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Ref: ESPS Manuscript NO: 851, entitled "Steroid-refractory ulcerative colitis and associated primary sclerosing cholangitis treated with infliximab", Duca I, et al., revised version

Dear Dr Lian-Sheng Ma:
Through the web-based system at http://www.wjgnet.com/esps/ we have uploaded the revised version of this manuscript in which changes have been introduced in response to comments made by the reviewer. In addition, our point-by-point comments to each suggestion are also provided. For easy identification, the new additions in the manuscript are highlighted with the pen function of word.

All changes requested in the edited version are included.

Sincerely yours,

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AUTHORS' COMMENTS TO SUGGESTIONS OF REVIEWER #1

I consider the study valuable in that there are few cases in the existing literature and in that it demonstrates a positive evolution in primary sclerosing cholangitis (PSC) after anti-TNF-α treatment.

- We appreciate your supporting comments to our contribution.

Currently the use of anti-TNF-α therapy is controversial because there are several studies which demonstrate no improvement in PSC after using infliximab or etanercept (Epstein MP et al. Dig Dis Sci. 2004). Contrarily and consequently adding to this controversy, Bo X's research (Gut 2001) is worthy of note as their findings provide sound reasons for the use of anti-TNF therapy in PSC cases.

The use of anti-TNF-α therapy remains controversial. The average time from diagnosis to liver transplantation is approximately twelve years. If we were to increase this timeframe by altering the natural progression of the disease with anti-TNF-α, the use of this medication for over ten years raises financial concerns. In addition, we must consider the secondary effects of this prolonged use.

In fact, perhaps the focus of the discussion should consider how the use of anti-TNF-α alters the natural history of the disease. This discussion would have a marked significance in daily medical practice.

- We have added this new paragraph in the Discussion, including the references of Epstein et al. and Bo et al., as well as concerns regarding prolonged use of anti-TNF-α therapy: "Currently, the use of anti-TNF-α treatment in primary sclerosing cholangitis is not well established. The observation that reduced T cell reactivity in liver infiltrating cells obtained from patients with primary sclerosing cholangitis was due to high local production of TNF-α provides support for the use of anti-TNF antibodies as an alternative treatment for these patients[21]. Contrarily, in the experience of Epstein et al.[22] etanercept was well tolerated but not effective in a clinical series of 10 patients with clinically active primary sclerosing cholangitis. It is unknown whether early treatment with anti-TNF-α drugs may change the natural history of primary sclerosing cholangitis. Also, the use of this medication over years may raise financial concerns and secondary effects of this prolonged use. In the case here presented, although treatment with infliximab is expensive, the patient did not present recurrent episodes of colitis, uveitis, sacroiliitis or new episodes of cholangitis, allowing prompt resumption of work and social activities with an excellent quality of life and without further admissions to the hospital or the need of surgical operations, as a result of which direct and indirect costs have been markedly reduced in this particular case."

Nevertheless, I think that the use of anti-TNF-α in a well established PSC is not advisable due to immunosuppression and the high risk of cholangitis, which in these patients could prove fatal.

- A comment regarding the careful balance at the time of using anti-TNF-α agents in well established primary sclerosing cholangitis is added in the Discussion: "However, indications of anti-TNF-α in well established primary

sclerosing cholangitis should be carefully balanced due to immunosuppression and the risk of potentially fatal cholangitis."

In the case report section would have to confirm if during the two year follow-up the patient remained with infliximab or when exactly treatment was suspended. Finally, was the cholangio-MRI repeated in follow-up?

- Yes, the patient remained with infliximab and cholangio-MRI was repeated at follow-up. We have added these sentences: "At present, after two years of follow-up, the patient is still on treatment with infliximab and has remained asymptomatic …" and "Repeated cholangio-MRI performed during the follow-up was also unrevealing."

The language used is acceptable but I would make some changes:
- On page 6 on the line 12, I would change "poor prognosis" for "worse prognosis"
- In the Introduction, on page 3 on the line 17, I would change " (TNF)" for "(TNF-α)"
- On page 4 on the line 24, I would change " secondary sclerosis colangitis" for "secondary sclerosing cholangitis"

- All these linguistic improvements kindly mentioned by the reviewer are made.

In references, I think Bo X's research and Epstein's research should be included.

- These two studies are included, references #21 and #22.

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AUTHORS' COMMENTS TO SUGGESTIONS OF REVIEWER #2

The authors describe a patient who had ulcerative colitis (UC), spondylarthropathy and uveitis and who developed primary sclerosing cholangitis (PSC). Because UC was refractory to cortocosteroids, treatment with infliximab with standard induction and maintainance doses was prescribed. After two years of follow-up, the patient is asymptomatic and the liver tests are within normal limits.

The case and it's presentation

Impact of TNF blockers on PSC is not widely studied. The observation presented by the authors is new and it deserves to be published. The manuscript is clearly written and easy to read. However, some questions arise concerning the course of events. The authors mention that the causes of secondary sclerosing cholangitis were excluded as the diagnosis of PSC was made. This should be clarified. Especially, was the serum IgG4 level measured? What was the dose and duration of the costicosteroid treatment and what was the time span between the corticosteroid treatment and infliximab. Was the cholangio-MRI repeated? Sclerosing cholangitis associated with elevated IgG4 levels could have responded to costocosteroid treatment. The authors should discuss this in more detail.

- We have clarified that the causes of secondary sclerosing cholangitis were excluded and indicate that IgG4 levels were negative for autoimmune pancreatitis or cholangitis associated with IgG4 (levels < 100 mg/dL). Also, the patient showed increased values serum bilirubin and alkaline phosphatase of a lower magnitude that those suggestive of autoimmune pancreatitis, and radioimaging findings for pancreatic gland abnormalities were absent. Also, the patient did not complain of abdominal symptoms suggestive of pancreatitis. All these data together with the presence of ulcerative pancolitis directed us to confirm the diagnosis of primary sclerosing cholangitis associated to inflammatory bowel disease and to exclude an autoimmune pancreatitis. This information is added in the description of the Case Report.
- The time span between corticosteroid treatment and infliximab was 6 years. We have added this information in the text: "The patient received full doses of methylprednisolone, 1 mg/kg/day, with subsequent dose reductions at least on seven occasions over the course of 6 years."
- This sentence is added: "Repeated cholangio-MRI performed during the follow-up was also unrevealing."

Language

The English used in the manuscript is acceptable after some corrections. However, the text would benefit from language consultation by a person whose native language is english. Personally, I suggest the following changes to the text:
1) In the abstract on the line 11, on page 5 on the line 8 and on page 6 on the line 15, the use of the word "analytical" is maybe a little odd. The authors mean that the liver tests were normal at that time. In my opinion, it would be better to speak about "biochemical remission" or simply about "normal liver tests".
2) On page 4, on the second last line: "secondary sclerosis cholangitis" should be " secondary sclerosing cholangitis".
3) On page 6 on the line 8: "poor prognosis" should be "worse prognosis".

- All these modifications have been included in the text.

References

1) In the introduction the authors claim that 20- 40 % of patients with IBD have extraintestinal manifestations including musculosceletal ones. However, they refer to the article by Bernstein et al (reference No 1) in which musculosceletal manifestations were not included and thus, only 6,2 % of patients had extraintestinal manifestions. The authors should refer to a study in which musculosceletal manifestations are included (maybe Rankin et al 1979).
2) On page 6 on the lines 1 and 2. The authors claim that the longer duration and greater extent of colitis has been shown to be associated with PSC. The articles they refer (12 – 14) support the association of PSC with the greater anatomic extent of colitis but do these particular articles show that PSC is associated with longer duration of colitis?

- We only mention that extraintestinal manifestations in patients with inflammatory bowel disease can involve nearly any organ or system, including the musculoskeletal system. However, we have rewritten the first sentences of the Introduction as follows: "Inflammatory bowel diseases are associated with extraintestinal manifestations involving almost every organ system in the body, including the musculoskeletal, dermatologic, hepatic, pancreatic, biliary, ocular, renal, and pulmonary systems and can cause a significant challenge to physicians managing patients with Crohn's disease and ulcerative colitis[1-3]. The reference to the article of Bernstein et al. is now added at the end of this sentence.

- We have clarified that "Primary sclerosing cholangitis has been shown to be associated with greater anatomic extent of colitis". The previous mention of "longer duration of colitis" is deleted.