ANSWERING TO REVIEWERS

May 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9718-edited.doc).

Title: Inflammatory Bowel Disease and Thromboembolism

Author: Petros Zezos, Georgios Kouklakis, Fred Saibil

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9718

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) **R: Throughout the paper there is a lot of emphasis on odds ratios and relative risk, whilst this is fine for epidemiological studies, this is difficult for the clinical to translate into risk for the patient. What are the absolute risks of DVT for hospitalized/ambulant IBD patient?**

A: In the "epidemiology section" of the review we maintained the statistical terms of every paper cited. The absolute risks of DVT for hospitalized or ambulant IBD patients are stated in page 8 (highlighted) in the manuscript (Grainge *et al*[25]).

(2) **R: Relative risks are only useful when the comparison group is well defined. It seems clear that IBD does increase the risk of TE compared to controls but how does the risk compare to other, perhaps more comparable inflammatory conditions (diverticulitis or pancreatitis perhaps?). The authors have provided some data on the comparison with coeliac disease but in terms of inflammatory burden, these are very different diseases.**

A: Miehsler *et al*[22] demonstrated that VTE is a specific feature of IBD because neither rheumatoid arthritis, another chronic inflammatory disease, nor celiac disease, another chronic bowel disease, was accompanied by an increased risk of VTE compared with controls. (page 11)

Case reports for acute diverticulitis or acute pancreatitis and observational studies for acute pancreatitis have shown that there is an increased tendency for TE in both conditions. However, diverticulitis and pancreatitis are acute inflammatory conditions and not chronic inflammatory disease. Hence, comparisons between IBD and acute diverticulitis or acute pancreatitis are not applicable.

(3) **R: On page 14, there is a whole paragraph expanding on the possible pathway of IBD pathogenesis: whilst this is interesting conjecture, the many statements in this section**

do need appropriate referencing. This is in contrast to the over referencing in other areas. For instance, it does seem unnecessary to cite 6 different references about prophylaxis in IBD patients (also page 14).

A: References have been added in the aforementioned paragraph (page 15, highlighted).

(4) **R: The authors cites that management of TE in IBD is challenging (page 14) and the present no data showing this is any more challenging than managing TE in any other group of patients and in fact present a completely standard management pathway.**

A: The word "challenging" has been deleted (page 15) (strikethrough highlighted).

(5) **R: The authors have provided a fairly convincing link between vascular thrombosis and exacerbation of pathogenesis in IBD, except they have much skimmed over the negative results obtained in the trials of anticoagulation for the treatment of active IBD, these argues against thrombosis being integral to the pathogenesis of IBD and deserve further discussion.**

A: The following paragraph has been added to the manuscript (page 16, highlighted): "Heparin could be an ideal drug for IBD treatment, especially UC, because of its anticoagulant, heparin, anti-inflammatory, immunomodulatory and mucosal healing properties. The failure of the existing trials to prove its efficacy for the UC treatment could be related to the small patient number and the heterogeneity of these studies regarding the compound of LMWH and the dosage administered, the duration of treatment and the definition of response to treatment. Larger studies may be needed clarify this issue and to reveal the optimal dosing of heparin and the features of a subgroup of patients with active UC who may benefit from LMWH administration."

(6) **R: Page 17. Data are plural, it should be there are no data.**

A: Corrected (highlighted)

(7) **R: Page 17. The discussion on the merits of standard versus higher doses of heparins for prophylaxis is important but difficult to interpret given the different dose regimens of the different LMW heparins and this dose of 4000 IU/day needs to be placed in the context of the different available drugs.**

A: Dose "4000IU/day" deleted (strikethrough highlighted).

(8) **R: Whilst many guidelines are quotes discussing prophylactic anticoagulation in IBD inpatients: what is the evidence that this actually works?**

A: The following paragraph has been added to the manuscript in page 18 (highlighted): "There is no direct data that anticoagulation for VTE prophylaxis in IBD patients actually works since there are no randomized controlled trials that have evaluated this issue yet. However, indirect evidence demonstrated that in acutely ill medical patients pharmacological prophylaxis significantly reduces the incidence of VTE and mortality".

(9) **R: Page 18. It seems very draconian to say that management of cardiovascular risk factors always requires consultation with a specialist: this is standard internal medicine or primary care and surely should be within the remit of most competent physicians**

and including the IBD physicians. This comment may well relate more to specific health care systems but is not generalizable. Similarly, I am sure than in many health care systems, thromboembolism in IBD patients is managed absolutely safely and appropriate without any recourse to either hematology or interventional radiology. Again this is a health service design (and/ or payment?) related issue and in no way can this be mandatory (page 19).

A: Corrected in the manuscript pages 18 and 19 (strikethrough highlighted) as the reviewer suggested.

(10) **R: The authors do not once mention vitamin K antagonist therapy specifically. Are there any data suggesting that these drugs are less reliable in patients with small bowel disease and /or diarrhoea? Although I suspect data are very limited, a paper like this should really mention the new novel orally acting anticoagulants: are these approved and safe for the management of TE in IBD? There is a theoretical increase risk in GI bleeding, if so how safe are these drugs? Should they be avoided at the moment?**

A: The following paragraph has been added to the manuscript in page 18 (highlighted): "In general, LMWH, vitamin K antagonists (VKAs) or even the new direct oral anticoagulants (NOACs; dabigatran or rivaroxaban) can be used for the long term treatment of TEs. For NOACs new evidence from studies suggests that they have comparable efficacy to that of VKAs with a more favorable safety profile, but there is no direct evidence for their use in IBD patients yet."

3 Correction in epidemiology data in page 7

4 References and typesetting were corrected

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

Sincerely yours,

Petros Zezos, MD, PhD
Division of Gastroenterology,
Department of Medicine, University of Toronto,
Sunnybrook Health Sciences Centre (SHSC),
H52–2075 Bayview Avenue, Toronto, Ontario M4N 3M5 Canada
email: zezosp13@hotmail.com
Telephone: +1 416-480-4727; Fax: +1 416-480-5977