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To:
Ze-Mao Gong,
Science Editor, Editorial Office
Baishideng Publishing Group Inc
World Journal of Gastroenterology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China

Submission of the revised invited review ESPS Manuscript NO: 28679

13.09.2016

Dear Doctor Ze-Mao Wang,

We are pleased to submit a revised version of our review (ESPS Manuscript No: 28679) entitled **“Molecular mechanism of action of anti-TNF antibodies in inflammatory bowel diseases”** for publication in “World Journal of Gasroenterology”. We have revised our manuscript to fully address the thoughtful comments by the reviewers. We now have even more emphasized that the anti-TNF agent etanercept showed no therapeutic efficacy in a clinical trial with Crohn’s disease patient to differentiate it from the other mentioned anti-TNF antibodies. We would nevertheless propose to still include the presented molecular mechanism data of Etanercept, as these clearly show the differences in comparison to the other anti-TNF agents, which are approved for the treatment of IBD patients. Some of the missing characteristic features of the approved anti-TNF agents in etanercept, might explain its absent clinical efficacy from a mechanistic point-of-view. The pharmacokinetic data of the anti-TNF agents and the predictors of clinical response have been presented in a table format, as requested by the reviewers. Moreover, a mistake in the numbering of the figure legends has been corrected, as rightfully noticed by the reviewer. We have also followed the editor’s comments and revised the language of the manuscript in order to reach Grade A in the language evaluation.

We have also included the sections “abstract”, “key words” and “core tip” in the revised manuscript as requested. All relevant changes have been highlighted in the manuscript by underlining.

We believe that the additional clarifications greatly strengthen the manuscript and hope that the revised paper will meet the high requirements for publication in *World Journal of Gastroenterology*. We are looking forward to hearing from you.

Sincerely yours,

Raja Atreya
for the authors

Point by point reply

Reviewer's code: 00069458

This is a very well-written and comprehensive review regarding molecular mechanisms of action of anti-TNF antibodies in inflammatory bowel diseases.

We thank the reviewer for these comments on the relevance of our manuscript.

Major points:

1. As this review refers to the molecular mechanisms of action of anti-TNF antibodies in inflammatory bowel diseases information regarding etanercept should be omitted.

We thank the reviewer for this comment. We fully agree that information regarding etanercept should not necessarily be included in a review regarding the mechanism of action of anti-TNF agents in IBD, as etanercept failed to show clinical efficacy in a trial with Crohn's disease patients. We would nevertheless propose to still include data regarding etanercept in the manuscript. Differences between the molecular characteristics of etanercept and the other approved anti-TNF agents for IBD give valuable information regarding important and required mode of action features of anti-TNF antibodies in IBD. The apparent differences in comparison to other anti-TNF agents, for example regarding affinity and avidity, might very well explain the missing clinical efficacy of etanercept in IBD treatment. We would therefore like to include the etanercept data, as they emphasize important mechanistic characteristics for clinical efficacy of anti-TNF antibodies in IBD. We sincerely hope, that the reviewer agrees with our justification for the inclusion of etanercept data. To emphasize this very important point and the suggestion by the reviewer, we have additionally included more references regarding the absent clinical efficacy of etanercept in IBD.

2. In order the review to be more comprehensive, pharmacokinetic data of all anti-TNF agents used in IBD and predictors of clinical response should be better described in a table format.

We thank the reviewer for this suggestion. We have now provided data of all anti-TNF agents and predictors of clinical response in a table format.

Reviewer's code: 02445239

Excellent review written in a precise manner and definitely going to be useful for the readers of esteemed WJG. This new strategy of Anti TNF therapy in IBD will be definitely going to prove utility in treatment of IBD to reduce the global burden of IBD. So it is suitable for publication in WJG.

We thank the reviewer for this evaluation and for finding the manuscript suitable for publication in WJG.

Reviewer's code: 02848336

The manuscript presents in a very comprehensive and clear way the complexity of mechanisms of action of anti-TNF antibodies in IBD.

We thank the reviewer for this supportive review of our manuscript.

In my opinion the paper deserves publication after some minor corrections: 1. I would suggest to present the data on the avidity and affinity of different anti-TNF agents in the table, not in the text. In the present form the comparison of IFX, ADA, ETA, CER and GOL is a little bit difficult to follow.

We have added a table to present the data on avidity and affinity of the different anti-TNF agents. We have nevertheless left the paragraphs in the text, where these properties are explained in more detail for each anti-TNF agent. The interested reader can therefore comprehend the presented data in the table more comprehensively.

2. There is a mistake in the numbering of the figure legends (the Figure 1 legend refers to Figure 2 and the Figure 2 legend refers to Fig. 1!).

We have re-numbered the figure legends as suggested by the reviewer.