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REVIEW

ANCA-associated vasculitis with renal involvement

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Abstract Systemic vasculitis is a rare but severe group of diseases characterized by inflammation and necrosis of blood vessels. The size of the vessel affected varies among the different forms of vasculitis and there are three main subgroups: large, medium and small vessel vasculitis. Among small vessel vasculitis, the antineutrophil cytoplasmic antibody (ANCA)-associated forms are of particular importance. This subgroup includes: microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg–Strauss) and the form limited to the kidney. ANCA are serum autoantibodies directed against proteins present in the cytoplasmic granules of neutrophils and represent the serological markers of small vessel vasculitis. Renal involvement is present in the majority of patients with ANCA-associated vasculitis (AAV) and the consequences of a missed or delayed diagnosis of renal vasculitis are potentially life threatening. Patient survival and the risk of end-stage renal disease are closely associated with renal function at presentation. The gold standard for diagnosis remains renal biopsy. In 2010, a new histopathological classification based on the percent of normal glomeruli, cellular crescent or global sclerotic glomeruli was proposed. The aim of this classification was to predict the renal prognosis. Nowadays, remission can be achieved and maintained in most cases with a combination of high-dose steroid and immunosuppressive drugs. This therapy has to be continued for at least 24 months after a substantial remission has been obtained because early cessation of treatment is associated with an increased risk of relapse. For this reason, patients should be regularly monitored in order to promptly diagnose and treat a possible recurrence of AAV. This review will focus on kidney involvement in AAV with an overview of the clinical–pathological characteristics and therapeutic strategy for these conditions.

Keywords Vasculitis · ANCA · Pathology · Therapy

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Introduction

The term systemic vasculitis includes a group of autoimmune disorders characterized by inflammation and necrosis of blood vessels. Vasculitis is a rare group of disorders with a heterogeneous clinical presentation and unknown etiology. The size of the vessel affected varies among the different forms of vasculitis and it is used for the classification of the disease. There are three main subgroups: large vessel, medium vessel and small vessel vasculitis, although any size artery can be affected in all the major categories [1, 2]. Other features used for classification are primitive versus secondary forms, characteristics of inflammatory infiltrates, association with antineutrophil cytoplasmic antibodies (ANCA) and different types of ANCA, presence or absence of immune deposits and genetic variants [3] (Table 1).

Recently this journal published a review on kidney involvement in medium and large vessel vasculitis [4]. The subgroup of small vessel vasculitis (SVV) includes ANCA-associated vasculitis (AAV) and immune-complex

Table 1 Different classifications of vasculitis

Size of vessel involved	
Large vessel vasculitis	Takayasu arteritis
	Giant cell arteritis
Medium vessel vasculitis	Polyarteritis nodosa
	Kawasaki disease
Small vessel vasculitis	
ANCA associated vasculitis	Microscopic polyangiitis (MPA)
	Granulomatosis with polyangiitis (GPA)
	Eosinophilic granulomatosis with polyangiitis (EGPA)
	Renal limited vasculitis (RLV)
Immune complex vasculitis	Anti-glomerular basement membrane disease
	Cryoglobulinemic vasculitis
	IgA vasculitis
	Hypocomplementemic urticarial vasculitis
Primitive or secondary	
Primitive form	
Secondary form	Lupus vasculitis
	Rheumatoid vasculitis
	Hepatitis B and C associated vasculitis
	Drugs associated vasculitis
	Cancer associated vasculitis
Type of ANCA	
P-ANCA	ANCA specific for myeloperoxidase (MPO-ANCA)
C-ANCA	ANCA specific for proteinase 3 (PR3-ANCA)
Atypical ANCA	Neither MPO nor PR3
Negative ANCA	
Histopathologic classes	
Focal	≥50% normal glomeruli
Crescentic	≥50% glomeruli with cellular crescents
Mixed	<50% normal, <50% crescentic, <50% globally sclerotic glomeruli
Sclerotic	≥50% globally sclerotic glomeruli
Genetic variants	
33 genetic variant (S and Z alleles of SERPINA1, HLA-B, HLA-DP,HLA-DQ and HLA DR, CTLA-4)	

vasculitis. This review will focus on kidney involvement in AAV with an overview of the clinical–pathological and histopathological classifications of these conditions.

The nomenclature established in 1994 by the Chapel Hill International Consensus Conference and revised in 2012 describes different forms of AAV, all characterized by few or no immune deposits in the vessel walls and the presence of ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). The major clinical-pathologic variants of AAV are: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's) (GPA), eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) and forms limited to the kidney (renal-limited vasculitis, RLV) [1, 2]. Although these forms show some differences in clinical and epidemiological characteristics, it is still controversial whether these different types of AVV are part of a single disease or represent distinct diseases.

Epidemiology

Vasculitis is a rare disease and until 1989 there were very few data on the incidence and prevalence of AAV. During the last 25 years, studies on the epidemiology of AAV have been reported from Europe, Japan, USA, New Zealand and Australia [5]. AAV are relatively rare in non-Caucasian populations [6, 7]. GPA is more common in the north of Europe and MPA more common in the south of Europe. The overall incidence rates of AAV in Europe are reported to be from 13 to 20/million inhabitants. The combined annual incidence of GPA and MPA in the UK

was 1.5/million at the beginning of 1980s and increased significantly to 6.1/million by the end of the 1980s [8]. The incidence of GPA tripled between 1975 and 2001 in a large population in Sweden (with an increase of prevalence from 36/million in 1993 to 112/million in 2001) [9]. This increased incidence was mainly due to enormous progress in the diagnosis of these forms that has been made since the 1980s due to the development of ANCA testing and to the implementation of classification criteria.

The gender distribution is fairly similar in most studies with a slight male predominance. Although AAV may occur at any age, the typical age of disease onset is between the fifth and the seventh decades of life [5]. Geographical factors such as environmental factors and exposure to certain substances may play a role. It is also now known that genetic factors play a major role [3]. The environmental risk factors most investigated as the trigger of vasculitis are infections, ultraviolet radiation, silica, heavy metal exposure, drugs or tobacco smoke [5].

ANCA subtypes

ANCA are serum autoantibodies which are directed against proteins present in the cytoplasmic granules of neutrophils. ANCA represent the serological markers of SVV and are commonly tested to confirm diagnosis when a SVV is suspected [10]. ANCA are generally tested by immunofluorescence technique as a first step, followed for confirmation by enzyme-linked immunosorbent assay (ELISA). The great majority of patients with SVV and renal involvement have detectable ANCA at indirect immunofluorescence. There are two main fluoroscopic patterns: diffuse, granular cytoplasmic (C-ANCA) and perinuclear (P-ANCA). A positive immunofluorescence finding needs to be confirmed by an ELISA test specific for the two major antigens in the primary granules of neutrophils: serine protease proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). The granular pattern is largely due to the presence of autoantibodies targeting PR3-ANCA, while the perinuclear pattern is caused by antibodies directed against many antigens. MPO-ANCA is the most frequently observed form in AAV. The sensitivity of indirect immunofluorescence is high while the specificity is low due to the presence of P- and C-ANCA in other diseases evaluated as controls. ELISA tests are highly specific, so combining indirect immunofluorescence and ELISA assures the highest diagnostic specificity (up to 98%) [11].

Besides PR3 and MPO, other neutrophil-related proteins can be targeted by ANCA at indirect immunofluorescence: bactericidal permeability increasing protein (PBI), elastase, cathepsin G and lactoferrin are some of these minor antigens. The presence of these atypical ANCA is not clearly associated with specific disease and their clinical significance remains unclear [12–14]. In most cases these antibodies are benign and are not associated with disease, but may be markers of inflammation [12].

Antibodies targeting lysosomal membrane protein 2 (LAMP-2) cause pauci-immune glomerulonephritis in rats and activate neutrophils in vitro [15]. LAMP-2 have been found in patients with necrotizing glomerulonephritis, suggesting that LAMP-2 could be a new ANCA subtype, but their role in disease pathogenesis and their utility in clinical practice is still debated [16].

Ten to 20% of patients with pauci-immune vasculitis do not have circulating ANCA. It is unclear what the underlying etiologic autoimmune agent in ANCA-negative vasculitis is, or if ANCA detection could be masked in patients with circulating fragments of ceruloplasmin. Other proteins may be responsible for the decreased recognition of ANCA. Sometimes it is possible that ANCA have been searched at the wrong timing of the disease or that the antibody levels are too low to be detected with the currently available assays. In any case, it seems that ANCA-positive and -negative vasculitis have the same course and outcome [17, 18].

ANCA specificity generally correlates with the clinical syndrome: PR3-ANCA are present in the majority of patients with GPA whereas MPO-ANCA are present in the majority of patients with MPA, although it is possible to find PR3-ANCA in MPA patients and MPO-ANCA in GPA patients. In AAV, only immunoglobulin (Ig)G ANCA are considered relevant. The pathogenicity of ANCA remains controversial but both clinical evidence and in vitro and in vivo experimental data support a direct pathogenic role of these autoantibodies (reviewed in [19]).

In vitro studies have demonstrated that ANCA plays a role in the stimulation of cytokine-primed neutrophils, thereby inducing the degranulation of neutrophils, and the release of oxygen free radicals and lytic enzymes which results in the lysis and disruption of endothelial cells [18]. Furthermore, ANCA-activated neutrophils release factors that activate the alternative complement pathway, which generates C5a, a chemoattractant that determines the accumulation of more neutrophils at the site of activation [20].

Multiple convincing models of MPO-ANCA-associated disease have been described and confirmed. Disease can be induced by injecting mouse anti-MPO IgG into immunocompetent or immunodeficient mice, by injecting splenocytes containing anti-MPO B cells into immunodeficient mice, or by transplanting bone marrow that contains MPO-positive myeloid cells into MPO-knockout mice. In these models, a pathogenic level of anti-MPO antibodies induces necrotizing and crescentic glomerulonephritis in all mice, systemic necrotizing SVV and granulomatous inflammation in some, but not all, animals. The inflammatory lesions in these mouse models closely mimic human AAV.

Furthermore, in patients and experimental animal models the acute vascular and extravascular lesions of AAV are neutrophil-rich necrotizing inflammation. In animal models, during the first days of necrotizing inflammation, neutrophils are the predominant cells within glomeruli. Subsequently they are replaced by monocytes and macrophages [19].

Targeted therapies that reduce autoantibodies and deplete B cells are effective treatments in AAV, supporting a pathogenetic role for ANCA [20].

Healthy individuals have circulating autoantibodies against MPO and PR3. Compared with pathogenic MPO-ANCA, natural MPO-ANCA has lower titers, lower avidity, less subclass diversity and less capability to activate neutrophils in vitro. There are many factors (genetic, environmental and immunological events) that can break autoimmune homeostasis inducing the development of pathogenic ANCA [19]. The proposed autoantigens that induce the pathogenetic ANCA response can be exogenous, such as infections or drugs, or endogenous like antisense peptides and peptides derived from alternatively spliced transcripts. Several microbial agents such as *Staphylococcus aureus* and *Ross River virus* have been implicated in the pathogenesis of AAV [21], and many drugs such as propylthiouracil, hydralazine, cocaine-containing levamisole or isoniazid have been shown to induce AAV [22].

The role of ANCA in monitoring disease activity in patients with vasculitis is still controversial: some studies found that ANCA levels was associated with disease activity and with an early prediction of relapse, but other studies did not find this association. Severe active disease without ANCA positivity is very rare [23]. It is reasonable to consider the increase of ANCA alone without clinical manifestation as a warning for a strict monitoring of the patient but not an indication to change the treatment [10].

There is evidence suggesting that identification of the ANCA subtype could be better than clinical diagnosis for defining homogeneous groups of patients, because PR3-ANCA and MPO-ANCA have been found to be associated with different genetic backgrounds [24, 25]. The large genome-wide study that has confirmed the role of genetic factors in the pathogenesis of AAV is the study of Lyons et al. [26]. It found that AAV forms have both major histocompatibility complex (MHC) and non-MHC associations and that GPA and MPA have a different genetic background. Anti-proteinase 3 ANCA was associated with HLA-DP and the genes encoding alfa1 antitrypsin (SERPINA1) and proteinase 3 (PRTN3) while anti-myeloperoxidase ANCA was associated with HLA-DQ. Several other polymorphisms have been associated to the risk of developing AAV and to the risk of relapse [26–29]. Recently, a meta-analysis confirmed that the classification of AAV based on ANCA serotype (MPO or PR3) has a stronger genetic basis than the subdivision based on clinical diagnosis [3].

Clinical features

The diagnosis of vasculitis is a challenge because its presentations are heterogeneous as regards severity and organ distribution. Clinically, the onset of AAV is often preceded by prodromal symptoms such as fatigue, articular pain, fever, weight loss, and headache. Laboratory tests show an elevation of the inflammatory markers: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), normocytic anemia and microscopic hematuria [30]. Constitutional disturbance can occur even several months before the organ-specific presentation or may be absent in the organ-limited presentation. Patients with all forms of AAV commonly present with upper respiratory tract symptoms such as sinusitis, dyspnea, rhinitis, nasal polyps and conductive deafness.

Renal involvement is present in the majority of patients with MPA and GPA and is asymptomatic until advanced renal failure occurs. Therefore, renal involvement in AAV must be diagnosed before the creatinine increase through detection in urine of microscopic hematuria, erythrocyte casts and non-nephrotic proteinuria. The consequences of a missed or delayed diagnosis of renal involvement are potentially life threatening, because the survival and the risk of end-stage renal disease (ESRD) are closely associated with renal function at presentation [31].

Clinicopathological variants

Microscopic polyangiitis

MPA is a necrotizing vasculitis predominantly affecting small vessels (capillaries, venules or arterioles). Multiple organs are generally affected in MPA, the kidneys and the lungs being the most frequently reported [32]. Necrotizing glomerulonephritis and pulmonary capillaritis are very common, while granulomatous inflammation is absent. A diagnosis of MPA is appropriate when there is systemic necrotizing SVV without evidence for granulomatous inflammation or asthma. The kidney involvement is present in almost 100% of patients with MPA and is characterized by a necrotizing and crescentic pauci-immune glomerulonephritis. The gold standard for diagnosis remains renal biopsy.

Patients with active disease have glomerular necrosis usually segmental without substantial endocapillary hypercellularity, segmental or circumferential crescents, disruption of Bowman's capsule and frequent periglomerular

infiltrates of leukocytes. Glomeruli without crescentic lesions have little or no histological abnormalities. At immunofluorescence, there is no evidence of glomerular immune complex deposits or linear IgG deposits typical of anti-GBM disease. These histological features are defined as pauci-immune forms. The crescents evolve from cellular to fibrocellular to fibrotic phases. This process is accompanied by a comparable degree of progressive sclerosis of glomerular tuft, interstitial fibrosis and tubule atrophy.

Arteriolar fibrinoid necrosis with associated mural and perivascular infiltration of neutrophils or mononuclear leukocytes lesions can be present in the renal specimen. Mononuclear interstitial infiltration is frequently present in active phases of the disease [33].

The clinical course of MPA is characterized by acute and quiescent phases and it is not uncommon to find in the same biopsy active and chronic lesions.

The urinary manifestations are oliguria, hematuria, erythrocyte casts and non-nephrotic proteinuria. Pauci-immune glomerulonephritis is the most common cause for rapidly progressive glomerulonephritis (RPGN) with a very rapid decline of renal function. Deterioration of renal function often carries a poor prognosis, with a high rate of ESRD and mortality. In addition to the renal involvement, pulmonary involvement can be present in about 50% of patients with MPA and its manifestations vary from transient infiltrate of alveoli to severe pulmonary hemorrhage. Neurologic involvement is found in about 30% of patients, generally in the form of peripheral neuropathy. Some patients have skin involvement in the form of purpura, and skin biopsy often shows leukocytoclastic vasculitis [32]. Most patients with MPA (65–90%) have ANCA directed against myeloperoxidase (MPO-ANCA) but a minority of patients (15–20%) have ANCA directed against proteinase 3 (PR3-ANCA). Not all patients, however, have ANCA [10, 18].

Granulomatosis with polyangiitis (former Wegener's)

GPA is a necrotizing granulomatous inflammation where the upper and lower respiratory tract are usually involved. A diagnosis of GPA is appropriate when there is evidence for necrotizing granulomatous inflammation accompanied by necrotizing SVV. The diagnosis of generalized GPA requires the involvement of an extra-respiratory tract organ (e.g. kidney, skin or nervous system) [34].

Also in this form necrotizing glomerulonephritis is frequent (about 70–80% of patients) and represents, together with the pulmonary involvement, the most severe complication of the disease. The pathology is similar, with extracapillary proliferation and glomerular necrosis in the absence of immune deposits. The distinctive trait of GPA is granulomatous inflammation with local tissue destruction that can be found in the upper and lower respiratory tract as well as in the kidney.

Renal failure is common and the course is generally ominous. If not treated promptly, RPGN can lead to ESRD in a very short period. Some patients require hemodialysis at diagnosis. Furthermore, renal involvement is associated with increased morbidity and mortality. Less frequently in GPA as well as in MPA renal disease may present as subacute or chronic nephritis.

In almost 90% of patients with GPA the lung and upper respiratory tract are involved. The initial symptoms of GPA begin in the head and neck region with a wide spectrum of involvement of any site ranging from the nasal septum, paranasal sinuses, oral mucosa, ocular area, larynx and even the external, middle and internal ear [35, 36]. Pulmonary hemorrhage is the most severe complication of the lower respiratory tract and is associated with a higher incidence of long-term mortality despite treatment. Other pulmonary symptoms are infiltrates, excavated nodules, pleural effusion and bronchitis. From 10 to 50% of the patients with GPA have skin involvement in the form of purpura, while a peripheral neuropathy is also possible (25% of patients) [37].

Most patients with GPA (40–90%) have ANCA directed against proteinase 3 (PR3-ANCA) but a minority of patients can have ANCA directed against myeloperoxidase (MPO-ANCA) or no detectable ANCA [10].

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

EGPA represents only 10–20% of patients with AAV and is treated as a separate entity in the latest guidelines and in most clinical trials [5, 6]. Although EGPA belongs to the AAV, a diagnosis of this syndrome is appropriate when there is a history of asthma and eosinophilia and granulomatous pulmonary disease is present. The pathology is similar to GPA and MPA, but with a prevalence of eosinophilic infiltration and/or granulomatous inflammation and less frequent extracapillary proliferations and glomerular necrosis.

EGPA has traditionally been described as evolving from a prodromal phase characterized by asthma and rhino-sinusitis, through an eosinophilic phase marked by peripheral eosinophilia and organ involvement, to a vasculitis phase with clinical manifestations due to SVV. Asthma is the main manifestation during the prodromal phase and is present in 96–100% of patients, often with upper respiratory symptoms (47–93% of patients) such as nasal polyps, allergic rhinitis and recurrent or chronic sinusitis. The eosinophilic phase is characterized by eosinophilic pneumonia or gastroenteritis. Involvement of the lung parenchyma occurs in up to two-thirds of

EGPA patients and the finding of migratory infiltrates on the chest radiograph is one of the key features of EGPA. Gastrointestinal involvement is often due to eosinophilic infiltration of the gastrointestinal mucosa and frequently affects the small bowel.

The heart, peripheral nerves, kidney and skin are commonly affected in the vasculitic phase. Symptomatic cardiac involvement occurs in as many as 27–47% of EGPA cases and is the leading cause of patient deaths, while peripheral neuropathy affects 70% of the patients and skin lesions are a prominent feature too. Although less frequent and severe than in the other forms of AAV, renal manifestations occur in 25% of EGPA patients and range from isolated urinary abnormalities to RPGN.

ANCA-positivity ranges from 30 to 70% of EGPA patients but is usually less frequently observed than in other AAV. An MPO pattern is the most common EGPA ANCA-positive finding (40% of cases) [38]. Two recent studies show that in EGPA ANCA positivity is associated with a higher prevalence of renal disease, pulmonary hemorrhage, skin involvement and peripheral neuropathy. ANCA negativity is strongly associated with heart involvement and non-hemorrhagic lung involvement [39, 40].

Renal-limited vasculitis

Isolated pauci-immune necrotizing, crescentic glomerulonephritis, typically known as idiopathic RPGN, has many features to suggest that it represents a renal-limited form of MPA, including the presence of circulating ANCA, mostly MPO-ANCA, in about 40–50% of cases [10]. The histologic features of renal-limited pauci-immune crescentic glomerulonephritis are indistinguishable from those of pauci-immune crescentic glomerulonephritis that occurs as a component of systemic vasculitis. Constitutional symptoms, generally present in these patients, indicate that the disease is active and systemic.

Histological classification OF AAV

In 2010, a new histopathological classification based on the percent of normal glomeruli, cellular crescents or global sclerotic glomeruli was proposed for the purposes of predicting the renal prognosis [41]. The four categories of glomerular lesions proposed were: focal, crescentic, mixed and sclerotic. The focal category is defined by the presence of more than 50% of normal glomeruli; the crescentic category by more than 50% of glomeruli with cellular crescents, the mixed class by less than 50% of normal glomeruli and crescentic or sclerotic lesions, while the sclerotic class by more than 50% of glomeruli with global sclerosis. In the validation study of Berden et al. the sequence of categories was found to correspond to the order of severity of renal function loss at 1 year as well as at 5-year follow-up. Renal survival at 5 years was 93, 76, 61 and 50% respectively. With such promising results, many studies since 2010 have tested the value of the proposed classification. All studies agreed about the best prognosis of the focal class [42–47] and many about the sclerotic class as having the worst prognosis [42, 43, 45, 47, 48]. The difference in survival between crescentic and mixed forms varies in several studies [42, 43, 46, 47, 49, 50] (Fig. 1). In our experience the renal survival at 5 years was worse in the crescentic subgroup compared to the mixed subgroup. This may be due to the fact that in the crescentic subgroup we found only 12% of normal glomeruli and that more than half of the crescents present were circumferential. Moreover, the Kaplan–Meier curves estimating survival without development of ESRD did not show significant differences between the outcome of focal and mixed groups or between crescentic and sclerotic groups. Consequently, survival without ESRD was significantly better for the focal and the mixed groups in comparison to that of the crescentic and the sclerotic groups. At multivariate analysis, independent predictors of ESRD were <20% of normal glomeruli at kidney biopsy, high serum creatinine and arterial hypertension at presentation [44].

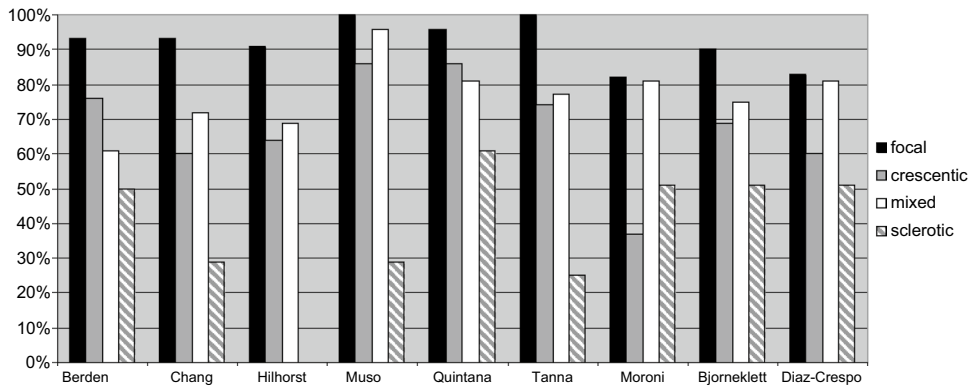

Fig. 1 Renal survival of the histological classes—focal, crescentic, mixed and sclerotic—from several studies that report the 5-year renal survival

Another matter of debate is that the classification is based on glomerular lesions only, while there are other lesions such as the chronic tubule-interstitial damage that can predict poor outcomes.

Treatment

Due to the rarity and heterogeneous nature of these disorders, the management of SVV can be extremely challenging. The initial therapeutic approach has to be tailored to each patient, and to the type and severity of the vasculitis phenotype. Two different steps are suggested: first, therapy to induce remission and then that to maintain remission and avoid relapses of disease. Although AAV are potentially fatal diseases, nowadays remission can be achieved and maintained in most cases with a combination of high-dose steroids and immunosuppressive drugs. The European League Against Rheumatism (EULAR) ethylenediamine tetraacetic acid (EDTA) recommendations have been recently published and are very useful for managing the treatment of AVV patients [51].

Treatment with glucocorticoids (GC) and either cyclophosphamide (CYC) or rituximab (RTX) is recommended for remission-induction of new onset organ-threatening or life-threatening AAV [52–59]. GC are the first line treatment to rapidly control inflammation and prevent further organ damage. Intravenous methylprednisolone (at a dosage of 7.5–15 mg/kg/day) is generally used for 3 consecutive days, followed by oral prednisone at a daily starting dose of 1 mg/kg. After about 1 month, prednisone can be gradually tapered. At the moment there is no internationally validated tapering regimen. CYC may be given as intravenous pulses (15 mg/kg) or 0.5 gr every 2–3 weeks or orally at a dose of 2 mg/kg/day. During therapy, the CYC dosage is to be adjusted for renal function, polymorphonuclear neutrophil (PMN) count and age. Therapy with CYC can be continued for 3 months after remission. An open-label randomized controlled clinical trial (CYCLOPS study) demonstrated no differences in remission between the pulse and daily oral CYC regimens. A reduced cumulative CYC dose and consequently fewer infections were observed with the intravenous CYC administration than with oral therapy, but in the long term follow-up pulse CYC was associated with a higher relapse rate [53].

The effectiveness of RTX in inducing the remission of severe AAV has been demonstrated by two different trials involving GPA and MPA patients. In the RAVE trial, 99 patients received 4 weekly RTX pulses (375 mg/m²) plus daily placebo-CYC. The other 98 patients received placebo-RTX infusion plus 2 mg/kg/day CYC. Patients in this group who achieved remission between 3 and 6 months were switched to 2 mg/kg/day of azathioprine. The two groups received the same GC regimen. The rate of remission and the adverse events were not significantly different between the two regimens. RTX tended to be superior in relapsing diseases [58]. RITUXVAS is a randomized trial involving 44 patients with a diagnosis of renal AAV. Thirty-three patients received a GC plus 4 weekly RTX infusions (375 mg/m²) and two intravenous CYC pulses. The other 11 patients received monthly intravenous CYC for 3 or 6 months, followed by azathioprine. The RTX regimen was comparable to the standard CYC regimen in terms of sustained remission rates and severe adverse events [57]. In refractory patients, a switch from cyclophosphamide to rituximab or the opposite is recommended. The same induction therapy is suggested for severe flares.

Plasma exchange is normally recommended for patients with rapidly progressive glomerulonephritis and serum creatinine greater than 5 mg/dl or for patients with severe diffuse alveolar hemorrhage [60]. PEXIVAS is an ongoing global trial that aims to provide definitive answers regarding the use of plasma exchange in AAV [61].

For the maintenance of remission one of the following drugs is recommended in association with low-dose steroids: azathioprine, RTX, methotrexate or mycophenolate mofetil [62–65]. Azathioprine (2 mg/kg/day), once remission is reached, is safer than CYC and as effective at 18 months in preventing relapses (CYCARAZEM trial) [62]. For maintaining remission, azathioprine was compared to RTX in the MAINRITSAN trial: 58 patients were treated with azathioprine (2 mg/kg/day for 12 months, then reduced to 1 mg/kg/day) from remission until month 22, while 57 patients were treated with RTX 500 mg e.v. on days 0 and 14 and at months 6, 12 and 18 after study entry. More patients treated with RTX had sustained remission at month 28 (5% on RTX versus 29% on azathioprine had a major relapse). No significant differences were noted in the rate of adverse events between the two groups [63]. Methotrexate for remission maintenance in AAV is not safer than azathioprine and it cannot be used if serum creatinine is >1.5 mg/dl [64]. Mycophenolate mofetil can be used at a dose of 2 g/day, but was proven to be less effective than azathioprine in the maintenance phase in an open-label randomized controlled trial (IMPROVE) [65]. Therapy has to be continued for at least 24 months after a substantial remission has been obtained with the induction therapy because early cessation of treatment is associated with an increased risk of relapse [51].

Prognosis

Patients with AAV have a very poor outcome if the vasculitis is not diagnosed and treated promptly. The introduction of immunosuppressive therapy has improved patient

survival dramatically, with over 90% of patients achieving remission compared to a mortality of 80% at 1 year in untreated patients [66]. Patient survival has been reported to be ~70% at 5 years of follow-up in cohorts comprising GPA and MPA, while in cohorts with exclusively GPA it is ~79% (reviewed in [67]). Many studies have documented a worse patient outcome for elderly patients and those with renal insufficiency at the time of diagnosis of AAV. AAV patients have a 2.6-fold increased risk of death compared to a matched general population [66]. Mortality is high in the first year after diagnosis, but the excess risk of mortality persists after the first year for patients with AAV. However, with the improvement of survival in the short term, AAV have become chronic diseases.

The main causes of death within the first year after diagnosis are infections and active vasculitis, and later cardiovascular (CV) events, malignancy and infections. Patients with AAV have a two- to fourfold increased risk of coronary heart disease compared to control subjects, and older age is associated with a higher risk for CV death. Many studies reported an overall increased risk for cancer in AAV patients, particularly high for urinary bladder cancer, lymphoma and non-melanoma skin cancer [67].

The identification of prognostic factors is a key element for the clinician in balancing the risks against the benefits of the treatment. The follow-up in patients with AAV is characterized by phases of exacerbation and phases of remission induced by therapy. Vasculitis recurs in 50% of patients, often after the reduction or discontinuation of therapy. In the prospective CYCAZAREM trial, patients with GPA had a greater chance of relapse than patients with MPA [62]. A number of studies have shown that relapses are much more frequent in patients with PR3-AAV than in those with MPO-AAV. PR3-ANCA positivity emerged as the most important risk factor for relapses in a multivariate analysis (reviewed in [24]).

Among genetic factors, Chang et al. found that DRB1*0405 was an independent risk factor due to the poor response to treatment and to the deterioration of renal function, and DPB1*0402 for all causes of mortality [68]. HLA-DPB1 haplotype could be an important determinant in relapse risk [29]. Genetic factors are promising, but their use in clinical practice is not routinely available. The prognostic significance of histological characteristics at kidney biopsy is still controversial. In addition to the proposed histological classification, there are other recognized factors correlating with poorer renal outcomes, such as the lower percentage of normal glomeruli or greater degree of tubular atrophy [44, 45].

Among the prognostic clinical features identified, some are associated with renal survival and others are associated with poor patient survival.

The principal negative predictors for patient survival are age >65 years, dialysis dependence at presentation, high creatinine in the first month, PR3-ANCA positivity, a high score on the Vasculitis Damage Index or a high Birmingham Vasculitis Activity Score [69, 70]. The main prognostic factors for renal survival are: GPA compared with MPA or RLV, the occurrence of a renal relapse during follow-up, less than 20% of normal glomeruli at kidney biopsy, high serum creatinine and arterial hypertension at presentation [44]. However, there is not an absolute level of serum creatinine above which treatment is always ineffective [71].

From January 1995 to December 2011, we hospitalized 93 patients with newly diagnosed AAV and renal involvement. The clinical characteristics at presentation, the therapy and the outcome of these patients are reported in Table 2. After the hospitalization and execution of a renal biopsy, the patients were followed in our Unit for a mean period of 62.7 ± 62.9 months. Patients were classified according to the 2012 Chapel Hill Consensus

Table 2 Clinical characteristics at presentation, therapy and outcome of the patients

Clinical characteristics	All 93 patients
At onset	
Follow-up, months	62.7 ± 62.9
Female/male, n	44/49
Age at diagnosis of renal involvement, years	58.8 ± 16.3
Serum creatinine, mg/dl	5.6 ± 4.4
Glomerular filtration rate, ml/min	23.2 ± 30.3
Proteinuria, g/day	1.9 ± 3.2
Urinary erythrocytes/high power field	63.5 ± 38.1
Arterial hypertension	55.9%
Hemoglobin, g/dl	9.63 ± 1.69
Eosinophils, %	3.2 ± 4.91
Erythrocyte sediment rate	84.6 ± 33.3
C-reactive protein, mg/dl	9.3 ± 9.2
C3, mg/dl	110.5 ± 29.5
C4, mg/dl	31.1 ± 9.9
Serum albumin, g/dl	3.2 ± 0.7
Therapy	
Methylprednisolone pulses	89.3%
Oral prednisone	10.7%
Oral cyclophosphamide	88%
Azathioprine	12%
Plasma exchange	12.9%
Outcome at last observation	
Normal renal function	38.7%
Chronic renal insufficiency	10.7%
Dialysis	35.5%
Death	15.1%

Conference on the nomenclature of systemic vasculitis as follows: 34 patients had MPA (36.5%), 38 patients had GPA (40.9%) and 21 patients had the renal limited form (22.6%). None of our patients had EGPA. Thirty-nine percent of patients were PR3 positive, 46.4% MPO positive and 14.6% ANCA negative. Of the 93 patients, 49 were males and 44 females, and the mean age at renal biopsy was 58.8 ± 16.3 years. The mean time between the first systemic manifestations of vasculitis and renal manifestations was 4.4 ± 12.7 months. The most frequent extra-renal manifestations at presentation were fever (51 patients), malaise (41 patients), arthralgia (36 patients), anorexia (33 patients), lung involvement (24 patients), upper respiratory tract involvement (25 patients), myalgia (18 patients), skin involvement (14 patients), central nervous system involvement (7 patients) and ocular involvement (5 patients). All but two patients presented with an impairment of renal function with a mean serum creatinine of 5.6 ± 4.4 mg/dl and a mean glomerular filtration rate of 23.2 ± 30.3 ml/min. The mean proteinuria was 1.9 ± 3.2 g/24 h and was in the nephrotic range in 12 patients (13%); at urinary sediment examination, the mean number of erythrocytes was 63.5 ± 38.1/HPF.

In this retrospective cohort, the choice of therapy was dictated by clinical and histological characteristics that were evaluated patient by patient. All patients received induction therapy. Eighty-three patients (89.3%) were treated with one methylprednisolone pulse (0.5–1 g according to body weight) for 3 consecutive days followed by oral prednisone 0.5–1 mg/kg/day for 1–2 months then progressively reduced. The other ten patients (10.7%) were treated with oral prednisone 1–2 mg/kg/day for 1–2 months then gradually reduced. In 82 patients (88%), oral cyclophosphamide 1.5–2 mg/kg/day was added to steroids and continued for a median of 7.5 months (25th–75th percentile: 5–12.7 months). In the other 11 patients (12%), azathioprine 2 mg/kg/day was added to prednisone. In addition, 12 patients (12.9%) received a course of plasma exchange. Plasma exchange has been employed since 2007 when the randomized trial of Jayne et al. [60] demonstrated its efficacy for patients with RPGN and serum creatinine greater than 5 mg/dl. As maintenance therapy, all patients received azathioprine associated with prednisone that was reduced by 2.5 mg every 2 weeks until 5–10 mg per day and then continued indefinitely.

Renal and patient outcome: At last observation after a mean follow-up of 62.7 ± 62.9 months, 36 patients (38.7%) had normal renal function (mean serum creatinine 1.1 ± 0.2 mg/dl; proteinuria 0.5 ± 0.7 g/24 h), 10 patients (10.7%) had chronic renal insufficiency (mean serum creatinine 3.0 ± 1.5 mg/dl), 33 (35.5%) are on chronic dialysis and 14 patients (15%) died (6 with normal renal function, and 8 with chronic renal insufficiency). Twelve other patients died in a median 12.3 months (2–44) after starting dialysis. Causes of death were: uncontrolled vasculitis in 6 patients, neoplasia in 5, myocardial infarction in 2, sepsis in 4, and unknown in the remaining 9 patients.

Among the 21 patients with the renal limited form of systemic vasculitis, the outcome was as follows: after a mean follow-up of 62.3 ± 63 months, 11 patients were on dialysis, 4 had chronic renal insufficiency (2 of these patients died), and the other 6 patients had normal renal function (1 of them died). Their outcome was not significantly different from that of the patients with other forms of vasculitis. Indeed 52.4% (11/21) of patients with the renal limited form entered dialysis in comparison to 30% (22/72) of the patients with the other vasculitic forms ($p = 0.11$). The pure kidney survival rate (without ESRD) was 83% at 1 year, 66% at 5 years, and 60% at 10 years. Patient survival was 92% at 1 year, 84% at 5 years and 81% at 10 years (Fig. 2).

We evaluated the predictors of renal outcome: at univariate analysis, among the clinical features at presentation patients who developed ESRD had higher serum creatinine ($p = 0.00001$), and higher CRP ($p = 0.01$), higher proteinuria ($p = 0.03$), lower glomerular filtration rate ($p = 0.001$), and more frequent arterial hypertension ($p = 0.001$) than those who did not develop ESRD. Among the histological features at renal biopsy, patients who developed ESRD had a percent of normal glomeruli <20 ($p = 0.00007$), a higher percentage of glomeruli with crescents ($p = 0.0007$), with cellular crescents ($p = 0.0007$), with circumferential crescents ($p = 0.001$), more frequent moderate-severe interstitial infiltration ($p = 0.02$), and more frequent severe tubulointerstitial fibrosis ($p = 0.04$). At multivariate analysis, taking into account only the histological features, less than 20% of normal glomeruli [$p = 0.011$, odds ratio (OR) 3.38, 95%

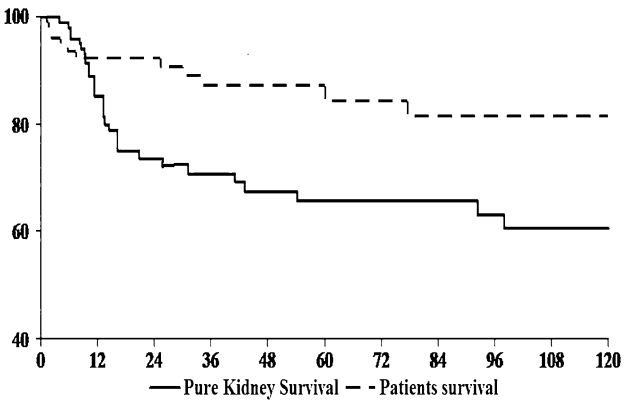

Fig. 2 Kaplan–Meier estimates of patient survival (*dashed line*) and of survival without end-stage renal disease censored for death (*solid line*) in ANCA-associated renal small-vessel vasculitis

confidence interval (CI) 1.32–8.65], circumferential crescents (p = 0.026, OR 1.02, CI 1.002–1.03), and tubulointerstitial fibrosis (p = 0.01, OR 1.88, 95% CI 1.16–3.04) were independent predictors of ESRD.

Including clinical and histological features, at multivariate analysis, serum creatinine [p = 0.009, relative ratio (RR) 1.11 for every mg of serum creatinine, 95% CI 1.03–1.21], presence of arterial hypertension (p = 0.006, RR 5.54, 95% CI 1.6–18.8) and less than 20% of normal glomeruli (p = 0.022, RR 3.05, 95% CI 1.17–7.93) emerged as the independent predictors of development of ESRD [44]. Our results confirm the importance of both clinical and histological features in predicting the renal outcome.

Conclusion

Renal AAV continues to be a severe disease with poor patient survival in the long term, particularly in elderly people. There are still questions about how to treat patients with very severe disease and/or refractory manifestations (subglottic stenosis, orbital tumors) and/or continually relapsing disease. Other questions of importance are how to further decrease the damage associated with the disease (ESRD, peripheral nerve damage) or its treatments [37]. An early diagnosis of renal involvement is of paramount importance to improve renal and patient survival. A prompt institution of therapy modulated on the severity of the disease is recommended.

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Compliance with ethical standards

Conflict of interest We declare no conflicts of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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