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The use of intravenous immunoglobulin in rheumatic diseases

KEY POINTS:

The postulated immunomodulating effects of high-dose intravenous immunoglobulin (IVIg) therapy and its relatively low toxicity profile make it an attractive alternative to corticosteroids or cytotoxic agents.

Serious toxicity is infrequent, but nonetheless possible. Transmission of hepatitis C via IVIg is extraordinarily rare, chemical procedures incorporated into the preparation of IVIg inactivate hepatitis viruses and human immunodeficiency virus (HIV), and no cases of HIV transmission have been reported to date.

The efficacy of IVIg for vasculitides other than Kawasaki disease is debatable. The high cost of IVIg is an important concern, especially when it is utilized in a setting of questionable efficacy.

In recent years, numerous studies have explored the immunosuppressive properties of high-dose intravenous immunoglobulin (IVIg) therapy. IVIg is clearly effective in Kawasaki disease and idiopathic autoimmune thrombocytopenia.[1,2] However, its utility in other diseases is less clear.

This edition of Clinical Decision-Making reviews IVIg therapy in a variety of rheumatic autoimmune diseases and provides a case example in which an empiric trial was attempted, but failed.

A CASE OF SYSTEMIC VASCULITIS

The patient's condition

A 57-year-old man was referred to the Cleveland Clinic because of an illness of 2 years' duration. He had biopsy-proven cutaneous leukocytoclastic vasculitis, peripheral sensory-motor neuropathy, fever, night sweats, and weight loss.

Skin biopsies had revealed IgG deposition in the walls of numerous dermal vessels. He subsequently developed episodes of transient blindness, right wrist drop, and left foot drop.

A sural nerve biopsy revealed vasculitis. Stains for amyloid were negative. Extensive workup failed to reveal other organ involvement or underlying infectious or malignant processes.

Serum protein electrophoreses either yielded normal results or revealed polyclonal increases in immunoglobulin. Modest quantities of cryoglobulins (polyclonal IgG and IgM, with kappa and lambda light chains) were present in concentrations that varied from less than 50 µg/mL to 96 µg/mL. Hypocomplementemia (low C2, C4, and CH_{50} levels) was repeatedly demonstrated.

The results of serologic studies for hepatitis A, B, and C were negative. Antineutrophil cytoplasmic antibodies (ANCA) were not present.

Problems with glucocorticoid and cyclophosphamide treatment

The patient's condition improved after treatment with "pulse" methyl-

prednisolone (1 g intravenously daily for 3 days), methotrexate (20 mg/week), and plasmapheresis. He subsequently received maintenance therapy with daily doses of prednisone, which were titrated to minimize toxicity and avoid relapse. However, the patient developed prednisone-induced diabetes, erosive gastritis, and hypertension.

When attempts were made to taper the prednisone to less than 30 mg/day, vasculitic skin lesions reappeared and neuropathy worsened. Cyclophosphamide therapy (2 mg/kg daily) was added, resulting in stabilization of the mononeuritis and resolution of the skin lesions and enabling discontinuance of prednisone. However, cystitis developed, forcing discontinuance of cyclophosphamide.

Five months later, subcutaneous nodules and purpuric lesions reappeared and were demonstrated on biopsy to be due to necrotizing vasculitis of small- and medium-sized vessels.

Would IVIg help?

At this point, IVIg was considered for the following reasons: IVIg has demonstrated efficacy in another form of vasculitis (Kawasaki disease); it may have efficacy in ANCA-associated vasculitides; the patient had recurrent vasculitis in the course of tapering conventional immunosuppressive therapies (glucocorticoids and cytotoxic agents); previous immunosuppressive therapy had unacceptable toxicity; and IVIg therapy is relatively safe.[3–5]

It was recognized that the utility of IVIg therapy for immune complex-mediated vasculitis had not been established. If it proved effective, however, it could be justified in this difficult-to-treat patient, despite its high cost (approximately $5000 per monthly infusion).

An empiric trial fails

IVIg was given in a dose of 2 g/kg (500 mg/kg/day intravenously for 4 days). During the fourth infusion, the skin lesions markedly increased, and a biopsy revealed necrotizing vasculitis. These lesions resolved in response to prednisone, 60 mg daily.

Plasmapheresis was subsequently employed to try to minimize or eliminate the need for corticosteroids. Unfortunately, even after 10 treatments given over 3 weeks, the patient still needed corticosteroids for disease control, and he remains corticosteroid-dependent.

This case is an example of immune complex-associated vasculitis. Side effects of high-dose prednisone and of cyclophosphamide prompted the use of IVIg. However, improvement did not follow, and cutaneous lesions became more severe.

Side effects of immunoglobulin

Worsening disease, as seen in this patient, and deterioration of renal function in patients with lupus glomerulonephritis have been reported with IVIg therapy.[6] Circulating immune complexes can form large aggregates and activate complement. Rather than leading to accelerated clearance of complexes, tissue deposition of immune complexes may aggravate glomerulonephritis. The mechanisms by which IVIg therapy may worsen renal function remain unclear, but formation of nephritogenic antigen-antibody complexes[6] and transient hyperosmolar influences[7] may play a role.

Nevertheless, IVIg is relatively safe. Reactions such as fever, headache, myalgias, chills, low back pain, nausea, vomiting, tachycardia, and chest tightness occur in 1% to 15% of patients. Hypersensitivity reactions in patients with IgA deficiency can be severe. Rare neurological complications, including aseptic meningitis and stroke, may be caused by transient hyperviscosity.

Transmission of hepatitis C via IVIg is extraordinarily rare.[7] Chemical procedures incorporated into the preparation of IVIg inactivate hepatitis viruses and human immunodeficiency virus (HIV), and no cases of HIV transmission have been reported to date.

IVIg IN RHEUMATIC DISEASES

ANCA-associated vasculitides

Because of the dramatic response of Kawasaki disease to IVIg, it has been evaluated in studies in ANCA-associated vasculitides (eg, Wegener's granulomatosis, microscopic polyangiitis).[8–10] IVIg has been shown to contain anti-idiotypic antibodies to ANCA that bind to pathogenic antibodies, which may then undergo enhanced clearance.[8] Some researchers have observed that in patients with this subset of vasculitis, ANCA titers decreased as the disease abated.

In two open studies, adjunctive use of IVIg led to clinical improvement and reduction of cyclophosphamide and prednisone doses in some patients.[8,10] One report of 15 patients revealed that IVIg was of no benefit for oph-

thalmologic, pulmonary, pericardial, or renal manifestations. Complete remission did not occur in any patient. The researchers concluded that only patients with limited forms of disease achieved partial remission.[10]

In the second study, 15 of 16 patients were reported to have improved, 8 having achieved remission. However, most of the patients in this study were concurrently receiving glucocorticoid and/or cytotoxic therapies prior to study enrollment and 5 to 18 months after treatment with IVIg. Consequently, the degree to which immunosuppressive therapies contributed to improvement is uncertain.[8]

Idiopathic inflammatory myopathy

IVIg therapy appears effective in at least some patients with idiopathic inflammatory myopathy, particularly dermatomyositis.[11–13] In a double-blind, placebo-controlled crossover trial in 15 patients with biopsy-proven disease,[12] all eight patients who received a single infusion of IVIg (2 g/kg) demonstrated a significant clinical response and histopathologic improvement. In contrast, neuromuscular symptoms did not improve in the seven patients who received placebo. Of these seven patients, four improved after crossing over to IVIg therapy.

Rheumatoid arthritis

In a double-blind study, 32 patients with rheumatoid arthritis of 3 to 6 months' duration received either IVIg 1 g/kg followed by 0.5 g/kg/month for 6 months, or placebo.[14] Significant improvement was noted after the first infusion, but no statistically significant difference between the two groups was evident during subsequent months.

In other uncontrolled studies in juvenile and adult rheumatoid arthritis, although 60% or more of patients showed improvement in clinical and laboratory parameters, the benefits did not persist after discontinuation of IVIg treatment.[15–18]

Other rheumatic diseases

The efficacy of IVIg in other rheumatic diseases has been addressed in small open studies and anecdotal reports, but the results have been mixed. Its effect in lupus-associated thrombocytopenia appears similar to that in chronic idiopathic thrombocytopenic purpura (ITP), ie, efficacy is quite variable and limited in many patients.[19]

CONCLUSIONS

The postulated immunomodulating effects of high-dose IVIg therapy and its relatively low toxicity profile make it an attractive alternative to corticosteroids or cytotoxic agents. However, efficacy of IVIg for vasculitides other than Kawasaki disease is debatable. Serious toxicity is infrequent, but nonetheless possible. The high cost of IVIg is an important concern, especially when IVIg is utilized in a setting of questionable efficacy. ■

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