

ANSWERING REVIEWERS



January 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7321-review.doc).

Title: Need for Infliximab Dose Intensification in Crohn's Disease and Ulcerative Colitis

Author: Carlos Taxonera, David Olivares, Juan L. Mendoza, Manuel Díaz-Rubio, Enrique Rey

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7321

The manuscript has been improved according to the suggestions of the editor and of the reviewers. The following revisions have been made:

Format has been updated according to format for brief article:

We have likewise modified the abstract according to the WJG guidelines.

The revised abstract is now shorter and clearer.

Editor's suggestions:

1. Title: The title must be informative, specific, and brief (Title should be no more than 10~12 words/60 bytes. Please revise it).

Revised title: Need for Infliximab Dose Intensification in Crohn's Disease and Ulcerative Colitis

2. Please reformat all the reference numbers like this one (superscript with square brackets).

Reference numbers were reformatted

3. Please add PubMed citation numbers and DOI citation to the reference list and list all authors.

We have included PMID numbers and DOI citations

4. At least 26 references should be included.

We have included 26 references

5. Please provide the "Highlighted contents"

Highlighted contents were provided

Revision has been made according to the suggestions of the reviewers:

Referee 01489500

This is a well-written original article about the need for infliximab dose intensification in patients with CD and UC. I think it can be published after few points are addressed.

INTRODUCTION, LINE 2: and it is indicated instead of that is. **Done**

Methods, criteria for dose intensification, paragr 3: "the presence of" is not needed. **Done**

Discussion, first paragraph, line 2: rephrase to dose intensification between patients with ulcerative colitis and Crohn's disease.... **Done**

Discussion, 2nd paragr, line 2: correct reference number of Gisbert et al. **Done**

Discussion, paragr 4, line 6: therapeutic approach and furthers our understanding? please revise as it

makes no sense. **We have deleted "and furthers our understanding of the impact that the disease type may have on dose escalation"**

Discussion, paragr 5, line 10: thought to arise from instead of because.

Thank you for your comments and suggestions.

Referee 02520511

Well-done and well-written. Congratulations!

Major comments: Need for dose escalation is higher in UC. This likely represents the fact that UC is a completely different entity than Crohn's. The fact that colectomy is a viable option for UC patients might have affected the treating physician's judgement whenever a UC patient had a need for dose escalation (vs Crohn's).

Also, in your cohort, it appeared that UC patients were sicker (higher proportion with need for steroids at baseline). This was evaluated in multivariate analysis and appears non-significant on its impact on dose escalation. However, the low "n" could have affected statistics.

We have added the sentence: **Neither the need for steroids at baseline nor having a steroid-refractory disease at baseline were associated with the need for infliximab dose intensification.**

Please consider adding to the paper how many patients with UC ended up requiring colectomy, if such data is available. **Data were not available; outcomes after intensification were not evaluated.**

Minor comment: Under "Discussion" 4th paragraph: 3rd line from the end of the paragraph: "significantly" should be replaced by "significant". **Done**

Thank you for your comments and suggestions.

Referee 02520845

ESPS Manuscript NO: 7321 Title: Need for Infliximab Dose Intensification in Patients with Crohn's Disease and Ulcerative Colitis General comments: The investigation has profound therapeutically implication highlighting the problem of intensification of infliximab in both forms of inflammatory disease, Crohn's disease and ulcerative colitis incorporating the administration cost as well. Specific comments Title: It reflects the major topics and contents of the study. Abstract: It gives a clear delineation of the research objective and the results. Material and methods: The study design, criteria for dose intensification, administration cost and outcomes are well described but the number of patients is not stated (it is mentioned in the results section). Appropriate statistical methods are selected and made. Results & Discussion: The data is clearly presented and the discussion is well organized. Tables & Figure: Reflects the major findings. In conclusion, this is a very interesting research.

Thank you for your comments.

Referee 00722601

This is an interesting and well written article.

Minor revision: - Describe "response to induction doses" criteria.

We have added: **according to standard criteria**

- Indicate "p" value in the phrase "The rate of infliximab dose intensification per patient-month was not significantly different between perianal and luminal Crohn's disease". **We have included p value**

- Because a high proportion of patients with ulcerative colitis is treated with infliximab because of steroid-refractory ulcerative colitis, could be interesting to show in the results, point "Predictors of the need for infliximab dose intensification" that there wasn't found a relation between this indication and the outcomes. We have added the sentence: **Neither the need for steroids at baseline nor having a steroid-refractory disease at baseline were associated with the need for infliximab dose**

intensification.

Thank you for your comments and suggestions.

Referee 02548901

This article addresses an important topic and to my mind may be the first to do so I have only minor suggestions to strengthen the article. Regarding methodology - was institutional approval obtained?

Yes, the study was approved by the local hospital ethics committee.

There are minor spelling errors throughout that could be resolved with a spell-check.

Discussion: Two points should be referenced to provide a balanced appraisal - firstly, evidence is emerging that other modalities (cyclosporin - Chang et al, Int J Colorectal Disease, 2013), can be equally as efficacious as infliximab with certain advantages over it. I think this point should just be referenced.

We have added the sentence: **"Cyclosporine is also useful when used as rescue therapy in acute severe steroid-refractory ulcerative colitis, but patients need to be hospitalized". We have added 2 References, including the article by Chang et al.**

Also, genetic heterogeneity plays a major role in determining outcomes (responsivity to treatment, see Solon et al, Infl Bowel Disease, 2013) and although this study is not powered and designed to deal with this point, I think it should also be referenced, at least to balance the overall discussion.

We have added the sentence: **"Genetic test were not available in our study. Genetic polymorphisms may contribute to predict efficacy of infliximab". We have added 2 References more regarding this issue.**

Thank you for your comments and suggestions.

The copyright transfer agreement form has been completed, signed and send.

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

Sincerely yours,

A handwritten signature in blue ink, appearing to be 'CT' or similar initials, with a long horizontal stroke extending to the right.

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