UPMC RHEUMATOLOGY GRAND ROUNDS

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Small- and Mixed-Vessel Vasculitis: An Update on Therapeutic Approaches

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Introduction

Vasculitis is defined by the presence of inflammatory infiltrate and reactive damage to blood vessel walls. This can compromise the lumen and result in ischemia and necrosis of downstream tissues. Different vasculitides can affect many different organs. Classification of the vasculitides has been challenging. Vasculitis may be a primary process or may occur secondary to other disease processes.[1]

Traditionally, the vasculitides have been categorized based on the dominant size or type of the vessels most commonly affected by a given disease.[1-4] The initial classification scheme suggested by Zeek in 1952 did not include several forms of vasculitis.[5] Currently, the most widely accepted classification schemes include the American College of Rheumatology (ACR) classification criteria introduced in 1990 and the subsequent revisions in the Chapel Hill Consensus Conference (CHCC) in 1994 and 2012 *(see Table 1 on Page 2)*. The classification of vasculitis syndromes continues to evolve. The association with antineutrophil cytoplasmic antibodies (ANCA) and the concept of ANCA-associated vasculitis (AAV) have been recently added to proposed classification schemes, including a new consensus algorithm.[1,6,7]

TABLE 1:

Vasculitis: Classification

Dominant size and type of the vessels affected	Vasculitis syndromes
Small vessels (arterioles, capillaries, and venules)	• Cutaneous small-vessel vasculitis • IgA vasculitis (formerly Henoch-Schönlein purpura) • Cryoglobulinemic vasculitis • Urticarial vasculitis (UV)
Mixed-size vessels (arterioles, capillaries, venules, small arteries, and small veins)	• Granulomatosis with polyangiitis (formerly Wegener's) • Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome)
Medium-size vessels (medium-size arteries and occasionally small muscular arteries)	• Polyarteritis nodosa
Large vessels (large- to medium-size arteries)	• Giant cell arteritis • Takayasu's arteritis
Vessels of all sizes (medium- to large-size arteries, medium-size arteries, small arteries, arterioles, capillaries, venules, and veins)	• Behçet's disease

In this edition of *UPMC Rheumatology Grand Rounds*, we summarize the current therapies and new developments in the management of small- and mixed-vessel (small- and medium-vessel) vasculitides.

Cutaneous Small-Vessel Vasculitis

The management of cutaneous small-vessel vasculitis (CSVV) should begin with a thorough history and physical examination focusing on new medications, and a workup for potential infection or underlying systemic disease that could guide therapy. Conservative management includes leg elevation, reduction of activity, and avoiding cold temperatures and sunlight, which is often successful.[8] Antihistamines and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to relieve itching and burning if not contraindicated (e.g., renal disease). Although topical corticosteroid and antibiotic creams have historically been used in the treatment of CSVV, there are no data to support their use.[9] Colchicine and dapsone have been used for the treatment of more severe or extensive cutaneous symptoms. The use of these medications has been based on anecdotal studies or small case series.[10] The only randomized controlled trial to date to investigate the efficacy of colchicine in CSVV did not show any significant therapeutic effect.[11] Some believe that colchicine should be combined with dapsone, while other experts recommend that colchicine should be used as a first-line therapy and dapsone as a second-line therapy in CSVV.[10,12] Refractory or extensive cases may require brief periods of high-dose oral glucocorticoid or immunosuppressive agents, including methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide.[10,13-16] Anti-TNF therapy and rituximab have shown some efficacy in recent case reports.[17,18]

IgA Vasculitis (previously termed Henoch-Schönlein purpura)

IgA vasculitis *(see Figure 1 on Page 3)* is usually self-limited, and treatment largely consists of supportive care. However, in adults it can be associated with significant renal disease and a worse prognosis compared to the pediatric population.

Symptomatic therapy includes NSAIDs or acetaminophen, which can be used for the relief of arthralgia, arthritis, and gastrointestinal symptoms. The risk of gastrointestinal hemorrhage has not been shown to increase by the use of cyclo-oxygenase inhibitors.

The use of glucocorticoids in the treatment of IgA vasculitis is controversial. In a recent Cochrane Review, there was no significant difference in the risk of serious persistent kidney disease at six months (three studies, 379 children: RR 0.51, 95% CI 0.24 to 1.11) and 12 months (three studies, 498 children: RR 1.02, 95% CI 0.40 to 2.62) in children treated with prednisone for 14 to 28 days at presentation of IgA vasculitis compared to those who received placebo or supportive therapy.[19] A recent prospective study of 223 children in Finland reported that prednisone did not affect the timing of the appearance of nephritis and did not alter the clinical course of IgA vasculitis during six months of follow-up.[20] Furthermore, there were no differences between the prednisone and placebo groups eight years after treatment at disease onset.[21] Many clinicians use glucocorticoids in patients whose symptoms are severe enough to require hospitalizations (including patients with an inability to maintain adequate oral hydration, severe abdominal pain or gastrointestinal bleeding, altered mental status, debilitating arthralgia/arthritis, and significant renal involvement).

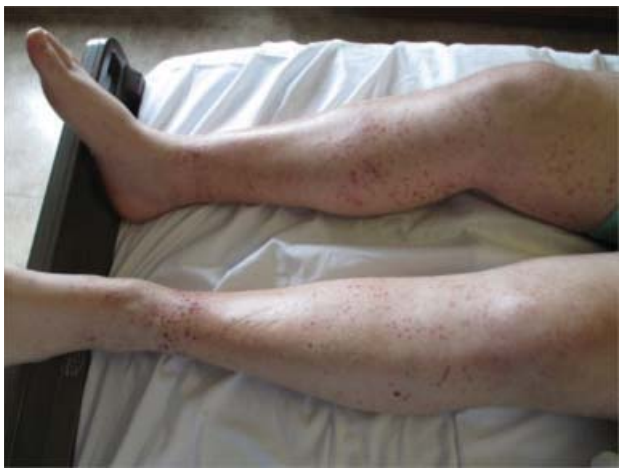

FIGURE 1: **Symmetrically distributed palpable purpura in gravity-dependent areas (lower extremities) in a patient with IgA vasculitis.**

Intravenous immune globulin (IVIG), plasmapheresis, and a variety of cytotoxic agents have been used as the treatment for severe nephritis. However, the most effective treatment remains unclear, and there is currently no consensus regarding the indications for more aggressive therapy.[22]

Cryoglobulinemic Vasculitis

Hepatitis C viral (HCV) infection should be investigated in all patients diagnosed with cryoglobulinemic vasculitis. Patients with hepatitis C-related cryoglobulinemic vasculitis should be treated for the underlying infection.[23,24] Induction therapy with pegylated interferon alfa and ribavirin is currently used for patients with HCV genotype 2, 3, or 4 infections. In patients with HCV genotype 1 infection, who typically have suboptimal response to treatment, a protease inhibitor, preferably boceprevir, is added to the antiviral regimen, provided the patients have normal renal function.

In patients presenting with rapidly progressive and severe disease, plasmapheresis, glucocorticoids, rituximab, and cyclophosphamide have been used.[25] In severe cases, concomitant combination of antiviral therapy with rituximab has been suggested as well.[26] Rituximab has been well-tolerated and effective in the treatment of patients with cryoglobulinemic vasculitis and severe hepatitis C-related cases where antiviral therapy failed to induce remission.[26,27]

Interferon alpha also has been reported to be efficacious for hepatitis C-negative cryoglobulinemic vasculitis, which is possibly due to its immunomodulatory effects. It is important to note that the titer of cryoglobulins does not correlate with disease severity, and should not be used to monitor treatment responsiveness.[28]

Urticarial Vasculitis

Treatment recommendations for urticarial vasculitis (UV) have been based on small case series. Antihistamines are used for symptomatic therapy of pruritus. Colchicine, hydroxychloroquine, systemic glucocorticoids, dapsone, and mycophenolate mofetil have been used for treatment of cutaneous disease and prevention of further urticarial lesions.[29] The use of rituximab was effective in the treatment of hypocomplementemic urticarial vasculitis in a patient with systemic lupus erythematosus who was unresponsive to high-dose methylprednisolone and mycophenolate.[30]

Granulomatosis With Polyangiitis (previously termed Wegener's)

Initial Immunosuppressive Treatment (Induction Therapy)

Treatment depends on the organs involved, as well as the severity of the disease. Initial immunosuppressive treatment in granulomatosis with polyangiitis (GPA) includes three to six months of glucocorticoids and cyclophosphamide or rituximab.

Cyclophosphamide can be administered as daily oral or monthly intravenous infusions. Daily oral cyclophosphamide (1.5 to 2 mg/kg per day) is typically favored because of a lower rate of relapse; however, it is associated with more leucopenia and infectious complications.[31,32]

Treatment with high-dose pulse methylprednisolone (500 to 1000 mg/day) for three days has been used by many clinicians in patients with severe renal or respiratory disease, but this treatment modality remains controversial. Oral glucocorticoid therapy consists of 1 mg/kg prednisone-equivalent per day. Depending on the clinical status, the oral glucocorticoid dosage should be tapered slowly, with the goal of reaching 20 mg/day prednisone (or its equivalent) by the end of two months. Glucocorticoid use beyond six months is not associated with a reduced risk of relapse, but is associated with a significantly greater risk of infections.[33]

Rituximab also can be used for induction therapy. In two multicenter noninferiority trials (RAVE and RITUXVAS), rituximab was as effective as cyclophosphamide for the initial immunosuppressive treatment of GPA; however, both trials are limited in the duration of follow-up. Also, both patients with disease manifestations, such as alveolar hemorrhage severe enough to require ventilator support and patients with advanced renal dysfunction (serum creatinine level greater than 4 mg per deciliter), were excluded. Therefore, the comparative efficacy of rituximab and cyclophosphamide for such patients remains unclear.[34,35]

Low-dose oral methotrexate has been used as an alternative for initial immunosuppressive therapy in GPA patients with non-organ-threatening and non-life-threatening disease.[36]

Some patients with severe disease may benefit from plasma exchange in conjunction with glucocorticoids and cyclophosphamide or rituximab; however, plasma exchange has not been formally evaluated for this indication. A multicenter, international, open-label, randomized control trial (PEXIVAS study) is currently being performed to determine the efficacy of plasma exchange in addition to immunosuppressive therapy and glucocorticoids in reducing death and end-stage renal disease.

Maintenance Immunosuppressive Treatment

Maintenance therapy can be initiated a few days after the last dose of oral cyclophosphamide and a few weeks after the cessation of monthly intravenous cyclophosphamide.

Azathioprine (2 mg/kg per day) or methotrexate (0.3 mg/kg once weekly) are the preferred agents for maintenance immunosuppressive therapy. Azathioprine is preferred to methotrexate in patients with impaired renal function, in particular those with an estimated glomerular filtration rate (GFR) of less than 50 mL/min. Maintenance therapy

usually is continued for 12 to 18 months, but select patients with multiple relapses may require longer or indefinite therapy. The glucocorticoid dose is gradually tapered to the lowest dose required for control of extrarenal symptoms of active GPA, and can be tapered off in asymptomatic patients.

In a recent multicenter, randomized, double-blind, noninferiority trial, a single course of rituximab (375 mg per square meter of body-surface area, once a week for four weeks) followed by placebo, was compared with conventional immunosuppressive therapy consisting of three to six months of cyclophosphomide followed by azathioprine for 12 to 15 months. A total of 197 patients with severe ANCA-associated vasculitis were enrolled. In the rituximab group, 64% of the patients had a complete remission by six months, whereas 53% of patients in the cyclophosphamide-azathioprine group had a complete remission in that same time frame. At 12 and 18 months, 48% and 39% respectively of the patients in the rituximab group had maintained the complete remissions, as compared to 39% and 33% in the cyclophosphamide-azathioprine group. There was no significant difference between the groups in any efficacy measures, and rituximab met the criterion for noninferiority (less than 20% difference in risk; $P<0.001$). The authors concluded that a single course of rituximab as administered in the trial was as effective as conventional immunosuppressive therapy for the remission induction and maintenance over the course of 18 months. The trial had some limitations, because patients with alveolar hemorrhage severe enough to require ventilator support, patients with advanced renal dysfunction (serum creatinine level greater than 4 mg per deciliter), and ANCA-negative patients were excluded.[37]

An international controlled trial (RITAZAREM) is currently being performed to compare rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis.

Eosinophilic Granulomatosis With Polyangiitis (previously termed Churg-Strauss Syndrome)

Therapy depends on the severity of the disease. The most commonly used scoring system to assess the disease severity is the five-factors score (FFS). The FFS was revised in 2009 and now is based on the presence of several factors: age over 65 years, cardiac insufficiency, renal insufficiency (stabilized peak creatinine 1.7 mg/dL), gastrointestinal involvement, and absence of ear, nose, and throat manifestations.[38]

The initial therapy for mild eosinophilic granulomatosis with polyangiitis, or EGPA, (FFS of 1) is systemic glucocorticoids. The therapy is initiated with 0.5 to 1.5 mg/kg per day of prednisone or equivalent. Patients with acute multiorgan involvement may require high-dose intravenous pulse methylprednisolone (1 gram daily for three consecutive days) prior to oral glucocorticoid therapy. The glucocorticoid dose can then be gradually tapered over 12 to 18 months.[39,40]

In patients with more severe disease (FFS of 2 or higher), or in those with central nervous system or cardiac involvement, cyclophosphamide is usually added to systemic glucocorticoid therapy for remission induction. After initial immunosuppressive therapy with three to six months of cyclophosphamide, maintenance therapy should be started. Azathioprine is the preferred agent for maintenance therapy. Methotrexate and leflunomide are the alternatives for maintenance therapy.

Maintenance immunosuppressive therapy is usually continued for approximately 12 to 18 months. Concurrent glucocorticoid therapy, using the lowest dose required for control of active EGPA, is also recommended during this treatment period.[39,40]

There have been several recent reports of successful use of rituximab in the treatment of refractory and severe cases of EGPA.[41,42]

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