Author's response to reviews

Title: Validation of the new Classification of Pauci-Immune Glomerulonephritis in a United States cohort and its Correlation with Renal Outcome

Authors:

Carla L Ellis (cellis22@jhmi.edu)
Rebecca L Manno (rmanno2@jhmi.edu)
John P Havill (johnhavill@yahoo.com)
Lorraine C Racusen (lracusen@jhmi.edu)
Duvrruru Geetha (gduvura@jhmi.edu)

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Author's response to reviews:

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Hans-Joachim Anders, Section Editor

BMC Nephrology

SUBJECT: MANUSCRIPT REVISION SUBMISSION FOR THE “ORIGINAL ARTICLE” SECTION

Dear Dr. Anders,

It is with great pleasure that we submit this revised manuscript for your consideration.

We would like to thank you for the opportunity to respond to the Reviewer’s comments and to submit a revised version of the manuscript. This letter includes a point-by-point response to the Reviewer’s comments including changes we made to the manuscript in response to each specific point. We also provide a “Clean” version of the revised manuscript and a “Marked” version. We are grateful for the Reviewer’s suggestions and in response to the recommendations the manuscript has been modified. As a result, the manuscript has been substantially strengthened. We have re-stated the Reviewer’s comments in full before our response.

Reviewer: Guy Neild

Reviewer’s report:

Validation of the new Classification of Pauci-Immune Glomerulonephritis in a United States cohort and its Correlation with Renal Outcome.

This is a single centre audit of the outcome of their patients with pauci-immune glomerulonephritis (1995-2011) according to the recent Histopathologic Classification of ANCA-Associated Glomerulonephritis (JASN 2010).
I found the paper very difficult to understand until I had read the primary paper carefully (Histopathologic Classification of ANCA-Associated Glomerulonephritis).

The problems with this paper are:
1. 18% of patients were ANCA negative compared with 2% in the original paper (although the sums do not quite add up in the original).
2. The ratio of the different categories was quite different in this paper with fewer ‘crescentic’
3. The paper is padded out with detailed information on therapy given to the different groups.
4. The follow up is 1 year versus 5 in the JASN paper.

All that is required with this study is to reproduce the renal survival figure (figure 4 in the JASN paper). In the JASN paper it can be seen at a glance that when the patients are stratified according to the 4 groups they separate out clearly.

It has been known for at least 30 years that if you want to predict the long-term GFR from a biopsy you evaluate the tubulo-interstitial damage. The authors of the JASN paper acknowledge this but do not produce any data (although they have subsequently published a separate paper addressing this (Tubular Lesions Predict Renal Outcome in Antineutrophil Cytoplasmic Antibody–Associated Glomerulonephritis after Rituximab Therapy).

The authors could resubmit a paper that had some genuine novelty and interest if they
1) omitted all the irrelevant therapy information and analysed the tubulo-interstitial damage, and
2) Comparing it with the glomerular analysis and with outcome.

Major Compulsory:

to reproduce the renal survival figure (figure 4 in the JASN paper).

We thank the reviewer for careful review and comments. We have included renal survival figure and have included tubule-interstitial damage in table 2. Since we are reporting one year e-GFR and renal survival, we feel it is important to include details of therapy

Reviewer: Ruth Pepper
Reviewer’s report:
This paper validates the recently described Berden/EUVAS classification of AAV
which was published in 2010. The classification was validated using patients in 2 large multicentre European vasculitis trials, with 1 year follow-up. The patients included a mixture of both MPO-ANCA and PR3-ANCA patients. The Berden ANCA-associated glomerulonephritis classification describes 4 categories: focal, crescentic, mixed and sclerotic. The classification system demonstrated that the different classes correlated with renal outcome, with focal the best renal outcome and sclerotic the least favourable outcome.

The paper by Ellis et al, describes a retrospective cohort of patients from 1995 to 2011 with a diagnosis of pauci-immune glomerulonephritis and a renal biopsy containing at least 10 glomeruli. Similar to Berden et al, patients were followed up for a minimum of 1 year. The majority of patients were ANCA positive although 14 patients were ANCA negative.

Major compulsory revisions

Methods
The patients were included over a time span of 16 years.

1. How many pathologists analysed the renal biopsy samples over this extensive time period?

The original biopsies were read by 3 different pathologists. For the purposes of this study, all biopsies were re-analyzed by a single pathologist blinded to the clinical data and we have included this in the “methods” section of the revised manuscript

Results

2. The number of biopsies in the sclerotic group were small. Additionally, the number of patients with c-ANCA and the sclerosed class is very small with only 1 patient, as well as a small number of patients in the group with pANCA/microscopic polyangiitis and a crescentic glomerulonephritis. Can the numbers be expanded in these 2 groups?

This is a single center study and we have included only patients that had clinical data and minimum of 10 glomeruli. We are unable to increase the sample size for this study

3. Unlike the other classes of GN, a significant number of patients in the sclerotic class had relapsing disease. Can any more information be obtained? Number of renal flares? Previous immunosuppression prior to the relapse described in the paper? Did these patients already have significant scarring on a previous renal biopsy with baseline poor renal function? This point may be particularly relevant considering that none of the sclerotic patients who presented requiring dialysis
were able to discontinue dialysis. In the Berden classification, 1 year renal survival was 50% in the sclerotic class, this paper has a much poorer renal survival.

Although patients had relapsing disease, the biopsies represent the first renal biopsy from all except one patient and these patients had extra-renal disease prior to the biopsy. Due to the retrospective nature of the study, the details of immunosuppressive therapy prior to renal biopsy are not available in all patients and we are unable to provide this information.

4. The immunosuppression that the patients received was very heterogeneous. Four patients (2 in focal, 2 mixed) only received steroids. The majority of patient received similar immunosuppression with steroids and oral cyclophosphamide (52 patients), however, 17 patients had a mixture of steroids plus another immunosuppressant. The 2 patients with sclerotic class of GN who did not receive any treatment unsurprisingly remained on dialysis. Although these patients have a worse renal outcome, the initiation of treatment may stabilise renal function, so any patients not treated should be excluded.

We did not exclude these patients since we wished the manuscript to reflect the practice patterns

5. Renal survival at 1 year was highest in the focal group (90%), followed by mixed (81%) and then crescentic (78%). Could the authors expand on this point? In the Berden paper renal survival was highest in focal, followed by crescentic, mixed and finally sclerotic. Can any more histopathological information regarding the mixed biopsies be obtained? This can be a very heterogenous group, but since the renal survival is better than the Berden paper, can any explanation be obtained?

This survival pattern has been reported in 2 other cohorts, Chinese cohort and recent paper from Netherland and could be due to differences in the percent of normal glomeruli. We have included this information in the “Discussion” section of the revised manuscript

6. It is of interest to investigate whether the Berden classification is applicable to other patient populations/ethnicity. This US based population has a proportion of patients who are African-American. How about the remainder of the patients? More information of the ethnicity of the entire cohort would be interesting.

In this cohort, 82% were Caucasian and remainder African American. This is mentioned in the “Results” section

Discussion

7. The crescentic patients also had the highest death % (17%). This is also in
contrast to the original classification paper in which patients with sclerotic ANCA GN run the highest risk of death. Could any explanation be given for this? Did outcomes improve during the latter period of 1995-2011?
We did not find any differences in the number of deaths in different time periods. In summary, this study broadly agrees that patients with a focal GN have the best renal outlook with sclerotic the worst. The main weakness is regarding the different treatment regimes used over a long time period.

Minor revisions.

Methods
1. Did the assays/commercially available kits used to measure ANCA change over this time period?
The ANCA assays did not change during this time period.

Thank you in advance for your consideration. Please do not hesitate to contact us for any further questions or clarifications.

Sincerely,
Duvuru Geetha, M.D., M.R.C.P. (U.K.)
Assistant Professor of Medicine
Division of Nephrology
Johns Hopkins Bayview Medical Center
Johns Hopkins University School of Medicine