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JOURNAL CLUB
Article Summary by: Mehrnaz Maleki Fischbach, MD

ARTICLE

Avacopan for the Treatment of ANCA-Associated Vasculitis. Jayne et al. (Feb. 18, 2021)
N Engl J Med 2021;384:599-609.

CLINICAL QUESTION

Avacopan: Is this the end of the reign of corticosteroids in treatment of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis?

SUMMARY

Patients were randomly assigned in a 1:1 ratio to receive 30 mg of avacopan twice daily orally plus prednisone-matching placebo or a tapering oral regimen of prednisone plus avacopan-matching placebo in a double-dummy design.

A total of 331 patients underwent randomization; 166 were assigned to receive avacopan, and 165 were assigned to receive prednisone. The mean BVAS at baseline was 16 in both groups. All the patients received one of three regimens: cyclophosphamide intravenously at a dose of 15 mg per kilogram of body weight up to 1.2 g on day 1 and at weeks 2, 4, 7, 10, and 13; cyclophosphamide orally at a dose of 2 mg per kilogram of body weight up to 200 mg per day for 14 weeks (see the Supplementary Appendix, including Table S2); or intravenous rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks. From week 15 onward, cyclophosphamide was followed by oral azathioprine at a target dose of 2 mg per kilogram per day. No rituximab was given beyond the first 4 weeks.

Remission at week 26 (**the first primary end point**) was observed in 120 of 166 patients (72.3%) receiving avacopan and in 115 of 164 patients (70.1%) receiving prednisone (estimated common difference, 3.4 percentage points; 95% confidence interval [CI], −6.0 to 12.8; P<0.001 for noninferiority; P=0.24 for superiority).

Sustained remission at week 52 (**the second primary end point**) was observed in 109 of 166 patients (65.7%) receiving avacopan and in 90 of 164 patients (54.9%) receiving prednisone (estimated common difference, 12.5 percentage points; 95% CI, 2.6 to 22.3; P<0.001 for noninferiority; P=0.007 for superiority).

Serious adverse events (excluding worsening vasculitis) occurred in 37.3% of the patients receiving avacopan and in 39.0% of those receiving prednisone.

Table S8. Remission at Week 26 for Each Subgroup*

	Prednisone (N=164)	Avacopan (N=166)
All Patients*	115 / 164 (70.1%)	120 / 166 (72.3%)
Disease Status		
Newly diagnosed patients	76 / 114 (66.7%)	76 / 115 (66.1%)
Relapsing disease	39 / 50 (78.0%)	44 / 51 (86.3%)
ANCA Type		
Anti-proteinase 3 positive	50 / 70 (71.4%)	51 / 72 (70.8%)
Anti-myeloperoxidase positive	65 / 94 (69.1%)	69 / 94 (73.4%)
Background Treatment		
Cyclophosphamide	34 / 57 (59.6%)	37 / 59 (62.7%)
Rituximab	81 / 107 (75.7%)	83 / 107 (77.6%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	65 / 90 (72.2%)	65 / 91 (71.4%)
Microscopic polyangiitis	50 / 74 (67.6%)	55 / 75 (73.3%)

* Results are shown for n / N (%), where n = the number of remitters and N = the number of patients in each stratum. Remission at week 26 was defined as achieving a BVAS of zero and not having received any glucocorticoid treatment for vasculitis within 4 weeks prior to the week 26 visit.

Table S9. Sustained Remission at Week 52 for Each Subgroup*

	Prednisone (N=164)	Avacopan (N=166)
All Patients*	90 / 164 (54.9%)	109 / 166 (65.7%)
Disease Status		
Newly diagnosed patients	66 / 114 (57.9%)	70 / 115 (60.9%)
Relapsing disease	24 / 50 (48.0%)	39 / 51 (76.5%)
ANCA Type		
Anti-proteinase 3 positive	40 / 70 (57.1%)	43 / 72 (59.7%)
Anti-myeloperoxidase positive	50 / 94 (53.2%)	66 / 94 (70.2%)
Background Treatment		
Cyclophosphamide	30 / 57 (52.6%)	33 / 59 (55.9%)
Rituximab	60 / 107 (56.1%)	76 / 107 (71.0%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	52 / 90 (57.8%)	56 / 91 (61.5%)
Microscopic polyangiitis	38 / 74 (51.4%)	53 / 75 (70.7%)

*Results are shown for n / N (%), where n = the number of remitters and N = the number of patients in each stratum. Sustained remission was defined as remission at week 26 and remission at week 52 (BVAS of 0 and not taking glucocorticoids for treatment of vasculitis within 4 weeks prior to Week 52) and without relapse between week 26 and 52.

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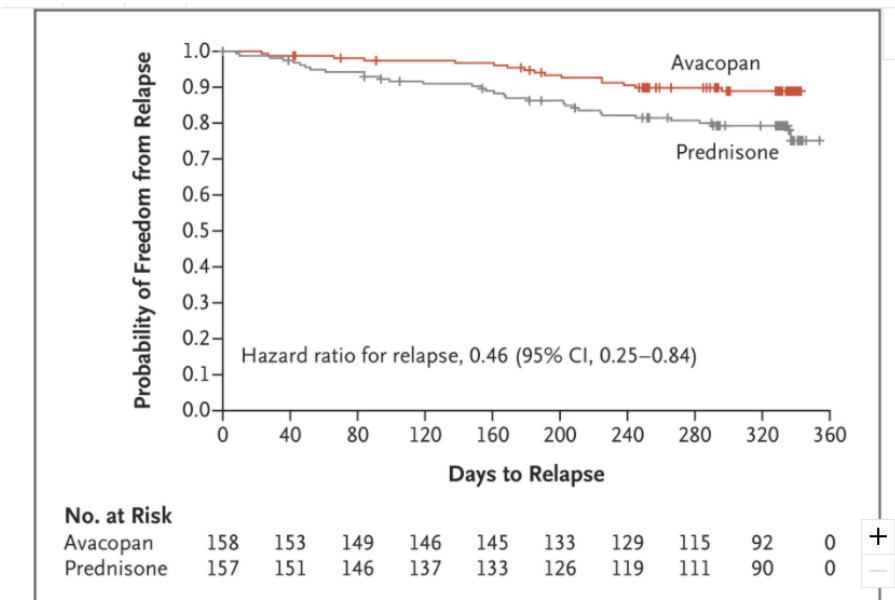

Figure 2. Kaplan–Meier Plot of Time to Relapse.

A relapse was defined as worsening of disease, after previous achievement of a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity), that involved one or more major items in the BVAS, three or more minor items in the BVAS, or one or two minor items in the BVAS recorded at two consecutive trial visits. A total of 16 of 158 patients (10.1%) in the avacopan group and 33 of 157 patients (21.0%) in the prednisone group had relapses. A test of proportionality was performed by incorporating a time-varying covariate in the Cox regression model by creating an interaction of the treatment groups and log of the time to relapse. The Wald chi-square test for the interaction term was 0.48. The corresponding P value was 0.49, which indicates no significant evidence of nonproportionality of the hazard. Tick marks indicate censored data.

In this trial involving patients with ANCA-associated vasculitis, avacopan was noninferior but not superior to prednisone taper with respect to remission at week 26 and was superior to prednisone taper with respect to sustained remission at week 52. All the patients received cyclophosphamide or rituximab. The safety and clinical effects of avacopan beyond 52 weeks were not addressed in the trial.

GROUP OPINION

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of disorders involving severe, systemic, small-vessel vasculitis and are characterized by the development of autoantibodies to the neutrophil proteins leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). The current treatment modalidities for severe AAVs include tapering doses of costicosteroid with either rituximab or cyclophasphamide.[1] These regimens are used with tapering dose of corticosteroid, which has significant adverse effect.

Activation of the alternative complement pathway, which results in terminal C5a production, is a component of the pathogenesis of ANCA-associated vasculitis.[2] Avacopan is an orally administered small-molecule C5a receptor antagonist that selectively blocks the effects of C5a through the C5a receptor (C5aR, also called CD88), including blocking neutrophil chemoattraction and activation. In a murine model of ANCA-associated vasculitis, avacopan prevented the development of glomerulonephritis induced by antimyeloperoxidase antibodies.[3] The ADVOCATE trial enables us to use lower doses of corticosteroid and have another treatment option for severe active ANCA vasculitis.

The FDA approved avacopan in October of this year as an add-on treatment to standard therapy including glucocorticoids for adult patients with severe active ANCA-associated vasculitis. Avacopan is the first oral complement C5a receptor inhibitor to be approved by the FDA.

References:

1. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, Kullman J, Lyons PA, Merkel PA, Savage COS, Specks U, Kain R. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020 Aug 27;6(1):71. doi: 10.1038/s41572-020-0204-y. PMID: 32855422.

2. Kettritz R. With complements from ANCA mice. J Am Soc Nephrol. 2014 Feb;25(2):207-9. doi: 10.1681/ASN.2013101043. Epub 2013 Oct 31. PMID: 24179172; PMCID: PMC3904575.

3. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T, Wang Y, Seitz LC, Penfold ME, Gan L, Hu P, Lu B, Gerard NP, Gerard C, Schall TJ, Jaen JC, Falk RJ, Jennette JC. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol*. 2014 Feb;25(2):225-31. doi: 10.1681/ASN.2013020143. Epub 2013 Oct 31. PMID: 24179165; PMCID: PMC3904560.

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