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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Predictors of Poor Outcome in ANCA-Associated Vasculitis (AAV)

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Abstract It is important to recognize factors that might predict poor outcome and prognosis in patients with AAV. The predictors reported in the literature encompass genetic, histopathological, and clinical ones. Genetic studies (genetic predictors) have found genes that are associated with prediction of poor response to treatment, deterioration of renal function, and risk of mortality. Histopathological studies (histopathological predictors) have shown that sclerotic renal lesions are associated with increased risk of progression to end-stage renal disease and death. Lastly, scores (clinical predictors) obtained with tool as FFS, Maldini risk score, VDI, and emerging new biomarkers could potentially be helpful in assessment of prognosis in the future.

Keywords ANCA-associated vasculitis · Granulomatosis with polyangiitis · Eosinophilic granulomatosis with polyangiitis · Microscopic polyangiitis · Poor outcome · Biomarkers

Introduction

The ANCA-associated vasculitis (AAV) is a group of multisystem disorders characterized by inflammatory and necrotizing changes of the vessel wall that leads to ischemia and tissue damage, organ dysfunction and, if untreated, to organ failure. Morbidity, outcomes, and mortality associated with this group of disorders have significantly decreased in the past several years due mostly to prompt recognition of the severity of symptomatology and early therapeutic intervention with immunosuppressive agents including corticosteroids, cytotoxic and biologic agents, and most recently plasmapheresis [1].

As a group, ANCA-associated vasculitis includes granulomatosis with polyangiitis (formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (formerly Church-Strauss disease), microscopic polyangiitis, and the variant limited to the kidney (renal vasculitis). This group of disorders may severely affect any organ system, especially the kidney, which may threaten the lives of patients; therefore, it is important to recognize and characterize the risk factors that might predict the clinical manifestations associated with poor outcome and prognosis. On the other hand, high costs and potentially serious adverse events, associated with uncertainties over long-term effects of existent therapeutic modalities, make careful selection and stratification of patients for treatment imperative if unnecessary toxicity and expense are to be avoided.

There are published reports in the literature concerning predictors of poor outcome that include genetic, histopathological, and clinical, which can be used for patient selection and optimal treatment.

Genetic Predictors

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are the two major syndromes in AAV, with GPA carrying a poorer prognosis. Both disorders share many clinical and histopathological findings, and until recently they were thought to represent each end of a single disease

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spectrum and typically treated similarly. However, striking differences can be found in terms of clinical outcomes and ANCA specificities. And more recently, Lyons et al. have clearly demonstrated that there are genetic distinctions between GPA and MPA, which are associated with ANCA specificity, and supporting the notion that the response against the autoantigen proteinase 3 is a central pathogenic feature of proteinase 3 ANCA-associated vasculitis [2•].

In their study, a genome-wide association study was performed in a cohort of 1233 UK patients with ANCA-associated vasculitis and 5884 controls, and the study was also performed in 1454 Northern European case patients and 1666 controls. They found both major-histocompatibility-complex (MHC) and non-MHC associations with AAV. Strong genetic associations were found with the antigenic specificity of ANCA, not with the clinical syndrome. Anti-proteinase 3 ANCA was associated with HLA-DP and the genes encoding α (1)-antitrypsin (SERPINA 1) and proteinase 3 ANCA-associated vasculitis.

AAV has long been thought to have a genetic component in disease susceptibility, familial cases of AAV have been described, and also a number of studies have shown an association of HLA genes, including both class I and class II, with disease susceptibility of AAV [3].

More recently, Chang et al. investigated the association between HLA genes and the outcomes of patients with AAV [4]. The objective of their study was to determine the predictive value of the HLA alleles for renal outcome, response to treatment, and all-cause mortality. They found a higher proportion of patients with treatment failure in DRB1*0405-positive patients than in DRB1*0405-negative patients (41.7 vs 12.9 %; $P = 0.008$; corrected $P = 0.02$). After adjusting for the other potential predictors, DRB1*0405 remained an independent predictor for the poor response to treatment (HR, 5.91; 95 % CI, 1.23–28.52; $P = 0.03$). In addition, renal survival was worse in patients with DRB1*0405 than those without DRB1*0405 ($P < 0.001$; corrected $P < 0.001$). And after adjusting for the other potential predictors, DRB1*0405 remained an independent predictor for end-stage renal disease (ESRD) (HR, 5.50; 95 % CI, 2.18–13.88; $P = 0.001$). All-cause mortality in patients with DPB1*0402 was significantly higher than those without DPB1*0402 ($P = 0.02$; corrected $P = 0.04$). After adjusting for the other potential predictors, DPB1*0402 remained an independent predictor for all-cause mortality (HR, 2.52; 95 % CI, 1.21–5.28; $P = 0.01$). They conclude that in AAV patients, DRB1*0405 might be considered an independent risk factor for the poor response to treatment and the deterioration of renal function, whereas DPB1*0402 might be an independent risk factor for all-cause mortality.

Persson et al. studied the associations between ANCA-associated vasculitis and polymorphisms in the genes of four key molecules possibly involved in different pathogenic pathways: complement C3, CTLA-4, Fcγ-RIIa, and IL1-Ra [5]. In their study, 105 patients with AAV subgrouped as MPA or GPA or PR3 ANCA positive were compared to a control group of 200 blood donors. Polymorphisms in the genes were analyzed with PCR amplification of DNA. The gene frequency of C3F was 0.27 in the PR3-ANCA subgroup ($P = 0.041$) compared to 0.19 in the control group. The number of patients homozygous for the shortest 86-bp allele of CTLA-4 was significantly decreased in the whole group of patients ($P = 0.049$). No differences were evident in the Fcγ-RIIa and IL1-Ra polymorphisms when compared to controls, neither in the whole group of patients nor in any of the sub-groups. Authors concluded that the aberrant gene frequency of the C3F allele among PR3-ANCA positive patients and the findings with the CTLA-4 polymorphisms indicates that complement may be involved in pathogenesis and that T cell activation is of importance in these diseases.

Cao et al. recently conducted a meta-analysis on the PTPN22 R620W polymorphism across four studies in 1399 White patients with ANCA disease and 9934 normal control subjects [6••]. They found a statistically significant association between the A allele and ANCA disease in all subjects (OR 1.44, 95 % CI 1.26–1.64, $P < 0.00001$), and further stratification by disease category determined that the A allele was associated with GPA (OR 1.72, 95 % CI 1.35–2.20, $P < 0.0001$) and MPA (OR 1.53, 95 % 1.08–2.15, $P = 0.02$) as compared to controls. Furthermore, when stratified by ANCA specificity, the association of the A allele was statistically evident among those with PR3 ANCA disease (OR 1.74, 95 % CI 1.25–2.430, $P = 0.001$), with the same trend but not statistically associated with myeloperoxidase ANCA disease. Marked associations were also shown between this allele and lung, ENT, skin, and peripheral neuropathy involvement.

Grayson et al. recently reported on their studies aimed at discovering biomarkers involved in the pathophysiology of AAV and to determine whether low-density granulocytes (LDGs) contribute to gene expression signatures in AAV [7••]. Gene expression was measured and compared between patients who met versus those who did not meet the primary trial outcome of clinical remission at 6 months (responders vs no responders). In addition, measurement of neutrophil-related gene expression was confirmed in peripheral blood mononuclear cells (PBMCs) to validate the findings. Differential expression between responders ($n = 77$) and no responders ($n = 35$) was detected in 2346 transcripts at the baseline visit ($P = 0.05$). Unsupervised hierarchical clustering demonstrated a cluster of granulocytes-related genes, including MPO and PR3. A granulocyte multigene composite score was significantly higher in no responders than in responders ($P < 0.01$) and during active disease than during remission ($P < 0.01$). This finding

strongly overlapped an LDG signature also seen in lupus (false discovery rate by gene set enrichment analysis <0.01). Transcription of PR3 measured in PBMCs was associated with active disease and treatment response ($P < 0.01$). LDGs isolated from patients with AAV spontaneously formed neutrophils extracellular traps containing PR3 and MPO. Authors concluded that in AAV, increased expression of a granulocyte gene signature is associated with disease activity and decreased response to treatment. LDGs appeared to be the source of this signature.

The genetics findings discussed are promising, but of limited value as predictor of poor outcome. It will be necessary for sufficiently powered longitudinal studies in well-characterized cohorts to assess the utility of these novel genetics patterns. It is difficult to predict response to a particular treatment with the currently available studies. These tests are not currently available or not routinely used in clinical practice. Also, the cost/effectiveness and add value cannot be determined due to the lack of solid and consistent evidence.

Histopathological Predictors

AAV, especially GPA and MPA, often affect the kidney, and renal involvement is an important factor regarding patient morbidity and mortality. Therefore, morphologic changes in the renal biopsy remain the gold standard for establishing a diagnosis with great certainty. The diagnostic value of kidney biopsy is well recognized, while its value in predicting renal and patient outcomes is less clear and the reported results are to a certain extent controversial. Renal biopsy in AAV provides precise information of the extent and severity of the underlying renal injury; therefore, it is recommended that all patients with renal involvement should have a biopsy. Four general categories of renal lesions have been proposed in AAV: focal, crescentic, mixed, and sclerotic. The first two categories denote activity while the last two denote chronicity and irreversibility of changes; therefore, therapy will be aggressive in focal and crescentic categories and conservative in the last two to avoid toxicity and unnecessary risk of infection. This classification was devised in 2010 by an international group of renal pathologists and nephrologists, and it is purely based on glomerular lesions as assessed by light microscopy [8]. However, it was acknowledged that tubulointerstitial lesions may also be of prognostic value in AAV. Berden et al. also performed a validation study in 100 biopsies from patients with clinically and histologically confirmed ANCA-associated glomerulonephritis. Results showed that the proposed classification criteria are of prognostic value for 1- and 5-year renal outcomes. Patients with AAV and sclerotic class were at higher risk for death within the first year after diagnosis [9].

Subsequent published reports have confirmed that the group of patients with sclerotic lesions has the worst renal and patient outcomes.

Chang et al. re-evaluated the classification for its prognostic significance in an independent Chinese series [10]. They studied 121 patients with ANCA-associated glomerulonephritis, diagnosed from 1997 to 2010. The predictive value of the classification for renal outcome and renal response to treatment was analyzed. Thirty-three (27.3 %), 24 (19.8 %), 53 (43.8 %), and 11 (9.1 %) patients were classified as focal, mixed, crescentic, and sclerotic ANCA-associated glomerulonephritis, respectively. The renal biopsy findings correlated with initial serum creatinine and the renal response to treatment ($P < 0.001$, $P < 0.01$, respectively). The probability of progressing to ESRD increased with ascending categories of focal, mixed, crescentic, and sclerotic glomerulonephritis ($P < 0.01$). Patients with lower histopathological classification such as focal, mixed, and crescentic ANCA-associated glomerulonephritis were all at decreased risk for developing ESRD compared with the patients in the sclerotic category ($P < 0.05$). They concluded that the histopathological classification criteria reflect the severity of the initial renal involvement and can predict, at least to some degree, the renal response to treatment. It can also independently predict renal outcome, especially development of ESRD.

Muso et al. also evaluated the classification in order to ascertain its predictive value and reproducibility in 87 Japanese patients diagnosed with MPA (all MPO-ANCA). The renal survival was worse for the sclerotic class, similar to the Chinese and Caucasian studies [11]. Mortality was higher for patients with sclerotic class in both studies. Comparison was made with European and Chinese series, and results yielded similar findings, sclerotic class predicts ESRD.

Validation in USA and Australia have also showed worse outcome in patients with sclerotic class biopsies [12–15].

Tanna et al. also evaluated the 2010 international histological classification criteria for ANCA-associated glomerulonephritis (AAGN) as a predictor of renal outcome when used in conjunction with other prognostic factors [16]. One hundred and four patients with AAGN were studied: 23 were classified as focal, 26 as crescentic, 48 as mixed, and 7 as sclerotic. Renal outcomes were based on estimated glomerular filtration rate (eGFR) at 1 and 5 years, and on renal survival. Consistent with previously published reports, patients in the focal class had the best renal outcome, those in the sclerotic class the worst outcome, and those in the mixed and crescentic classes had intermediate renal survival. In addition, lower percentage of normal glomeruli, greater degree of tubular atrophy, MPO-ANCA positivity, increasing age, and lower starting eGFR all correlated with poorer renal outcomes. They concluded that the international histological classification is predictive of renal outcome in AAGN, but did not appear to provide

additional information over other established prognostic factors in multivariate analysis. They suggest that it may be of value to combine the current histological classification with other established parameters, such as tubular atrophy and percentage of normal glomeruli.

Ford et al. also conducted an observational cohort study to assess the reproducibility of the new classification and clinical variables that predict outcomes [17]. One hundred sixty-nine patients with AAV were identified; 145 were included in the reproducibility study, and 120, in the outcomes study. Kidney biopsies were classified according to the predominant glomerular lesion: focal, mixed, crescentic, and sclerotic. An assessment of tubular atrophy was also performed. The primary outcome was time to ESRD or all-cause mortality. Reproducibility of the classification was seen only in patients with sclerotic patterns of glomerular injury. Sclerotic pattern of glomerular injury, advanced chronic interstitial injury, and decreased kidney function all predicted poor outcomes.

Recently, Moroni et al. validated the classification criteria in 93 patients with ANCA-associated vasculitis and also compared their findings with the previously published reports [18]. The 10-year renal and patient's survival were 60 and 81 %, respectively. Biopsy findings were classified as 21 % focal, 30 % crescentic, 39 % mixed, and 10 % sclerotic. Survival without ESRD at 5 years was 82 % in focal, 37 % in crescentic, 81 % in mixed, and 51 % in sclerotic group. Renal survival was no different between sclerotic and crescentic groups but both had a significantly worse prognosis than focal ($P = 0.04$ and 0.015, respectively) and mixed groups ($P = 0.05$ and 0.03, respectively). Renal survival was similar in focal and mixed groups. At multivariate analysis, the independent predictors of ESRD were less than 20 % of normal glomeruli at kidney biopsy ($P = 0.022$), high serum creatinine ($P = 0.009$), and arterial hypertension at presentation ($P = 0.006$). Authors concluded that the proposed histological classification was not predictive of renal prognosis.

It can be concluded that the degree of glomerular sclerosis seems to be predictive of renal outcome, with a higher degree of sclerosis correlating with a worse renal prognosis. In addition, the proposed classification criteria have not been shown to be useful for therapeutic guidance, but there have been some suggestions for its use in this area.

The renal biopsy and histopathology is a tool available in most tertiary medical centers; it has good cost/benefit and provides an added value to the assessment of patients with renal damage in clinical practice.

Clinical Predictors

The clinical outcome of AAV has been significantly impacted by more effective immunosuppressive therapy over the past few decades. Mortality rate has significantly declined to less than 25 % at 10 years, and while the quality of life continues to improve, it remains affected by the relapsing nature of the disease, and also the long-term consequences of the disease and treatment, as well as by the presence of comorbidities, which will contribute to the patient's clinical outcome. A series of standardized validated clinical instruments to quantify disease activity and damage have been developed over the years, which provide a solid basis for clinical management in patients with vasculitis.

In 1996, the French Vasculitis Study Group (FVSG) published the so-called Five-Factor Score (FFS), revised in 2009, and only validated for patients with ANCA-associated vasculitis. The only role of the FFS was to evaluate necrotizing vasculitis prognosis and identify clinical manifestations associated with death and thus could stratify individuals with a worse prognosis to receive a more aggressive therapy than those with a better prognosis. The current version includes four negative factors: age (older than 65 years), GI involvement, cardiac involvement, and renal involvement (associated with poor prognosis), and one positive factor: ENT involvement (associated with better outcome) (Table 1) [19]. A number of clinical reports from the FVSG using the FFS appear to validate the initial observation.

There are other risk scores reported to predict short-term incidence of death or relapse in AAV. Maldini et al. performed a study aimed at developing a risk score that could be used to predict 1-year risk of death or relapse in newly diagnosed AAV [20]. Each variable have a score. The variables used was age >60 years [1], ENT involvement [1], creatinemia >3.39 mg/dL [3], PR3-ANCA [1], MPO-ANCA [1], peripheral neutrophil count >7000 mm^3 [2•], hemoglobin level <10 g/dL [1], and C reactive protein level >10 mg/dL [2•]. Each patient was assigned a risk score between 0 and 15. The risk of death or relapse was low, medium, and high. This instrument may be useful in predicting a patient's risk of death

Table 1 Current version of the Five-Factor Score

Age	≥65 years
Renal	Renal insufficiency: creatinine ≥150 μmol/L
Cardiac	Cardiac insufficiency: based only on the presence of its clinical symptoms
Gastrointestinal	Severe symptoms: perforation, bleeding, and pancreatitis
Ear, nose, and throat (ENT)	Presence of clinical symptoms confirmed by physical examination by a specialist

or relapse in short-term follow-up and may contribute to better risk-stratified characterization and management of AAV.

Other predictors of treatment resistance and relapse have been identified including older age as a predictor of treatment resistance, and the presence of PR3-ANCA, heart, and lung involvement as predictors of relapse, while Black ethnicity, female sex, and presentation with severe kidney disease are associated with treatment resistance. In addition, the Vasculitis Damage Index has been shown to predict higher mortality in patients with higher scores [21, 22].

The development of these clinical instruments have proven to be very useful for evaluating disease progress in AAV, but the development of biomarkers may provide a more representative description of the natural history of AAV and identify potential targets for more selective or specific therapies as well as better predictors of clinical response to drugs.

Recent reports have described the presence of promising biomarkers in the serum of patients with AAV including relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

Kronbichler et al. aimed at validating some of the most promising markers of GPA and MPA identified by literature search and to create biomarkers panels [23•]. Following a systematic review, they identified 161 marker molecules that were ranked by their quantitative differential expression between active and inactive disease. They identified several promising biomarkers including CRP, C3a, C5a, IL-18BP in blood, and MCP-1 and C5a in urine samples. In addition, they proposed a biomarker panel comprising CRP and urinary MCP-1 in patients with AAV and renal involvement.

Grayson et al. assessed the clinical value of absolute eosinophil count, serum IgE, ESR, and CRP as longitudinal biomarkers of disease activity and predictors of relapse in EGPA-Church-Strauss [24]. Data obtained showed that the absolute eosinophil count, IgE, ESR, and CRP have limitations as longitudinal biomarkers of disease activity or predictors of flares in EGPA, and concluded that novel biomarkers of disease activity for EGPA are needed.

Dejaco et al. studied the role for eotaxin-3, TARC/CCL 17, and IgG4 in newly diagnosed patients with EGPA-Church-Strauss with highly active disease [25]. Findings showed that serum levels of TARC/CCL 17, eotaxin-3, IgG4, and IgG4/IgG ratio do not differentiate active and inactive disease in established EGPA. They concluded that the search for biomarkers in EGPA remains a challenge especially during concomitant glucocorticoid use.

Several other potential biomarkers have been described in patients with AAV, especially in patients with renal involvement, active disease activity, response to rituximab therapy or to distinguish infection from active disease. These studies, however, should be considered preliminary studies and there is a need to validate them in larger number of patients, and in a prospective and control manner.

Brix et al. have shown that CC chemokine ligand 18 drives renal inflammation through CCR8-expressing cells and may potentially be of use as a biomarker for disease activity and renal relapse in ANCA-associated crescentic GN [26]. deSouza et al. have recently reported that urinary high mobility group box 1 levels are increased in AAV patients with active nephritis when compared with healthy controls and patients in remission. They suggest that urinary HMGB 1 may be of additional value in identifying active glomerulonephritis in AAV [27].

Zhang et al. have described significantly higher levels of cathelicidin LL37 and IFN-α in AAV patients, particularly those with crescentic formation [28]. Other studies have suggested the use of platelet counts, naïve B cell population, low serum complement C3, and circulating microRNA profiles as potential biomarkers of disease activity or response to therapy. It has also been reported that the CD4 count has a higher predictive value than the total lymphocyte count for overall infection, while CD14 expression with ANCA autoantigen expression in AAV may reflect cell activation, PR3 ANCA and lung involvement predicts relapse and female gender, and severity of renal disease predicts treatment resistance [29–38]. More recently, the presence of circulating levels of neutrophil extracellular traps (NETs) has been reported play a role in the pathogenesis and disease activity of patients with AAV, but recent evidence with larger number of patients has shown that circulating levels of NETs can not be used to assess disease activity in AAV [39–41].

Newer biomarkers detected in urine or blood could greatly assist with diagnosis, disease activity assessment, and prognosis of patients with AAV; however, at present there is a need for prospective and longitudinal studies followed by validation in different groups of AAV patients to confirm their clinical value.

Table 2 Predictors of poor outcome

Genetic	HLA-BP: SERPINA-1, PRTN3 DRB1*0405, DPB1*0402 C3F Allele, CTLA-4 A Allele-PR3:PTPN22 R620W Granulocyte Gene Signature (LDG)
Histopathological	Renal lesion type sclerotic Renal lesion type crescentic?
Clinical	FFV ≥1 Maldini Risk Score Vasculitis Damage Index ≥5 Biomarkers: CRP, C3a, C5a, IL-18BP, CCR8, cathecilidin LL37, IFNα (blood) and MCP-1, HMGB-1(urine), NETs Miscellaneous: platelet counts, naïve B cell populations, C3 levels, circulating microRNA,, CD4 count, CD14 expression, PR3 ANCA, lung involvement, female gender

In conclusion, important risk factors or predictors of disease activity, renal damage, morbidity and mortality, and response to therapy have been described in AAV (Table 2). However, there is a need for novel biomarkers that could predict more accurately disease activity, relapse, prognosis, and facilitate therapy.

Conclusion

- Recognition and understanding of predictors of poor outcome should allow better selection and stratification of patients for more specific treatment modalities and at the same time avoid toxicity and high costs.

- There is a need for future collaborative studies that may help to generate, test hypotheses, and identify novel biomarkers in blood and urine that may assist with prompt diagnosis, early therapy, and prognosis of patients with AAV.

Compliance with Ethical Standards

Conflict of Interest Luis E. Vega and Luis R. Espinoza declare that they have no conflict of interest.

Human and Animal Right and Informed Consent This article does not contain any studies with human and animal subjects performed by any of the authors

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