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How the Availability of Anti-C5a Agents Could Change the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Keywords

Renal biopsy · Antineutrophil cytoplasmic antibody-associated vasculitis · Anticomplement therapy · Avacopan · Glucocorticosteroid-sparing strategies

Abstract

Background: Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a cluster of potentially life-threatening disorders, often involving the kidney with a necrotizing crescentic glomerulonephritis with scanty deposition of immunoglobulins and complement. Historically the role of complement has been considered ancillary. Recently, an anti-myeloperoxidase (MPO) AAV model in complement-deficient mice has shown an involvement for the complement cascade in the development of the renal injuries. Further animal studies showing that in contrast to mice deficient for factor B and C5 animals deficient for C4 were susceptible to AAV development by injection of anti-MPO antibodies emphasized the specific involvement of the alternative pathway. Consonantly, the C5a receptor (Cd88) blockade was found to protect mice from MPO-AAV. CCX168, i.e., avacopan, a powerful inhibitor of C5a receptor that can be administered orally, was shown to reduce the proinflammatory effects of C5a and abolish the activation of neutrophils, their migration and adherence to endothelium, and the vascular endothelial cell retraction that increases permeability. ***Summary:*** Avacopan was found to be safe in healthy volunteers given a wide range of doses in a phase 1 clinical trial. The phase 2 trial CLEAR assessed the possibility to decrease dose or entirely replace glucocorticosteroids in the standard-of-care therapy of AAV. Avacopan, added to CYC or RTX either in combination with GCs or not, shortened the time to remission in patients with either newly diagnosed or relapsing AAV. The phase 3 ADVOCATE study compared the ability of an avacopan-associated regimen to induce and sustain remission in AAV patients versus a conventional GC-associated scheme. Remission at week 26 was observed in 72.3% of patients given avacopan and in 70.1% of those given prednisone. Sustained remission at week 52 (second primary endpoint) was obtained in 65.7% of patients given avacopan and in 54.9% receiving prednisone. The avacopan-associated regimen was noninferior at week 26 and superior at week 52 in sustaining remission as compared to the GC-based scheme. ***Key Messages:*** The results of the ADVOCATE trial opened new prospects for the treatment of AAV and also other immune-mediated diseases with renal involvement. The possible position of avacopan in a routine clinical setting and its possible indications in specific subsets of patients with AAV are extensively discussed.

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a cluster of systemic immune-mediated disorders comprising microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis [1]. Genetic, epigenetic, and environmental factors are involved in a complex pathogenetic interplay. ANCAs are directed against constituents of primary neutrophil granules, especially proteinase 3 (PR3) and myeloperoxidase (MPO) [2]. There is strong clinical in vitro and in vivo evidence that ANCAs are pathogenic [3]. How autoantibodies directed to the PR3 and MPO occur is not entirely clarified. The process could involve mechanisms of molecular mimicry [4] and exposure to peptides that are complementary to the human autoantigen [5–7]. Bacteria, such as *Staphylococcus aureus*, have peptides that mimic the complementary PR3 [8]. Moreover, altered regulation of neutrophil extracellular traps (NETs) contributes to ANCA production. NETs are part of the innate immune (primarily essential for host defense), but NET formation must be strictly regulated because excessive production causes angiopathy [9]. The association between NETs and vasculitis was first described by Kessenbrock, who showed that anti-PR3 IgG ANCA (and sera from AAV patients as well), triggered NETosis in vitro and that NETs contain both MPO and PR3 [10]. Notably, NETs have also been subsequently shown to activate the complement system [11].

The renal histological hallmark of AAV is crescentic necrotizing glomerulonephritis with scanty deposition of reactants, such as the complement [12–14]. Historically, the role of complement has been considered ancillary in AAV. This concept was first challenged by an anti-MPO-AAV model of complement-deficient mice demonstrating the involvement of the alternate pathway of complement [14]. Current data suggest that both IgG and IgM can activate complement via the classical pathway by binding of C1q to the Fc regions of these immunoglobulins [15]. In turn, there is evidence that complement is important in regulating the antibody response.

The Complement Cascade

The interactions between antibody response and complement system are well known [15, 16], but the role of the latter in AAV is a relatively recent acquisition. Indeed, opposite to animals with C4 deficiency, factor B and C5 deficient mice did not develop vasculitis following anti-MPO antibody injection [17]. C5a receptor (Cd88) blockade was found to protect against MPO vasculitis in mice [18], and other models confirmed the involvement of the alternative pathway and, among the other complement components, of C5a in the pathogenesis of AAV [19, 20]. Plasma levels of C3a, C5a, soluble C5b-9, and Bb were found to be higher in active disease than in remission, whereas levels of properdin were significantly lower in active than in remission phase [21–27]. C5a is of most importance for several inflammatory disorders. It triggers mast cell degranulation and is a powerful chemoattractant that promotes recruitment phagocytic cells at sites of inflammation. C5a enhances recruitment and adherence of neutrophils [28–30]. C5a also primes neutrophils to express PR3, allowing binding of ANCA [31] (Fig. 1). The consequent release of proinflammatory cytokines further activates the alternative complement pathway, the formation of C5a breakdown product, and the amplification of the inflammatory response [32]. Another known complement abnormality in active AAV is the decrease of the expression of factor H [33]. Factor H is a critical regulatory protein that inhibits neutrophil activation by ANCA. Its deficiency induces a dysregulation of C3b and favors the activation of neutrophils that accelerate AAV progression [34]. Other regulators of the complement alternative pathway such as intercellular adhesion molecule-1, decay-accelerating factor, and glycoprotein CD59 are altered in patients with AAV [35]. Hypocomplementemia is uncommon in AAV but, when present, correlates with less favorable outcomes [36–40]. Different studies reported an association between hypocomplementemia and poor renal prognosis and/or life prognosis. The reported incidence of hypocomplementemia in AAV in the Japanese population ranged between 4.2 and 14.8% [41]. Molad et al. [42] reported that 20% with MPO-ANCA-positive AAV had low C3 at the disease onset. Fukui et al. [43] reported that 20% of the AAV patients had hypocomplementemia at the disease onset and that 38% of the AAV patients had immune complex deposits in renal biopsy specimens, and the AAV patients with hypocomplementemia had significantly more immune complex deposits in renal biopsy specimens than the AAV patients without hypocomplementemia [43]. Histologically, positive staining in renal specimens of complement components or complement breakdown products, such as properdin and C3d, was found to be associated with extracapillary proliferation [44]. Furthermore, in a critical revision of the extent of deposition of immune reactants in AAV, 41% (40/97) of unselected

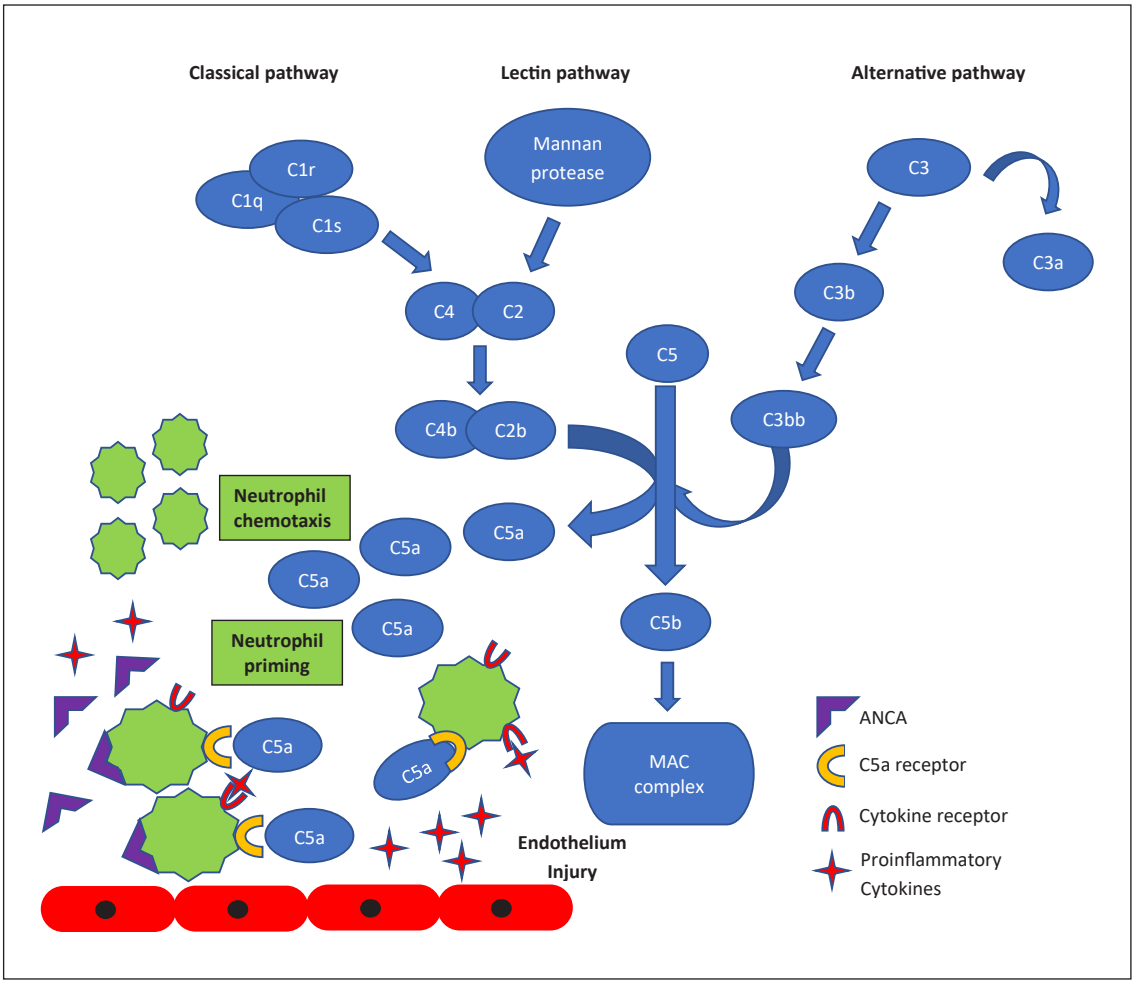

Fig. 1. Complement involvement in AAV. Complement system activation leads to the generation of C5a, which amplifies the inflammatory response via enhanced neutrophil recruitment. C5a also primes neutrophils to express antigens allowing binding of ANCA. The consequent release of proinflammatory cytokines further activates the alternative complement pathway, the formation of C5a breakdown product, and the amplification of the inflammatory response.

cases had positive ≥2 + immunofluorescence for at least one of the six immunoglobulin or complement components tested. Notably, these cases had lower serum C3 and higher serum creatinine than patients with negative immunofluorescence [45].

The New Challenge of Anticomplement Treatment of AAV

The two phases of induction of remission and remission consolidation or maintenance are the paradigm for AAV treatment. In spite of the improvement of AAV prognosis over the years, a consistent minority of patients reaches the end-stage renal disease. Furthermore, the agents that have substantially reduced the overall mortality, especially cyclophosphamide (CYC), are penalized by short- and long-term morbidity due to side effects.

In the last 15 years, rituximab (RTX) has been shown to effectively replace CYC in several pilot studies and in two randomized trials [46, 47]. RTX, given four times weekly at the dose of 375 mg/m^2, and glucocorticosteroids (GCs) were found to be comparably effective as GC and CYC 2 mg/day for 3–6 months for induction of remission and azathioprine (AZA) for maintenance in newly diagnosed AAV patients with nonsevere renal impairment (RAVE trial). RTX was more effective than CYC plus AZA in AAV with relapsing course, PR3-AN-

CA pattern, and granulomatous phenotype. In cases with severe renal impairment (RITUXVAS trial), i.e., GFR <20 mL/min, a combined therapy of RTX and low-dose CYC was equally effective as intravenous CYC for 3–6 months followed by AZA [44]. In both arms, similar doses of GCs were administered. Notably, in these patients with extreme renal impairment, the occurrence of relapses at 24 months was 21% and 18%, respectively, even though no maintenance therapy was administered in the study group.

The ongoing challenges about AAV management consist first, on the identification of treatments able to spare GCs, quickly effective, and safe; second, development of strategies for remission maintenance more personalized and safer in the long run than those currently in use; and third, effective management of the most severe AAV.

The discovery of the decisive role of the complement in AAV could address all these issues. The newly developed CCX168, i.e., avacopan, is an orally administered small-molecule C5a receptor antagonist that selectively blocks the effects of C5a through the C5a receptor (C5aR, also called CD88), including blocking neutrophil chemoattraction and activation. Avacopan does not block C5a-like receptor 2 (C5L2), and that is why it may be more effective than eculizumab that blocks C5 all together for management of AAV. In contrast to eculizumab that inhibits the formation of the membrane attack complex, which is cardinal to host defense, it does not interfere with membrane attack complex formation [48]. CCX168/avacopan blocks the activation and recruitment of neutrophils and tempers the inflammation of small vessels in target organs [49]. Safety and pharmacokinetics of CCX168/avacopan were addressed in a phase 1 study in 48 healthy young subjects (24 males, 24 females, mean 38 years). Over a wide range of doses, no major side effect could be detected. Only mild dizziness and nausea were observed in a greater proportion of subjects receiving avacopan compared to placebo. As regards the pharmacodynamics properties, avacopan reaches its maximum blood concentration within 2.5 h and has biexponential curve of elimination with a fast first component followed by a slow decline [49].

The phase 2 study named CLEAR assessed the possibility to treat patients with GPA and MPA with a decreased GC dose or even without GC using avacopan in combination with CYC (81% of cases) or RTX (19%). The study arm was administered CCX168/avacopan with either low-dose or no prednisone for 3 months, while the control group was treated with placebo and prednisone at standard dose tapered to 10 mg/day within 3 months. The avacopan-based scheme was as effective as the GC-based protocol [50].

Another phase 2 trial, named CLASSIC, randomized GPA and MPA patients to receive for 12 weeks either two doses of avacopan (10 mg or 30 mg in 13 and 16 patients, respectively) given twice daily combined with SOC (consisting of GC + CYC or RTX) or SOC only (13 patients) [51]. No concern about safety has arisen with either avacopan dose added to SOC. Compared to the group under SOC only and the cohort treated with avacopan 10 mg, the patients treated with avacopan 30 mg reached remission earlier and had a greater improvement in eGFR (+6.2 mL/min vs. + 2.0 mL/min and +1.3 mL/min). The questionnaire of quality of life showed an improved score in patients treated with avacopan, while the Vasculitis Damage Index increased only in the group receiving SOC only.

The phase 3 ADVOCATE study evaluated if avacopan could replace GCs in remission induction of AAV patients equally distributed among GPA and MPA [52]. In this 52-week trial, oral avacopan was given twice daily at a dose of 30 mg in 166 patients, and the effects were compared to those obtained in a similar control group (165 subjects) receiving oral prednisone. Randomized patients had a mean Birmingham Vasculitis Activity Score (BVAS) at baseline of 16. They all were also given CYC-AZA or RTX. Achieving a BVAS of 0, i.e., clinical remission, at week 26 represented the first primary endpoint. Remission at both weeks 26 and 52, i.e., sustained remission, was the second primary endpoint. On hundred and twenty patients out of 166 (72.3%) given avacopan and 115 of 164 patients (70.1%) who received prednisone reached remission at week 26. Interestingly, the urinary abnormalities reversed earlier in the avacopan than in the prednisone group. Indeed, at week 4, a 40% decrease in the urinary albumin/creatinine ratio was observed with the avacopan-based regimen versus no change in patients given GCs. At week 52, 109 of 166 patients (65.7%) given avacopan and 90 of 164 (54.9%) having prednisone ($p < 0.001$) had a sustained remission ($p = 0.007$ for superiority). Improvement of eGFR at week 52 was greater in the avacopan group than in the control sample. Notably, the greatest improvements were achieved in the patients with the greater impairment in renal function at baseline. Greater improvements with avacopan were also shown in the physical component score and in mental SF-36 domain scores. Side effects were comparable (37.3% vs. 39.0%).

In summary, compared to the GC-based regimen, the avacopan scheme was noninferior in inducing remission at week 26 and superior in sustaining remission at week

Table 1. Issues to be addressed with the use of avacopan in the real life

Patients with more severe diseases (limited data)
Patients with extrarenal disease activity (limited data)
Diabetic patient
Efficacy in the long term
Safety in the long term
Use of avacopan as a maintenance treatment possible a lower dose
Efficacy in different disease phenotypes
Future combination therapies other than RTX or CYC

Table 2. Putative specific indications of avacopan

Patients at risk of bone fractures
Diabetic patients
Patients with glaucoma
Patients with ANCA-negative small-vessel vasculitis
Patient with a C_3 level lower than normal
Patient at risk of infection (?)

52. However in the ADVOCATE trial, avacopan (30 mg twice daily) or matching placebo was given for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks. This difference could be important in the interpretation of the apparent superiority of avacopan compared to prednisone. It is worth to remind that the mean total prednisone-equivalent dose of oral and intravenous glucocorticoids was significantly lower in the avacopan than in the prednisone group in which a greater incidence of glucocorticoid-induced toxic effects has been reported. Whether an additional RTX dose at 6 months could increase patient remission rate will require further investigation.

Moreover, avacopan was noninferior by less than a 20-percentage-point margin but not superior to tapered prednisone in inducing remission of vasculitis at 26 weeks and was superior to prednisone at 52 weeks in patients who received RTX or CYC. However, the heterogeneity of patients and the lack of differentiation between patients treated with RTX and those treated with CYC make the superiority of avacopan in the two separate groups unrecognizable.

The results of the ADVOCATE trial opened new prospects for AAV patients and possibly for other forms of glomerulonephritis [53]. While the efficacy of avacopan in different disease phenotypes was correctly examined by collecting comparable cohorts of GPA and MPA patients [53], a number of issues remain to be addressed: avacopan as a maintenance treatment, its role in patients with more severe diseases and in patients with extrarenal disease, and its effects in combination therapies other than RTX or CYC remain to be clarified (Table 1). Available data are limited but promising, also given the more rapid improvement in urinary sediment in patients treated with avacopan, which allow us to glimpse a consistent anti-inflammatory potential. Finally, the efficacy and safety of the agent in the long term should be defined.

Another point to be addressed concerns the phase of consolidation of remission. The agents currently used include AZA, mycophenolate mofetil, and RTX. In the MAINRITSAN study, RTX resulted superior to AZA for preventing relapse following remission induction [54]. In the MAINRITSAN 2 trial, RTX was similarly effective when given on demand or at fixed doses [55]. Prolonged administration of RTX (two more years) further reduced the relapse rate in the MAINRITSAN 3 study [56]. However, induction regimens combining RTX and CYC seem to achieve long-lasting remission without a maintenance regimen, especially in MPO-AAV [57–60]. Could avacopan have a role as a maintenance regimen? Due to its safety profile, it could be given for long, especially in MPO-AAV which are less susceptible of relapse. For what is concerning the most critical patients of AAV, i.e., those with eGFR <15 mL/min/1.73 m^2 and >50% crescents in nonsclerotic glomeruli at the renal biopsy, in a single-center pilot trial, a combination of RTX, low-dose CYC, and GCs (the so-called intensive B-cell depletion protocol) added to plasma exchange achieved a BVAS = 0 at 6 months in 14 out 15 patients (93%) with recovery of renal function, allowing dialysis discontinuation in 6 out of 10 dialysis-dependent patients [61]. Similar findings were observed in 64 patients (50% dialysis-dependent) having a mean eGFR 9 mL/min/1,73 m^2 treated with a similar regimen [58].

In the ADVOCATE study, avacopan showed superior efficacy compared to steroids in reversing renal impairment in severely compromised patients. Could we envisage to replace steroids with avacopan in these extremely severe cases? Available data are limited but promising, also given the more rapid improvement in urinary sediment in patients treated with avacopan, which allow us to glimpse a consistent anti-inflammatory potential.

Data are more limited in extrarenal manifestations because avacopan was specifically used in renal patients

[50–52]. Finally, only the use of avacopan in the real life can assure us on the long-term safety. In this context, Table 2 summarizes the putative indications of avacopan as a front-line treatment. Diabetic patients and patients at risk of bone fractures or glaucoma could specifically benefit of this new option. Another potential indication for the use of avacopan could concern patients with pauci-immune necrotizing crescentic glomerulonephritis with negative ANCA serology. Previously Sethi et al. [62] reported the detection of large amounts of C3 and moderate amount of C9 in the ANCA-negative glomerulonephritis. This observation on the activation of the alternate and terminal pathways of complement candidates ANCA-negative patients to treatment with avacopan.

Patients with a level of C3 lower than normal could be another subset of possible indications. Detection of serum levels of C3 and possibly of complement breakdown products, such as C3d, could be useful in identifying the subset of patients with specific indications to avacopan. More than in the past, pathologists should recognize even trace amounts of complement deposition in order to identify this sample of patients.

Separate considerations merit the patient at risk of infection. The difference in adverse effects (including infections) compared to standard GC treatment in trials assessing avacopan was not impressive, and handling of the complement cascade, which represents the more ancestral barrier against infections of primates, must require caution.

Conclusions

The currently available treatments of AAV achieve long-lasting remission in most cases often at the cost of severe side effect morbidity. Anticomplement therapy with a C5a receptor blocker proved to temper therapy toxicity and putatively replace GCs. This new approach could revolutionize our approach in the management of AAV both in the induction of remission and in maintenance. Several novel complement-directed therapies including monoclonal antibodies are under investigation. Apart from the already reported successful use of eculizumab, AAV could be a new indication for the anti-C5a MoAb-IFX-1.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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