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Review

New Insights into Pathogenesis and Treatment of ANCA-Associated Vasculitis: Autoantibodies and Beyond

Marino Paroli *, Chiara Gioia and Daniele Accapezzato

Division of Clinical Immunology, Department of Clinical, Anesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, 00185 Rome, Italy
* Correspondence: marino.paroli@uniroma1.it

Abstract: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a group of rare systemic diseases affecting small-caliber vessels. The damage caused by AAV mainly involves the lung and kidneys. AAV includes three different types: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Although the different phenotypic forms of AAV share common features, recent studies have shown that there are significant differences in terms of pathogenetic mechanisms involving both the adaptive and innate immune systems. Advances in our understanding of pathogenesis have enabled the development of immuno-targeted therapies. This review illustrates the characteristics of the various forms of AAV and the new therapies available for this disease that can have lethal consequences if left untreated.

Keywords: ANCA; vasculitis; pathogenesis; B-cells: complement; neutrophils; eosinophils

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1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic diseases affecting small vessels. AAV causes damage to several organs and tissues, including the upper and lower respiratory tracts, kidneys, nerves, and skin [1]. AAV comprises three main forms: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [2]. Another type is drug-induced AAV [3]. AAV is characterized by the presence in the serum of ANCA specific for zymoproteins present in the cytoplasm of neutrophils, namely myeloperoxidase (MPO) and proteinase3 (PR3) [4,5]. The frequency of the presence of these antibodies varies widely among different types of AAV [6]. The most serious complications of AAV are diffuse alveolar hemorrhage and renal failure, both of which can be life-threatening [7,8]. The diagnosis of this condition is still based on Watts' criteria [9] but a new classification has recently been proposed by ACR/EULAR [10–12] to highlight differences in pathogenesis and response to treatment between conditions previously considered most similar. The purpose of this review is to discuss new knowledge about the pathogenesis of different forms of AAV and the latest therapeutic approaches for this complex disease.

2. Epidemiology

The introduction of the ANCA test about three decades ago made it possible to identify previously undiagnosed cases of AAV. However, epidemiological data on the incidence and prevalence of AAV have always been hampered by the rarity of the disease [13,14]. In recent years, there has been a gradual increase in the number of patients diagnosed as having AAV. Several explanations have been proposed, including climate change, improved classification criteria, more common use of ANCA testing, and increased awareness of the disease. However, the epidemiology of AAV seems to have stabilized in the early 2000s [15]. The incidence of GPA and MPA seems similar, with up to 30 new cases per

million population and a prevalence of up to 250 cases per million population according to epidemiological studies [16,17]. EGPA is much rarer, with an incidence of up to four cases per million population and a prevalence of up to 25 cases per million population [18]. Several studies have shown that the peak incidence of AAV occurs in the age group of 60 to 79 years [19,20]. The higher incidence of AAV in elderly individuals may be partly explained by improved testing for ANCAs in serum, which has made it possible to detect previously undiagnosed forms [19,21]. The ratio of male-to-female prevalence was reported as slightly in favor of women [19,22–24]. However, this result has not been confirmed by other studies. Therefore, the question of whether there is a sex-dependent susceptibility to the disease has not yet been definitively answered [25].

Epigenetics and Environmental Factors

Some environmental factors have been reported to be responsible for the induction or course of AAV. These mainly include infectious agents, drugs, and silica dust. Some studies indicate that toxic shock syndrome toxin-1 (TSST-1) produced by some strains of *S. aureus* is a risk factor for GPA recurrence [26]. It has been hypothesized that this bacterium is involved in the pathogenesis of AAV through a mechanism of molecular mimicry [27]. The hypothesis of the possible involvement of *S. aureus* in AAV is also based on the observation of the therapeutic effect of antibiotic treatment in GPA, as reported by some studies [28,29]. The association between silica dust exposure and the development of AAV was first suggested by a comprehensive meta-analysis [30]. In this regard, it was reported that the severity of the disease increased in patients with AAV after the earthquakes in Japan [31,32]. This observation suggested that silica dust in the air due to the destruction and reconstruction of cities may have influenced the course of AAV, especially at the respiratory level. However, no difference was observed in the incidence of AAV before and after the 2011 New Zealand earthquake [33]. Therefore, the role of earthquakes in the onset or flares of AAV has not yet been conclusively demonstrated.

3. Classification and Diagnostic Criteria

The first American College of Rheumatology (ACR) criteria for vasculitis including AAV were published in 1990 and included only GPA and EGPA, but not MPA [34]. Subsequently, new definitions from the Chapel Hill Consensus Conference (CHCC) were published in 1994 and then revised in 2012. On this occasion, the classification took into account the new etiopathogenetic knowledge of the different types of AAV. A tree hierarchy was developed, emphasizing that some conditions cannot be classified simply by vessel size, but require the presence of surrogate markers of disease. AAV was recognized as a specific type of small vessel vasculitis in which the surrogate marker is the presence of serum ANCA [2]. This classification revision was preceded by a stepwise diagnostic algorithm formulated by experts and widely used in clinical practice [9]. The presence of ANCA can be assessed by several tests, the first of which to be proposed was the indirect immunofluorescence test on ethanol-fixed human neutrophils [35]. Alternative and more practical methods are enzyme immunoassay and chemiluminescence. In detail, the c-ANCA describes an indirect immunofluorescence pattern that consists of diffuse granular cytoplasmic staining, characteristic of PR3-ANCA, while the p-ANCA pattern consists of perinuclear staining, typical of MPO-ANCA [36,37]. The pattern most commonly associated with GPA although not exclusively, is c-ANCA [38]. Patients with MPA often show a p-ANCA pattern, but they can also exhibit PR3-ANCA [39]. In EGPA, <50% of patients have detectable ANCA. If present, these are typically MPO-ANCA [40]. More recently, diagnostic criteria for AAV have been proposed that aim to provide more accurate distinctions of individual forms based on their clinical features [10–12]. It has also been suggested by some authors that the classification of AAV types was based on the specificity of circulating ANCA rather than clinical features [41].

4. Pathogenesis

4.1. The Role of Genetic

Through genome-wide association studies (GWAS), several genes have been identified that may be involved in AAV susceptibility. In particular, the major histocompatibility complex class II genes appear to play a major role [42–44]. In some studies, GPA with PR3-ANCA is significantly associated with *HLA-DP* genes, while the presence of MPO-ANCA is associated with *HLA-DQ* genes [42,43]. It has also been reported that the *HLA-DPB1*04* allele is associated with the risk of developing GPA in North America, while the *HLA-DRB1*09* allele is associated with GPA with MPO-ANCA in the Japanese population. These differences reflect the predominance of GPA with PR3-ANCA in European white populations, while GPA with MPO-ANCA is more common in Asian populations [45]. Several associations of AAV with non-MHC genes have also been described. These include *PTPN22* [46], *SERPIN1*, *PRTN3*, and *SEMA6A* genes [42–44]. It has been reported that the frequency of a single nucleotide polymorphism (SNP) in the *PTPN22* gene is higher in patients with AAV than in healthy subjects. It has also been shown that this mutated variant is associated with increased production of interleukin (IL)-10 characterized by anti-inflammatory activity. This would result in decreased disease activity in patients with AAV bearing this mutation [46]. An SNP near the *SERPIN1* gene is associated with PR3-ANCA-associated GPA resistance [47]. An SNP in the *PRTN3* gene is associated with resistance to developing PR3-ANCA AAV, while an SNP in the *SEMA6A* gene is associated with resistance to developing GPA. [43,44]. Future studies are needed to better clarify how mutations in these genes are involved in the pathogenesis of AAV. Epigenetic modifications of histones and DNA have been implicated in the regulation of the expression of genes encoding for MPO and PR3 [48,49]. Promoter methylation of *MPO* and *PRTN3* genes was found to be negatively correlated with their transcription [49] and is inversely related to disease activity [49].

4.2. The Role of ANCA and Neutrophils

Several studies conducted initially in animal models have shown that ANCA play an important role in the pathogenesis of AAV. For example, injection of MPO-ANCAs into wild-type mice can induce necrotizing and crescentic glomerulonephritis (NCGN) [50]. In other experimental models, the presence of MPO-ANCA has been shown to cause pulmonary hemorrhage [51]. These animal models indicate the pathogenicity of ANCAs and not only their utility as biomarkers of disease. To understand the pathogenic mechanism of ANCAs, their interaction with neutrophils is crucial. Neutrophils play a central role in mediating and amplifying tissue damage. In genetically predisposed individuals and with the contribution of environmental factors, proinflammatory cytokines induce neutrophils to express MPO and PR3 antigens on their cell surface making them visible to autoreactive cells of the adaptive immune system [52]. These antigens can then become the target of ANCA. Such antibodies further activate circulating neutrophils that transmigrate through the endothelium and accumulate at the level of the vascular wall. Here, they can release superoxide radicals and oxygen enzymes, molecules that are extremely damaging to the vessels and can cause their necrosis [53]. Damaged vascular endothelium allows plasma to reach perivascular tissue triggering the coagulator cascade and inducing thrombosis of small vessels [54,55]. Neutrophil activation activates by chemotaxis the arrival of monocytes into the tissue, which in turn induces the release of cytokines, other proinflammatory mediators, reactive oxygen species, and lytic enzymes, further amplifying the inflammatory reaction and tissue damage [56]. A key contribution to tissue damage is also made by the formation and release of neutrophil extracellular traps (NETs) associated with neutrophil apoptosis (NETosis). NETs are extracellular fibrillar arrays containing DNA that constitute an important defense tool of neutrophils against extracellular pathogens [57]. Their activation is very harmful to small vessels [58] and is involved in complement activation [59] and ANCA production [60].

4.3. The Role of B- and T-Cells

MPO and PR3 antigens are discharged in the extracellular environment by neutrophils dying of apoptosis after NETs release. These proteins are phagocytosed by antigen-presenting cells for induction of MPO- and PR3-specific T lymphocytes which are then expanded and activated in the peripheral blood [61]. Abnormal immune responses are thus induced that promote the chronicity of the inflammatory process through the release of cytokines, enzymes, and reactive oxygen species [62]. The T-cell response is mediated mainly by T helper (Th)1 and Th17 cells with pro-inflammatory activity. This process is accompanied by a decrease in circulating regulatory T cells (Tregs) that contribute to the immune reaction against the self-antigens MPO and PR3 [63]. Th17 cells stimulate the recruitment of neutrophils to inflamed sites with the amplification of tissue damage [64]. Conversely, neutrophils provide to induce the enrolment of effector T-cell types and amplification of T-cell memory [65]. Some of these effector T-cells also contribute to natural killer (NK) cell proliferation [66]. Th2 cells provide to help B-cells to produce ANCA [67,68]. Several other factors have been found to contribute to the development of AAV, including defective apoptosis or failure to eliminate apoptotic cells. These may expose self-antigens normally invisible to the immune system [69]. It has also been observed that nasal colonization with S. aureus is often present in GPA, especially in relapsing patients. It has been suggested that this pathogen might contribute to an inflammatory microenvironment necessary for the activation of autoreactive T cells in AAV [70,71]. The direct pathogenicity of ANCA is supported by both experimental and clinical observations [72,73]. In animal models, ANCA have been shown to interact with neutrophils by inducing their degranulation and production of oxygen radicals [74,75]. ANCA can also induce the adhesion properties of neutrophils to the endothelial cells [76,77], inducing vessel wall inflammation of different target organs [50,78–80]. The pathogenic role of ANCAs is also supported by clinical data. For example, in drug-associated AAV, remission induced by drug withdrawal is directly related to a significant reduction in circulating ANCA titer [81–83]. In support of the pathogenetic role of ANCA, a case of neonatal pulmonary hemorrhage secondary to transplacental passage of MPO-ANCA by the mother has been well described [84]. Another similar clinical case in which an infant of a mother with AAV developed pulmonary hemorrhage and renal kidney damage. The MPO-ANCA assay revealed that the antibody titer in serum was the same as that of the mother. This finding is highly suggestive of the passive transfer of ANCAs by the placental route [85]. More evidence of ANCA pathogenicity includes the observation that targeted therapies that reduce autoantibodies depleting B-cells are effective treatments in AAV [86–88]. It is noteworthy, however, that in a mouse model of MPA made B-cell deficient, crescentic glomerulonephritis developed equally in the absence of MPO-ANCA. Depletion of CD4+ effector cells attenuated glomerulonephritis, demonstrating a possible ANCA-independent role of T-cells in the immunopathogenesis of AAV [89]. It has also been reported that regulatory B cells (Breg) induce the trans-differentiation of effector T cells into regulatory T cells (Treg), contributing to reduced ANCA production by B cells. A defect in Breg may therefore be an additional factor promoting the production of AAV [90]. Figure 1 illustrates the pathogenesis of AAV, involving ANCA, neutrophils, dendritic cells, and cells of the adaptive immune system.

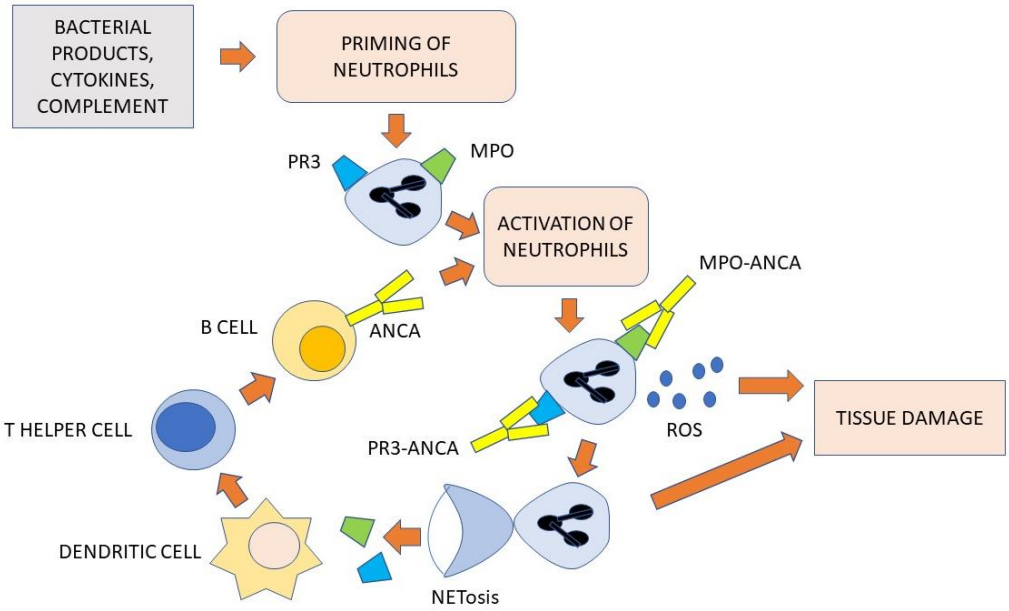

Figure 1. Pathogenesis of AAV. Environmental factors induce neutrophils to express MPO and PR3 on their surface. These cells are then further activated and induce tissue damage through the production of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps (NETs). Exposure of NETs, through a process termed NETosis, is associated with apoptosis of the neutrophils themselves, which release the antigens MPO and PR3 into the extracellular space. These proteins are processed by dendritic cells and then presented to T helper cells. The latter help the B cells to produce ANCA, which further activate the neutrophils thus maintaining the inflammatory process.

4.4. The Role of Complement

AAV is considered a pauci-immune disease because immunoglobulin and complement deposits are absent or greatly reduced in patients with AAV [91–93]. However, recent experimental and clinical studies suggest that the complement system is actively involved in the pathogenesis of AAV, particularly through the alternative pathway. In this regard, it has been shown that factor B- and C5-deficient mice do not develop the disease after MPO-ANCA administration [94]. On the other hand, the blockade of the C5a receptor (CD88) in mice protects animals from MPO-ANCA-induced vasculitis [95]. Many other studies support the role of C5a factor in AAV pathogenesis [96,97]. Clinical data confirmed that there is an activation of the alternative complement pathway in AAV. Plasma levels of soluble C3a, C5a, C5b-9, and Bb have been described to be higher during active disease than during remission phases [98–101]. C5a released through the action of C5 convertase can induce mast cell degranulation. This molecule has chemoattractive properties, being able to induce the recruitment of phagocytic cells into tissues and facilitate the migration of antigen-presenting cells into lymph nodes resulting in the activation of the adaptive immune response [102–104]. C5a also induces neutrophils to express PR3 on the cell membrane, allowing specific ANCA to bind this protein [105]. In AAV in an active phase, decreased expression of factor H was observed [106]. Factor H not only regulates the alternative complement pathway, but can also bind neutrophils by inhibiting their activation by ANCA. A deficiency of factor H can induce alteration in C3b production, resulting in neutrophil activation with subsequent progression of AAV [107]. Other factors that regulate alternative complement pathways are intercellular adhesion molecule-1 (CD54), decay-accelerating factor (DAF or CD55), and CD59 glycoprotein. The levels of all these proteins can be altered during AAV [108]. Another observation in favor of the role of complement is the evidence that a condition of hypocomplementemia at diagnosis is associated with a worse prognosis and severe renal damage in patients with AAV, due to complement deposition in the small vessels of target organs [109,110]. Figure 2 summarizes the role of complement in the pathogenesis of AAV.

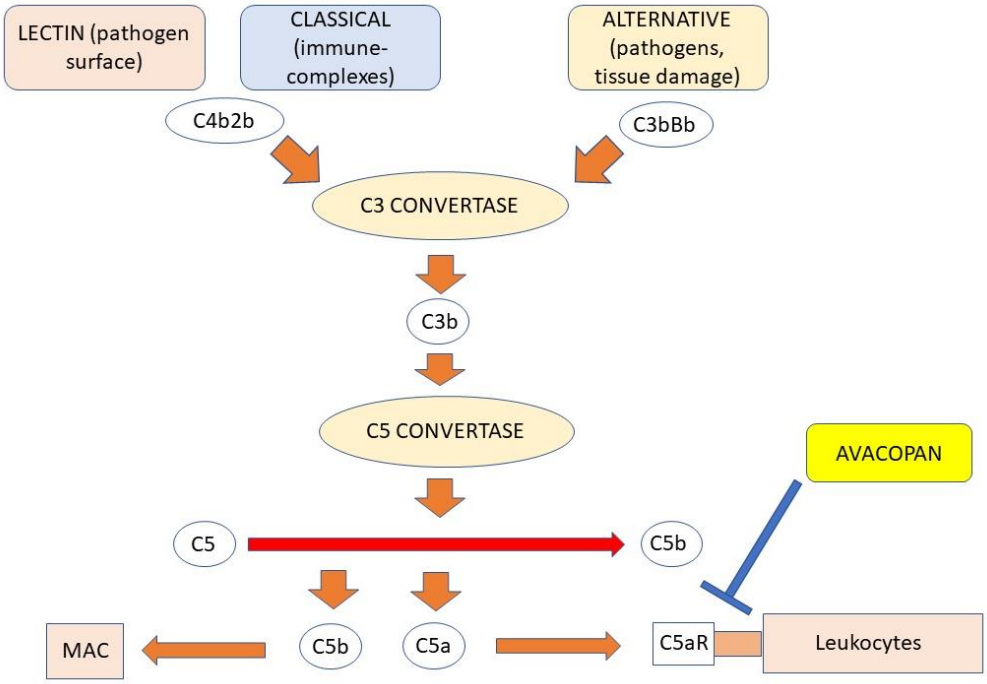

Figure 2. The role of complement. Activation of the alternative complement pathway results by a cascade mechanism in the synthesis of factor C5a, which after recognition of its C5aR receptor on the surface of leukocytes activates them to produce factors that mediate tissue damage. Avacopan, a C5aR agonist, inhibits C5a binding thereby blocking activation of leukocytes including neutrophils.

4.5. The Role of Eosinophils

EGPA is an AAV characterized mainly by asthma associated with eosinophilia. EGPA can affect several organs, including the skin, lungs, and peripheral nerves [2,111]. EGPA differs mainly from GPA and MPA in the expression of ANCA, which are present in only 30–40% of patients with EGPA [112–114]. In addition, some patients with EGPA may not show histological signs of vasculitis and are defined by some authors as having hyper-eosinophilic syndromes (HES) or eosinophilia or suffering from eosinophilic lung disease [115]. EGPA is associated with several immunological dysregulations. CD4+ T-cells, mainly of Th2 phenotype, play a pathogenic role in EGPA. In particular, eosinophils are responsible for most tissue damage [116]. Th2-related cytokines, including IL-5, IL-10, and IL-13, can effectively promote the maturation of eosinophils in the bone marrow and play a key role in their activation peripherally [117]. The success of therapy based on blocking IL-5 by monoclonal antibodies underscores the importance of Th2 cells and eosinophils in disease pathogenesis. In addition, CD4+ T lymphocytes can protect eosinophils from apoptosis, helping them survive longer [118]. Moreover, some studies have revealed that eosinophil proliferation can be triggered by signaling pathways by tyrosine kinases [119]. In addition, endothelial cells can produce eotaxin-3, which can induce the eosinophils to infiltrate tissues and release cytotoxic mediators [120]. Eosinophil cationic protein (ECP) can promote cell death, allowing the presentation of cryptic autoantigens to Th cells, thus perpetuating a vicious cycle [121]. Interferon produced mainly by Th1 cells may also mediate granuloma development, and it has been reported that IL-17 levels, which promote neutrophil recruitment and activation, are significantly increased in EGPA in the active phase [122]. B-cells play also an important role in EGPA immunopathogenesis, as suggested by the therapeutic success achieved with CD20+ B-cell depletion using the monoclonal antibody (mAb) rituximab.

5. Clinical Presentation

The clinical features of AAV are heterogeneous and depend largely on the type of AAV considered. These include GPA which primarily affects the upper and lower respiratory tracts, MPA which preferentially affects the kidneys, and EGPA initially characterized by allergy-like symptoms, including asthma, which evolves into definite vasculitis [10–12]. The clinical picture and severity are associated with the number of affected vessels, target organs, and disease activity [123]. As this is a systemic disease, patients often present with constitutional symptoms and in particular fever, asthenia, weight loss, and arthralgias [124]. Upper respiratory tract manifestations consist of recurrent nose bleeding, damage to the cartilage of the nasal septum which can collapse, sinusitis, and otitis media [125,126]. Pulmonary manifestations include pulmonary nodules and diffuse alveolar hemorrhage. Alveolar hemorrhage is a particularly severe complication and presents with hemoptysis and dyspnea. An increased incidence of interstitial lung disease has been reported especially in subjects with MPA and MPO-ANCA [127]. The eye can also be affected with several manifestations, among which one of the most frequent is scleritis [128]. In some cases, skin, neurological, or enteric involvement is present [129–131]. A more recently recognized co-morbidity is cardiovascular involvement. Cardiovascular disease in AAV is thought to be associated with the acceleration of atherosclerosis. It has been reported that the incidence of cardiovascular events in patients with AAV is three times higher than in the general population, while the risk of cerebrovascular events is increased eightfold compared with healthy controls [132]. An important target organ of AAV is the kidney. The renal disease typically manifests as pauci-immune NCGN. Usually, this condition is characterized by nephritic syndrome with hematuria and proteinuria. Less frequently, renal involvement presents as subacute or chronic nephritis. Renal disease in AAV can progress to end-stage renal failure. Importantly, the frequency of renal involvement differs according to the type of AAV, being higher in MPA than in GPA or EGPA, and is associated with the presence of MPO-ANCA rather than PR3-ANCA [124]. Conversely, involvement of the upper and lower airways is more frequent in patients with GPA than in those with MPA [133]. EGPA presents with a characteristic picture of hypereosinophilia, respiratory allergy, and asthma progressing toward definite vasculitis [134,135].

6. Disease Activity

To assess disease activity, the Birmingham Vasculitis Activity Score (BVAS) is commonly used. This score includes 10 categories of symptoms calculated differently depending on whether they are new onset or have worsened for no more than 4 weeks after detection or are present in stable patients. A BVAS score of 0 represents remission, and a BVAS ≥ 1 represents active disease and/or treatment-refractory disease of varying severity. The maximum score is 63 or 33, depending on the patient category considered [136]. The five-factor score (FFS) was validated first for MPA and EGPA and later for GPA. It includes the calculation of serum creatinine, proteinuria, presence of cardiomyopathy, gastrointestinal involvement, and CNS manifestations. It is used to predict the five-year survival rate of AAV patients [137]. The vasculitis damage index (VDI) is a useful clinical tool to distinguish chronic vasculitis-induced damage. To obtain the score, manifestations of the disease must have been present for at least three months. The VDI considers 11 items referring to different organs and systems [138].

7. Treatment of AAV

7.1. Treatment with Conventional Immunosuppressants

Treatment of AAV has long depended on the use of glucocorticoids and conventional immunosuppressive drugs [88,139]. AAV therapy consists of a first phase for induction of remission and a second phase for maintenance of disease remission. The conventional immunosuppressant commonly used to induce disease remission is cyclophosphamide (CYC) combined or not with steroids. For maintenance therapy, several immunosuppressants, particularly azathioprine, methotrexate, and mycophenolate, are used to spare steroids.

CYC is an alkylating agent whose inhibitory effects on B-cells have been recognized, particularly the inhibition of autoantibody production, including autoantibodies [140]. However, serious adverse events secondary to the use of this drug have been reported, including the occurrence of cancer [141,142]. In patients with particularly severe conditions, such as alveolar hemorrhage and rapidly progressive glomerulonephritis, plasmapheresis, which allows rapid and effective removal of ANCAs from serum, may be considered [88]. Regarding maintenance therapy, methotrexate and azathioprine have been found to have similar safety profiles [143]. Mycophenolate was found to be superior to azathioprine in suppressing cytokine production by B-cells in a small cohort of patients [144].

7.2. Rituximab

CYC is associated with severe side effects. Therefore, many studies have been devoted to finding safer alternative therapies. Deletion of B lymphocytes to reduce the serum level of ANCA has been considered critical for the treatment of the disease. Research interest has therefore focused on rituximab (RTX), a chimeric murine/human mAb that recognizes and deletes the B lymphocytes [145]. RTX eliminates CD20-expressing B lymphocytes through several mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and induction of apoptosis [146]. The possibility of RTX in inducing remission in AAV has been evaluated in several clinical trials. Two randomized, controlled trials, RAVE and RITUXVAS evaluated the efficacy of RTX for remission induction in GPA and MPA [87,147]. Inclusion criteria for the RAVE study included patients with a diagnosis of GPA or MPA according to the recent AAV definition and positive serum tests for PR3-ANCA or MPO-ANCA with the new onset and relapsing disease but without severe renal failure. The RTX arm was combined with pulse methylprednisolone treatment, and prednisone dosing was reduced to zero within six months. The RITUXVAS study enrolled patients with newly diagnosed vasculitis and more severe renal disease, including patients requiring dialysis. In the RITUXVAS study, the RTX arm received two doses of intravenous CYC and was able to use plasmapheresis. Both studies demonstrated that RTX therapy was non-inferior to CYC therapy for induction of remission, with comparable mortality rates and adverse events. In addition, an analysis of secondary data from the RAVE trial concluded that RTX was superior to CYC in patients with non-severe relapses, who were more likely to be PR3-ANCA positive than MPO-ANCA positive, to have a diagnosis of GPA than MPA, and to have a history of the relapsing disease at baseline [148]. Based on this evidence, current guidelines recommend RTX as the first-line treatment for patients with PR3-ANCA, relapsed disease, refractory disease, and those with contraindications to CYC [88,149]. It should be emphasized, however, that specific measures, such as preventing the reactivation of the hepatitis B virus in patients with occult hepatitis B, controlling antibody production, and preventing the reactivation of latent tuberculosis, are necessary in the case of RTX therapy [150]. In this regard, low levels of IgG class immunoglobulin are observed after RTX therapy in an average of 50–60% of patients [151]. However, in most cases, hypogammaglobulinemia is mild and transient, and IgG levels return to normal within six months of RTX treatment. Only in a small percentage of patients can hypogammaglobulinemia be severe. In that case, intravenous administration of human IgG-class immunoglobulin is required to prevent infectious diseases [152]. Finally, a rare side effect of RTX observed in patients with AAV is sudden and severe neutropenia that occurs within 2–6 months after the last dose of RTX. this event may require the administration of granulocyte growth factors [153]. However, it is necessary to establish the long-term efficacy of RTX as a maintenance therapy. In addition, it should be considered that RTX treatment does not impair the survival of long-lived plasma cells, resulting in the continued production of ANCA, albeit in smaller amounts than in untreated patients [87]. Given the significant toxicity associated with the use of CYC and the relapsing nature of AAV, the use of RTX has nonetheless been approved for the treatment of MPA and GPA as both induction and maintenance therapy [154]. To find safer treatments in AAV therapy and possibly reduce the use of B-cell depleting agents, a study was conducted on the efficacy

and safety of plasma exchange in combination with glucocorticoids in patients with severe AAV (PEXIVAS study). However, this treatment approach was not found to reduce the incidence of mortality or end-stage renal disease in treated patients. Therefore, the main conclusion of this study was that the addition of plasma exchange to standard therapy of severe AAV is not indicated [155]. It should be emphasized that the non-approval of RTX for patients with EGPA was because in the studies that led to the drug's approval such patients were not included [87,147,156]. However, given the role of B cells in the pathogenesis of EGPA, further case series and cohort studies were conducted. The reported results suggest that RTX may also have a role in severe, refractory, or relapsed EGPA, especially if ANCA-positive [157–160]. The results of two recent systematic reviews have also confirmed the validity of the results obtained from observational studies [161,162]. Response rates similar to those of patients with MPA or GPA were found in patients with EGPA treated with RTX in the European Collaborative Study, a retrospective review of the use of biologics in refractory and/or relapsed EGPA [163]. It is noteworthy that, in most patients with EGPA, RTX has no significant effect on steroid-sparing if asthma is present. Also noteworthy are the results from the REOVAS trial, a randomized, double-blind, controlled trial of RTX in EGPA whose conflicting results still published only as congress abstracts raise doubts about the real efficacy of RTX even in ANCA-positive patients [164]. However, the 2021 ACR/VF guidelines recommend considering RTX for the induction of severe new-onset or relapsing EGPA, particularly in ANCA-positive patients with active glomerulonephritis or at high risk for CYC toxicity if in the absence of cardiac involvement [139]. Conventional immunosuppressants are recommended in the maintenance phase. However, further studies are needed to clarify the role of RTX in EGPA as well as in maintaining disease remission.

7.3. C5aR Antagonist Avacopan

Avacopan is an antagonist of C5aR. C5aR is a receptor for C5a that belongs to the G-protein-coupled receptor family. This receptor is expressed on myeloid cells such as granulocytes, macrophages, dendritic cells, mast cells, and various nonmyeloid tissue cells. Activation of this receptor causes inflammation and degranulation of granulocytes, macrophages, and mast cells and vascular permeability as well [165]. The mechanism of action of avacopan is blocking the C11b-induced upregulation of C5a on neutrophils by inhibiting their activation and chemotaxis [95]. In a phase I study, avacopan administered to healthy people produced C5aR inhibition in most subjects at a dose of 30 mg orally twice daily [166]. The phase II, double-blind, placebo-controlled CLEAR trial recruited patients with AAV who were randomized into placebo group with high-dose prednisone, avacopan 30 mg twice daily with low-dose prednisone, or avacopan 30 mg twice daily without prednisone. All patients received standard therapy for induction of remission. The endpoint was a reduction of BVAS $\geq$ 50% at 12 weeks. This was achieved by 70%, 86%, and 81% of patients in the three groups, respectively [167]. The CLASSIC study, a phase II, randomized, double-blind, placebo-controlled trial, demonstrated the safety and efficacy of avacopan 10 or 30 mg twice daily when added to standard therapy [168]. The ADVOCATE, multicenter, phase III, randomized, double-blind, placebo-controlled trial included patients with AAV randomized to receive avacopan 30 mg twice daily or oral prednisone. These patients also received standard therapy for induction of remission. Maintenance of remission at week 26 indicated that avacopan was non-inferior to prednisone, while sustained remission at week 52 demonstrated the superiority of the avacopan group [169]. Avacopan has thus been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for AAV in combination with standard therapy. Eculizumab, a mAb targeting complement protein C5, although not approved for the treatment of AAV, has been effective in refractory cases with an aggressive form of AAV [170–172]. Other agents capable of blocking complement are currently being studied. One phase II study evaluated the safety and tolerability of IFX-1, a mAb that binds C5a, in patients with GPA and MPA.

The plasma C1 protease inhibitor (C1INH), currently used for the treatment of hereditary angioedema, has also been tested in patients with AAV [173].

7.4. The Blockage of Eosinophils in EGPA

Interleukin-5 (IL-5) is a very important cytokine in the growth, maturation, and differentiation of eosinophils [174]. Mepolizumab is a humanized monoclonal mAb specific for the alpha subunit of IL-5. This antibody blocks the binding of the IL-5 receptor (IL-5R). This mAb widely used in the treatment of asthma was the first drug approved by the FDA for the exclusive treatment of EGPA and no other forms of AAV [175]. The pivotal study that led to the approval of mepolizumab for the treatment of EPGA is the MIRRA study. This double-blind, placebo-controlled study recruited patients with relapsed or refractory EGPA. These were randomized to receive mepolizumab 300 mg subcutaneously every four weeks or placebo in combination with glucocorticoids with or without immunosuppressive therapy. Treated patients achieved the primary endpoint of at least 24 weeks of remission, which was a BVAS of 0. In addition, a 50% lower recurrence rate was observed in the mepolizumab-treated group compared with the placebo group, and a significant reduction in steroid use. However, the MIRRA study included only patients with mild disease. In addition, patients with the presence of ANCA in serum were a minority. This limits the generalizability of the results to ANCA-positive patients. Although a substantial percentage of patients in the treatment group did not achieve remission at 52 weeks, a secondary analysis of the data still showed an absence of flares and confirmed the reduction in glucocorticoid use [175,176]. Several subsequent retrospective studies have confirmed the efficacy of mepolizumab [163,177,178] even at the lower dose of 100 mg per month, such as that used for asthma [163,178]. Two other anti-IL-5 agents currently approved for asthma are being studied in EGPA. Reslizumab, a mAb specific for the IL-5 alpha chain, showed promising results in reducing glucocorticoid use in an open-label pilot study of a small number of patients with EGPA [179]. Benralizumab, a mAb directed against IL-5R, also showed efficacy in treating EGPA in another pilot study. Half of the treated patients stopped taking glucocorticoids at the end of the study [180]. The MANDARA study, which aims to compare benralizumab with mepolizumab in relapsed or refractory EGPA, is still ongoing. Interestingly, this will be the first study to compare head-to-head two biologics for the treatment of EGPA Table 1 shows the main clinical trials conducted on novel AAV therapies. Table 2 shows the drugs approved for the treatment of different phenotypes of AAV and the specific conditions for their use. Figure 3 illustrates the treatment algorithm for the induction of AAV remission and its maintenance.

Table 1. Trials on currently approved new drugs for AAV.

Target	Drug	Trial	Primary Endpoint Results
B cells	RTX	RAVE	Non inferiority to oral CYC for remission induction, superior for relapsing or PR3-ANCA patients
B cells	RTX	RITUXVAS	Non inferiority to CYC in pulses for remission induction
B cells	RTX	MAINRISTAN	Superiority to AZA for maintenance of remission
B cells	RTX	MAINRITSAN 2	No difference between standard and customized infusion based on B-cell count for relapse rate
B cells	RTX	REOVAS	Non inferiority to conventional therapy for remission (CYC/CS) in EGPA
C5aR	AVACOPAN	CLASSIC	Safe and effective at day 85
C5aR	AVACOPAN	ADVOCATE	Non inferiority to CS for remission induction
C5aR	AVACOPAN	CLEAR	Non inferiority to CS for remission induction
IL-5	MEPO	MIRRA	Non inferiority to placebo for relapsing or refractory EPGA

RTX = Rituximab; MEPO = Mepolizumab; CYC = Cyclophosphamide; AZA = Azathioprine; CS = Corticosteroids.

Table 2. FDA approved indications for new AAV drugs.

Drug	AAV	Specifications
Rituximab	GPA and MPA	In adult and pediatric patients 2 years of age and older in combination with glucocorticoids.
Avacopan	GPA and MPA	As an adjunctive treatment of adult patients with severe active GPA and MPA in combination with standard therapy.
Mepolizumab	EGPA	Adult patients with EGPA.

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; EPGA = eosinophilic granulomatosis with polyangiitis.

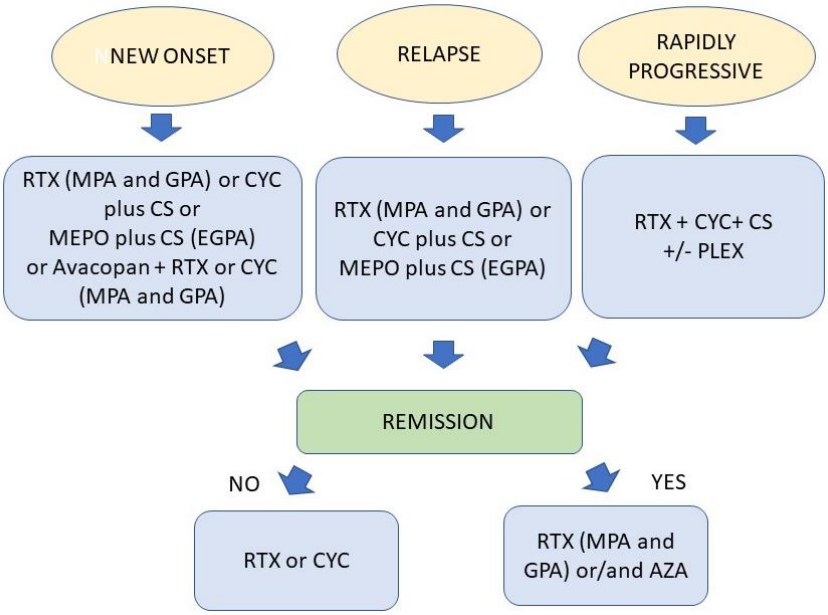

Figure 3. Algorithm for the treatment of AAV. Several strategies are used for induction of remission and maintenance of remission. In addition to conventional drugs such as cyclophosphamide (CYC) corticosteroids (CS) and azathioprine (AZA), new drugs that are able to selectively inhibit immunologic targets such as rituximab (RTX), avacopan, and mepolizumab (MEPO) have been approved by regulatory agencies. PLEX = plasmapheresis. Therapeutic strategies are periodically updated according to new knowledge by EULAR and ACR.

8. Conclusions

Several forms of AAV make such vasculitis a very complex disease. Despite its rarity, it can have lethal effects on the lung and kidneys. Fortunately, several aspects of the immunopathogenesis of AAV have been clarified in recent years. This has led not only to greater knowledge and earlier identification of the disease, but also to the possibility of developing sufficiently effective and safe targeted therapies that can replace traditional immunosuppressants characterized by high toxicity. The main target of therapy remains the inhibition of ANCA production as these autoantibodies play a pathogenic role. RTX was effective in both remission and maintenance of the disease, with far fewer side effects than CYC. However, the discovery of the key role played by alternative complement pathways in MPA and GPA has made C5aR agonist available in the treatment of these types of AAV. Moreover, the anti-IL-5 antibody mepolizumab, already approved for asthma, has been the first drug specifically approved for the treatment of EGPA due to its inhibitory effect on various functions of eosinophils. Future studies will further elucidate the pathogenetic basis of AAV, allowing the design of innovative drugs for an increasingly efficacious and safe therapy.

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