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CLINICAL SCIENCE

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

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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.

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.

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 (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

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/m^2 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 m^2 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.2[9] 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 m^2 was also analysed. eGFR (in mL/min/1.73 m^2) 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 reproportions 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 m^2 from a mean (SD) of 50.8 (29.8) mL/min/1.73 m^2 at baseline. In the prednisone taper group, the LS mean change was 2.8 mL/min/1.73 m^2 from a mean (SD) of 46.8 (26.4) mL/min/1.73 m^2 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 m^2 at baseline, the LS mean increase in eGFR at week 52 in the avacopan group was 8.7 mL/min/1.73 m^2 from a mean (SD) of 21.0 (3.7) mL/min/1.73 m^2 at baseline. In the prednisone taper group, the LS mean change was 6.6 mL/min/1.73 m^2 from a mean (SD) of 21.0 (4.5) mL/min/1.73 m^2 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 m^2 in the avacopan group and 4.1 mL/min/1.73 m^2 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 m^2 in the avacopan group and 2.8 mL/min/1.73 m^2 in the prednisone taper group at week 52. Patients with baseline eGFR<30 mL/min/1.73 m^2 had even higher increases of 8.7 mL/min/1.73 m^2 and 6.6 mL/min/1.73 m^2, 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

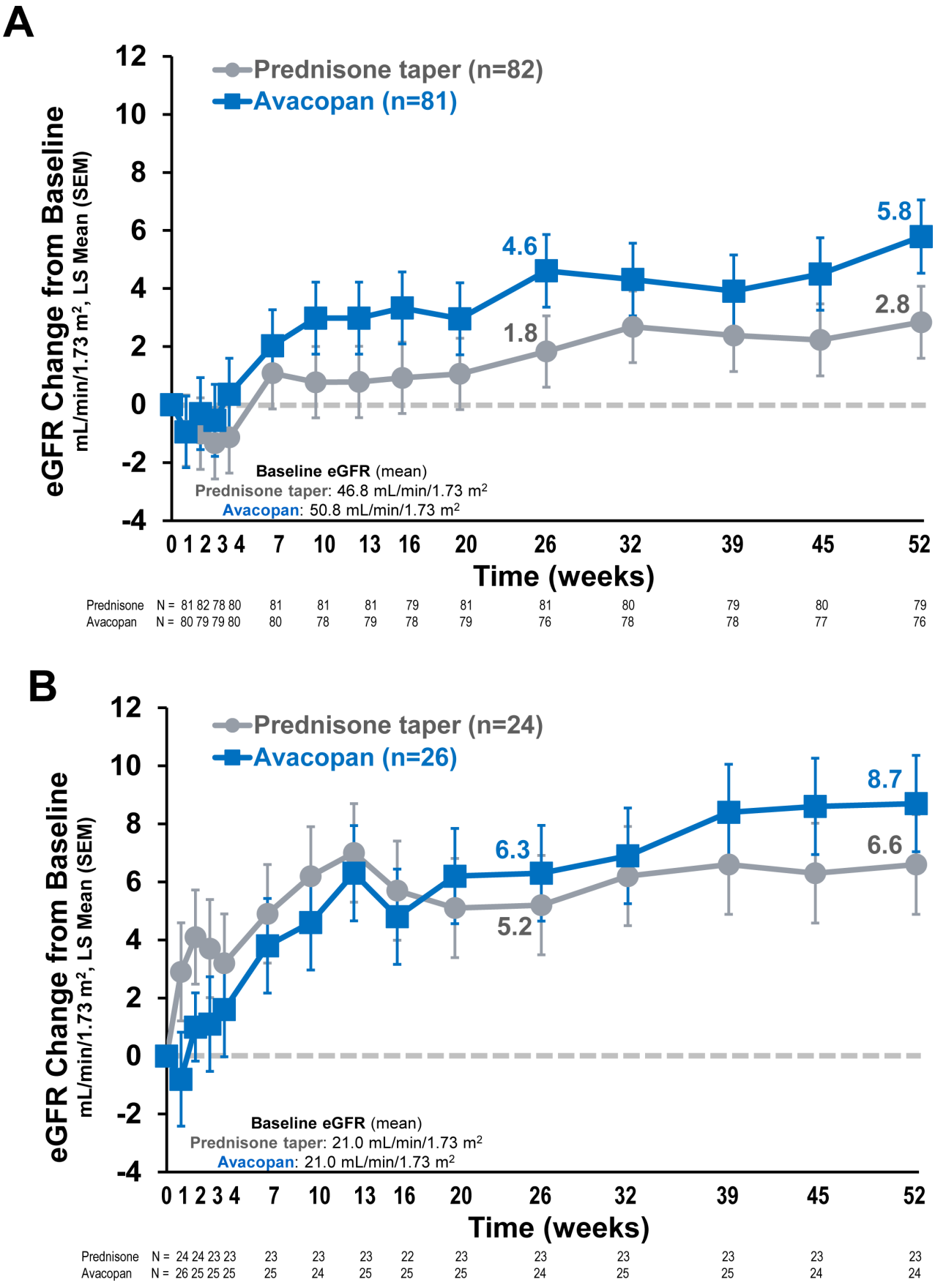

Figure 1 Change from baseline in estimated glomerular filtration rate in patients with (A) renal disease at baseline and (B) renal disease and an estimated glomerular filtration rate <30 mL/min/1.73 m^2 at baseline. LS mean and SEM are from mixed effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a covariate. eGFR, estimated glomerular filtration rate; LS mean, least squares mean.

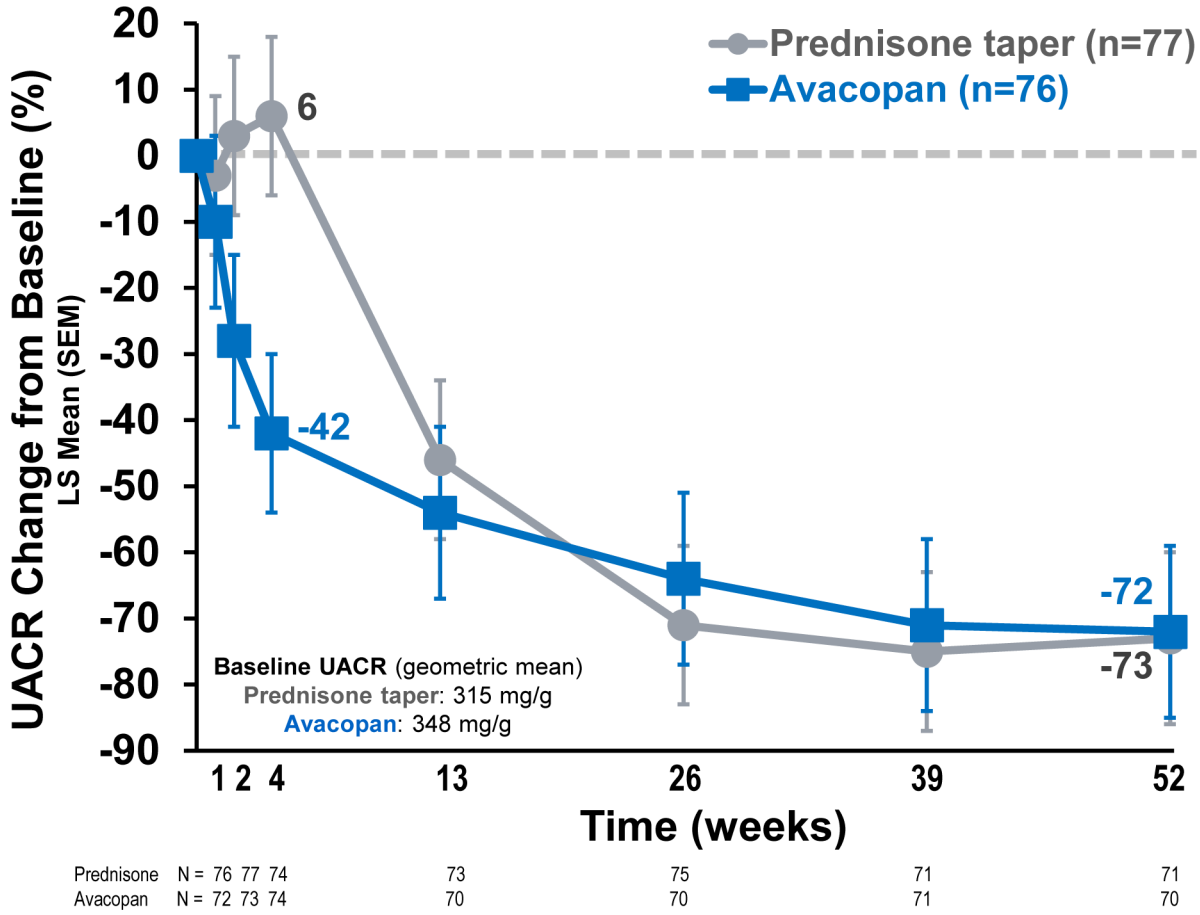

Figure 2 Percent change from baseline in urinary albumin to creatinine ratio in patients with albuminuria (≥10 mg/g creatinine) at baseline. LS mean and SEM are from mixed effects models for repeated measures with treatment group, visit and treatment-by-visit interaction as factors and baseline as a 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.

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)

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 m^2 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

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.

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