Reviewer’s report

Title: Response to Immunosuppressive Therapy in PLA₂R-associated and Non-PLA₂R-associated Idiopathic Membranous Nephropathy: A Retrospective, Multicenter Cohort Study

Version: 0 Date: 15 Mar 2017

Reviewer: Eva Languille

Reviewer's report:

I read with great interest this article proposed to BMC Nephrology. The authors investigated whether PLA2R status on renal biopsy influenced the response to immunosuppressive treatment of idiopathic GEMs. By retrospectively monitoring the follow-up of 91 GEM over 15 months, they looked at their rate of remission under CTX or anti-calcineurins, depending on the PLA2R status on the initial renal biopsy. Remission at 3 months and 6 months was more frequent in PLA2R negative patients than PLA2R positive. They then conclude that PLA2R status on renal biopsy may be a predictor factor of response to immunosuppressive therapy and that PLA2R negative patients respond faster.

I have a few remarks, listed in order of importance:

1 / Major comments:

1) The authors state that 1/3 of the patients received IEC / ARA2 from an average of 1 month before inclusion. It is known that 1/3 of the idiopathic GEMs enter spontaneous remission under IEC / ARA2 after 6 months. Given the short time lag between the onset of IEC / ARA2 and the onset of immune-suppressants (IS), we can imagine that some patients would have remission spontaneously without any immunosuppressant therapy. Can the authors explain this attitude i.e the initiation of immunosuppressive therapy less than 6 months after the beginning of IEC / ARA2 (cf KDIGO) ?

To clarify more, it would be necessary to explicitly state what the T0 of inclusion in the study corresponds to. From what I understand, this is the beginning of the IS treatment (and not the diagnosis of GEM).

It should be interesting, if possible for the authors, to specify the delay between the diagnosis of GEM and the onset of IS treatment.

2) In the stratified analysis, the difference in the remission rate appears in M3 and M6 only for patients under CNIs (and not CTX). What is the hypothesis of the authors to explain this
result? This might suggest that CNIs act on a different antigen from PLA2R, which is already suggested p918 but could be related to CNIS treatment.

3) How long were patients treated on average? It might be interesting to show the reader how the immunosuppressive treatment was conducted: systematized duration for all patients (6 months, 12 months or 15 months) or as a function of remission?

4) Regarding the immunosuppressive treatment: at what time of the treatment are observed the side effects presenting in table 2? How many patients become diabetic or compound their kidney function under CNIs? It could also be interesting to explicit how many patients received tacrolimus and how many CsA. Finally, what were the criteria for choosing the type of the immunosuppressive therapy?

2 / Minor comments by order of appearance in the text:

1) P4l47: Are the targets for Tacrolimus and CsA blood concentrations consistent with residual T0 or T2?

2) P7l1 : There is an error in the text: higher serum creatinine in the "CTX" group and not in CNIs group.

3) P8l21: the authors could compare the study (19) with their results and also show that, like the antibody, the presence of the PLA2R antigen on renal biopsy leads to a more severe nephrotic syndrome (table 1).

4) P8l43: specify that the total remission rate is at "Month 3"

5) In order to attenuate the limit of the low number of PLA2R- patients, the authors could recall that this population is under-represented here compared to the literature: 85% here of PLA2R + whereas in general the PLA2R + GEMs represent rather 75% of idiopathic GEMs (Debiec H, NEJM, 2011)

6) Table 3 : It could be more clear if the authors presenting the main results with a graphic.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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