ANSWER TO EDITOR'S AND REVIEWERS' COMMENTS

EDITOR

The comments were taken into consideration and the manuscript was corrected respectively.

REVIEWER 1

COMMENT: Title: Do not abbreviate any word in the title.

ANSWER: The title is modified accordingly

COMMENT: A role of mycophenolate in the treatment of ANCA associated Vasculitis has already been established by a number of empirical studies and used clinically. In-depth review on the pharmacodynamic and pharmacokinetic would be more appreciated by the potential readers of this manuscript.

ANSWER: Mycophenolate though effective in AAV is second or third or even fourth line choice according to European recommendations. However in clinical practice mycophenolate is useful and this mini-review analyses published experience trying to signify that mycophenolate is an important alternative in the treatment of AAV. The pharmacodynamic and pharmacokinetic profile of mycophenolate is well known however the relevant part in the manuscript was supplemented. Its efficacy is proven by clinical data mostly and not by experimental models. Extensive work has been published by Allison A and Eugui E.

COMMENT: Page 5, line3; What does MPA represent? • Page 5, line 5; Microscopic polyangiitis (MPA). Question; MPA in line 3 and MPA in line 5 do they have similar manning? Defining abbreviation before use is the ideal thing to do for clarity. The use of MPA throughout the manuscript is confusing as to what it represents. Is it Mycophenolic Acid or Microscopic polyangiitis? Other abbreviations not defined before use in the manuscript include; PR3-ANCA BVAS EUVAS CSS IMPROVE WG AAV MPO-ANCA PR3-ANCA MMF EULAR/ERA-EDTA

ANSWER: Abbreviations are explained in the manuscript. Mycophenolate and microscopic polyangiitis are also clearly defined.

COMMENT: Page 7, line 2; "… remission rates that the CYS" Question; is it than or that?

ANSWER: corrected to "….remission rates than the CYC group."

COMMENT: Page 9, paragraph 1, lines 9-11; Question; More relapse in MMF group than AZA group, why?

ANSWER: Hiemstra *et al* conducted the International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) study to "*test the hypothesis that mycophenolate mofetil is more effective than azathioprine for preventing relapses in AAV*" and they concluded "*mycophenolate mofetil was less effective than azathioprine for maintaining disease remission*." They analyzed that "*Relapses were more common in the mycophenolate mofetil group (42/76 patients; 18 with major and 24 with minor relapses) compared with the azathioprine group (30/80 patients; 10 with major and 20 with minor relapses), with an unadjusted HR for mycophenolate mofetil use of 1.69 (95%CI, 1.06-2.70; P=.03)"*. In their conclusion the authors comment "*One explanation is that our mycophenolate mofetil regimen provided an inadequate dose. However, our starting dose of mycophenolate mofetil*

was the same as that found effective in both autoimmune disease and solid organ transplantation rejection prophylaxis, and is similar to or greater than doses previously reported for remission maintenance in AAV. Furthermore, in pharmacokinetic studies of mycophenolate mofetil in autoimmune disease, 2000 mg/d (the dose our patients were taking when the majority of relapses occurred) provided adequate trough levels of mycophenolic acid in the majority of patients." JAMA. 2010;304(21):2381-2388

COMMENT: Page 10, line 24; Question; "… active of partial controlled" is it of ?

ANSWER: corrected to "….active or partially controlled AAV."

COMMENT: This paper summarizes previous studies on the role of Mycophenolate in the induction and maintenance of remission of antineutrophil cytoplasmic antibody (ANCA) and associate vasculitis. The authors simply reported previous study findings with no in-depth analysis of results to unmark new areas for further research. For instance, which aspect of the therapy was myclophenolate more preferable to other therapies e.g., induction or maintenance or both. Are there some baseline demographic or biochemical indices that could enhance or hinder effectiveness of the therapy with Mycophenolate? For instance, in a study by Draibe et al 2015, the authors found that Mycophenolate demonstrated to be more effective and well tolerated option for maintenance treatment, whereas for induction treatment, Mycophenolate seems to be similar to cyclophosphamid for patients with moderate renal failure. In another study comparing the effectiveness of MMF versus Azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis, the authors reported that MMF was less effective than AZA for maintaining diseases remission in a study population that was mainly constituted by patients with positive PR3 (70%). It is also

reported that patients who are PR3-ANCA positive are more likely to relapse than patients with MPO-ANCA (Frassen et al 1995 and Hogan et al 1996). The readers of this manuscript will be more appreciative if more information is given concerning therapy with MMF.

ANSWER: Mycophenolate has been introduced in the therapeutics of AAV since the middle of the decade of 1990'. Relatively few clinical studies have been published, usually as cohorts of patients, describing single –centre experience. The EUVAS study group has led important clinical trials, two of which concern the efficacy of mycophenolate as induction and as remission maintenance agent in AAV including significant number of patients. Published experience could not provide plausible explanations for the reasons that mycophenolate even though a potent immunosuppressive with great and superior efficacy in organ transplantation, was not superior to other treatment options in AAV. The hypothesis of inadequate dosing or the type of positivity of ANCA, PR3 or MPO, vasculitis were not proven or supported by clinical data. This is a mini-review to summarize published clinical studies with mycophenolate in AAV and describe the experience of our centre. It seems unlikely that another clinical trial of mycophenolate as induction or remission agent will be conducted in the near future. Mycophenolate's efficacy in AAV is not doubted, could still be a useful treatment alternative in cases of toxicity with life threatening side effects or intolerance to cyclophosphamide or azathioprine, in cases with high cumulative dose of cyclophosphamide but also in cases with insufficient response and should not be considered obsolete.

COMMENT: Methods: I have not seen the method section of this manuscript. How did the authors select the articles included in this review? What were the search strategies including the search terms and inclusion/exclusion criteria?

ANSWER: According to "Guidelines for Manuscript Preparation and Submission: Minireviews – WRITING REQUIREMENTS: Main text. The main

text contains content, Acknowledgments, and References." Methods section was not included. If required though could be added.

COMMENT: Drugs interaction: A section discussing the interaction of mycophenolate with other ancillary drugs should be added. Drug interaction can change how drug works. Interactions between drugs can increase or decrease potency. At some instances dose adjustment may be done to produce optimum effect especially when co-administering drugs that share similar metabolic fate with Mycophenolate e.g., Rosiglitazone. For instance, Cattaneo et al 2008 reported how MMF interacted with Rosiglitazone with a resultant high serum level of MMF (almost 2times) and leading to severe anaemia which gradually resolved on withdrawal of Rosiglitazone.

ANSWER: The drug to drug interaction is an interesting point but the available knowledge is described in each drug spc. A comment is added in the test.

COMMENT: References: Intext references are not presented according to journal format.

ANSWER: References are written according to journal format

REVIEWER 2

We would like to express our appreciation for reviewing our manuscript.