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Author

Soulsby, William

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JOURNAL CLUB

Journal Club Review of "Avacopan for the Treatment of ANCA-Associated Vasculitis"

William Daniel Soulsby

Journal Club. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599-609.

Objective. The C5a receptor inhibitor avacopan is being studied for the treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Methods. In this randomized, controlled trial, we assigned patients with ANCA-associated vasculitis in a 1:1 ratio to receive oral avacopan at a dose of 30 mg twice daily or oral prednisone on a tapering schedule. All the patients received either cyclophosphamide (followed by azathioprine) or rituximab. The first primary endpoint was remission, defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) at week 26 and no glucocorticoid use in the previous 4 weeks. The second primary endpoint was sustained remission, defined as remission at both weeks 26 and 52. Both endpoints were tested for noninferiority (by a margin of 20 percentage points) and for superiority.

Results. A total of 331 patients underwent randomization; 166 were assigned to receive avacopan, and 165 were assigned to receive prednisone. The mean BVAS at baseline was 16 in both groups. Remission at week 26 (the first primary endpoint) was observed in 120 of 166 patients (72.3%) receiving avacopan and in 115 of 164 patients (70.1%) receiving prednisone (estimated common difference, 3.4 percentage points; 95% confidence interval [CI], -6.0 to 12.8; $P < 0.001$ for noninferiority; $P = 0.24$ for superiority). Sustained remission at week 52 (the second primary endpoint) was observed in 109 of 166 patients (65.7%) receiving avacopan and in 90 of 164 patients (54.9%) receiving prednisone (estimated common difference, 12.5 percentage points; 95% CI, 2.6 to 22.3; $P < 0.001$ for noninferiority; $P = 0.007$ for superiority). Serious adverse events (excluding worsening vasculitis) occurred in 37.3% of the patients receiving avacopan and in 39.0% of those receiving prednisone.

Conclusion. In this trial involving patients with ANCA-associated vasculitis, avacopan was noninferior but not superior to prednisone taper with respect to remission at week 26 and was superior to prednisone taper with respect to sustained remission at week 52. All the patients received cyclophosphamide or rituximab. The safety and clinical effects of avacopan beyond 52 weeks were not addressed in the trial. (Funded by ChemoCentryx; ADVOCATE ClinicalTrials.gov number, NCT02994927.).

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ANCA-associated vasculitis (AAV) is a chronic autoimmune disease characterized by progressive pauci-immune glomerulonephritis and inflammation of the respiratory tract traditionally requiring treatment with corticosteroids. The ADVOCATE trial was a phase III randomized double-blind placebo-controlled clinical trial to investigate whether avacopan, a C5a receptor inhibitor involved in blocking complement activation, could replace steroids in induction therapy for AAV in addition to standard-of-care therapy via a noninferiority trial design. The ADVOCATE trial met its primary endpoint of clinical remission at week 26 (3.4% difference between treatment and placebo; 95% CI: –6.0 to 12.8%; $P < 0.001$ for noninferiority) and at week 52 (12.5% difference; 95% CI: 2.6% to 22.3%; $P = 0.007$ for superiority).

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No potential conflicts of interest relevant to this article were reported.

Address correspondence to William Daniel Soulsby, MD, University of California, San Francisco, Division of Pediatric Rheumatology, 550 16th Street, 4th Floor, Box #0632, San Francisco, CA 94158. Email: daniel.soulsby@ucsf.edu.

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Strengths of this study include its international and multicenter involvement, rigorous study design and analysis, and minimal loss to follow-up. Potential weaknesses of this study include the lack of rituximab maintenance as part of standard-of-care treatment beyond week 4 of induction therapy and complete wean off prednisone by week 21, much faster than steroid weans in prior trials (including PEXIVAS), which may somewhat limit our interpretation of the noninferiority of avacopan to prednisone. Overall, the ADVOCATE trial yielded thought-provoking clinical implications that may revolutionize AAV treatment moving forward, including less reliance on corticosteroids to achieve clinical remission in AAV.

BACKGROUND

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a chronic autoimmune disease characterized by rapidly progressive pauci-immune glomerulonephritis and granulomatous inflammation of the respiratory tract. C5a is a split product resulting from the activation of the complement pathway. Its interaction with the C5a receptor plays a key role in the pathogenesis of AAV. C5a acting on the C5a receptor is a potent neutrophil chemoattractant that decreases neutrophil deformability and slows their movement across small blood vessels, especially in the presence of ANCAs that have activated and primed neutrophils. These activated neutrophils will then release reactive oxygen species and create neutrophil extracellular traps, leading to endothelial cell damage and inflammation (1–3). Avacopan is an orally administered small molecule C5aR antagonist that blocks the effects of C5a and has been studied as a potential therapeutic for the treatment of AAV. C5a receptor blockade was first demonstrated in murine models of AAV to prevent the development of glomerulonephritis by anti-myeloperoxidase (MPO) antibodies (4,5). Prior phase II trials (including the CLEAR Trial: A randomized, double-blind, placebo-controlled, phase 2 study to evaluate the safety and efficacy of CCX168 in subjects with AAV on background of cyclophosphamide or rituximab treatment) demonstrated safety and efficacy in humans (6). The avacopan development in vasculitis to obtain corticosteroid elimination and therapeutic efficacy (ADVOCATE) trial was a phase III 1:1 randomized double-blind placebo-controlled clinical trial to investigate whether avacopan could replace a glucocorticoid-tapering regimen, in addition to standard of care, for the treatment of AAV (7).

METHODOLOGY

In the ADVOCATE trial, patients were eligible if they were 12 years of age or older with newly diagnosed or relapsing granulomatosis with polyangiitis or microscopic polyangiitis, requiring treatment with cyclophosphamide or rituximab. Important inclusion criteria included the following: the presence of ANCAs (anti-MPO or proteinase-3 (PR3) antibodies); an estimated glomerular filtration rate (eGFR) greater than 15 mL/min/1.73 m^2 BSA; and one major, three nonmajor, or two renal items on the Birmingham Vasculitis Activity Score (BVAS). Patients were excluded if they received more than 3 g of IV steroids within 4 weeks of trial enrollment, received greater than 10 mg of an oral prednisone equivalent for greater than 6 weeks, or needed dialysis or plasmapheresis within 12 weeks of enrollment. Other exclusion criteria included the presence of diffuse alveolar hemorrhage or active infection, among others.

Eligible patients were randomized into a treatment group receiving 30 mg of oral avacopan daily versus a control group receiving a placebo equivalent daily. In addition, patients were treated with standard of care therapy, including IV rituximab at 375 mg/m^2 dosing for a total of 4 weeks or cyclophosphamide (IV 15 mg/m^2 every 2 weeks vs. oral 2 mg/kg daily for 14 days), followed by oral azathioprine 2 mg/kg/d. Of note, no rituximab was given beyond the first 4 weeks of therapy. For steroids, those in the avacopan group received a 0 mg placebo taper, whereas those in the prednisone group started at 30-60 mg (depending on their weight) daily followed by rapid taper to 5 mg daily by week 15 and 0 mg by week 21.

Primary endpoints for the trial were clinical remission at week 26, defined as a BVAS score of 0 and no need for glucocorticoids for at least 4 weeks prior, and sustained remission at week 52, defined as persistent BVAS score of 0 with no need for glucocorticoids for at least 4 weeks prior and no relapse between weeks 26 and 52. Several secondary endpoints were assessed, including time to relapse and change in eGFR, among others.

This was a noninferiority trial analyzed via a modified intention-to-treat analysis, meaning that those participants who received at least one dose of the study drug were analyzed per their assigned randomized group. Assuming an expected incidence of remission in the prednisone group of 60% and 150 participants per group, the study would have 90% power to detect a δ of a –20% between the two trial arms. The gatekeeping method was used to maintain statistical significance, meaning that each primary endpoint was tested for statistical significance at a P value of 0.05 in sequence: first starting with noninferiority at 26 weeks, followed by noninferiority at 52 weeks, followed by superiority at 52 weeks.

STUDY FINDINGS

In total, 331 subjects were enrolled in the trial, with a mean age of 61 years and a male-to-female ratio of approximately 50% in both groups. Of subjects, 57% had a positive MPO status, and 43% had a positive PR3 status; 81% had renal disease.

There were no significant differences in steroid doses during screening between the two groups. Approximately two thirds received standard of care with rituximab, whereas approximately one third received cyclophosphamide.

The ADVOCATE trial met its primary endpoint at 26 weeks: 72.3% in the avacopan group versus 70.1% in the prednisone group demonstrated remission by week 26 (δ: 3.4%; 95% CI: –6.0 to 12.8), achieving noninferiority (boundary: 20%; $P < 0.001$), and 65.7% in the avacopan group versus 54.9% in the prednisone group had sustained remission at week 52 (δ: 12.5%; 95% CI: 2.6 to 22.3), achieving superiority ($P = 0.007$; boundary: 0%).

Although there were several secondary outcomes analyzed, we will focus on two key findings, including Kaplan-Meier analysis predicting time to relapse between the prednisone and avacopan groups. Whereas 10.1% in the avacopan group had relapse, 21.0% had relapse in the prednisone group, yielding a hazard ratio of 0.46 (95% CI: 0.25-0.84). This means that patients in the avacopan group were 54% less likely to relapse compared with the prednisone group. Additionally, there was a higher mean improvement in eGFR from baseline in the avacopan group (7.3 mL/min/1.73 m^2) compared with the prednisone group (4.1 mL/min/1.73 m^2).

STUDY IMPLICATIONS

In analyzing the implications of this trial's contribution to the field of rheumatology, it is important to analyze the study's criteria for and adherence to the noninferiority trial design. To justify conducting a noninferiority trial, a drug under investigation should either be more cost effective, more convenient, better tolerated, or less toxic than the standard-of-care equivalent (8). In this case, rheumatologists are keenly aware of the significant toxicities of steroid therapy, as well as the implications of having an orally available equivalent option, especially true for pediatric patients. In this regard, the choice of noninferiority trial appears justified.

To better understand the statistics, we must understand the concept of the noninferiority margin, or δ, which captures the essence of a treatment "not being worse." This δ sets the boundary not to be exceeded by the lower limit (in this trial) of the confidence interval for the difference between the event rate for the standard of care versus new treatment groups. It corresponds to the smallest clinical evidence of inferiority that would warrant nonacceptance of the new therapy. It should be chosen in advance and clinically justified (9).

In this case, a –20% δ was set in advance of trial conduction. Although the authors do not discuss in the manuscript their clinical rationale for the cut off of –20%, it is also recognized that too conservative of a margin may lead to a large and unfeasible trial. On the contrary, too liberal a margin could allow potentially inferior therapies to become accepted based on insufficient evidence (7). In this case, a –20% δ means that we would accept at least a 20% difference in clinical remission between the avacopan group and the standard of care. Greater than this margin would mean that the drug is inferior. The clinical justification of this δ was missing from the manuscript and would have facilitated interpretation of the study findings.

Another important consideration in the analysis of a noninferiority trial is a critical analysis of the comparator (standard-of-care) group regarding both design and adherence during the trial. Low adherence and loss to follow-up tend to make two treatments' results appear similar and would therefore bias toward the noninferiority hypothesis. This is not likely a major issue of this trial, in which there was minimal loss to follow-up or cross-over, although we cannot assume that adherence to the trial is synonymous with adherence to medications (including prednisone, placebo prednisone, avacopan, and placebo avacopan) by study subjects.

Finally, in the analysis of a noninferiority trial, we must consider the rigor of the standard-of-care group, which is being used as the gold standard to determine noninferiority. If the standard of care is not rigorously applied, it will be easier to achieve noninferiority, which may bias our interpretation of the results. One potential pitfall of the trial is the dosing regimen for rituximab. As established by the rituximab versus azathioprine as therapy for maintenance of remission for AAV (RITAZAREM) trial, standard-of-care therapy for AAV with rituximab requires re-dosing as part of maintenance therapy on an every-6-month basis (10). However, participants in this trial, two thirds of whom received rituximab, only received initial induction doses, at least as described by the article and its supplement. It is theoretically possible that those individuals in the prednisone group who were receiving rituximab could have had improved outcomes with regular 6-month-interval dosing of rituximab, thus biasing study findings towards noninferiority. Additionally, the prednisone taper in the prednisone group was an intentionally fast taper, weaning off steroids completely by week 21 of the trial. By comparison, the most recent large clinical trial assessing reduced steroid dosage in the AAV literature was the plasma exchange and glucocorticoids for the treatment of AAV (PEXIVAS) trial, which analyzed the effect of plasmapheresis on outcomes (11). In this trial, study subjects in both the standard and reduced-dose arms continued 5 mg of daily prednisone through week 52. It can be argued that steroid dosing was higher in PEXIVAS because these patients were classified as having severe AAV, requiring plasmapheresis, which was an exclusion criterion for ADVOCATE. Nevertheless, one could argue that those in the ADVOCATE trial may not have truly received the established standard of care for low steroid dosing in AAV. It is possible that the 5 mg of prednisone sustained through 1 year of the trial could have improved outcomes, thus (similar to those receiving rituximab) biasing toward noninferiority. This is less likely to be a major limitation of the trial given that the superiority margin was achieved by week 52, corresponding to the window in which both groups were completely off steroids (weeks 26-52).

Finally, when considering a new drug as a standard of care therapy, it is important to consider its safety. The results from the ADVOCATE trial suggest a favorable safety profile. There were 116 serious adverse events in the avacopan group versus 166 in the prednisone group, the most common of which was worsening of vasculitis (10.2% in the avacopan vs. 14.0% in the prednisone groups). Excluding vasculitis events, 37.3% and 39.0% of patients experienced a serious adverse event in the avacopan and prednisone groups, respectively. There were two deaths in the avacopan group (one due to worsening vasculitis and the other due to pneumonia) compared with four deaths in the prednisone group (one due to fungal infection, one with an infectious pleural effusion, one with acute myocardial infarction, and one with unknown cause of death). Serious infections occurred in 13.3% and 15.2% of those in the avacopan and prednisone groups, respectively.

Of note, avacopan may be of particular benefit to patients with low serum complements at disease onset. As neutrophil and complement activation are central to the pathophysiology of AAV, several studies have suggested that low serum C3 levels may portend an increase in AAV activity. For example, a recent cross-sectional analysis has shown that low serum C3 levels in drug-naïve patients at the time of diagnosis is associated with severe AAV activity and worse renal outcomes (12). The use of avacopan, then, as a direct target of complement activation at disease diagnosis, especially in patients with low complement levels, could be of benefit and should be one focus of future study.

In conclusion, the ADVOCATE trial represents a large international multicenter trial with rigorous study design and analysis (with minimal loss to follow-up) with thought-provoking clinical implications that may revolutionize AAV treatment moving forward. Avacopan was demonstrated to be a safe, well-tolerated oral drug noninferior to a prednisone-based treatment regimen by week 26 and superior by week 52 in achieving clinical remission along with significantly lower likelihood of relapse across 1 year. The results of this trial suggest that avacopan may have the potential to completely replace our reliance on oral steroids for AAV induction therapy, when combined with standard-of-care treatments, including rituximab and cyclophosphamide. The ability to adequately treat moderate disease activity in rheumatology without the use of steroids is an enticing prospect. Nevertheless, lack of rituximab maintenance as part of standard of care and complete wean off prednisone by week 21 may somewhat limit our interpretation of the noninferiority of avacopan to prednisone in this trial. Future studies should investigate the role for avacopan as a potential maintenance agent as well as its role in induction therapy for severe disease, including patients requiring dialysis or plasmapheresis. It can be hypothesized that avacopan could play an important therapeutic role in such patients, albeit possibly with the use of some corticosteroids.

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AUTHOR CONTRIBUTIONS

Dr. Soulsby drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Noone D, Hebert D, Licht C. Pathogenesis and treatment of ANCA-associated vasculitis-a role for complement. Pediatr Nephrol 2018; 33:1–11.
2. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol 2019;15:91–101. Erratum in: Nat Rev Rheumatol 2019;15:123.
3. Trivioli G, Vaglio A. The rise of complement in ANCA-associated vasculitis: from marginal player to target of modern therapy. Clin Exp Immunol 2020;202:403–6.
4. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol 2014;25:225–31.
5. Huugen D, van Esch A, Xiao H, Peutz-Kootstra CJ, Buurman WA, Tervaert JW, et al. Inhibition of complement factor C5 protects against anti-myeloperoxidase antibody-mediated glomerulonephritis in mice. Kidney Int 2007;71:646–54.
6. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al; CLEAR Study Group. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol 2017;28:2756–67.
7. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609.
8. Angeli F, Verdecchia P, Vaudo G, Masnaghetti S, Reboldi G. Optimal use of the non-inferiority trial design. Pharmaceut Med 2020;34: 159–65.
9. Macaya F, Ryan N, Salinas P, Pocock SJ. Challenges in the design and interpretation of noninferiority trials: insights from recent stent trials. J Am Coll Cardiol 2017;70:894–903.
10. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyousi R, et al; RITAZAREM co-investigators. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis 2020;79:1243–9.
11. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al; PEXIVAS Investigators. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020; 382:622–31.
12. Choi H, Kim Y, Jung SM, Song JJ, Park YB, Lee SW. Low serum complement 3 level is associated with severe ANCA-associated vasculitis at diagnosis. Clin Exp Nephrol 2019;23: 223–30.