THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Review

A glance into the future of anti-neutrophil cytoplasmic antibody-associated vasculitis

Marta Casal Moura, Carolina Branco, Joana Martins-Martinho, José Luís Ferraro, Alvise Berti, Estela Nogueira and Cristina Ponte

***Abstract*:** In the past decade, unprecedented progress has been made in understanding the pathogenesis, diagnosis, assessment, and treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). International collaborations and input from several fields (e.g. immunology, rheumatology, and nephrology) have been critical for analyzing demographics, disease manifestations, and outcomes in clinical research studies. Such efforts opened new avenues for generating novel questions and rationale to design better clinical trials. In addition, clinical research has been a source of several biological discoveries and the starting point for knowledge seeking on the pathophysiology of AAV. Interestingly, the blending of clinical and basic research provides a platform for personalized medicine. Despite recent revisions on AAV classification, the incorporation of new findings on disease genetics and immunologic responses may soon result in changes in clinical practice. These advances will enhance the selection of more specific and targeted therapies. However, current unmet needs in the management of AAV are still sizable and heavily impact long-term survival. Especially, frequent relapses, damage accrual, and high morbidity contribute to poor outcomes. Finally, the lack of defined biomarkers for disease activity and the prognosis is a permanent challenge in AAV research. Our work provides an overview of the current state of the art in AAV literature and suggests bridges for the remaining knowledge gaps. It offers potential future directions for the clinical assessment, management, and research in the field toward a more personalized medicine approach.

Keywords: ANCA-associated vasculitis, classification, prognosis, treatment

Received: 10 February 2022; revised manuscript accepted: 26 August 2022.

Ther Adv Musculoskelet Dis

2022, Vol. 14: 1–30

DOI: 10.1177/1759720X221125979

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of small vessel vasculitis disorders characterized by neutrophil-driven inflammation of blood vessels leading to endothelial injury and tissue damage.[1] Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) are the three types of AAV with different definitions according to the Chapel Hill nomenclature (Table 1).[2–4] In MPA, kidney involvement is predominant. In contrast, GPA and EGPA are characterized by extravascular granulomatous inflammation, predominantly involving the respiratory tract.[1,2] Severe disease occurs with capillaritis, manifesting more commonly as glomerulonephritis (GN) or alveolar hemorrhage.[5] The loss of tolerance to neutrophilic proteins, namely proteinase 3 (PR3) and myeloperoxidase (MPO), plays a central role in AAV pathogenesis.[1,2] Immunofluorescence shows minimal deposition of immunoglobulins and complement, hence the so-called 'pauci-immune' vasculitis.[1,2] AAV are rare diseases with

an estimated prevalence of 200–400 cases per million people, and there was an apparent increase in incidence over time due to higher awareness for the diagnosis and higher yield in ANCA testing methodologies.[6–9]

In the last decade, several research goals in AAV have been attained. AAV genetic background is now better characterized.[10–12] Due to efficient immunosuppressive agents, the prognosis for patients with AAV has evolved from a fatal outcome to a potentially treatable disease.[13] After the PEXIVAS and ADVOCATE trials, it became apparent that reducing exposure to glucocorticoids (GCs) is possible and safe.[14,15] The benefits of using plasma exchange (PLEX) are currently being questioned.[16] Moreover, remission-maintenance treatment with rituximab (RTX) is now recommended as the primary strategy for relapse prevention.[17,18] However, several critical needs remain unmet in the management of AAV. Many patients still progress to kidney failure (KF), associated with increased morbidity and mortality.[19–22] The risk of relapse is high, contributing to damage accrual and decreased survival.[23] In addition, especially during remission-induction treatment, the incidence of infectious complications related to immunosuppressants is high.[1] Finally, remission-maintenance strategies are not protocolized or guided by specific biomarkers, which does not help to subside the exposure to unnecessary treatments.[16]

Our work shows how pathogenesis, disease classification, and assessment can be combined for a unified approach. Consequently, we expect improvements in phenotypic and biologic disease characterization and in selecting specific treatments to potentially step towards personalized medicine and mitigate some of the knowledge gaps that remain in AAV (Figure 1).

Pathogenesis

The pathogenic hallmark of AAV is the loss of immunologic T- and B-cell tolerance to neutrophilic proteins, namely PR3 or MPO.[1] The loss of tolerance is multifactorial and occurs in the presence of risk factors, such as genetic background and age, in combination with environmental factors and, more commonly, in the context of inflammation or infection.[1] MPO and PR3 are released from neutrophils and presented for T-cell recognition resulting in proinflammatory cytokine production and recruitment of effector leukocytes.[1] After the loss of tolerance, the generated ANCA activate the neutrophils in the endothelium microvasculature, leading to local injury and inflammation.[1] Endothelial and tissue injury ensues, facilitating extravascular inflammation, fibrosis, and progressive loss of function.[1]

Genetics

Genome-wide association studies (GWASs) have shown that GPA and MPA are genetically distinct. In contrast, EGPA encompasses two genetically different subtypes (MPO-ANCA-positive EGPA and ANCA-negative EGPA). Shared genetic risk factors for vasculitis might underlie the susceptibility to the disease.[10–12] Major histocompatibility complex (MHC) genes and non-MHC genes lead to an increased susceptibility to AAV. In PR3-AAV, the presentation of PR3 antigen to the immune system is ruled by the HLA-DPB1*04:01 allele, and increased plasma levels of PR3 result from the balance between α1-antitrypsin (*SERPINA1*) and PR3 (*PRTN3*) gene expression, contributing the immune system awareness and reactivity to PR3.[10] MPO-AAV and MPA have been mainly associated with HLA-DQ.[10] In EGPA, the GWAS studies allowed the differentiation of EGPA into two distinct subtypes. The authors identified 11 loci associated with the disease.[11] Furthermore, the general risk for vasculitis seems to be conveyed by polymorphisms in the *PTPN22* gene and further modified by epigenetics.[12,24]

Infection

The loss of tolerance is promoted by infection through the priming of neutrophils for ANCA-induced activation, molecular mimicry, and autoantigen exposure included in neutrophil extracellular traps (NETs).[1,25,26] The presence of infectious triggers in AAV pathogenesis has been suggested in observational studies and in particular the contribution of *Staphylococcus aureus* as a trigger for relapse in GPA or as a source of molecular mimicry in MPO-AAV.[27,28]

Loss of tolerance

In combination with the appropriate genetic background and as a response to an adequate

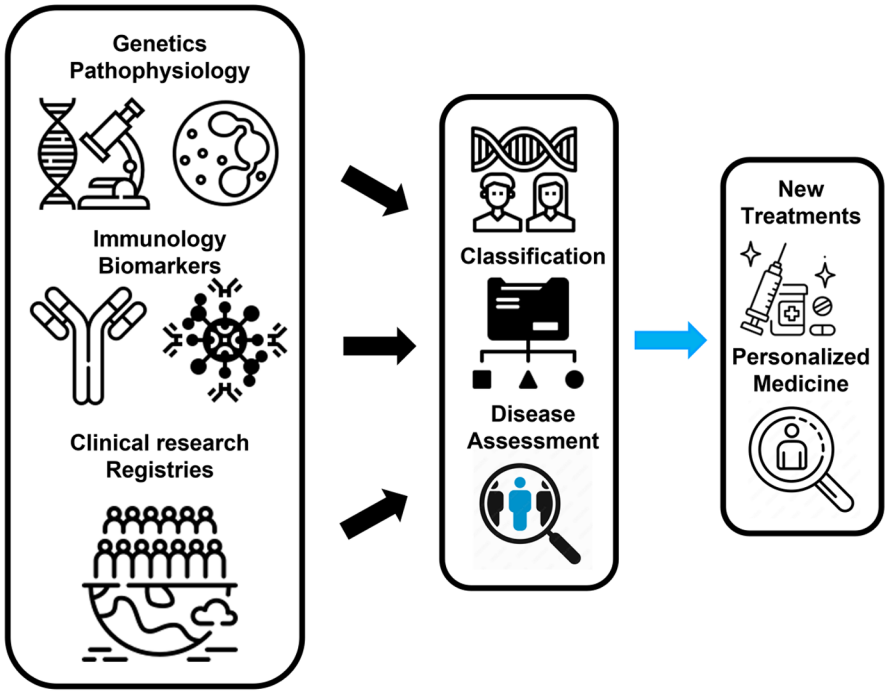

Figure 1. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis framework. Integrating genetic and immunologic background on the phenotypical characterization of patients with ANCA-associated vasculitides (AAVs) will potentially add precision to the selection and development of new treatments. In addition, new classification criteria, adjusted to current practice, will aid correct recruitment of patients into clinical trials and research studies, ultimately improving patients' management. Finally, the continuous development of AAV registries will allow for more meaningful research based on a multidisciplinary approach and using real-world data. These will potentially converge to personalized medicine in AAV.

trigger, the loss of immunologic T- and B-cell tolerance to PR3 or MPO is necessary for the pathogenesis of AAV.[1] This occurs before the onset of AAV symptoms.[1] Loss of T-cell tolerance results in the differentiation of autoantigen-specific T-cells into a T-helper phenotype, including T follicular helper (Tfh), type 1 T helper (Th1), and interleukin 17A (IL-17A)-producing T helper (Th17) cells.[1,29–31] Furthermore, CD4 $^{+}$ promotes ANCA production, generates effector memory T-ells, and is present in local organ lesions (with CD8 $^{+}$). The immune response will be perpetuated, particularly when there is reduced expression of T-cell exhaustion markers, associated with an increased risk of relapse.[1,32,33]

The emergence of autoreactive B-cells and plasma cells occurs after the loss of B-cell tolerance, and this has been identified in AAV patients. Autoreactive PR3 $^{+}$ and MPO $^{+}$ B-cells represent the source of high-affinity pathogenic autoantibodies in AAV.[34–36] The maturation of B-cells occurs in germinal centers of secondary lymphoid tissues or tertiary lymphoid organ structures of inflamed target tissues, which promotes the interaction of the recruited autoreactive B-cells with the Tfh. The Tfh are a specialized subset of CD4 $^{+}$ T-cells with a critical role in the germinal center formation, contributing to high-affinity maturation, clonal selection, and class switch of B-cells leading to expansion, differentiation, and positive selection of the memory subsets.[37–39] Among B-cells, a small fraction is defined as autoreactive B-cells (i.e. cells bearing a B-cell receptor that recognizes autoantigens).[34] In addition, detection of *in situ* PR3^{+} B-cells in inflamed tissues has been pursued based on the hypothesis that granuloma formation in AAV might represent ectopic lymphoid structures, potentially leading to autoantibody production.[40,41] Clinical studies have been highlighting the role of CD19^{+} B-cells as an immunologic

biomarker for disease monitoring since B-cell reappearance after immunosuppressive treatment precludes the occurrence of relapses in most patients with AAV.[42,43]

ANCA

The clinically relevant neutrophil antigens that ANCA targets are PR3 and MPO, and only rarely different targets such as bactericidal permeability–increasing protein (BPI), elastase, lysosome-associated membrane protein-2 (LAMP-2), cathepsin G, lysozyme, and lactoferrin are documented.[44,45] Clinical *in vitro* and *in vivo* studies have supported the hypothesis of the pathogenic role for ANCA in the development of AAV.[46] This evidence is more robust for MPO-ANCA than for PR3-ANCA, which has shown the same proinflammatory effects in *in vitro* experimentation.[47]

Neutrophil priming, activation by ANCA, and promotion of antigen recognition

The so-called effector phase in AAV is best documented by the presence of capillaritis (such as GN). The effector phase happens in two steps.[47] First, neutrophils are primed by low-level exposure to proinflammatory cytokines, such as tumor necrosis factor (TNF) and IL-1, by pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern (DAMP) engagement with toll-like receptors, (TLRs) and by the binding of C5a to the C5a receptor on neutrophils.[1] Priming of neutrophils results in surface expression of MPO, PR3, and other substances of neutrophil granules (e.g. lactoferrin, gelatinase, and elastase) and promotes neutrophil adhesion to the endothelial surface of blood vessels.[1] In the second step, neutrophils are activated by interactions with ANCA by binding to neutrophils Fc receptors and/or to antibody substrate, leading to the rapid release of reactive oxygen species (respiratory burst), preformed proteases, mediators of inflammation, and chemotactic factors for neutrophils and other cells of the immune system, ultimately leading to inflammation, endothelial injury, and tissue damage.[47,48] ANCA-stimulated neutrophils can also release chromatin fiber leading to NETs formation, in which autoantigens MPO and PR3 can be stored, further representing a persistent source of autoantigens contributing to inflammation maintenance.[49]

Complement

ANCA has been shown to have an *in vitro* cytolytic effect on endothelial cells through the activation of neutrophils and the interaction with the complement system's alternative pathway (especially with C5a and the C5a receptor).[50] The importance of complement was shown in mouse models and renal histologic samples.[51,52] C5-deficient mice failed to develop GN and vasculitis. Similarly, C5-deficient and factor B-deficient mice were completely protected from the disease. In contrast, the wild-type and C4-deficient mice were not protected from developing disease, reinforcing the role of complement activation *via* the alternative pathway in the pathogenesis of AAV. Furthermore, mice lacking the C5a receptor (C5aR, also known as CD88) were protected from AAV-GN development. The description of immunologic phenotypes and genetic background, might help to a more precise classification of patients, better correlated with outcomes, contributing to a more accurate prognostic assessment. This will potentially be helpful for the selection of therapeutic targets in AAV.

Diagnosis and classification

There are no AAV diagnostic criteria published so far. Hence, current diagnosis is mostly based on clinical features and supported, whenever possible, by the presence of ANCA and typical histological findings. Patients may present with various symptoms, from constitutional features (e.g. malaise, fatigue, weight loss, fever, arthralgia, and myalgia) to specific organ-related manifestations.[53] Although there are many overlapping features between the three subtypes of AAV, differences in organ manifestations and ANCA specificity may offer excellent clues to help in their distinction (Table 1).

Diagnosis and clinicopathologic entities. GPA is more often associated with upper and lower respiratory tract involvement, particularly with ear, nose, and throat (ENT) manifestations such as nasal crusting, epistaxis, sinusitis, otitis, and

Table 1. Definitions, clinical features, and classification criteria of ANCA-associated vasculitis (AAV).

	GPA	MPA	EGPA
		Definitions	
Chapel Hill Consensus Conference (2012)	Necrotizing granulomatous inflammation usually involves the upper and lower respiratory tract, and necrotizing vasculitis predominantly affects small to medium vessels.	With few or no immune deposits, Necrotizing vasculitis predominantly affects small vessels (i.e., capillaries, venules, or arterioles). Necrotizing GN is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.	Eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract and necrotizing vasculitis predominantly affecting small to medium vessels, associated with asthma and eosinophilia.
		Specific organ involvement	
Eye	27%–58% Keratitis, conjunctivitis, (epi)scleritis, uveitis, optic neuropathy, oculomotor nerve palsy, retinal vasculitis, orbital granuloma	1%–9% Keratitis, conjunctivitis, (epi)scleritis, uveitis, optic neuropathy, oculomotor nerve palsy, retinal vasculitis, etc.	3%–11% Keratitis, conjunctivitis, (epi)scleritis, uveitis, optic neuropathy, oculomotor nerve palsy, retinal vasculitis, orbital granuloma
Skin	10%–50% Palpable purpura is the most common manifestation; nodules, papules, ulceration/necrosis, livedo reticularis	30%–60% Palpable purpura is the most common manifestation, livedo reticularis, nodules, urticarial lesions, ulceration/necrosis, bullae, plaques	30%–69% Palpable purpura and nodules as the most common manifestations, livedo reticularis, vesicles, aseptic pustules, urticarial lesions, papules, ulceration/necrosis
ENT	75%–99% The most typical manifestations of the disease; rhinosinusitis which might progress to nasal septum perforation and saddle-nose deformity; chronic otitis media; sensorineural hearing loss; "strawberry" gingival hyperplasia; subglottic stenosis	9%–30% Not considered a typical feature; mostly mild, non-granulomatous, non-erosive, and non-specific sinus inflammation; sensorineural hearing loss.	48%–98% Allergic rhinitis, sinusitis/polyposis (not typically destructive), otitis media, sensorineural hearing loss
Lung	62%–94% Nodules/cavities and pulmonary infiltrates as the most common manifestations; alveolar hemorrhage and pleurisy may also occur	25%–66% Diffuse alveolar hemorrhage, interstitial pneumonitis/pulmonary fibrosis	91%–100% Asthma as disease hallmark 61%–91% Pulmonary infiltrates, nodules/cavities, pleural effusion, alveolar hemorrhage
Heart	<4%–16% Pericarditis/pericardial effusion, cardiomyopathy, coronary artery disease, valvular disease, arrhythmia (subclinical involvement in up to 64%)	2%–15% Pericarditis/pericardial effusion, cardiomyopathy, heart failure, valvular disease, arrhythmia	14%–58% Pericarditis/pericardial effusion, cardiomyopathy, endocarditis, heart failure, coronary artery disease, arrhythmia (subclinical involvement in up to 71%)
GI	0%–7% Abdominal pain, bleeding, diarrhea, organ perforation, pancreatitis,	2%–56% Abdominal pain, bleeding, diarrhea, abnormal liver tests, hepatomegaly, pancreatitis, organ perforation, cholecystitis, appendicitis	6%–44% Abdominal pain, organ perforation, diarrhea, bleeding, pancreatitis, organ perforation, mesenteric ischemia, colitis, cholecystitis, appendicitis
Kidney	38%–85% Rapidly progressive GN (pauci-immune necrotizing GN)	75%–100% Disease hallmark with rapidly progressive GN (pauci-immune necrotizing GN with more diffuse and chronic damage than GPA)	10%–27% Indistinguishable from the other AAV but less severe
PNS	14%–40% Vasculitic neuropathy, mainly multiple mononeuropathy	14%–58% Vasculitic neuropathy, mainly multiple mononeuropathy	50%–92% Vasculitic neuropathy, mainly multiple mononeuropathy
CNS	5%–11% Pachymeningitis, pituitary gland involvement, CNS vasculitis	0%–18% Headache, convulsions, confusion, stroke, intracranial hemorrhage	5%–15% CNS vasculitis, stroke, eosinophilia in CSF, central affection of cranial nerves, cognitive disorders, intracranial hemorrhage

(Continued)

Table 1. (Continued)

	GPA	MPA	EGPA
		ANCA subtype	
PR3-ANCA	Limited forms: 40%–59% Systemic forms: 78%–87%	3%–28%	2%–6%
MPO-ANCA	Limited forms: 6%–8% Systemic forms: 13%	61%–100%	30%–40%
		Classification criteria	
ACR 1990	1. Nasal or oral inflammation 2. Abnormal chest radiograph (nodules, fixed infiltrates, or cavities) 3. Abnormal urinary sediment 4. Granulomatous inflammation on biopsy **Presence of at least 2/4 criteria**		1. Asthma 2. Eosinophilia > 10%, 3. Peripheral neuropathy 4. Pulmonary infiltrates 5. Para-nasal sinus abnormalities 6. Extravascular eosinophils **Presence of at least 2/6 criteria**
ACR-EULAR 2022			
Clinical criteria	• Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/ perforation 3 • Cartilaginous involvement 2 • Conductive or sensorineural hearing loss 1	• Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/ perforation 3	• Obstructive airways diseases 3 • Nasal polyps 3 • Mononeuritis multiplex 1
Laboratory, imaging, and biopsy criteria	• cANCA or PR3-antibody 5 • Pulmonary nodules, mass, or cavitation on chest imaging 2 • Granuloma, extravascular granulomatous inflammation or giant cells on biopsy 2 • Inflammation, consolidation, or effusion of the nasal/ paranasal sinuses on imaging 1 • Pauci-immune GN on biopsy 1 • pANCA or MPO-antibody –1 • Blood eosinophil count ≥ 1×10^9 /L –4	• pANCA or MPO-antibody 6 • Fibrosis or ILD on chest imaging 3 • Pauci-immune GN on biopsy 3 • cANCA or PR3-antibody –1 • Bloods eosinophil count ≥ 1×10^9 /L –4	• Blood eosinophil count ≥ 1×10^9 /L 5 • Extravascular eosinophilic-predominant inflammation on biopsy 2 • cANCA or PR3-antibody –3 • Haematuria –1
	Presence of at least ≥ 5 points	**Presence of at least ≥ 5 points**	**Presence of at least ≥ 6 points**

References: Definitions[2], specific organ involvement[54-83], ANCA subtype[55, 56, 59-62, 68, 79, 84, 85], classification criteria[3, 4, 86-91]

ACR: American College of Rheumatology; ANCA: Anti-neutrophil cytoplasmic antibodies; CNS: Central nervous system; CSF: cerebrospinal fluid; EGPA: Eosinophilic granulomatosis with polyangiitis; ENT: Ear, nose, and throat; EULAR: European Alliance of Associations for Rheumatology; GI: Gastrointestinal; GN: glomerulonephritis; GPA: Granulomatosis with polyangiitis; ILD: Interstitial lung disease; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; PR3: Proteinase 3; PNS: Peripheral nervous system

hearing loss.[69] Continued nasal inflammation may lead to severe damage with perforation of the nasal septum and saddle nose deformity, a very specific feature of GPA.[92] Moreover, eye involvement may commonly occur, in some cases with the presence of orbital pseudotumor, another clinical feature extremely suggestive of GPA.[54] While some patients may only present with localized forms of the disease (i.e., mainly limited to the upper respiratory tract with no life-threatening manifestations), others may progress to a more systemic clinical picture, usually involving the lungs and/or kidneys.[55,84] Serologic testing showing positive ANCA with a cytoplasmic pattern (C-ANCA) directed against PR3 is strongly associated with GPA.

In MPA, renal involvement is a significant feature of the disease.[56] Some patients may also present with lung involvement, mainly diffuse alveolar hemorrhage (DAH), and pulmonary fibrosis has been increasingly recognized in MPA, sometimes as the initial manifestation of the disease.[93,94] ANCA positivity with a perinuclear pattern (P-ANCA) directed against MPO is typically seen in patients with MPA, although PR3-ANCA may also be present. Of note, it is essential to highlight that either MPA or GPA may present with positive PR3-ANCA or positive MPO-ANCA, making the differential diagnosis between both diseases challenging and, in some cases, impossible to achieve. By contrast, EGPA is classically characterized by late-onset asthma, nasal polyposis, and eosinophilia of the peripheral blood and/or tissue.[60] Cardiac involvement is a recognized hallmark of EGPA, with endomyocarditis representing its most severe form of manifestation.[95] Renal disease is rarely seen, and ANCA is only detected in up to 40% of patients, usually MPO-ANCA.[62,96,97]

In some patients, the combination of highly suggestive clinical features and the detection of ANCA may be sufficient to make the diagnosis of AAV and begin treatment. Nevertheless, histologic confirmation of AAV should be sought whenever possible. Necrotizing vasculitis, with no or few immune deposits, predominantly affecting small vessels, is the most typical finding in AAV.[2] However, the diagnostic sensitivity of biopsy may be very low and highly dependent on the location it is performed. It is estimated that nasal and sinus biopsies may contribute to the diagnosis of vasculitis in only 28% and 37% of cases, respectively.[98] Moreover, the diagnostic yield of transbronchial biopsies in GPA is below 50%.[99] The combination of superficial peroneal nerve and peroneus brevis muscle biopsies has shown an estimated sensitivity of around 60–75% for vasculitis neuropathy. However, it can lead to a definitive sensory deficit at the procedure site.[100,101] Skin biopsies are easy to perform but often show non-specific findings such as leukocytoclastic vasculitis. When renal involvement is suspected, kidney biopsy is advisable to confirm pauci-immune GN and exclude other causes of renal disease (e.g. drug toxicity) and assess prognosis in terms of renal recovery.[102] In 2010, a histologic classification for renal AAV was established by a group of pathologists and nephrologists from the European Vasculitis Society (EUVAS).[103] Patient biopsies were divided into four classes (1) focal ($\geqslant$50% normal glomeruli), (2) crescentic ($\geqslant$50% glomeruli with cellular crescents), (3) sclerotic ($\geqslant$50% sclerotic glomeruli), and (4) mixed ($<$50% normal, $<$50% crescentic, and $<$50% sclerotic glomeruli), with a subsequent validation study confirming the prognostic value of this histopathologic classification for 1- and 5-year renal outcomes.[103] Since then, several other validation studies have been published worldwide.[102,104–112] In addition, the renal risk score for ANCA-associated GN was developed based in clinical and histologic characteristics and highlights the contribution of unaffected glomeruli to renal recovery.[113] More recently, a kidney biopsy chronicity grading score – the Mayo Clinic Chronicity Score – has also been developed and validated, additionally showing an impact on prognostic prediction.[114]

Classification criteria. Classification criteria define a homogeneous group of patients with a specific disease for correct recruitment into clinical research studies.[115] Classification criteria for GPA and EGPA were established by the American College of Rheumatology (ACR) in 1990 (Table 1) to differentiate these cases from other forms of vasculitides but not from non-vasculitic diseases.[3,4] Therefore, these criteria should not be used for diagnostic purposes and have been proven to perform poorly when used in this manner.[116] In addition, the 1990 ACR criteria were established before the routine testing of ANCA and the widespread use of advanced imaging modalities. More importantly, the criteria did not include separate classification criteria for MPA. Between 2011 and 2017, a multinational, observational study was conducted to develop diagnostic criteria and update classification criteria for systemic vasculitis: the Diagnostic and

Classification Criteria for Vasculitis (DCVAS) study.[117] It recruited 6991 patients from 136 different sites and 32 countries. The final ACR-EULAR endorsed classification criteria for AAV have now been published (Table 1).[86–91]

There is an ongoing debate on classifying patients with AAV based on their clinical phenotype *versus* ANCA specificity (PR3 *vs* MPO).[118] Patients with positive PR3-ANCA have been shown to have a different response to treatment, relapse rate, and long-term survival when compared to patients with positive MPO-ANCA.[13,19,23,119–123] Furthermore, data from GWAS have found genetic distinctions to be more closely aligned with ANCA status than clinicopathologic manifestations of the disease in patients with MPA and GPA.[10–12] However, it is still unclear which fraction of patients with EGPA or negative ANCA would fit in this ANCA-based classification.[124] In addition, despite the controversy, no clinical trials to date have used this different classification system as the sole inclusion criteria to recruit patients with AAV. ANCA serology is usually just included as one of the eligibility items.[125]

It is possible that in the future, diagnosis and classification of patients with AAV may include genetic findings paired with ANCA specificity. However, at least for the next few years, the new classification criteria are expected to optimize the way we include patients with AAV in clinical trials and research studies, hence improving their management and outcomes.

Disease assessment

AAV is a chronic and relapsing inflammatory disease requiring careful assessment of its activity, damage, and prognosis to ensure the appropriate use of potentially toxic therapies and accurate monitoring of disease progression. Moreover, patients with AAV perceive the burden of their illness differently from clinicians, which should be considered when evaluating these patients.[53,126] The regular use of assessment tools allows for a structured approach in clinical practice and is helpful to ensure homogeneous definitions of response to treatment and outcomes in clinical trials.[69,127,128]

Activity

After establishing the diagnosis of AAV, defining organ involvement is critical to evaluate response to treatment and outcomes (i.e. remission and relapse). The Birmingham Vasculitis Activity Score (BVAS) is endorsed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group to assess the level of disease activity, allowing the comparison between different disease states for individual patients or across groups of patients.[129–132] The most recent version of this tool (BVAS v3) consists of a list of items that typically occur in patients with active systemic vasculitis and provides an overall measure of disease activity using a score from 0 to 63.[131] Each item is only recorded as present if the clinician judges it to be due to active vasculitis.

Damage

After controlling disease activity, persistent organ lesions might ensue because of disease extension, cumulative relapses, treatment adverse effects, and comorbidities.[127] The resultant damage can be quantified using the Vasculitis Damage Index (VDI), assessed on a scale of 0 to 64 items, which can only be applied 3 months after the diagnosis of vasculitis has been established.[127,133] When monitoring patients with AAV, it is essential to distinguish clinical manifestations resulting from damage or activity to avoid unnecessary immunosuppressive treatment.[127] Moreover, estimating damage helps to record the presence of comorbidities.[127]

Function, quality of life, and patient-reported outcomes

Independent of disease activity and damage, the performance of daily life activities can be impaired in AAV. The assessment of function encompasses the overall impact of the disease on physical, social, and psychologic functions, including quality of life and employment.[127] Patients with AAV show a reduction in quality of life like that found in other chronic diseases. Therefore, these patients are suitable to be evaluated by generic instruments like Short Form 36 (SF-36).[134] Recently, a disease-specific measurement tool for patients with AAV became available to fully capture patient-related outcomes (AAV-PRO).[135,136] However, it still requires further validation using real world cohorts, which is expected to occur in the next few years.

Prognosis

A cumulative VDI score $\geqslant 5$ has been associated with increased mortality risk after 2 years. Higher levels of BVAS at disease presentation have been

linked with worst prognostic outcomes.[13,133,137] Nevertheless, in patients with AAV, the prognosis is most frequently assessed using the 5-Factor Score (FFS).[138,139] This prognostic tool was first validated in 1996 for patients with EGPA, polyarteritis nodosa (PAN), and MPA, and revised in 2009 to also include patients with GPA.[138,139] The original FFS encompasses five positive baseline items: creatinine >1.58 mg/dL, proteinuria >1 g/24 h, and central nervous system, gastrointestinal, and cardiac involvement.[138] The revised FFS includes one negative item (ear, nose, and throat involvement) in addition to the following four positive items: age > 65 years, creatinine ⩾150 μmol/L, and central nervous system and cardiac involvement.[139] Mortality rate at 5 years was estimated at 12%, 26%, or 46% for the original FFS, and 9%, 21%, and 40% for the revised FFS if the patient punctuates 0, 1, or 2, respectively.[138,139]

Laboratory testing and imaging techniques

Conventional inflammatory markers – C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – are of limited value for assessing disease activity in AAV due to the lack of specificity. It has been challenging to determine the utility of ANCA serial testing for relapse prediction. In the RAVE trial, patients with PR3-ANCA, relapsing disease, or who had the diagnosis of GPA were at a higher risk of relapse when compared to patients with MPO-ANCA, new disease onset, or who were diagnosed with MPA.[42,123,140] The most recent guidelines on AAV do not recommend monitoring ANCA titres.[16] This was mainly based on the conclusions from a meta-analysis that included studies in which the relapse risk was assessed in cohorts that combined patients with MPO- and PR3-AAV.[16,141] Previous studies have shown that rise in ANCA titres correlated better with relapses in patients with AAV-GN than in patients without renal disease.[142,143] Therefore, the potential use of ANCA as a biomarker for guiding treatment strategies of remission-maintenance and relapse monitoring may depend on organ involvement and ANCA specificity. Finally, routine use of imaging techniques has shown to be of small value for monitoring patients with AAV.[128]

Composite measures

The development of composite assessment tools has been desirable to evaluate response to treatment in AAV, particularly in the setting of clinical trials.[144,145] The evaluation of patient-related outcomes (PROs) and damage measures in AAV is lacking in many clinical trials.[144] Therefore, the development of a composite assessment tool for vasculitis has recently become a focus of the OMERACT Vasculitis Working Group.[145] The objective is to generate an instrument capable of capturing the entire burden of the disease across multiple domains, paired with the ability to detect response to treatment during different disease states.[145] A systematic review, a Delphi exercise, and a planned methodology were performed and discussed, and domains and high-quality instruments were defined.[145] The next step is to determine a scoring system that allows outcome measurement.[145] It is possible that in future clinical trials, patients' perspectives will be better captured on the measures of efficacy used.

Treatment

Following diagnosis or reasonable suspicion of AAV, treatment should be initiated as soon as possible.[146] In order to tailor therapy for each patient, a careful evaluation should be carried out to assess the individual risk of infection (including concurrent viral and bacterial infections), immunodeficiency, and comorbidities associated with stratification of the impact of GC treatment (e.g. diabetes, osteopenia/osteoporosis, psychiatric diseases). The treatment of AAV consists of two phases: remission-induction and remission-maintenance. Inducing long-term remission is one of the main goals of immunosuppressive therapy, which might be disrupted by the clinical reappearance of disease activity (relapse).[144] For this reason, after controlling disease manifestations, remission-maintenance treatment is instituted. The recommendations for each phase of treatment are currently stratified according to the severity of the disease and the AAV subtype (GPA/MPA *vs* EGPA). Severe disease can be defined as vasculitis with life- or organ-threatening manifestations and non-severe disease as vasculitis without life- or organ-threatening manifestations.[16,140] In addition, assessment of disease severity may also be aided by the BVAS and FFS (e.g. FFS ⩾ 1 and FFS = 0 for severe and non-severe disease, respectively).[129,130,147]

Remission-induction treatment

The main goal of the remission-induction treatment is to suppress and control inflammation as fast and steadily as possible to minimize organ

damage. During the last two decades, research in AAV management has taken significant steps toward reducing immunosuppression toxicity, with the decreasing of cyclophosphamide (CYC) cumulative doses (CYCLOPS, CORTAGE), progressive reduction of GCs (PEXIVAS, LoVAS) and introduction of new immunosuppressants like RTX (RAVE, RITUXVAS).[14,140,148–152]

GPA and MPA. In severe AAV, current standard therapy includes a combination of GCs and RTX or CYC, as proposed by the most recent guidelines (Figure 2).[16,146,153] Following the RAVE and RITUXVAS trials, the use of RTX for remission-induction treatment has been favored over CYC, particularly in cases of relapsing or PR3-ANCA positive disease, to preserve fertility, in frail older adults, in children and adolescents, or when GC-sparing is strongly needed.[16,140,146,152,153] When CYC is the treatment of choice, intravenous (IV) pulses are favored to reduce cumulative doses.[16] In patients with markedly reduced or rapidly declining estimated glomerular filtration rate (eGFR) (serum creatinine [SCr] $>$ 4 mg/dL [354 µmol/L]) and/or KF (eGFR $<$ 15.0 mL/min per 1.73 m)^2, some debate remains regarding the choice of RTX *versus* CYC for remission-induction.[16,146,153] The efficacy of RTX in patients with KF has not been directly tested in clinical trials. However, some studies have reported that both RTX and CYC therapies seem to be equivalent in severe kidney disease.[154,155] A post hoc analysis of the RAVE trial showed that patients enrolled with an eGFR $<$ 30.0 mL/min per 1.73 m^2 at baseline responded similarly to RTX (18 patients) and CYC (14 patients).[156] There was no statistically significant difference in the mean eGFR increase over the 18 months of follow-up.[156] In addition, in a cohort of 251 patients with an eGFR $<$ 30.0 mL/min per 1.73 m^2, a propensity score matching analysis that adjusted for the severity of kidney disease (eGFR $<$ 15.0 mL/min per 1.73 m)^2 showed no differences between the frequency of remission and renal events between patients who received RTX *versus* CYC for remission-induction (64 *vs* 161 patients, respectively).[154] In another study that included 37 patients with eGFR $<$ 20.0 mL/min per 1.73 m^2, there were no differences in remission, renal recovery from KF, or death when patients were treated with RTX and GC, with or without CYC (25 *vs* 12 patients, respectively).[155] Similarly, it is unclear whether the combination of RTX with CYC would benefit the treatment of these patients.

In the last decade, several combined schemes of CYC and RTX have emerged to reduce both CYC and GC cumulative doses.[152,157–160] Kavita Gulati *et al.*[158] recently reported a reduction in KF at 36 months from 67% to 52% with a low-dose CYC and GC regimen with two doses of RTX and PLEX. In addition infection rates were similar.[158] The SMARTVAS (Rituximab/Cyclophosphamide and Minimal Dose Glucocorticoid in AAV) study, in which the induction regimen consisted of two doses of RTX, 3 months of low-dose CYC, and a short course of GCs, provided an important breakthrough in achieving a substantial reduction of the CYC and GC doses (median of 3–3.2 g and median of 1–1.2 g after 1–2 weeks, respectively). It reported similar outcomes to other EUVAS trials, although with fewer GC-related adverse events, namely severe infections, and diabetes.[159] Previously, similar results were found in the CYCLowVasc study that included patients with more severe kidney disease.[157] Results from randomized clinical trials to further support these combined options are awaited.[161] Consequently, reflecting the controversy regarding the treatment of patients with severe kidney disease, the main guidelines have different positions on this subject: the Kidney Disease Improving Global Outcomes (KDIGO) 2021 guidelines for the management of glomerular diseases favor the use of CYC alone or combined with RTX, whereas in the 2021 ACR/Vasculitis Foundation (VF) guidelines for the management of AAV, the use of CYC as the preferred induction treatment for these patients is considered controversial, and the combination of both induction agents is not endorsed due to the currently limited data.[16,153] New EULAR recommendations, which are expected to be published by the end of 2022, will incorporate other studies and perhaps expand on current guidelines.

GCs have an essential role in the AAV remission-induction therapy. Methylprednisolone IV pulses of 500–1000 mg per day or high doses of oral prednisone (1 mg/kg/day) are used as an adjuvant to rapidly reduce inflammation until the biologic effect of the immunosuppressive agent occurs.[16,146,153] The need for methylprednisolone IV pulses to control disease activity, instead of only high doses of oral prednisone, has been recently questioned following a retrospective study which reported that its avoidance significantly reduced diabetes and severe infections without compromising efficacy.[162] The PEXIVAS

trial provided strong evidence for a new reduced prednisone tapering regimen which proved to be efficient and equivalent in the achievement of remission and is currently recommended for remission-induction.[14]

Advances in AAV pathogenesis research have shed light on the crucial role of the alternative complement pathway and allowed the development of new drugs that can potentially replace GCs.[50] In the ADVOCATE trial, the anti-C5a receptor (avacopan, 30 mg twice daily) proved to be noninferior at 26 weeks and superior at 52 weeks compared to GCs, with improved kidney outcomes.[15] This was reflected on the increase of eGFR and decrease in albuminuria, consistent with what has been previously reported in phase 2 trials.[163–165] In addition, there was a decrease in relapses within the first 52 weeks from 21% to 10% when compared with a prednisone tapering regimen, and quality of life patient-reported outcomes significantly improved.[15] However, there are still uncertainties about the best duration of treatment and its efficacy in patients under kidney replacement therapy and/or eGFR below 15 mL/min.[15] Two recent case series using avacopan have confirmed its steroid-sparing effect and safety profile, including in one patient with an eGFR of 11 mL/min who was able to recover stable kidney function (eGFR 23 mL/min) at 12 months.[166,167] Nevertheless, further studies documenting the results of avacopan in patients with a long-term follow-up in real-life settings are still needed.

The use of PLEX in DAH or rapidly progressive crescentic GN decreased considerably following the PEXIVAS study, which did not show a benefit in mortality or the incidence of KF compared to standard remission-induction treatment.[14] Strong evidence favoring PLEX in DAH is lacking, with different studies showing no difference in mortality, even in patients with hypoxemia.[168] A cohort study used propensity score matching analysis that adjusted for the severity of kidney disease (eGFR $<$ 15.0 mL/min per 1.73 m^2) and showed no differences between the frequency and risk for renal events between patients who received PLEX *vs* those who did not (51 *vs* 200 patients, respectively).[154] However, in patients with severe kidney disease (SCr $>$ 5.7 mg/dL) studies have reported conflicting results regarding the role of PLEX and international community is divi ded.[14,169–172] These controversies are reflected in the most recent guidelines, with KDIGO considering PLEX in patients with SCr $>$ 5.7 mg/dL, rapidly increasing SCr or who require dialysis, and in patients with DAH who have hypoxemia, while ACR/VF recommend *against* its routine use, but may consider PLEX in critically ill patients at high risk for progression to KF.[16,153]

IV immunoglobulin may also be a therapeutic option as adjunctive therapy for patients with refractory or relapsing AAV. It may induce rapid improvement in disease activity and related biomarkers.[16,173,174]

In non-severe disease, methotrexate (MTX) and mycophenolate mofetil (MMF) are considered the alternative options to CYC, based on the NORAM and MYCYC trials, respectively (Figure 2).[146,175–177] Azathioprine (AZA) may present as an alternative for remission-induction in cases of pregnancy or intolerance to MTX or MMF.[17]

EGPA. Patients with EGPA were not included in the main AAV clinical trials since the disease pathophysiology is substantially different from GPA and MPA, with higher rates of ANCA negativity and eosinophilic-driven inflammation. Hence, recommendations for severe EGPA disease are like those employed in GPA/MPA (Figure 2).[16] For non-severe EGPA, mepolizumab is recommended as the first choice of treatment for remission-induction in new-onset, relapsing and refractory disease. Mepolizumab improved remission rates and reduced the risk of relapse.[16,178]

Ongoing clinical trials of remission-induction in AAV. Table 2 summarizes the most relevant clinical trials, already terminated or currently ongoing, for remission-induction in AAV.

In patients with positive PR3-ANCA (GPA or MPA), treatment with belimumab plus RTX (COMBIVAS) is being compared with RTX alone with regard to improvement in biologic endpoints, functional outcomes, and clinical status (ClinicalTrials.gov: NCT03967925). The combination of RTX with CYC is also being compared to RTX alone in the ENDURRANCE-1 study to achieve a favorable immunologic state of minimal residual autoimmunity and reduce the need for retreatment (ClinicalTrials.gov Identifier: NCT03942887). In addition, the IXPLORE (ClinicalTrials.gov Identifier: NCT03712345)

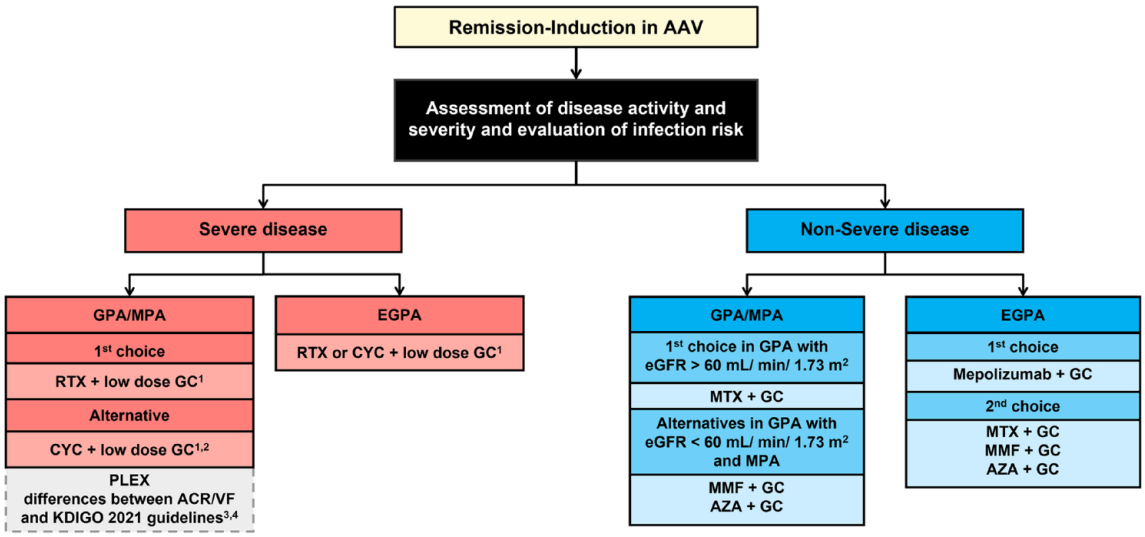

Figure 2. Algorithm for remission-induction treatment in ANCA-associated vasculitis (AAV).
AAV, ANCA-associated vasculitis; ACR/VF, American College of Rheumatology/Vasculitis Foundation; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; DAH, diffuse alveolar hemorrhage; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; IV, intravenous; KDIGO, Kidney Disease Improve Global Outcomes; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PEXIVAS, plasma exchange and glucocorticoid dosing in the treatment of severe ANCA-associated vasculitis; PLEX, plasma exchange; RTX, rituximab; SCr, serum creatinine.
[1,2]The low GC dose is based on the PEXIVAS trial scheme.
[2]In the KDIGO 2021 guidelines, IV CYC alone or combination with RTX is recommended for patients with SCr>4 mg/dL or rapidly declining eGFR.
[3]In ACR/VF 2021 guidelines: PLEX is considered in critically ill patients with active GN refractory to therapy.
[4]In the KDIGO 2021 guidelines: PLEX is considered in patients SCr > 5.7 mg/dL, rapidly decreasing eGFR, DAH.

and the Ixchange phase II trials (ClinicalTrials.gov Identifier: NCT03895801) focus on GC replacement by a monoclonal antibody specifically binding to C5a (IFX-1-vilobelimab) in patients with GPA and MPA. Moreover, there is an ongoing pilot study assessing the efficacy and safety of tofacitinib in active AAV (ClinicalTrials.gov: NCT04973033). In patients with EGPA, benralizumab, an anti-IL-5 monoclonal antibody, is currently being compared to mepolizumab in a phase III trial in efficacy and safety (ClinicalTrials.gov: NCT04157348).

Remission-maintenance treatment

The choice of remission-maintenance treatment is challenging and attempts to define strict criteria or biomarkers for its guidance have been insufficient. The main objective of the remission-induction phase is to prevent relapse while avoiding long-term drug toxicities and resultant comorbidities.[1] Several factors should be considered while choosing the best regimen: the remission-induction regimen used, disease severity, patient comorbidities, drug contraindications, and potential toxicities.[16,146,153]

GPA and MPA. The most recent guidelines on the treatment of AAV recommend remission-maintenance regimens according to disease severity (Figure 3).

In patients with severe GPA/MPA, RTX has the best evidence for the maintenance of remission when compared with AZA.[17,18] On the MAINRITSAN trial, the efficacy of RTX (500 mg on days 0 and 14, and months 6, 12, and 18) for remission-maintenance was compared to AZA (tapering regimen of 2 mg/kg/d for 12 months; 1.5 mg/kg for 6 months; 1 mg/kg for 4 months) in patients who previously received CYC for remission-induction.[17] The authors showed lower relapse rates at 28-months in the RTX arm.[17] Subsequently, the RITAZAREM trial showed that RTX was efficient in reinducing and maintaining remission in patients with relapsing GPA/MPA.[18] RTX for remission-maintenance has

Table 2. Clinical trials of remission-induction treatment in ANCA-associated vasculitis (AAV).

Cyclophosphamide (CYC)			
Name	**Population**	**Intervention**	**Main results/Status**
CYCLOPS, 2009[148]	Newly diagnosed GPA/MPA, Renal involvement, ANCA + or –if biopsy; No Immediately life-threatening disease ($n = 149$)	IV CYC (15 mg/kg every 2–3 weeks) + GC Oral CYC (2 mg/kg/day) + GC	• IV CYC non-inferior to oral CYC • ~50% Cumulative CYC dose in iv group IV CYC had ↓ leukopenia but ↑ relapse rate
CORTAGE, 2015[150]	⩾65 years old + newly diagnosed GPA, MPA, EGPA, or PAN ($n = 104$)	IV CYC 500 mg (⩽6 doses every 2–3 weeks) + 9 months of GC IV CYC 500 mg/m^2 (every 2–3 weeks until remission- ~5.5 g) + 26 months of GC	• Low-dose CYC and GC had ↓ serious adverse effects • Similar remission, relapse, and mortality rates
Rituximab (RTX)			
Name	**Population**	**Intervention**	**Main results/status**
RAVE, 2010[140]	Newly diagnosed or relapsing GPA/MPA with ANCA + (Cr clearance ~54 ml/min) $n = 197$)	RTX (375 mg/m^2 x 4 doses) + GC Oral CYC (2 mg/kg/day) + GC (+ AZA maintenance)	• RTX non-inferior to CYC • RTX is better for relapsing AAV/PR3-ANCA • Similar short-term adverse effects and relapse rates
RITUXVAS, 2010[152]	Newly diagnosed AAV With severe renal involvement (median eGFR~ 20 mL/min) ($n = 44$)	RTX (375 mg/m^2 × 4 doses) + CYC (15 mg/kg × 2 doses) + GC IV CYC for 3–6 months + GC (+ AZA maintenance)	• RTX + CYC regimen not superior IV CYC similar remission rates and adverse events
CYC sparing, clucocorticoid (GC), and plasma exchange (PLEX)			
Name	**Population**	**Intervention**	**Main results/Status**
CycLowVas, 2011[157]	23 patients with newly diagnosed or relapsed AAV with renal involvement No SCr > 5.7 mg/dL, DAH, Cerebral vasculitis, Previous RTX EUVAS controls trial	RTX (1 g x 2 doses) + IV CYC (10 mg/kg, max 750 mg × 2 doses + max 500 mg × 4 doses) + reduced GC regimen CYC regimens (from previous EUVAS trials)	• Median cumulative dose 3.4 *vs* 8.2–15 g (CYCLOPS) • Less infection and leucopenia than CYCLOPS • Prolonged disease-free remission
Kavita Gulati *et al.*[158] (same CycLowVas regimen with PLEX) non-RCT	64 patients with life-threatening AAV (DAH and/or SCr > 5.7 mg/dl or RRT in the first 48 hours No anti-GBM antibodies. (median eGFR 9 mL/min) Controls (40 patients with similar inclusion criteria with CYCLOPS regimen)	RTX (1 g × 2 doses) + IV CYC (10 mg/kg, max 750 mg × 2 doses + max 500 mg × 4 doses) + reduced GC regimen + PLEX (7 daily sessions) + maintenance with AZA or MMF) IV/oral CYC (CYCLOPS) + corticosteroids + PLEX (from historic severe AAV cohort)	• 94% achieved remission at six months • Improved KF-free survival at 36 months (67% *vs* 52.5% in controls with CYCLOPS) • Similar risk of infection
SMARTVAS (non-RCT), 2019[159]	49 patients with a new diagnosis or relapsing AAV No anti-GBM antibodies No long-term corticosteroids Median eGFR 29 mL/min Controls (CYCAZAREM, CYCLOPS; MEPEX, RITUXVAS)	IV CYC (500–750 mg every 2 weeks, x 6 doses) + RTX (2 1 g × 2 doses) + IV MP (250 mg-1 g) + prednisolone (1–2 weeks) + PLEX if dialysis dependent) EUVAS clinical trials and RITUXVAS	• Cumulative GC dose 1.1 *vs* 6.7 g (EUVAS trials) with similar remission rates and kidney outcomes • 0% *vs* 8% DM in EUVAS trials • Less severe infection (12.2% *vs* 30%) compared to RITUXVAS (possibly related to higher GC dose)
LoVAS, 2021[151]	Newly diagnosed GPA/MPA No severe GN or DAH. ($n = 140$)	Reduced dose prednisolone (0.5 mg/kg per day) + RTX (375 mg/m^2 × 4 doses) High-dose prednisolone (1 mg/kg/day) + RTX (375 mg/m^2 × 4 doses)	• Reduced GC dose non-inferior and associated with ↓ serious adverse effects

(Continued)

Table 2. (Continued)

CYC sparing, clucocorticoid (GC), and plasma exchange (PLEX)			
Name	**Population**	**Intervention**	**Main results/Status**
MEPEX, 2007[171]	Newly diagnosed and biopsy proven AAV with SCr > 5.7 mg/dL. (n = 137)	PLEX (7 sessions) + oral CYC + prednisolone. IV methylprednisolone (3000 mg) + oral CYC + prednisolone	• PLEX ↓ KF at 3 and 12 months but similar outcomes post 12 months
PEXIVAS, 2020[14]	Relapsing or newly diagnosed GPA/MPA + GFR < 50 mL/min or DAH (n = 704) 18% SCr > 5.7 mg/dL 6% DAH with hypoxemia	First intervention PLEX (7 sessions within 14 days) as add on to CYC or RTX + GC CYC or RTX + GC Second intervention - standard dose GC + CYC or RTX - reduced dose GC + CYC or RTX	• PLEX did not ↓ mortality or progression to KF • Similar serious adverse effects • Reduced GC regimen non-inferior to standard GC dose (death and KF) • Less severe infections with reduced GC dose
ADVOCATE, 2021[15]	Newly diagnosed or relapsed ANCA + MPA/GPA eGFR ⩾ 15 mL/min + 1 major BVAS item or 2 minor BVAS items or ⩾ 2 renal BVAS items. (n = 331)	Avacopan (30 + 30 mg /day) + CYC or RTX Prednisolone + CYC or RTX	• Avacopan non-inferior to GC at 26 weeks and superior at 52 weeks • Beneficial effect on kidney function • Less GC related adverse effects
Methotrexate (MTX) and mycophenolate mofetil (MMF)			
Name	**Population**	**Intervention**	**Main results/Status**
NORAM, 2005[175]	Newly diagnosed GPA/MPA SCr < 1.7 mg/dL No critical organ involvement. (n = 100)	Oral MTX (20–25 mg/week) + GC Oral CYC (2 mg/kg/day) + GC	• MTX non-inferior to CYC • MTX had ↑ relapses and ↓ disease control in extensive disease/pulmonary involvement treated with MTX
MYCYC, 2019[176]	Newly diagnosed with GPA or MPA No life-threatening disease, RPRF or GFR < 15 mL/min. (n = 140)	MMF (2–3 g/day) + GC (+ AZA maintenance) IV CYC (15 mg/kg/day every 2–3 weeks) + GC (+ AZA maintenance).	• MMF non-inferior to CYC • Relapse rates > MMF (mainly in PR3-ANCA)
Anti-IL5			
Name	**Population**	**Intervention**	**Main results/Status**
MIRRA, 2017[178]	136 patients with relapsing or refractory EGPA + treatment for at least four weeks No organ/life-threatening disease or SCr > 2.5 mg/dL	Mepolizumab (300 mg every 4 weeks for 52 weeks) + SOC Placebo (for 52 weeks) + SOC	• Mepolizumab ↑ accrued weeks and rate of remission, ↓ relapse rates, and GC dose at weeks 48–52 • Similar safety profile
Ongoing clinical trials for remission-induction in AAV (www.clinicaltrials.gov)			
Clinical trial	**Population**	**Objective**	**Intervention**
MANDARA NCT04157348	Patients with relapsing EGPA	IL5-Rα antagonist for relapsing EGPA (Phase III)	Benralizumab 30 mg SC *vs* 3x mepolizumab 100 mg SC for 12 months
COMBIVAS NCT03967925	30 patients with PR-3 positive AAV	RTX + BEL for remission-induction (Phase II)	RTX (1 g × 2 doses) + GC RTX (1 g × 2 doses) + BEL (200 mg SC weekly) + GC
ENDURRANCE-1 NCT03942887	47 patients with GPA/MPA + generalized disease + ANCA positive	RTX + CYC to decrease minimal residual autoimmunity (Phase III)	RTX (1 g x 2 doses) GC RTX (1 g x 2 doses) + Low dose CYC (500 mg x 6 doses) + GC

(Continued)

Table 2. (Continued)

Ongoing clinical trials for remission-induction in AAV (www.clinicaltrials.gov)			
Clinical trial	**Population**	**Objective**	**Intervention**
IXPLORE NCT03712345	19 patients with GPA/MPA requiring CYC or RTX and GC + ANCA positive + 1 major BVAS item or ⩾3 minor BVAS items or ⩾2 renal BVAS items	IFX-1 (anti-C5a) for remission-induction in GPA/MPA (Phase II)	Main intervention: SOC + IFX-1 + low dose GC SOC + Placebo IFX-1 + high dose GC Followed by: SOC + Placebo IFX-1 + high dose GC SOC + IFX-1 + Placebo GC
Exchange NCT03895801	57 patients with GPA/MPA, requiring CYC or RTX and GC ⩾ 1 "major" item, or ⩾3 other items, or ⩾2 renal items on the (BVASv3)	IFX-1 (anti-C5a) as a replacement for GC in remission-induction in GPA/MPA (Phase II)	SOC + low dose GC + IFX-1 SOC + standard dose GC SOC + IFX-1

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; Anti-GBM, anti glomerular basal membrane; AZA, azathioprine; BEL, belimumab; BVAS, Birmingham Vasculitis Activity Score; C5a, complemente factor 5ª; CYC, cyclophosphamide; DAH, diffuse alveolar hemorrhage; DM, diabetes mellitus; EGPA, eosinophilic granulomatosis with polyangiitis; EUVAS, European Vasculitis Association; GC, glucocorticoid; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; IL, interleukin; IV, intravenous; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis nodosa; PLEX, plasma exchange; PR3, proteinase 3; RRT, renal replacement therapy; RTX, rituximab; SC, subcutaneous; SCr, serum creatinine; SOC, standard of care.

been used either in fixed intervals or guided by B-cell reconstitution (CD19 $^{+}$ monitoring) and/or ANCA reappearance. The MAINRITSAN2 trial showed no differences between the two strategies.[179] However, the most recent ACR/VF guidelines endorsed the fixed regimen.[17] The possible maintenance doses for RTX reported include: (1) IV 500 mg every 6 months (FDA-approved), (2) IV 1000 mg every 4 months, and (3) IV 1000 mg every 6 months.[17,18] Comparative studies are still warranted.[17] MTX or AZA are viable alternatives for cases in which RTX cannot be used (e.g. due to limited access, intolerance), with both drugs exhibiting a similar efficacy and safety profile.[180] Other immunosuppressants like MMF and leflunomide may also be considered.[16,146,181,182] In patients that remain dialysis-dependent following remission-induction, there is still some debate regarding the institution of remission-maintenance therapy. Recent KDIGO guidelines recommend avoiding further immunosuppression, especially in patients with MPO-ANCA vasculitis. The relapse rate is low and risk of infection related to therapy is high. The ongoing Maintaining or Stopping Immunosuppressive Therapy in Patients With ANCA Vasculitis and End-stage Renal Disease (MASTER-ANCA) will provide future guidance. In non-severe GPA/MPA, it is recommended to continue the same treatment used for remission-induction (Figure 3).[16,146]

EGPA. Evidence regarding remission-maintenance therapy for EGPA is not as strong as for GPA/MPA.[16,146] In patients with severe disease manifestations who have attained remission after induction with CYC, maintenance treatment with MTX, AZA, or MMF is preferred over RTX or mepolizumab (Figure 2).[16] By contrast, the use of mepolizumab over MTX, AZA, and MMF is indicated for remission-maintenance in cases of non-severe disease (Figure 3).[16] In the last couple of years, RTX has frequently been used in EGPA as a GC-sparing agent. It is currently the treatment of choice for remission-induction and maintenance in cases of relapsing disease with severe manifestations.[16,146,183,184] In patients who present with non-severe relapses while receiving MTX, AZA, or MMF, adding mepolizumab should be considered.[16]

Duration of remission-maintenance treatment. The optimal time of the remission-maintenance treatment is still a matter of debate. The general recommendations are for at least 18–24 months of treatment.[16,146] Results of the MAINRITSAN 3 study showed that in patients who underwent RTX maintenance treatment and were in

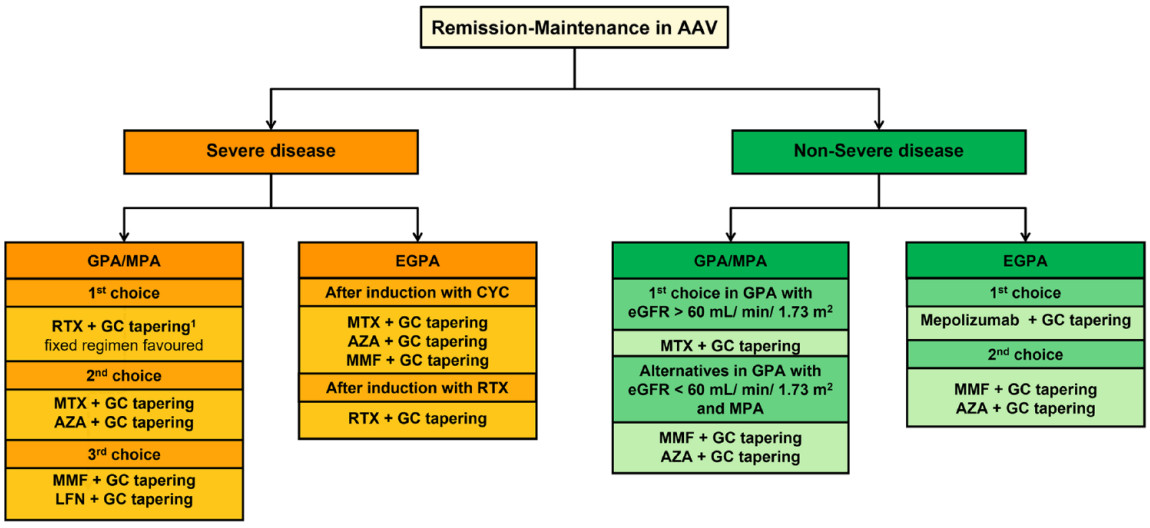

Figure 3. Algorithm for remission-maintenance treatment in ANCA-associated vasculitis (AAV).
AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; LFN, leflunomide; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab.
[1]The GC tapering is the standard of care at this point since avacopan was only recently approved as GC sparing strategy.

sustained remission for 2 years, two additional years of treatment with RTX decreased the relapse rate.[185]

Ongoing clinical trials of remission-maintenance in AAV. Table 3 summarizes the most relevant clinical trials on remission-maintenance for AAV.

The TAPIR (ClinicalTrials.gov: NCT01933724) and the MAINEPSAN trials (ClinicalTrials.gov: NCT03290456) focus on assessing the best duration of GC treatment to maintain remission in patients with GPA and with GPA or MPA, respectively. The HAVEN trial (ClinicalTrials.gov: NCT04316494) will provide information regarding the potential role of hydroxychloroquine in reducing disease activity in AAV. The STATVAS study (ClinicalTrials.gov Identifier: NCT02117453) will assess whether rosuvastatin can reduce AAV subclinical atherosclerosis. The

Table 3. Clinical trials of remission-maintenance treatment in ANCA-associated vasculitis.

Rituximab (RTX)			
Name	**Population**	**Intervention**	**Main results/Status**
MAINRITSAN, 2014[17]	Newly diagnosed or severe GPA or MPA or renal-limited vasculitis in complete remission vasculitis after induction with GC and CYC ($n = 115$)	RTX 500 mg IV at days 0 and 14 (then months 6, 12, 18, total 18 months) AZA 2 mg/kg/day for 12 months, 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months (total 22 months)	• Reduction of relapse was superior with RTX at 28 months • Improved survival and increased major relapse-free survival with RTX at 60 months
MAINRITSAN-2, 2018[179]	Newly diagnosed or severe relapse of GPA or MPA in complete remission after induction ($n = 162$)	Fixed: RTX 500 mg IV at days 0 and 14 (then months 6,12,18) Individualized: 500 mg IV at randomization and then reinfusion only if reappearance of CD19 or ANCA or increased titer of ANCA or increased titer of ANCA; measured every three months, until month 18	• No difference in relapse rate at 28 months of follow-up • ANCA and CD19 did not predict relapse

(Continued)

Table 3. (Continued)

Rituximab (RTX)			
Name	**Population**	**Intervention**	**Main results/Status**
MAINRITSAN-3, 2020[185]	Newly diagnosed or severe relapse of GPA or MPA in complete remission following the completion of MAINRITSAN-2 trial (*n* = 97)	Four additional 500 mg IV doses of RTX at months 34, 40, and 46 *vs* placebo	• Relapse-free survival rates are superior with extended therapy with RTX at 56 months • No difference in severe adverse events at 56 months
RITAZAREM, 2020[18]	Maintenance therapy after major relapse of GPA or MPA after induction with CG + RTX (*n* = 170)	RTX 1000 mg IV every 4 months x5 doses *vs* AZA 2 mg/kg/day	• RTX was superior in preventing relapses at 24 months • No difference in severe adverse events
Azathioprine (AZA)			
Name	**Population**	**Intervention**	**Main results/Status**
CYCAZAREM, 2003[186]	Newly diagnosed GPA or MPA after induction with GC and CYC (*n* = 144)	Continued CYC therapy (1.5 mg/kg/day) *vs* substitute regimen of AZA (2 mg/kg/day) Both arms continued to receive prednisolone (follow-up 18 months)	• No difference in relapse and adverse events at 18 months of follow-up. • The duration of exposure to CYC may be safely reduced.
WEGENT, 2008[180] WEGENT – long term, 2016[122]	Newly diagnosed GPA or MPA after induction with GC and CYC (*n* = 126 and *n* = 112)	AZA 2 mg/kg/day for 12 months *vs* MTX 0.3 mg/kg/week (oral or SC)	• No difference in relapse and adverse events at 29 months and ten years
REMAIN, 2009[187]	Newly diagnosed GPA or MPA or renal-limited vasculitis after induction with GC and CYC (*n* = 117)	Maintenance with AZA and prednisone low dose for 24 *vs* 48 months	• Significant reduction of relapse at 48 months • ANCA positivity is associated with relapse risk • More serious adverse events at 48 months
Mycophenolate Mofetil (MMF)			
Name	**Population**	**Intervention**	**Main results/Status**
IMPROVE, 2010[188]	Newly diagnosed GPA or MPA after induction with GC and CYC (*n* = 156)	AZA 2 mg/kg/day for 12 months, 1.5 mg/kg/day for 6 months, 1 mg/kg/day until month 42 *vs* MMF 2000 mg/day for 12 months, 1500 mg for 6 months and 1000 mg until month 42	• Increased incidence of relapse in the MMF group at follow-up of 39 months • Both treatments had similar adverse event rates
Leflunomide (LFN)			
Name	**Population**	**Intervention**	**Main results / Status**
Metzler *et al.*, 2004[189]	GPA incomplete or partial remission	LEF 30 mg/day *vs* MTX 7.5–20 mg/week after 8 weeks	• Relapse rate was inferior in the LEF group • Adverse events in LEF group
Belimumab (BEL)			
Name	**Population**	**Intervention**	**Main results/Status**
BREVAS, 2019[190]	Newly diagnosed or relapse of severe GPA or MPA after induction with GC + RTX	BEL 10 mg/kg IV on days 0,14 and 28 (then every 28 days) *vs* placebo of BEL	No difference in relapse rate at 12 months
Ongoing clinical trials for remission-maintenance in AAV (www.clinicaltrials.gov)			
Clinical trial	**Population**	**Objective**	**Intervention**
ABROGATE NCT02108860	Patients with relapsing non-severe GPA (*n* = 66)	ABA for remission-maintenance in GPA (Phase III)	ABA 125 mg SC weekly for 12 months *vs* placebo

(Continued)

Table 3. (Continued)

Ongoing clinical trials for remission-maintenance in AAV (www.clinicaltrials.gov)			
Clinical trial	**Population**	**Objective**	**Intervention**
TAPIR NCT01933724	GPA in remission ($n = 60$)	Low dose GC in GPA (Phase III)	All patients tapered to 5 mg of daily prednisone Prednisone: continue 5 mg daily No prednisone: taper to 0 mg
MAINEPSAN NCT03290456	Patients with GPA or MPA in remission, 12 months following induction therapy	Low dose GC in GPA/MPA (Phase III)	Prednisone: continue 5 mg daily for 12 months No prednisone: taper to 0 mg in 1 month
NCT04944524	Patients with GPA in remission after induction with CG + CYC	TOF for remission-maintenance (Phase IV)	TOF 5 mg twice a day for 12 months *vs* MTX 15–20 mg/weekly for 12 months
NCT04973033	10 patients with active AAV No organ/life-threatening disease	TOF for remission-maintenance (Interventional)	SOC + tofacitinib 5 mg twice a day
NCT03385668	Seven patients with MPO-ANCA (with or without vasculitis) with definite or possible UIP or NSIP No active vasculitis (BVAS > 3)	Pirfenidone in AAV-ILD	Pirfenidone at a dose of 2403 mg/day for 50 weeks, after 2 weeks of titration (801 mg/day 1 week, 1602 mg/day 1 week)
HAVENNCT04316494	76 patients with GPA/MPA/ EGPA + treated AAV + BVAS > 3	HCQ in AAV (Phase IV)	SOC + HCQ SOC + Placebo
STATVAS NCT02117453	121 patients with GPA/MPA/ EGPA remission no subclinical atherosclerosis with high cardiovascular risk	Rosuvastatin for the reduction of atherosclerosis and major cardiovascular events (Phase 3)	Rosuvastatin 20 mg/day Placebo
Ongoing clinical trials for remission-maintenance in AAV (www.clinicaltrials.gov)			
Clinical trial	**Population**	**Objective**	**Intervention**
MAINRITSEG NCT03164473	Patients with newly diagnosed or relapsing EGPA in remission within the past year	RTX for remission-maintenance in EGPA (Phase IV)	RTX fixed dose 500 mg IV every 6 months (total of 18 months) *vs* AZA (2 mg/kg/day) for 24 months
NCT03906227	Subjects with normalized CD5 + B cells are thought to be at lower risk and relapse and, therefore, may not need maintenance immunosuppression.	CD5 + B cell count as a marker of relapse risk	Patients were randomized to either maintenance immunosuppression *vs* close clinical observation without maintenance immunosuppression
MASTER-ANCA NCT03323476	Patients with KF related to AAV	Need for maintenance-remission treatment	Arm 1: discontinuation (or not initiation) of maintenance treatment) Arm 2: maintenance (or initiation) of immunosuppressive treatment

AAV, ANCA-associated vasculitis; ABA, abatacept; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; BEL, belimumab; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; HCQ, hydroxychloroquine; IV, intravenous; KF, kidney failure; LEF, leflunomide; LFN, leflunomide; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; RTX, rituximab; SC, subcutaneous; SCr, serum creatinine; SOC, standard of care; TOF, tofacitinib; UIP, usual interstitial pneumonia.

ABROGATE trial is currently recruiting patients with relapsing, non-severe GPA (ClinicalTrials.gov: NCT02108860) to evaluate the efficacy of abatacept (CTL4-Ig) in achieving GC-free remission. The role of tofacitinib (ClinicalTrials.gov: NCT04944524) is also being assessed in patients with non-severe GPA (new-onset or relapsing patients) in comparison to MTX as a

remission-maintenance treatment. In addition, treatment of specific organ involvement is now being studied in clinical trials due to the impact on morbidity and survival in AAV. Pirfenidone, an oral antifibrotic agent, used to reduce the progression of idiopathic pulmonary fibrosis,[191–193] has been evaluated to treat pulmonary fibrosis in a pilot study including patients with MPO-ANCA, with or without AAV (ClinicalTrials.gov Identifier: NCT03385668); results are still pending. For patients with newly diagnosed or relapsing EGPA, RTX is under further study as a maintenance agent compared to AZA in the MAINRITSEG trial (ClinicalTrials.gov Identifier: NCT03164473). Other treatment approaches focusing on tailoring treatment to avoid relapse are also being explored. For instance, there is a clinical trial that focuses on determining CD5 $^{+}$ regulatory B cells as patients with low levels have a higher need to keep remission-maintenance treatment to avoid relapse. (ClinicalTrials.gov Identifier: NCT03906227).

Potential new management strategies

The ability to target immunologic pathways will become increasingly possible. Hence the rationale for investigation is expected to be driven by pathophysiology. The analysis of specific populations might help with personalized care. Decreasing immunosuppressant drug toxicity, damage accrual, and morbidity are at the center of drug development.

The treatment to target has been explored using different strategies. The complement inhibition has now been studied as an adjuvant of remission-induction. It has been shown that avacopan has the potential for GC sparing.[15] New drugs targeting the complement system, such as IFX-1, a monoclonal antibody specifically binding to C5a, are under development. Inhibition of MPO has been recently proposed as a valuable target, as shown in a preclinical crescentic GN study where it suppressed kidney damage without augmenting adaptive immune responses.[194] Emerging cell therapies with tolerogenic dendritic cells, regulatory T cells (CAR-T cells), and stem cells (namely human amniotic epithelial cells) will probably emerge due to their selective immunosuppressive capacity.[195] In addition, the use of cytokines for the treatment of autoimmune rheumatic diseases has been studied.[196] It was shown that administration of low dose IL-2 allows expansion of T reg repertoire without effector T cell activation.[196] This could be a potential approach to maintaining immune tolerance, particularly in antibody-mediated diseases. The loss of tolerance to particular antigens is generally the starting point of antibody generation.[196,197] When and whether these newer strategies will be translated into improved management of patients with AAV in clinical practice is uncertain. In EGPA, depemokimab, an IL-5 receptor antagonistic monoclonal antibody, is currently being investigated to treat patients with severe eosinophilic asthma with an eosinophilic phenotype (ClinicalTrials. gov: NCT04718103 and NCT04718389).

Although most efforts in AAV research have focused on immunomodulating agents, therapies that address cellular and molecular mechanisms of tissue repair and regeneration, reducing evolution to tissue fibrosis, are also unmet needs in the AAV treatment approach. Blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) has been central in retarding progression of chronic kidney disease (CKD). However, patients still progress to KF, and research studies targeting the critical components of the fibrogenic pathway are currently ongoing, with a particular interest in TGF-β1 BMP-7, CTGF, CC motif chemokines, PDEs, Nox1/4, ET-1 and TNF-α.[198,199] The role of antifibrotic drugs in different kidney diseases is being evaluated in several clinical trials. However, their effect on AAV is still unknown.[198,199] More recently, sodium-glucose co-transporter 2 inhibitors (SGLT2i), which are reno-protective in diabetic and nondiabetic kidney disease, could be a potential adjunctive therapy in AAV.[200] However, to date, patients with AAV have been excluded from these clinical trials.

Registries

Collaborative networks have been synergic in the study of rare diseases. The clinical heterogeneity of AAV is particularly prone to benefit from registries and data accrued from different real-world practices. Furthermore, incidence, prevalence, and geographic differences regarding risk factors are better characterized using this overview type. Therefore, registries are a vital source of clinical data and can be particularly useful in facilitating research in disease biomarkers, optimizing recruitment for clinical trials, and deepening our understanding of the natural course of AAV.[201] There

are currently various vasculitis registries available or in development in different European and North American countries, for example: France [the French Vasculitis Study Group (FVSG)]; UK and Ireland [the UK and Ireland Vasculitis Rare Disease Group (UKIVAS)]; Spain [*Registro Español de Vasculitis Sistémicas* (REVAS)]; Poland (the Polish Vasculitis [POLVAS] registry); Czech Republic (Czech Registry of AAV); Norway [Norwegian Vasculitis Register & Biobank (NorVas)]; Portugal [Portuguese vasculitis registry [Reuma.(Reuma.]);)]; Germany, Austria, and Switzerland [Joint Vasculitis Registry in German-speaking countries (GeVas)]; Greece (AAV Patient Registry); USA and Canada [Vasculitis Patient-Powered Research Network (VPPRN)].[121,202–215] However, these existing registries exhibit significant differences in terms of content, data collection (retrospective *vs* prospective), stages of development, and aims, primarily influenced by the medical specialties involved (e.g. nephrology, rheumatology, internal medicine, immunology) and local resources.[201]

Ideally, AAV databases should have a common language and terminology, and patients should be recruited by all health care providers involved in management of AAV. Harmonizing data collection is crucial for attaining homogeneous communication and the correct merging of information between registries. Two initiatives are already underway to align vasculitis registries across Europe: 1) 'Model registry' initiative to define a long list of items using a REDCap (Research Electronic Data Capture) platform, led by the EUVAS working group for registries; 2) FAIRVASC, a collaboration between the EUVAS and the European Reference Network for Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune diseases (ERN – RITA) which aims to use semantic-web technologies to link vasculitis registries, establishing a common platform and reaching agreement on data governance.[201,216]

Improvements in registries interoperability and compatible joint exports of data, will facilitate research in AAV with an accrual of a sizable number of patients.

Conclusion

AAV is a group of challenging and complex conditions with overlapping clinical and laboratory manifestation patterns. Our increasing understanding of pathogenesis and early diagnosis has helped us choose a more tailored treatment and reshape the use of potential biomarkers for monitoring these patients. Mortality has significantly improved over the years, and survival rates are now close to 80% after remission-induction. Nevertheless, patients with AAV still have a relapsing course that impacts long-term survival and accrual of morbidity. Integrating genetic and immunologic backgrounds in the phenotypical characterization of patients with AAV will potentially add precision to the selection and development of new treatments. In addition, new classification criteria, adjusted to current practice, will aid correct recruitment of patients into clinical trials and research studies, ultimately improving patients' management. Finally, the continuous development of AAV registries will allow for more meaningful research based on a multidisciplinary approach and using real-world data. Although 10 years from now, the future of AAV is still uncertain, knowledge in this field is rapidly evolving. Thus, patients are expected to achieve higher rates of sustained remission with more individualized therapies while being exposed to less treatment toxicity.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Acknowledgements

The Scientific Publications staff at Mayo Clinic provided copyediting support and English-language review.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

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