

January 17, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6893-review.doc).

Title: OPTIMIZATION OF THE TREATMENT WITH IMMUNOSUPPRESSANTS AND BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

Authors: Sara Renna, Mario Cottone

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6893

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:

REVIEWER 1

I would like to suggest authors to use these two articles and provided enough comparison in discussion. The articles are: Efficacy and tolerability of immunoregulators and antibiotics in fistulizing Crohn's disease: A systematic review and meta-analysis of placebo-controlled trials. *Curr Pharm Des.* 2010; 16: 3684-3698. PMID: 21143147. A systematic review and meta-analysis of the effects of infliximab on the rate of colectomy and post-operative complications in patients with inflammatory bowel disease. *Arch Med Sci* 2011; 7(6): 1000-1012. DOI: 10.5114/AOMS.2011.26612 The Abstract of paper is too defective and needs rewriting. Also I suggest authors to write a better conclusion in terms of efficacy of each treatment separated for CD or UC.

The suggested studies have been included in the manuscript. Abstract and conclusion have been rewritten

REVIEWER2

It should be addressed about the importance of measuring concentrations of metabolites of thiopurines (e.g., 6-thioguanine, etc) and antibodies (serum concentration of infliximab and adalimumab). It should also be included about the development of antibodies to biologics (ATI, AAA) in relation to the serum concentration of biologics.

The suggested data have been included in the manuscript

The authors concluded about the combination therapy in IBD as "In clinical practice the use of combination therapy should be reserved to patients who do not respond to monotherapy." However, it should be reminded that combination therapy in the early phase of induction of biologics will prevent development of autoantibodies to biologics and is considered to improve the efficacy of biologics. This issue should be further discussed.

The suggested data have been included in the manuscript

Tacrolimus should be added as an effective immunosuppressant therapy for IBD in this manuscript.

The suggested data have been included in the manuscript

In the section of “Biologic therapies in ulcerative colitis”, the meaning of the sentences is unclear. “Regarding the timing of treatment one year scheduled treatment with Infliximab is indicated in patients who have responded to infliximab induction. [2,3] In patients who are thiopurines naïve, maintenance therapy with thiopurines may be a valuable option as maintaining treatment. The duration of therapy over 1 year should be evaluated case-by-case.”

The sentences have been corrected

There are several typing and grammatical errors found in this manuscript such as comma, space, etc. This manuscript requires English editing. 2. In ref 25, [] should be deleted.

The manuscript has been English edited

REVIEWER3

Abstract: - The use of thalidomide and mycophenolate mofetil is not recommended whether in the AGA-guidelines nor in the ECCO-guidelines. Therefore, these drugs should not be mentioned in the abstract. - In addition, it should become clear in the abstract, that methotrexate is an option in CD patients, but it's evidence for the use in UC is insufficient.

Abstract has been rewritten

Immunosuppressant therapies in CD - Please point out clearly, that there are no recommendations for thalidomide and mycophenolate mofetil in the guidelines. The decision to use these drugs might only be made on a by-case basis after failure of all other options including optimisation of anti-TNF-therapies and surgical strategies.

The suggested data have been included in the manuscript

Biologic therapies in Crohn's disease - Certolizumab pegol has no approval in the European Union, but in the USA and Switzerland. This should be included in the manuscript. - At the beginning of the section, the reader gets the impression of infliximab being the first line anti-TNF-therapy. Here, one sentence should be included to point out, that adalimumab and infliximab are both equal options in patients with moderate to severe steroid-refractory or -dependent disease (it is only mentioned later in this section “up to now, no trial compared the efficacy and safety of infliximab and adalimumab in CD patients, thus the only factor that can guide the choice of one of the two biologics as first line therapy is the route of administration....”). - Concerning dose-optimisation strategies, not only the possible decrease in interval between infusions of infliximab, but also the possibility to decrease the interval of subcutaneous applications of adalimumab should be mentioned. - Please clarify the term “dose intensification” in patients on infliximab treatment in the study cited (Ref. 35) - similar to the description of the study on intensification of adalimumab. How many patients had an increase in infliximab dose, a decrease in the interval of application or both? Please provide the reference number of the studies after referring to them.

The suggested data have been included in the manuscript

Immunosuppressant therapies in UC - In the introduction (page 7), not only the use of cyclosporine should be mentioned in patients not responding to intravenous steroids, also infliximab should be discussed. - As mentioned for CD, also in UC patients no recommendations exist from guidelines to use thalidomide and mycophenolate mofetil. This fact should clearly be addressed. - Mycophenolate mofetil: the studies cited here included both, UC and CD patients (Ref: 55-57). Please differentiate in the section “Immunosuppressant therapies in UC” between CD and UC. For example, of the 40% of patients (n=16) achieving remission in the study of Ford et al. (Ref. 55), only 4 patients were UC patients. In addition, in the study of Palaniappan et al. only 19 out of 70 patients were included having UC.

The suggested data have been included in the manuscript

. Biologic therapies in UC - Page 11: “Up to now adalimumab is not licensed for the treatment of active UC in Europe.” This statement is not correct – adalimumab has approval for the treatment of active UC, also in Europe. - Please include golimumab as option in UC patients, which is now approved by the FDA, in Canada and in Europe. Minor points: - According to possible side effects of azathioprine also long-term risks as malignancies (lymphoma/cutaneous malignancies) should be mentioned.

The suggested data have been included in the manuscript

Page 10: please give a reference after citation of the studies. - The manuscript should be read carefully again; some examples: page 1: responding to corticosteroids; page 1: evaluating their efficacy; page 4: the superiority of MTX compared to placebo; page 5:

The manuscript has been corrected

3 References and typesetting were corrected

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

Sincerely yours,

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