Are Intravenous Immunoglobulin Infusions Beneficial in the Treatment of Inflammatory Myopathies?

Inflammatory myopathies include polymyositis, dermatomyositis and inclusion-body myositis. They share characteristic immune-mediated tissue damage and can be treated similarly. However, the pathogenesis of individual myopathies is somehow different; in polymyositis and inclusion-body myositis, sensitized CD8+ cytotoxic T cells recognize unidentified muscle antigens, leading to phagocytosis and fiber necrosis. Dermatomyositis, a clinically distinct entity because of the skin rash, is characterized by an intramuscular microangiopathy mediated by the complement C5b-9 membranolytic attack complex, leading to loss of capillaries, muscle ischemia, muscle-fiber necrosis, and perifascicular atrophy (1).

Because of the immune mechanisms, inflammatory myositis is treated with various immunosuppressive agents. One of the new approaches in the treatment of the patients refractory to conventional therapies has been high-dose intravenous immunoglobulin infusion (2).

Intravenous immunoglobulin is a new modality used to treat conditions associated with immune dysregulation. In 1981, Imbach et al reported successful treatment of children with idiopathic thrombocytopenic purpura using high-dose intravenous immunoglobulin (3). Thereafter, many autoimmune diseases were treated similarly. A number of hypotheses have been proposed for the mechanisms for the possible efficacy of intravenous immunoglobulin (4). A subset of circulating antibodies, known as anti-idiotypic antibodies, serves a regulatory function for the immune system. Anti-idiotypic antibodies bind to the variable region of other antibodies and may form a regulatory network that suppresses the production of pathogenic antibodies. Therapeutic immunoglobulin preparation contains diverse array of antibody molecules, some of which are anti-idiotypic antibodies. Such anti-idiotypic antibodies in therapeutic immunoglobulin may neutralize autoantibodies in some patients in certain autoimmune diseases, thereby increasing their clearance and perhaps also downregulating their production.

Another action of intravenous immunoglobulin is to inhibit the binding of activated complements to target cells. Complement-mediated damage to cell membranes is involved in the pathogenesis of dermatomyositis as described. Activated complement complexes generated by the action of autoantibodies may bind to either cell membranes bearing the target antigens, antibodies that are bound to the target antigens, or soluble bystander IgG. By increasing the ambient concentration of IgG, intravenous immunoglobulin may favor the binding of activated complements to “bystander” IgG instead of target cells, thereby acting as an absorbant of complements. Thus, intravenous immunoglobulin reduces complement deposition in capillaries of patients with dermatomyositis. Intravenous immunoglobulin also may reduce antibody production of B cells by a feedback regulation mechanism; lymphocytes from patients who have received intravenous immunoglobulin show reduced immunoglobulin synthesis in vitro cell cultures.

Intravenous immunoglobulin blocks or down-regulates Fc-receptors expressed on reticuloendothelial cells. This effect is responsible for the prolongation of platelet survival, leading to the therapeutic effect of intravenous immunoglobulin in idiopathic thrombocytopenic purpura. In addition, intravenous immunoglobulin neutralizes viruses that potentially provoke certain autoimmune diseases, inhibits cytokine production by pathologic lymphocytes and inhibits expansion of such lymphocytes.

In 1987, intravenous immunoglobulin was reported to be beneficial for the treatment of refractory polymyositis. Subsequent studies have confirmed the efficacy of intravenous immunoglobulin in the treatment of polymyositis and dermatomyositis. However, in other trials of intravenous immunoglobulin, the efficacy of this new treatment was not seen (5–7).

Although it was an uncontrolled study, Moriguchi et al (8) reported that their patient was improved with intravenous immunoglobulin treatment. They also summarized the results of therapeutic trials in 87 patients with various inflammatory myopathies who were treated with intravenous immunoglobulin. Improvement was noted in about 71% of the patients. Notably, the best outcome was recorded for juvenile dermatomyositis and the worst for inclusion-body myositis. Sussman and Pruzanski have summarized the therapeutic trials of intravenous immunoglobulin in inflammatory myopathy reported to date, and reached a similar conclusion (9). The main criticism of the clinical trials for treating inflammatory myositis with intravenous immunoglobulin is that they were generally open, unblinded studies of small numbers of patients. In addition, other drugs such as steroids were usually given simultaneously. Treatment with intravenous immunoglobulin was given only after immunosuppressive medications had failed in most patients, late in the disease course.

Other considerations that make comparative analysis difficult are variability in therapeutic immunoglobulin preparations.
infused, dosage, dose interval, and duration of treatment. Long-term outcome has not been assessed, and repeat muscle biopsies were usually not done. However, the overall efficacy seems to be most promising in the treatment of juvenile dermatomyositis. In a well designed double-blind placebo-controlled crossover study, efficacy in nine of 12 dermatomyositis patients who were treated with high-dose intravenous immunoglobulin (2g/kg/month) was demonstrated. Muscle biopsy specimens showed decreased microvascular deposits, lymphocytic infiltrates, and necrotic muscle fibers, which were associated with a restoration of capillary circulation and increased size of surviving muscle fibers. There was also reduced expression of major histocompatibility complex class I antigens on muscles. However, three of the above-mentioned 12 patients did not respond to intravenous immunoglobulin treatment.

The therapeutic benefit of intravenous immunoglobulin in the treatment of inflammatory myopathy is still unclear. Although promising, until more exact pathologic mechanisms of the diseases are defined and a clearer definition of the various inflammatory myopathies is completed, the therapeutic effectiveness of intravenous immunoglobulin cannot be adequately assessed. However, it appears that the treatment with intravenous immunoglobulin may be useful, at least in some patients, in certain inflammatory myopathies, and thus the efficacy of intravenous immunoglobulin for the treatment of various inflammatory myopathies should be demonstrated by long-term, well-controlled double-blind cross-over studies.

References