ANCA-associated vasculitis is a systemic autoimmune disease affecting numerous organs and tissues (1). Traditionally, the anti-inflammatory effects of glucocorticosteroids rapidly induce remission, and drugs like cyclophosphamide or rituximab suppress adaptive immunity to control and prevent relapse of the underlying autoimmune disease activity (1). Infections, diabetes, fractures, and other classic steroid toxicity keep contributing significantly to the morbidity and mortality of patients with ANCA vasculitis (2). Replacing steroids in the treatment of ANCA vasculitis would require drugs with equipotent and immediate anti-inflammatory effects, while sparing interferences with host defense and metabolic homeostasis. The solution was to identify molecular targets within the innate immune system because innate immunity largely contributes to autoimmune tissue injury (3). The complement system has long been considered in this context because it is not involved in metabolic control, but it is a key mediator in many forms of sterile inflammation, including autoimmune vasculitis (4). However, the complement system is also critically involved in host defense. It took decades of research to identify the optimal molecular target within the complex cascades of complement activation and regulation (4,5).

In 2017, the phase 2 Study to Evaluate the Safety and Efficacy of CCX168 in Subjects with ANCA-Associated Vasculitis (CLEAR) included patients with ANCA vasculitis receiving a standard induction regimen including cyclophosphamide or rituximab (6). CCX168, also named avacopan, is a small molecule antagonist to the receptor of complement factor C5a blocking the chemotactic and proinflammatory properties of C5a (Figure 1) (4). Oral treatment with capsules of avacopan in combination with no or low-dose prednisone was not inferior to standard-dose prednisone taper alone in achieving a clinical remission. In 2021, the phase 3 Clinical Trial of Avacopan in Patients with ANCA-Associated Vasculitis (ADVOCATE) now reports phase 3 trial results in 331 patients with ANCA vasculitis (7). Eligible patients had newly diagnosed or relapsing ANCA vasculitis including granulomatosis with polyangiitis and microscopic polyangiitis, with eGFR > 15 ml/min per 1.73 m². All patients received either cyclophosphamide (followed by azathioprine) or rituximab. Participants were assigned to receive either oral avacopan at a dose of 30 mg twice daily or oral prednisone on a tapering schedule. Additional (nonstudy-supplied) intravenous and oral glucocorticoids were allowed before enrollment and during the first 4 weeks if required for initial control of disease, to treat adrenal insufficiency, or to treat worsening or relapsing disease. The first and second primary end points were remission at week 26 and sustained remission at both weeks 26 and 52, respectively. Remission rates of the patients receiving avacopan and those receiving prednisone at week 26 were 72.3% and 70.1%, respectively, implying noninferiority for avacopan. Meanwhile, at week 52, sustained remission in the avacopan group was significantly more frequent with avacopan (65.7% versus 54.9% with prednisone). Furthermore, secondary end-point analyses revealed that patients treated with avacopan had favorable outcomes in kidney function, health-related quality of life, and an index of glucocorticoid toxicity. The rates of serious adverse events in the avacopan and prednisone groups (excluding worsening vasculitis) were 37.3% and 39.0%, respectively. No drug-specific adverse event, such as Neisseria meningitidis infections, occurred in avacopan-treated patients.

The ADVOCATE trial is remarkable in many ways. The attempt to replace steroids recognizes steroid toxicity as a meaningful unmet medical need. Indeed, infections remain a major cause of death in patients with ANCA vasculitis and relate to steroid dose among many other potentially disabling consequences of steroid treatment. Attempts to minimize steroids on the side of the immunosuppressants were only partially successful, and steroids have remained a constant in each drug regimen for the management of ANCA vasculitis. The idea to replace steroids by targeting the complement system was clever because the complement system is a central mediator of immunothrombosis and vascular necroinflammation in ANCA vasculitis (Figure 1). In ANCA vasculitis, ANCA binding to their target antigen on the cell surface of neutrophils sensitizes neutrophils to undergo NETosis (i.e., an explosion-like form of neutrophil death during which neutrophils expel their chromatin and granular content into the extracellular space). Mechanistically, NETosis represents what pathologists refer to as “leukocytoclastic” in vasculitic lesions (i.e., neutrophils broken in pieces). “Karyorrhexis” (i.e., disruption of the neutrophil nucleus) is part of this process. NETosis preferentially occurs when neutrophils have to squeeze through the microvasculature where mechanical forces and local complement mediators promote the rupture of cell membranes and neutrophil extracellular trap release of ANCA-sensitized neutrophils (8). Therefore, it does not come as a surprise that the combination
of high pressure and shear stress inside glomerular capillaries renders the kidneys particularly susceptible for NETosis to occur in the glomerular compartment. Hence, kidney involvement is frequent in ANCA vasculitis (9). After vascular injury occurred, the proinflammatory and cytotoxic roles of complement mediators prevailed even more during the crescendo of local necroinflammation and tissue destruction.

But why C5aR? Indeed, among the many possible molecular targets within the complex complement cascade, the C5aR was a particularly careful choice (5). C5a, the molecular target of eculizumab, splits into the two components: C5a and C5b, of which the latter fuels into formation of the membrane attack complex that is essential for host defense, whereas C5a acts as an anaphylatoxin recruiting immune cells to the site of tissue injury (Figure 1). Therefore, avacopan, in contrast to eculizumab, does not impair the formation of the membrane attack complex (4,5), a central mechanism in antibacterial host defense. This may explain why, in CLEAR and ADVOCATE, serious bacterial infections (e.g., with *N. meningitidis*) were not observed with this variant of a complement inhibitor (6,7). Obviously, selectively blocking C5a-mediated local inflammation is sufficient to control tissue necroinflammation in active ANCA vasculitis similar to steroids, which explains equipotent efficacy albeit with less adverse effects.

Beyond target selection, the main key to success in CLEAR and ADVOCATE was the clever trial design. The starting dose in the prednisolone arm of the trials was relatively low with fast tapering, which slightly favored a positive outcome. A traditional superiority trial design would have placed avacopan as an add-on to the standard dose of steroids, which would have likely failed to reach the primary efficacy end points for the overlapping mechanism of action of these two drugs. This mistake notoriously repeats in lupus nephritis trials. Maybe the success of ADVOCATE can help us to bypass this long-lasting hurdle because replacing...
steroids with more specific and less toxic anti-inflammatory drugs is a central unmet medical need in many forms of immune-mediated kidney diseases, not only in ANCA vasculitis (10).

Finally, the innovative trial design allowed avacopan to demonstrate not only noninferiority to steroids but also superiority to standard steroid dosing, which maximized the possibility for a positive outcome.

In conclusion, the results of the ADVOCATE trial are exciting and open new prospects for patients with ANCA vasculitis and all those who want to replace steroids in the management of autoimmune disease. These results clarify the pathogenic role of complement in ANCA vasculitis and create hope that similar results might be achievable in other forms of autoimmune kidney inflammation (e.g., C3 GN, lupus nephritis, membranous nephropathy, IgA nephropathy, and others). In addition, the innovative trial design itself may offer new opportunities in the future.

Disclosures
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