The Beneficial Effects of Intravenous Immunoglobulin for Antineutrophil Cytoplasmic Antibody-Positive Vasculitis

Nina Svetlicky PhD[1,3], Miri Blank PhD[1,3] and Gisele Zandman-Goddard MD[2,3]

[1]Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel
[2]Department of Medicine C, Wolfson Medical Center, Holon, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Antineutrophil cytoplasmic antibody-associated vasculitides, among them Churg-Strauss syndrome, are characterized by vascular necrosis, predominantly renal and pulmonary involvement, and antibodies to myeloperoxidase or proteinase 3. Patients often have relapses despite aggressive induction and maintenance with non-targeted, non-biologic immunosuppressive therapy including steroids and cyclophosphamide [1]. Intravenous immunoglobulin is an adjunct biologic agent that is beneficial and has a good safety profile for many autoimmune diseases [2].

In the current issue of IMAJ Ballanti et al. [3] describe a postpartum woman diagnosed with Churg-Strauss syndrome. The predominant clinical manifestation that was devastating for the patient was neurological, initially mononeuritis multiplex and then a symmetrical peripheral neuropathy. She was resistant to conventional treatment with steroids and oral cyclophosphamide over a 6 month period. The patient responded to six monthly high dose IVIG courses. Clinical improvement was rapid and sustained without the development of adverse events. During the short follow-up after discontinuation of IVIG, the patient maintained remission.

IVIG is beneficial for organ-specific and systemic autoimmune diseases. The monthly high dose protocol (2 g/kg over 5 days) is utilized primarily for systemic autoimmune diseases [4]. Low dose IVIG (400 mg/kg for 1 day) is beneficial for organ-specific diseases, particularly neurologic disease due to immunologic mechanisms [5].

One of the extensively studied mechanisms of IVIG is down-regulation of anti-idiotypic antibodies interacting with B cells and neutralizing pathogenic idiotypes. These anti-idiotypic antibodies can inhibit the binding of the pathogenic autoantibodies to their corresponding antigen in vitro and in vivo, thereby ameliorating or preventing disease manifestations. Other possible explanations for the beneficial effect of anti-idiotypic antibodies include their inhibitory effect on the maturation of B cells towards autoantibodies secreting plasma cells in vitro, or shifting Th2 response towards Th1 response [6].

Molecular targeting of anti-dsDNA in an experimental systemic lupus erythematosus mouse model, using specific anti-anti-dsDNA anti-idiotypic antibodies fractionated from IVIG (sIVIG-aID) preparations, inhibited the idiotypic activity of anti-dsDNA in vitro. When the sIVIG-aID was infused to NZBxW/F1 mice, there was a decline in anti-dsDNA antibody titers, amelioration of glomerulonephritis, and prolonged survival. The treatment with sIVIG-aID was 200 times more efficient in suppressing the humoral reaction and clinical manifestations of than the native form of IVIG. Furthermore, IVIG affinity purified on synthetic peptide columns was defined as psIVIG (peptide-specific IVIg). The psIVIG compound significantly inhibited the binding of lupus patients' idiotypes to the dsDNA in vitro [7].

Employing the same approach, our group produced specific IVIG for antiphospholipid syndrome: specific anti-anti-beta-2-glycoprotein-1 anti-idiotypic antibodies from IVIG compound (APS-sIVIG-aID). In an experimental model of antiphospholipid syndrome, IVIG neutralized the activity of anticardiolipin-β2GP1-dependent antibodies, preventing fetal resorptions, improving platelet count and coagulation time, and promoting in vitro human trophoblast invasiveness associated with up-regulation of metalloproteinases-2/9 activity [8]. This concept has been applied to other experimental models including pemphigus vulgaris [9] and myasthenia gravis [10].

Among patients with Churg-Strauss syndrome, 40% have elevated titers of anti-myeloperoxidase autoantibodies, which are considered a pathogenic factor of vascular disease. The patient reported by Ballanti et al. in this issue [3] had an elevated level of 86.9 UI/ml perinuclear ANCA (anti-MPO antibodies). A central pathogenic function of anti-MPO antibodies is neutrophil activation, which leads to the generation of reactive oxygen species and degranulation contributing to vascular inflammation. Recently, our group tested the influence of IVIG on

IVIG = intravenous immunoglobulin

β2GP1 = beta-2-glycoprotein-I
MPO = myeloperoxidase

human neutrophils in vitro. We found that IVIG contains a fraction of anti-MPO naturally occurring antibodies; nevertheless, these antibodies are non-pathogenic and do not induce oxidative burst production in human neutrophils [11]. Moreover, IVIG inhibited binding of pathogenic anti-MPO antibodies by 35%, affinity purified from patients with small vessel vasculitis to MPO. In addition, IVIG leads to a 39% reduction of the superoxide production and oxidative burst in neutrophils induced by anti-MPO monoclonal antibodies ($P < 0.001$). IVIG contains a fraction of anti-anti-MPO (sIVIG) that we purified on the anti-MPO column and compared its activity to the original IVIG. We demonstrated that anti-MPO sIVIG was able to eliminate the neutrophil activation by anti-MPO monoclonal antibodies and was 100 times more efficient in preventing oxidative burst than the original IVIG. The benefits and safety profile of sIVIG have yet to be established in the clinical setting.

Among the advantages of IVIG compared to other agents in the conventional immunosuppressive and biologic armamentarium is the drug's good safety profile. In the patient without IgA deficiency, thrombophilia, renal failure or substantial cardiovascular disease, IVIG has an excellent safety profile, with only minor and transient adverse events in most cases. The immediate adverse events that appear during the first 30 minutes of infusion usually include a flu-like response and blood pressure changes. For the most part, mild adverse events are not an indication for the cessation of IVIG therapy, and many patients respond to adjustment of the infusion rate for a brief period. In our experience, intravenous hydrocortisone (100–200 mg) administered prior to the initiation of the IVIG course resulted in fewer adverse events [12]. We recommend a single treatment with low molecular weight heparin at a prophylactic dose before the initiation of the IVIG course to prevent the development of thromboembolism.

Long-term therapy with IVIG remains safe without compromising its beneficial effects [13]. IVIG possesses steroid-sparing properties [14]. It may be useful for patients with autoimmune diseases and concomitant infectious diseases. Furthermore, IVIG is an option for pregnant women, for those who refuse the possible toxicities of cyclophosphamide, and for those who develop unacceptable serious adverse events.

While randomized controlled trials with IVIG are lacking, many anecdotal and case series report on IVIG for off-label indications [2,4]. IVIG is recommended for some immune neurologic diseases including Guillain-Barre syndrome, refractory myasthenia gravis, and chronic inflammatory polyneuropathy [15]. We have shown that IVIG is beneficial and safe for vasculitic neuropathy of different etiologies [16]. IVIG was advantageous in Churg-Strauss patients who presented with neuropathy or cardiomyopathy as a second-line agent [17].

In the largest open trial of 22 patients with relapsing ANCA vasculitis, treatment with IVIG led to a partial remission in most, and a complete remission in 50% of the patients [18]. In conclusion, IVIG is a beneficial and safe biologic drug for many autoimmune diseases including ANCA-positive vasculitis.

Corresponding author:
Dr. G. Zandman-Goddard
Dept. of Medicine C, Wolfson Medical Center, Holon, 58100, Israel
Phone: (972-3) 502-8674 **Fax:** (972-3) 502-8810
email: goddard@wolfson.health.gov.il

ANCA = antineutrophil cytoplasmic antibodies

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