ANSWERING REVIEWERS

September 16, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4761-review.doc).

Title: Frequency and prognostic role of mucosal healing after one-year period of biological therapy

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) This is an interesting study that shows the prognostic role of mucosal healing at one year of biologic therapy in CD and UC. The important message is that mucosal healing does not predict "sustained" clinical remission. Maybe you could define "sustained clinical remission". The relapse rates are higher than similar studies (78% in CD and 100% in UC), please comment on that. The authors must also state the time period of patient's inclusion in the study and should also generally revise the manuscript with regard to English language use. In line 7 of Discussion, change the sentence to: mucosal healing after 12 months of treatment was not associated to sustained clinical remission. In paragraph 3, line 11,12 you state that biologic therapy was more effective in achieving mucosal healing in CD than UC. Is there a reason for that? Please comment. In last paragraph of Discussion, line 8, change to mucosal healing could correlate with clinical activity.
-Thank you for your comment. Sustained clinical remission was defined as a stable, steroid-free clinical remission (defined by CDAI of <150 points or a Mayo score of <2 points) during the 1-year follow-up period. The higher relapse rates in patients who achieved mucosal healing may be explained by the shorter duration of biological therapy and the less frequent use of combined immunosuppressive therapy than in similar studies. The study was conducted between January 2010 and December 2011. The English language of the text was revised by the American Journal Experts company. In our study biological therapy was more effective in CD than in UC. Although the accurate explanation of this result is unfortunately not known, the difference in the extent of the inflamed area, the number of the enrolled patients and the proportion of patients with previous biological therapy between CD and UC may explain it. The recommended corrections were made and the asked comments were added.

(2) The paper by the Hungarian group is interesting, as it shows that mucosal healing does not predict any sustained clinical remission in patients with IBD if biologicals are stopped one year of treatment. Major comments It should be stated for how long time the study was open for inclusion of patients with IBD into the study (not mentioned on p. 5). Was a power calculation performed before initiation of the experiment to ensure statistically valid conclusions of the statement provided? Is TNF inhibitor treatment also discontinued after one year in Hungary if patients have symptoms of their IBD? The conclusion of the present manuscript is rather important even it is a limited material from only two departments. However, it is strongly recommended that the authors take a little more care of the English expression throughout so the reader does not get the impression that the paper was written in Hungarian and then put in Google Translate. Please, highlight the statements of this study more

precisely in a revised manuscript. Minor comments Line 2 in the Introduction: I suggest that after IBD it is stated that it comprises UC and CD as the two most frequent entities. The authors should specify the second ECCO scientific workshop (p. 3), if they think it is important to mention or perhaps delete this workshop and just add a reference. On p. 5, six lines from the button, azathioprine is stated, however, on Table 1 says thiopurines. Did any of the patients receive 6-mercaptopurine? In that case this should be stated as well on p. 5. Did the authors use a CDAI including haematocrit value or was it a modified CDAI score index used clinically? I believe it is questionable that terminal ileum was reached in all cases (p. 8). On p. 8: In some cases a decimal is added to the percentage, but not in others. However, this matter should be more consequent throughout the whole manuscript. I suggest deleting any decimals in percentages. On p. 10: The UC Success trial should be with capital letters like SONIC and ACCENT1. On p. 10: "Respectively" should be added, e.g. line 2 ("56% and 32% of the patients, respectively").

- Thank you for the observations and comments. The study was conducted between January 2010 and December 2011. No power calculation was performed before the initiation of the experiment, we enrolled every patient who underwent ileocolonoscopy before and after the one-year biological therapy and in whom anti-TNFs were discontinued at the end of the year. TNF inhibitor treatment should be discontinued after one year in every case, however, it can be readministered if patient still have symptoms. The English language of the text was revised by the American Journal Experts company. We did every change as recommended in the minor comments. Thiopurine was corrected to azathioprine in Table 1 (none of the patients received mercaptopurine). We used CDAI with hematocrit value. Terminal ileum was reached in every case at the first examination and after the one year therapy ileoscopy was repeated only in case of previous ileal location. Decimals were deleted.

(3) The subject of the study is interesting, and the unique regulation of the Hungarian government provides an optimal setting to ask the question how long does mucosal healing sustain after cessation of biologics. The work, while observational in nature, does provide some insight into the response to therapy. However, there are a couple of important issues that need to be clarified: 1. The authors described "sustain clinical response". What does that mean? How long after cessation of the biologics do patients maintain clinical remission? Summary from the literature is needed. 2. Patients who need to be restarted on biologics: response after restarting the medication needs to be provided. In my view, only those who respond to the restarted medication can be attributed to premature cessation of the drugs. 3. Histology evaluation has been proposed to provide additional information that may complement endoscopy findings. Have the authors performed biopsy on these patients? If so, what did they show?

Thank you for the comments. Sustained clinical remission was defined as a stable, steroid-free clinical remission (defined by CDAI of <150 points or a Mayo score of <2 points) during the 1-year follow-up period. Response rates of retreatment were 81% in CD and 54% in UC within an average of 8 weeks after the reintroduction of the therapy. Histological examination was performed at the diagnosis of the disease in every case. Since endoscopic finding is enough to evaluate the activity indices of the disease, biopsy was not taken in every patient when biological therapy was introduced, thus histological evaluation was not involved in the study. The manuscript was completed with the additional data. Summary from the literature about the maintenance of clinical remission after cessation of the biologics was added to the text.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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