Author’s response to reviews

Title: Successful long-term remission through tapering tocilizumab infusions: a single-center prospective study

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Author’s response to reviews:

Dear Editor,

Thank you for your useful comments and suggestions on the structure of our manuscript. We have modified the manuscript accordingly. You will find the corrections highlighted in the manuscript and detailed corrections are listed below point by point:

REVIEWER 1

MAJOR ISSUES

1/ This study analyses only 13 patients; even if the Authors claim that it is only an exploratory study this number is quite small for a common disease like RA.
Response:

As we mentioned in the manuscript, we would like to have included a larger sample of patients in our study. However, given the monocentric nature of the study, carried out over a period of 15 months, we were limited in our recruitment possibilities. In our department, only 30% of a cohort of about 80 patients who had been treated with TCZ for more than 6 months met the inclusion criteria. In particular, the study was limited by finding patients with DAS28 < 2.6, which is consistent with low remission rates highlighted in a recent meta-analysis. There the authors show that only 26.1% of patients on anti-TNF alpha treatment achieve remission after 1 year and for non-anti-TNF alpha biotherapy the remission rate drops to 13.8% (C. Yu. Clin Rheumatol 2019; 38:727-38). The remission rate is even lower when patients with more than one swollen joint using the DAS44 score are excluded. In addition, some patients in our cohort declined to participate because they felt that therapeutic de-escalation entailed too many risks of relapse.

2/ There are at least two studies (Bouman CAM, Tweehuysen L, Haverkort D, van den Ende CH, van der Maas A, den Broeder AA. Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA-a retrospective, exploratory cohort study. Rheumatol Adv Pract. 2018 Apr 12;2(1) and Saiki O, Uda H. Successful extension of tocilizumab infusion intervals from 4 weeks to 6 or 5 weeks in 90% of RA patients with good response to 4-week intervals. Clin Exp Rheumatol. 2017 Jul-Aug;35(4):666-670.) that analyze the possible reduction of the Tocilizumab dose or the extension of the infusion interval.

Response:

As requested, we have taken these two new references into consideration and included them in the discussion section of our manuscript. We also added another paper from Saiki et al (Rheumatol Int. 2018 Dec;38(12):2307-2313. doi: 10.1007/s00296-018-4149-3. Epub 2018 Sep 11. PMID: 30206670) (e.g. Discussion section, page 17, lines 396-403; references 25, 25 and 27)

3/ The absence of significativity in many comparisons between patients with successful long term maintenance and patient with secondary failure is probably due to the low number of the patients recruited. For example, the disease duration, and the previous number of DMARDs appears higher in patients with secondary failure than in patients with successful long term maintenance; the Authors could recruit a higher number of patients to better understand these possible associations.
Response:

We totally agree and we would have liked to increase the number of subjects included, but the recruitment requirements outlined in the answer 1, and the minimum 2-year follow-up period for each patient, would not allow us to complete the current analysis.

4/ At the lines 327-330, the Authors claim that "The risk of relapse could likely be reduced by slowly tapering infusions. Indeed, the relatively quick tapering may be responsible of some relapses observed." However, in the Paper, there is not any evidence supporting these claims.

Response:

Our conclusion is based on our own data as well as the most recent data from the literature. Indeed, three of the five patients (P10, P11, and P12) who had to switch to a new biotherapy showed a flare (Table 2) within 3 months after initiating spacing. Furthermore, Saiki's recent study found that more progressive spacing, initially at 5 weeks and then at 6 weeks, led to good response rates that were maintained at more than 90% (Saiki 2017). Conversely, if TCZ therapy was reduced directly from 4 to 6 weeks, the maintenance of a low activity level was reduced to about 60% (Saiki 2018), all of which support the benefit slowly tapering infusions (e.g. Discussion section, page 18-19, lines 443-458)

MINOR ISSUES

1/ The Authors could use a multivariate analysis instead than comparisons of single variables to analyze the predictors of remission maintenance or flare after tapering.

Response:

As suggested, we conducted a complementary multivariate analysis but no variables were found to be significant due probably to the small sample size in each group. We have added this point in the manuscript (e.g. Results section page 13, lines 287-289).
2/ It is essential to know the type of previous drugs used to treat the patients and not only their number (line 153-154); for example, would be useful to know if the patients were treated with anti-TNF agents or with anti CD20 because the type of previous therapies could correlate with the success of long term maintenance after the extension of dose interval.

Response:

None of the patients in the study had received rituximab treatment before TCZ. It should also be pointed out that the average duration of exposure to TCZ before spacing was 18 months, limiting the impact of a previous therapy on the success of the response to spacing. We have specified this in the manuscript (e.g. Results section, page 9, lines 188-189).

3/ A native English speaker must correct the Paper.

Response:

The paper had been corrected by a native English speaker.

REVIEWER 2:

In this paper the authors aim to evaluate the long term maintenance of remission after progressive tocilizumab tapering in RA patients. The paper adds some concepts for defining patients eligible for TCZ tapering and potential future strategies in using clinical parameters in predicting the risk for disease relapse after initiation of TCZ tapering are addressed.

The most important features of the study are:

1/ The sample size is small
Response

We agree that the weakness of our study is related to the low number of patients. However, given the monocentric nature of the study, carried out over a period of 15 months, we were limited in our recruitment possibilities. In our department, only 30% of a cohort of about 80 patients who had been treated with TCZ for more than 6 months met the inclusion criteria. In particular, the study was limited by finding patients with DAS28 $\leq$ 2.6, which is consistent with low remission rates highlighted in a recent meta-analysis. There the authors show that only 26.1% of patients on anti-TNF alpha treatment achieve remission after 1 year and for non-anti-TNF alpha biotherapy the remission rate drops to 13.8% (C. Yu. Clin Rheumatol 2019; 38:727-38). The remission rate is even lower when patients with more than one swollen joint using the DAS44 score are excluded. In addition, some patients in our cohort declined to participate because they felt that therapeutic de-escalation entailed too many risks of relapse.

2/ The absence of data about the long-term impacts of these strategies on efficacy, safety and cost.

Response

One of the strengths of our manuscript is the extended follow-up time (2 years), which is unlike most studies published to date. Of course, a longer follow-up period would be better. Moreover, our study was not designed for a medico-economic analysis (cost-effectiveness/ cost-utility/ cost-benefits). Clearly, future studies should address this objective, as in a recent publication comparing therapeutic de-escalation of anti-TNF drugs versus synthetic DMARDs (van Mulligen E et al. Ann Rheum Dis. 2019 Jun;78(6):746-753. doi: 10.1136/annrheumdis-2018-214970. Epub 2019 Apr 6. PMID: 30954969). We added the reference and discussed this point in the discussion section (e.g. Page 16, lines 366-370, reference 24).

3/ However the manuscript is well written and the conclusions are supported.

Response

We really appreciate your support.