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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **1 33137-Revised manuscript-**.doc).

Manuscript Title: Inflammatory bowel disease in liver transplanted patients

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewer:

All performed changes are bolded in red.

1. **MINOR POINTS:**

- **Review-er comment: INTRODUCTION:** *This is brief and could include additional information on the following: The indications for OLT in PSC patients should be discussed; The differences in prognosis and management in PSC in CD vs UC; Small duct vs large duct PSC?*

The separate subheading (bolded in red): PRIMARY SCLEROSING CHOLANGITIS AND LIVER TRANSPLANTATION is added after INTRODUCTION. In this subheading PSC course, indications for LT and prognostic factors are explained in more details compared to original text. Also in this subheading PSC relation with IBD, differences in presentation of PSC in small or large ducts and its relation with types of IBD (UC or CD) are explained.

- **Review-er comment: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION:** *Page 2 – Type – "Tree different patterns of disease….."? Is risk of recurrent or de novo IBD after OLT different between CD and UC patients? ?*

Explanation on this question is provided in page 9 (bolded red) of this subheading starting with: The possible different patterns of disease… Risk of recurrent UC and CD is explained in study of Verdonk et. al. [41] were it seems that more patients with UC experience recurrence of disease. But, as stated in text, the overall conclusion on this issue is hard to provide because in most studies number of patents with CD is very small, authors are not reporting separate results for two IBD entities and there is possibility of other factors influence on disease course. In all other referenced studies

number of patients with CD is small, disease type in post-LT period is only colitis without specific data on subtype of IBD.

- **Review-er comment: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION:** *CMV mismatching is only discussed briefly – how important is this in work up for transplantation?*

In this subheading on page 9 (bolded in red) we have provided more data related to influence of CMV disease on the course of IBD after LT. Especially regarding the: role of donor end recipient screening tools for CMV serology, possible pathogenesis of CMV infection in development of de novo IBD after LT, prophylactic and therapeutic interventions in CMV viremia and CMV disease.

Review-er comment: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION: *Is the protective effect of 5-ASA against disease flares in only UC patients – presumably so?*

In referenced studies treatment with 5-ASA is related to lower risk of IBD flare up. According to ECCO guidelines 5-ASA is recommended for patients with colonic or ileocolonic disease. As stated in text (page 9), almost all PSC/IBD patients in published studies have UC (around 90%) with only minority CD with colonic or ileocolonic involvement. So data regarding effects of 5-ASA are related to IBD patients with colonic or ileocolonic involvement. Unfortunately authors in provided studies did not provide details on type of IBD (separately for CD or UC) and effects of 5-ASA on this separate entities. (bolded in red)

Review-er comment: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION: *Regarding post OLT immunosuppressive regimens it is suggested to use cyclosporine instead of tacrolimus and azathioprine instead of mycophenylate – are these recommendations supported by guidelines – eg from ECCO?*

In the subheading: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION (starting with page 7) we have made few major and minor changes (bolded in red) related to explanation of the role of immunosuppressive therapy (CsA, Tac, AzA, MMF, mTOR, corticosteroids) on the IBD course after LT. As stated in text: The interpretation of the results from previously published studies is complicated because of the small number of included patients, the differences in inclusion and exclusion criteria, diagnostic and treatment procedures, statistical analyses and duration of follow up.

In subheading TREATMENT OF POST-TRANSPLANTATION INFLAMMATORY BOWEL DISEASE, page 13 starting with: *Comparing effect...* we have provided more data on the role of different types of CNI in post-LT setting and their effects on IBD course. Since there are no guidelines, and data on this issue are scarce, we have concluded that: Although strong data is missing, knowing the possible negative effects

of tacrolimus and MMF on course of post-transplant IBD, in case of active IBD with low risk of graft rejection, preferential immunosuppressive regimens may be based on cyclosporine (over tacrolimus) and/or azathioprine (over MMF). While performing decision on optimal immunosuppressive approach for individual PSC/IBD patient, it of great importance to evaluate for the potentially increased risk of acute and chronic graft rejection for non-tacrolimus based regimens, especially because this risk appears to be relatively high in patients transplanted for PSC or AIH. To fully compare the two CNI further studies are needed. A prospective study comparing this triple regimen (cyclosporine/azathioprine/prednisolone) with others such as azathioprine/tacrolimus or rapamycin containing regimens would be useful. (bolded in red)

Review-er comment: RISK FACTORS ASSOCIATED WITH EXACERBATION OR DE NOVO IBD AFTER LIVER TRANSPLANTATION: *Similarly, in patients on azathioprine (or anti-TNF agents) prior to OLT should these be routinely stopped after OLT?*

Experience with IBD treatment in perioperative period is only briefly published in study of Verdonk et. al. with positive effects of reinitiating 5-ASA on IBD recurrence (page 9 in this subheading and also in subheading TREATMENT OF POST-TRANSPLANTATION INFLAMMATORY BOWEL DISEASE, page 13).
We have also pointed (in subheading PRIMARY SCLEROSING CHOLANGITIS AND LIVER TRANSPLANTATION, page 6 starting with: *At this moment there are no ...*) that study data is scarce and there are no prospective controlled studies regarding perioperative continuation of therapy or optimal post-transplant timing for reinitiating of earlier stopped therapy. Especially, there is no general recommendation regarding azathioprine or anti-TNF-alfa and decision should be based on assessment of risk of perioperative infections and wound complications like in all other operations in IBD patients. (bolded in red)

Review-er comment: TREATMENT OF POST-TRANSPLANTATION INFLAMMATORY BOWEL DISEASE : *These recommendations are not specific to IBD management in the post OLT patient ?*

We have stated in text (page 14) that, due to lack of high quality studies data: For patients with active IBD the recommended IBD therapy in post-transplant setting is equivalent to therapy recommendations in overall IBD population. (bolded in red)

Review-er comment: TREATMENT OF POST-TRANSPLANTATION INFLAMMATORY BOWEL DISEASE : *These two sentences are contradictory - "No significant drug interaction between 5-ASA and immunosuppressant's are observed. In some cases 5-ASA may interact with azathioprine and increase the risk of leukopenia" There are several papers showing the interaction of 5-ASA and thiopurines leading to increased 6TGN levels (Eg. . 5-aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. Hande S, Wilson-Rich N, Bousvaros A, Zholudev A, Maurer R, Banks P, Makrauer F, Reddy S, Burakoff R, Friedman S. Inflamm Bowel Dis. 2006 Apr;12(4):251-7).*

We have removed sentence *"No significant drug interaction between 5-ASA and immunosuppressant's are observed."* since it is contradictory to next one and left information on possible interaction of 5-ASA and Aza.

Review-er comment: *Table 1 is a large table that describes only 31 patients on A-TNFs. Of more value would be a larger table showing response rates to all agents used to treat IBD post IBD – it would not need to be so detailed for each agent.*

We have changed Table 1 into new one with data about effects and risks of overall immunosuppressive agents prescribed in post-transplant setting for IBD and anti-rejection purposes.

Review-er comment: *There should be a separate subheading on management of recurrent PSC post OLT.*

We have provided separate subheading on management of recurrent PSC post OLT named PSC AFTER LIVER TRANSPLANTATION (bolded in red) with more details on course of PSC after LT, diagnostic procedures, risk factor (especially related to IBD) and treatment. (bolded in red)

Review-er comment: *There should be a separate subheading on management of rejection post OLT*

We have provided separate subheading MANAGEMENT OF GRAFT REJECTION AFTER LIVER TRASPLANTATION with more data on risk of rejection in PSC patients and role of CNI inhibitor in prevention of rejection. (bolded in red)

Review-er comment: COLORECTAL CARCINOMA (CRC): *With reference to CRC surveillance the scenic guidelines and chromoendoscopy should be referenced. ?*

Data on role of chromendoscopy in colonoscopic evaluation is provided in subheading PRIMARY SCLEROSING CHOLANGITIS AND LIVER TRANSPLANTATION on page 5 in paragraph starting with: *In PSC patients without…* (bolded in red)
In paragraph COLORECTAL CARCINOMA we have stated that yearly endoscopy with chromendoscopy should be performed.
Also we have provided more data on risk of CRC in post-LT setting. (bolded in red)

Review-er comment: CONCLUSIONS: *The authors suggest "considering" cyclosporine and azathioprine as anti-rejection therapy. This is vague and the readers need stronger recommendations.*

According to review-er suggestion and due to lack of hard data we have revisited conclusions on optimal immunosuppressive protocol with suggestion (page 22): Decisions regarding optimal immunosuppressive drugs should be performed on an individual basis because patients with PSC are at a higher risk of acute and chronic graft rejection. When deciding treatments for individual patients with PSC/IBD, it is important to consider the risk of active treatment-resistant IBD occurrence (which is

related to an increased risk of colon neoplasia, PSC recurrence, hepatic artery thrombosis, etc.) in addition to the potentially increased risk of graft rejection for non-tacrolimus based regimens. (bolded in red)
Also we have made some more minor changes in Conclusions text in order to be more informative subheading, (bolded in red)

2. MAJOR POINTS:

Review-er comment: *This manuscript is too brief and inconclusive in its present form. More information is required in several areas as is suggested above. Most important is specific data, and therefore recommendations, on IBD management in the post OLT population versus the non-transplant population. A table summarizing key recommendations in this population would be useful.*

According to all specific review-er comments and this general one in all subheadings we have presented more data about published studies results, constraints regarding lack of specific treatment recommendations for PSC/IBD transplant recipients and possible approach until more data will be available. We have stated that this moment patients should be treated based on guidelines for overall IBD population. Based on results form studies on transplanted patients with IBD, we have made some suggestions on approach to specific problems in transplant setting; specificities of transplanted patients due to higher rate of co morbidities, drugs interactions and adverse events, infections, other autoimmune disease (especially PSC), risk of CRC, risk of rejection and contradictory role of immunosuppressive drugs in anti-rejection and IBD treatment. Table summarizing this data is presented in Table 1. Approach to patient in peri-transplant setting is provided in Table 2. At the end we concluded that in this filed more data is needed in order to make specific guidelines and also proposed the way further studies should be performed.

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

Best regards

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