Author’s response to reviews

Title: Use of Rituximab in Idiopathic Retroperitoneal Fibrosis

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Author’s response to reviews:

Manuscript entitled "Use of Rituximab in Idiopathic Retroperitoneal Fibrosis" which was submitted to BMC Rheumatology.

Response to reviewers:

We are grateful to the reviewers for their insightful comments and suggestions and thank BMC Rheumatology for the opportunity to re-submit our work. We have responded to each comment made by the reviewers, on a point-by-point basis, and re-state each comment before our response. In addition to responding to the reviewers’ comments, we have added another citation (13) to our manuscript, which reflects a relevant study that has been published since the submission of our manuscript. Discussion of this study was added to the manuscript (Discussion section, page 13, line 7).

T Kuijper, Ph.D. (Reviewer 1):

1) In the results section, it is stated that 4 patients were treated with at least one course of prednisone, 3 of whom continued to use prednisone during the treatment with rituximab.
Did the authors consider to do a sensitivity analysis excluding these patients? Also, it may be of interest to be able to identify these patients in the profile plots to see whether their response profiles differ.

Author Response:

Thank you for your suggestion. Using the Wilcoxon signed rank test, we re-analyzed our data when excluding patients on concurrent prednisone (patients 2, 3, and 7) and found that the axial RPF diameter was still statistically significantly smaller post-rituximab (p=0.35). However, the difference in the craniocaudal RPF was no longer statistically significantly smaller post-rituximab (p=0.1). We have added a sentence to our Figure 1 description to clearly identify the patients who were on concurrent prednisone (Results section, page 9, line 7).

2) The number of patients with ureter involvement and renal stents increased after treatment with rituximab. This seems like an outcome relevant to patients and also somewhat curious given that the retroperitoneal lesions decreased in size. Could rituximab treatment be expected to be effective against urinary tract and renal complications of the disease and had disease simply progressed too far? Or could this be an adverse effect of rituximab treatment? Please elaborate a bit more on this.

Author Response:

Thank you for your insightful comment. The presence of stents was assessed based on the pre-treatment imaging studies, which were often done months prior to the start of treatment with rituximab (mean time pre-rituximab was 6.5 months). Because of this, the reported stent data does not accurately reflect the number of stents that our patients had just prior to treatment with rituximab. Having looked back at the data, the number of ureteral stents did not increase from pre-treatment to post-treatment. Prior to treatment, 2 patients had unilateral stents, 2 patients had bilateral stents, and 6 patients had no stents. Following rituximab, 3 patients had unilateral stents and only 1 patient had bilateral stents, while 6 patients had no stents. Therefore, 1 patient had a stent removed (went from bilateral to unilateral stent) following treatment with rituximab. We believe that rituximab can be effective against renal complications and our re-analyzed data supports this. However, it is likely that the chronicity of the disease caused irreversible renal damage. It is possible some of this damage may have been avoided with earlier successful treatment of the iRPF (we found a moderate relationship between disease duration and response for axial RPF diameter – see response to Reviewer 3, comment 13). We do not believe urinary tract or renal complications are an adverse effect of rituximab itself. Several sentences were added to address this data collection issue (Discussion section, page 13, line 13).

3) For variables known to have a skewed distribution (e.g. most laboratory parameters), a paired non-parametric test (Wilcoxon signed rank test) may be more appropriate and have more statistical power compared to the paired t-test.

Author Response:
We agree with the Reviewer. The data for RPF measurements on imaging (both axial and craniocaudal), GFR, Creatinine, and CRP were graphed and determined not to follow a normal distribution curve, as per your prediction. Given this, we agree that the Wilcoxon signed rank test is a more appropriate test for this statistical analysis. The p values were recalculated using the Wilcoxon signed rank test and were adjusted in the manuscript based on these calculations (Abstract section, page 2, line 21; Abstract section, page 3, lines 3-4; Methods section, page 6, line 21; Results section, page 9, lines 15-16). The p values remained similar to those calculated using the paired t test.

Giacomo Quattrocchio (Reviewer 2):

1) Why did the number of patients with necessity of renal stents increase in spite of treatment?

Author Response:

Thank you for your question. The presence of stents was assessed based on the pre-treatment imaging studies, which were often done months prior to the start of treatment with rituximab (mean time pre-rituximab was 6.5 months). Because of this, the reported stent data does not accurately reflect the number of stents that our patients had just prior to treatment with rituximab. Having looked back at the data, the number of ureteral stents did not increase from pre-treatment to post-treatment. Please see our response to Reviewer 1 in comment 2 for more discussion on this. Several sentences were added to address this data collection issue (Discussion section, page 13, line 13).

2) Why did unilateral ureteral involvement increase in spite of treatment?

Author Response:

Thank you for your comment. As with renal stents, the ureter involvement was assessed based on the pre-treatment imaging studies, which were often done months prior to the start of treatment with rituximab (mean time pre-rituximab was 6.5 months). Because of this, the reported ureter involvement data may not accurately reflect the true extent of ureter involvement patients had prior to treatment with rituximab. Given that the number of renal stents was reduced, as addressed in your previous comment, we suspect the number of ureters involved did not increase, and possibly decreased. Several sentences were added to address this data collection issue (Discussion section, page 13, line 13).

3) Have you performed any 18F-FDG PET CT pre and post rituximab?

Author Response:
Thank you for your comment. At our institution, PET CT is not a modality that is readily available and can only be done through our Cancer Agency. Although PET CT is a useful imaging tool, our patients did not have access to this modality.

Riccardo Capecchi (Reviewer 3):

1) At page 3, line 9 (and also at page 9, line 29) you declare "15.9± 4.9 cm" of RPF diameter around the aorta. Is it correct? Moreover, at line 12 you don't define a measure unit (please specify).

Author Response:

Thank you for your comment. We have corrected the mistake and changed the units to millimeters (Abstract Section, page 3, line 3; Results section, page 9, lines 14, 16). The units have also been defined where previously missing (Abstract Section, page 3, line 4).

2) At page 5, line 38 you affirm that "patients with clinical, serologic or pathologic evidence of IgG4-related disease were excluded". What do you mean with "clinical evidence" of IgG4-RD?

Author Response:

Thank you for your comment. On clinical exam, we looked for evidence of sialadenitis, orbital involvement, lymphadenopathy, Reidel thyroiditis, pulmonary involvement or cutaneous nodules. Our primary way to exclude IgG4-related disease and other RPF etiologies was through histopathology (Deshpande, Carruthers, et. al., 2012). New classification criteria for IgG4-related disease suggests that retroperitoneal fibrosis and an elevated IgG4 level is sufficient for diagnosis of IgG4-related disease (Wallace et. al., 2020), but at the time of this manuscript, this was not the standard of care.

3) At page 5, line 54 you declare that one patient refused biopsy. In such case, how can you classify him as an idiopathic retroperitoneal fibrosis? According to Umehara 2012, a diagnosis of IgG4-RD is still possible with a positive biopsy, also with IgG4 lower than 135 mg/dL. Please exclude this patient from your group in order to demonstrate that your findings are still significant.

Author Response:

Thank you for your comment. The patient who declined a biopsy had normal serum IgG4 levels. Using the new classification by Wallace et. al. mentioned in our response to the previous comment, this patient would be excluded from an IgG4 diagnosis based on this. Furthermore, this patient had no evidence of extra-organ involvement suggestive of IgG4-related disease. For thoroughness, we completed statistical analysis excluding the patient without a biopsy, and the
reduction in both the axial RPF diameter and craniocaudal RPF measurements remained statistically significant (p=0.01, p=0.035, respectively).

4) Did your expert pathologist perform EBER in situ hybridization for EBV or research for ALK rearrangement?

Author Response:

These tests were not performed as part of our study. However, further research into the use of these tests is promising (Takeuchi et.al., 2014).

5) At page 6, line 33 you wrote that all 10 patients were previously treated with rituximab as part of their routine care. How do you justify the choose of rituximab as therapy in "routine care"? Did they fail other treatments?

Author Response:

Thank you for your comment. To our knowledge, there are no randomized control trials showing benefit from DMARDs in the treatment of retroperitoneal fibrosis. Therefore, the choice of a steroid-sparing agent is part of routine clinical care. Many patients in our study had contraindications to prednisone where the risk of serious side effects was too great.

6) In the table 1, IgG4 baseline range suggest that one or more patients present basal IgG4 level higher than 135 mg/dL. This could identify a subpopulation of IgG4-RD patients with negative biopsy for various reasons (e.g. residual fibrosis, nonuniform infiltrate, older lesions, post-steroid modifications etc). How these patients respond to rituximab in comparison with the others?

Author Response:

Thank you for your comment. The one patient (patient 9) who had an elevated IgG4 level had a biopsy that was not consistent with IgG4-related disease. Serum IgG4 levels have a sensitivity of 90% but a specificity of 60%, with a positive predictive value of only 34% (Carruthers et.al., 2015). We used the now outdated IgG4-related disease criteria to classify this patient as idiopathic (Deshpande, Carruthers, et.al., 2012). We have added several sentences to the manuscript addressing the new classification criteria that have been recently released by Wallace et. al.in January 2020 (Discussion section, page, 15 line 12; Citations section, page 20, line 17).

7) At page 8, line 17 you declare that 4 patients were treated with at least one course of prednisone. Please include the mean dose (daily dose and total dose). Similarly, include mean daily dose of prednisone for the patients still on treatment with steroid. Moreover, did you use bolus steroid during infusion protocol of rituximab?

Author Response:
Thank you for your comment. The chart was reviewed to assess prednisone doses. The precise dose collection was difficult given previous records indicating exact start and stop dates were not available for all patients. There was variable use of prednisone, as indicated in the manuscript. The 3 patients who were on concurrent prednisone at time of rituximab treatment had the following doses: 20mg daily, 12.5mg daily, and 10mg daily. This study did not aim to assess patient response to prednisone, and further study of precise prednisone dosing for this patient population is required. As part of the rituximab infusion protocol, patients were given 50mg of oral prednisone prior to the rituximab infusion.

8) 3 patients were on azathioprine. Please specify dose and duration of the treatment.

Author Response:

Thank you for your comment. All 3 patients were started on azathioprine 50mg for 2 weeks, followed by azathioprine 100mg if tolerated. Patients 2 and 3 were on azathioprine for approximately 5 weeks. Patient 7 was on azathioprine for approximately 6 weeks. All 3 patients were unable to tolerate this treatment due to side effects which included transaminitis, pruritis, and nausea with emesis. A comment on azathioprine dosing was added to the manuscript (Results section, page 8, line 8).

9) Page 9, line 21: please define a mean interval between pre-rituximab and post-rituximab imaging.

Author Response:

Thank you for your helpful suggestion. The mean interval between pre-rituximab imaging and treatment was 6.5 months. The mean interval between treatment and post-rituximab imaging was 5 months. These intervals have been added to the manuscript (Results section, page 9, line 18).

10) The relatively high proportion (50%) of renal atrophy pre-rituximab could justify the limited reduction of creatinine after the treatment. Please comment.

Author Response:

Thank you for your comment. We agree that the relatively high proportion of renal atrophy pre-rituximab could explain the limited reduction of creatinine after the treatment. In addition, further renal deterioration occurred in the timeframe between pre-rituximab imaging to the time of treatment, as most pre-RTX imaging was months prior to treatment. Please see our response to comment 2 by reviewer 1 for further commentary on this.

11) Ureteral stenting was performed in at least 3 cases after rituximab. EGF and creatinine post-rituximab reported are pre- or post-stenting? Please specify in the paper.

Author Response:
Thank you for your comment. The GFR and creatinine reported were post-stenting, as all stents were placed prior to patient treatment. Please see our response to comment 2 by reviewer 1 for further commentary on this. A sentence was added to address the stenting data discrepancy, which should clarify the reported GFR and creatinine (Discussion section, page 13, line 13).

12) Page 12, line 22: what type of premedication taked the patient with rituximab allergy?

Author Response:

Thank you for your question. Only two patients had an allergic reaction during their infusion, but this was quickly mitigated with diphenhydramine 50mg IV and both patients were able to complete treatment. The patient who developed a more severe reaction initially took prednisone 50mg orally in the evening prior to first infusion. During the infusion, the patient received diphenhydramine 50mg IV over 2-3 minutes followed by hydrocortisone 100mg IV to mitigate the allergic reaction. Prior to the second infusion, the patient took the prednisone 50mg orally in the morning prior to infusion (instead of in the evening) and was then able to tolerate the infusion well. Clarification was added to the manuscript (Discussion section, page 15, line 3).

13) Please verify if a shorter disease duration pre-rituximab is associated to a better response to treatment (e.g. thickening reduced, creatinine, etc).

Author Response:

Thank you for your suggestion. We performed a Spearman analysis to determine the relationship between disease duration and response to rituximab. There was a moderate correlation between greater percent reduction of RPF in the axial plane and shorter disease duration prior to treatment with rituximab (Spearman’s coefficient = 0.58), and a weak correlation between greater percent reduction of RPF in the craniocaudal plane and shorter disease duration prior to rituximab (Spearman’s coefficient = 0.25). These results have been added to the manuscript (Results section, page 11, line 20).