Intravenous Immunoglobulin and Autoimmunity

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Mixed cryoglobulinemia is associated with vasculitis and hepatitis C virus infection, which reflects the impact of environmental triggers in autoimmune diseases [1]. In this issue of *IMAJ*, Almog and co-researchers [2] provide further evidence for the beneficial effects of intravenous immunoglobulin in yet another autoimmune disorder – mixed cryoglobulinemia. The patient described in this case report had mixed cryoglobulinemia with evidence of cytomegalovirus infection (IgM positive) but without HCV exposure. The initial clinical manifestations were purpura and arthralgia. Renal involvement and peripheral neuropathy developed later. The patient's disease worsened and she suffered a relapse despite conventional immunosuppressive therapy. Rapid improvement and remission occurred with adjuvant high dose IVIG therapy [2].

IVIG is a potent biological drug that is used routinely for idiopathic thrombocytopenic purpura, Kawasaki's disease, and dermato/polymyositis. In addition, it is administered experimentally for neuroimmunological, infectious, skin, blood, cardiac, inflammatory and malignant disorders [3-5]. Over the past two decades, IVIG has been used extensively for various manifestations of the prototypic systemic autoimmune disease – systemic lupus erythematosus. The manifestations include autoimmune hemolytic anemia, acquired von Willebrand disease, pure red cell aplasia, thrombocytopenia, pancytopenia, pleural effusion, pericarditis, myocarditis, nephritis, psychosis, vasculitis and others [6-8]. IVIG was administered for renal disease in more than 100 cases [8].

In Europe, therapy with IVIG in neurological diseases, such as Guillain-Barré syndrome, acute exacerbations of myasthenia gravis, and chronic inflammatory demyelinating polyradiculoneuropathy, is well established [9].

Evidence for the therapeutic effect of IVIG in vasculitic disorders also exists. High dose IVIG was beneficial for vasculitic neuropathies, as reported in a case series on patients with vasculitic peripheral neuropathy [10]. The French Vasculitis Study Group examined the role of short-term high dose IVIG in 22 patients with anti-neutrophil cytoplasmic antibody-positive relapsing disease. After 6 months of monthly therapy, 14 patients reached remission and no serious adverse events were encountered [11].

While therapy with high dose IVIG is significantly beneficial, there is some evidence that non-specific low dose IVIG therapy may be warranted not only in neurologic diseases but also in systemic autoimmune disease [12]. The beneficial effect of targeted specific IVIG in lupus and antiphospholipid syndrome in experimental models is mounting [13,14].

MECHANISMS OF ACTION OF IVIG

IVIG has multiple effects on the innate and adaptive immune systems. Mechanisms of action comprise Fc-receptor blocking by binding inhibitory Fc receptors (FcgR2b) and activating Fc receptor (FcgR1 and FcgR3), anti-cytokine effects, inhibition of complement activation, complement system regulation, enhanced suppressor activity, down-regulation of B and T cell function, idiotype network regulation, enhanced clearance of endogenous pathogenic autoantibodies, neutralization of autoantibodies, neutralization of superantigens, and augmentation of the reticuloendothelial clearance by increasing the size of inflammatory circulating immune complexes due to the addition of exogenous antibodies. The therapeutic effects of IVIG in antibody-mediated diseases such as SLE include direct effects on B cells. IVIG suppresses the expansion of autoreactive B lymphocytes through signaling of the FcgRIIB, idiotype-mediated inhibition of B cell receptors and neutralization of cytokines such as the B cell survival factors (BAFF and APRIL). IVIG can induce the secretion of IgG, which reacts against various self and non-self antigens from a unique set of human B lymphocytes [15].

Recently, a novel regulatory pathway with anti-inflammatory effects towards members of the Siglec family inhibitory lectin receptors and their influence on death signals was discovered [16].

SAFETY PROFILES

Among the advantages of IVIG compared to other biologic agents is its good safety profile. In a patient who is not IgA deficient and who does not have thrombophilia, renal failure, or

IgM = immunoglobulin M
HCV = hepatitis C virus
IVIG = intravenous immunoglobulin G
SLE = systemic lupus erythematosus

substantial cardiovascular disease, and the use of IVIG agents that do not include sucrose, IVIG has an excellent safety profile with only minor adverse events in most cases [17]. IVIG therapy is associated predominantly with mild and transient adverse effects and has an overall estimated rate of 36% adverse effects in high dose IVIG-treated patients [18]. The immediate adverse effects usually comprise headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnea, back pain, nausea, vomiting, diarrhea, blood pressure changes, tachycardia, and anaphylactic reactions especially in IgA-deficient patients. Immediate adverse effects appear early, and in many cases during the first 30 minutes of the infusion. Late adverse effects are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia, autoimmune hemolytic anemia, pseudo-hyponatremia, skin reactions, and rare events of arthritis [17].

IVIG may have a steroid-sparing effect, although this needs further investigation. Our group evaluated the clinical outcome and the steroid-sparing effect in 17 patients with autoimmune diseases. All patients were treated with high dose IVIG (2 g/kg over a 5 day period once a month for 6 months, followed by therapy every 2–3 months) and steroids. IVIG harbored a steroid-sparing effect. The average prednisone consumption decreased by 11.25 mg/day [19].

The annual cost of IVIG is of course dependent on the protocol used. Therapy with IVIG is not more expensive than other biologics, such as tumor necrosis factor blockers or rituximab.

IVIG is a reasonable option for therapy in organ-specific or multi-organ involvement in autoimmune diseases. While it is consistently potent for patients with concomitant acute infections, its role has yet to be established for chronic infectious diseases that may reactivate, such as hepatitis virus or cytomegalovirus. HCV, while shown to be involved in polyarteritis nodosa and mixed cryoglobulinemia, may also be a factor in other autoimmune diseases, such as pemphigus vulgaris, vasculitis, secondary antiphospholipid syndrome, Hashimoto's thyroiditis, and inflammatory bowel disease [20].

With this reported case of mixed cryoglobulinemia, as part of the vasculitic spectrum and with overt multi-organ involvement, IVIG may be considered as yet another beneficial and safe therapy for this condition.

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"Age is mind over matter. If you don't mind, it doesn't matter"

Mark Twain (1835-1910), American author and humorist. Twain is most noted for his novels *Adventures of Huckleberry Finn*, which has since been called the Great American Novel, and *The Adventures of Tom Sawyer*. During his lifetime, Twain became a friend to presidents, artists, industrialists, and European royalty. Twain enjoyed immense public popularity, and his keen wit and incisive satire earned him praise from both critics and peers. Upon his death he was lauded as the "greatest American humorist of his age."