Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

ABSTRACT

BACKGROUND

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 end point 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 end point was sustained remission, defined as remission at both weeks 26 and 52. Both end points 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 end point) 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 end point) 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.

CONCLUSIONS

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.)

PATIENTS WITH ANTINEUTROPHIL CYTOplasmic antibody (ANCA)–associated vasculitis may have life-threatening complications, including impairment in kidney function[1-6] caused by progressive focal necrotizing glomerulonephritis.[1,2] ANCA-associated vasculitis can also result in deterioration of health-related quality of life[7-9] because of organ damage, as well as toxic effects from medications used to treat the disorder, including from long-term use of glucocorticoids.[10-13]

Activation of the alternative complement pathway, which results in terminal C5a production, is a component of the pathogenesis of ANCA-associated vasculitis.[14-17] 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. In a murine model of ANCA-associated vasculitis, avacopan prevented the development of glomerulonephritis induced by antimyeloperoxidase antibodies.[17] Avacopan showed an effect on vasculitis in phase 2 trials.[18,19] We conducted a phase 3 randomized trial (ADVOCATE) that compared avacopan with a tapering schedule of prednisone in patients with ANCA-associated vasculitis concurrently treated with immunosuppressive drugs.

METHODS

TRIAL DESIGN AND PATIENTS

The trial design has been described previously, and the protocol is available with the full text of this article at NEJM.org.[20] Patients were enrolled at 143 centers in an international, randomized, double-blind, double-dummy, controlled trial. The aim was to evaluate whether avacopan could replace a glucocorticoid-tapering regimen used in the treatment of ANCA-associated vasculitis.[21] 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 (60 mg per day tapered to discontinuation by week 21) (Table S1 in the Supplementary Appendix, available at NEJM.org).

The screening period for trial eligibility was not to exceed 14 days. Eligible patients had newly diagnosed or relapsing granulomatosis with polyangiitis or microscopic polyangiitis, according to the Chapel Hill Consensus Conference definitions,[2] for which treatment with cyclophosphamide or rituximab was indicated; had tested positive for antibodies to either proteinase 3 or myeloperoxidase; had an estimated glomerular filtration rate (eGFR) of at least 15 ml per minute per 1.73 m[2] of body-surface area; and had at least one major or three nonmajor items or at least two renal items of hematuria and proteinuria on the Birmingham Vasculitis Activity Score (BVAS), version 3 (a composite of signs and symptoms in nine organ systems; total range, 0 to 63, with higher scores indicating more disease activity) (see the Supplementary Appendix).[22] All use of immunosuppressants had to cease before trial entry. Patients were excluded if they had received more than 3 g of intravenous glucocorticoids within 4 weeks, or more than 10 mg per day of oral prednisone (or equivalent) for more than 6 weeks continuously, before screening. Complete inclusion and exclusion criteria are described in the Supplementary Appendix.

The trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics committees and institutional review boards at participating sites approved the research protocol. All the patients or a parent or guardian gave written informed consent before entry. ChemoCentryx sponsored the trial and provided trial medication. Medpace conducted the trial with guidance from ChemoCentryx. The first two authors had confidentiality agreements with the sponsor. All the authors vouch for the completeness and accuracy of the data, the complete reporting of adverse events, and the adherence of the trial to the protocol. All the authors participated with the sponsor in the design of the trial, the analysis of the data, and the writing of the manuscript.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive 30 mg of avacopan twice daily orally plus prednisone-matching placebo or a tapering oral regimen of prednisone plus avacopan-matching placebo in a double-dummy design. Randomization was stratified according to vasculitis disease status (newly diagnosed or relapsing), ANCA status (antiproteinase 3 positive or antimyeloperoxidase positive), and immunosuppressive treatment (cyclophosphamide or rituximab, as-

signed at the discretion of the investigators at the inception of the trial for each patient and continued throughout the trial). Randomization was performed centrally through an interactive Web-response system with the use of a minimization algorithm to maintain balance between the treatment groups.[23] Glucocorticoid treatment during the screening period had to be tapered to 20 mg or less of prednisone equivalent before the patient began the trial, and this open-label glucocorticoid treatment was further tapered to discontinuation by the end of week 4 of the trial. Patients in either trial group who had a worsening of disease that involved a major item in the BVAS could be treated with rescue therapy consisting of intravenous glucocorticoids (typically 0.5 to 1 g of methylprednisolone per day for 3 days), oral glucocorticoids, or both, tapered according to the patient's condition.

All the patients received one of three regimens: cyclophosphamide intravenously at a dose of 15 mg per kilogram of body weight up to 1.2 g on day 1 and at weeks 2, 4, 7, 10, and 13; cyclophosphamide orally at a dose of 2 mg per kilogram up to 200 mg per day for 14 weeks (see the Supplementary Appendix, including Table S2); or intravenous rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks. From week 15 onward, cyclophosphamide was followed by oral azathioprine at a target dose of 2 mg per kilogram per day. No rituximab was given beyond the first 4 weeks. Investigators were instructed that the use of additional glucocorticoids, not supplied as trial medication, was to be avoided as much as possible (see the Supplementary Appendix). Prophylactic therapy for infection, including for *Pneumocystis jirovecii*, was required according to the protocol.

Patients, trial personnel, and sponsor representatives involved in the conduct of the trial were unaware of the trial group assignments. The trial drugs and their matching placebos were provided to trial centers in identical bottles.

END POINTS

The two primary efficacy end points were clinical remission at week 26, defined as a BVAS of 0 and no receipt of glucocorticoids for 4 weeks before week 26, and sustained remission, defined as remission at week 26 and at week 5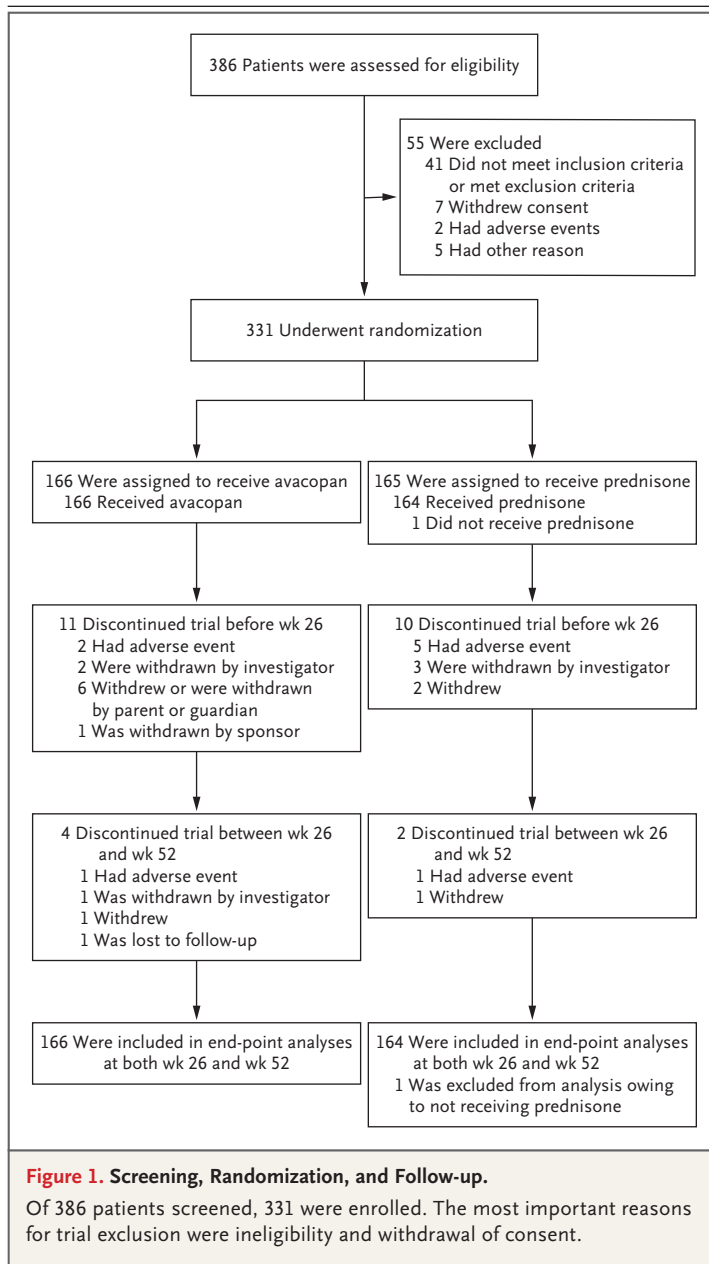2 and no receipt of glucocorticoids for 4 weeks before week 52. Patients were not considered to be in sustained remission if they had remission at week 26 but a relapse thereafter; relapse was defined as a return of vasculitis activity on the basis of at least one major BVAS item, at least three minor BVAS items, or one or two minor BVAS items for at least two consecutive trial visits.

Secondary end points were glucocorticoid-induced toxic effects according to the Glucocorticoid Toxicity Index (GTI) during the first 26 weeks (measured by both the Cumulative Worsening Score [GTI-CWS], which ranges from 0 to 410, and the Aggregate Improvement Score [GTI-AIS], which ranges from −317 to 410; on both scales, higher scores indicate greater severity of toxic effects) (Table S3)[24,25]; a BVAS of 0 at week 4; change from baseline in health-related quality of life, assessed with the 36-Item Short Form Health Survey (SF-36), version 2, and the EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) (range, 0 to 100 for both, with higher scores indicating better quality of life)[26,27]; relapse (assessed in a time-to-event analysis); change from baseline in the eGFR; urinary albumin:creatinine ratio; urinary monocyte chemoattractant protein 1:creatinine ratio; and the Vasculitis Damage Index (range, 0 to 64, with higher scores indicating more damage).[28] Details of the trial assessments are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that a planned sample size of 150 patients per group would provide the trial with at least 90% power to show the noninferiority of avacopan to prednisone with respect to the primary end point of remission at week 26, assuming a noninferiority margin of −20 percentage points and an incidence of remission in the prednisone group of 60%. The primary efficacy analyses were conducted in the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of trial medication.

With respect to the primary end points, if the lower boundary of the two-sided 95% confidence interval for the difference (avacopan minus prednisone) in the incidence of remission was greater than −20 percentage points, avacopan would be considered not inferior to prednisone. If the lower boundary of the 95% confidence interval

Figure 1. Screening, Randomization, and Follow-up.

Of 386 patients screened, 331 were enrolled. The most important reasons for trial exclusion were ineligibility and withdrawal of consent.

52, and superiority at week 26. Data were analyzed after all the patients had completed the 52-week treatment period. No interim analyses were performed.

Secondary end-point analyses of continuous variables were performed with the use of mixed-effects models for repeated measures. Least-squares means, standard errors, and confidence intervals are from models incorporating treatment group, visit, treatment-by-visit interaction, and stratification factors as covariates. Longitudinal measurements from the same patients were considered as repeated-measure units in the model. The Kaplan–Meier method was used to estimate the time to relapse of vasculitis, and the proportionality assumption was upheld. There was no prespecified plan for adjustment of confidence intervals for multiplicity of the secondary end points; point estimates and 95% confidence intervals only are presented, and no definite conclusions can be drawn from these data. Prespecified subgroup analyses were performed, but the trial was not powered to make conclusions from these data.

RESULTS

PATIENTS

The trial was conducted from March 15, 2017, until November 1, 2019 (last trial visit). Details of the screening, randomization, and follow-up of the patients are provided in Figure 1. The demographic and clinical characteristics of the patients at baseline were similar in the two treatment groups (Table 1). The mean age was 61 years in both groups. Men constituted 59.0% of the avacopan group and 53.7% of the prednisone group. In each group, 43% of the patients were positive for antiproteinase 3 antibodies, and 57% were positive for antimyeloperoxidase antibodies. A total of 81.2% of the patients had renal vasculitis. The glucocorticoid doses during screening were similar in the two groups. In both groups, approximately two thirds of the patients received rituximab and one third received cyclophosphamide (Table 1).

END POINTS

Remission at week 26 (the first primary end point) was observed in 120 of 166 patients (72.3%) in the avacopan group and in 115 of 164 patients (70.1%) in the prednisone group (estimated common difference, 3.4 percentage points;

was greater than 0.0 percentage points, avacopan would be considered superior to prednisone. Summary score estimates of the common difference in the incidences of remission were calculated with the use of inverse-variance stratum weights (see the Supplementary Appendix). For the primary end points, missing data at week 26 and week 52 were imputed as no remission. To preserve the type I error, the two primary end points were tested in a gatekeeping procedure in the following sequence: noninferiority at week 26, noninferiority at week 52, superiority at week

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Age — yr	61.2±14.6	60.5±14.5
Sex — no. (%)		
Male	98 (59.0)	88 (53.7)
Female	68 (41.0)	76 (46.3)
Race — no. (%)†		
White	138 (83.1)	140 (85.4)
Asian	17 (10.2)	15 (9.1)
Black	3 (1.8)	2 (1.2)
Other	8 (4.8)	7 (4.3)
Body-mass index‡	26.7±6.0	26.8±5.2
Median duration of ANCA-associated vasculitis (range) — mo	0.23 (0–362.3)	0.25 (0–212.5)
Vasculitis disease status — no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status — no. (%)		
Antiproteinase 3 positive	72 (43.4)	70 (42.7)
Antimyeloperoxidase positive	94 (56.6)	94 (57.3)
Type of vasculitis — no. (%)		
Granulomatosis with polyangiitis	91 (54.8)	90 (54.9)
Microscopic polyangiitis	75 (45.2)	74 (45.1)
Birmingham Vasculitis Activity Score§	16.3±5.9	16.2±5.7
Vasculitis Damage Index¶	0.7±1.5	0.7±1.4
Immunosuppressant induction treatment — no. (%)		
Intravenous rituximab	107 (64.5)	107 (65.2)
Intravenous cyclophosphamide	51 (30.7)	51 (31.1)
Oral cyclophosphamide	8 (4.8)	6 (3.7)
Organ involvement — no. (%)‖		
Renal	134 (80.7)	134 (81.7)
General	111 (66.9)	114 (69.5)
Ear, nose, and throat	75 (45.2)	69 (42.1)
Chest	71 (42.8)	71 (43.3)
Nervous system	38 (22.9)	31 (18.9)
Mucous membranes or eyes	26 (15.7)	40 (24.4)
Cutaneous	24 (14.5)	23 (14.0)
Cardiovascular	6 (3.6)	3 (1.8)
Abdominal	4 (2.4)	1 (0.6)
Glucocorticoid use during screening period		
Use of any glucocorticoids — no. (%)	125 (75.3)	135 (82.3)
Intravenous use	63 (38.0)	73 (44.5)
Oral use	99 (59.6)	113 (68.9)
Total prednisone-equivalent dose — mg**	907.3±1145.9	978.0±1157.5
Daily prednisone-equivalent dose — mg**	64.8±81.9	69.9±82.7
Previous immunosuppressant use — no. (%)††		
Cyclophosphamide	4 (2.4)	2 (1.2)
Rituximab	1 (0.6)	4 (2.4)

* Data are shown for the modified intention-to-treat population. Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ANCA denotes antineutrophil cytoplasmic antibody.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Birmingham Vasculitis Activity Score is a composite measure of signs and symptoms in nine organ systems. Scores range from 0 to 63, with higher scores indicating more extensive disease activity.
¶ The Vasculitis Damage Index pertains to 11 organ systems. Values range from 0 to 64, with higher scores indicating more extensive organ damage. Patients with a new diagnosis typically have a score of 0.
‖ Organ involvement was based on the Birmingham Vasculitis Activity Score.
** The prednisone-equivalent dose includes both intravenous and oral use of glucocorticoids.
†† Shown are patients who used immunosuppressants within the previous 12 months.

Table 2. Primary and Key Secondary End Points.*

End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖
Secondary end points			
GTI-CWS**			
Wk 13			
Patients evaluated	160	161	
Least-squares mean	25.7±3.4	36.6±3.4	–11.0 (–19.7 to –2.2)
Wk 26			
Patients evaluated	154	153	
Least-squares mean	39.7±3.4	56.6±3.4	–16.8 (–25.6 to –8.0)
GTI-AIS††			
Wk 13			
Patients evaluated	160	161	
Least-squares mean	9.9±3.4	23.2±3.5	–13.3 (–22.2 to –4.4)
Wk 26			
Patients evaluated	154	153	
Least-squares mean	11.2±3.5	23.4±3.5	–12.1 (–21.1 to –3.2)
eGFR — ml/min/1.73 m^2‡‡			
Baseline			
Patients evaluated	131	134	
Mean	44.6±2.4	45.6±2.4	
Change from baseline to wk 26			
Patients evaluated	121	127	
Least-squares mean	5.8±1.0	2.9±1.0	2.9 (0.1 to 5.8)
Change from baseline to wk 52			
Patients evaluated	119	125	
Least-squares mean	7.3±1.0	4.1±1.0	3.2 (0.3 to 6.1)
SF-36 physical component score§§			
Baseline			
Patients evaluated	165	160	
Mean	39.2±0.8	40.1±0.8	
Change from baseline to wk 26			
Patients evaluated	153	147	
Least-squares mean	4.45±0.73	1.34±0.74	3.10 (1.17 to 5.03)
Change from baseline to wk 52			
Patients evaluated	147	144	
Least-squares mean	4.98±0.74	2.63±0.75	2.35 (0.40 to 4.31)
Score on EQ-5D-5L visual-analogue scale¶¶			
Baseline			
Patients evaluated	166	162	
Mean	65.8±1.5	63.4±1.8	
Change from baseline to wk 26			
Patients evaluated	153	150	
Least-squares mean	9.1±1.4	5.5±1.4	3.6 (–0.1 to 7.2)
Change from baseline to wk 52			
Patients evaluated	149	146	
Least-squares mean	13.0±1.4	7.1±1.4	5.9 (2.3 to 9.6)
Urinary albumin:creatinine ratio‖			
Baseline			
Patients evaluated	125	128	
Geometric mean (range)	433 (20–6461)	312 (11–5367)	
Percent change from baseline to wk 4			
Patients evaluated	121	124	
Least-squares mean ±SE	–40±10	0±9	–40 (–53 to –22)

Table 2. (Continued.)

End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Percent change from baseline to wk 13			
Patients evaluated	116	121	
Least-squares mean	−55±10	−49±9	−12 (−32 to 13)
Percent change from baseline to wk 26			
Patients evaluated	113	118	
Least-squares mean	−63±10	−70±10	25 (−3 to 61)
Percent change from baseline to wk 52			
Patients evaluated	109	114	
Least-squares mean	−74±10	−77±10	12 (−14 to 45)

* Plus–minus values are means or least-squares means ±SE.

† Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and no receipt of glucocorticoids for vasculitis within 4 weeks before the week 26 visit.

‡ Shown are estimated common differences in percentage points and two-sided 95% confidence intervals.

§ One-sided P value for noninferiority, <0.001; P value for superiority, 0.24.

¶ Sustained remission was defined as remission at week 26 and remission at week 52 (BVAS of 0 and no receipt of glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks before week 52) and no relapse between week 26 and 52.

‖ One-sided P value for noninferiority, <0.001; P value for superiority, 0.007.

** The Glucocorticoid Toxicity Index Cumulative Worsening Score (GTI-CWS) ranges from 0 to 410, with higher scores indicating greater severity of toxic effects.

†† The Glucocorticoid Toxicity Index Aggregate Improvement Score (GTI-AIS) ranges from −317 to 410, with higher scores indicating greater severity of toxic effects.

‡‡ Shown is the estimated glomerular filtration rate (eGFR) in patients with renal disease at baseline on the basis of the BVAS.

§§ The physical component score on the 36-Item Short Form Health Survey (SF-36), version 2, ranges from 0 to 100, with higher scores indicating better quality of life.

¶¶ Scores on the visual-analogue scale of the EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L) range from 0 to 100, with higher scores indicating better quality of life.

‖‖ Values are for patients with renal disease (on the basis of the BVAS) and a urinary albumin:creatinine ratio (with albumin measured in milligrams and creatinine in grams) of at least 10 at baseline. Percent changes from baseline are based on ratios of geometric means of visit over baseline.

95% confidence interval [CI], −6.0 to 12.8; P<0.001 for noninferiority; P=0.24 for superiority) (Table 2). Sustained remission at week 52 (the second primary end point) was observed in 109 of 166 patients (65.7%) in the avacopan group and in 90 of 164 patients (54.9%) in the prednisone group (estimated common difference, 12.5 percentage points; 95% CI, 2.6 to 22.3; P<0.001 for noninferiority; P=0.007 for superiority). The prespecified 20-percentage-point difference between groups was not exceeded in the confidence interval for the between-group difference at 26 weeks or 52 weeks; therefore, the criteria for noninferiority of avacopan were met, but superiority was met only at week 52 (Fig. S1). Remission results for per-protocol analyses are shown in Table S7, and results of subgroup analyses based on vasculitis disease status, ANCA status, immunosuppressive treatment, and type of vasculitis are shown in Tables S8 and S9.

For glucocorticoid-induced toxic effects, the least-squares mean for the GTI-CWS at week 26 was 39.7 in the avacopan group and 56.6 in the prednisone group, and the difference between groups was −16.8 points (95% CI, −25.6 to −8.0) (Table 2 and Fig. S2). The least-squares mean for
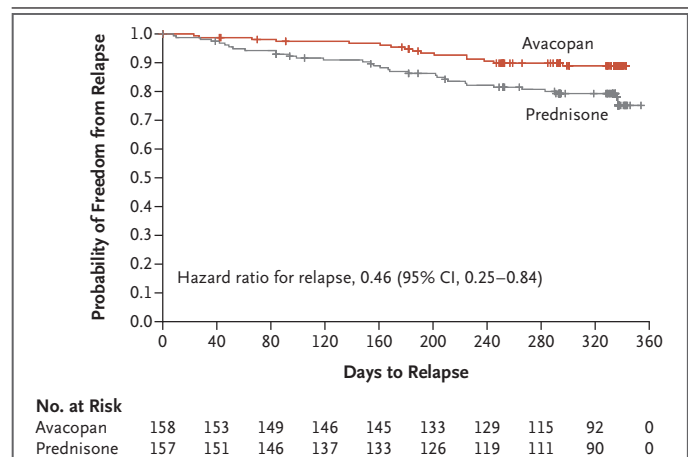
Figure 2. Kaplan–Meier Plot of Time to Relapse.

A relapse was defined as worsening of disease, after previous achievement of a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), that involved one or more major items in the BVAS, three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive trial visits. A total of 16 of 158 patients (10.1%) in the avacopan group and 33 of 157 patients (21.0%) in the prednisone group had relapses. A test of proportionality was performed by incorporating a time-varying covariate in the Cox regression model by creating an interaction of the treatment groups and log of the time to relapse. The Wald chi-square test for the interaction term was 0.48. The corresponding P value was 0.49, which indicates no significant evidence of nonproportionality of the hazard. Tick marks indicate censored data.

the GTI-AIS at week 26 was 11.2 in the avacopan group and 23.4 in the prednisone group, and the difference between groups was –12.1 points (95% CI, –21.1 to –3.2).

At week 52, the least-squares mean change from baseline in the eGFR was 7.3 ml per minute per 1.73 m^2 in the avacopan group and 4.1 ml per minute per 1.73 m^2 in the prednisone group, and the difference between groups was 3.2 ml per minute per 1.73 m^2 (95% CI, 0.3 to 6.1) (Table 2 and Fig. S3A). Among the patients with stage 4 kidney disease (i.e., baseline eGFR of <30 ml per minute per 1.73 m^2), the least-squares mean change at week 52 was 13.7 ml per minute per 1.73 m^2 in the avacopan group and 8.2 ml per minute per 1.73 m^2 in the prednisone group, and the difference between groups was 5.6 ml per minute per 1.73 m^2 (95% CI, 1.7 to 9.5) (Fig. S3B). Two patients in the avacopan group and four in the prednisone group received dialysis during the treatment period.

Results for health-related quality of life, as measured by the SF-36 and EQ-5D-5L, are shown in Table 2, Table S10, and Figures S4 and S5. Most results are in the same direction as those for sustained remission. Relapse results are shown in Figure 2 and Table S10. The hazard ratio for relapse after remission (avacopan vs. prednisone) was 0.46 (95% CI, 0.25 to 0.84). Other secondary end-point results, for which there was no plan for adjustment of multiple comparisons, are shown in Table 2 and Table S10.

The mean total prednisone-equivalent dose of oral and intravenous glucocorticoids was 1676 mg (equating to 5 mg per patient per day) in the avacopan group and 3847 mg (equating to 13 mg per patient per day) in the prednisone group (Table S5). Glucocorticoid use according to week is shown in Figures S6 and S7, and use according to trial period is shown in Table S6. Immunosuppressants, other than those specified in the protocol, for worsening of vasculitis or relapses were used in 29 patients (17.5%) in the avacopan group and in 36 patients (22.0%) in the prednisone group (Table S6).

SAFETY

The incidences of serious adverse events, life-threatening adverse events, and death are shown in Table 3. There were 116 serious adverse events in the avacopan group and 166 in the prednisone group. The most common serious adverse event was worsening of vasculitis (10.2% in the avacopan group and 14.0% in the prednisone group).

The percentage of patients with serious adverse events (excluding vasculitis events) was 37.3% in the avacopan group and 39.0% in the prednisone group.

There were two deaths in the avacopan group (due to worsening of vasculitis and pneumonia) and four deaths in the prednisone group (generalized fungal infection, infectious pleural effusion, acute myocardial infarction, and death of unknown cause). Fatal infections and life-threatening infections were reported in one patient each in the avacopan group and in two patients each in the prednisone group (Table 3). Serious infections occurred in 13.3% of the patients in the avacopan group and in 15.2% of those in the prednisone group (median time to infection, 126 days vs. 97 days), and serious opportunistic infections occurred in 3.6% and 6.7%, respectively. Serious herpes zoster infections occurred in no patients in the avacopan group and in two patients in the prednisone group. No *Neisseria meningitidis* or *P. jirovecii* infections were observed.

Nine patients in the avacopan group and six in the prednisone group had a serious adverse event of an abnormality on liver-function testing. All events resolved with the withdrawal of trial medication and other potentially hepatotoxic drugs, including trimethoprim–sulfamethoxazole. One patient in the avacopan group, who had a history of drug hypersensitivity, had a serious adverse event of angioedema that resolved after treatment with avacopan was discontinued. The incidence of adverse events possibly related to glucocorticoids on the basis of European League against Rheumatism criteria (see Table S4 for included terms)[29] was 66.3% in the avacopan group and 80.5% in the prednisone group (difference, –14.2 percentage points; 95% CI, –23.7 to –3.8).

DISCUSSION

This trial tested the hypothesis that the orally administered C5a receptor inhibitor avacopan could be effective in patients with ANCA-associated vasculitis without daily oral prednisone treatment. Avacopan was noninferior but not superior to tapered prednisone with respect to remission at week 26 and was superior to prednisone with respect to sustained remission at week 52. In subgroup analyses, patients in the rituximab stratum who did not receive rituximab after the first 4 weeks had an incidence of sustained remission at week 52 of 71.0% in the

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
Severe adverse event†		
No. of patients (%)	39 (23.5)	41 (25.0)
No. of events	71	94
Life-threatening adverse event		
No. of patients (%)	8 (4.8)	14 (8.5)
No. of events	8	22
Death — no. (%)	2 (1.2)	4 (2.4)
Any serious adverse event‡		
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166
Any serious event related to vasculitis worsening§		
No. of patients (%)	17 (10.2)	23 (14.0)
No. of events	18	36
Any serious event not related to vasculitis worsening		
No. of patients (%)	62 (37.3)	64 (39.0)
No. of events	98	130
Discontinuation of trial medication due to adverse event — no. (%)	26 (15.7)	29 (17.7)
Any infection		
No. of patients (%)	113 (68.1)	124 (75.6)
No. of events	233	291
Any serious infection¶		
No. of patients (%)	22 (13.3)	25 (15.2)
No. of events	25	31
Any serious opportunistic infection — no. (%)	6 (3.6)	11 (6.7)
Death due to infection — no. (%)	1 (0.6)	2 (1.2)
Life-threatening infection — no. (%)‖	1 (0.6)	2 (1.2)
Serious adverse event of abnormality on liver-function testing — no. (%)	9 (5.4)	6 (3.7)
Any adverse event potentially related to glucocorticoids — no. (%)**	110 (66.3)	132 (80.5)
Cardiovascular	72 (43.4)	85 (51.8)
Infectious	22 (13.3)	25 (15.2)
Gastrointestinal	3 (1.8)	4 (2.4)
Psychological	27 (16.3)	39 (23.8)
Endocrine or metabolic	23 (13.9)	48 (29.3)
Dermatologic	14 (8.4)	28 (17.1)
Musculoskeletal	19 (11.4)	21 (12.8)
Ophthalmologic	7 (4.2)	12 (7.3)
Any adverse event potentially related to glucocorticoids as assessed by the investigators — no. (%)	107 (64.5)	131 (79.9)
Any serious adverse event potentially related to prednisone as assessed by the investigators — no. (%)	11 (6.6)	24 (14.6)

*   Incidence is expressed as number and percentage of patients having at least one event.
†   Severe adverse events were defined as those events that caused an inability of a patient to carry out usual activities.
‡   Serious adverse events were defined as any adverse event that resulted in death, was immediately life-threatening, required or prolonged hospitalization, resulted in persistent or clinically significant disability or incapacity, was a birth defect, or was an important event that might jeopardize the patient or might have required intervention to prevent any of the above.
§   Data are for patients who had a serious adverse event of ANCA-positive vasculitis (worsening), granulomatosis with polyangiitis (worsening), or microscopic polyangiitis (worsening).
¶   All serious infections are summarized in Table S11.
‖   The life-threatening infections were not the same as the fatal infections. One patient in the prednisone group had sepsis and another had bacteremia and meningitis. One patient in the avacopan group, who also received two rituximab infusions before the event, had hepatitis C reactivation during the trial drug–free follow-up period.
** Predefined *Medical Definition for Regulatory Activities* preferred terms based on the European League against Rheumatism search criteria[29] were included for each cluster (see Table S4 for included terms).

avacopan group, as compared with 56.1% in the prednisone group; however, the subgroup analyses were not conclusive.

The greater incidence of glucocorticoid-induced toxic effects in the prednisone group than in the avacopan group was consistent with higher glucocorticoid use in the prednisone group. The effects of avacopan on eGFR and albuminuria in this trial were consistent with those in previous studies in mice[17] and humans[18,19] that showed a beneficial effect of avacopan on kidney function in the context of vasculitis. The effects of avacopan on eGFR and albuminuria in vasculitis may be due to blockade in the glomeruli of the C5a–C5aR axis, arresting the potent chemoattraction and activation of neutrophils that damage the glomeruli.[17,30] Quality of life improved in both treatment groups. The EQ-5D-5L results did not differ substantially between the two groups at 26 weeks; however, the EQ-5D-5L results at week 52 and health-related outcomes assessed by SF-36 were in the same direction as the primary outcome, which was consistent with findings in previous trials.[18,19]

The number of serious adverse events (excluding events of worsening vasculitis) was 33% higher in the prednisone group than in the avacopan group, a finding consistent with a higher exposure to glucocorticoids in that group, and there were more deaths, life-threatening or serious adverse events, and infections in the prednisone group than in the avacopan group. Because avacopan does not block the formation of C5b and the membrane attack complex, as occurs with C5 blockers such as eculizumab,[31] *N. meningitidis* infections were an adverse event of special interest; no cases were observed. Serious adverse events of an abnormality on liver-function testing occurred in 5.4% of the patients in the avacopan group and 3.7% of those in the prednisone group.

This trial had limitations. Glucocorticoids were used by patients in the avacopan group, although the mean daily glucocorticoid dose in the avacopan group was one third of that in the prednisone group. The incidence of additional glucocorticoid use was higher in the prednisone group than in the avacopan group. Rituximab and cyclophosphamide were used as immunosuppressive treatments during the trial in patients positive for antiproteinase 3 antibodies and in those positive for antimyeloperoxidase antibodies, and patients with newly diagnosed vasculitis and those with relapsing disease were both included; thus, the trial population was heterogeneous.

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 rituximab or cyclophosphamide. Longer trials are required to determine the durability and safety of avacopan in patients with ANCA-associated vasculitis.

REFERENCES

1. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 1988;318:1651-7.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
3. Jayne D. Evidence-based treatment of systemic vasculitis. Rheumatology (Oxford) 2000;39:585-95.
4. Koldingsnes W, Nossent H. Predictors of survival and organ damage in Wegener's granulomatosis. Rheumatology (Oxford) 2002;41:572-81.
5. Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, Lerma-Márquez JL. Overall survival, renal survival and relapse in patients with microscopic polyangiitis: a systematic review of current evidence. Rheumatology (Oxford) 2011;50:1414-23.
6. Takala JH, Kautiainen H, Finne P, Leirisalo-Repo M. Wegener's granulomatosis in Finland in 1981-2000: risk of dialysis-dependent renal disease. Scand J Rheumatol 2011;40:283-8.
7. Koutantji M, Harrold E, Lane SE, Pearce S, Watts RA, Scott DGI. Investigation of quality of life, mood, pain, disability, and disease status in primary systemic vasculitis. Arthritis Rheum 2003; 49:826-37.
8. Tomasson G, Boers M, Walsh M, et al. Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's).

Arthritis Care Res (Hoboken) 2012;64: 273-9.

9. Basu N, McClean A, Harper L, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis 2014;73:207-11.

10. Charlier C, Henegar C, Launay O, et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis 2009;68:658-63.

11. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol 2012;7: 240-7.

12. Goupil R, Brachemi S, Nadeau-Fredette A-C, et al. Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis. Clin J Am Soc Nephrol 2013;8:416-23.

13. Robson J, Doll H, Suppiah R, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitis: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford) 2015;54: 471-81.

14. Halbwachs L, Lesavre P. Endothelium-neutrophil interactions in ANCA-associated diseases. J Am Soc Nephrol 2012;23: 1449-61.

15. Furuta S, Jayne DR. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. Kidney Int 2013;84: 244-9.

16. Kettritz R. With complements from ANCA mice. J Am Soc Nephrol 2014;25: 207-9.

17. Xiao H, Dairaghi DJ, Powers JP, et al. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol 2014;25:225-31.

18. Jayne DRW, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. J Am Soc Nephrol 2017;28: 2756-67.

19. Merkel PA, Niles J, Jimenez R, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody–associated vasculitis. ACR Open Rheumatol 2020;2:662-71.

20. Merkel PA, Jayne DR, Wang C, Hillson J, Bekker P. Evaluation of the safety and efficacy of avacopan, a C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: protocol for a randomized, double-blind, active-controlled, phase 3 trial. JMIR Res Protoc 2020;9(4):e16664.

21. Jones RB, Cohen Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.

22. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.

23. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.

24. Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017; 76:543-6.

25. McDowell PJ, Stone JH, Zhang Y, et al. Quantification of glucocorticoid-associated morbidity in severe asthma using the Glucocorticoid Toxicity Index. J Allergy Clin Immunol Pract 2020 September 1 (Epub ahead of print).

26. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: manual and interpretation guide. Boston: Health Institute, New England Medical Center, 1993.

27. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.

28. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371-80.

29. Duru N, van der Goes MC, Jacobs JWG, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2013;72:1905-13.

30. Bekker P, Dairaghi D, Seitz L, et al. Characterization of pharmacologic and pharmacokinetic properties of CCX168, a potent and selective orally administered complement 5a receptor inhibitor, based on preclinical evaluation and randomized phase 1 clinical study. PLoS One 2016; 11(10):e0164646.

31. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nat Biotechnol 2007;25:1256-64.
Copyright © 2021 Massachusetts Medical Society.