Author's response to reviews

Title: Interventions for renal vasculitis in adults. A systematic review.

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Author's response to reviews: see over
Reviewer's report
Title: Interventions for renal vasculitis in adults. A systematic review.
Version: 2 Date: 13 December 2009
Reviewer: David Jayne
Reviewer's report:
This review is of high quality and covers most of the relevant literature in this area, it will be of use to practitioners and clinical researchers. The methodology appears sound. The comments below reflect suggestions which would enhance the manuscript.

1. Renal vasculitis has other presentations such as, cortical infarctions and aneurysms in PAN and renal artery stenosis in Takayasu’s arteritis.
   Agreed

2. Also, renal vasculitis can present without RPGN, such as, asymptomatic urinary abnormality, chronic kidney disease or FSGS.
   Agreed

3. HSP and cryoglobulinemia are causes of renal vasculitis
   entered in manuscript

4. Methodological issues in the MMF and leflunomide trials preclude conclusions.
   More detailed comment below in similar point

5. In the results of IV versus daily oral cyclophosphamide trials it is important to add that some trials used no remission maintenance treatment when referring to an increased relapse risk.
   There are 4 studies examining this issue. There is remission maintenance treatment for Adu and de Groot studies but not for haubitz and Guillevin. However, the cyclophosphamide treatment continues for 1 year after remission for both studies with a further year of reduced dose cyclophosphamide in Guillevin. Considering that the analysis in most studies is up to 18 months or 2 yearssm the only study where some patients are without maintenance treatment is haubitz. The figures of this study are not at variance with the others, ie there is little heterogeneity in the study outcomes

6. In the Stegeman study there was no difference in non-respiratory relapse rates, after co-trimaoxazole /placebo. A problem with this study was disentangling the reduction in respiratory tract infections related to the antibiotic and the reduction in respiratory tract relapses.
   Agreed. It is a very difficult study to interpret.

7. The Hu trial was conducted in China with a majority of MPO-ANCA associated MPA. Any conclusions may not be transferable to populations with higher frequencies of PR3-ANCA disease, Wegener’s. Page 11 “Mycophenolate Mofetil may be equivalent to cyclophosphamide”.
   Added “in this limited population” on the comments. The limited external validity of this trial is mentioned in the discussion of this study.

Wrong reference quoted – should say
32 , i.e. Hu et al, NDT 2008 (not reference 22- Glockner et al ‘88).
Thanks, corrected. I had not finally updated the reference list. Hu has now jumped to 22.

Short follow-up
( only 6 months), also only patients with mild ANCA vasculitis were included so results cannot be extrapolated to those with creat >500 or lung hemorrhage.
Agreed.
8. Could include a note about the ongoing MYCYC trial by the EUVAS group. 
*Added to Implications for practice.*

9. The leflunomide trial was stopped early by the data monitoring committee. The summary of the trial is misleading as the number of excess SAEs in the leflunomide group exactly matched the number of severe vasculitis flares in the MTX group. Any conclusions must be guarded in view of these observations. 
*Added to discussion.*

10. The etanercept trial was not able to show a benefit of etanercept on remission induction due to its design, only on remission maintenance. 
*I do not agree. This was a study that randomised patients at relapse or diagnosis to be treated with etanercept or placebo plus standard treatment for severe or limited disease. The primary outcome was sustained remission. Relapse rate was a secondary outcome in the study.*

11. There is of mention of the WEGENT trial (Pagnoux, New Eng J Med 2008) presumably because it was not picked up by the search. Yet the leflunomide trial was picked up. Neither focus on renal vasculitis but both are relevant to the discussion of remission maintenance agents. 
*Entered into the review.*

12. Although not an aim for the RCTs, plasma exchange is often used for lung hemorrhage, a major vasculitic cause of death. At least, the absence of evidence might be referred to here. 
*The focus of this review has been renal involvement in vasculitis. I have therefore not mentioned this.*

13. As mentioned above the earlier trials of pulse cyclophosphamide did not use remission maintenance therapy and this will have influenced the relapse rates. 
*Answered above. There are only 4 studies. This problem does not seem to impact on the figures.*

14. Definitions of remission and relapse vary between trials which may influence remission and relapse rates. 
*Agreed.*

15. There is no mention of the two rituximab RCTs reported in abstract form (ASN 2008 and ACR 2009). 
*Both now added.*

16. There is no mention of the IMPROVE, MMF vs AZA trial (ASN 2009). 
*added*

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: 
I have received research grant support and consulting fees from ASPREVA and Roche.
Reviewer's report
Title: Interventions for renal vasculitis in adults. A systematic review.
Version: 2 Date: 18 November 2009
Reviewer: Catherine Meads
Reviewer's report:

major compulsory revisions
1. you must explain why you have included quasi-RCTs as normally this will not be included unless there is a specific reason. What forms of Quasi-RCT were you willing to include?
Quasi RCTs were included in the protocol prior to the search strategy being implemented. Good quality RCTs are very hard to come by in Renal Medicine, we therefore used as wide a search as possible to maximise the available data. In the final event, there are no quasi RCTs in the study.

2. did you search for unpublished studies?
Yes we have not found any as yet

3. did you include studies in foreign languages?
Yes, this included getting a chinese abstract translated, only to find it was not a randomised study.

4. did you check reference lists to find other studies?
Yes, lots of them

5. You MUST put in a flow diagram of the study selection process. How many titles and abstracts did you sift? How many full papers did you examine? What were the reasons for the excluded full papers?
Agreed, included.

6. What was the quality of the included studies? You say you assessed but how did you use the assessment to indicate the believeability of the results?
The quality of the studies is highly variable but, in most of the outcomes, heterogeneity is low. There are no major issues as to interpretation of the studies. Whilst some of the early, small and poor quality studies are rather difficult to interpret, the larger higher quality studies show similar results. The issue of “believeability” is therefore not a major problem in the current study.

7. Which studies were the Quasi-RCTs? Did their results differe systematically from the true RCTs?
As above, there are none.

8. You need to give some details of the patients in the trials. What ages were they? Gender? Ethnicity? Etc
Yes, currently this is not in the paper. It is a table in the review but I was not sure that this detail was essential for the paper. It could go in the text or as a table and I would be happy to add it. Most appropriate would probably be a table but there are quite a few of them already.

minor essential revisions
1. the review needs to be written according to the PRISMA guidelines, including the abstract
I have worked to format the paper according to the instructions for authors. I have also gone through the 27 item PRISMA worklist. The full Cochrane Review complies with the worklist but a paper summarising the full review simply cannot fulfill all the Prisma criteria. If there are any thought to be essential that I have missed I am happy to put them in.

2. the abstract conclusions seem to just have more results in . Please move these to the results section and put what you conclude from the systematic review in the conclusions section.
The Conclusions are a summary of the most notable results of the available evidence. They are a significant departure from some currently held beliefs.
3. p4 the sentence "The treatment of goodpastures....." in the background section does not make sense to the general reader as you say you are reviewing PRGN then exclude some forms RPGN but don't explain why these are any different from other forms of RPGN and why they should be excluded. - your figure captions don't explain what the forest plots show but seem to be statements of conclusion. Please change them to say exactly what the forest plot is.

Added an explanatory phrase in background.

4. you don't explain about induction and maintenance agents in the background section yet an understanding of this is expected in the discussion section. Please make the two sections match. For example, exactly what is Ser<500uM???
The concept of inducing remission was present in the second paragraph of the background followed by scaling back of treatment. I have specifically included the words remission induction and maintenance therapy to clarify.

Ser is referred to in the table of abbreviations as Serum Creatinine. 500 uM is a concentration in SI units.

5. You start to describe cost benefit studies in your implications for research. Do you mean cost-effectiveness as it is very rare to estimate the financial cost of health effects and much more common to estimate utility. Are you actually describing a cost minimisation activity?
Yes, you are correct, I should have termed it cost effectiveness. This is a critical issue for example in the use of rituximab where it has equivalent efficacy but costs probably several hundred times as much as cyclophosphamide. It is widely held that rituximab has fewer long term side effects but that is not well proven.

discretionary revisions
1. If you were developing a guideline for treatment of this condition, which drug would come first and which next etc? What additional information would you need to be able to construct the guideline (ie which comparative studies are missing?)
The guideline I have already co-authored.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests