



OPEN ACCESS

CLINICAL SCIENCE

Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial

Duvuru Geetha ,¹ Anisha Dua ,² Huibin Yue,³ Jason Springer ,⁴ Carlo Salvarani ,^{5,6} David Jayne ,⁷ Peter Merkel ,⁸ ADVOCATE Study Group

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ard-2023-224816>).

For numbered affiliations see end of article.

Correspondence to

Dr Duvuru Geetha, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA; dgeetha1@jhmi.edu

Received 4 August 2023
Accepted 6 October 2023
Published Online First
18 November 2023

ABSTRACT

Objectives To evaluate the efficacy and safety of avacopan in the subgroup of patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis receiving background induction therapy with rituximab in the phase 3 ADVOCATE trial.

Methods Key efficacy outcomes were remission at week 26 and sustained remission at week 52. Additional outcomes included the Glucocorticoid Toxicity Index, estimated glomerular filtration rate, urinary albumin to creatinine ratio, health-related quality of life and safety.

Results Of the 330 patients who received study medication, 214 (64.8%) received rituximab (once weekly for 4 weeks), with a mean age of 59.8 years; 163 (76.2%) had renal vasculitis and 125 (58.4%) were newly diagnosed. Remission at week 26 and sustained remission at week 52 were achieved by 83/107 (77.6%) and 76/107 (71.0%) patients in the avacopan group and 81/107 (75.7%) and 60/107 (56.1%) in the prednisone taper group, respectively. The relapse rate, recovery of renal function, speed of reduction in albuminuria and glucocorticoid toxicity favoured the avacopan group. Serious adverse events occurred in 34.6% and 39.3% of patients in the avacopan and prednisone taper groups, respectively.

Conclusions These data suggest that in patients with ANCA-associated vasculitis receiving rituximab, efficacy of treatment with avacopan compared with a prednisone taper was similar at week 26 and greater at week 52, with a favourable safety profile. In addition, avacopan was associated with improved renal outcomes and lower glucocorticoid toxicity. These results demonstrate the efficacy and safety of avacopan in patients receiving background induction therapy with rituximab.

Trial registration number NCT02994927.

INTRODUCTION

Successful treatment of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) focuses on suppressing disease activity while minimising treatment-related toxicity. Cyclophosphamide (CYC) plus glucocorticoids (GCs) was the standard therapy for induction of remission for nearly four decades.¹ Use of rituximab (RTX) plus GCs for remission became more common in recent years based on the results of randomised trials.^{2,3} However, there remains an unmet need for additional agents to maintain remission.

In the phase 3 ADVOCATE randomised trial in patients with AAV (granulomatosis with polyangiitis

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Rituximab is now considered the standard of care for induction of remission in antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. However, there remains an unmet need for additional agents to maintain remission.
- ⇒ Prior analyses of the ADVOCATE trial concluded that avacopan was superior to a prednisone taper in sustaining remission at week 52.

WHAT THIS STUDY ADDS

- ⇒ These data confirm and add to the current evidence of the role of avacopan as a therapeutic agent to sustain remission to 52 weeks and reduce the risk of relapses.
- ⇒ These data suggest that in patients with ANCA-associated vasculitis receiving background induction therapy with rituximab, avacopan has a favourable safety profile and is associated with improved recovery of renal function, faster reduction in albuminuria and lower glucocorticoid toxicity compared with a prednisone taper.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ As a new therapeutic agent, avacopan may be considered as a standard therapy along with rituximab for treatment of ANCA-associated vasculitis to induce and sustain remission.

(GPA) or microscopic polyangiitis (MPA)) who received background immunosuppressive therapy (RTX or CYC/azathioprine), avacopan—a selective oral C5a receptor antagonist—was non-inferior to a prednisone taper in achieving remission at week 26 and superior in sustaining remission at week 52.⁴ Because RTX is currently standard of care for induction of remission and maintenance of remission in AAV, this subgroup analysis of the ADVOCATE trial was conducted to evaluate the efficacy and safety of avacopan in patients with GPA or MPA receiving background induction therapy with RTX.

METHODS

Study design

This analysis of patients treated with RTX was a prespecified subgroup of the ADVOCATE study, a

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Geetha D, Dua A, Yue H, et al. *Ann Rheum Dis* 2024;**83**:223–232.

multicentre, randomised, double-blind, double-dummy, active-controlled trial (NCT02994927).⁴ Avacopan (30 mg two times per day) or matching placebo was administered for 52 weeks, randomly assigned (1:1) using an interactive web-response system, with the use of a minimisation algorithm, to maintain balance between the treatment groups. Prednisone or a matched placebo was administered on a tapering schedule over 20 weeks (60 mg per day tapered to discontinuation by week 21). Study medication was given within hard gelatin capsules to maintain blinding. Randomisation was performed centrally and stratified according to vasculitis disease status (newly diagnosed or relapsing), ANCA type (anti-proteinase 3 (PR3) positive or anti-myeloperoxidase (MPO) positive) and immunosuppressive therapy (CYC (followed by azathioprine) or RTX with no redosing). The dose of intravenous RTX was 375 mg/m² of body surface area per week for 4 weeks. The study protocol and any changes made are available online as part of supplementary material of the original ADVOCATE report.⁴

Patients

Patients with GPA or MPA were enrolled in 143 centres across 20 countries. Detailed inclusion and exclusion criteria for each study were previously reported.⁴ Briefly, eligible patients had newly diagnosed or relapsing GPA or MPA, according to the Chapel Hill Consensus Conference definitions,⁵ a history of a positive test result for antibodies to either PR3-ANCA or MPO-ANCA, an estimated glomerular filtration rate (eGFR) of at least 15 mL/min/1.73 m² of body surface area, and at least one major or three non-major items or at least the two renal items of haematuria and proteinuria on the Birmingham Vasculitis Activity Score (BVAS), V.3.⁶

Efficacy analyses

The key efficacy outcomes were remission at week 26, defined as a BVAS of 0 and no receipt of GCs for AAV 4 weeks before week 26, and sustained remission, defined as remission at week 26 and at week 52 with no receipt of GCs for AAV 4 weeks before week 52 and no relapse between weeks 26 and 52. Relapse was defined as a return of active vasculitis after previous achievement of a BVAS of 0 at any time that involved 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. Exploratory analyses summarised the proportion of patients experiencing a relapse under two conditions: (1) for the first time after achieving remission at week 26, and (2) for the first time after achieving remission (BVAS of 0) at any time for which the Cox proportional model was used to estimate the hazard ratio (HR) of time to relapse.

Additional outcomes in exploratory analyses included the Glucocorticoid Toxicity Index (GTI),^{7 8} GC use (presented as mg prednisone equivalent), and change from baseline in health-related quality of life (HRQoL), assessed with the Short-Form 36 questionnaire (SF-36) V.2⁹ and the EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L).¹⁰ For both the GTI Cumulative Worsening Score (GTI-CWS) and the GTI Aggregate Improvement Score (GTI-AIS), lower scores indicate lesser severity of toxic effects. In patients with renal disease at baseline on the basis of BVAS, eGFR and urinary albumin to creatinine ratio (UACR) were assessed (in patients with albuminuria (UACR ≥ 10 mg/g)). eGFR for patients with a baseline eGFR less than 30 mL/min/1.73 m² was also analysed. eGFR (in mL/min/1.73 m²) was calculated using the serum creatinine-based formula (Modification of Diet in Renal Disease) for adults,¹¹

the Japanese equation for Japanese adults,¹² and the modified Schwartz equation for adolescents.¹³

Safety analyses

Safety outcomes included incidence of adverse events (AEs) and serious AEs (SAEs). Data were collected and coded using the Medical Dictionary for Regulatory Activities (v19.1)¹⁴ and graded according to the Common Terminology Criteria for Adverse Events Version 5.0.¹⁵

Statistical analysis

The efficacy and safety analysis sets comprised the intention-to-treat population, which included all randomised patients who received at least one dose of blinded study drug. The summary statistics for the outcome measures of the subgroup analysis were prespecified. No statistical inference or hypothesis testing for the subgroup was conducted.

Data were summarised descriptively by the treatment group. For continuous variables, means, medians, ranges SDs and SEMs were calculated. Frequency counts and percentages were presented for categorical variables.

The proportion of patients achieving disease remission at week 26, sustained disease remission at week 52, and two-sided 95% CIs for the difference in proportions (avacopan minus prednisone taper) were estimated. CIs for group response proportions were calculated using the Clopper-Pearson method. CIs for the difference in proportions were calculated using the stratified summary score estimate for the common difference in proportions adjusted for randomisation strata (newly diagnosed or relapsed AAV, and anti-PR3 or anti-MPO ANCA). Missing data were imputed as not achieving remission (for week 26) or not achieving sustained remission (for week 52).

For changes from baseline, least squares mean (LS mean) and SEM were calculated from mixed effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. These analyses were exploratory. Patients were considered as repeated measure units over visits. Logarithmic transformations were applied to the UACR data before fitting the model, and 95% CIs were transformed back to the original scale. Percent changes from baseline in UACR were calculated based on ratios of geometric means of visit over baseline. No imputation was performed for missing data. All statistical analyses were performed using Statistical Analysis System (SAS) software (V.9.4 of SAS for Windows, SAS Institute).

Site investigators collected data, and ChemoCentryx (a wholly owned subsidiary of Amgen) sponsored the trial and provided trial medication. Medpace conducted the trial and data analysis with guidance from ChemoCentryx. All authors interpreted the data and collaborated in manuscript preparation with support from professional medical writers funded by Amgen. All authors made the decision to submit the manuscript and attested to the veracity and completeness of data and analyses and to the fidelity of this report.

RESULTS

Patients

The ADVOCATE trial was conducted from 15 March 2017 (first patient enrolled) to 1 November 2019 (last study visit). There were 331 patients randomised, 1 of which did not receive study medication. Of the 330 patients who received study medication, 214 (64.8%) received RTX and comprised the subgroup analysis set. The demographic and baseline clinical characteristics of the

Table 1 Baseline demographics and clinical characteristics of study participants

| | Prednisone taper+rituximab group (N=107) | Avacopan+rituximab group (N=107) | Total (N=214) |
|---|--|----------------------------------|---------------|
| Age (years), mean (SD) | 59.9 (16.0) | 59.7 (15.4) | 59.8 (15.7) |
| Sex, n (%) | | | |
| Male | 52 (48.6) | 61 (57.0) | 113 (52.8) |
| Female | 55 (51.4) | 46 (43.0) | 101 (47.2) |
| Race, n (%) | | | |
| Asian | 8 (7.5) | 11 (10.3) | 19 (8.9) |
| Black or African American | 2 (1.9) | 2 (1.9) | 4 (1.9) |
| White | 92 (86.0) | 89 (83.2) | 181 (84.6) |
| Other | 4 (3.7) | 5 (4.7) | 9 (4.2) |
| Multiple | 1 (0.9) | 0 (0.0) | 1 (0.5) |
| Body mass index (kg/m ²), mean (SD) | 26.6 (5.1) | 26.6 (6.1) | 26.6 (5.6) |
| Vasculitis disease status, n (%) | | | |
| Newly diagnosed | 62 (57.9) | 63 (58.9) | 125 (58.4) |
| Relapsed | 45 (42.1) | 44 (41.1) | 89 (41.6) |
| ANCA type, n (%) | | | |
| Anti-proteinase-3 | 49 (45.8) | 50 (46.7) | 99 (46.3) |
| Anti-myeloperoxidase | 58 (54.2) | 57 (53.3) | 115 (53.7) |
| Type of vasculitis, n (%) | | | |
| Granulomatosis with polyangiitis | 64 (59.8) | 65 (60.7) | 129 (60.3) |
| Microscopic polyangiitis | 43 (40.2) | 42 (39.3) | 85 (39.7) |
| Duration of ANCA-associated vasculitis (months), median (range) | 0.8 (0–213) | 0.5 (0–362) | 0.6 (0–362) |
| Birmingham Vasculitis Activity Score, mean (SD) | 15.6 (6.1) | 15.5 (5.7) | 15.5 (5.9) |
| Vasculitis Damage Index, mean (SD) | 1.0 (1.6) | 0.9 (1.7) | 0.9 (1.7) |
| Diabetes mellitus at baseline, n (%) | 14 (13.1) | 18 (16.8) | 32 (15.0) |
| Renal disease at baseline, n (%) | 82 (76.6) | 81 (75.7) | 163 (76.2) |
| Estimated glomerular filtration rate, mL/min/1.73 m ² , mean (SD)* | 46.8 (26.4) | 50.8 (29.8) | - |
| Glucocorticoid use during screening period, n (%) | | | |
| Any | 86 (80.4) | 83 (77.6) | 169 (79.0) |
| Oral | 76 (71.0) | 69 (64.5) | 145 (67.8) |
| Intravenous | 37 (34.6) | 40 (37.4) | 77 (36.0) |

*Shown is the baseline estimated glomerular filtration rate in patients with renal disease at baseline on the basis of the Birmingham Vasculitis Activity Score. ANCA, antineutrophil cytoplasmic autoantibody.

RTX subgroup were similar between the two treatment groups (table 1) and did not differ appreciably from the full study population, except that the proportion of newly diagnosed patients was lower in the subgroup (58.4%) than in the full study population (69.4%).⁴ The mean (SD) age was 59.8 (15.7) years; 52.8% of patients were male and 84.6% were white. The rate of anti-PR3-AAV was 46.7% in the avacopan group and 45.8% in the prednisone taper group. In total, more patients had GPA (60.3%), renal vasculitis (76.2%) and were newly diagnosed (58.4%). The mean (SD) baseline eGFR for patients with renal involvement was 50.8 (29.8) in the avacopan group and 46.8 (26.4) in the prednisone taper group.

Outcomes

Remission

Remission at week 26 was observed in 83/107 patients (77.6%) in the avacopan group and 81/107 patients (75.7%) in the prednisone taper group (estimated common difference 3.0 percentage points; 95% CI -8.3 to 14.2) (table 2). Sustained remission at week 52 was observed in 76/107 patients (71.0%) in the avacopan group and 60/107 patients (56.1%) in the prednisone taper group (estimated common difference, 16.5 percentage points; 95% CI 4.3 to 28.6).

Relapse

The relapse rate after remission at any time was 8.7% (9/104 patients) in the avacopan group compared with 20.2% (21/104 patients) in the prednisone taper group (table 2). The HR for relapse after remission at any time (avacopan vs prednisone taper) was 0.42 (95% CI 0.19 to 0.91), a reduction of relapse risk of 58%. The relapse rate for patients who achieved remission at week 26 was 7.2% (6/83 patients) in the avacopan group and 13.6% (11/81 patients) in the prednisone taper group.

GC toxicity

GC-induced toxicity, as assessed by GTI, was greater in the prednisone taper group than in the avacopan group (table 3). The LS mean (95% CI) difference between groups for the AIS at week 13 was -11.0 (-21.6 to -0.5), based on LS mean (95% CI) scores of 11.9 (4.4 to 19.4) and 22.9 (15.5 to 30.3) for the avacopan and prednisone taper groups, respectively. The LS mean (95% CI) difference between groups for the CWS at week 13 was -10.0 (-20.5 to 0.5) based on LS mean (95% CI) scores of 25.5 (18.1 to 33.0) for the avacopan group and 35.6 (28.2 to 43.0) for the prednisone taper group. The LS mean (95% CI) difference between groups for the AIS at week 26 was -7.3 (-18.0 to 3.3), based on LS mean (95% CI) scores of 12.8 (5.3 to 20.3) and 20.2

Table 2 Rates of remission and sustained remission by treatment group

| | Prednisone taper+rituximab group (N=107) | Avacopan+rituximab group (N=107) |
|--|--|----------------------------------|
| Remission* at week 26, n (%) | 81 (75.7) | 83 (77.6) |
| Estimate of common difference in percentages (95% CI) | | 3.0 (−8.3 to 14.2) |
| Sustained remission† at week 52, n (%) | 60 (56.1) | 76 (71.0) |
| Estimate of common difference in percentages (95% CI) | | 16.5 (4.3 to 28.6) |
| Relapse rate after remission at week 26, n (%) | 11 (13.6) | 6 (7.2) |
| Estimate of common difference in percentages (95% CI) | | −7.9 (−17.7 to 2.0) |
| Relapse rate after remission (BVAS of 0) at any time, n (%)‡ | 21 (20.2) | 9 (8.7) |
| HR (95% CI) | | 0.42 (0.19 to 0.91) |

*Remission was defined as a BVAS of 0 and no receipt of glucocorticoids for vasculitis within 4 weeks before the week 26 visit.
†Sustained remission defined as BVAS of 0 at week 26 and week 52 without any use of glucocorticoids for vasculitis during the 4-week periods preceding and including the week 26 and week 52 visits and no relapse between week 26 and week 52.
‡The number of patients who achieved remission at any time was 104 in the prednisone taper group and 104 in the avacopan group.
BVAS, Birmingham Vasculitis Activity Score.

(12.7 to 27.7) for the avacopan and prednisone taper groups, respectively. The LS mean (95% CI) difference between groups for the CWS at week 26 was -14.9 (-25.5 to -4.4) based on LS mean (95% CI) scores of 38.0 (30.5 to 45.4) for the avacopan group and 52.9 (45.5 to 60.4) for the prednisone taper group.

GC use

Consistent with the trial protocol, the total GC use over 52 weeks was lower in the avacopan group than in the prednisone taper group (table 3). The mean total prednisone-equivalent dose of all oral and intravenous GCs was 1731 mg in the avacopan group and 3687 mg in the prednisone taper group, with respective median doses of 625 mg (range: 0–21 680 mg) and 3130 mg (range: 1520–13 383 mg).

Kidney function

Kidney function recovered in patients with renal disease at baseline in both treatment groups (figure 1). The LS mean increase in eGFR at week 52 in the avacopan group was 5.8 mL/min/1.73 m² from a mean (SD) of 50.8 (29.8) mL/min/1.73 m² at baseline. In the prednisone taper group, the LS mean change was 2.8 mL/min/1.73 m² from a mean (SD) of 46.8 (26.4) mL/min/1.73 m² at baseline. The LS mean (95% CI) difference between groups at week 52 was 3.0 (−0.5 to 6.4). For patients with eGFR <30 mL/min/1.73 m² at baseline, the LS mean increase in eGFR at week 52 in the avacopan group was 8.7 mL/min/1.73 m² from a mean (SD) of 21.0 (3.7) mL/min/1.73 m² at baseline. In the prednisone taper group, the LS mean change was 6.6 mL/min/1.73 m² from a mean (SD) of 21.0 (4.5) mL/min/1.73 m² at baseline. The LS mean (95% CI) difference between groups at week 52 was 2.1 (−2.6 to 6.8).

In patients with renal disease and albuminuria at baseline, improvement in UACR occurred more rapidly in the avacopan group compared with the prednisone taper group (figure 2). At week 4, there was an LS mean change of -42% in UACR in the avacopan group compared with a change of 6% in the prednisone taper group; the LS mean (95% CI) difference between groups was -45 (-60 to -24). By week 52, the improvements in UACR were similar in both treatment groups, with a $>70\%$ decrease.

Health-related quality of life

HRQoL, measured by the SF-36 and EQ-5D-5L, tended to improve in both treatment groups (online supplemental eTable 1). The LS mean change from baseline in the SF-36 Physical

Component Summary (PCS) score was greater in the avacopan group at week 26, with a between-group difference of 2.8 (95% CI 0.4 to 5.2). The LS mean change from baseline was greater in the avacopan group than in the prednisone taper group across all of the SF-36 domains measured except social functioning at week 26, with larger relative between-group difference for the role physical, bodily pain and vitality domains at week 26.

Trends of greater changes from baseline in the avacopan group than in the prednisone taper group were reported for EQ-5D-5L Visual Analogue Scale (VAS) and EQ-5D-5L index at both week 26 and week 52. The LS mean (95% CI) difference between groups for change from baseline was 4.7 (95% CI 0.0 to 9.3) at week 52 for the EQ-5D-5L VAS and 0.04 (95% CI 0.00 to 0.09) for the EQ-5D-5L index.

Safety

Safety results for the overall study population were previously published.⁴ For the 214 patients who received RTX as background induction therapy, SAEs occurred in 37/107 patients (34.6%) in the avacopan group, with 62 events, and 42/107 patients (39.3%) in the prednisone taper group, with 91 events (table 4). For serious infections, there were 11/107 patients (10.3%) with 12 events in the avacopan group and 15/107 patients (14.0%) with 19 events in the prednisone taper group. Three patients (2.8%) in the avacopan group and four (3.7%) in the prednisone group had an SAE of an abnormality on liver-function testing. There were no deaths in the avacopan group and three deaths attributed to generalised fungal infection with diarrhoea and vomiting, acute myocardial infarction, and death of unknown cause in the prednisone taper group.

DISCUSSION

The results of this subgroup analysis suggest that avacopan with background induction therapy with RTX showed comparable efficacy to a prednisone taper with background RTX in achieving remission at week 26 and a higher rate of sustained remission at week 52. The results regarding efficacy in this current subgroup analysis are similar to those of the full study population, in which avacopan was non-inferior to the prednisone taper for achieving remission at week 26 (72.3% for avacopan vs 70.1% for prednisone) and superior for sustaining remission at week 52 (65.7% for avacopan vs 54.9% for prednisone).⁴ The data presented here provide evidence for improved treatment options over the current treatment guidelines, which recommend the use of GCs with RTX or CYC. The American College of Rheumatology/

Table 3 Measurements of the Glucocorticoid Toxicity Index by treatment group and glucocorticoid use among study participants

| | Prednisone taper+rituximab group (N=107) | Avacopan +rituximab group (N=107) |
|---|--|-----------------------------------|
| Glucocorticoid Toxicity Index | | |
| Cumulative Worsening Score* | | |
| Week 13 | 35.6 (28.2 to 43.0) | 25.5 (18.1 to 33.0) |
| Difference | | -10.0 (-20.5 to 0.5) |
| Week 26 | 52.9 (45.5 to 60.4) | 38.0 (30.5 to 45.4) |
| Difference | | -14.9 (-25.5 to -4.4) |
| Aggregate Improvement Score* | | |
| Week 13 | 22.9 (15.5 to 30.3) | 11.9 (4.4 to 19.4) |
| Difference | | -11.0 (-21.6 to -0.5) |
| Week 26 | 20.2 (12.7 to 27.7) | 12.8 (5.3 to 20.3) |
| Difference | | -7.3 (-18.0 to 3.3) |
| Glucocorticoid use | | |
| Screening (week -2 to 0) | | |
| n (%) | 86 (80.4) | 83 (77.6) |
| Dose (mg prednisone equivalent)† | | |
| Mean | 823 | 863 |
| Median (range) | 290 (0-4465) | 392 (0-5805) |
| Weeks 0-26‡ | | |
| n (%) | 107 (100.0) | 103 (96.3) |
| Dose (mg prednisone equivalent)† | | |
| Mean | 3265 | 1417 |
| Median (range) | 3026 (1520-11 815) | 625 (0-19 492) |
| Weeks 26-52 | | |
| n (%) | 42 (39.3) | 28 (26.2) |
| Dose (mg prednisone equivalent)† | | |
| Mean | 443 | 330 |
| Median (range) | 0 (0-6333) | 0 (0-4565) |
| Weeks 0-52‡ | | |
| n (%) | 107 (100.0) | 103 (96.3) |
| Dose (mg prednisone equivalent)† | | |
| Mean | 3687 | 1731 |
| Median (range) | 3130 (1520-13 383) | 625 (0-21 680) |
| *Data represent LS mean (95% CI). The Glucocorticoid Toxicity Index Cumulative Worsening Score ranges from 0 to 410, with higher scores indicating greater severity of toxic effects. The Glucocorticoid Toxicity Index Aggregate Improvement Score ranges from -317 to 410, with higher scores indicating greater severity of toxic effects. | | |
| †All doses were converted to prednisone equivalent (mg) and are calculated as total dose during a specified period. The prednisone-equivalent dose includes both intravenous and oral use of glucocorticoids. The n (%) data are the number of patients who used any glucocorticoids during the period and the mean and median (range) data are for all patients in the period. | | |
| ‡All patients received rituximab; however, there were 7 patients in the prednisone taper group and 10 patients in the avacopan group with no recorded use of intravenous glucocorticoids during the initial 4-week study period. | | |
| LS mean, least squares mean. | | |

Vasculitis Foundation guidelines recommend using RTX with GC as the first-line approach for induction of remission for AAV.¹⁶ The Kidney Disease Improving Global Outcomes and the 2022 European Alliance of Associations for Rheumatology (EULAR) recommend the combination of GC with either RTX or CYC, with the EULAR guidelines suggesting consideration of avacopan to reduce GC exposure.^{17 18}

Although the use of RTX has improved treatment options for patients with AAV,¹⁹ challenges to maintain remission still exist, including increased risk of infections and

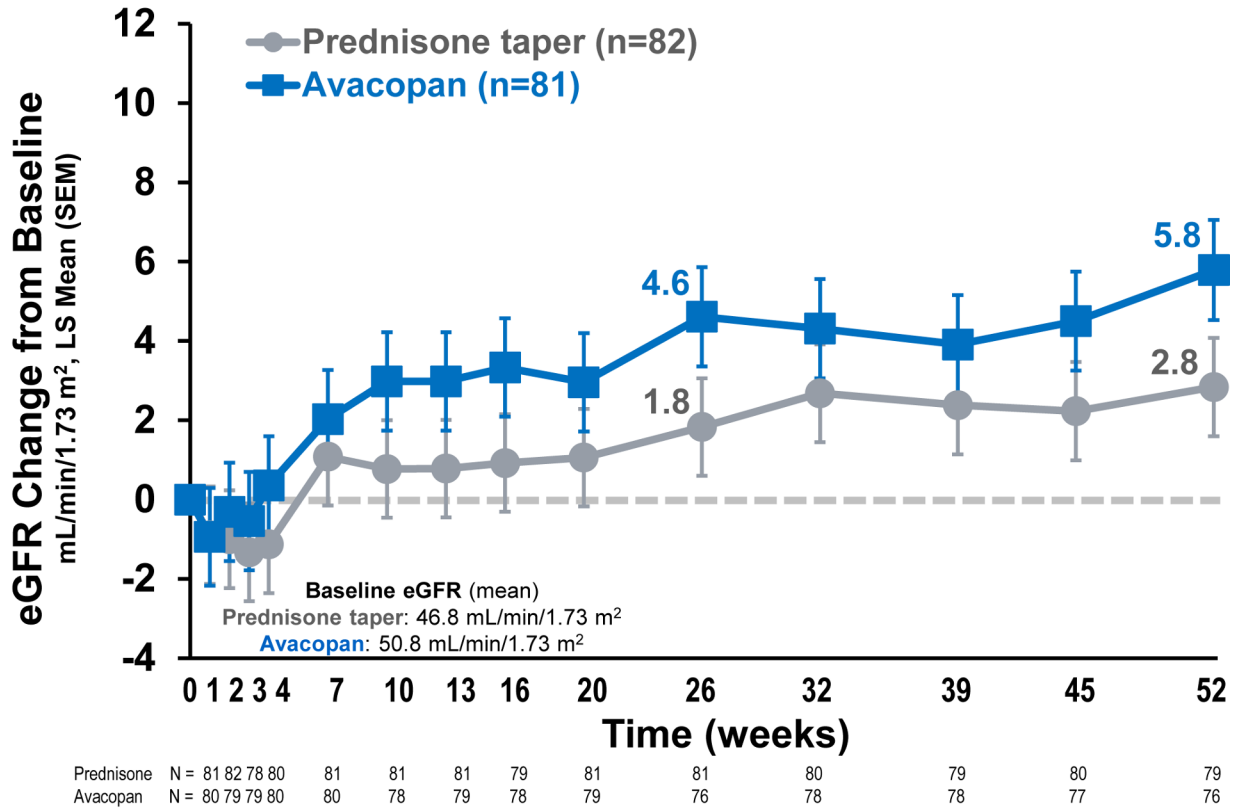
hypogammaglobulinaemia with repeat doses of RTX and risk of relapse after cessation of treatment with RTX.²⁰⁻²⁴ Management of patients with AAV on RTX was particularly challenging during the coronavirus disease (COVID-19) pandemic since RTX is associated with increased severity of COVID-19 infection,²⁵ there is impaired humoral response to vaccination,²⁶ and delays in administration of RTX for maintenance of remission were common.²⁷ Currently, there are no data available on the use of avacopan in patients who have contracted COVID-19, and further research is needed.

The rate of sustained remission at 12 months is low in patients treated with RTX with no maintenance therapy, with one trial estimating it to be less than 50%.²⁸ The rate of sustained remission can be increased by continuing treatment with prednisolone, as in the RITUXVAS trial in which sustained remission at month 12 was achieved by 76% of patients receiving RTX for induction of remission with continued prednisolone at a dose of 5 mg daily for 12 months.²⁹ Sustained remission can also be achieved by repeated doses of RTX; however, more than 40% of patients experience a relapse after the withdrawal of RTX.³⁰⁻³³ For comparison, this subgroup analysis reports relapse rates after remission at any time of 20.2% for the prednisone taper group and 8.7% for the avacopan group at 52 weeks among patients who achieved BVAS of 0 at any time, suggesting that the addition of avacopan reduced the rates of relapse. Consistent with the rates of remission reported in other trials, in the current analysis, patients who received background therapy with RTX without redosing and were randomised to a 20-week prednisone taper had a rate of sustained remission of 56.1% at week 52. In contrast, the rate of sustained remission at week 52 was much higher (71.0%) among patients who received avacopan. These results indicate the benefit of avacopan for the treatment of AAV among patients also receiving RTX induction.

Beyond the efficacy outcomes of remission and relapse rates, other outcomes reported in this study indicate benefits of avacopan with background induction RTX therapy, including trends of renal recovery and improvement in HRQoL outcomes. For context, in the overall ADVOCATE trial, LS mean eGFR increased by 7.3 mL/min/1.73 m² in the avacopan group and 4.1 mL/min/1.73 m² in the prednisone taper group at week 52.⁴ In this subgroup analysis among patients who received RTX, LS mean eGFR increased by 5.8 mL/min/1.73 m² in the avacopan group and 2.8 mL/min/1.73 m² in the prednisone taper group at week 52. Patients with baseline eGFR < 30 mL/min/1.73 m² had even higher increases of 8.7 mL/min/1.73 m² and 6.6 mL/min/1.73 m², respectively. Other improvements of note were observed in UACR at weeks 2 and 4, SF-36 role physical and vitality domains and PCS at week 26, and SF-36 general health domain and EQ-5D-5L VAS at week 52. HRQoL results described here are similar to those of the overall trial.³⁴

Data from trials in vasculitis showed that treatment-related damage occurs secondary to GCs and that higher levels of damage are independently associated with the duration of use of GCs.³⁵ Two trials for induction of remission in AAV demonstrated that a reduced-dose GC regimen was non-inferior to a high-dose GC regimen.^{36 37} From a patient's perspective, the minimal clinically important difference in GTI is reported to be 10 points, and was evaluated at this threshold, as well as 20-point and 30-point thresholds previously used for such analyses.³⁸ The LS mean value for GTI-AIS at weeks 13 and 26 exceeded the 20-point threshold in the prednisone taper group and exceeded the 10-point threshold in the avacopan group, indicating a perceptible difference to patients. For GTI-CWS, the LS mean value for the prednisone taper group exceeded the 30-point threshold at

A



B

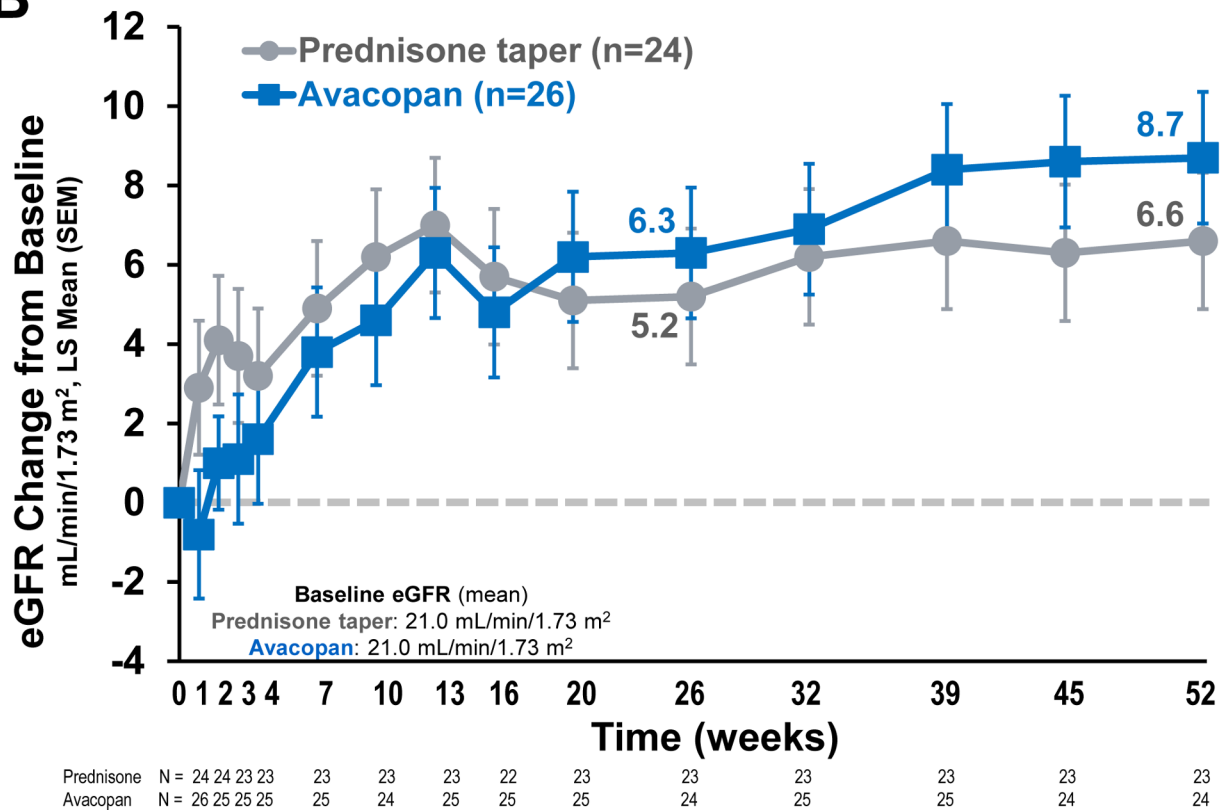
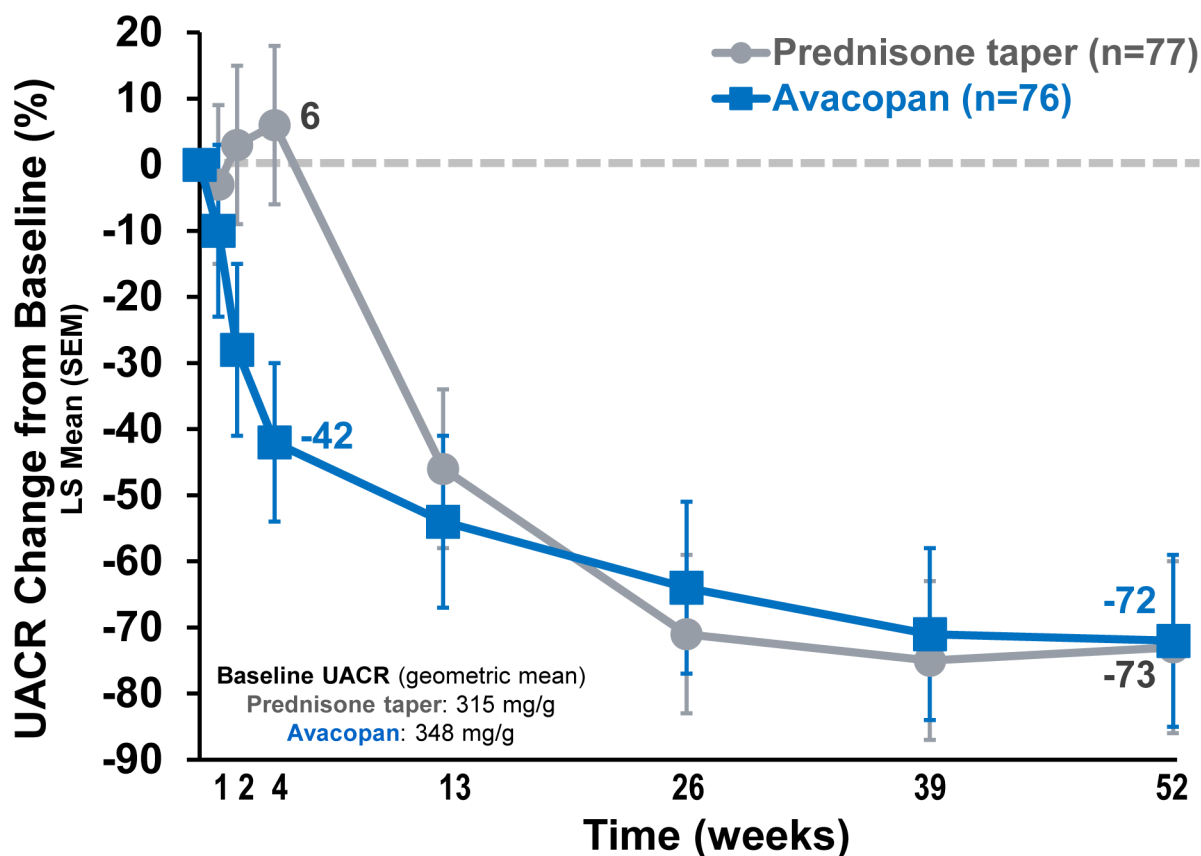


Figure 1 Change from baseline in estimated glomerular filtration rate in patients with (A) renal disease at baseline and (B) renal disease and an estimated glomerular filtration rate <30 mL/min/1.73 m² at baseline. LS mean and SEM are from mixed effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. eGFR, estimated glomerular filtration rate; LS mean, least squares mean.



Prednisone N = 76 77 74 73 75 71 71
 Avacopan N = 72 73 74 70 70 71 70

Figure 2 Percent change from baseline in urinary albumin to creatinine ratio in patients with albuminuria (≥ 10 mg/g creatinine) at baseline. LS mean and SEM are from mixed effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. Logarithmic transformations were applied to the data before fitting the model. Percent changes from baseline are based on ratios of geometric means of visit over baseline. LS mean, least squares mean; UACR, urinary albumin to creatinine ratio.

weeks 13 and 26, while in the avacopan group, this threshold was reached at week 26 only. This current subgroup analysis of the ADVOCATE trial demonstrates that among patients treated with RTX induction, use of avacopan, compared with a prednisone taper, can reduce GC toxicity potentially ameliorating the burden of chronic, treatment-related harms for patients, without compromising efficacy.

Among patients treated with RTX, the number of SAEs was 47% higher in the prednisone taper group than in the avacopan group, and there were numerically more infections, serious infections and deaths in the prednisone taper group than in the avacopan group. SAEs of an abnormality on liver-function testing occurred in 2.8% of the patients in the avacopan group and 3.7% of those in the prednisone taper group.

Strengths of this study include involvement of a large cohort of patients with GPA or MPA recruited into a clinical trial with recruitment from 143 centres internationally, with the trial cohort representative of other trial populations in AAV. There was also a rigorous study design and analysis with minimal loss to follow-up. In addition, the results of this report are largely consistent with the overall results of the ADVOCATE trial.

This study has some limitations to consider. Based on the approved treatment at the time of the trial, patients who received RTX did not receive repeat dosing at week 26 in the ADVOCATE trial. However, repeat dosing of RTX is currently the recommended treatment approach.^{16–18} Thus, the efficacy and safety of avacopan when used alongside RTX for maintenance of remission are unknown. Yet, rates of remission and sustained remission are substantial even without redosing of RTX. In addition, patients with an eGFR of less than 15 mL/min/1.73 m² and those with alveolar haemorrhage requiring mechanical ventilation were not included in this study, and these findings need to be confirmed in this cohort. Lastly, limited data on the use of avacopan beyond week 52 is available. Longer follow-up

Table 4 Summary data on adverse events among study participants

| | Prednisone taper+rituximab group (N=107) | Avacopan+rituximab group (N=107) |
|---|--|----------------------------------|
| Any adverse event, n (%) | 105 (98.1) | 105 (98.1) |
| No. of events | 1239 | 1074 |
| Any infection, n (%) | 77 (72.0) | 68 (63.6) |
| No. of events | 188 | 136 |
| Any serious adverse event, n (%) | 42 (39.3) | 37 (34.6) |
| No. of events | 91 | 62 |
| Any serious infection, n (%) | 15 (14.0) | 11 (10.3) |
| No. of events | 19 | 12 |
| Discontinuation of trial medication due to adverse event, n (%) | 16 (15.0) | 13 (12.1) |
| Serious adverse event of abnormality on liver-function testing, n (%) | 4 (3.7) | 3 (2.8) |
| Fatal, n (%) | 3 (2.8) | 0 (0.0) |

is important to better understand the benefits and risks of the adjunctive use of avacopan therapy for AAV.

In conclusion, similar to the overall ADVOCATE trial, the results of the current subgroup analysis suggest that in patients with GPA or MPA receiving background induction therapy with RTX, the addition of avacopan, compared with a prednisone taper, provides a favourable safety profile and achieves similar rates of remission at week 26, higher rates of sustained remission at week 52, improved recovery of renal function, faster reduction in albuminuria and lower GC toxicity.

Author affiliations

¹Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

²Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

³Department of Biostatistics, Amgen Inc, San Carlos, California, USA

⁴Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

⁵Department of Medical Specialties, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy

⁶Department of Surgical, Medical, Dental and Morphological Sciences with Interests in Transplantology, Oncology and Regenerative Medicine, Università di Modena e Reggio Emilia, Reggio Emilia, Italy

⁷Department of Medicine, University of Cambridge, Cambridge, UK

⁸Department of Medicine, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Twitter Anisha Dua @anisha_dua

Acknowledgements The authors thank all the many study coordinators, investigators and patients involved for their valuable contributions. Jon Nilsen, PhD and Rachel Gurlin, PhD (Amgen), provided medical writing support for this manuscript.

Collaborators ADVOCATE Study Group. Collaborators from the ADVOCATE trial (Presented by country, with National Coordinating Center followed by participating centres, in alphabetical order by principal investigator.). Australia: National Coordinating Center: Royal Adelaide Hospital, Adelaide SA (C Au Peh); Sir Charles Gairdner Hospital, Nedlands, WA (A Chakera); Royal North Shore Hospital, St Leonards (B Cooper); Griffith University, Southport (J Kurtkoti); Wesley Medical Research, Auchincloss (D Langguth); Western Health, St Albans Victoria (V Levidiotis); Prince of Wales Hospital, Randwick NSW (G Luxton); Austin Health, Heidelberg Victoria (P Mount); Princess Alexandra Hospital, Woolloongabba, QLD (D Mudge); Sunshine Coast University Hospital, Birtinya (E Noble); Westmead Hospital, Westmead NSW (R Phoon); Royal Brisbane and Women's Hospital, Herston QLD (D Ranganathan); Concord Repatriation General Hospital, Concord (A Ritchie); Monash Medical Centre, Clayton Victoria (J Ryan); Liverpool Hospital, Liverpool, NSW (M Suranyi). Austria: National Coordinating Center: Medizinische Universitätsklinik Graz, Graz (A Rosenkranz); Landeskrankenhaus Feldkirch, Feldkirch (K Lhotta); Medical University of Innsbruck, Innsbruck (A Kronbichler). Belgium: National Coordinating Center: Cliniques Universitaires Saint-Luc, Brussels (N Demoulin); Centre Hospitalier Universitaire (CHU) de Liege, Liege (C Bovy); Antwerp University Hospital (UZ), Edegem (R Hellemans); Université Libre de Bruxelles (ULB) - Hôpital Erasme, Brussels (J Hougardy); University Hospital (UZ) Leuven, Leuven (B Sprangers); University Hospital Brussels, Brussels (K Wissing). Canada: National Coordinating Center: University of Toronto, Toronto (C Pagnoux); St Paul Hospital, Vancouver (S Barbour); Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal (S Brachemi); CISSS de la Montérégie-Centre – Hôpital Charles LeMoine, Greenfield Park (S Cournoyer); University of Calgary, Calgary (L Girard); Hôpital Maisonneuve-Rosemont, Montreal (L Laurin); Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke (P Liang); CHUQ-L'Hotel-Dieu de Quebec, Quebec City (D Philibert); St Josephs Healthcare, Hamilton (M Walsh). Czech Republic: Department of Nephrology, General University Hospital, Prague (V Tesar); Rheumatology Institute, Prague (R Becvar); University Hospital Olomouc, Olomouc (P Horak); University Hospital Vinohrady, Prague (I Rychlik). Denmark: National Coordinating Center: Copenhagen University Hospital, Copenhagen (W Szpirt); Odense University Hospital, Odense (H Dieperink); Aalborg University Hospital, Aalborg (J Gregersen); Aarhus University Hospital - Skejby, Aarhus (P Ivarsen); Herlev Hospital, Herlev (E Krarup); Sjællands Universitets hospital Roskilde, Roskilde (C Lyngsoe). France: National Coordinating Center: CHU Bordeaux - Hôpital Pellegrin, Bordeaux (C Rigother); CHU Angers, Angers (J Augusto); CHU Lyon - Hôpital Femme- Mere-Enfant, Bron (A Belot); CHU de Toulouse - Hôpital Rangueil, Toulouse (D Chauveau); CHU de Brest - Hôpital de la Cavale Blanche, Brest (D Cornec); APHM - Hôpital de la Conception, Marseille (N Jourde-Chiche); CHU de Caen, Caen (M Ficheux); Hôpital Européen Georges Pompidou, Paris (A Karras); Hôpitaux Civils de Colmar, Colmar (A Klein); Hôpitaux Prives de Metz, Metz (F Maurier); Centre Hospitalier Boulogne sur Mer, Boulogne sur

Mer (R Mesbah); CHU Nîmes – Hôpital Caremeau, Nîmes (O Moranne); CHU Nantes Medicine Interne, Nantes (A Neel); Centre Hospitalier de Valenciennes, Valenciennes (T Quemeneur); Hôpital Pitie Salpetriere, Paris (D Saadoun); Hôpital Cochin, Paris (B Terrier); CHU de Grenoble, Grenoble Isere Cedex (P Zaoui). Germany: National Coordinating Center: University Clinic Heidelberg, Heidelberg (M Schaefer); University Clinic Mannheim, Mannheim (U Benck); Clinic of Ludwigshafen am Rhein, Ludwigshafen (R Bergner); University Clinic Jena, Jena (M Busch); University Clinic Aachen, Aachen (J Floege); University Clinic Cologne, Cologne (F Grundmann); Medizinische Hochschule Hannover, Hannover (H Haller); Klinikum Fulda, Fulda (M Haubitz); Medius Clinic Kirchheim, Kirchheim-unter-Teck (B Hellmich); University Hospital Tuebingen, Tuebingen (J Henes); Nephrological Center Villingen-Schwenningen, Villingen-Schwenningen (B Hohenstein); University Clinic Carl Gustav Carus, Dresden (C Hugo); Klinikum Bad Bramstedt GmbH, Bad Bramstedt (C Iking-Konert and F Arndt); Asklepios Klinik, Hamburg (T Kubacki and I Kotter); University Clinic Schleswig-Holstein, Luebeck (P Lamprecht); University Clinic Leipzig, Leipzig (T Lindner and J Halbritter); Charité - Universitätsmedizin Berlin, Berlin (H Mehling); Universität München – Großhadern, Munich (U Schönermark); University Clinic Freiburg, Freiburg (N Venhoff); University Clinic Munich, Munich (V Vielhauer); University Clinic Essen, Essen (O Witzke). Hungary: Qualiclinic Kft, Budapest (I Szombati); DEOEC Rheumatology Faculty, Debrecen (G Szucs). Italy: National Coordinating Center: IRCCS Azienda Ospedaliera Universitaria San Martino, Genova (G Garibotto); ASST Santi Paolo e Carlo-Presidio Ospedale San Carlo, Milan (F Alberici); Istituto Clinico Humanitas, Rozzano (E Brunetta); IRCCS Ospedale San Raffaele, Milan (L Dagna); Azienda Sanitaria Universitaria Integrata di Udine, Udine (S De Vita); Azienda Ospedaliero-Universitaria Careggi, Florence (G Emmi); AOU Ospedali Riuniti di Ancona, Torrette Ancona (A Gabrielli); Azienda Ospedaliero Universitaria di Parma, Parma (L Manenti); ASST di Monza-Ospedale San Gerardo, Monza (F Pieruzzi); ASL Città di Torino - Ospedale San Giovanni Bosco, Torino (D Roccatello); Azienda Unità Sanitaria Locale di Reggio Emilia, Reggio Emilia (C Salvarani). Japan: National Coordinating Investigator: Prof M Harigai, Tokyo Women's Medical University, Tokyo; Kagawa University Hospital, Kagawa (H Dobashi); Hokkaido University Hospital, Hokkaido (T Atsumi); University of Miyazaki Hospital, Miyazaki (S Fujimoto); Teikyo University Chiba Medical Center, Chiba (N Hagino); National Hospital Organization Yokohama Medical Center, Yokohama (A Ihata); Kyorin University Hospital, Tokyo (S Kaname); Keio University Hospital, Tokyo (Y Kaneko); Juntendo University Shizuoka Hospital, Shizuoka (A Katagiri); Nagoya Medical Center, Aichi (M Katayama); Yokohama City University Hospital, Kanagawa (Y Kirino); National Hospital Organization Kanazawa Medical Center, Ishikawa (K Kitagawa); Akita University Hospital, Akita City (A Komatsuda); Teikyo University Hospital, Tokyo (H Kono); Saitama Medical Center, Saitama (T Kurasawa); National Hospital Organization Chiba East Hospital, Chiba (R Matsumura); Saitama Medical University Hospital, Saitama (T Mimura); Kobe University Hospital, Hyogo (A Morinobu); Shimane University Hospital, Shimane (Y Murakawa); Nagoya City University Hospital, Aichi (T Naniwa); Toho University Omori Medical Center, Tokyo (T Nanki); Hamamatsu University Hospital, Shizuoka (N Ogawa); National Hospital Organization Tokyo Medical Center, Tokyo (H Oshima); Okayama University Hospital, Okayama (K Sada); Hiroshima University Hospital, Hiroshima (E Sugiyama); Osaka Medical College Hospital, Osaka (T Takeuchi); Toyama University Hospital, Toyama (H Taki); Juntendo University Hospital, Tokyo (N Tamura); Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka (T Tsukamoto); University of Tsukuba Hospital, Ibaraki (K Yamagata); Okayama Saiseikai General Hospital, Okayama (M Yamamura). The Netherlands: Erasmus MC, Rotterdam (P van Daele); Groningen Universitair Medisch Centrum, Groningen (A Rutgers); Leids Universitair Medisch Centrum, Leiden (Y Teng). New Zealand: National Coordinating Center: Dunedin Hospital, Dunedin (R Walker); Christchurch Clinical Studies Trust, Christchurch (I Chua); Auckland City Hospital, Auckland (M Collins); Waikato Hospital, Hamilton (K Rabindranath); North Shore Hospital, Takapuna, Auckland (J de Zoysa). Norway: National Coordinating Center: Akershus Universitetssykehus, Nordbyhagen (M Svensson); Oslo Universitetssykehus, Oslo (B Grevbo); University Hospital of North Norway, Tromsø (S Kalstad). Republic of Ireland: National Coordinating Center: Beaumont Hospital, Dublin (M Little); Cork University Hospital, Cork (M Clarkson); St Vincent's University Hospital, Dublin (E Molloy). Spain: Hospital Vall D Hebron, Barcelona (I Agraz Pamplona); Hospital Sant Joan de Deu, Barcelona (J Anton); Hospital Universitario Infanta Sofia, San Sebastian de los Reyes, Madrid (V Barrio Lucia); Hospital Da Costa, Burela (S Cigarran); Hospital Clinic Barcelona – Autoimmune Diseases Department, Barcelona (M Cinta Cid); Fundacio Puigvert, Barcelona (M Diaz Encarnacion); Hospital Universitari de Bellvitge, Barcelona (X Fulladosa Oliveras); Hospital del Mar, Barcelona (M Jose Soler); Hospital Germans Trias i Pujol, Badalona (H Marco Rusinol); Hospital 12 de Octubre, Madrid (M Praga); Hospital Clinic Barcelona, Barcelona (L Quintana Porras); Hospital Universitari Arnau de Vilanova, Lleida (A Segarra). Sweden: National Coordinating Center: Karolinska University Hospital, Stockholm (A Bruchfeld); Linköping University, Linköping (M Segelmark); Uppsala University Hospital, Uppsala (I Soveri); Örebro University Hospital, Örebro (E Thomaidi); Skane University Hospital, Malmö (K Westman). Switzerland: National Coordinating Center: Kantonsspital St Gallen, St Gallen (T Neumann); CHUV Lausanne, Lausanne (M Burnier); University Hospital Basel, Basel (T Daikeler); Hôpital Fribourgeois, Fribourg (J Dudler); Immunologie- Zentrum Zürich, Zürich (T Hauser); Universitätsspital Zürich, Zürich (H Seeger); Inselspital,

Universitätsspital Bern, Bern (B Vogt). United Kingdom: National Coordinating Center: Addenbrooke's Hospital - Cambridge University Hospitals, Cambridge (D Jayne); Leicester General Hospital, Leicester (J Burton and R Al Jayoussi); Leeds Childrens Hospital, Leeds (T Amin); Leeds Teaching Hospitals NHS Trust, Leeds (J Andrews); Freeman Hospital, Newcastle upon Tyne (L Baines); Great Ormond Street Hospital for Children, London (P Brogan); Southend University Hospital, Westcliff on Sea (B Dasgupta); Kent and Canterbury Hospital, Canterbury – Kent (T Doulton); Royal Berkshire Hospital, Reading, Berkshire (O Flossmann); University Hospital of Wales, Cardiff (S Griffin); Royal Liverpool University Hospital, Liverpool (J Harper); University of Birmingham, Birmingham (L Harper); University Aberdeen, Aberdeen (D Kidder); Russells Hall Hospital, Dudley (R Klocke); Queens Medical Centre, Nottingham (P Lanyon); Nuffield Orthopaedic Centre, Oxford (R Luqmani); Whytemans Brae Hospital, Fife (J McLaren); St Helier Hospital, Carshalton (D Makanjuola); Alder Hey Children's NHS Foundation Trust, Liverpool (L McCann); Basildon University Hospital, Basildon (A Nandagudi and S Selvan); Salford Royal NHS Foundation Trust Manchester, Salford (E O'Riordan); University of Manchester, Manchester Royal Infirmary, Manchester (M Patel); Queen Elizabeth University Hospital, Glasgow (R Patel); Imperial College Healthcare NHS Trust, London (C Pusey); The Royal London Hospital, London (R Rajakariar); Bristol Royal Infirmary, Bristol (J Robson); Guy's and St Thomas's NHS Foundation Trust, London (M Robson); UCL Centre for Nephrology Royal Free, London (A Salama); Royal Devon and Exeter Hospital, Exeter (L Smyth); Raigmore Hospital, Inverness (J Sznajd); Dorset County Hospital, Dorchester (J Taylor). United States of America: University of Pennsylvania, Philadelphia (P Merkel and A Sreih); Winthrop University Hospital, Mineola (E Belilos); Columbia University Medical Center, New York (A Bomback); Virginia Mason Medical Center, Seattle (J Carlin); University of South Florida, Tampa (Y Chang Chen Lin); University of North Carolina Hospitals, Chapel Hill (V Derebail); MedStar Georgetown University Hospital, Washington (S Dragoi); University of Chicago Medical Center Rheumatology, Chicago (A Dua); Cedars-Sinai Medical Center, Los Angeles (L Forbess); Johns Hopkins Bayview Medical Center, Baltimore (D Geetha); University of Michigan, Ann Arbor (P Gipson); Rhode Island Hospital, Providence (R Gohh); Brookview Hills Research Associates, Winston-Salem (G T Greenwood); Indiana University Nephrology, Indianapolis (S Hugenberg); Western Washington Arthritis Clinic, Bothell (R Jimenez); Northwest Louisiana Nephrology, Shreveport (M Kaskas); University of California, Los Angeles, Santa Monica (T Kermani); Altoona Center for Clinical Research, Duncansville (A Kivitz); University of Utah, Salt Lake City (C Koenig); Cleveland Clinic, Cleveland (C Langford); Northwell Health, Great Neck (G Marder); University of Kentucky Medical Center, Lexington (A Mohamed); Boston University, Boston (P Monach); Arizona Kidney Disease and Hypertension Center Flagstaff, Flagstaff (N Neyra); Arthritis Healthcare Group, Charleston (G Niemer); Massachusetts General Hospital, Boston (J Niles); East Carolina University, Greenville (R Obi); Renal Disease Research Institute, Dallas (C Owens); Washington University School of Medicine, St Louis (D Parks); Colorado Kidney Care, Denver (A Podoll); Ohio State University, Columbus (B Rovin); San Francisco General Hospital Dialysis Center, San Francisco (R Sam); Rheumatology Associates of North Alabama, Huntsville (W Shery); Boise Kidney & Hypertension, PLLC – Meridian, Caldwell (A Silva); Mayo Clinic - Division of Pulmonary & Critical Care Medicine, Rochester (U Specks); Hospital for Special Surgery, New York (R Spiera); University of Kansas Medical Center, Kansas City (J Springer); University of Colorado Denver - School of Medicine, Aurora (C Striebich); Arizona Arthritis & Rheumatology Research, Phoenix (A Swarup); University of Minnesota, Minneapolis (S Thakar); Emory University School of Medicine, Atlanta (A Tiliakos); Arthritis, Autoimmune and Allergy LLC, Daytona Beach (Y Tsai); University of Texas Health Sciences Center, Houston (D Waguespack); Allegheny General Hospital, Pittsburgh (M Chester Wasko).

Contributors DG, DJ and PAM conceived and designed the study. HY performed statistical analyses of the data. DG, AD, JS, CS, DJ and PAM acquired the data. All authors contributed to the analysis and interpretation of data. DG wrote the manuscript. All authors provided critical appraisal of the final manuscript. DG is guarantor for the manuscript.

Funding Funding for this study was provided by ChemoCentryx (a wholly owned subsidiary of Amgen). Some data analysis and medical writing support was provided by Amgen.

Competing interests DG reports consultant fees from Amgen, ChemoCentryx (a wholly owned subsidiary of Amgen), Aurinia, Otsuka, Calliditas Therapeutics, and GlaxoSmithKline (GSK). AD reports consultant fees from Amgen, ChemoCentryx (a wholly owned subsidiary of Amgen), Novartis, Sanofi, AbbVie and GSK, grants from the Rheumatology Research Foundation, advisory board participation for Sanofi and GSK, honoraria and travel support for lectures from GSK, and a leadership role at the Vasculitis Foundation and Chicago Rheumatism Society. HY reports stocks from and was an employee of ChemoCentryx (a wholly owned subsidiary of Amgen) and Amgen. JS reports consultant fees from ChemoCentryx (a wholly owned subsidiary of Amgen). CS reports royalties from UpToDate and consultant fees from Amgen, Novartis, CSL Vifor, Lilly, Boehringer Ingelheim, Pfizer and Janssen. DJ reports consultant fees from AstraZeneca, Boehringer Ingelheim, ChemoCentryx (a wholly owned subsidiary of Amgen), GSK, Novartis, Roche and CSL Vifor, and grant or research support from GSK and Roche. PM reports royalties from UpToDate,

consultant fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ChemoCentryx (a wholly owned subsidiary of Amgen), Eicos, Electra, Forbuis, Genentech/Roche, GSK, InflaRx, Neutrolis, Novartis, Sanofi and Takeda, support for travel to a scientific meeting from ChemoCentryx (a wholly owned subsidiary of Amgen), stock options from Kyverna and Sparrow, and grants to his institution from the National Institutes of Health, Food and Drug Administration, Vasculitis Foundation, American College of Rheumatology and EULAR.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The ADVOCATE study was conducted in compliance with the Declaration of Helsinki, International Council for Harmonisation Guidelines for Good Clinical Practice and local country regulations. Study protocols were approved by each centre's Institutional Review Board or Independent Ethics Committee. Patients or a parent or guardian provided written informed consent before study initiation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request>.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Duvuru Geetha <http://orcid.org/0000-0001-8353-5542>
Anisha Dua <http://orcid.org/0000-0002-3508-9290>
Jason Springer <http://orcid.org/0000-0002-3903-6049>
Carlo Salvarani <http://orcid.org/0000-0001-5426-5133>
David Jayne <http://orcid.org/0000-0002-1712-0637>
Peter Merkel <http://orcid.org/0000-0001-9284-7345>

REFERENCES

- 1 Fauci AS, Katz P, Haynes BF, *et al*. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979;301:235–8.
- 2 Stone JH, Merkel PA, Spiera R, *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
- 3 Aqeel F, Xu L, Tomar O, *et al*. Practice patterns of induction therapy in severe anti-neutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep* 2022;7:2704–8.
- 4 Jayne DRW, Merkel PA, Schall TJ, *et al*. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021;384:599–609.
- 5 Jennette JC. L17. What can we expect from the revised Chapel hill consensus conference nomenclature of vasculitis? *Presse Med* 2013;42:550–5.
- 6 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.
- 7 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.
- 8 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* 2021;9:365–72.
- 9 Ware JE. SF-36 health survey update. *Spine (Phila Pa 1976)* 2000;25:3130–9.
- 10 Herdmann 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.
- 11 Levey AS, Coresh J, Greene T, *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–54.
- 12 Kasai T, Miyauchi K, Kajimoto K, *et al*. Prognostic significance of glomerular filtration rate estimated by the Japanese equation among patients who underwent complete coronary revascularization. *Hypertens Res* 2011;34:378–83.
- 13 Schwartz GJ, Muñoz A, Schneider MF, *et al*. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629–37.

- 14 International Conference on Harmonisation (ICH. Introductory guide Meddra version 19.1. 2016. Available: https://admin.meddra.org/sites/default/files/guidance/file/intguide_19_1_english.pdf [Accessed 20 Mar 2023].
- 15 U.S Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0. 2017. Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf [Accessed 20 Mar 2023].
- 16 Chung SA, Langford CA, Maz M, *et al.* American college of rheumatology/vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol* 2021;73:1366–83.
- 17 Rovin BH, Adler SG, Barratt J, *et al.* KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney International* 2021;100:S1–276.
- 18 Hellmich B, Sanchez-Alamo B, Schirmer JH, *et al.* EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis* 2024;83:30–47.
- 19 Sanders JSF, Abdulahad WH, Stegeman CA, *et al.* Pathogenesis of antineutrophil cytoplasmic autoantibody-associated vasculitis and potential targets for biologic treatment. *Nephron Clin Pract* 2014;128:216–23.
- 20 Vassilopoulos A, Vassilopoulos S, Kalligeros M, *et al.* Incidence of serious infections in patients with ANCA-associated vasculitis receiving immunosuppressive therapy: a systematic review and meta-analysis. *Front Med (Lausanne)* 2023;10:1110548.
- 21 Terrier B, on behalf of French Vasculitis Study Group. SP0120 current controversies in the use of Rituximab for induction and maintenance of AAV disease. *Ann Rheum Dis*; 2018;77 32
- 22 Roberts DM, Jones RB, Smith RM, *et al.* Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015;57:60–5.
- 23 Tieu J, Smith RM, Gopaluni S, *et al.* Rituximab associated hypogammaglobulinemia in autoimmune disease. *Front Immunol* 2021;12:671503.
- 24 Thery-Casari C, Euvrard R, Mainbourg S, *et al.* Severe infections in patients with anti-neutrophil cytoplasmic antibody-associated vasculitides receiving rituximab: a meta-analysis. *Autoimmun Rev* 2020;19:102505.
- 25 Strangfeld A, Schäfer M, Gianfrancesco MA, *et al.* Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2021;80:930–42.
- 26 Floyd L, Elsayed ME, Seibt T, *et al.* SARS-CoV-2 vaccine response in patients with antineutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep* 2022;7:629–32.
- 27 Kant S, Morris A, Ravi S, *et al.* The impact of COVID-19 pandemic on patients with ANCA associated vasculitis. *J Nephrol* 2021;34:185–90.
- 28 Specks U, Ikle D, Stone JH. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013;369:1865–6.
- 29 Jones RB, Tervaert JWC, Hauser T, *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363:211–20.
- 30 Alberici F, Smith RM, Jones RB, *et al.* Long-term follow-up of patients who received repeat-dose Rituximab as maintenance therapy for ANCA-associated vasculitis. *Rheumatology (Oxford)* 2015;54:1153–60.
- 31 Habibi MA, Alesaeidi S, Zahedi M, *et al.* The efficacy and safety of Rituximab in ANCA-associated vasculitis: a systematic review. *Biology (Basel)* 2022;11:1767.
- 32 Smith RM, Jones RB, Specks U, *et al.* Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. *Ann Rheum Dis* 2023;82:937–44.
- 33 Terrier B, Pagnoux C, Perrodeau É, *et al.* Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 2018;77:1150–6.
- 34 Strand V, Jayne DRW, Horomanski A, *et al.* The impact of treatment with Avacopan on health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis: a post-hoc analysis of data from the ADVOCATE trial. *The Lancet Rheumatology* 2023;5:e451–60.
- 35 Robson J, Doll H, Suppiah R, *et al.* Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European vasculitis study group trials. *Rheumatology (Oxford)* 2015;54:471–81.
- 36 Furuta S, Ikeda K, Nakajima H. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA* 2021;326:1536–7.
- 37 Walsh M, Merkel PA, Peh C-A, *et al.* Plasma exchange and glucocorticoids in severe ANCA associated vasculitis. *N Engl J Med* 2020;382:622–31.
- 38 Stone JH, McDowell PJ, Jayne DRW, *et al.* The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum* 2022;55:152010.