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ORIGINAL ARTICLE

Complement blockade in the management of antineutrophil cytoplasmic antibody-associated vasculitis

José Salvador García-Morillo[1], Ricardo Blanco-Alonso[2], and Enrique Morales-Ruiz[3]*

[1]Autoimmune and Minority Diseases Unit. Internal Medicine Department. Hospital Universitario Virgen del Rocío, Sevilla. Systemic Autoimmune Diseases Working Group (GEAS-SEMI), Spain; [2]Rheumatology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain; [3]Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain

Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are characterized by the presence of ANCA, particularly those directed against proteinase 3 (PR3) or myeloperoxidase (MPO). At present, the most accepted pathogenic pathway is based on the pathogenic nature of ANCA, which stimulate neutrophils with the consequent activation of the alternative complement pathway, leading to the production of C5a, an anaphylatoxin which plays a key role in amplifying the inflammatory process in AAV. Remission induction in patients with AAV continues to depend on the use of glucocorticoids (GC) in combination with rituximab or cyclophosphamide. Indeed, there are very limited treatment options and a clear need for strategies that reduce the use of GC without compromising efficacy. Avacopan is the first drug specifically developed for patients with AAV as its mechanism of action inhibits C5aR1, thus acting on one of the pathophysiological mechanisms of AAV.

Keywords: Complement. Antineutrophil cytoplasmic antibodies-associated vasculitis. Avacopan.

Introduction

ANCA-associated vasculitis (AAV) is a group of systemic autoimmune diseases characterized by necrotizing inflammation of small-caliber blood vessels. AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)[1]. The clinical presentation is heterogeneous. Renal (pauci-immune necrotizing glomerulonephritis), pulmonary (alveolar hemorrhage and lung nodules), and otorhinolaryngological (ENT) (nasal crusting, epistaxis, sinusopathy, and hearing loss) involvement, are very frequent[2,3]. EGPA has clinical and pathological characteristics that differ from GPA and MPA. Therefore, the recommendations for its management also differ and have not been included in this review.

AAV are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA), the most common of which are those that directed against proteinase 3 (PR3) or myeloperoxidase (MPO)[3]. At present, the most accepted pathogenic pathway is based on the pathogenic nature of ANCA, which stimulate neutrophils with the consequent activation of the alternative complement pathway and production of C5a, an anaphylatoxin which plays a key role in amplifying the inflammatory process in AAV. C5a, through its binding to the C5aR1 receptor, attracts, and activates more neutrophils and increases vascular permeability, thus contributing to the injury produced in the blood vessel (Fig. 1)[4,5].

In Spain, the estimated incidence of GPA is 2.1-2.9 cases per million residents/year, the incidence of

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***Correspondence:**
José Salvador García-Morillo
E-mail: salvaymar@gmail.com

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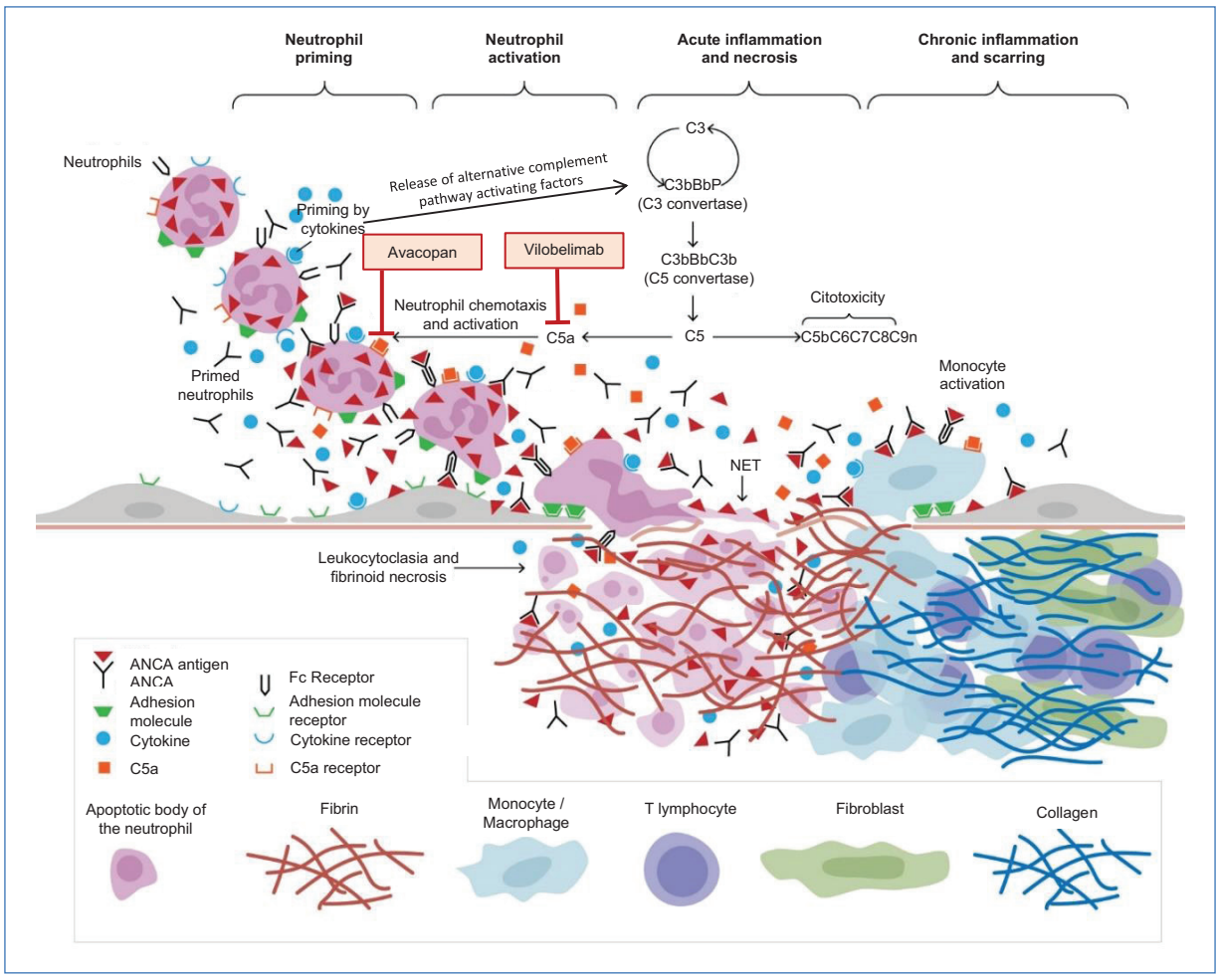

Figure 1. Diagram representing the pathogenesis of vascular lesions in ANCA-associated vasculitis. The events indicated from the left to right occur sequentially in each injury site and start in multiple sites until remission induction. Neutrophil priming — for example, through cytokines generated by an infection — entails exposure to ANCA antigens on the neutrophils' surface and microenvironment. ANCA contribute to neutrophil activation, which adhere to the endothelium and penetrate the vessel walls, in addition releasing destructive inflammatory mediators. ANCA-activated neutrophils also produce factors that activate the alternative complement pathway, which results in the generation of C5a which, through its binding to the C5aR1 receptor, amplify the inflammation, attracting and activating more neutrophils. Avacopan (CCX168), C5aR1 antagonist (NCT02994927, NCT01363388, NCT02222155), and Vilobelimab (IFX-1), anti-C5a antibody (NCT03895801, NCT03712345) are complement-blocking therapies with trials in patients with GPA or MPA. In vessel wall rupture sites, the plasma spills into the necrotic area and coagulation factors are activated to produce fibrin, leading to fibrinoid necrosis in the tissue vessels and glomerular crescents. Leukocytoclasia is also produced as a consequence of leukocytic apoptosis or necrosis and due to neutrophil NETosis. In few days, infiltration of macrophages and lymphocytes occurs, starting the scarring process through the deposit of collagen from activated fibroblasts and myofibroblasts (only the activation of monocytes by ANCA is shown on the right side, but this occurs in parallel with neutrophil activation in all acute injury sites).
NET: neutrophil extracellular trap.
Adapted from Jennette et al.[5]

MPA is 3.4-7.9 cases per million residents/year, and the estimated prevalence of AAV is 44.8 cases per million residents and has been increasing in recent decades[6,7]. Given that its prevalence is < 50 cases/100,000 residents, AAV are considered a rare disease[8].

Treatment of AAV

At present, there are few treatment options for patients with severe GPA or MPA. The recommendation is to use rituximab (RTX), cyclophosphamide (CYC), or the combination of both together with glucocorticoids (GC) to

induce disease remission. In regard to the use of oral GC, it is recommended to start treatment with a high dose of oral prednisone (50-75 mg/day) during the 1st week and continue with a rapid dose reduction regimen. In addition, intravenous pulses of methylprednisolone (dose of 1-3 g) are commonly used. There are various factors to take into account in the choice of immunosuppressive treatment. For example, RTX is recommended as the preferred option in patients in relapse whereas in patients with severe renal involvement (serum creatinine > 300 μmol/L), the preferred option is CFM or combination therapy of CFM with RTX; plasmapheresis in addition to the immunosuppressive treatment can be considered in these patients[9-12].

Once disease remission is achieved, it is recommended to continue with immunosuppressive treatment to prevent relapses. The most recent recommendations propose the use of RTX as the treatment of choice in maintaining remission. Alternatives to consider include azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF)[10-12]. The use of low-dose GC is also considered, but the evidence is limited and its recommendation varies according to factors such as the concomitant immunosuppression or the type of ANCA. The duration of maintenance therapy is not well-defined, though the recommendation is between 18 months and 4 years, depending on factors such as risk of relapse, ANCA-PR3 positivity, the patient's preferences, and the risk of maintaining the immunosuppression[11].

Relevant clinical problems in patients with AAV

In recent decades, advances in diagnostic techniques, greater knowledge of the disease, and the introduction and optimization of immunosuppressive treatment regimens have improved the prognosis of AAV. The mortality rate at 1 year was reduced 80% in untreated patients to 11% after the introduction of treatment with GC and CFM[13,14]. In consequence, AAV have become chronic diseases with frequent relapses; it is estimated that 30-50% of patients will have a relapse of their disease in a 5-year period[15].

Despite the aforementioned advances[14,16], mortality among patients with AAV remains 2.6 times higher than in the general population, mainly due to complications of the disease, such as renal failure or pulmonary hemorrhage, and complications of the immunosuppressive treatment such as infections, which cause up to 50% of deaths during the 1st year. The cumulative GC dose in these patients, in whom prolonged use is frequent, directly contributes to the onset of common complications such as infections, cardiovascular disease (CVD), diabetes, hypertension, and osteoporosis[17]. Therefore, there is a need to identify new treatment approaches that contribute to minimizing the use of GC without any additional risk.

One of the main objectives in AAV is to minimize the irreversible organ damage that occurs in these patients, especially in the kidney. It has been demonstrated that renal, ENT, and treatment-related damage (CVD, diabetes, osteoporosis, and cancer) increases with time. Indeed, it is estimated that one out of every three patients with AAV has severe organ damage (VDI ≥ 5) at 7 years of follow-up[18]. Of note among the factors that contribute to increasing organ damage are the disease's severity at diagnosis, age, the number of relapses, and prolonged use of GC[17]. Therefore, strategies that facilitate an early diagnosis or faster disease control, that reduce the relapse rate, and that allow for decreasing the use of GC could be decisive for mitigating organ damage in patients with AAV. Likewise, the identification of early biomarkers of activity could be key for evaluating treatment response or the early identification of relapses, thus contributing to a more rational, individualized use of immunosuppression.

One of the most relevant problems is undoubtedly the prevalence of chronic kidney disease in patients with AAV, given that it is associated with a worse prognosis and high morbidity[19,20]. In Spain, it has been described that up to 35% of patients with AAV and renal involvement progress to end-stage kidney disease (ESKD) after a median follow-up time of 43 months[21]. Among the factors associated with risk of progression to ESKD are relapses and the degree of renal involvement at diagnosis[19,22], again highlighting the importance of an early diagnosis, the prevention of relapses, and the development of treatment strategies that improve renal function, with the overall aim of delaying progression to ESKD.

Avacopan in AAV

Avacopan selectively and competitively interferes with the binding of C5a to the C5aR1 receptor, thus reducing chemotaxis and neutrophil activation and, with this, the characteristic inflammatory process of AAV[4,5,23].

Two Phase II clinical studies with avacopan have been conducted in patients with AAV: CLEAR[24] and CLASSIC[25].

The CLEAR study evaluated the efficacy and potential GC-sparing effect of avacopan, comparing the following treatment groups: (1) prednisone (60 mg/day at the start; n = 20), (2) avacopan (30 mg twice/day) with a reduced dose of prednisone (20 mg/day at the start; n = 22), and (3) avacopan without prednisone (n = 21). All patients also received immunosuppressive treatment with CFM or RTX. Avacopan demonstrated non-inferiority in the response rate at 12 weeks (70% prednisone, 86.4% avacopan with prednisone, 81% avacopan without prednisone) with a similar safety profile in terms of adverse events (AE) reported (91% prednisone, 86% avacopan with prednisone, and 96% avacopan with prednisone)[24].

The CLASSIC study evaluated the safety and possible efficacy of two doses of avacopan, 10 mg (n = 13) or 30 mg (n = 16) twice/day compared to a placebo (n = 13), in addition to standard treatment (CFM or RTX + GC, 60 mg/day at the start with a gradual 20-week dose reduction regimen). No differences were observed between the groups in regard to safety, with severe AE reported in 15% of patients treated with the placebo and 17% in the combination of the two groups treated with avacopan. In addition, avacopan 30 mg was numerically superior in some secondary outcome measures, such as early remission, recuperation of the estimated glomerular filtration rate (eGFR), and lifestyle evaluations[25].

The pivotal phase III ADVOCATE clinical trial[26] is a multicenter, double-blind, randomized, placebo-controlled study that included 331 patients with active and severe AAV (GPA or MPA). Patients were randomized into receiving avacopan (30 mg twice/day) for 52 weeks or an oral prednisone regimen (60 mg/day at the start with a 21-week dose reduction regimen). All patients also received RTX or CFM followed by AZA. Avacopan demonstrated non-inferiority in remission induction at 26 weeks (72.3% avacopan vs. 70.1% prednisone; $p < 0.001$ for non-inferiority) and superiority in maintaining remission at 52 weeks (65.7% avacopan vs. 54.9% prednisone; $p = 0.007$ for superiority). In addition, significant differences were observed in several relevant secondary outcome measures such as: (i) Greater recuperation of eGFR, mainly in patients in stage 4 chronic kidney disease at the start (eGFR < 30 mL/min) with a difference between groups of 5.6 mL/min/1.73 m^2 at 52 weeks (95% CI 1.7-9.5), (ii) lower GC toxicity index and fewer GC-related AE (66.3% avacopan vs. 80.5% prednisone), and (iii) improvements in health-related quality of life.

It should be noted that a lower relapse rate was also observed in patients who received treatment with avacopan (10.1% avacopan vs. 21.0% prednisone; HR 0.46; $p < 0.01$). The frequency of severe AE was similar in both groups (40.2% avacopan vs. 45.1% prednisone), although the number of events was lower in patients who received avacopan (116 vs. 166). Severe infections were reported in 13.3% of patients who received avacopan and 15.2% of those treated with prednisone while opportunistic infections were reported in 3.6% and 6.7%, respectively. No infections by encapsulated organisms such as *Neisseria meningitidis* were observed, which had been reported with complement C5 blockers[27]. In patients treated with avacopan, elevations in liver enzyme levels were observed more often (5.4% avacopan vs. 3.7% prednisone), which resolved after the discontinuation of avacopan and other hepatotoxic drugs such as cotrimoxazol[26].

Based on these results, the European Medicines Agency (EMA) authorized avacopan in combination with an RTX or CFM regimen for the treatment of adult patients with severe, active GPA or MPA on January 11, 2022.

Conclusions

Remission induction in patients with AAV continues to depend on the use of GC in combination with RTX or CFM. There are few treatment options in these patients and a clear need for strategies that allow for reducing the use of GC without compromising efficacy.

Avacopan is the first drug specifically developed for patients with AAV due to its mechanism of action targeted at C5aR1 inhibition, thus acting on one of the pathophysiological mechanisms of AAV. It is also the first treatment alternative to GC for this disease, achieving better efficacy outcomes in terms of remission maintenance and improvement in some renal parameters. In fact, the outcomes of the CLEAR, CLASSIC, and ADVOCATE studies suggest that complement blockade may favor a greater degree of renal recovery than the few treatment options available at present and with a favorable safety profile for avacopan.

Studies with longer follow-up periods are needed to evaluate the safety of treatment with avacopan over a longer period of time as well as possible interactions with other drugs, especially those that are hepatotoxic.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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