RESPONSE LETTER FOR REVISIONS

Reviewed by 00034489

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.

- The title was changed to say "anti-TNF antibodies" rather than "drug antibodies," as per the reviewers' recommendations; however, this may exceed the word limit for the title (14 words instead of 12).
- We added additional details to the case series and also implemented some changes in the case series recommended by the other reviewers (see below). We feel that the review flows better into the case series, but do feel that inclusion of the case series is appropriate.

Reviewed by 02998238

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

- Main text page 1 – we changed "identification" to "intensification" and also added the reference for this statement
- With regard to adding more detail to the case series, we added additional columns to the table (now entitled table 3) as recommended above so that

the pre and post drug levels are available for review. We also added additional baseline patient characteristics (table 2) as recommended by another reviewer. Hopefully, this added detail will allow for the review and case series to flow better together. We also added an additional paragraph to the conclusion to better tie the review and case series together

Reviewed by 03658316

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, 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)

- We added additional information regarding factors predictive of immunogenicity, as recommended

- Reviewed the Matsumoto paper; this shows that efficacy of ADA vs. ADA + immunomodulator is no different in patients with Crohn's. The study did exclude patients who had been on prior anti-TNF, which is not true of our study and is an important distinction, as many of our patients had prior exposure to anti-TNF which may have contributed to development of immunogenicity/drug antibodies. Additionally, as our paper is discussing therapeutic drug monitoring and formation of drug antibodies, we feel that the conclusions our this paper are outside of the scope of our brief review. Additionally, the study did show a trend toward lower levels of antibodies to ADA in the combination therapy group which supports findings of other studies cited in our paper
- We added an additional table with the patient data as recommended

Reviewed by 03254146

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.

- There were no clear predictive factors in the 25% of patients who did not have resolution of ADAs. All four of these patients had CD rather than UC, so this was noted in the paper though significance is unknown given small sample size
- We changed the wording of sentence on page 3, line 28 to be more clear
- With regard to differences between old vs. new drug level assays, this was actually referenced from source 4 (not 5) therefore we fixed the citation
- With regard to low vs. high titers of ADA, we included clinically significant cutoffs as described under the section "anti-drug antibodies"; however, a definition for low level of drug antibodies has not been clearly defined therefore remains subjective at this point, which we state in the case series portion of the paper. The addition of the ADA levels into table 3 helps to specify the levels in our study
- In the case series portion, we added our own experience as far as cost. It is difficult to find costs listed/cited in any published studies or reviews, based on our search
- With regard to the *Journal of Crohn's and Colitis* paper referred to above, we reviewed this paper by Matsumoto et al; this shows that efficacy of ADA vs. ADA + immunomodulator are no different in pts with Crohn's. As stated in the comments to the previous reviewer, we felt that the findings of this study were outside the scope of our brief review, and additionally, the study did show a trend toward lower levels of antibodies to ADA in the combination therapy group which supports findings of other studies cited in our paper
- Clarified that the Ben-horin study did not include ADA patients (only IFX)
- Changed "addition or" to "addition of" (this was a typo)
- We provided the age range of patients, as recommended
- We provided the ranges of ADA levels in table 3, as recommended
- In our experience, patient concern regarding side effects of immunomodulator therapy generally includes lymphoma/cancer risk, infection risk, amongst other risks but as the exact concern regarding side effect was not always clearly documented in the chart of the patients

included in this case series; therefore, we cannot comment with regard to these specific patients

- We added age/sex data along with additional patient characteristics in table 2
- The authors typically do not de-escalate anti-TNF dosing or discontinue immunomodulator therapy in patients in who overcome drug antibodies given concern for re-developing antibodies. We added a statement reflecting this opinion
- Approval for the data collection and study was approved by our institution's IRB

Reviewed by 00009292

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.

- We added reference values for the antibody levels, as recommended
- We cited a meta analysis from *Clinical Gastroenterology and Hepatology* 2015, which found no significant difference adverse events for combination therapy vs. monotherapy (added a statement about this)