



September 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

**Title:** Inflammatory bowel disease of primary sclerosing cholangitis

: a distinct entity ?

**Author:** Takahiro Nakazawa, Itaru Naitoh, Kazuki Hayashi, Hitoshi Sano, Katsuyuki Miyabe, Shuya Shimizu, Takashi Joh

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 5302

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

**Reviewer 00001390**

This review article provide useful information regarding IBD with PSC and differentiation among sclerosing cholangitis, that will be published in World Journal of Gastroenterology. To polish it, I have some questions and proposal.

1. Major If possible, could you add the section of "IBD with type 2 AIP"? In addition, we eager to know the comparison between IBD with PSC and that with type 2 AIP. Type 1 AIP and IgG4-SC are included in the same disease entity of IgG4 related disease. If PSC-IBD is useful for the differentiation between IgG4-SC and PSC, type2 AIP-IBD may also be useful for the differentiation between type 1 and type 2 AIP.

Association with IBD is characteristic findings with type2 AIP. This association is

incorporated into the diagnostic criteria of type 2 AIP in ICDC. We are also interested in IBD with type2 AIP. However, there were no reports about the details of association between type2 AIP and IBD. We could not find the article which mentioned the clinical characters of associated IBD with type 2 AIP. In addition, type 2 AIP cases are very rare in Japan. I have never experienced type 2 AIP and cannot discuss the character of IBD associated with type2 AIP.

However, we inserted your advice in the section of “The usefulness of PSC-IBD characteristics in the diagnosis of sclerosing cholangitis”

2. Minor 1. Title, “Inflammatory bowel disease associated with primary sclerosing cholangitis shows unique characteristics and is a useful marker in the diagnosis of sclerosing cholangitis” may be changed to “Inflammatory bowel disease associated with primary sclerosing cholangitis shows characteristic findings and provides a useful marker in the diagnosis of sclerosing cholangitis” or more suitable expression.

We agreed with the reviewer, but writing requirements of topic highlight demand that title should be less than 12 words. Therefore, I followed the other reviewer’s advice.

A new title is “ Inflammatory bowel disease of primary sclerosing cholangitis: a distinct entity ?”

3. In Abstract, line 3 “IBD-associated PSC” may be changed to “IBD-associated with PSC”

We agreed with the reviewer and corrected the mistake as the reviewer advised.

#### **Reviewer 00054089**

This is a review of IBD, PSC and IgG4 cholangitis. It combines a review of the literature and some of the authors' own experience. The topic is reasonably well covered but offers little new insight. It suffers, in my view, from two main defects:

1. there is a lack of critical assessment and the layout is muddled. It is difficult to draw any novel conclusions from this. For example, they outline much of the published literature but do not critically assess reasons for differences between Asian and

Western findings. Is there a real difference or is this methodology: there is no discussion and no conclusion.

We agreed with the reviewer and added our conclusion critically in each section.

2. The data on IgG4 cholangitis is hampered by a clear definition and conclusions are weak.

Figure 4 is a key figure of two main topics. We added the detailed figure legend of figure 4 because we would like many readers to easily understand the contents. Furthermore, we added the significance of PSC-IBD clearly in the last part of *The usefulness of PSC-IBD characteristics in the diagnosis of sclerosing cholangitis*

3. There should be more discussions about the HLA and other genetic actors

We agreed with the reviewer and added the recent two studies about the topic reviewer recommended. However, this invited review article is one of 25 review articles for the special issue celebrating the 20th anniversary of *World Journal of Gastroenterology* (III: Inflammatory bowel disease review: Pathogenesis, prevention, diagnosis, treatment, and evidence-based medicine). We are afraid that other authors might argue the detail of pathogenesis.

#### **Reviewer 0006992**

1. Nakazawa et al. wrote an review article about primary sclerosing cholangitis and inflammatory bowel disease. In the abstract it should already be stated that the article is an review and no original report.

We agree with the reviewer and inserted the following sentence in the beginning of abstract. "This is a review of the characteristic findings inflammatory bowel disease (IBD) associated with primary sclerosing cholangitis (PSC) and the usefulness in the diagnosis of sclerosing cholangitis."

2. In Material and Methods the source of articles should be mentioned exactly. Was

there only a literature search in PubMed? Why did the authors avoid Cochrane Databases and Medline? Where the keywords connected by AND or OR? The screening strategy should be metioned as exactly as possible.

We searched references using Cochrane library as reviewer advised , but did not find new useful studies for this review article.

We connected the keywords by OR. We clearly mentioned it.

3. The authors stated that they have an own >20-year clinical experience in the treatment of PSC-IBD. These authors should evaluate single paragraphs (e.g. frequency, mechanisms, or usefulness of PSC-IBD characteristics in the diagnosis of sclerosing cholangitis) and sign the opinion as their own for example at the end of the paragraphs.

We agreed with the reviewer and added our conclusion critically in each section.

#### **Reviewer4 00036868**

This is a review article on the inflammatory bowel disease associated with primary sclerosing cholangitis. The topic is of interest.

1. In general the article should be shortened particularly in the introduction section that should be limited to the definitions and to the aim of the study since many elements such as frequency will be reported later in the paper.

We agree with the reviewer. We shortened the introduction by deleting the data repeated in the next sections.

2. The title should be more general such as “ Inflammatory bowel disease of primary sclerosing cholangitis: a distinct entity ?”

We agree with the reviewer. We changed our title as the reviewer advised.

3. It should be clearly indicated that the study is limited to adults patients, if not a section dedicated to pediatric patients should be inserted.

We agree with the reviewer. We inserted the sentence” this study is mainly limited to

adults patients except the section of *frequency of PSC-IBD*

4. On page 4 = PSC can still develop after colectomy and IBD can still develop after liver transplantation” please give reference for each of the items.

We agree with the reviewer. We cited references.

5. In table 2. Our data should be changed in “ name of the first author” year and referenced as personal communication

We agree with the reviewer. We cited a reference.

6. The figure 4 is confusing and should be omitted

We are sorry, but we cannot omit figure 4 because figure 4 is a key figure of two main topics.

We added the detailed figure legend for figure 4 for readers to easily understand. .

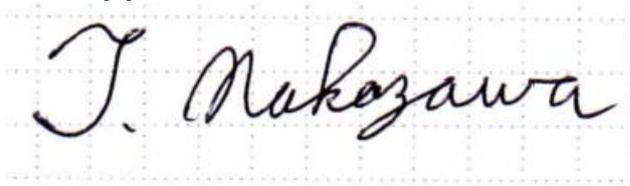
**Reviewer 00005986**

This manuscript by Nakazawa et al reports a revision of the literature on PSC and IBD. They quoted the available studies on this area but the discussion is quite plan. Studies have to be discussed more critical.

We agreed with the reviewer and added our conclusion critically in each section.

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

Sincerely yours,

A handwritten signature in black ink on a light gray dotted grid background. The signature reads "T. Nakazawa" in a cursive, flowing script.

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