High Dose Intravenous Immunoglobulins: A New Step in the Treatment of Systemic Lupus Erythematosus

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Key words: intravenous immunoglobulin, systemic lupus erythematosus, lupus nephritis, anti-DNA, anti-idiotypes

IMAJ 2000;2:388–392

Systemic lupus erythematosus is a multisystemic autoimmune disease with diverse clinical manifestations, ranging from mild clinical findings with typical abnormal laboratory tests to a life-threatening condition. Laboratory abnormalities include high titers of autoantibodies against a vast array of tissue antigens [1]. The most characteristic antigens are those directed against components of the cell nucleus such as DNA, RNA, histones, nuclear proteins, and protein-nucleic complexes. The interaction of these antibodies with their specific antigens results in immune complexes forming and the excessive activation of complement system, which produces other typical laboratory symptoms such as low serum levels of complement components (C3, C4, CH50), leukopenia, trombocytopenia and anemia.

The clinical course of SLE is highly variable and unpredictable, frequently involving periods of remissions and relapses. The most common clinical signs are fever, weakness, arthritis, photosensitivity, skin rashes, alopecia and serositis. The major determinant of the course and prognosis of SLE and one of the major causes of mortality is kidney involvement. The various neuropsychiatric manifestations include both the central and the peripheral nervous system. Heart involvement presents most commonly as pericarditis or Libman-Sacks endocarditis. Myocardial damage can also occur as a coronary artery disease in longstanding SLE or more rarely as true myocarditis.

The etiology of SLE is uncertain, with the interaction of genetic, hormonal and environmental factors resulting in polyclonal B cell activation and excessive autoantibody production. Body tissues are damaged by autoantibodies and immune complex deposition, which activate the complement system and generate a membrane-attack complex and complement split products that damage the tissues. The tissue injury may also result from either cell-mediated cytotoxicity or direct antibody attack on target tissues.

Therapy for SLE

The standard therapy for SLE consists of non-steroidal anti-inflammatory drugs, followed by low dose corticosteroids and antimalarial compounds. A second line of therapeutics includes cytotoxic agents, cyclophosphamide, methotrexate and azathioprine. Severe cases are usually managed with high dose steroids and pulse cyclophosphamide or oral cyclosporin A. Other immunosuppressive agents such as FK506 and mycophenolate mofetil, and immunoablative therapy with extremely high doses of cyclophosphamide (50 mg/kg/day for 4 days) have been investigated in some patients with autoimmune disease refractory to other modalities. This therapy provides broad-spectrum immunosuppression with the consequent high risk of secondary infection and myelosuppressive side effects. High dose cytotoxic therapy followed by autologous stem cell transplantation has been proposed as a novel treatment for severe autoimmune diseases including SLE. However, a safe and efficient mode of immunomodulatory therapy for this disorder is still lacking.

The aim of modern therapy for SLE is to regulate rather than suppress the immune response. This can be achieved by manipulation of idiotypes by intravenous immunoglobulins; manipulation of the hormonal axis by DHEA and bromcriptine; manipulation of second signal pathways in T and B cell interaction by anti-CD4, anti-CD40L or CTLA4Ig; manipulation of cytokines (interleukin-10); or inducing tolerance to DNA by administration of blocking peptides [For review see Ref. 2].

IVIG in immunodeficiency and autoimmunity

Human normal immunoglobulin for intravenous administration is highly purified IgG preparation made from pooled human plasma collected from thousands of healthy blood donors. The spectrum of antibody specificity expressed is extremely large, and IVIG not only recognizes a large number of bacterial, viral and other infectious antigens, but also exhibits anti-idiotypic specificity. Therefore, in addition to traditional replacement therapy in immunodeficient conditions, IVIG is currently being used also as an immunomodulatory agent in autoimmunity and allogeneic bone marrow transplantation [Table 1].

SLE = systemic lupus erythematosus

IVIG = intravenous immunoglobulins

Table 1. Well-established indications for IVIG

Replacement therapy in:
- ***Primary immunodeficiency syndrome with hypo- or agammaglobulinemia:***
  Congenital agammaglobulinemia and hypogammaglobulinemia
  Common variable immunodeficiency
  Severe combined immunodeficiencies
  Wiskott-Aldrich syndrome
- ***Myeloma and chronic lymphatic leukemia with severe secondary hypogammaglobulinemia and reccurent infections***
- ***Children with congenital AIDS and recurrent infection***

Immunomodulatory effects in:
- Idiopathic thrombocytopenic purpura in children or adults at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain-Barré syndrome
- Kawasaki disease
- Allogeneic bone marrow transplantation

The current high dose IVIG therapy was initiated by Imbach et al. [3] following their observation that children with Wiskott-Aldrich syndrome, characterized by hypogammaglobulinemia, often demonstrate an unexpected rise in platelet count after IVIG administration. Since this observation in 1981, the immunomodulatory potential of IVIG in autoimmune diseases has been studied extensively. In addition to its "well-established" effect in idiopathic thrombocytopenic purpura, Kawasaki disease and Guillain-Barre syndrome, controlled trials have shown the clinical efficacy of IVIG in immune neutropenia, myasthenia gravis, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, relapsing-remitting multiple sclerosis, myasthenia gravis, and refractory dermatomyositis [4]. IVIG has been known to be used in the treatment of 50 to 60 unapproved indications with beneficial effect in most of them, including recurrent abortions of unknown cause [5], heparin-induced thrombocytopenia [6], systemic vasculitis [7] and systemic sclerosis [8]. In addition, a few animal models have shown the beneficial effect of IVIG in both prevention and treatment of experimental antiphospholipid syndrome and SLE [9].

The therapeutic dose of IVIG in autoimmunity is empirically set at 2 g/kg, with the total dose divided into five daily doses of 400 mg/kg each to lower the risk of adverse reactions. Dividing the total dose into two daily doses of 1 g/kg each may enhance efficacy, provided that the patient does not have such underlying conditions as congestive heart failure, renal insufficiency or high serum viscosity. In children with Kawasaki syndrome, one 2 g/kg dose of IVIG given in a 10 hour infusion was more effective than four daily infusions of 400 mg/kg each. The rate of infusion should not exceed 200 ml/hour or 0.08 ml/kg per min. After the total dose, the patient's serum IgG level increases fivefold and then declines by 50% during 72 hours before returning in 21 to 28 days to the pretreatment level. In long-term therapy the IVIG infusion is repeated every 4 to 8 weeks according to the patient's response and objective signs of disease recurrence. The efficacy of lower doses of IVIG in maintaining improvement remains to be determined [4].

IVIG in SLE

Despite encouraging reports on the efficacy of IVIG in autoimmune disorders, the clinical efficacy and indication in SLE patients remains undetermined. The successful results of IVG-treated secondary complications represented the first experience with IVG in the treatment of SLE. Particularly in severe SLE-associated thrombocytopenia, IVIG usually induces a prompt rise in platelet count [10–13].

IVIG has also been successfully used to treat SLE patients with a broad spectrum of clinical manifestations [Table 2], including refractory pleural effusion [14], central nervous system involvement [15,16] and myelofibrosis [17]. Several studies have reported the beneficial effect of IVIG on skin lesions [13,18,19], as well as an improvement in the immunofluorescence pattern in cutaneous tissues [20]. However, in a study of seven patients, the only study that focused specifically on cutaneous manifestations, the results showed no significant modifications of the typical malar rash or oral ulcers [21]. In fact the reverse was true: there was increasing exacerbation of the skin lesions in patients with subacute cutaneous lupus erythematosus, in contrast to the reduction of autoantibody titers, disappearance of clinical manifestation (asthenia, arthromyalgia and fever) and reduction of immunoglobulin deposits in skin biopsies [21].

Table 2. Clinical manifestations of SLE successfully treated by IVIG

- Thrombocytopenia
- Leukocytopenia
- Pancytopenia
- Autoimmune hemolytic anemia
- Pure red cell aplasia
- Myelofibrosis
- Acquired factor VIII inhibitor
- Pleural effusion
- Pneumonitis
- Pericarditis
- Myocarditis with cardiogenic shock
- Cerebritis
- Psychosis
- Polyradiculoneuropathy
- Lupus nephritis
- Secondary antiphospholipid syndrome

IVIG in lupus nephritis

There is still controversy regarding the treatment of kidney involvement in SLE. While a deterioration in renal function has been described as a potential side effect of IVIG [10,22–24], many reports have shown a beneficial effect of IVIG in lupus nephritis [25–27], proteinuria [18,28] and end-stage renal disease [29].

IVIG has been used in patients with nephritis since 1982 and was shown to improve nephrotic syndrome [30]. Moreover, it was demonstrated *in vitro* that glomerular IgG deposits in an affected kidney could be dissociated in frozen sections of biopsy specimens after incubation with human gamma globulin [25]. This mechanism may also work *in vivo*, as several studies have shown a reduction in the IgG deposits in the subsequent renal biopsy specimens obtained from patients after IVIG therapy in concert with an improvement in their clinical condition [25,28]. In a large

study that included nine patients with lupus nephritis, three of five patients with class IV lupus nephritis had a good response after one course of IVIG, with decreased proteinuria and serum creatinine, increased serum complement, and decrease of IgG deposits in the follow-up biopsy. Four patients with class V lupus nephritis had only a partial response [25]. In other two long-term studies, no detrimental clinical effects or laboratory abnormalities during or after the IVIG treatment were observed. In the group of 12 patients treated for 24 months with IVIG, all 5 patients with renal involvement showed improvement in renal function [19]. In the second study [27], exacerbation of nephritis occurred in one of the patients, despite IVIG therapy but not because of it, and the IVIG therapy was continued without any side effect. In contrast, after 3 months of IVIG therapy, renal complications (acute renal failure, increased proteinuria and developing proliferative glomerulonephritis) developed in three of seven SLE patients treated with IVIG, while one patient showed no change and three showed improvement in renal function [24]. Pirner and co-workers [22] also observed renal failure in three of six SLE patients treated with IVIG. Acute renal failure was observed in two patients with preexisting reduced renal function, and the third patient demonstrated a decrease of renal function 1 month after IVIG treatment. Corvetta et al. [10] had to discontinue IVIG treatment in one SLE patient with encephalitis and nephritis after 3 days because of rapid deterioration in renal function. The response of another two patients with encephalitis and cytopenia was good. Finally, in a pilot randomized trial [31] that assessed and compared the efficacy and safety of monthly intravenous immunoglobulin therapy with cyclophosphamide in patients with proliferative lupus nephritis, 5 of the 14 SLE patients were treated with IVIG and in none of them was IVIG withdrawn because of toxic effect or deterioration in renal function. Over the 18 months of the study IVIG maintained remission similar to that with standard intravenous cyclophosphamide treatment.

All these data suggest that IVIG may be a useful alternative therapy for lupus nephritis. The limiting factor might be renal function and the grade of renal involvement. The patient with renal insufficiency may be at considerably higher risk of developing renal failure due to IVIG. The renal impairment due to IVIG is usually transient. More than 80% of cases are reversible and resolve within 2 weeks. Higher risk occurs in patients with preexisting kidney disease and volume depletion, especially elderly, diabetic, or poorly hydrated individuals. This risk can be minimized by diluting the IVIG preparation and slowing the rate of infusion, and by close monitoring of blood urea nitrogen and serum creatinine during and several days after treatment [32]. The cause of IVIG-induced acute renal failure remains unknown. One hypothesis holds that glomerular damage from newly formed nephritogenic circulating immune complexes is the product of anti-anti-idiotype antibodies, but it seems more likely that the tubular damage secondary to increased blood viscosity and osmotic nephrosis is due to the large sucrose load [32]. The high sucrose concentration is used as a preservative in some IVIG products to reduce immunoglobulin aggregation. In a large cohort of 56 patients with several autoimmune diseases treated with IVIG preparation stabilized by saccharose, renal failure did not occur in any patient [33].

IVIG and disease activity

Several studies have demonstrated a significant effect of IVIG on overall disease activity. The beneficial effects are usually prompt, with marked improvement within a few days, but they are of limited duration. Clinical improvement lasts several weeks after the last infusion, and the clinical response could be maintained by continuous monthly IVIG infusions [18,27]. Even the first study on the beneficial effect of IVIG advocated it for acute exacerbation only [18], yet several later studies showed significant improvement in chronic refractory SLE [19,28]. The general efficacy in several small case series involving 3 to 12 patients ranged between 33 and 100% [summarized in 13]. In the largest study reported recently, which included 20 SLE patients with a 85% response rate, the authors advocate using IVIG as a useful steroid-sparing agent in SLE patients requiring high doses of steroids. However, this should be confirmed in a double-blind placebo-controlled study [13].

Due to the small numbers of patients and the conflicting results presented in the literature, it is impossible to ascertain which signs or symptoms will usually respond to IVIG. Moreover, in view of reports about flare-ups or the appearance of immune-mediated disease following IVIG treatment [12,23], it cannot be excluded that IVIG may cause paradoxical exacerbation of an autoimmune disease instead of inducing a remission.

IVIG and laboratory parameters

IVIG treatment usually results in reduction of autoantibody and circulating immune complex levels in various autoimmune and immune-mediated diseases [3]. In SLE, IVIG therapy led to decreased anti-dsDNA antibody levels, increased C3, C4 and total hemolytic complement activity, and no change in antinuclear antibody level, antibodies to RNP, Sm and SSA/SSB. Reduction of circulating immune complexes was also observed.

Laboratory examinations following IVIG treatment have shown subclinical anemia due to enhanced erythrocyte sequestration [34], increased erythrocyte sedimentation rate up to sixfold or more that persisted for 2 to 3 weeks, increased antiviral and antibacterial antibodies levels up to 30 days, and false hyponatremia due to high protein concentration in the sample [4].

Adverse effects of IVIG

The most notable advantage in the use of IVIG to treat autoimmune disease is the relative lack of side effects, especially when compared to the usual immunosuppressive therapy. Overall, it is well tolerated and safe. Although IVIG use in autoimmune diseases is associated with adverse

effects in about 10–30% of patients, these effects are usually mild and transient. The presence of adverse effect is not related to either the clinical response to the treatment or to the nature of autoimmune disease; rather, the occurrence of an adverse effect in the first treatment course is significantly associated with a greater chance for an adverse effect in the subsequent courses [33]. The most common effects are mild to moderate headache responding to non-steroidal anti-inflammatory drugs, chills, myalgia and chest discomfort. These usually resolve within an hour of discontinuing or slowing the infusion and respond to symptomatic treatment. Fatigue, fever and nausea may occur after infusion and may last as long as 24 hours. In patients with a history of migraine, IVIG may trigger a migraine attack or cause rare but serious aseptic meningitis, but the symptoms respond to strong analgesia and subside within 24 to 48 hours. Skin reactions are rare; they may develop 2 to 5 days after infusion and could persist for as long as 30 days. They include urticaria, pruritus of the palms, and petechiae of the extremities [4]. Elderly patients and patients with cryoglobulinemia, monoclonal gammopathies, high lipoproteins, or preexisting vascular disease are at higher risk to develop thromboembolic events due to an increase in serum viscosity. Moreover, patients with additional vascular risk factors such as hypertension, a history of stroke or coronary artery disease may develop acute myocardial infarction during or soon after IVIG treatment [35]. Patients with a marked deficiency of IgA with anti-IgA antibodies may develop a severe anaphylactic reaction. The most serious adverse effect of IVIG is renal tubular necrosis mentioned above.

As with all blood products, the use of IVIG may cause transmission of blood-borne infection. Viral safety is ensured by rigorous selection of plasma donors screened for hepatitis B surface antigen, antibody to hepatitis C virus and antibody to human immunodeficiency virus 1+2, together with virus inactivation and removal using appropriate inactivation method and nanofiltration. Potential viral contamination is controlled in the source plasma pool and at appropriate stages of production against contaminating viruses by means of plasma pool testing for hepatitis C virus RNA using nucleic acid amplification technology. This procedure is considered to be highly effective and demonstrative of the viral safety of IVIG with respect to enveloped viruses.

Mechanism of action

The precise mode of action of IVIG in SLE is unknown. IVIG appears to provide large amounts of immunoregulatory substances that have the capacity to regulate the immune system in various ways. The mechanism of action was best studied in idiopathic thrombocytopenic purpura where the beneficial effect was mainly attributed to the interference with Fc receptor-mediated platelet clearance by phagocytic cells. However, in SLE, additional mechanisms are involved. They include inhibition of complement-mediated damage, modulation of production of cytokines and cytokine antagonists, modulation of T and B lymphocyte functions, induction of apoptosis in lymphocytes and monocytes, selection of immune repertoires or down-regulation of autoantibody production and manipulation of the idiotypic network, and neutralization of pathogenic autoantibodies.

Table 3. Autoantibodies towards which anti-idiotypic antibodies were detected in IVIG

- Anti-factor VIII antibodies
- Anti-intrinsic factor antibodies
- Anti-thyroglobulin autoantibodies
- Anti-DNA autoantibodies
- Anti-neutrophil cytoplasmatic antibodies
- Anti-MPO antibodies
- Anti-microsomal antibodies
- Anti-neuroblastoma antibodies
- Anti-phospholipid antibodies
- Anti-platelet antibodies
- Anti-Sm idiotype (4B4)
- Anti-GM1 antibody

Commercial IVIG preparations contain anti-idiotypic antibodies against several autoantibodies [Table 3]. These anti-idiotypic antibodies can inhibit the binding of the pathogenic autoantibodies to their corresponding antigen both *in vitro* [36] and *in vivo* and thus treat or prevent disease manifestations [37]. The dissociated soluble CIC may also be aggregated with IVIG through the idiotypic network mechanism, becoming insoluble and then removable by the reticuloendothelial system. In addition, high IgG serum levels obtained after IVIG therapy could produce an antibody excess state capable of dissociating IgG deposits. Thus IVIG is able to interfere with the deposition of anti-DNA antibodies by solubilizing immune complexes. Another possible explanation for the beneficial effect of anti-idiotypes is their inhibitory effect on the spontaneous secretion of anti-dsDNA by peripheral B lymphocytes, as was demonstrated *in vitro* [38]. Since the amount of specific anti-idiotypes in commercial IVIG preparations is extremely low, it is natural to speculate that the use of isolated anti-idiotypes against pathogenic autoantibodies will result in more effective treatment with amounts of IgG that are hundreds of times smaller. Although the beneficial effect of monoclonal anti-idiotypic antibodies was shown in several mice models of SLE, human SLE is characterized by the presence of numerous autoantibodies and it is not known which are pathogenic. Therefore, treatment with monoclonal anti-idiotypic antibody may produce an inhibitory effect in only a few patients, while being useless in others. Silvestris et al. [39] reported on the treatment of two SLE patients with enriched specific anti-idiotypes affinity purified on Sepharose column coupled with DC-305-39 myeloma protein. Infusion of the eluate induced a prompt resolution of proteinuria and marked decrease of anti-dsDNA antibodies. These investigators suggest that reduction of active lupus nephritis by enriched specific anti-idiotypes is the result of at least two mechanisms: suppression of pathogenic idiotypes at the cellular level and improvement in the mesangium of the secretion anti-inflammatory cytokines, such as interleukin-6, whose defective function is related to the autoimmune disorder.

Conclusion

IVIG represents a promising immunoregulatory agent that

has the ability to control autoimmune disorders without subsequent predisposition to infectious complications. However, it is extremely expensive: the approximate average wholesale price is $1,800 per dose for a 70 kg patient. Future work and controlled clinical trials will be necessary to prove the efficacy of this therapy for specific autoimmune and vasculitic disorders. At present, using IVIG in SLE is indicated in either severe cases that are non-responsive to other therapeutic modalities, or whenever "milder" signs and symptoms of SLE can be controlled only with high dose steroids.

This treatment is immunoregulatory but not immunosuppressive or myelotoxic. Additionally, IVIG obviates ovarian/testicular toxicity, hemorrhagic cystitis, and carcinogenicity caused by cyclophosphamide.

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