Reviewer: 00189619

Author responses in blue font.

This is a well written comprehensive review of the topic.
Thank you for your kind comments!

Minor comments:
1. The section on MTX treatment for IBD on page 18 (lines 360-364) should be placed under the RA section (page 13).
We elected to keep the MTX treatment for IBD section with the section on IBD such that the information about MTX mediated risk of LD in IBD patients can be compared with other treatment risk of LD in IBD patients.

2. The following reference should probably be cited: "A Systematic Review of Factors That Contribute to Hepatosplenic T-Cell Lymphoma in Patients With Inflammatory Bowel Disease" KOTLYAR, DS et al. CGH 2011.
This reference has now been included in the MS on page 20 in the section on HSTCL (Line 405-411)

3. Although the authors underscore (in the discussion) the need for more information and studies on IBD-EBV-LPD- it may be useful to add a flow chart/ diagram that suggests a risk stratification and follow up and preferable therapies for IBD patients according to their EBV status. This should be based on the available data presented by the authors regarding IBD and the other lymphoma associated immune disorders.
A great suggestion. Such a flow chart has now been included in the revised MS.

Reviewer: 00055096

Author responses in blue font.

The manuscript analyzes the relationship between EBV infection, lymphoproliferative disorders and the immunosuppressant drugs. Authors utilized the experiences from patients undergoing transplantation and rheumatologic patients trying to translate them in the setting of IBD patients. The paper appears well written and clearly gives the information available in the current literature. Some minor comments.
Thank you for your kind feed back!

1.We know that it is not easy to extrapolate data from different specialties, as demonstrated by the lack of efficacy in IBD by some drugs successfully utilized by rheumatologist. Probably a comment on this aspect could be added in the discussion.
We have now done so on page 21 one lines 422-429.

2. Since the paper is intended as a review, it could be appropriate to also cite data regarding adalimumab (i.e. Ikeda T et al, Mod Rheumatol 2012;22,3:458-62. Shale MJ et al Aliment Pharmacol Ther 2010,31,1:20-34), in that only infliximab is reported as an anti-TNF drugs throughout the manuscript.
We have now included the currently known risk of adalimumab on LD development in both RA (p13-14; lines 261-267) and IBD (p19; lines 368-374).

3. Basicly all the recent guidelines in Gastroenterology consider the importance of EBV in the management of IBD patients undergoing immunosuppression and/or anti-TNF treatment. I wonder whether a brief flow-chart or a summary table could be placed in the manuscript as a final conclusion of the discussion.
Great suggestion! We have done added a treatment algorithm to the MS.

Reviewer: 00189171

Author responses in blue font

Lam et al highlighted the significance of Ebstein Barr virus infection and immunosuppressive agents regarding the development of lymphoproliferative disorders (LPD) in inflammatory bowel diseases. The topic is current, as more and more patients with IBD are treated with immunosuppressant therapy even in combination with biologics. The structure of the manuscript is relevant, the authors summarize the scientific data regarding EBV infection in post-transplantation setting and in other IMID disorders and try to find the similarities and differences compared to IBD patients. Notwithstanding I have some remarks regarding the manuscript.

Authors state that LPD is a consequence of IBD and its treatment (row 80), and later (row91) there is an opposite statement. This discrepancy is dissolved later, but it should clarify in this section also in my opinion.
The sentence in row 91 has been updated to clarify the discrepancy.

Authors use the term "immunosuppressive" very general in the introduction section. It is not clear form me if this nomenclature includes the anti-TNF agents in this section.
The inclusion of biologics in "immunosuppression" has now been further clarified in line 108.

Regarding classical immunosuppressives, I believe that more infrequent use of MTX in IBD compared to RA should be emphasized - while this agent has a cyclosporine, which is an important member of our arsenal in sever UC.
This distinction has now been highlighted in rows 332 and 334-5

Age, as a major risk factor regarding LPD should be also discussed. RA population is older, than IBD population in my best knowledge.
Age is a tricky risk factor to discuss regarding LPD and perhaps is beyond the scope of this review. The reason being those that are older have different risk factors for LPD development (ie: unlikely to be due to EBV seroconversion) and as such develop different types of LPD whereas those that are younger have a higher incidence of being EBV negative and the age at which the normal population show peak seroconvert rates (ie: 3-10 years of age and 18-30 years of age) are thereby more prone to develop EBV-associated LPD.

It is stated that IBD is predisposes to infections (row 278). This statement is expeditious in my opinion; risk factors for having an infection in IBD should be mentioned more detailed.
It is not clear why IBD patients have higher rates of specific infections. As such, the sentence has been edited to merely report this increased rate and that the reason for it remains unclear. (row 281-3)

Authors conclude that there is a significant risk of LPD development from EBV seroconversion while on immunosuppressants in IBD patients based on three case reports. However the message is clear for me, more data are needed to get this conclusion. Anyway, this sentence (in row 321-323) should be reviewed.
The sentence has been edited and an additional comment on how more data is needed has been added.

I'm lacking the data regarding the LPD in patients treated anti-TNF other than infliximab. Is there any data regarding ADA or CZP?
We have now included the currently known risk of adalimumab on LPD development in both RA (p13-14; lines 261-267) and IBD (p19; lines 368-374). We are not aware of any data on CZP in either the RA or IBD literature.

Statement that risk of LPD in IBD is mechanistically is the same than the risk of LPD in RA is unreasonable in my opinion (row 423-424).
This statement has now been edited.
In summary, this manuscript is very interesting and thought-provoking, however some minor change, refinements and complementary data may improve the quality of the paper.
Thank you for the encouraging comments!