

Dear Editors:

Great thanks to you and the anonymous referees for the time and efforts you spent on our manuscript. According to the comments, we have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers' comments are listed below. We hope that the revised version of the manuscript is now acceptable for publication in your journal.

#### Response to the comments of Reviewer #1

"The manuscript is well written, comprehensive, described an up to date revision of the evolution of the small molecules and biological therapies of inflammatory bowel disease; the abstract is competent and inclusive, and manuscript is well categorized and organized some typo errors in the manuscript (attached)"

Response: Thank you for the help for this manuscript. We have amended the grammars in this article according to your advice.

#### Response to the comments of Reviewer #2

1: "To provide the readers with a better overview a table could be suggested naming the different drugs, their immunological targets and relevant references."

Response: Thanks for your constructive suggestion. We have added a table to summarize the emerging biologics and SMDs in IBD. (Table 1)

2: Abstract: "The sentence starting with "Additinally, identifying the subgroup..." should be corrected in that the word "pattern" should be removed and it may seem as though it would be more correct to use the word "responding" instead of sensitive. Introduction: I would prefer to start with the statement that " The inflammatory bowel diseases ulcerative colitis (UC) and

Crohn's disease (CD) are progressive inflammatory diseases..."

Response: Thank you. We have corrected the sentences marked with red font color according to your suggestion.

3: "Emerging (correct the spelling) biologics and SMDs in IBD: It is mentioned that the efficacy of monotherapies is limited to 15-40% compared to placebo. I think it would be advisable to split the response into induction phase and long time effects. Likewise it could be suggested to put in a few words on end-points (clinical response/remission, endoscopic respons/remission)"

Response: Thanks for the suggestion. We have adjusted the statements of these sentences to be more clear. (The first paragraph of Emerging biologics and SMDs in IBD)

4: "Anti-TNF agents: Here it should be added that immunogenicity is also a problem and that it can be partly overcome by adding immunomodulators."

Response: Thanks. We added more context about the effect of immunomodulators on immunogenicity of anti- TNF in IBD. (In the Anti-TNF agents section of Emerging biologics and SMDs in IBD paragraph)

5: "Anti IL 12/23 agents: Data regarding Gusulkumab should be added."

Response: Thank you for the suggestion, and we added some data about Gusulkumab in this part of manuscript. (In the *Anti-IL-12/23 agents* section of Emerging biologics and SMDs in IBD paragraph)

6: "JAK inhibitors: It is not evident that filgotinib and upadacitinib have better safety profiles than tofacitinib."

Response: Thank you. We have re-wrote this part according to the suggestion to make the information of new JAK inhibitors more comprehensive. (In the JAK inhibitors section of Emerging biologics and SMDs in IBD paragraph)

7: "I think a sentence or two should be added addressing the fact that practical all knowledge on the effect of combination of drugs stems from data on patients rather resistant to therapy and who may have failed several lines of monotherapy."

Response: Thanks. We have rephrased some sentences in this part to make our expression more convincing. (In the beginning of The current status of biological combinations in IBD paragraph)

8: "The sentence "A better understanding of the pathology..." should read "understanding of the pathophysiology"."

Response: Thank you for the advice and we have re-write the sentence. (At the end of The current status of biological combinations in IBD paragraph )

9: "What can we do to improve the response to DTT: I think this part of the manuscript could be shortened without loss of important information."

Response: Thank you. We have deleted the sentences "Another prospective TAXIT study... Lower than that in the symptom-based group (7% vs. 17%, p=0.017)" and "However, given the uncertainty...maintained above 5 ug/ml and 7.5 ug/ml, respectively" in the TDM enhanced the response of DTT section and the sentences "As an important marker of inflammation CRP detection of biologics" and reorganized the part of this manuscript according to your suggestion.

Lastly, we thank you again for giving us a chance to revise and improve the quality of our article.