Format for ANSWERING REVIEWERS

March 17, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 32577-review.doc).

Title: Clinical course of ulcerative colitis patients who developed acute pancreatitis

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
A:
COMMENTS TO AUTHORS
In this large cohort, authors aimed to investigate clinical course of ulcerative colitis patients who developed acute pancreatitis prospectively. First recognized result is that a rate of the thiopurine induced acute pancreatitis is lower than western studies. That lower rates should be mentioned in discussion explaining causes.
Reply: We thank the reviewer for the valuable comments. We have added this point to the Discussion on p.12 lines 6-10, as follows:

"The incidence of thiopurine-induced pancreatitis is reported to be 3-4% among IBD patients [27-29]. Among our patients, thiopurine-induced pancreatitis developed less frequently (1.75% of thiopurine users). The reason for this is not clear, but it might represent a distinct characteristic of our cohort."

And also autoimmune pancreatitis seems to be higher than other studies without Japanese results. Authors should also highlight this clinical importance.
Reply: We are not sure which non-Japanese study to which the reviewer refers. As noted by Ramos et al. (Dig Liver Dis. 2016 Aug;48(8):893-8), there have been only two studies reporting the prevalence of AIP in IBD patients: one is the Japanese study by Ueki et al, (Pancreas 2015;44:434–40), and the other is a Korean study (Journal of Clinical Gastroenterology 2013;47:520–5.), both of which reported a similar frequency of AIP among UC patients. We wrote about this in the Discussion (p.11, lines 3-5). Ramos et al. described a case series of five AIP patients who had IBD,

but the prevalence of AIP among IBD was not analyzed in this report (Dig Liver Dis. 2016 Aug;48(8):893-8).

Types of acute pancreatitis should be mentioned in the result and discussion at least as mild and severe forms. This study could be accepted after added detailed information.
Reply: We classified the severity of acute pancreatitis using the revised Atlanta classification. This is mentioned in the Methods section, p.6, lines 13-14. We found one case of AIP with moderate severity; the severity was mild for all other patients. We added this in the Results section as follows (p. 8, lines 29-30):

"There was one patient with AIP whose severity was classified as moderate; all other patients had mild acute pancreatitis."

B.

COMMENTS TO AUTHORS

The authors can extend with correlations between pancreatitis and other extra-GI manifestations of CU about the risk of colectomy

Reply: We thank the reviewer for the comment. However, there was only one case of primary sclerosing cholangitis who had aminosalicylate-induced acute pancreatitis. There were no cases of extraintestinal manifestation among autoimmune or thiopurine-induced pancreatitis patients. We feel that the frequency of extraintestinal manifestation was too low for further analysis.

C.

COMMENTS TO AUTHORS

? Among the patients with UC who developed acute pancreatitis, there were two patients in whom the appearance of acute autoimmune pancreatitis preceded the clinical diagnosis of UC, and three more patients in whom acute autoimmune pancreatitis appeared concurrently with the clinical manifestations of UC. This is an interesting observation which should be emphasized in the discussion section as so far, very few cases have described in the international literature (mainly referring to patients with Crohn's disease) See the following references: (Triantafillidis JK, Cheracakis P, Hereti IA, Argyros N, Karra E. Acute idiopathic pancreatitis complicating active Crohn's disease: favorable response to infliximab treatment. Am J Gastroenterol. 2000 Nov;95(11):3334-6. Triantafillidis JK, Cheracakis P, Merikas EG, Peros G. Acute pancreatitis may precede the clinical manifestations of Crohn's disease. Am J Gastroenterol. 2003 May;98:1210-1. Triantafillidis JK, Merikas E, Malgarinos G, Panteris V, Peros G. Acute idiopathic pancreatitis preceding diagnosis of Crohn's disease. Description of three cases. Rev Med Chir Soc Med Nat Iasi. 2009;113:97-102.) ?

Reply: First of all, we deeply thank the reviewer for the valuable comments.

We also found it interesting that several cases of acute pancreatitis occurred at or before the time of UC diagnosis. We found more articles that reported AIP preceding CD, but none reported AIP before UC. We have noted this in the discussion section, p. 11, lines 11-16, as follows:

"It is interesting that two cases of AIP occurred before the diagnosis of UC. There have been several reports of AIP occurring before the diagnosis of CD [31,32,39-41], but to the best of our knowledge, there have been no reports of AIP that preceded UC. Our results suggest that patients with repeated episodes of unexplained acute pancreatitis should be evaluated for inflammatory bowel disease."

I wonder if there are epidemiological data concerning the incidence of acute pancreatitis in the country of origin of the work. If the answer is yes, then the readers of the paper might be interested to learn about the size of differences in the epidemiological features of pancreatitis between patients with UC and the general population. (Chen YT, Su JS, Tseng CW, Chen CC, Lin CL, Kao CH. Inflammatory bowel disease on the risk of acute pancreatitis: A population-based cohort study. J Gastroenterol Hepatol. 2016 Apr;31(4):782-7. doi: 10.1111/jgh.13171). ?

Reply: According to the JGH paper by Chen et al., UC patients were at a 2.49-fold (95% CI, 1.91-3.26) increased risk of acute pancreatitis compared to the general population (J Gastroenterol Hepatol 2016 (31) 782–787). According to a study performed in 2003, the annual incidence of acute pancreatitis in Korea was 19.4 per 100,000 persons (Korean J Gastroenterol. 2003; 42(1):1-11). In our UC patients, the annual incidence of acute pancreatitis was 152.9 (95% CI, 113.4-206-1) per 100,000 persons. Direct comparison of the figures suggests that the incidence of acute pancreatitis is in fact higher among UC patients, but further analysis using data from the general population is required to draw firm conclusions. We have added this in the

Discussion section, p. 10, line 26 - p.11 line 2, as follows:

"UC patients are reported to be at an increased risk of developing acute pancreatitis compared to the general population [31]. According to a study performed in 2003, the annual incidence of acute pancreatitis in Korea was 19.4 per 100,000 persons [32]. In our patients, the annual incidence of acute pancreatitis was 152.9 (95% CI, 113.4-206-1) per 100,000 persons (data not shown). Although the incidence was high among our patients, further analysis using data from the general population is required to draw firm conclusions."

What was the incidence of other extraintestinal manifestations in patients with acute pancreatitis compared to those without acute pancreatitis? These data would be of interest for the readers of the article.
Reply: Among our acute pancreatitis patients, one patient with primary sclerosing cholangitis developed aminosalicylate-induced acute pancreatitis (1/51 [1.96%]). Among non-pancreatitis patients who were evaluated, there were 41/650 (6.31%) patients with PSC (p = 0.353). Since our study and cohort were not exactly designed to compare extraintestinal manifestations, this result is only speculative and thus we did not include this in the manuscript.

? What was the proportion of asymptomatic elevation of serum amylase in the whole cohort of UC patients?
Reply: Unfortunately, we do not routinely measure serum amylase in our cohort, and thus the rate of asymptomatic amylase elevation could not be analyzed.

Finally, it is well established that the rate of colectomy represents an important index of severity of the course of UC. In the discussion section the authors should use and discuss these data as an index of severity of the underlying UC.
Reply: In a previous study that described our UC cohort, the overall colectomy rate was 7.5% (Journal of Crohn's and Colitis, 2015, 147–155). The colectomy rate in our study was 7.3%, as described in the manuscript. Colectomy rates have been reported to be 7.5-18.9% in previous studies, which seems to be comparable to that of our study (Am J Gastroenterol 2012;107:1228–35, Gut 2014;63:1–10, Gastroenterology 2013;145:996–1006, Scand J Gastroenterol 2009;44:431–40, Inflamm Bowel Dis 2013;19:1858–66). We have included this in the Discussion, as suggested by the reviewer, as follows (p. 12 lines 23-24):

"The colectomy rate in our cohort was 7.3%, which is comparable to those of previous studies [46-50]."

D.

COMMENTS TO AUTHORS

There is an interesting study that evaluates the clinical course of UC patients who developed acute pancreatitis of all etiologies. One shortcoming is the lack of the date related to the types of acute pancreatitis, especially its severity; these could also influence the outcome of inflammatory disease.

Reply: We reviewed the clinical data and found one patient with moderate severity; all other patients had mild acute pancreatitis. This was added in the Results section as follows (p. 8 lines 29-30):

"There was one patient with AIP whose severity was classified as moderate; the severity was mild for all the other patients."

I also recommend evaluating if there is any correlation between acute pancreatitis and other extra intestinal manifestations.

Reply: There was only one case of primary sclerosing cholangitis who had aminosalicylate-induced acute pancreatitis. There were no cases of extraintestinal manifestation among autoimmune or thiopurine-induced pancreatitis patients. We feel that the frequency of extraintestinal manifestation was too low for further analysis.

E.

COMMENTS TO AUTHORS

The author present interesting data on pancreatitis in UC.

1. The data has been obtained from a database and hence it is possible that all cases may not have been documented if the follow up was not systematic. There is large vaiability in follow up interval. This may explain the apparently low rate of AZT induced pancreatitis.

Reply: We agree with the reviewer, and we added this as a limitation in the Discussion, p. 13, lines 10-11, as follows:

"Fourth, the follow-up interval was variable among patients, which could have led to the apparently low rate of thiopurine-induced pancreatitis."

2. Table 3 and 4 show odds ratio for use of surgery and biologicals. However the need for surgery and biologicals depends on multiple factors which have to be analysed instead of acute pancreatitis alone (the number of outcomes in this study are insufficient to do multivariate analysis).

Reply: It is true that the risk of colectomy and disease course including anti-TNF use are multifactorial and cannot be attributed to prior history of acute pancreatitis alone. We think, however, that there is also a need for analyzing what impact acute pancreatitis might have on such important clinical events.

Although the number of cases was small for a multivariate analysis, we were greatly interested in adjusting for baseline UC severity, since it can influence the disease course tremendously.

3. The authors can perhaps focus on AIP patients and their course of illness .

Reply: We were most interested in disease course of AIP during the initial analyses, but comparing the disease course among different types of acute pancreatitis such as autoimmune, aminosalicylate-, and thiopurine-induced pancreatitis could attract more interest among the readers of this paper. The severity of acute pancreatitis was mild in most patients with AIP, and pancreatitis resolved uneventfully in all cases, which we described in the manuscript on p. 9 lines 10-12, as follows:

"All 13 patients with AIP showed a good response to corticosteroids, and there were no cases of recurrence during the median follow-up of 27.8 months (range, 3.2–81.9) following diagnosis of AIP."