Intravenous Immunoglobulins: Myth and Reality

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Intravenous immunoglobulins have been used as therapeutic proteins since the early 1980s. They were initially used as replacement therapy for primary or secondary humoral immunodeficiency syndromes and were rapidly shown to provide effective treatment for autoimmune thrombocytopenic purpura. Since then, IVIg have been used in a large range of autoimmune or systemic inflammatory diseases. This review relates to the main clinical indications for IVIg therapy and not to the more than 80 clinical situations in which they have been used.

IVIg composition

IVIg preparations are mainly composed of intact immunoglobulin G (approximately 97–98%) and their IgG subclass distribution is similar to that observed in human normal plasma. They also contain trace amounts of IgA that can cause anti-IgA immunization in patients presenting with total deficiencies of this isotype. These therapeutic preparations are manufactured from plasma collected from a pool of blood donors (generally 7000 to 10,000). Because a large number of donors contribute to the pool, these preparations offer a wide range of antibody specificities that are directed particularly against bacterial or viral antigens as well as against other pathogens. This property is especially important for replacement therapy in patients with humoral immunodeficiencies.

IVIg also contain "natural" antibodies, so called because they were not generated through prior contact with external antigens or active immunization [1]. These antibodies are present in the IgG, IgM or IgA isotypes and their repertoire remains constant throughout life. Since these natural antibodies are often able to bind to several antigens, they are considered to be more polyreactive than immune antibodies (directed against an exogenous antigen).

Natural antibody activity is considered crucial for the immunoregulatory properties of IVIg, particularly their ability to recognize other autoantibodies in the same patient [2].

Mechanisms of action

Several mechanisms have been described for the action of IVIg in autoimmune diseases over the last 20 years. Often acting together in a given pathology, they include the following: a) blockage and modulation of the expression of IgG Fc fragment receptors on the surface of macrophages; b) modulation of the complement system; c) modulation of cytokine synthesis and release; d) modulation of cell proliferation, apoptosis and remyelination; e) neutralization of circulating autoantibodies; f) selection of B and T lymphocyte repertoires; and g) interaction with other B and T lymphocyte surface molecules [2].

IVIg = intravenous immunoglobulins

Therapeutic indications for IVIg

Regulatory context

In 1996, European health authorities published guidelines for the clinical investigation of IVIg [3]. This document, revised in 2000, defines the nature and quantity of the minimum clinical data required to obtain marketing authorization for a given IVIg preparation. These data requirements are described in Table 1. Completion of these trials is sufficient for approval of the product in question for the indications recognized by the European Agency for the Evaluation of Medicinal Products [Table 2].

Humoral immunodeficiency syndromes

IVIg were first used for replacement therapy in patients with primary humoral immunodeficiency syndromes. They were

Table 1. Minimum clinical data required to obtain marketing authorization

	Data required
Pharmacokinetics	Minimum 15 patients with humoral immunodeficiencies, including at least 10 patients with primary immunodeficiencies
Efficacy	
Replacement therapy	The data must be applicable to all types of IgG deficiencies. They must derive from the clinical follow-up of the 15 patients included in the pharmacokinetics study, describing the frequency of infections and antibiotic use over a period of minimum 6 months
Immunomodulation therapy	Data must be demonstrated in at least 15 adult patients with AITP in the acute phase (platelet count below 20 x 10^9/L)
Guillain-Barré syndrome	Data from the literature for this indication in association with efficacy data for humoral immunodeficiencies and AITP
Kawasaki disease	Data from the literature for this indication in association with efficacy data for humoral immunodeficiencies and AITP
Allogeneic bone marrow transplant	Data from replacement therapy for humoral immunodeficiencies and immunomodulation treatment for AITP
Safety	Data concerning adverse events observed during 180 infusions in at least 30 patients

Table 2. Indications recognized by the European Agency for the Evaluation of Medicinal Products [4]

Replacement therapy	Immunomodulation
Primary humoral immunodeficiencies with hypogammaglobulinemia or agammaglobulinemia	Idiopathic thrombocytopenic purpura in children and adults at high risk for bleeding or before surgery
X-linked agammaglobulinemia/ congenital hypogammaglobulinemia	Guillain-Barré syndrome
Common variable immunodeficiency	Kawasaki disease
Severe combined immunodeficiencies	
Wiskott-Aldrich syndrome	
Multiple myeloma and chronic lymphocytic leukemia with severe hypogammaglobulinemia and recurring infections	
Allogeneic bone marrow transplant	

shown to be effective in reducing the incidence and severity of bacterial infections compared to treatment with intramuscular immunoglobulins [4]. The indications for replacement therapy were extended to other patient populations with, in particular, secondary humoral immunodeficiencies (chronic lymphocytic leukemia, multiple myeloma) and presenting with hypogammaglobulinemia and recurring infections [5].

IVIg were also shown to prevent recurring bacterial infections in children infected with the human immunodeficiency virus [6]. However, the use of IVIg for this indication is relatively controversial since the advent of anti-retroviral triple therapies and prophylaxis with cotrimoxazole.

Autoimmune thrombocytopenic purpura

AITP is the most common autoimmune cytopenia. Severe thrombopenia can occur during the acute phase (platelet count below 30 x 10^9/L), putting the patient at serious risk for bleeding, especially in the cerebrum and meninx. The first to demonstrate the efficacy of IVIg were Imbach et al. [7]. Their findings were later confirmed and this indication is now validated. A recent randomized study comparing the efficacy of IVIg with that of corticosteroids (bolus of methylprednisolone) showed that a regimen successively combining IVIg infusions with oral prednisone induced a more rapid increase in platelet count than a regimen combining methylprednisolone bolus injections with prednisone [8].

Autoimmune or parvovirus B19-mediated pure red cell aplasia

Pure red cell aplasia is defined as the absence of mature erythroid precursors in a bone marrow that otherwise exhibits normal cellularity. Acquired PRCA may occur in association with neoplasms, thymoma, autoimmune disorders, pregnancy, or due to chronic human parvovirus B19 infection in an immunologically incompetent host. PRCA of autoimmune origin was first treated successfully with IVIg more than 20 years ago.

IVIg contain anti-parvovirus B19 antibodies able to neutralize B19 and constitute a reference treatment for AIDS-related PRCA (IVIg infusion might be necessary if CD4+ count is below 80/μl) and solid-organ transplant recipients who develop B19 infection. IVIg may also be effective against PRCA associated with lymphoproliferative disorders and autoimmune diseases [9].

Allogeneic bone marrow transplant

IVIg were shown to reduce the incidence of systemic and local gram-negative germ infections and interstitial lung disease in patients who underwent allogeneic bone marrow transplant. In these same patients, prospective randomized trials showed that IVIg reduced the risk of graft versus host disease [10]. However, these results were reported 10 years ago and were recently contested in a controlled double-blind study comparing the efficacy of three doses of IVIg (100 mg/kg, 250 mg/kg, 500 mg/kg) administered each week for 90 days and then each month for one year after the transplant. This study found no difference, regardless of IVIg dose, in the incidence of GVHD or infection [11]. It would, however, be justified to consider IVIg for allogeneic bone marrow transplant in patients with severe hypogammaglobulinemia [12].

Kawasaki disease

The efficacy of IVIg was also confirmed for the treatment of Kawasaki disease in a prospective, multicenter, randomized trial comparing the association of acetylsalicylic acid (100 mg/kg/day until the 14th day followed by 3 to 5 mg/kg/day) and IVIg (400 mg/kg/day for 4 days) with acetylsalicylic acid alone [13]. Two weeks after inclusion, coronary artery abnormalities were observed in 23% (18/78) of children having received only acetylsalicylic acid compared to 8% (6/75) of the children who received the combined treatment (P = 0.01). Seven weeks later, 18% (14/79) of patients in the acetylsalicylic acid group presented with abnormalities compared with only 4% (3/79) in the other group (P = 0.005). No serious adverse events were reported during this trial. Since publication of this work, the association of IVIg and acetylsalicylic acid initiated within 12 days following the appearance of clinical symptoms is recognized as the reference treatment for Kawasaki disease.

Guillain-Barré syndrome

The first controlled randomized study comparing the effects of IVIg and plasma exchange for the treatment of Guillain-Barré syndrome was coordinated by Van der Meché [14]. The protocol compared the efficacy of five plasma exchanges with that of one IVIg infusion at a dose of 0.4 g/kg/day for 5 days. Efficacy was evaluated 4 weeks later using a motricity score on a scale of 0 to 6. The study group comprised 150 patients. The muscular

AITP = autoimmune thrombocytopenic purpura
PRCA = pure red cell aplasia
GVHD = graft versus host disease

score improved by at least one point in 34% of the patients treated with plasma exchange and in 53% of those who received IVIg ($P = 0.024$). There were also fewer complications in the IVIg group. The conclusion of this trial was that IVIg are at least as effective as plasma exchange and perhaps even more effective.

Another prospective randomized study compared the clinical efficacy of IVIg (0.4 g/kg/day for 5 days), plasma exchange (5 sessions) and a combination of the two in 379 patients with Guillain-Barré syndrome [15]. The improvement in functional score at 4 weeks after randomization was 0.9 in the plasma exchange group, 0.8 in the IVIg group and 1.1 in the combined treatment group. The authors concluded that there was no significant difference between the three therapeutic options. They did, however, encourage preference for IVIg, the simplest treatment with comparable efficacy.

All these results prompted European authorities to include this indication in the group of "well-established" indications [3]. Health authorities require pertinent clinical data for the approval of all other indications for treatment with IVIg. Several indications not currently included in the list of "well-established" have, however, been studied in controlled clinical trials showing the efficacy of IVIg. The results for the main indications are shown below.

Chronic inflammatory demyelinating polyradiculoneuropathy

The efficacy of IVIg for the treatment of CIDP was evaluated in six randomized trials. Four of the trials compared IVIG with placebo [16–19], and the other two with plasma exchange [20] and oral prednisone [21] respectively. These studies showed that IVIg are more effective than placebo and that the efficacy of these three treatments is comparable (approximately two-thirds of the patients were responders to the first-line treatment). In addition, a Cochrane meta-analysis [22] of these six trials demonstrated that IVIg ameliorated neurologic impairment for 2–6 weeks and that its efficacy was equivalent to those of the other two therapeutic options. Certain authors believe that IVIg could be used as first-line treatment since they induce rapid improvement, are associated with minor adverse events and are simple to administer. A comparison of safety, ease of administration and cost would help to define the most appropriate treatment.

Acute myasthenia

Gajdos and colleagues [23] conducted a prospective, randomized trial comparing IVIg and plasma exchange in 87 patients presenting with an acute myasthenia exacerbation. Forty-six patients were included in the IVIg group, of whom 23 received 0.4 g/kg/day for 3 days and 23 received the same dose for 5 days. The efficacy of the two IVIg doses was similar but the patient population was too small to identify the most appropriate dose. Forty-one patients were included in the plasma exchange group. The clinical efficacy of the two treatments was comparable as evaluated by muscular score on the 15th day after treatment. Safety was found to be significantly superior in the IVIg group (9 adverse events in the IVIg group compared with 14 in the plasma exchange group, $P = 0.01$).

Dermatomyositis

Corticosteroid-resistant dermatomyositis was evaluated in a prospective, randomized, placebo-controlled crossover trial in 15 adult patients [24]. The switch was proposed after 3 months of treatment. An IVIg preparation was administered to eight patients during the first phase of the study at a dose of 2 g/kg/month. Placebo was administered during the same phase to seven patients. The muscular scores in the IVIg group patients improved significantly as compared to the placebo group ($P < 0.018$). This is the only controlled trial performed for this indication.

Polymyositis

Polymyositis is an inflammatory myositis; its pathophysiology differs from that of dermatomyositis. Only open studies in corticosteroid-resistant polymyositis have been reported; these showed improvement in muscular testing and reductions in blood levels of muscular enzymes in the treated patients [25–27]. A recent study showed that after administration of IVIg two-thirds of the treated patients (resistant to conventional treatments) responded. After termination of the treatment, this efficacy was maintained in 50% of the patients with an average follow-up period of more than 3 years [28].

Multifocal motor neuropathy with conduction block

Based on clinical and electrophysiologic criteria, multifocal motor neuropathy with conduction block was described in 1982 as a clinical entity different from CIDP. The clinical symptoms are predominantly distal motor impairment in association with fasciculations and cramps. Several clinical studies have been performed for this indication [29,30]. In particular, the prospective randomized study of Léger et al. [29] compared the efficacy of an IVIg preparation at a dose of 500 mg/kg/day for 5 days with placebo in 19 patients. After the third treatment session, the patients who were responsive to treatment continued the same treatment while those who were not responsive changed therapy. Seven of the nine patients treated with IVIg responded, as compared to two of the nine patients who received placebo as first-line treatment. This difference was statistically significant ($P = 0.03$).

IVIg in eye involvement

In autoimmune diseases with intraocular inflammation, uveitis may be the first clinical manifestation and may represent the most severe sign. The conventional treatment of intraocular inflammation includes corticosteroids and immunosuppressive agents, which are efficient in about 50% of the patients but their effectiveness is also limited by their iatrogenicity. Most of the published reports are case series or open trials. They show favorable results in a subset of indications including mainly ocular cicatricial pemphigoid, Vogt-Koyanagi-Harada syndrome, or birdshot disease. Birdshot retinochoroiditis is a rare, chronic,

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy

progressive, bilateral inflammatory eye disease affecting the posterior segment. Treatment with oral corticosteroids with or without immunosuppressants (such as cyclosporine) induces serious side effects over the long term. The efficacy of IVIg for this condition was studied in an open study of 18 patients [31]. The dose used was 1.6 g/kg every 4 weeks for 6 months followed by 1.2–1.6 g/kg every 6–8 weeks. The average follow-up period in this population was 39 months (limit 6–8 years). Visual acuity improved by more than two lines in 14/36 eyes (38.8%) and by more than one line in 24/36 eyes (66.66%). It remained stable in 8/36 eyes. Visual acuity deteriorated in two eyes (by one line in one and by four lines in the other). No serious adverse events during the trial were reported. In five of these patients the mean daily intake of prednisone was decreased sixfold, from 55 ± 16 to 9 ± 7 mg (P = 0.04); in one patient who received steroid therapy for 72 months before IVIg, steroid treatment was discontinued after 12 courses of IVIg. These results suggest that IVIg may represent a therapeutic alternative for patients requiring long-term treatment.

Multiple sclerosis

The efficacy of IVIg was also studied in controlled trials in patients with multiple sclerosis, especially the relapsing-remitting form. A study by Achiron and co-workers [32] showed a significant reduction in the rate of relapse in the group treated with IVIg compared with the placebo group (P = 0.003). In addition, Fazekas and associates [33] also reported the efficacy of IVIg versus placebo in a prospective controlled trial. The authors showed that the functional handicap score decreased in the IVIg group and increased in the placebo group (P = 0.008). A Swedish team also studied the efficacy of IVIg in this same population using nuclear magnetic resonance imaging [34]. The results were also similar, showing significantly fewer lesions in the IVIg group. Nevertheless, several authors state that additional studies are necessary to justify the use of IVIg for this disease.

Stiff-man syndrome

Stiff-man syndrome is a disease of the central nervous system characterized by rigidity and highly debilitating muscle spasms in association with high levels of anti-glutamate decarboxylase antibodies. The results of a randomized, crossover study comparing the effects of IVIg with placebo in patients with this disease were recently reported [35]. In this study, stiffness scores decreased significantly in patients initially treated with IVIg (P = 0.02) and increased after the switch to placebo. On the other hand, stiffness scores in the patients initially treated with placebo remained stable during the first phase and then dropped significantly during treatment with IVIg (P = 0.01). This work will no doubt serve to validate the use of IVIg for this entity.

ANCA-positive vasculitis

Encouraging results from an open study on the efficacy of IVIg for the treatment of relapsing vasculitis with antineutrophil cytoplasmic antibodies (ANCA-positive vasculitis) prompted the authors to perform a randomized IVIg versus placebo trial. In this prospective study of 34 patients, significant clinical improvement was observed in 14/17 patients who received an injection of IVIg at immunomodulation doses compared with 6/17 in the placebo group [36].

Hemophagocytic syndrome of infectious origin

Pathologic macrophage activation may occur in the context of several systemic diseases (autoimmune diseases, malignancies, Langerhans cell histiocytosis); it may also be secondary to infections. The abnormal accumulation and stimulation on monocytes/macrophages leads to the phagocytosis of blood cells in bone marrow liver and spleen. The clinical presentation includes mainly refractory fever, hepato- or splenomegaly, and lymphadenopathy (treatment with dexamethasone, cyclosporin A, etoposide, and allogeneic bone marrow transplantation is proposed by some authors). IVIg has been successfully used alone or in combination with etoposide [37]; nevertheless, the results presented so far come from case reports or open studies. A clear demonstration of the efficacy of IVIg is awaited.

Streptococcal/staphylococcal toxic shock syndrome

The number of diagnoses and reports of this syndrome has increased dramatically since the 1980s. The clinical feature is shock with organ failure with or without necrotizing fasciitis. This dramatic syndrome is associated with high mortality rates ranging between 30% and 70%. The treatment includes antibiotic therapy, shock treatment and often extensive surgical debridement including amputation with prolonged hospital stay. IVIg has been reported as an efficient adjunctive treatment in case reports and open studies. A European randomized controlled double-blind placebo trial was performed in the early 2000s in streptococcal toxic shock syndrome [38], but unfortunately the trial was terminated early because of slow patient recruitment. The results were obtained for 21 patients (10 IVIg recipients and 11 placebo recipients). The mortality rate at day 28 was 3.6-fold higher in the placebo group (not significant). Nevertheless, a significant decrease in sepsis-related organ failure assessment score at days 2 and 3 was observed in the IVIg group.

Blistering diseases

The potency of IVIg has been investigated in several blistering diseases, especially Lyell syndrome. In 1998 Viard et al. [39] reported on the spectacular efficacy of IVIg in 10 consecutive patients [39]. Disease progression was rapidly reversed and the outcome was favorable in all cases. Unfortunately, these observations were not reproduced in further studies. The subject remains controversial.

Ocular cicatricial pemphigoid is a chronic sub-epithelial blistering disease of autoimmune origin. Clinical manifestations include lesions of various mucosal sites; around 80% of the patients with OCP have ocular lesions, which is the most severe expression of the disease. Several open studies, mainly by the same team, showed a favorable outcome after IVIg treatment

OCP = ocular cicatricial pemphigoid

[40]. These authors also reported a correlation between the clinical efficacy of IVIg in OCP and a decrease in serum titers of anti-β4-integrin antibodies. An effective demonstration should be provided by prospective trials.

Conclusion

Over the last 25 years, medical and scientific knowledge about IVIg has made spectacular progress and the number of prescriptions has increased significantly. This review did not discuss all the potential therapeutic indications for IVIg such as systemic diseases (systemic lupus erythematosus, Crohn's disease, antiphospholipid syndrome), anti-HLA allo-immunization in chronic hemodialysed patients, or recurrent and early spontaneous abortion. These pathologic conditions require additional clinical data to assess the potential benefit of IVIg. In the coming years, some indications considered as valid by the experts but not recognized by health authorities as "well-established" will probably be validated by health authorities based on published clinical trials. A great number of potential new entities remain to be evaluated. As most of these diseases are rare, new study designs adapted to small populations, such as randomized crossover trials, should be used in the future to assess the efficacy of IVIg for new clinical indications.

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