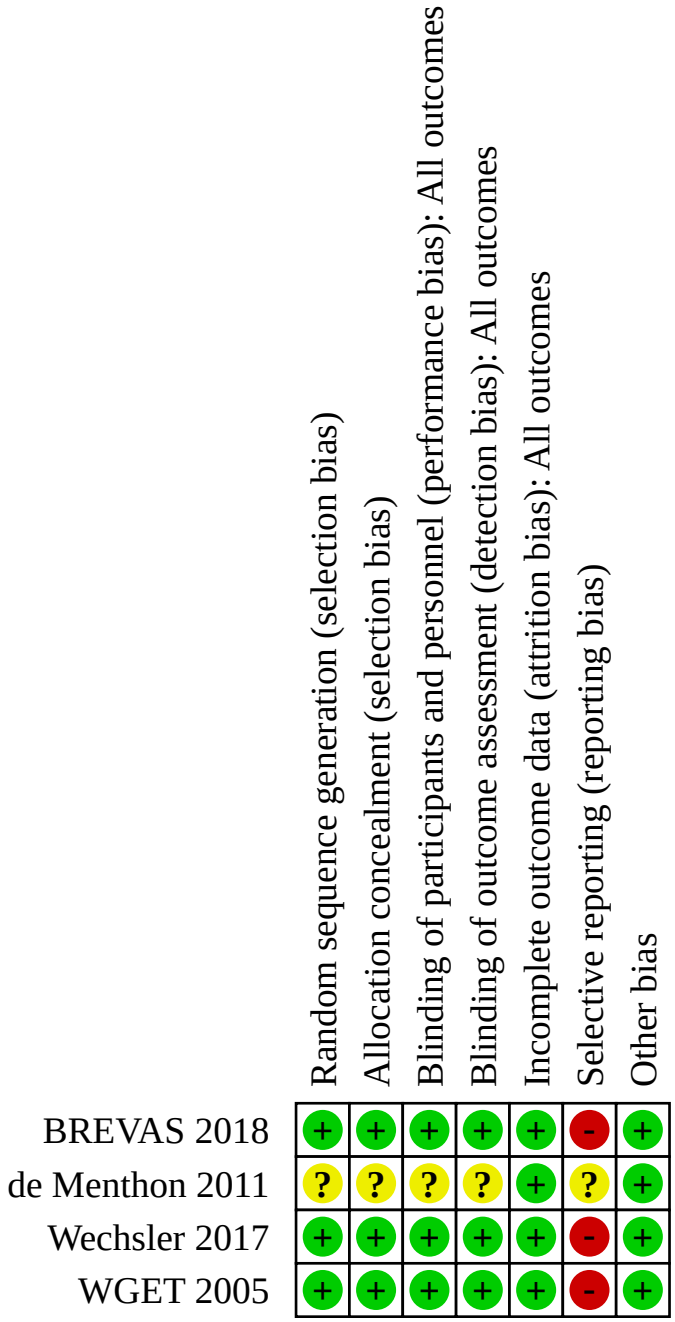


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



All included studies were published in full articles. None of the studies was at low risk of bias in all domains.

Random sequence generation

Randomisation methods were not reported in one study (de Menthon 2011). In BREVAS 2018 the authors reported the use of an interactive web-response system, so we assume that the sequence generation was computer-based. In the two remaining studies,

randomisation was stratified, including generating permuted blocks of varying length (WGET 2005), and centralised computer-generated permuted-block schedule (Wechsler 2017).

Allocation

Allocation concealment was at unclear risk of bias in one study (de Menthon 2011) and at low risk of bias in the three remaining studies (BREVAS 2018; Wechsler 2017; WGET 2005).

Blinding

Three studies stated that they were double-blind, with participants blinded (BREVAS 2018; Wechsler 2017; WGET 2005). One study did not report detailed information about blinding we assessed the risk of bias as unclear (de Menthon 2011). Three studies reported blinding of investigators (BREVAS 2018; Wechsler 2017; WGET 2005). However, in one study the authors highlighted that one potential source of bias in blinding personnel was injection site reactions in the treatment group (WGET 2005). Blinding of outcome assessors was reported in three studies and those trials were judged to be at low risk of bias (BREVAS 2018; Wechsler 2017; WGET 2005). In one study, blinding of outcome assessors was not reported and we assessed the risk of bias as unclear (de Menthon 2011).

Incomplete outcome data

We judged all four studies contributing data to be at a low risk of attrition bias (BREVAS 2018; de Menthon 2011; Wechsler 2017; WGET 2005).

Selective reporting

For one study, no protocol was available, so it was not possible to judge if all outcomes were reported. However, the study reported all important vasculitis outcomes and AEs (de Menthon 2011). In another study, all of its protocol-specified major and minor outcomes were reported, but other benefit endpoints listed in the protocol were not reported (BREVAS 2018). We judged two studies with protocols to be at high risk of bias, as data on treatment outcomes were reported incompletely (Wechsler 2017; WGET 2005).

Other potential sources of bias

Three studies appeared free of other potential sources of bias (BREVAS 2018; de Menthon 2011; Wechsler 2017; WGET 2005).

Effects of interventions

See: **Summary of findings 1** Mepolizumab compared to placebo for adults with EGPA ANCA-associated vasculitis; **Summary of findings 2** Active drug (etanercept or belimumab) with standard therapy compared to standard therapy with placebo for adults with GPA ANCA-associated vasculitis; **Summary of findings 3** Infliximab compared to rituximab for adults with refractory GPA ANCA-associated vasculitis

The studies included in the review enrolled participants with GPA (three studies: BREVAS 2018; de Menthon 2011; WGET 2005) or EGPA (one study: Wechsler 2017) or MPA (one study: BREVAS 2018). Studies compared a single drug with placebo or with another active drug. The population in BREVAS 2018 was mixed and included mostly participants with GPA (79%), but also with MPA (21%). Therefore, we summarised the results from all studies for the GPA and EGPA populations separately, as well as for comparisons of active drug with placebo and active drug with another active drug.

Comparison 1: Mepolizumab compared to placebo in adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis

Major outcomes

Mortality

In Wechsler 2017, one death was reported in mepolizumab group and no deaths in placebo group (Peto OR 7.39, 95% CI 0.15 to 372.38; Analysis 1.1).

Remission

Wechsler 2017 reported this outcome as accrued weeks of remission over a 52-week period. Overall, more participants had any remission (for at least one week) in the mepolizumab group compared with the placebo group (RR 2.77, 95% CI 1.62 to 4.74; Relative benefit increase 177%, 95% CI 62 to 374%; RD 33.8%, 95% CI 11.9% to 71.5%; NNTB 3, 95% Cl 2 to 6; Analysis 1.2) and more participants had at least 24 weeks of accrued remission (28% versus 3%; RR 9.5, 95% CI 2.3 to 39.2; Relative benefit increase 850%, 95% CI 130 to 3820%; RD 25%, 95% Cl 3.8% to 112%; NNTB 4, 95% Cl 3 to 8; Analysis 1.2).

In the analysis of accrued weeks of remission over follow-up, more participants in the mepolizumab group (28%) had ≥ 24 weeks of accrued remission over 52 weeks of follow-up than in the placebo group (3%) (OR 5.91, 95% CI 2.68 to 13.0).

Durable remission

In Wechsler 2017, durable remission was defined as remission within the first 24 weeks that was sustained until week 52. More participants in the mepolizumab group, compared with control group, experienced durable remission (13 versus 1 participants; RR 13.0, 95% CI 1.75 to 96.33; Relative benefit increase 1200%, 95% CI 75 to 9563%; RD 17.6%, 95% CI 1.1 to 140.2%; NNTB 6, 95% Cl 4 to 13); Analysis 1.3).

Disease relapse

Wechsler 2017 reported time to first relapse over 52 weeks of the study, and the number of participants with first EGPA relapse. Fewer participants relapsed in the mepolizumab group than in the placebo group (56% versus 82%; RR 0.68, 95% CI 0.53 to 0.86; RRR 32%, 95% CI 14 to 47%; RD -26.4%, 95% CI from -38.7 to -11.5; NNTB 4, 95% CI 3 to 9; Analysis 1.4). The time to relapse was longer in active treatment, compared with the placebo group (hazard ratio (HR) 0.32, 95% CI 0.21 to 0.5). The study reported details regarding relapses in the mepolizumab and placebo groups in the following categories: any vasculitis relapses (43% versus 65% of participants); any asthma (37% versus 60%); any sinonasal relapses (35% versus 51%); vasculitis only (18% versus 22%); asthma only (19% versus 32%); sinonasal only (6% versus 12%); and any combinations of these.

Total AEs

Wechsler 2017 reported similar rates of participants with any AEs in the mepolizumab and placebo groups (97% versus 94%; RR 1.03, 95% CI 0.96 to 1.11; RD 3%, 95% CI from -4 to 1; Analysis 1.5), and also reported any event considered by the investigator to be related to the trial agent (51% versus 35%; RR 1.46, 95% CI 0.98 to 2.17; RD 16%, 95% CI from -0.3 to 33; Analysis 1.5). The most common AEs reported in the study were headache (32% versus 18%), nasopharyngitis (18% versus 24%), arthralgia (22%

versus 18%), sinusitis (21% versus 16%), and upper respiratory tract infection (21% versus 16%). The number of participants who experienced local injection-site reactions and systemic reaction was similar in the two groups (15% versus 13% and 6% versus 1% respectively). For serious AEs, see Analysis 1.6.

Serious and severe AEs

Wechsler 2017 defined all serious AEs as "any untoward medical occurrence that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of existing hospitalisation, resulted in disability or incapacity, was a congenital anomaly or birth defect, or was indicative of possible drug-induced liver injury with hyperbilirubinaemia" and specific serious events defined as serious AE which was considered by the investigator as related to the trial agent. The most common serious AE was exacerbation or worsening of asthma (3% of the participants in the mepolizumab group versus 6% of participants in the placebo group).The percentages of participants with any serious AEs or any serious AEs considered to be related to the trial agents were similar in the mepolizumab and placebo groups (18% versus 26%, RR 0.67, 95% CI 0.35 to 1.28; RD -8.7, 95% CI from -17.2 to 7.4; and 4% versus 4%; RR 1.0, 95% CI 0.21 to 4.78; RD 0, 95% CI from -3.5% to 16.7%; Analysis 1.6). One participant in the mepolizumab group died from cardiac arrest during the trial, this participant had a history of coronary artery disease.

Withdrawals due to AEs

Wechsler 2017 reported similar number of participants withdrawn from the mepolizumab and placebo groups due to AEs (3% versus 1%; RR 2.0, 95% CI 0.19 to 21.54; RD 1.5% 95% CI -1.2% to 30.2%; Analysis 1.7).

Minor outcomes

Treatment response

Wechsler 2017 did not analyse treatment response as an outcome.

Health-related quality of life

Wechsler 2017 provided no results of quality of life assessments.

Control of asthma/sinonasal disease

Wechsler 2017 reported changes from baseline in ACQ-6 and SNOT-22 scores, but only on graphs. We contacted the study authors to obtain numeric data, without success. To estimate the effect, we used software to read the values from the graph. Values were presented as mean change from baseline in both groups (Analysis 1.8; Analysis 1.9). For ACQ-6, the change from baseline was similar in both groups; the estimated difference was -0.3 (95% CI -0.6 to 0.00) (Analysis 1.8). The minimal clinically important difference, as reported by the authors, is 0.5.

For SNOT-22, the change from baseline was similar in both groups; the estimated difference was -4.66 (95% CI -10.69 to 1.36) (Analysis 1.9). The minimal clinically important difference, as reported by the authors, is 8.9.

Disease damage

Wechsler 2017 reported data on change from baseline in the VDI in the form of a graph. We contacted the study authors to obtain numeric data, without success. To estimate the effect, we used software to read the values from the graph. Values were presented as mean change from baseline in both groups (Analysis 1.10). The change from baseline was similar in both groups; the estimated difference was -0.07 (95% CI -0.37 to 0.23) (Analysis 1.8). The minimal clinically important difference has not been determined.

Comparison 2: Etanercept or belimumab compared with placebo in adults with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis

Major outcomes

Mortality

In WGET 2005, four deaths were observed in the group receiving etanercept and two deaths in the group receiving placebo. In BREVAS 2018, one death was observed in the belimumab group and no deaths were observed in the placebo group. When we pooled the results of two studies comparing active drug with placebo, we found similar odds of death in both groups (Peto OR 2.45, 95% CI 0.55 to 10.97; Analysis 2.1).

Remission

WGET 2005 reported remission, defined as a BVAS/WG of 0 at any time during the trial (as a minor outcome), in 80 participants in the etanercept group and 84 participants in the placebo group (RR 0.07, 95% CI 0.89 to 1.07; Analysis 2.2). WGET 2005 stratified participants at randomisation according to the disease severity at baseline (severe or limited) and found similar effect in both groups (HR 0.91, 95% CI 0.63 to 1.32 and HR 0.8, 95% CI 0.44 to 1.43, P for interaction = 0.77).

Durable remission

In WGET 2005, sustained remission was defined as BVAS/WG = 0 for ≥ 6 months. The number of participants with sustained remission in the etanercept and placebo groups was similar (62 versus 64 participants; RR 0.93, 95% CI 0.77 to 1.11; RD -5.3%, 95% CI -17.3% to 8.3%; Analysis 2.3). The study stratified participants at randomisation according to the disease severity at baseline (severe or limited) and found similar effects in both groups (HR 0.91, 95% CI 0.6 to 1.37; and HR 0.82, 95% CI 0.42 to 1.6; P for interaction = 0.85).

At baseline, all participants in BREVAS 2018 were in remission. In our analysis, we used the total number of participants included in an intention-to-treat (ITT) analysis. BREVAS 2018 reported that, at the year one, week 48 time point, 38 (71.7% of all included in ITT) participants were in remission in the belimumab group and 43 (82.69% of all included in ITT) were in remission in the placebo group (RR 0.87, 95% CI 0.7 to 1.07; calculated using RevMan calculator). At the year two, week 28 time point, 21 (39.62% of all included in ITT) participants were in remission in the belimumab group and 26 (50% of all included in ITT) were in remission in the placebo group (RR 0.79, 95% CI 0.52 to 1.22; calculated using RevMan calculator) .

Disease flare/relapse

WGET 2005 reported that similar percentage of participants in etanercept and placebo groups had no disease flares during the study (42.7% versus 42.9%; RR 0.98, 95% CI 0.76 to 1.27; RD -1.1%, 95% CI -13.7% to 15.4%; Analysis 2.5) and the number of any disease flares per 100 person-years was similar between the groups (66.3 versus 74.1 per 100 person-years, HR 0.89, 95% CI 0.62 to 1.28) as was the number of severe flares (14.9 versus 12.8 per 100 person-years, HR 1.05, 95% CI 0.61 to 1.8). Similar percentages of

participants who achieved sustained remission relapsed in both groups (30.6% of 62 participants in etanercept versus 32.8% of 64 participants in placebo group).

BREVAS 2018 reported a similar percentage of participants in the belimumab and placebo groups who experienced vasculitis relapse as the first relapse (11.3% versus 15.4%; RR 0.74, 95% CI 0.27 to 1.97; RD -4%, 95% CI from -17 to 9; Analysis 2.4) and among participants with relapse the time to first vasculitis relapse was similar in the belimumab and placebo group (median 251 (range 25-371) days, 105.5 (range 15-789) days; HR 0.88, 95% CI 0.29 to 2.65). In BREVAS 2018, the first protocol-specified event that included relapse was defined as a BVAS score of ≥ 6, presence of at least one predefined major BVAS item, or the receipt of prohibited medications for any reason. One participant in the belimumab group had a major relapse during the double-blind phase of the study. In the placebo group, none of participants experienced major relapse (RR 2.94, 95% CI 0.12 to 70.67; RD 2%, 95% CI from -3 to 7; Analysis 2.4).

Total AEs

WGET 2005 reported AEs defined as any medical condition in participants who received etanercept and were graded according to the National Cancer Institute Toxicity Grading Scale. The study reported three types of AEs: severe (grade 3), life-threatening (grade 4) and deaths as fatal AEs (grade 5). For serious or severe AEs, see Analysis 2.8).

WGET 2005 reported specific types of AEs such as cytopenias, infections, congestive heart failure and venous thrombotic events. The frequency of cytopenias, infections, venous trombotic events and congestive heart failure was similar in etanercept and placebo group. Similar numbers of participants experienced grade 2 to grade 5 infections (49.4% in each group) and venous thrombotic events (10 events in each group; P = 0.92).

BREVAS 2018 defined AEs as an untoward medical occurrence in a participant, temporally associated with the use of a drug, whether or not it was considered to be related to the medicinal product. In this study, 92.5% participants in belimumab group experienced at least one adverse event, compared to 82.7% participants in the placebo group, at any time during the study (see Analysis 2.6). Most AEs were infections and infestations (56.6% of participants in the belimumab group and 57.7% of participants in the placebo group). The study reported similar percentages of participants in both the belimumab and placebo groups with AEs other than serious (60.38% versus 63.46%; RR 0.95, 95% CI 0.7 to 1.28; RD -3.2%, 95% CI from -19 to 17.8; Analysis 2.7).

Serious and severe AEs

WGET 2005 provided the definition of severe AEs as adverse event grade 3, life-threatening events as adverse event grade 4 and fatal AEs as grade 5. The study reported similar percentages of participants with such events in the etanercept and placebo groups (56.2% versus 57.1%), which included deaths (four versus two cases). WGET 2005 did not report serious AEs.

BREVAS 2018 defined serious AEs as AEs that resulted in death, were life-threatening, required hospitalisation or prolongation of hospitalizations, or resulted in disability or incapacity. There was one death in the belimumab group and no deaths in the placebo group (see Analysis 2.1). The study reported similar percentage of participants with serious AEs in the belimumab and placebo groups (33.96% versus 30.77%). The study reported that there were four cases of any malignancies (including non-melanoma skin cancer) in the belimumab group (anal cancer, basal cell carcinoma, plasma cell myeloma and one malignancy not specified) with no such events in control group. There was also one case of ischaemic stroke (resulting in death). One participant in the control group was diagnosed with anaemia, one with pancytopenia, and one with sinus bradycardia. One participant in the belimumab group experienced acute kidney injury. Severe AEs were reported in 11 (20.8%) participants in the belimumab group and seven (13.5%) participants in the placebo group. When we pooled the results of both studies (BREVAS 2018; WGET 2005) we found non significant difference between the groups in frequency of serious or severe AEs (RR 1.0, 95% CI 0.8 to 1.27; RD 0, 95% CI from -9.5% to 12.8%; Analysis 2.8).

WGET 2005 reported six solid cancers (two cases of mucinous adenocarcinoma of the colon, one metastatic cholangiocarcinoma, one renal-cell carcinoma, one breast carcinoma, and one liposarcoma), all in the etanercept group (RR 13.29, 95% CI 0.76 to 232.45; RD 0, 95% CI 0 to 0; Analysis 2.9). The rate of cancers in the etanercept and placebo groups were similar (three cases versus four cases of cutaneous basal-cell or squamous-cell carcinomas). It is also important to mention AEs during long-term post-trial follow-up. These data were available for 153 participants (85% of the original cohort), with a median follow-up time of 43 months. During the follow-up, the rates of cancer were similar in the etanercept and placebo groups (10% versus 7%; RR 1.58, 95% 0.54 to 4.61; RD 3.8%, 95% CI from -3% to 23.4%; Analysis 2.9). However, the combined risk of solid malignancy from time of trial enrolment remained higher for the etanercept group (relative risk increase (RRI) 186%, 95% CI 8 to 662; RD 10%, 95% CI 1% to 19%) (WGET 2005).

Withdrawals due to AEs

WGET 2005 reported nine withdrawals due to AEs in etanercept group and three withdrawals in placebo group. In the BREVAS 2018 publications we identified some discrepancies in the numbers of participants withdrawn from the study. In a figure depicting participant flow, the authors reported seven withdrawals due to AEs in the belimumab group and three withdrawals in placebo group. However, in the results section describing AEs, the authors reported that eight participants in the belimumab group and six participants in the placebo group had AEs leading to study withdrawal. We contacted the authors to clarify this and we received information that the discrepancies were due to different categorisation of AEs in those two study sites, specifically vasculitis flares (classified as lack of efficacy on in the patient flow figure and as AE in the AEs section). The study authors suggested that we use of the number of withdrawals due to AEs presented on the figure depicting patient flow. When we pooled the results from both studies, we observed an increased risk of withdrawal due to AEs in the active drug group as compared with the placebo group (RR 2.66, 95% CI 1.07 to 6.59; RRI 166%, 95% CI 7 to 559%; RD 7%, 95% CI 0.3% to 23.5%; NNTH 15, 95% CI 8 to 100; Analysis 2.10). We used the number of participants withdrawn reported in AEs section of BREVAS study in sensitivity analysis, where the difference became non-significant (Analysis 4.1).

Minor outcomes

Treatment response

Treatment response was reported in WGET 2005 study as sustained low level of disease activity (BVAS/WG < 3 for at least 6 months) and no significant difference was found between the etanercept and control groups (RR 0.96, 95% CI 0.86 to 1.06; RD -4% 95%CI -13% to 5%; Analysis 2.11). The study stratified participants at randomisation according to the disease severity at baseline (severe or limited) and found a similar effect in both groups (HR 0.7, 95%CI 0.48 to 1.03 and 1.24, 95% CI 0.69 to 2.24, P for interaction = 0.11).

Health-related quality of life

In WGET 2005, the assessment of health-related quality of life was based on the SF-36 questionnaire. The results were only reported as improvements in physical and mental health domains in the etanercept and placebo groups (7.7 and 5.7 versus 8.4 and 8.0).

Control of asthma/sinonasal disease

WGET 2005 and BREVAS 2018 did not report on on this outcome.

Disease damage

WGET 2005 reported a mean score of VDI at baseline and at the end of the trial. The increase in the score was similar in the etanercept and control groups (from 1.6 to 2.0 versus from 1.0 to 1.7, P = 0.5). In all participants the most frequently reported items were hearing loss (25.6%) and proteinuria (> 0.5 g of protein in 24 hours; 18.9%).

BREVAS 2018 reported minimal changes in VDI score in the belimumab group (year one, week 48: 0.1 ± 0.38; year two, week 24: 0.2 ± 0.50) and no change in the placebo group (year one, week 48: 0.0 ± 0.15; year two, week 24: 0.0 ± 0.00).

Comparison 3: Infliximab versus rituximab added to steroids and cytotoxic agents in adults with refractory GPA

Major outcomes

Mortality

In a single study comparing two active drugs, one participant died in each group (de Menthon 2011) during 12 months of the study (Peto OR 0.88, 95% CI 0.05 to 15.51; Analysis 2.1). In additional follow-up (mean 30.6 months SD 15.4), two more deaths were reported, one in the infliximab group and one in the rituximab group.

Remission

A single study by de Menthon 2011 reported complete remission (CR), defined as BVAS = 0. During 12 months of the study, two participants in the infliximab group had complete remission, while in the rituximab group four participants had complete remission. No beneficial effect in complete remission was found in the case of infliximab in comparison with rituximab (RR 0.44, 95% CI 0.11 to 1.81; RD -28%, 95% Cl -44.5% to 40.5%; Analysis 2.2). During follow-up, in the infliximab group, one participant remained in remission. Two participants relapsed, were switched to other treatments and achieved remission. In the rituximab group, three participants remained in remission in the long term. One participant relapsed, achieved remission again and remained in remission.

Durable remission

de Menthon 2011 reported long-term complete remissions, defined as persistent remission during additional follow-up beyond 12 months. The study reported one long-term remission in the infliximab group during 28.9 +/- 15.4 months and four long-term complete remissions during 32.9 +/- 16.7 months of follow-up in rituximab group (RR 0.22, 95% CI 0.03 to 1.60; RD -39%, 95% Cl -48.5% to 30%; Analysis 2.3).

Disease flare/relapse

de Menthon 2011 reported that during long-term follow-up, two out of three participants in remission relapsed, while in rituximab one out of five participants in remission relapsed but achieved complete response again.

Total AEs

de Menthon 2011 reported AEs graded according to the World Health Organization classification (2003), defined AEs as severe, moderate and mild events. Two participants in the infliximab group experienced incidental or mild allergic reactions during infusion. These were one facial erythema and one transient bronchospasm that was described as severe and resulted in withdrawal from the trial. Two participants (one in the infliximab group, one in the rituximab group) experienced severe AEs and died. During the additional long-term follow-up in the infliximab group, with mean time of follow-up 30.6 ± 15.4 months and with all participants available, one participant had infliximab-related skin rash; one participant experienced hepatitis subsequent to cytomegalovirus infection nine months after the end of the treatment protocol. In the rituximab group, one participant was diagnosed with prostate carcinoma 27 months after the last rituximab infusion. One participant was diagnosed with pancreatic carcinoma two months after the last rituximab infusion, and died three months later.

Serious and severe AEs

de Menthon 2011 reported severe AEs and deaths. There was one severe allergic reaction (transient bronchospasm) in one participant in the infliximab group, and there were two deaths during the study (one in each group) (RR 1.78, 95% CI 0.2 to 16.1; RD 9.8%, 95% Cl -10% to 188.8%; Analysis 2.8). Two additional deaths occurred during follow-up (one in each group). One participant in infliximab group died of invasive aspergillosis at month 2, 60 days after first infusion (severe AE). One participant in the rituximab group experienced sudden death on day 23 of the trial, with no autopsy and no obvious explanation.

Withdrawals due to AEs

de Menthon 2011 reported one withdrawal due to AEs in the infliximab group and did not report withdrawals in the rituximab group (RR 2.7, 95% CI 0.13 to 58.24; RD 0 95% Cl 0% to 0%; Analysis 2.10).

Minor outcomes

Treatment response

de Menthon 2011 reported partial remission (PR), defined as partial regression of the disease and < 50% BVAS (as a part of major outcome). During 12 months of the study, one participant in the infliximab group and one participant in the rituximab group had PR (RR 0.89, 95 CI 0.07 to 12.0; RD -1.4% 95%Cl -11.6% to 137.5%; Analysis 2.11).

Health-related quality of life

de Menthon 2011 did not report on quality of life.

Control of asthma/sinonasal disease

de Menthon 2011 did not report on this outcome.

Disease damage

de Menthon 2011 did not report on this outcome.

Sensitivity analysis

We carried out sensitivity analyses for WGET 2005 in Comparison 2, including all randomised and control group participants, assumed to have the best possible outcome. Sensitivity analyses did not change the results of the trial reported for the main analyses (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7).

Our primary plan outlined in the protocol was to perform analyses across all types of ANCA-associated vasculitis, but based on clinical heterogeneity as outlined above, we decided to pool the data separately for each type of AAV. We performed sensitivity analysis by pooling the different AAV types together for the outcomes for which we had data from more than one study (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6). The results were similar across AAV-type and treatment comparisons subgroups for mortality, disease relapse, any serious or severe AEs and withdrawals due to AEs (Analysis 5.1; Analysis 5.4; Analysis 5.5; Analysis 5.6, but the effects differed across AAV-type and treatment comparisons for any remission and durable remission (Analysis 5.2; Analysis 5.3). This analysis is limited by the low number of studies (single studies in most subgroups).

DISCUSSION

Summary of main results

The aim of this review was to provide an overview of the benefits and harms of anti-cytokine targeted therapies in patients with ANCA-associated vasculitis. The review identified four RCTs investigating the effects of anti-cytokine interventions on mortality, remission, durable remission, disease flare, any AEs, any serious AEs, and any withdrawals due to AEs. Due to differences in studied populations and treatments, the results were not pooled together, but were analysed in three comparisons: 1) mepolizumab versus placebo in relapsing or refractory EGPA; 2) etanercept/belimumab added to standard therapy versus standard therapy with placebo in GPA (with 8% participants with MPA); and 3) infliximab versus rituximab in refractory GPA.

A single trial of mepolizumab compared with placebo in relapsing or refractory EGPA showed that the use of experimental treatment probably decreases the risk of disease relapse (moderate-certainty evidence) and may increase the probability of accruing at least 24 weeks of remission and durable remission (low-certainty evidence). However, due to low-certainty evidence and a low number of events there is uncertainty regarding the effect of mepolizumab on mortality. The evidence on any AEs, any severe adverse effects and any withdrawals due to adverse effects was limited, as the study included a low number of participants.

We found low-certainty evidence that in patients with GPA (with 8% participants with MPA), etanercept or belimumab added to standard therapy as compared with standard therapy alone may increase the probability of withdrawal due to AE; etanercept or belimumab may have little or no impact on serious AEs; etanercept may have little or no impact on durable remission, and belimumab may have little or no impact on major relapse. Moderate-certainty evidence suggests little or no improvement in disease flare with the use of etanercept. Low-certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy, when compared with standard therapy, does not increase or reduce mortality.

Due to very low-certainty evidence for all outcomes, the effects of infliximab as compared to rituximab in the management of patients with refractory GPA is uncertain.

Overall, based on obtained data, there is low- to moderate-certainty evidence of the clinically relevant effect of one specific anti-cytokine, mepolizumab, in one form of ANCA-associated vasculitis (relapsing or refractory EGPA), with uncertain side effect risk; but none for any other anti-cytokines in any vasculitis.

Overall completeness and applicability of evidence

It should be highlighted that only four studies were included in the review, of which three had major limitations and one was conducted in a small number of participants. This is a significant limitation of the available data. Three additional studies were planned, but were withdrawn prior to enrolment or closed without being completed, and do not add evidence to our systematic review. We have also identified four ongoing studies that may add evidence in future updates of the review.

The majority of included studies (three of the four included) were conducted mainly in participants with GPA. However, one of these studies included a small group of participants with refractory disease, so it had to be analysed separately and its results may not be applicable to patients with non-refractory disease. The remaining two studies included mainly participants with GPA, but also a small subgroup of participants with MPA, who comprised 8% of the overall pooled population from those two studies. Therefore, the results of these three studies, mainly in participants with GPA, may not be applicable to patients with MPA or other form of ANCA-associated vasculitis, such as EGPA.

One study was conducted in participants with EGPA. The authors reported that compared to placebo in relapsing or refractory EGPA participants, mepolizumab resulted in higher rates of remission (including durable remission) and fewer disease relapse events. The results of this study may not be applicable to patients with other forms of ANCA-associated vasculitis, such as GPA and MPA.

The studies included in the review assessed all or most of the major outcomes defined by this review, but they included small numbers of patients and for several outcomes the confidence intervals were wide and imprecise. Wechsler 2017 showed the beneficial effect of mepolizumab in relapsing or refractory EGPA, which maybe considered clinically relevant. However, the risk of side effects is uncertain, as the number of patients in the study was not large enough to assess safety.

None of the studies included in this systematic review address potential benefit in lowering the mortality in ANCA-associated vasculitis, as the number of death events was too low to draw any conclusions.

To summarise, the studies identified by this review addressed questions for single drugs in single groups of patients. There are still many gaps in evidence, suggesting the need for further studies. The effects of interventions in patients with other forms of ANCA-associated vasculitis are not sufficiently covered by current evidence. Further investigation of safety of these interventions is also needed.

Quality of the evidence

All the included studies were described as double-blind, randomised placebo-controlled trials. Two studies were judged to be at low risk of bias in all domains except selective reporting, which was judged to be at high risk of bias (Wechsler 2017; WGET 2005). One study was judged to be at unclear risk of bias for random sequence generation, high risk of bias for blinding, unclear risk of bias for allocation and low risk of bias for incomplete outcome data (de Menthon 2011). Additionally for this study, we had concern about risk of bias in selective outcome reporting, as there was no protocol available (de Menthon 2011). One study did not provide information about all outcomes specified in the protocol (BREVAS 2018). Three studies appeared free of other potential sources of bias. The studies enrolled different types of patients. Patients with GPA were included in three studies (BREVAS 2018; de Menthon 2011; WGET 2005). However, BREVAS 2018 included a mixed population, with the majority of participants with GPA and one fifth of the participants with MPA, analysed together. Another study enrolled participants with relapsing or refractory EGPA (Wechsler 2017). For this reason, we analysed these separately. However, all of the analyses provided imprecise results with wide CIs. Publication bias was not assessed due to the low number of studies. For the comparison of mepolizumab and placebo in patients with EGPA, we judged the certainty of the evidence for the following outcomes to be low: mortality, remission accrued for at least 24 weeks, durable remission, any AE, any serious AEs and any withdrawals due to AEs. We judged the cetertainty of evidence to be moderate for disease relapse. The certainty of evidence was downgraded due to imprecision. For the comparison of etanercept/belimumab and placebo in patients with GPA/MPA, we judged the certainty of evidence to be low for mortality, remission, durable remission, major relapse, any severe or serious AEs, and any withdrawals due to AEs. We judged the certainty of evidence to be moderate for disease flare. The certainty of evidence was downgraded due to risk of bias (high risk of selective outcome reporting in both studies) and/or for imprecision. For the comparison of infliximab with rituximab, the certainty of evidence was very low for all outcomes. It was downgraded for risk of bias in the study and imprecision.

Potential biases in the review process

We conducted an extensive search to identify relevant studies. In addition to a comprehensive database search we sought information from other sources, such as registries of clinical trials, the websites of regulatory agencies, pharmacovigilance agencies and drug safety updates. We checked for additional data in all primary studies, review articles and relevant manufacturer websites. We searched PubMed for errata or retractions from included studies published in full-text. Study selection on the basis of titles and abstracts and on the basis of full texts, data extraction and risk of bias assessments were done by two review authors independently and additionally checked by a senior review author to reduce chance of errors, while our GRADE assessment was done by a junior review author and checked by two senior review authors.

Agreements and disagreements with other studies or reviews

This Cochrane Review stays in agreement with other literature reviews in this topic (Silva-Fernandez 2014, Lutalo 2015; Souza 2017), pointing out that there is insufficient evidence regarding use most of biological treatments in ANCA-associated vasculitis. However, Silva-Fernandez 2014 had broader scope and addressed all types of vasculitis and all types of biological therapies. Silva-Fernandez 2014 was not focused only on evidence from RCTs, but also included previously published systematic reviews, RCTs, cohort studies and case series. That review had its last search in April 2014 and included two RCTs that we also identified. Silva-Fernandez 2014 concluded that etanercept is not effective in maintaining remission in patients with GPA and that large RCTs on biological therapies in systemic vasculitis are needed. Lutalo 2015 was not described as a systematic review. It aimed to summarise both the clinical trials and clinical practice regarding use of biological therapies in the treatment of ANCA-associated vasculitis. They searched literature up to November 2014, described three of the RCTs that were included in our review (BREVAS 2018 was still ongoing at the time). Lutalo 2015 concluded that drugs belonging to anti-TNF-α agents are not recommended in inducing remission in patients with ANCA-associated vasculitis and that the data for other biological agents (including those assessed in our review) is limited. The guidelines of the Brazilian Society of Rheumatology, based on a systematic review with literature searched up to October 2016, recommended not to use etanercept in the induction of remission in patients with ANCA-associated vasculitis (Souza 2017). Our review adds to the evidence from previous reviews the results of two studies on anti-cytokine agents: the results of BREVAS 2018 in patients with GPA and the results of Wechsler 2017 on mepolizumab in relapsing or refractory EGPA.

AUTHORS' CONCLUSIONS

Implications for practice

We found only four studies, of which three had major limitations and one was conducted in a small number of patients. There is thus limited evidence for drawing conclusions about the benefit and risk of anti-cytokine therapy in ANCA-associated vasculitis. In patients with relapsing or refractory EGPA, compared to placebo, we found moderate-certainty evidence that mepolizumab probably decreases disease relapse, and low-certainty evidence that mepolizumab may increase disease remission. There was low-certainty evidence on the similar frequency of AEs and serious AEs in both groups. The effect of mepolizumab as compared with placebo is uncertain, due to low-certainty evidence.

We found low-certainty evidence that etanercept/belimumab may increase the probability of withdrawal due to AEs, and low-certainty evidence that etanercept/belimumab may have little or no impact on durable remission, major relapse and serious AEs. We found moderate-certainty evidence of no improvement in disease flare. Low-certainty evidence suggests that active drug (etanercept or belimumab) added to standard therapy when compared with standard therapy does not increase or reduce mortality.

Due to very low-certainty evidence for all outcomes, the effects of infliximab, as compared to rituximab, in the management of patients with refractory GPA, is uncertain.

Implications for research

Future research should be adequately powered and should ensure proper adherence to treatment to assess the effects of the intervention on clinically important outcomes in patients with ANCA-associated vasculitis (AVV). It should also be reported properly, which will enable meaningful conclusions regarding the long-term benefits and harms of anti-cytokine targeted therapy. Due to the high heterogeneity of enrolled cases, especially concerning the uneven population of GPA and MPA in BREVAS 2018, further investigations on belimumab benefits and harms are justified. Due to limited evidence on the safety of mepolizumab, further investigations are justified.

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CHARACTERISTICS OF STUDIES

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

BREVAS 2018

Study characteristics

Methods	**Study design:** double-blind parallel RCT (initially planned as phase 3 trial)
	Location: Australia, Belgium, Canada, Czech Republic, Germany, Ireland, Italy, Mexico, Peru, Poland, Russian Federation, Spain, Switzerland, United Kingdom, United States
	Setting: Not reported
	Number of centres: 37
	Time frame of the study: 20 March 2013 through 06 February 2017
	Duration of follow-up: approximately up to 4 years

BREVAS 2018 *(Continued)*

Participants	**Inclusion criteria:** • Diagnosis of Wegener's granulomatosis or microscopic polyangiitis (Chapel Hill criteria). • Disease flare in the past 26 weeks, which required treatment with high dose corticosteroids and one of the following drugs: rituximab or intravenous or oral cyclophosphamide. • Anti-proteinase 3 (anti-PR3) or anti-myeloperoxidase (anti-MPO) antibodies positive at any time prior to enrolment. • Achieved remission in up to 26 weeks after first dose of induction treatment. • Maintenance therapy start no more than 2 weeks after confirmation of remission. **Exclusion criteria:** • The coexistence of another autoimmune disease. • Pregnant or breastfeeding. • Other than rituximab a B cell targeted therapy at anytime. • Investigational biological agent therapy within the last 60 days. • Acute or chronic infections within the past 60 days which required management . • Current drug or alcohol abuse or dependence. • HIV, hepatitis B, or hepatitis C positive status (current and past). • History of severe allergic reaction to contrast agents or biological agents. **Total number of participants:** 106 participants randomised, Belimumab group N = 53, Placebo group N = 52, N = 1 participant randomised in error **Characteristics:** GPA 79%, MPA 21% (The results of MPA patients were added to the GPA patient analysis) Mean (SD) age: Belimumab 56 ± 14, Placebo 54 ± 14 Female sex: Belimumab 49.1%, Placebo 48.1% CrCl value: NR Disease duration (time since diagnosis, median(SD)): Belimumab 2.3 years (range 0.3-14.9), placebo 1.3 years (0.01-20.6) Age at onset of symptoms: NR Race/ethnic group: Belimumab: African American/African Heritage 1, American Indian or Alaskan Native 6, Central/South Asian Heritage 0, White 46. Placebo: African American/African Heritage 1, American Indian or Alaskan Native 5, Central/South Asian Heritage 2, White 44 Disease diagnosed at the enrolment of the study: NR Disease assessment index BVAS (mean(SD)): NR Damage index: NR Global assessment: NR Quality of life: NR Disease severity (limited vs severe): NR Organ involvement: NR Prior treatment: NR ANCA type: anti-PR3 77%, anti-MPO 23%

BREVAS 2018 *(Continued)*

Interventions	**Belimumab group:** Belimumab 10 mg/kg administered intravenously over 1 hour, on days 0, 14, 28 and every 28 days thereafter until 12 months after the last participant was randomised (In Belgium- all participants received belimumab at dose 10mg/day every 28 days until Week 24, and a final evaluation was at Week 28). **Placebo group:** Placebo administered intravenously over 1 hour on days 0, 14, 28 and every 28 days thereafter until 12 months after the last participant was randomised. (In Belgium-only open-label extension, all participants received belimumab 10mg/day every 28 days until Week 24, and a final evaluation was at Week 28). Mean or median treatment duration not reported. **Description of treatment and concomitant treatment:** All participants received oral azathioprine at a target dose of 2 mg/kg/day.
Outcomes	**Major outcomes:** • Information on Clinicaltrials.gov register: Time to first relapse; Information in the full text publication: Time to first protocol-specified event. The same definition: the number of days from Day 0 until the patient experienced a relapse (relapse date – treatment start date +1), a BVAS score of ≥ 6, or at least 1 predefined major item on the BVAS, or receiving medications which were prohibited for any reason - which resulted in treatment failure • Vasculitis relapse (used for sensitivity analysis only, not described on Clinicaltrials.gov register): defined as a minimum total BVAS score of 6, at least one pre-defined major BVAS item or receiving prohibited medications for vasculitis **Minor outcomes:** • Information on Clinicaltrials.gov register: major relapse - number of patients experiencing at least 1 major BVAS item during the double-blind phase of the trial, while in full text publication it was defined as time to the first major vasculitis relapse **Other outcomes:** • AEs - serious and non serious AEs. All AE were collected through 8 weeks following administration of the last dose of drug (Safety Endpoints of Special Interest: all cause mortality, serious and/or severe infections, opportunistic infections, malignant neoplasms, selected serious psychiatric events, suicidality assessment, infusion reactions including hypersensitivity reactions, immunogenicity) • Time from Day 0 to first minor or major relapse (defined as experiencing at least 1 minor BVAS item and/or using a dose of rescue medication). At double-blind Week 48 of year 1 and double-blind Week 28 (specified in protocol) of year 2 and by visit; • Proportion of patients in remission (BVAS=0 and corticosteroid dose < 10 mg/day); • Absolute change in VDI (reported at week 48 of year 1 and week 24 of year 2) • Proportion of participants with any increase in VDI (not reported); • Absolute change in BVAS (not reported); • Proportion of participants with any increase in BVAS (not reported); • Proportion of participants with any increase in BVAS organ domains, also by domain (not reported); • Proportion of patients with no relapse (not reported, but could be calculated from reported data)
Notes	**Discontinuation:** 32 (9.52%) participants (12 participants from placebo group and 20 participant from belimumab group): 10 (9.52%) due to AEs, 11 (10.48%) lack of efficacy, 1 (0,95%) protocol violation, 2 (1.9%) other-study closed/terminated, 5 (4.76%) physician decision, 3 (2.86%) consent withdrawal. **Funding:** GlaxoSmithKline The study was initially planned as phase 3 trial with planned enrolment of approximately 300, then it ws changed to exploratory trial with enrolment of approximately 100 patients, the design changed

BREVAS 2018 *(Continued)*

	from "event-driven" to "fixed completion" specified as 12 months after the randomisation of the last patient.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A total of 164 participants were screened and 106 were enrolled and randomised in a 1:1 ratio to receive placebo or belimumab" - information from EudraCT and clinicaltrials.gov. Authors reported the use of interactive web response system so it was assumed that the sequence generation was computed based.
Allocation concealment (selection bias)	Low risk	Central randomisation: Use of interactive web response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" - information from EudraCT and clinicaltrials.gov.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" - information from EudraCT and clinicaltrials.gov.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT was performed (all randomised participants who received at least one dose of study drug) and all patients were included in primary analysis, no missing outcome data identified, all reasons of withdrawn were described.
Selective reporting (reporting bias)	High risk	Full protocol available; not all outcomes specified in protocol were reported (see in the description of outcomes).
Other bias	Low risk	No other biases were identified.

de Menthon 2011

Study characteristics

Methods	**Study design:** double-blinded parallel RCT **Location:** France: Dijon, Nancy, Lyon, Bordeaux, Rennes, Caen, Nantes, Reims, Rouen, Paris **Setting:** Hospitals **Number of centres:** Not reported **Time frame of the study:** June 2004 through June 2007 **Duration of follow-up mean (SD):** 30.6 ± 15.4 months (28.9 ± 15.4 months for the infliximab group and 32.9 ± 16.7 months for the rituximab group)
Participants	**Inclusion criteria:** Wegeners granulomatosis according to Chapel Hill criteria, refractory disease despite optimal treatment: failure to respond to steroids and several immunosuppressants (alone or combination), among the latter - at least pulses and then oral cyclophosphamide. **Exclusion criteria:** not reported

de Menthon 2011 *(Continued)*

Total number of participants: 17 participants randomised, Infliximab group N=9, Rituximab group N=8

Characteristics:

Mean (SD) age: Infliximab 52.9 ± 17, Rituximab 51.4 ± 15

Female sex: Infliximab 88.9%, Rituximab 12.5%

CrCl value: Not reported

Disease duration (time since diagnosis, mean(SD)): Infliximab 74.8 ± 70 months, Rituximab 76.3 ± 47 months

Age at onset of symptoms: Not reported

Race/ethnic group: Not reported

Disease diagnosed at the enrolment of the study: Not reported

Disease assessment index BVAS (mean(SD)): Infliximab 13.1 ± 5.5 Rituximab 12.6 ± 7

Damage index: Not reported

Global assessment: Not reported

Quality of life: Not reported

Disease severity (limited vs severe): 100% refractory

Organ involvement: Infliximab: Diagnosis: Poor General Condition 5 (56%), Ear nose and throat involvement 8 (89%), lung nodules 9 (100%), purpura 2 (22%), arthralgias 3 (33%), scleritis 3 (33%), mononeuritis multiplex 3 (33%), rapidly progressing glomerulonephritis 4 (44%)
Inclusion: Poor General Condition 6 (67%), Ear nose and throat involvement 6 (67%), lung nodules 8 (89%), mononeuritis multiplex 1 (11%), rapidly progressing glomerulonephritis 2 (22%), renal insufficiency 1 (11%)

Rituximab: Diagnosis: Poor General Condition 6 (75%), Ear nose and throat involvement 4 (50%), lung nodules 5 (62.5%), purpura 1 (12.5%), arthralgias 4 (50%), mononeuritis multiplex 2 (25%), rapidly progressing glomerulonephritis 2 (25%), tracheal stenosis 2 (25%), pericarditis 1 (12.5%), orchitis 1 (12.5%), subcutaneus nodules (12.5%), retroocular pseudotumour 1 (12.5%)
Inclusion: Poor General Condition 5 (67.5%), Ear nose and throat involvement 5 (67.5%), lung nodules 4 (50%), mononeuritis multiplex 2 (25%), rapidly progressing glomerulonephritis 2 (25%),pleural effusion 1 (12.5%), tracheal stenosis 2 (25%), subcutaneus nodules 1 (12.5%), retroocular pseudotumour 1 (12.5%)

Prior treatment: Not reported

ANCA positive in immunofluorescence (14 c-ANCA and 1 p-ANCA) at inclusion: infliximab: 6, Rituximab: 7

Interventions	**Infliximab group:** The initial IV dose (3 mg/kg) administered on days 1 and 14 and the response was assessed on day 42. In case of a complete remission, the dose maintained for the next 6 months. In case of a partial remission or no response - the dose increased to 5 mg/kg, and the therapeutic response re-evaluated 4 weeks later (day 73). In case of a complete remission after dose increase - the dose unchanged for the rest of the study (14 infusions). In case of no response on day 73 - infliximab stopped. **Rituximab group:** Administered IV (0.375g/m2) on days 1, 8, 15 and 22.

de Menthon 2011 *(Continued)*

	In case of a partial or complete remission at month 2, the same dose maintained for subsequent infusions (months 4, 8 and 12). In case of no response at month 2 - rituximab stopped. **Description of treatment and concomitant treatment:** Infliximab: One patient (12.5%) was taking corticosteroid (CS) at inclusion, with mean ± SD doses of 19.4 ± 11.8 mg/day for the infliximab group, 3 patients did not receive oral cyclophosphamide (CYC) after failure of IV CYC (cytopenia, haemorrhagic cystitis and high cumulated doses of CYC) Rituximab: One patient was taking CS at inclusion 41.4 ± 28 mg/day for the rituximab group (P = 0.34), 1 patient did not receive oral CYC after IV CYC failure because of high cumulated doses of CYC.
Outcomes	**Major outcomes:** • Complete remission - defined as the absence of active vasculitis manifestation with BVAS score of 0 • Partial remission - defined as partial regression of the disease manifestations and decrease in BVAS score of >50% **Minor outcomes:** • Treatment tolerance and adverse effects - AEs were classified according to the World Health Organization classification (2003): severe for fatal or life-threatening events; moderate for events requiring treatment, medical procedure or hospitalisation; mild for symptoms requiring only drug discontinuation, and incidental for very mild symptoms that did not contraindicated continuing therapy.
Notes	**Discontinuation:** 10 (58.82%) participants (7 participants from infliximab group and 3 participant from rituximab group): 7 (41.17%) due to progressive disease, 1 (5.88%) due to AE, 2 (11.76%) died, **Funding:** This trial was supported by a grant from the Programme Hospitalier de Recherche Clinique (PHRC 2003 n. P020931).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After inclusion, patients were randomly assigned to receive either infliximab or rituximab". Authors do not describe methods of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information how participants and personnel were blinded and the outcome is likely to be influenced by lack or insufficient of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information how participants and personnel were blinded and the outcome is likely to be influenced by lack or insufficient of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No protocol available, so insufficient information to judge if all outcomes reported; outcomes that are of interest in the review have been reported.
Other bias	Low risk	No other biases were identified.

Wechsler 2017

Study characteristics	
Methods	**Study design:** double-blinded parallel RCT **Location:** USA: Boston, Denver, Cleveland, Salt Lake City. Italy: Pisa, Firenze, Milano. France: Montpellier, Marseille, Bron, Paris, Suresnes. UK: Portsmouth, Leicester. Spain: Barcelona. Belgium: Bruxelles. Canada: Hamilton, Toronto. Germany: Kirchheim Gunter Teck, Neumünster, Hessen, Thueringen, Kiel, Freiburg. Japan: Miyagi, Kanagawa. **Setting:** clinical centres **Number of centres:** 31 **Time frame of the study:** February 2014 through June 2015 **Duration of follow-up:** continued until September 2016 (8 weeks)
Participants	**Inclusion criteria:** • Informed consent • Participants ≥ 18 years • A diagnosis of EGPA for at least six months based on the history or presence of: asthma and eosinophilia and two or more of the following additional features: histopathological evidence of eosinophilic vasculitis or perivascular eosinophilic infiltration, or eosinophil–rich granulomatous or Inflammation in biopsy; mono- or polyneuropathy, non-fixed pulmonary infiltrates; sino–nasal abnormality, cardiomyopathy (confirmed in echocardiography or MRI); glomerulonephritis (hematuria, red cell casts, proteinuria); alveolar haemorrhage (confirmed by bronchoalveolar lavage); palpable purpura; positive test for ANCA (MPO or PR3). • Relapsing or refractory disease. • CS at stable dose at least 4 weeks prior to baseline (Visit 2). • Immunosuppressive therapy in stable dose for the 4 weeks prior to baseline and during the study. • ECG measurements: QTc(F) < 450 msec or QTc(F) < 480 msec if bundle branch block. • Females of childbearing potential practicing an acceptable method of birth control during a clinical trial and for 4 months after the last study drug administration. • French participants if either affiliated to, or a beneficiary of, a social security system. **Exclusion criteria:** • Diagnosis of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. • Organ-threatening EGPA according to EULAR criteria. • Life–threatening EGPA defined as any of the following features within 3 months before screening: requirement for intensive care; severe alveolar haemorrhage or haemoptysis which required transfusion or ventilation or haemoglobin level below 8 g/dL (< 80 g/L) or drop in haemoglobin level of more than 2 g/dL (> 20 g/L) within 48-hour period due to alveolar haemorrhage; rapidly progressive glomerulonephritis (creatinine over 2.5 mg/dL (> 221 µmol/L) or rise in creatinine over 2 mg/dL (> 177 µmol/L) within 48-hour period; severe involvement of gastrointestinal system, central nervous system, heart; • other diseases: a current cancer or history of cancer in remission for less than 12 months before screening; unstable liver disease, cirrhosis or any known biliary abnormalities (except Gilbert's syndrome or asymptomatic gallstones); severe or clinically significant cardiovascular disease not controlled with standard therapy. and other clinically significant diseases not associated with EGPA and not controlled with standard therapy. • Chronic or ongoing active infectious disease which required systemic treatment. • Parasitic infection within 6 months before screening . • Chronic hepatitis B according to the study definitions, but participants HBsAb positive, only (i.e. negative for HBsAg and HBcAb) with a history of hepatitis B vaccination can be included. • Known HIV infection.

Wechsler 2017 *(Continued)*

- Known allergy or intolerance to a monoclonal antibody or biologic therapy.
- Mepolizumab within a year before screening .
- Receiving prohibited treatment: CS 4 weeks prior to baseline (oral dose of >50 mg/day prednisolone/prednisone or any dose IV or subcutaneous CS); Omalizumab within 130 days before screening; CYC (oral within 2 weeks before baseline, IV within 3 weeks before baseline, if total white blood cell count is at least $4x10^9$/L); rituximab within 12 months before screening and recovery of peripheral B-cell count to within the normal range; immunoglobulin (IV or SC within 6 months before screening); interferon-α within 6 months before screening; anti–tumour necrosis factor agent within 12 weeks before screening; anti-CD52 (alemtuzumab) within 6 months before screening.
- Creatinine above 2.5 mg/dL (221 µmol/L), White blood cell count below 4 x109/L, Platelet count below 120,000/mm^3, Hemoglobin below 8 g/dL (< 80 g/L).
- Pregnant or breastfeeding or plan to become pregnant during the time of trial.
- Alcohol or substance abuse within 2 years before screening.
- Treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug before screening.
- Current participation in any other interventional clinical study.
- French participant - had participated in any study using an investigational drug during the previous 30 days or 5 half-lives.

Total number of participants: 136 participants randomised, Mepolizumab group n = 68, Placebo group n = 68

Characteristics:

Mean age: Mepolizumab 49 ± 12 Placebo 48 ± 14

Female sex: Mepolizumab 42 (62%); Placebo 38 (56%)

BMI mean (SD): Mepolizumab 27.5 (4.4); Placebo 28.2 (5.7)

CrCl value: not reported

Disease duration (time since diagnosis; mean (SD)): Mepolizumab 5.2 (4.4) years; Placebo 5.9 (4.9) years

Age at onset of symptoms: not reported

Race/ethnic group (%): Mepolizumab white 89.7% other 10.3% Placebo white 94.1% other 5.9%

Disease diagnosed at enrolment to the study: not reported

Disease assessment BVAS > 0 Mepolizumab 37 (54%) Placebo 48 (71%)

VDI mean (SD): Mepolizumab 4.7 (3.4) Placebo 4.4 (2.8)

Global assessment: NR

Quality of life assessment: NR

Disease severity (limited /severe): NR

Organ Involvement n (%): Mepolizumab Asthma and eosinophilia 68 (100%), Neuropathy (mono or poly) 32 (47%), Pulmonary infiltrates (non-fixed) 50 (74%), sinonasal abnormality 64 (94%), cardiomyopathy 13 (19%), glomerulonephritis 1 (1%), alveolar haemorrhage 3 (4%), palpable purpura 9 (13%), biopsy evidence 25 (37%) Placebo Asthma and eosinophilia 68 (100%), Neuropathy (mono or poly) 24 (35%), Pulmonary infiltrates (non fixed) 48 (71%), sinonasal abnormality 64 (94%), cardiomyopathy 7 (10%), glomerulonephritis 0 (0%), alveolar haemorrhage 1 (1%), palpable purpura 8 (12%), biopsy evidence 31 (46%)

Prior treatment:

Mepolizumab: Prednisolone or prednisone dose — mg/day median (range) 12 (7.5-40) Immunosuppressive therapy at baseline 41 (60%)

Wechsler 2017 *(Continued)*

	Placebo: Prednisolone or prednisone dose — mg/day median 11 (7.5-50) Immunosuppressive therapy at baseline number (%): 31 (46%) Patients with ANCA laboratory results number (%): Mepolizumab: ANCA positive (MPO or PR3) 13 (19) Placebo: ANCA positive (MPO or PR3) 13 (19)
Interventions	**Mepolizumab group:** mepolizumab 300 mg - 3 separate injections (100 mg each) every 4 weeks, in addition to standard care for 52 weeks. **Placebo group:** subcutaneously, placebo 0.9% sodium chloride 300 mg every 4 weeks, in addition to standard care for 52 weeks **Description of treatment and concomitant treatment:** Participants taking glucocorticosteroids during treatment period: Mepolizumab: Prednisone 47 (69%) Prednisolone 22 (32%) Methylprednisolone sodium succinate 6 (9%) Methylprednisolone 4 (6%) Dexamethasone 1 (1%) Hydrocortisone sodium succinate 1 (1%) Hydrocortisone 1 (1%) Triamcinolone acetonide 1 (1%) Placebo: Prednisone 49 (72%) Prednisolone 22 (32%) Methylprednisolone sodium succinate 4 (6%) Methylprednisolone 4 (6%) Dexamethasone 3 (4%) Hydrocortisone sodium succinate 2 (3%) Triamcinolone 1 (1%)
Outcomes	**Major outcomes:** • The total accrued weeks of remission - the proportions of participants who had remission for a certain period of time, i.e. 0 weeks, > 0 weeks but < 12 weeks, >= 12 weeks but < 24 weeks, >= 24 weeks but <36 weeks, >= 36 weeks. The accrued number of weeks where BVAS = 0 (scale from 0 to 63) and the dose of prednisolone/prednisone below 4 mg/day over the 52 week study treatment period • Remission at both week 36 and week 48 - the proportion of participants who were in remission (i.e., BVAS=0 and prednisolone/prednisone dose below 4 mg/day) at both weeks 36 and 48 of the study treatment period.. **Minor outcomes:** • Remission within the first 24 weeks and continued to have remission until week 52 (proportion of participants). Remission defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day. • The time to first confirmed relapse of EGPA - relapse was defined as any of the following categories: active vasculitis (BVAS > 0), active asthma symptoms or signs and worsening in the score on the Asthma Control Questionnaire (ACQ-6; range, 0 to 6 points,with higher scores indicating worse disease control; minimal clinically important difference, 0.5 points), or active nasal or sinus disease and worsening in at least one of the sinonasal-symptom items which lead to an increase in the glucocorticoid dose to more than 4.0 mg /day of prednisolone (or equivalent), an initiation of or increase in immunosuppressive therapy, or hospitalisation. • The proportion of participants with an average daily prednisolone/prednisone dose during the last 4 weeks of the treatment period within the study (week 48 through 52). The following categories were used: zero, > 0 to ≤ 4.0 mg, > 4.0 to ≤ 7.5 mg, > 7.5 mg. • Total accrued weeks of remission over the 52-week period - number of participants in each category of remission duration. Less stringent definition of remission according to the European League against

Wechsler 2017 *(Continued)*

Rheumatism (EULAR) recommendations for clinical studies in systemic vasculitis was used: a BVAS of 0 and a prednisolone or prednisone dose <= 7.5 mg /day.

- Remission at both week 36 and week 48 and remission within the first 24 weeks and continued to have remission until week 52 with less stringent EULAR definition of remission.
- AEs - Number of participants with local and systemic AEs. An AE is any untoward medical occurrence in a participant of clinical investigation, which is temporally associated with the use of a medicinal product, regardless if considered or not to be related to the medicinal product. AEs which included systemic allergic and non-allergic reactions and local site injection-related reactions were counted throughout the study.

Other outcomes:

- Total duration of sustained remission, i.e., longest period of uninterrupted remission, i.e. BVAS=0 and prednisolone/prednisone ≤ 4 mg/day over the 52 week study treatment period, reported as proportion of participants achieving sustained remission in the following categories: Zero, > 0 to < 12 weeks, >=12 to < 24 weeks, >=24 to < 36 weeks, ≥ 36 weeks.

Notes

Discontinuation: 14 (10.29%) participants (9 participants from placebo group and 9 participant from mepolizumab group): 2 (1.47%) due to AEs, 3 (2.21%) lack of efficacy, 3 (2.21%) met protocol-defined stopping criteria, 1 (0.74%) physician decision, 5 (3.68%) withdrawal from the trial.

Funding:

Supported by grants from GlaxoSmithKline (115921) and the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (U01AI097073), and by the Division of Intramural Research, NIAID, National Institutes of Health.

Ongoing study: Mepolizumab Long-term Access Programme for Subjects who Participated in Study MEA115921. Placebo-controlled Study of Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis in Subjects Receiving Standard-of-care Therapy (ID: MEA116841, ClinicalTrials.gov Identifier: NCT03298061). A Phase III, multi-centre, multinational, non-randomised, open with one arm: mepolizumab 100mg SC.

Estimated Primary Completion Date: September 7, 2018 (Final data collection date for major outcome measure)

Authors contacted for the data reported only on the graphs and not usable for the reporting in the systematic review - information that the results will be posted on clinicaltrials.gov, but not posted yet.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed with the use of a centralized computer–generated, permuted-block schedule, stratified according to three subgroups: participation in a mechanistic–biomarker substudy in the United States, recruitment in Japan, and the remainder of recruited participants."
Allocation concealment (selection bias)	Low risk	"The randomization schedule was generated using the GSK validated randomization software RandAll. Equal numbers of subjects were allocated to each treatment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The randomization schedule was sent as a signed, hard copy, controlled document, marked as private, for the attention of the unblinded qualified designee at each centre or sent as a GSK Secure email to the attention of the unblinded qualified designee. Clinicians who were treating and evaluating patients were unaware of the preparation of the trial agents, the trial-group assignments, and the white-cell counts and white-cell differential counts for the duration of the trial."

Wechsler 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Procedures must be in place to ensure the blind is maintained by any site staff involved in administration of the drug or clinical care or assessment of the subject, and by the subject themselves."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT was performed and all patients were included in primary analysis, no missing outcome data identified.
Selective reporting (reporting bias)	High risk	Not all of the study's pre-specified major outcomes have been reported in the publication such as SF-36 score or WPAI index. ACQ-6 and SNOT-22 score were shown on Figures (and read from them).
Other bias	Low risk	No other biases was identified.

WGET 2005

Study characteristics	
Methods	**Study design:** double-blinded parallel RCT **Location:** USA: Michigan, San Francisco, Rochester, Maltimore, Durham, Cleveland, Boston, New York **Setting:** clinical centres **Number of centres:** 8 **Time frame of the study:** June 2000 through September 2003 **Duration of follow-up mean:** 27 months
Participants	**Inclusion criteria:** • Body weight ≥ 40 kg • GPA diagnosis: at least two of the five criteria of modified Americal College of Rheumatology (ACR) a criteria for the classification of GPA (nasal or oral inflammation; abnormal chest radiograph; active urine sediment; granulomatous inflammation and/or necrotizing vasculitis on tissue biopsy; positive enzyme immunoassay for antibodies to serine proteinase 3). • BVAS/WG of 3 or more within 28 days before the baseline assessment • Completion of all baseline procedures within 14 days before enrolment to trial • Readiness to limit alcohol intake to one drink/week while on methotrexate • Females of childbearing potential practicing an acceptable method of birth control during a clinical trial and no breastfeeding **Exclusion criteria:** • Active systemic infection • White blood cell count < 4000/mm^3 • Platelet count < 120000/mm^3 • Creatinine > 2 mg/dL not associated with GPA for a patient with limited GPA • Hepatic dysfunction of severity which may interfere with trial participation • A history of cancer within the last 5 years except fully excised basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ which has been treated or excised in a curative procedure. • Pregnancy • History of a demyelinating neurological syndrome • Previous therapy with anti-tumour necrosis factor specific therapies

WGET 2005 *(Continued)*

Total number of participants: 181 participants randomised. Etanercept group: 89 Placebo group: 91

Characteristics:

- Mean (SD) age: Etanercept: 52.4 ± 13.9; Placebo: 47.5 ± 16.5
- Mean age at onset of symptoms: Etanercept: 52.4 ± 13.9; Placebo: 47.5 ± 16.5
- Female sex: Etanercept: 33 (37.1%); Placebo: 39 (42.9%)
- BMI value: not reported
- Mean (SD) CrCI value: Etanercept: 1.85 ± 2.05; Placebo: 1.62 ± 1.76
- Disease duration (time since diagnosis, median (IQR)): Etanercept: for new diagnosis: 0.79 months IQR: 0.36–1.38; for previous diagnosis: 36 months IQR:19–61; Placebo: for new diagnosis: 0.66 months IQR: 0.36–1.12; for previous diagnosis: 25 months IQR: 10–50.
- Race/ethnic group (%) Etanercept: white, non-Hispanic 91%; black, non-Hispanic 2.3%; Hispanic 4.5%; other 2.2%; Placebo: white, non-Hispanic 93.4%); black, non-Hispanic 1.1%; Hispanic 3.3%; other 2.2%
- Disease diagnosed at enrolment to the study (%): Etanercept: 34.8%; Placebo: 53.9%
- Disease assessment index BVAS/WG (mean(SD)): Etanercept: 6.5 ± 3.0; Placebo: 7.5 ± 3.7
- Disease assessment VDI: mean ± SD: Etanercept: 1.6 ± 1.9; Placebo: 1 ± 1.4
- Disease assessment index Global assessment (Physicians' global assessment), mean±SD: Etanercept: 5.3 ± 2.3; Placebo: 5.8 ± 2.3
- Disease assessment index baseline Global assessment (Patients' global assessment), mean ±SD: Etanercept: 6.5 ± 2.8; Placebo: 6.4 ± 2.7
- Quality of life mean ± SD: SF-36 physical score: Etanercept: 34.4 ± 9.7; Placebo: 32.6 ± 9.6; SF-36 mental score: Etanercept: 45.4 ± 12.2; Placebo: 42.9 ± 10.9
- Disease severity (limited /severe) [%]: Etanercept: 30.3%; Placebo: 27.5%
- Organ involvement (%): Etanercept: systemic (65.2%); skin (15.7%); mucous membranes/eyes (24.7%); ears, nose, throat (69.7%); cardiovascular (0%); gastrointestinal (0%); pulmonary (51.7%); renal (52.8%); nervous (6.7%); other (44.9%); Placebo: systemic (78%); skin (24.2%); mucous membranes/eyes (27.5%); ears, nose, throat (83.5%); cardiovascular (2.2%); gastrointestinal (2.2%); pulmonary (68.1%); renal (55%); nervous (12.1%); other (35.2%)
- Prior treatment: not reported
- ANCA laboratory results: ever positive by IF (%): Etanercept 85.4%; Placebo: 89.0%: C-ANCA (% of total ANCA positive by IF) Etanercept: 85.3%; Placebo: 89.7%; P-ANCA (% of total ANCA positive by IF) Etanercept: 14.7%; Placebo: 10.3%; ANCA ever positive by EIA (%): Positive for PR3-ANCA Etanercept: 70.8%; Placebo:74.7%; Positive for MPO-ANCA Etanercept: 16.9%; Placebo: 6.6%

Interventions	All participants were followed for 12 months after randomization of the last participant. **Etanercept group**: 25 mg twice a week, subcutaneous; for 25 months (median value) **Placebo group:** lyophilised powder containing 40 mg of mannitol, 10 mg of sucrose, and 1,2 mg of tris(hydroxymethyl)methylamine twice a week, subcutaneous; for 19 months (median value) **Concominant treatment for both groups:** - Patients with severe GPA received cyclophosphamide + glucocorticoids at the time of enrolment. Those with limited GPA receive methotrexate and glucocorticoids. After control of the patients' disease, the standard medications are tapered according to regimens consistent with patient safety to reduce the risk of medication-associated morbidity and to test the benefit of etanercept in sustaining disease remissions. - All patients received prophylaxis against pneumocystis infection and osteoporosis.
Outcomes	**Major outcome:** • Sustained disease remission: defined as a BVAS/WG of 0 for >= six months (three follow-up visits, excluding the first follow-up visit, because of its shorter interval) **Minor outcomes:**

WGET 2005 *(Continued)*

- The number and rate of flares during the treatment phase: defined as an increase of >= one point in the BVAS/WG.
- Percentage of patients with a sustained low level of disease activity: defined by a BVAS/WG of less than 3 for at least six months.
- Remission: the percentage of patients with remission defined as a BVAS/WG score of 0.
- Cumulative area under the curve for the BVAS/WG.
- AEs related to Wegener's granulomatosis or its treatment: defined as any untoward medical occurrences in patients who received etanercept, regardless of their presumed relationships to treatment, were graded according to the National Cancer Institute Toxicity Grading Scale.
- Quality of Life: defined as results from SF-36 scale.
- Mortality.
- Time to mortality; but not reported.
- Number achieving BVAS ≤ 2; but not reported.
- Time from randomisation to first BVAS/WG=0; but not reported.
- Time from sustained remission to first disease flare; but not reported.
- Number of severe flares.
- Number of limited flares.
- End-stage renal disease; but not reported.
- Physician's global assessment of GPA activity.
- Patient's global assessment of GPA activity.
- Birmingham Vasculitis Damage Index.

Other outcomes:

- Change from baseline in Westergren erythrocyte sedimentation rate; but not reported.
- Change from baseline in serum C-reactive protein; but not reported.
- Change from baseline in ANCA titers; but not reported.
- Completion of prednisone taper regimen; but not reported.
- Switch from cyclophosphamide to methotrexate at 3 to 6 months after randomisation; but not reported.
- Cumulative doses of cyclophosphamide and methotrexate; but not reported.
- Cumulative doses of prednisone; but not reported.

Notes

Discontinuation: 69 (38.12%) participants (34 participants from placebo group and 35 participant from etanercept group): 12 (6.63%) due to AEs, 4 (2.21%) died, 20 (11.94%) had treatment failure, 9 (4.97%) physician decision, 18 (9.94%) participant decision, 6 (3.31%) other reasons.

Funded by:

- A contract (N01-AR-9-2240) with the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases;
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- General Clinical Research Center grants to Johns Hopkins University School of Medicine (M01-RRO-2719), Boston University (M01-RRO-00533), the University of Michigan (M01-RRO-0042), and Duke University (M01-RR-30) from the National Institutes of Health,
- National Center for Research Resources;
- Amgen.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment assignments are generated in permuted blocks of varying lengths."

WGET 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation. "Patients are assigned to one of six experimental medication “bins”: A1, B2, C3, D4, E5, or F6" (information obtained from the author of the study)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants receive medicinal dosage from the same bin. "The packaging of etanercept and placebo into identical vials". Blinding of study personnel ensured. "One potential source of unmasking among clinical personnel is the occurrence of injection site reactions. Injection site reactions have been reported in both the placebo- and etanercept-assigned groups in other trials, albeit more commonly among etanercept-assigned patients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The board is masked to the specific treatment assignment of each group. In the evaluation of all data regarding the harm and benefit, the board receives data relating to treatment group (i.e., either etanercept or placebo) labelled as either treatment “A” or “B.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, however 7% of patients in control group were excluded from primary analysis because lost to follow-up and 0% were excluded in etanercept group. Including those patients would not have clinically relevant impact on the intervention effect estimate for major outcome
Selective reporting (reporting bias)	High risk	One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
Other bias	Low risk	No other biases were identified.

AE – adverse event
ANCA – antineutrophil cytoplasmic antibody
anti-MPO – anti-myeloperoxidase
anti-PR3 – Anti-proteinase 3 -
BMI – body mass index
BREVAS- Belimumab in Remission of VASculitis
BVAS – Birmingham Vasculitis Activity Score
BVAS/WG – Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis
CrCl – creatinine clearance
EGPA – eosinophilic granulomatosis with polyangiitis
EudraCT - European Union Drug Regulating Authorities Clinical Trials Database
EULAR – European League against Rheumatism
GPA – granulomatosis with polyangiitis
HBcAb – hepatitis B core antibody
HBsAg – hepatitis B Surface antigen
HIV - human immunodeficiency virus
ITT – intention to treat
IV – intravenous
MPA – microscopic polyangiitis
NR – not reported
QTc(F) – QT interval corrected using Fridericia formula
RCT – randomized controlled trial
SC – subcutaneous
SD – standard deviation
VDI – Vasculitis Damage Index
WGET - Wegener's Granulomatosis Etanercept Trial

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

Study	Reason for exclusion
Anwar 2017	Wrong study design - not RCT (editorial)
Berti 2017	Wrong study design - not RCT (non-systematic review)
BIANCA-SC	Withdrawn prior to enrolment
Booth 2002	Wrong study design - not RCT (letter)
Booth 2004	Wrong study design - not RCT (open-label, multi-centre, prospective trial, not randomised); patients in both study subgroups received infliximab
Bosch 2007	Wrong study design - not RCT (systematic review)
Cattran 2011	Wrong intervention - mycophenolate mofetil vs azathioprine, not anti-cytokine drugs was assessed
Eculizumab 2011	Withdrawn (the study failed to enrol any patient and sponsor wished to stop)
Fraser 2016	Wrong study design - not RCT
Guillevin 2005	Wrong study design - not RCT (editorial)
Herrmann 2012	Wrong study design - not RCT; single arm study
Jayne 2015	Wrong study design - not RCT (non-systematic review)
Kahn 2010	Wrong study design - not RCT (letter to the editor)
Kontkanen 2010	Wrong study design - not RCT (letter to the editor)
Krishna 2017	Wrong study design - not RCT (non-systematic review)
Lamprecht 2004	Wrong study design - not RCT (letter)
Lamprecht 2005	Wrong study design - not RCT (letter to the editor)
Lau 2011	Wrong study design - not RCT (case report)
Lee 2008	Wrong study design - not RCT (non-systematic review)
Lutalo 2015	Wrong study design - not RCT (non-systematic review)
MEPOCHUSS 2006	Wrong study design, not RCT, single arm study
Merkel 2013	Wrong study design - not RCT (non-systematic review)
Moosig 2011	Wrong study design - not RCT (clinical trial, phase II, letter)
Moosig 2013	Wrong study design - not RCT (non-systematic review)
Mukhtyar 2011	Wrong study design - not RCT
Mukhtyar 2016	Wrong study design - not RCT (abstract of recommendation)
Murgia 2014	Wrong study design - not RCT (non-systematic review)

Study	Reason for exclusion
Niles 2017	Wrong study design - not RCT (prospective, observational safety study)
Puéchal 2017	Wrong study design - not RCT (non-systematic review)
Rhee 2018	Wrong study design - post hoc analysis
Rheumatology Annual Meeting 2013	Wrong study design - not RCT
Rozin 2003	Wrong study design - not RCT (letter to the editor)
Ruppert 2008	Wrong study design - not RCT (letter to the editor)
Saadoun 2016	Wrong study design - not RCT (editorial)
Sakai 2015	Wrong study design - not RCT (case report)
Samson 2013	Wrong study design - not RCT, mixed participants with eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa and microscopic polyangiitis from prospective studies
Samson 2014	Wrong intervention - intervention included azathioprine versus cyclophosphamide, not anti-cytokine drugs
Scherer 2006	Wrong study design - not RCT (non-systematic review)
Seror 2010	Wrong intervention - intervention included methotrexate versus azathioprine, not anti-cytokine drugs. Results from pre-randomisation phase of the prospective multicentre randomised open-label Wegener's Granulomatosis-Entretien (WEGENT) trial
Silva 2012	Wrong study design - not RCT
Silva 2013	Wrong study design - not RCT
Silva-Fernandez 2014	Wrong study design - not RCT (systematic review which include systematic reviews and meta-analysis, clinical trials, cohort studies, and case series)
Singer 2017	Wrong study design - not RCT (non-systematic review)
Solans 2008	Wrong study design - not RCT (editorial)
Spina 2009	Wrong study design - not RCT (letter which describes case report)
Tanaka 2012	Wrong study design - not RCT (non-systematic review)
Watts 2010	Wrong study design - not RCT (preliminary results of randomised, placebo-controlled trial of rituximab therapy)
Westman 2013	Wrong study design - not RCT (conference abstract of non-systematic review)

BIANCA-SC - A Study of the Efficacy, Safety, and Tolerability of Blisibimod in Addition to Methotrexate During Induction of Remission in Subjects With ANCA-Associated Small Vessel Vasculitis
MEPOCHUSS - Safety and Efficacy Study of Mepolizumab in Churg Strauss Syndrome
RCT – randomized controlled trial

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

ABAVAS 2008

Methods	A phase III, multi-centre, randomised, double-blind, placebo-controlled trial with two arms: 1. arm - abatacept 250 mg intravenous 2. arm - placebo
Participants	**Inclusion criteria:** 1. Informed consent 2. Participants (females not nursing and not pregnant) ≥18 years of age. 3. Females of childbearing potential practicing an acceptable method of birth control. 4. First diagnosis of acute AAV or relapse of AAV (Wegener's Granulomatosis, microscopic polyangiitis or Churg-Strauss syndrome and ANCA positivity (positive for anti-MPO or anti-PR3) or historical ANCA positivity, and a BVAS score of > 8. **Exclusion criteria:** 1. Severe life-threatening condition, i.e. lung haemorrhage, renal impairment with serum creatinine > 150 µmol/l, or severe central nervous system dysfunction regarded as associated with vasculitis. 2. Current symptoms of any severe, progressive, or uncontrolled disease or medical conditions which may cause an unacceptable risk for participation in this trial. 3. Any other non-vasculitic multisystem autoimmune disease. 4. Any serious acute bacterial infection not resolved completely with antibiotics before enrolment 5. Any severe chronic or recurrent bacterial infection, 6. Hepatitis B or C or HIV positive status. 7. Herpes zoster infection resolved <2 months before enrolment. 8. Received a live vaccine within 3 months before the first dose of study drug or a need of a live vaccine during the year following enrolment. 9. Active or latent tuberculosis (clinical or laboratory evidence) or active tuberculosis within the last three years 10. Any previous cancer, except properly treated non-melanoma skin cancer 11. Any mammogram suspicious for malignancy performed within 6 months before study 12. Hemoglobin below < 8.5 g/dL, white blood count below 3,000/mm3 (3 x 10^9/L), Platelets count below 100,000/mm3 (100 x 109/L), serum aminotransferase (alanine or aspartate) above 2 times upper limit of normal or any other results of laboratory tests which might be associated with an unacceptable risk for study participation. 13. Concurrent participant in another clinical trial. 14. Pregnant or breast feeding. 15. Allergy to a study medication or intolerance to methotrexate. 16. Previous treatment: abatacept any time investigational drug within 28 days (or >5 terminal half-lives) currently treated with biological agent methotrexate within 3 months rituximab, anti-TNF therapy, or IL-1 receptor antagonists within last year cyclophosphamide within last six months.
Interventions	Arm 1: Abatacept 500 mg for patients under 60kg 750mg for patients 60-100kg

ABAVAS 2008 *(Continued)*

	1g for patients > 100kg given as IV infusion over 30 minutes at day 0, 14, 28 and then monthly for a further 11 months 914 infusions in total) Arm 2: saline placebo only IV
Outcomes	Major outcome: 1. Relapse rate over 24 months. Minor outcomes: 1. The proportion of patients in sustained remission at 6, 12, 18 months and 24 months 2. The time to remission 3. The average steroid dosage at 6, 12,18 and 24 months 4. The time to ANCA negativity by immunofluorescence or negative anti-PR3 or anti-MPO anitbody test by ELISA 5. Urinary MCP-1 measurement to assess disease activity 6. Proportion of patients defaulting to cyclophosphamide (mycophenolate mofetil, azathioprine or other rescue) therapy 7. Proportion of patients unable to stick with trial protocol. 8. Degree of chronic disease activity 9. Health related quality of life
Notes	Contact person: Alan Salama Imperial College London ClinicalTrials.gov Identifier: NCT00482066 EudraCT number 2006-001859-35

NIAID 1999

Methods	No information available; study data were never published
Participants	
Interventions	
Outcomes	
Notes	

NIAID 2002

Methods	No information available; study data were never published
Participants	
Interventions	
Outcomes	
Notes	

AAV – Anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis
ABAVAS - Abatacept in ANCA Associated Vasculitis
ANCA – antineutrophil cytoplasmic antibody
anti-MPO – anti-myeloperoxidase
anti-PR3 – Anti-proteinase 3 -
BVAS – Birmingham Vasculitis Activity Score
ELISA – enzyme-bound immunosorbent analysis
HIV – human immunodeficiency virus
IV – intravenous
MCP-1 – monocyte chemoattractant protein-1
NIAID – National Institute of Allergy and Infectious Diseases

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

AAVTCZ

Study name	Clinical trial of tocilizumab versus cyclophosphamide for microscopic polyangiitis and granulomatosis with polyangiitis
Methods	A phase II, randomised, open - but assessors are blinded, controlled trial with two arms: 1. arm: intravenous tocilizumab (TCZ) plus high dose glucocorticoids 2. arm: intravenous cyclophosphamide (IVCY) plus high dose glucocorticoids
Participants	**Inclusion criteria:** 1. Informed consent. 2. ANCA positive active MPA or GPA meeting the diagnostic criteria of Japanese Ministry of Health, Labor and Welfare, or ANCA positive pauci-immune glomerulonephritis with no non-renal vasculitis. 3. Participant ≥ 20 years of age and <80 years old. 4. Body weight ≥ 40 kg. 5. Active disease with BVAS v3 >3 with one or more of the major BVAS items or active organ threatening disease requiring treatment with CY according to the discretion of site investigators. 6. Serum C-reactive protein > 1.0 mg/dl. 7. Both women and men willing to use an effective means of birth control until 70 days after the last administration of TCZ and until 90 days after the last administration of IVCY or azathioprine. 8. No breastfeeding throughout the trial. 9. Able to comply with treatment and follow-up procedures. **Exclusion criteria:** 1. Eosinophilic granulomatosis with polyangiitis or anti-glomerular basement membrane antibody disease 2. Other collagen diseases. 3. Systemic autoimmune diseases. 4. Limited disease according to EUVAS criteria. 5. Serious lung, renal or heart disease, infarction or bleeding of gastrointestinal tract or having diverticulitis. 6. A history of severe allergic reactions to drugs. 7. An active or a deep-seated infection within 6 months of the study. 8. Active hepatitis B (HB) or a history of HBV infection, positive anti-HB surface antibody or anti-HB core antibody, and DNA of HBV, active hepatitis C or a history of hepatitis C. 9. An alanine aminotransferase or aspartate aminotransferase level >2.5 times of the upper limit of normal. 10.Active tuberculosis or mycosis or active cytomegalovirus infection. 11.A history of malignancy, leukaemia, lymphoma or lymphoproliferative disease in the last 5 years. 12.Uncontrolled other disease. 13.A white blood cell count <4,000/mm3 or a platelet count <120,000/mm3.

AAVTCZ *(Continued)*

	14.Intolerant to cyclophosphamide or azathioprine. 15.Previous treatment with tocilizumab or other biologics. 16.Started CS or increased a dosage of CS within 4 weeks before the study. 17.Started CS at or increased a dosage of CS to a prednisone-equivalent dose >25mg per day between 5 and 8 weeks before the study. 18.Started or increased a dosage of immunosuppressive drugs except for CS within 8 weeks before the study. 19.Treatment with plasma exchange or Intravenous immune globulin within 4 weeks before the study. 20.Received any live vaccines within 4 weeks before the study. 21.Participating in another clinical trial and received an investigational medicine within 12 weeks before the study.
Interventions	Arm 1 Week 0-16: tocilizumab (8 mg/kg) IV every 2 weeks. Week 20 and 24: tocilizumab (8 mg/kg) IV every 4 weeks. If no response (a participant does not achieve BVAS v3=0) at week 16, tocilizumab continued every 2 weeks until week 24. Week 28-52: If a complete remission achieved at week 24, tocilizumab (8 mg/kg) continued IV every 4 weeks until week 48. Arm 2 Week 0-24: cyclophosphamide (15 mg/kg, doses modified for renal dysfunction) IV (IVCY) every 4 weeks (at least 3 times and up to 6 times). 4 weeks after the last dose of IVCY to week 52: If a complete remission achieved azathioprine orally every day until week 52. Prednisolone (PSL) prescribed by the same schedule to both treatment groups. Week 0-24: Oral PSL at a dose of 0.8 mg/kg/day for the first 4 weeks, then tapered according to the prefixed schedule. Week 25-52: Continued oral PSL at a dose of 7.5mg per day.
Outcomes	Major outcome measures: 1. Complete remission at week 24 after randomisation Minor outcome measures: 1. Maintaining complete remission (BVAS v3 = 0 and daily prednisolone at a dose of 7.5mg) during week 24 to 52 after randomisation. 2. Percentage of participants who achieved BVAS v3 = 0 at two consecutive visits during 52 weeks after randomisation. 3. Time from randomisation to achieving BVAS v3 = 0 at two consecutive visits. 4. Percentage of participants who were able to taper daily prednisolone to a dose of 7.5 mg during 52 weeks after randomisation. 5. Time from randomisation to tapering daily prednisolone to a dose of 7.5 mg. 6. Total dosage of prednisolone. 7. Percentage of participants who had flare. 8. Time from randomisation to first flare. 9. Changes of BVAS score by categories. 10.VDI 11.SF-36

AAVTCZ *(Continued)*

	12.EQ5D 13.Safety 14.Pharmacokinetics
Starting date	1 May 2018 (date of first enrolment)
Contact information	Masayoshi Harigai - Tokyo women's medical university Institute of Rheumatology harigai.masayoshi@twmu.ac.jp UMIN000024574
Notes	

ABROGATE

Study name	Abatacept (CTLA4-Ig) for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (Wegener's) (ABROGATE)
Methods	A phase III, multi-centre, randomised, double-blind, placebo-controlled trial with two arms: 1. arm: 125 mg abatacept 2. arm: placebo administered by subcutaneous injection once a week.
Participants	Inclusion criteria: 1. Informed consent. 2. Patients with GPA (not microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA)) and met at least 2 of the 5 modified ACR classification criteria for GPA. 3. Relapse of GPA within the 28 days before the screening and not meeting the definition of severe disease. 4. Participants ≥ 15 years old. 5. Willing to comply with study procedures. 6. Willing to use an effective means of birth control (men and women) during study treatment. Women willing to continue the use of those birth control means for a=>=14 weeks after the last dose of study drug. Exclusion criteria: 1. Presence of involvement that meets the criteria for severe disease. 2. Treatment prior to screening with: Cyclophosphamide within 3 months, Methylprednisolone 1000 mg within 28 days, Prednisone/prednisolone > 30 mg/day for > 28 days. 3. Begininng or increasing the dose of the immunosuppressive agent used for the disease maintenance (methotrexate, azathioprine, mycophenolate) within 3 months before the study. 4. Active infection (including chronic infection). 5. Pregnant or nursing. 6. HIV, hepatitis C positive status, or a positive hepatitis B surface antigen. 7. Inability to comply with study guidelines.

ABROGATE *(Continued)*

	8. Cytopenia: platelet count below 100,000/mm3, white blood cell count below 3,000/mm3 (3 x 109/L), absolute neutrophil count below 1500/mm3, haemoglobin below 8.5 g/dL. 9. Chronic renal insufficiency with a creatinine clearance of <= 20 ml/min. 10. Known current use of illegal drugs. 11. Other uncontrolled disease (co-morbidity) that could interfere with fulfilling the study requirements or substantially increase the risk of study procedures. 12. Any previous or current history of cancer except properly treated basal cell or squamous cell carcinomas of the skin, or cervical carcinoma in situ treated or excised in a curative procedure. 13. Investigational agent or device within 30 days before the study or 5 half lives of the drug (whichever is longer). 14. A live vaccination <3 months before enrolment. 15. Current active tuberculosis (clinical, radiographic, or laboratory evidence). 16. Any history of active tuberculosis within the past 3 years and >3 years ago if proper treatment not documented. 17. Latent tuberculosis not properly treated or currently treated with isoniazid or other therapy recommended in the guidelines for up to 4 weeks before the study. Participants with a positive tuberculosis screening test indicative of latent tuberculosis can be eligible for the study if there is no evidence of current tuberculosis on chest X-ray at screening and they are receiving treatment with isoniazid or other therapy for latent tuberculosis recommended in the guidelines (e.g., CDC) for at least 4 weeks before the study and complete this treatment according to the guidelines. 20. History of herpes zoster resolved <2 months before the study. 21. Treatment with: Rituximab or any other biologic agent depleting B cell within the last 6 months Alemtuzumab or anti-thymocyte globulin within the past 12 months. Intravenous immunoglobulin or plasma exchange within the last 3 months. Infliximab, etanercept, adalimumab, tocilizumab, or any other biologics within the last 3 months or 5 half lives of the agent (whichever is longer).
Interventions	Arm 1 abatacept 125 mg administered by subcutaneous injection once a week for at least 12 months. Participants may be removed from treatment earlier due to a disease relapse, disease worsening, or if they have not achieved remission by treatment month 6. Arm 2 blinded placebo administered by subcutaneous injection once a week for at least 12 months. Participants may be removed from treatment earlier due to a disease relapse, disease worsening, or if they have not achieved remission by treatment month 6.
Outcomes	Major outcome measures: 1. Treatment failure after 12 months of study treatment (defined as relapse, disease worsening, or failure to achieve a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) = 0 or 1 by 6 months). Minor outcome measures: 1. Duration of glucocorticoid-free periods 2. Duration of remission

ABROGATE *(Continued)*

	3. Severity of relapses 4. Health-related quality of life 5. Number and severity of AEs
Starting date	April 2015
Contact information	Cristina Burroughs 1-888-772-8315 abrogate@epi.usf.edu
Notes	Estimated Primary Completion Date: August 2019 (Final data collection date for major outcome measure) ClinicalTrials.gov Identifier: NCT02108860

ALEVIATE

Study name	Alemtuzumab for ANCA Associated Refractory Vasculitis - a Study of Safety and Efficacy
Methods	A open label, randomised, multi-centre study with two arms: 1. arm: Alemtuzumab - high dose (60mg) 2. arm: Alemtuzumab - low dose (30mg)
Participants	**Inclusion criteria:** 1. Active AAV with >=one severe or >=three non severe items of BVAS/WG (BVAS/WG>3). 2. Previous treatment with cyclophosphamide or methotrexate, and prednisolone for >= three months. **Exclusion criteria:** 1. Age < 18 or > 60 years. 2. Creatinine above 150µmol/l (1.7mg/dl). 3. Total white blood cells count below 4x109/l or lymphocyte count below 0.5x109/l, or Immunoglobulin G below 5g/L, or neutrophil count below 1.5x109/l. 4. Severe lung haemorrhage with hypoxia (<85% on room air). 5. Severe gastrointestinal, central nervous system or cardiac vasculitis. 6. Previous therapy with: Any alemtuzumab Within the past 3 months: IVIg, infliximab, etanercept, adalimumab, abatacept, anti-thymocyte globulin or plasma exchange Within the past 6 months: rituximab. 7. Required intensive care unit treatment. 8. Active infection with HIV, hepatitis B or hepatitis C or other infection which requires parenteral or long-term oral antibiotics. 9. History of idiopathic thrombocytopenic purpura or platelet count below 50,000 x 106/l at screening. 10. Pregnancy or nursing or not adequate contraception in pre-menopausal women. 11. Any condition which can be associated with detrimental effect of the study to the participant. 12. Any other multisystem autoimmune disease, such as Churg Strauss angiitis, systemic lupus erythematosus,anti-glomerular basement membrane disease and cryoglobulinaemia.

ALEVIATE *(Continued)*

	13. Any previous or current history of cancer (other than resected basal cell carcinoma).
Interventions	Arm 1: Alemtuzumab (Campath 1H)- high dose (60mg) - Alemtuzumab will be administered on Day 1 and Day 2 at 0 and 6 months. Arm 2: Alemtuzumab (Campath 1H)- low dose (30mg) - Alemtuzumab will be administered on Day 1 and Day 2 at 0 and 6 months.
Outcomes	Major outcome: 1. Proportion of patients with a vasculitis response at 6 months - includes patients in complete and partial remission. Complete remission is defined as a BVAS/WG of 0 for >=one month. Partial response is defined as the absence of severe BVAS/WG items and >= 50% fall in BVAS/WG score from baseline. Minor outcomes: 1. Proportion of patients with treatment failure within 12 months defined as the failure to achieve a response by six months or a relapse between 6 and 12 months. 2. Combined damage assessment scores within 12 months. 3. Non severe AEs within 12 months. 4. Cumulative dose of corticosteroids within 12 months. 5. Time to complete and partial remission within 6 months . 6. Relapse within 12 months. 7. Change in SF-36 within 12 months.
Starting date	February 2011
Contact information	David Jayne FMedSci Professor of Clinical Autoimmunity Department of Medicine School of Clinical Medicine University of Cambridge CB2 2QQ Tel 01223 325039 dj106@cam.ac.uk
Notes	We received information that the trial has completed recruitment but follow-up is ongoing.

COMBIVAS

Study name	A Randomised, Double Blind, Controlled Mechanistic Study of Rituximab and Belimumab Combination Therapy in PR3 ANCA-associated Vasculitis
Methods	A phase II randomised, double-blind, multi-centre study with two arms: 1. arm: 200 mg belimumab with rituximab 2. arm: rituximab with placebo administered by subcutaneous injection once a week
Participants	nclusion Criteria: 1. Participants ≥ 18 years old. 2. Active disease of granulomatosis with polyangiitis or microscopic polyangiitis defined by one major or three minor items on BVAS/WG. 3. Proteinase 3 ANCA detected by ELISA at screening. 4. Informed consent. Exclusion Criteria:

COMBIVAS *(Continued)*

	At screening: 1. Positive for Myeloperoxidase (MPO)-ANCA or anti-glomerular basement membrane antibody detected by ELISA. 2. Lung haemorrhage with hypoxia. 3. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2. 4. Acute serious or chronic infection. 5. Patients with undetectable peripheral blood B cells. 6. Patients with Immunoglobulin G < 400mg/dl 7. Previous treatment before Day 1: Any B cell targeted therapy within 364 days, Cyclophosphamide within 180 days, Any steroid injection within 60 days (unless provided during or 14 days before screening period) Methylprednisolone (IV) >1.5mg between 14 days prior to screening and Day 1 (including Day 1). 8. Prednisolone on average >10mg/day (or equivalent) orally during 30 days prior to screening.
Interventions	Arm 1 Belimumab (Benlysta) 200 mg administered by subcutaneous injection once a week for 12 months co-administration of rituximab Arm 2 Placebo administered by subcutaneus injection once a week for 12 months. co-administration of rituximab
Outcomes	Major outcome measures: 1. Time to PR3 ANCA negativity - ELISA analysis at different time points to determine when PR3 ANCA can no longer be detected. Minor outcomes measures: 1. Percentage of participants with PR3 ANCA negativity - measured by ELISA at various time points. 2. Change from baseline of certain cell subsets - measured by flow cytometry at various time points. 3. Time to clinical remission - measured by BVAS/WG. 4. Incidence of serious AEs (SAEs) - hospitalisation or serious events.
Starting date	February 2019
Contact information	Kim Mynard 01223 349350 kim.mynard@addenbrookes.nhs.uk Principal Investigator: Rachel Jones
Notes	Estimated Primary Completion Date: February 2022 (Final data collection date for major outcome measure) ClinicalTrials.gov Identifier: NCT03967925

AAV – Anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis
AAVTCZ - Clinical trial of tocilizumab versus cyclophosphamide for microscopic polyangiitis and granulomatosis with polyangiitis
ABROGATE - Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis
ACR – American College of Rheumatology
AE – adverse event

ALEVIATE - Alemtuzumab for ANCA Associated Refractory Vasculitis
ANCA – antineutrophil cytoplasmic antibody
anti-MPO – anti-myeloperoxidase
anti-PR3 – Anti-proteinase 3 -
BVAS – Birmingham Vasculitis Activity Score
BVAS/WG – Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis
CDC – Centre for Disease Control
COMBIVAS - A Randomised, Double Blind, Controlled Mechanistic Study of Rituximab and Belimumab Combination Therapy in PR3 ANCA-associated Vasculitis
CS – corticosteroid
DNA – deoxyribonucleic acid
eGFR – Estimated glomerular filtration rate
EGPA – eosinophilic granulomatosis with polyangiitis
ELISA – enzyme-bound immunosorbent analysis
EQ5D – The EuroQol (European Quality of Life) Five Dimension Scale
EUVAS - European Vasculitis Study Group
GPA – granulomatosis with polyangiitis
HB - hepatitis B
HBV - hepatitis B virus
HIV – human immunodeficiency virus
IV – intravenous
IVCY – intravenous cyclophosphamide
Kg – kilogram
MCP-1 – monocyte chemoattractant protein-1
MPA – microscopic polyangiitis
PSL - prednisolone
SAE – serious adverse event
SF-36 – Short Form-36
TCZ – tocilizumab

DATA AND ANALYSES

Comparison 1. EGPA - mepolizumab vs placebo

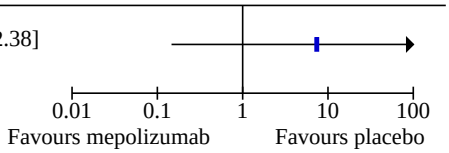
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Any remission (for at least 1 week)	1	136	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.62, 4.74]
1.2.2 Remission for at least 24 weeks	1	136	Risk Ratio (M-H, Random, 95% CI)	9.50 [2.30, 39.21]
1.3 Durable remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4 Disease relapse	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5 Any AE	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.5.1 Any event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.2 Any event related to trial agent	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6 Any serious AE	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6.1 Any serious event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6.2 Any serious event related to trial agent	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.7 Any withdrawals due to AE	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.8 Control of asthma symptoms with ACQ6 - change from baseline	1	136	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.60, 0.00]
1.9 Control of sinonasal symptoms with SNOT22 - change from baseline	1	136	Mean Difference (IV, Random, 95% CI)	-4.66 [-10.69, 1.36]
1.10 Disease damage in VDI - change from baseline	1	136	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.37, 0.23]

Analysis 1.1. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 1: Mortality

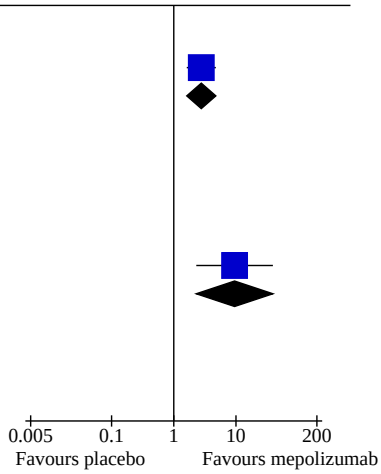
Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
Wechsler 2017	1	68	0	68	7.39 [0.15 , 372.38]

Test for subgroup differences: Not applicable



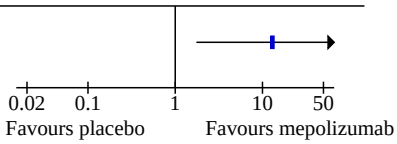
Analysis 1.2. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 2: Remission

Study or Subgroup	Mepolizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Any remission (for at least 1 week)						
Wechsler 2017	36	68	13	68	100.0%	2.77 [1.62 , 4.74]
Subtotal (95% CI)		**68**		**68**	**100.0%**	**2.77 [1.62 , 4.74]**
Total events:	36		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.71 (P = 0.0002)						
1.2.2 Remission for at least 24 weeks						
Wechsler 2017	19	68	2	68	100.0%	9.50 [2.30 , 39.21]
Subtotal (95% CI)		**68**		**68**	**100.0%**	**9.50 [2.30 , 39.21]**
Total events:	19		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.11 (P = 0.002)						



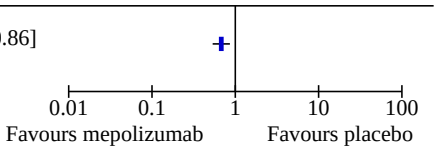
Analysis 1.3. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 3: Durable remission

Study or Subgroup	Mepolizumab Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Wechsler 2017	13	68	1	68	13.00 [1.75 , 96.63]
Test for subgroup differences: Not applicable					



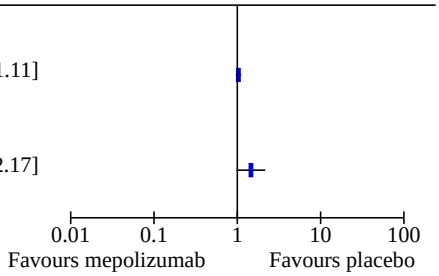
Analysis 1.4. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 4: Disease relapse

Study or Subgroup	Mepolizumab Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Wechsler 2017	38	68	56	68	0.68 [0.53 , 0.86]
Test for subgroup differences: Not applicable					



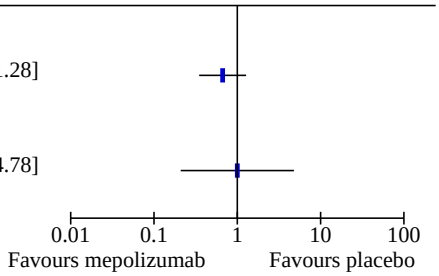
Analysis 1.5. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 5: Any AE

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.5.1 Any event					
Wechsler 2017	66	68	64	68	1.03 [0.96 , 1.11]
1.5.2 Any event related to trial agent					
Wechsler 2017	35	68	24	68	1.46 [0.98 , 2.17]



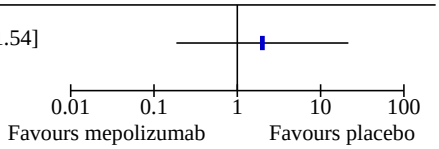
Analysis 1.6. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 6: Any serious AE

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.6.1 Any serious event					
Wechsler 2017	12	68	18	68	0.67 [0.35 , 1.28]
1.6.2 Any serious event related to trial agent					
Wechsler 2017	3	68	3	68	1.00 [0.21 , 4.78]



Analysis 1.7. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 7: Any withdrawals due to AE

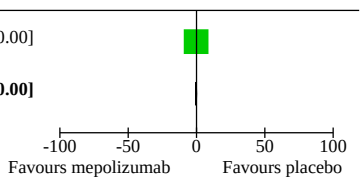
Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Wechsler 2017	2	68	1	68	2.00 [0.19 , 21.54]



Analysis 1.8. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 8: Control of asthma symptoms with ACQ6 - change from baseline

Study or Subgroup	Mepolizumab Mean	Mepolizumab SD	Mepolizumab Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Wechsler 2017	-0.45974	0.894	68	-0.16269	0.894	68	100.0%	-0.30 [-0.60 , 0.00]
Total (95% CI)			**68**			**68**	**100.0%**	**-0.30 [-0.60 , 0.00]**

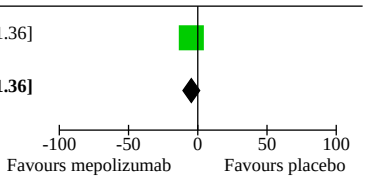
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 9: Control of sinonasal symptoms with SNOT22 - change from baseline

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wechsler 2017	-7.4375	17.93	68	-2.7742	17.93	68	100.0%	-4.66 [-10.69 , 1.36]
Total (95% CI)			**68**			**68**	**100.0%**	**-4.66 [-10.69 , 1.36]**

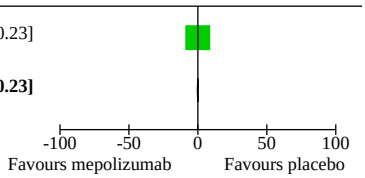
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: EGPA - mepolizumab vs placebo, Outcome 10: Disease damage in VDI - change from baseline

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wechsler 2017	0.23593	0.876	68	0.30451	0.921	68	100.0%	-0.07 [-0.37 , 0.23]
Total (95% CI)			**68**			**68**	**100.0%**	**-0.07 [-0.37 , 0.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



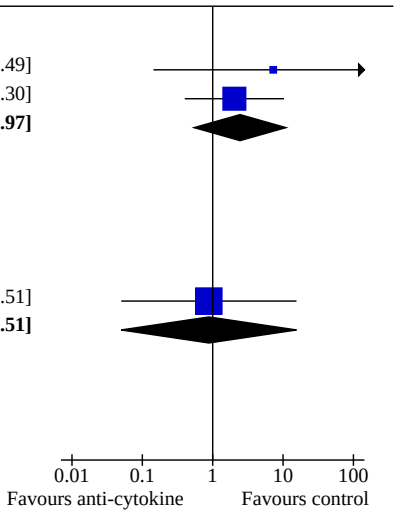
Comparison 2. GPA - anticytokine therapy vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1.1 Active drug vs placebo	2	285	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.45 [0.55, 10.97]
2.1.2 Infliximab vs rituximab	1	17	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.05, 15.51]
2.2 Remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Etanercept vs placebo, remission at any time during study	1	180	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.07]
2.2.2 Infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.11, 1.81]
2.3 Durable remission	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 Etanercept vs placebo	1	174	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.11]
2.3.2 Infliximab vs rituximab long term	1	17	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.60]
2.4 Disease relapse	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.1 Any relapse - belimumab vs placebo	1	105	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.27, 1.97]
2.4.2 Major relapse - belimumab vs placebo	1	105	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.12, 70.67]
2.5 No disease flare	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 Etanercept vs placebo	1	180	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.27]
2.6 Any AE	1	105	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.29]
2.7 Any non serious AE	1	105	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
2.7.1 Belimumab vs placebo	1	105	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.28]
2.8 Any severe or serious AE	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.8.1 Active drug vs placebo	2	285	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.80, 1.27]
2.8.2 Infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.20, 16.10]
2.9 Any solid malignancy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.9.1 During trial and follow up	1	180	Risk Ratio (M-H, Random, 95% CI)	2.86 [1.08, 7.62]
2.9.2 During trial	1	180	Risk Ratio (M-H, Random, 95% CI)	13.29 [0.76, 232.45]
2.9.3 During follow up	1	153	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.54, 4.61]
2.10 Any withdrawals due to AE	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 Active drug vs placebo	2	285	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.07, 6.59]
2.10.2 Infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	2.70 [0.13, 58.24]
2.11 Treatment response	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.11.1 Sustained low level of disease activity (Etanercept vs placebo)	1	174	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.06]
2.11.2 Partial remission (infliximab vs rituximab)	1	17	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.07, 12.00]

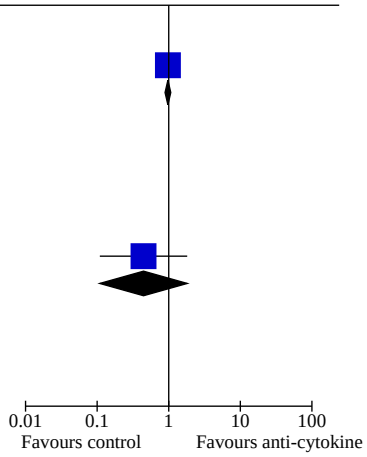
Analysis 2.1. Comparison 2: GPA - anticytokine therapy vs control, Outcome 1: Mortality

Study or Subgroup	Anti-cytokine therapy Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.1.1 Active drug vs placebo						
BREVAS 2018	1	53	0	52	14.6%	7.25 [0.14 , 365.49]
WGET 2005	4	89	2	91	85.4%	2.03 [0.40 , 10.30]
Subtotal (95% CI)		**142**		**143**	**100.0%**	**2.45 [0.55 , 10.97]**
Total events:	5		2			
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
2.1.2 Infliximab vs rituximab						
de Menthon 2011	1	9	1	8	100.0%	0.88 [0.05 , 15.51]
Subtotal (95% CI)		**9**		**8**	**100.0%**	**0.88 [0.05 , 15.51]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%						



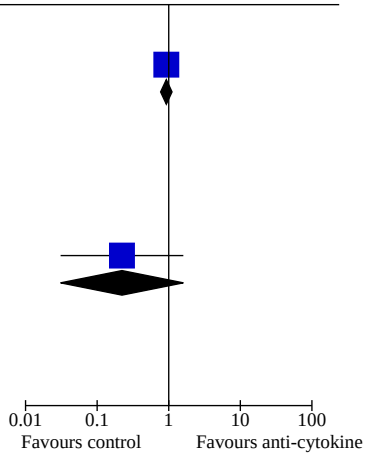
Analysis 2.2. Comparison 2: GPA - anticytokine therapy vs control, Outcome 2: Remission

Study or Subgroup	Anti-cytokine therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Etanercept vs placebo, remission at any time during study						
WGET 2005	80	89	84	91	100.0%	0.97 [0.89 , 1.07]
Subtotal (95% CI)		**89**		**91**	**100.0%**	**0.97 [0.89 , 1.07]**
Total events:	80		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
2.2.2 Infliximab vs rituximab						
de Menthon 2011	2	9	4	8	100.0%	0.44 [0.11 , 1.81]
Subtotal (95% CI)		**9**		**8**	**100.0%**	**0.44 [0.11 , 1.81]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 1.19, df = 1 (P = 0.27), I² = 16.1%						



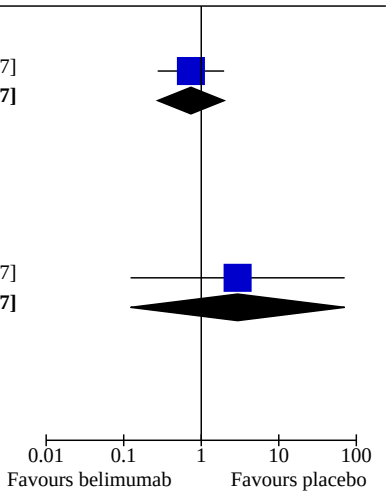
Analysis 2.3. Comparison 2: GPA - anticytokine therapy vs control, Outcome 3: Durable remission

Study or Subgroup	Anti-cytokine therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Etanercept vs placebo						
WGET 2005	62	89	64	85	100.0%	0.93 [0.77 , 1.11]
Subtotal (95% CI)		**89**		**85**	**100.0%**	**0.93 [0.77 , 1.11]**
Total events:	62		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
2.3.2 Infliximab vs rituximab long term						
de Menthon 2011	1	9	4	8	100.0%	0.22 [0.03 , 1.60]
Subtotal (95% CI)		**9**		**8**	**100.0%**	**0.22 [0.03 , 1.60]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: Chi² = 1.99, df = 1 (P = 0.16), I² = 49.7%						



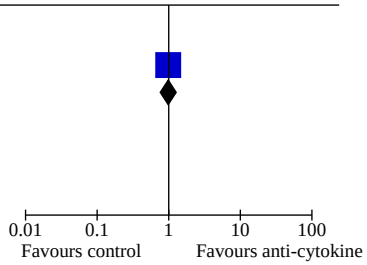
Analysis 2.4. Comparison 2: GPA - anticytokine therapy vs control, Outcome 4: Disease relapse

Study or Subgroup	Belimumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Any relapse - belimumab vs placebo						
BREVAS 2018	6	53	8	52	100.0%	0.74 [0.27 , 1.97]
Subtotal (95% CI)		**53**		**52**	**100.0%**	**0.74 [0.27 , 1.97]**
Total events:	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.4.2 Major relapse - belimumab vs placebo						
BREVAS 2018	1	53	0	52	100.0%	2.94 [0.12 , 70.67]
Subtotal (95% CI)		**53**		**52**	**100.0%**	**2.94 [0.12 , 70.67]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%						



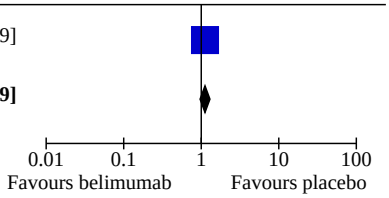
Analysis 2.5. Comparison 2: GPA - anticytokine therapy vs control, Outcome 5: No disease flare

Study or Subgroup	Anti-cytokine therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Etanercept vs placebo						
WGET 2005	50	89	52	91	100.0%	0.98 [0.76 , 1.27]
Subtotal (95% CI)		**89**		**91**	**100.0%**	**0.98 [0.76 , 1.27]**
Total events:	50		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Not applicable						



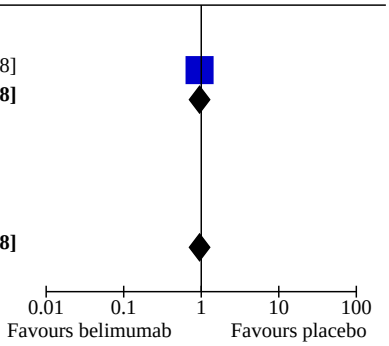
Analysis 2.6. Comparison 2: GPA - anticytokine therapy vs control, Outcome 6: Any AE

Study or Subgroup	Belimumab Events	Belimumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
BREVAS 2018	49	53	43	52	100.0%	1.12 [0.97 , 1.29]
Total (95% CI)		**53**		**52**	**100.0%**	**1.12 [0.97 , 1.29]**
Total events:	49		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
Test for subgroup differences: Not applicable						



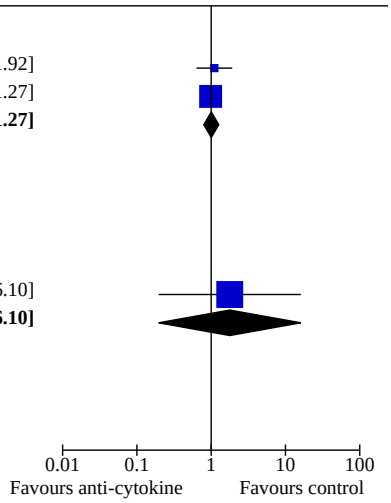
Analysis 2.7. Comparison 2: GPA - anticytokine therapy vs control, Outcome 7: Any non serious AE

Study or Subgroup	Belimumab Events	Belimumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Belimumab vs placebo						
BREVAS 2018	32	53	33	52	100.0%	0.95 [0.70 , 1.28]
Subtotal (95% CI)		**53**		**52**	**100.0%**	**0.95 [0.70 , 1.28]**
Total events:	32		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**53**		**52**	**100.0%**	**0.95 [0.70 , 1.28]**
Total events:	32		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



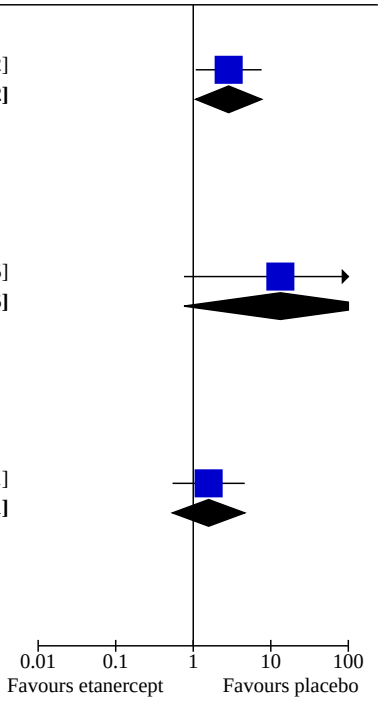
Analysis 2.8. Comparison 2: GPA - anticytokine therapy vs control, Outcome 8: Any severe or serious AE

Study or Subgroup	Anti-cytokine therapy Events	Anti-cytokine therapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Active drug vs placebo						
BREVAS 2018	18	53	16	52	17.5%	1.10 [0.63 , 1.92]
WGET 2005	50	89	52	91	82.5%	0.98 [0.76 , 1.27]
Subtotal (95% CI)		**142**		**143**	**100.0%**	**1.00 [0.80 , 1.27]**
Total events:	68		68			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
2.8.2 Infliximab vs rituximab						
de Menthon 2011	2	9	1	8	100.0%	1.78 [0.20 , 16.10]
Subtotal (95% CI)		**9**		**8**	**100.0%**	**1.78 [0.20 , 16.10]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



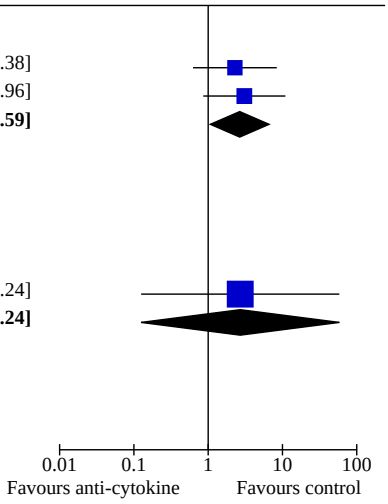
Analysis 2.9. Comparison 2: GPA - anticytokine therapy vs control, Outcome 9: Any solid malignancy

Study or Subgroup	Etanercept Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 During trial and follow up						
WGET 2005	14	89	5	91	100.0%	2.86 [1.08 , 7.62]
Subtotal (95% CI)		**89**		**91**	**100.0%**	**2.86 [1.08 , 7.62]**
Total events:	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.11 (P = 0.04)						
2.9.2 During trial						
WGET 2005	6	89	0	91	100.0%	13.29 [0.76 , 232.45]
Subtotal (95% CI)		**89**		**91**	**100.0%**	**13.29 [0.76 , 232.45]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
2.9.3 During follow up						
WGET 2005	8	77	5	76	100.0%	1.58 [0.54 , 4.61]
Subtotal (95% CI)		**77**		**76**	**100.0%**	**1.58 [0.54 , 4.61]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 2.08, df = 2 (P = 0.35), I² = 4.0%						

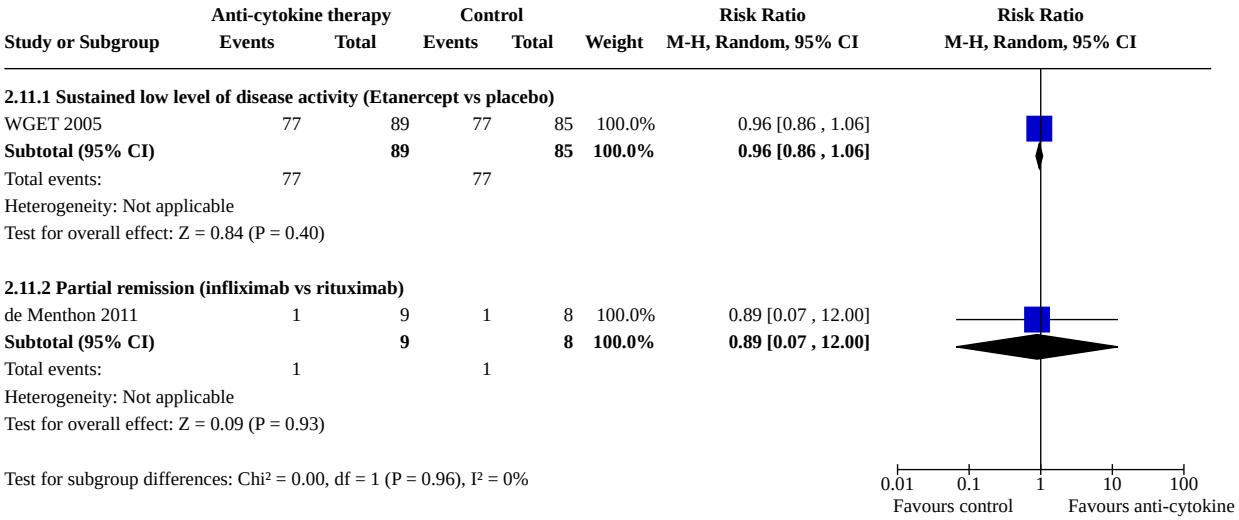


Analysis 2.10. Comparison 2: GPA - anticytokine therapy vs control, Outcome 10: Any withdrawals due to AE

Study or Subgroup	Anti-cytokine therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Active drug vs placebo						
BREVAS 2018	7	53	3	52	49.1%	2.29 [0.63 , 8.38]
WGET 2005	9	89	3	91	50.9%	3.07 [0.86 , 10.96]
Subtotal (95% CI)		**142**		**143**	**100.0%**	**2.66 [1.07 , 6.59]**
Total events:	16		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.11 (P = 0.04)						
2.10.2 Infliximab vs rituximab						
de Menthon 2011	1	9	0	8	100.0%	2.70 [0.13 , 58.24]
Subtotal (95% CI)		**9**		**8**	**100.0%**	**2.70 [0.13 , 58.24]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



Analysis 2.11. Comparison 2: GPA - anticytokine therapy vs control, Outcome 11: Treatment response



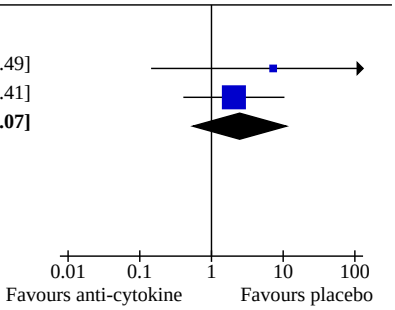
Comparison 3. GPA - sensitivity analysis regarding WGET trial

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mortality	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1.1 Active drug vs placebo	2	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [0.55, 11.07]
3.2 Remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Etanercept vs placebo	1	181	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.08]
3.3 Durable remission	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.3.1 Etanercept vs placebo	1	181	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.21]
3.4 Disease flare	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 Etanercept vs placebo	1	181	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.77, 1.28]
3.5 Any severe or serious AE	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.5.1 Active drug vs placebo	2	286	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.28]
3.6 Any withdrawals due to AE	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.6.1 Active drug vs placebo	2	286	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.08, 6.63]
3.7 Treatment response	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7.1 Sustained low level of disease activity (Etanercept vs placebo)	1	181	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.17]

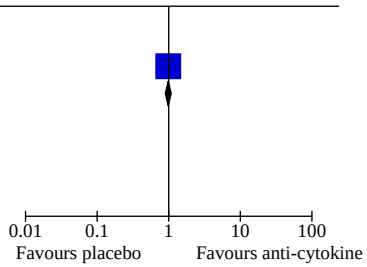
Analysis 3.1. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 1: Mortality

Study or Subgroup	Anti-cytokine therapy Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.1.1 Active drug vs placebo						
BREVAS 2018	1	53	0	52	14.6%	7.25 [0.14 , 365.49]
WGET 2005	4	89	2	92	85.4%	2.05 [0.41 , 10.41]
Subtotal (95% CI)		**142**		**144**	**100.0%**	**2.47 [0.55 , 11.07]**
Total events:	5		2			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Not applicable						



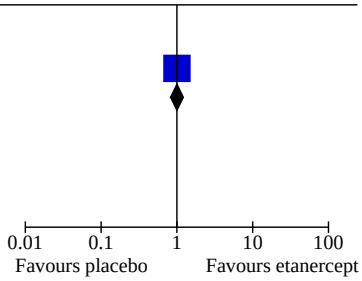
Analysis 3.2. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 2: Remission

Study or Subgroup	Anti-cytokine therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Etanercept vs placebo						
WGET 2005	80	89	84	92	100.0%	0.98 [0.90 , 1.08]
Subtotal (95% CI)		**89**		**92**	**100.0%**	**0.98 [0.90 , 1.08]**
Total events:	80		84			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



Analysis 3.3. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 3: Durable remission

Study or Subgroup	Etanercept Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Etanercept vs placebo						
WGET 2005	62	89	64	92	100.0%	1.00 [0.83 , 1.21]
Subtotal (95% CI)		**89**		**92**	**100.0%**	**1.00 [0.83 , 1.21]**
Total events:	62		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Not applicable						

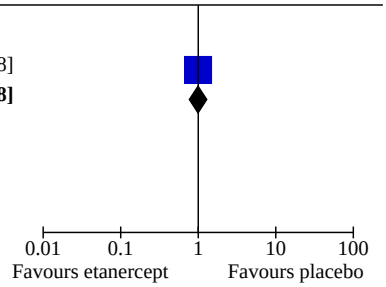


Analysis 3.4. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 4: Disease flare

Study or Subgroup	Etanercept Events	Etanercept Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Etanercept vs placebo						
WGET 2005	50	89	52	92	100.0%	0.99 [0.77 , 1.28]
Subtotal (95% CI)		**89**		**92**	**100.0%**	**0.99 [0.77 , 1.28]**
Total events:	50		52			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

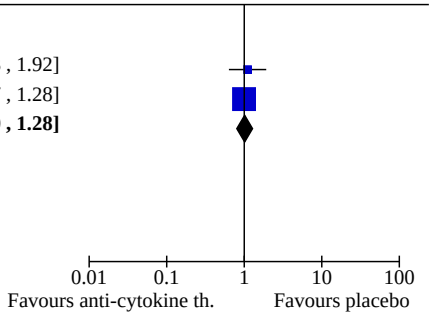


Analysis 3.5. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 5: Any severe or serious AE

Study or Subgroup	Anti-cytokine Events	Anti-cytokine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Active drug vs placebo						
BREVAS 2018	18	53	16	52	17.6%	1.10 [0.63 , 1.92]
WGET 2005	50	89	52	92	82.4%	0.99 [0.77 , 1.28]
Subtotal (95% CI)		**142**		**144**	**100.0%**	**1.01 [0.80 , 1.28]**
Total events:	68		68			

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable

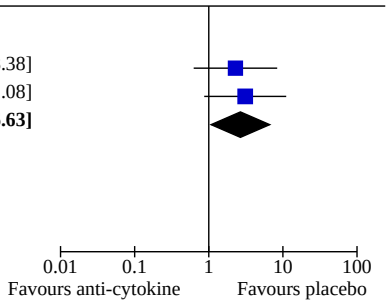


Analysis 3.6. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 6: Any withdrawals due to AE

Study or Subgroup	Anti-cytokine therapy Events	Anti-cytokine therapy Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Active drug vs placebo						
BREVAS 2018	7	53	3	52	49.1%	2.29 [0.63 , 8.38]
WGET 2005	9	89	3	92	50.9%	3.10 [0.87 , 11.08]
Subtotal (95% CI)		**142**		**144**	**100.0%**	**2.67 [1.08 , 6.63]**
Total events:	16		6			

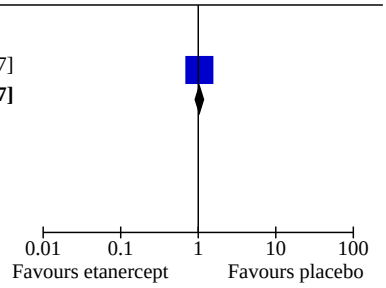
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: GPA - sensitivity analysis regarding WGET trial, Outcome 7: Treatment response

Study or Subgroup	Etanercept Events	Etanercept Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Sustained low level of disease activity (Etanercept vs placebo)						
WGET 2005	77	89	77	92	100.0%	1.03 [0.92 , 1.17]
Subtotal (95% CI)		**89**		**92**	**100.0%**	**1.03 [0.92 , 1.17]**
Total events:	77		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
Test for subgroup differences: Not applicable						

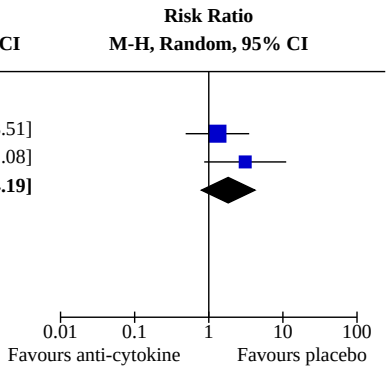


Comparison 4. GPA - sensitivity BREVAS withdrawn due to adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Any withdrawals due to AE	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Active drug vs placebo	2	286	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.80, 4.19]

Analysis 4.1. Comparison 4: GPA - sensitivity BREVAS withdrawn due to adverse events, Outcome 1: Any withdrawals due to AE

Study or Subgroup	Anti-cytokine therapy Events	Anti-cytokine therapy Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Active drug vs placebo						
BREVAS 2018	8	53	6	52	61.2%	1.31 [0.49 , 3.51]
WGET 2005	9	89	3	92	38.8%	3.10 [0.87 , 11.08]
Subtotal (95% CI)		**142**		**144**	**100.0%**	**1.83 [0.80 , 4.19]**
Total events:	17		9			
Heterogeneity: Tau² = 0.04; Chi² = 1.12, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Not applicable						

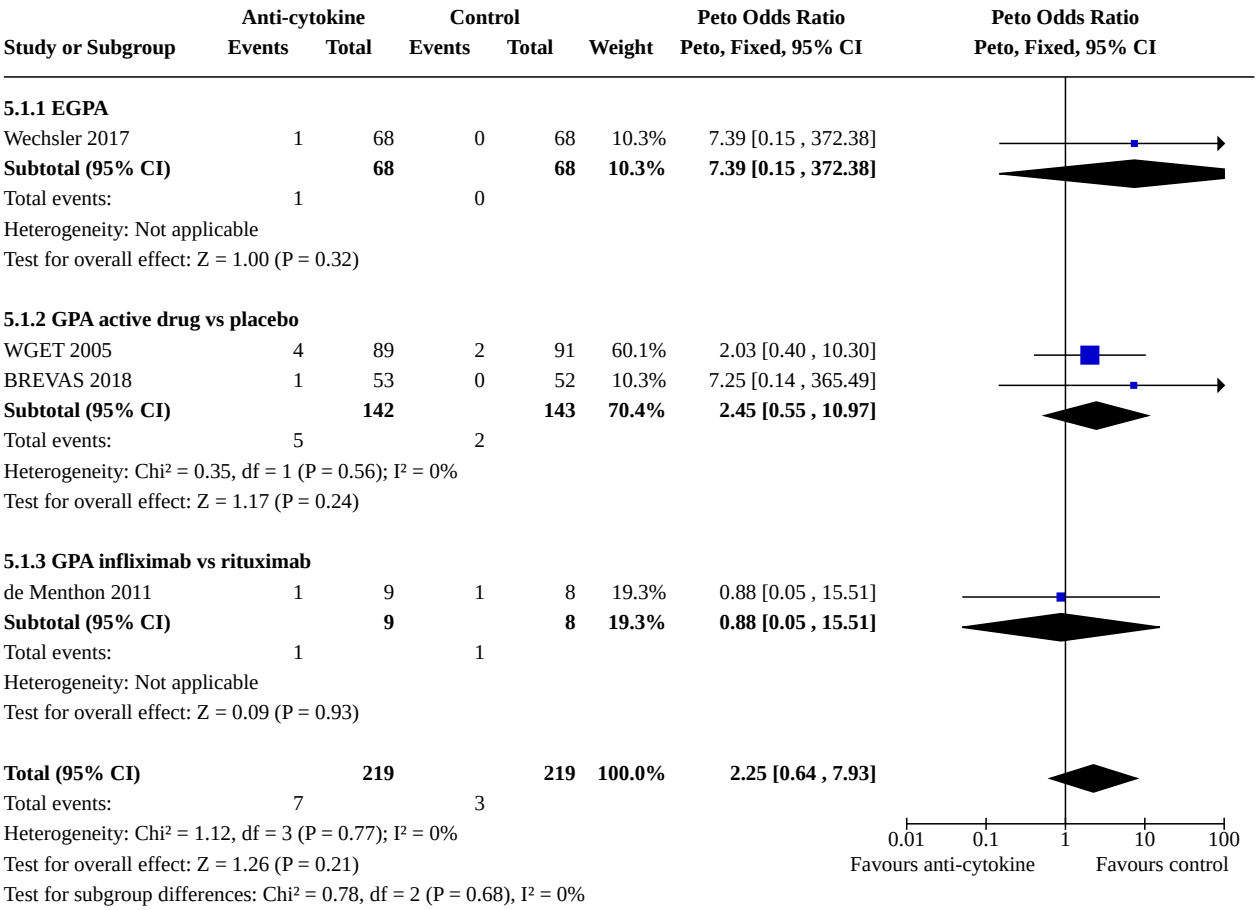


Comparison 5. Sensitivity analysis - all AAV together

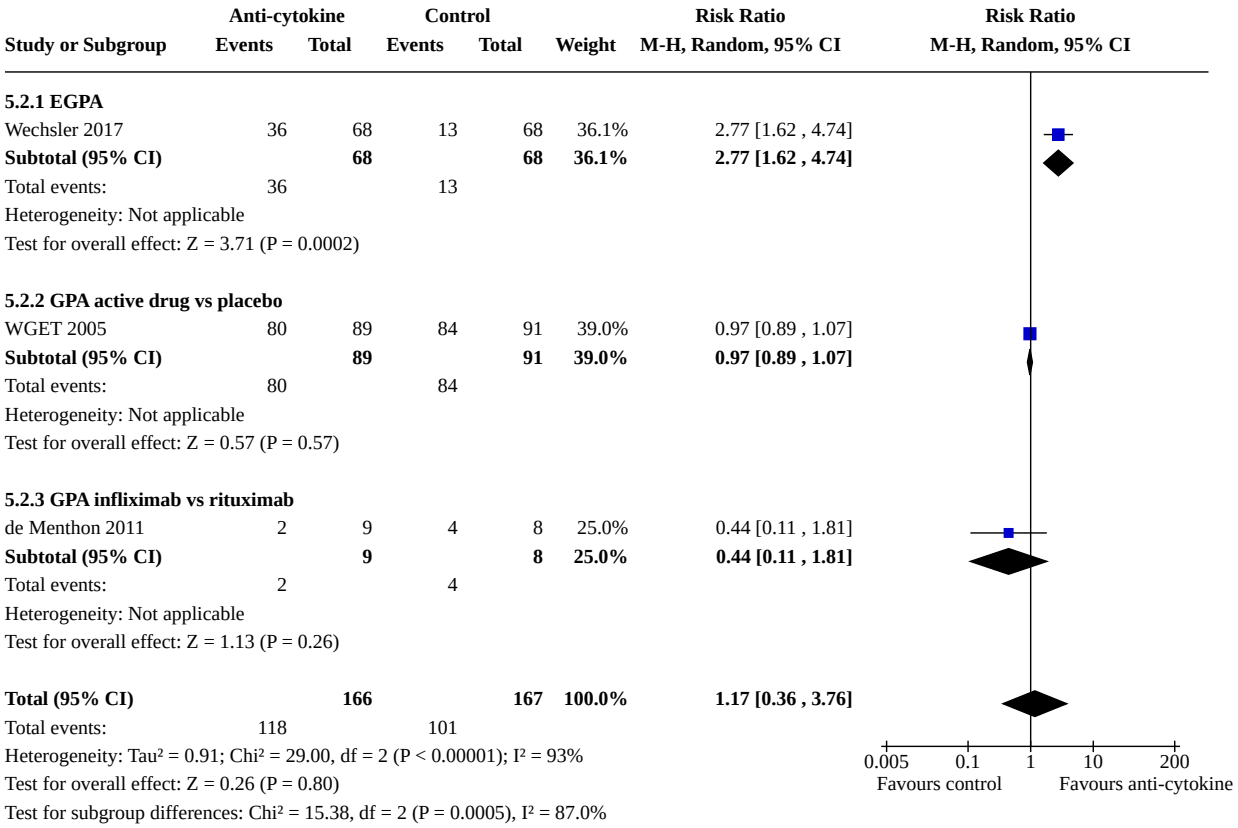
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Mortality	4	438	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [0.64, 7.93]
5.1.1 EGPA	1	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
5.1.2 GPA active drug vs placebo	2	285	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.45 [0.55, 10.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.3 GPA infliximab vs rituximab	1	17	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.05, 15.51]
5.2 Any remission	3	333	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.36, 3.76]
5.2.1 EGPA	1	136	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.62, 4.74]
5.2.2 GPA active drug vs placebo	1	180	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.07]
5.2.3 GPA infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.11, 1.81]
5.3 Durable remission	3	327	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.20, 8.61]
5.3.1 EGPA	1	136	Risk Ratio (M-H, Random, 95% CI)	13.00 [1.75, 96.63]
5.3.2 GPA active drug vs placebo	1	174	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.11]
5.3.3 GPA infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.60]
5.4 Disease relapse	2	241	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.86]
5.4.1 EGPA	1	136	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.53, 0.86]
5.4.2 GPA active drug vs placebo	1	105	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.27, 1.97]
5.5 Any serious or severe AE	4	438	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.20]
5.5.1 EGPA	1	136	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.35, 1.28]
5.5.2 GPA active drug vs placebo	2	285	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.80, 1.27]
5.5.3 Infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.20, 16.10]
5.6 Any withdrawals due to AE	4	438	Risk Ratio (M-H, Random, 95% CI)	2.57 [1.13, 5.83]
5.6.1 EGPA	1	136	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 21.54]
5.6.2 GPA active drug vs placebo	2	285	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.07, 6.59]
5.6.3 GPA infliximab vs rituximab	1	17	Risk Ratio (M-H, Random, 95% CI)	2.70 [0.13, 58.24]

Analysis 5.1. Comparison 5: Sensitivity analysis - all AAV together, Outcome 1: Mortality

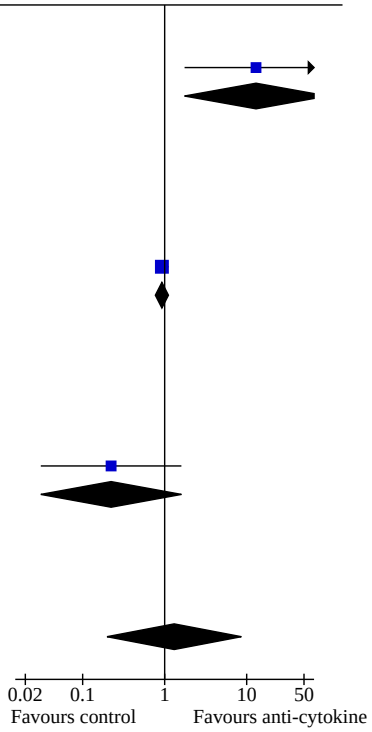


Analysis 5.2. Comparison 5: Sensitivity analysis - all AAV together, Outcome 2: Any remission



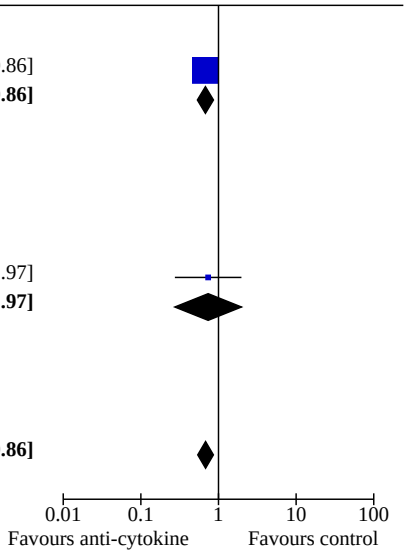
Analysis 5.3. Comparison 5: Sensitivity analysis - all AAV together, Outcome 3: Durable remission

Study or Subgroup	Anti-cytokine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 EGPA						
Wechsler 2017	13	68	1	68	28.7%	13.00 [1.75 , 96.63]
Subtotal (95% CI)		**68**		**68**	**28.7%**	**13.00 [1.75 , 96.63]**
Total events:	13		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
5.3.2 GPA active drug vs placebo						
WGET 2005	62	89	64	85	42.3%	0.93 [0.77 , 1.11]
Subtotal (95% CI)		**89**		**85**	**42.3%**	**0.93 [0.77 , 1.11]**
Total events:	62		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
5.3.3 GPA infliximab vs rituximab						
de Menthon 2011	1	9	4	8	29.0%	0.22 [0.03 , 1.60]
Subtotal (95% CI)		**9**		**8**	**29.0%**	**0.22 [0.03 , 1.60]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**166**		**161**	**100.0%**	**1.31 [0.20 , 8.61]**
Total events:	76		69			
Heterogeneity: Tau² = 2.18; Chi² = 10.35, df = 2 (P = 0.006); I² = 81%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 8.66, df = 2 (P = 0.01), I² = 76.9%						



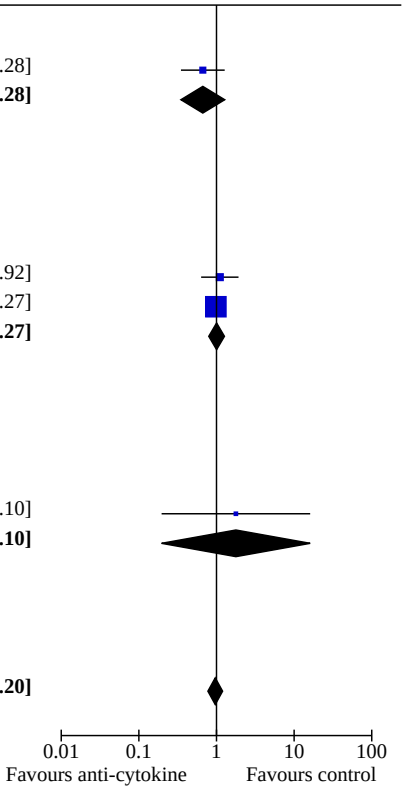
Analysis 5.4. Comparison 5: Sensitivity analysis - all AAV together, Outcome 4: Disease relapse

Study or Subgroup	Anti-cytokine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 EGPA						
Wechsler 2017	38	68	56	68	94.5%	0.68 [0.53 , 0.86]
Subtotal (95% CI)		**68**		**68**	**94.5%**	**0.68 [0.53 , 0.86]**
Total events:	38		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.19 (P = 0.001)						
5.4.2 GPA active drug vs placebo						
BREVAS 2018	6	53	8	52	5.5%	0.74 [0.27 , 1.97]
Subtotal (95% CI)		**53**		**52**	**5.5%**	**0.74 [0.27 , 1.97]**
Total events:	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**121**		**120**	**100.0%**	**0.68 [0.54 , 0.86]**
Total events:	44		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

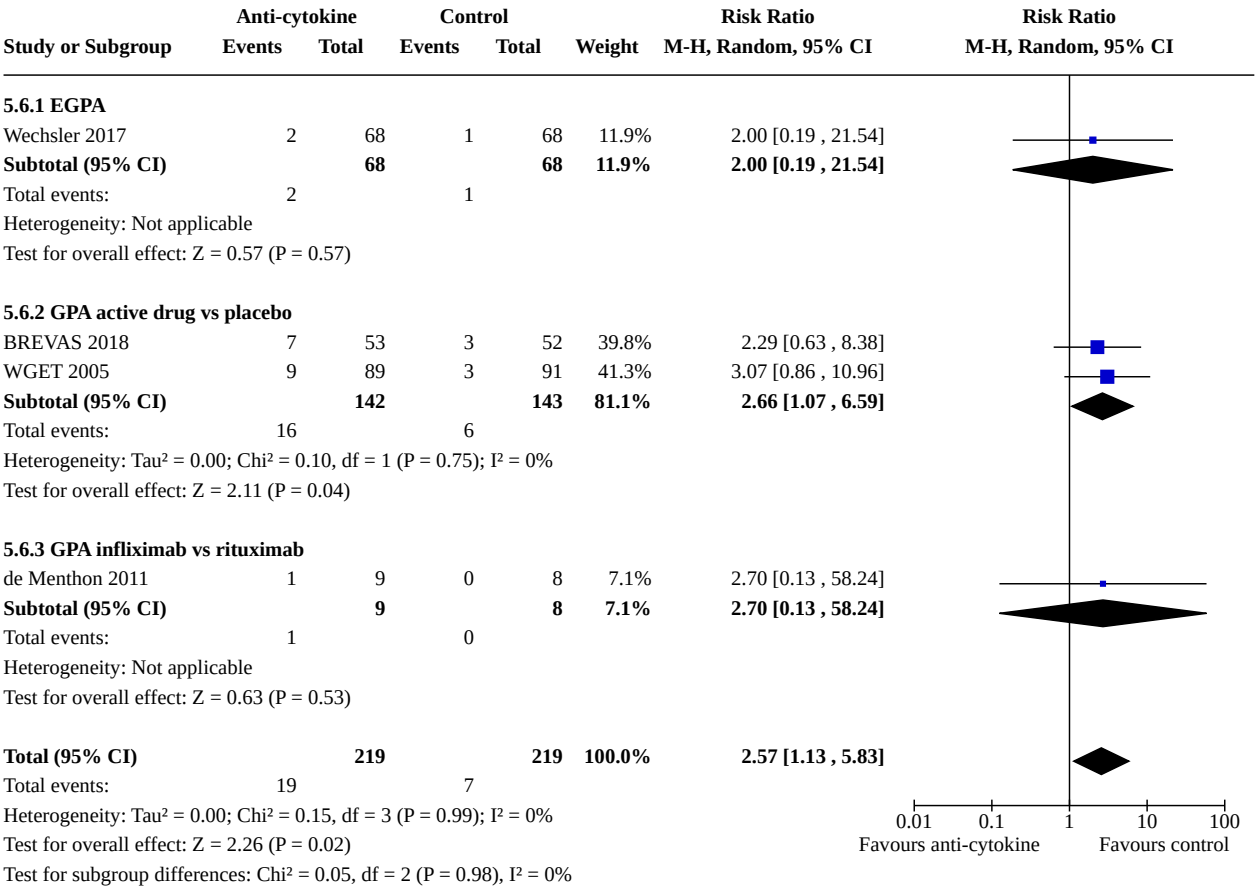


Analysis 5.5. Comparison 5: Sensitivity analysis - all AAV together, Outcome 5: Any serious or severe AE

Study or Subgroup	Anti-cytokine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 EGPA						
Wechsler 2017	12	68	18	68	11.2%	0.67 [0.35 , 1.28]
Subtotal (95% CI)		**68**		**68**	**11.2%**	**0.67 [0.35 , 1.28]**
Total events:	12		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
5.5.2 GPA active drug vs placebo						
BREVAS 2018	18	53	16	52	15.4%	1.10 [0.63 , 1.92]
WGET 2005	50	89	52	91	72.4%	0.98 [0.76 , 1.27]
Subtotal (95% CI)		**142**		**143**	**87.8%**	**1.00 [0.80 , 1.27]**
Total events:	68		68			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 0.03 (P = 0.98)						
5.5.3 Infliximab vs rituximab						
de Menthon 2011	2	9	1	8	1.0%	1.78 [0.20 , 16.10]
Subtotal (95% CI)		**9**		**8**	**1.0%**	**1.78 [0.20 , 16.10]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**219**		**219**	**100.0%**	**0.96 [0.78 , 1.20]**
Total events:	82		87			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.81$, df = 3 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: $Chi^2 = 1.65$, df = 2 (P = 0.44), $I^2 = 0\%$						



Analysis 5.6. Comparison 5: Sensitivity analysis - all AAV together, Outcome 6: Any withdrawals due to AE



APPENDICES

Appendix 1. MEDLINE search strategy

1. Granulomatosis with Polyangiitis.sh.
2. (Polyangiitis adj2 Granulomatosis).tw.
3. (Wegener$ adj2 Granulomatosis).tw.
4. Microscopic Polyangiitis.sh.
5. Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis.sh. or (anca associated vasculitis).mp.
6. Eosinophilic granulomatosis with polyangiitis.tw.
7. Microscopic Polyangiitis.tw.
8. Eosinophilic Granulomatous Vasculiti$.tw.
9. EGPA.tw.
10. Churg-Strauss Syndrome.sh.
11. Churg-Strauss Syndrome.tw.
12. Churg-Strauss vasculitis.tw.
13. Allergic Granulomato$.tw.
14. Allergic Angiiti$.tw.
15. Allergic Granulomato$ Angiiti$.tw.
16. GPA.tw.
17. MPA.tw.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19.randomized controlled trial.pt.
20.randomized controlled trials.mp.
21.random allocation.mp.
22.controlled clinical trial.pt.
23.controlled clinical trials.mp.
24.randomized.ab.
25.clinical trials.mp.
26.(clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
27.placebo.ab.
28.drug therapy.fs.
29.randomly.ab.
30.(random$ or RCT or RCTs).tw.
31.(controlled adj5 (trial$ or stud$)).tw.
32.(clinical$ adj5 trial$).tw.
33.((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
34.(quasi-random$ or quasi random$ or pseudo-random$ or pseud or random$).tw.
35.((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
36.placebo$.tw.
37.trial$.ab.
38.groups.ab.
39.animals.sh. not (humans.sh. and animals.sh.)
40.Tumor Necrosis Factors.sh.
41.Tumo?r Necrosis Factor-alpha antagonist$.tw.
42.anti-tumo?r necrosis factor$.tw.
43.Tumo?r Necrosis Factor-alpha inhibitor$.tw.
44.anti-tnf.tw.
45.antibodies monoclonal.sh.
46.Interleukin$ receptor$ antagonist$.tw.
47.Receptors, Interleukin.sh.
48.Interleukin$ antagonist$.tw.
49.Interleukin$ inhibitor$.tw.
50.Interleukin 1 Receptor Antagonist Protein.sh.
51.(Interleukin-$ adj2 antagonist$).tw.
52.(Interleukin-$ adj2 antagonist$).nm.
53.(IL-$ adj2 antagonist$).tw.
54.(IL-$ adj2 antagonist$).nm.
55.(Etanercept or Enbrel or TNF Receptor Type II IgG Fusion Protein or tnr001OR Recombinant Human Dimeric TNF Receptor Type II IgG Fusion Protein or TNFR-Fc Fusion Protein or TNFR-Fc Fusion Protein or TNFR-Fc Fusion Protein or TNR 001 or TNR-001).nm. or (Etanercept or Enbrel or TNF Receptor Type II IgG Fusion Protein or tnr001OR Recombinant Human Dimeric TNF Receptor Type II IgG Fusion Protein or TNFR-Fc Fusion Protein or TNFR-Fc Fusion Protein or TNFR-Fc Fusion Protein or TNR 001 or TNR-001).tw.
56.(Infliximab or Remicade or Remsima or MAb cA2 or Monoclonal Antibody cA2 or CT-P13).tw. or (Infliximab or Remicade or Remsima or MAb cA2 or Monoclonal Antibody cA2 or CT-P13).nm.
57.(Adalimumab or Humira or D2E7 Antibody).tw. or (Adalimumab or Humira or D2E7 Antibody).nm.
58.(Golimumab or Simponi or Belimumab).tw. or (Golimumab or Simponi or Belimumab).nm.
59.(Certolizumab pegol or Cimzia or Cimzias or CDP870 or CDP870s or CDP 870 or Certolizumab Pegols).tw. or (Certolizumab pegol or Cimzia or Cimzias or CDP870 or CDP870s or CDP 870 or Certolizumab Pegols).nm.
60.(Anakinra or Kineret or Urine-Derived IL1 Inhibitor or IL1 Febrile Inhibitor or Urine IL-1 Inhibitor or IL-1Ra or Antril or recombinant interleukin 1 receptor antagonist or recombinant interleukin 1 receptor blocker).nm. or (Anakinra or Kineret or Urine-Derived IL1 Inhibitor or IL1 Febrile Inhibitor or Urine IL-1 Inhibitor or IL-1Ra or Antril or recombinant interleukin 1 receptor antagonist or recombinant interleukin 1 receptor blocker).tw.
61.(Rilonacept or interleukin-1 Trap or Arcalyst).nm. or (Rilonacept or interleukin-1 Trap or Arcalyst).tw.
62.(canakinumab or Ilaris or Novartis Pharma or ACZ 885 or ACZ-885 or ACZ885 or anti-interleukin-1beta monoclonal antibody).nm. or (canakinumab or Ilaris or Novartis Pharma or ACZ 885 or ACZ-885 or ACZ885 or anti-interleukin-1beta monoclonal antibody).tw.

63. (Tocilizumab or Atlizumab or Actemra or monoclonal antibody, MRA or il -6 or anti-IL-6 or anti-interluekin-6 or interleukin 6).nm. or (Tocilizumab or Atlizumab or Actemra or monoclonal antibody, MRA or il -6 or anti-IL-6 or anti-interluekin-6 or interleukin 6).tw.
64. (Siltuximab or Sylvant or CNTO 328 monoclonal antibody or cClB8 monoclonal antibody or monoclonal antibody CNTO 328 or monoclonal antibody CNTO-328 or monoclonal antibody CNTO328).nm. or (Siltuximab or Sylvant or CNTO 328 monoclonal antibody or cClB8 monoclonal antibody or monoclonal antibody CNTO 328 or monoclonal antibody CNTO-328 or monoclonal antibody CNTO328).tw.
65. (Daclizumab or Zenapax or dacliximab or dacluzimab or Ro 24-7375 or Ro-24-7375 or Zinbryta).nm. or (Daclizumab or Zenapax or dacliximab or dacluzimab or Ro 24-7375 or Ro-24-7375 or Zinbryta).tw.
66. (Basiliximab or Simultec or Simulect or CHI 621 or SDZ CHI 621).nm. or (Basiliximab or Simultec or Simulect or CHI 621 or SDZ CHI 621).tw.
67. (Mepolizumab or Nucala or SB-240563 or SB24056 or Bosatria).nm. or (Mepolizumab or Nucala or SB-240563 or SB24056 or Bosatria).tw.
68. (Reslizumab or Cinquil or Cinqair or sch 55700 or sch-55700 or DCP-835 or DCP835).nm. or (Reslizumab or Cinquil or Cinqair or sch 55700 or sch-55700 or DCP-835 or DCP835).tw.
69. (Benralizumab or medi 563).nm. or (Benralizumab or medi 563).tw.
70. (Tralokinumab or cat 354).nm. or (Tralokinumab or cat 354).tw.
71. (Lebrikizumab il -13 or anti-IL-13 or anti-interluekin-13 or interleukin 13).nm. or (Lebrikizumab il -13 or anti-IL-13 or anti-interluekin-13 or interleukin 13).tw.
72. (Pitrakinra or binetrakin).nm. or (Pitrakinra or binetrakin).tw.
73. (Dupilumab or REGN668).nm. or (Dupilumab or REGN668).tw.
74. (Ustekinumab or Stelara or CNTO 1275 or CNTO-1275).nm. or (Ustekinumab or Stelara or CNTO 1275 or CNTO-1275).tw.
75. (Ixekizumab or Taltz or LY-2439821 or LY2439821 or il -17 or anti-IL-17 or anti-interluekin-17 or interleukin 17).nm. or (Ixekizumab or Taltz or LY-2439821 or LY2439821 or il -17 or anti-IL-17 or anti-interluekin-17 or interleukin 17).tw.
76. Sarilumab.nm. or Sarilumab.tw
77. Olokizumab.nm. or Olokizumab.tw
78. Sirukumab.nm. or Sirukumab.tw
79. (Clazakizumab or ALD518 or BMS-945429).nm. or (Clazakizumab or ALD518 or BMS-945429).tw
80. (Secukinumab or Cosentyx or AIN 457 or AIN-457 or AIN457).nm or (Secukinumab or Cosentyx or AIN 457 or AIN-457 or AIN457).tw
81. (Brodalumab or AMG-827).nm. or (Brodalumab or AMG-827).tw
82. (interleukin-2 or interleukin 2 or IL-2 or IL2 or IL 2 or Il-2 antagonist or Il-2 receptor antagonist).nm. or (interleukin-2 or interleukin 2 or IL-2 or IL2 or IL 2 or Il-2 antagonist or Il-2 receptor antagonist).tw
83. (interleukin-3 or interleukin 3 or IL-3 or IL3 or IL 3 or Il-3 antagonist or Il-3 receptor antagonist).nm. or (interleukin-3 or interleukin 3 or IL-3 or IL3 or IL 3 or Il-3 antagonist or Il-3 receptor antagonist).tw
84. (Il-4 antagonist or Il-4 receptor antagonist or Il-4 receptor or interleukin 4 or interleukin-4 or Il-4 or Il 4).nm. or (Il-4 antagonist or Il-4 receptor antagonist or Il-4 receptor or interleukin 4 or interleukin-4 or Il-4 or Il 4).tw
85. (interleukin-7 or interleukin 7 or IL-7 or IL7 or IL 7 or Il-7 antagonist or Il-7 receptor antagonist).nm. or (interleukin-7 or interleukin 7 or IL-7 or IL7 or IL 7 or Il-7 antagonist or Il-7 receptor antagonist).tw
86. (interleukin-8 or interleukin 8 or IL-8 or IL8 or IL 8 or Il-8 antagonist or Il-8 receptor antagonist).nm. or (interleukin-8 or interleukin 8 or IL-8 or IL8 or IL 8 or Il-8 antagonist or Il-8 receptor antagonist).tw
87. (interleukin-9 or interleukin 9 or IL-9 or IL9 or IL 9 or Il-9 antagonist or Il-9 receptor antagonist).nm. or (interleukin-9 or interleukin 9 or IL-9 or IL9 or IL 9 or Il-9 antagonist or Il-9 receptor antagonist).tw
88. (interleukin-10 or interleukin 10 or IL-10 or IL10 or IL 10 or Il-10 antagonist or Il-10 receptor antagonist).nm. or (interleukin-10 or interleukin 10 or IL-10 or IL10 or IL 10 or Il-10 antagonist or Il-10 receptor antagonist).tw
89. (interleukin-11 or interleukin 11 or IL-11 or IL11 or IL 11 or Il-11 antagonist or Il-11 receptor antagonist).nm. or (interleukin-11 or interleukin 11 or IL-11 or IL11 or IL 11 or Il-11 antagonist or Il-11 receptor antagonist).tw
90. (interleukin-12 or interleukin 12 or IL-12 or IL12 or IL 12 or Il-12 antagonist or Il-12 receptor antagonist).nm. or (interleukin-12 or interleukin 12 or IL-12 or IL12 or IL 12 or Il-12 antagonist or Il-12 receptor antagonist).tw
91. (interleukin-14 or interleukin 14 or IL-14 or IL14 or IL 14 or Il-14 antagonist or Il-14 receptor antagonist).nm. or (interleukin-14 or interleukin 14 or IL-14 or IL14 or IL 14 or Il-14 antagonist or Il-14 receptor antagonist).tw
92. (interleukin-15 or interleukin 15 or IL-15 or IL15 or IL 15 or Il-15 antagonist or Il-15 receptor antagonist).nm. or (interleukin-15 or interleukin 15 or IL-15 or IL15 or IL 15 or Il-15 antagonist or Il-15 receptor antagonist).tw
93. (interleukin-16 or interleukin 16 or IL-16 or IL16 or IL 16 or Il-16 antagonist or Il-16 receptor antagonist).nm. or (interleukin-16 or interleukin 16 or IL-16 or IL16 or IL 16 or Il-16 antagonist or Il-16 receptor antagonist).tw
94. (interleukin-18 or interleukin 18 or IL-18 or IL18 or IL 18 or Il-18 antagonist or Il-18 receptor antagonist).nm. or (interleukin-18 or interleukin 18 or IL-18 or IL18 or IL 18 or Il-18 antagonist or Il-18 receptor antagonist).tw
95. (interleukin-19 or interleukin 19 or IL-19 or IL19 or IL 19 or Il-19 antagonist or Il-19 receptor antagonist).nm. or (interleukin-19 or interleukin 19 or IL-19 or IL19 or IL 19 or Il-19 antagonist or Il-19 receptor antagonist).tw

96. (interleukin-20 or interleukin 20 or IL-20 or IL20 or IL 20 or Il-20 antagonist or Il-20 receptor antagonist).nm. or (interleukin-20 or interleukin 20 or IL-20 or IL20 or IL 29 or Il-20antagonist or Il-20 receptor antagonist).tw
97. (interleukin-21 or interleukin 21 or IL-21 or IL21 or IL 21 or Il-21 antagonist or Il-21 receptor antagonist).nm. or (interleukin-21 or interleukin 21 or IL-21 or IL21 or IL 21 or Il-21 antagonist or Il-21 receptor antagonist).tw
98. (interleukin-22 or interleukin 22 or IL-22 or IL22 or IL 22 or Il-22 antagonist or Il-22 receptor antagonist).nm. or (interleukin-22 or interleukin 22 or IL-22 or IL22 or IL 22 or Il-22 antagonist or Il-22 receptor antagonist).tw
99. (interleukin-23 or interleukin 23 or IL-23 or IL23 or IL 23 or Il-23 antagonist or Il-23 receptor antagonist).nm. or (interleukin-23 or interleukin 23 or IL-23 or IL23 or IL 23 or Il-23 antagonist or Il-23 receptor antagonist).tw
100. (interleukin-24 or interleukin 24 or IL-24 or IL24 or IL 24 or Il-24 antagonist or Il-24 receptor antagonist).nm. or (interleukin-24 or interleukin 24 or IL-24 or IL24 or IL 24 or Il-24 antagonist or Il-24 receptor antagonist).tw
101. (interleukin-25 or interleukin 25 or IL-25 or IL25 or IL 25 or Il-25 antagonist or Il-25 receptor antagonist).nm. or (interleukin-25 or interleukin 25 or IL-25 or IL25 or IL 25 or Il-25 antagonist or Il-25 receptor antagonist).tw
102. (interleukin-26 or interleukin 26 or IL-26 or IL26 or IL 26 or Il-26 antagonist or Il-26 receptor antagonist).nm. or (interleukin-26 or interleukin 26 or IL-26 or IL26 or IL 26 or Il-26 antagonist or Il-26 receptor antagonist).tw
103. (interleukin-27 or interleukin 27 or IL-27 or IL27 or IL 27 or Il-27 antagonist or Il-27 receptor antagonist).nm. or (interleukin-27 or interleukin 27 or IL-27 or IL27 or IL 27 or Il-27 antagonist or Il-27 receptor antagonist).tw
104. (interleukin-28 or interleukin 28 or IL-28 or IL28 or IL 28 or Il-28 antagonist or Il-28 receptor antagonist).nm. or (interleukin-28 or interleukin 28 or IL-28 or IL28 or IL 28 or Il-28 antagonist or Il-28 receptor antagonist).tw
105. (interleukin-29 or interleukin 29 or IL-29 or IL29 or IL 29 or Il-29 antagonist or Il-29 receptor antagonist).nm. or (interleukin-29 or interleukin 29 or IL-29 or IL29 or IL 29 or Il-29 antagonist or Il-29 receptor antagonist).tw
106. (interleukin-30 or interleukin 30 or IL-30 or IL30 or IL 30 or Il-30 antagonist or Il-30 receptor antagonist).nm. or (interleukin-30 or interleukin 30 or IL-30 or IL30 or IL 30 or Il-30 antagonist or Il-30 receptor antagonist).tw
107. (interleukin-31 or interleukin 31 or IL-31 or IL31 or IL 31 or Il-31 antagonist or Il-31 receptor antagonist).nm. or (interleukin-31 or interleukin 31 or IL-31 or IL31 or IL 31 or Il-31 antagonist or Il-31 receptor antagonist).tw
108. (interleukin-32 or interleukin 32 or IL-32 or IL32 or IL 32 or Il-32 antagonist or Il-32 receptor antagonist).nm. or (interleukin-32 or interleukin 32 or IL-32 or IL32 or IL 32 or Il-32 antagonist or Il-32 receptor antagonist).tw
109. (interleukin-33 or interleukin 33 or IL-33 or IL33 or IL 33 or Il-33 antagonist or Il-33 receptor antagonist).nm. or (interleukin-33 or interleukin 33 or IL-33 or IL33 or IL 33 or Il-33 antagonist or Il-33 receptor antagonist).tw
110. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
112. 111 not 39
113. 18 and 112 and 110

Appendix 2. Embase search strategy

1. 'granulomatosis'/exp OR granulomatosis:ab,ti
2. 'wegener granulomatosis'/exp OR wegener AND granulomatosis
3. 'microscopic polyangiitis'/exp OR 'microscopic polyangiitis':ti,ab
4. 'churg strauss syndrome'/exp OR 'churg strauss syndrome':ti,ab
5. 'vasculitis'/exp OR vasculitis:ti,ab OR 'anca associated vasculitis'
6. 'allergic granulomato* angiiti*':ti,ab
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. random*
9. factorial* OR crossover* OR cross AND over* OR 'cross over*' OR placebo* OR doubl* AND adj5 AND blind* OR singl* AND adj5 AND blind* OR assign* OR allocat* OR volunteer*
10. 'crossover procedure' OR 'double blind' AND procedure OR randomized AND controlled AND trial OR 'single blind' AND procedure
11. group*:ti,ab
12. trial*:ab
13. 8 OR 9 OR 10 OR 11 OR 12
14. 'cytokine'/exp OR cytokine:ti,ab
15. 'interleukin'/exp OR interleukin:ti,ab
16. 'tumor necrosis factor':ti,ab
17. 'cytokine receptor'/exp OR 'cytokine receptor':ti,ab
18. 'tumor necrosis factor inhibitor'/exp

19.'tumor necrosis factor inhibitor'/exp OR 'tumor necrosis factor inhibitor':ti,ab
20.'etanercept'/exp OR etanercept:ti,ab OR enbrel:ti,ab OR (tnf AND receptor AND type AND ii AND igg AND fusion AND protein) OR tnr001 OR (recombinant AND human AND dimerictnf AND receptor AND type AND ii AND igg AND fusion AND protein) OR ('tnfr fc' AND fusion AND protein) OR (tnr AND 001) OR 'tnr 001' OR 'belimumab'/exp OR belimumab:ti,ab
21.'infliximab'/exp OR infliximab:ti,ab OR remicade:ti,ab OR remsima:ti,ab OR (mab AND ca2) OR (monoclonal AND antibody AND ca2) OR 'ct p13'
22.'adalimumab'/exp OR adalimumab:ti,ab OR humira:ti,ab OR (d2e7 AND antibody)
23.'monoclonal antibody'/exp OR 'monoclonal antibody':ti,ab
24.golimumab:ti,ab OR simponi:ti,ab OR 'golimumab'/exp
25.'certolizumab pegol*':ti,ab OR cimzia*:ti,ab OR cdp870 OR cdp870s OR 'cdp 870' OR 'certolizumab'/exp
26.'anakinra'/exp OR anakinra:ti,ab OR kineret:ti,ab OR ('urine derived':ti,ab AND il1:ti,ab AND inhibitor:ti,ab) OR (il1:ti,ab AND febrile:ti,ab AND inhibitor:ti,ab) OR (urine:ti,ab AND 'il 1':ti,ab AND inhibitor:ti,ab) OR 'il 1ra':ti,ab OR antril:ti,ab OR (recombinant:ti,ab AND interleukin:ti,ab AND 1:ti,ab AND receptor:ti,ab AND antagonist:ti,ab) OR (recombinant:ti,ab AND interleukin:ti,ab AND 1:ti,ab AND receptor:ti,ab AND blocker:ti,ab)
27.rilonacept:ti,ab OR ('interleukin 1':ti,ab AND trap:ti,ab) OR arcalyst:ti,ab
28.'rilonacept'/exp
29.canakinumab:ti,ab OR ilaris:ti,ab OR (acz AND 885) OR 'acz 885' OR acz885 OR ('anti interleukin 1beta':ti,ab AND monoclonal:ti,ab AND antibody:ti,ab)
30.'canakinumab'/exp
31.tocilizumab:ti,ab OR atlizumab:ti,ab OR actemra:ti,ab OR (monoclonal:ti,ab AND antibody,:ti,ab AND mra:ti,ab) OR (il:ti,ab AND -6:ti,ab) OR 'anti il 6':ti,ab OR 'anti interluekin 6':ti,ab OR 'interleukin 6':ti,ab
32.'tocilizumab'/exp
33.siltuximab:ti,ab OR sylvant:ti,ab OR (cnto AND 328 AND monoclonal AND antibody) OR (cclb8 AND monoclonal AND antibody) OR (monoclonal AND antibody AND 'cnto 328') OR (monoclonal AND antibody AND cnto328)
34.'siltuximab'/exp
35.daclizumab:ti,ab OR zenapax:ti,ab OR dacliximab:ti,ab OR dacluzimab:ti,ab OR (ro AND '24 7375') OR 'ro 24 7375' OR zinbryta:ti,ab
36.'daclizumab'/exp
37.basiliximab:ti,ab OR simultec:ti,ab OR (chi AND 621) OR (sdz AND chi AND 621)
38.'basiliximab'/exp
39.mepolizumab:ti,ab OR nucala:ti,ab OR 'sb 240563' OR sb24056 OR bosatria
40.'mepolizumab'/exp
41.reslizumab:ti,ab OR cinquil:ti,ab OR cinqair:ti,ab OR (sch AND 55700) OR 'sch 55700' OR 'dcp 835' OR dcp835
42.'reslizumab'/exp
43.benralizumab:ti,ab OR (medi AND 563)
44.'benralizumab'/exp
45.tralokinumab:ti,ab OR (cat AND 354)
46.'tralokinumab'/exp
47.lebrikizumab:ti,ab OR 'il 13'/exp OR 'il 13':ti,ab OR (anti AND il AND 13) OR (anti AND interluekin AND 13) OR (interleukin AND 13)
48.'lebrikizumab'/exp
49.pitrakinra:ti,ab OR binetrakin:ti,ab
50.'pitrakinra'/exp
51.dupilumab:ti,ab OR regn668
52.'dupilumab'/exp
53.ustekinumab:ti,ab OR stelara:ti,ab OR (cnto AND 1275) OR 'cnto 1275'
54.'ustekinumab'/exp
55.ixekizumab:ti,ab OR taltz:ti,ab OR 'ly 2439821' OR ly2439821 OR (il:ti,ab AND 17:ti,ab) OR 'il 17'/exp OR 'anti il 17' OR 'anti interluekin 17':ti,ab OR 'interleukin 17':ti,ab OR 'interleukin 17'/exp
56.'ixekizumab'/exp
57.'sarilumab'/exp OR sarilumab:ti,ab
58.'olokizumab'/exp OR olokizumab:ti,ab
59.'sirukumab'/exp OR sirukumab:ti,ab
60.clazakizumab:ti,ab OR ald518 OR 'bms 945429'
61.'clazakizumab'/exp
62.secukinumab:ti,ab OR cosentyx:ti,ab OR (ain AND 457) OR 'ain 457' OR ain457

63.'secukinumab'/exp
64.'brodalumab'/exp OR brodalumab:ti,ab OR 'amg 827'
65.14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64
66.'human'/exp OR human*
67.7 AND 13 AND 65 AND 66
68.67 AND [embase]/lim NOT [medline]/lim

Appendix 3. CENTRAL search strategy

1. random* or trial* crossover* or 'cross over*' or double near blind* or singl* near blind or assign* or allocat*
2. MeSH descriptor: [Double-Blind Method] explode all trees
3. MeSH descriptor: [Randomized Controlled Trial] explode all trees
4. MeSH descriptor: [Single-Blind Method] explode all trees
5. MeSH descriptor: [Cross-Over Studies] explode all trees
6. 1 or 2 or 3 or 4 or 5
7. granulomatosis or 'wegener granulomatos*' or 'microscopic polyangi*' or 'churg strauss syndrome' or 'allergic granulomato* angiiti*'
8. MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees
9. MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees
10. MeSH descriptor: [Churg-Strauss Syndrome] explode all trees
11. 7 or 8 or 9 or 10
12. Tumor Necrosis Factor-alpha' and (antagonist* or inhibitor*)
13. 'Tumor Necrosis Factor-alpha receptor*' and (antagonist* or inhibitor*)
14. Interleukin* and (antagonist* and inhibitor*)
15. MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees
16. MeSH descriptor: [Interleukins] explode all trees
17. 12 or 13 or 14 or 15 or 16
18. Etanercept or Enbrel or 'TNF Receptor Type II IgG Fusion Protein' or tnr001 or 'Recombinant Human Dimeric TNF Receptor Type II IgG Fusion Protein' or 'TNFR-Fc Fusion Protein' or 'TNFR-Fc Fusion Protein' or 'TNFR-Fc Fusion Protein'
19. MeSH descriptor: [Etanercept] explode all trees
20. 18 or 19
21. Infliximab or Remicade or Remsima or 'MAb cA2' or 'Monoclonal Antibody cA2' or CT-P13
22. MeSH descriptor: [Infliximab] explode all trees
23. 21 or 22
24. Adalimumab or Humira or 'D2E7 Antibody'
25. MeSH descriptor: [Adalimumab] explode all trees
26. 24 or 25
27. Golimumab or Simponi
28. Certolizumab pegol* or Cimzia* or CDP870*
29. MeSH descriptor: [Certolizumab Pegol] explode all trees
30. 28 or 29
31. Anakinra or Kineret or 'Urine-Derived IL1 Inhibitor' or 'IL1 Febrile Inhibitor' or 'Urine IL-1 Inhibitor' or IL-1Ra or Antril or 'recombinant interleukin 1 receptor antagonist' or 'recombinant interleukin 1 receptor blocker'
32. MeSH descriptor: [Interleukin 1 Receptor Antagonist Protein] explode all trees
33. 31 or 32
34. Rilonaept or 'interleukin-1 Trap' or Arcalyst
35. Canakimumab or Ilaris or 'Novartis Pharma' or 'ACZ 885' or 'anti-interleukin-1beta monoclonal antibody'
36. Tocilizumab or Atlizumab or Actemra
37. Siltuximab or Sylvant or 'CNTO 328 monoclonal antibody' or 'cClB8 monoclonal antibody'
38. Daclizumab or Zenapax or dacliximab or dacluzimab or 'Ro 24-7375'
39. Basiliximab or Simultec or 'CHI 621' or 'SDZ CHI 621'
40. Mepolizumab or Nucala or 'SB-240563' or Bosatria
41. Reslizumab or Cinquil or 'sch 55700'

42.Benralizumab or 'medi 563'
43.Tralokinumab or 'cat 354'
44.Lebrikizumab
45.Pitrakinra or binetrakin
46.Dupilumab or 'REGN 668'
47.Ustekinumab or Stelara or 'CNTO 1275'
48.MeSH descriptor: [Ustekinumab] explode all trees
49.47 or 48
50.Ixekizumab or taltz or 'ly 2439821'
51.sarilumab or belimumab
52.olokizumab
53.sirukumab or clazakizumab or secukinumab or brodalumab or 'amg 827'
54.17 or 20 or 23 or 26 or 27 or 30 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 49 or 50 or 51 or 52 or 53
55.6 and 11 and 54

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 9, 2020

Date	Event	Description
6 January 2016	Amended	New review authors added, protocol updated in accordance with newer classification of vasculitis and Cochrane MECIR standards
11 November 2009	Amended	CMSG ID C162-P

CONTRIBUTIONS OF AUTHORS

MMB, TMM and WS developed the concept of the study; JZ, MK and MMB developed the search strategy. All review authors contributed to preparation of the protocol and agreed upon this final version of the review.

We thank the authors of the previous version of this protocol for their contributions.

DECLARATIONS OF INTEREST

We are not aware of any direct conflicts of interest.

TMM, JZ, and JDJ declared no conflicts of interest.

MMB receives honoraria (as a freelancer) from a company that works for pharmaceutical companies.

MK received honoraria for articles with topics not related to the topic of the review from a publishing company which does work for several pharmaceutical companies.

WS participates in a trial sponsored by a pharmaceutical company that is not related to vasculitis but to non-cardiac surgery.

SOURCES OF SUPPORT

Internal sources

- Jagiellonian University Medical College, Poland

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we indicated that type of AAV will be a subject of subgroup analysis. However, we decided not to pool the results from two types of AAV together (i.e. GPA and EGPA) due to their clinical heterogeneity, as it would not be clinically meaningful to combine the results and derive conclusions for all types of AAV on the basis of studies targeted to two separate populations of AAV (i.e. not mixed).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis [*drug therapy] [mortality]; Antibodies, Monoclonal, Humanized [administration & dosage] [adverse effects]; Churg-Strauss Syndrome [drug therapy]; Etanercept [administration & dosage] [adverse effects]; Granulomatosis with Polyangiitis [drug therapy]; Immunosuppressive Agents [*administration & dosage] [adverse effects]; Infliximab [administration & dosage] [adverse effects]; Microscopic Polyangiitis [drug therapy]; Numbers Needed To Treat; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Rituximab [administration & dosage] [adverse effects]; Secondary Prevention; Steroids [administration & dosage]

MeSH check words

Humans; Middle Aged