

## ESPS PEER-REVIEW REPORT

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

**ESPS manuscript NO:** 17943

**Title:** Immunosuppression And Epstein-Barr Virus Associated-Lymphoproliferative Disorders In Inflammatory Bowel Disease: Lessons From Immunosuppression Use In Other Medical Disorders

**Reviewer's code:** 00189619

**Reviewer's country:** Israel

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2015-03-31 11:38

**Date reviewed:** 2015-04-02 16:08

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ Y ] Grade A: Excellent	[ Y ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ Y ] No	[ Y ] Minor revision
[ ] Grade E: Poor		BPG Search:	[ ] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ Y ] No	

## COMMENTS TO AUTHORS

This is a well written comprehensive review of the topic. 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). 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. 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.

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**Reviewer's code:** 00055096

**Reviewer's country:** Italy

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2015-03-31 11:38

**Date reviewed:** 2015-04-03 16:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

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. 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. 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. 3. Basically 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



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or a summary table could be placed in the manuscript as a final conclusion of the discussion.

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**Reviewer's code:** 00189171

**Reviewer's country:** Hungary

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2015-03-31 11:38

**Date reviewed:** 2015-04-09 02:34

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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## COMMENTS TO AUTHORS

Lam et al highlighted the significance of Epstein 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. Authors use the term "immunosuppressive" very general in the introduction section. It is not clear from me if this nomenclature includes the anti-TNF agents in this section. Regarding classical immunosuppressives, I believe that more infrequent use of MTX in IBD compared to RA should be emphasized - while this



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agent has a cyclosporine, which is an important member of our arsenal in sever UC. Age, as a major risk factor regarding LPD should be also discussed. RA population is older, than IBD population in my best knowledge. 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. 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. I'm lacking the data regarding the LPD in patients treated anti-TNF other than infliximab. Is there any data regarding ADA or CZP? 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). 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.