Reviewer's report

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

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Reviewer: Ruth Pepper

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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?

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?

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
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.

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?

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.

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?

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

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests'