Dear reviewers,

Thank you for your comments which greatly contributed to the improvement of the article and its comprehension for future readers.
The corrections were made in the original article, but you can also find them below, in this letter.

Hoping to have met your expectations,
Best regards,

Laura Sirmai

Reviewer#1->answer

Specific Comments to Authors: Overall the manuscript is well prepared and provides useful clinical information. The main manuscript imperfection is the ADA concentration measuring because its time point was not the same through the centers. Some centers had performed ADA concentration measurements during induction, while others – during treatment. This circumstance undoubtedly influences the ADA values. To ensure that it is the ADA concentration and not the duration of treatment that affects PAFs remission, I suggest supplementing the study with regression analysis. It will strengthen the conclusions of this study.

→ As you judiciously propose, we made a regression analysis with adjustment on the duration of treatment. The results remain significant, as following : « *Median serum ADA concentrations were significantly higher in assessment visits of patients in clinical remission than in those not in clinical remission (14 [10–16] vs. 10 [2–15] µg/mL, p = 0.02 after adjustment on the duration of treatment) (Figures 1 and 2).”*

Reviewer#2->answer

Specific Comments to Authors:

– Please avoid ADL concentrations “needed” - it is just association please correct to »associated« or similar - → corrected as requested

– Abstract: »Serum ADA concentrations tended to be higher in patients whose treatment was optimized than in those whose treatment was not optimized (14 [5–16] µg/mL vs. 10 [4–13] µg/mL, p=0.20) and in patients receiving combination therapy than in those receiving ADA alone (12 [5–16] µg/mL vs. 11 [5–14] µg/mL, p=0.11).” – none of the reported comparisons are significant – would suggest to remove from the abstract (can comment in discussion) → corrected as requested

– Abstract: A target concentration that is associated with remission has not yet been determined by a prospective study – this was not studied by the authors – should be removed from the abstract → corrected as requested

– - Please add definitions of outcomes reported in the abstract already in the abstract: i.e. define clinical remission of fistula in the abstract (important to reach broader readership) → corrected as requested

– - Fig 1: please make it clear and self-explanatory (name the axes, remove abbreviations - Fig: the same as for Fig 1. Also add titles: - please change the y axis to

proportions (%) – the number of pts with achieved remission can still be added to the top of the column. - Please work on the figure appearance – → corrected as requested

– Discussion: o You mention no correlation of drug concentration to adverse events – this is important as would enable clinicians to use higher dose of tnf-inhibitors – perhaps you could make and extra paragraph and discuss this in line with other literature on this topic (e.g. infliximab some suggest no link to infections/ DOI: 10.1080/00365521.2018.1486882, DOI: 10.1093/ibd/izy066 …….but others do not: • DOI: 10.1016/j.cgh.2020.03.018)– should deserve a separate paragraph since you stress the safety of high ADL concentrations in both, the first and the last paragraph: → corrected as requested : *«In our study, high serum ADA concentrations was not associated with an increased incidence of adverse events, knowing that we only took into account the serious adverse events leading to a stop of ADA. In the literature, Drobne et al.[33] and Greener et al.[34] studies found that higher infliximab serum concentrations are not associated with a higher frequency of infections. Interestingly, Landemaine et al.[35] study found that infection risk was individually correlated with cumulative increase in drug exposure, but not infliximab trough level."*

– . o 3rd paragraph: you suggest to measure drug concentrations if no remission – but you also suggest that higher concentrations are needed for fistula healing – since the ceiling concentration was not reached I think it is difficult to rely on certain drug level (i.e. we do not have a concentration to target as you conclude –so why measuring drug levels at all (perhaps only to exclude immunogenicity issue) → corrected as requested: *«Serum ADA concentrations have shown considerable variability and overlap between patients with and without clinical remission, as previously described[13]. It is likely that not all patients need to reach these high concentrations. For patients not achieving remission, we suggest measuring serum ADA concentrations and antibodys to exclude immunogenicity issue. Optimizing ADA dosage or adding combination therapy (or both) should be considered, even if we don't have yet a concentration to target."*

– o "We identified a trend but not a significant difference in serum ADA concentrations according to healing status (11 [7–14] µg/mL vs. 10 [4–16] µg/mL, p = 0.69)." – with medians so close and p completely insignificant it is difficult to say that this is trend – I would suggest change this → corrected as requested*: «We found no significant difference in serum ADA concentrations according to healing status (11 [7–14] µg/mL vs. 10 [4–16] µg/mL, p = 0.69). We think the lack of statistical significance is attributable to our small sample size,and our low rate of healing of PAFs, likely due to the accuracy of this robust criteria."*

– (perhaps the ADA concentrations that would associate with this very robust endpoint were not reached with 40 mg weekly dose in this cohort – this could be one explanation for this result (i.e. what do you think about off-label dose of ADL 80mg weekly to reach this more difficult endpoint?)

→ We think that this would be a good recommendation for selected patients (complex PAFs, no remission with 40 mg weekly ...), but our work does not allow us to conclude on this.