Rheumatology Advances in Practice, 2024, **8(3)**, rkae100
https://doi.org/10.1093/rap/rkae100
Advance access publication 24 August 2024
Letter to the Editor

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Letter to the Editor (Case report)

Is it possible to use avacopan alone in the induction of remission in ANCA-associated vasculitis?

Soichiro Kubota[1], Shunichiro Hanai[1], Nakako Tanaka-Mabuchi[1], Ryosuke Ito[1], Daiki Nakagomi*

[1]Department of Rheumatology, University of Yamanashi Hospital, Yamanashi, Japan
*Correspondence to: Daiki Nakagomi, Department of Rheumatology, University of Yamanashi, Yamanashi 4093898, Japan. E-mail: dnakagomi@hotmail.co.jp

Key message
- The effectiveness of avacopan as a standalone therapy has yet to be established.

Dear Editor, Avacopan inhibits ANCA-associated vasculitis (AAV) by blocking C5a receptors and inhibiting neutrophils via the complement pathway [1]. It is a novel agent that may offer a glucocorticoid-independent therapy, considered essential for treating vasculitis. However, in practice, avacopan is often used in combination with cyclophosphamide or rituximab (RTX) to sustain remission in accordance with the ADVOCATE trial (NCT02994927) [2, 3]. Here we report on five patients with clinically defined minor relapses of AAV treated with avacopan alone, without glucocorticoid escalation or immunosuppressive agents.

The first patient was a 74-year-old man with granulomatosis polyangiitis (GPA). The patient presented with hypertrophic meningitis (HP), mastoiditis and interstitial pneumonia. The patient was in remission with prednisolone (PSL; 30 mg/day) and i.v. CYC; however, his HP flared after 1 year. Remission was achieved with RTX and PSL was tapered off. The patient remained drug-free for the next 2 years. However, fever and headache developed, MPO-ANCA levels increased and MRI revealed HP recurrence. Attempts to induce remission with avacopan (60 mg/day) alone, without PSL, were unsuccessful. The patient's symptoms worsened, his antibody titre continued to increase and purpura and dysarthria developed. After 12 weeks, the treatment was deemed ineffective. Subsequently, avacopan was discontinued and remission was induced using PSL and RTX, leading to improvement in the patient's condition.

The second patient was an 88-year-old woman diagnosed with microscopic polyangiitis (MPA). She presented with fever, myositis in both thighs and glomerulonephritis and was initially in remission with PSL (40 mg/day) and RTX. Subsequently she was maintained on a lower dose of PSL (8 mg/day) due to fatigue, myalgia, an increased inflammatory response and the development of MPO-ANCA. However, due to gradual exacerbations, avacopan (60 mg/day) was administered. Six weeks after administration, the drug was ineffective and the patient's condition improved only after increasing the dose of PSL to 30 mg/day and intensifying treatment with RTX.

The third patient, a 79-year-old man also diagnosed with MPA, initially presented with fever, general malaise and myositis. Remission was induced with PSL (40 mg/day) and RTX and was maintained with azathioprine (AZA) at a dose of 100 mg/day. However, PSL dose reduction was challenging due to symptom flares, and PSL (7 mg/day) was continued for 2.5 years. Mild visual impairment and MRI findings led to a diagnosis of optic neuritis, prompting the administration of avacopan (60 mg/day) as a standalone therapy. However, after 6 months of treatment, there was no improvement in visual acuity or inflammatory response.

The fourth patient was a 75-year-old man with GPA. The patient presented with fever, mononeuritis multiplex, cutaneous vasculitis, HP and otitis media. Initially he achieved remission with PSL (30 mg/day) and RTX, maintained with AZA (50 mg/day) and PSL (10 mg/day) for 5 years. However, the patient relapsed with worsening otitis media and elevated MPO-ANCA levels. Despite administration of avacopan (60 mg/day), the patient's condition did not improve.

The fifth patient was a 74-year-old woman with GPA. She presented with a pulmonary mass, mononeuritis multiplex and sinusitis and received remission induction therapy with PSL (50 mg/day) and i.v. CYC, followed by remission maintenance with PSL (5 mg/day) and AZA (75 mg/day) for 3 years. However, the patient relapsed with an elevated CRP level and an increased pulmonary mass shadow. Avacopan (60 mg/day) was administered for 6 months, but there was no improvement. None of the five patients who underwent intensified avacopan treatment alone, as described above, showed any improvement in symptoms (Table 1).

The ADVOCATE trial, a phase 3 study of avacopan, compared the group receiving immunosuppressants and glucocorticoids with the group receiving immunosuppressants and avacopan. The avacopan group showed superior sustained remission at 52 weeks [2, 3]. However, it should be noted that the avacopan group received a sufficient dose of glucocorticoids before screening and both groups received concomitant immunosuppressive agents. Therefore, the results did not conclusively prove the efficacy of avacopan as a single agent. In Japan, avacopan can be used alone

Accepted: 19 August 2024

Table 1. Characteristics of patients treated with avacopan

Patient	Diagnosis	Age (years)/sex	Maintenance therapy	Duration of remission (years)	Main relapse symptoms	MPO-ANCA (IU/ml)	Avacopan administration period (weeks)	Clinical course after avacopan
1	GPA	74/M	Drug free	2	Hypertrophic meningitis	101	12	Induction of remission PSL and RTX
2	MPA	88/F	PSL 8 mg/day	1	Myositis	6.4	6	Induction of remission PSL and RTX
3	GPA	79/M	PSL 7 mg/day, AZA 100 mg/day	2.5	Optic neuritis	265	26	No change
4	GPA	75/M	PSL 10 mg/day, AZA 50 mg/day	5	Otitis media	3.4	52	No change
5	GPA	74/F	PSL 5 mg/day, AZA 75 mg/day	3	Pulmonary mass	0.2	36	No change

to treat clinically defined minor relapses of AAV at the discretion of individual physicians and patients' consent is not required. Furthermore, two pathways are thought to exist in the pathogenesis of AAV: the neutrophil activation cycle pathway (priming of neutrophils by complement, activation of neutrophils by ANCA binding, damage to vascular endothelial cells via neutrophil extracellular traps and activation of further complement pathways) and the pathway of antibody production from B cell activation. Avacopan inhibits C5a receptors and affects neutrophil activation [4]. It has been reported that antibody titres do not decrease with the addition of avacopan to AAV treatment, suggesting that the neutrophil activation cycle and B cell–mediated antibody production pathway may not be completely correlated [5]. Based on the response to treatment in the five cases presented here, it appears that the effect of avacopan alone on the complement activation pathway may not be sufficient to suppress overall vasculitis. Therefore, a combination of immunosuppressive drugs such as i.v. CYC and RTX, which act on B cell and antibody production pathways, may be necessary [6, 7].

Data availability

The data underlying this article are available in the article.

Authors' contributions

D.N. and S.K. designed and conceived this study. S.K., S.H., N.T. and R.I. collected data. D.N. and S.K. analyzed and interpreted the results and drafted the manuscript. All authors read and approved the final manuscript.

Funding

This study received no specific funding from any bodies in the public, commercial or not-for-profit sectors.

Disclosure statement: The authors have declared no conflicts of interest. Informed consent for the publication of this report was provided by the patients.

References

1. Jayne DRW. Complement inhibition in ANCA vasculitis. Nephrol Ther 2019;15:409–12.
2. Jayne DRW, Merkel PA, Schall TJ *et al.* Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609.
3. Geetha D, Dua A, Yue H *et al.* Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. Ann Rheum Dis 2024;83:223–32.
4. Shiratori-Aso S, Nakazawa D. The involvement of NETs in ANCA-associated vasculitis. Front Immunol 2023;14:1261151.
5. Abe Y, Minowa K, Kogami M *et al.* Avacopan is possibly associated with the improvement of ANCA-associated vasculitis activity without decreasing ANCA titres: a four-case series. Rheumatology (Oxford) 2023;62:e317–8.
6. Furuta S, Nakagomi D, Kobayashi Y *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.
7. Furuta S, Nakagomi D, Kobayashi Y *et al.* Reduced-dose versus high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: predefined 2-year follow-up study. Ann Rheum Dis 2024;83:96–102.

Rheumatology Advances in Practice, 2024, 8, 1–2
https://doi.org/10.1093/rap/rkae100
Letter to the Editor