

Adjunctive Treatment With Avacopan, an Oral C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. This study aimed to evaluate the safety of avacopan, an orally administered C5a receptor inhibitor, for the treatment of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis in addition to standard-of-care (SOC) treatment with glucocorticoids with cyclophosphamide or rituximab.

Methods. In this randomized 12-week study, twice daily avacopan (10 mg or 30 mg) plus SOC was assessed versus SOC only in patients with newly diagnosed/relapsing ANCA-associated vasculitis. Efficacy measurements included 50% or greater reduction in Birmingham Vasculitis Activity Score (BVAS) at day 85, rapid reduction (day 29) of BVAS to a score of 0 that was sustained through day 85, change in Vasculitis Damage Index (VDI), renal response (improvement in estimated glomerular filtration rate [eGFR], hematuria, and albuminuria), and health-related quality of life (HRQoL).

Results. Forty-two patients were randomized (n = 13 SOC, n = 13 avacopan 10 mg, and n = 16 avacopan 30 mg). Serious adverse events occurred in 15% and 17% of patients receiving SOC only and patients receiving avacopan with SOC, respectively. In the intent-to-treat population, BVAS response was high across arms (11 of 13 SOC, 11 of 12 avacopan 10 mg, and 12 of 15 avacopan 30 mg); increases in mean VDI were greater with SOC only than with avacopan plus SOC (0.3 versus 0.1). Avacopan 30 mg was numerically superior to placebo and avacopan 10 mg in early remission (15%, 8%, and 20% for SOC only, avacopan 10 mg, and avacopan 30 mg, respectively), improved eGFR (+2.0 ml/min/1.73m², +1.3 ml/min/1.73m², and +6.2 ml/min/1.73m², respectively), renal response (17%, 40%, and 63%, respectively), and measures of HRQoL.

Conclusion. Avacopan in addition to SOC for ANCA-associated vasculitis was well tolerated, and at the higher study dose, it appeared to improve time to remission (ClinicalTrials.gov identifier NCT02222155).

INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides are a group of related organ- and life-threatening,

systemic autoimmune diseases characterized by vessel inflammation and necrosis. Standard-of-care (SOC) therapy for moderate to severe ANCA-associated vasculitis consists of a combination of high-dose glucocorticoids and either cyclophosphamide or

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rituximab (1). These combinations have markedly improved management of ANCA-associated vasculitis, achieve high rates of treatment response, and improve survival (2,3) compared with historic experience. Treatment for ANCA-associated vasculitis is also associated with significant toxicity, especially because of glucocorticoids (4,5). Thus, there is a significant unmet need for safer options for inducing and maintaining remission in these patients.

There is evidence that activation of the alternative complement pathway, which acts principally through the proinflammatory C5a receptor (C5aR) on neutrophils, plays an important role in the pathogenesis of ANCA-associated vasculitis (6,7,8). Avacopan, an orally administered small-molecule antagonist of C5aR (9), is the focus of a clinical development program to evaluate avacopan as targeted therapy in patients with ANCA-associated vasculitis.

Avacopan's potential to reduce or eliminate the need for chronic dosing of glucocorticoids was demonstrated in the CLEAR study, a randomized, placebo-controlled, phase 2, 12-week study in 67 patients with ANCA-associated vasculitis. The CLEAR trial compared a standard prednisone dosing regimen with avacopan plus reduced-dose prednisone (20 mg) or avacopan without daily prednisone, with all given with either cyclophosphamide or rituximab. Treatment with avacopan was numerically superior and not statistically different from the prednisone-containing SOC control group in control of disease activity, and no significant differences were seen in frequency or severity of adverse events (AEs), suggesting that C5aR inhibition by avacopan may enable a significant reduction in prednisone dosing for the treatment of vasculitis (10).

Reported here are the results of a second phase 2 study, the CLASSIC (Clinical ANCA Vasculitis Safety and Efficacy Study of Inhibitor of C5aR) trial, which was conducted to provide an assessment of the safety and tolerability of avacopan when administered in addition to the current SOC. Assessments to further establish the impact of avacopan on clinical outcomes in patients with ANCA-associated vasculitis were also performed.

PATIENTS AND METHODS

Study design. CLASSIC was a phase 2, randomized, double-blind, placebo-controlled, three-arm study evaluating two doses of avacopan plus SOC versus SOC only in patients with ANCA-associated vasculitis. All patients received SOC treatment consisting of cyclophosphamide or rituximab plus standard oral glucocorticoids (Supplementary Figure S1). The study was conducted in accordance with the Declaration of Helsinki and all applicable regional or country-specific laws and regulations and in compliance with good clinical practice guidelines. Ethics committees and institutional review boards at each participating institution approved the protocol. All patients gave written informed consent. The CLASSIC trial was registered with Clinicaltrials.gov (identifier NCT02222155).

Patients. Patients were 18 years old or older with newly diagnosed (within 4 weeks of screening) or relapsing ANCA-associated vasculitis in which SOC treatment would be considered appropriate by the treating physician. Other eligibility criteria included each of the following: 1) clinical diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) per the 2012 Chapel Hill Consensus Conference definitions (11), 2) current or historical positive test for anti-myeloperoxidase (MPO) or anti-proteinase 3 (PR3)-ANCA, 3) an eGFR of 20 ml/min/1.73m² or greater according to the Modification of Diet in Renal Disease (MDRD) method (12), and 4) either one or more major items on the BVAS (version 3), or three or more non-major BVAS items, or two or more renal BVAS items at screening. Patients were not eligible if they had rapidly progressive glomerulonephritis anticipated to require renal replacement therapy within 7 days or alveolar hemorrhage leading to grade 3 or greater hypoxia (decreased oxygen saturation at rest [eg, pulse oximeter of less than 88% or partial pressure of arterial oxygen of 55 mm Hg or less]). Full eligibility criteria are provided in Supplementary Table S1.

Treatment. Patients were randomized through a central interactive web response system 1:1:1 to one of three treatment groups and treated for 12 weeks with the following: 1) placebo plus SOC (SOC only), 2) avacopan 10 mg orally twice daily plus SOC (avacopan-10), and 3) avacopan 30 mg orally twice daily plus SOC (avacopan-30). SOC consisted of 15 mg/kg intravenous (IV) cyclophosphamide on days 1, 15, 29, 57, and 85 or 375 mg/m² IV rituximab on days 1, 8, 15, and 22 (Supplementary Figure S1). All patients also received 60 mg/day oral prednisone, steadily tapering to 10 mg/day by week 11 and to 0 mg/day by week 20 (Supplementary Table S2). Avacopan or SOC only was administered for 84 days (12 weeks), followed by an additional 84-day (12-week) follow-up period without avacopan (SOC only). This analysis covers the initial 12-week period of the study. Per protocol, the blinding was maintained for all patients and personnel involved in the study until the end of study and database finalization.

For patients receiving cyclophosphamide, a maximum dose of 1.2 g was allowed per infusion; doses were reduced for any of the following reasons: age of 60 years or more, eGFR of less than 30 ml/min/1.73 m², and white blood cell count of 3.9×10⁹/L or less at the time of dosing or 3×10⁹/L or less between dosing. For patients receiving rituximab, premedication with acetaminophen, an antihistamine, and methylprednisolone (100 mg IV or equivalent) was recommended before each infusion.

Glucocorticoids were given as needed to patients with worsening disease. All patients received treatment to prevent *Pneumocystis jirovecii* pneumonia. Prophylactic treatment for osteoporosis, gastroprotection, and treatment-related nausea was given according to local practice.

Outcome assessments. Before randomization, patients were stratified in the following ways: 1) newly diagnosed or relapsing disease, 2) anti-MPO or anti-PR3-ANCA, and 3) choice of cyclophosphamide or rituximab.

The primary endpoint was the incidence of AEs. The main efficacy endpoint was the proportion of patients achieving disease response at day 85, which was defined as a 50% or greater reduction of BVAS (version 3) from baseline with no worsening in any body system component. The rate of achievement of a BVAS of 0 was also measured, as was early achievement of a BVAS of 0 at day 29 and sustained through day 85; both time points were prespecified in the protocol for analysis. For the day 29 BVAS assessment only, disease activity present within the 7 days before the visit was recorded. For all other study visits, the BVAS disease activity present within the 28 days prior to the visit was recorded. Other endpoints included incidence of infections, laboratory parameters, vital signs, VDI score, eGFR, renal response (defined below), hematuria (based on central laboratory microscopic count of urinary red blood cells [RBCs]), albuminuria (first morning urinary albumin:creatinine ratio [UACR]), and renal inflammatory activity based on urinary monocyte chemoattractant protein-1 [MCP-1]:creatinine ratio and on serum C-reactive protein (CRP) level. Health-related quality of life (HRQoL) was measured by Short Form 36 version 2 (SF-36v2) and EuroQOL-5D-5L (EQ-5D-5L). The EQ-5D-5L visual analog score (VAS) is comprised of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) scored on a scale from 1–5, whereas weighted index scores are calculated based on mapped responses of VAS scores to country-specific index values. Renal responses among patients with renal vasculitis (who had hematuria or albuminuria at baseline determined secondary to ANCA-associated vasculitis) were defined as improvement in the following parameters of renal vasculitis: 1) increase from baseline to day 85 in eGFR (MDRD equation), 2) decrease from baseline to day 85 in hematuria (microscopic count of urinary RBCs), and 3) decrease from baseline to day 85 in albuminuria (first morning UACR). The BVAS and SF-36v2 were assessed on days 1, 29, and 85, whereas the VDI was assessed on days 1 and 85.

Statistical analysis. The safety population included all randomized patients who received at least one dose of study medication (avacopan). The modified intent-to-treat (ITT) population consisted of all randomized patients who received at least one dose of study medication and had at least one postbaseline, on-treatment BVAS assessment. The main efficacy analysis was conducted in the modified ITT population.

Because this study was primarily a safety study, efficacy results are descriptive, and neither safety nor efficacy outcomes were powered statistically. Data were summarized overall and by treatment group. For continuous variables, summary statistics included the sample size, mean, median, SD, standard error of the mean, minimum, and maximum. Continuous variables with

skewed distributions were log-transformed for analysis, including UACR and urinary RBCs. Because of the relatively small sample size, no inferential statistical analysis was performed on BVAS response.

RESULTS

Patients. From February 4, 2015, to July 19, 2016, 42 patients with ANCA-associated vasculitis were enrolled at 15 sites in the United States and Canada (Supplementary Figure S2). In total, 13 patients were randomized to receive SOC only, 13 to receive avacopan-10, and 16 to receive avacopan-30 (Supplementary Figure S2). Mean age was similar across the treatment groups at study entry, 55% of patients were female, and 91% were Caucasian (Table 1). Twenty-nine (69%) patients had a diagnosis of GPA, and half of the patients had ANCA serology positive for anti-PR3. Twenty-seven (64%) patients had renal involvement, and 27 patients (64%) had newly diagnosed disease. At screening, the mean BVAS was 15.3 and the mean eGFR was 59.4 ml/min/1.73m².

Baseline characteristics were balanced across treatment arms, with the exception of a greater proportion of female patients, Caucasian patients, and patients with higher VDI scores receiving SOC only. Thirty-nine (93%) patients received rituximab as part of SOC treatment in this study.

Safety. During the 84-day treatment period, the overall rates of AEs appeared similar across all treatment arms. In the SOC-only treatment arm, 100% of patients experienced at least one treatment-emergent AE, compared with 85% and 94% in the avacopan-10 and avacopan-30 treatment arms, respectively (Table 2). The most commonly reported AE in both the SOC-only arm and the combined avacopan plus SOC group was hypertension (31% and 21%, respectively). For patients receiving SOC only, other common AEs included fatigue (23%), scab (15%), weight increase (15%), headache (15%), fall (15%), epistaxis (15%), and paranasal sinus discomfort (15%), with the latter two likely related to underlying disease. In the combined avacopan plus SOC treatment group, other common AEs included peripheral edema (14%), ecchymosis (10%), nausea (10%), infusion-related reaction (10%), and insomnia (10%). The majority of AEs (74%) were mild or moderate in severity across treatment groups.

Across treatments, mean neutrophil counts decreased $\sim 2\text{--}3 \times 10^9/\text{L}$ from baseline to day 85. Two patients (6.9%) experienced neutropenia (one at each dose of avacopan).

Infections occurred in two (15%) patients receiving SOC only and in seven (24%) patients in the combined avacopan plus SOC group (not statistically different). No type of infection occurred in more than one patient receiving any treatment. Seven infections that were considered possibly related to study medication occurred among 4 patients. In the SOC-only treatment arm, one patient had viral gastroenteritis and herpes zoster; in the

Table 1. Demographics and baseline characteristics of study patients

Characteristic	Placebo + SOC (n = 13)	10 mg Avacopan + SOC (n = 13)	30 mg Avacopan + SOC (n = 16)	All Patients (n = 42)
Age, mean (SD), y	58.5 (15.4)	60.0 (10.2)	55.3 (13.8)	57.7 (13.2)
Sex, n (%)				
Male	4 (31)	8 (62)	7 (44)	19 (45)
Female	9 (69)	5 (38)	9 (56)	23 (55)
Race, n (%)				
White	13 (100)	11 (85)	14 (88)	38 (91)
Black	0	2 (15)	1 (6)	3 (7)
Other	0	0	1 (6)	1 (2)
Type of ANCA-associated vasculitis, n (%)				
Granulomatosis with polyangiitis	9 (69)	8 (62)	12 (75)	29 (69)
Microscopic polyangiitis	4 (31)	5 (38)	4 (25)	11 (26)
ANCA-associated vasculitis disease status, n (%)				
Newly diagnosed	8 (62)	10 (77)	9 (56)	27 (64)
Relapsing	5 (38)	3 (23)	7 (44)	15 (36)
Renal involvement at baseline, n (%)	9 (69)	8 (62)	10 (63)	27 (64)
Duration of ANCA-associated vasculitis, median (range), mo	1.0 (0-95)	1.0 (0-347)	2.5 (0-170)	1 (0-347)
ANCA type, n (%)				
Anti-MPO	7 (54)	6 (46)	8 (50)	21 (50)
Anti-PR3	6 (46)	7 (54)	8 (50)	21 (50)
Background treatment, n (%)				
Rituximab	12 (92)	13 (100)	14 (88)	39 (93)
Cyclophosphamide	1 (8)	0	2 (13)	3 (7)
Disease assessment scores, mean (SD)				
BVAS	15.0 (4.5)	15.8 (2.5)	15.1 (1.6)	15.3 (6.6)
VDI score	1.2 (1.8)	0.8 (2.5)	0.6 (1.2)	0.8 (1.8)
Renal assessments				
eGFR, mean (SD), ml/min/1.73 m ²	60.1 (24.3)	56.4 (26.8)	61.4 (7.8)	59.4 (27.2)
Albumin:creatinine ratio, GMR (range), mg/g	n = 12; 135.4 (7-3262)	n = 13; 76.1 (3-1771)	n = 16; 111.9 (4-5540)	n = 41; 104.7 (3-5540)
Urinary MCP-1:creatinine ratio, GMR (range), pg/mg creatinine	n = 11; 651.7 (163-7291)	n = 11; 499.0 (103-3466)	n = 16; 463.5 (98-2693)	n = 38; 522.6 (98-7291)
Urinary RBCs per hpf, n (%)				
30-49	1 (8)	1 (8)	1 (6)	3 (7)
50-75	1 (8)	1 (8)	0	2 (5)
>75	0	0	0	0

ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio; MCP-1, monocyte chemoattractant protein-1; MPO, myeloperoxidase; PR3, proteinase 3; RBC, red blood cell; hpf, high-powered field; SOC, standard of care; VDI, Vasculitis Damage Index.

avacopan-10 treatment group, one patient had abscesses of the left thigh and perirectal region; and in the avacopan-30 treatment group, one patient had oral candidiasis, one patient had sepsis, and one patient had urinary tract infection.

The frequency of serious AEs (SAEs) was similar across the treatment groups. Two patients (15%) receiving SOC only had SAEs, with one patient, who was also receiving dapsone, having methemoglobinemia and one patient having gangrene. Five patients (17%) in the combined avacopan plus SOC groups had SAEs, including neutropenia, staphylococcal cellulitis, atrial fibrillation, sepsis (in a patient with biliary stricture and history of sepsis), and urinary tract infection. No patients died during the study.

Two patients (15%) in the SOC-only arm discontinued treatment because of adverse events of maculopapular rash (nonserious) and gangrene (serious). Four (14%) patients in the combined avacopan plus SOC groups discontinued treatment because of SAEs of limb and perirectal abscesses in the avacopan-10 arm,

atrial fibrillation and sepsis in the avacopan-30 arm, and a nonserious event of pain in the avacopan-30 arm.

Vasculitis endpoints. As expected with the use of SOC therapy by all patients in this study, response rates were high across all treatment groups. A similar proportion of patients achieved clinical responses in each arm, as follows: 85% (11/13) SOC-only arm versus 92% (11/12) avacopan-10 arm versus 80% (12/15) avacopan-30 arm (Table 3). The mean percentage decrease in BVAS from baseline was also similar between arms (−82% versus −96% versus −82%, respectively). Individual patient BVAS response appeared to be more consistent in the two avacopan arms compared with the SOC-only arm (Figure 1). The proportion of patients who achieved a BVAS of 0 by day 85 was 54% (7/13) in the SOC-only group, 67% (8/12) in the avacopan-10 group, and 47% (7/15) in the avacopan-30 group. The number of patients with early BVASs of 0 was 2/13 (15%) in the SOC-only

Table 2. Adverse events occurring in >10% of patients in any treatment group during the 84-day treatment period

	Placebo + SOC (n = 13)	10 mg Avacopan + SOC (n = 13)	30 mg Avacopan + SOC (n = 16)	Combined Avacopan (n = 29)
Any adverse event	13 (100)	11 (85)	15 (94)	26 (90)
Hypertension	4 (31)	2 (15)	4 (25)	6 (21)
Edema peripheral	0 (0)	1 (8)	3 (19)	4 (14)
Ecchymosis	1 (8)	1 (8)	2 (13)	3 (10)
Infusion-related reaction	0 (0)	2 (15)	1 (6)	3 (10)
Insomnia	0 (0)	1 (8)	2 (13)	3 (10)
Nausea	1 (8)	2 (15)	1 (6)	3 (10)
Back pain	1 (8)	0 (0)	2 (13)	2 (7)
Oropharyngeal pain	1 (8)	0 (0)	2 (13)	2 (7)
Arthralgia	0 (0)	0 (0)	2 (13)	2 (7)
Blood creatinine increased	0 (0)	0 (0)	2 (13)	2 (7)
Diarrhea	0 (0)	0 (0)	2 (13)	2 (7)
Dizziness	0 (0)	0 (0)	2 (13)	2 (7)
Fall	2 (15)	1 (8)	1 (6)	2 (7)
Fatigue	3 (23)	1 (8)	1 (6)	2 (7)
Flatulence	0 (0)	0 (0)	2 (13)	2 (7)
Headache	2 (15)	0 (0)	2 (13)	2 (7)
Myalgia	0 (0)	0 (0)	2 (13)	2 (7)
Tachycardia	0 (0)	0 (0)	2 (13)	2 (7)
Epistaxis	2 (15)	0 (0)	0 (0)	0 (0)
Paranasal sinus discomfort	2 (15)	0 (0)	0 (0)	0 (0)
Scab	2 (15)	0 (0)	0 (0)	0 (0)
Weight increased	2 (15)	0 (0)	0 (0)	0 (0)

SOC, standard of care.

Data are presented as n (%).

group, 1/12 (8%) in the avacopan-10 group, and 3/15 (20%) in the avacopan-30 group (Table 3).

The avacopan treatment response was similar between subgroups by disease status (newly diagnosed or relapsed), ANCA type (anti-MPO or anti-PR3), type of ANCA-associated vasculitis (MPA or GPA), background SOC treatment (cyclophosphamide or rituximab), and among those with or without renal involvement at baseline (Table 3).

Patients in this study initiated oral prednisone on day 1 at 60 mg per day, and this dose was tapered down to 0 mg by day 141. No patients received rescue glucocorticoids during the study. Median doses of study-supplied prednisone and total systemic glucocorticoids (including study-supplied prednisone, new glucocorticoid, and maintenance glucocorticoid) did not differ between treatment groups.

Cumulative vasculitis damage, based on the VDI, appeared to be lower with the addition of avacopan to the SOC, suggesting improved disease control. Mean VDI scores increased in all treatment arms from baseline to day 85, but the rate and magnitude of change was numerally higher in the SOC-only treatment arm than in the avacopan-10 or avacopan-30 treatment arms (0.31 versus 0.09 versus 0.14, respectively) (Table 3).

Renal endpoints. Among patients with renal vasculitis at study entry, eGFR improved in all treatment groups, with the highest degree of improvement in the avacopan-30 arm compared with the SOC-only and avacopan-10 arms (increases of

2.0, 1.3, and 6.2 ml/min/1.73m² for placebo, avacopan-10, and avacopan-30, respectively; Figure 2 and Table 4). These improvements occurred early, reaching significance in a post hoc analysis ($P < 0.05$) by week 4 in the avacopan-30 arm compared with the placebo control arm.

Albuminuria improved in all three treatment groups based on decreasing geometric mean ratios (GMRs) of first morning UACR at day 85 (Table 4). In patients with hematuria at baseline, the GMR of urinary RBC count decreased more than 90% in all three arms at day 85. The improvement appeared to occur more rapidly in the avacopan arms, based on day 8 GMR showing greater magnitudes of decrease in the avacopan arms (Table 4).

Among patients with both hematuria and albuminuria at baseline, renal responses were achieved in 17% (1/6) patients in the SOC-only arm, 40% (2/5) patients in the avacopan-10 arm, 63% (5/8) patients in the avacopan-30 arm, and 54% (7/13) in the combined avacopan plus SOC arms versus the SOC-only arm (post hoc analysis, $P = 0.0353$), with $P = 0.0227$ for avacopan-30 arm versus the SOC-only arm (Table 4).

High levels of the renal inflammatory marker urinary MCP-1:creatinine ratio correlate with poorer outcomes in patients with active renal vasculitis and other renal diseases (13–15). The onset of MCP-1 level decrease appeared to be more pronounced in the avacopan-30 group compared with the other two treatment groups based on greater mean change from baseline on day-15 measurements of first morning urinary MCP-1:creatinine

Table 3. Clinical responses in intent-to-treat population

	Placebo+ SOC (n = 13)	10 mg Avacopan+ SOC (n = 12)	30 mg Avacopan+ SOC (n = 15)
BVAS-based outcomes in the ITT population			
Response at week 12 ^a	11 (85)	11 (92)	12 (80)
Mean decrease in BVAS from baseline, %	82	96	82
Early disease remission ^b	2 (15)	1 (8)	3 (20)
Remission at week 12 ^c	7 (54)	8 (67)	7 (47)
Response by subgroup			
Disease status			
Newly diagnosed	6/8 (75)	8/9 (89)	6/8 (75)
Relapsed	5/5 (100)	3/3 (100)	6/7 (86)
ANCA status			
MPO-positive	6/7 (86)	5/6 (83)	6/8 (75)
PR3-positive	5/6 (83)	6/6 (100)	6/7 (86)
Type of ANCA-associated vasculitis			
GPA	7/9 (78)	7/7 (100)	8/11 (73)
MPA	3/3 (100)	3/4 (75)	4/4 (100)
Background treatment			
Cyclophosphamide	1/1 (100)	0/0 (0)	2/2 (100)
Rituximab	10/12 (83)	11/12 (92)	10/13 (77)
Disease location			
Renal involvement at baseline	7/9 (78)	7/8 (88)	8/10 (80)
No renal involvement at baseline	4/4 (100)	4/4 (100)	4/5 (80)
Vascular Damage Index			
Day 85	1.46	1.0	0.86
Mean increase from baseline	0.31	0.09	0.14

ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; GPA, granulomatosis with polyangiitis; ITT, intent-to-treat; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; SOC, standard of care.

Data presented as n (%) unless otherwise noted.

^a Defined as BVAS decrease of at least 50% from baseline and no worsening in any body system component at day 85.

^b Defined as BVAS = 0 at day 29 and sustained at day 85.

^c Defined as BVAS = 0 at day 85.

ratio (Table 4). Similarly, improvement in serum CRP levels also appeared to occur more rapidly in patients receiving avacopan, particularly those receiving avacopan-30, compared with those receiving SOC only based on a greater mean change from baseline on day-15 measurements (Table 4). Serum CRP levels continued to decrease with avacopan treatment over time in contrast to an increase observed in the SOC-only arm relative to baseline on day 85 (Table 4).

Assessment of HRQoL. Based on the SF-36v2, patients who received avacopan showed improvements in a variety of aspects of self-perception of health status compared with patients who received SOC only. Patients who received avacopan showed improvement in bodily pain, vitality, mental health, physical functioning, and emotional role that was evident as early as 4 weeks (day 29) after starting avacopan (Supplementary Figures S3 and S4). Compared with patients who received SOC only, patients receiving avacopan appeared to feel a greater improvement in their health relative to 1 year prior based on the Reported Health Transition aspect of the instrument (Supplementary Table S3).

Similarly, EQ-5D-5L-VAS scores and health scale index values increased in all treatment groups. VAS scores increased

the most in the avacopan-30 arm (44.1% in the SOC-only arm versus 39.7% in the avacopan-10 arm versus 61.4% in the avacopan-30 arm). Health scale index values increased 6.4% with SOC only, 9.6% with avacopan-10, and 7.2% with avacopan-30 (Supplementary Table S4).

DISCUSSION

The potential of C5aR antagonism as a therapeutic option for vasculitis, with the added potential to markedly reduce or eliminate chronic glucocorticoid use, was previously evaluated in a clinical study of avacopan in patients with ANCA-associated vasculitis (10), which yielded promising safety and efficacy findings. The present study was conducted to further establish the safety and tolerability profile of avacopan when added to SOC therapy. Although considered primarily a safety study, with efficacy and HRQoL as secondary objectives, the current study found that the addition of avacopan (10 mg or 30 mg) appeared to be well tolerated, neither increasing the rate of AEs compared with placebo in patients with newly diagnosed or relapsing severe ANCA-associated vasculitis. Response rates remained high with the addition of avacopan, with no differences seen between treat-

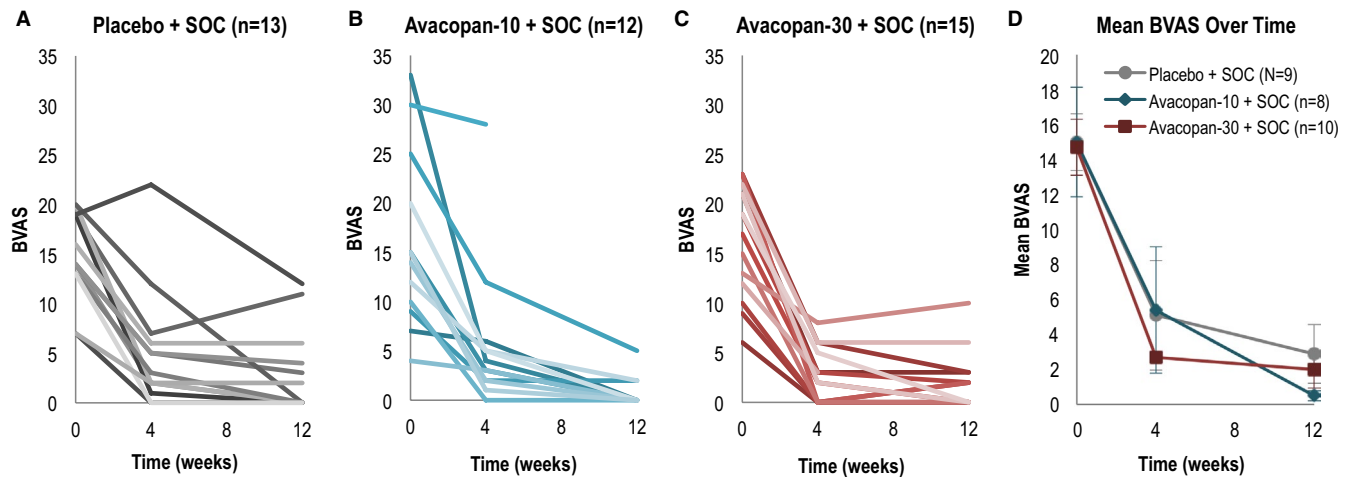


Figure 1. BVAS over time in patients receiving **A** placebo + SOC, **B** avacopan 10 mg twice-daily + SOC, and **C** avacopan 30 mg twice-daily + SOC, **D** Mean BVAS \pm SEM by treatment group. BVAS, Birmingham Vasculitis Activity Score; SOC, standard of care; SEM, standard error of the mean. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

ment arms. Interestingly, consistent with findings from the CLEAR study (10), the addition of avacopan (particularly at the 30-mg dose) appeared to improve several vasculitis endpoints, including early remission and renal outcomes, to reduce cumulative organ damage, and to improve patient HRQoL.

Patients with severe ANCA-associated vasculitis frequently have complications because of organ damage and are at risk of infections and other complications associated with immunosuppressive medications such as glucocorticoids, cyclophosphamide, and rituximab (4). In the present study, recognizing the small sample size, there were no apparent major differences in

the incidence of AEs among the treatment groups, with the maximum severity being mild or moderate for the majority of patients. The study discontinuation rate because of AEs was also similar between the combined avacopan group (14%) and placebo group (15%). These rates are similar to those observed in the randomized controlled Rituximab in ANCA-Associated Vasculitis study that compared rituximab-based and cyclophosphamide-based treatments plus glucocorticoids (14% and 17%, respectively), regimens that are comparable to the SOC used in this study (16). No deaths occurred in the current study, and the overall rate of SAEs was similar for SOC-only therapy and avacopan added to SOC

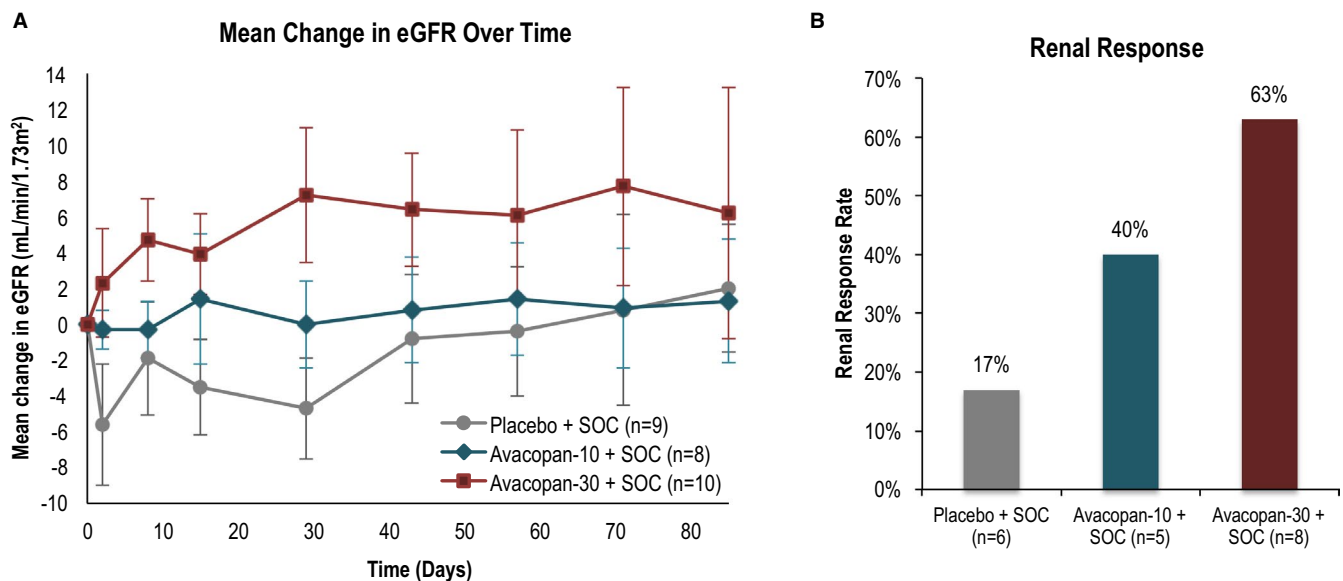


Figure 2. Renal endpoints. **A** Mean change \pm SEM in eGFR over time in patients with renal vasculitis according to treatment group. **B** Renal response rate according to treatment group. Renal response was defined as follows: (1) Increase from baseline to day 85 in eGFR (MDRD equation), (2) decrease from baseline to day 85 in hematuria (microscopic count of urinary red blood cells), and (3) decrease from baseline to day 85 in albuminuria (first morning urinary albumin:creatinine ratio). eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SEM, standard error of the mean; SOC, standard of care. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

Table 4. Renal outcomes

	Placebo + SOC	10 mg Avacopan + SOC	30 mg Avacopan + SOC
eGFR (MDRD) baseline ^a , ml/min/1.73 m ²	n = 9	n = 8	n = 10
Day 85	59.2	49.1	64.0
Change from baseline, mean (%)	2.0 (10.2)	1.3 (15.4)	6.2 (4.4)
Renal response, n (%)	1 (17)	2 (40)	5 (63) ^b
Urinary albumin:creatinine ratio ^c	n = 9	n = 8	n = 10
GMR, day 85/baseline	0.27	0.49	0.32
Mean change from baseline, %	-73	-51	-68
Urinary RBC ^d	n = 7	n = 5	n = 8
GMR, day 8/baseline	0.76 ^e	0.20	0.16
Mean change from baseline, %	-24	-80	-84
GMR, day 85/baseline	0.08	0.06	0.03
Mean change from baseline, %	-92	-94	-97
Urinary MCP-1:creatinine ratio	n = 11	n = 9	n = 14
GMR, day 15/baseline	0.92	0.80 ^e	0.72
Mean change from baseline, %	-8	-20	-28
GMR, day 85/baseline	0.51	0.50	0.78
Mean change from baseline, %	-49	-50	-22
Serum CRP	n = 13	n = 12	n = 15
GMR, day 15/baseline	0.82 ^e	0.63	0.46
Mean change from baseline, %	-18	-37	-54
GMR, day 85/baseline	1.41	0.42	0.97
Mean change from baseline, %	41	-3	-33

ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio; MCP-1, monocyte chemoattractant protein-1; MDRD, Modifications of Diet in Renal Disease; RBC, red blood cell; SOC, standard of care.

^a In patients with renal ANCA-associated vasculitis.

^b In post hoc analysis, $P=0.0227$ versus placebo + SOC group; $P=0.0353$ for comparison of all avacopan versus placebo + SOC.

^c In patients with albuminuria at baseline.

^d In patients with hematuria at baseline.

^e One patient not evaluable.

(15% and 17%, respectively), which is also similar to the 17% rate observed with SOC in the CLEAR study (10). Collectively, these data suggest that avacopan does not appear to increase the rate of AEs or their severity level when added to SOC.

As anticipated with the use of cyclophosphamide or rituximab together with high-dose glucocorticoids, most SAEs were infections, with similar rates occurring across all treatment arms. No specific infection event was reported in more than one patient in any treatment arm. These observations are encouraging when considering the hypothetical risk of infection associated with other complement inhibitors, such as eculizumab, which blocks the formation of the membrane attack complex. In contrast, C5aR inhibition with avacopan does not compromise the innate immune system's ability to generate the membrane attack complex (17), which plays an important role in defense against pathogenic bacteria such as *Neisseria meningitidis* (18).

This study, collectively with findings from the CLEAR study, offers insights about the potential impact of avacopan for the treatment of ANCA-associated vasculitis based on improvement in overall disease activity, renal parameters, and HRQoL. Although the CLEAR study was designed to evaluate glucocorticoid-sparing potential of avacopan, the present study was a follow-up

study designed specifically to evaluate the safety of avacopan in patients receiving SOC.

The potential clinical benefit of avacopan was further supported in this study by dose-dependent effects seen in several of the outcomes, with the 30-mg dose of avacopan appearing to confer the greatest benefit. Early disease remission, renal responses in patients with hematuria and albuminuria, and renal function (eGFR) were all highest in the avacopan-30 group compared with the avacopan-10 and SOC-only groups. These observations were evident in patients who had renal disease at baseline, in whom a significant improvement in eGFR in the avacopan-30 arm appeared to occur more quickly by day 29 compared with the SOC-only arm. Additionally, both urinary MCP-1 (a renal inflammatory marker that correlates with poorer outcomes) and serum CRP also improved more quickly with avacopan-30. Collectively, these data suggest that avacopan may provide additional benefit when added to SOC, and when considering all available data to date, 30 mg avacopan twice daily appears to be the optimal dose based on the various clinical outcomes measures in this study.

Interestingly, the assessments of HRQoL showed that the addition of avacopan to SOC led to broad improvements in

various aspects of well-being, including bodily pain, vitality, mental health, physical functioning, and emotional role. Findings from the current study suggest that the clinical benefits derived from avacopan underlie the observed improvement in HRQoL relative to that seen with SOC alone.

This study has important limitations to consider. First, the study had a relatively small sample size and was not powered to detect differences between avacopan or SOC-only arms, among subgroups of patients such as those with newly diagnosed versus relapsed disease status, or on the basis of characteristics such as ANCA type. Second, the 12-week treatment duration does not allow the evaluation of the long-term effects of avacopan. Third, a minority of patients received a cyclophosphamide-based regimen. However, based on results of the CLEAR study, in which a cyclophosphamide-based regimen was used in the majority of patients, avacopan appeared to be well tolerated and showed clinical activity when administered with either rituximab or cyclophosphamide.

Finally, it is important to note that all patients in the CLASSIC study were given what is considered a standard dose of glucocorticoids. Avacopan is not intended to be an add-on therapy, but rather one that reduces risk of AEs by reducing or eliminating the need for glucocorticoids. As such, approval of avacopan-based regimens is expected to be based on demonstration of noninferiority to SOC combined with improving safety and tolerability of reduced exposure to glucocorticoids (19).

In summary, treatment with avacopan did not appear to exacerbate the toxicities of SOC treatment. The addition of avacopan, particularly the 30-mg twice daily dose, appeared to improve the clinical activity of the SOC and improve HRQoL. Based on these observations and those of the CLEAR study, avacopan may have an important role in the treatment of patients with severe ANCA-associated vasculitis. A phase 3 study of 12 months' duration evaluating avacopan in the absence of high-dose glucocorticoid versus the standard high-dose glucocorticoid SOC regimen in patients with ANCA-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine has been completed (NCT02994927; 19).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Merkel, Schall, Bekker.

Acquisition of data. Merkel, Niles, Jimenez, Spiera, Rovin, Bomback, Pagnoux, Potarca, Shall, Bekker.

Analysis and interpretation of data. Merkel, Schall, Bekker.

ROLE OF THE STUDY SPONSOR

ChemoCentryx, Inc. was directly involved in the design of this study, the collection, analysis, and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. Publication of this article was contingent upon approval by ChemoCentryx, Inc., in collaboration with the other authors.

REFERENCES

1. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis [published erratum appears in *Ann Rheum Dis* 2017;76:1480]. *Ann Rheum Dis* 2016;75:1583–94.
2. Bajema IM, Bruijn JA, Casian A, Cid MC, Csernok E, van Daalen E, et al. The European Vasculitis Society 2016 Meeting Report. *Kidney Int Rep* 2017;2:1018–31.
3. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488–94.
4. King C, Harper L. Avoidance of harm from treatment for ANCA-associated vasculitis. *Curr Treatm Opt Rheumatol* 2017;3:230–43.
5. Little MA, Nightingale P, Verburgh CA, Hauser T, de Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2010;69:1036–43.
6. Jennette JC, Xiao H, Hu P. Complement in ANCA-associated vasculitis. *Semin Nephrol* 2013;33:557–64.
7. Schreiber A, Xiao H, Jennette JC, Schneider W, Luft FC, Kettritz R. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J Am Soc Nephrol* 2009;20:289–98.
8. 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.
9. Bekker P, Dairaghi D, Seitz L, Leleti M, Wang Y, Ertl L, et al. Characterization of pharmacologic and pharmacokinetic properties of CCX168, a potent and selective orally administered complement 5a receptor inhibitor, based on preclinical valuation and randomized phase 1 clinical study. *PLoS One* 2016;11:e0164646.
10. Jayne DR, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 2017;28:2756–67.
11. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461–70.
13. Kim MJ, Tam FW. Urinary monocyte chemoattractant protein-1 in renal disease. *Clin Chim Acta* 2011;412:2022–30.
14. Liu S, Li N, Zhu Q, Zhu B, Wu T, Wang G, et al. Increased serum MCP-1 levels in systemic vasculitis patients with renal involvement. *J Interferon Cytokine Res* 2018;38:406–12.
15. Haller H, Bertram A, Nadrowitz F, Menne J. Monocyte chemoattractant protein-1 and the kidney. *Curr Opin Nephrol Hypertens* 2016;25:42–9.

16. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221–32.
17. Bunch DO, Deng J, McInnis EA, Bekker P, Hillson JL, Schall TJ, et al. Effect of a selective c5ar antagonist, avacopan (CCX168), on plasma complement levels in anca associated vasculitis (AAV). *Ann Rheum Dis* 2018;77(Suppl 2):OP0046.
18. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991;4:359–95.
19. 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:e16664.

Appendix A

CLASSIC collaborators in addition to the authors are as follows: Louis-Philippe Girard, Yih Chang Chen Lin, Galina Marder, Jennifer Murphy, William Shergy, Christopher Charles Striebich, Areena Swarup, and James Tumlin.