CONTACT HOUR: 2.0 HRS

Emerging therapies for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

By Aileen Liu, Vanessa Raco, and Marisa Battistella

LEARNING OBJECTIVES

1. Describe clinical presentation and pathophysiology of vasculitis
2. Recognize complications associated with vasculitis
3. Summarize current treatment options for ANCA-associated vasculitis
4. Discuss the role of avacopan in the treatment of vasculitis

Vasculitis is a rare disease that refers to the inflammation of blood vessel walls and comprises a large group of diseases characterized by inflammation of the vascular wall and perivascular tissues (Morita et al., 2020). The size of vessels is used to classify vasculitis types (Morita et al., 2020). They are generally grouped by the vessels with main involvement such as (1) large vessels vasculitides (associated with the aorta), (2) medium vessels vasculitides (associated with vessels of the arterial and venous systems), and (3) small vessels vasculitides (associated with arterioles and capillaries) (Shavit et al., 2018). See Table 1 for the classification of vasculitides. Small vessel vasculitis is the most common group of vasculitis, and it is further divided to include immune complex small vessel

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Table 1

Classification and Example Types of Vasculitis

Classification	Type
Large vessels vasculitides	Takayasu arteritis Giant Cell Arteritis (GCA)
Medium vessels vasculitides	Polyarteritis nodosa (PAN) Kawasaki disease
Small vessels vasculitides	ANCA-associated vasculitides: Microscopic polyangiitis (MPA) Granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis) Eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strau yndrome) Immune complex vasculitis: Anti-glomerular basement membrane disease (formerly known as Goodpasture syndrome) Cryoglobulinemic vasculitis IgA vasculitis (formerly known as Henoch-Schonlein purpura) Hypocomplementemic urticarial vasculitis
Variable vessels vasculitides	Behçet's Disease (BD) Cogan's syndrome
Single organ vasculitides	Cutaneous leukocytoclastic angiitis
Vasculitides associated with systemic disease	Lupus vasculitis Rheumatoid vasculitis
Vasculitides associated with probable etiology	Hepatitis C virus-associated vasculitis Hepatitis B virus-associated vasculitis Drug-associated immune complex vasculitis Drug-associated ANCA-positive vasculitis Cancer-associated vasculitis

Note. Adapted from Morita et al. (2020) and Shavit et al. (2018).

vasculitis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The purpose of this article is to review the clinical presentation, pathophysiology, and treatment for vasculitis, with a focus on ANCA-associated vasculitis and a new medication for its treatment, avacopan.

PATHOPHYSIOLOGY

The pathophysiology of ANCA-associated vasculitis is not fully understood. ANCAs are autoantibodies groups that are produced by B-cells (Turgeon et al., 2023). These autoantibodies bind to proteinase 3 and myeloperoxidase that are expressed on neutrophils, thus activating neutrophils. Neutrophil activation releases reactive oxygen species and toxic enzymes that lead to vascular inflammation. C5a is a cytokine with anaphylatoxic and chemotactic properties that recruits neutrophils to affected tissues to amplify this process (Trivioli & Vaglio, 2020).

DIAGNOSIS AND CLINICAL PRESENTATION

There is no standard diagnostic test for vasculitis. Diagnosis is guided by conducting physical examination, identifying the underlying cause and organ involvement, and completing a skin biopsy (Morita et al., 2020). ANCA-associated vasculitis is characterized by determining ANCAs that bind to proteinase 3 or myeloperoxidase. However, this on its own is not diagnostic of ANCA-associated vasculitis (Kitching et al., 2020; Morita et al., 2020).

Vasculitis predominantly presents as skin manifestations such as purpura, nodules, purpuric urticaria, skin ulcers (Shavit et al., 2018). Less commonly, they may present as bullae, pustules, or necrotizing lesions (Shavit et al., 2018). Most vasculitis cases also present with non-specific inflammatory signs, such as elevated C-reactive protein or leukocytosis, and symptoms, such as fatigue and arthralgia (Morita et al., 2020). Differential diagnosis for vasculitis is listed in Table 2. Vasculitis is a systemic disease that involves vessels of any organ or tissue; therefore, its presentation is not only limited to the skin as it commonly also affects other organs, such as the kidneys, lungs, or eyes (Kronbichler et al., 2020).

ANCA-associated vasculitis presents as necrotizing vasculitis in the small vessels (Mendel et al., 2021). Sub-types of ANCA-associated vasculitis include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The clinical presentation of GPA and MPA includes general signs of inflammation, such as fever, weight loss, malaise, and fatigue. GPA is associated with purpura, ulcers and necrosis, as well as involvement of the ear, nose and throat tract (i.e., nasal and oral ulcers), eyes (i.e., eye pain, uveitis), lungs (i.e., cough, dyspnea), and kidneys (i.e., increased serum creatinine, urine abnormalities, proteinuria). MPA presents similarly to GPA where kidney and skin effects are frequent, but ear, nose and throat presentations are less common (Kitching et al., 2020).

GENERAL TREATMENT FOR ANCA-ASSOCIATED VASCULITIS

Treatment of ANCA-associated vasculitis comprises (1) remission induction therapy with a glucocorticoid and immunosuppressant, followed by (2) maintenance therapy when remission is achieved (Pagnoux, 2016). Medications traditionally used for remission induction therapy include immunosuppressant therapies rituximab, or cyclophosphamide along with a high-dose glucocorticoid (Mendel et al., 2021). Maintenance therapy includes rituximab, azathioprine, methotrexate, mycophenolate mofetil (MMF), or leflunomide (Mendel et al., 2021).

Table 2

Vasculitis Differential Diagnosis

Differential Diagnoses	Examples
Drug reactions	Antibiotics (i.e., beta-lactams, fluoroquinolones), sulfa drugs, NSAIDS
Infections	Viral infections (i.e., HBV, HCV, HIV), bacterial infections (i.e., *Staphylococcus*, *Streptococcus*), fungal infections (i.e., *Candida*)
Inflammatory conditions	Auto-immune connective tissue disease, neutrophilic dermatoses, bowel bypass syndrome
Neoplasms	Hematologic malignancies (i.e., Non-Hodgkin's lymphoma, multiple myeloma) Solid tumours (i.e., lung, colon, prostate, breast, head, and neck cancers)

Note. Adapted from Shavit et al. (2018).
NSAIDS = non-steroidal anti-inflammatory drugs; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus

Remission Induction Therapy

Prednisone 1 mg/kg/day (maximum dose of 80 mg/day) is recommended as initial remission induction therapy for adults with severe GPA and MPA (Mendel et al., 2021). Lower doses of prednisone (0.5 mg/kg/day) can be considered in patients in non-severe cases (Mendel et al., 2021). Prednisone tapers should be initiated within two weeks of starting induction therapy. There is no ideal tapering protocol or duration of therapy; rather, tapering is completed based on the patient's clinical status (Mendel et al., 2021).

Pulse steroids, such as intravenous methylprednisolone 0.5 to 1 g/day for one to three days may be considered in patients with severe or life-threatening GPA or MPA. However, therapy with pulse steroids overall lacks efficacy and has higher risk of side effects compared to prednisone dosing. Thus, pulse steroids should be used with caution. Steroids are associated with a variety of short- and long-term side effects. Common side effects include hyperglycemia, hypertension, psychiatric disturbances (agitation or insomnia), gastrointestinal events (gastritis or ulcer formation) osteoporosis, ocular conditions (cataracts or glaucoma), and immunosuppression increasing the risk of infection.

Steroids may be given in combination with cyclophosphamide or rituximab for remission induction therapy. Rituximab is generally preferred over cyclophosphamide as *post hoc* analyses showed rituximab was more effective than cyclophosphamide (Mendel et al., 2021). However, cyclophosphamide may be considered in individuals who have a contraindication to rituximab, such as intolerance to rituximab infusion. Use of cyclophosphamide or rituximab allows for a

steroid taper within the first one to two weeks of induction therapy, limiting steroid exposure and associated side effects (Mendel et al., 2021).

Maintenance Therapy

Patients who achieve remission with cyclophosphamide or rituximab induction therapy should receive maintenance therapy rituximab infusions given every four to six months (Mendel et al., 2021). Maintenance therapy with rituximab should be continued for at least two years. Alternatives for maintenance therapy include azathioprine, methotrexate, MMF, and leflunomide in patients who cannot tolerate or do not respond to rituximab. Despite advances in vasculitis treatments, patients remain at high risk of mortality due to complications from the disease or treatments. Complications include chronic kidney disease or infections largely caused by prolonged steroid use. As a result, efforts to limit steroid exposure are crucial for vasculitis treatment. In 2022, the Canadian Vascular Research Network (CanVasc) updated its ANCA-associated vasculitis guidelines to include avacopan recommendations due to new available evidence demonstrating efficacy while limiting prolonged steroid use (Turgeon et al., 2023).

Avacopan

Avacopan (Tavneos®) is a novel small molecule drug that blocks factors involved in the pathogenesis of ANCA-associated vasculitis. Avacopan works by selectively inhibiting C5a, which prevents neutrophil chemoattraction and activation to reduce inflammation (Pfizer, 2022).

Avacopan was approved for the adjunctive treatment of adults with ANCA-associated vasculitis, with the combination of steroids, in Canada in 2022. The CanVasc guidelines recommend avacopan can be added for induction remission with a diligent corticosteroid taper in patients with GPA or MPA treated with cyclophosphamide or rituximab. Adjunctive therapy with avacopan may achieve a faster steroid taper where steroids should be discontinued in four weeks (Turgeon et al., 2023). Avacopan should be continued for one year when starting induction therapy.

Avacopan is dosed as 30 mg orally twice daily with food, and the capsules should not be crushed, chewed, or opened (Pfizer, 2022). No dose titrations are required or dose adjustments for patients with any degree of kidney impairment. However, patients with estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73m^2 were excluded. Avacopan is a CYP3A4 substrate and should be checked for drug interactions. It should be reduced to 30 mg daily when co-administered with a strong CYP 3A4 inhibitor, such as voriconazole, clarithromycin, or ritonavir (Pfizer, 2022). Avacopan should be avoided with strong or moderate CYP 3A4 inducers, such as carbamazepine, phenytoin, or rifampin (Pfizer, 2022).

Common side effects associated with avacopan include headache, nausea, and vomiting. Serious adverse effects include hepatic injury, pneumonia, and urinary tract infections (Pfizer, 2022). Patients receiving avacopan should obtain liver functions tests at baseline and every three weeks for the first six months of therapy. If the asparate aminotransferase (AST) or alanine aminotransferase (ALT) level is greater than three times the upper limit of normal, avacopan should be stopped (Pfizer, 2022). Avacopan may be offered as an adjunctive therapy for patients with ANCA-associated vasculitis to limit prolonged steroid therapy and minimize complications associated with steroids (Hellmich et al., 2023). Table 3 summarizes the medications used for both induction and maintenance therapy for ANCA-associated vasculitis.

Table 3

Summary of ANCA-Associated Treatment

Medication	Common Dosing Regimens	Side Effects	Monitoring Parameters
Steroids	Induction: *Standard*: prednisone 1 mg/kg (maximum 80 mg/day) orally daily. May start at lower dose 0.5 mg/kg/day in non-severe cases. Taper should commence within two weeks of induction therapy *Pulse steroid*: methylprednisolone IV 0.5–1 g/day for 1 to 3 days	Hyperglycemia, hypertension, osteoporosis, infection, cataracts, glaucoma, insomnia, agitation, psychosis	Blood glucose, blood pressure, nausea, vomiting
Rituximab	Induction: 375 mg/m^2 IV weekly for 4 weeks Maintenance: 500 mg IV every 4 to 6 months for at least two years	Fatigue, nausea, vomiting, headache, hypertension, abdominal pain, neutropenia, infection, pulmonary reaction, Hepatitis B reactivation, infusion related reaction	Blood pressure, complete blood count, respiratory rate, temperature, infusion reaction
Cyclophosphamide	Induction: 2 mg/kg orally daily for 14 days or 15 mg/kg IV every 2 weeks for 3 doses, followed by every 3 weeks	Nausea, vomiting, infection, urinary bladder toxicity (IV), bone marrow suppression (anemia, neutropenia)	Nasal congestion, facial discomfort, headache, dizziness, complete blood count, white blood cell count, infusion reaction (IV)
Avacopan	Induction: 30 mg orally twice daily for 1 year	Headache, nausea, vomiting, hepatotoxicity, hypertension	Nausea, vomiting, liver function tests, blood pressure

Note. IV = intravenous.

SUMMARY

Vasculitis is a rare disease that consists of a large group of diseases that cause inflammation of blood vessels. It is a systemic disease that mostly presents as skin manifestations and can cause complications in other organs, such as the kidneys, lungs, or eyes. ANCA-associated vasculitis is a form of small vessel vasculitis where ANCAs activate neutrophils, leading to vascular inflammation. Treatment of ANCA-associated vasculitis comprises of induction remission and maintenance therapy with the use of immunosuppressants, such as steroids, cyclophosphamide, and rituximab. Despite these therapies, patients are at high risk of mortality due to complications from the disease or treatments. Avacopan is a novel medication that inhibits the vascular inflammation process of ANCA-associated vasculitis. It is approved as an adjunctive treatment with the combination of steroids for adults with ANCA-associated vasculitis. This adjunctive therapy can allow for a faster steroid taper minimizing side effects associated with long-term steroid use.

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