Author’s response to reviews

Title: Hepatobiliary and Pancreatic Manifestations in Inflammatory Bowel Diseases: A Referral Center Study

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To BMC Gastroenterology

Dear Editor,

I hereby submit for your consideration the revised article, titled “Hepatobiliary and Pancreatic Manifestations in Inflammatory Bowel Diseases: A Referral Center Study”. My colleagues — co-authors and I sincerely hope that you will deem it appropriate for publication in BMC Gastroenterology.

We would like to thank the Reviewers for their useful comments.

A great emphasis has been placed on the revision of the manuscript, following the instructions/comments posed by the Reviewers.
The responses to the Reviewers are presented in details as follows:

Responses to reviewers

Reviewer #1:
In this retrospective study, the authors wanted to document the strong prevalence of manifestations of the liver, pancreas and biliary tree in patients with inflammatory bowel disease. This topic is novel but the application proposed is not so novel. It is difficult for us to understand the conclusions because of poor statistical approaches being used and statistical significant differences in respective groups does not prove (see Remark 1). Based on the statistical results conducted by the un-precise methods, the conclusions are overstated and unscientific and therefore this manuscript does not bring any meaningful knowledge. And beyond that, the following are furthermore detailed modifications and questions in this manuscript. Attached, please find referee comments/suggestions on your paper. It would be ideal if you could also draft a response to our referees stating what has been rectified in the revised copy as this will help speed up the finalization process.

1. The clinical data from this research is summarized as means and standard deviation. However, it is hard to obtain statistical significant data through above methods of data analysis. Hence, the clinical value of the study is almost meaningless. And the Chi-square test should be applied to compare the experimental and the control group.

2. It should be noted that the study scope of manifestations of the liver, pancreas and biliary tree is so abroad that the highest association is difficult to distinguish. Due to aforesaid disease also can be resulted in the side effects of drugs, especially the hepatitis and drug-induced hepatotoxicity. There is no experimental comparison of the algorithm with previously known work, so it is impossible to judge whether the algorithm is an improvement on previous work. Further researches and experimental scheme should be conducted.

3. On the other side, more detailed explanation of methodology should be provided. Because of the inflammatory bowel disease and/or therapeutics may have an indeterminate influence on the patients and may cause the undesirable side effects. Therefore, it's important to take a careful observation of IBD development from the beginning. The manuscript ought to reset the criteria for inclusion and give more detailed about the criteria.

4. More importantly, this manuscript does not mention that the selected patients had signed the informed consent and this study had not been recommended by the ethics committee.

Response:
In our retrospective study, we tried to register the extra intestinal manifestations from liver, biliary tract and pancreas in IBD patients and their frequency rates. Also, we emphasized to the side effects of medical treatment in hepatobiliary system and pancreas. Through our study, we report the hepatic and pancreatic manifestations and complications in a large number of IBD patients and their relative frequency.

On comment 1: our study sufficiently demonstrates the spectrum of hepatobiliary manifestations in IBD and we compare our results with another study.

On comment 2: in our study there is special part about drug-induced hepatotoxicity and in addition cases of reactivation of viral hepatitis during immunosuppressant therapy are analyzed in detail.

On comment 3: we added information about the methodology and the inclusion criteria of study. On 5
Page, we added “Inclusion criteria for the study were diagnosis of IBD and regular follow-up from time of diagnosis with frequent laboratory tests. Consequently” and “All patients were followed up from the time of diagnosis of IBD in our referral center”.

On comment 4: the present study was approved by the Ethics Review Committee of University of Ioannina. No additional permissions were required to review the patient records, including the hospitals from which the records were obtained.

Reviewer #2: The authors in this retrospective study have tried to shed light on essentially the extraintestinal GI manifestations of IBD. It is important to identify patterns of extraintestinal manifestations and other organ involvement of the GI tract. However, the study fails to add meaningfully to the literature on IBD at present.

1) The methodology is weak, given this is a retrospective study, it is not possible to find out the prevalence of other GI organ involvement, especially in setting of imaging modalities available for review in less than half of the cases. The methods need to be defined more clearly. A clear description of diagnostic process is needed. Is there a protocol in place on imaging and testing in IBD at the center? etc.

2) The imaging modalities are available only in a select few, thus the results are heavily skewed. Was imaging done in patients with more severe disease? This should be discussed as limitations.

3) It would not be appropriate to compare the incidences of other manifestations, such as PSC, with other studies with different methodology.

4) It is difficult to identify results which are going to add meaningfully to the already available data.

5) One way this study could be written differently would be to compare it with other studies from Greece, to compare differences in extra intestinal findings and trying to identify patterns to better characterize risks in various patient populations.

Response:
On comment 1: In summary, imaging was performed, when there was a relative indication, such as mild abdominal pain or abnormal liver function tests. Despite this limitation, more than third of patients underwent imaging evaluation and a significant number of abnormal findings were observed.

On comment 2: we added the following explanation to the text “Imaging evaluation was performed, when there was an appropriate indication, such abnormal biochemical hepatic tests, and this is one of the limitations of our study”, on page 8.

On comment 3: It is a correct comment, but we think that the reader should be informed about epidemiological data from other studies, recognizing the limitations of our study.

On comment 4: Despite the existing limitations, the study shows the range and frequency of hepatobiliary manifestations in a large group of IBD patients, in Northwestern Greece.

On comment 5: It is an interesting idea. However, due to limited data from other local studies and different methodology, such a comparison would not add to the value of our study.
Reviewer #3: The study of Fousekis et al. evaluates the frequency of liver, biliary and pancreatic diseases in patients with IBD. This is a retrospective study conducted in a tertiary center from Greece

Major comments:
1. This is a retrospective study from a tertiary center and has the drawbacks of this kind of study: selection bias (tertiary center) and classification bias (quality of the data in a retrospective data)
2. There is no new information but there are interesting results about the epidemiology of drug induced liver and pancreatic injuries (DILI and DIPI). I think, you should give more details on these 2 populations and less on biliary diseases (see below)
3. To improve the quality of the manuscript, we need more information on the way the diagnosis was affirmed as drug induced injury is an exclusion diagnosis.
4. It is necessary to use standardized definitions. For example use the criteria of Aithal et al. (Clinical pharmacology & Therapeutics 2011) for DILI and Badalov et al. for DIPI (Clin Gastroenterol Hepatol 2007). How did you evaluate the causality? Roussel Uclaf Causality Assessment Method for DILI?
5. Can you give a clear message to the readers: when do they have to stop for example azathioprine when ALT is increased ? ALT > 3N or 5N?
6. Some studies have shown that DILI with azathioprine is cytolytic in roughly in one third of the patients, cholestatic 1/3, mixte 1/3. Did you observe a cholestatic injury?
7. DILI by AZA can be dose dependent or dose independent, did you observe the 2 types?
8. For steatosis, do you have information on BMI and the metabolic syndrome (waist size, lipids, glycemia, hypertension). Is steatosis nowadays associated with the activity of the disease or denutrition or metabolic syndrome?
9. How many patients had excessive consumption of alcohol?
10. Use also standardized epidemiological words as person-years when you give results of incidence
11. How do you explain the low number of PSC? When did your center started to use biliary MRI?

Minor comments:
1. Page 5, lane 23; several patients underwent imaging evaluation: how many? This is a selection bias. Then the frequency of biliary lithiasis has a very limited interest.
2. Page 6 lane 10: I think Table 1 does not add information
3. Lane 16: The most "a word is missing" were males
4. Lane 26: did you look for thrombophilia?
5. Page 7 Lane 8: this message is confusing as amylase should not be tested if the patient has no abdominal pain
6. Lane 18: what was the interval for sulfasalazine
7. Lane 21: You use ALT > 2 ULN, what are the percentage of patients with ALT > 3 ULN, 5 ULN and Hy's Law?
8. Lane 27: please say clearly that the patient received both drugs for 2 months and that azathioprine was started 6 months before methylprednisolone
9. Page 8 Lane 2: What was the value of HBVDNA and ALT in the second patient with reactivation?
10. Lane 24: associated instead of correlated
11. Page 9 Lane 3: in patients with PSC
12. Lane 8: did you observe common bile duct lithiasis?
13. Lane 15: can you comment on differential diagnosis of DIPI as autoimmune pancreatitis (IgG4) and familial pancreatitis? Other causes like duodenal inflammation…….
Response:

On major comments

On comment 1: We agree that almost all the retrospective studies from tertiary centers have important disadvantages, but they offer useful information and help essentially in research.

On comment 2: We followed your instructions.

On comment 3, 4 and 5: We added on page 7 lines 8-10 “Drug-induced pancreatitis was established as diagnosis, when there was a reasonable temporal sequence between AP development and administration of the drug and withdrawal of drug caused clinical improvement. Re-exposure (re-challenge) was not used in any patient” and on page lane “drug induced liver injury (DILI). DILI was defined when other causes of liver injury, such as hepatitis viruses and PSC, had been excluded and withdrawal of drug caused laboratory improvement. Also, we used the Roussel Uclaf Causality Assessment Method (RUCAM) for the definition of DILI”.

On comment 5: Azathioprine should be stopped with a constant elevation of ALT > 3N

On comment 6: We added on page 11 lines 13-14 “According to R factor for liver injury, in 8 of 9 AZA-hepatotoxicity cases hepatotoxicity liver injury was observed (R>5) and in only one case the liver injury was mixed (R: 2-5)”.

On comment 7: we added on page 11 lines 11-13 “In addition, hepatotoxicity from AZA was dose independent and occurred only few weeks after administration of AZA, while many patients received AZA for more than one year without manifesting liver injury. AZA-induced DILI was dose independent”.

On comment 8 and 9: We have no data in all patients about the BMI of patients and alcohol consumption. Most patients did not consume alcohol at all and the remainder were rare social drinkers. Most of them had normal BMI. We added on page 9 lines “Unfortunately, there was no accurate information about alcohol consumption, BMI and factors-related with metabolic syndrome of our patients. Despite that, most patients did not consume alcohol at all and the remainder were barely social drinkers. In addition most of them had normal BMI. So it is unlikely that these factors had played a significant role on steatosis”.

On comment 10: We followed your instruction and we added on page 11 “(1.1 per 100 person-months)” and “(1 per 35 person-years)”.

On comment 11: A possible explanation is the limited use of MRCP in the first two decades of our retrospective study. Our center started to use biliary MRCP from 1993. We added on text “The
decreased incidence of PSC in our study may be due to limited use of MRCP in the first two decades of our retrospective study. Our tertiary center has started to use MRCP since 1993”.

On minor comments
On comment 1: We changed “several patients” to “220 patients”.

On comment 2: We would like the Table 1 to remain if possible.

On comment 3: We added “The most patients”.

On comment 4: We investigated for thrombophilia. We added on page 6 “In case of portal vein thrombosis, the risk factors for portal vein thrombosis, such as myeloproliferative disorders, protein S and C deficiency and antiphospholipid syndrome, were investigated. In our patient with portal vein thrombosis, these factors were negative. So, IBD was implicated as the main risk factor. The patient had moderately severe ulcerative colitis”.

On comment 5: We just want to mention drug induced-hyperamylasemia. We can remove this sentence, if it is necessary.

On comment 6: The interval of sulfasalazine exists in Table 3.

On comment 7: We added “From them, there were 3 patients with ALT >5 ULN and one patient with ALT > 3 ULN, while there was not any patient with Hy’s Law.”.

On comment 8: We followed your instruction and added “The patient received both drugs for 2 months”.

On comment 9: We added “with HBV-DNA: 10,000 IU/mL, ALT: 94 U/L and AST 83 U/L”.

On comment 10: It was done.

On comment 11: It was done.

On comment 12: In our follow-up time, cholelithiasis was not observed.

On comment 13: We added “Additionally, it is worth mentioning that the differential diagnosis of causes of acute pancreatitis in IBD patients should include the duodenal involvement of CD and autoimmune pancreatitis”.

On comment 14: We would like to maintain the structure of text, thereby giving greater emphasis to viral hepatitis in IBD.

On comment 15: we added “anti-HCV positive and HCV RNA positive”.

On comment 16: We followed your instructions

On comment 17: It was done.
On comment 18: We would like to keep the Table.

On comment 19: We changed the title of table.

On comment 20: We followed your instructions and added additional information to the Table.

We hope that the revised manuscript will vouch for a position among other relative studies already published in your Journal. Once more we would like to thank the Section Editor and their reviewers for their fruitful comments and their important contribution.

This work is part of thesis of the first author Dr Fotios Fousekis, who tried hard and gave a lot of effort and energy to gather the data and draft the initial manuscript.

On behalf of the co-authors with my great appreciation

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