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【 CASE REPORT 】

Effectiveness and Safety of Avacopan as a Combination Therapy with Glucocorticoids or Monotherapy in Patients with Microscopic Polyangiitis

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Abstract:
We herein report three cases of microscopic polyangiitis (MPA). Two patients were administered avacopan in combination with glucocorticoid (GC), whereas one patient was treated with avacopan monotherapy; none of the patients were co-administered either rituximab or cyclophosphamide. The doses of GC were successfully reduced after the introduction of avacopan in the two patients, and the serum C-reactive protein levels decreased in the patient treated with avacopan monotherapy. Avacopan may therefore be effective either in combination with GC or as monotherapy, even for patients at a high risk of developing adverse effects when administered rituximab or cyclophosphamide.

Key words: avacopan, glucocorticoid, microscopic polyangiitis

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Introduction

Avacopan is a C5a receptor inhibitor, and its effects on microscopic polyangiitis (MPA) and granulomatous polyangiitis (GPA), which are two forms of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), have been proven in a phase 3 randomized controlled trial (RCT) (ADVOCATE study) (1). A subgroup analysis of the ADVOCATE study suggested that the efficacy and safety of avacopan in Japanese patients are comparable to those in the global population (2). Avacopan supposedly replaced high-dose glucocorticoids (GCs) in the 2023 updated clinical practice guidelines for MPA and GPA in Japan (3). A rapid progressive glomerulonephritis (RPGN) is a life-threatening manifestation of AAV. However, the appropriateness of avacopan for AAV with severe renal dysfunction is unclear. This can be attributed to the exclusion criteria based on the reduced estimated glomerular filtration rate (eGFR) set for the above-mentioned RCT. Avacopan was administered as a combination therapy with cyclophosphamide (CY) or rituximab (RTX) in the ADVOCATE study. The appropriateness of avacopan for patients without CY or with RTX co-administration, that is, for reasons such as a very old age, comorbidities, and infection concerns, is unclear. Previous reports have suggested concerns over severe liver damage during avacopan administration (4-6). Avacopan was introduced into clinical practice after approval in Japan in 2022. However, robust evidence for its efficacy and safety in Japanese AAV patients in real-world settings is lacking.

In this report, we investigated three cases of AAV at risk of infection admitted to the Sasebo City General Hospital between September 2022 and September 2023 and successfully treated them with avacopan in combination with GC or as monotherapy. These cases suggest that avacopan may be considered in combination with GC or as a monotherapy for patients at high risk of adverse effects from RTX or CY, such as in those with an infection.

Case Reports

In Case 1, a 69-year-old woman presented with RPGN,

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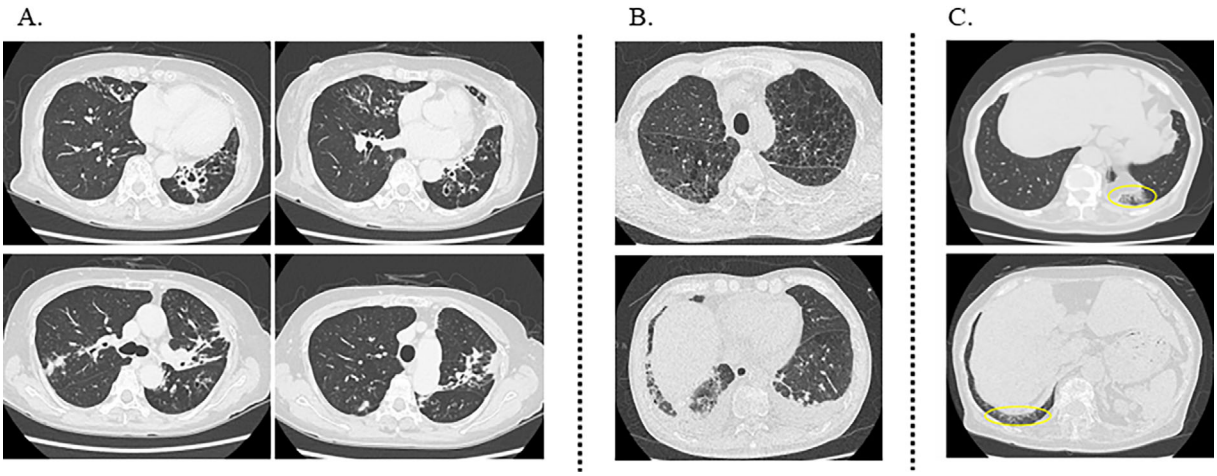

Figure 1. Chest computed tomography at the time of referral to our department. A: (Case 1) Bronchial wall thickening and ectasis, irregularly shaped shadows in both lung fields. B: (Case 2) Pulmonary emphysema and interstitial changes in the lower lung fields. C: (Case 3) Ground-glass opacities in the lower lung fields (yellow circles).

pulmonary hemorrhage, mononeuritis multiplex, *Pseudomonas aeruginosa*-induced acute pneumonia were detected one month prior to the diagnosis of MPA, and congestive heart failure was present as a comorbidity. In Case 2, an 82-year-old man presented with interstitial lung disease (ILD) and pulmonary emphysema as comorbidities. In Case 3, an 88-year-old woman presented with ILD. The chest computed tomography findings of the patients are shown in Fig. 1. All patients tested positive for myeloperoxidase-antineutrophilic cytoplasmic antibodies and were diagnosed based on the criteria proposed by the Japanese Ministry of Health, Labour and Welfare (7). Case 3 was also positive for antiglomerular basement membrane (anti-GBM) antibody; we did not diagnose the patient as having anti-GBM antibody disease considering the lack of any characteristic symptoms, such as the presence of bronchoalveolar hemorrhage and glomerulonephritis. Hemodialysis (HD) was initiated in Case 1. Substantially elevated transaminase and biliary enzyme levels were not observed before the administration of avacopan (Table 1).

Avacopan was administered (without CY or RTX) concomitantly with GC in Cases 1 and 2, but without GC in Case 3 (avacopan monotherapy) through shared decision-making with each patient for the following reasons: (i) Case 1, because of old age and comorbidities including *P. aeruginosa* pneumonia; (ii) Case 2, because of the risk of infection caused by ILD and pulmonary emphysema; and (iii) Case 3, due to a very old age (88 years) and the presence of ILD. We initiated 20 mg/day of avacopan and increased it to 60 mg/day in Case 1. We initiated 40 mg/day of avacopan and increased the dose to 60 mg/day in Case 2. We continued treatment with 60 mg/day avacopan in Case 3. A decrease in the Birmingham Vasculitis Activity Score was observed in all patients. Urinary tract infection was observed in Case 1 at 6 weeks after the introduction of avacopan, which was treated with antibacterials without terminating avacopan. In addition, skin eruption was observed in Case 1 at 7.5 weeks after introducing avacopan, which was treated with topical GC and oral antihistamines without terminating avacopan. Cytomegalovirus reactivation was observed in Case 2 at 8 weeks after the introduction of avacopan, which was treated with valganciclovir without terminating avacopan. We observed elevated biliary enzyme levels in Case 3 at 8 weeks after introducing avacopan, which improved with ursodeoxycholic acid (UDCA) without avacopan termination. UDCA was initiated upon the introduction of avacopan in Case 2, and no liver dysfunction was observed (Table 2) (Fig. 2-4). The drugs prescribed in combination with avacopan were as follows: prednisolone (PSL), omeprazole, lansoplazole, vonoprazan, meropenem, furosemide, dobutamine, tolvaptan, cefcapene pivoxil, levofloxacin, cefepime, mecobalamin, sulfamethoxazole/trimetprim, atovaquone, sennoside, lubiprostone, linaclotide, lactulose, atorvastatin, potassium L-aspartate, alfacalcidol, fexofenadine, fungizone, sodium picosulfate, metclopramide, lemborexant, insulin aspart and betamethasone and hydrocortisone for Case 1, clopidogrel, cilostazol, rabeprazole, pitavastatin, ethyl icosapentate, PSL, UDCA, teneligliptin, sulfamethoxazole/trimetprim, amlodipine, canagliflozin, alfacalcidol, potassium L-aspartate, valganciclovir, olodaterol/tiotropium and insulin aspart for Case 2, vonoprazan, vibegron, and UDCA for Case 3 (Table 3).

Discussion

This report suggests that avacopan can be effective in combination with GC or as monotherapy, even in patients at a high risk of adverse effects from RTX or CY. In the ADVOCATE study, the avacopan group served as the control group for the GC group, and both groups required concomitant administration of CY or RTX (1). However, a considerable number of patients with AAV refrained from CY and

Table 1. Clinical Features of Patients.

Case	Age/Sex	Form of AAV	Symptoms of MPA			Complicatons
			Kidney	Lung	Other than lung and kidney	
1	69F	MPA	+	+	Mononeuritis multiplex	Acute pneumonia caused by *P. aeruginosa*
2	82M	MPA	-	+	-	Pulmonary emphysema
3	88F	MPA	-	+	-	-

Case	CRP (mg/dL)	MPO-ANCA (IU/mL) (reference range: 0-5)	PR3-ANCA (IU/mL) (reference range: 0-3)	Anti-GBM antibody (U/mL) (reference range: 0-7)	Serum Cr (mg/dL)	eGFR (mL/min/1.73 m^2)	HD
1	7.24	444.0	<0.6	Not tested	5.22	7.0	Yes
2	11.16	28.2	<0.6	Not tested	0.82	68.0	No
3	10.85	1,300.0	<0.6	68.4	0.78	52.1	No

Case	T-Bil (mg/dL)	AST (IU/L)	ALT (IU/L)	LDH (IU/L)	ALP (IU/L)	γGTP (IU/L)
1	0.5	15	20	302	83	92
2	0.6	24	37	233	54	46
3	0.7	23	13	145	90	57

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANCA: anti-neutrophil cytoplasmic antibody, Anti-GBM antibody: anti-glomerular basement membrane antibody, AST: asparate aminotransferase, CHF: congestive heart failure, Cr: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, γGTP: gamma-glutamyl transpeptidase, HD: hemodialysis, LDH: lactate dehydrogenase, MPA: microscopic polyangiitis, MPO: myeloperoxidase, P: Pseudomonas, PR3: proteinase3, T.Bil: total bilirubin

Table 2. Therapeutic Regimen and Clinical Courses of Patients.

Case	GC	CY or RTX	Doses of avacopan
1	PSL 40 mg/day	No	20 mg/day → 60 mg/day
2	PSL 50 mg/day	No	40 mg/day → 60 mg/day
3	No	No	60 mg/day

Case	Outcomes of MPA BVAS at diagnosis → 1 month → 3 months	Adverse effects of avacopan			Remarks
		Manifestations	Onset (weeks from introduction of avacopan)	Interventions	
1	Recovered, gradual decrease of GC and withdrawal of HD 36 (arthralgia/arthritis, fever, PE, infiltrate, alveolar hemorrhage, respiratory failure, CHF, HT, proteinuria, hematuria, serum Cr 250-499 μmol/L, >30 % rise in Cr or >25% fall in CCr, MM) → 10 (PE, proteinuria, hematuria, MM) → 3 (MM)	Urinary tract infection	6	Avacopan continued, antibacterials	
		Skin eruption	7.5	Avacopan continued, topical GC, oral antihistamine	
2	Recovered and gradual decrease of GC 13 (myalgia, weight loss, wheeze, pleural effusion, proteinuria) → 2 (proteinuria) → 0	Cytomegalovirus reactivation	8	Avacopan continued, valganciclovir	UDCA was initiated at the introduction of avacopan
3	Recovered 2 (fever) → 0 → 0	Elevated biliary enzyme levels (γGTP 274 U/L, ALP 197 U/L)	8	Avacopan continued, additional UDCA	

ALP: alkaline phosphatase, BVAS: Birmingham Vasculitis Activity score, CHF: congestive heart failure, CCr: creatinine clearance, Cr: creatinine, CY: cyclophosphamide, GC: glucocorticoid, HD: hemodialysis, HT: hypertension, γGTP: gamma-glutamyl transpeptidase, MM: mononeuritis multiplex, MPA: microscopic polyangiitis, PE: pleural effusion, PSL: prednisolone, RTX: rituximab, UDCA: ursodeoxycholic acid

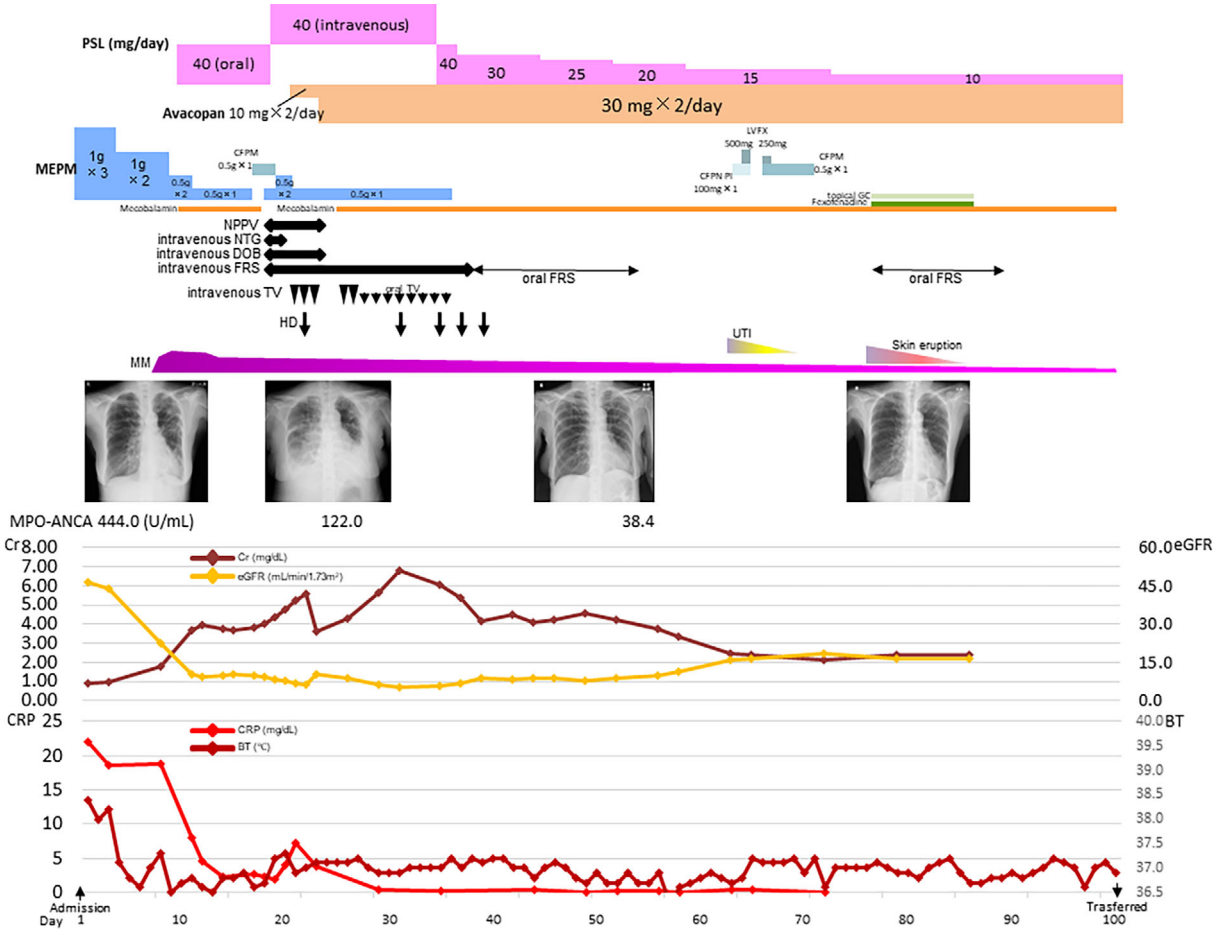

Figure 2. Clinical course of Case 1. BT: body temperature, CFPM: cefepime, CFPN-PI: cefcapene pivoxil, Cr: creatinine, CRP: C-reactive protein, DOB: dobutamine, eGFR: estimated glomerular filtration rate, HD: hemodialysis, FRS: furosemide, GC: glucocorticoid, LVFX: levofloxacin, MEPM: meropenem, MM: mononeuritis multiplex, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, NPPV: non-invasive positive pressure ventilation, NTG: nitroglycerin, PSL: prednisolone, TV: tolvaptan, UTI: urinary tract infection

RTX administration in Japan (8). In 2017, the clinical practice guidelines for AAV in Japan indicated that GC monotherapy might be used for patients at risk of infection (9). This survey was conducted by the Japanese Ministry of Health, Labour and Welfare before the approval of avacopan for AAV. However, these results reflect the actual clinical practice of AAV in Japan. Sato et al. reported three cases of MPA with RPGN, in which avacopan and GC were prescribed in combination, but not CY or RTX immunosuppressants, which thus improved the renal function. Sato et al. demonstrated that they refrained from the concomitant use of CY or RTX because of the patient's age (75-79 years) and his clinical condition, which was mostly limited to the kidneys with nonsevere lung symptoms (10). Although these findings should be interpreted with caution since the number of patients was limited, reports from Sato et al. and ours suggest that avacopan in combination with GC might be beneficial for managing MPA, depending on each patient's overall condition.

Patients with severe renal dysfunction (eGFR <15 mL/min/1.73 m^2) were excluded from the ADVOCATE study (1). On the other hand, the label of avacopan mentions that its pharmacokinetics in patients with mild-to-severe renal dysfunction is closely comparable to that in patients with a healthy renal function (https://med.kissei.co.jp/dst01/pdf/di_tv.pdf) (in Japanese). The ADVOCATE study included 50 patients with eGFR ≤20 mL/min/1.73 m^2 (27 in the avacopan group and 23 in the GC group). The avacopan group demonstrated a better eGFR recovery than did the GC group (11). Cortazar et al. reported three cases of AAV with RPGN requiring HD; avacopan was prescribed in combination with GC and immunosuppressants, which led to the successful withdrawal from HD (12). Clinicians should consider avacopan monotherapy or combination therapy comprising avacopan and GC, depending on the severity, general condition, and complications observed in each case.

In the ADVOCATE study, the incidence of severe adverse events was lower in the avacopan group than in the GC group; however, the incidence of serious adverse events such as abnormalities on liver function testing was relatively high in the avacopan group (5.4% vs. 3.7%) (1). Three reports described Japanese cases of avacopan-related severe liver ab-

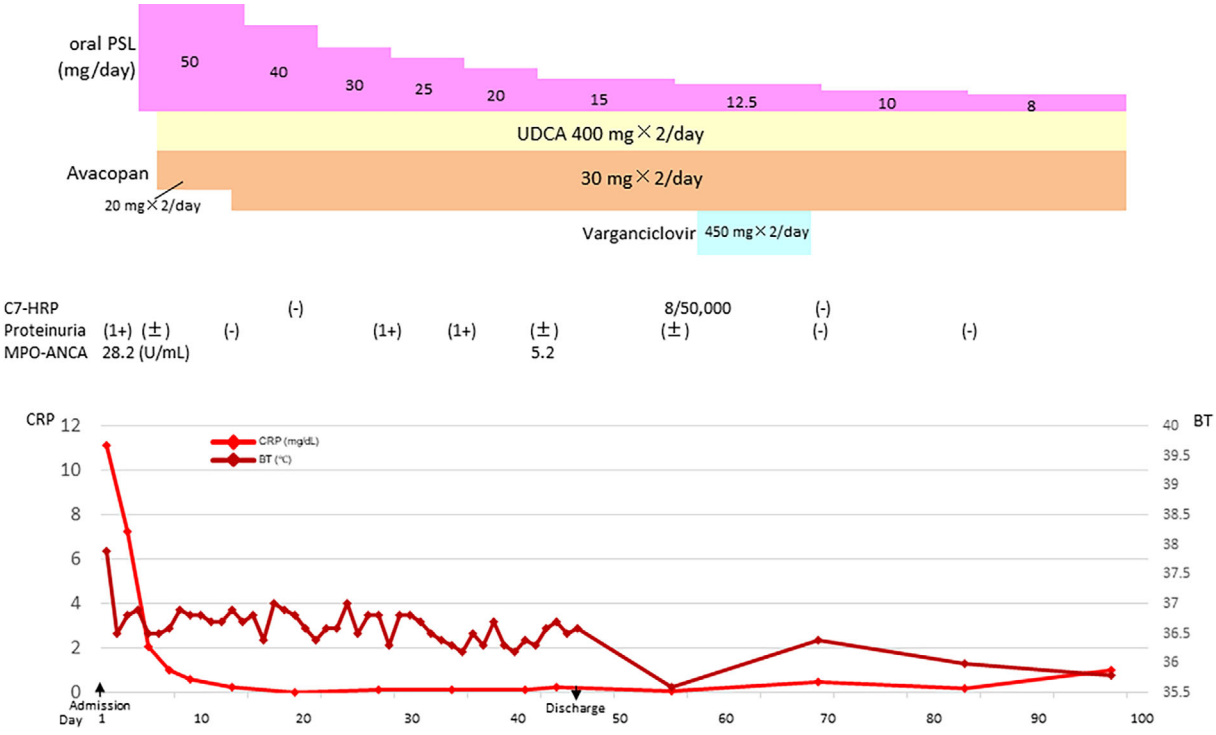

Figure 3. **Clinical course of Case 2. BT: body temperature, CRP: C-reactive protein, C7-HRP: cytomegalovirus pp65 antigen, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, PSL: prednisolone, UDCA: ursodeoxycholic acid**

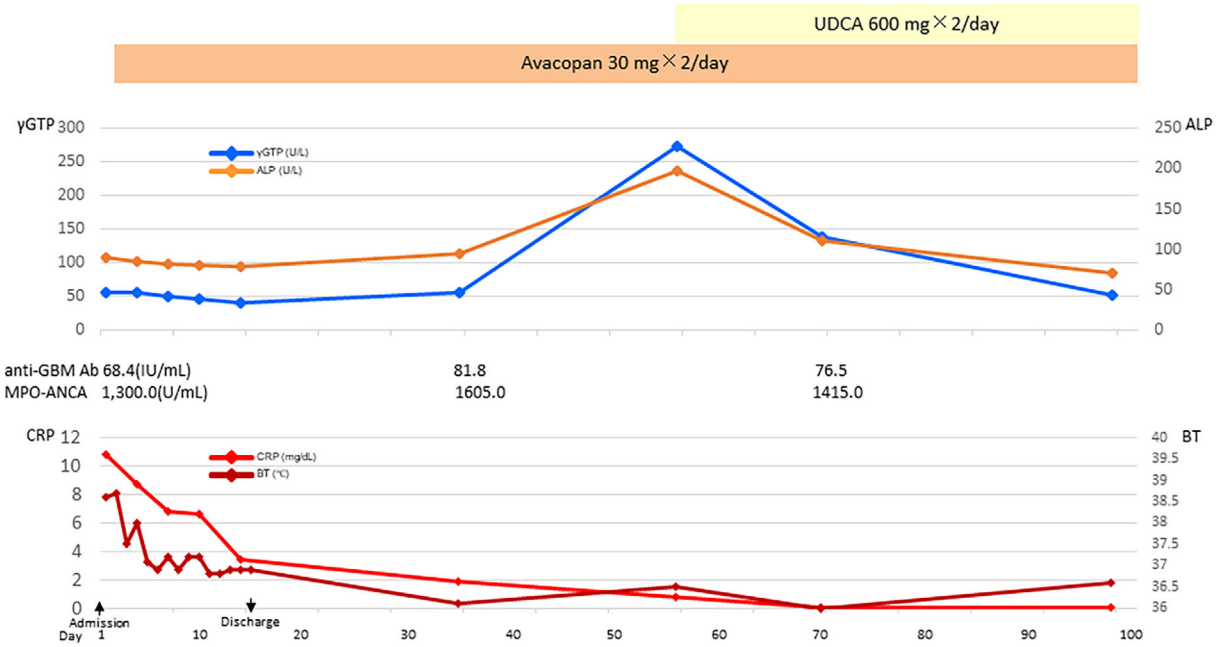

Figure 4. **Clinical course of Case 3. anti-GBM Ab: anti-glomerular basement membrane antibody, ALP: alkaline phosphatase, BT: body temperature, CRP: C-reactive protein, γGTP: gamma-glutamyl transpeptidase, MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody, UDCA: ursodeoxycholic acid**

normalities. In one woman with GPA, a liver abnormality developed 4 weeks after avacopan administration, which was treated by terminating avacopan and adding UDCA (4). In another woman with GPA, a liver abnormality developed 9 weeks after avacopan administration. Her treatment comprised avacopan interruption and UDCA addition, with an increase in avacopan dose (5). In another woman with MPA, liver abnormalities resulted in vanishing duct syndrome 45 days after avacopan administration; the treatment included avacopan termination and UDCA addition (6). Collectively,

Table 3. Concomitant Drugs Prescribed for the Patients until Three Months after the Introduction of Avacopan.

Case	Drugs
1	・Intravenous injection PSL 40 mg/day (continued for two weeks from the introduction of avacopan), Omeprazole 40 mg/day (continued for four days from the introduction of avacopan), Meropenem 0.5 g/day (continued for two weeks from the introduction of avacopan), Furosemide 400 mg/day (continued for one week from the introduction of avacopan), 200 mg/day (following 400 mg/day, for five days), 100 mg/day (following 200 mg/day, for one day), 40 mg/day (following 100 mg/day, for five days), Dobutamine 150 mg/day (contiuned for two days from the introduction of avacopan), Tolvaptan 100 mg/day (four times within one week from the introduction of avacopan), Cefepime 0.5 g/day (for five days, switched from oral levofloxacin) ・Oral PSL 40 mg/day (following intravenous PSL, for two days), 30 mg/day (following 40 mg/day, for one week), 25 mg/day (following 40 mg/day, for one week), 20 mg/day (following 25 mg/day, one week), 15 mg/day (following 20 mg/day, for two weeks), 10 mg/day (following 15 mg/day), Lansoplazole 15 mg/day (following intravenous omeprazole, for eight weeks), Vonoprazan 10 mg/day (switched from omeprazole), Mecobalamin 1,500 μg/day (resumed from one week after the introduction of avacopan), Tolvaptan (for eight days, following intravenous tolvaptan), Furosemide 80 mg/day (switched from 40 mg/day of intravenous furosemide, for ten days), 160 mg day (following 80 mg/day, for five days), 20 mg/day (after the interval of three weeks, 12 days), Sulfamethoxazole/trimetprim 0.5 tablet/day, three times a week (for one week, starting from one week after the introduction of avacopan), Atovaquone 1,500 mg/day (switched from sulfamethoxazole/trimetprim, for three weeks, terminated on the suspicion of drug eruption), Sennoside 12 mg/day (for five days, starting from two weeks after the introduction of avacopan), Lubiprostone 24 μg/day (for three days, switched from sennoside), 48 μg/day (for two days, following 24 μg/day, terminated due to nausea), Linaclotide 0.5 mg/day (switched from 48 μg/day of lubiprostone), Lactulose 20 mg/day (for ten days, starting from four weeks after the introduction of avacopan), Atorvastatin 10 mg/day (starting from five weeks after the introduction of avacopan), Potassium L-aspartate 900 mg/day (for one week, starting from five and half weeks after the introduction of avacopan), Alfacalcidol 0.25 μg/day (starting from six weeks after the introduction of avacopan), Cefcapene pivoxil 100 mg/day (for one day, starting from six weeks after the introduction of avacopan), Levofloxacin 250 mg/day (for one day, switched from cefcapene pivoxil), Fexofenadine 60 mg/day (for ten days, starting from seven and half weeks after the introduction of avacopan), Fungizone 180 mg/day (oral suspencion, starting from nine weeks after the introduction of avacopan), Sodium picosulfate ten drops (in case of constipation), Metclopramide 5 mg (in case of nausea), Lemborexant 5 mg (in case of insomnia) ・Subcutaneous injection Insulin aspart (subcutaneous injection, dose was dependent on blood glucose level) ・Topical Betamethasone (for skin eruption on the trunk, starting from seven and half weeks after the introduction of avacopan), Hydrocortisone (for skin eruption on the face, starting from seven and half weeks after the introduction of avacopan)
2	・Oral Clopidogrel 75 mg/day, Cilostazol 100 mg/day, Rabeprazole 10 mg/day, Pitavastatin 2 mg/day, Ethyl icosapentate 1,800 mg/day, PSL 50 mg/day (continued for one week from the introduction of avacopan), 40 mg/day (following 50 mg/day, for one week), 30 mg/day (following 40 mg/day, for one week), 25 mg/day (following 30 mg/day, for one week), 20 mg/day (following 25 mg/day, for one week), 15 mg/day (following 20 mg/day, for two week), 12.5 mg/day (following 15 mg/day, for two week), 10 mg/day (following 12.5 mg/day, for two week), 8 mg/day (following 10 mg/day), UDCA 400 mg/day (started at the introduction of avacopan), Teneligliptin 20 mg/day (from the week of the introduction of avacopan), Sulfamethoxazole/trimetprim 0.5 tablet/day (from the week of the introduction of avacopan), Amlodipine 5 mg/day (from the week of the introduction of avacopan), Canagliflozin 100 mg/day (starting from two weeks after the introduction of avacopan), Alfacalcidol 0.5 μg/day (starting from four weeks after the introduction of avacopan), Potassium L-aspartate 900 mg/day (for five days, starting from five weeks after the introduction of avacopan), Valganciclovir 900 mg/day (for 12 days, starting from seven weeks after the introduction of avacopan) ・Inhalation Olodaterol/tiotropium (inhalation, starting from four weeks after the introduction of avacopan) ・Subcutaneous injection Insulin aspart (subcutaneous injection, dose was dependent on blood glucose level)
3	・Oral Vonoprazan 10 mg/day, Vibegron 50 mg/day, UDCA 600 mg/day (starting from eight weeks after the introduction of avacopan)

PSL: prednisolone, UDCA: ursodeoxycholic acid

the concomitant use of UDCA and a gradual increase in avacopan might therefore prevent or alleviate avacopan-related liver abnormalities.

The authors state that they have no Conflict of Interest (COI).

References

1. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med **384**: 599-609, 2021.

2. Harigai M, Kaname S, Tamura N, Dobashi H, Kubono S, Yoshida T. Efficacy and safety of avacopan in Japanese patients with anti-neutrophil cytoplasmic antibody-associated vasculitis: a subanalysis of a randomized Phase 3 study. Mod Rheumatol **33**: 338-345, 2023.

3. Sada KE, Nagasaka K, Kaname S, et al. Clinical practice guidelines of the Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis for the management of microscopic polyangiitis and granulomatosis with polyangiitis: the 2023 update - secondary publication. Mod Rheumatol **34**: 559-

567, 2024.
4. Kojima K, Fukui S, Tanigawa M, et al. Severe prolonged liver abnormality with jaundice during treatment for granulomatosis with polyangiitis with rituximab and avacopan. Rheumatology (Oxford) **63**: e101-e103, 2024.
5. Kataoka H, Tomita T, Nakanowatari M, Kondo M, Mukai M. Gradual increase of avacopan dose with concomitant ursodeoxycholic acid use may help avoid the risk of C5a receptor inhibitor-induced liver injury in antineutrophil cytoplasmic antibody-associated vasculitis. Mod Rheumatol Case Rep **7**: 444-447, 2023.
6. Yamaguchi S, Yamazaki M, Kido T, et al. A case of vanishing bile duct syndrome during treatment of microscopic polyangiitis with avacopan. Rheumatology (Oxford) **63**: e120-e122, 2024.
7. Ozaki S. ANCA-associated vasculitis: diagnostic and therapeutic strategy. Allergol Int **56**: 87-96, 2007.
8. Miyawaki Y, Fujii T, Anan K, et al. Concordance between practice and published evidence in the management of ANCA-associated vasculitis in Japan: a cross-sectional web-questionnaire survey. Mod Rheumatol **33**: 990-997, 2023.
9. Harigai M, Nagasaka K, Amano K, et al. 2017 Clinical practice guidelines of the Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis for the management of ANCA-associated vasculitis. Mod Rheumatol **29**: 20-30, 2019.
10. Sato A, Nakata K, Moriya RF, et al. Microscopic polyangiitis presenting as rapidly progressive glomerulonephritis treatment with the complement C5a receptor inhibitor, Avacopan: three case report. Fukushima Med J **73**: 29-35, 2023 (in Japanese, Abstract in English).
11. Cortazar FB, Niles JL, Jayne DRW, et al.; the ADVOCATE Study Group. Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of avacopan. Kidney Int Rep **8**: 860-870, 2023.
12. Cortazar FB, Cerda J, Dhanani R, Roglieri J, Santoriello D. Avacopan in patients with rapidly progressive glomerulonephritis requiring dialysis. Kidney Int Rep **8**: 1687-1691, 2023.

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