Journal Club
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Title: Avacopan for the Treatment of ANCA-Associated Vasculitis

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a term used to define a group of rare autoimmune diseases that cause inflammation and necrosis of blood vessels.[2] Overall, the cause of ANCA-associated vasculitis is unknown with a prevalence of 46-184 per million.[2,3] Clinically, patients can present in a variety of ways, and the Birmingham Vasculitis Activity Score (BVAS) can be used to determine the patients disease score across nine organ systems that may be affected by vasculitis.[2,4] Prior to this trial, the treatment of ANCA-associated vasculitis consisted of induction therapy with rituximab or cyclophosphamide in combination with glucocorticoids.[5] Glucocorticoids are associated with a variety of adverse events including increased risk of infections, osteoporosis, or adrenal suppression.[6] The ADVOCATE trial seeks to evaluate the use of avacopan, a novel C5a receptor antagonist which blocks neutrophil chemoattraction and activation in ANCA-associated vasculitis.[1]

Primary Objective: To determine if the use of avacopan is non-inferior to a tapering schedule of prednisone in patients with ANCA-associated vasculitis with concurrent use of immunosuppressive medications.

Primary Efficacy Measure:
First Primary Endpoint: The number of patients achieving clinical remission at week 26 as shown by a BVAS of zero and no glucocorticoids administered for 4 weeks.
Second Primary Endpoint: The number of patients sustaining remission at week 52.

Study Design: This was a phase III, multicenter, multinational, randomized, double-blind, double-dummy, active control trial. Patients were screened for up to 14 days prior to beginning the 52-week treatment period followed by an 8-week follow-up period. Outside of both treatment groups, patients were also administered a regimen of cyclophosphamide followed by azathioprine or rituximab.

Subjects: 1:1 randomization resulted in similar groups regarding age, race, body-mass index, median duration of ANCA-associated vasculitis, vasculitis disease status, ANCA status, type of vasculitis, and BVAS. The distribution of sex did differ between groups with males accounting for 59% of avacopan group versus 53.7% for the prednisone group.

Inclusion Criteria:
- Aged 18 or older with the following:

- Newly diagnosed or relapsing granulomatosis with polyangiitis or microscopic polyangiitis according to the Chapel Hill Consensus Conference definitions for which treatment with cyclophosphamide or rituximab was indicated
- Positive for antibodies to either proteinase 3 or myeloperoxidase
- Estimated eGFR of $\geq$ 15 mL/1.73m^2
- Had at least one major or three nonmajor items or at least two renal items of hematuria and proteinuria on the BVAS.

Exclusion Criteria:

- Patients who received more than 3 g of intravenous glucocorticoids within 4 weeks prior to screening
- Patients who received more than 10 mg per day of oral prednisone (or equivalent) for more than 6 weeks continuously prior to screening
- Patients who received cyclophosphamide within 12 weeks prior to screening
- Patients with evidence of hepatic disease

Study Period: This study took place from March 2017 to November 2019 with a maximum of 14-day screening period prior to randomization to receive 30 mg avacopan by mouth twice daily plus prednisone matched placebo or an oral tapering prednisone schedule plus avacopan matching placebo twice daily. The taper occurred from week 1 to 20 and differed based on patient weight and age.

Study Day	**Avacopan Group**	**Prednisone Group**			
	Daily Prednisone Dose				
	All	Adults		Adolescents	
		$\geq$ 55 kg	< 55 kg	> 37 kg	$\leq$ 37 kg
Week 1	0 mg	60 mg	45 mg	45 mg	30 mg
Week 2	0 mg	45 mg	45 mg	45 mg	30 mg
Week 3	0 mg	30 mg	30 mg	30 mg	30 mg
Week 4 to 6	0 mg	25 mg	25 mg	25 mg	25 mg
Week 7 and 8	0 mg	20 mg	20 mg	20 mg	20 mg
Week 9 and 10	0 mg	15 mg	15 mg	15 mg	15 mg
Week 11 to 14	0 mg	10 mg	10 mg	10 mg	10 mg
Week 15 to 20	0 mg	5 mg	5 mg	5 mg	5 mg
Week $\geq$ 21	0 mg	0 mg	0 mg	0 mg	0 mg

Monitoring: Patients were monitored for safety, BVAS, and pharmacokinetic/pharmacodynamic parameters on study day 1, weeks 4, 10, 16, 26, 39, 52, and 60.

Data Analysis: Analysis of a modified intent-to-treat population was performed with 162 patients assigned to avacopan and 161 patients assigned to prednisone. Power was set at 90% with 150 patients per group required to show non-inferiority. The non-inferiority margin was set at -20%. Alpha was set at 0.05.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Number of patients achieving clinical remission at week 26 Number of patients achieving clinical remission at week 52	Nominal	Stratified Newcombe hybrid-score method to calculate 95% CI	Appropriate

Results: Avacopan was non-inferior to prednisone in patients achieving clinical remission as at week 26 and sustained remission at week 52. The authors chose to present this information as a mirrored image where the lower bound of the confidence interval was not to cross the prespecified NI margin of -20%, which did not occur, and is further shown by the p-value less than alpha. A statistically significant difference was shown only in the sustained remission endpoint at week 52 as evidenced by the lower bound of the confidence interval not crossing the absolute equivalency of zero and further shown by p-value less than alpha.

	avacopan (n=162)	prednisone (n=164)	Difference (95% CI)	P-value for Difference Between Groups
Remission at week 26 (%)	120 (72.3)	115 (70.1)	3.4 -6.0 – 12.8	<0.001 (non-inferiority) = 0.24 (superiority)
Sustained remission at week 52 (%)	109 (65.7)	90 (54.9)	12.5 2.6 – 22.3	<0.001 (non-inferiority) = 0.007 (superiority)

While a modified intent-to-treat population is not preferred for a non-inferiority trail, the authors also performed an analysis with a per-protocol population, where Avacopan was non-inferior to prednisone in patients achieving clinical remission as at week 26 and sustained remission at week 52 as evidenced by the lower bound of the 95% confidence interval not crossing the prespecified NI margin and p-value less than alpha. As with the modified intent-to-treat population, the per-protocol population only had a statistically significant difference in the sustained remission at week 52 as shown by the lower bound of the confidence interval not crossing the absolute equivalency of zero and further shown by p-value less than alpha.

	avacopan (n=162)	prednisone (n=161)	Difference (95% CI)	P-value for Difference Between Groups
Remission at week 26 (%)	110 (67.9)	109 (67.7)	2.0 -7.6 – 11.6	<0.001 (non-inferiority) = 0.35 (superiority)
Sustained remission at	95 (58.6)	81 (50.3)	11.0	<0.001 (non-inferiority)

week 52 (%)			1.0 – 21.1	= 0.016 (superiority)

Tolerability: The total amount of patients affected by adverse events were similar between groups (164/166 avacopan vs. 161/164 prednisone); however, the number of events was higher in the prednisone group (1779 avacopan vs. 2139 prednisone). Severe adverse events were also similar between groups with the most common reported serious adverse being worsening of vasculitis (10.2% avacopan vs. 14.0% prednisone). There were 2 deaths in the avacopan group caused by worsening vasculitis and pneumonia versus 4 deaths in the prednisone group due to generalized fungal infection, infectious pleural effusion, acute myocardial infarction, and death of unknown cause. 9 patients from the avacopan group and 6 from the prednisone group had abnormal liver function tests which resolved after discontinuation of trail medication and other hepatotoxic medications.

Author's Conclusion: The use of avacopan is non-inferior to the use of prednisone in achieving clinical remission at 26 weeks in patients with ANCA-associated vasculitis, and superior to prednisone in sustaining remission at week 52 with concurrent use of an immunosuppressive agent.

Strengths:

- Power set and met
- Treatment was appropriate and accepted
- Length of study was appropriate to show effect
- Inclusion and exclusion criteria were appropriate
- Blinding was present
- Randomization produced fairly similar groups
- Biostatistical test was appropriate
- Primary outcome is standard and accepted
- Authors' conclusion supported by results
- Performed per-protocol analysis which is preferred in non-inferiority trials

Limitations:

- Mostly white population
- Prednisone taper occurred faster than other trials
- Glucocorticoids were used by patients in the avacopan group
- Incidence of additional glucocorticoid use was higher in the prednisone group than in the avacopan group
- Trial population was heterogenous due to use of rituximab and cyclophosphamide in patients positive for antiproteinase 3 antibodies, antimyeloperoxidase antibodies, and patients with newly diagnosed vasculitis or relapsing disease

Level of Evidence: Level I – interventional, placebo-controlled, randomized trial that met power with Minor Limitations

Recommendation: I recommend the use of avacopan with or without glucocorticoids as an adjunctive treatment to immunosuppressive treatment regimens for patients with ANCA-

associated vasculitis versus the use of glucocorticoids plus an immunosuppressive treatment regimen only.

- Efficacy
  - Avacopan was shown to be non-inferior to prednisone in achieving clinical remission at week 26 and sustaining remission at week 52.
  - Avacopan was shown to have a statistically significant difference versus placebo in sustaining remission at week 52
- Safety
  - Overall, rates of adverse events were higher in the prednisone group
  - Worsening vasculitis was higher in the prednisone group
  - Deaths were slightly higher in the prednisone group
- Cost
  - According to Lexicomp, the cost of one 10 mg capsule is $96.32[7]
    - 30-day supply cost is $17,337.60
  - According to Lexicomp, the cost of prednisone can differ from $0.18 to $1.50 per tablet[8]
- Special Considerations/Populations
  - Majority of patients received intravenous rituximab (64.5% avacopan and 65.2% prednisone) and of those patients over 75% in each group achieved remission at week 26 versus around 60% of the intravenous and oral cyclophosphamide treatment subgroups.
  - Primarily white population makes it harder to generalize these results to other races with ANCA-associated vasculitis

*Grade of Recommendation:*A

References:

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