Author’s response to reviews

Title: Adverse Infusion Reactions to Rituximab in Systemic Lupus Erythematosus: A Retrospective analysis

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Dear Editor and Reviewers,

Thank you very much for your kind, diligent and thorough review of our manuscript, which have helped improve it. We have studied your comments carefully and made corrections, which we trust will meet with your approval. Please see each comment addressed in turn below.

Shereen Oon (Reviewer 1):

Table 4 - in text, two of three patients who were retreated had further reaction - according to table, only one is listed, can the other patient data be added to the table?
Thank you for pointing this out. The data has been added to the table page 17 Line 3 (in bold).
Table 5 - could you include further detail on how proposed mechanism was determined as unlikely/likely due to cytokine release vs likely Ig mediated, given that clinically they can be difficult to distinguish?
We agree with the reviewer that the mechanism of infusion reactions, even at the time of the reaction, can be difficult to determine and more so on retrospective review. We used terms such as “unlikely/likely” to indicate the uncertainty regarding this dilemma. The Allergist who retrospectively evaluated these reactions used her clinical experience of 15 years of direct drug, including biologics, challenges in order to estimate the likelihood of these categories. And although these mechanisms cannot be confirmed with absolute certainty, there are certain features of infusion reactions that point towards one mechanism rather than another. Features such as: isolated skin flushing, patient tolerating
the rest of the infusion following simple measures such as infusion rate reduction or treatment with paracetamol and/or antihistamine were considered to be more likely a result of cytokine release rather than allergic reaction. However, combination of any of the following: shortness of breath, skin rash, vomiting, wheezing, +/- recurrence of symptoms on restarting the infusion at the lower rate lead to the assumption of likely immune-mediated reaction. We added the following paragraph to the manuscript page 7, line 2 to explain this.

“To differentiate between likely cytokine release and likely immunoglobulin mediated reactions, we used the following criteria: the timing of the onset of the reaction, signs and symptoms (skin flushing and nonspecific symptoms v. combination of signs/symptoms involving at least two body systems), response to treatment (able to continue infusion following rate reduction or simple treatment v. recurrence/deterioration of symptoms on continuation) and finally treatment used to terminate the reaction.”

There are a few minor editing errors throughout e.g. page 5, line 5; page 7, line 45. Both amended at corresponding places in text with tracked changes.

Consider embedding reference to tables with the corresponding sentence e.g. 'We then went on to classify the reaction by proposed mechanism…(Table 5)'

This has been amended with tracked changes in the document.

Laura Ross (Reviewer 2):

The manuscript would be improved if the statistical significance of the differences between the patient characteristics in the no reaction vs IR groups were presented. It is difficult to draw conclusions about the differences in these patient populations with only numerical differences are presented. There is one p value presented in the discussion section, this should be in the Results section and the p-values for the differences should be presented as an extra column in table 1. The statistical test used to compare each group should be stated in the Methods section.

A column has been added to the table to illustrate that the proportion of male patients in the reaction group is the only significant variable. See bolded text in table 1 page 16. See also text line 14 page 7.

Also, it is unclear what 1 2 3 4 ENA refers to in Table 1.

Apologies, Line 23 of table 1, page 16 explanation added to table.

It would be useful to know what other concurrent medications patients were receiving and whether this had any effect on IR. This is particularly relevant for cyclophosphamide which was given as per institutional protocol for some of the time reviewed in this study. Was there a difference in the number of IR in patients receiving cyclophosphamide? Did this increase or decrease the rates of RTX IR? Reference is made within the text to some reactions being excluded from analysis because of concurrent administration of cyclophosphamide. How many infusions included in the analyses were co-administered with cyclophosphamide and RTX?

Unfortunately the data on concurrent medications was not available for analysis. However, the protocol for care is to continue oral steroids and hydroxychloroquine and stop other immunosuppressive medications before being started on rituximab. There is no expected difference between groups. Line 13 page 6 added text to reflect this.

Cyclophosphamide 750mg iv infusion was given the day after both rituximab infusions in the initial protocols (pre 2007). Following this it was clinical discretion. Unfortunately though the data is not available to make accurate inferences about the influence of cyclophosphamide on the rate of infusion reactions. We are hoping to explore this in our planned prospective study. Only one reaction was excluded from the analysis of the cause (the death) as the timing of her severe Acute Respiratory
Distress Syndrome (ARDS) was during the administration of the cyclophosphamide. Given this, the treating team attributed this as the cause. Given this is a retrospective review the clinical decisions of the treating team were taken into consideration.

How was it determined which infusions co-administered with cyclophosphamide were to be excluded? Given this is a retrospective analysis of IR, including delayed reactions, attribution of IR is difficult, particularly when a drug is co-administered with cyclophosphamide given its high toxicity. Apologies if this was misleading, no patients were excluded from analysis. The only patient who did not have a proposed mechanism of the infusion reaction (Table 5) was the patient who died during the cyclophosphamide infusion. Text reworded to below: page 8 line 24.

“Several of these reactions were unable to be assessed due to lack of clinical information, the reaction probably due to cyclophosphamide was excluded from analysis.”

Also, the one death in your study is variably referred to as a complication of cyclophosphamide therapy and a RTX IR. If this was thought due to cyclophosphamide, why was this included in table 3 listing the severity of RTX IR?

This was listed as although it was not felt to be due to RTX is it important to record all outcomes for the patients and include them in the table. An important outcome such as death should not be excluded. Can a comment be made about the treatment response to these patients given RTX?

Reference is made to 50% of patients with IR being not treated with further RTX for an unknown reason, could this be because they responded to RTX and didn't require any further therapy? A response rate of 50% would be consistent with the response rate for treatment with RTX from your centre quoted elsewhere in the paper. Further discussion added line 11 and 13 page 9.

It is worth commenting on the observation that whilst a high number of patients who had a RTX IR were not re-treated, numerically, the patients who experienced an IR received the same number of cycles of RTX as those who had no reaction, from Table 1. Further discussion added page 10 line 21-24.

What was the compliance with pre-medications?

Pre-medications were universally prescribed as part of the protocol. We are not aware of any patients having had rituximab without the premedication, consisting of iv methylprednisolone, an anti-histamine and oral paracetamol.

Did this have an effect on IR rates? Please see above.

Is it possible to obtain this information from the electronic medical records reviewed for this study? Unfortunately the medication records are not electronic.

Patients were most likely to have an IR with their 2nd infusion, could this be in part attributable to the faster infusion rates used for the second RTX infusion?

The infusion rates given to the patients in this study is slower that the current accepted care of rapid infusion rate of RTX, these studies have shown that if the first infusion is tolerated then there is no significant increase in rate of adverse events with a faster rate than in our retrospective study, therefore not explaining the phenomenon that we have seen (1).

It would be useful to quote the infusion reaction rates for other rheumatological conditions such as RA and ANCA vasculitis. How significant is the difference between the IR noted in this study compared to the published data in other rheumatological conditions?

Discussion expanded in text added to page 9 line 13.

This rate is similar to published IR rates in SLE (5) however in a small study looking at the safety of rapid infusion of rituximab the quoted rates of reaction was overall 18.5%, highest in RA (9.2%) lowest in ANCA associated vasculitis 3.7% (29). In another study 9.4-17.5% is quoted for autoimmune diseases (comprising of RA, sjögrens and ITP)(30).
Can a comment be made about why the IR rate was so much higher in this study compared to the cohort study from your centre quoted in your paper (17.6% vs 6.1%)? There has been the addition of further patients compared to the previous study at the same centre, in addition, the methodology of our study required the further examination of the infusion itself perhaps with greater sensitivity for mild infusion reactions, reflected by the significant number of grade 1 reactions (25%).

We hope the above clarifies and addressed the issues raised. Thank you for taking the time to consider our revised manuscript.

With Kind regards,

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on behalf of the authors - Joanna Lukawska, Geraldine Cambridge David Isenberg & Maria Leandro.

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Bibliography