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OUTCOMES OF PROTEINASE 3- AND MYELOPEROXIDASE ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY ASSOCIATED VASCULITIS IN DENMARK 2014-2017

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Background and Aims: Anti-neutrophil cytoplasmic antibody associated vasculitis (AAV) defines an uncommon group of autoimmune diseases with antibodies directed against proteinase 3 (PR3) or myeloperoxidase (MPO). Incidence rates of PR3- and MPO-AAV differ geographically, and current evidence based on genetic variations and cluster analyses supports discrimination of associated vasculitis based on PR3- and MPO-positivity. Such discrimination could provide insights of scope for clinical trials with ramifications for improvement of treatment. With the aim of comparing patient characteristics and outcomes between PR3- and MPO-AAV, we report on results from a nationwide retrospective cohort study.

Method: Incident patients positive for PR3- and MPO-anti-neutrophil cytoplasmic antibodies were identified in central laboratories of three of four administrative regions (covering 80% of the population) in Denmark between 1/1-2014 and 31/12-2017. Patient characteristics were identified by cross-referencing of data from multiple national health care registers. Baseline renal function was calculated based on the CKD-EPI equation using plasma creatinine measurements recorded 365 to 7 days prior to index. Incidences of all-cause mortality and end-stage renal disease stratified on baseline eGFR were computed using the Aalen-Johansen estimator. Hazard ratios for specific predictors including strata of baseline eGFR were calculated based on a multiple Cox proportional hazards model adjusted for relevant confounders.

Results: In total 770 patients were included in the study (PR3 n=399 and MPO n=371). Annual incidence rates of PR3- and MPO-AAV were 22.6 and 21.1 per million, respectively. PR3-AAV was associated with greater preponderance for male gender (54.4% vs. 42.3%, p=0.001), lower patient age (61.9 years [IQR 41.6-73.0 years] vs. 64.9 years [IQR 50.0-74.0 years], p=0.016), and greater baseline renal function (eGFR 87 ml/min [IQR 56-101 ml/min] vs. 75 ml/min [IQR 36-92 ml/min] compared with MPO-AAV. Comorbid burden was comparable; 26% of patients had history of hypertension, 15% of patients had a history of ischemic heart disease, and 12% of patients had a history of cancer.

Acute dialysis was initiated in 5.3% and 6.7%, plasmapheresis in 12.8% and 13.7%, and mechanical ventilation in 4.8% and 4.3% of patients with PR3- and MPO-AAV, respectively. Median follow-up was 564 days [234 – 932]. A total of 86 deaths and 25 end-stage renal disease endpoints were recorded during follow-up. Cumulative incidences of all-cause mortality and end-stage renal disease stratified on baseline eGFR are shown in Figure 1.

Adjusted hazard ratios for all-cause death and/or end-stage renal disease showed increased risk associated with PR3-AAV, HR 1.51 (95% CI 1.03 – 2.25, p=0.036), non-European descent, HR 3.63 (95% CI 1.29-10.25, p=0.015) and patient age, HR 1.05 (95% CI 1.03-1.07, p<0.001). In both PR3- and MPO-AAV, only baseline eGFR $\leq$ 20ml/min/1.73m^2 was associated with poorer prognosis (ref.: baseline eGFR >90 ml/min/1.73m^2); MPO-AAV: eGFR 51-90 ml/min/1.73m^2: HR 2.34 (95% CI 0.75 – 7.34, p=0.145), eGFR 21-50 ml/min/1.73m^2: HR 2.11 (95% CI 0.60 – 7.47, p=0.246), and eGFR $\leq$ 20ml/min/1.73m^2: 5.05 (95% CI 1.55 – 16.45, p=0.007); PR3-AAV: eGFR 51-90 ml/min/1.73m^2: HR 1.54 (95%CI 0.53 – 4.46, p=0.427), eGFR 21-50 ml/min/1.73m^2: HR 1.70 (95% CI 0.51 – 5.64, p=0.386), and eGFR $\leq$ 20ml/min/1.73m^2: 8.06 (95% CI 2.83 – 23.0, p=<0.001).

Conclusion: In a nationwide cohort study comparing PR3- and MPO-AAV, PR3-AAV was associated with poorer 24-month outcomes in spite of superior renal function at baseline. Overall, poor prognosis was limited to patients with severe renal insufficiency (eGFR $\leq$20ml/min/1.73m^2) at time of diagnosis in both PR3- and MPO-AAV.

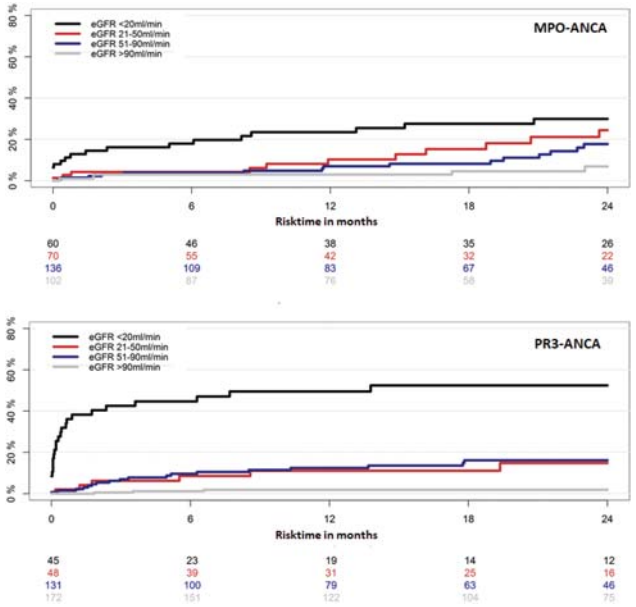

Figure 1: Cumulative incidence of end-stage renal disease and death