Avacopan with combined cyclophosphamide and rituximab for induction therapy in severe ANCA-associated vasculitis: retrospective observational study of 30 patients in two German referral centres

G. Assmann[1,2], E. Adjailia[3], S. Klapa[3], K. von Allwoerden[3], K. Amann[4], R. Turkiewicz[5], J. Radermacher[6], P. Lamprecht[3]

[1]Department of Rheumatology, RUB University Hospital Minden JWK; [2]Jose-Carreras Centre for Immunogenetics and Gene Therapy, University Medical School of Saarland; [3]Department of Rheumatology and Clinical Immunology, University of Luebeck; [4]Department of Nephropathology, University Hospital of Erlangen; [5]Department of Pulmonology, RUB University Hospital Minden JWK; [6]Department of Nephrology, RUB University Hospital Minden JWK, Minden, Germany.

Abstract

Objective

Combination therapy of rituximab (RTX) and cyclophosphamide (CYC) can be considered for the induction of remission in severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The presented study reports on the safety and efficacy of the complement C5a receptor inhibition with avacopan in the patients with severe ANCA-associated vasculitis treated with RTX and CYC in combination.

Methods

Retrospective analysis of the clinical course, response to and safety of avacopan in combination with RTX and CYC in 30 patients with severe ANCA-associated vasculitis with renal and at least two further organ-threatening involvement treated in two German referral centres.

Results

The median observation time was 49 weeks (range 26-52). All patients achieved remission by week 24. Mean BVAS score was 22.8 (range 12-53) at baseline; mean eGFR increased from 44.0 ml/min per 1.73m^2 at baseline to 57.6 ml/min per 1.73m^2 by week 52. GC comedication was discontinued in 17 of 29 (58.6%) patients by week 24, and in 23 of 28 (82.1%) by week 52. One patient discontinued avacopan treatment due to urosepsis, another due to refractory disease. There was a significant difference in dialysis dependency of GC-free patients versus GC-treated patients at week 24 (n=1 vs. 4, p=0.048, OR 0.12, CI:0.01-1.25).

Conclusion

In this observational study, avacopan as GC-sparing agent appeared safe and efficacious in combination with RTX and CYC for remission induction in severe ANCA-associated vasculitis. In this subgroup, prospective studies are needed to determine the efficacy and safety of avacopan in combination with RTX and CYC for guidance of a GC-sparing strategy.

Key words

granulomatosis with polyangiitis, vasculitis, ANCA, avacopan, cyclophosphamide, rituximab

*Gunter Assmann, MD, Prof**
*El-Baraa Adjailia, MD**
Sebastian Klapa, MD
Katja von Allwoerden, MD
Kerstin Amann, MD
Ryszard Turkiewicz, MD
Joerg Radermacher, MD, Prof
Peter Lamprecht, MD, Prof

**Contributed equally.*

Please address correspondence to:
Prof Gunter Assmann
Department of Rheumatology,
RUB University Hospital JWK Minden,
D-32429 Minden, Germany.
E-mail:
gunter.assmann@muehlenkreiskliniken.de
ORCiD: 0000-0002-3216-9340

Received on December 5, 2024; accepted in revised form on April 30, 2025.

Competing interests: G. Assmann has received research grant from Boehringer Ingelheim, CLS Vifor Pharm, AstraZeneca, UCB, AbbVie. S. Klapa has received grant support from the Federal Ministry of Defence, German Society for Rheumatology, consulting fees from AstraZeneca and Galapagos, honoraria for lectures from AbbVie, AstraZeneca, Galapagos, Novartis and Pfizer and participation at advisory boards from AstraZeneca and Galapagos.
P. Lamprecht has received grant support from the German Research Society, Federal Ministry of Education and Research, German Society for Rheumatology, John Grube Foundation and Vifor Pharma, consulting fees from AbbVie, GSK, Novartis, UCB and Vifor Pharma, honoraria for lectures from AstraZeneca, Boehringer Ingelheim, GSK, Janssen, Novartis, UCB and Vifor Pharma, support for meeting attendance from Vifor Pharma, and participation at advisory boards from AstraZeneca, GSK and Vifor Pharma.
The other authors have declared no competing interests.

Introduction

Life- and organ-threatening manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represent a major challenge for treatment. Glomerulonephritis in particular continues to have a critical long-term prognosis for the preservation of organ function and overall survival (1, 2). Moreover, infections and active vasculitis have remained the major causes of death in the first year after diagnosis (1).

In AAV with severe ANCA-associated GN, the combination of rituximab (RTX) and cyclophosphamide (CYC) can be considered for remission induction as an alternative for CYC alone with glucocorticoid (GC)-taper or the oral C5a receptor (C5aR) inhibitor avacopan according to the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guideline (3,4). Lack of experience with RTX with concomitant CYC in severe AAV with ANCA-associated GN with or without further organ-threatening involvement is emphasised in the 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations (5). Randomised controlled trials showing a benefit of the combination therapy with RTX and CYC over RTX alone are missing (5). A retrospective study (CycLowVas) suggested a superior long-term outcome of the combination therapy with RTX and CYC in severe ANCA-associated GN in comparison to historical group of propensity-matched controls from 4 previous European Vasculitis Study Group (EUVAS) trials (6). In detail, the patients' characteristics of the study showed additional extrarenal manifestations which includes further organ-threatening manifestations resulting in a high BIVAS score of 18.5 (mean). According to the 2022 EULAR recommendations and 2024 KDIGO guideline for the management of AAV, avacopan may be considered as an alternative to GC-taper for vital organ- and life-threating AAV in combination with RTX or CYC or combined RTX and CYC, respectively (3, 5, 6). In the ADVOCATE trial, a randomised controlled phase 3 trial comparing the efficacy and safety of avacopan *versus* GC taper in combination with RTX or CYC for the induction of remission, avacopan was superior to GC-taper with respect to sustained remission at week 52. Moreover, avacopan improved renal recovery and efficiently reduced GC exposure and GC-related toxicity and serious adverse events including infections (7, 8). A retrospective postmarketing analysis of AAV patients (which also be included from the ADVOCATE trial) from 12 centres in the USA was previously published to demonstrate well promising results due to remission rate und GC-sparing effect by acavopan; moreover, a subgroup of the cohort with severe renal manifestation was also treated with the combination of RTX and CYC (9).

In this retrospective observational study, we assessed the outcomes of 30 patients from two German referral centres treated with avacopan and a combination therapy with RTX and CYC for remission induction in severe AAV with renal and additionally at least two organ-threatening manifestations.

Patients and methods

Study population

We conducted a retrospective observational study on 30 patients treated with avacopan aiming at reduction of GC exposure using the combination therapy with RTX and CYC for remission induction in severe AAV presenting ANCA-associated GN, reduced kidney function and at least two additional organ-threatening manifestations (26 of them with lung manifestation) between February 2022 and December 2023. In particular, severe AAV was defined according to the PEXIVAS study, the status of organ-threatening manifestations was outlined in the 2022 EULAR recommendations (5, 10). Fifteen patients each from the RUB University Hospital Minden JWK and University Medical Centre Schleswig-Holstein campus Luebeck were included. All patients fulfilled the Chapel Hill Consensus Conference (CHCC) definitions for AAV, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA), and the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatol-

ogy (EULAR) classification criteria for GPA and MPA (11, 12). Patients were either proteinase 3 (PR3)- or myeloperoxidase (MPO)-ANCA positive. In all patients, renal involvement was histologically confirmed showing pauci-immune necrotising glomerulonephritis, consistent with renal involvement in AAV. For disease activity and damage assessment, Birmingham Vasculitis Activity Score (BVAS) V3.0 and Vasculitis Damage Score (VDI) were applied (13, 14). The AAV renal risk score (basing on percentage of normal glomeruli score, tubular atrophy score and eGFR score) were evaluated out of the renal biopsy combined with the eGFR at baseline (15).

This was a retrospective study meeting the criteria for a service evaluation study and hence did not require approval from a research ethics committee. All patients gave their consent for treatment and received standard care according to our accepted unit protocols.

Treatment regime

For the induction of remission, combination therapy of RTX and CYC was administered according to the RITUXVAS protocol with 375 mg/m^2 RTX i.v. weekly for 4 consecutive weeks and CYC at a dose of 15 mg/kg i.v. with the first and third RTX infusion (n=15) (16) or the CycLowVas protocol with 1 g RTX i.v. at a two-week interval and CYC at a dose of 10 mg/kg i.v. for the first two infusions at a two-week interval and at least 500 mg i.v. for the subsequent four biweekly infusions (n=15) (6). Patients received methylprednisolone at a maximum dose of 500 mg i.v. per day initially for three consecutive days. Subsequently, oral GC at 1 mg/kg daily (maximum 75 mg) was started and the GC dose tapered at the physician`s discretion. Avacopan was initiated in all patients within 4 weeks of induction therapy. All AAV patients received pneumocystis prophylaxis with cotrimoxazole according to current treatment guidelines (3 x 960mg weekly with respective dose reduction depending on renal function). Following remission induction, all AAV patients received RTX maintenance therapy according to the MAINRITSAN regimen starting with 1 g RTX i.v. 4 months after combined RTX and CYC remission induction (RITUXVAS regimen) and 4 weeks after the last CYC infusion (CycLowVas regimen), respectively. Thereafter, RTX maintenance therapy was continued with 500 mg RTX i.v. every 6 months (17). Patients undergoing plasma exchange (PLEX) received 7 treatments within 14 days with 60 ml of albumin replacement per kilogram (kg) of body weight by means of centrifugation similar to the use of PLEX in the PEXIVAS trial (10).

Table I. Baseline clinical characteristics of the AAV patients (n=30).

age (years; median, range)	59, 20-81
female/male (n/n)	15/15
new-onset/relapsing disease (n/n)	27/3
PR3-/MPO-ANCA positive AAV (n/n)	20/10
GPA/MPA (n/n)	20/10*
renal biopsy with necrotising glomerulonephritis (n)	30
ANCA renal risk score (at diagnosis) [22]	
Low n (%)	6 (20%)
Medium n (%)	9 (30%)
High n (%)	6 (20%)
Unclassified #	9 (30%)
extra-renal organ involvement (n)	30
lung (n)	26
CNS (n)	5
heart (n)	3
Eye (n)	7
ENT (n)	18
GIT (n)	3
peripheral nervous system (n)	13
C-reactive protein (mg/l ± SEM)	64.1 (15.1)
Serum creatinine (umol/l)	241.5 (37.5)
eGFR (ml/min ± SE) 44.0 (5.6)	
eGFR <50 ml/min (n)	21
eGFR < 15 ml/min (n) (%)	6 (20)
ESKD followed by dialysis (n) (%)	5 (16.5)
albumin/creatinine (urine) ± SEM	494.2 (104.0)
BVAS V3.0 (mean, range)	23, 12-53

AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PR3: proteinase 3; MPO: myeloperoxidase; GN: glomerulonephritis; CNS: central nervous system; ENT: ear, nose and throat; GIT: gastrointestinal part; ± SEM: ± standard error; eGFR: estimated glomerular filtration rate; BVAS: Birmingham vasculitis activity score V3.0 [11].
*GPA patients (n=20) were PR-3, MPA patients (n=10) were MPO-positive.
#AAV-GN was diagnosed by pathologist in specimen with 3 or less glomeruli.

Subgroup analysis and statistics

The analysis of AAV subgroups was stratified into two groups according to whether GC had been successfully discontinued at week 24 or by week 52. Differences in the respective disease-related activity parameters between the groups of GC-free and ongoing GC treated AAV patients were determined according to parametric test procedures with t-test for continuous variables and with chi-square testing (with indication of the odd-ratio) for numerical variables using SPSS (v. 29.0.1.1) as statistical software, a p-value <0.05 was evaluated as significant. Furthermore, the treatment effects on the extra-renal manifestations were analysed due to the categories: improvement, no change, and aggravation in week 24, respectively; hereby, improvement was defined as any improvement compared to baseline reflecting (partial) remission.

Results

Overall outcome

Thirty patients with AAV with ANCA-associated GN and at least two organ-threatening manifestations treated with

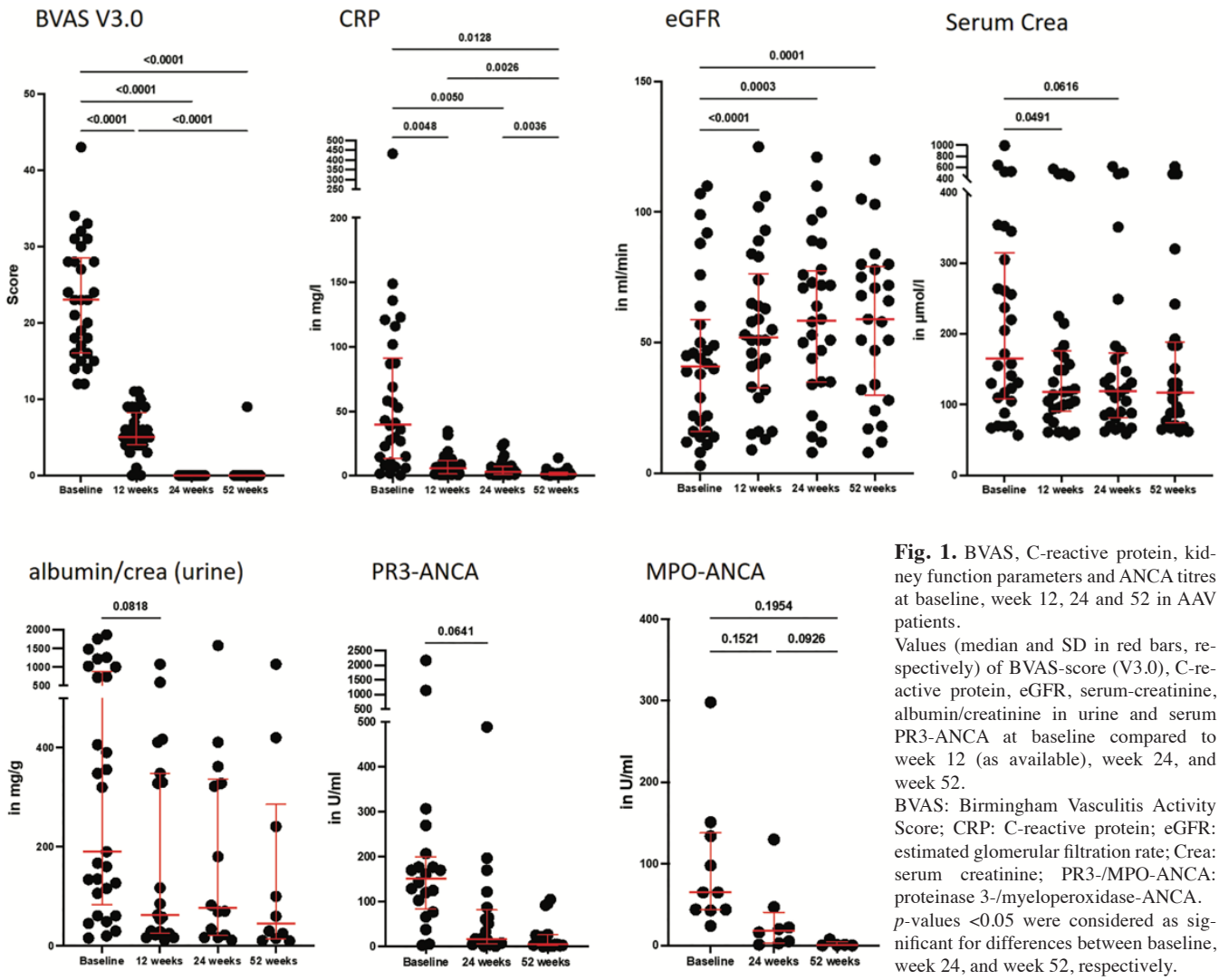

Fig. 1. BVAS, C-reactive protein, kidney function parameters and ANCA titres at baseline, week 12, 24 and 52 in AAV patients.
Values (median and SD in red bars, respectively) of BVAS-score (V3.0), C-reactive protein, eGFR, serum-creatinine, albumin/creatinine in urine and serum PR3-ANCA at baseline compared to week 12 (as available), week 24, and week 52.
BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Crea: serum creatinine; PR3-/MPO-ANCA: proteinase 3-/myeloperoxidase-ANCA.
p-values <0.05 were considered as significant for differences between baseline, week 24, and week 52, respectively.

combined RTX and CYC therapy and avacopan for GC-taper for the induction of remission were included in this retrospective study. Twenty-seven patients had new-onset disease with initial diagnosis of AAV. Three patients had a relapse of known AAV while being on remission maintenance therapy with methotrexate (n=1), azathioprine (n=1) each with low dose GC, and one patient on RTX maintenance. Apart from renal involvement with biopsy-proven necrotising glomerulonephritis, all patients had at least two other organ-threatening manifestations. At baseline, mean BVAS V3.0 was of 22.8 (range 12-53), mean CRP 64.1 mg/l (SD±82.5; SEM±15.1), mean creatinine 241.5 μmol/I (SD±205.4; SEM37.5) and mean eGFR 44.0 ml/min per 1.73m^2 (SD±30.8; SEM±5.6); the renal biopsy confirmed in all AAV-patients the ANCA-associated GN, resulting in AAV-renal risk score of medium in 9 (30%) and high in 6 (20%) patients (Table I).

Remission was induced with combined RTX and CYC therapy according to the RITUXVAS protocol in 15 patients and according to the CycLowVas protocol in another 15 patients. Avacopan was added and GC tapered in all patients. Three patients received PLEX. Mean creatinine levels declined from 241.5 µmol/l (median:165 µmol/l; SD±205.4; SEM±37.5) at baseline to 171.8 µmol/l (median:117 µmol/l; SD±149.3; SEM±30.0) by week 52. Mean eGFR increased from 44.0 ml/min per 1.73m^2 (SD±30.8; SEM±5.6) at baseline to 57.6 ml/min per 1.73m^2 (SD±30.5; SEM±6.1) by week 52 (Fig. 1). The median observation time was 49 weeks (range 26–52). The mean BVAS score was 22.8 (range 12–53) at baseline, all patients achieved remission by week 24 resulting in a BVAS score of 0 (Fig. 1).

Tapering glucocorticosteroids

In 17 of 29 patients (58.6%) GC comedication was discontinued by week 24 and in 23 of 28 (82.1%) patients by week 52 (Fig. 2). In one patient, treatment with avacopan was terminated due to urosepsis at week 8 and in another patient during GC-tapering at week 32 due to a relapse of glomerulonephritis. In this case, therapy was switched to high dose GC and mycophenolate mofetil. One patient in remission choose to stop avacopan therapy on his own decision at week 48. Five patients suffered prolonged neutropenia (>7 days, neutrophils <1.500/µl) during the remission induc-

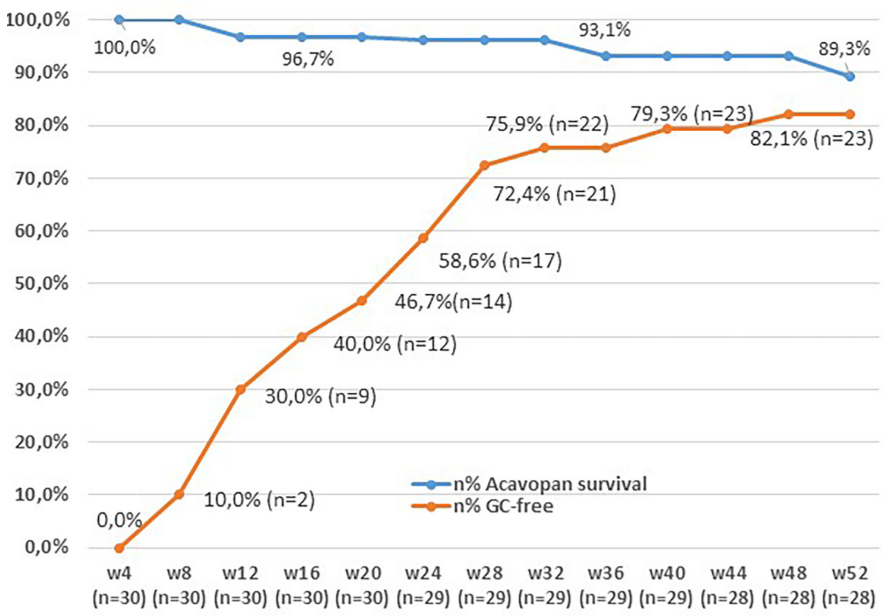

Fig. 2. Survival of AVV patients on avacopan and glucocorticoids over 52 weeks.
N% patients GC-free (orange line) and being on avacopan (blue line) from week 4 to week 52. GC: glucocorticoids.

tion treatment period. Three of them received G-CSF for 3–5 days, whereas the dose of CYC was not adjusted. There were no deaths from the underlying disease or due to comorbidities during the 52-week observation period. Figure 1 summarises the treatment effects on BVAS V3.0, C-reactive protein, eGFR, serum creatinine, albumin/creatinine (urine), PR3- and MPO-ANCA in week 12, 24, and 52 comparing to baseline. Treatment courses resulted in significant reduction of BVAS V3.0 from baseline not only to week 24, but already to week 12 (22.8±1.4 SEM *vs.* 5.7±0.5 SEM, p=0.0001); furthermore, the kidney function parameters eGFR improved significantly from baseline to week 12 (44 µmol/l ±5.6 SEM *vs.* 55.4±5.4 SEM, p=0.0001), week 24 (59.0±5.7 SEM, p=0.0003), and week 52 (57.6±6.1 SEM, p=0.0001).

Table II shows the results of a subgroup analysis of the 27 patients categorised into two groups according to whether GC therapy was discontinued at week 24 or by week 52 (n=16 *vs.* n=11). There was a significant difference in dialysis dependency of GC-free patients versus patients treated with ongoing GC therapy at week 24 (n=1 *vs.* 4, OR 0.12, CI: 0.01–1.25; p=0.048). One of the 5 patients initially requiring haemodialysis, belonging to the ongoing GC treated patient group, remained dialysis dependent. Serum creatinine and albuminuria tended to be higher in the group of patients in whom GC was discontinued at week 24 compared to patients in whom GC therapy was discontinued by week 52. However, reduction of the albumin/creatinine quotient appeared to be more pronounced in the first group than in the latter, but without significant differences between both groups. Differences between the two groups regarding other clinical parameters, *i.e.* VDI, RITUXVAS *vs.* CycLowVas regimen, cumulative CYC dose, seroconversion of PR3-and MPO-ANCA, were not significant.

Extrarenal manifestations

Table III shows the outcome of the 29 AAV patients with regard to their non-renal involvement at week 24; two of them stopped avacopan (n=1 due to infection, one due to relapse). All AAV patients had renal and at least two further organ-threatening involvement (26 of them of the lung), and the following manifestations were also evaluated: CNS, peripheral nervous system, heart and/or gastrointestinal tract (major events), and ENT, eye, skin, joints (minor events). Based on the BVAS, the outcome after 24 weeks was stratified into improvement, no change, and aggravation. There was no deterioration over 24 weeks in any non-renal organ involvement, except of two patients dropped out (see above); however, a persistent *versus* residual manifestation was most frequently seen in peripheral neuropathy (n=7 of 13), CNS (2/5), and arthritis (4/10); in 5 patients residual lung granuloma was observed after 24 weeks.

Discussion

In this retrospective observational study, treatment with avacopan aiming for reduction of GC exposure and improvement of renal function together with combined RTX and CYC therapy appeared to be safe for the induction of remission in severe AAV including ANCA-associated GN as well as two further organ-threatening manifestations. Remission was achieved by week 24 in all patients, and improvement of renal function measured by eGFR was shown in 27 of 30 patients in our study. Although all patients had significant renal involvement, the cohort studied was characterised by severe multi-organ involvement, which was reflected in the high BVAS of 22.8. According to the new KDGIO guidelines, combination therapy with RTX and CYC can be considered if renal function is severely impaired (>serum creatinine 350 µmol/I), however, the KDIGO guidelines had not yet been formulated for the observation period of our study between 2022 and 2024; against this background the retrospective long-term data from McAdoo have already shown positive effects in patients with severe renal involvement less than serum creatinine 350 µmol/I (eGFR ranging from 8 to 86) but multiple organ including involvement (BVAS ranging from 12 to 31) (4, 6, 18). In general, the simultaneous involvement of the kidney and lung in AVV as we observed in our study (in 26 of 30 cases, five of them with alveolar haemorrhage) has been shown to further limit the prognosis which potentially requires intensified treatment (19).

Treatment adherence to avacopan was high (85% in 52 weeks). Avacopan was

Table II. Baseline and follow-up characteristics, respectively, of AAV patients stratified into glucocorticoid-free treatment at week 24 *versus* glucocorticoid treatment past week 24 until maximum week 52 (n=27).

	Glucocorticoid-free at week 24 (n=16)	Glucocorticoid beyond week 24 (n=11)	*p*-value	OR*;CI
Treatment				
treatment regime cyclophosphamide and rituximab according to RITUXVAS vs. CycLowVas regimen	10 vs. 6	5 vs. 6	*0.311*	1.243; 0.64-2.07
cumulative cyclophosphamide dosages g (mean, ± SEM)*	5.2 ± 0.5	5.5 ± 0.7	*0.738*	-1.54-2.14
glucocorticoid tapering in weeks (n± SEM)	18.1 ± 1.8	28.1 ± 5.4	*0.030*	0.48-2.36
Outcome				
CRP (mg/l) week 0 (mean ± SEM)	60.6 ± 12.2	77.3 ± 37.2	*0.678*	-68.54-101.86
CRP max. reduction from week 0 (mean ± SEM)	58.0 ± 12.4	72.9 ± 37.2	*0.711*	-70.42-100.15
Kidney function tests				
urine sediment positive/negative week 24 (n/n)	5/11	2/9	*0.445*	2.05;0.32-13.16
eGFR (ml/min) week 0 (±SEM)	48.2 ± 8.6	46.6 ± 7.5	*0.893*	-25.13-22.04
eGFR increase (ml/min) week 24(±SEM)	17.1 ± 5.0	17.5 ± 4.2	*0.953*	-13.09-13.88
serum crea (µmol/l) week 0 (±SEM)	237.6 ± 55.6	179.6 ± 42.4	*0.415*	-202.03-86.05
albumin/crea (mg/g) week 0 (±SEM)	570.9 ± 154.6	312.2 ± 106.7	*0.182*	-647.18-129.78
albumin/crea reduction at week 24 (mg/g) /±SEM)	497.2 ± 154.6	179.0 ± 106.7	*0.347*	-1102.4-466.1
PR3-/MPO-ANCA				
seroconversion (n=yes /n=no)**	7/8	6/5	*0.691*	0.87;0.45-1.69
Haemodialysis				
transient/permanent (n/n)	1/0	3/1	***0.048***	**0.12;0.11-1.25**
PLEX (n)	1	2	*n.a.*	n.a.
VDI	1.3 ± 0.4	1.3 ± 0.3	*0.991*	-1.15-1.16
BVAS	22.3 ± 1.5	23.6 ± 3.0	*0.705*	-5.06-7.65
ANCA renal risk score [22] low *vs.* medium+high	3 *vs.* 5	3 *vs.* 7	*0.098*	1.67;-0.34-3.41

CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; crea: creatinine; AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; PLEX: plasma exchange; VDI: vasculitis damage index; SE: standard error.
*Dosages including previous applications; **Data only from 26 of 27 patients.

Table III. Outcome of extrarenal manifestations of AAV patients in week 24 (n=29*).

Extrarenal manifestation	Improvement	No change	Aggravation
Lung (n=26)	21 (80,8%)	5 (19.2%)	0
Granuloma/infiltrate (n=24)	19 (79.2%)	5 (20.8%)	0
Alveolar haemorrhage (n=5)**	5 (100%)	0	0
Ear-nose-throat (n=18)	17 (94.4%)	1 (5.6%)	0
CNS (n=5)	3 (60%)	1 (20%)	1 (20%)*
Peripheral N (n=13)	6 (46.2%)	6 (46.2%)	1 (7.6%)*
Heart (n=3)	3 (100%)	0	0
Eye (n=7)	6 (85.7%)	1 (14.3%)	0
GIT (n=3)	3 (100%)	0	0
Skin (n=9)	9 (100%)	0	0
Arthritis (n=10)	6 (60%)	4 (40%)	0

AAV: ANCA-associated vasculitis; CNS: central nervous system; peripheral N: peripheral nervous system; GIT: gastrointestinal part.
*Twenty-nine patients (of n=30) completed observation of 24 weeks being still on avacopan, two of them dropped out because of relapse (n=1) and infection (n=1; but included in analysis).
**Three patients have both granuloma and alveolar haemorrhage, one of them diffuse alveolar haemorrhage (DAH).

stopped due to urosepsis at week 8 in one patient. Another patient had a relapse of glomerulonephritis during GC-taper in week 32. During the remission induction period, prolonged neutropenia was observed in 5 patients. In our case series, no deaths occurred during the 52-week observation period. In the thus far largest and only randomised controlled trial comparing avacopan *versus* GC-taper in combination with RTX or CYC for remission induction in AAV (ADVOCATE trial), serious adverse events were related to relapse of vasculitis and serious infections in 10-15% of the patients during the 52-week observation period (7). Thus, we observed no apparent excess of adverse events in our study despite the use of combined RTX and CYC rather than RTX or CYC alone together with avacopan for the induction of remission. However, this finding is limited by the observational and non-randomised and -controlled character of our study, potentially underreporting and -estimating adverse events compared to controlled studies. Compared to the retrospectively reported data from Zonozi *et al*. (9) the rate of discontinuation of avacopan within 52 weeks were higher

(18/92 AAV patients) due to transaminitis and gastrointestinal-related side effects. It should be emphasised that 43 of the 92 AAV patients also received a combination of CYC and RTX, but were not specifically evaluated with regard to the side effects of avacopan. In addition, the study documented significantly lower disease activity than in our cohort as measured by BVAS 14 *versus* 22.8.

In the ADVOCATE trial, the protocol devised GC-taper to discontinuation within a period of 4 weeks in the avacopan arm and by week 21 in the placebo arm following the screening period (7). However, patients in the avacopan arm received additional GC medication for pre-medication and other reasons. The mean daily GC dose was about one third compared to that of the GC-taper group resulting in lower GC exposure with less serious adverse events, deaths, and infections (7). In the present observational study, tapering of concomitant GC in avacopan-treated patients was left to the physician's discretion. Lack of experience with newly approved avacopan may have biased GC-tapering, thereby impeding faster reduction in our study. Nevertheless, GC was discontinued in more than a half of the patients by week 24 and nearly all patients by week 52 in our study. By contrast, in the PEXIVAS trial which evaluated the use of PLEX and two GC regimens in patients treated with RTX or CYC for the induction of remission, GC treatment was continued at least until week 52 in the reduced-dose and standard-dose GC regimens for remission induction in severe AAV (10). Reduced-dose GC showed similar efficacy compared to standard-dose GC therapy in PEXIVAS trial and was recommended for GC-taper in the 2022 EULAR recommendations (5). However, subgroup analysis showed a trend toward the primary composite outcome of death from any cause or ESKD for patients treated with reduced-dose GC and RTX and a creatinine >300 μmol/l, respectively (10). Thus, the 2024 KDIGO guideline recommended a longer period for GC-tapering (3, 4). Thus, at this time further studies are needed for guidance of tapering concomitant GC therapy in avacopan-treated AAV patients for clinical practice.

In this observational cohort, we included PR3- and MPO-AAV patients with renal involvement and at least two further organ-threatening manifestations. In the PEXIVAS trial, severe AAV was defined as PR3- or MPO-AAV with renal involvement and an eGFR of <50 ml/min per 1.73 m^2 and pulmonary involvement. Contrasting with the PEXIVAS trial (10), renal activity and involvement was histologically confirmed by showing pauci-immune necrotising glomerulonephritis in our study. Patients in our cohort displayed vasculitis activity with a mean baseline BVAS of 23. In the PEXIVAS trial using BVAS/GPA score, a lower baseline score was reported (10). In the RITUXVAS and CycLowVas studies using elder BVAS versions, comparable scores to that in our study were reported (6, 16). In our study, renal recovery with an increase in eGFR from 44.0 at baseline to 57.6 at week 52 was shown. Consistent with disease activity and severity of the patients included in our observational cohort, five patients had initially renal replacement therapy, and one patient of them remained permanently haemodialysis-dependent. Haemodialysis requirement at initial disease presentation was significant less frequent in the group of GC-free AVV patients at week 24 compared to non-GC-free patients (11 *vs*. 4 patients, OR 0.12, CI 0.01-1.25) in our study, whereas the ANCA risk score did not resulted in significant differences. In the ADVOCATE trial, one patient in the avacopan arm and 2 patients in the GC-taper arm required transient haemodialysis (7). Avacopan seems to be of added value to AAV patients with high risk for kidney failure and low eGFR. However, the extent to which these play a causal role in the differences we observed between the early *versus* late GC-free cohort cannot be assessed due to the small number of cases, especially since 4 out of 5 ESKD patients in our cohort received both avacopan and low-dose GC (4, 20). Basically, randomised controlled trials such as the ADVOCATE trial are conducted on selected patient populations, whereas observational studies as the one presented here report on real-world evidence from a non- or less selected patient group (21, 22).

Reporting on the safety and outcomes of the use of avacopan as GC-sparing agent in combination with RTX and CYC for remission induction in severe AAV in a real-world setting represents the strength of this study. In addition, the study also showed an effective response with regard to the most extra-renal manifestations, in detail manifestations of the lung improved in 80.8%, of ENT in 94.4%, of eye in 85.7%, of heart and GIT in all cases; however, joints as well as peripheral nerves the peripheral nervous system showed in 46.2% and 40.0%, respectively, persistent deficits, which most likely indicates a defect healing, according to the VDI. At the same time, limitations in the presented study are the retrospective observational design, potential underreporting and -estimating of adverse events, lack of a control arm and lack of an unequivocally recommended GC-tapering regimen for avacopan-treated patients due to missing data from a randomised controlled study in support of a specific GC-tapering strategy. However, treatment principles applied were relatively uniform due to the cooperation of the two participating referral centres and with regard to the protocols applied based on the RITUXVAS or CycLowVas protocols. The relatively short observation period of the median of 10.8 months and the limited number of cases of 30 AAV patients should be considered in the context of avacopan being available in Germany for less than two years.

In summary, avacopan for reduction of GC-exposure in combination with RTX and CYC appeared to be safe and efficacious for induction of remission in severe AAV showing renal and further organ-threatening involvement, predominantly lung manifestations. Prospective studies are needed to determine (1) the efficacy and safety of avacopan in combination with RTX and CYC compared to RTX alone, (2) the impact on prognosis and mortality, and (3) for guidance of a GC-sparing strategy in clinical practice in this subgroup of AAV patients.

Take home messages

- Avacopan appeared safe and efficacious in combination with RTX and CYC for remission induction in severe ANCA-associated vasculitis.
- All AAV patients achieved remission at week 24 of treatment, GC could be stopped in 58% of the cases within 24 weeks and 82% over 52 weeks.

References

1. SÁNCHEZ ÁLAMO B, MOI L, BAJEMA I *et al*.: Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 2023; 38: 1655-65. https://doi.org/10.1093/ndt/gfac320
2. HEIJL C, MOHAMMAD AJ, WESTMAN K, HÖGLUND P: Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. *RMD Open* 2017; 3: e000435. https://doi.org/10.1136/rmdopen-2017-000435
3. FLOEGE J, JAYNE DRW, SANDERS JF, TESAR V, BALK EM, GORDON C: Executive summary of the KDIGO 2024 Clinical Practice Guideline for the management of ANCA-associated vasculitis. *Kidney Int* 2024; 105: 447-49. https://doi.org/10.1016/j.kint.2023.10.009
4. KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES (KDIGO) ANCA VASCULITIS WORK GROUP: KDIGO 2024 Clinical Practice Guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Kidney Int* 2024; 105: S71-S116. https://doi.org/10.1016/j.kint.2023.10.008
5. 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. https://doi.org/10.1136/ard-2022-223764
6. MCADOO SP, MEDJERAL-THOMAS N, GOPALUNI S, TANNA A, MANSFIELD N, GALLIFORD J: Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephrol Dial Transplant* 2019; 34: 63-73. https://doi.org/10.1093/ndt/gfx378
7. JAYNE DRW, MERKEL PA, SCHALL TJ *et al*.: Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384: 599-609. https://doi.org/10.1056/nejmoa2023386
8. CORTAZAR FB, NILES JL, JAYNE DRW *et al*.: Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of avacopan. *Kidney Int Rep* 2023; 8: 860-70. https://doi.org/10.1016/j.ekir.2023.01.039
9. ZONOZI R, AQEEL F, LE D *et al*.: Real-world experience with avacopan in antineutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep* 2024; 9(6): 1783-91. https://doi.org/10.1016/j.ekir.2024.03.022
10. WALSH M, MERKEL PA, PEH CA *et al*.: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382: 622-31. https://doi.org/10.1056/nejmoa1803537
11. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81: 315-20. https://doi.org/10.1136/annrheumdis-2021-221795
12. SUPPIAH R, ROBSON JC, GRAYSON PC, PONTE C, CRAVEN A, KHALID S: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81: 321-26. https://doi.org/10.1136/annrheumdis-2021-221796
13. MUKHTYAR C, LEE R, BROWN D, CARRUTHERS D, DASGUPTA B, DUBEY S: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32. https://doi.org/10.1136/ard.2008.101279
14. EXLEY AR, BACON PA, LUQMANI RA *et al*.: Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997; 40: 371-80. https://doi.org/10.1002/art.1780400222
15. BRIX SR, NORIEGA M, TENNSTEDT P *et al*.: Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 2018; 94(6): 1177-88. https//doi.org/10.1016/j.kint.2018.07.020
16. JONES RB, TERVAERT JW, HAUSER T *et al*.: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20. https://doi.org/10.1056/nejmoa0909169
17. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80. https://doi.org/10.1056/nejmoa1404231
18. CASAL MOURA M, GAUCKLER P, ANDERS HJ *et al*.: Management of antineutrophil cytoplasmic antibody-associated vasculitis with glomerulonephritis as proposed by the ACR 2021, EULAR 2022 and KDIGO 2021 guidelines/recommendations. *Nephrol Dial Transplant* 2023; 38(11): 2637-51. https://doi.org/10.1093/ndt/gfad090
19. COHEN SP, WODARCYK AJ, WONG A *et al*.: Impact of concurrent glomerulonephritis on outcomes of diffuse alveolar haemorrhage in antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol* 2024; 42(4): 811-15. https://doi.org/10.55563/clinexprheumatol/s9su9e
20. PATEL NJ, JAYNE DRW, MERKEL PA *et al*.: Glucocorticoid Toxicity Index scores by domain in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated with avacopan versus standard prednisone taper: post-hoc analysis of data from the ADVOCATE trial. *Lancet Rheumatol* 2023; 5(3): e130-e138. https://doi.org/10.1016/S2665-9913(23)00030-9
21. KIM HS, LEE S, KIM JH: Real world evidence versus randomized controlled trial: clinical research based on electronic medical records. *Korean Med Sci* 2018; 33: e213. https://doi.org/10.3346/jkms.2018.33.e213
22. TREPPO E, MONTI S, DELVINO P *et al*.: Systemic vasculitis: one year in review 2024. *Clin Exp Rheumatol* 2024; 42(4): 771-81. https://doi.org/10.55563/clinexprheumatol/gkve60