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Invited Review

Updates in ANCA-associated vasculitis

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Abstract

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are small-vessel vasculitides that include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg - Strauss syndrome). Renal-limited AAV can be considered a fourth entity. Despite their rarity and still unknown cause(s), research into AAV has been very active over the past decades and has allowed for the development of new therapeutic regimens. The pathogenesis is a complex process of immune dysregulations with genetic and environmental influences. Recent genome-wide association studies have identified multiple genetic predisposing variants, especially at the major histocompatibility complex region. The pathogenic role of antimyeloperoxidase ANCA (MPO-ANCA) is well supported by several animal models, but that of antiproteinase 3 ANCA (PR3-ANCA) is not as strongly demonstrated. B cells likely play a major role in the pathogenesis because they produce ANCAs, as do neutrophil abnormalities, imbalances in T-cell subtypes, and/or cytokine - chemokine networks. The role of the alternative complement pathway was established more recently, and studies of the antagonist of human C5a receptor (avacopan) in AAV have just been completed, with promising results. The current standard management of severe AAV still consists of remission induction therapy with glucocorticoids combined with rituximab or, less often now, cyclophosphamide. Several studies showed that reduced-dose regimens of glucocorticoids are noninferior to the previously used heavier regimens, for therefore less cumulative exposure to glucocorticoids. Avacopan use may even lead to new steroid-free therapeutic approaches, at least for some selected patients. Several trials and studies have now shown the superiority of rituximab over azathioprine or methotrexate as maintenance therapy. However, the optimal dosing regimen and duration for maintenance remain to be better defined, at the individual patient level. Many changes have occurred in the standard of care for AAV over the past decades, and more are expected soon, including with use of avacopan, but also, likely, a few other agents under investigation or development.

Keywords: Anti-neutrophil cytoplasm antibody-associated vasculitides, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, cyclophosphamide

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Introduction

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are small-vessel vasculitides that include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (Table 1).[1–4] Renal-limited ANCA-associated vasculitis can be considered a fourth entity and is characterized by pauci-immune crescentic glomerulonephritis without systemic involvement and, in most cases, is an ANCA-positive disease with myeloperoxidase (MPO)-ANCA in 70%-80% of patients.[1] Despite the rarity and still unknown cause(s) of AAV, research into these diseases has been very active and steadily increasing over the past three decades. The results of several clinical and more basic fundamental studies demonstrated that each of these diseases has some different pathogenic mechanisms and genetic backgrounds.[5] From a therapeutic point of view, treatment strategies have been gradually better defined, and several targeted biologic agents, initially developed for other diseases, have been studied for AAVs and/or are still under investigation.[6–9] As demonstrated in two randomized controlled trials, the monoclonal anti-CD20 antibody rituximab has become an alternative to the conventional cytotoxic cyclophosphamide to induce remission in adults with severe GPA or MPA, combined with glucocorticoids.[10–12] Later, rituximab was also found more effective than azathioprine in maintaining disease remission.[13] Other agents more recently studied to optimize treatment options in AAV include avacopan, an oral antagonist of human C5a receptor (C5aR), which could become the alternative to glucocorticoids in AAV, and belimumab, with more mitigated, nuanced results for maintaining remission in GPA. This article provides a brief overview of AAV characteristics and summarizes the results of some of the main recently published studies of AAV that may impact practice.

Epidemiology

AAV affect men and women equally. The average age at diagnosis is in the fifth or sixth decade, but young children and older adults can be affected.[14–17] Although AAV have been described in all ethnicities, most patients are Caucasian or Hispanic (93%-98%). The global incidence of AAV between Japan and the United Kingdom is similar, but MPO-AAV is 10 times more frequent than PR3-AAV in Japan.[18]

The estimated annual incidences of GPA or MPA are close and vary from 2 to 30 cases per million population each, with prevalences of 25-250 cases per million population.[19,20] EGPA is much rarer than GPA or MPA, with an incidence of 1-4 cases per million population and a prevalence of about 10-25 cases per million population.[21] Intriguingly, the overall incidence rates of AAV increased steadily in the 1980s and 1990s but appear to have stabilized since the early 2000s.[14,22,23] The improvements in the recognition of AAV and increased availability of ANCA testing are possible explanations.[14,22] Indeed, the increased awareness of physicians has led to shorter diagnostic delay, with some studies in Sweden reporting a median time of only 2 months between the first symptoms and the diagnosis of GPA.[23] Finally, a few studies suggested some seasonal variations in the incidence of AAV but not reproducibly during the same periods of the year.[19]

Main Points

- Despite their rarity and still unknown cause(s), research into AAV has been very active over the past decades and has allowed for the development of new therapeutic regimens.
- Management of severe GPA and MPA still consists of remission induction therapy with glucocorticoids combined with rituximab or, less often now, cyclophosphamide.
- Several studies have now shown superiority of rituximab over azathioprine or methotrexate as maintenance therapy in GPA and MPA.
- More changes are expected soon, including with use of avacopan, the antagonist of human C5a receptor (avacopan), which may allow new steroid-free therapeutic approaches in GPA and MPA.
- Treatment of EGPA also consists of a remission induction therapy followed by a maintenance phase. Mepolizumab, an anti-IL-5 humanized monoclonal antibody, showed clinical benefit, especially for the frequent steroid-dependent asthma or ear-nose-throat manifestations.

Genetics

AAV are not considered inherited diseases, and familial occurrence is rare.[24] However, several genetic associations have been found with AAV, especially for molecules of the major histocompatibility complex. The strongest associations are with the ANCA antigenic specificity rather than clinical syndrome (MPA vs GPA). PR3-AAV is associated with HLA-*DP*, the genes encoding alpha1-antitrypsin (*SERPINA1*) and PR3 (*PRTN3*), whereas MPO-AAV is associated more often with HLA-*DQ*. Previous studies already showed an association with more severe forms of GPA and allele deficiency of alpha-1 antitrypsin (homozygosity for deficiency ZZ, SS, or SZ).[25] *PTPN22* and the *CTLA4* locus appear to have a role in AAV susceptibility.[26–28] *SEMA6A* has been associated with an increased risk of GPA, but more studies are needed to validate this association.[26,28] A study demonstrated a 73-fold increased frequency of *HLA-DRB1*15* alleles in African Americans with PR3-AAV, a minority of the AAV population.[29]

HLA-DRB4 gene, present in carriers of *HLA-DRB1*04*, *HLA-DRB1*07*, or *HLA-DRB1*09* alleles, is a genetic risk factor for the development of vasculitic manifestations of EGPA, whereas *HLA-DRB3* and *HLA-DRB1*13* are associated with decreased likelihood.[25] Also, the HLA-*DQ* region is associated with MPO-ANCA–positive but not ANCA–negative EGPA,[30] which reinforces the idea of two subtypes of EGPA, as discussed later in this article.

Clinical and Biological Findings, Diagnosis

Classification but not diagnostic criteria are available for AAV. Updated classification criteria from the Diagnostic and Classification Criteria for Vasculitis, American College of Rheumatology, and European League Against Rheumatism have been recently developed and should be published in early 2022, after having been fully endorsed. The previous classification criteria and the nomenclature definitions of AAV are in Table 1.

The main characteristics and differences for GPA, MPA, and EGPA are summarized in Table 2, and Figures 1 to 8 show some of the most typical manifestations. AAV are all potentially life-threatening, but limited and/or less severe forms exist. The limited form of GPA has slightly different definitions according to different study groups but is defined, as in the WGET trial, as GPA without life- or organ-threatening manifestations and without gastrointestinal, ocular, or central nervous system involvement.[31] GPA localized to the upper airway is often persistent and refractory to treatment, with frequent relapses. The main target organs of GPA are the upper and lower respiratory tracts, lungs, and kidneys. MPA is a nongranulomatous vasculitis, and mostly affects the lungs and kidneys, like GPA but without the formation of nodules. EGPA's hallmark is late-onset asthma and eosinophilia, with other vasculitic manifestations.[32–34] Other than the most common disease manifestations listed in Table 2, some rarer include parotid gland involvement, retroperitoneal fibrosis, pancreatitis, splenic infarct, and genitourinary lesions, such as prostatitis, orchitis, and penile necrosis.

Besides these classical and well-known manifestations of AAV, an association between interstitial lung disease (ILD) and AAV has been established over the last few years. This complication is mostly seen in patients over 65 years of age, Japanese patients, and/or those with MPO-ANCA–positive disease (70% of cases of AAV-associated ILD). The prevalence of ILD is reported in 23% of patients with GPA and up to 45% of patients with MPA.[35] Lung fibrosis can precede the development of AAV, as seen in almost half of the reported patients, by a few months to 12 years.[35,36] On imaging, patterns encountered are usual interstitial pneumonia in 50%-71% of cases, nonspecific interstitial pneumonia in 7%-31%, and desquamative interstitial pneumoniae in up to 14%.[35,37] The presence of ILD implies poor prognosis, with increased mortality and a median survival of 5 years,[35,36] but more studies are needed to confirm this point and determine the best treatment approach for these patients.

Patients with AAV are also at increased risk of venous thromboembolism, with an estimated frequency of 8%. Venous thrombosis is reported especially when the disease is active, just prior to, then within the first 6 months after a disease flare (diagnosis or relapse) but can also occur, at lesser frequency, during phases of remission.[38,39]

Several studies showed an increased likelihood of cardiovascular events (CVEs) in patients with AAV, mostly because of accelerated atherosclerosis, and these events usually occur in the first 5 years after diagnosis.[40,41] Patients have a threefold higher risk of CVEs than the general population, and the risk is more than eightfold increased with cerebrovascular accidents.[41] The incidence rates of CVEs were 19 per 1000 patient-years in a Canadian study and 27.8 per 1000 patient-years in France.[42,43]

Table 1. Classification criteria and definitions of the antineutrophil cytoplasm antibody (ANCA)-associated vasculitides according to the American College of Rheumatology (ACR, 1990; microscopic polyangiitis was not yet individualized as a specific entity at that time), and the 2012 Chapel Hill nomenclature.[1–3]

1990 ACR classification criteria for Wegener's granulomatosis

For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.

1. Nasal or oral inflammation: Development of painful or painless oral ulcers or purulent or bloody nasal discharge.
2. Abnormal chest radiograph: Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities.
3. Urinary sediment: Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment.
4. Granulomatous inflammation on biopsy: Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

1990 ACR classification criteria for Churg–Strauss syndrome

For purposes of classification, a patient shall be said to have Churg–Strauss syndrome if at least four of these six criteria are present. The presence of any four or more criteria yields a sensitivity of 85% and a specificity of 99.7%.

1. Asthma: History of wheezing or diffuse high-pitched expiratory rhonchi.
2. Eosinophilia greater than 10% on differential white blood cell count.
3. Mononeuropathy (including multiplex) or polyneuropathy: Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (glove/ stocking distribution) attributable to systemic vasculitis.
4. Nonfixed pulmonary infiltrates: Migratory or transitory pulmonary infiltrates (not including fixed infiltrates) attributable to vasculitis.
5. Paranasal sinus abnormality: History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses.
6. Extravascular eosinophils: Biopsy including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas.

Definition of ANCA-associated vasculitides in the nomenclature of systemic vasculitis adopted in 2012 by the Chapel Hill consensus conference

Large vessel vasculitis: Giant-cell arteritis; Takayasu arteritis.

Medium-sized-vessel vasculitis: Polyarteritis nodosa; Kawasaki disease.

Small vessel vasculitis*:

ANCA-associated vasculitides**

Granulomatosis with polyangiitis (Wegener's).

Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (eg, capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common.

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

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.

Microscopic polyangiitis.

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, 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.

Immune complex small-vessel vasculitides

IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Antiglomerular basement membrane (antiglomerular basement membrane) disease

Variable vessel vasculitis: Behcet's disease; Cogan's syndrome

Single-organ vasculitis: Cutaneous leukocytoclastic angiitis; cutaneous arteritis; primary central nervous system vasculitis; isolated aortitis; others

Vasculitis associated with systemic disease: Lupus vasculitis; rheumatoid vasculitis; sarcoid vasculitis; others

Vasculitis associated with probable etiology: Hepatitis C virus–associated cryoglobulinemic vasculitis; hepatitis B virus–associated vasculitis; syphilis-associated aortitis; drug-associated immune complex vasculitis; drug-associated ANCA-associated vasculitis; cancer-associated vasculitis; others

The final version of the revised 2020 Diagnostic and Classification Criteria for Vasculitis, American College of Rheumatology and European League Against Rheumatism) criteria were not been published at the time of this review article (see the text for details).

*Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intraparenchymal arteries, arterioles, capillaries, venules, and veins.

**Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (ie, capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity (eg, MPO-ANCA, PR3-ANCA, ANCA-negative).

The diagnosis of AAV relies on the combination of clinical findings and results of imaging studies, basic and nonspecific biology tests (inflammatory markers such as C-reactive protein level, complete blood count, renal parameters, and urine sediment analysis), and more specific ones, including ANCA testing of course and, when feasible, a biopsy of an affected organ. For quantitative detection of ANCA, the recommendation is to use high-quality antigen-specific immunoassays such as enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay as the preferred first screening test.[44] Many centers have almost abandoned ANCA testing by indirect immunofluorescence (to detect c-ANCA with a cytoplasmic labeling pattern, p-ANCA with a perinuclear pattern, and

Table 2. Main characteristics of the three ANCA-associated vasculitides.

	Microscopic polyangiitis	Eosinophilic granulomatosis with polyangiitis (Churg - Strauss syndrome)	Granulomatosis with polyangiitis
Clinical manifestations			
Constitutional symptoms (fever, arthralgia, myalgia)	55%-80%	30%-50%	70%-100%
Skin	Purpura (35-60%)	Purpura, pseudourticarial rash (50-70%)	Purpura (10-50%)
ENT manifestations	Few patients (2-30%), not specific, not destructive, and not granulomatous	Frequent (20-80%): Allergic rhinitis, sinus polyposis (not destructive)	Frequent (50-95%): Crusting rhinitis, destructive sinusitis, saddle-nose deformity, nasal septum deformity, otitis media, decreased/loss of smell or taste, gum hypertrophy/pain
Lung involvement	Frequent (60-80%): Alveolar hemorrhage	Frequent (50%): transient patchy infiltrates, eosinophil pleural effusion, rarely nodules, alveolar hemorrhage (rare; 3-10%)	Frequent (60-80%): lung solid and/or excavated nodules, alveolar hemorrhage, bronchial and/or subglottic stenosis
Asthma	No	Yes ($\sim$100%)	No
Kidney involvement	Very frequent: Glomerulonephritis (necrotizing extracapillary), 80%	Not frequent: Glomerulonephritis (necrotizing extracapillary), 20%	Frequent: Glomerulonephritis (necrotizing extra-capillary): 60-80%
Peripheral neuropathy (mononeuritis multiplex)	Possible (35%)	Very frequent (65-75%)	Possible (25%)
Other "classical" manifestations	Venous thrombosis 7-8%	Cardiac manifestations (10-50%; cardiomyopathy); venous thrombosis 7-8%	Eye manifestations (scleritis, orbital tumor); pachymeningitis; venous thrombosis 7-8%
Biology			
Standard	Nonspecific inflammatory syndrome; check creatinine and urine analysis (red blood cell casts?)	Eosinophilia, often $>$3,000/mm^{3}Nonspecific inflammatory syndrome	Nonspecific inflammatory syndrome; check creatinine and urine analysis (red blood cell casts?)
ANCA	Yes (60-80%): mainly MPO-ANCA, peri-nuclear-ANCA (p-ANCA)	Yes (30-40%): mainly MPO-ANCA, peri-nuclear-ANCA (p-ANCA)	Yes (90% if systemic disease): mainly PR3-ANCA, cytoplasmic-ANCA (c-ANCA)
Radiology	Check chest X-ray and/or CT scan for alveolar hemorrhage (ground-glass opacities); other imaging studies according to clinical presentation	Check chest X-ray and/or CT scan for labile and transient lung infiltrates (rarely alveolar hemorrhage or nodules); sinus X-ray and/or CT scan for nonerosive sinusitis, polyps; other imaging studies according to clinical presentation	Check chest X-ray and/or CT scan for alveolar hemorrhage (ground-glass opacities), lung nodules, excavated or not, subglottic and/or bronchial stenosis; sinus X-ray and/or CT scan for erosive sinusitis, pseudotumor; other imaging according to clinical presentation
Histology	Necrotizing vasculitis of small-sized vessels; no granuloma (rare cases)	Granuloma, including eosinophils (frequent); necrotizing vasculitis of small-sized vessels	Granuloma (frequent but not always); necrotizing vasculitis of small-sized vessels

ANCA, antineutrophil cytoplasm antibody; CT, computed tomography; ENT, ear - nose - throat; MPO, myeloperoxidase; PR3, proteinase 3.

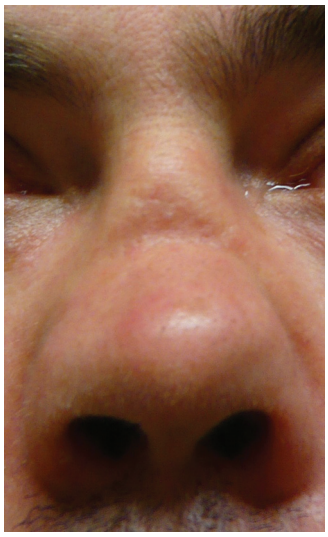

Figure 1. Saddle-nose deformity in a patient with granulomatosis with polyangiitis (GPA).

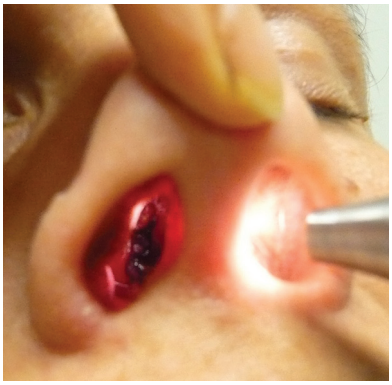

Figure 2. Nasal septum perforation in a patient with GPA. Note the light going from one nostril to the other through the perforated nasal septum and the crusty bleeding posterior wall of the sinonasal cavity.

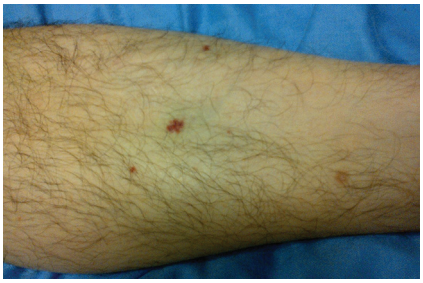

Figure 3. Purpuro-ecchymotic skin lesions on the legs of a patient with eosinophilic granulomatosis with polyangiitis (EGPA). Legs are the most involved areas for skin lesions in antineutrophil cytoplasm antibody (ANCA)-associated vasculitides.

sometimes x-ANCA for an atypical pattern). In all, 60%-80% of patients with MPA are ANCA-positive, mostly MPO-ANCA, whereas 90% of patients with severe GPA are ANCA-positive,

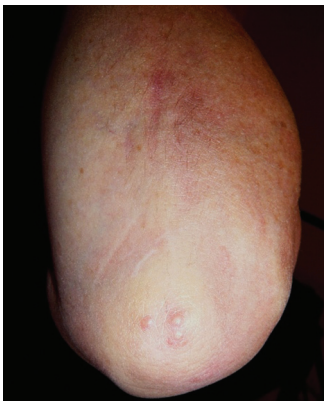

Figure 4. Nodular cutaneous lesions in a patient with GPA. Elbows are a frequent location for such skin lesions in GPA and EGPA.

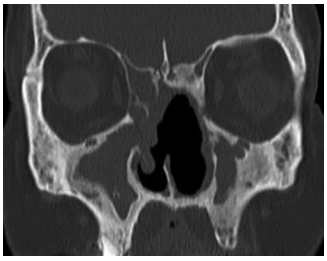

Figure 5. Computed tomography (CT) scan of sinuses in a patient with GPA. Note the perforated nasal septum and bilateral opacification of maxillary sinuses - sinusitis.

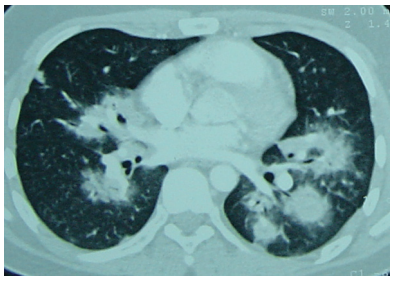

Figure 6. Chest CT of a patient with GPA. Note the multiple solid lung nodules, surrounded by ground-glass opacities, suggestive of associated peri-nodular alveolar hemorrhage.

mostly PR3-ANCA.[31] Patients with ANCA-negative GPA most often have limited disease, but the disease can progress to a more severe form and sometimes become ANCA-positive. Approximately 30%-40% of EGPA patients are ANCA-positive, mostly MPO-ANCA.[32,45]

Ruling out the differentials, including infections or malignancy, is mandatory when suspecting the diagnosis or a relapse, as well as complications of therapy for the latter. Of note, a positive ANCA test result can be observed in other conditions, such as auto-immune hepati-

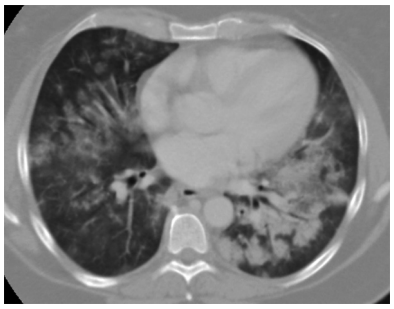

Figure 7. Chest CT in a patient with microscopic polyangiitis (MPA). Note the diffuse ground-glass opacities, suggestive of alveolar hemorrhage, with some pseudonodular consolidation appearance in the left lung.

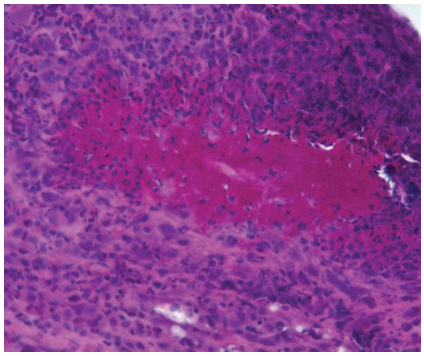

Figure 8. Histology of muscle-nerve biopsy in a patient with EGPA. Note the massive vessel wall and peri-vascular infiltrate by inflammatory cells, mainly eosinophils, the vessel wall necrosis and subsequent vessel lumen occlusion.

tis, ulcerative colitis, infection with hepatitis C virus or HIV, or infectious endocarditis, without associated vasculitis. In the latter condition, the specificity of ANCA is often different from PR3- or MPO-ANCA.[44] Some drugs can induce AAVs (propylthiouracil is the most famous one), usually with high titers of MPO-ANCA.[44,46] Levamisole-cocaine use can trigger a vasculopathy with high titers of ANCA (PR3- and/or MPO-ANCA, sometimes with antielastase specificity, that can be detected by nonroutine ELISA). The vasculopathy closely resembles GPA and occasionally requires a similar treatment approach, at least initially, along with cocaine discontinuation.[47] Finally, all patients with renal and/or alveolar hemorrhage should also be tested for antiglomerular basement membrane antibody disease, which can mimic AAVs or be an additional condition. ("Double ANCA and antiglomerular basement membrane positivity" patients have worse renal prognosis and require a slightly different treatment approach.)

Biopsies of skin lesions, present in up to 40%-60% of patients with AAVs, are easy to

perform and will usually reveal vasculitis, although most medium- or small-sized vessel vasculitis can cause the same type of histological lesions.[48] Vascular and extravascular eosinophilic granulomas are more suggestive of EGPA. Nasal or sinus biopsies have low sensitivity (20%-50%) even when performed by trained surgeons on ulcerated areas and with deep mucosa samples. Open lung biopsy yields high sensitivity (80%-90%) but is invasive. The diagnostic value of transbronchial biopsy is only about 10%.[49] In patients with renal involvement, renal biopsy can show the hallmark features of pauci-immune necrotizing and crescentic glomerulonephritis and can further be classified according to pathologic activity. Focal glomerular lesions (≥50% of normal glomeruli) have the best prognosis and usually do not progress to end-stage renal disease (ESRD), whereas sclerotic glomerular lesions (≥50% sclerotic glomeruli) have the worst prognosis and high mortality rates. Crescentic and mixed categories have an intermediate risk of progression to ESRD.[50] On initial presentation, the degree of chronic damage on kidney biopsy seems associated with overall survival and is one of the best predictors of renal outcome.[51] In practice, the need for an invasive biopsy in an ANCA-positive patient with typical clinical manifestations of AAV and no evidence of infection, cancer, or drug-induced disease remains a case-based decision.

Pathogenesis

The pathogenesis of AAV is a complex process of immune dysregulations with genetic and environmental influences, but the exact cause is not fully elucidated.

The hypothesis of an infectious agent, such as *Staphylococcus aureus* for GPA, which would (over) activate the immune system, has been repeatedly suggested. However, the infection can barely be sufficient to cause or explain the full-blown disease by itself and its multiple facets.[52]

The pathogenic role of MPO-ANCA has been supported by animal models by passive transfer of MPO-ANCAs and a single case of MPA in the newborn of a mother with anti-MPO antibodies (passive transplacental transfer).[53,54] Additional experiments demonstrated the major importance of neutrophils, the neutrophil activation pathway, and the alternative complement pathway (mainly through C5a) in the MPO-ANCA-induced animal model.[55,56] Recent studies showed that blockade of the C5a receptor (CD88) with CCX168 (now known as avacopan) could prevent but also limit renal disease in this murine model.[57]

Conversely, we lack convincing evidence to support the pathogenic role of PR3-ANCA or to explain why some patients with biopsy-confirmed GPA or MPA have typical clinical manifestations despite being ANCA-negative. There may be several explanations. First, the homology between human and murine PR3 is less than that for MPO. Hence, animal models are more difficult to generate, and complex alterations in mice are required before achieving some vasculitic changes close to those seen in GPA.[58,59] Second, only a fraction of ANCAs are pathogenic in an individual (ie, only those ANCAs directed toward one or a few specific epitopes). A study of MPO-ANCA - positive patients demonstrated only a subset of MPO-ANCAs associated more strongly and specifically with disease activity than others directed toward different MPO epitopes.[60] Moreover, these specific ANCAs, directed toward the linear amino-acid sequence 447-459 of the MPO molecule were detected in many ANCA-negative patients with MPA, were well associated with disease activity and, when injected in mice, triggered the development of (proliferative, but not necrotizing) glomerulonephritis. Routine ANCA tests do not properly detect these specific MPO-epitope-ANCAs$^{447\text{-}459}$ because such tests are based on total serum. Serum immunoglobulins (Ig) first need to be purified for detection of these specific MPO-epitope-ANCAs$^{447\text{-}459}$. A serum factor (likely a fraction of ceruloplasmin) indeed bound to these specific MPO-epitope-ANCAs$^{447\text{-}459}$, thereby preventing detection of the most clinically relevant ANCAs with routine tests. Specific alterations and "maturation" of ANCAs may also be necessary for them to become pathogenic, including the selection of higher-affinity PR3-ANCAs in nasal mucosa granulomas or modulation of their sialylation levels.[61]

An excessive and abnormally sustained antigenic presentation of PR3 and/or MPO has also been implicated (in patients with GPA or MPA) through their overexpression on neutrophils, genetically determined, as well as endothelial cell membranes and the formation by neutrophils of neutrophil extracellular traps and microparticles, which include the PR3 and/or MPO molecules.[52,62]

B cells likely play a major role in the pathogenesis, not only because they produce ANCAs. Studies have reported elevated serum levels of B-lymphocyte stimulator (BLys) in patients with AAV, with good association with disease activity. After anti-B-cell treatment with rituximab, serum BLys level is increased in patients with AAVs.[63] Imbalances in the different T-cell subtypes (T helper 1 [Th1], Th2, Th17, regulatory CD4+ CD25+ FoxP3+ T cells, etc) and/or cytokine - chemokine networks can also lead to, or at least participate in, rupture of tolerance, triggering autoimmunity and/or an oxidative burst aggressive toward endothelial cells.

The pathogenesis of EGPA is less studied than that of GPA and MPA. Only 30%-40% of patients with EGPA are positive for ANCA, mainly perinuclear MPO-ANCAs.[21] We lack an animal model of EGPA, and MPO-ANCA - induced murine models do not show any of the main features of EGPA (ie, blood eosinophilia, tissue eosinophilic granulomas, or obstructive lung disease). Eosinophils likely play a central and/or additional role in the development of EGPA, directly or through their granule degradation products. Th2 lymphocytes are also a key part of the disease because they produce specific cytokines (interleukin 4 [IL-4], IL-5, and IL-13). In particular, IL-5 is known to play a key role in the maturation process, activation, proliferation, and survival of eosinophils and is associated with disease activity.[64] IL-25, with an increased level in EGPA patients, is secreted by activated eosinophils and enhances Th2 cytokine production, thus promoting an inflammatory cycle.[65] IL-10 level is also increased in EGPA, mostly in ANCA-negative patients, via gene polymorphisms, and promotes the dysregulated Th2 pathway and increases IgG4 level.[65] Finally, the efficacy of B-cell depletion with rituximab, at least in some patients with EGPA, has questioned the contribution of B lymphocytes to the pathogenesis of EGPA. Patients with relapsing EGPA show an elevated number of CD80+, CD27+, and CD95+ B cells and lower percentages of CD19+ cells.[66]

Treatment Approaches

Current standard of care for induction therapy in GPA and MPA

The current treatment of severe AAV involves two phases: Remission induction therapy based on the combination of glucocorticoids and another immunosuppressive agent, then once remission is achieved, maintenance therapy (to maintain remission). New treatment regimens have been developed and studied over the past three decades to limit the toxicity of agents that have been used as conventional therapies for many years, such as cyclophosphamide and glucocorticoids.[9] Table 3 summarizes the indications and adverse events associated with the most commonly used treatments.[67]

Remission is usually achieved by a combination of high doses of glucocorticoids with cyclophosphamide or rituximab for 3-6 months.[68] The optimal dose, tapering

Table 3. Main current medications for the treatment of ANCA-associated vasculitides: Principles of use and main risks. See text for details and latest published guidelines or recommendations.

Medication	Current validated indications	Dosage	Adverse events
Glucocorticoids	Cornerstone treatment for remission induction Continuous low-dose glucocorticoids might have an additive role as maintenance therapy	Induction: Oral prednisone (or prednisolone-equivalent) 1 mg/kg/day Often preceded by IV methylprednisolone pulses (7.5-15 mg/kg/day, up to 1000 mg, daily for 1-3 days)	Infections, diabetes, hypertension, osteoporosis, gastritis, peptic ulcers, weight gain, avascular necrosis, myopathy, neuropsychiatric manifestations, cataracts, skin thinning, cardiovascular disease, fluid retention.
Cyclophosphamide	Remission induction therapy in patients with severe AAVs	Oral: 2 mg/kg/day (maximum 200 mg/day) or Intravenous: 15 mg/kg (maximum 1200 mg) every 2 weeks for the first three doses, then every 3 weeks for the next 3-6 doses Dose to adjust according to age and renal function (fixed-500 mg per pulse can be considered in older patients)	Infections (patients must receive prophylactic therapy against Pneumocystis jiroveci pneumonia), myelosuppression and cytopenias, nausea, vomiting, myocarditis, hemorrhagic cystitis (mesna to consider for bladder protection with IV cyclophosphamide), infertility, primary ovarian failure, teratogenicity. - Increased risk of malignancy, such as skin cancers, acute leukemia, myeloid malignancies, bladder cancer.
Rituximab	Remission induction therapy in patients with severe AAVs Maintenance of remission in patients with severe AAVs	Induction: 375 mg/m^2 IV weekly for four doses or 1000 mg IV at days 1 and 15 Maintenance: 500-1000 mg IV every 4-6 months (500 mg every 6 months most commonly used) for at least 18 months (four doses)	Infections, including hepatitis B virus reactivation (screening for hepatitis B virus prior to treatment) or P. jiroveci pneumonia (patients must receive prophylactic therapy), infusion reactions, arthralgias, skin rash, hypogammaglobulinemia (IgG, M and A levels to monitor in patients with serious or recurrent infections), late-onset neutropenia.
Methotrexate	Remission induction therapy in patients with limited AAVs and/or without life-threatening disease Maintenance of remission	0.3 mg/kg/week (oral or subcutaneous) Maximum dose of 25 mg/week Avoid in renal impairment (glomerular filtration rate $<$30 mL/min)	Infections, oral ulcers (folic acid supplementation to limit this risk), transaminitis and hepatotoxicity, gastrointestinal symptoms (nausea/vomiting, diarrhea, abdominal pain), skin rashes, alopecia, headache, fatigue, myelosuppression, pneumonitis, pericarditis, teratogenicity, impairment of fertility. - Can increase the risk of neoplasia, such as lymphoproliferative disorders.
Azathioprine	Maintenance of remission	2 mg/kg/day (oral) Maximum 200 mg/day	Cytopenias (patients with homozygous deficiency of thiopurine methyltransferase at high risk), infection, hepatotoxicity, pancreatitis, skin rashes, nausea and vomiting, diarrhea, alopecia. - Can increase the risk of neoplasia, such as lymphoproliferative disorders and nonmelanoma skin cancers. - Safe in pregnancy.
Mycophenolate mofetil	Remission induction therapy in patients with limited AAVs and/or without life-threatening disease Maintenance of remission in patients with contraindications or adverse events to azathioprine or methotrexate	2 g/day (oral) Maximum dose of 3 g/day	Infections, gastrointestinal symptoms (diarrhea, abdominal pain, nausea/vomiting), cytopenias, teratogenicity. - Can increase the risk of neoplasia, such as lymphoproliferative disorders and nonmelanoma skin cancers.
Mepolizumab	Refractory and/or relapsing nonsevere EGPA and/or glucocorticoid-dependent patients (prednisone $\geq$7.5 mg/day)	Subcutaneous injection of 300 mg every 4 weeks	Headache, nasopharyngitis, sinusitis, upper respiratory tract infections, arthralgias (including back pain) and myalgias, abdominal pain, infusion reactions, pruritis and eczema, shingles.

ANCA, antineutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; IV, Intravenous.

regimen, and duration of glucocorticoid treatment are still uncertain. For severe organ involvement, such as alveolar hemorrhage or rapidly progressive glomerulonephritis, patients typically receive intravenous pulses of methylprednisolone (500-1000 mg for 1-3 days), although strong evidence for this practice is lacking and the treatment seems associated with severe infection.[69] Prednisone is typically given afterward at 1 mg/kg/day (not exceeding 80 mg/day) and progressively tapered after 2 weeks, by about 10% every 2 weeks. Hence, in most studies, the prednisone dose was tapered to 5-10 mg/day at 4-6 months of induction therapy. The randomized multicentric trial PEXIVAS, recently published, studied a reduced-dose regimen of glucocorticoids (prednisone tapered from 1 to 0.5 mg/kg/day after only 1 week, then weekly or biweekly, until reaching 5 mg/day at the end of month 4). The regimen was found noninferior to the standard regimen in patients with severe AAV in terms of deaths and ESRD. At 6 months, the cumulative dose of oral glucocorticoids in the reduced-dose group was less than 60% of that in the standard-dose group and was associated with a reduced rate of severe infections.[70]

Cyclophosphamide and rituximab are the two possible agents for remission induction, combined with glucocorticoids, in patients with severe GPA or MPA. The drugs can induce remission in more than 80% of patients. Cyclophosphamide was first used in the mid-1970s, and its efficacy is well proven. The CYCAZAREM trial showed that oral cyclophosphamide (2 mg/kg/day) combined with glucocorticoids for 3-6 months induced remission in 93% of patients.[7] Subsequently, two trials showed that intravenous pulsed (see Table 3 for dosing regimen) or oral daily cyclophosphamide were as effective in inducing remission.[71,72] However, long-term follow-up showed more relapses with intravenous cyclophosphamide but no differences between the administrations in renal function or survival.[72] Conversely, intravenous pulses were associated with less cumulative cyclophosphamide dose exposure, thereby less risk of infertility, late cancer (mainly bladder cancer or lymphoma), and leukopenia.[71] Cyclophosphamide toxicity can be minimized by reducing the dose in older patients.[73]

Given the associated risk with cumulative use of cyclophosphamide, rituximab was studied as an alternative therapy in the early 2000s. The RAVE trial enrolled patients with newly diagnosed or relapsing severe GPA or MPA and showed that rituximab (375 mg/m^2 weekly for four doses) was noninferior to cyclophosphamide in inducing remission. The trial found a trend toward superiority of rituximab for relapsing disease and, in a posthoc subgroup analysis, for patients with PR3-ANCA–positive AAV.[10,74] Whereas there was no difference in terms of infection rates between the arms in the RAVE trial, some subsequent real-life data showed that RTX-based induction therapy was also associated with less serious infectious complications, and was less risky to use than cyclophosphamide in patients with known, concurrent infections.[75,76] The RITUXVAS trial randomized patients with severe, newly diagnosed AAV with renal involvement to receive glucocorticoids and rituximab plus two intravenous pulses of cyclophosphamide (experimental arm) or the standard intravenous cyclophosphamide pulse therapy for 3-6 months. Both groups achieved similar sustained remission rates at 12 months.[12] Rituximab should clearly be preferred in patients with contraindications and/or at risk of infertility with cyclophosphamide. A different dosing regimen of rituximab (1 g on days 1 and 15) has also been used for induction. The regimen is more practical, and a recent meta-analysis revealed equivalency to the 375-mg/m^2-weekly-for-4-weeks regimen, as used in the RAVE and RITUXVAS trials.[77] To help minimize glucocorticoid exposure (and cyclophosphamide toxicity), two small observational studies studied a combination of rituximab and cyclophosphamide, not so different from that used in the experimental arm of RITUXVAS. More than 80% of patients achieved remission at 6 months, with fewer cumulative doses of glucocorticoids.[78,79] Clinical controlled trials are needed to confirm these findings and better delineate the place, if any, of the combined use of cyclophosphamide and rituximab, which may carry an increased risk of infections.

The additive role of plasma exchange has been debated for years for severe AAV, especially for patients with renal involvement and/or alveolar hemorrhage. In the MEPEX trial in the early 2000s, plasma exchange reduced the risk of progression to ESRD by 24% at month 12 ($P = .03$), but the long-term follow-up (4 years) revealed no difference in mortality and ESRD.[80,81] The factorial-designed PEXIVAS trial, mentioned above, enrolled 704 patients with severe AAV, most with glomerulonephritis and some with diffuse alveolar hemorrhage. Patients were randomly assigned to undergo plasma exchange (7 plasma exchanges within 14 days) or no plasma exchange. The study did not find any reduced incidence of ESRD or death at up to 7 years of follow-up, in the entire study population or in any subgroup analyses, although the latter analyses were underpowered.[70] The results of a recent cohort analysis of more than 400 patients with severe renal disease further support the results of PEXIVAS.[82]

Mycophenolate mofetil (MMF) and methotrexate combined with glucocorticoids can be considered for remission induction in patients with nonsevere GPA or renal but nonsevere MPA. Methotrexate was compared to cyclophosphamide for remission induction in nonsevere, nonrenal GPA or MPA, and remission at 6 months was similar in both groups. However, methotrexate was associated with a longer time to remission in patients with more severe disease and with a higher number of relapses at 18 months.[83] MMF was compared to intravenous cyclophosphamide for remission induction in a randomized controlled trial in newly diagnosed GPA or MPA without life-threatening disease and was also found noninferior at 6 months. However, at 18 months, high relapse rates also occurred in the MMF group, mostly in PR3-ANCA–positive patients.[84] Abatacept (CTLA4-Ig) is currently being studied as another possible therapeutic option for relapsing and nonsevere GPA (ABROGATE; ClinicalTrials.gov Identifier: NCT02108860) based on the promising results of a small open-label series.

Glucocorticoids may also be used alone, as first-line therapy, to induce remission in the rare patients with nonsevere, nonrenal MPA (ie, with a five-factor score of 0[85]) However, more than half of these patients eventually require the addition of another immunosuppressant because of progressive, refractory or relapsing disease. The CHUSPAN2 study showed no benefit of a combination of glucocorticoids and azathioprine (vs glucocorticoids and a placebo of azathioprine) as first-line treatment for these rare patients.[86] In France, a study is evaluating a combination of glucocorticoids and rituximab (vs glucocorticoids and a placebo of rituximab) in these patient populations (RITUXGOPRO; ClinicalTrials.gov Identifier: NCT03920722).

Forthcoming, probable changes in induction treatment of GPA and MPA

As emphasized in the pathogenesis section, the alternative complement pathway is important in AAV. A few years ago, a small open-label study of avacopan, the oral selective C5a receptor inhibitor, showed that it could be noninferior to prednisone as a remission-induction treatment in AAV, combined with cyclophosphamide or rituximab.[87] The larger, randomized, and double-blinded ADVOCATE trial then evaluated avacopan (30 mg twice daily for 1 year) versus prednisone (1 mg/kg/day initially, then tapered and stopped at month 6) as additional therapy to cyclophosphamide or rituximab in AAV.[88] The results of this study showed that 72% of patients achieved disease remission at 26 weeks in the avacopan group (and no

glucocorticoids) as compared with 70% in the standard-treatment group with glucocorticoids (noninferior, but not significantly better). This response was sustained at 52 weeks, with disease remission rates of 66% and 55% ($P < .01$), respectively. Subgroup analyses also suggested even better results with avacopan in the patients treated with rituximab for induction, those MPO-ANCA - positive and/or relapsers. The proportion of serious adverse events was comparable with avacopan and glucocorticoids (37% and 39%), and improvement in renal function was significantly greater with avacopan at both 26 and 52 weeks.[88] The use of avacopan instead of (or with much less) glucocorticoids may be the next "revolution" in AAV treatment since the discovery of the efficacy of rituximab. However, there may still be someplace for high-dose glucocorticoids, at least initially, in very severe and/or refractory disease, or maybe at a lower dose (5 mg per day) for maintenance, as detailed below. The optimal duration of avacopan also needs to be established and its long-term safety determined.

Current standard of care for maintenance therapy in GPA and MPA

Following induction therapy with glucocorticoids and cyclophosphamide or rituximab, 70-90% of patients will achieve remission. However, continued treatment with an immunosuppressant is required to prevent disease relapse.[89] Cyclophosphamide is not continued beyond the time of remission as maintenance therapy because of its significant toxicity. A switch to azathioprine was found equally effective at preventing relapses, occurring at about 14% at 1-year postremission.[7] In the WEGENT trial, azathioprine and methotrexate were compared as maintenance agents, following cyclophosphamide-based induction, and showed similar relapse rates and proportion of adverse events.[6] Conversely, MMF was found less effective than azathioprine for maintaining remission in the IMPROVE trial, but it can still be considered in patients intolerant to all the other maintenance options.[8] Leflunomide can also be used, but the evidence is more limited. Rituximab has now been studied in many cohorts and trials for maintenance therapy in AAV and was found the most efficient agent to date at preventing relapses. Hence, many groups now recommend rituximab as the first choice for maintenance in AAV. In investigating maintenance of remission, following induction with glucocorticoids and cyclophosphamide, the French MAINRITSAN trial showed the superiority of rituximab (500 mg at remission, again 15 days later, then every 6 months for a total of 2 years) at 28 months as compared with azathioprine in patients with newly diagnosed or relapsing GPA or MPA.[13] The extended follow-up at 60 months confirmed the clear and sustained superiority of rituximab, even after it had been stopped (major relapse-free survival rates at 60 months of 72 vs 49%; $P = .003$).[90] Subsequent studies showed that the second maintenance dose (500 mg at day 15) could be omitted. The more recently completed RITAZAREM trial followed 170 patients with relapsing disease who received induction therapy with rituximab and glucocorticoids. Patients were then maintained with rituximab (1000 mg every 4 months, for 2 years) or azathioprine. Rituximab was again found superior to azathioprine in preventing disease relapse (18% vs 38% of major relapses at 24 months; $P < .001$).[91] The optimal regimen needed for rituximab infusions for maintenance may still need refinements and likely patient-based adjustments. Most patients may receive 500 mg every 6 months once remission has been achieved; some may need 1000 mg every 4 months, perhaps those with more severe, relapsing disease. The MAINRITSAN-2 trial studied another approach: A group of patients received 500 mg every 6 months, and the other group received 500 mg at the time of remission but then repeat infusions only when CD19+ B lymphocytes reappeared or with markedly increased ANCA titers (reappearance or twofold increase) based on measurements every 3 months. The relapse rates did not differ between the two groups, and the "tailored-arm" group received fewer infusions.[92] This tailored regimen could be an alternative maintenance regimen in some patients, either immediately after the remission has been achieved or after the 2-year mark of maintenance with systematic rituximab infusions. It is associated with lower infusion costs but requires close clinical and biological monitoring.

Other treatments have been studied for the maintenance of remission. Sulfamethoxazole/trimethoprim (800 mg/160 mg twice daily; cotrimoxazole) can be used as an adjunct maintenance treatment in patients with limited GPA, but its efficacy at preventing relapse is debated and not retained in recent meta-analyses.[93,94] Etanercept has not been found effective and was associated with an increased risk of malignancy.[95] Belimumab is a human monoclonal antibody against BLyS that was studied in combination with azathioprine for maintenance of remission in newly diagnosed or relapsing severe AAVs. The trial results did not show a reduction in relapse risk as compared with controls receiving placebo and azathioprine. However, patients who achieved remission after induction with rituximab (rather than cyclophosphamide) and who subsequently received belimumab did not experience any disease relapses.[96] A clinical trial is ongoing to compare rituximab monotherapy to a sequential combination of rituximab and belimumab for remission maintenance in patients with PR3-ANCA–positive disease (COMBIVAS; ClinicalTrials.gov Identifier: NCT03967925).

The optimal duration of maintenance therapy should be at least 24 months.[68] Past the 24-month mark, the continuation or not of maintenance therapy is, in practice, often individualized according to several patient characteristics, including the ANCA serotype (PR3-ANCA - positive patients relapse more), persistence of ANCAs after induction therapy (associated with a higher risk of relapse as well), previous relapse history (associated with higher risk for further relapses), organ involvement and/or the patient's or physician's preference. The REMAIN trial showed that prolonged use of azathioprine and low-dose prednisone beyond 24 months was associated with a further reduction in relapse risk and improved renal survival at 48 months after diagnosis.[97] The MAINRITSAN-3 randomized placebo-controlled trial enrolled 97 patients with AAVs who had achieved remission after 18 months of rituximab maintenance therapy in MAINRITSAN-2 trial. Patients then received rituximab 500 mg or placebo every 6 months for an additional 18 months. Rituximab continuation beyond 2 years was again associated with lower relapse rates than with placebo, with no increase in adverse event rates. At 56 months, relapse-free survival rates were 96% versus 74% in the rituximab and placebo groups ($P = .008$).[98] Although this difference was statistically significant, it is debatable to treat all patients for 4 years, when three-quarters of them will remain disease-free if rituximab is stopped at year 2. As mentioned above, the longer treatment may be preferable for PR3-ANCA - positive patients with relapsing disease until an alternative even more effective than rituximab is available.

Treatment of EGPA

Treatment of EGPA also consists of a remission induction therapy followed by a maintenance phase, but there are several nuances and differences as compared with that for GPA and MPA. An internal consensus task force for EGPA established that most patients with nonsevere forms of the disease can initially be treated with glucocorticoids alone.[99] The French CHUSPAN trial showed that in 72 patients with newly diagnosed EGPA without poor prognosis factors, a treatment solely with glucocorticoids achieved remission in 93% of cases. However, 35% of the patients showed relapse, mostly upon glucocorticoid tapering and in the first year of treatment, which required the addition of another immunosuppressant.[100] The addition of azathioprine to glucocorticoids for such patients,

tested as first-line treatment, versus glucocorticoids alone in the CHUSPAN2 trial did not result in lower relapse rates, lower exacerbation rates of asthma or ear-nose-throat manifestations or any significant glucocorticoid sparing.[86] Other agents may achieve better results, but only rituximab (still combined with glucocorticoids) is being investigated as possible first-line therapy in patients with nonsevere EGPA (REOVAS; ClinicalTrials.gov Identifier: NCT02807103; results expected late 2021 or early 2022).

Patients with life- and/or organ-threatening EGPA should unequivocally receive glucocorticoids and an additional immunosuppressant (cyclophosphamide) for 3-6 months.[99] A study comparing 6 or 12 intravenous cyclophosphamide pulses in patients with EGPA showed six pulses associated with more relapses (86% vs 62%; $P = .07$). However, patients were not receiving subsequent maintenance therapy, and, eventually, a large proportion, 74%, exhibited clinical relapse.[101] Thus, maintenance therapy is needed, and usually azathioprine or methotrexate is used.[99] Leflunomide or MMF can also be used, but data are lacking to clearly recommend one agent over another for remission maintenance in EGPA.[45] A study is comparing azathioprine to rituximab for maintenance therapy in patients with EGPA (MAINRITSEG; ClinicalTrials.gov Identifier: NCT03164473; recruiting). The optimal duration of treatment is definitely not known in EGPA, but the consensus is that it should be given for at least 18-24 months following remission induction.[68] The duration can also be adjusted based on individual patient characteristics. Patients with ANCA-positive EGPA showed a higher risk of relapse despite better survival rates than ANCA-negative patients.[32] The latter patients have more frequent cardiac manifestations and lung infiltrates, whereas patients with ANCA-positive EGPA have more frequent purpura, mononeuritis multiplex, lung hemorrhage, and renal manifestations.[32]

Glucocorticoids should be gradually tapered until withdrawal, when possible, but many EGPA patients require long-term prednisone because of steroid-dependent asthma and/or ear - nose - throat manifestations. In a French cohort, 84% of patients required ongoing glucocorticoids.[32]

The evidence for rituximab as part of the induction therapy in EGPA is limited, definitively not yet as strong as for GPA and MPA. Rituximab can be considered in selected patients, especially ANCA-positive patients with refractory disease or renal involvement.[99] In one study of 41 patients with EGPA, mainly with refractory or relapsing disease, rituximab achieved remission in 49% by 12 months; ANCA-positive patients achieved remission more frequently. However, only 6% of patients completely tapered their glucocorticoids at 12 months.[102] Another recent study showed similar results in 69 patients, but rates of asthma or sinonasal relapses remained frequent.[103] Case reports have also described severe bronchospasms after rituximab infusions, so caution is warranted in EGPA. The French REOVAS and MAINRITSEG studies, mentioned earlier, will help determine the place of rituximab for EGPA induction and/or maintenance.

Mepolizumab, an anti-IL-5 humanized monoclonal antibody, was recently studied in a randomized placebo-controlled study. In this MIRRA study, 136 patients with relapsing or refractory EGPA received monthly subcutaneous injections of 300 mg mepolizumab over 52 weeks versus placebo. Importantly, the trial excluded patients with the newly diagnosed disease and/or active severe disease. Remission, as defined in the protocol, lasting more than 24 cumulative weeks, was achieved in 28% of patients in the mepolizumab group versus 3% with placebo. Glucocorticoids had been discontinued at month 12 in (only) 18% of mepolizumab patients as compared with 3% of placebo patients.[104] Hence, clinical benefit was significantly higher for patients receiving mepolizumab than placebo, but 47% of the former patients still failed to achieve remission, and 56% showed relapse. Patients with higher eosinophil count had a better response to mepolizumab.[105] The glucocorticoid-sparing effect of mepolizumab, especially for asthma or other ear-nose-throat manifestations, was further supported by smaller case series.[106] Some data recently published suggested that mepolizumab at only 100 mg monthly, instead of 300 mg, could achieve some improvement, although to a slightly lesser extent and with some concern about a rebound of disease if control is not optimal with this lower dosage.[107,108] More studies of mepolizumab in EGPA are needed and of other anti-IL-5 agents, including benralizumab (MANDARA; ClinicalTrials.gov Identifier: NCT04157348) or reslizumab (ClinicalTrials.gov Identifier: NCT02947945).

Immunoglobulins can be considered second-line therapy for EGPA flares refractory to other treatments, especially in pregnancy or, based mostly on case reports, in the context of myocardial or nerve involvement.[99] Omalizumab, a humanized anti-IgE monoclonal antibody, has some proven efficacy in allergic asthma and rhinitis. A study of 17 patients with EGPA and severe steroid-dependent asthma showed that omalizumab had a steroid-sparing effect, but the medication was discontinued during follow-up because of refractory disease in 25% of patients, with relapse in half of them.[109] Another recent study showed similar results in 18 other patients, with mild improvement of asthma and/or sinonasal symptoms, some glucocorticoid-sparing effect, but a significant number of patients showed relapse after the tapering of glucocorticoids.[110] The risk of severe EGPA flares after reduction of glucocorticoids raises the question of the safety of omalizumab, and its benefit in EGPA is limited.

Follow-up, Prognosis, and Disease Assessment

As mentioned above, with current optimal therapies, the rate of remission at 6 months in all AAV is 80%-90%.[90,111] Patients with major organ involvement have poorer prognosis, and mortality rate remains around 10%, especially during the first year of treatment, because of the underlying vasculitis, or its treatment-related side effects, mainly infections.[112,113] Relapses remain frequent in GPA (up to 30% at 4 years from diagnosis, when using maintenance rituximab for 2 years), a little bit less in MPA (around 10% at 4 years, from diagnosis, when using maintenance rituximab for 2 years) and EGPA (up to 35%). However, in EGPA, up to 80% of the patients have persistent and/or "relapsing" asthma or sinus problems, thus remain steroid-dependent.[32,114,115]

Diagnosing and treating promptly relapses can be challenging, as there are no good predictive or diagnostic markers. Serial measurement of ANCA is by default still the "best" available predictive option but lacks both specificity and sensitivity.[116] Following ANCA (and CD19+ B cells) in patients treated with rituximab may have better predictive value than with conventional immunosuppressive drugs such as azathioprine.[74,92,117] When a relapse is suspected, it is important to rule out mimickers, especially (opportunistic) infections or, more rarely, other complications of treatments, such as hematuria due to cyclophosphamide-related bladder cancer, or new lung nodules related to malignancy.

A few disease assessment tools exist, such as the Birmingham Vasculitis Activity Score (BVAS, version 3) or the BVAS/WG (Wegener's granulomatosis).[118–120] Because they have been developed to assess disease activity in clinical trials, they have limited interest in routine practice, other than reminding physicians of all the main organ manifestations to check in patients with AAV. Damage can also be assessed in trials using scores such as the Vasculitis Damage Index. Studies in AAV showed

that no more than 10%-20% of patients will keep a VDI = 0, which supports the need to identify treatment strategies with fewer side effects and more rapidly effective.[121,122]

Conclusions

Management of AAV has evolved tremendously in the past two decades, with substantial improvements in survival and quality of life. Induction treatment is now well codified, but some major changes may again occur soon. Our expanding knowledge of the pathogenesis and genetic contribution has provided new therapeutic targets, such as the C5a receptor antagonist (avacopan) for GPA and MPA. The optimal duration of low-dose glucocorticoids therapy and the most effective regimen for rituximab-based maintenance therapy are still under study. Reducing the need for or, at least, the cumulative use of glucocorticoids may become a reality with some of these newly developed treatments. The identification of reliable biological markers remains needed to better assess disease activity, predict disease relapse, and further personalize the treatment approach.

A few patients still experience refractory disease and/or unrelenting relapses, which underscores the continuing need for newer and more effective therapies. Treatment of multirelapsing or refractory disease, with or without complex manifestations, such as subglottic and tracheobronchial stenoses, orbital tumor, or pachymeningitis, goes beyond the scope of this review article. Such diseases should ideally be managed in reference centers with expertise in vasculitis.

Many other questions of importance remaining to be answered include how to reduce the damage associated with the disease (ESRD, peripheral nerve damage, saddle-nose deformity in GPA) or its treatments and how best to treat associated nonvasculitic manifestations, such as asthma in EGPA. Finally, because all these new treatments and/or biologics reviewed in this article are expensive, cost-effectiveness studies are needed. Biosimilars of these agents are not as expensive, and their preferential use over the originator is now mandated in many countries, but data on their safety and efficacy in AAV remain very limited.[123,124]

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