



January 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6000-Review.docx).

**Title:** Venous thrombosis and pro-thrombotic factors in inflammatory bowel disease.

**Authors:** Fernando Magro, João-Bruno Soares and Dália Fernandes.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6000

The manuscript has been improved according to the suggestions of editor and reviewers (changes highlighted with yellow). Point-by-point response to comments from the editor and reviewers is provided below:

#### Editor

**Comment#1:** For manuscripts submitted by non-native speakers of English, please provide language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for TOPIC HIGHLIGHT'.

**Response#1:** The revised manuscript was edited by the following English language editing company:XXX. A recommendation letter is also attached. Moreover, "Abstract" and "Core tip" were reformulated in order to be in agreement with the 'The Revision Policies of BPG for TOPIC HIGHLIGHT'.

**Comment#2:** Please put all figures and tables at the end of your paper.

**Response#2:** In the revised manuscript all tables were put at the end of the manuscript.

#### Reviewer 1

**Comment#1:** The review should be focused in a more specific question. Authors should describe with more detail how the electronic search was done and what were the inclusion criteria to include paper in the review.

**Response#1:** In the revised manuscript a new section regarding the strategy of electronic search was added.

#### Reviewer 2

**Comment#1:** Abbreviation of venous thrombosis "VT" is not universal, use DVT or VTE

**Response#1:** In the revised manuscript "VT" thrombosis was changed by "VTE".

**Comment#2:** The article is globally too long, with some useless chapters. Delete: page 12-17 "overview of coagulation system" and "mechanisms of VT".

**Response#2:** In the revised manuscript chapters on "overview of coagulation system" and "mechanisms of VT" were deleted.

**Comment#3:** The table 2 "risk factors for the development of VT" (Page 16) can be included and associated with table 3 "pro-thrombotic abnormalities associated with IBD" (page 19).

**Response#3:** In the revised manuscript tables 2 and 3 were merged.

**Comment#4:** Table 4 (pages 23-28) is clearly detailed in the text. It is not useful.

**Response#4:** As tables are more reader-friendly and as suggested by reviewer 3, in the revised manuscript the table 4 was maintained while the corresponding chapter on the manuscript was shortened.

**Comment#5:** The chapter 3 “pharmacological effect on risk factors” (page 10) should come after the chapter 6 “pro-thrombotic abnormalities in IBD” (page 17)

**Response#5:** In the revised manuscript chapter “pharmacological effect on risk factors” comes after chapter “pro-thrombotic abnormalities in IBD”.

**Comment#6:** One point must be discussed somewhere about the overlap diagnosis between Behcet’s disease with deep vein thrombosis and intestinal involvement and the outcome of DVT in IBD: presentation may be very similar

**Response#6:** In the revised manuscript a statement was added in the chapter “Impact of inflammation on coagulation” emphasizing that there may be an overlap in the differential diagnosis between Behcet’s disease with VTE and intestinal involvement and the outcome of VTE in IBD.

**Comment#7:** Table 1 : “controlled variables” should be shorter for the references [22] and [23].

**Response#7:** In table 1 of the revised manuscript “controlled variables” were reduced for the references [9], [12], [23] and [24]. There were no “controlled variables” for the reference [22].

**Comment#8:** Page 10 : the title of the chapter 2.4 “IBD-specific disease risk factors” should be more precise like for example “type of lesions in IBD” ?

**Response#8:** In the revised manuscript the title of the chapter “IBD-specific disease risk factors” was changed to “IBD-phenotype risk factors”.

**Comment#9:** Page 17 : line 22 : It is not correct to use the terms of “inflammatory machinery”.

**Response#9:** In the revised manuscript the expression “inflammatory machinery” was changed to “inflammatory pathways”.

**Comment#10:** Page 17 line 25-26 : You cannot compare IBD and DVT with systemic lupus or Behcet syndrome because DVT may be part of the presentation of those 2 diseases.

**Response#10:** In the revised manuscript a statement was added in the chapter “Impact of inflammation on coagulation” emphasizing that in many inflammatory diseases as systemic lupus erythematosus and Behcet’s syndrome, VTE may be part of the presentation of those diseases.

**Comment#11:** The style need to be more concise and precise. Page 11: first and second chapters. Page 18 : the second chapter beginning with “TNF a ....” Is too long with many repetitions.

**Response#11:** In the revised manuscript the first and second paragraphs of chapter “Pharmacological effect on risk factors” and the second paragraph of chapter “Impact of inflammation on coagulation” were shortened.

**Comment#12:** The chapters 6.1 and the introduction of the chapter 6.2 (page 19) may be associated.

**Response#12:** In the revised manuscript the chapter “Impact of inflammation on coagulation” and the introduction of the chapter “Abnormalities of haemostasis associated with IBD” were associated.

**Comment#13:** Chapter 6.2.2: Discuss more precisely the role and value of D-Dimers.

**Response#13:** In the chapter “Abnormalities of fibrinolysis” of the revised manuscript we discuss more precisely the role and value of D-dimer, mainly its role as a marker of recent or ongoing intravascular blood coagulation and its relation to IBD activity.

**Comment#14:** Chapter 6.2.5 : page 22. The chapter about hyperhomocysteinemia must be re-discussed because the data associating hyper homocysteinemia and atherosclerosis are not that clear.

**Response#14:** Although early data on the relationship between elevated blood homocysteine concentrations and coronary heart disease and stroke have been somewhat inconsistent, several meta-analyses (Homocysteine Studies

Collaboration, JAMA 2002; Klerk M et al, JAMA 2002; Humphrey LL et al, Mayo Clin Proc. 2008) showed that high homocysteine levels appear to be clearly associated with an increased risk of cardiovascular and cerebrovascular disease.

**Comment#15:** Chapter 2.5 : repetition!!! Just axe the text on factors not already discussed before

**Response#15:** In the chapter "IBD-nonspecific acquired risk factors" of the revised manuscript only text on factors not previously discussed was maintained.

**Comment#16:** Recall chapters. 6.2: Abnormalities of haemostasis associated with IBD. 6.2.5→6.3: Thrombophilia and IBD. 6.3.1: acquired risk factors. 6.3.2 : inherited risk factors.

**Response#16:** In the revised manuscript, chapter "Abnormalities of haemostasis associated with IBD" was recalled as suggested by the reviewer.

### Reviewer 3

**Comment#1:** 1. Introduction: a more specific background should be summarized and more clarified aims should be provided. Certain contents in current Introduction section should be shortened or removed into Discussion section.

**Response#2:** In the revised manuscript "Introduction" was shortened and the aims of the review were clarified.

**Comment#2:** 2. Risks of VT in IBD: this is the major topic that readers are interested in. Congratulations to authors that they have described very well regarding this topic.

**Response#2:** We appreciated this comment from the reviewer.

**Comment#3:** 2.1-2.5: this part should be shortened because many refs have already been described in Table 1.

**Response#3:** In the revised manuscript chapter 2 was shortened.

**Comment#4:** 4 and 5: personally, I don't think these two parts should be discussed in current paper since most of contents can be found in textbook and other more general reviews and they are less IBD-specific.

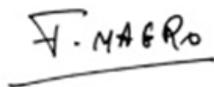
**Response#4:** In the revised manuscript chapters 4 and 5 were deleted.

**Comment#5:** 6.Pro-thrombotic abnormalities in IBD: Similar to section 2, Table 4 has provided a very good summary of current literature, therefore certain contents should be deleted from manuscript. The whole manuscript seems too long to be published.

**Response#5:** In the revised manuscript section "Inherited risk factors" was shortened.

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

Sincerely yours,



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