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The Management of ANCA-associated Vasculitis: We Only See the Tip of the Iceberg

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Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) encompasses a group of rare autoimmune diseases affecting small blood vessels, including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis. Diagnosing AAV relies on clinical, biological, radiological, and histological findings. Despite advancements in understanding and treating these conditions, challenges remain in accurate prognosis and therapy management. The Five-Factor Score and Birmingham Vasculitis Activity Score are used to evaluate disease severity and guide treatment decisions, yet these tools have limitations and may not fully capture disease complexity. Recent epidemiological studies have highlighted the geographic variability in AAV incidence and the role of ANCAs as diagnostic and prognostic markers. Treatment involves an initial remission induction phase followed by maintenance therapy, often corticosteroids and immunosuppressants like rituximab and cyclophosphamide. However, newer agents such as mepolizumab and avacopan show promise, particularly for specific AAV subtypes. Evaluating sequelae using indices like the Vasculitis Damage Index is critical, given the increased survival rates and focus on quality of life. While current treatment protocols aim to reduce relapse and manage complications, including infections and metabolic issues, there is a need for more tailored approaches. The revised Chapel Hill classification has improved disease definitions, but the absence of ANCAs sometimes complicates diagnosis. This review underscores the necessity for developing more refined prognostic and activity scores to enhance the clinical management of AAV and calls for ongoing research to optimize treatment strategies and outcomes for affected patients.

Keywords: Vasculitis • ANCA • Management • Classification • Prognosis • FFS • BVAS • VDI • Contraindications • Complications

Introduction

Antineutrophil Cytoplasmic Antibodies (ANCA) Associated Vasculitis (AAV) comprises heterogeneous diseases affecting small-caliber vessels, including arterioles, capillaries, and venules. The main types of AAV are Granulomatosis With Polyangiitis (GPA), formerly known as Wegener's granulomatosis; Eosinophilic Granulomatosis With Polyangiitis (EGPA), formerly known as Churg-Strauss syndrome; and Microscopic Polyangiitis (MPA) [1]. The diagnosis of AAV is based on clinical suspicion, supported by biological, radiological, and histological findings. Due to the potential for severe visceral manifestations and fatal localizations, it is crucial to initiate appropriate treatment promptly to prevent life-threatening or functional complications. While severity and activity scores can be useful, they are not without limitations, as they may overestimate or underestimate the extent of damage in AAV. The Five-Factor Score (FFS) is not a reliable tool for therapeutic decision-making due to its lack of specificity and limited criteria, which make it inadequate for selecting the appropriate treatment. It is necessary to enhance this score to better identify severe conditions. In parallel, activity scores are mainly represented by the Birmingham Vasculitis Activity Score (BVAS), which is used for all types of vasculitis, including AAV. Despite its comprehensive nature, combining BVAS with FFS may be beneficial for determining the need to add an Immunosuppressant (IS) to Corticosteroid (CS) therapy. There are also several evaluation scores for assessing sequelae in AAV, with the Vasculitis Damage Index (VDI) being the most widely used [2]. The treatment of AAV typically involves an initial phase of remission induction followed by a longer phase of remission maintenance [3]. Understanding the indications, contraindications, and potential complications of any prescribed medications is essential. Therefore, we conducted this review to evaluate the current diagnostic criteria, prognostic tools, and treatment strategies for ANCA-associated vasculitis, highlighting recent advancements and identifying areas for future research to improve patient outcomes.

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Literature Review

Epidemiology

AAVs are rare conditions, making their epidemiological study challenging. The incidence of AAVs in France is comparable to hat in Germany and the United Kingdom. GPA is the most studied disease within AAVs and is twice as common as MPA in France [4]. In New Zealand, a five-year study showed a significantly higher incidence of AAVs in the southern regioncompared to the northern region. This geographic difference is similar to that between northern and southern Europe [5]. The highest incidence rate of EGPA was reported in Norwich, United Kingdom, at 2.7 cases per million people [6]. The incidence of AAVs varies between men and women worldwide, with most studies showing a moderate male predominance. Over the past 20 to 30 years, the incidence of AAVs has increased with age, likely due to greater awareness of the disease and more diagnoses in older individuals [7].

Basic concepts

Vasculitis, or angiitis, refers to inflammation of blood vessels, including arteries, capillaries, or veins. This inflammation can affect the intima, media, and/or adventitia layers of the vessel wall, leading to infiltration by cells such as Neutrophil Polynuclears (NPN), eosinophilic polynuclears, lymphocytes, plasma cells, histiocytes, and/or giant cells. AAVs are rare, multisystem autoimmune diseases of unknown etiology, characterized by inflammatory cell infiltration causing necrosis of blood vessels. ANCAs serve as diagnostic and prognostic markers of AAV. These autoantibodies, mainly immunoglobulin G, target antigens in the azurophilic granules of NPNs and monocyte lysosomes. Three types of ANCAs are based on the indirect immunofluorescence test [8]. PR3-ANCA (c-ANCA) produces diffuse cytoplasmic staining and mainly reacts with Proteinase 3 (PR3). MPO-ANCA (p-ANCA) targets Myeloperoxidase

(MPO), producing a perinuclear staining pattern. Atypical ANCA (x-ANCA) is directed against other constituents of cytoplasmic granules, not PR3 or MPO. PR3-ANCA is most frequently associated with GPA (75%), while MPO-ANCA is found in 60% of MPA cases [9]. The presence of x-ANCA is common in non-vasculitic diseases, such as chronic inflammatory bowel diseases, malignancies, and autoimmune disorders. PR3-ANCA or MPO-ANCA can also be present in chronic infections, including endocarditis, tuberculosis, human immunodeficiency virus, hepatitis C, and bartonellosis. When both PR3-ANCA and MPO-ANCA are detected simultaneously in the same patient—a rare occurrence—drug-induced vasculitis is a likely diagnosis [9].

Classification of vasculitis

In 1990, the American College of Rheumatology established a classification system for major vasculitis types based on clinical, biological, and histological criteria [10]. The Chapel Hill nomenclature, introduced in 1994, became a reference standard, classifying vasculitis by the size of the affected vessels, although it did not address some relatively common forms, such as secondary vasculitis. In 2012, the Chapel Hill Consensus Conference revised the classification, incorporating new types of vasculitis and terminology [10]

Table 1. Definitions of ANCA-associated vasculitis proposed in Chapel Hill Consensus Conference.

CHCC 2012 Name	CHCC 2012 Definition [10]
Granulomatosis with Polyangiitis	Necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract, and necrotizing vasculitis, predominantly affecting small-to-medium vessels. Necrotizing glomerulonephritis is common.
Microscopic Polyangiitis	Necrotizing vasculitis, predominantly affecting small vessels. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Eosinophilic Granulomatosis With Polyangiitis	Eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract, and necrotizing vasculitis, predominantly affecting small-to-medium vessels. Associated with asthma and eosinophilia.

Abbreviations: ANCA: Antineutrophilic Cytoplasmic Antibody; CHCC: Chapel Hill Consensus Conference

Table 2. 2012 Revised international chapel hill classification.

Type of Vasculitis [10]	Specific Conditions [10]
Large Vessel Vasculitis	Takayasu arteritis
	Giant cell arteritis
Medium Vessel Vasculitis	Polyarteritis nodosa
	Kawasaki disease
Small Vessel Vasculitis	ANCA-associated vasculitis
	Granulomatosis with polyangiitis
	Eosinophilic granulomatosis with polyangiitis
	Microscopic polyangiitis MPA
	Immune complex vasculitis
	Antiglomerular basement membrane disease
	Cryoglobulinemic vasculitis
	IgA vasculitis
	Hypocomplementemic urticarial vasculitis
Variable Vessel Vasculitis	Behçet disease
	Cogan syndrome
Single-Organ Vasculitis	Cutaneous leukocytoclastic angiitis
	Cutaneous arteritis
	Primary central nervous system vasculitis
	Isolated aortitis
Vasculitis Associated With Systemic Disease	Lupus vasculitis
	Rheumatoid vasculitis
	Sarcoid vasculitis
	Others (Sjögren's disease, dermatomyositis, scleroderma, antiphospholipid syndrome)
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 vasculitis
	Cancer-associated vasculitis

Abbreviations: ANCA: Anti-Neutrophil Cytoplasmic Antibody; Microscopic Polyangiitis

(Table 1). New definitions were proposed for AAVs, and ANCA testing has become an essential classification criterion [10] (Table 2).

Prognostic factors

The FFS is used to guide treatment decisions for patients with AAV. The FFS includes five clinical and biological criteria correlating with the five-year mortality rate. In its original 1996 version, the FFS identified factors impacting overall survival in patients with polyarteritis nodosa and EGPA, but it did not apply to other necrotizing vasculitides [11]. The FFS was revised in 2011 to include other systemic necrotizing vasculitides, particularly GPA and MPA. This revision removed nervous system involvement and 24-hour proteinuria as factors. Using the original 1996 criteria, the five-year mortality was 11.9% without any prognostic factors. However, mortality increased to 25.9% with one factor and exceeded 45.95% with two or 3 of 7 more factors [12]. In the revised FFS, age over 65 became a negative prognostic factor, while Ear, Nose and Throat (ENT) involvement was considered protective, with a very low relative risk of death. According to the 2011 criteria, the five-year mortality rates were 9%, 21%, and 40% for FFS scores of 0, 1, and 2, respectively [12]. The revised FFS is a simplified score for prognostic evaluation and therapeutic decision-making. However, it is limited because it considers only the prognostic parameters at diagnosis and not over time. The revised FFS can underestimate the severity of disease since it only accounts for digestive, renal, cardiac, and ENT disorders and may overestimate severity for patients older than 65. Clinicians may encounter lifethreatening visceral involvement, such as rapidly progressing intra-alveolar hemorrhage, where an FFS of 0 might suggest CS therapy alone, but aggressive IS treatment is necessary for AAV control. Similarly, in GPA with ENT involvement, CS therapy alone is ineffective due to frequent recurrences, requiring repeated CS use, which is suboptimal and increases the risk of infectious and metabolic complications. Adding IS agents not only reduces the need for CS but also helps control unpredictable relapses and flare-ups. AAVs differ in their life-threatening and functional implications, so using a single score to unify theirprognosis might not be appropriate. The revised FFS should be more specific and detailed and should be combined with an activity score. In such a score, IS agents could be categorized as "light",aggressive", such as Azathioprine (AZA)," Cyclophosphamide (CYC), to facilitate therapeutic decisions.

Antineutrophil cytoplasmic antibodies

ANCAs are crucial for predicting responses to induction therapies and long-term prognosis. Rituximab (RTX) is more effective than CYC in patients with PR3-ANCA type AAV, while both treatments have similar effects in MPO-ANCA type AAV. Patients with PR3-ANCA are at greater risk of relapse than those with MPO-ANCA [13].

Activity scores

Activity scores assess the severity of AAV at diagnosis or during relapses. Several clinical and biological scores exist, but the BVAS is the most widely used. BVAS applies to all types of vasculitis. It was initially proposed in 1994 and revised in 1997 and 2009. The 2009 version is the most reliable and current. BVAS includes a list of nine organ systems to evaluate vasculitis activity and define treatment response to medications such as CYC, methotrexate, mycophenolate mofetil, intravenous immunoglobulins, and RTX. BVAS version 3 comprises 56 items, and the point values differ between recent lesions (less than 28 days) and persistent ones. Higher scores indicate more active disease, with scores of 25 to 35 reflecting very active disease affecting multiple organs. In 2001, the French Vasculitis Study Group proposed a specific BVAS for GPA [14]. Although BVAS is commonly used for AAV, it cannot distinguish between active vasculitis and progressive generalized infections due to overlapping clinical features such as fever, purpura, and headache. The infectious symptoms may be secondary to the vasculitis itself, its treatment, or a comorbidity. Therefore, including C-Reactive Protein (CRP) and Procalcitonin (PCT) in BVAS could help differentiate between sepsis and significant disease activity. A high CRP with a negative PCT would indicate a disease flare-up. During inflammation or viral infections, PCT usually does not increase, whereas high CRP and PCT levels suggest a generalized bacterial or fungal infection. Additionally, ANCA levels could be included in BVAS since their persistence despite treatment indicates residual activity and a risk of relapse. An increase or return of ANCA positivity suggests a disease flare-up. Combining FFS and BVAS for AAVs would better determine the necessity of adding IS treatment.

Evaluation scores of sequelae

Limiting sequelae has become a critical focus with the overall improvement in survival rates among patients with vasculitis. The Short Form 36 is a global scale used to assess the impact of diseases on quality of life. It originates from the Medical Outcomes Study, which aims to measure quality of life objectively, and includes 36 questions covering eight health domains [15]. The VDI is more specific to vasculitis. While the BVAS records current disease activity, the VDI highlights the consequences of vasculitis and/or its treatment or other comorbidities that occur after diagnosis, regardless of cause. The VDI score can remain stable or increase, but it cannot decrease even if sequelae fade months or years after remission. The VDI is simple to calculate, with each element contributing one point to the totalscore. Each time the VDI is evaluated, it includes all elements from the previous evaluation plus any new ones. This cumulative nature distinguishes it from the non-cumulative BVAS. The VDI defines chronic damage and record any condition that has occurred and lasted at least three months since the onset of vasculitis [16].

Treatment

Induction of remission: During the induction phase, the main objective is to improve patient survival. CS are initially administered at a dose of 1 mg/kg/day, not exceeding 60 to 80 mg per day, with the attack treatment often lasting four weeks. Depending on the severity, one or more boluses of methylprednisolone (7.5 to 15 mg/kg/day) may precede oral intake [17]. Boluses of CYC are combined with CS, initially administered every two weeks for one month (days 1, 14, and 28) at a dose of 0.6 g/m². Dosage is adjusted according to renal function [18]. RTX, an anti-CD20 agent, is the standard treatment for AAV and is preferable in cases of relapse, nonresponse to CYC, and in patients of childbearing age [19]. In contraindications or refractory disease cases, obinutuzumab, another anti-CD20 agent, could be an effective alternative for AAV treatment. Since obinutuzumab causes deeper and longer-lasting depletion of B lymphocytes, it may theoretically provide better control of vasculitis than RTX [20]. Plasma exchanges are beneficial for patients with severe alveolar hemorrhage, persistent worsening of renal insufficiency despite treatment with CS in combination with CYC or RTX, glomerulonephritis, and/or rapidly progressive alveolar hemorrhage without a definitive diagnosis, at least until results for antibodies against the glomerular basement membrane are available [21].

Maintenance of remission: During maintenance treatment, the therapeutic objectives are to reduce relapse risk and prevent complications related to treatment and vasculitis. The optimal duration of treatment is not yet defined. CS are used with a decreased dosage maintained for 12 to 18 months. CYC is administered at a 0.7 g/m2 dose every three weeks, typically with six to eight boluses. However, CYC is not the preferred IS due to its association with some long-term neoplasms. AZA at a dose of 2 to 3 mg/kg/day or methotrexate at 0.3 mg/kg/week are often used and are nearly equivalent in tolerance and effectiveness [22]. Mycophenolate mofetil (MMF) is another IS used during maintenance, which can advantageously replace CYC. However, MMF is less effective than AZA in preventing relapse, so it is not a first-line treatment butremains a valuable alternative in MPO-ANCA vasculitis [23]. RTX can achieve remission without additional treatment. A dosage of 500 mg or 1000 mg is administered at fixed intervals every six months for two years. This regimen is recommended after the end of induction therapy. The risk of relapse persists after stopping RTX, necessitating ongoing monitoring [24].

Particularities

Mepolizumab: In EGPA, treating residual asthma primarily involves inhaled CS and long-acting beta-2 agonists, with the occasional addition of anticholinergics. If triple-inhaled therapy fails, mepolizumab, an anti-

interleukin-5 agent, may provide satisfactory results. Mepolizumab is approved for severe eosinophilic asthma and is currently under study for preventing relapses in EGPA patients. In refractory asthma, mepolizumab is administered subcutaneously at a dose of 100 mg every four weeks; for maintaining remission, the dose is 300 mg every four weeks [25].

Avacopan: The activation of the alternate complement pathway results in the terminal production of C5a, which plays a role in AAV pathogenesis. Avacopan is an oral C5a receptor antagonist that selectively blocks C5a effects *via* the C5a receptor (C5aR, also known as CD88). It inhibits the chemoattraction and activation of neurophils. In a mouse model of AAV, avacopan prevented the development of glomerulonephritis induced by MPO-ANCA [26]. Phase 2 trials have demonstrated its effectiveness in AAVs. The recommended dose is 30 mg twice daily [27].

Contraindications

True contraindications to CS are rare and include severe progressive infections, glaucoma, cataracts, and certain psychiatric disorders. Diabetes is not an absolute contraindication, but CS may temporarily worsen glycemic control. CS should be limited in osteoporosis or severe hypertension [28]. Vaccines that are contraindicated during CS treatment include measles, mumps, rubella, tuberculosis, and varicella. For other IS, absolute contraindications include serious progressive infections (viral, bacterial, parasitic, or fungal), any live vaccine, and certain neoplasms. Precautions are necessary in cases of hepatic and renal insufficiency. IS should be discontinued during pregnancy and breastfeeding, except for AZA, which is allowed during pregnancy [29].

Complications

Infectious complications are common after CS therapy or IS use and include bacterial pneumonia, 5 of 7 septicemia, viral infections, and opportunistic infections e.g. pneumocystosis, aspergillosis, candidiasis). Anti-infective prophylaxis has proven effective in GPA using trimethoprim-sulfamethoxazole (160 mg/800 mg) three times per week and in patients with leukopenia (CD4 <300/mm^3) treated by CYC [30]. CYC and AZA are the IS most associated with carcinogenic risk. Hemorrhagic cystitis and bladder cancer are known complications of CYC [30,31]. The toxicity arises from the direct oncogenic effect of CYC metabolites, such as acrolein, on the bladder mucosa. Preventative measures include increased fluid intake to reduce mucosal contact with acrolein and cytostatic treatment (mesna). Long-term AZA use in chronic inflammatory bowel disease is linked to an increased risk of lymphoma [32]. Prolonged and/or high-dose CS therapy is associated with metabolic complications, including glycemic, lipid, and blood pressure dysregulation, which may require antihyperglycemic agents or insulin, lipidlowering drugs, and antihypertensive medications. While a strict salt-free and/or sugar-free diet has not been scientifically validated and remains controversial, adequate daily intake of vitamin D (800 IU) and calcium (1g) appears beneficial. Patients should also be advised to maintain a balanced diet and exercise regularly. Osteonecrosis of the hip and humeral head is a frequent complication of prolonged CS therapy [33]. Osteoporotic fractures can result from CS use or menopause secondary to IS. Therefore, systematic prevention with vitamin D and calcium and anti-osteoporosis treatment with bisphosphonates is recommended for patients on CS therapy ≥7.5 mg/day for more than three months in postmenopausal women and men over 50 years [34].

Conclusion

The revised Chapel Hill classification has provided clearer definitions of AAVs, emphasizing the presence of ANCAs. However, the absence of ANCAs does not exclude the diagnosis of primary vasculitis, making diagnostic confirmation challenging for clinicians. AAV treatment has advanced significantly in recent years, with remission maintenance becoming a major therapeutic goal. Prognostic scores like the FFS and activity indices like the BVAS help manage AAVs, yet their practical contribution remains limited. Developing new, more relevant scores would be beneficial.

Conflicts of Interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info

All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declalared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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