

Format for ANSWERING REVIEWERS

July 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12064-review.doc).

Title: Risk of infections associated with biological treatment in inflammatory bowel disease

Author: Nynne Nyboe Andersen and Tine Jess

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12064

The manuscript has been improved according to the suggestions of reviewers and references and typesetting were corrected:

Reviewer 1:

ESPS Manuscript NO: 12064 Title: Risk of infections associated with biological treatment in inflammatory bowel disease. The manuscript is concise and informative reading on the topical subject and is very welcome.

1. I would have only slight comment about the first sentence in the introduction section – IBD – I would recommend to delete the words “systemic , chronic” from the sentence – IBD (UC or CD) affects gastrointestinal tract not the entire body and the course of the inflammation/disease is acute and/or chronic – depending on the time course.

Reply: We thank you for the corrections which has been modified in the revised manuscript

Reviewer 2:

Congratulations on a well written and comprehensive review. Please address the following minor comments:

1. A few lines referencing the updated ECCO consensus on prevention of opportunistic infection would be of interest to the reader and could potentially be added to the last paragraph or conclusion.

Reply: Thank you for this suggestion. A few lines referring to the up-dated ECCO consensus have been added to the manuscript at the end of the section: Latent viral infections.

2. Minor grammatical errors : A] In your "OVERALL INFECTION RISK" section: line 8: should read "infection" B] ;Line13: "Similarly" C] Line 17: "populations IS not..." D] Line 22: "In CONTRAST" not contrary E] Line 28: "attributed" not contributed

Reply: The errors has now been corrected in the revised manuscript.

Reviewer 3:

This manuscript nicely summarizes the available evidences on infection risks in IBD patients treated with biological therapies. It was a pleasure to review this well writing and updated manuscript.

Reviewer 4:

Thank you for the opportunity to review this manuscript. This short review is a synopsis of the infectious risks of anti-TNF agents. I congratulate the authors for a well-written review.

1. I would have loved if the authors had a section on the risk of postoperative infections but this is not essential.

Reply: We agree that the risk of postoperative infections is an important concern. As this is a brief overview of the risk of infections related to TNF- α inhibitor exposure we find it beyond the scope of the present topic highlight to present literature regarding the risk of postoperative infections.

2. Also, a table on the required testing before initiation of anti-TNF therapy is strongly suggested.

Reply: A table 1 summarizing the required testing prior to TNF- α inhibitor exposure has been added to the manuscript.

Minor comments:

1. Please spell tuberculosis once before using TB. - et al and per se should be in italic. - Last sentence of MYCOBACTERIAL INFECTIONS: change to..."evidence of latent TB infection" - Change to "VZV in children causes chickenpox" - The sentence "A German study including 5040 patients with RA authors revealed that exposure to the TNF- α inhibitors infliximab and adalimumab was associated with a 82% significant increased risk" does not make sense. Should it be "A German study including 5040 patients with RA authors revealed that exposure to the TNF- α inhibitors infliximab and adalimumab was associated with an 82% significant increased risk"? - Numbers such as 5,040 and 33,324 should include a comma. - Change from "or ankylosing spondylitis" to "and ankylosing spondylitis" - Change from "in the light" to "in light" - Hepatitis B virus should be abbreviated (HBV) the first time it is referenced. - This sentence does not make sense: Attention towards hepatitis B virus infections has been paid following several case reports of severe hepatitis B virus reactivation with consequent fulminant HBV infection in patients exposed to TNF- α inhibitors. Suggestion: The awareness of hepatitis B virus infection has increased because of several case reports of severe hepatitis B virus reactivation in patients exposed to TNF- α inhibitors. - Change to "limited, there is evidence" - The following sentence is long and confusing. I would recommend shortening or dividing in two sentences. "Although the role of TNF- α in chronic viral hepatitis is limited there is evidence that TNF- α synergizes with interferons in suppressing viral replication[44] and is essential in clearing HBV45 and hence, inhibiting the TNF- α cytokine could potentially increase HBV replication leading to active disease" - Change "IBD are screened" to "IBD be screened" - Change "patients on concomitant treatment with corticosteroids and comorbidity" to "patients receiving concomitant corticosteroids and with comorbidities" - Change "minimalized" to "minimized" - Change "in high TB incidence countries" to "in countries with high TB incidence" - Change "are no current consensus " to "is no current consensus" - The last sentence of the conclusions is long and confusing. I would recommend shortening or separating into two sentences.

Reply: All the listed minor comments has been corrected in the updated manuscript.

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

Sincerely yours,

Nynne Nyboe Andersen

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