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Comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: a systematic review

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ABSTRACT

Objective To compare the efficacy and safety of alternative glucocorticoids (GCs) regimens as induction therapy for patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis.

Design Systematic review of randomised controlled trials (RCTs).

Data sources Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials up to 10 April 2020.

Study selection and review methods RCTs comparing two (or more) different dose regimens of GC in ANCA-associated vasculitis during induction of remission, regardless of other therapies. Pairs of reviewers independently screened records, extracted data and assessed risk of bias. Two reviewers rated certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Results Of 3912 records identified, the full texts of two records met the eligibility criteria. Due to the heterogeneity of population and dose regimen of GCs between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Compared with the standard-dose regimen, the reduced-dose regimen of GC may reduce death risk difference (RD): from −1.7% to −2.1%, low certainty), while not increasing end-stage kidney disease (ESKD) (RD: from −1.5% to 0.4%, moderate certainty). The reduced-dose regimen probably has an important reduction in serious infections at 1 year (RD: from −12.8% to −5.9%, moderate certainty). Reduced-dose regimen of GCs probably has trivial or no effect in disease remission, relapse or health-related quality of life (moderate to high certainty).

Conclusions The reduced-dose regimen of GC may reduce death at the follow-up of 6 months to longer than 1 year and serious infections while not increasing ESKD.

PROSPERO registration number CRD42020179087.

Strengths and limitations of this study

- This systematic review included a comprehensive search of literatures without limitation on language.
- This systematic review applied Grading of Recommendations Assessment, Development, and Evaluation approach assessing the quality of evidence.
- This systematic review included the largest global trial and the latest trial on the subject so far that have improved the generalisability of the results through the efforts of national and international vasculitis networks and extensive selection criteria.
- Despite the excellent methodological quality, the two eligible trials were open labelled and were subject to bias.
- This systematic review is mainly based on evidence from patients with severe antineutrophil cytoplasmic antibodies-associated vasculitis is uncertain.

INTRODUCTION

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) comprises a subgroup of systemic vasculitis affecting small-sized to medium-sized vessels, a chronic inflammatory disease of the blood vessel wall,[1] and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[2] Patients with AAV usually test positive for ANCA. The cause of the disease remains unclear. Genetic and environmental factors play an important role in the onset of the disease.[3 4] The annual incidence of AAV is about 20 per million inhabitants, and the prevalence is about 100 per million inhabitants.[5] AAV has multiple clinical manifestations, characterised by leucocytes infiltrating the vessel walls, fibrinoid necrosis and vascular damage with occlusion or aneurysm formation.[6] The severity of AAV varies greatly, but after months to years of non-severe manifestations, patients with non-severe diseases often progress to severe

diseases.[7] The most common severe AAV manifestation is glomerulonephritis, which leads to renal failure and alveolar capillaritis causing pulmonary haemorrhage.[8] Previous studies have shown that untreated AAV is typically fatal,[9] with 6-month and 1-year mortality rates of 60% and 80%, respectively.[10]

Since the 1950s, glucocorticoids (GCs), as immunosuppressants and anti-inflammatory drugs with a fast-acting and powerful anti-inflammatory effect, became the basis of therapy for AAV.[11 12] The main mechanism of action is genomic and non-genomic effects mediated by cytosolic GC receptors or specific and non-specific interactions with membrane-bound GC receptors resulting in reduced production of proinflammatory proteins (transrepression).[13] However, monotherapy has incomplete efficacy.[14] Subsequently, standard therapy emerged using the combination of high-dose GC and cyclophosphamide to achieve remission in AAV.[15–17] This combination therapy proved to reduce mortality to 25% at 5 years and has high remission rates of 80%–90%.[18] In addition to cyclophosphamide, clinical remission can also be achieved with rituximab-based or methotrexate-based therapies.[19] Although the combination of high-dose GC and cytotoxic drugs greatly enhances the therapeutic efficacy, high-dose GC may increase the toxicity associated with treatment. Infections and cardiovascular diseases due to the treatment are main causes of fatal side effects that reduced quality of life (QOL) in patients.[20 21] Previous studies have shown that lower GC doses during the induction period were associated with higher relapse rates and longer term of GC use that might expose patients to the potential toxicity of high-cumulative GC.[22 23]

The purpose of this systematic review is to evaluate the comparative efficacy and safety of alternative GC regimens (two or more different doses of GC) in patients with ANCA-associated vasculitis. Our systematic review is part of a BMJ Rapid Recommendations project, which is based on the shared vision of the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and The BMJ. When there is evidence that may change the clinical practice, the cooperative organisations will act quickly to provide a timely, trustworthy practice guideline. Under such circumstance, the exciting evidence was the PEXIVAS trial.[24] The systematic review informed an associated BMJ Rapid Recommendations.

METHODS

Registration and report

A priori protocol of this systematic review is presented at PROSPERO (CRD42020179087). We reported this systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (see online supplemental appendix 1).[25]

Patient and public involvement

According to the process of the BMJ Rapid Recommendations, the guideline panel on this target provides critical process oversight and content guidance for the systematic review. The guideline panel consisted of clinicians, methodologists, pharmacists, patient partners with AAV and caregiver partner. Patients received relevant training and support to meet patient involvement content throughout the guideline development process, including critical feedback on outcome and subgroup selection, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) judgments and manuscript feedback.

Study selection

We included studies of patients with a diagnosis of active AAV. AAV is defined as the following categories according to the Chapel Hill Consensus Conference 2012 classification method: MPA, GPA and EGPA (Churg-Strauss syndrome).[26] In addition, single organ damage AAV (eg, renal limited vasculitis or idiopathic rapidly progressive glomerulonephritis) can be considered the fourth entity, although in practice it eventually corresponds to the kidney-limited form of MPA or GPA.[27]

Eligible studies are defined as comparing two or more doses of GC in patients with AAV during induction of remission, regardless of the use of other therapies. Other therapies include, but are not limited to cyclophosphamide, azathioprine, rituximab, methotrexate, mycophenolate mofetil and plasma exchange. We included only randomised controlled trial (RCTs). Outcomes of interest included death, end-stage kidney disease (ESKD), serious infections, serious adverse events other than serious infection, sustained remission and any other patient-important outcomes. The time point for the outcome assessment depends on what was specified in individual studies.

Data sources and searches

A professional medical librarian developed a literature search strategy and searched Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies from the inception to 10 April 2020 with no restriction on language. Online supplemental appendix 2 presents the literature search strategies and results. We also reviewed the reference lists of included studies for additional references. Pairs of reviewers (YX, JED, TAB, MMA) independently screened titles and abstracts, and reviewed the full texts of potentially eligible studies to determine the final eligible studies. Disagreements were resolved by discussion. To ensure the validity and consistency of the process, we provided reviewers with review instruction and conducted calibration exercises before the formal start of each process.

Data extraction and risk of bias assessment

We collected data through a predesigned excel extraction form. Pairs of reviewers (YX, JED, TAB, MMA) extracted data independently. We resolved disagreements by discussion. For each eligible study, we collected the following: country/region, design of the study, patient characteristics (mean age, sex and disease diagnosis), treatment

strategy, outcomes and measures and follow-up duration. Pair of reviewers (YX, JED, TAB, MMA) independently assessed the risk of bias of each RCT using a revised Cochrane risk of bias tool that includes sequence generation, concealment of allocation, blinding (participants, personnel and outcome assessors), loss to follow-up, selective outcome reporting and other potential sources of bias.[28] The reviewers judged each criterion as definitely or probably low risk of bias, or probably or definitely high risk of bias.

Data synthesis or analysis, and grading of evidence

If data permitted, we planned to conduct meta-analysis for each of the outcomes. For continuous outcomes, we planned to use inverse variance statistical method to calculate mean difference and 95% CI. For binary outcomes, we would use the Mantel-Haenszel statistical method to calculate risk ratio and 95% CI. We planned to conservatively use a priori random effects model assuming a great variability in treatment effects across the study. We planned to use the I^2 statistic to assess statistical heterogeneity. And when the effect-estimated I^2 value is >30%, we would attempt to determine the reason for the heterogeneity. Subgroups would depend on the outcomes of the included studies report. We planned to check the funnel plot for potential publication bias if the number of eligible studies in the analysis exceeded ten. We set significance at p=0.05 and would use RevMan .5.3 for all statistical analyses.

We used the GRADE approach[29] to assess the quality of evidence at outcome level by two reviewers (LZ and YX). We focused on the grading of the following outcomes after our team discussion: death, ESKD, serious infections at 1 year, serious adverse events and health-related QoL. Disagreements were resolved by discussion or through a third reviewer (GG) adjudication. RCTs started as high quality. We summarised the quality of evidence in GRADE summary of findings using the MAGICapp platform.[30 31]

RESULTS

Literature search

The search yielded, after removal of duplicates, 3912 records, 38 of which were considered for full-text review. The PRISMA flow chart (figure 1), presents the reasons for excluding studies at the stage of full-text screening. Ultimately, two RCTs met the inclusion criteria.[18 24] The full text of one of the two RCTs[18] was published after our initial submission of this systematic review. We updated our results after the full text was published.

Included studies

The RCT by Walsh *et al*[24] was a multicentre trial including 704 patients with severe AAV at 95 centres in 16 countries (median duration of follow-up: 2.9 years). This study was a 2-by-2 factorial design and compared the efficacy of plasma exchange with or without plasma exchange for AAV, as well as the efficacy of a reduced-dose regimen and

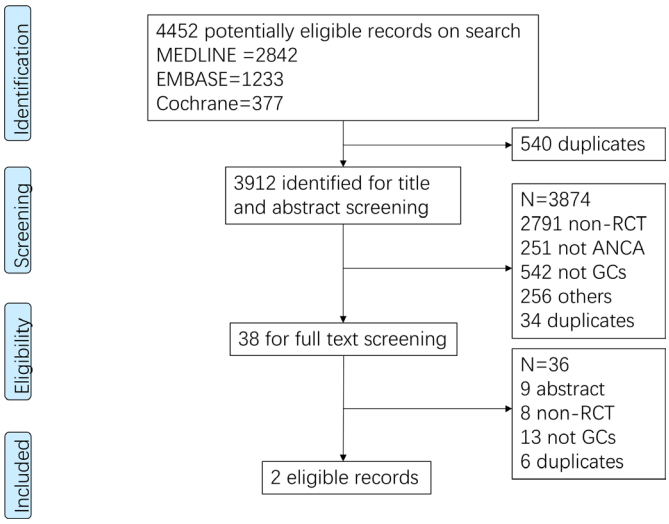

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of literature search and screening process. ANCA, antineutrophil cytoplasmic antibodies; GCs, glucocorticiods; RCT, randomised controlled trial.

a standard-dose regimen of GC over the first 6 months of the treatment period. The two regimens of oral GC, specifically, patients in the reduced-dose regimen and standard-dose regimen received the same treatment in the first week —the dose was determined according to the patients' weight (50.0 mg/<50 kg, 60.0 mg/50–75 kg, 75.0 mg/>75 kg). The reduced-dose regimen and the standard-dose regimen began to decrease gradually in the second and third weeks, respectively. Finally, at sixth month, the cumulative dose of oral GC in the reduced-dose regimen was <60% of the standard-dose regimen (table 1).

The RCT by Furuta *et al*[18] was a multicentre trial enrolling 140 patients with newly diagnosed AAV at 34 centres in Japan (with a follow-up of 6 months). This trial evaluated whether a low-dose GC regimen (initial dose at 0.5 mg/kg/day) is non-inferior to a high-dose regimen (initial dose at 1.0 mg/kg/day) in efficacy when combined with rituximab for the treatment of AAV. In the low-dose group, prednisolone was discontinued at 5 months, while in the high-dose group, prednisolone was reduced to 10.0 mg/ day until 6 months (table 1).

Risk of bias

Both trials were open-label trials and patients and investigators were aware of the group assignments due to the complexity of the GC regimen. However, the recorded treatment adherence, lack of available cointerventions and objective, easily ascertained nature of the outcomes, the lack of blinding may have introduced minimal bias. Considering the low risk of bias in the other domains, overall risk of bias of both trials was low(online supplemental appendix 3).

Table 1 Characteristics of studies originally planned to be included

Author (year)	Name of the study (Clinicaltrials.gov number)	Country	Study design	Intervention and comparison (number of patients)*	Patients	Outcomes
Walsh *et al* (2020)[24]	PEXIVAS (NCT00987389)	Multiple countries	Phase III, randomised, open label, 704 patients	Intervention: reduced-dose GC therapy (initial dose: 50–75 mg; maintenance dose continues at 5 mg/day from the end of week 23 until at least week 52; accumulative dose less than 60% of the standard)	353 patients with severe AAV (mean age 63 years, 44% female)	Primary outcome: a composite of death from any cause or ESKD. Secondary outcomes: death from any cause, ESKD, sustained remission, serious adverse events, serious infections within 1 year and health-related quality of life.
				Comparison: standard-dose GC therapy (initial dose: 50–75 mg; maintenance dose continues at 5 mg/day from the end of week 23 until at least week 52)	351 patients with severe AAV (mean age 63 years, 43% female)	
Furuta *et al* (2021)[18]	LoVAS (NCT02198248)	Japan, multicentric	Phase IV, randomised, open label, 140 patients	Intervention : low-dose GC treatment (initial dose : 0.5 mg/kg/day; discontinued at 5 months)	70 patients with new diagnosis of AAV (median age: 73; 43% female)	Primary outcome: remission rate at 6 months. Secondary outcomes: time to remission, death, relapse, ESKD and the first serious adverse event, proportion of death, relapse and ESKD for efficacy at 6 months.
				Comparison : high-dose GC treatment (initial dose : 1 mg/kg/day; reduced to 10 mg/day by 5 months)	70 patients with new diagnosis of AAV (median age: 74; 37% female)	

*Although these two trials are comparisons of different doses of GCs, the regimens are different, and the details are in the text.
AAV, antineutrophil cytoplasmic antibodies associated vasculitis; ESKD, end-stage kidney disease; GCs, glucocorticoids.

Effect of interventions

Due to the heterogeneity in the population and in the regimens of GCs between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis. Since the results of the Walsh's study[24] showed no interaction between the GC regimen and the plasma exchange, we only focus on the use of GC in conjunction with the purpose of this review.

Online supplemental appendix 4 summarises the GRADE summary of findings for these two trials. Compared with standard-dose regimen, reduced-dose regimen of GC may reduce death (risk difference (RD): from −1.7% to −2.1%, low certainty), while not increasing ESKD (RD: from −1.5% to 0.4%, moderate certainty). Results showed that the rate of serious infection at 6 months to 1 year in the reduced-dose regimen tended to be lower than in the standard-dose regimen (RD: from −12.8% to −5.9%, moderate certainty). As one trial showed reduced-dose regimen might increase the risk of serious adverse events (RD: 3.1%, 95% CI: −3.7% to 11.2%), while another trial showed reduced-dose regimen might reduce the risk (RD: −18.1%, 95% CI: −33% to 3.2%), we are uncertain about the effect of reduced-dose regimen on serious effect (very low certainty). Reduced-dose regimen of GCs probably has trivial or no effect in disease remission, relapse or health-related QoL (Mmoderate to high certainty).

DISCUSSION

After full-text screening, we identified two studies[18 24] involving 844 patients who met our selection criteria for studies comparing different dose regimens of GC for the treatment of AAV. According to this systematic review, the results of the absolute effects of low certainty of evidence showed that reduced-dose regimen of GC may reduce death at a follow-up from 6 months to longer than 1 year, while not increasing the rate of ESKD (moderate certainty) among patients with AAV when compared with standard-dose regimen. However, due to the wide CIs, the absolute effects of any intervention on these two outcomes were minimal, and the results were not significantly different. This may be due to the fact that the improvement of the disease by other treatments may mask the benefits of reduced-dose regimens.

In addition, relative to the standard-dose regimen, moderate certainty of evidence indicated that the reduced-dose regimen probably has an important reduction in serious infections at 6 months to 1 year (moderate certainty). This study showed that reduced-dose regimen does have an obvious advantage in reducing infections, which echoes previous studies.[17 32] For example, Jayne *et al* reported that when high-dose GC was used, infection was most common in the first 6 months of treating severe renal vasculitis.[17] Therefore, considering that the most common cause of death more than 1 year after diagnosis

of AAV is infection or uncontrolled vasculitis,[16 33–35] this is particularly important to support the practice of the conclusion of this study.

We are, however, uncertain about the effect of the reduced-dose regimen on other serious adverse events. While Furuta *et al*'s trial showed a significant reduction in serious adverse events by reduced-dose regimen,[18] Walsh *et al*'s trial showed the reduced-dose regimen might increase the risk with a wide CI.[24] In Walsh *et al*'s trial, although the reduced-dose regimen group had more renal/urinary adverse events than the standard-dose regimen, there was no significant difference in the incidence of ESKD between the two regimen groups as described above. This may be related to the treatment status of the included patients. Among the patients included in the study, the number of patients in the standard-dose regimen who had undergone dialysis before the start of the trial was more than that in the reduced-dose regimen.

The use of GC transformed AAV from an almost uniformly fatal condition to one characterised by remissions and relapses complicated by drug-induced adverse events. Despite the ubiquitous use of GC for AAV, there was no standardisation of dose regimens, guidelines were ambiguous and practice patterns varied substantially. The two trials[18 24] supported the important role GC plays in causing adverse events and highlight the need to optimise their use. Although the two trials found evidence to support one regimen of GC over another, further research is needed to determine whether the GC regimen can be further improved for the treatment of AAV.

The advantages of this systematic review include a comprehensive search of emerging and past evidence across databases without being restricted by study design or publication language, and the use of GRADE approach to assess the quality of evidence. Decisions regarding eligible studies, data extraction and risk of bias assessments were all performed in duplicate, and calibration exercises were conducted before the formal start of the project. By excluding non-RCT studies, we limited the risk of bias. The RCTs we included are of sound methodological quality. AAV is a rare disease, and the PEXIVAS trial is the largest global trial on the subject so far which has improved the generalisability of the results through the efforts of national and international vasculitis networks and extensive selection criteria.

The results of our systematic review also have some limitations. First, only two trials were included and although they were broadly inclusive and contained more events than any other trial in this disease, the total statistical information remains low. This is particularly obvious for serious adverse events other than serious infection. However, the reduced-dose GC regimen should not result in more treatment-related adverse events (ie, it is illogical that a lower exposure to GC would have anything but the same or lower rate of GC caused side effects) and there is reasonable precision around the efficacy outcomes. This limitation is expected to result in an underappreciation of the benefits of reducing the GC dose, a limitation that is supported by observational studies of GC which suggests reducing GC exposure may also reduce fractures, peptic ulcer disease, psychiatric disease, weight gain and dysglycaemia. In addition, despite the excellent methodological quality of the included trial, this is an open label and is subject to biases despite our relative confidence that differential treatment or outcome ascertainment was at low risk. Despite the large scale of this study for a rare disease, the degree to which the results can be generalised to patients with non-severe AAV is uncertain, although it is likely safer to extrapolate the safety of the regimen from more severe illness to less severe illness rather than less severe to more severe.

CONCLUSION

An important general rule is that in routine clinical practice, the use of conventional GC should be 'as much as necessary, but as little as possible'.[36] Therefore, compared with the standard-dose regimen, the reduced-dose regimen of GC may reduce death, probably has little or no effect on ESKD among patients with AAV, and resulted in a lower risk of serious infections at 6 months to 1 year. Future clinical trials should evaluate whether GC dosing can be further safely reduced.

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Contributors MW, AM, DJ, PAM and GG conceived the study idea. RJC performed the literature search. YX, JED, TAB and MMA performed the screening, data abstraction and risk of bias assessments. YX, LZ and MW performed the data analysis. YX, GG, LZ, RS, DJ, PAM and MW interpreted the data. YX, GG and LZ performed the certainty assessment. YX, GG, LZ and MW drafted the manuscript. All authors critically revised the manuscript. All authors approved the final version of the manuscript. YX and MW had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YX and MW are the guarantors.

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Patient consent for publication Not applicable.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-17
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: Search strategies and results for The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review

Database	No of records
MEDLINE	2842
EMBASE	1233
Cochrane Library	377
Subtotal	4452
-dupes	-540
Total	3912

Database: OVID MEDLINE

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1 Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (1682)
2 Churg-Strauss Syndrome/ (2090)
3 Microscopic Polyangiitis/ (507)
4 Granulomatosis with Polyangiitis/ (6902)
5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4968)
6 churg strauss.mp. (2876)
7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4297)
8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp. (9268)
9 wegener*.mp. (6572)
10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (797)
11 or/1-10 (18126)
12 exp Glucocorticoids/ (190619)
13 prednisolone/ or methylprednisolone/ (49855)
14 Prednisone/ (39084)
15 Adrenal Cortex Hormones/ (63823)

16 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (283874)
17 Corticosterone/ or corticosteron*.mp. (34191)
18 Hydrocortisone/ or hydrocortison*.mp. (76765)
19 Cortisone/ or cortison*.mp. (23710)
20 steroids.mp. or Steroids/ (112972)
21 Cortodoxone/ or cortodoxon*.mp. (856)
22 Hydroxycorticosteroids/ or hydroxycorticosteroid*.mp. (6731)
23 Dexamethasone/ or dexamethason*.mp. (71052)
24 adrenocorticosteroid*.mp. (313)
25 adrenocorticoid*.mp. (177)
26 corticoid*.mp. (6458)
27 or/12-26 (547377)
28 11 and 27 (4782)
29 randomized controlled trial.pt. (503644)
30 controlled clinical trial.pt. (93611)
31 randomized.ab. (475606)
32 placebo.ab. (206694)
33 drug therapy.fs. (2193818)
34 randomly.ab. (330775)
35 trial.ab. (501000)
36 groups.ab. (2031658)
37 or/29-36 (4675601)
38 exp animals/ not humans.sh. (4689197)
39 37 not 38 (4053127)
40 28 and 39 (2842)

Database: EMBASE

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1 ANCA associated vasculitis/ (5871)
2 Churg Strauss syndrome/ (4947)
3 microscopic polyangiitis/ (3039)
4 Wegener granulomatosis/ (12860)
5 (vasculit* adj3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (9651)
6 churg strauss.mp. (5425)
7 ((angiit* or vasculit*) adj3 (granulom* or necrot* or allergic)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug

manufacturer, device trade name, keyword, floating subheading word, candidate term word] (7160)
8 ((polyangiit* or polyarterit*) adj3 (microscop* or MPA or granulom*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (7171)
9 wegener*.mp. (14257)
10 (glomerulonephrit* adj3 necrot*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1243)
11 or/1-10 (29983)
12 exp glucocorticoid/ (700322)
13 prednisolone/ (122582)
14 methylprednisolone/ (93152)
15 prednisone/ (167298)
16 corticosteroid/ (229322)
17 (corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (688798)
18 corticosterone/ or corticosteron*.mp. (38497)
19 hydrocortisone/ or hydrocortison*.mp. (135041)
20 cortisone/ or cortison*.mp. (17205)
21 steroids.mp. or steroid/ (245681)
22 cortodoxone/ or cortodoxon*.mp. (2044)
23 hydroxycorticosteroid*.mp. or hydroxycorticosteroid/ (2310)
24 dexamethasone/ or dexamethason*.mp. (161446)
25 adrenocorticosteroid*.mp. (286)
26 adrenocorticoid*.mp. (169)
27 corticoid*.mp. (7745)
28 or/12-27 (1111323)
29 11 and 28 (13676)
30 randomized controlled trial/ (598366)
31 Controlled clinical study/ (463908)
32 random$.ti,ab. (1520687)
33 randomization/ (86548)
34 intermethod comparison/ (258594)
35 placebo.ti,ab. (303776)
36 (compare or compared or comparison).ti. (505122)
37 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2085158)
38 (open adj label).ti,ab. (78322)
39 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (230181)
40 double blind procedure/ (171296)
41 parallel group$1.ti,ab. (25234)

42 (crossover or cross over).ti,ab. (104111)
43 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (326088)
44 (assigned or allocated).ti,ab. (383843)
45 (controlled adj7 (study or design or trial)).ti,ab. (343989)
46 (volunteer or volunteers).ti,ab. (244774)
47 human experiment/ (490852)
48 trial.ti. (296188)
49 or/30-48 (4957675)
50 29 and 49 (1233)

Database: Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees	157
#2	MeSH descriptor: [Churg-Strauss Syndrome] explode all trees	27
#3	MeSH descriptor: [Microscopic Polyangiitis] explode all trees	40
#4	MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees	82
#5	vasculit* near/3 (ANCA or AAV or antineutrophil or anti-neutrophil or cytoplasm* or RLV or renal or churg or strauss or pauci immune)	470
#6	churg strauss	112
#7	((angiit* or vasculit*) near/3 (granulom* or necrot* or allergic))	102
#8	((polyangiit* or polyarterit*) near/3 (microscop* or MPA or granulom*))	277
#9	wegener*	394
#10	(glomerulonephrit* near/3 necrot*)	13
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	867
#12	MeSH descriptor: [Glucocorticoids] explode all trees	4445
#13	MeSH descriptor: [Prednisolone] explode all trees	4804
#14	MeSH descriptor: [Methylprednisolone] explode all trees	2679
#15	MeSH descriptor: [Prednisone] explode all trees	3909
#16	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	14135
#17	corticosteroid* or glucocorticoid* or methylprednisolon* or prednison* or prednisolon*	41757
#18	MeSH descriptor: [Corticosterone] explode all trees	38
#19	MeSH descriptor: [Hydrocortisone] explode all trees	5886
#20	MeSH descriptor: [Cortisone] explode all trees	143
#21	MeSH descriptor: [Steroids] explode all trees	57500
#22	MeSH descriptor: [Cortodoxone] explode all trees	30
#23	MeSH descriptor: [Cortodoxone] explode all trees	30
#24	MeSH descriptor: [Hydroxycorticosteroids] explode all trees	7002
#25	MeSH descriptor: [Dexamethasone] explode all trees	4409

#26	corticosteron* or hydrocortison or cortison* or steroids or cortodoxon* or hydroxycorticosteroid* or dexamethason* or adrenocorticosteroid* or adrenocorticoid* or corticoid*	22688
#27	#12 or #13 or #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	95898
#28	#11 and #27 in Trials	377

Appendix 3 Risk of Bias assessment for outcomes of included RCTs

Outcomes of Trials	Sequence generation	Allocation concealment	Blinding (patients)	Blinding (health care providers)	Blinding (outcome assessors)	Blinding (data collectors)	Blinding (data analyst)	Loss to follow-up
Walsh et al. 2020								
Death	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
ESKD	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Remission	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Serious adverse events	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Serious infections	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Health-related quality of life	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Furuta et al. 2021								
Death	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
ESKD	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Remission	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Relapse	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Serious adverse events	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Serious infections	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low
Health-related quality of life	Definitely Low	Definitely Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Definitely Low

ESKD: end-stage kidney disease；RCT：randomized controlled trial.

Appendix 4 GRADE summary of findings on the use of reduced-dose regimen versus standard-dose regimen of glucocorticoids in patients with ANCA-associated vasculitis

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard-dose regimen of glucocorticoids / Reduced-dose regimen of glucocorticoids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Death	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported death from any cause. In Walsh et al's trial, death occurred in 46 of 353 patients (13.0%) in the reduced-dose GC therapy group and in 53 of 351 patients (15.1%) in the standard-dose GC therapy group (Risk difference, -2.1%; 95% confidence interval, -6% to 3.6%). In Furuta et al's trial, death occurred in 2 of 69 patients (2.9%) in the reduced-dose GC treatment group and in 3 of 65 patients (4.6%) in the high-dose GC treatment group (Risk difference, -1.7%; 95% confidence interval, -4.7% to 8.2%).	**Low** Due to very serious imprecision[1]	Reduced dose of glucocorticoids may reduce death at follow-up of 6 months to 2.9 years
End-stage kidney disease	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported end-stage kidney disease. In Walsh et al's trial, end-stage kidney disease occurred in 70 of 353 patients (19.8%) in the reduced-dose GC therapy group and in 68 of 351 patients (19.4%) in the standard-dose GC therapy group (Risk difference, 0.4%; 95% confidence interval, -4.7%	**Moderate** Due to serious imprecision[2]	Reduced dose of glucocorticoids probably has little or no effect on end-stage kidney disease at follow-up of 6 months to 2.9 years

		to 7.4%). In Furuta et al's trial, end-stage kidney disease occurred in none of 69 patients (0%) in the reduced-dose GC treatment group and in 1 of 65 patients (1.5%) in the high-dose GC treatment group (Risk difference, -1.5; 95% confidence interval, -4.5 to 1.5).		
Remission	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported remission rate. In Walsh et al's trial, remission was analyzed in the two GC groups with the use of Cox proportional-hazards models resulting a hazard ratio of 1.04 (95% confidence interval, 0.81 to 1.33). In Furuta et al's trial, remission occurred in 49 of 69 patients (71.0%) in the reduced-dose GC treatment group and in 45 of 65 patients (69.2%) in the high-dose GC treatment group (Risk difference, 1.8%; 97.5% confidence interval, -13% to ∞).	**Moderate** Due to serious imprecision[1]	Reduced dose of glucocorticoids probably has little or no effect on disease remission at follow-up of 6 months to 2.9 years
Relapse	Based on data from 838 patients in 2 study Follow up: 6 months to 2.9 years	Two RCTs reported remission rate. In Walsh et al's trial, relapse occurred in 32 of 353 patients (9.1%) in the reduced-dose GC therapy group and in 23 of 351 patients (6.6%) in the standard-dose GC therapy group (Risk difference, 2.5%; 95% confidence interval, -1.45% to 6.47%). In Furuta et al's trial, relapse occurred in 3	**Moderate** Due to serious imprecision[3]	Reduced dose of glucocorticoids probably has little or no effect on relapse in patients at follow-up of 6 months to 2.9 years

		of 69 patients (4.3%) in the reduced-dose GC treatment group and in none of 65 patients (0%) in the high-dose GC treatment group (Risk difference, 4.4%; 95% confidence interval, -0.5% to 9.2%).		
Serious adverse events	Based on data from 838 patients in 2 study Follow up: 6 months to 1 year	Two RCTs reported serious adverse events. In Walsh et al's trial, serious adverse events occurred in 230 of 353 patients (65.2%) in the reduced-dose GC therapy group and in 218 of 351 patients (62.1%) in the standard-dose GC therapy group (Risk difference, 3.1%; 95% confidence interval, -3.7% to 11.2%). In Furuta et al's trial, serious adverse events occurred in 13 of 69 patients (18.8%) in the reduced-dose GC treatment group and in 24 of 65 patients (36.9%) in the high-dose GC treatment group (Risk difference, -18.1%; 95% confidence interval, -33.0% to -3.2%).	**Very Low** Due to serious imprecision[4] Due to very serious inconsistency	We are uncertain whether reduced dose of glucocorticoids increases or reduce the risk of serious adverse events at 6 months to 1 year
Serious infections	Based on data from 838 patients in 2 study Follow up: 6 months to 1 year	Two RCTs reported serious infections. In Walsh et al's trial, serious infections occurred in 230 of 353 patients (27.1%) in the reduced-dose GC therapy group and in 218 of 351 patients (33.0%) in the standard-dose GC therapy group (Risk difference, -5.9%;	**Moderate** Due to serious imprecision[3]	Reduced dose of glucocorticoids probably reduces the risk of serious infections at 6 months to 1 year

		95% confidence interval, -11.2% to 1.0%). In Furuta et al's trial, serious infections occurred in 5 of 69 patients (7.2%) in the reduced-dose GC treatment group and in 13 of 65 patients (20.0%) in the high-dose GC treatment group (Risk difference, -12.8%; 95% confidence interval, -24.2% to -1.3%).		
Health related quality of life (SF-36 PCS)	Measured by: SF-36 PCS Scale: - High better Based on data from 838 patients in 2 study Follow up: 6 months to 1 years	Two RCTs reported health related quality of life assessed by SF-36 PCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36PCS was 39.13 in the reduced-dose GC therapy group and 37.84 in the standard-dose GC therapy group (Mean difference, 1.29 higher; 95% confidence interval, 0.26 lower to 2.84 higher). Furuta et al's trial reported that the median score of health related quality of life measured by SF-36PCS was 38.3 (IQR : 21.1 to 47.4) in the reduced-dose GC treatment group and 31.7 (IQR : 22.0 to 49.4) in the high-dose GC treatment group (Mean difference, 6.3 higher; 95% confidence interval, 2.6 lower to 15.2 higher).	**Moderate** Due to serious imprecision	Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (SF-36PCS) at 6 months to 1 years

Health related quality of life (SF-36 MCS)	Measured by: SF-36 MCS Scale: - High better Based on data from 838 patients in 2 study Follow up: 6 months to 1 years	Two RCTs reported health related quality of life assessed by SF-36 MCS. Walsh et al's trial reported that the mean score of health related quality of life measured by SF-36MCS was 52.16 in the reduced-dose GC therapy group and 51.19 in the standard-dose GC therapy group (Mean difference, 0.97 higher; 95% confidence interval, 0.24 lower to 2.18 higher). Furuta et al's trial reported that the median score of health related quality of life measured by SF-36MCS was 49.8 (IQR : 45.1 to 56.6) in the reduced-dose GC treatment group and 50.4 (IQR : 46.3 to 57.2) in the high-dose GC treatment group (Mean difference, 0.4 lower; 95% confidence interval, 4.7 lower to 4.0 higher).	**High**	Reduced dose of glucocorticoids has little or no effect on health related quality of life (SF-36MCS) at 6 months to 1 years
Health related quality of life (EQ-5D Index) at 1 year	Measured by: EQ-5D Index Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year	**0.77** Mean **0.79** Mean Difference: **MD 0.02 higher** (CI 95% 0.01 lower - 0.05 higher)	**Moderate** Due to serious imprecision[5]	Reduced dose of glucocorticoids probably has little or no effect on health related quality of life (EQ-5D) at 1 year
Health related quality of life (EQ-5D Thermometer) at 1 year	Measured by: EQ-5D Thermometer Scale: - High better Based on data from 704 patients in 1 study Follow up at 1 year	**71.07** Mean **72.11** Mean Difference: **MD 1.04 higher** (CI 95% 1.09 lower - 3.17 higher)	**High**	Reduced dose of glucocorticoids has little or no effect on health related quality of life (EQ-5D Thermometer) at 1 year

1. **Imprecision: Very serious.** Because the 95% CI includes both the minimally important difference for benefit (20 fewer death in 1000 patients) and minimally important difference for harm (20 more death in 1000 patients, we rated down two levels for imprecision;

2. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit (30 fewer ESKD in 1000 patients) and minimally important difference for harm (30 more ESKD in 1000 patients) ;

3. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (50 fewer serious infections in 1000 patients);

4. **Imprecision: Serious.** The 95% CI includes an increase in serious adverse event over 10%;

5. **Imprecision: Serious.** The 95% CI crosses the minimally important difference for benefit and the minimally important difference for harm (0.03 reduction or increase in EQ-5D Index) ;

ESKD: end-stage kidney disease; SF-36 = short form 36; PCS = physical component score; MCS = mental component score; EQ = EuroQol; RR: relative risk; MD: mean difference; CI: confidence interval. IQR = interquartile range