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

Bala MM, Malecka-Massalska TJ, Koperny M, Zajac JF, Szczeklik W

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[Intervention Protocol]

Anti-cytokine targeted therapies for ANCA-associated vasculitis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of anti-cytokine targeted therapy for patients with ANCA-associated vasculitis in terms of the following primary outcomes: mortality, disease activity (remission, durable remission, disease relapse) and adverse events such as withdrawals due to adverse events, total adverse events and serious adverse events.

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 (Levine 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 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 diameter of 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) affects predominantly 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 preva-

lence 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 condition 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 to establish 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 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 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 dose-dependent rates of bladder cancer over time (Knight 2004). To overcome these treatment-related toxicities, strategies for introducing less toxic immunosuppressive agents such as 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 efficacy of rituximab (Riminton). Molecules other than anti-TNF agents and rituximab (such as abatacept, mepolizumab - anti-IL5 antibody; alemtuzumab - humanised monoclonal antibody anti-CD52) 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 assessed in a recently completed randomised trial called MIRRA (NCT02020889).

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) - 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 treatment of affected mice with anti-TNF-alpha has improved their outcomes (Feldmann 2006). In another chronic immune-mediated inflammatory disease - rheumatoid arthritis (RA) - 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, the 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 the 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 efficacy in RA is well established (Berli 2015). Inhibition of pro-inflammatory cytokines has therefore emerged as an attractive prospect for 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-inducted adverse events; or whether to employ novel

biological anti-cytokine therapies with the potential for greater efficacy 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 systematic review has yet been published.

We will conduct 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 patients with ANCA-associated vasculitis in terms of the following primary outcomes: mortality, disease activity (remission, durable remission, disease relapse) and adverse events such as withdrawals due to adverse events, total adverse events and serious adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) and controlled clinical trials (CCTs) for inclusion in this review. We will include studies reported as abstracts without data in the 'Studies awaiting assessment' category and will contact study authors for additional detailed data. We will apply no restrictions on length of follow-up or language.

Types of participants

We will restrict inclusion in this review to trials that meet the following criteria.

- All studies primarily concerning ANCA-associated vasculitis in adult populations (18 years of age or older).
- Specific confirmed diagnoses of patients including granulomatosis with polyangiitis (GPA) - formerly Wegener's granulomatosis - eosinophilic granulomatosis with polyangiitis (EGPA) - formerly Churg-Strauss syndrome - and microscopic polyangiitis (MPA).

We will exclude patients with other types of vasculitides.

Types of interventions

We will consider all randomised controlled comparisons of specifically targeted anti-cytokine therapy versus placebo, standard therapy or another modality; and of varying types and dosages of anti-cytokine therapy.

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

Types of outcome measures

Primary outcomes

Primary efficacy outcomes include:

- mortality;
- remission (as defined by study authors, typically as complete absence of disease activity (Merkel 2011) measured by Birmingham Vasculitis Activity Score (BVAS), BVAS for Wegener's granulomatosis (WG) 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).

Primary safety outcomes include:

- total adverse events;
- serious adverse events; and
- withdrawals due to adverse events.

Secondary outcomes

Secondary outcomes include:

- 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 will collect data at six months, at 12 months and after 12 months, as well as during active treatment and after treatment cessation.

Search methods for identification of studies

We will search all databases from their inception to the present, and we will impose no restriction on language and date of publication.

Electronic searches

We will search the following electronic databases and sources to identify studies.

- Cochrane Central Register of Controlled Trials.
- MEDLINE (OVID).
- Embase (OVID).

We will search the following ongoing trial registries.

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

For assessments of adverse effects, we will search the web sites of regulatory agencies such as the US Food and Drug Administration-MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm), the European Medicines Evaluation Agency (http://www.emea.europa.eu), the Australian Adverse Drug Reactions Bulletin (http://www.tga.gov.au/adr/aadrb.htm) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) for pharmacovigilance and drug safety updates (http://www.mhra.gov.uk).
See Appendix 1 for the MEDLINE search strategy.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' web sites for trial information. When we identify unpublished trials, we will contact relevant authors for further information. We will check http://www.clinicaltrialresults.org/ and the web sites of regulatory agencies such as the US Food and Drug Administration-MedWatch (http://www.fda.gov) and the European Medicines Evaluation Agency (http://www.emea.europa.eu) for unpublished data.
We will search for errata and retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and will report in the review the date this was done.

Data collection and analysis

Selection of studies

For study selection, we will use Covidence (www.covidence.org), a new tool recommended by Cochrane to facilitate production of systematic reviews. Two review authors (JZ, MK, TMM or MMB) will independently screen titles and abstracts of articles identified by the search to determine their potential for inclusion in the review and will code them as 'yes/maybe' (eligible or potentially eligible/unclear) or 'no'. We will retrieve full-text study reports/publications, and two review authors (JZ, MK, TMM or MMB) will independently screen full texts to identify studies for inclusion and will identify and record reasons for exclusion of ineligible studies. We will resolve disagreements through discussion, or, if required, we will consult a third review author (WS). We will identify and exclude duplicates and will collate multiple reports of the same study, so that each study, rather than each report, will be the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (PRISMA Group) (http://prisma-statement.org/PRISMAStatement/Default.aspx) and 'Characteristics of excluded studies' tables.

Data extraction and management

If Covidence allows for adjustment of data extraction forms, we will use this tool for data extraction; otherwise, we will prepare a data extraction form in Microsoft Excel. We will record study characteristics and outcome data on a data collection form that has been piloted on at least one study in the review. One review author (JZ or MK) will extract the following study characteristics from included studies. A second review author (MMB or TMM) will spot-check study characteristics for accuracy against the trial report.

- 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: primary and secondary 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.

Two review authors (JZ and MK) will independently extract outcome data from included studies. We will extract 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 will extract confidence intervals and P values. We will 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 will resolve disagreements by reaching consensus or by involving a third review author (MMB). One review author (MK) will transfer data into the Review Manager (RevMan 2014) file. We will double-check that data have been entered correctly by comparing data presented in the systematic review against study reports.

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

Assessment of risk of bias in included studies

Two pairs of review authors (JZ, MK, MMB, TMM) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion or by consultation with another review author (WS). We will assess 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 will grade each potential source of bias as high, low or unclear and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements per outcomes within a study and per outcomes across studies.

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

When considering treatment effects, we will take into account risk of bias for studies that contribute to that outcome.

We will present figures generated by the risk of bias tool to provide summary assessments of risk of bias.

We will consider a study to have low risk of bias if we assess low risk in all domains for each outcome; otherwise, we will consider the study to have high risk of bias.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

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

We will 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 are reported only as mean differences with standard errors or 95% confidence intervals, we will pool them using the generic inverse variance method available in RevMan5.

We will analyse time-to-event data as hazard ratios.

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

For dichotomous outcomes, such as serious adverse events, we will calculate the NNTB/number needed to treat for an additional harmful effect (NNTH) from the control group event rate and the

risk difference using the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB/NNTH for continuous measures using the Wells calculator (available at the CMSG Editorial Office; http://musculoskeletal.cochrane.org/).

For dichotomous outcomes, we will calculate the absolute risk difference using the risk difference statistic in RevMan software (RevMan 2014) and will express the result as a percentage. For continuous outcomes, we will calculate the absolute benefit as improvement in the intervention group minus improvement in the control group, in original units, and will express this as a percentage.

We will calculate the relative percent change for dichotomous data as the risk ratio - 1 and will express this as a percentage. For continuous outcomes, we will 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 are reported in a single trial, we will include only relevant arms. If two comparisons (e.g. drug A vs placebo and drug B vs placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified as abstract only, when data are not available for all participants). When this is not possible, and missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis. We will clearly describe assumptions and imputations required to handle missing data and will explore the effect of imputation by performing sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will 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 will calculate the MD or the SMD by using the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, we will use the number of randomised participants in each group at baseline.

When possible, we will compute missing standard deviations from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (see Chapter 7). If standard deviations cannot be calculated, we will impute them (e.g. from other studies in the meta-analysis) (refer to the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 7).

Assessment of heterogeneity

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

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), interpretation of an I^2 value from 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity; and 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions*, we will keep 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 will interpret the Chi^2 test with a P value ≤ 0.10 as evidence of statistical heterogeneity.

If we identify substantial heterogeneity, we will report this and will investigate possible causes by following the recommendations provided in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Assessment of reporting biases

If possible, we will create and examine a funnel plot to explore possible small study biases. In interpreting funnel plots, we will examine different possible reasons for funnel plot asymmetry, as outlined in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* and will relate this to review results. If we are able to pool more than 10 trials, we will 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 will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialssearch) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes has occurred.

Data synthesis

We will 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 will pool results for the longest follow-up available.

We will use a random-effects model and will perform a sensitivity analysis based on the fixed-effect model.

We will restrict the primary analysis of self-reported outcomes in this review to trials at low risk of detection and selection bias.

'Summary of findings' table

We will create a 'Summary of findings' (SoF) table using the following outcomes: mortality, remission, durable remission, disease flare/relapse, total adverse events, serious adverse events and withdrawals due to adverse events. The first SoF table will present the comparison of placebo or standard therapy, followed by another modality.

Two people (MK and MMB) will independently assess the quality of the evidence. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contribute data to meta-analyses for prespecified outcomes. We will use 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 2011; Schünemann 2011a; Schünemann 2011b). We will use GRADEpro software to prepare SoF tables (GRADEpro GDT 2015). We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes, and we will provide comments to aid the reader's understanding of the review when necessary.

In the Comments column of the 'Summary of findings' table, we will provide the absolute percent difference, the relative percent change from baseline and the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) (only when the outcome shows a statistically significant difference).

For dichotomous outcomes, such as serious adverse events, we will calculate the NNTB/NNTH from the control group event rate, and the relative risk with use of the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB/NNTH for continuous measures by using the Wells calculator (available at the CMSG Editorial Office; http://musculoskeletal.cochrane.org/).

For dichotomous outcomes, we will calculate the absolute risk difference by using the risk difference statistic in RevMan and will express the result as a percentage. For continuous outcomes, we will calculate absolute benefit as improvement in the intervention group minus improvement in the control group (mean difference), in original units, and will express this value as a percentage.

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

Subgroup analysis and investigation of heterogeneity

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

- Newly diagnosed or relapsing - as treatment effects may differ in cases of first-timers and 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 will use the following outcomes in subgroup analyses.

- Remission.
- Total adverse events.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014) and will apply caution in interpreting subgroup analyses, as advised in Section 9.6 of the *Cochrane Handbook for Systematic Reviews of Interventions*. We will 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.

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

- Effect of assessing study quality - 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).

Interpreting results and reaching conclusions

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

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* *Indicates the major publication for the study*

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.
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 as Topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21. Random Allocation.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. controlled clinical trial.pt.
23. Controlled Clinical Trials as Topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. randomized.ab.
25. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
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. Placebos/
29. placebo effect/
30. drug therapy.fs.
31. Drug Evaluation/
32. Research Design/

33. double-blind method/
34. single-blind method/
35. randomly.ab.
36. (random$ or RCT or RCTs).tw.
37. (controlled adj5 (trial$ or stud$)).tw.
38. (clinical$ adj5 trial$).tw.
39. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
40. (quasi-random$ or quasi random$ or pseudo-random$ or pseud or random$).tw.
41. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
42. placebo$.tw.
43. trial$.ab.
44. groups.ab.
45. control groups/
46. controls.tw.
47. (animals not humans).sh.
48. Tumor Necrosis Factors.sh.
49. Tumo?r Necrosis Factor-alpha antagonist$.tw.
50. anti-tumo?r necrosis factor$.tw.
51. Tumo?r Necrosis Factor-alpha inhibitor$.tw.
52. anti-tnf.tw.
53. antibodies monoclonal.sh.
54. Interleukin$ Receptor$ antagonist$.tw.
55. Receptors, Interleukin.sh.
56. Interleukin$ antagonist$.tw.
57. Interleukin$ inhibitor$.tw.
58. Interleukin 1 Receptor Antagonist Protein.sh.
59. (Interleukin-$ adj2 antagonist$).tw.
60. (Interleukin-$ adj2 antagonist$).nm.
61. (IL-$ adj2 antagonist$).tw.
62. (IL-$ adj2 antagonist$).nm.
63. (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.
64. (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.
65. (Adalimumab or Humira or D2E7 Antibody).tw. or (Adalimumab or Humira or D2E7 Antibody).nm.
66. (Golimumab or Simponi).tw. or (Golimumab or Simponi).nm.
67. (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.
68. (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.
69. (Rilonacept or interleukin-1 Trap or Arcalyst).nm. or (Rilonacept or interleukin-1 Trap or Arcalyst).tw.
70. (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.
71. (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.

72. (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.
73. (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.
74. (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.
75. (Mepolizumab or Nucala or SB-240563 or SB24056 or Bosatria).nm. or (Mepolizumab or Nucala or SB-240563 or SB24056 or Bosatria).tw.
76. (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.
77. (Benralizumab or medi 563).nm. or (Benralizumab or medi 563).tw.
78. (Tralokinumab or cat 354).nm. or (Tralokinumab or cat 354).tw.
79. (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.
80. (Pitrakinra or binetrakin).nm. or (Pitrakinra or binetrakin).tw.
81. (Dupilumab or REGN668).nm. or (Dupilumab or REGN668).tw.
82. (Ustekinumab or Stelara or CNTO 1275 or CNTO-1275).nm. or (Ustekinumab or Stelara or CNTO 1275 or CNTO-1275).tw.
83. (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.
84. Sarilumab.nm. or Sarilumab.tw
85. Olokizumab.nm. or Olokizumab.tw
86. Sirukumab.nm. or Sirukumab.tw
87. (Clazakizumab or ALD518 or BMS-945429).nm. or (Clazakizumab or ALD518 or BMS-945429).tw
88. (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
89. (Brodalumab or AMG-827).nm. or (Brodalumab or AMG-827).tw
90. (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
91. (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
92. (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
93. (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
94. (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
95. (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
96. (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
97. (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
98. (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
99. (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
100. (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
101. (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

102. (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
103. (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
104. (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
105. (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
106. (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
107. (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
108. (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
109. (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
110. (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
111. (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
112. (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
113. (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
114. (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
115. (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
116. (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
117. (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
118. 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 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118
119. 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
120. ((randomized controlled trial or Randomized Controlled Trials as Topic or Random Allocation or controlled clinical trial or Controlled Clinical Trials as Topic or randomized or (clinical trials as topic or clinical trials, phase i as topic or clinical trials, phase ii as topic or clinical trials, phase iii as topic or clinical trials, phase iv as topic) or (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv) or placebo or Placebos or placebo effect or drug therapy or Drug Evaluation or Research Design or double-blind method or single-blind method or randomly or (random$ or RCT or RCTs) or (controlled adj5 (trial$ or stud$)) or (clinical$ adj5 trial$) or ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)) or (quasi-random$ or quasi random$ or pseudo-random$ or pseud or random$) or ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)) or placebo$ or trial$ or groups or control groups or controls) not (animals not humans)).sh.
121. 18 and 118 and 120 (203)

WHAT'S NEW

Date	Event	Description
6 January 2016	Amended	New review authors added, protocol updated in accordance with newer classification of vasculitis and Cochrane MECIR standards

HISTORY

Protocol first published: Issue 1, 2010

Date	Event	Description
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 this protocol and have agreed upon this final version.

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 and JZ have declared no conflicts of interest.

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

In 2011-2014, MK received honoraria as a freelance analyst from a company that performed analyses and HTA reports for the Agency for Health Technology Assessment and Tariff System and for pharmaceutical companies.

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

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