Author’s response to reviews

Title: Immunoglobulin abnormalities are frequent in patients with lupus nephritis

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Author’s response to reviews:

Dr Savino Sciascia MD PhD
BMC Rheumatology

Dear Dr Sciascia,

Many thanks for the detailed reviewer comments.

We had prepared the article in a short report/concise communication format, as we did not feel that the data justified a full original article. We deliberately restricted the article to 1500 words & 15 references. We were aware that BMC Rheumatology does not have a specific short report format, but were keen for publication in this journal.

We have responded to the Reviewer Comments as follows, our answers are given below each Reviewer comment

Reviewer 1: Thanks for the opportunity of reviewing this study. This, manuscript gives exhaustive evidences about the immunoglobulin abnormalities in lupus nephritis.

This paper adds more informations a still not so clear about immunologic system alteration in SLE. Moreover the conclusions are interesting for clinical practice.

It would be useful to add the protocol of immunoglobulin replacement therapy.
We have added the protocol of immunoglobulin replacement therapy to both the Results (page 4, line 154) and Discussion (page 5 line 229) sections.

Reviewer 2: In this research article, Maria-Jose Cuadrado and co-workers calculated the rates of aberrant immunoglobulin levels in patients with lupus nephritis. I have the following concerns and suggestions.

1. In the Background, the authors make a number of statements without providing references to support them, e.g. that hypogammaglobulinaemia is gaining recognition as a complication following B cell depleting therapy, or that patients with lupus nephritis are likely to "have multiple factors contributing to immunoglobulin abnormalities". Could the authors explain which these factors are and provide the appropriate references?

The multiple factors contributing to immunoglobulin abnormalities have been added to the Background, and appropriate references included (page 2, line 94).

2. What was the aim of the study? There is no clear junction between the Background and the Methods. What is the knowledge gap and what is the question?

The specific aim of the study has been added at the end of the Background section (page 3, line 96).

For the next points 3-7, we do very much appreciate Reviewer 2’s comments. We absolutely agree that in a full original article that points 3-7 are very important, and that responses should definitely be included in the paper. However, as we no longer had the full clinical information, we instead submitted this manuscript in the concise communication/short report format.

3. Please provide a Table with the patient characteristics, including disease duration and activity at the time of nephritis and Ig level testing. Were these cases incident or recurrent nephritides? It is not clear when the Ig testing was performed in relation to the renal biopsy.

Unfortunately, we no longer have this detailed information.

4. It would be informative to provide the readers with the treatment regimens used as induction and maintenance therapies for the patients' nephritides, as well as the ISN/RPS lupus nephritis class and NIH activity and chronicity index scores. E.g. cyclophosphamide is not mentioned in the list of regimens in the Methods, but is discussed in the Results (last sentence). It is not clear to this reviewer when and why cyclophosphamide was used to that specific patient.

We have added a sentence regarding cyclophosphamide, and the use of the EuroLupus protocol (page 3, line 109).
Unfortunately, we no longer have this detailed information regarding the renal biopsy data or specific regimens used for individual patients.

5. What treatment(s) were patients who showed aberrant immunoglobulin levels receiving and for how long? What was the current dose and cumulative exposure to glucocorticoids?

Unfortunately, we no longer have this detailed information regarding the specific treatment regimens and glucocorticoid dosage used for individual patients.

6. Could the authors also provide leukocyte counts (total and different lines), especially in the patients with aberrant Ig levels?

Unfortunately, we no longer have this detailed information regarding the leukocyte counts for individual patients.

7. How many patients of the ones surveyed here received rituximab at a later stage?

Unfortunately, we no longer have this detailed information regarding subsequent rituximab therapy for individual patients.

8. IgG has a molecular mass that is double as high as the one of albumin. How possible (or impossible) is it according to the authors that the association between hypogammaglobulinaemia and nephrotic syndrome is due to IgG losses? In either case, how does Ig monitoring guide the choice of treatment?

We agree that in the majority of nephrotic syndrome patients, immunoglobulin levels are not significantly affected. However in severe patients, there may be urinary Ig loss. This is shown in the Smilek study, and we have added the reference of our own patient whom we reported. Page 4 line 193, Page 4 line 197

9. Again, if post-rituximab hypogammaglobulinaemia is not associated with increased frequencies of infections, why is it important to monitor IgG levels?

We have added a section in the discussion outlining that a significant minority of patients with post-rituximab hypogammaglobulinemia do develop infection (page 4, line 186; page 4, line 208).
10. It is unclear to this reviewer how the authors end up with the recommendation that clinical immunologists (rather than rheumatologists) should assess the suitability for Ig therapy.

We have added a sentence in the discussion to justify this (page 5, line 225).

11. The authors may want to consider revising their article to a Review article summarising current literature on Ig aberrancies.

We are keen to share our immunoglobulin data, rather than a Review article. We have recently published a Systematic Literature Review in this area (now added as Reference 1).

We would be grateful for consideration of our revised manuscript in the Concise Communication format.

With very best wishes

Dr M Y Karim