Response to Reviewers Manuscript 20321 "How Should Immunomodulators be Optimized When Used as Combination Therapy with Anti-TNF"

We would like to thank the reviewers for their helpful and thoughtful comments.

Reviewer One (50345)

In this paper, the authors precisely reviewed how best to optimize immunomodulators when used in combination therapy with anti-TNFs. This paper has been well written and the contents are clinically interesting. I suggest that the authors should address the following point to improve the paper. The authors should show the full spellings of "6-TGN"and "TPMT.

Thank you for your comments. We have amended the manuscript to include the full spelling of both TGN and TPMT.

Reviewer Two (49331)

Anti-TNF therapy and immunomodulators (IM) are effective in the treatment of IBD, however they have many side effects. They may also cause opportunistic infections and malignancies. The Authors mentioned the benefits and risks of mono or combination therapy, the selection of immunomodulators and their dosage thoroughly. My comments; In deep remission or active period (mild activation), whether the treatment can be stopped and also when to stop it should be mentioned under the heading "Can immunomodulators be stopped at any time when used in combination therapy?" and in the summary and key points.

Thank you for your comments. We have provided data and a recommendation in the section "Can Immunomodulators be stopped at any time when used in combination therapy" as "From these three studies it can be concluded that the lowest risk of relapse is in patients who are in deep remission (clinical remission and normalized biomarkers including mucosal healing), with good anti-TNF drug levels, after a prolonged period of combination therapy (ideally at least 12 months) before IMs are withdrawn." We have further clarified this by adding a sentence that those with active disease are more likely to require treatment optimisation if they subsequently have their IM withdrawn. We have added a point to highlight this in the summary/key point table.

Reviewer Three (38879)

Thank you for your thoughtful comments.

1. The issue of the anti-TNF levels and antibodies to biologics is overemphasized here in my opinion. We really do not know at this point whether there is a universal therapeutic threshold level truly predictive of clinical response. In addition as the authors point out the antibodies to anti-TNF might at times have minimal or no clinical impact. In most studies in addition there is no proof that IM impact anti-TNF PK. Yet the authors seem to equate the benefit of combination therapy to improvement in anti-TNF PK. I suggest the authors reduce the lengthy discussions on this issue and downplay it in the conclusions (Summary and key points). As of today this is a very imperfect science - and much needs to be learnt.

We agree with the reviewer that more data is needed before we equate an improvement in clinical outcomes on combination therapy, (compared to anti-TNF monotherapy) with an improvement in anti-TNF

pharmacokinetics. We have altered the manuscript to be more balanced by including a lack of clinical benefit seen in some papers of anti-TNF pharmacokinetics and have edited the summary accordingly.

2. This is a very, very long manuscript and the reader is often left wondering why the authors did not include a few tables summarizing the results of the literature. It would greatly help

Thank you for these suggestions. As this was not a systematic review we did not perform extensive tabulation of all of the referenced studies. We have expanded the summary and key points table to improve readability of the manuscript. We have also shortened the manuscript as per below.

3. The data related to toxicity, infections, risk of cancer etc are spread all over the manuscript. Again, this is a bit frustrating for the reader. I suggest you discuss this once only in a single section and refer to that as needed.

Thank you for highlighting this point. We have consolidated data on infection and lymphoma risk into one section for brevity.

4. It would be nice to see the authors recommendations represented in a concise figure (or two)

We thank the reviewer for this suggestion. We planned a diagram summarising management, (and optimisation) of combination therapy in the first 12-24 months of treatment before consideration of withdrawal to anti-TNF monotherapy after evaluation for deep remission. After consideration we felt several components of such a figure represented expert opinion and were not well enough supported in the literature and hence would detract from the overall manuscript.

5. I would add the issue of teratogenicity for methotrexate.

We thank the reviewer for this important suggestion and have included two sentences in the manuscript to address this issue.

6. The authors proposal of starting IM and biologics at the same time makes sense based on the literature. However it is unclear - WHO should be subjected to such treatment. I do understand the present data do not clarify it, but the reader would appreciate a stronger stand on this - which is after all the most important point of the entire review.

We agree with the reviewer that it a critical issue is to define which group of patients with IBD should be treated with combination therapy rather than anti-TNF monotherapy. We have altered the manuscript to suggest that those with moderate to severe IBD should be considered for combination therapy. The thrust of the manuscript is to describe in detail how IM are best optimised in combination therapy once a decision is made to use combination therapy. A more detailed discussion on the merits of combination therapy over anti-TNF monotherapy is beyond the scope of the paper and has also recently been reviewed by Dulai et al – Gut 2014 Dec; 63(12): 1843-53.