

Format for ANSWERING REVIEWERS

March 3, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 8748-review.doc).

Title: Predictors of Response to anti-TNF therapy in Ulcerative Colitis

Author: Evanthia Zampeli, Michalis Gizis, Spyros I. Siakavellas, Giorgos Bamias

Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 8748

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 reviewers
A point-by point response to the reviewers follows.

Reviewer 1

The number of UC patients is increasing on the worldwide, and recently anti TNFa therapy is a standard therapy for moderate to severe UC. So this manuscript is timely and clinically very important and should be accepted in the WJGP. Minor comments There are some misspelling and grammatical errors. Add table Authors should show the prodnostic factors on the table.

Reply: We thank the reviewer for his/her comments. In the revised manuscript we have corrected the misspelling and grammatical errors. In accordance with the reviewer's recommendation we have added a table in the revised manuscript that depicts all proposed prognostic factors.

Reviewer 2

The review "predictors of response to anti-TNF therapy in ulcerative colitis by E.Zampeli et al. analyzes the use of anti-TNF in moderate and severe UC refractory to corticosteroids and immunosuppressants. Not all patients respond and anti-TNF can have severe side effects. In addition, the treatment is expensive. Therefore the authors considered it important to search for parameters that could predict response. The introduction is informative, but too verbous and should be cut by half.

Reply: We thank the reviewer for his/her comments. In the revised manuscript we have considerably decreased the Introduction.

The authors proceed with introducing the two anti-TNF antibodies mostly used, IFX and ADA,

where only for IFX data exist on patients with severe, steroid refractory disease. The short term response rate to both drugs is similar, long term response appears somewhat better with IFX. Non-responsiveness or loss of responsiveness is poorly predictable and reasoning is many described for patients with CD. The authors first discuss the clinical outcome, which is summarized in Table 1. They then report on the laboratory investigations, where CRP is the most common marker and was predictive of response. Besides CRP, hemoglobin was also a response predictor, which, however, was not as clear for serum albumin. In concern of immunological markers, absence of p-ANCA correlates with better response. Pretreatment mucosal TNF, IL-17 and IFN γ were also predictive. An array analysis revealed a correlation with adaptive immune response genes. Studies on genetic polymorphisms are at too early a state, but IL23R polymorphism may play a role. Expectedly, response is better without immunosuppressive treatment. In the following the authors describe the prognostic factors during treatment. Early responders will profit for long term. A drop in CRP, changes in T helper genes, Treg and mucosal healing were additional parameters of some predictive value. Treatment related factors provided not much information, except those to be judged by common sense. The review finishes with a statement that response markers are not yet appropriately well defined. This is a fair review, but is boring to read and in view of the authors conclusion that not sufficient data are available, I suggest to strikingly shorten the review not to steal readers time. Some constructive criticism based on integrating the individual puzzles is strongly recommended.

Reply: We thank the reviewer for his/her comments. We present now a much shorter version of our manuscript, according to the reviewer's suggestion. We include in our manuscript a specific section where the advantages and disadvantages of the individual markers are summarized and criticized.

Reviewer 3

I have read this manuscript and my observations are as follows:

1. It is a review article, where the authors have reviewed various studies, on Anti-TNF therapy has been used in patients with CL. It appears, the authors collected the data from a large number of trial studies and tried to put together in the form of case study reports.
2. Is the article written on the pattern of journal needs? This must be examined.

Reply: We believe that the manuscript fulfills the Journal's requirements.

3. No specific conclusion has been made by the authors for anti-TNF therapy in UC patients. Since there are overlapping between CD,IBD and UL, as far as the inflammatory response is concerned, the results are non-conclusive, therefore of little clinical implications.

Reply: We include our conclusions in the last two sections of the manuscript.

4. There is lot of repetition of the statements in the paper, which must be avoided.

Reply: We thank the reviewer for his/her comments. In the revised manuscript we have tried to avoid repetitive statements and have removed several parts of the original text.

5. Paper may be considered for publication as minireview, after considerable changes are made in the text format.

Reply: We believe that the manuscript fulfills the Journal's requirements for a full review.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Pathophysiology*

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Giorgos Bamias', with a long horizontal stroke extending to the left.

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