Author’s response to reviews

Title: Optimizing biologic treatment in IBD: objective measures, but when, how and how often?

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Reviewer #1: The authors Shomron Ben-Horin et al. submitted a fine and exhaustive review about the use of laboratory and imaging markers in assessing patients with inflammatory bowel diseases. They cover the area by looking at the following situations:

- before and during induction phase
- after induction
- at loss of response
- before and after stopping therapy
- role of endoscopy for optimizing treatment

I only have very few comments:

1. In the section "before and during induction phase" the authors give an exhaustive review on the role of CRP. They should also discuss the role of fecal calprotection and abdominal ultrasound in this situation. In countries where ultrasound is routinely used by gastroenterologists themselves at the bedside, e.g. Italy, Switzerland, or Germany, this technology proved to be excellent for verifying inflammation without relying on more invasive or complex imaging modalities, i.e. endoscopy or MRI, especially in terminal ileitis, where calprotectin is often false negative.

R1: We have added information about role of fecal calprotectin and abdominal ultrasound as per the reviewer’s request, as follows:

Thickened bowel wall and increased blood perfusion are typical features of inflammation and can be assessed by bowel ultrasound, which could be used as a simple and non-invasive technique for monitoring and optimizing the biological treatment. In a study of 24 consecutive patients receiving biological therapy, sonographic changes including reduction in the thickness
of the bowel wall and Doppler blood flow were significantly more marked in Crohn's patients who achieved clinical-biological response, compared to those patients who did not respond to treatment (Dig Dis Sci. 2010 Feb;55(2):404-10). In another prospective longitudinal study of 30 patients receiving immunomodulators and/or biological treatment, 18 (60%) patients exhibited endoscopic remission (CDEIS <6 points); of these patients, 15 (83.3%) had normalized sonographic findings, with a good correlation between endoscopic remission and sonographic normalization (κ=0.73, p<0.001) (J Crohns Colitis. 2014 Sep;8(9):1079-87). Transmural healing evaluated by bowel ultrasound can be achieved in 17 of 66 patients with CD treated with anti-TNF-[alpha] agents and significantly correlates with MH. (Inflamm Bowel Dis. 2013 Aug;19(9):1928-34).

Fecal calprotectin (FC) has been shown to be useful in predicting relapse of quiescent IBD patients (Inflamm Bowel Dis. 2012 Oct;18(10):1894-9). In a prospective study of UC patients on IFX, baseline FC was not associated with risk of relapse, whereas two consecutive FC>300 mg/kg had 100% specificity for relapse (Inflamm Bowel Dis. 2013 Sep;19(10):2111-7). In another prospective study of UC patients in clinical and endoscopic remission, FC>100 had 65% of specificity and 88% of NPV for relapse in 3 months, while FC>250 had 85% specificity, 88% NPV for relapse in 3 months (Inflamm Bowel Dis. 2014 Jul;20(7):1187-93).

2. At the end of the section about therapeutic drug monitoring the authors give a caveat about this method: optimal thresholds need to be established. The authors mention themselves that "patients with adequate drug levels and active inflammation will USUALLY respond better to switch to another class of drugs". Relying to heavily on these algorithms might miss a few patients in whom a higher drug level will lead to clinical response therby unnecessarily foregoing one of the few drugs that exist for Crohn's disease. I feel the authors need to discuss this caveat too.

R2: We absolutely agree with the reviewer that some patients with ‘adequate’ drug levels may nevertheless prove to respond to intensified dose (and even higher drug concentrations). However, this is true for any biologic or pharmacokinetic diagnostic parameter (levels of cyclosporine, ‘normal’ CRP value, etc.), as no parameter is perfect with AUC of ROC of 1, to be 100% correct about distinguishing two diagnoses or guiding between two interventions with 100% accuracy. Nonetheless, in light of the reviewer’s comment, we further underscored now in the text that "patients with adequate drug levels and active inflammation will usually respond better to switch to another class of drugs. However, in selected cases, optimizing the anti-TNF class may sometimes still be warranted for individual patients who may require higher concentrations for response especially if they have exhausted other therapeutic modalities".
3. In discussing the role of mucosal healing the authors will have to mention the POCER study and the role of endoscopy in optimizing post-operative treatment.

R3: We have added information about POCER study and role of endoscopy in optimizing post-operative treatment as per the reviewer’s request, as follows:

In the randomised postoperative Crohn’s endoscopic recurrence (POCER) trial, 177 consecutive patients with Crohn’s disease undergoing intestinal resection of all macroscopic disease received standard prophylactic treatment with metronidazole and thiopurine, the later given to patients with high-risk features. Patients were then randomized into parallel groups: colonoscopy at 6 months (active care group, 122 patients) or no colonoscopy (standard care group, 52 patients). In the case of endoscopic recurrence (Rutgeerts score ≥i2) at 6 months, patients in active group stepped-up to thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab. The trial demonstrated that endoscopic recurrence at 18 months occurred in 60 (49%) patients in the active care group and 35 (67%) patients in the standard care group (p=0.03). Complete mucosal normality was maintained in 27 (22%) patients in the active care group versus four (8%) in the standard care group (p=0.03). This suggests that treatment according to clinical risk of recurrence coupled with early colonoscopy could play important role in optimizing post-operative treatment (Lancet2015; 385: 1406–17).