PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: A systematic review
AUTHORS	xiao, yingqi; Guyatt, Gordon; Zeng, Linan; Jayne, David; Merkel, PA; Siemieniuk, Reed; Dookie, Jared E; A Buchan, Tayler; Ahmed, Muhammad Muneeb; Couban, Rachel; Mahr, Alfred; Walsh, Michael

VERSION 1 – REVIEW

REVIEWER	Rossi, Giovanni Unità Operativa di Nefrologia, Azienda Ospedaliero-Universitaria di Parma, Dipartimento di Medicina e Chirurgia, Università di Parma
REVIEW RETURNED	19-Apr-2021

GENERAL COMMENTS	This systematic review of the literature pertaining the evidence of different glucocorticoid (GC) regimens performed by the Authors could only have one results, for the reasons they very well note in their paper. The only RCT comparing different GC at the time of their writing was PEXIVAS, which, therefore, is the only included in their analysis. While not RCTs, and not strictly necessary in this kind of work, I think a table listing good quality but retrospective or non-randomized prospective trials and the different GC regimens they compared would be very useful for the reader. Finally, the results of the avacopan trial became available in the meantime, which might be worth including.

REVIEWER	Mendel, A McGill University
REVIEW RETURNED	16-May-2021

GENERAL COMMENTS	The systematic review by Xiao et al is interrogating the literature about a very important question. Strengths of the paper include following the GRADE methodology and PRISMA checklist. 1. It is unfortunate that the rapid review was completed before LoVAS results were available, given that the LoVAS protocol uses a RTX-based induction regimen. Perhaps the main area of uncertainty with the PEXIVAS results is the effect of the reduced-dose GC regimen in the subgroup of patients treated with rituximab– RTX recipients were only 15% of patients enrolled in PEXIVAS, and I think one of the remaining questions is whether the results of PEXIVAS are generalizable to this group. Given that

	more and more patients with GPA/MPA are receiving RTX for induction rather than CYC, the authors should highlight that the results of this only study included in the meta-analysis (despite being large and multi-centre), may lack generalizability for this reason. Will the rapid review be repeated after the completion of LoVAS? I think there should be a plan to do so. 2. I do not have experience with GRADE but I am not sure the RR of death of 0.86 with 95% confidence interval of 0.6-1.24 ought to be interpreted as “may reduce death”, especially since the quality of evidence is “low” with “very serious imprecision”. The estimate seems rather inconclusive - it may reduce death but it also may not. 3. If such an interpretation (#2) is to be made, RR of vasculitis relapse 1.38 (95% CI 0.83-2.32) would be an estimate worth commenting on in the discussion, even if the effect is inconclusive, especially since I this would a theoretical consequence for patients taking a reduced-dose regimen. This was named as an a priori outcome of interest in this review (sustained remission). 4. Several sentences, including within the abstract (results section), introduction (second last paragraph) require grammatical and structural corrections. For example, there are 2 sentences in the paper that start with the word 'And'. 5. Page 17 line 40 “it is well known that dialysis reduces the occurrence of SAE in the urinary system” – perhaps a supporting reference/brief explanation would be useful

REVIEWER	Hagman, Henning University Hospital Cologne, Nephrology, Rheumatology
REVIEW RETURNED	20-Jul-2021

GENERAL COMMENTS	The systematic review aimed to include RCTs investigating different dosing regimens for GC in AAV. Authors planned to employ an elaborate and extensive search strategy. However, only two studies met eligibility criteria for in depth review of which one had no published results available. The authors therefore stick with data from the PEXIVAS trial. PEXIVAS was an RCT published in 2020 with a 2-by-2 factorial design enrolling 704 patients to test PLEX vs. no PLEX and two different dosing regimens of GC in patients with severe AAV. PEXIVAS results show that low dose GC compared to a standard GC regimen is non-inferior with regard to death of any cause and death of ESKD. Reduced dose GC was associated with reduce serious infections at >1 year follow-up and does not convey additional risk for ESKD. No additional risk of side effects was detected in the reduced dose GC group. In addition to these results published in PEXIVAS, the present study poses the question whether there might be a signal towards reduced rate of death at the follow-up of longer than 1 year, while not increasing the rate of ESKD. However, broad confidence intervals cannot resolve uncertainty in this regard. PEXIVAS informed clinicians on the feasibility and safety of reduced steroid doses which has become part of clinical practice in many centers, already. Additional data is needed to confirm this

	management strategy which seems to be beneficial with regard to less infections. This systematic review, however, does not provide any additional evidence. In general, the reviewer does not comprehend the added value of this systematic review article compared to the data already available through PEXIVAS. That said, a metaanalyis of the use of GC in AAV is highly relevant and urgently needed when additional studies e.g. the study by Furuta are published.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Giovanni Rossi, Unità Operativa di Nefrologia
Comments to the Author:

This systematic review of the literature pertaining the evidence of different glucocorticoid (GC) regimens performed by the Authors could only have one results, for the reasons they very well note in their paper. The only RCT comparing different GC at the time of their writing was PEXIVAS, which, therefore, is the only included in their analysis.

While not RCTs, and not strictly necessary in this kind of work, I think a table listing good quality but retrospective or non-randomized prospective trials and the different GC regimens they compared would be very useful for the reader.

Finally, the results of the avacopan trial became available in the meantime, which might be worth including.

Response: Thanks for your comments and suggestions. After we submitted the first version of our manuscript to the BMJ Open, an open-label, randomized, non-inferiority trial comparing the effect of reduced-dose versus high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis (LoVAS trial) (JAMA 2021;325(21):2178-2187) was published. We included this RCT in this revised version of our systematic review. Due to the heterogeneity between these two included trials in the population (severe AAV in PEXIVAS trial vs. newly diagnosed AAV in LoVAS trial) and in the regimens of glucocorticoids (e.g. prednisolone was stopped at 5 months in the reduced-dose group of the LoVAS trial, while prednisolone was continued from the end of week 23 at a dose of 5mg/day until at least week 52 in the reduced-dose group of the PEXIVAS trial), we descriptively presented the two trials and did not combine the results using meta-analysis. The two RCTs consistently revealed that compared with standard dose regimen, reduced dose regimen of oral glucocorticoids reduced the risk of serious infections without increasing the risk of end-stage kidney disease or risk of disease remission.

Reviewer: 2
Dr. A Mendel, McGill University
Comments to the Author:

The systematic review by Xiao et al is interrogating the literature about a very important question. Strengths of the paper include following the GRADE methodology and PRISMA checklist.

1. It is unfortunate that the rapid review was completed before LoVAS results were available, given that the LoVAS protocol uses a RTX-based induction regimen. Perhaps the main area of uncertainty

with the PEXIVAS results is the effect of the reduced-dose GC regimen in the subgroup of patients treated with rituximab– RTX recipients were only 15% of patients enrolled in PEXIVAS, and I think one of the remaining questions is whether the results of PEXIVAS are generalizable to this group. Given that more and more patients with GPA/MPA are receiving RTX for induction rather than CYC, the authors should highlight that the results of this only study included in the meta-analysis (despite being large and multi-centre), may lack generalizability for this reason. Will the rapid review be repeated after the completion of LoVAS? I think there should be a plan to do so.
Response:
Thanks for your comment. Please see our response to Reviewer 1, Comment 1.

2. I do not have experience with GRADE but I am not sure the RR of death of 0.86 with 95% confidence interval of 0.6-1.24 ought to be interpreted as “may reduce death”, especially since the quality of evidence is “low” with “very serious imprecision”. The estimate seems rather inconclusive - it may reduce death but it also may not.

Response: The target of certainty rating (i.e. what it is in which the authors rate their certainty) depends in the relative location of the point estimate and the threshold of interest (GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. Journal of Clinical Epidemiology Volume 137, September 2021, Pages 163-175). And GRADE suggests to use absolute effect rather than relative effect when rate certainty of evidence. As both of the trials indicated that reduced-dose regimen of GC reduced the risk of death (measured by risk difference). The target of certainty rating is that there is an effect. As the confidence interval appreciably crossed the threshold of interest (i.e. risk difference = 0%), we rated down two levels for imprecision and came to a low certainty of evidence. According to GRADE plain language statement (GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions.

Journal of Clinical Epidemiology. Volume 119, March 2020, Pages 126-135), for low certainty of evidence, the plain language is the reduced-dose regimen “may” reduce mortality.

3. If such an interpretation (#2) is to be made, RR of vasculitis relapse 1.38 (95% CI 0.83-2.32) would be an estimate worth commenting on in the discussion, even if the effect is inconclusive, especially since I this would a theoretical consequence for patients taking a reduced-dose regimen. This was named as an a priori outcome of interest in this review (sustained remission).

Response: The absolute effect of reduced-dose regimen of GC in disease relapse is 2.5% with a 95% CI (-1.45% to 6.47%) in Walsh et al’s study and 4.4% with a 95% CI (-0.5% to 9.2%) in Furuta et al’s trial. As we have set a minimally important difference for disease relapse at 5%, both trials indicated that the reduced-dose regimen has trivial or no effect on disease relapse. We added a summary in the results section as below:

Reduced-dose regimen of glucocorticoids probably has trivial or no effect in disease remission, relapse or health related quality of life (Moderate to high certainty).

4. Several sentences, including within the abstract (results section), introduction (second last paragraph) require grammatical and structural corrections. For example, there are 2 sentences in the paper that start with the word 'And'.
Response: We corrected grammatical and structural errors.

5. Page 17 line 40 “it is well known that dialysis reduces the occurrence of SAE in the urinary system” – perhaps a supporting reference/brief explanation would be useful
Response: Thanks for your review. We have already deleted it.

Reviewer: 3
Dr. Henning Hagman, University Hospital Cologne
Comments to the Author:

The systematic review aimed to include RCTs investigating different dosing regimens for GC in AAV. Authors planned to employ an elaborate and extensive search strategy. However, only two studies met eligibility criteria for in depth review of which one had no published results available. The authors therefore stick with data from the PEXIVAS trial.

PEXIVAS was an RCT published in 2020 with a 2-by-2 factorial design enrolling 704 patients to test PLEX vs. no PLEX and two different dosing regimens of GC in patients with severe AAV.
PEXIVAS results show that low dose GC compared to a standard GC regimen is non-inferior with regard to death of any cause and death of ESKD. Reduced dose GC was associated with reduce serious infections at >1 year follow-up and does not convey additional risk for ESKD. No additional risk of side effects was detected in the reduced dose GC group. In addition to these results published in PEXIVAS, the present study poses the question whether there might be a signal towards reduced rate of death at the follow-up of longer than 1 year, while not increasing the rate of ESKD. However, broad confidence intervals cannot resolve uncertainty in this regard.

PEXIVAS informed clinicians on the feasibility and safety of reduced steroid doses which has become part of clinical practice in many centers, already. Additional data is needed to confirm this management strategy which seems to be beneficial with regard to less infections. This systematic review, however, does not provide any additional evidence. In general, the reviewer does not comprehend the added value of this systematic review article compared to the data already available through PEXIVAS. That said, a metaanalyis of the use of GC in AAV is highly relevant and urgently needed when additional studies e.g. the study by Furuta are published.

Response: Thanks for your comments and suggestions. Please see our response to Reviewer 1, Comment 1.

VERSION 2 – REVIEW

REVIEWER	Rossi, Giovanni Unità Operativa di Nefrologia, Azienda Ospedaliero-Universitaria di Parma, Dipartimento di Medicina e Chirurgia, Università di Parma
REVIEW RETURNED	13-Sep-2021

GENERAL COMMENTS	This paper addresses an important problem: the evidence supporting the efficacy of different GC regimens in AAV, and does so with sound statistical methodology, i.e. a systematic review of RCTs without using a meta-analysis approach since it would be futile, as only two RCTs have been performed. For this very reason, I don't see the point of this paper. The interested reader can simply refer to the only two published RCTs. Although I appreciate the effort put into this paper, I don't see how this can be turned around even with a major revision.

REVIEWER	Mendel, A McGill University

REVIEW RETURNED	01-Sep-2021

GENERAL COMMENTS	The authors have incorporated the recently published LOVAS trial which renders the SLR more complete and worthwhile. I have no concerns about the scientific content of the manuscript. However, I do think it still needs to be carefully proofread and edited for language issues, some examples below Page 7, line 5, abstract conclusion "...while not increase ESKD" should be changed to "while not increasing ESKD" Page 7, line 38-39 "this systematic review is mainly based on evidence from patients with severe AAV is uncertain" - some words are missing Page 8, line 13 consider spelling out what ANCA stands for as this is a general medicine audience Page 8 line 21 "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" - i do not think this latter half of the sentence is generally true and is not supported by the paper cited. Page 8 line 43 - sentence starting with "And" Page 9 line 5 "randomized controlled trails started as high quality" - what does this mean? is this sentence needed Page 16 line 25 "Since the results of the Walsh's study" - consider changing to Walsh et al, remove "the" Page 16 line 48 "serious effect" should be changed to "serious adverse events"

REVIEWER	Hagman, Henning University Hospital Cologne, Nephrology, Rheumatology
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	By including results from the LoVAS trial, authors broadened the view on the topic, especially since the study population of LoVAS contained patients with newly diagnosed AAV and excluded severe glomerulopathy and pulmonary hemorrhage. In contrast, besides severe AAV PEXIVAS also allowed recurrent AAV and previous treatment. More information on LoVAS is needed in the introduction and differences to PEXIVAS need to be addressed in the discussion section. Does LoVAS inform on treatment of the less severe cases of AAV? Minor points: 1. Page 3 line 16 –must be „randomized clinical trials“ 2. Page 3 line 23 – please correct the date 3. Page 4 line 38 – please correct grammar 4. Page 5 line 25 – incorrect grammar: must read “the most common manifestations are…”

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Giovanni Rossi, Unità Operativa di Nefrologia

Comments to the Author:

This paper addresses an important problem: the evidence supporting the efficacy of different GC regimens in AAV, and does so with sound statistical methodology, i.e. a systematic review of RCTs without using a meta-analysis approach since it would be futile, as only two RCTs have been performed.

For this very reason, I don't see the point of this paper. The interested reader can simply refer to the only two published RCTs.

Although I appreciate the effort put into this paper, I don't see how this can be turned around even with a major revision.

Response: We appreciate the reviewer's comment but we do not agree. Beyond looking at the two papers, the interested reader will benefit from our review in the following ways: i) Because of the comprehensive literature search, one can be confident that this review includes all the RCT evidence available; ii) the review provides ratings of the certainty of the evidence; iii) the systematic review presents the absolute effects of the reduced-dose regimen of glucocorticoids in the PEXIVAS trial that were not reported in the original trial paper. iv) The systematic review also compared the effects of reduced-dose regimens of glucocorticoids in newly diagnosed AAV and severe AAV, and the discussion clearly identifies areas in which we have at least moderate certainty of effects and those in which high uncertainty remains.

Reviewer: 2

Dr. A Mendel, McGill University

Comments to the Author:

The authors have incorporated the recently published LOVAS trial which renders the SLR more complete and worthwhile. I have no concerns about the scientific content of the manuscript.

However, I do think it still needs to be carefully proofread and edited for language issues, some examples below

Page 7, line 5, abstract conclusion "...while not increase ESKD" should be changed to "while not increasing ESKD"

Response: We changed "...while not increase ESKD" into "while not increasing ESKD".

Page 7, line 38-39 "this systematic review is mainly based on evidence from patients with severe AAV is uncertain" - some words are missing

Response: We removed this sentence.

Page 8, line 13 consider spelling out what ANCA stands for as this is a general medicine audience

Response: We spelt out what ANCA stands for when it first presents in the main context of the paper, as follows:

Antineutrophil cytoplasmic antibodies (ANCA) -associated vasculitis (AAV) comprises a subgroup of systemic vasculitis affecting small- to medium-sized vessels, a chronic inflammatory disease of the blood vessel wall1,

Page 8 line 21 "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" - i do not think this latter half of the sentence is generally true and is not supported by the paper cited.

Response: We removed the latter half of the sentence.

Page 8 line 43 - sentence starting with "And"

Response: We removed “And”.

Page 9 line 5 "randomized controlled trails started as high quality" - what does this mean? is this sentence needed

Response: We removed this sentence.

Page 16 line 25 "Since the results of the Walsh's study" - consider changing to Walsh et al, remove "the"

Response: We removed “the” and have changed to Walsh et. al.

Page 16 line 48 "serious effect" should be changed to "serious adverse events"

Response: We changed “serious effect” into “serious adverse events”.

Reviewer: 3

Dr. Henning Hagman, University Hospital Cologne

Comments to the Author:

By including results from the LoVAS trial, authors broadened the view on the topic, especially since the study population of LoVAS contained patients with newly diagnosed AAV and excluded severe glomerulopathy and pulmonary hemorrhage. In contrast, besides severe AAV PEXIVAS also allowed recurrent AAV and previous treatment. More information on LoVAS is needed in the introduction and

differences to PEXIVAS need to be addressed in the discussion section. Does LoVAS inform on treatment of the less severe cases of AAV?

Response: We have removed the description of the PEXIVAS trial in the introduction section. We added a description of the patients and the differences between these two trials in eligible patients in the result section under “Included studies” as follows:

The RCT by Walsh et al 24 was a multicenter trial including 704 patients with severe AAV at 95 centers in 16 countries (median duration of follow-up 2.9 years). Eligible patients were 15 years of age or older, had new or relapsing granulomatosis with polyangiitis or microscopic polyangiitis, and kidney involvement or pulmonary involvement……

The RCT by Furuta et al 18 was a multicenter trial enrolling 140 patients with newly diagnosed AAV at 34 centers in Japan (with a follow-up of 6 months). Patients with severe glomerulonephritis or pulmonary hemorrhage were excluded.

Under “Effect of interventions”, we emphasized the heterogeneity in the characteristics of patients between the two trials as follows:

Due to the heterogeneity in the population and in the regimens of glucocorticoids between the two trials, we descriptively presented the two trials and did not combine the results using meta-analysis.

And we reported the effect of the intervention both newly diagnosed and severe ANCA-associated vasculitis as follows:

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 probably not increasing ESKD in either patients with newly diagnosed ANCA-associated vasculitis or patients with severe ANCA-associated vasculitis (RD: from -1.5% to 0.4%, moderate certainty). The rate of serious infections at six months to one year in the reduced-dose regimen tended to be lower than in the standard-dose regimen in both newly diagnosed and severe ANCA-associated vasculitis (RD: from -12.8% to -5.9%, moderate certainty). The PEXIVAS trial showed reduced-dose regimen might increase the risk of serious adverse events in a follow-up period of longer than one year (RD: 3.1%, 95% CI -3.7% to 11.2%) while the LoVAS trial showed reduced-dose regimen might reduce the risk at six month (RD: -18.1%, 95% CI -33% to 3.2%). We are uncertain about the effect of reduced-dose regimen on serious adverse events (Very low certainty).

Minor points:

1. Page 3 line 16 –must be „randomized clinical trials“

Response: We revised into “randomized controlled trial (RCTs)”.

2. Page 3 line 23 – please correct the date

Response: The date is correct. We searched Medline, Embase, Clinicaltrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies from the inception to 10 April 2020. Two eligible trials (i.e. the PEXIVAS trial, and the LoVAS trial) were found, one of which (i.e. the LoVAS trial) was only published as a protocol. The full text of the LoVAS trial was published after our initial submission of this systematic review. We updated our results when we re-submitted this paper.

3. Page 4 line 38 – please correct grammar

Response: We corrected the grammar throughout the paper.

4. Page 5 line 25 – incorrect grammar: must read “the most common manifestations are…”

Response: We removed “severe AAV” and changed the sentence into “The most common manifestation is”.