Clinical utility of intravenous immunoglobulins in autoimmune diseases

J.A. Gómez-Puerta, R. Cervera, J. Font

Department of Autoimmune Diseases, Institut Clinic d’Infeccions i Immunologia (ICII), Hospital Clinic, Barcelona, Catalonia, Spain

INTRODUCTION

Intravenous immunoglobulins (IVIG) were initially used for the treatment of primary immunodeficiency syndromes. However, during the last years IVIG have proven useful for the treatment of a wide variety of other clinical conditions such as infectious processes (i.e., sepsis, parvovirus B19 or HIV infection)\(^1\), neuroimmunological diseases (i.e., multiple sclerosis, chronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome or myasthenia gravis)\(^2\) and in different systemic autoimmune diseases\(^3\)–\(^5\), neurological inflammatory disorders and autoimmune diseases. IVIG are a highly purified IgG preparation made from pooled human plasma from 3,000 to 10,000 healthy blood donors and typically contain more than 95% unmodified IgG, which has functionally intact Fc-dependent effector functions and only trace amounts of

ABSTRACT

Intravenous immunoglobulins (IVIG) were initially used for the treatment of primary immunodeficiency syndromes. However, during the last years IVIG have proven useful for the treatment of a wide variety of other clinical conditions such as infectious processes, neuroimmunological disorders and autoimmune diseases. IVIG are a well tolerated and safe therapy, but with a high cost. Despite the low number of randomised clinical trials, IVIG have been of high efficacy for the treatment of several autoimmune diseases such as autoimmune blistering diseases, dermatomyositis (DM), systemic lupus erythematosus (SLE) and some systemic vasculitis refractory to conventional immunosuppressive agents. In other conditions such as Sjögren syndrome, systemic sclerosis (SSc), antiphospholipid syndrome (APS), rheumatoid arthritis (RA) and inclusion body myositis (IBM), the efficacy of IVIG is still controversial.

KEY WORDS: Intravenous immunoglobulins / Autoimmune diseases.

RESUMEN

Durante los últimos años, la utilización de las inmunoglobulinas endovenosas (Ig ev) se ha extendido desde las inmunodeficiencias primarias, a una serie de entidades clínicas como los procesos infecciosos, las enfermedades neurológicas inflamatorias y las enfermedades autoinmunes. Las Ig ev son una terapia bien tolerada, con pocos efectos adversos, aunque con un elevado coste económico. Aunque el número de ensayos cínicos aleatorizados es escaso, se ha demostrado su eficacia en entidades autoinmunitarias como las enfermedades autoinmunes ampollosas, la dermatomiositis, el lupus eritematoso sistémico y ciertas vasculitis refractarias al tratamiento inmunodepresor habitual. En otras enfermedades como el síndrome de Sjögren, la esclerosis sistémica, el síndrome antifosfolípido, la artritis reumatoide o la miopatía con cuerpos de inclusión, su utilidad aún es controvertida.

PALABRAS CLAVES: Inmunoglobulinas endovenosas / Enfermedades autoinmunes.
IgA, IgM, soluble CD4+, CD8+, HLA molecules and certain cytokines. Some cytokines present in commercially available IVIG preparations such as the transforming growth factor (TGF)-β, could contribute to the therapeutic effects of IVIG in autoimmune diseases(1).

In 1981, the food and drug administration (FDA) licensed the use of IVIG for six conditions: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, chronic B-cell lymphocytic leukemia, bone marrow transplantation in adult patients, and pediatric HIV infection.

MECHANISMS OF ACTION, KINETICS AND SIDE EFFECTS

The mechanisms of action of IVIG are complex, and may differ among diseases and even among patients. They can be partially explained by the numerous immuno-modulatory properties mediated by the Fc portion of the IgG and by the spectrum of variable (V) regions contained in the IVIG preparations. Additionally, IVIG interfere with the cytokine network and the activation of complement, provide antiidiotype antibodies, and play an important role on the activation, differentiation, and effector functions of T and B cells. The relative importance of each mechanism depends on the circumstances in which IVIG are used(5, 6).

Figure 1 shows the different mechanisms of action and properties of IVIG, such as immunomodulation, Fc receptor-mediated effects, substitutive therapy and antiinflammatory effects.

Immunoglobulins can be administrated through different ways (intramuscular, subcutaneous or intravenous) and have a half-life of 21 to 30 days. All available commercial preparations for IVIG are similar in efficacy, safety and cost. Conventional doses are 0.4g/kg/day during 5 days or 1g/kg/day during 2 days, once a month(6).

IVIG are usually well tolerated. Mild and self-limited adverse effects can appear in 5 to 10% of the patients, including headache, nausea or vomiting, chills, fever, hypertension or hypotension, myalgias, flushing, and tachycardia. These symptoms appear within the first minutes or hours after the infusion, and disappear or may be relieved by reducing the infusion rate, stopping the infusion or administering hydrocortisone or an antihistamine agent before the infusion(1,3,7). However, severe anaphylactic reactions may occur in patients with IgA deficiency. For these particular patients, the use of IgA-depleted IVIG preparations is recommended(10). The NIH consensus conference on IVIG did not recommend screening for anti-IgA antibodies to patients who receive IVIG(10), but, nevertheless, that screening is often done.

The amount of infused IVIG correlates with blood viscosity and the potential risk of thromboembolic complications, especially in patients with previous hyperviscosity conditions (cryoglobulinemia, monoclonal gammopathies, high density lipoproteins, among others). There are several reports of thromboembolic events after IVIG infusions, including myocardial infarction(9), pulmonary embolism(10), cerebrovascular accidents (11) and transverse sinus thrombosis(12).

A few cases have been reported on the association of acute renal failure with IVIG therapy. Levy and Pusey(13) recently analysed 119 patients who had received IVIG and disclosed renal insuficiency in only 8 patients (6.7%), 2 of them requiring renal support therapy. There was no relationship with the previous patient’s characteristics, IVIG preparations or dose infused. Finally, neurologic adverse effects are rarely noted but aseptic meningitis with pleocytosis can appear even 1 week after
IVIG administration. Other adverse side effects, such as haemolytic reactions or skin rash, are less frequent.

CLINICAL UTILITIES
IVIG are useful in a wide spectrum of diseases mediated by autoantibodies. In this review, we will focus on their use in autoimmune cutaneous diseases and systemic autoimmune disorders, such as dermatomyositis (DM), systemic lupus erythematosus (SLE), systemic vasculitis, antiphospholipid syndrome (APS), rheumatoid arthritis (RA), systemic sclerosis (SSc) and Sjögren syndrome. Table I shows the list of autoimmune conditions where IVIG have utility.

AUTOIMMUNE BLISTERING DISEASES
Autoimmune blistering diseases are a group of chronic autoimmune diseases characterised by blister formation in the skin. Recently, Jolles(14) reviewed the clinical benefit of IVIG in different blistering disorders, including pemphigus vulgaris (PV), pemphigus foliaceus (PF), bullous pemphigoid (BP), pemphigoid gestationis (PG), mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA) and linear IgA disease and disclosed interesting results. About 42 patients with PV have been treated with high dose IVIG with an overall rate of response of around 90%. The conventional dose used in these patients was 1 to 2 g/kg/month. Most of the patients had previously received immunosuppressive therapy without response or with side effects. All responders used IVIG treatment as an adjunctive therapy, with unsuccessful results when IVIG was given as monotherapy.

Regarding other blistering disorders, several open trials and case reports have been published, involving 43 patients with MMP, 32 patients with BP, 28 patients with PF, 7 with EBA and only one case report with PG. Most of them had a good response to IVIG therapy, in some cases even as monotherapy. Additionally, many patients were able to reduce the dose of other immunosuppressive drugs. However, all these results must be interpreted with caution, due to the heterogeneity of the studies. There is evidence that administration of IVIG is useful in other immune mediated or inflammatory skin diseases, such as chronic autoimmune urticaria, atopic dermatitis, and pyoderma gangrenosum or toxic epidermal necrolysis(15).

DERMATOMYOSITIS AND POLYMYOSITIS
The three major forms of immune-mediated inflammatory myopathies are dermatomyositis (DM), polymyositis (PM), and inclusion-body myositis (IBM). The literature describes almost 100 DM patients that have been in trials of IVIG. This includes a mixture of case reports, uncontrolled trials, and a placebo-controlled crossover trial. Dalakas et al.(16) found that in patients with therapy-resistant DM, IVIG administered at 2 gm/kg/month for 3 months offered significant improvement in more than 70% of patients. Muscle biopsy specimens taken after treatment and compared with those taken before treatment demonstrated an increase in muscle fiber diameter, resolution of complement deposition on capillaries, and decreased intercellular adhesion molecule (ICAM)–1 and MHC class I antigens. In DM, IVIG is a reasonably therapeutic alternative and must be considered as a steroid sparing agent.

There are a few numbers of controlled studies with long-term follow-up in patients with PM. Cherin et al.(17) studied 35 adult patients with therapy-resistant PM that were treated with IVIG as a third-line therapy, with a followup of over 3 years. Significant clinical and biochemical improvement was noted in 25 of 35 patients (71.4%), allowing a prednisone dose reduction. Seven patients relapsed after discontinuation of IVIG. Response seemed to be more favorable in patients with shorter duration of disease and higher baseline enzyme levels.

The benefit of IVIG in IBM remains controversial. Despite the finding that some studies have shown some benefit(18), no significant changes in muscle strength were noted in a recent study(19). The pathogenic mechanism that leads to IBM involves amyloid deposit in muscle fibers rather than
Inflammatory processes. This is probably the reason why IVIG are not such an effective treatment for IBM patients.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

IVIG have an established therapeutic role in SLE patients with haematological manifestations, including severe thrombocytopenia(20), neutropenia(21), haemolytic anaemia(22), neonatal thrombocytopenia(23), red cell aplasia(24), acquired factor VIII deficiency(25), hypoprotrombinemia(26) and haemophagocytic syndrome(27). Their role in treating other SLE features is less clear. Many reports on the use of IVIG for the treatment of SLE have been published; most of them showed the efficacy and safety of this therapy. A number of series(20,23, 28-37) involving 135 SLE patients treated with IVIG have been published, showing a global response rate of 80%. Clinical features with better response include arthritis, thrombocytopenia, fever, myalgias, and cutaneous involvement including vasculitis lesions, serositis and nephritis. Levy et al.(28) not only found a clinical improvement in those SLE patients who received IVIG, but also a significant reduction in activity score and steroid dose.

Boletis et al.(39) studied 14 patients with type III or IV glomerulonephritis in a pilot randomized trial and compared IVIG treatment with cyclophosphamide as maintenance therapy for proliferative lupus nephritis. After 18 months of follow-up, they found similar results in both groups, in terms of creatinine levels, creatinine clearance and proteinuria, without significant differences of active extrarenal SLE. These results suggest that IVIG is a safety and effective therapeutic alternative to be used as maintenance treatment in lupus nephritis, though this needs to be confirmed in larger randomised controlled studies.

**ANTIPHOSPHOLIPID SYNDROME**

The antiphospholipid syndrome (APS) is a non-inflammatory autoimmune disease, characterised by arterial and venous thrombosis, recurrent pregnancy loss and the presence of antiphospholipid antibodies (aPL) (anticardiolipin antibodies and/or lupus anticoagulant). Thrombocytopenia is the most frequent haematologic manifestation of APS: it is present in one quarter of the patients but it is rarely severe (50,000 to 100,000). When necessary, treatment of aPL-related thrombocytopenia is usually based on corticosteroids. Some resistant cases may require additional immunosuppressive therapies or IVIG(38).

Stos et al.(39) analysed a wide series of patients with idiopathic thrombocytopenia, some of them related to aPL antibodies. The presence of aPL did not modify treatment response to steroids, splenectomy or IVIG. Twenty-five patients received IVIG with a good initial response, but without an adequate sustained response. Most of the reports about the use of IVIG in APS focused on its obstetric complications. IVIG, in contrast to heparin, do not increase the risk of osteopenia or potentially peripartum bleeding. Although several case reports suggest that treatment of women with APS during pregnancy with IVIG reduces the rates of obstetric complications, recent randomised clinical trials(38) failed to achieve a better response in comparison to conventional treatment with low molecular weight heparin and aspirin. Another possible field of action for IVIG is the infertility related to aPL antibodies, and initial data suggested promising results(39). At present time, treatment with IVIG offers a hope of successful outcome with low risk in patients with APS and obstetric complications when standard therapy has failed.

The catastrophic APS syndrome is an uncommon but often fatal form of presentation of APS, characterised by multorgan failure due to microcirculation thrombosis. The treatment of this dramatic condition is based on anticoagulation, steroids and other immunosuppressive agents. Although a recent analysis(40) failed to demonstrate efficacy of IVIG in terms of mortality, this therapy could be a useful co-adjuvant therapy for the treatment of this life-threatening condition.

**VASCULITIS**

One of the first illnesses in which IVIG was used was the childhood vasculitic disorder known as Kawasaki disease. Clear evidence have proven the benefit of IVIG treatment on coronary artery abnormalities related with Kawasaki disease(41,42). Subsequently, various case reports have suggested beneficial effect in other vasculitis such as Wegener’s granulomatosis (WG)(43), microscopic polyangiitis (MPA)(44), Churg-Strauss syndrome(45), polyarteritis nodosa(46), Henoch-Schönlein purpura(47), and Behcet’s disease(48). However, only one prospective, double-blind, randomised controlled trial using IVIG in systemic vasculitis has been performed(49). This study included 24 patients with WG and 10 with MPA with more than 5 organs involved. A significant decrease of vasculitic activity measured by BVAS score and in the C-reactive protein levels were found in 14 of 17 patients in the IVIG group during the first 3 months. After this time, however, there were no differences between IVIG and placebo groups.

**OTHER AUTOIMMUNE DISEASES**

Experience on the use IVIG in other autoimmune diseases is based on anecdotal case reports and few open trials.
Regarding RA, the apparent benefit is temporal and in some cases positive results measured by cytokine response are contradictory. Published data on Sjögren’s syndrome is limited; however, there are reports with good response in neurological features such as dysautonomia or neuropathy and in associated vasculitis. A few case reports indicate that IVIG may be used as an alternative treatment in systemic sclerosis (SSc). Levy et al. noted an improvement in skin thickness measured by modified Rodnan total store, but not in the titres of PM-Sc antibodies, after six months of therapy of IVIG in 3 patients with SSc.

CONCLUSIONS

IVIG are a safe and useful alternative therapy for many autoimmune conditions. It is important to underline that IVIG are a heterogeneous product and it is difficult to determine the exact mechanism of action in every disease and in every patient. Their role in the treatment of autoimmune diseases is clear in some conditions, such as Kawasaki disease, DM, haematological manifestations of SLE, refractory autoimmune blistering diseases and refractory vasculitis. However, the current experience regarding the duration of treatment is scarce in these conditions. A single IVIG bolus administration could be enough in some patients with autoimmune thromboctopenia or catastrophic APS, while in other patients with autoimmune blistering diseases, DM, SLE or systemic vasculitis, the usual treatment schemes range from 2 months to 1 year. The real utility of this therapy in other autoimmune disorders will have to be analysed during the following years.

CORRESPONDENCE TO:
Ricard Cervera MD PhD
Servei de Malalties Autoimmune
Hospital Clínic. Villarroel 170
Phone: +34 93 2275774. Fax: +34 93 2275774.
E-mail: rcervera@clinic.ub.es

REFERENCES

63. Dupoil JL, Ge H, de Vazaries B. Five-year efficacy of intravenous