Author’s response to reviews

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

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Version: 2 Date: 15 May 2019

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15th May 2019

Dear Editor and Reviewers,

Thank you very much for your kind, diligent and thorough review of our manuscript, which have further 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):
Methods: consider adding statistical program used to analyse data page 7 added : “Using GraphPad PRISM version 7”

Table 3: clarify asymp if using abbreviation, amend symptomatic. changed to “Asymptomatic”

If data is available, add detail regarding how many patients received concurrent CYC (per protocol < 2007), and how many received 4 x rituximab infusion.

Cyclophosphamide 750mg iv infusion was given the day after both rituximab infusions in the initial protocols (pre 2007). From 2007 onwards cyclophosphamide was given with rituximab at clinical discretion. Unfortunately though the data are not available to make accurate inferences about the influence of cyclophosphamide on the rate of infusion reactions. We are planning to explore this in our prospective study.
Five patients required more than two doses of RTX to achieve clinical response (2 cycles comprised of 3 infusions and 4 cycles comprised of 4 infusions)."

Table 5: perhaps add comment in text in Results section that most infusion reactions were immediate hypersensitivity and probably immune related (cytokine release and Ig related)

Page 8 Added “immediate reactions were the most common reaction type and were then broadly classified as likely immune mediated and likely non-immune mediated."

Page 9 line 22 - meaning of sentence is unclear - 'This (is?) high…)

reworded paragraph to:
“The 17.6% reaction rate is high when considering that these were all clinically significant reactions with 86.3% of these patients not retreated, compared to 13.9% patients overall who only received one cycle implying that the reactions influenced clinical decisions not to retreat."

Laura Ross (Reviewer 2):
There is a typographical error in line 7, page 7 of the manuscript. 
Apologies. This has been corrected with the language re-edit.

Does the % range quoted in line 18 on page 9 refer to the infusion reaction rate quoted in this paper?
Yes this is correct.

I would consider re-wording the paragraph on page 9 lines 22-27 as the meaning of this paragraph is not entirely clear as currently stated.
“The 17.6% reaction rate is high when considering that these were all clinically significant reactions with 86.3% of these patients not retreated, compared to 13.9% patients overall who only received one cycle implying that the reactions influenced clinical decisions not to retreat."

Consider listing the abbreviations used in each table below to clarify the meaning of acronyms for the reader.
Acronyms used in the tables are expanded in the footer: updated to:
Table 1. NB. “x ENA” refer’s to the number of antibodies to extractible nuclear antigen’s detectable in an individual patient
Table 2 - RTXa first infusion of the cycle, RTXb second, RTXc third and RTXd fourth.

Thank you for your comment in your response to reviewers, it is worth considering adding in the paragraph you have stated in this letter about the difference in infusion reaction rates quoted in the study between this publication and the previous publication from your centre. It will explain to the reader of the manuscript why the IR rates are very different between publications in a cohort of patients from the same treatment centre.

Added page 9 “This is the first time a detailed description of IRR in a consecutive patient cohort has been explored with the addition of further patients since the earlier published safety data. [1]"

PEER REVIEWER ASSESSMENTS:
I apologize for this comment, but the written English is really difficult to follow. I barely understand the design of the study as well as the result and discussion session. I suggest a profound revision of the English Language and Grammar by a native english speaking colleague before resubmitting the
manuscript. I cannot comment on the methodology, results and conclusion without a proper understanding. Happy to review the manuscript again after English Language editing.

Thank you for your feedback. We have undertaken a re-edit of the manuscript with all tracked changes marked in the document. There have been changes in the language used however not in the content of the discussion. We hope that these changes clarify the intent and findings from this study.

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

With Kind regards,

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

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