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REVIEW

Evaluating Avacopan in the Treatment of ANCA-Associated Vasculitis: Design, Development and Positioning of Therapy

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Abstract: Recently, avacopan has been approved for the treatment of ANCA-associated vasculitis (AAV). Avacopan is an inhibitor of the C5a-receptor, which plays an important role in chemotaxis and the amplification loop of inflammation in AAV. In the most recent, international guidelines avacopan is recommended as steroid-sparing agents for the management of AAV. Here, we review the clinical trials that have led to demonstrate that avacopan is an effective treatment option in the management of AAV, where it can significantly reduce the cumulative dosage of glucocorticoids (GC). Despite the new guideline recommendations, clear guidance on how to employ avacopan in real-world clinical practice is lacking. We therefore also address in this review the data and clinical experience with avacopan obtained from real-world evidence. Combining preclinical studies, clinical trials, and real-world evidence helps to provide a better position of avacopan for the management of AAV in routine clinical practice, taking advantage of the GC-sparing effects of avacopan as a possible solution for the current challenge of reducing GC-toxicity in AAV patients. Furthermore, we delineate current knowledge gaps and future research areas that need to be addressed.

Keywords: antineutrophil cytoplasmic antibody, ANCA, pauci-immune glomerulonephritis, complement, C5a inhibition, glucocorticoid toxicity

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare, potentially life-threatening, systemic autoimmune disease with a high relapse rate.[1–3] AAV comprises three subtypes (granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA)), which can affect nearly all organs, with severe forms leading to kidney failure and diffuse alveolar haemorrhage (DAH).[1–3] The pathophysiology of AAV is related to auto-antibodies against two types of neutrophil proteins: proteinase 3 (ANCA-PR3) or myeloperoxidase (ANCA-MPO). PR3 and MPO migrate to the outer cell membrane when neutrophils are primed for activation. Subsequently, the binding of ANCA's activates primed neutrophils, which initiates a cascade of inflammation, leading to neutrophil extracellular trap formation, release of cytoplasmatic components including PR3 and MPO, activation of the alternative complement system, and injury of the small vessels, which ultimately leads to organ damage.[1,4]

In the last two decades, it has become apparent that the alternative complement activation pathway is pivotal to sustaining and enhancing inflammation in AAV.[5] Notably, in murine studies, the blockade of alternative complement up to the level of C5/C5a prevented the formation of crescentic vasculitis lesions in kidney glomeruli.[6–8] As one of the split products from an activated alternative complement system, C5a induces chemotaxis of immune cells, particularly

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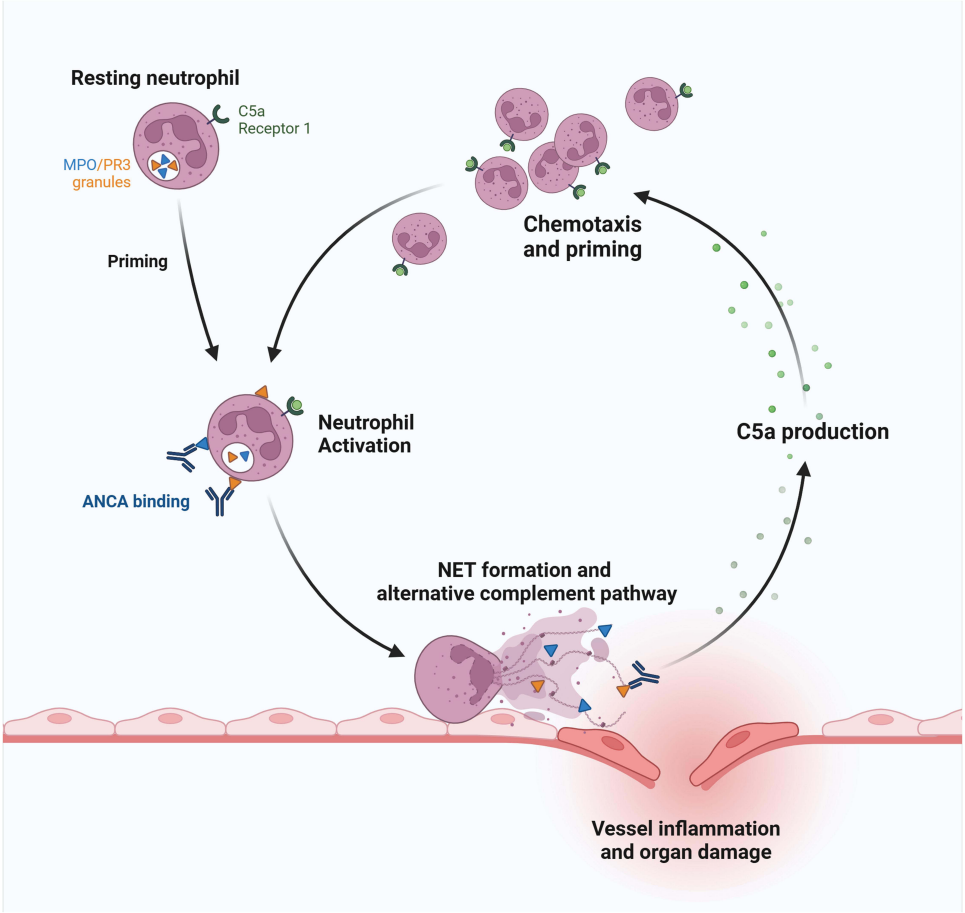

Figure 1 The amplification loop of AAV targeted by avacopan: binding of ANCA-antibodies to PR3 or MPO on primed neutrophils activates the alternative complement pathway resulting in generation of C5a. In turn, C5a will induce chemotaxis of more neutrophils and primes them for further activation by ANCAs. Blocking of the C5a receptor with avacopan prevents this amplification loop and reduces vessel injury and organ damage.

neutrophils. In addition, binding of C5a to the C5a-receptor 1 (C5aR) on neutrophils induces priming of neutrophils, an important step in AAV pathophysiology.[9] C5a-induced priming of neutrophils creates a vicious amplifying loop for neutrophil activation and inflammation in AAV patients (Figure 1).[1,5,9]

The treatment of AAV consists of anti-inflammatory and immunosuppressive treatments. Guidelines recommend the initiation of remission induction treatment that combines high-dose corticosteroids with rituximab (RTX) and/or cyclophosphamide (CYC), followed by remission maintenance treatment with rituximab.[2,3] High-dose glucocorticoids (GC) are tapered to low-doses or discontinuation in 6–12 months.[2,3] The use of these immunosuppressive drugs has tremendously decreased the mortality of AAV and increased remission rates to more than 90%.[1–3] As a result, maintaining remission and managing long-term complications require increasing attention since disease and treatment make AAV patients at high risk for relapses, organ damage, treatment toxicity, (cardiovascular) comorbidities and infections.[1–3,10]

There is ample evidence that GCs are related to multiple complications, such as diabetes, hypertension, cardiovascular disease, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems, and neuropsychological problems.[11,12] Importantly, severe infections are currently the main cause of death for patients within the first year of vasculitis and are strongly related to high-dose GCs.[3] Additionally, GCs have shown a negative impact on patients' health-related quality of life (HRQoL).[13,14] And most recently, steroid-use in AAV patients has also been associated with higher healthcare costs.[15,16] Taken together, a high priority to improve outcomes for AAV patients is to reduce infectious complications and increase HRQoL by reducing steroids within immunosuppressive treatment strategies without compromising control of vasculitis-related inflammation.[3]

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In the most recent EULAR guidelines, avacopan is recommended as a steroid-sparing agent for the management of AAV. In this review, we will cover the clinical development of the C5a-blocking agent avacopan (Tavneos®), leading to the approval by the FDA and EMA, summarize early access clinical experiences with avacopan, and discuss the treatment positioning and duration of avacopan in the management of AAV patients.

Design and Development

The first therapeutic potential for complement blockage was demonstrated in preclinical, murine studies that showed that complement depletion with cobra venom factor, blockage of the alternative pathway through factor B depletion and blockage of the final step of the complement pathways by C5 knockout protected against the development of MPO-induced glomerulonephritis.[6] Of note, a C4-knockout model, blocking the classical and lectin pathway, could not prevent or reduce inflammation.[6] Additionally, it was demonstrated that blockage of the alternative complement pathway at level of C5 and C5a in mouse could protect against the development of MPO-induced glomerulonephritis and could reduce the number of crescent after the disease started.[7] Subsequently, it was shown that C5a and its receptor on neutrophils (C5aR) were responsible for priming neutrophils for activation by ANCA's.[9] This led to the development of an antagonist for C5aR, CCX168 (now known as avacopan). In a pivotal study Xiao et al (2014) demonstrated avacopan was able to block human C5aR in mice, which reduced the formation of crescents of MPO-induced glomerulonephritis from 30.4% to 3.3%.[8]

In a Phase 1 trial, avacopan was tested in different dosages in 48 healthy volunteers, which showed that a bidaily 30mg of avacopan blocked 94% of C5aR as measured by CD11b upregulation. CCX168 was well tolerated without any safety concerns.[17]

The phase 1 trial was followed by two phase-2 trials, the CLASSIC and the CLEAR, and one phase-3 trial, the ADVOCATE.[18–20] All three studies were double blinded randomized studies on AAV patients with comparable inclusion criteria, as summarized in Table 1. Clinically relevant outcomes of all these studies, including a subgroup and post-hoc-analysis of ADVOCATE, are summarized in Table 2.

In the CLEAR study (2017), 67 patients were treated for 12 weeks with a follow-up visit at 24 weeks.[18] All patients received a standard induction with RTX or intravenous CYC (CYC-IV) and patients were randomized between addition of a) prednisone 60 mg taper schedule with avacopan placebo, b) prednisone 20 mg taper + 30 mg avacopan bidaily or c) 30 mg avacopan bidaily with prednisone placebo. Patients randomized to the prednisone 60 mg group were tapered to 0 mg in 20 weeks, and patients randomized to the prednisone 20 mg group were tapered to 0 mg in 14 weeks. The primary endpoint for efficacy was a Birmingham Vasculitis Activity Score (BVAS) reduction of >50% at week 12, which showed non-inferiority between the groups. Secondary renal outcomes showed urine albumin/creatinine ratio (UACR) decreased more quickly in both avacopan groups, but the UACR difference was not sustained at follow-up. No significant differences in change of estimated glomerular filtration rate (EGFR) or urinary red blood cells (RBC) were seen.[18]

In the CLASSIC study (2020), 42 patients were treated for 12 weeks.[20] All patients received a prednisone taper combined with a standard induction with RTX or CYC-IV and patients were randomized between addition of a) avacopan placebo, b) avacopan 10 mg bidaily or c) avacopan 30 mg bidaily. In all groups, prednisone was tapered from 60 mg to

Table 1 Inclusion and Exclusion Criteria in the Avacopan Trials

Inclusion Criteria	Exclusion Criteria
• New or relapsing MPA or GPA • PR3 or MPO positivity (ever) • At least 1 major item, 3 minor items or 2 renal items on BVAS • EGFR ≥20mL/mL/1.73m^2 (CLEAR and CLASSIC) • EGFR ≥15 mL/mL/1.73m^2 (ADVOCATE)	• Severe kidney disease expected to require dialysis (CLEAR and CLASSIC) • Severe alveolar haemorrhage expected to require invasive ventilation (ADVOCATE) • >3000 mg IV methylprednisolone 12 weeks before/during screening • >10 mg GC for >6 weeks continuously before screening • Cyclophosphamide 12 weeks before screening • RTX <26 weeks before screening or <52 weeks without B-cell repopulation

Abbreviations: EGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; GC, glucocorticoids; IV, intravenous; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RTX, rituximab;

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Table 2 Important Outcomes in the Avacopan Trials

			CLEAR			CLASSIC			ADVOCATE		ADVOCATE Sub: RTX Treated		ADVOCATE Post-hoc: EGFR ≤20	
	Randomization Arm		**Pred 60 (n=20)**	**Pred20+ AVA 30 (n=22)**	**AVA 30 (n=21)**	**Pred 60 (n=13)**	**Pred 60+ AVA 10 (n=12)**	**Pred 60+ AVA 30 (n=15)**	**Pred 60 (n=164)**	**AVA 30 (n=166)**	**Pred 60 (n=107)**	**Ava 30 (n=107)**	**Pred 60 (n=23)**	**AVA 30 (n=27)**
	Primary Outcome		**Efficacy**			**Safety**			**Efficacy**		**Efficacy**		**Renal Recovery**	
Treat-ment	RTX, n (%)		3 (15)	5 (23)	5 (24)	12 (92)	13 (100)	14 (88)	107 (65)	107 (64)	107 (100)	107 (100)	13 (57)	12 (44)
	CYC-IV, n (%)		17 (85)	17 (77)	16 (76)	1 (8)	0	2 (13)	51 (31)	51 (31)	-	-	9 (39)	13 (48)
	CYC-PO, n (%)		–	–	–	–	–	–	6 (4)	8 (5)	–	–	1 (4)	2 (7)
Efficacy out–comes	BVAS <50%	Week 12	70	86	81	85	92	80	–	–	–	–	–	–
	BVAS 0 + Pred 0 (% pts)	Week 26	–	–	–	–	–	–	70.1	72.3	76	78	60.9	70.4
		Week 26–52	–	–	–	–	–	–	54.9	**65.7***	56	**71***	60.9	66.7
	Relapses (% pts)	EoS	8.7	4.5	13.6	0	0	0	21.0	**10.1***	20.2	**8.7***	17.4	7.4

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Renal outcomes	EGFR change in %	Week 4	−0.8	+2.0	−1.2	Est# −5	Est# 0	**Est# +7***	Est# +4.5	Est# +3.5	–	–	–	–
		Week 12	+5.6	+6.0	+0.8	+2.0	+1.3	+6.2	Est# +8	Est# +9	–	–	–	–
		Week 26	–	–	–	–	–	–	+2.9	**+5.8***	+1.8	+4.6	+6.1	**+11.9***
		Week 52	–	–	–	–	–	–	+4.1	**+7.3***	2.8	+5.8	+7.7	**+16.1***
	UACR change in %	Week 4	+15	**−40***	**−47***	–	–	–	0	**−40***	+6	**−42***	+66	**−16***
		Week 12–13	−21	**−56***	−43	−73	−51	−68	−49	−55	–	–	+20	**−35***
		Week 24–26	−48	−61	−30	-	-	-	−70	−63	–	–	−40	−55
		Week 52	–	–	–	–	–	–	−77	−74	−73	−72	−62	−62
	RBC count change in %	Week 1	–	–	–	−24	**−80***	**−84***	–	–	–	–	–	–
		Week 4	−76	−72	−65	–	–	–	–	–	–	–	–	–
		Week 12	−91	−83	−85	−92	−94	−97	–	–	–	–	–	–
Safety,	Pts with AEs (%)	EoS	91	86	96	100	85	94	98	99	98	98	100	100
	Pts with SAEs (%)	EoS	17	14	36	15	17		45	42	39	35	70	48
	AEs related to GC	EoS	65	**34***		–	–	–	80.5	**66.3***	–	–	–	–

(*Continued*)

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Table 2 (Continued).

			CLEAR			CLASSIC			ADVOCATE		ADVOCATE Sub: RTX Treated		ADVOCATE Post-hoc: EGFR ≤20	
	Randomization Arm		**Pred 60 (n=20)**	**Pred20+ AVA 30 (n=22)**	**AVA 30 (n=21)**	**Pred 60 (n=13)**	**Pred 60+ AVA 10 (n=12)**	**Pred 60+ AVA 30 (n=15)**	**Pred 60 (n=164)**	**AVA 30 (n=166)**	**Pred 60 (n=107)**	**Ava 30 (n=107)**	**Pred 60 (n=23)**	**AVA 30 (n=27)**
Damage, toxicity and QoL	VDI change	EoS	+0.7	+0.3	+0.2	+0.31	+0.09	+0.14	+1.17	+1.15	–	–	–	–
	GTI-CWS	Week 26	–	–	–	–	–	–	56.6	**39.7***	52.9	**28.0***	–	–
	GTI-AIS	Week 26	–	–	–	–	–	–	23.4	**11.2***	20.2	12.8	–	–
	EQ-5D-5L VAS[&]	EoS	−3%	+28%	+5%	+44.1%	+39.7%	+61.4%	+7.1	**+13.0***	+9.0	+13.6	–	–
Steroids	GC dose protocol	Week 20	2450	805	0	2450	2450	2450	2450–2800[$]	0–350[$]	2450–2800[$]	0–350[$]	2450–2800[$]	0–350[$]
	Mean cum. dose	EoS	–	–	–	–	–	–	3847	**1676***	3687	**1731***	3875	**1376***

Notes: *P<0.05 for comparison of avacopan versus prednisone 60. [#]Estimated based on figures in the manuscript. [$]Including a four week open-label taper of prednisone according to 20–15-10-5mg/week. [&]Percentual change for CLEAR and CLASSIC, least-squares mean change in ADVOCATE.

Abbreviations: AE, adverse event; AVA, avacopan; BVAS, Birmingham Vasculitis Activity Score; cum, cumulative; CYC, cyclophosphamide; EGFR, estimated glomerular filtration rate; EoS, end of study; GC, glucocorticoids; GTI-CWS /AIS, Glucocorticoid Toxicity Index Cumulative Worsening Scores and Aggregate Improvement Scores; IV, intravenous; post-hoc, post-hoc analysis; PO, per os; pred, prednisolone; pts, patients; RBC, urinary red blood cells; RTX, rituximab; SAE, severe adverse event; sub, subgroup analysis; UACR, urine albumin/creatinine ratio, VDI, vasculitis damage index; VAS, visual analogue scale.

0 mg over 20 weeks. The primary endpoint was safety based on the incidence of adverse events (AEs), which showed non-inferiority between the groups. The incidence of severe AEs (SAEs) also did not differ between patients treated with and without avacopan. The main efficacy endpoint was the same as that in the CLEAR trial, that is, a BVAS reduction of >50% at week 12, which showed non-inferiority between the groups. Secondary renal endpoints showed EGFR gain was slightly higher in patients treated with avacopan 30mg bidaily, but the difference was only significant at week 4. Urinary RBCs decreased faster at week 1 in the avacopan arms but did not differ at week 12. UACR change did not differ between groups at week 12.[20]

In the ADVOCATE study (2021), 330 patients were treated for 52 weeks.[19] All patients received a standard induction with CYC-IV, CYC per-os (CYC-PO) or RTX and were randomized between addition of a) prednisone 60 mg taper with avacopan placebo and b) avacopan 30 mg bidaily with prednisone placebo. During the screening period, which was maximized to 14 days, open-label prednisone, including IV methylprednisolone of maximum 3000 mg, was allowed but had to be tapered to 20 mg or less before the start of the trial and had to be discontinued within the first 4 weeks of the trial. Patients randomized to the prednisone group were tapered to 0 mg over 20 weeks. Open-label prednisone during the course of the study was allowed for non-vasculitis reasons up to 10 mg/day and for worsening disease or disease without improvement, according to the physicians' opinion. Maintenance treatment consisted of azathioprine in patients who received CYC induction. Patients who received RTX induction therapy did not receive maintenance treatment. The primary endpoint was clinical remission at week 26, defined as a BVAS score of 0 with at least 4 weeks of GC discontinuation, which showed non-inferiority between the two groups. The secondary efficacy endpoints of sustained remission from 26 to 52 weeks and the number of relapses showed superiority for the avacopan group over the prednisone group.[19] This impact was even clearer in a subgroup-analysis of patients treated with rituximab.[21] Supplementary data also indicated a numerically higher impact of avacopan on sustained remission in MPA (+19.3%) than in GPA patients (+3.7%), in MPO+ (+17%) than in PR3+ patients (+2.6), and in relapsing (+28.5%) than in new disease (+3%). Secondary renal endpoints showed a larger gain of EGFR in the avacopan group compared to the prednisone group at week 26 and 52.[19] The difference in EGFR gain was even larger in a post-hoc-analysis of patients with a EGFR <20 mL/min at baseline.[22] UACR reduced more in the avacopan group at week 4, but there was no difference at later timepoints.[19] The 1-year mean cumulative GC dose in the avacopan group was significantly lower than in the prednisone group (1676 mg versus 3847 mg). There was no difference in the incidence of AEs, SAEs, or (serious) infections between groups; however, the avacopan group had a significantly lower incidence of AEs categorized as possibly related to GC. Indeed, the avacopan group had significantly lower Glucocorticoid Toxicity Index (GTI) Cumulative Worsening Scores (GTI-CWS) and GTI Aggregate Improvement Scores (GTI-AIS), and significantly more improvement of HRQoL.[19]

In conclusion, the Phase 2 CLEAR and CLASSIC studies showed that avacopan could replace steroids with the same short-term efficacy with non-inferior safety. The Phase 3 ADVOCATE study demonstrated that avacopan is an effective co-immunosuppression in remission induction treatment that allows a significant reduction in cumulative GCs, leading to beneficial effects on GC-related toxicity and kidney function recovery.[18–20] Based on these trials, both the FDA and the EMA have approved avacopan for the treatment of ANCA-associated vasculitis. The FDA indicated avacopan can be used in adult patients with severe GPA or MPA as adjunctive treatment combined with standard therapy including GCs. It specifically stated that avacopan cannot eliminate GCs.[23] The EMA indicated avacopan can be used in adult patients with severe GPA or MPA in combination with RTX or CYC and GC as clinically needed.[24] In both the EMA and FDA approval, the primary safety warning is for hepatotoxicity for which regular testing of hepatic transaminases and bilirubin are recommended.[23,24]

Since the approval of avacopan, the EULAR, KDIGO, and CAN-VASC guidelines on AAV have been updated to include recommendations about avacopan (Table 3).[2,3,25] The 2022 EULAR update recommends that avacopan can be considered as part of a remission induction treatment with RTX or CYC to substantially reduce GC. Patients most likely to benefit from avacopan are patients at risk for GC-related toxicity and patients with rapidly deteriorating kidney function.[3] The KDIGO 2024 guideline recommends that avacopan can be used as an alternative to GC and indicates that patients most likely to benefit from avacopan are patients with an increased risk for GC toxicity and patients with a low EGFR (<20 mL/min).[2] The CAN-VASC 2022 addendum recommends to taper GCs in 4 weeks when using avacopan as

Table 3 Current Guidelines on Avacopan

Guideline	EULAR	KDIGO	CAN-VASC
Treatment recommendation	Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.	We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV. Avacopan may be used as an alternative to glucocorticoids	The addition of oral avacopan can be considered for induction of remission in patients with newly diagnosed or relapsing GPA or MPA treated with cyclophosphamide or rituximab. After starting avacopan, a faster glucocorticoid tapering protocol aiming for discontinuation by the end of week 4 should be considered.
Patients most likely to benefit	• Patients at risk of development or worsening of GC-related adverse effects and complications. • Patients with active glomerulonephritis and rapidly deteriorating kidney function	• Patients at increased risk of GC toxicity, including those with high infection risk, preexisting diabetes mellitus, psychiatric disorders, and osteoporosis. • Patients with lower kidney function (eGFR <20 mL/min per 1.73 m2).	• Patients at increased risk of GC toxicity • Patients with renal involvement • Patients refractory to conventional treatments
Treatment duration	Stop avacopan after duration of treatment of 6–12 months; there are no data on use of avacopan beyond 1 year, so longer-term use cannot be recommended.	There is a lack of long-term data on avacopan usage.	When initiated as part of induction therapy, avacopan can be continued for one year.

Abbreviations: EGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; GC, glucocorticoids; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3.

part of a remission induction treatment and indicates that patients most likely to benefit are patients at risk of GC toxicity, patients with renal involvement, and patients refractory to conventional therapy.[25]

Since the ADVOCATE study, a large number of real-world evidence (RWE) studies have been reported in cohort studies, case series, and case reports (Table 4).[26–54] RWE is of added-value because it addresses the gap between the homogenous trial population versus the heterogeneous AAV patients in clinical practice. Consequently, RWE studies often include patient groups not included in the original AAV trials, such as AAV patients with refractory disease, severe glomerulonephritis, or severe diffuse alveolar hemorrhage (DAH).

Refractory patients were described in one cohort study, two case series and four case report. In a German cohort (n = 31) where a remission rate of 87.5% was reported after 6 months, 51% of patients started avacopan because of uncontrolled disease.[28] In a Spanish cohort (n = 29) with an overall remission rate of 86% at 6 months, 20.6% started avacopan because of refractory disease.[27] In a Dutch case series, 6 refractory and relapsing patients were described, who received multiple remission induction treatments in the year before avacopan and all achieved remission within 6 months of avacopan, with only 1 relapse during follow-up of 1–2 years.[37] One case report described avacopan halted recurrent

Table 4 Real-World Evidence on Avacopan

	Number of Studies	Studies Reporting Outcomes on		
		Refractory Disease	Severe RPGN	Severe DAH
Retrospective cohorts	**5**	2	3	2
Case series	**8**	2	2	1
Case reports	**16**	4	3	0

Abbreviations: DAH, diffuse alveolar haemorrhage; RPGN, rapid progressive glomerulonephritis.

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subglottic and bronchial stenosis which was previously not achieved with several other immunosuppressives.[42] Two cases of severe DAH refractory to multiple immunosuppressives for over a month were reported to show improvement within 1 month after the start of avacopan.[34] Three case reports detailed AAV patients with RPGN with insufficient renal response upon standard remission induction treatment, where avacopan initiation resulted in EGFR improvement.[39,41,43]

Substantial EGFR improvements have also been reported in patients with EGFR <15 mL/min in an American cohort (n = 21), a German cohort study (n = 15), and a small case series (n = 3).[28,29,33] The mean improvement of EGFR after 12 months in both cohort studies (+25 and +27 mL/min respectively) were higher than that reported for the <20 mL/min subgroup of ADVOCATE (+16 mL/min).[19,29] Across multiple studies, 23 patients were dialysis-dependent when starting avacopan and 17 (74%) were able to discontinue dialysis, but the time range until discontinuation was very large (maximum 13 months).[26,28,29,33,35]

Outcomes for patients with severe DAH are scarce and have only been reported in two cohort studies and one case series.[28,30,34] A German cohort study reported on seven patients with DAH, including two patients requiring invasive ventilation, who had a remission rate of 83% after 6 months.[28] Another small cohort study described 15 patients with DAH, including three patients needing oxygen support. One patient with concomitant kidney failure died due to a severe infection. All others achieved remission with 10 (71%) patients being able to discontinue GCs after a median of 52 days.[30] One case series reported 8 patients with severe DAH requiring oxygen support, including 4 needing mechanical ventilation, who all achieved remission. In all 8 patients, oxygen support could be stopped after a median of 6.5 days (range 2–40).[34]

Positioning of Avacopan Therapy

Indications

Based on the phase 2 and 3 trials, it is clear that avacopan has a beneficial impact on the cumulative dose of GC needed to effectively treat patients with AAV and that avacopan reduced GC-related toxicity with subsequent higher HRQoL. In addition, in two out of three trials, avacopan had a beneficial effect on kidney function recovery, with the highest improvement in a subgroup of patients with an EGFR 15–20 mL/min/1.72 m^2 at initiation. Based on all data and guidelines, we can firmly establish that avacopan has added value when employed in AAV patients with an increased risk for GC-toxicity. Based on guidelines, we can identify two subgroups of patients at risk for GC-toxicity: a) patients with a high risk for GC toxicity based on their medical history and b) patients with a high risk for GC toxicity based on disease severity.[2,3]

A high risk for GC toxicity based on medical history can be either based on pre-existing comorbidities that are easily worsened by GC or previous episodes of GC-toxicity. Pre-existing comorbidities can include but not limited to obesity, diabetes, osteoporosis, psychiatric conditions and severe infections. Additionally, the risk for severe infections is higher in older and frail patients and is associated with cumulative GC-dose.[12,55] Previous episodes of GC toxicity can include, but not limited to, multiple or severe infections, difficult to treat diabetes, psychological burden, or weight gain.

A high risk for GC toxicity based on disease severity can be expected in patients with refractory or relapsing disease. Patients who received multiple remission induction treatments or are unable to taper GC will have a higher cumulative dosage of GC, which increases the risks for GC-toxicity. To reduce the cumulative GC dose needed, avacopan can be initiated. This might also increase disease control, but this needs to be further studied.

Avacopan also seems to be of added value to patients with a high risk for kidney failure, defined as a low EGFR or a rapidly decreasing kidney function. Although patients with an EGFR <20 mL/min/min2 or dialysis were excluded from the avacopan trials, and formal proof in a well-designed controlled study is lacking, the promising results reported from RWE allow the consideration of avacopan in this subgroup of AAV patients to optimize the chances for recovery of kidney function.

Taken together, we describe three subgroups of AAV patients that could most benefit from the use of avacopan as part of the treatment strategy to manage active AAV (Table 5).

Table 5 Positioning of Avacopan in Routine Clinical Practice

Patients Most likely to Benefit	Concomitant Treatment	GC Taper	Treatment Duration
I. Patients at high risk for GC toxicity based on medical history: a. Comorbidities likely to worsen due to GC b. Previous episodes of GC toxicity	RIT with RTX and GC taper. RTX maintenance treatment.	Week 1: 60mg Week 2: 30mg Week 3: 5mg Week 4: 0mg Consider faster taper or no GCs at all.	Consider discontinuation after 6 months only if remission is achieved.
II. Patients at high risk for GC toxicity based on high cumulative GC dose due to disease severity: a. Relapsing disease b. Refractory disease	RIT with RTX and GC taper. Consider addition of MP, PLEX or low dose CYC-IV if needed. RTX maintenance treatment.	*Refractory patients*: PEXIVAS taper schedule. *Relapsing patients*: Week 1: 60mg Week 2: 30mg Week 3: 5mg Week 4: 0mg Consider a longer GC taper if needed.	Prolonged use beyond one year might be considered.
III. Patients at high risk for kidney failure: a. Low kidney function at start treatment, including EGFR <15mL/min/m^2 or dialysis b. Rapidly decreasing EGFR at start or during treatment	RIT with RTX and GC taper. Consider addition of MP, PLEX or low dose CYC-IV if needed. RTX maintenance treatment.	Week 1: 60mg Week 2: 30mg Week 3: 5mg Week 4: 0mg Consider a longer GC taper if needed.	Consider discontinuation after 6 months only if remission is achieved

Abbreviations: CYC, cyclophosphamide; EGFR, estimated glomerular filtration rate; GC, glucocorticoids; IV, intravenous; MP, methylprednisolone; PLEX, plasma exchange; RIT, remission induction treatment; RTX, rituximab.

Concomitant Immunosuppressive Treatment

Although avacopan can effectively reduce GCs, it has not yet been studied as a completely steroid-free treatment regimen. Thus, the optimal GC tapering schedule when using avacopan remains unclear and can only be deducted from extrapolating experiences from the phase 2 and 3 studies. In CLEAR, faster UACR reduction and fewer GC-related AEs were observed for both avacopan groups, ie both without concomitant GC and with a 20 mg prednisone taper of 14 weeks (805 mg cumulative). In ADVOCATE, patients with avacopan received a mean of 907 mg GC during screening and a mean of 1676 mg during the complete study, with the highest proportion of mean 625 mg during the first 4 weeks of open-label GC taper.[19] The KDIGO and EULAR guidelines do not specify a taper schedule for avacopan, but the Canadian guidelines recommend to taper GC to discontinuation in 4 weeks, based on the open label taper of the ADVOCATE.[2,3,25] The lack of recommended taper schedules is reflected in the RWE, where cumulative GC dosages are very heterogeneous. American and German cohort studies reported higher GC dosages than in ADVOCATE (>2 gram and >3 gram respectively).[28,29] A Spanish cohort showed higher dosages for relapsing (3 gram) than for newly diagnosed patients (2 gram).[27] One French cohort study reported a lower median dosage of 700 mg with a median time till GC discontinuation of <1 month.[26] Simultaneously with the development of Avacopan, the search for optimal GC reduction also continued in other trials. Based on the PEXIVAS trial the recommended taper is now faster which reduced cumulative GC dosage by 40% compared to previous tapers.[56] The LoVas trial showed a fast reduction starting at 0.5 mg/kg/day tapered to 5 mg by week 7 can safely reduce cumulative GCs to 1817 mg.[57] A retrospective cohort study even showed promising outcomes after a minimalized GC taper schedule of 2 weeks with a cumulative dosage of 1100 mg.[58] Altogether, there is a continuous trend towards minimizing GCs, while the most important added value of employing avacopan is also in the safe and

significant reduction of GC exposure. Based on the available evidence and study designs, there can be suggested to comply to reported study procedures where steroids are stopped by 4 weeks after initiation of avacopan, exemplified by a tapering schedule summarized in Table 5. This would add up to a cumulative dose of 665 mg.

Notwithstanding, the GC sparing effect of avacopan is notably of added value in patients with refractory disease who either do not achieve to taper GCs adequately or already have been exposed to high cumulative dosages of steroids over time. Due to the lack of evidence in this group of severe, refractory patients, caution should be employed to taper steroids as fast as proposed for the average ADVOCATE AAV patients. As evidenced by RWE, a regular PEXIVAS taper seems most appropriate while allowing room for a personalized based taper in real clinical practice.

Lastly, one should note that avacopan is a true solution for AAV patients with severe contraindications for GC, where the promising results described in GC-free patients in the CLEAR trial and multiple cases in RWE support treatment strategy completely free from oral glucocorticoids.[18,26,36,44,50]

In addition to avacopan and GC, all patients should be treated with rituximab or cyclophosphamide.[2,3,19,25] In ADVOCATE, 65% of the patients were treated with RTX and 35% with CYC. The primary endpoints remained non-inferior in subgroup analysis based on treatment (76 vs 78% for RTX and 60 vs 63% for CYC). The secondary endpoint of sustained remission only reached superiority for avacopan in the RTX-treated group (56 vs 71%) and not in the CYC-treated group (53 vs 56%).[19] It can be speculated that the high rate of relapses in the RTX-treated patients without avacopan might be explained by the absence of maintenance treatment. The majority of patients in RWE received avacopan combined with rituximab maintenance treatment.[26–29,34–37] Interestingly, remission rates after 1 year reported in RWE are higher than reported in ADVOCATE although direct comparison is difficult.[26–29,36,37] Overall, there is ample evidence for the use of avacopan during remission induction with either rituximab or cyclophosphamide, after which repeated RTX is the cornerstone of maintenance therapy in line with the recommendations of most recent guidelines.

The combination of RTX with low dose CYC-IV and plasma-exchange (PLEX) was not used in the ADVOCATE study but have been reported in RWE without safety concerns.[27–29,34,35,37] The decision for additional treatments with low dose CYC-IV or PLEX should be made according to the current guidelines and generally does not influence the decision to initiate avacopan.[2,3]

Avacopan Treatment Duration

In ADVOCATE, the treatment duration of avacopan was 52 weeks and therefore guidelines recommend to not continue avacopan beyond 1 year (Table 3).[2,3,19,25] However, as also mentioned in the EULAR guideline, shorter treatment duration of 6–12 months might be considered since the major GC-sparing effect is achieved within the first 6 months.[3] If after 6 months remission is achieved and maintenance RTX-therapy is started, avacopan discontinuation can be considered, comparable to GC discontinuation in an RTX-based treatment strategy.[2,3,59] Data on treatment with avacopan beyond 1 year are scarce and has only been reported in a few patients in one cohort, one case series and one case report without any new safety concerns.[27,37,42] As such, treatment beyond 1 year might only be worthwhile considering in patients with refractory disease where achieving sustained remission was difficult and patients with frequent relapses during regular maintenance treatment. This is also a patient category that would profit from treatment at a center of expertise on AAV.

The impact of avacopan as maintenance treatment agent to prevent relapses remains unclear.[19] It therefore remains speculative whether there is an additive relapse preventing the effect of avacopan combined with RTX maintenance, but high remission rates after 1 year are reported in RWE for this combination.[26,28,29,37] This issue on maintenance treatment and several important clinical issues around the use of avacopan in AAV remain unaddressed thus far and inevitably require further, controlled studies. Optimal treatment regimen, beneficial effects on achieving and maintaining disease control and the exact pathophysiological effects remain the most pressing issues for the research agenda (Table 6).

Table 6 Research Agenda for Avacopan

Research Agenda
• Determine optimal GC tapering schedule for patients with life-threatening, major and minor disease activity treated with avacopan.
• Determine if avacopan can be discontinued when remission is achieved.
• Determine if avacopan in combination with GC can beneficially impact disease control in severe disease
• Determine for which organs or symptoms avacopan can beneficially impact disease control and recovery.
• Determine if avacopan has a beneficial impact on relapse prevention during maintenance in addition to RTX maintenance treatment.
• Determine effects and safety of long-term avacopan usage (>1 year).
• Determine pathophysiological impact of avacopan.
• Collect large cohorts of real-world evidence for sub-analysis

Abbreviations: GC, glucocorticoids; RTX, rituximab.

Conclusion & Discussion

The development of avacopan has led to a new treatment option in active AAV patients, which can reduce GC toxicity and improve kidney function recovery. Although the GC-sparing effect of avacopan has been established in the phase 3 ADVOCATE study, the extent of this effect and the optimal way to employ avacopan are more complex in real clinical practice.

Therefore, to produce high level evidence relevant to practicing physicians, controlled studies could address whether in severe, generalized AAV patients avacopan can replace GCs or should be used as add-on to GCs. Additionally, the impact of continuing or discontinuing avacopan after achieving remission could be addressed in a controlled study with standard-of-care maintenance treatment with rituximab. Such studies could be complemented with biomarker studies to assess beneficial control of tissue-related inflammation underpinning disease control. Moreover, to consider avacopan as maintenance treatment in frequently relapsing patients, we will need studies to obtain data on long-term avacopan use.

In addition to improving guidance for clinical practice, many questions regarding the beneficial effects of C5a-receptor blockade by avacopan in AAV remain unanswered. For example, it remains unclear if avacopan can play a synergistic role with other immunosuppressive agents to increase control of inflammation in specific organs. This could be especially relevant to patients with life-threatening diseases, such as DAH, kidney failure or neurological involvement, where quick resolution of inflammation is essential, and treatment options sometimes fall short. However, also for AAV patient with grumbling disease, (refractory) ENT involvement, or persistent fatigue, there is a need for better control of inflammation. Understanding the impact of avacopan on local or systemic inflammation can be clinically relevant for these patients. Interestingly, persistent fatigue has been related to complement usage, and a large decrease of fatigue was seen in ADVOCATE.[60]

Therefore, it would help to understand the exact effect of avacopan on pathophysiological processes. Studies have shown that local and systemic complement usage are associated with poor outcomes in AAV, but the impact of avacopan on systemic and local complement usage, including NET-osis, vessel damage, and fibrosis, has not been studied yet.[61–63] It has been suggested that the rapid reduction of UPCR observed at week 4 of ADVOCATE and CLEAR is a reflection of quick control of inflammation at the kidney tissue level; however, it is also possible that the difference in UPCR is due to hemodynamic changes related to high steroids in the control patients.[18,19] This may also explain why this rapid reduction is not reported in RWE where higher dosages of GC were used and/or avacopan initiation was delayed. Unfortunately, UPCR changes were not reported for week 4 in CLASSIC, where all patients received high-dose GC.[20,28] A better understanding of (organ-specific) pathophysiological mechanisms and timing of effects can help personalize avacopan treatment and identify novel biomarkers to assess treatment efficacy of avacopan.

Until new randomized controlled studies are planned, high-quality RWE can be generated for many open questions regarding the use of avacopan. Assembling of large AAV patient cohorts treated with avacopan allows analysis of

relevant subgroups, which can help determine if the efficacy of avacopan differs between subgroups. For example, these analyses will be able to validate or refute the higher remission rates reported for MPO+, MPA and relapsing patients in the ADVOCATE study. Even though RWE is often uncontrolled, it is easier, cheaper, and less time-consuming than conducting global, multicenter RCTs and results in impactful evidence that outweighs multiple, individual small cohorts, case series, and case reports.

Based on currently available data, avacopan has an established role as part of a remission induction treatment strategy for patients with active GPA and MPA. Especially those AAV patients with high cumulative GC exposition, at high risk for GC toxicity and/or progressive kidney failure will have the largest benefit of an avacopan-based treatment strategy.

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