

Answers for the Reviewers:

November 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14473-review.doc).

Title: Autoimmune hepatitis and anti-TNF-alpha therapy: A single center report of 8 cases

Running Title: Eight cases of anti-TNF-alpha-induced autoimmune hepatitis

Author: Rodrigues Susana, Lopes Susana, Magro Fernando, Cardoso Hélder, Horta e Vale Ana Maria, Marques Margarida, Mariz Eva, Bernardes Miguel, Lopes Joanne, Carneiro Fátima, Macedo Guilherme

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14473

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) Reviewer: "This nice study reports the one centre experience on suspected AIH after anti-TNK. However, some major criticism does exist. Firstly, diagnosis was not supported by histology, making any conclusion debatable. Moreover, data are not fully elucidated, in particular differential diagnosis. Furthermore, tables are very badly designed and illegible. Finally, some minor language revision is needed"

Answer: Thank you for your pertinent comments. All of the patients had liver biopsies as explained in the case description and the biopsy results were all indicative of autoimmune disease. The biopsy results are found on table 1.

Addition information was added to the manuscript explicitly detailing the differential diagnoses: "All of the patients had a complete work-up to exclude other etiologies including viral (anti-HCV, anti-HBs and HBe antibodies and HBs antigen), toxic, metabolic (alpha-1 antitrypsin, iron saturation, ferritin, ceruloplasmin), other autoimmune liver diseases (anti-mitochondrial and ANCA antibodies), in particular those associated

to IBD, such as primary sclerosing cholangitis (liver MRI). Liver histology was obtained in all cases and each case showed signs of autoimmune hepatitis (chronic lymphoplasmocytic infiltrate and interface hepatitis)."

I was born and raised in the USA and my native language is English.

(2) Reviewer: The present study is original and well conducted. However, English is poor and should be revised by a native speaker. I strongly suggest that patient 2 might be excluded from the sample as the anti-TNF agent was different from the other cases. Moreover, the dose use of adalimumab was 5 times the dose of infliximab. This fact might compromise the comparison with the other cases. Also, histological findings should be showed within results.

Answer: Thank you for your pertinent comments. I am an American citizen and English is my native tongue, therefore I will not by requesting language revision.

I chose not to exclude the patient 2 because I would like to underline to clinicians that the risk exists in both of the anti-TNF-alpha antagonists using in inflammatory bowel disease.

Furthermore the dose described is the dose used in everyday clinical practice.

Histological findings are found on table 1.

(3) Reviewer " Case report is not very well organized (introduction is very short; it should present background information that provide clarity to the subject of discussion and pertinent definition - type of liver injury induced by Tumor Necrosis Factor-alpha antagonists (immune-mediated DILI and AIH).

Introduction: is very short, it should present background information that provides clarity to the subject of discussion and pertinent definition - type of liver injury induced by Tumor Necrosis Factor-alpha antagonists (immune-mediated DILI and AIH).

May be few words about these patients?

Thank you for your pertinent comments. In response to your comments, I have added the highlighted section to the manuscript: One of the major discussions is the importance of the distinction between autoimmune hepatitis and drug-induced autoimmunity because of the long-term repercussions that the disease may hold for these patients.

In our center, we have analyzed the medical records of our patients undergoing anti-TNF alpha therapy (over 600 patients), in order to detect cases of AIH associated to anti-TNF biologic agents. This population included patients with inflammatory bowel disease (IBD) and autoimmune rheumatological (rheumatoid arthritis, ankylosing spondylitis) and dermatological diseases (psoriasis) undergoing treatment with infliximab (IFX), adalimumab (ADA) or etanercept.

3 References and typesetting were corrected

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

Sincerely yours,

Susana Rodrigues, MD

Department of Gastroenterology

Centro Hospitalar de São João

Avenida Professor Hernani Monteiro

4200-319 Porto

Fax: +351 225096093

Telephone: +351963109863

E-mail: susanagrodrigues@gmail.com