A past medical history of autoimmune disease predicts a future with fewer relapses in patients with ANCA-associated vasculitis

S. Lionaki[1], S. Marinaki[2], S. Fragkioudaki[2], I. Bellos[1], E. Kalaitzakis[2], P. Kalogeropoulos[2], G. Liapis[3], A.G. Tzioufas[4], J.N. Boletis[2]

[1]Department of Nephrology, Attikon Hospital, National and Kapodistrian University of Athens; [2]Department of Nephrology and Transplantation Unit, Laiko Hospital, National and Kapodistrian University of Athens; [3]Department of Pathology, Laiko Hospital, National and Kapodistrian University of Athens; [4]Department of Pathophysiology, Laiko Hospital, National and Kapodistrian University of Athens, Greece.

Abstract

Objective

To explore the frequency and impact of an autoimmune disease past-medical history (PMH) in the clinical picture and outcomes of patients with antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV).

Methods

This was a retrospective study of patients with biopsy-proven AAV, >16 years old, with detailed information about their PMH. Outcomes of interest included remission, treatment resistance, relapse, end-stage kidney disease (ESKD), and death.

Results

206 patients with biopsy-proven AAV and available information regarding their PMH were studied. 63(30.6%) of them had a history of autoimmune disease prior to AAV diagnosis. The mean age overall was 54.1 years. One hundred and five patients (51%) were positive for PR3-ANCA, 101 (49%) for MPO-ANCA. Granulomatosis with polyangiitis was diagnosed in 79 (38.3%), microscopic polyangiitis in 97 (47.1%) and renal-limited vasculitis in 30 (14.6%) individuals. Remission rate was similar among patients with and without a PMH of autoimmune disease. Time-to-event analysis indicated that the relapse-free survival was significantly longer in patients with PMH of autoimmune disease (148.2 vs. 61.9 months, p-value <0.001). After adjusting for covariates, autoimmune disease history was associated with significantly lower risk of relapse (HR: 0.33, 95% CI: 0.15-0.72), which remained significant in males, patients ≥60 years old and those with C/PR3-ANCA, kidney and lung involvement.

Conclusion

Patients with a PMH of autoimmune disease, prior to AAV diagnosis, experienced significantly fewer relapses after achievement of remission, compared to patients without such a history, underlining the importance of individualisation of maintenance immunosuppressive therapy, given the different aetiopathogenetic settings the disease was developed.

Key words

pauci-immune, vasculitis, disease-course

Sophia Lionaki, MD
Smaragdi Marinaki, MD
Sophia Fragkioudaki, MD
Ioannis Bellos, MD
Emmanuel Kalaitzakis, MD
Petros Kalogeropoulos, MD
George Liapis, MD
Athanasios G. Tzioufas, MD
John N. Boletis, MD

Please address correspondence to
Sophia Lionaki,
1, Rimini Street
12462 Athens, Greece.
E-mail: sophial@med.uoa.gr

Received on September 2, 2021; accepted in revised form on November 29, 2021.

Competing interests: none declared.

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) is a group of diseases characterised by necrotising vasculitis, absence or paucity of immune deposits, and predominant involvement of small vessels, that is, capillaries, venules, arterioles, and small arteries (1-2). The clinical phenotype of the disease includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (3). The vast majority of patients are positive for antineutrophil cytoplasmic antibodies (ANCAs), which are autoantibodies specific for antigens located in the cytoplasmic granules of neutrophils and lysosomes of monocytes (3) and targeting two major autoantigens *i.e.* myeloperoxidase (MPO) and proteinase 3 (PR3). Beyond its diagnostic importance, clinical, animal model, and in vitro experimental evidence suggests that ANCAs are pathogenic (4). Current knowledge regarding the pathogenesis of AAV, although not complete, has been enhanced significantly through the last two decades, pointing to a multifaceted process involving infections, genetic influences, environmental exposures, and abnormalities of the innate and acquired immune system (5-11). Besides, there are individuals and/or families with a certain propensity to autoimmunity (12), which is reflected in experiencing more than one autoimmune disorder during their life. This phenomenon is believed to be a result of the fact that autoimmune diseases may share a common background, including genetic, hormonal, environmental and immune system defects (12-13). Clinical experience has shown that a proportion of AAV patients report a PMH of another autoimmune disorder at the time of AAV diagnosis. We aimed to explore the frequency of a PMH of autoimmunity in these patients, and its impact, if any, in the clinical picture and treatment outcomes of vasculitis.

Patients and methods

Study population and definitions

Patients with AAV, diagnosed between 1991 and 2019, were studied retrospectively. All included patients were 16 years old or older, had-biopsy proven AAV at any organ/tissue, with available and precise information regarding their PMH prior to diagnosis of vasculitis. Also, included patients were required to have a minimum follow up time of 1 year to be included in the analysis of outcome. Patients with renal involvement were required to have a minimum of ten glomeruli in the diagnostic kidney biopsy to be included in the evaluation of renal histopathology. Accordingly, exclusion criteria were lack of information regarding the PMH, insufficient follow-up data, diagnosis of EGPA, and non-compliance issues. The observation period lasted from the date of AAV diagnosis until end-stage kidney disease (ESKD) *i.e.* initiation of chronic dialysis, or death or the last visit to the nephrology clinic.

All patients were tested for ANCA by immunofluorescence or ELISA (14) or both. Clinical phenotypes of AAV were assigned according to the Chapel Hill vasculitides nomenclature consensus conference (15). Thus, a diagnosis of GPA was defined by the presence of necrotising granulomatous inflammation in any tissue by histopathology, or by documentation of pauci-immune vasculitis at any organ/system in combination with imaging studies showing pulmonary nodules or cavities (non-infectious) and/or bony erosions, and/or subglottic stenosis in the upper respiratory tract (2). Accordingly, EGPA was defined by the presence of the triad asthma, eosinophilia, and necrotising granulomatous inflammation. Microscopic polyangiitis (MPA) was defined by systemic necrotising small-vessel vasculitis without evidence of granulomatous inflammation or asthma (2). Patients with a PMH of autoimmune disease, either organoid or systemic, were grouped together since both types have been associated with AAV in the literature.

Organ involvement of AAV

Organ involvement was defined according to previously described criteria (2); extra renal manifestations of AAV included pulmonary involvement defined by the presence of haemoptysis, pulmonary haemorrhage, respiratory

failure or radiographic proof of infiltrates in the absence of any infectious aetiology. Upper respiratory tract involvement was defined by clinical or radiographic evidence of sinusitis, the presence of ulcers of the nasal passages, with or without epistaxis, or otitis media. Skin vasculitis was inferred when a typical purpuric rash with or without ulceration was present. Gastrointestinal involvement included abdominal pain and/or gastrointestinal bleeding. Neurological involvement included seizures or multifocal neural deficit (2). Patients with upper respiratory tract involvement were not considered to have EGPA if there was no evidence of invasive bony disease or granulomatous inflammation. Involvement of the joints was defined by arthritis. Patients with necrotising granulomatous inflammation at any site, *i.e.* the respiratory tract, nodular or cavitary lesions on chest imaging studies or significant facial bone erosion, or mass lesion in the sinuses were considered to have EGPA.

Table I. Demographics and baseline characteristics of AAV patients with and without a past medical history of autoimmune disease at diagnosis of vasculitis.

Characteristics	Overall (n=206)	Autoimmune PMH (n=63)	No. Autoimmune PMH (n=143)	*p*-value
Age (years)	54.1 ± 16.6	55.6 ± 15.6	55.4 ± 16.9	0.372
Sex (male)	115 (55.8%)	28 (44.4%)	87 (60.8%)	0.042
ANCA type				
C/PR3	105 (51.0%)	26 (41.3%)	79 (55.2%)	0.090
P/MPO	101 (49.0%)	37 (58.7%)	64 (44.8%)	
Clinical phenotype				
Granulomatosis with polyangiitis	79 (38.3%)	17 (27.0%)	62 (43.4%)	0.073
Microscopic polyangiitis	97 (47.1%)	34 (54.0%)	63 (44.1%)	
Renal limited vasculitis	30 (14.6%)	12 (19.0%)	18 (12.5%)	
Organ involvement				
Kidney	158 (76.7%)	52 (82.5%)	106 (74.1%)	0.267
Lung	92 (44.7%)	24 (38.1%)	68 (47.6%)	0.494
Ear, nose & throat	58 (28.2 %)	14 (22.2%)	44 (30.8%)	0.579
Eye	12 (5.8%)	5 (7.9%)	7 (4.9%)	0.320
Skin	51 (24.8%)	9 (14.3%)	42 (29.4%)	0.045
Acute dialysis requirement	22 (10.7%)	11 (17.5%)	11 (7.7%)	0.021
Baseline serum creatinine (mg/dl)	0.8 [0.7-1.0]	0.8 [0.7-1.1]	0.9 [0.7-1.0]	0.990
Serum creatinine at biopsy (mg/dl)	1.9 [1.1-3.9]	2.4 [1.0-4.5]	1.7 [1.2-3.6]	0.465
eGFR at biopsy (ml/min/1.73 m^2)	33.3 [12.8-58.6]	22.4 [11.2-57.1]	34.4 [14.0-58.6]	0.272
BVAS at biopsy	15 [12-20]	14.5 [12-18.5]	15 [12-20]	0.294

PMH: past medical history; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase-3; MPO: myeloperoxidase; eGFR: estimated glomerular filtration rate; BVAS: Birmingham Vasculitis Activity Score.

Treatment for AAV

In patients with GPA or MPA who had organ- or life-threatening disease, an induction regimen consisting of glucocorticoids in combination with cyclophosphamide was initiated. The regimens which were employed included IV cyclophosphamide (0.5–1 g/m^2 body surface area in a monthly basis) or cyclophosphamide orally (1.5–2 mg/kg per day) with appropriate dose reductions made in older adults and patients with impaired kidney function. Therapy was continued until a stable remission was induced, which was typically achieved within three to six months. The white blood cell count was closely monitored (*e.g.* weekly), and the cyclophosphamide dose was adjusted to avoid leukopenia. When using intermittent pulses of cyclophosphamide, we administered either mercaptoethane sulfonate or intensive hydration iv to prevent cystitis. If a rituximab-based regimen was selected,1g of rituximab was administered followed 14 days later by another 1 g dose) or 375 mg/m^2 per week for four weeks was used. Selection of cyclophosphamide *versus* rituximab as induction therapy was based on the severity of the disease as said above. Oral glucocorticoid therapy was typically started at 1 mg/kg per day (maximum of 80 mg/day of oral prednisone) for most patients with organ- or life-threatening disease. Pulses methyl-prednisone (7 mg/kg to a maximum dose of 1000 mg/day for 3 consecutive days) were given to patients presenting with manifestations such as rapidly progressive glomerulonephritis, pulmonary haemorrhage, mononeuritis multiplex, or optic neuritis. Daily oral glucocorticoids were started after the IV therapy. Plasma exchange was applied in patients with pulmonary haemorrhage and/or rapidly progressive glomerulonephritis with acute dialysis initiation around diagnosis. If plasma exchange was used, 6–7 sessions were performed over two weeks (60 mL/kg at each session). Fresh frozen plasma and albumin was used as replacement fluid. For patients with active haemorrhage, the replacement fluid was exclusively fresh frozen plasma. Maintenance therapy consisted of azathioprine (1.5–2 mg per kg of body weight) or mycophenolate mofetil (2 g per day). Patients who experienced more than one relapse received rituximab as maintenance therapy.

Treatment outcome of AAV

Outcomes of interest included treatment resistance, remission, ESKD, relapse and death. Treatment-resistant AAV was defined as a progressive decline in kidney function, with persistently active urine sediment, and/or new or persistent extrarenal vasculitic manifestations or death attributed to active vasculitis despite appropriate therapy (16). Remission was defined as the stabilisation or improvement of kidney function, as measured by serum creatinine levels, with resolution of glomerular haematuria and of all other vasculitic manifestations. Persistent proteinuria with bland urine sediment was not considered indicative of active renal vasculitis. Relapse could only be recorded among patients who had achieved remission and was characterised by recurrent or new signs and symptoms of active vasculitis in any organ (16). Diagnosis of disease relapse was established by histology of the related tissue (skin, kidney, upper respiratory, lung) and exclusion of any

condition that might mimic vasculitic symptoms. Yet, escalation of immunosuppressive therapy was typically associated with significant clinical improvement in relapsing patients. A patient was considered to have a positive PMH of autoimmune disease if he had received the related diagnosis by the associated medical specialty or the primary care physician, based on tissue biopsy, serological findings and/or imaging studies.

Collection of data

Recorded information at diagnosis included clinical, laboratory and serological variables: demographics, clinical phenotype, organ-system involvement, renal indexes *i.e.* serum creatinine, and estimated glomerular filtration rate (eGFR), as well as acute dialysis requirement. Estimated GFR was determined using the four-variable modification of diet in renal disease formula equation (17) and disease activity was estimated using the Birmingham Vasculitis Score (BVAS) (18). Information regarding the type and management of autoimmune disease prior to AAV was requested. This was a retrospective observational study, (no interventions took place), and thus, approval by the ethics or Institutional Animal Care and Use Committee that approved was not required according to the regulations of our institution. All included patients had provided written informed consent for medical chart reviewing.

Evaluation of renal histopathology

Histologic confirmation was based on a kidney, lung, or upper respiratory tract biopsy, consistent with pauci-immune small-vessel vasculitis or glomerulonephritis, with or without granulomatous inflammation. Diagnosis of pauci-immune vasculitis was made by histopathology based on the utilisation of the combined use of light microscopy and immunofluorescence parameters at any tissue and/or by histopathological confirmation of necrotising granulomatous inflammation in any tissue by histology. Histopathological evaluation was performed by an experienced renal pathologist (GL), by review of the data in diagnostic pathology reports, following a detailed scoring system according to the concept presented by Lee *et al.* (19). Specifically, the number of normal glomeruli was presented as a percentage of the total; grade 4 if <10%, 3 if ≥10 <25%, 2 if ≥25% <50%, 1 if ≥50%. Glomerular and tubulointerstitial lesions were scored separately, and as part of the activity index, and chronicity index scores. The activity index score represented the sum of scores from 6 categories: glomerular necrosis, cellular crescents, interstitial leukocyte infiltration, fibrinoid necrosis in vessel walls, red blood cell (RBC) cast, and circumferential crescents. Red blood cell cast (0 for absent, 1 for present). Circumferential crescent (0 for absent

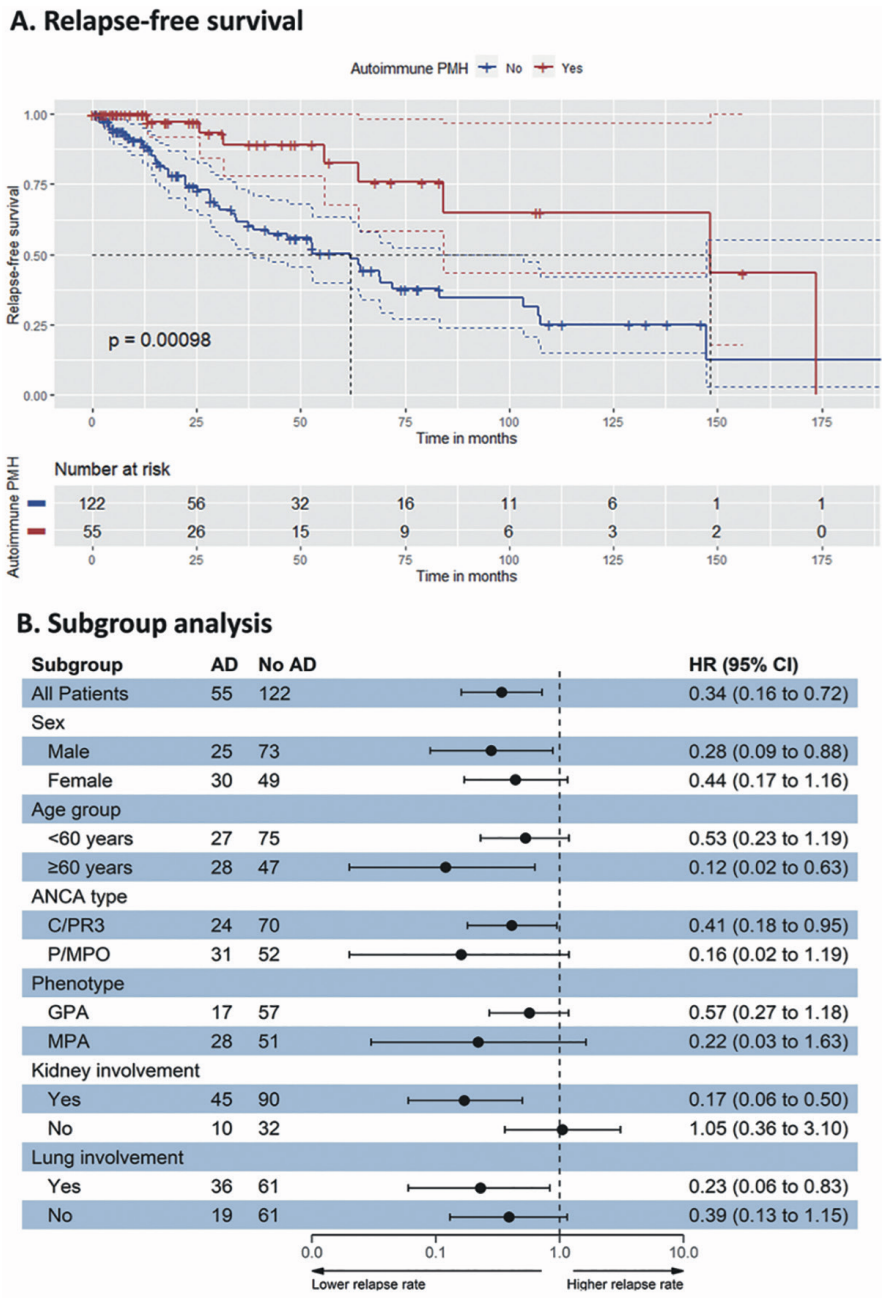

Fig. 1. Relapse-free survival and risk of relapse in patients with and without PMH of autoimmunity. (**A**) Kaplan-Meier curves of relapse-free survival among patients with and without PMH of autoimmune disease. Dotted lines indicate 95% confidence intervals. (**B**) Competing risk regression analysis of relapse in patient subgroups.
PMH: past medical history; AD: autoimmune disease; ANCA: anti-neutrophil cytoplasmic antibodies; PR3: proteinase-3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; HR: hazard ratio; CI: confidence intervals.

Table II. Association of autoimmunity past medical history with relapse-free and dialysis-free survival in patients with AAV.

Outcome	Univariate		Age & sex-adjusted		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Relapse								
Composite outcome[1]	0.30 (0.14-0.64)	0.002*	0.31 (0.14-0.65)	0.002*	0.33 (0.15-0.72)	0.005*	0.33 (0.15-0.72)	0.005*
Competing risk	0.34 (0.16-0.72)	0.004*	0.35 (0.16-0.73)	0.005*	0.40 (0.20-0.80)	0.010*	0.42 (0.21-0.83)	0.013*
Long-term end-stage renal disease								
Composite outcome[2]	0.79 (0.40-1.56)	0.494	0.76 (0.38-1.51)	0.433	0.65 (0.32-1.32)	0.234	0.63 (0.31-1.27)	0.158
Competing risk	0.94 (0.46-1.92)	0.870	0.91 (0.46-1.82)	0.800	0.79 (0.39-1.61)	0.520	0.74 (0.36-1.54)	0.420

Multivariate model 1 adjusts for age, sex, ANCA type and clinical phenotype and model 2 for age, sex, ANCA type, clinical phenotype, kidney involvement and lung involvement.
[1]relapse or end-stage kidney disease or death; [2]ESKD: end-stage kidney disease or death.
*p-value <0.05; HR: hazard ratio; CI: confidence intervals; AAV; ANCA associated vasculitis; PMH; past medical history.

1 for present). Necrosis in the wall of arterioles, interlobular or arcuate arteries (0, 1, absent/present). The chronicity index score represented the sum of scores from 4 categories, *i.e.* global glomerulosclerosis, interstitial fibrosis, tubular atrophy and fibrotic crescents/segmental sclerosis, which were scored semi-quantitatively from 1 to 3; (grade 1 for 0–25%, grade 2 for 26–50%, and grade 3 for >50%) for a maximum of 12 points. Immunofluorescence examination on frozen tissue was applied in all cases for immunoglobulins (IgG, IgA, IgM), complement components (C3 and C1q), Fibrinogen and k and l light chains (DAKO FITC, Polyclonal Rabbit 1/50 dilution). All patients with renal involvement had biopsy proven disease (in any tissue), but 100 of them had a kidney biopsy performed at diagnosis of glomerulonephritis and were eligible to be included in the analysis regarding of renal histopathology using the scoring system described above.

Methods

Statistical analysis was conducted in R-4.0.5 (packages "*survival*" (20), "*survminer* (21) and "*cmprsk*" (22)]. Statistical significance was defined by a two-sided *p*-value below the threshold of 0.05. The normality of continuous variables was assessed by the visual inspection of histograms and was tested by the Kolmogorov-Smirnov method (23). Normally distributed variables were described by their mean and standard deviation and were compared with the Student's *t-test*; otherwise, the median and interquartile range were reported and the Mann-Whitney U-test was applied (24). Categorical data were compared with the chi-squared test; in case its assumptions were not met, the Fisher's exact test was implemented (25). For the outcome of remission, logistic regression analysis was used to obtain estimates of odds ratio (OR) and 95% confidence intervals (CI). Both univariate and multivariate logistic regression models were applied, adjusting for potential confounders (age, sex, ANCA type, clinical phenotype, kidney and lung involvement).

Time to relapse was evaluated among patients who have achieved remission. Competing risk regression analysis was conducted by considering first-occurring end-stage renal disease and death as competing events (26). Competing events should be considered, as the occurrence of the outcome of interest may be precluded by other events, especially in case the exposure effect may differ among the competing events and the primary event of interest. Moreover, the composite outcome of relapse, ESKD or death was assessed by Cox proportional hazards regression analysis. For the analysis of long-term ESKD, all patients were included and death was treated as a competing event. Similarly, competing risk regression was implemented, while the composite outcome of ESKD or death was evaluated by Cox proportional hazards regression analysis. The plausibility of the proportional hazards assumption was assessed graphically and by the Schoenfeld's global test. Multivariate models included age, sex ANCA type, clinical phenotype, kidney and lung involvement. Subgroup analysis was also performed based on the above covariates.

The histopathologic parameters were compared between patients with and without a PMH of autoimmune disease. In addition, multivariate Cox proportional hazards regression analysis was conducted regarding relapse and dialysis-free survival, by fitting models including EUVAS class, activity and chronicity scores. For regression analyses, missing data were statistically imputed using the k-nearest neighbour method.

Results

Description of study population

Of 304 patients with biopsy-proven AAV at any site, 206 patients (male: 55.9%) satisfied the inclusion criteria. Excluded patients were as following: 14 were ANCA negative, 61 did not have any information available regarding their PMH, 19 were followed for less than one year, and 4 had EGPA. Of the included patients 63 (30.6%) reported PMH of any autoimmune disease prior to AAV diagnosis. Of these, 31 (49.2%) patients had a PMH of autoimmune thyroiditis, 16 (25.4%) rheumatoid arthritis, 6 (9.5%) psoriasis, 5 (7.9%) Sjögren syndrome, 4 (6.3%) Crohn disease and 1 (1.6%) scleroderma. The mean age of the population at AAV diagnosis was 54.1 years (SD: 16.6, range: 12–91), while the vast majority of patients were Caucasians (98.5%). The mdian time from diagnosis of the autoimmune disorder to the

diagnosis of AAV diagnosis was 5.8 years, range (3.5–11.8).

Furthermore, 105 patients (51.0%) were positive for PR3-ANCA and 101 (49.0%) for MPO-ANCA. Granulomatosis with polyangiitis was diagnosed in 79 (38.3%), microscopic polyangiitis in 97 (47.1%) and renal limited vasculitis in 30 (14.6%) individuals. Kidney involvement was present in 158 (76.7%) and lung involvement in 92 (44.7%) cases. Table I summarises the baseline characteristics of the patients; overall, no significant differences were noted between patients with and without PMH of autoimmune disease, with the exception of sex (p-value=0.042), skin involvement (p-value: 0.045) and acute dialysis requirement (p-value: 0.021).

Exposure to immunosuppression prior to AAV diagnosis was recorded for patients with a PMH of autoimmunity. Specifically, among patients with a PMH of autoimmunity, there were thirteen patients (6.04%) had received at least one course of glucocorticoids orally, two patients who had been treated with methotrexate and one who had been treated with an anti-tumour necrosis factor monoclonal antibody, for rheumatoid arthritis or Sjögren's syndrome. All those patients were treated for rheumatoid arthritis. Yet, three patients with Graves thyroiditis had received propyl-thiouracil for hyperthyroidism (1.4%).

Treatment outcomes of AAV

Remission. Remission rate was similar among patients with and without PMH of autoimmune disease (87.3% *vs*. 85.3%, χ^2 p=1). The difference remained non-significant after adjusting for age and gender (adjusted OR: 0.97, 95% CI: 0.38-2.33). No significant change was evident after adding ANCA type and clinical phenotype (adjusted OR: 0.84, 95% CI: 0.32–2.06), as well as kidney and lung involvement (adjusted OR: 0.76, 95% CI: 0.28–1.88) in the multivariate model.

Relapse. The composite endpoint of relapse, ESKD or death was present in 59 cases; of them, 8 (13.6%) reported a PMH of autoimmune disease (χ^2: 11.478, p<0.001). Time-to-event analysis indicated that the median relapse-free survival was significantly longer in patients with autoimmune disease history (148.2 *vs*. 61.9 months, log-rank p<0.001) (Fig. 1a). No violation of the proportional hazards assumption was observed (Schoenfeld's global test p=0.510). After adjusting for covariates, autoimmune disease history was associated with significantly lower risk of developing the composite outcome (adjusted HR: 0.33, 95% CI: 0.15–0.72). Similarly, the competing risk model demonstrated that patients with history of autoimmune disease was at significantly lower risk of relapse (adjusted HR: 0.42, 95% CI: 0.21–0.83) (Table II). Subgroup analysis indicated that the outcome remained significant in males, patients ≥60 years old and

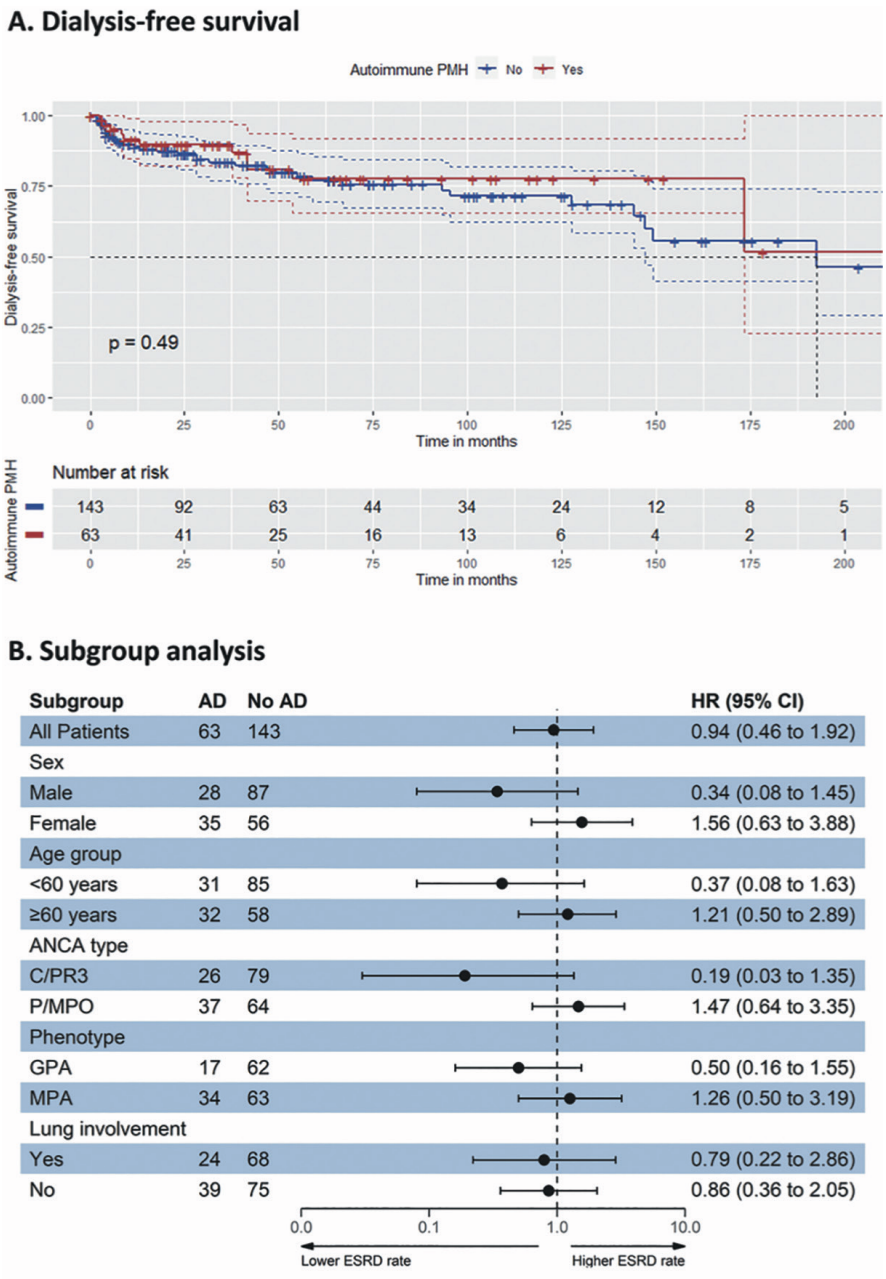

Fig. 2. Dialysis-free survival and risk of ESKD in patients with and without PMH of autoimmunity.
A: Kaplan-Meier curves of dialysis-free survival among patients with and without PMH of autoimmune disease. Dotted lines indicate 95% confidence intervals.
B: Competing risk regression analysis of end-stage kidney disease in patient subgroups.
PMH: past medical history; AD: autoimmune disease; ANCA: anti-neutrophil cytoplasmic antibodies; PR3: proteinase-3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; HR: hazard ratio; CI: confidence intervals; ESKD: end-stage kidney disease.

those with C/PR3 positivity, kidney and lung involvement (Fig. 1b).

ESKD or death. The composite outcome of long-term ESKD or death was observed in 45 patients, 11 of whom reported history of autoimmune disease (χ^2: 0.685, p=0.408). The dialysis-free survival was estimated to be similar between the compared groups (log-rank, p=0.340) (Fig. 1a). The proportional hazards assumption was not violated (Schoenfeld's global test, p=0.810). No significant dialysis-free survival difference was noted after adjusting for age, gender, ANCA type, clinical phenotype, kidney involvement and lung involvement (adjusted HR: 0.63, 95% CI: 0.31-1.27). Correspondingly, the competing risk model indicated that the ESKD risk did not differ between groups (adjusted HR: 0.74, 95% CI: 0.36–1.54) (Table II). Subgroup analysis demonstrated no significant difference in any subgroup of sex, age, ANCA type, clinical phenotype and lung involvement (Fig. 2b).

Renal histopathology evaluation

Renal histopathological parameters were evaluated in a sub cohort of 100 patients. Comparison of histopathological variables between groups are presented in Table III. The median activity score was estimated at 5 (interquartile range: 4-6.5) and the median chronicity score at 6 (interquartile range: 4 to 8). Classification of patients according to the European Vasculitis Society (EUVAS) schema revealed the following: focal in 22 (22%), crescentic in 25 (25%), mixed in 38 (38%) and sclerotic in 15 (15%) cases. No significant differences of histopathological parameters were observed among the two groups, with the exception of an increased frequency of cellular crescents among patients without history of autoimmune disease (Table III).

Remission rate was not affected by the PMH status after adjusting for EUVAS class, activity and chronicity score. Conversely, relapse-free survival remained significantly longer in patients with autoimmune disease history after adjusting for EUVAS class (adjusted HR: 0.30, 95% CI: 0.12–0.76) or for activity and chronicity score (adjusted HR: 0.31, 95% CI: 0.12–0.77). Dialysis-free survival was not associated with autoimmune disease status after adjusting for histopathology covariates (Table IV). It should be noted that higher chronicity score was linked with significantly shorter dialysis-free survival (adjusted HR: 1.21, 95% CI: 1.01–1.46).

Table III. Histopathologic parameters among AAV patients with and without a past medical history of autoimmune disease.

Histopathology	Overall (n=100)	Autoimmune PMH (n=34)	No. Autoimmune PMH (n=66)	p-value
EUVAS classification				
Focal	22 (22%)	10 (29.4%)	12 (18.2%)	0.144
Crescentic	25 (25%)	4 (11.8%)	21 (31.8%)	
Mixed	38 (38%)	15 (44.1%)	23 (34.8%)	
Sclerotic	15 (15%)	5 (14.7%)	10 (15.2%)	
Normal glomeruli				
Grade 1 (>50%)	11 (11%)	2 (5.9%)	9 (13.6%)	0.313
Grade 2 (25-50%)	27 (27%)	12 (35.3%)	15 (22.7%)	
Grade 3 (10-24%)	25 (25%)	10 (29.4%)	15 (22.7%)	
Grade 4 (<10%)	37 (37%)	10 (29.4%)	27 (40.9%)	
Severe arteriosclerosis	18 (18%)	3 (8.8%)	15 (22.7%)	0.148
Activity				
Cellular crescents				
None/mild (<25%)	44 (44%)	19 (55.9%)	25 (37.9%)	**0.043**
Moderate (25-50%)	29 (29%)	11 (32.4%)	18 (27.3%)	
Severe (>50%)	27 (27%)	4 (11.8%)	23 (34.8%)	
Glomerular necrosis				
None/mild (<25%)	71 (71%)	25 (73.5%)	46 (69.7%)	0.318
Moderate (25-50%)	20 (20%)	8 (23.5%)	12 (18.2%)	
Severe (>50%)	9 (9%)	1 (2.9%)	8 (12.1%)	
Interstitial leucocyte infiltration				
None/mild (<25%)	75 (75%)	26 (76.5%)	49 (74.2%)	0.911
Moderate (25-50%)	23 (23%)	7 (20.6%)	16 (24.2%)	
Severe (>50%)	2 (2%)	1 (2.9%)	1 (1.5%)	
Circumferential crescents	40 (40%)	12 (35.3%)	28 (42.4%)	0.636
Red blood cell casts	36 (36%)	13 (38.3%)	23 (34.8%)	0.909
Fibrinoid necrosis in vessel wall	8 (8%)	4 (11.8%)	4 (6.1%)	0.439
Activity score	5 [4-6.5]	5 [4-6]	6 [4-7]	0.112
Chronicity				
Global glomerulosclerosis				
None/mild (<25%)	61 (61%)	19 (55.9%)	42 (63.6%)	0.752
Moderate (25-50%)	21 (21%)	8 (23.5%)	13 (19.7%)	
Severe (>50%)	18 (18%)	7 (20.6%)	11 (16.7%)	
Fibrotic crescents/Segmental sclerosis				
None/mild (<25%)	72 (72%)	25 (73.5%)	47 (71.2%)	0.944
Moderate (25-50%)	17 (17%)	6 (17.6%)	11 (16.7%)	
Severe (>50%)	11 (11%)	3 (8.8%)	8 (12.1%)	
Tubular atrophy				
None/mild (<25%)	53 (53%)	21 (61.8%)	32 (48.5%)	0.179
Moderate (25-50%)	42 (42%)	13 (38.2%)	29 (43.9%)	
Severe (>50%)	5 (5%)	0 (0.0%)	5 (7.6%)	
Interstitial fibrosis				
None/mild (<25%)	46 (46%)	17 (50.0%)	29 (43.9%)	0.748
Moderate (25-50%)	48 (48%)	16 (47.1%)	32 (48.5%)	
Severe (>50%)	6 (6%)	1 (2.9%)	5 (7.6%)	
Chronicity score	6 [4-8]	6 [4-7]	6 [4-8]	0.650

AAV: ANCA associated vasculitis; PMH: past medical history; EUVAS: European Vasculitis Society.

Discussion

This is the first study to our knowledge exploring the frequency of existence of an autoimmune disease PMH in patients, who are diagnosed with AAV and its impact, if any, in the clinical picture and outcome following immunosuppressive therapy. It was found that 30.6% of patients with AAV had received a diagnosis of either a systemic or organ-specific autoimmune disorder prior to vasculitis diagnosis. Patients with and without a PMH of autoimmunity were similar regarding the baseline and disease-related character-

Table IV. Outcomes of regression analyses adjusting for histopathologic parameters in patients with AAV.

Outcome	Age and sex-adjusted		Multivariate model 1		Multivariate model 2	
	ES † (95% CI)	*p*-value	ES † (95% CI)	*p*-value	ES † (95% CI)	*p*-value
Remission	0.64 (0.19-1.89)	0.429	0.68 (0.19-2.21)	0.528	0.96 (0.27-3.37)	0.949
Relapse or ESKD or death	0.30 (0.12-0.73)	0.008*	0.30 (0.12-0.76)	0.011*	0.31 (0.12-0.77)	0.012*
Long-term ESKD or death	0.67 (0.30-1.53)	0.347	0.66 (0.29-1.47)	0.304	0.79 (0.34-1.82)	0.578

Multivariate model 1 adjusts for age, sex and EUVAS class and model 2 for age, sex, activity and chronicity score.
†Effect size (ES) refers to odds ratio in remission outcome and hazard ratio in composite outcomes. *p-value <0.05; CI: confidence intervals.

istics, while the majority of patients with a positive PMH had MPA or renal limited disease. The rates of remission were similar between patients with a history of autoimmunity and those without, but the risk of relapse was significantly lower in patients with a PMH of autoimmunity, a finding which remained significant after adjusting for covariates. Specifically, patients with a PMH of an autoimmune disorder prior to AAV diagnosis had a 67% lower probability of experiencing a relapse with the median relapse-free survival being significantly longer in this group (148.2 *vs*. 61.9 months, $p<0.001$). Importantly, subgroup analysis indicated that the outcome remained significant in males, patients ≥60 years old and those with C/PR3-ANCA positivity, kidney and lung involvement. Appliance of a detailed histopathological evaluation scoring system with adjustment for the activity and chronicity score, and the EUVAS class revealed that the remission rate was not affected by the PMH status, and the relapse-free survival remained significantly longer in patients with a PMH of autoimmune disease. The reported rates of relapse in AAV vary substantially across studies, ranging from approximately 10–60% (28-32). Certain risk factors for relapse have been identified including PR3-ANCA seropositivity, lung involvement, upper respiratory tract involvement, prior history of relapse or persistently elevated ANCA levels (30). Importantly, the rate of relapse in the present study, was much higher in patients with the first three of these risk factors, compared with those who had none of them. Other cohorts have found a higher relapse rate in patients with lung involvement and in those with PR3-ANCA (31-34). This difference in the risk of relapse, between patients with and without a PMH of autoimmune disorder, remained significant after adjusting for these covariates, and thus, we may speculate that is associated with differences in the underlying cascade of events that caused the disease. Genetic influences, environmental exposures or abnormalities (35-37) of the innate and acquired immune system have been implicated in the pathogenesis of AAV (1). Each of these factors seem to play a particular role in the induction and perpetuation of the disease. Still, there is less understanding of the initial trigger, which is associated with ANCA genesis. In general, it is widely known that there are individuals with a certain propensity to autoimmunity (13), which is reflected in experiencing more than one autoimmune disorder during their life. As shown here, this is also the case for one third of patients with AAV. Potential mechanisms, which might have been involved include HLA associations, that have been revealed by genome-wide association studies in patients with MPO-ANCA and PR3-ANCA vasculitis (8, 38) or epigenetically controlled modifications, such as, increased expression of ANCA autoantigens, *i.e*. increased expression of MPO and PR3 genes, which may influence disease pathogenesis, either by augmenting ANCA-induced neutrophil activation, or stimulating the pathogenic autoimmune response, or both (39-40). Yet, 30% of patients with AAV have been shown to have an anti-idiotypic antibody directed to a non-pathogenic antibody against the anti-sense strand of PR3, complementary PR3, which are reactive with PR3 (41-42). Finally, one might speculate that the difference in the relapse rate between AAV patients with or without a PMH of autoimmunity might reflect distinctions between patients who have a propensity to autoimmunity due to genetically driven pathways or epigenetic alterations, which might be more potent.

Therefore, it comes forward that the management of patients with AAV should follow a personalised approach, since the pathogenetic setting is variable, while cumulative toxicity associated with immunosuppressive therapy over time is problematic. Clinical studies have pointed out that extended maintenance therapy has only a limited effect on the prevention of relapse (43-45), while selective therapy discontinuation, for 2 or more years may be feasible in 50% of patients with AAV and 5 or more years among 22% of them (43-44).

The main limitation of this study pertains to its retrospective design and the fact that the time frame of disease diagnosis of included patients was spread in three decades. Yet, although all patients with renal involvement had a kidney biopsy performed at the time of diagnosis, detailed histopathological evaluation using the activity/chronicity scoring system was performed in 65% of kidney biopsies. Certain strengths of the study were its sample size, which is relatively large considering that the disease is rare, the long term follow up, and the fact all patients had biopsy-proven disease with thorough histopathological assessment of kidney biopsies and immunosuppressive therapy. In addition, a competing risk analysis was performed to evaluate the questioned issues.

In conclusion, patients with a PMH of autoimmune disorders prior to AAV diagnosis were shown to have a different disease course following immunosuppressive therapy, compared to patients

without such a history. The risk of relapse was significantly lower in the presence of a PMH of autoimmunity at the time of AAV diagnosis, a finding that remained significant after adjusting for sex, age and ANCA positivity. Most of all, these findings are clinically meaningful, as they underline the importance of individualisation of the intensity and duration of therapy, which is given to maintain remission, considering the different aetiopathogenetic backgrounds of AAV, and in order to avoid increasing the burden of immunosuppression if not needed. Until a therapy able to eradicate the disease is in our hands.

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