Author's response to reviews

Title: Serum levels and renal deposition of C1q complement component and its antibodies reflect disease activity of lupus nephritis

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Author's response to reviews: see over
Institute of Nephrology, Peking University First Hospital

Dear Dr. Hayley Henderson,

Re: Serum levels and renal deposition of C1q complement component and its antibodies reflect disease activity of lupus nephritis

MS: 6754618758207509

Thank you very much for your consideration. We had carefully revised our manuscript in accordance with the editors’ and reviewers’ comments. Briefly speaking, the revision included the following issues:

1. The section of Authors’ contribution was added in the revised manuscript and the revised manuscript was conformed to the journal style.
2. Figure 2, Figure 3, Table 2 and 3 was revised and added in the revised version.
3. Kaplan-Meier analysis of renal survival and relapse-free renal survival for our cohort of patients was shown in Figure 3.
4. References to support the hypothesis of an endothelial production of C1q and the immuno-regulatory properties of C1q was cited in the revised version.
5. The cut-off points for the detection of C1q and anti-C1q antibodies, the number of patients with glomerular C1q deposits simultaneously positive or not for anti-C1q antibodies have been provided in the revised version.
6. Patients were divided into two groups according to the cut-off point of levels of C1q. The statistical analysis were revised according to the new group.

Separate point-by-point answers to the reviewers are attached. We would like to submit the revised version of the above manuscript to your journal and hope that it will be suitable for publication.

Yours sincerely,

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Answers to Reviewer #1

1) Tan et al provide valuable information on serum C1q, serum anti-C1q antibodies and renal C1q deposits and their relations with histopathological lesions in a large cohort of patients with lupus nephritis. The manuscript could be more didactic and even more precise on the characterization of this interesting cohort.

Answer: Thank you for your suggestion. More detailed information about the cohort of patients with lupus nephritis was added in the Table 2, Table 3 and revised Figure 1 in the revised manuscript.

2) Figure 1 is not very informative. SLE group should be divided in 2 groups: "anti-C1q positive" and "anti-C1q negative" patients, in addition to the control group. The reader could then compare C1q levels in patients with/without anti-C1q.

Answer: Thank you for your suggestion. Figure 1 was revised as you recommended.

3) Levels of C1q are the lowest in patients with class IV lupus nephritis, and are inversely correlated with renal activity indices, but are not associated with renal outcome. Could the authors discuss this result? If possible, authors could also provide data on the renal outcome of this cohort (Kaplan-Meier analysis of renal survival and relapse-free renal survival) according to C1q level at inclusion. Three groups could be compared: patients with "normal C1q" (> 40
µg/mL), "low C1q" (20-40 µg/mL) and "very low C1q" (<20 µg/mL).

Answer: Thank you for your inquiry. Our study found that the levels of serum C1q were closely associated with clinico-pathological renal active features, but not a risk factor for renal outcomes, which might be explained by the following reason: previous studies found that chronicity index (CI), instead of activity index (AI), was an independent risk factors for progression to ESRD or death in lupus nephritis (Contreras G, et al. Factors associated with poor outcomes in patients with lupus nephritis. Lupus. 2005;14(11):890-5; Singh S, et al. A retrospective analysis of clinical presentation of lupus nephritis. Am J Med Sci. 2011 Dec;342(6):467-73).

Kaplan-Meier analysis of renal survival and relapse-free renal survival, among 3 groups according to C1q level, were added as Figure 3 in the revised paper as you recommended.

4) Could the authors provide references to support the hypothesis of an endothelial production of C1q (discussion section, page 10, line 12)?

Answer: Thank you for your comments. The references were added in the revised manuscript (Bulla R, et al. Decidual endothelial cells express surface-bound C1q as a molecular bridge between endovascular trophoblast and decidual endothelium. Mol immunol. 2008 May;45(9):2629-40; Ghebrehiwet B, et al. The C1q family of proteins: insights into the emerging non-traditional functions. Front Immunol. 2012 Apr 5;3. pii: 52.)
5) *The paragraph on CRP and PTX3 immune complexes (page 10, lines 19-25) is confusing and should be clarified. The ability of PTX3 to bind C1q could be mentioned.*

Answer: Thank you for your inquiry. We are sorry for the unclear presentation. The part of CRP and PTX3 immune complexes was revised and made more clearly in “Discussion”. The ability of PTX3 to bind C1q was also added in the corrected manuscript as you recommended.

6) *Recent literature on the immuno-regulatory properties of C1q in SLE, beyond clearance of immune complexes and apoptotic cells, could be mentioned: C1q limits the differentiation of monocytes into dendritic cells [Son et al, PNAS 2012] and immune complexes-induced production of IFN# by pDC [Lood et al, Ann Rheum Dis 2009], and participates in neutrophil extracellular traps (NETs) clearance [Elkon et al, Curr Opin Immunol 2012]*

Answer: Thank you for your suggestion. The references were added in the “Background” of the revised manuscript as you recommended.
Answer to Reviewer #2

1) *First of all, the cut-off points for the detection of C1q and anti-C1q antibodies have not been provided.*

Answer: Thank you for your inquiry. The cut-off points for the detection of C1q and anti-C1q antibodies were added in “Methods” and “Results” of the revised version as you recommended.

2) *Secondly, it would be much easier to read the paper when the obtained data were organized into tables and/or figures comparing the patients with low and normal levels of C1q, as well as anti-C1q antibodies positive and negative.*

Answer: Thank you for your suggestion. The tables and figures were revised and added as you recommended. (New Table 2, Table 3 and revised Figure 2)

3) *Apart from this, the authors try to convince a reader that the presence of anti-C1q antibodies was associated with the intensity of glomerular deposition of C1q. However, the data supporting this point of view are lacking. Namely, the authors provide the number of patients with vascular and glomerular C1q deposits, but they did not give the numbers of those with glomerular C1q deposits simultaneously positive or not for anti-C1q antibodies.*

Answer: Thank you for your inquiry. The data was added in “Results” of the revised version as you recommended.

4) *It would be advisable for the authors to get in touch with a native speaker to*
correct the grammatical and spelling mistakes in the paper.

Answer: Thank you for your suggestion. Our manuscript has been carefully run a spelling test to correct spelling mistakes and revised with the help of an experienced editor of English journals.
Answer to Reviewer #3

1) Please indicate the line 19 in Page 7. Should the interpunction between the minimum value and the maximum value be comma instead of dash?

Answer: Thank you for your inquiry. We are sorry for the mistake that it should be a comma and it was corrected in the revised manuscript as you recommended.

2) Please summarize Result 2 and 3 into tables or/and figures which will be open-and shut, and present the data which only have P value shown. eg. “including hematuria (P=0.033), neurologic disorder (P=0.028), 23 leukocytopenia (P<0.001), anemia (P<0.001), thrombocytopenia (P=0.017), hypocomplementemia 24 (P<0.001), compared with those without these manifestations in lupus nephritis.”

Answer: Thank you for your suggestion. The results were summarized into tables and revised in the new version of manuscript as you recommended.