EDITORIALS

Avacopan — Time to Replace Glucocorticoids?

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In recent decades, substantial advances in the treatment of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis have led to a decrease in disease-related morbidity and mortality. The regimen for inducing remission in patients with severe ANCA-associated vasculitis has evolved on the basis of data from randomized clinical trials and typically consists of a tapering course of glucocorticoids in combination with cyclophosphamide or rituximab.[1] Despite these advances, glucocorticoids have remained an anchoring medication in updated regimens, and they contribute to treatment-related toxic effects. Along with evaluation of the efficacy and safety of newer agents such as rituximab, there has been a drive to reduce glucocorticoid doses and toxic effects and to evaluate the glucocorticoid-sparing effect of other treatments. The results of the previously published PEXIVAS trial,[2] which used a factorial design that randomly assigned patients to plasma exchange or no plasma exchange and to an accelerated or standard prednisone-tapering schedule, showed that the accelerated schedule was noninferior to the gradual tapering schedule with respect to the combined outcome of death or end-stage kidney disease. At 6 months, the cumulative dose of oral glucocorticoids in the reduced-dose group was less than 60% of that in the standard-dose group and was associated with a reduction in the risk of serious infections. An even more rapid reduction in glucocorticoid dosing over a period of 1 to 2 weeks was evaluated in a study involving 49 patients with ANCA-associated vasculitis and showed that favorable outcomes could be achieved while reducing the incidences of infection and diabetes.[3]

The background for the use of avacopan, an oral small-molecule inhibitor of the complement C5a receptor, in vasculitis is that activation of the alternative complement pathway has been identified as a key mechanism in the pathogenesis of ANCA-associated vasculitis. In a murine model of the disease, both C5a knockout and blockade of the neutrophil C5a receptor with avacopan protected against ANCA-induced glomerulonephritis.[4] Avacopan was also initially evaluated in the phase 2 CLEAR trial,[5] in which patients with ANCA-associated vasculitis received a standard induction regimen with either cyclophosphamide or rituximab and were randomly assigned to one of three treatment groups: avacopan, avacopan with low-dose prednisone, or standard high-dose prednisone alone (control group). The results in both avacopan groups were noninferior to those in the control group; clinical response at 12 weeks was achieved in 70% of the patients receiving standard-dose prednisone, 86% of those receiving avacopan with low-dose prednisone, and 81% of those receiving avacopan without prednisone. Patients receiving avacopan also had a more rapid decrease in urinary albumin levels and greater improvement in quality of life than those receiving standard-dose prednisone.

We now have a report in this issue of the *Journal* by Jayne and colleagues of a phase 3 clinical trial in ANCA-associated vasculitis that in effect replaced glucocorticoids with avacopan.[6] In the ADVOCATE trial, 331 patients were randomly assigned to avacopan at a dose of 30 mg twice daily or a tapering schedule of oral prednisone; all patients received standard remission-induction therapy with cyclophosphamide (followed by azathioprine) or rituximab. Patients with newly diagnosed or relapsing ANCA-associated vasculitis were eligible for the trial, and

approximately 80% of the patients had renal vasculitis.

The ADVOCATE trial was designed with two primary end points: the first was remission at week 26, and the second was sustained remission at week 52. Remission at week 26 was achieved in 72% of the patients receiving avacopan and 70% of those receiving prednisone; thus, a prespecified definition of noninferiority of avacopan to prednisone was met. Furthermore, the incidence of sustained remission at week 52 was significantly higher among those receiving avacopan (66%) than among those receiving prednisone (55%). In secondary end-point analyses, improvement in renal function and health-related quality of life generally favored the avacopan group as compared with the prednisone group, but significant differences between groups for these end points could not be established because of a lack of adjustment for multiple comparisons.

The ADVOCATE trial heralds a change in the treatment of ANCA-associated vasculitis that was previously unthinkable — the possibility of inducing disease remission without glucocorticoids. However, patients in this trial did receive a brief course of glucocorticoids during the screening phase or early in the trial as prednisone was being tapered off and could receive glucocorticoids as rescue medication. The average total prednisone-equivalent glucocorticoid dose was approximately 1.3 g (equating to 4 mg per patient per day) in the avacopan group and approximately 3.7 g (12 mg per patient per day) in the prednisone group.

An innovative aspect of the ADVOCATE trial was the use of a Glucocorticoid Toxicity Index that captures common glucocorticoid-related toxic effects, including change in body weight, glucose tolerance, blood pressure, lipids, myopathy, neuropsychiatric features, and infection. Using this tool, the investigators found that patients in the avacopan group had fewer glucocorticoid-related adverse events. Given concern about the potential risk of infections related to complement inhibition by avacopan, it is noteworthy that 13% of the patients in the avacopan group and 15% of those in the prednisone group had serious infections, but no *Neisseria meningitidis* infections occurred. The overall incidence of serious adverse events was also similar in the two groups. The safety of avacopan was recently confirmed in a smaller trial involving 42 patients with ANCA-associated vasculitis in which avacopan was added to standard-of-care treatment.[7]

The success of the ADVOCATE trial will probably encourage the evaluation of other complement-directed therapeutics for ANCA-associated vasculitis. A monoclonal antibody against the C5a molecule (IFX-1) is being evaluated in phase 2 clinical trials (ClinicalTrials.gov numbers, NCT03712345 and NCT03895801), and case reports suggest that eculizumab may be effective for the treatment of refractory ANCA-associated vasculitis.[8] Glucocorticoids are not only used in the remission-induction phase of severe ANCA-associated vasculitis but are also often used to manage minor disease relapses, thus contributing to the cumulative burden of glucocorticoid toxicity. Therefore, it will be of interest to explore whether avacopan could also replace glucocorticoids during management of minor relapses. The ADVOCATE trial is a milestone in the treatment of ANCA-associated vasculitis; complement inhibition with avacopan has glucocorticoid-sparing effects and results in superior disease control.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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