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Safety of Avacopan for the Treatment of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: Combined Data From Three Clinical Trials

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Objective. This study aimed to report the safety of avacopan, an oral selective complement C5a receptor antagonist, using pooled data from clinical trials in patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA]).

Methods. Data were included from two phase 2 (CLEAR [NCT01363388] and CLASSIC [NCT02222155]) and one phase 3 (ADVOCATE [NCT02994927]) double-blind randomized controlled trials comparing the safety and efficacy of avacopan with active non-avacopan control regimens to induce remission in patients with GPA or MPA. In CLEAR and ADVOCATE, avacopan-treated patients received either no or lower doses of study-supplied prednisone than the control groups; in CLASSIC, all groups received the same dose of study-supplied prednisone. Assessments included rates of exposure-adjusted adverse events (AEs), serious AEs (SAEs), and AEs of special interest.

Results. Overall, 439 patients with GPA or MPA (avacopan: n = 239; non-avacopan: n = 200) were included. The exposure-adjusted rates of AEs, SAEs, white blood cell (WBC) count reductions, and infections were lower with avacopan versus control (between-group differences in rate per 100 patient-years −151.9 [95% confidence interval (CI) −218.6 to −85.3], −20.8 [95% CI −38.3 to −3.3], −11.6 [95% CI −22.2 to −1.2], and −24.3 [95% CI −48.5 to −0.1], respectively). SAEs associated with hepatic function abnormalities occurred in 4.4% of the avacopan group and 2.8% of the control group.

Conclusion. In clinical trials of GPA or MPA, use of avacopan was associated with fewer AEs, SAEs, and WBC count reductions and fewer infections than non-avacopan treatment. Safety data support the use of avacopan in patients with GPA or MPA.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a complex, systemic, organ- or life-threatening relapsing autoimmune disorder characterized by inflammation of small- to medium-sized blood vessels affecting multiple organ systems.[1] AAV encompasses the three clinical syndromes of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis.[1]

The standard treatment for patients with new-onset or relapsing AAV involves the use of high-dose glucocorticoids with rituximab (RTX) or cyclophosphamide (CYC) to achieve and sustain remission, limit further organ damage, and reduce mortality rates.[1–3] Although effective, the toxic effects of these treatments can have a profound impact on patients with AAV, especially during the first year of treatment.[4–6] Adverse events (AEs) include short-term complications, such as hyperglycemia and infection (a major cause of early mortality in people with AAV[5–7]), and long-term complications, including hypogammaglobulinemia and infertility.[1,4,5,8–10] In some patients, the risk of AEs is increased by frequent relapses that necessitate the re-introduction of glucocorticoids and other immunosuppressive drugs.[11] The unmet

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Qualified researchers may request data from Amgen Clinical Trials. Complete details are available at: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/.

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need for treatment strategies for AAV that reduce the risk of AEs by reducing glucocorticoid exposure has led to multiple clinical trials.[11–17]

The alternative complement pathway is an important component of the pathogenesis underlying the autoimmune dysregulation associated with AAV.[18,19] Avacopan is a first-in-class, small molecule, selective C5a receptor antagonist.[20] Avacopan does not interfere with the formation of the terminal complement complex or the membrane attack complex, C5b-9, which is necessary for the clearance of pathogenic encapsulated bacteria, such as *Neisseria meningitidis*.[20–23] The phase 2 CLASSIC trial demonstrated that avacopan was well tolerated and improved time to remission when used as adjunctive therapy to standard care in patients with GPA and MPA.[15] In the phase 2 CLEAR trial[14] and the phase 3 ADVOCATE trial,[16] avacopan improved remission rates, sustained remission over time, and improved kidney function (albuminuria and/or estimated glomerular filtration rate) in patients with GPA and MPA treated with RTX or CYC and reduced glucocorticoid exposure. The aim of this integrated analysis was to evaluate the safety of avacopan using pooled data from the CLEAR, CLASSIC, and ADVOCATE trials.

PATIENTS AND METHODS

Trial designs. This integrated analysis includes data from patients with GPA or MPA treated with an avacopan or non-avacopan active control-based regimen in two phase 2 trials (CLEAR [NCT01363388[14]] and CLASSIC [NCT02222155[15]]) and one phase 3 trial (ADVOCATE [NCT02994927[16]]). Characteristics of these trials are published[14–16] and are summarized in Figure 1.

Briefly, CLEAR was a randomized, double-blind, placebo-controlled, phase 2 clinical trial designed to evaluate the safety and efficacy of avacopan in 67 patients with newly diagnosed or relapsing GPA or MPA from 11 countries in Europe.[14] Patients received CYC or RTX at doses consistent with the current standard of care and were randomized to receive one of the following treatments for 12 weeks: avacopan 30 mg twice daily (BID) with a prednisone placebo (n = 22), avacopan 30 mg BID with a prednisone taper starting at 20 mg/day (n = 22), or non-avacopan treatment (active control) with a prednisone taper starting at 60 mg/day (n = 23). Patients were observed for a further 12 weeks.

The randomized, double-blind, placebo-controlled, phase 2 CLASSIC trial evaluated the safety and efficacy of avacopan in addition to standard therapy in 42 patients with newly diagnosed or relapsing GPA or MPA in the United States or Canada.[15] Patients were randomized to receive either avacopan 30 mg BID (n = 16) or 10 mg BID (n = 13) as an add-on to standard therapy or standard therapy alone (n = 13) for 12 weeks with an additional 12 weeks of observation. Standard therapy consisted of a prednisone taper starting at 60 mg/day plus CYC or RTX.

ADVOCATE was a 52-week randomized, double-blind, double-dummy, active-controlled, phase 3 trial conducted in 331 patients with newly diagnosed or relapsing GPA or MPA in the United States, Canada, Europe, New Zealand, Australia, and Japan.[16] The study design was based on the findings from the two phase 2 trials.[14,15] Patients received oral avacopan 30 mg BID (n = 166) or oral prednisone on a tapering schedule (60 mg/day tapered to discontinuation by week 21; n = 165). Per protocol, open-label glucocorticoid treatment during the screening period was tapered to ≤20 mg of prednisone equivalent before the start of the trial and was further tapered to discontinuation by the end of week 4. All patients received RTX without maintenance therapy or CYC followed by azathioprine (AZA) or mycophenolate mofetil.

The total systemic glucocorticoid dose of study- and non–study-supplied glucocorticoids varied across trials. This was partly because of differences in the per-protocol dosing of glucocorticoids and partly because some patients received non–study-supplied glucocorticoids during the screening period, as premedication for RTX, as tapering doses during the study period to reduce the risk of adrenal crisis, and/or as short-term rescue therapy for flares of AAVGPA/MPA.

All three trials adhered to the tenets of the Declaration of Helsinki and were conducted in accordance with the International Conference on Harmonization E6 for Good Clinical Practice. Trial sites received institutional review board approval before trial initiation, and all patients (or a parent or guardian) provided written informed consent.

Efficacy outcomes. The primary efficacy endpoint for the CLEAR and CLASSIC trials was the proportion of patients achieving a ≥50% reduction in Birmingham Vasculitis Activity Score (BVAS) by week 12 and no worsening in any body system component (Figure 1).[14,15] For the ADVOCATE trial, the first primary endpoint was the proportion of patients achieving remission (BVAS 0) at week 26 with no use of glucocorticoid in the previous 4 weeks for the treatment of GPA/MPA, and the second primary endpoint was the proportion achieving sustained remission at week 52 with no use of glucocorticoid in the previous 4 weeks for the treatment of GPA/MPA.[16] Additional efficacy endpoints for each of the trials have been previously described.[14–16]

Safety outcomes. Safety outcomes for each of the three trials included AEs, serious AEs (SAEs), AEs leading to study drug discontinuation, hospitalizations, deaths, and AEs of special interest. AEs and SAEs were defined according to International Conference on Harmonization guidelines, and the reported AEs were assigned preferred terms using the Medical Dictionary for Regulatory Activities (version 19.1). AEs of special interest were identified as AEs related to hepatic abnormalities, infections, white blood cell (WBC) count reductions (neutropenia and/or lymphopenia), and hypersensitivity events, including angioedema. Hepatic abnormalities were identified by an abnormal liver function test result, the presence of a hepatobiliary disorder, and/or elevations

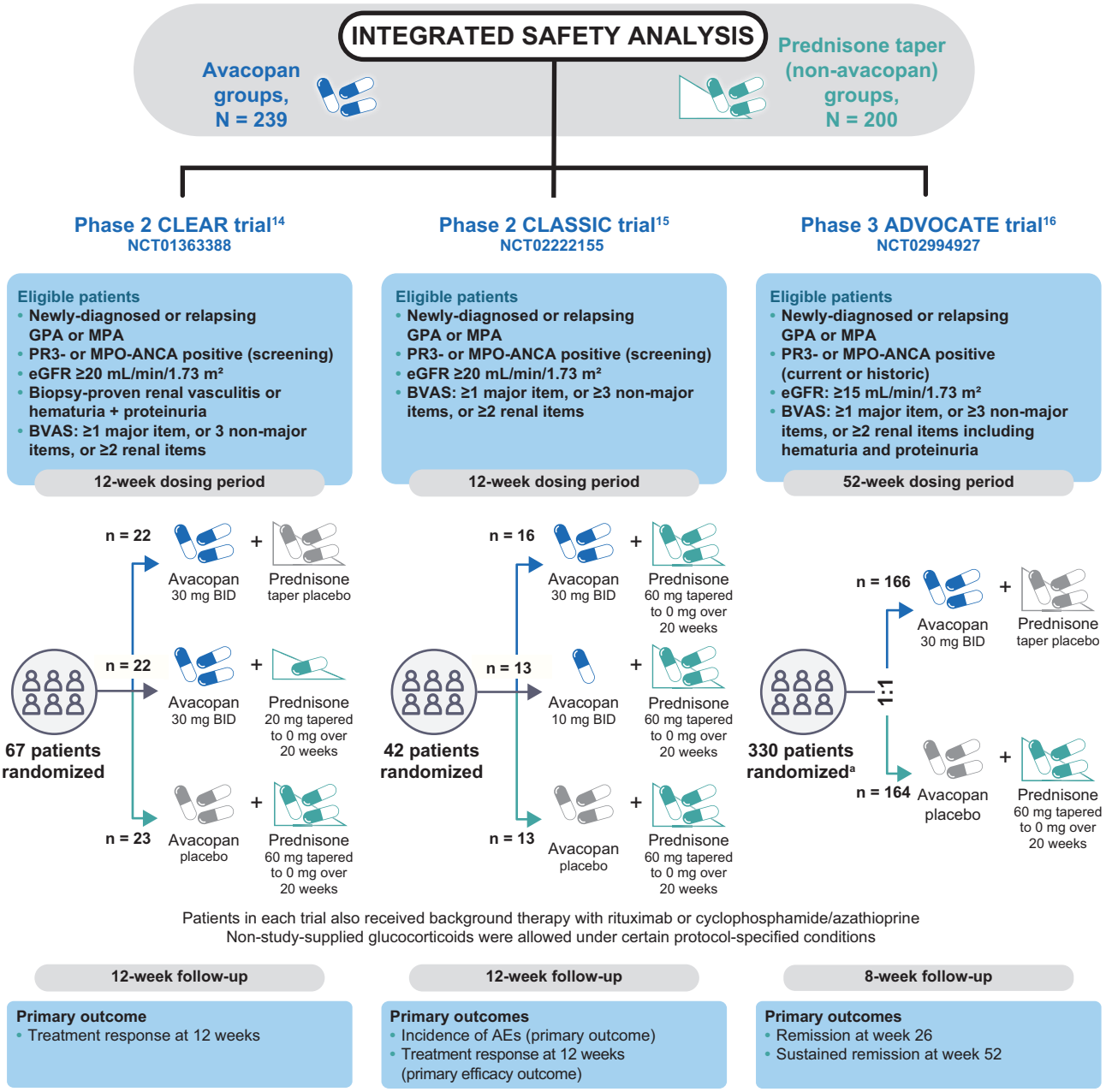

Figure 1. Study characteristics for the CLEAR,[14] CLASSIC,[15] and ADVOCATE[16] trials. [a]Excludes patients who were randomized but did not receive treatment. AE, adverse event; ANCA, antineutrophil cytoplasmic antibody; BID, twice daily; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3.

in liver enzymes above the normal range (6–41 U/L for alanine aminotransferase [ALT], 9–34 U/L for aspartate aminotransferase [AST], 37–116 U/L for alkaline phosphatase [ALP], and 0.1–1.1 mg/dL for bilirubin). Infections were identified using the AE System Organ Class (SOC) of "Infections and Infestations." Neutropenia and lymphopenia were defined as WBC counts below the normal range (1 to 8 × 10^3/μL for neutrophils and 1 to 5 × 10^3/μL for lymphocytes). Pre-existing conditions worsening during a trial were reported as AEs. For the phase 2 trials, AE summaries included all events in the 24-week study period (including the 12-week treatment period and the 12-week follow-up period).

Statistical analysis. Details of the sample size calculations and statistical analyses for each of the three trials are published.[14–16] Efficacy outcomes were analyzed for the intention-to-treat populations, defined as all patients with at least one post-baseline on-treatment BVAS assessment in the CLEAR

and CLASSIC trials and all randomized patients receiving at least one dose of study medication in the ADVOCATE trial. Safety data were analyzed for the safety populations, which included all patients receiving at least one dose of study medication.

Safety data for the phase 3 trial and the pooled phase 2 trials were summarized descriptively by treatment group, phase of the study, and overall. For continuous variables, numbers, means, medians, ranges, SDs, and SEMs were calculated. Categorical variables were described using frequency counts and percentages.

The integrated analyses of pooled safety data from the phase 2 and 3 trials were conducted according to the methodology outlined by the Pharmaceuticals User Software Exchange (https://phuse.global/Working_Groups). Exposure-adjusted event rates and exposure-adjusted first incidence rates of AEs and SAEs were presented as point estimates and 95% confidence intervals (CIs) for the between-group differences in rates per 100 patients. Exposure-adjusted event rates were calculated based on the total number of events experienced for each Medical Dictionary for Regulatory Activities–preferred term divided by the total duration of follow-up (on or off treatment) for all patients. Exposure-adjusted first incidence rates were calculated based on the number of patients with a specific event divided by the total time at risk (the time to the first event for patients who experienced the event and the time during the study for patients who did not experience the event).

RESULTS

Demographics and baseline characteristics. A total of 440 patients were randomized to treatment in the CLEAR, CLASSIC, and ADVOCATE trials.[14–16] Of these, 439 (239 receiving avacopan and 200 not receiving avacopan) were included in the safety population, and 1 (a patient in the ADVOCATE trial control group) was excluded after a renal biopsy failed to confirm the presence of vasculitis. Patient demographics and baseline characteristics for the pooled phase 2 trials, the phase 3 trial, and the pooled phase 2 and 3 trials are described in Table 1.

Exposure to glucocorticoids and avacopan. The total doses and durations of use of study- and non–study-supplied systemic glucocorticoids varied across the three trials (Table 2). In the combined trials, the total exposure to avacopan treatment was 212.3 patient-years, and the total exposure to the non-avacopan treatment regimen was 195.7 patient-years (Table 3).

Exposure-adjusted rates of adverse events. Exposure-adjusted rates of AEs (1,099.8 vs 1,251.7; difference –151.9 [95% CI –218.6 to –85.3]), infection (142.2 vs 166.6; –24.3 [95% CI –48.5 to –0.1]), and neutropenia/lymphopenia (22.6 vs 34.2; –11.6 [95% CI –22.0 to –1.2]) per 100 patient-years were significantly lower in the avacopan group than in the non-avacopan group (Table 3). Although not statistically significant, rates of first infection were slightly lower in the avacopan group (139.1 vs 148.5; difference –9.4 [95% CI –42.6 to 23.7]), whereas rates of AEs related to hepatic abnormalities (18.4 vs 17.4; 1.0 [95% CI –7.2 to 9.2]) and hypersensitivity reactions (68.8 vs 61.8; 6.9 [–8.7 to 22.6]) were slightly higher. The rates of AEs leading to study drug discontinuation (21.7 vs 21.5; 0.2 [95% CI –8.8 to 9.2]) were similar between treatment groups.

Exposure-adjusted rates of seroius adverse events. Although the exposure-adjusted rate of SAEs was lower in the avacopan group than in the non-avacopan group (70.7 vs 91.5; difference –20.8 [95% CI –38.3 to –3.3]), rates of first incidence SAEs were similar between treatments (61.6 vs 60.1; 1.5 [95% CI –16.5 to 19.6]) (Table 3). Overall, the exposure-adjusted rates of SAEs by SOC were similar for the phase 3 trial and the integrated phase 2 and 3 trials.

Serious adverse events related to hepatic abnormalities. Across the three trials, SAEs associated with hepatic abnormalities occurred in 4.4% of patients in the avacopan group versus 2.8% of patients in the non-avacopan group (difference 1.7 [95% CI –1.8 to 5.1]) (Table 4). Trial medication was interrupted or discontinued because of hepatic abnormalities in 7 of the 10 patients with liver-related SAEs in the avacopan group versus three of six patients in the non-avacopan group (all issues resolved). None of the patients with liver abnormalities met the Hy's law criteria for potentially fatal drug-induced liver injury (ALT or AST ≥3 times the upper limit of normal [ULN], total bilirubin ≥2 times the ULN, and ALP <2 times the ULN with no obvious cause[24]), with all patients having either confounding factors (other hepatotoxic drugs, viral etiology, or alcohol abuse), bilirubin levels within the normal range, and/or evidence of cholestasis. In the ADVOCATE trial, there was a higher incidence of grade 1 (ALP >1 to 2.5 times the ULN if baseline levels were normal or 2.0–2.5 times the baseline if baseline levels were abnormal) and grade 2 ALP elevation (>2.5 to 5.0 times the ULN or >2.5 to 5.0 times baseline, respectively) in the avacopan group compared with the non-avacopan group and a greater mean decrease in ALP in the non-avacopan versus the avacopan group over the first 20 weeks of the study. Grade 3 ALP elevations (ALP >5.0 to 20.0 times the ULN or >5.0 to 20.0 times the baseline) were observed in one patient in the non-avacopan group and none in the avacopan group.

Infection-related seroius adverse events. In the phase 3 ADVOCATE trial, 25 infection-related SAEs were reported in 22 patients (13.3%) in the avacopan group compared with 31 events in 25 patients (15.2%) in the non-avacopan group. In the phase 2 trials, 12 serious infections were reported by seven patients (9.6%) in the avacopan group, and four events were reported by three patients (8.3%) in the non-avacopan group. Three patients (0.7%) died because of infection across the three trials, with all three deaths occurring in the ADVOCATE trial (one in the avacopan group and two in the non-avacopan group).

Table 1. Demographics and baseline characteristics of patients with GPA and MPA treated with avacopan- versus non-avacopan-based regimens in the phase 2 CLEAR[14] and CLASSIC[15] trials and the phase 3 ADVOCATE[16] trial

Characteristic	Avacopan-based regimen		Non-avacopan-based regimen		Combined (3) trials (n = 439/440)
	Pooled phase 2 (n = 73)	Phase 3 (n = 166)	Pooled phase 2 (n = 36)	Phase 3 (n = 164/165)[a]	
Age at screening, mean (SD), y	57.5 (13.2)	61.2 (14.6)	59.2 (14.4)	60.6 (14.5)	60.2 (14.3)
Duration of AAV, mean (SD), mo	27.1 (60.0)	22.9 (52.5)	16.4 (34.4)	20.1 (40.5)	22.0 (48.3)
Male patients, n (%)	45 (61.6)	98 (59.0)	21 (58.3)	89 (53.9)	253 (57.5)
Race,[b] n (%)					
Asian	0	17 (10.2)	0	15 (9.1)	32 (7.3)
Black or African American	3 (4.1)	3 (1.8)	0	2 (1.2)	8 (1.8)
White	69 (94.5)	138 (83.1)	36 (100.0)	141 (85.5)	384 (87.3)
Other	1 (1.4)	8 (4.8)	0 (0.0)	7 (4.2)	16 (3.6)
Baseline eGFR, mean (SD), mL/min/1.73 m^2	CLEAR: 53.6 (23.2) CLASSIC: 59.1 (28.8)	44.6 (2.4)	CLEAR: 47.6 (15.1) CLASSIC: 60.1 (24.3)	45.6 (2.4)	52.5 (30.0)
Disease history, n (%)					
Newly diagnosed	50 (68.5)	115 (69.3)	26 (72.2)	114 (69.5)	305 (69.3)
Relapsed	23 (31.5)	51 (30.7)	10 (27.8)	50 (30.5)	134 (30.5)
Type of AAV, n (%)					
GPA	43 (58.9)	91 (54.8)	19 (52.8)	90 (54.9)	243 (55.4)
MPA	26 (35.6)	75 (45.2)	13 (36.1)	74 (45.1)	188 (42.8)
Renal limited vasculitis	4 (5.5)	0 (0.0)	3 (8.3)	0 (0.0)	7 (1.6)
Other	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.1)
ANCA type, n (%)					
Anti-MPO	39 (53.4)	94 (56.6)	17 (47.2)	94 (57.3)	244 (55.6)
Anti-PR3	33 (45.2)	72 (43.4)	17 (47.2)	70 (42.7)	192 (43.7)
Anti-MPO and anti-PR3	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.2)
ANCA equivocal	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
ANCA negative	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.2)
Prior medications, n (%)					
Cyclophosphamide	1 (1.4)	4 (2.4)	0	2 (1.2)	7 (1.6)
Rituximab	0	1 (0.5)	0	4 (2.4)	5 (1.1)
Other immunosuppressive drugs	14 (19.2)	26 (15.7)	4 (8.1)	26 (15.9)	70 (15.9)
Glucocorticoids	52 (71.2)	125 (75.3)	21 (58.3)	135 (82.3)	333 (75.9)
Induction treatment, n (%)					
Rituximab	37 (50.7)	107 (64.5)	15 (41.7)	107 (65.2)	266 (60.6)
Intravenous cyclophosphamide	36 (49.3)	51 (30.7)	21 (58.3)	51 (31.1)	159 (36.2)
Oral cyclophosphamide	0	8 (4.8)	0	6 (3.7)	14 (3.2)

Organ involvement, n (%)	Avacopan		Non-avacopan		Combined (2) trials (n = 398)
	Phase 2[c] (n = 44)	Phase 3 (n = 166)	Phase 2[c] (n = 23)	Phase 3 (n = 165)	
Pulmonary	15 (34.1)	71 (42.8)	9 (39.1)	71 (43.3)	166 (41.7)
Neurologic	7 (15.9)	38 (22.9)	3 (13.0)	31 (18.9)	79 (19.8)
Cardiovascular	3 (6.8)	6 (3.6)	0	3 (1.8)	12 (3.0)
Ear, nose, and throat	13 (29.5)	75 (45.2)	9 (39.1)	69 (42.1)	166 (41.7)
Mucous membranes and eye	5 (11.4)	26 (15.7)	1 (4.3)	40 (24.4)	72 (18.1)
Cutaneous	5 (11.4)	24 (14.5)	4 (17.4)	23 (14.0)	56 (14.1)
Kidney	42 (95.5)	134 (80.7)	23 (100.0)	134 (81.7)	333 (83.7)

AAV, antineutrophil cytoplasmic antibody–associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.
[a]n = 164 for age at screening, duration of AAV, male patients, race, baseline eGFR, and prior medications received. n = 165 for disease history, type of AAV, ANCA type, and induction treatment.
[b]Race was identified by the patient using a fixed set of categories.
[c]Organ involvement data are only provided for the CLEAR trial. Data are not available for the CLASSIC trial.

In the ADVOCATE trial, the most common infection-related SAE in both treatment groups was pneumonia (8 of 166 patients [4.8%] in the avacopan group versus 6 of 164 [3.7%] in the non-avacopan group). Infections in the avacopan group included pneumonia, sepsis, infective exacerbation of chronic obstructive pulmonary disease, *Campylobacter* gastroenteritis, and hepatitis B. The distribution of individual infections was similar during the first 20 weeks of the trial and from weeks 21 to 52. Six patients (3.6%) in the avacopan group and 11 (6.7%) in the non-avacopan group had serious opportunistic infections. No infections caused by *Neisseria meningitidis* have been observed in clinical trials with avacopan.

Neutropenia or lymphopenia. In the ADVOCATE trial, a lower proportion of patients in the avacopan group had serious neutropenia or lymphopenia compared with those in the non-

Table 2. Total systemic glucocorticoid dose and treatment duration in patients with granulomatosis with polyangiitis and microscopic polyangiitis treated with avacopan-based versus non-avacopan-based regimens in the CLEAR,[14] CLASSIC,[15] and ADVOCATE[16] trials (intention-to-treat populations)

	CLEAR			CLASSIC			ADVOCATE	
	84 days			84 days			12 months	
Treatment regimen group	Avacopan 30 mg BID (n = 21)	Avacopan + low-dose prednisone (n = 22)	Placebo + full-dose prednisone (n = 20)	Avacopan 30 mg BID + prednisone (n = 14)[a]	Avacopan 10 mg BID + prednisone (n = 12)	Non-avacopan + prednisone (n = 13)	Avacopan 30 mg BID (n = 166)	Non-avacopan + prednisone (n = 164)
Mean/median dose of study-supplied GCs, mg	0/0	701/721	2,092/2,100	2,015/2,093	1,900/2,050	2,109/2,090	0/0	2,389/2,448
Mean/median dose of GC received, mg	698[b]/500[b]	1,064/743	2,414/2,108	2,397/2,490	2,532/2,455	2,484/2,435	1,676/600	3,847/3,098

BID, twice daily; GC, glucocorticoid.
[a]Data from 14 of the 15 patients who took study-supplied prednisone during the designated study period.
[b]Seven patients used non–study-supplied GCs.

avacopan group (2.4% vs 4.9%). One case of neutropenic sepsis was reported on day 59 (neutrophil count 1.4 × 10^3/μL on day 50) in a patient in the avacopan group receiving oral CYC. The patient was treated with antibiotics and recovered without interruption of avacopan.

The distribution of individual WBC-related SAEs was similar throughout the ADVOCATE trial. The incidence of grade 3 lymphopenia (lymphocyte counts 0.2 to <0.5 × 10^3/μL) in the ADVOCATE trial was similar between treatment groups (28.3% in the avacopan group and 30.1% in the non-avacopan group),

Table 3. Exposure-adjusted adverse event/serious adverse event rates per 100 patient-years in patients with granulomatosis with polyangiitis and microscopic polyangiitis treated with avacopan-based versus non-avacopan-based regimens in the CLEAR,[14] CLASSIC,[15] and ADVOCATE[16] trials

Exposure-adjusted rate/100 patient-years	Avacopan (n = 239)	Non-avacopan (n = 200)	Difference in rate (95% CI)
Total exposure to avacopan/non-avacopan treatment, patient-years[a]	212.3	195.7	–
Overall AEs			
First incidence rate[b]	1,328.5	1,626.5	−298 (−583.0 to −13.0)
AE rate[c]	1,099.8	1,251.7	−151.9 (−218.6 to −85.3)[d]
Overall SAEs			
First incidence rate[b]	61.6	60.1	1.5 (−16.5 to 19.6)
SAE rate[c]	70.7	91.5	−20.8 (−38.3 to −3.3)[d]
Discontinuation of study medication owing to AEs			
First incidence rate[b]	18.2	18.0	0.2 (−8.4 to 8.9)
Event rate[c]	21.7	21.5	0.2 (−8.8 to 9.2)
Infections[e]			
First incidence rate[b]	139.1	148.5	−9.4 (−42.6 to 23.7)
AE rate[c]	142.2	166.6	−24.3 (−48.5 to −0.1)[d]
Hepatic function AEs[e]			
First incidence rate[b]	14.7	12.3	2.3 (−5.2 to 9.8)
AE rate[c]	18.4	17.4	1.0 (−7.2 to 9.2)
WBC count decrease AEs[e]			
First incidence rate[b]	18.9	25.0	−6.1 (−16.0 to 3.8)
AE rate[c]	22.6	34.2	−11.6 (−22.0 to −1.2)[d]
Hypersensitivity AEs[e]			
First incidence rate[b]	57.7	58.0	−0.3 (−18.1 to 17.5)
AE rate[c]	68.8	61.8	6.9 (−8.7 to 22.6)

AE, adverse event; CI, confidence interval; SAE, serious AE; WBC, white blood cell.
[a]Exposure is calculated as the follow-up time for all patients in the treatment group (irrespective of whether an event occurred).
[b]First incidence rate calculated as the number of patients with at least one event divided by the total follow-up time per 100 patient-years. Follow-up time is the total time at risk (in years), defined as the sum of (1) the follow-up time of patients who did not have an AE and (2) the time to first occurrence of the event in patients who had a treatment-emergent AE.
[c]The rate was calculated as the total number of events divided by real follow-up time per 100 patient-years; it thus included multiple events per patient.
[d]$P < 0.05$ based on 95% CI.
[e]Prespecified AE of special interest; AE-preferred terms identified before unblinding.

Table 4. Patient incidence of serious adverse events associated with hepatic abnormalities in patients with granulomatosis with polyangiitis and microscopic polyangiitis treated with avacopan-based versus non-avacopan-based regimens in the CLEAR,[14] CLASSIC,[15] and ADVOCATE[16] trials

Serious Adverse Events	Avacopan (n = 239), n (%)[a]	Non-avacopan (n = 200), n (%)[a]	Difference in rate (95% CI), %
Any treatment-emergent SAE associated with hepatic function abnormalities	10 (4.4)	6 (2.8)	1.7 (−1.8 to 5.1)
Hepatobiliary disorders	5 (2.3)	1 (0.5)	1.8 (−0.3 to 4.0)
Hepatic function abnormal	2 (0.9)	0 (0.0)	0.9 (−0.3 to 2.2)
Drug-induced liver injury[b]	1 (0.5)	0 (0.0)	0.5 (−0.4 to 1.3)
Hepatitis cholestatic	1 (0.5)	0 (0.0)	0.5 (−0.4 to 1.3)
Hepatocellular injury	1 (0.5)	1 (0.5)	−0.0 (−1.3 to 1.3)
Investigations	5 (2.2)	5 (2.3)	−0.1 (−2.9 to 2.6)
Hepatic enzyme increased	3 (1.2)	3 (1.4)	−0.1 (−2.2 to 2.0)
AST increased	1 (0.5)	1 (0.5)	−0.0 (−1.3 to 1.3)
Liver function test increased	1 (0.5)	0 (0.0)	0.5 (−0.4 to 1.3)
ALT increased	0 (0.0)	1 (0.5)	−0.5 (−1.4 to 0.4)
Transaminases increased	0 (0.0)	1 (0.5)	−0.5 (−1.4 to 0.4)

ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CI, confidence interval.
[a]The number of patients with at least one event. Patient incidence of SAEs is reported as the study-size adjusted percentage.
[b]The reported term is azathioprine-induced liver toxicity.

whereas the incidence of grade 4 lymphopenia (<0.2 × 10^3/μL) was lower in the avacopan than in the non-avacopan group (2.4% vs 8.0%). The integrated analysis of data from the phase 2 trials reported one case of grade 4 neutropenia (neutrophils <0.5 × 10^3/μL) in the avacopan group and no grade 3 neutropenia (0.5 to <1.0 × 10^3/μL) in either group. One SAE of neutropenia was reported in one patient (also treated with RTX) in the avacopan group in the CLASSIC study. No grade 4 lymphopenia events were observed in the phase 2 trials, and the incidence of grade 3 lymphopenia was 23.3% in the avacopan group and 5.9% in the non-avacopan group.

Hypersensitivity. Across the three trials, AEs related to hypersensitivity occurred in 37.3% of patients in the avacopan group versus 36.9% in the non-avacopan group. Most cases of hypersensitivity occurred in the skin and subcutaneous tissues, with rash affecting 21.5% of the avacopan group versus 22.7% of the non-avacopan group. No cases of angioedema were observed in the phase 2 trials. In the phase 3 ADVOCATE trial, two cases of angioedema were observed in two patients treated with avacopan, with a negative re-challenge in one of the two patients. No cases of angioedema were reported in the non-avacopan group.

All-cause hospitalizations. The rates of SAEs resulting in hospitalizations were similar across groups (Table 5). The mean duration of hospitalization was 11.7 days in the avacopan group and 17.6 days in the non-avacopan group.

Deaths. Seven deaths were reported across the three trials, all of which occurred in the phase 3 ADVOCATE trial. Of these, one death occurred during the screening period and six after randomization (two in the avacopan group and four in the non-avacopan group). Causes of death in the avacopan group were serious infection (pneumonia) and worsening GPA; both the

Table 5. Exposure-adjusted rate of serious treatment-emergent adverse events leading to hospitalizations while receiving treatment in patients with granulomatosis with polyangiitis and microscopic polyangiitis treated with avacopan-based versus non-avacopan-based regimens in the CLEAR,[14] CLASSIC,[15] and ADVOCATE[16] trials

Category	Avacopan (N = 239), n/time[a] (rate[b])	Non-avacopan (N = 200), n/time[a] (rate[b])	Difference in rate[b] (95% CI)
Any SAE resulting in hospitalization while on treatment[c]	73/148.7 (49.1)	70/157.9 (44.3)	4.8 (−10.6, 20.1)
Hospitalization due to glucocorticoid-related SAE	13/157.0 (8.3)	9/152.3 (5.9)	2.4 (−3.6, 8.3)
Hospitalization due to infection SAE	28/151.9 (18.4)	25/144.2 (17.3)	1.1 (−8.5, 10.7)
Summary of hospitalizations[d]	**Avacopan (N = 239)**	**Non-avacopan (N = 200)**	**Difference between treatment groups**
Number of patients hospitalized	73	70	3
Number of events	106	119	−13
Mean (SD) duration of hospitalization[d]	11.7 (13.0)	17.6 (28.3)	−5.9

[a]Time = total time at risk (in years), defined as the sum of (1) treatment duration in patients who did not have a treatment-emergent occurrence of the adverse event and (2) time to first occurrence of the event in patients who had a treatment-emergent occurrence of the adverse event.
[b]Rate = incidence per 100 patient-years ([n/time] × 100).
[c]Treatment-emergent SAEs resulting in a hospitalization with a start date between first and last dose date of the study drug.
[d]Hospitalization length of stay is calculated from treatment-emergent serious adverse events resulting in hospitalization with a start date between first and last dose date of study drug.
CI, confidence interval; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; n, number of patients with at least one incidence in specified category; SAE, serious adverse event; SD, standard deviation.

patients had been without avacopan treatment for ≥79 days at the time of death. Two patients in the non-avacopan group died from serious infection (fungal sepsis and infectious pleural effusion), one from acute myocardial infarction, and one from unknown causes.

DISCUSSION

Previous studies demonstrated that C5a receptor inhibition using avacopan improved remission rates, sustained remission over time, and, in the subset of patients with ANCA-associated glomerulonephritis, improved kidney function in patients with GPA and MPA treated with RTX or CYC and reduced exposure to glucocorticoids.[14,16] This report presents an integrated analysis of safety data from the CLEAR, CLASSIC, and ADVOCATE trials,[14–16] which included 239 patients with GPA or MPA and a total of 212.3 patient-years of avacopan exposure. Results suggest that, compared with standard (non-avacopan) treatment, the use of avacopan with a reduced-dose glucocorticoid regimen was associated with a lower incidence of AEs, SAEs, and infections without increasing the rates of neutropenia or lymphopenia. These benefits were likely due to the reduced exposure to glucocorticoids in the avacopan versus non-avacopan group. Together, these results suggest a favorable benefit-risk profile for avacopan and support the EULAR (2022) and KDIGO (2024) recommended the use of avacopan to reduce glucocorticoid exposure in patients with GPA or MPA.[3,25]

Overall, 4.4% of patients treated with avacopan had SAEs related to hepatic abnormalities compared with 2.8% of patients treated with a non-avacopan regimen. This, together with recent reports of hepatic toxicities in a small proportion of patients treated with avacopan in case studies,[26,27] suggests that patients receiving avacopan should be closely monitored for changes in liver function.

The 52-week phase 3 ADVOCATE trial reported 25 cases of infection-related SAEs in 22 patients (13.3%) in the avacopan group versus 31 cases in 25 patients (15.2%) in the non-avacopan group, with similar rates reported by the 24-week combined phase 2 trials (12 cases in seven patients [9.6%] versus four cases in three patients [8.3%], respectively). In comparison, the RITAZAREM trial (in which patients with relapsed GPA or MPA received RTX and glucocorticoids to reinduce remission followed by RTX or AZA for ≥36 months in patients achieving remission within 4 months) identified 19 severe infections in 15 patients (18%) in the RTX group compared with 27 cases in 19 patients (22%) in the AZA group.[28]

Although rates of infection in the avacopan trials were lower in patients receiving avacopan than in those not receiving avacopan, the risk of infection was substantial in both groups despite a much lower cumulative exposure to glucocorticoids in patients receiving avacopan. This is likely because many patients in the avacopan group received some glucocorticoids, albeit at a lower dose, and because AAV itself, comorbidities, and other non-glucocorticoid immunosuppressive drugs are key contributors to infections. Importantly, both the PEXIVAS[13] and LoVAS[17] trials demonstrated that substantial reductions in total early dosing of glucocorticoids are associated with a significantly reduced risk of serious infection in patients with AAV. Additional studies may be warranted to establish whether avacopan-based regimens can reduce the rates of infection-related SAEs compared with other treatment options in patients with GPA and MPA.

Overall rates of neutropenia or lymphopenia were lower in patients receiving avacopan than in those not receiving avacopan. Two severe events of neutropenia were noted in the avacopan group. However, there is no known method for establishing whether neutropenia was caused by avacopan or by RTX or CYC and no scientific rationale for a relationship between avacopan and neutropenia. Notably, the US Food and Drug Administration does not deem neutropenia to be an AE of concern for avacopan, whereas the European Union recommends monitoring patients treated with avacopan for changes in WBC counts.

This integrated safety analysis has several limitations, including differences between trials in glucocorticoid dosing and reported safety outcomes. Compared with the phase 3 ADVOCATE trial,[16] the phase 2 CLEAR and CLASSIC trials[14,15] had smaller sample sizes and shorter durations of therapy, both of which were accounted for using exposure-adjusted rates per 100 patients. Nonetheless, the study provides important information about the safety profile of avacopan among the large numbers of patients with GPA and MPA in randomized controlled trials.

Overall, avacopan represents an advancement in the treatment of GPA and MPA, providing potential improvements in remission rates, sustained remission, and improved kidney function while reducing the need for glucocorticoids.[14,16] In this integrated analysis of safety data from the CLEAR, CLASSIC, and ADVOCATE trials,[14–16] avacopan demonstrated a favorable safety profile compared with standard treatment with a prednisone taper. No new safety signals have been identified since avacopan became commercially available, and its safety continues to be closely monitored. Additional studies, including the post-authorization AvacoStar safety study (NCT05897684) and a phase 4 randomized, double-blind, placebo-controlled clinical trial (NCT06072482) will provide a greater understanding of the long-term safety of avacopan in patients with GPA or MPA.

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