

Real-World Experience with Avacopan in ANCA-Associated Vasculitis in Portugal

Sofia Oliveira Correia^{1,2,3*}, Ivo Laranjinha^{3,4}, Estela Nogueira^{3,5,6}, Anita Cunha⁷, Catarina Tenazinha⁸, Helena Pinto^{3,9,10}, Inês Ferreira^{3,11}, João Fernandes Serodio^{12,13}, José Silvano^{1,2}, Maria João Gonçalves^{14,15}, Miguel Gonçalves¹⁶, Lídia Teixeira¹⁷, Vítor Silvestre Teixeira¹⁸, Alice Lança^{3,5}, António Inácio^{3,18}, Clara Santos^{3,19}, Iolanda Godinho^{3,5,6}, Raquel Vaz^{3,20}, Teresa Moura Jerónimo^{3,21}, Nuno Afonso^{3,9,10}

1. Department of Nephrology, Centro Hospitalar Universitário de Santo António, Unidade Local de Saúde de Santo António, Porto, Portugal.
2. UMIB- Unit for Multidisciplinary Research in Biomedicine, ICBAS- School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; ITR- Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal.
3. Immunonephrology working group of the Portuguese Society of Nephrology, Lisbon, Portugal.
4. Nephrology Department, Unidade Local de Saúde de Lisboa Ocidental, Lisbon, Portugal.
5. Nephrology and Renal Transplantation Department, Unidade Local de Saúde Santa Maria, Lisbon, Portugal.
6. Lisbon Academic Medical Center, Lisbon, Portugal.
7. Rheumatology Department, Unidade Local de Saúde do Alto Minho, Ponte de Lima, Portugal.
8. Rheumatology Department, Unidade Local de Saúde do Algarve, Faro, Portugal.
9. Nephrology Department, Unidade Local de Saúde de Coimbra, Coimbra, Portugal.
10. Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
11. Nephrology Department, Unidade Local de Saúde São João, Porto, Portugal.
12. Systemic Immune-Mediated Diseases Unit, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal.
13. Immune Response and Vascular Disease Group, iNOVA4Health, NOVA Medical School, Lisbon, Portugal.
14. Rheumatology Department, Hospital Egas Moniz, ULSLO, Lisbon, Portugal.
15. Comprehensive Health Research Centre (CHRC), NOVA Medical School, Lisbon, Portugal.
16. Nephrology Department, Hospital Central do Funchal, Funchal, Portugal.
17. Rheumatology Department, SESARAM-EPE, Funchal, Portugal.
18. Nephrology Department, Unidade Local de Saúde da Arrábida, Setúbal, Portugal.
19. Nephrology Department, ULS Gaia/Espinho, Gaia, Portugal.
20. Nephrology Department, Unidade Local de Saúde de Braga, Braga, Portugal.
21. Nephrology Department, Unidade Local de Saúde do Algarve, Faro, Portugal.

<https://doi.org/10.71749/pkj.103>

Abstract

Introduction: Avacopan, a selective C5a receptor inhibitor, has emerged as a potential corticosteroid-sparing treatment in ANCA-associated vasculitis (AAV). This study aims to evaluate its real-world efficacy and safety in Portuguese patients with active AAV.

Methods: We conducted a multicenter retrospective analysis of 15 adult patients with newly diagnosed or relapsing AAV treated with avacopan across nine academic centers in Portugal. Patients received avacopan 30 mg twice daily in conjunction with standard induction and maintenance therapy. Clinical outcomes, including Birmingham Vasculitis Activity Score (BVAS), prednisolone use, renal function, and adverse events, were assessed at 3, 6 and 12 months.

Results: The median patient age was 65 (interquartile range (IQR): 51.5–75.5), and 60% had *de novo* AAV. Most patients (93.3%) presented with systemic manifestations, and renal involvement was seen in 60%. Median time to start avacopan was 3.45 months. Prednisolone was discontinued in eight patients, with a median time to cessation of 44 days post-avacopan initiation. Median BVAS at baseline, 3 and 12 months was 23 (13–28.5), 2 (2–4.5) and 0 (0–0), respectively. This consistent downward trend indicates effective disease control ($p < 0.05$). The median estimated glomerular filtration rate

Received: 03/07/2025 Accepted: 04/09/2025 Published Online: 10/09/2025 Published: 13/10/2025

* **Corresponding Author:** Sofia Oliveira Correia | soacorreia@gmail.com | Department of Nephrology, Centro Hospitalar Universitário de Santo António, Largo do Prof. Abel Salazar, 4099-001 Porto, Portugal

© Author(s) (or their employer(s)) and PKJ 2025. Re-use permitted under CC BY-NC 4.0. (<https://creativecommons.org/licenses/by/4.0/>)

(eGFR) at baseline, 3 and 12 months was 15 (9-31), 38 (20-62) and 48 (36.5-83.5), respectively ($n=9$, $p<0.05$). Safety was generally acceptable; one patient discontinued avacopan due to reversible hepatotoxicity, and one died from sepsis.

Conclusion: In this real-world Portuguese cohort, avacopan was effective in achieving and maintaining clinical remission in AAV, with a notable steroid-sparing effect. In this sample, we have shown the stability of eGFR in patients with renal involvement, a reduction in disease activity (BVAS improvement), a favorable safety profile, and the potential for use as maintenance monotherapy. These results support avacopan's potential role in AAV management and warrant further investigation in larger prospective studies.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/drug therapy; Avacopan; Glomerular Filtration Rate/drug effects; Kidney Diseases; Portugal; Registries

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) comprises a group of challenging diseases that can course with multiple organ involvement. Although immunosuppression has significantly reduced mortality in the last decades, patients continue to evolve with chronic organ damage due to treatment limited efficacy and toxicity. As a result, patients' health-related quality of life remains substantially impaired.

The current standard-of-care for severe AAV involves the use of glucocorticoids (GCs) in combination with either rituximab (RTX) or cyclophosphamide (CYC).¹ However, prolonged high-dose GC therapy is associated with significant adverse effects. Research has shown that it is possible to substantially reduce GC doses when inducing remission in moderate to severe AAV, thereby decreasing treatment-related side effects without compromising effectiveness.^{2,3} Avacopan, an oral C5a receptor antagonist, was recently approved as an adjunctive therapy for AAV, being the first effective glucocorticoid-sparing alternative. In the phase 3 ADVOCATE trial, patients with AAV randomized to avacopan had a non-inferior rate of remission at week-26 and a superior rate of sustained remission at week-52 compared with patients randomized to standard-of-care prednisone. Among the 81% of the study population with kidney involvement, patients treated with avacopan experienced more rapid reductions in albuminuria and greater improvements in estimated glomerular filtration rate (eGFR) at 26 and 52 weeks.⁴ In patients with $eGFR<30$ mL/min/1.73 m², the mean improvement in eGFR by week 52 was 13.7 and 8.2 mL/min/1.73 m², in the avacopan and prednisone groups, respectively.^{1,4}

Avacopan was approved for the treatment of AAV by the US Food and Drug Administration in October 2021,⁵ Health Canada in April 2022,^{2,6} and approval was recommended by a committee of the European Medicines Agency to the European Commission.

Real-world data on avacopan is limited and unknown in Portugal. We conducted a multicenter retrospective cohort analysis of 15 patients who received avacopan for the treatment of new or relapsing AAV. Our objective was to describe the real-world experience and outcomes with avacopan in Portugal.

METHODS

Study Design and Patient Cohort

We conducted a multicenter retrospective observational study of 15 patients with active AAV who received avacopan treatment at nine academic medical centers across Portugal. Eligible participants were aged ≥ 18 years and had either newly diagnosed or relapsing AAV, fulfilling the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA).⁷ All patients had a minimum follow-up of three months after initiating avacopan. Data was collected retrospectively and up to 31/12/2024 from electronic medical records. Collected variables included demographic information, AAV subtype, renal involvement, Birmingham Vasculitis Activity Score (BVAS), laboratory markers (e.g., serum creatinine, eGFR, C-reactive protein (CRP), urinary protein-to-creatinine ratio), treatment regimens, and adverse events. Patients with missing data were censored from the calculation of medians and frequencies.

Treatment Regimen

Induction therapy varied between units according to the treating physician's discretion and included oral or intravenous CYC, RTX alone or combined, as well as GC and plasmapheresis (PLEX). Remission maintenance therapy consisted of RTX (500 mg or 1000 mg i.v. dose every 4–6 months) or azathioprine (target dose of 2 mg/kg/day). Most patients started prophylaxis to avoid *pneumocystis jirovecii* infection, osteoporosis and gastrointestinal ulceration.^{3,4} Avacopan was added to induction therapy depending on local drug availability and authorization, at a dose of 30 mg twice daily, intended for a 1-year treatment duration.

Outcomes and Follow-Up

The primary outcome was clinical remission at 3, 6 and 12 months, which was defined as no signs or symptoms of vasculitis activity (BVAS=0) and a prednisolone dose ≤ 5 mg/day. Secondary outcome measures included prednisolone dose at 6 and 12 months, cumulative GC dose, BVAS and Vasculitis Damage Index (VDI) scores, ANCA

titers evolution, changes in eGFR, reduction in proteinuria at 3, 6 and 12 months, resolution of hematuria, disease relapse, infection requiring hospitalization, and both kidney and patient survival.

Assessment of changes in eGFR (calculated using the race-free 2021 chronic kidney disease epidemiology collaboration equation), proteinuria, and hematuria was limited to patients with kidney involvement. Disease relapse was defined as a recurrence of AAV activity (BVAS>0) requiring intensification of immunosuppression therapy at any point during treatment.

All patients in our series had at least 3 months of follow-up after avacopan initiation at the time of data analysis, with none excluded due to treatment discontinuation, adverse events or death.

Statistical Analysis

Due to the small sample size, continuous variables were summarized as medians, minimum and maximum or interquartile ranges (IQR). Categorical variables were presented as counts and percentages. Group comparisons for continuous variables were performed using the Wilcoxon signed-rank test for matched samples.

Associations between avacopan and various outcome measures (creatinine, proteinuria, and BVAS) were explored using mixed-effects models to account for intra-individual variability. Results were reported as beta coefficients with corresponding 95% confidence intervals (CI) and *p*-values. A two-tailed *p*-value < 0.05 was considered statistically significant for all analyses. Statistical analyses were conducted using R version 4.1.1.

RESULTS

Study Population

A total of 15 adult patients with GPA and MPA were treated within the avacopan compassionate use program. Patient demographics and AAV-related relevant clinical characteristics are summarized in Table 1.

Table 1. Clinical characteristics of the study population

Variable	Summary
Age, years (IQR)	65.0 (51.5–75.5) min. 25- max. 81
Sex	Female (8, 53.3%)
Hypertension	11, 73.3%
Diabetes mellitus	3, 20.0%
Cardiac disease	3, 20.0%
Previous chronic kidney disease	3, 20.0%
BVAS (IQR)	23.0 (13.0- 28.5) min. 7- max. 38
ANCA titers baseline (IQR)	159 (62.25- 416.7)
<i>De novo</i> AAV	9, 60.0%
Systemic manifestations	14, 93.3%
Hematological manifestations	13, 86.7%
Respiratory manifestations	12, 80%
Upper airway vasculitis	4
Alveolar haemorrhage	8
Renal manifestations	9, 60.0%
Articular manifestations	6, 40.0%
Skin manifestations	6, 40.0%
Neurologic manifestations	5, 33.3%

AAV- ANCA-associated vasculitis; ANCA- antineutrophil cytoplasmic antibody; BVAS- Birmingham Vasculitis Activity Score; IQR- interquartile range

The study population had a median age of 65 years (IQR: 51.5- 75.5), with similar numbers of both genders (53.3% female patients). Comorbidity prevalence varied, with hypertension affecting 73.3% of the patients, diabetes mellitus 20.0%, cardiac disease 20% and chronic kidney disease (CKD) also 20.0%. Two patients had CKD as a result of renal involvement from vasculitis at the time of presentation. Patient number 14 (Table 2) had end-stage renal disease (ESRD), undergoing hemodialysis and patient number 8 had CKD stage 4.

Regarding clinical manifestations, systemic involvement was frequent (93.3%), followed by hematological (86.7%) and respiratory manifestations (80%). Renal involvement was present in 60% of patients. Neurological manifestations were the least common (33.3%), while skin and articular manifestations were present in 40% of cases. One patient had orbital inflammatory pseudotumor and another had recurrent pericarditis. The median baseline BVAS score was 23.0 (IQR: 13.0- 28.5), reflecting a moderate-to-severe disease burden. Nine (60%) had anti-MPO antibodies and 6 (40%) had anti-PR3 antibodies. A total of 9 patients (60%) had *de novo* AAV, while 6 were relapses. The median follow-up period was 12 months (IQR: 7.8 - 18.5), providing a longitudinal perspective on disease progression.

Table 2. Individual demographics, clinical characteristics at baseline, treatment and outcome

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
	76 / M	32 / F	65 / F	81 / M	55 / M	76 / M	48 / M	25 / F	63 / F	25 / F	75 / F	70 / F	80 / F	57 / M	65 / M
ANCA serology	MPO	PR3	PR3	MPO	MPO	MPO	MPO	PR3	MPO	PR3	MPO	MPO	MPO	PR3	PR3
Organ involvement	renal	Orbital inflammatory pseudo-tumor	ENT; renal	Cutaneous; nervous system; Lung; renal	Cutaneous; peripheral nerves; Lung; ENT	Cutaneous; Lung	ENT; renal	ENT; pericarditis	Cutaneous; peripheral nerves; Lung; ENT; renal	Lung; ENT	Lung; ENT; renal	cutaneous; renal	Lung; renal	Nervous system; Lung	Cutaneous; peripheral nerves; lung; renal
De novo / relapse	De novo	Relapse	De novo	De novo	De novo	Relapse	De novo	Relapse	Relapse	De novo	De novo	De novo	Relapse	Relapse	De novo
Previous flare number		4				1		3	2				1	1	
BVAS at presentation	12	7	25	23	38	20	23	8	34	28	29	14	18	12	38
Cr (mg/dL)/ eGFR *1	2.65/31		8/4	3.9/18			1.1/88		1.35/42		3.1/15	9.6/4	4.33/9		4.09/14
Cr 3/12 months	1.83/1.81		4.6/NA	3.22/2.8			0.96/0.71		0.8/0.73		1.35/NA	2.49/0.99	2.34/NA		1.23/2
Induction treatment	GC, Rtx	GC, Rtx	Cyc, GC, PEX, Rtx	Cyc, GC, Rtx	Cyc, GC, Rtx	GC, Rtx	GC, Rtx	GC, Rtx	Cyc, GC, PEX, Rtx	Cyc, GC, Rtx	GC, Rtx	GC, Rtx	GC, Rtx	GC, Rtx	GC, Rtx
Maintenance treatment	GC	GC	GC, Rtx	GC	GC, Rtx	GC, Aza	GC, Rtx	GC	GC, Rtx	GC, Rtx	GC, Rtx	GC	GC, Rtx	GC	GC, Rtx
Time from induction to avacopan (months)	2,7	6,4	2,2	2,6	6,0	5,9	3,1	4,2	0,1	5,3	3,7	2,2	0,6	NA *3	5,8
Time on avacopan (months)	28,7*2	27,1*2	4,07	20,4*2	10,4	15,8*2	12,2	17,2*2	29,3*2	7,9*2	8,1 *2	1,9	8,6 *2	7,6 *2	12,5
GC dose at the end of follow-up	stop	stop	stop	stop	5 mg	stop	stop	5 mg	2,5 mg	NA	2,5	NA	stop	5 mg	stop
BVAS 3/6/12 months	5/0/0	2/0/NA	0/0/NA*4	0/0/0	4/0/0	0/0/NA	0/0/0	3/0/0	0/0/0	0/0/NA	6/0/NA	1/0/0	5/5/NA	2/NA/NA	9/0/0

*1 values at disease presentation/current flare, considering only those with renal involvement; *2 still taking avacopan at the end of the study; *3 started avacopan 18 months after the induction due to severe adverse effects from the GC (avascular necrosis of the femur); *4 death at 6 months. ANCA- antineutrophil cytoplasmic antibody; Aza- azathioprine; BVAS- Birmingham Vasculitis Activity Score; Cyc- cyclophosphamide; ENT ear-nose-throat; F- feminine; GC- glucocorticoid; M- masculine; NA- not available; PEX- plasmapheresis; Rtx-rituximab

Patients with Renal Involvement

Only 9 patients were considered for this analysis, seven of whom had rapidly progressive glomerulonephritis (RPGN). Patients 8 and 14 were excluded, as they did not have acute renal involvement in the present/current flare, despite having renal involvement at initial presentation (causing CKD stage 4 and 5D). Compared with the whole cohort, patients with renal involvement were older (median age 70 years (IQR: 63.0 - 76.0)) and more frequently female (66.7%). The majority were positive for MPO antibodies (n=7). The median BVAS scores were slightly higher (25.0, IQR: 18.0 - 29.0) compared to the general cohort (23.0, IQR: 13.0 - 28.5). Systemic and hematological symptoms

were universally present (100%). Respiratory involvement was also common (77.8%), whereas neurological symptoms remained less frequent (33.3%) (Table 3).

Table 3. Renal patients' clinical characteristics

Variable	Summary
Age, years (IQR)	70.0 (65- 76) min 48- max 81
Sex	Female (6, 66.7%)
BVAS (IQR)	25.0 (18.0- 29.0)
Systemic manifestations	9, 100.0%
Hematological manifestations	9, 100.0%
Respiratory manifestations	7, 77.8%
Articular manifestations	5, 55.6%
Skin manifestations	4, 44.4%
Neurologic manifestations	3, 33.3%
Oliguria	2, 22.2%
Hypertension	4, 44.4%
eGFR at baseline, mL/min 1.73 m ² (IQR)	15 (9- 31)
Maximum Cr (mg/dL) at baseline (IQR)	3.9 (2.62 – 4.33) min 1.1- max 9.6
Hematuria (>5 erythrocytes per field) *1	6
Urinary protein-to-creatinine ratio at baseline, mg/g (IQR)	989 (461-1634)

*1 3 missing data; BVAS- Birmingham Vasculitis Activity Score; Cr – creatinine; eGFR- estimated glomerular filtration rate; IQR- interquartile range

Hematuria occurred in 6/9 (66.7%) at baseline, but 3 of the patients had no data. The evolution of proteinuria and eGFR are analyzed in the outcomes section. Oliguria was present in 22% (2/9) and both patients required dialysis temporarily (during 17 and 51 days). Five patients (55.6%) had $\text{ClCr} \leq 15$ mL/min at presentation. At 12 months, no information was available for 3 patients due to death (1/9) and short follow-up (2/9).

Treatment Regimens and GC Use

Treatment strategies (see Table 4) varied among patients, with GC being universally used (100%). Induction regimens included a combination of RTX with low-dose CYC (n=5, 33.3%) or RTX alone (n=10, 66.6%). Plasma exchange was less commonly used (n=2, 13.3%). The median cumulative GC was 8.17 g (methylprednisolone bolus was taken into account for the calculation).⁸

The reason given by the treating physicians for initiating avacopan was corticosteroid dependence (n=5, 25%) and contraindication to GC use (n=10, 75%), including osteoporosis, diabetes mellitus, avascular necrosis of the femoral head and pancreatitis.

Eight (53.3%) patients discontinued GC after initiating avacopan and the median time to GC discontinuation was 44 days (IQR: 25- 139), indicating variable treatment durations across the cohort. The remaining patients maintain a daily dose of ≤ 5 mg of prednisolone.

Table 4. Treatment characteristics

Variable	n, % (IQR)
Induction	
GC	15, 100.0%
RTX	11, 73.3%
CYC + RTX	5, 33.3%
PEX	2, 13.3%
Cumulative dose of GC, g	8,17 (3.42- 10,96)
Time from induction to avacopan initiation, months	3.45 (2.33- 5.68)*1
Treatment duration with avacopan, months	12.23 (8.0-18.8)
Time to stop GC after starting avacopan, days	44.0 (25- 139)*2

*1 one patient was excluded from this analysis because he started avacopan 18 months after the disease due to severe adverse effects from the GC (avascular necrosis of the femur); *2 eight patients stopped GC. CYC- cyclophosphamide; GC- glucocorticoids; PEX- plasmapheresis; RTX- rituximab

After induction of remission, all patients started maintenance therapy. In addition to GC and/or avacopan, eight patients received rituximab and one received azathioprine for maintenance. Six patients were maintained on avacopan and prednisolone alone, and among these, 3 discontinued GC. A total of 3 patients remain on maintenance therapy with avacopan alone. Patient number 1 underwent induction with rituximab and continued on avacopan monotherapy for maintenance. The treating physician decided to postpone rituximab due to the patient's frailty, heart disease and persistent B-cell depletion at 12 months. The patient remains stable, with a serum creatinine of 1.58 mg/dL (44 mL/min 1.73 m²), no symptoms, and a progressive decline in MPO levels over two years. Patient number 4 developed hypogammaglobulinemia secondary to rituximab and for this reason, only avacopan was maintained. Patients 2 and 8 had frequent relapsing disease and initiated avacopan to reduce glucocorticoid therapy. This led to the interruption of prednisolone in patient 2 and the dose reduction to 5 mg in patient 8. At 12 months, patient 8 still had B-cell depletion, but the decision to keep her on avacopan and prednisolone, without rituximab, was mainly due to the fact that she was well controlled clinically, had already been on multiple classes of therapy and had hypogammaglobulinemia, despite no infections. Patient 12 underwent less than two months of avacopan therapy, remained B-cell depleted and only received GC for maintenance therapy. Patient 14 started avacopan 18 months after the current episode of recurrence, due to severe adverse effects from the GC (avascular necrosis of the femur). No disease relapses have occurred to date.

Five patients had already stopped avacopan treatment at the time of recruitment into this study. Three patients discontinued treatment after one year based on the decision of the treating physician; 1 discontinued due to hepatotoxicity and one patient died. Six patients were treated

with avacopan for more than 13 months, given the clinical results obtained, the treating physician decided to extend therapy to at least two years.

Outcomes

The data on patient and renal outcome are shown in Table 5. A consistent downward trend in BVAS scores suggests effective disease control and response to therapy. Six patients (40.0%) had BVAS=0 at 3 months. At 6 months, of the 14 who had follow-up, 12 reached BVAS=0 (92.86%). BVAS showed statistically significantly lower values at 3 and 12 months ($p < 0.05$). No relapse occurred during the follow-up.

Table 5. Patient and renal outcomes

Variable		
BVAS		
at baseline	23.0 (13.0- 28.5), min. 7- max. 38	
3 months	2 (2-4.5), min 0 – max. 9	n=15, $p < 0.05$
6 months	0 (0-0), min. 0- max. 5	n=14, $p < 0.05$
12 months	0 (0-0), min. 0 – max. 0	n=8, $p < 0.05$
ANCA		
at baseline	159 (62.25- 416.7)	
6 months	6.7 (0- 34)	
12 months	2.1 (0-27.3)	
VDI		
at 3 months	3 (2- 5), min 0- max 11	
at 12 months	3 (2-5), min 0- max 6	
Recurrences at 12 months	0	
Creatinine		
	n = 9	
at baseline	3.9 (2.62 – 4.33)	
3 months	1.83 (1.23-2.49)	
6 months	1.52 (1.25- 2.26)	
12 months	1.4 (0.79 – 1.95)	
eGFR		
	n = 9	
at baseline	15 (9- 31)	
3 months	38 (20-62)	n=9, $p < 0.05$
6 months	42 (28- 64)	n=9, $p < 0.05$
12 months	48 (36.5 – 83.5)	n=6, $p < 0.05$
Urinary protein-to-creatinine ratio, mg/g		
at baseline	989 (461-1634)	
6 months	137 (103.5 – 397)	
12 months	203 (150-297)	
Hematuria		
at baseline	6/9, 3 missing	
at 6 months	1/9	
at 12 months	0/6	

ANCA- antineutrophil cytoplasmic antibody; BVAS- Birmingham Vasculitis Activity Score; VDI- Vasculitis Damage Index

The trajectory of eGFR is shown in Fig. 1, n=9. The time at which avacopan was started and when it was stopped are also marked on the graph. Patient number 12 discontinued therapy after 1.9 months due to hepatotoxicity. The patients whose end date is not marked are patients who were still taking the drug at the end of the study. All patients had improved or stabilized kidney function at 6 months. Similarly, improvement in renal function was sustained at one-year follow-up with median eGFR of 48 vs 15 mL/min/1.73 m². At 3 and 12 months, the eGFR was statistically significantly higher ($p < 0.05$).

Hematuria is frequent at the time of diagnosis, and after a year, it had resolved in all patients who had a 12-month follow-up. Proteinuria levels were elevated at presentation and reduced significantly at 12 months (median protein-to-creatinine ratio 989 vs 203 mg/g).

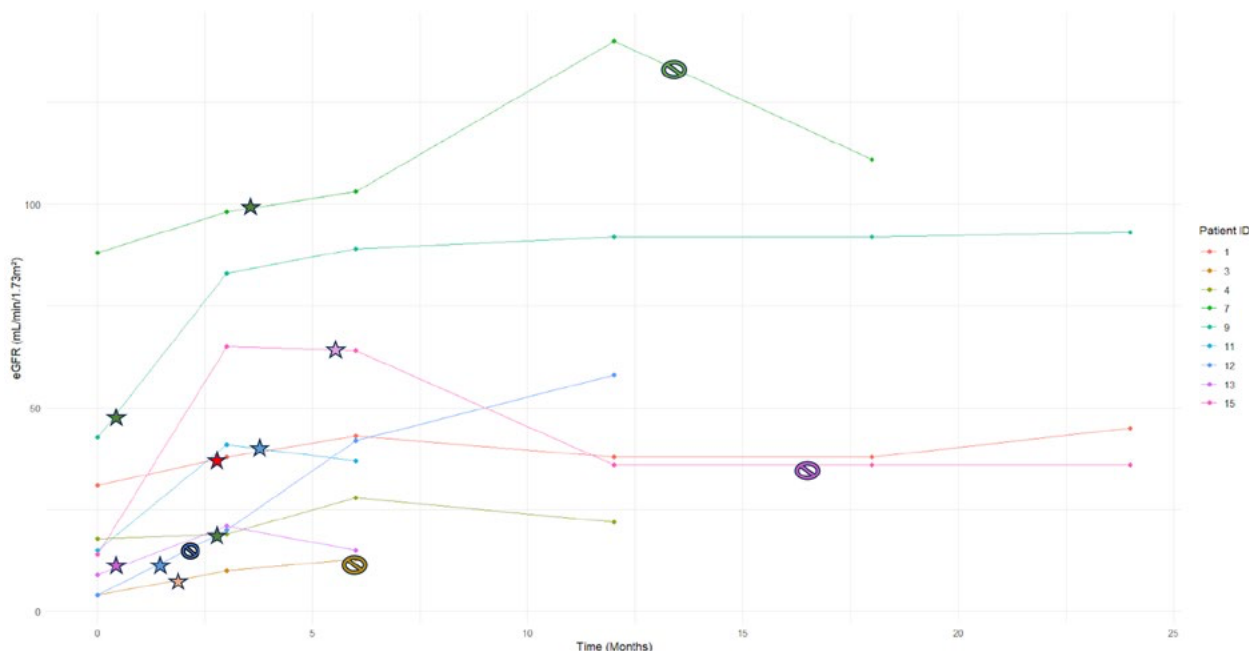


Figure 1. Estimated Glomerular Filtration Rate over Time (n=9)

The eGFR of each of the nine patients is shown in the figure, corresponding to the same numbering used in Table 2. The moment when avacopan was started (★) and suspended (⊗) is shown on each line.

Safety

Of the 15 patients, one had to abandon treatment due to liver toxicity (cholestasis), which was completely reversible after the drug was discontinued. Another patient died from sepsis three months after starting avacopan. One patient had community-acquired pneumonia requiring hospitalization about a month after starting avacopan. There were no further serious infections requiring hospitalization reported.

DISCUSSION

In this study, the use of avacopan as part of the induction and maintenance therapy in the novo or relapsing AAV was associated with successful induction of remission (as suggested by the marked reduction in BVAS and sustained decrease in ANCA levels, observed as early as three months) and good renal outcomes, including in patients requiring dialysis. The safety profile was overall acceptable.

These findings are in line with the ADVOCATE trial, which demonstrated that avacopan was non-inferior to prednisolone in inducing remission in AAV, with superior renal outcomes at 52 weeks, particularly among patients with kidney involvement.⁴ Other real-world studies have also confirmed improvements in disease control, renal function, and significant reductions in cumulative glucocorticoid exposure.^{9,10} These results suggest that avacopan may be especially valuable in reducing steroid-related toxicity, which is a major concern in long-term management of AAV.

This study has several limitations, mainly the small sample size with only 15 patients included. Also, there were significant delays in avacopan initiation, primarily due to early challenges in accessing the drug. In our series, patients were diagnosed with either *de novo* or relapsing, but not refractory AAV. Because of its retrospective nature, some data, such as urinary samples, was missing. Furthermore, the sample represents a very heterogeneous group of patients, limiting the ability to perform further statistical analysis.

Despite these limitations, this is the first study to report real-life setting experience with avacopan in patients with *de novo* or relapsing AAV in Portugal. Also, the study includes detailed clinical characterization and extended follow-up of patients treated in routine clinical practice, including those with severe renal involvement and dialysis dependency. The sustained disease control and successful steroid reduction or discontinuation across this diverse group adds valuable insight into the feasibility and utility of avacopan outside of controlled trial settings. Our data support the therapeutic potential of avacopan in the clinical practice as a standard-of-care, and not only in difficult-to-treat patients, as it has been previously published.¹¹ A series of five cases in which avacopan alone was used in the induction treatment of a relapse showed no efficacy in resolving the symptoms.¹² But could avacopan change the role or need for other maintenance therapies, such as regular rituximab infusions? In our cohort, six patients received avacopan (3 without GC) as their only

maintenance treatment, suggesting its potential as an alternative—an area that warrants investigation in randomized clinical trials. This approach may be particularly relevant in patients with hypogammaglobulinemia or contraindications to long-term immunosuppression, although further studies are needed to validate this strategy.

Patients with eGFR <20 mL/min, experienced improved renal function with avacopan treatment in the ADVOCATE trial, but patients with eGFR <15 mL/min per 1.73 m² were excluded.⁴ We present 5 cases describing the use of avacopan in individuals with AAV and eGFR ≤15 mL/min per 1.73 m² at presentation (two requiring dialysis), as has also been reported in another series of cases.¹³ Avacopan appeared to be safe, reduced glucocorticoid exposure, and resulted in substantial eGFR recovery in 4 individuals. One of the patients died at six months of sepsis.

The ideal duration of therapy with avacopan for maintaining remission is unknown. Data on treatment with avacopan beyond 1 year are scarce and has only been reported in a few patients.¹³ In our case series, six patients extended therapy beyond 13 months. When asked, the treating physician made this decision based on favorable clinical outcomes, with the possibility of reducing or discontinuing GC. This was particularly considered for patients with frequent relapses during standard maintenance therapy or in cases where rituximab was not included in the maintenance regimen, for reasons previously discussed.

Two patients were treated with PLEX and avacopan. Guidelines recommend integrating avacopan with standard induction therapies (rituximab or cyclophosphamide) for AAV, and PLEX is still recommended for specific

indications, even when avacopan is part of the protocol. Following the PEXIVAS study, PLEX use is generally reserved for severe patients, either with alveolar hemorrhage and hypoxemia or severe kidney involvement to optimize immunosuppression. A post-hoc analysis of the PEXIVAS trial indicates that PLEX improves early kidney function.¹⁴ Though the ADVOCATE trial did not include patients receiving PLEX, subsequent real-world cohort studies have safely combined avacopan with low-dose cyclophosphamide and plasmapheresis. No new safety concerns—such as increased infections or liver toxicity—were identified.¹⁵ Moreover, the efficacy of avacopan (remission rates, kidney function recovery, glucocorticoid sparing) remained robust even with adjunctive PLEX.¹³ Some authors suggest that the use of PLEX in conjunction with avacopan could perhaps be superfluous since therapy with avacopan seems to produce a rapid control of inflammatory processes, likely reducing the progression to ESKD.¹⁶ On the other hand, a multitarget approach with additional complement inhibition could possibly improve outcomes in this specific population, although the risk of infection should always be taken into consideration. More studies are needed to explore this hypothesis.

In conclusion, our findings support the use of avacopan as a safe and effective treatment option for patients with AAV. It was associated with disease remission, kidney function stabilization or improvement, and glucocorticoid tapering. Future prospective studies are needed to further clarify its role in remission induction and maintenance, particularly in high-risk or complex patient profiles, such as patients with severe kidney disease.

Ethical Disclosures

Conflicts of Interest: Sofia Correia – Occasional consulting and lecturing (Vifor pharma and Otsuka); Ivo Laranjinha – Occasional consulting and lecturing fees (Viforpharma and Novartis); Estela Nogueira – Occasional consulting and lecturing fees (GSK, Vifor pharma and Otsuka); Inês Ferreira – Occasional consulting (GSK and Vifor pharma); Teresa Jerónimo – Occasional consulting and lecturing fees (CSL Vifor); Nuno Afonso – Occasional consulting and lecturing fees (GSK, Viforpharma and Alexion). The remaining authors- Nothing to disclose.

Financing Support: This work has not received any grant. Support for statistical analysis was provided by Evidenze.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Contributorship Statement

SOC: Bibliographical search, data collection, analysis and interpretation of results, drafting the article, critical reviewing of the content of the article.

IL, EN: Data collection, analysis and interpretation of results, critical reviewing of the content of the article.

AC, CT, HP, IF, JFS, JS, MJG, MG, LT, VST: Data collection.

AC, HP, IF, JFS, AL, AI, CS, IG, RV, TMJ, NA: Critical reviewing of the content of the article.

All authors approved the final version to be published.

REFERENCES

1. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221-32. doi: 10.1056/NEJMoa0909905.
2. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *N Engl J Med*. 2020;382:622-31. doi: 10.1056/NEJMoa1803537.
3. Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, et al. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA*. 2021;325:2178-87. doi:10.1001/jama.2021.6615.
4. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med*. 2021;384:599-609. doi: 10.1056/NEJMoa2023386. Erratum in: *N Engl J Med*. 2024;390:388. doi: 10.1056/NEJMs230010.
5. Food and Drug Administration, fda.gov. FDA approves add-on drug for adults with rare form of blood vessel inflammation [accessed 13 Oct 2021]. Available at: <https://www.fda.gov/drugs/news-events/human-drugs/fda-approves-add-drug-adults-rare-form-blood-vessel-inflammation>.
6. Health Canada, Canada.ca. Notice: Multiple Additions to the Prescription Drug List; [accessed 17 Aug 2022]. Available at <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/notices-changes/multiple-additions-2022-08-17.html>.
7. Robson JC, Grayson PC, Ponte C, Suppiah R, Craven A, 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. doi: 10.1136/annrheumdis-2021-221795.
8. Montero-Pastor N, Sánchez-Costa JT, Guerra-Rodríguez M, Sánchez-Alonso F, Moriano C, Loricera J, et al. Development of a web tool to calculate the cumulative dose of glucocorticoids. *Reumatol Clin*. 2023;19:1-5. doi: 10.1016/j.reuma.2022.11.001.
9. Zonozi R, Aqeel F, Le D, Cortazar FB, Thaker J, Zabala Ramirez MJ, et al. Real-world experience with avacopan in antineutrophil cytoplasmic autoantibody-associated vasculitis. *Kidney Int Rep*. 2024;9:1783-91. doi: 10.1016/j.ekir.2024.03.022.
10. McAdoo SP, Medjeral-Thomas N, Gopaluni S, Tanna A, Mansfield N, Galliford J, et al. 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. doi: 10.1093/ndt/gfx378. Erratum in: *Nephrol Dial Transplant*. 2018;33:899. doi: 10.1093/ndt/gfy075.
11. Van Leeuwen JR, Bredewold OW, van Dam LS, Werkman SL, Jonker JT, Geelhoed M, et al. Compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int Rep*. 2021;7:624-8. doi: 10.1016/j.ekir.2021.11.036.
12. Kubota S, Hanai S, Tanaka-Mabuchi N, Ito R, Nakagomi D. Is it possible to use avacopan alone in the induction of remission in ANCA-associated vasculitis? *Rheumatol Adv Pract*. 2024;8:rkae100. doi: 10.1093/rap/rkae100.
13. Van Leeuwen JR, Quartuccio L, Draibe JB, Gunnarson I, Sprangers B, Teng YK. Evaluating Avacopan in the Treatment of ANCA-Associated Vasculitis: Design, Development and Positioning of Therapy. *Drug Des Devel Ther*. 2025;19:23-37. doi: 10.2147/DDDT.S341842.
14. Odler B, Riedl R, Geetha D, Szpirt WM, Hawley C, Uchida L, et al. The effects of plasma exchange and glucocorticoids on early kidney function among patients with ANCA-associated vasculitis in the PEXIVAS trial. *Kidney Int*. 2025;107:558-67. doi: 10.1016/j.kint.2024.11.029.
15. Draibe J, Espigol-Frigolé G, Cid MC, Prados MC, Guillén E, Villacorta J, et al. The real-world use and effectiveness of avacopan in routine practice for the treatment of ANCA vasculitis. First experiences in Spain. *Rheumatology*. 2025;64:2019-26. doi: 10.1093/rheumatology/keae534.
16. Casal Moura M, Crowson CS, Specks U, Warrington KJ, Zand L, Sethi S, Fervenza FC. PLEX in AAV-GN: insights from the meta-analysis results and impact on remission induction treatment recommendations. *Clin Kidney J*. 2022;16:432-6. doi: 10.1093/ckj/sfac221.