

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 33443

Title: Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature

Reviewer's code: 02441062

Reviewer's country: Italy

Science editor: Yuan Qi

Date sent for review: 2017-02-21

Date reviewed: 2017-02-23

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" 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
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input 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

It is a very interesting and well done paper. I only have a few comments. 1. the authors discuss the possibility of adding an immunosuppressant drug to therapy with anti-TNF; it would be useful to add a sentence about the possible risks of such an association, with some reference. 2. For some patients, the level of antibodies was measured by the ECLIA method: are reference values for this technique available? Authors should briefly comment on this point.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 33443

Title: Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature

Reviewer's code: 03254146

Reviewer's country: Japan

Science editor: Yuan Qi

Date sent for review: 2017-02-21

Date reviewed: 2017-02-25

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
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

I'm pleased to review the precious editorial entitled "Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature". The authors reviewed literature on therapeutic drug monitoring and overcoming strategy by dose escalation of anti-TNF therapy or addition of an immunomodulator and described their own case series. They concluded that low-level anti-TNF drug antibodies might be overcome by these strategy. Overall this editorial was well arranged and supported by their own experience. Minor points. 1) Are there any predictive factors for resolution of antibody (Eight of the twelve patients (75%)). 2) Page 3, line 28. It is difficult to understand the meaning of "presence of or when bound to drug antibodies(5)" and I read the reference 5, but I could not catch the difference of newer generation assays from old ones. 3) Although the thresholds of titer of ADAs for infliximab and adalimumab are provided, those of low and high of ADAs and the titer of their series were not provided. 4) Please provide approximate cost date for the measurement of anti-TNF and ADAs. 5)

Please refer to the following paper, which indicates no additional effect of IM on adalimumab for CD (J Crohns Colitis. 2016;10:1259-1266). 6) Page 6, line 9. The authors introduced Ben-Horin paper. Please provide adalimumab data including no previous data if so. 7) Page 6, line 27. "addition or " may be replaced to "addition of". 8) Page 6, line 33. Please provide the range of ages of the patients. 9) Page 7, line 7-11. Please provide the ranges of concentrations of antibodies. 10) Page 7, line 19. Please provide the patients' concern about side effects in detail. 11) Table 2. Please explain ? and ? at the bottom (abbreviation part) and provide sex and age data of the patients. 12) Please provide the authors' opinion on the de-escalation of anti-TNF or the discontinuation of IM after the resolution of ADAs and the enough increase of anti-TNF concentration. 13) Although this study is retrospective and need no informed consent by the patients, their institutional review (review board or ethics committee) should be done.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 33443

Title: Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature

Reviewer's code: 03658316

Reviewer's country: Italy

Science editor: Yuan Qi

Date sent for review: 2017-02-21

Date reviewed: 2017-02-26

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

COMMENTS TO AUTHORS

Discussion seems in part superficial or incomplete in some sections, leaving some outstanding issues. I suggest to analyze some topics: 1. Discuss risk factors that increase the immunogenicity and subsequent formation of ADAs (e.g. : Billiet et al. Immunogenicity to infliximab is associated with HLADRB1. Gut. 2015). 2. Examine literature data on the role of immunomodulators in patients treated with adalimumab, differentiating them by patients treated with infliximab (e.g.: Matsumoto et al. Adalimumab monotherapy and in combination with azathioprine for Crohn's disease: a prospective, randomized trial. 2016; Colombel et al. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. 2017). Moreover, given the number of patients in the case series, I suggest to implement "table 2" with additional data (eventually, I suggest to draw up two tables, one with the demographic and disease characteristics for each patient): - Indicate for each patient age,



BAISHIDENG PUBLISHING GROUP INC

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>

gender, disease duration, extent of disease according to the Montreal classification, smoking status; - Indicate for each patient how long was treated with anti-TNF prior to treatment failure and if prior to anti-TNF they were treated with immunomodulator; - Indicate for patients 4-6-8-12 when they started therapy with immunomodulators (prior to therapy with anti-TNF, in conjunction with anti-TNF beginning, etc); - Indicate how long time was maintained clinical response from the moment it has been optimized treatment with anti-TNF (if they still retain, how long you keep it at the end of the assessment - October 2016)

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 33443

Title: Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature

Reviewer's code: 02998238

Reviewer's country: Canada

Science editor: Yuan Qi

Date sent for review: 2017-02-21

Date reviewed: 2017-02-28

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

General Comments: Overall, these authors aim to review the literature on the use of TDM to overcome drug antibodies and show a 12 case series of how this was effective. However, the literature review and the case series do not complement each other. Furthermore, they do not report the individual levels found in these 12 patients or exactly what dose escalation strategy was used. Specific Recommendations: a) Major – - The literature review is too long and lacks a message – it would be better to focus on the case series - Table 1 – need to add several columns – dose/interval pre-levels, and new dose/interval, TDM levels, antibodies pre and post dose escalation – just reporting the median levels does not help us interpret the data. - The way the data is reported, we can only see that these 12 subjects had symptoms and were dose escalated and then some got better (and these were all the ones that the authors report resolved their antibodies....) We need to see if the levels or the dosing/interval can help distinguish those that resolved antibodies and those that did not. b) Minor – - Main text pg 1 -



BAISHIDENG PUBLISHING GROUP INC

7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>

Stated that "it is generally thought, --- needs reference - Main text pg 1 - dose identification? Do you mean intensification?

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Pharmacology and Therapeutics

Manuscript NO: 33443

Title: Strategies for Overcoming Drug Antibodies in IBD: Case Series and Review of Literature

Reviewer's code: 00034489

Reviewer's country: Japan

Science editor: Yuan Qi

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Date reviewed: 2017-03-04

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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		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors review the anti TNF antibodies for IBD from an antidrug antibodies' perspective and show a case series of their institution. The review is well written. There are only a few concerns with regards to the paper. 1) The title is just a little ditzy. "Drug antibodies" should be changed to "anti TNF antibodies etc.". 2) I think case series in authors' institution is inappropriate for Editorial. It is better to delete the case series in the paper.