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Avacopan for ANCA-Associated Vasculitis

By: Connor Aossey, Pharm.D.

Background: Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis is a specific type of small vessel vasculitis characterized by the presence of circulating ANCAs.[1] These circulating ANCAs cause life-threatening systemic inflammation and long-term complications due to multi-system organ damage.[2-5] The introduction of cyclophosphamide and corticosteroids in the 1960's led to a significant improvement in the prognosis of this type of vasculitis. With these treatments over 90% of the patients achieved remission compared to an 80% mortality rate at 1 year for untreated patients.[6] The 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of ANCA–associated Vasculitis recommends treating severe ANCA-associated vasculitis initially with corticosteroids and either rituximab (the preferred therapy) or cyclophosphamide to induce remission of this disease.[7] However, long-term steroid use is associated with various adverse effects (e.g., increased infection rate, new-onset diabetes).[8] Avacopan (Tavneos®; ChemoCentryx, Inc.), a novel agent for severe ANCA–associated vasculitis, may reduce total steroid exposure.[9] The Food and Drug Administration approved avacopan in October 2021 as an adjunctive treatment for adult patients with severe ANCA–associated vasculitis and microscopic polyangiitis in combination with standard therapy including glucocorticoids. Avacopan does not entirely eliminate the need for glucocorticoids.

Mechanism of Action: Avacopan is a complement 5a (C5a) receptor antagonist which prevents the binding of C5a to the C5a receptor present on neutro-

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Faricimab for Retinal Diseases

By: Jack Janosik, Pharm.D.

Background: Neovascular age-related macular degeneration (nAMD) and diabetic retinopathy, commonly attributed to diabetic macular edema (DME), are leading causes of blindness worldwide.[1] Upregulation of vascular endothelial growth factor (VEGF) worsens both nAMD and DME by promoting vascular permeability and leakage.[2,3] Therefore, the current standard of care for these retinal diseases includes anti-VEGF agents (e.g., aflibercept, ranibizumab).[4,5] Although effective, anti-VEGF therapy requires frequent intravitreal injections as often as every 4 weeks.[6] In January 2022, faricimab-svoa (Vabysmo®; Genentech, Inc.) received approval from the Food and Drug Administration to treat nAMD and DME.[7] Faricimab may have a longer duration of action than anti-VEGF agents with a lower injection burden.[8]

Mechanism of Action: Faricimab is a novel humanized bispecific antibody that inhibits both vascular endothelial growth factor-A (VEGF-A) and angio-

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phils.[9,10] Theoretically, the inhibition of the C5a receptor blocks C5a-mediated neutrophil activation, thereby reducing systemic inflammation.

Clinical Trial: The ADVOCATE 2021 trial attempted to determine whether avacopan could replace steroids as a part of the standard of care for severe ANCA–associated vasculitis.[11] This phase III, randomized, double-dummy, double-blind clinical trial was conducted at 143 international sites. Patients (N=331) received standard of care therapy with either cyclophosphamide (followed by azathioprine) or rituximab and were randomized to receive either prednisone 60 mg daily (n=165) on a tapering prednisone schedule which was discontinued by week 21, or avacopan 30 mg (n=166) twice daily for 52 weeks. Patients with new or relapsing ANCA–associated vasculitis for which treatment with cyclophosphamide or rituximab was indicated who had tested positive for ANCA were included. The primary efficacy endpoints were disease remission at week 26 and sustained remission at week 52. Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 (on a scale of 0 to 63 with higher scores indicating greater disease activity) and no glucocorticoid use in the previous 4 weeks. Patient characteristics were similar between treatment groups. The majority of patients were white (84%) males (55%), with an average age of 61 years who were newly diagnosed (69.4%) and had an average BVAS score of 16.2. Most patients were on steroids before enrollment in both groups, and these patients were required to taper to a 20 mg prednisone equivalent dose before beginning the trial. Patients in both groups were tapered off open-label steroids by week 4. The first primary endpoint of remission at 26 weeks was observed in 120 of 166 patients (72.3%) receiving avacopan and 115 of 164 (70.1%) who received prednisone (estimated common difference, 3.4 percentage points; 95% confidence interval (CI), -6.0 to 12.8; $p<0.001$ for non-inferiority; $p=0.24$ for superiority). Sustained remission at week 52 was achieved in 109 of 166 patients (65.7%) of those receiving avacopan and in 90 of 164 patients (54.9%) receiving prednisone (estimated difference, 12.5 percentage points; 95% CI, 2.6 to 22.3; $p<0.001$ for non-inferiority; $p=0.007$ for superiority). From these results, the authors concluded that avacopan was non-inferior to a prednisone taper in achieving remission at week 26, but superior to the prednisone taper for maintaining remission at week 52.

Safety: In the ADVOCATE trial adverse events of any severity were reported in 98.8% of patients in the avacopan group and 98.2% of patients in the control group.[11] Serious adverse events, with the exception of worsening vasculitis, occurred in 37.3% who received avacopan compared to 39% who received prednisone. The most common side effects were nausea (24%), headache (21%), hypertension (18%), vomiting (15%), diarrhea (15%) and hepatotoxicity (13%).

Dosing and Administration: The recommended dose of avacopan is 30 mg orally twice daily.[9] There are no dosage adjustments for patients with hepatic or renal impairment. However, the drug was not studied in patients with severe renal impairment (eGFR<15 mL/min/1.73 m^2) or dialysis patients and is not recommended in those with severe hepatic impairment. Avacopan is a major substrate of Cytochrome P450 (CYP) 3A4. Co-administration with a CYP3A4 inducer should be avoided and a dose reduction to 30 mg daily is recommended with concurrent use of a strong CYP3A4 inhibitor.

Cost and Availability: Avacopan is available as 10 mg capsules NDC 73556-0168-02 (30-count) and NDC 73556-0168-01 (180-count) and has an average wholesale price of $96.32 per capsule.[10] The estimated cost of therapy for 30 days at standard dosing is about $17,337.

Formulary Status: Avacopan is on the CCHS Formulary with initiation of therapy restricted to the Departments of Nephrology and Rheumatology. There are no restrictions for continuation of therapy.

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poietin-2 (Ang-2).[7] Through the dual inhibition of VEGF-A and Ang-2 pathways, blood vessel leakage, endothelial cell proliferation, and neovascularization are reduced.

Clinical Trials: YOSEMITE and RHINE were phase III, randomized, double-masked, non-inferiority trials that compared faricimab and aflibercept in patients with DME.[8] Patients were randomized 1:1:1 to receive faricimab 6 mg via intravitreal injection every 8 weeks (YOSEMITE n=315, RHINE n=317), faricimab 6 mg via intravitreal injection on a personalized treatment interval (PTI) with adjustable dosing up to every 16 weeks (YOSEMITE n=313, RHINE n=319), or aflibercept 2 mg via intravitreal injection every 8 weeks (YOSEMITE n=312, RHINE n=315). The primary endpoint was the change in Best Corrected Visual Acuity (BCVA) from baseline to 1 year assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Non-inferiority was demonstrated in each trial between both the faricimab every 8 week and PTI groups and the aflibercept every 8 week group. In YOSEMITE, the mean difference vs aflibercept every 8 weeks was -0.2 ETDRS letters [-2.0 to 1.6] in the faricimab every 8 week group and 0.7 ETRDS letters [-1.1 to 2.5] in the faricimab PTI group. In RHINE, the mean difference vs aflibercept every 8 weeks was 1.5 ETDRS letters [-0.1 to 3.2] in the faricimab every 8 week group and 0.5 ETRDS letters [-1.1 to 2.2] in the faricimab PTI group. More than 70% of patients in the faricimab PTI groups achieved a dosing interval of 12 weeks or longer (53% of patients in YOSEMITE and 51% of patients in RHINE achieved a 16-week dosing interval). The authors concluded that faricimab offered vision gains comparable to aflibercept with adjustable dosing up to every 16 weeks for patients with DME. TENAYA and LUCERNE were phase III, randomized, double-masked, non-inferiority trials that compared faricimab and aflibercept in patients with nAMD.[9] Patients were randomly assigned 1:1 to receive either an intravitreal injection of faricimab 6 mg up to every 16 weeks (TENAYA n=334, LUCERNE n=331) or aflibercept 2 mg every 8 weeks (TENAYA n=337, LUCERNE n=327). After their first four doses, patients in the faricimab group with active disease at week 20 would continue on every 8-week dosing, those with active disease at week 24 would continue on every 12-week dosing, and those without active disease at weeks 20 and 24 received faricimab at week 28 and would continue on every 16-week dosing. The primary endpoint was the change in BCVA from baseline to week 48 assessed using ETDRS letters. Non-inferiority was demonstrated in each trial with faricimab compared to aflibercept. The adjusted mean gains in BCVA at primary endpoint visits in TENAYA were 5.8 letters (95% CI, 4.6 to 7.1) in the faricimab group and 5.1 letters (3.9 to 6.4) in the aflibercept group (treatment difference 0.7 letters [95% CI, -1.1 to 2.5]). In LUCERNE, vision gains were 6.6 letters (95% CI, 5.3 to 7.8) in the faricimab group and 6.6 letters (5.3 to 7.8) in the aflibercept group (treatment difference 0.0 letters [95% Cl, –1.7 to 1.8). At week 48, approximately 80% of faricimab-treated patients received either 12- or 16-week dosing regimens, with 144 patients (45.7%) in TENAYA and 142 patients (44.9%) in LUCERNE on 16-week dosing. The authors concluded that faricimab, administered at up to 16-week intervals, demonstrated vision benefits for patients with nAMD comparable with aflibercept every 8 weeks.

Safety: In phase III clinical trials, faricimab was associated with conjunctival hemorrhage (7%), vitreous floaters (3%), increased intraocular pressure (3%), and intraocular inflammation (2%).[7]

Dosing and Administration: Faricimab is given as a 6 mg (0.05 mL) intravitreal injection, with different dosing regimens depending on the indication specified in the package insert.[7] The administration must be carried out under aseptic conditions with adequate anesthesia. A broad-spectrum microbicide should be provided before injection.

Cost and Availability: Faricimab is currently available as a 6 mg/0.05 mL solution (NDC 50242-096-01) supplied in a carton that contains a single-use vial and one sterile filter needle.[7] The average wholesale price for one vial is $2,628.[10] If a patient were to receive the every 16-week dosing regimen after their first four doses for DME, the average annual cost would be approximately $15,768 (six total doses in the year).

Formulary Status: Faricimab is on the CCHS Formulary restricted to the Department of Ophthalmology for outpatient use only.

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