

ANCA Associated Glomerulonephritis- An In-Depth Review

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Abstract

Inflammation of vasculature involving small to medium vessels associated with antineutrophil cytoplasmic antibodies or ANCA are collectively referred to as ANCA vasculitides. In a majority of such disorders there are a few or no immune deposits and hence the term- "pauci immune vasculitis". The three main conditions included in this group include microscopic polyangiitis, Granulomatosis with polyangiitis (GPA) - formerly known as Wegener's granulomatosis, and Eosinophilic Granulomatosis with Polyangiitis (EGPA)-formerly known as Churg-Strauss Syndrome. There have been several advances in the last two decades in the classification, understanding of the pathogenesis and management of these conditions. To provide an update on the classification, pathology and pathogenesis and therapeutic advances for management of ANCA vasculitis is the focus of this in depth review.

Keywords: ANCA; AAV; Myeloperoxidase; Granulomatosis

Introduction

ANCA Associated Vasculitides (AAV) comprises a group of multi-systemic diseases affecting small-to-medium-sized vessels and is characterized by the presence of Anti-Neutrophil Cytoplasmic Antibodies (ANCA) with specificity for either Proteinase-3 (PR3) or Myeloperoxidase (MPO). Absence or paucity of immune complex deposits in vessel walls is very characteristic, hence the name "Pauci immune vasculitis".

The kidneys are vascular organs and therefore are targets for different types of systemic vasculitides, in particular those affecting small vessels. The primary renal sites for small-vessel vasculitides are the glomeruli therefore, the most common clinical presentations are those of glomerulonephritis. The characteristic kidney lesions in these conditions are pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (NCGN). Active pauci-immune small vessel vasculitis is typically associated with circulating ANCA antibodies (ANCA vasculitis). NCGN may also occur without extra renal manifestations of disease.

ANCA-associated-vasculitis (AAV) comprises three different diseases entities:

- 1- Eosinophilic Granulomatosis with Polyangiitis (EGPA) formerly known as Churg-Strauss Syndrome (CSS)
- 2- Microscopic Polyangiitis (MPA)
- 3- Granulomatosis with Polyangiitis (GPA) previously known as Wegener's Granulomatosis (WG)

Nomenclature and classification of vasculitis

The American College of Rheumatology (ACR) in 1990 had proposed classification criteria for seven vasculitis syndromes. The ACR criteria were developed before wide spread ANCA testing, and PAN and MPA were not differentiated. Application of the ACR criteria alone results in frequent overlaps between syndromes of WG, CSS, and PAN [1].

The nomenclature of the primary systemic vasculitis syndromes was defined by the 1994 Chapel Hill Consensus Conference (CHCC). The CHCC system was limited by its requirement for histology resulting in many unclassified cases [2]. The CHCC definitions were revised in 2012 to cover a broader spectrum of vasculitis, and to implement the replacement of eponyms with descriptive nomenclatures for vasculitis syndromes (Table 1).

The European Vasculitis Study Group (EUVAS) criteria for a diagnosis of AAV:

- History of a chronic inflammatory disease
- Exclusion of other causes (such as infection)
- Tissue biopsy showing characteristic histology on biopsy and/or a positive
- And/ or positive ELISA for either PR3 or MPO antibodies with a classical ANCA on immunofluorescence [3].

Pathogenesis

Vasculitis is an inflammatory process of blood vessels, and is characterized histopathologically by inflammation and fibrinoid necrosis of the vessel wall. The recent years have witnessed substantial developments in our understanding of the pathogenesis of ANCA associated vasculitides. Animal models have finally proven a direct pathogenic role for ANCA, a subject debated since their original identification. We also developed a more clear understanding of how ANCA exert their effects to cause disease.

Role of ANCAs

ANCAs are antibodies directed against neutrophil cytoplasmic antigens, first described in 1982 and were believed to be associated with Ross River virus infections. By 1985, ANCA had been linked to GPA and eventually the link with MPA and pauci- immune glomerulonephritis had been established. ANCA testing currently plays a critical role in the diagnosis and classification of vasculitides [4].

There is ample evidence that ANCAs are themselves pathogenic when studied in different *in vitro* and *in vivo* models [5]. Membrane-

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|--|---|
| ANCA-associated vasculitis | Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity. e.g., PR3-ANCA, MPO-ANCA, and ANCA negative |
| Microscopic polyangiitis | Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent |
| Granulomatosis with polyangiitis (GPA) | Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common |
| Eosinophilic granulomatosis with polyangiitis (Churg– Strauss) | Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present |

Definitions of ANCA-associated vasculitis according to the Chapel Hill consensus conference in 2012 [2]

Table 1: Classification of Vasculitis.

bound MPO/PR3 are expressed on the neutrophils and enhanced by pro-inflammatory cytokines through the process of “priming” which also enhances adhesion to endothelial cells. ANCAs bind to PR3/MPO on neutrophils and this interaction results in activation and release of serine proteases and cytotoxic superoxide. In addition to cytotoxic mediators, degranulation of the vascular endothelium occurs resulting in endothelial damage and vasculitic lesions [6]. ANCAs also enhance firm attachment of neutrophils to the endothelial cells leading to enhanced transmigration and damage [5].

The Role of the anti-idiotypic response

In 2004, a new concept was proposed that might explain the link between infection and autoimmunity. It was suggested that antibodies against complementary-PR3 (cPR3) demonstrated homology to several bacterial proteins, and it was hypothesized that PR3-ANCA develop in response to anti-cPR3 antibodies, as a consequence of the anti-idiotypic network.

PR3- ANCA is formed during a secondary immune response to antibodies that have specificity for complementary PR3 (cPR3). The sense strand of the PR3 gene codes for the corresponding sense protein PR3, whereas the antisense strand of the PR3 gene codes for the corresponding complementary protein cPR3. According to Pendergraft et al. [7] an immune response against cPR3 is elicited in AAV patients. Subsequently, antibodies with specificity for cPR3 evolve. The antigen-binding region of these antibodies mimics epitopes of the sense protein PR3. An additional immune response against anti-cPR3 antibodies is initiated and defined as ‘anti-idiotypic response.’ According to this concept, antibodies against anti-cPR3 evolve throughout the disease process. These ‘anti’-anti-cPR3 antibodies bind the sense PR3 and resemble PR3-ANCA. However, Tadema et al. [8] investigated the presence of anti-cPR3 antibodies in a Dutch cohort of PR3-ANCA-associated vasculitis patients. It was found that anti-cPR3-reactivity was not increased in their studies patients group, in comparison to the control groups.

Role of lysosomal-associated membrane protein 2 (LAMP-2)

Kain et al. [9] discovered new autoantibodies, anti-LAMP-2, and suggested that those antibodies play important role in the pathogenesis of AAV. Those antibodies were only found in patients with active vasculitis even those who were lacking PR3 or MPO. Patients with AAV without renal involvement or in remission also were negative for Anti- LAMP-2. Kain has proposed evidence of molecular mimicry between LAMP-2 and Fim- H - a bacterial adhesion protein, which in turn points out to the role of bacterial infection.

Roth et al. [10], questioned the prevalence of anti-LAMP 2 and

its relation to AAV, and concluded that these antibodies are only occasionally found in population, anti- LAMP-2 reactivity was not prevalent in ANCA sera and; reactivity was not different from the control group with gram negative urinary tract infection. No correlation was found between anti-LAMP-2 antibodies and disease activity. Kain and her group later confirmed their original results and showed that anti-LAMP-2 autoantibodies have different kinetics to those of PR3 and MPO, and are less likely to be detectable when the disease is in remission. They suggested that the differences reported by Aleeza and his group were largely attributable to selection criteria of the AAV patients studied and the assays used [11].

The role of the complement system

AAV is characterized by pauci-immunity and absence of immune complexes; however compelling evidences suggest the role of complement. Alternative complement pathways are emerging as players in pathogenesis. Schreiber et al. discovered that C5a has a role in priming neutrophils and enhancing ANCA induced neutrophil activation. C5a receptors deficiency in animal models was protective against the development of GN [12]. Their findings link neutrophils to complement activation. Moreover, mice treated with anti -C5 treatment could prevent MPO induced vasculitis [13]. Complement depletion using cobra venom resulted in complete blockage of MPO induced vasculitis factor [14]. Complement activation results in release of inflammatory cytokines with further activation of the neutrophils leading to enhanced cells destruction. The role of complement activation might explain the associated increased in thromboembolic events in AAV [15].

The role of T cells

A change in circulating T cell populations and altered expression of co- stimulatory molecules and increased numbers of activated T cell has been described. T cells are usually found within granulomas of AAV and markers of T-cell activity correlate with disease activity. A specific subset of effector memory T cells (Tems) (CD134+) is expanded in GPA patients. Tems migrate from the circulation to inflammatory lesions. Tems are powerful immune cells that initiate and sustain immune responses [16].

On the other hand regulatory T cells (Tregs) limit immune responses. In some autoimmune diseases, Tregs defects have been described. Two studies suggest a functional impairment of Tregs in GPA [17,18]. These defective Tregs are unable to inhibit effector T cells proliferation or cytokine production. Also defective Tregs elaborate the Tems expansion with continued T-cell activation [19].

Other Factors

Genetics

Genetic basis of the disease has been suggested by segregation of GPA cases in some families. A polygenic model has been suggested with many of those genes described encoding proteins involved in the immune response, such as CD226, HLA, PTPN22, CTLA4, AAT and others. Willcocks et al. [20] reported a neonate who developed GN and pulmonary hemorrhage apparently caused by trans-placental passage of MPO-ANCA IgG.

An increased expression of CTLA-4 on CD4+ T cells has been reported in GPA. CTLA-4 is a negative co-stimulator which binds to CD80/CD86 on Antigen Presenting Cells (APCs) and inhibits CD28-dependent T-cell activation. CTLA-4 interferes with increased T-cell activation in AAV. Genetic polymorphisms and dinucleotide repeats within the gene encoding CTLA-4 has been reported in AAV. Those elongated repeats lead to instability of mRNA and contribute to hyper-reactivity of T cells. The co- occurrence of PD 1.5 T allele with CDLA-4 49+ AA homozygosity was less often present in patients with AAV than in healthy controls [21]. Other associated polymorphisms in the *CTLA-4* gene are known to reduce the availability and surface expression of this negative co-stimulator. Thus, associated polymorphisms might limit the efficacy of CTLA-4 up regulation [21]. Further studies in this field are in progress to provide more insight.

Environmental factors

Drugs such as the anti-thyroid agent propylthiouracil are known to induce myeloperoxidase (MPO)-ANCA and to trigger overt vasculitis. Other drugs that have been associated with vasculitis as hydralazine, anti-tumour necrosis factor- α (TNF- α) agents, sulfasalazine, D-penicillamine and minocycline, however, most of them were limited to case reports [22]. Evidence is emerging around silica as a potential activator of the inflammatory complex and cytokine interleukin (IL)-1 [23]. Seasonal variation with reported higher incidence of vasculitis in winter and a lower incidence in summer, also points to the role of environmental factors. Other risk factor that has been implicated is exposure to pesticides, fumes or construction materials [24] hydrocarbons exposure such as cleaning agents, paint, and diesel [25]. The link to infections has been suggested by the findings of relapse in nasal carriers of *Staphylococcus aureus* [26]. Additionally a toxin from *S. aureus* is also a potent activator of the NLRP3 inflammasome, also known as cryopyrin [27]. Vaccination against hepatitis B, pneumococci and influenza has been linked to onset of vasculitis in some case reports [28-30].

Epidemiology

The incidence is higher in men than in women. The overall annual incidence of vasculitis is 10-20/million with a peak between 65 and 74 years of age however in the United States, the peak age ranges seemed to be lower [31]. Prevalence of AAV is more difficult to assess due to inherent difficulties but published studies suggest that the less common in the USA (32/million) [32] compared with more recent studies from Europe (65/million) [33]. The incidence is disproportionately greater in Caucasians than in African Americans and it was shown in a French study that the risk is two times greater for patients of European ancestry [34].

Clinical Presentations and Diagnosis

AAV are characterized by a focal necrotizing vasculitis affecting small vessels which can involve any organ with varying degrees of

severity. Overall, in GPA the lungs and kidneys are the most commonly involved organs, in about 70%-80% of patients [35].

Renal manifestations

Patients with ANCA associated glomerulonephritis usually present with rapidly progressive glomerulonephritis with hematuria, proteinuria, and serum creatinine elevation [36]. These patients have the typical necrotizing and crescentic glomerulonephritis. A smaller subset of patient have subacute disease and on renal biopsy have glomerular sclerosis either alone or accompanied by focal active disease with necrosis and crescents [37]. In a cohort of patients with ANCA/G N the mean age was 56 years, male female ratio was 1.0:0.9, mean serum creatinine was 6.5 and proteinuria was 1.94 ranges of 0.11 to 18.00 g/dL [38]. Approximately 75% of patients with ANCA/G N glomerulonephritis have manifestations of systemic small vessel vasculitis at the time of initial presentation. Some patients report an antecedent illness to the onset of symptoms of renal disease or systemic vasculitis [39]. Patients with ANCA crescentic GN may later show manifestations of systemic AAV. Woodworth et al reported 19 cases with ANCA/GN who initially presented with isolated crescentic GN and developed features of GPA 4-78 months after their diagnosis [40].

Other manifestations

Microscopic polyangiitis, GPA, and EGPA share certain clinical features of small-vessel vasculitis, but each also has distinctive characteristics. Constitutional signs and symptoms, such as fever, myalgia, arthralgia, and malaise, often accompany small-vessel vasculitis. Cutaneous lesions, leukocytoclastic angiitis caused by vasculitis or granulomatous lesions, present as palpable purpura and nodules. Necrotizing arteritis in small dermal and subcutaneous arteries cause's erythematous tender nodules; focal necrosis, ulceration, and livido reticularis. These are more common in patients with EGPA than in MPA and GPA. Peripheral neuropathy caused by vasculitis affecting the epineural vessels, is also more common in EGPA, followed by GPA and MPA. Central nervous system disease usually results from involvement of the meningeal vessels. Gastrointestinal involvement has been reported in almost one half of the patients with AAV [41].

Eosinophilic GPA (also known as Churg-Strauss syndrome)

EGPA is characterized by a history of asthma or severe allergic rhinitis and blood eosinophilia. The heart is a major target f or this form of vasculitis, with the heart failure is the most common cause of death. Pulmonary, neural, and cutaneous manifestations are common [42]. Renal disease is usually mild, and it is less frequent than in other entities of AAV but severe crescentic disease can occur [43]. In a recent report 75% of patients were noted to have manifestations of ear nose or throat. Allergic rhinitis and nasal polyps were the most common of these problems [44]. Other problems included otitis media, progressive sensorineural hearing loss and chronic rhinosinusitis.

GPA

Characterized by necrotizing granulomatous inflammation of ten with vasculitis, GPA usually has major involvement of the upper or lowers respiratory tract or both simultaneously [35]. Pulmonary lesions characterized by pulmonary nodules, with or without subsequent cavity formation. Pulmonary hemorrhage can result from the alveolar capillaritis, granulomatous inflammation or pulmonary arte ritis, and can be a life threatening condition. Ocular and ear inflammation may occur. Sub glottic stenosis may develop secondary to inflammation and scarring. Upper respiratory and nasal manifestations are very common

in GPA. Rhinorrhoea, epistaxis, sinusitis, otitis media, and collapse of the nasal bridge are well described in GPA. Cartilage and bone destruction of the nose may cause collapse with saddle nose deformity. Acute and chronic sinusitis is common, sometimes with bone and soft tissues destruction.

Microscopic Polyangiitis (MPA)

MPA is characterized by necrotizing vasculitis that affects small vessels without granuloma formation. Over 80 percent of patients with MPA have ANCA, Most Often Perinuclear ANCA (MPO-ANCA). MPA is distinguished from Polyarteritis Nodosa (PAN) by presence of vasculitis in vessels smaller than arteries, ANCA positivity, and negative serologic tests for hepatitis B [45]. Approximately 90 percent of patients have glomerulonephritis and pulmonary-renal syndrome is a common presentation [41]. Upper respiratory tract with or without pulmonary involvement is very rare. The respiratory manifestations alone are not adequate for distinguishing between MPA and GPA. In the presence of active major organ damage, such as crescentic GN or pulmonary hemorrhage treatment of AAV can proceed even if it is not clear whether the patient MPA or GPA [46].

Assessment of Disease Severity

A variety of methods have been used to evaluate disease activity in patients with vasculitis. The Birmingham Vasculitis Activity Score for GPA (BVAS/WG) was designed to measure disease activity and has been validated and used to assess treatment efficacy in clinical trials [46,47]. The BAVS score was lately modified on 2008 and with updated version has been validated for assessment of systemic vasculitis [48]. The Vasculitis Damage Index (VDI) was first published in 1997 and its revised version the Combined Damage Assessment (CDA) Index can be used as measures of damage from vasculitis [49]. The European Vasculitis Study (EUVAS) group categorized AAV into clinical subtypes according to the extent and severity of the disease. This categorization serves as a tool for the assignment of different treatment protocol regimens [50] (Table 2).

Diagnostic Evaluations

Detailed patient history, physical examination, laboratory and radiological investigations are critical in diagnosing any vasculitic disorder. Initial investigation includes complete blood count, inflammatory markers like; Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP). Evaluation for renal involvement should be done immediately; early diagnosis allows treatment to be initiated early. Renal function tests with eGFR, urinalysis for proteinuria and hematuria presence or absence of red cell casts or active urine sediment, quantification of proteinuria with a 24-hour urine protein collection or by urine protein/creatinine ratio. Urine infection should also be ruled out [51].

Measurement of complement level is useful since it might be low in patients with other forms of vasculitis as immune complex vasculitis (e.g. cryoglobulinaemia). Liver function should also be assessed,

and hepatitis specially Hepatitis C serology needs to be checked to distinguish MPA from PAN. Histological examination of biopsy from affected tissues is useful in confirming a diagnosis in the context of clinical and laboratory data. It is considered the gold standard investigation. Renal pathological features provide a way for directing therapy and assessing the prognosis in ANCA-associated.

Radiographic tests

Chest x-ray and Computed Tomography (CT) scan should be done in all patients evaluated for ANCA vasculitis. Computed Tomographic (CT) scanning may disclose lesions that are not seen on the plain chest x-ray, Baseline radiographic studies (including chest x-ray and CT) are often obtained prior to initiating immunosuppressive therapy [52].

Detection of ANCA

Serologic detection of ANCA is an important diagnostic marker for AAV either localized or systemic forms. However it is important to emphasize that ANCA must be interpreted in right clinical context with other available data. Approximately 80% to 90% of patients with GPA or MPA [53], and approximately 40% of patients with EGPA [54], are ANCA-positive. ANCA has two major Immunofluorescence (IFA) patterns: The C-ANCA pattern, characterized by diffuse cytoplasmic staining. In most cases, antibodies directed against PR3 cause this pattern. The second pattern is perinuclear or P-ANCA staining pattern around the nucleus, among vasculitis patients, the antibody responsible for this pattern is usually directed against MPO [54]. However positive IFA result does not correspond to a positive MPO-ANCA or PR3-ANCA. Using enzyme linked immunoassay (ELISA), C-ANCA commonly has specificity for proteinase 3 (PR3-ANCA) and the most common P-ANCA commonly has specificity for Myeloperoxidase (MPO-ANCA). When used together, positive IFA with positive ELISA has a sensitivity of approximately 81% and a specificity of approximately 96% for pauci-immune crescentic GN. As the case with other diagnostic testing, the positive and negative predictive values of the test are dependent on the pretest probability of the disease, clinical signs of the test and the prevalence of the disease in the studied population. Patients with active GPA granulomatosis usually have C-ANCA (PR3-ANCA), patients with microscopic polyangiitis have slightly more P-ANCA (MPO-ANCA) than C-ANCA (PR3-ANCA), and patients with EGPA and renal-limited pauci-immune crescentic glomerulonephritis have predominantly P-ANCA (MPO-ANCA) [41].

Some patients (as many as 10% in some reports) [55,56] present with classic manifestations of the pauci-immune crescentic glomerulonephritis, microscopic polyangiitis, GPA granulomatosis, or EGPA, but are ANCA-negative. Thus, a negative ANCA result by no means rules out these diseases, and patients who are ANCA-negative have the same prognosis and should receive the same treatment as ANCA-positive patients [55].

Changes in ANCA titers have correlation with disease activity and can be used in the right clinical context to monitor response to treatment, relapses or exacerbation. However, it must be interpreted with much

Table 2: Assessment of disease severity.

| | |
|----------------|--|
| Localized | Upper and/or lower respiratory tract disease without any other Systemic involvement or constitutional symptoms |
| Early systemic | Any, without organ-threatening or life-threatening disease |
| Generalized | Renal or other organ threatening disease, serum creatinine >500 μmol/litre (5.6 mg/dl) |
| Severe | Renal or other vital organ failure, serum creatinine >500 μmol/litre (5.6 mg/dl) |
| Refractory | Progressive disease unresponsive to glucocorticoids and Cyclophosphamide |

caution. Most clinicians do not modify treatment on the basis of an increase in titer without supportive clinical or laboratory evidence of disease exacerbation [57].

It should be noted that P- ANCA can be positive in inflammatory diseases like ulcerative colitis, rheumatoid arthritis and autoimmune hepatitis, however this P-ANCA lacks specificity to MPO [58]. In about one third of cases of anti-GBM disease, ANCA has been positive. In patients with concomitant anti-GBM and ANCA antibodies, histology tends to be different from those with only anti-GBM and the renal survival in these patients is not better than in anti-GBM positive patients and is worse compared with patients with MPO -ANCAs only [59].

Pathologic findings

Grossly, the kidneys are either normal or slightly enlarged. In case of severe pauci-immune crescentic glomerulonephritis, the cut surfaces may have scattered small red dots due to blood within Bowman's spaces and in tubules [60].

Histologically, the characteristic glomerular lesions of acute pauci-immune ANCA glomerulonephritis are crescents (Figure 1) and fibrinoid necrosis (Figures 2 and 3). The glomerular lesions may be accompanied by necrotizing arteritis; however, this finding is not common (less than 10% of specimens). The histologic finding that correlates best with outcome is the percentage of normal-appearing glomeruli by light microscopy [61].

Interstitial edema is commonly seen with severe acute pauci-immune ANCA glomerulonephritis. RBC and tubular casts are often present. Interstitial leukocytes infiltration by leukocytes is also common. Interstitial eosinophils often occur in EGPA [43], but this is not a specific finding, as it can be observed in microscopic polyangiitis, GPA granulomatosis, and renal-limited pauci-immune crescentic glomerulonephritis. Presence of foci of tubular coagulative necrosis should raise the possibility of vasculitis causing infarction [60]. Tubular atrophy and interstitial fibrosis are often present.

The pauci-immune necrotizing glomerulonephritis in GPA granulomatosis or microscopic polyangiitis is histologically indistinguishable from glomerulonephritis of EGPA but is often more extensive [61]. Morphologically, pauci-immune ANCA glomerulonephritis and anti-GBM crescentic glomerulonephritis have similar features. They cannot be differentiated by light microscopy

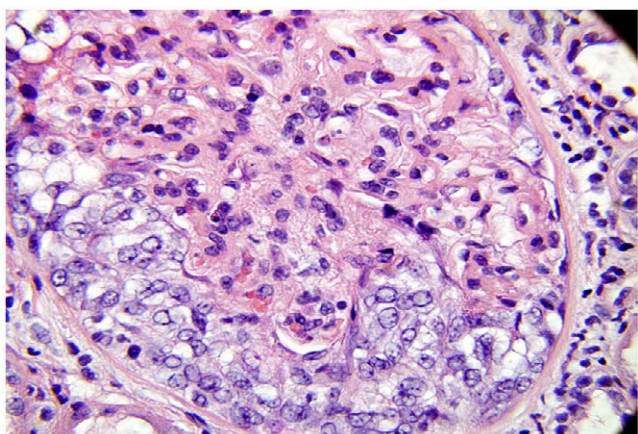


Figure 1: ANCA Vasculitis- Crescent formation.

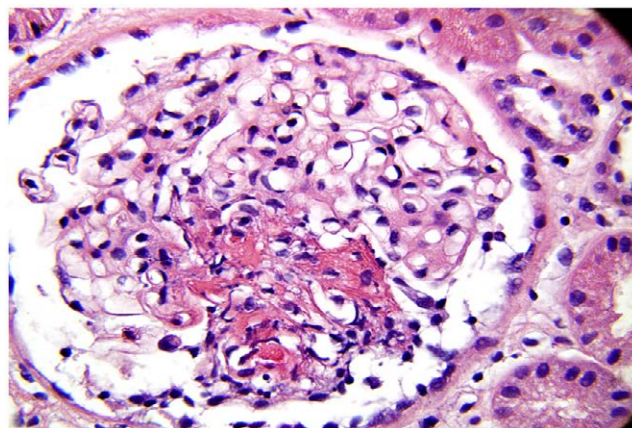


Figure 2: ANCA Vasculitis- Fibrinoid necrosis.

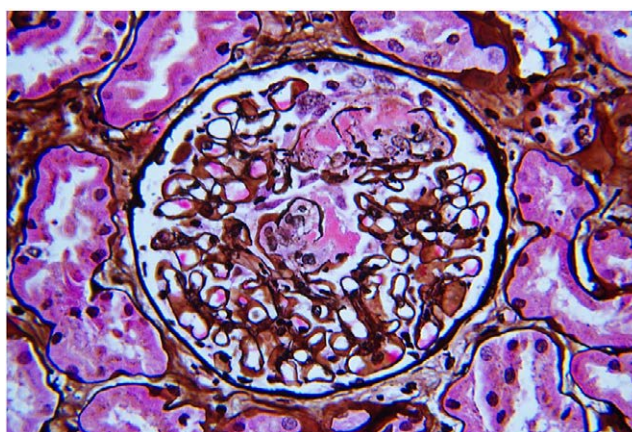


Figure 3: ANCA Vasculitis- Fibrinoid necrosis.

and electron microscopy; however, immunofluorescence microscopy can distinguish these two entities. Recently an international vasculitis working study group has proposed a histological classification of ANCA vasculitis into focal crescentic, sclerotic and mixed groups, to predict renal survival [62]. To validate the predictive value of this classification Hillhorst et al. [63] recently examined 164 consecutive patients with biopsy-proven ANCA- associated vasculitis with renal involvement. The study concluded that crescentic and mixed groups had the worst prognosis when the number of normal glomeruli was <25%. The study recommended considering the percentage of number of glomeruli in predicting the renal survival.

By immunofluorescence microscopy, pauci-immune crescentic ANCA glomerulonephritis, has very little staining with immunoglobulins; however, some non-specific staining for immunoglobulin is not uncommon [43]. Staining for fibrin at sites of fibrinoid necrosis is often present. Electron microscopy often shows no electron-dense deposits. However, occasionally, there may be a few small electron-dense deposits (especially, if staining for immunoglobulin was seen on immunofluorescence microscopy). Breaks in glomerular basement membrane breaks are often seen.

Differential diagnosis

Pauci-immune crescentic glomerulonephritis must be separated from immune complex mediated glomerulonephritis and anti-GBM

disease. Although, this may not be accomplished by light microscopy alone; immunofluorescence microscopy and serology usually lead to definitive diagnosis.

Immune complex glomerulonephritis often has more glomerular hypercellularity, in contrast to pauci-immune crescentic glomerulonephritis [41]. On the other hand, anti-GBM glomerulonephritis is indistinguishable from pauci-immune crescentic glomerulonephritis because both, typically, have prominent fibrinoid necrosis and crescent formation without significant endo-capillary proliferation. A typical linear staining for IgG in anti-GBM disease on immunofluorescence study and serology will allow the specific diagnosis.

Similarly, immune complex type deposits by immunofluorescence and electron microscopy will help separate Henoch-Schonlein purpura (IgA-dominant immune deposits) and cryoglobulinemic vasculitis (IgM-dominant deposits). Lupus nephritis will have characteristic full house positivity on immunofluorescence study and deposits on electron microscopy.

Drug-associated ANCA disease is another cause of pauci-immune crescentic glomerulonephritis, histologically similar to other etiologies. This entity characteristically has a positive antinuclear antibody test without systemic lupus erythematosus. An unusually high titer of MPO-ANCA raises suspicion of drug-induced disease [64]. Likely drugs include propylthiouracil, hydralazine, and methimazole.

Prognosis

AAV are associated with high morbidity and mortality. The survival rate was unfortunately low before the introduction of cyclophosphamide, with the median survival rate of five months in systemic GPA [65]. ESRD developed in over 20% of patients with renal vasculitis at five years [66]. On the other hand, remission induction is now achievable in almost 90% patients by six months [67] with survival rates are around 75% [68].

The relapse rate however, remains high- up to 50% over five years despite therapy [69]. Therapy its self is associated with serious unwanted effects for a substantial number of patients specially with high risk of infectious complications [70].

In another study it was found that incidence of cancer in AAV patients treated with conventional immunosuppressive therapy was higher than expected for the general population with non-melanoma skin cancer, bladder cancer, leukemia and lymphoma being the commonest type of cancers [71]. Lionaki et al. [72] studied the disease outcome in patients with renal involvement and concluded that, despite treatment advances, a quarter of patients with ANCA- vasculitis still develop ESRD. ESRD in this study was more as a result of new onset disease with severe renal involvement rather than relapsing or chronic vasculitis. (51 versus 43 % respectively) This finding again points out to the importance of prompt diagnosis and treatment with expedient use of immunosuppression specifically in ESRD patients with active vasculitis.

Other studies have been conducted to study prognostic factors for renal outcome. The EUVAS group conducted a prospective study to identify the clinical and histologic prognostic predictive factors for renal outcome in patients with ANCA- associated glomerulonephritis. It was shown that age, renal function at time of diagnosis, normal glomeruli percentage, and tubulointerstitial lesions were predictors of the GFR at 12 months. Dialysis dependency was predicted by the

percentage of fibrous crescents at entry, percentage of normal glomeruli and treatment arm [73].

Recent evidence suggests that Interleukin-10 (IL-10) secreting B cells [Breg] that regulate Tcell mediated immunity may have diagnostic and prognostic significance in AAV patients. Studies by Wilde et al. [74] showed that the fraction of Breg were decreased in AAV compared to healthy controls while IFN- γ + T helper cells were negatively correlated with AA V in remission but in active AAV or healthy controls. These studies indicate that Breg suppression of T helper cells may be decreased in active AAV.

Another recent study [75] found evidence for role of toll-like receptors (TLR)9 in AAV patients. A strong association was demonstrated between AAV and TLR-9 genotypes and haplotypes with significant differences between PR3A-NCA+ vasculitis and MPO-ANCA+ vasculitis.

A large retrospective study [76] that was published in 2013 analyzed prognostic factors in 273 consecutive patients that were diagnosed with AAV. In patients with renal involvement, advanced renal failure needing renal replacement was associated with worst prognosis; Multivariate analysis revealed that the main determinants of long term survival were renal function at 6 months and renal relapses.

Management

Treatment of AAV can be divided into three phases, initial immunosuppression and subsequent maintenance and third is treatment of relapse. Patients with concurrent anti-GBM disease or immune complex disease should be treated similarly to patients with ANCA disease alone.

Induction therapy

Complete remission is defined in some trials as absolute absence of clinical signs of disease activity and partial remission was defined as absence of acute or newer clinical activity [77]. Using the BVAS score in other trials, complete remission was defined as BVAS of 0 (no clinical, radiologic, or pathologic evidence of active disease) plus PCR < 10 mg/L, and partial remission as clinically relevant improvement of BVAS [78].

Induction of remission in ANCA-associated vasculitis

The EUVAS Group (EUVAS) has published guidelines on the management of vasculitis with different treatments recommended according to the disease category [50] (Tables 3 and 4).

Treatment with cyclophosphamide in combination with corticosteroid induces remission in approximately 75% of patients at 3 months and 90% at 6 months [79]. The National Institutes of Health (NIH) developed the initial regimen that consisted of oral CYC at a dose of 2 mg/kg/day and glucocorticoids at 1 mg/kg/day. The treatment continued for at least one year after remission with the steroid tapered to an alternate day regimen [80]. This regimen reliably induces remission in, but causes significant toxicity and morbidity [35] and relapses occur in up to 50% of patients, despite continued immunosuppression [35]. Numerous refinements of this approach have been tested in clinical trials.

IV versus oral cyclophosphamide

CYC is toxic in a dose-dependent manner and associated with severe side effects and high cumulative doses above 36g seem to increase the risk for leukemia and bladder cancer [81]. Regimens using IV CYC offer one third to one half of the total dose of CYC given

| Disease category | Induction therapy | Maintenance therapy |
|---------------------|---|--|
| Localized disease | Methotrexate and steroids | Low-dose steroids plus azathioprine or leflunomide or methotrexate |
| Early Systemic | Methotrexate or cyclophosphamide and steroids | Low-dose steroids plus azathioprine |
| Generalized disease | Cyclophosphamide and steroids | Low-dose steroids plus azathioprine or mycophenolate mofetil |
| Severe disease | Cyclophosphamide and steroids plus plasma exchange | Low-dose steroids plus azathioprine or mycophenolate mofetil |
| Refractory disease | Deoxyspergualin, mycophenolate mofetil, antithymocyte globulin or rituximab | No consensus |

Table 3: Assessment of Disease category.

| Drug | Dose | Other |
|------------------------------|--|---|
| Cyclophosphamide | IV Pulses: 0.75 g/m ² q 3–4 weeks. 15 mg/Kg 2-weekly for 3 pulses, then 3-weekly for 3-6 pulses. Decrease initial dose to 0.5 g/m ² if age >60 years or GFR <20 ml/min per 1.73m ² . Adjust subsequent doses to achieve a 2-week nadir leukocyte count <43000/mm ³ . | Oral cyclophosphamide (2 mg/Kg/day) might be used Adjusted to keep WBC >3,000/μL |
| Prednisone | 60 mg/day for 1 month tapered to 15 mg/day at 3 months | IV methylprednisolone 500-1,000 mg/day for 3 days in critical organ manifestations |
| Rituximab IV | 375 mg/m ² /week for 4 Pulses | Use in intolerance to CYC and in young patients |
| Plasmapheresis | 60 ml/kg volume replacement. Vasculitis: Seven treatments over 14 days. If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. | Use in critical organ manifestations (serum creatinine >5.6 mg/dL, or lung hemorrhage) Vasculitis in association with anti-GBM antibodies: Daily for 14 days or until anti-GBM antibodies are undetectable |
| Methotrexate | Starting dose 15 mg/week, increased to 20-25 mg/week at 2 months | Use in non-critical organ manifestations (normal serum creatinine) |
| Mycophenolate Mofetil | 2 g/day | In patients with moderate renal involvement who cannot take cyclophosphamide |

Table 4: The agents used in induction therapy and their dosage.

in oral regimens. Randomized trials to compare both approaches, including the EUVAS/ CYCLOPS trial demonstrated that pulsed IV CYP (used at a dose of between 7.5 and 15 mg/kg/pulse in this study) has the advantage of a lower total cumulative dose (8.2 versus 15.8 g) with no difference in the time to achieve remission or the percentage of patients who achieved it. The dose of CYC in CYCLOPS protocol must be adjusted for weight, age, and renal function which improved the safety of these agents [82].

A meta-analysis study showed i.v. CYC was as effective as oral CYC for inducing remission and was associated without a significant difference in mortality and a tendency toward an increased risk of relapse [83].

Glucocorticoids

There is no consensus agreement on the dosing of glucocorticoids because of lack of randomized trials. The usual initial dose is 1 mg/kg (maximum 60 to 80 mg) with subsequent tapering to maintenance dose not more than 15-20 mg/day at three months or when remission is achieved (whichever is later). IV methylprednisolone in doses of 0.5-1.0 g daily for three days can be used initially. Adverse steroid effects, including hypertension, obesity, hyperglycemia, cataracts, and osteoporosis, should not be underestimated and remain a considerable cause of morbidity [84]. Different steroids tapering regimen have been employed. The initial dose is typically continued for two to four weeks. If significant improvement is achieved, the dose is tapered slowly, with the goal of reaching 20 mg/day by the end of two months. The total duration of steroids therapy has been six to nine months. However, the use of prednisone beyond six months is not favorable because of associated morbidity related to adverse effects of the steroids [85]. During induction, pneumocystis jiroveci prophylaxis with

trimethoprim- sulphamethoxazole, gastric prophylaxis for protection from ulceration, and calcium- vitamin D supplementation is usually added to the regimen.

The role of plasma exchange (PE)

The likely mechanisms of PE are rapid removal of ANCA, and the reduction of circulating inflammatory cytokines, complement, and coagulation factors [84].

Plasma exchange may be of benefit in three specific conditions [86]:

- (1) life-threatening pulmonary hemorrhage
- (2) Dialysis-dependent renal failure at the time of presentation
- (3) Concurrent anti-Glomerular Basement Membrane (GBM) antibody disease.

The MEPEX trial aimed to study the effect of PE on the renal and patient survival in a cohort of patients with severe renal vasculitis and acute renal failure. Plasmapheresis in combination with oral CYC/PRED compared with concomitant courses of i.v. methylprednisolone instead of PE. It was shown that PE compared with pulse methylprednisolone increases the rate of recovery from renal failure. Patient survival and adverse events were not significantly different. Moreover, PE was associated with a 24% reduction of the risk of progression to end-stage renal disease (ESRD) [87]. A recent meta-analysis by Walch et al., which identified 9 trials including 387 patients with renal vasculitis, found that PE resulted in reduction in the composite end point of mortality and progression to ESRD. This outcome did not affect significantly across the range of baseline serum creatinine values or the number of PE treatment that was received [88]. PEXIVAS study received ethical approval and is actively recruiting and this trial aims to

study the influence of PE and a reduced dose of steroids on mortality and ESRD in patients with less advanced renal impairment (estimated glomerular filtration rate of <50 mL/min [88].

Rituximab (RTX)

A chimeric monoclonal anti-CD20 antibody that works by B-cell depletion, RTX has been studied as an alternative to CYC in the standard induction protocol. The non-inferiority of RTX to CYC induction protocol was evident in two RCTs. In the RAVE trial RTX was compared to CYC for induction of remission, in a multi-centric non-inferiority RCT. The patients studied were either newly diagnosed or with relapsing GPA or MPA disease, they were randomly assigned to receive either RTX (375 mg/m² per week for four weeks) or oral CYC (2 mg/kg per day). Both groups received one to three pulses of IV methylprednisolone (1000 mg) followed by oral prednisone (1 mg/kg per day). RTX was found to be non-inferior to CYC in inducing remission. RTX was superior to CYC in remission induction in patients with relapsing disease. No difference in the number of adverse events or relapse rate between the two protocols [89].

In the EUVAS/ RITUXVAS study, patients with ANCA-associated renal vasculitis were assigned in to receive iv methylprednisolone followed by oral methylprednisolone (tapered down to 5 mg per day by the end of six months) plus either rituximab (375 mg/m² per week for four weeks) with two i.v. CYC pulses (15 mg/kg) or IV CYC for three to six months. A third dose of CYC was given to the patients who received RTX if they develop progressive disease within the first six months. At 12 months, there was no difference in the rate of sustained remission nor the rate of adverse effects between the RTX and the CYC only groups [90]. These studies support the non-inferiority of RTX when compared with CYC for induction of remission with a less toxic profile. Rituximab can be used as an alternative to cyclophosphamide in generalized, severe or refractory AAV when there is contra-indication to CYC. However, no sufficient data available on the long term outcomes, or its use in localized and early systemic disease [91].

Maintenance therapy

In patients with newly diagnosed GPA or MPA, the maintenance therapy is usually given for 12 to 18 months after achieving remission. No RTC were conducted to compare the different duration of maintenance treatment [67] (Table 5).

Azathioprine

Azathioprine has been evaluated for maintenance of remission in patients with AAV. In the EUVS/CYCAZAREM trial, patients with

ANCA-positive vasculitis received induction therapy with oral CYC and prednisolone for a minimum period of three months. The patients, in whom remission was achieved, were randomly assigned to either continued oral CYC (1.5 mg/kg per day) or azathioprine (2 mg/kg per day) along with prednisolone 10 mg/day in each regimen. At one year, both groups were treated with azathioprine (1.5 mg/kg per day) plus prednisolone (7.5 mg/day). It was shown that there was no significant difference in the relapse rate or the number of severe adverse events during the maintenance of remission phase between the two groups [67].

Methotrexate

MTX has been used as an alternative to CYC in induction of remission in early systemic vasculitis without significant renal involvement or life threatening disease. The EUVAS NORAM trial compared MTX and CYC for both induction and remission of ANCA-associated vasculitis without significant renal involvement. MTX was found to be a less toxic alternative to CYC for patients with early systemic disease and mean serum creatinine 1.0 mg/dl achieving equal rates of disease remission, albeit at a slower rate [92]. Given the higher relapse rate MTX should be used primarily for limited disease not involving the kidney, and given its renal toxicity MTX is contraindicated in patients with significant renal impairment and should not be used with renal impairment when GFR is below 50 ml/min. The European League against Rheumatism (EULAR) 2008 guidelines recommended that oral or parenteral MTX in combination with glucocorticoids can be used as an alternative to CYC to induce remission in patients with localized ANCA associated vasculitis without organ or life threatening disease [50]. MTX dose usually starts at 10 mg/week increasing to 25 mg/week or 0.3 mg/kg if tolerated. Side effects are mainly myelotoxicity, hepatotoxicity and mucositis, which required monitoring with CBC and liver function tests. The (WEGENT) trial compared AZA and MTX for maintenance therapy in patients with GPA or MPA (with a mean serum creatinine was approximately 2.0 mg/dL at baseline and 1.5 mg/dL at randomization) who were in remission after treatment with CYC and oral glucocorticoids were randomly assigned to azathioprine (2 mg/kg per day) or methotrexate (0.3 mg/kg per week, progressively increased by 2.5 mg every week to a maximum of 25 mg per week) for 12 months followed by gradual withdrawal over three months. At the end of the follow up period, both groups had similar number of adverse effects with similar relapse rate and most of the relapses developed after cessation of the maintenance therapy [93].

Mycophenolate mofetil

MMF has been tried as an alternative to CYC for induction of

| Drug | Dose | Other |
|----------------------------------|--|---|
| Prednisolone | 15 mg/day at 3 months tapered to 7.5 mg/day at 12 months | Alternate-day schemes have been used to minimize side effects. Should not be used alone in generalized or severe forms of the disease |
| Cyclophosphamide IV pulse | 0.75 mg/m ² every 3 Months | Oral cyclophosphamide (1.5 mg/Kg/day) might be used in patients with frequent relapses |
| Azathioprine | 2 mg/kg/day for 12 months than 1.5 mg/kg/day | Considered the gold standard for maintenance of remission |
| Rituximab IV | 375 mg/m ² every 6 Months | Should be considered in Patients where AZA or MTX is either contraindicated or ineffective. |
| Mycophenolate mofetil | Starting dose 2000 mg/d reduced to 1500 mg/d after 12 months, 1000 mg/d after 18 months, and withdrawn after 42 months | In IMPROVE trial, when compared to AZA, relapses were less frequent among those who received AZA [97] |
| Methotrexate | Starting dose 0.3/kg per week, increased to 25 mg per week | For limited disease not involving the kidney. Should be avoided in patients with renal impairment |

Table 5: Agents used in maintenance therapy.

remission. For instance, A small open-label study compared MMF and CYP in 35 patients with AAV mainly MPO-positive, with serum creatinine <500 $\mu\text{mol/L}$. This showed higher rates of remission and maintenance of normal renal function in the MMF group compared with the CYP group at six months [94]. The EUVAS group conducting the MYCYC trial to Compare MMF and CYP for induction of remission but has yet to report the findings [95]. There has been greater interest in the use of MMF as a maintenance agent rather than as an induction agent until more data are available. Although recent IMPROVE trial results from EUVAS suggest it may be inferior to AZA. Gastrointestinal symptoms and opportunistic infections are not uncommon. The (IMPROVE) has been conducted to compare MMF to AZA for maintenance of remission in patients with newly diagnosed ANCA-associated vasculitis. Patients who achieved remission with cyclophosphamide and glucocorticoids were randomly assigned to received either AZA (starting at 2 mg/kg per day, then reduced to 1.5 and 1.0 mg/kg per day after 12 and 18 months, respectively) or MMF (starting at 2000 mg per day and reduced to 1500 and 1000 mg per day after 12 and 18 months respectively). Both agents were withdrawn after 42 months of treatment. The rate of adverse events was not significantly different between the two groups however; relapses were less frequent among those who received azathioprine [96].

TNF- α blocking agent

The use of TNF- α blockade in treatment of AAV is controversial. The WGET trial assessed Etanercept use in AAV. Serious concerns on safety of Etanercept (including increased incidence malignancies) have been raised [97]. Infliximab has been shown in some studies to be effective agent when used with the conventional therapy for induction and maintenance of remission in patients with AAV, although the rate of developing severe infection was higher [98]. The results of subsequent trials were conflicted and could not show clear additional benefit from its use in AAV [99].

The efficacy of adalimumab, was recently studied by Laurino et al. in patients with new-onset systemic GPA/MPA and renal involvement concomitantly with CYC and PRED induction protocol, The addition of adalimumab reduced prednisone exposure with remission rates and adverse events similar to standard therapy alone [100]. Further studies on those agents would be useful to understand whether their addition to the current protocols would confer additional advantage but such studies may never be undertaken in view of severe adverse effects and malignancy potential of these compounds.

Treatment of refractory and relapsing disease

The definition of refractory disease varies widely. In general, resistance is defined as unresponsiveness to standard induction treatment with CYC and steroids, the persistence or appearance of renal and/or systemic manifestation of vasculitis. Renal manifestations of resistance include presence of hematuria, red blood casts with continued decline of renal function. Resistance to corticosteroids and cyclophosphamide has been reported in as high as 20% of patients. Numerous agents have been suggested to be used in patients with refractory disease. Randomized trials to analyze the best therapy are lacking. The following agents have been tried.

Intravenous immunoglobulin

IVIG act by interfering with ANCAs binding to their antigens and by inhibiting ANCAs-mediated neutrophil activation. IVIGs have good safety and tolerance profiles, these agents can be included in a therapeutic strategy with other drugs used to treat relapses In one study

IVIG was administered for 6 months to treat relapses GPA or MPA (relapses occurred while under treatment or during the year following its discontinuation). IVIGs induced complete remissions in 13 of 22 patients at month 9 [101].

15-Deoxyspergualin

15-Deoxyspergualin was tested in two open-label trials in patients with refractory GPA, 70 % of patients in the first trial [77] and 95% in the second [102], achieved partial remission. The favorable safety profile of 15-Deoxyspergualin suggests that it could be a promising therapy.

Antithymocyte Globulin (ATG)

ATG causes rapid, deep depletion of T lymphocytes. In a prospective uncontrolled trial, ATG infusion induced remission in 13 of 15 patients with GPA in whom CYC was contraindicated, or with refractory disease while on CYC. Because of the ATG potential adverse events, it was suggested to avoid its use in cases of infections and to balance the benefit versus risk of its use in such patient's population [103].

Allogeneic hematopoietic stem cell transplantation

In selected cases with refractory disease, allogeneic hematopoietic stem cell transplantation has been recently tried. It was reported that this therapy might allow achieving control of disease activity [104].

Rituximab

In the previously mentioned RVE trial RTX was superior to CYC in remission induction in patients with relapsing disease [89]. In another retrospective study RTX was suggested to be possibly efficient to induce remission in patients with refractory AAV [105].

Treatment of relapses

Relapse is defined as the recurrence of signs or symptoms of active vasculitis in any organ system after a period of partial or complete remission. Severe relapse is defined as life-threatening (e.g pulmonary hemorrhage) or organ-threatening (e.g. active GN) relapse [106]. Relapse is common in patients with AAV and rate of relapse has that been reported ranges from 11 to 57 [107]. In a large cohort of 535 patients with AAV, Anti-proteinase 3 antibodies and cardiovascular involvement were associated with increased risk of relapse. On the other hand, a creatinine level >200 $\mu\text{moles/liter}$ at the time of diagnosis was associated with a reduced risk of relapse [108].

Nasal carriage of *S. aureus* in has been also associated with increased relapse rate. Antibiotic treatment as cotrimazole decreased the relapse rate in patients with GPA [109]. The preferred treatment of relapsing disease has not been defined. According to the KDIGO guidelines for GN, the protocol used for treatment of relapse is similar to the induction therapy; however it should be taken into consideration the severity of the relapsing disease and the previous cumulative CYC dose. Severe relapses should be treated with CYC, corticosteroids and plasmapheresis (whenever indicated). Patients who have received a high cumulative dose of CYC, were suggested to receive a rituximab-based regimen. For relapse that is not severe, increased immunosuppressive therapy should be used with more precaution of the cumulative CYC dose as possible.

In patients who develop relapse while not receiving maintenance therapy, treatment may include the reinstatement of MMF or AZA alone or in combination with steroids. In patients who suffer a relapse while

on maintenance therapy with azathioprine or MMF, IVIG can be tried [110].

Potential novel therapies

With the advances in understanding of the underlying disease mechanisms, targeting specific mechanisms provides potential new therapeutic options with possibly better outcome and with reduced adverse effects. The following examples are considered as potential options for patients with AAV. In addition to Rituximab, other monoclonal anti-CD20 antibody agents like ocrelizumab [111] and ofatumumab [112] have been tried in a number of autoimmune disorders.

Blockade of co-stimulatory pathways such as CD28/CD80 that controls T cell activation has been used with success in rheumatoid arthritis and might be a potential therapy for AAV [113]. Abatacept is a dimeric fusion protein (CTLA4-Ig) was developed to block the interactions of CD28 with CD80 and CD86. Abatacept acts to inhibit immune responses both *in vitro* and *in vivo*. The *in vitro* binding of CTLA4-Ig to CD80 and CD86 down-regulates T-cell proliferation and inhibits humoral immune responses. Abatacept was shown to be effective in the treatment of autoimmune disorders and has been FDA approved for the treatment of rheumatoid arthritis (RA).

Belatacept, a second-generation CTLA4-Ig, with superior binding to CD80 and CD86 compared with abatacept and provided more potent immunosuppressive effect [113]. IL-17 blockade is another target for autoimmune diseases that has potential use for AA. IL-17 is produced by the Th 17 cells, a subset of T helper cells [114]. Belimumab, an anti-BlyS (B-lymphocyte stimulator) monoclonal antibody, already has shown success in Phase III trials in SLE. BlyS is a TNF cytokine that plays a role in B cell proliferation [115]. Natalizumab targets α 4-integrin, which has a role in the adhesion of leukocytes to vascular endothelial cells, and thus prevents leukocyte migration. It has been tried in patients with inflammatory bowel disease and in cohorts with multiple sclerosis. In both cases, it was reported to be effective [116].

Repair of vascular damage induced by vasculitis is another therapeutic consideration. Vascular repair is mediated by Endothelial Progenitor Cells (EPCs) which present in the circulation. Thus, enhancing EPC mobilization and function might be beneficial for AAV. Agents like statins and angiotensin receptor blockers enhance EPC mobilization and should be considered as an adjunctive therapy in AAV in particularly with the increased risk of accelerated atherosclerosis. Erythropoietin is able to enhance EPC function and should be studied in AAV [19].

Eculizumab and Pexelizumab are monoclonal antibody agents to C5a, might have a therapeutic role in AAV based on the theoretical role of the complement pathway in the pathogenesis of AAV. The generation and engagement of the C5a-C5a receptor pathway is an extremely important event in the pathogenesis of ANCA-associated vasculitis. Therefore, pharmacologic intervention with Eculizumab and Pexelizumab might provide a novel and less toxic therapeutic strategy. Eculizumab is currently well approved for the treatment used in of paroxysmal nocturnal hemoglobinuria [12]. Natalizumab is a humanized recombinant monoclonal antibody against very late activation antigen. Blockade of α 4-integrins leads to inhibition of migration of T cells to tissue sites or T-cell-driven granuloma formation. Natalizumab is approved for the treatment of patients with Multiple Sclerosis (MS), and might provide another potential effective agent for AAV [117]. With expansion of our knowledge of the disease pathogenesis, more molecules that block key signaling pathways will

provide potential therapies, hopefully with a better tolerability and safety profile.

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