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High-dose intravenous immunoglobulin G treatment of myasthenia gravis

Abstract IVIg is a safe and effective adjunctive treatment for myasthenia gravis, but there are no well established guidelines for the use of IVIg in this disease, lacking controlled randomized trials to assess its efficacy in homogeneous group of patients. The main advantages of IVIg are the rapid onset of the effect, the lack of long-term toxicity, and the possibility to reduce the required doses of immunosuppressive drugs. IVIg appears to have a role as an acute treatment in rapidly progressive myasthenia gravis weakness, particularly in situations when therapeutic apheresis is not feasible. In addition, IVIg is safer than plasma exchange (PE) in patients with hypotension or autonomic instability, in children, in patients of older age (>65 years), and in those suffering from sepsis. For these reasons, at present, IVIg are recommended during crises of myasthenia gravis in older patients when PE is contraindicated or not feasible. IVIg can be also used as a chronic maintenance therapy when other immunosuppressive treatments have failed or cannot be used. Periodic administration of IVIg on a bimonthly or monthly basis may be able to stabilize chronic, nonresponding patients.

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Introduction

Acquired myasthenia gravis (MG) is an autoimmune disease characterized by muscular weakness, worsened by repeated activity and restored by rest. The disease course is usually progressive, sometimes with episodes of acute worsening of symptoms, often related to infections. Eye muscles are usually the first to be affected but, as the disease progresses, other muscles are involved, including pharyngeal and respiratory muscles [1].

According to the severity of muscle involvement, a recent clinical classification into 5 severity classes of disease has been proposed by the Myasthenia Gravis Foundation of America [2].

MG prevalence is variously estimated to be 4–12 per 100 000 people. The peak age of MG onset is between 20 and 30 years for women, while for men it is between 50 and 60 years.

The course of the illness is extremely variable, but spontaneous remission and stabilization are rare. In generalized disease, bulbar functions are frequently involved. Mortality is actually under 4% [1]. In about 90% of MG patients, pathological alterations of thymus gland are found, 10% referred to thymic tumors (predominantly in older males) and 80% to hyperplasia of lymphoid follicles with active germinal centers, confined to the medulla of the thymus.

The pathogenesis of MG is related to the presence of antibodies (Ab) to nicotinic acetylcholine receptors (AChR) of the neuromuscular junction. MG serum IgG reproduce myasthenic symptoms when administered to animals [3]. These antibodies crosslink AChR molecules, increasing their internalization on post-synaptic muscle membranes (Fig. 1a). Anti-AChR antibodies can also activate C3 component of complement, resulting in destruction of the AChR-containing segments of the post-synaptic membrane. These effects of anti-AChR antibodies reduce the width of post-synaptic membrane folds and the number of AChRs, with impairment of neuromuscular transmission. In addition, different amounts

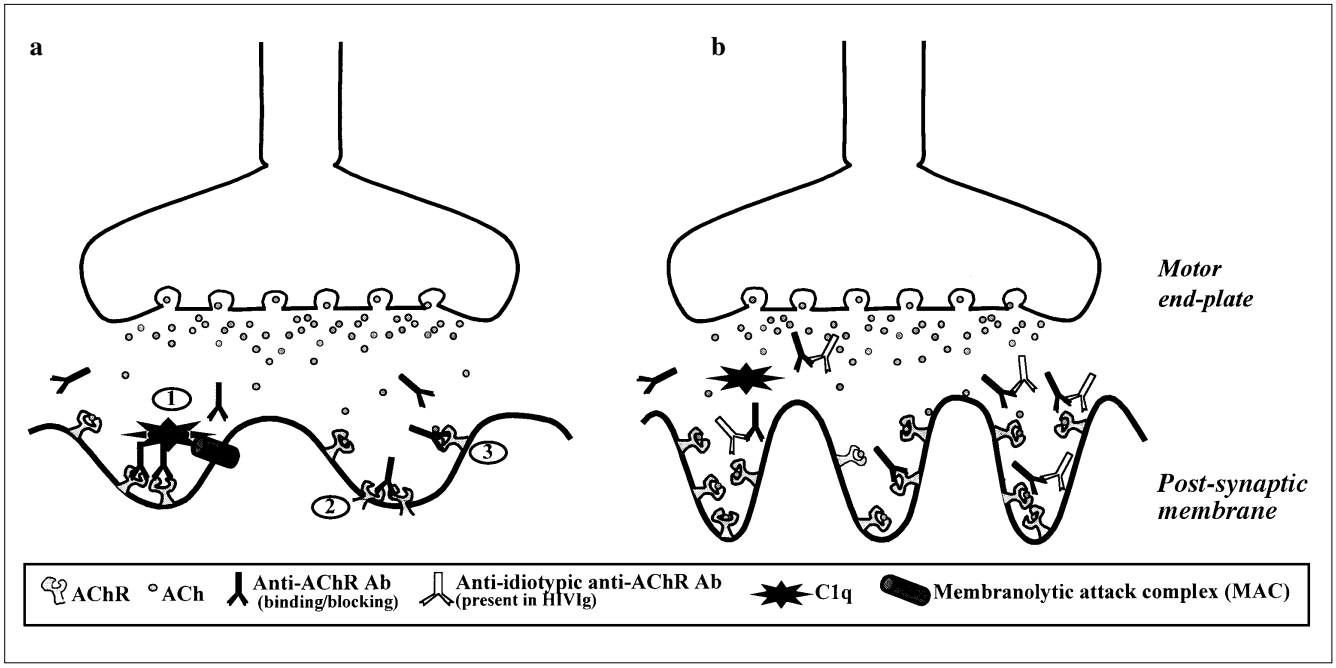

Fig. 1 a MG pathogenesis. *1*, Membranolytic attack complexes (MAC) deposit on post-synaptic membranes and lead to a reduction in AChR number and post-synaptic muscle membrane folds; *2*, Increase of AChR internalization at the post-synaptic membrane with alteration in AChR turnover; *3*, Allosteric block of ACh-AChR binding by anti-AChR-blocking antibodies with decrease of AChR-related ion-channel activity. **b** Mechanisms of action of IVIg at the neuromuscular junction. The pathogenetic mechanisms induced by anti-AChR antibodies are counteracted by anti-idiotypic anti-AChR antibodies present in IVIg

of anti-AChR antibodies able to block ACh-AChR interactions (anti-AChR blocking antibodies) are present in MG sera: these autoantibodies, when present, reduce the activity of AChR-related ion channels at the post-synaptic membrane, thereby decreasing neuromuscular transmission (Fig. 1a).

Initial anti-AChR antibody sensitization may occur in the thymus because of the presence in the "myoid" cells of the gland of a protein with structural and antigenic similarities to those of embryonic muscle AChR [4]. In normal thymus the T cell repertoire is shaped by deleting thymocytes expressing T cell receptors (TCR) with high affinity for self-peptides (such as AChR) presented by self-MHC molecules. In fact, these autoreactive clones usually undergo apoptotic death in thymic cortex, as proven by histological studies. For unknown reasons, the MG thymic microenvironment is altered, causing a proliferation of autoreactive clones and a loss of tolerance. For this reason, clones of AChR-reactive Th1 (stimulated by interleukin (IL)-12 and secreting IL-2, interferon (IFN)-gamma and tumor necrosis factor (TNF)-beta) and Th2 (stimulated by IL-4 and secreting IL-4 and IL-5) lymphocytes can proliferate and stimulate B cell-dependent anti-AChR antibody production [5]. This loss of immune tolerance has been associated with other immunological alterations found in MG patients (alteration both in T suppressor or natural killer subsets and in cytokine levels), but it is not clear if such alterations are the cause or an epiphenomenon of myasthenic immunological changes. However, since the thymus plays a central role in MG pathogenesis, thymectomy is recommended for most patients with MG.

Therapies for MG

The treatment of MG is mainly based upon the use of anticholinesterase drugs, increasing progressively their dosage to reach a sufficient clinical improvement. Anticholinesterase drugs are well tolerated with a few side effects. Thymectomy is indicated in all cases of thymoma (followed by radiotherapy) and recommended in all young patients with uncomplicated generalized myasthenia, poorly responding to anticholinesterase drugs and within two years after disease onset.

If the response to the appropriate dose of anticholinesterases both in thymectomized and in nonthymectomized patients is inadequate to counteract MG symptoms, corticosteroids (i.e. prednisone at 1–1.5 mg/kg body weight day) are usually the first-choice treatment. Marked improvement or complete relief of symptoms occurs in more than 75% of patients treated with prednisone. Adverse reactions include an initial, transient, steroid-induced exacerbation in about one-third of patients, usually within the first 7–10 days and lasting for up to a week, hypercorticism in about half of patients, diabetes mellitus and, less commonly, cataract formation, osteopenia, hypertension, gastric diseases and psychotic events.

If corticosteroid therapy is contraindicated or ineffective, immunosuppressants can be used. Azathioprine, given at a dosage of 2.5 mg/kg daily, reverses symptoms in most patients, but the effect is delayed by 4–8 months. Other less used therapies for MG include cyclosporine, cyclophosphamide, total lymphoid irradiation and, recently, mycophenolate mofetile. In spite of all described treatments for MG, several patients may remain refractory or develop severe contraindications to the therapies [6].

Plasma exchange (PE) is used as a short-term intervention for patients with a sudden worsening of MG symptoms. Usually, PE every other day for 4–6 procedures in total is the most commonly used approach. Almost all patients with acquired MG improve temporarily after PE, usually within 2 days after the first exchange. This form of treatment may be lifesaving during a MG crisis. It is also useful before and after thymectomy and at the start of corticosteroid or immunosuppressive drug therapy. PE is, however, a complicated treatment requiring the placement of a central venous catheter, technically not feasible in all patients (not recommended in elderly patients and in those suffering from sepsis) and often associated with the risk of an initial worsening of myasthenic symptoms [7]. For this reason PE has to be administered only in intensive care units.

High-dose intravenous immunoglobulin G (IVIg) infusion is a new therapeutic approach for MG. This therapy can be used virtually in all MG patients, without age or pathology-associated limitations, during both acute and chronic phases of the disease.

IVIg therapy in generalized and neurologic autoimmune diseases

Immunoglobulin G (IgG), prepared from pooled plasma (obtained from about 3000 normal blood donors) by ethanol cryoprecipitation (Cohn's fraction II), has been used intramuscularly, starting from the 1950s, in patients with primary immunodeficiency syndromes [8]. Immunoglobulin suitable for intravenous use was developed during the 1970s and used extensively since 1985. At the present, IVIg has assumed an important role in prophylaxis and therapy of bacterial (e.g. streptococcal necrotizing fasciitis) [9] and viral (e.g. human immunodeficiency virus) infectious diseases, as well as in the treatment of primary and secondary antibody deficiency syndromes. The demonstration that high doses of passively administered IgG inhibited antibody synthesis [10] prompted the use of such preparations for treatment of patients without a classic humoral antibody deficiency syndrome, such as hyperimmune and autoimmune conditions [11].

Although the mechanism of action of IVIg therapy is not well known, it is accepted as an effective and convenient alternative to PE for treating generalized diseases thought to be mediated by pathogenic autoantibodies or immune complexes. In idiopathic thrombocytopenic purpura, this approach has transformed the medical management, becoming a widely accepted form of therapy [12]. The effectiveness of IVIg treatment was then confirmed in patients with a pseudohemophilic bleeding syndrome due to auto- or alloantibodies inhibiting the procoagulant factor VIIIc [13]. These encouraging results prompted the use of IVIg in anecdotal cases of other non-neurologic and neurologic disimmune syndromes: autoimmune neutropenia [14], autoimmune pure red cell aplasia [15], systemic lupus erythematosus [11], chronic inflammatory demyelinating or monoclonal gammopathy-associated polyneuropathies [16–18], polymyositis [19, 20], Guillain-Barré syndrome [21, 22], Kawasaki's disease [23], multiple sclerosis [24, 25] and recurrent pregnancy loss [26].

More recent controlled therapeutic trials confirmed the benefical effect of IVIg in some autoimmune neurological diseases, such as Guillain-Barré syndrome [27], chronic inflammatory demyelinating polyneuropathy [28–30], myasthenia gravis [31, 32], Eaton-Lambert syndrome [33], multiple sclerosis [34], multifocal motor neuropathy [35–37], intractable childhood epilepsy [38] and steroid-resistent dermato-polymyositis [39, 40].

IVIg therapy in myasthenia gravis

Immunoglobulin therapy was proposed in the early 1970s as an effective and safe treatment for MG. Intramuscular injections of 10 ml human gamma globulin were administered to patients every three weeks, with a significant stabilization of the disease [41]. Initial reports using high-dose human intravenous IgG for MG appeared in the first years of the 1980s [42, 43], with encouraging results. MG patients with rapidly worsening bulbar symptoms or respiratory insufficiency, with adverse reaction to corticosteroids, cytostatic drugs, or PE were treated with IVIg (0.2–0.4 g/kg per day for five consecutive days). Improvement of MG symptoms was observed in most patients 5–10 days after starting IVIg and lasted up to 60 days. In all cases serum IgG levels were elevated simultaneously. In some patients, with high pretreatment titers, anti-AChR antibody levels fell between days 10–15, and rose again almost to baseline range by day 25. Often the improvement of MG symptoms was observed 4–5 days after starting IVIg.

Because of these encouraging results, since 1984 several small case series of MG patients treated with IVIg have been published. The most important of these open trials are sumarized in Table 1. These studies were non-controlled or used heterogeneous patient inclusion criteria regarding disease severity, disease duration, and concurrent or previous treatments, without standardization of IVIg preparations, assessment method (clinical or electrophysiologic) or definition of response. Gajdos et al. [44] performed the only randomized trial on 87 patients with acute MG who worsened when treated with IVIg and compared them to a population of patients

Table 1 Clinical trials of IVIg therapy for myasthenia gravis

References	Study design and IVIg dose	Patients n (% men)	Age, years[a]	Clinical stage[b, c]	Duration, months[a]	Thymic pathology[c]	Concomitant [c]therapies[c]	Improvement after IVIg		
								Patients, n (%)	Onset, days[a]	Duration, days[a]
Fath-Moghadan	Open 20 g/day for 6 days	4 (50)	29 (20–34)	Stable	87 (12–120)	NG	AZA (2)	4 (100)	<14	>45
Gajdos	Open 1–2 g/kg on 5 days	5 (60)	53 (30–75)	Stable III (5)	NG	NG	0	4 (80)	10–15	>25
Ippoliti	Open 2 g/kg on 5 days	7 (0)	39 (20–70)	Stable II (1), III (3), IV (3)	46 (7–100)	T (2), H (3)	(4), P+AZA (2), AZA (1)	6 (85)	<21	52
Arsura	Open 2 g/kg on 5 days	12 (50)	50 (15–70)	Acute II (2), III (6), IV (4)	42 (4–180)	T (4), H (4)	P (8)	11 (92)	4 (1–9)	52 (19–120)
Beisenger	Open 20 g/day for 6 days	9 (33)	41 (19–62)	Stable	72 (12–336)	NG	AZA (2)	7 (77)	<7	>25
Uchiyama	Open 10 g/day for 6 days	6	NG	Chronic	NG	NG	P+AZA+PE (5)	0	0	0
Gajdos	Open 3–4.5 g on 5 days	21	NG	Acute II (7), III (9), IV (5)	NG	NG	P (9)	10 (48)	<10	>25
Cosi	Open 2 g/kg on 5 days	37 (11)	38 (11–78)	Acute (11), stable (26) II (20), III (16), IV (1)	98 (2–384)	T (8), H (10)	P (18), P+AZA (8), AZA (4)	26 (70)	6–10	>60
Evoli	Open 2 g/kg on 5 days	12 (33)	51 (16–76)	Acute II (8), III (2), IV (2)	55 (5–193)	T (5), H (2)	P (7), P+AZA (2), AZA (3)	10 (83)	8 (3–20)	64 (24–120)
Ferrero	Open 2 g/kg on 5 days	15 (40)	48 (22–61)	Acute II (6), III (6), IV (3)	28 (4–103)	T (4), H (8)	–	13 (86)	8 (3–21)	41 (23–75)
Edan	Retrospective 2 g/kg on 5 days	10 (30)	53 (23–69)	Acute (6), stable (4)	6	T (2)	–	7 (70)	1–7	>60

Cont.→

Table 1 continued

References	Study design and IVIg dose	Patients n (% men)	Age, years[a]	Clinical stage[b, c]	Duration, months[a]	Thymic pathology[c]	Concomitant [c]therapies[c]	Improvement after IVIg		
								Patients, n (%)	Onset, days[a]	Duration, days[a]
Gajdos	Randomized 1.2 g/kg on 3 days; 2 g/kg on 5 days 3 PE on 5 days (1.5 x volume each PE)	87 (34)	50 (15–91)	Acute with bulbar symptoms	48 (0–324)	NG	P (25), AZA (15)	22 (48)	2–15	>15
Tatay	Open after 5 PE 2 g/kg on 5 days	10 (60)	48 (28–62)	Chronic	NG	NG	P (5), AZA (1), P+AZA (4)[d]	10 (100)	3 (1–8)	>100
Jongen	Retrospective 2 g/kg on 5 days	11 (18)	55 (14–86)	Acute (6), subacute (8) chronic (2) II (7), III (7), IV (2)	86 (6–220)	T (2), H (6)	P (1), P+AZA (2), AZA (2), CYCLO (2)	9 (56)	3 (1–12)	>30
Qureschi	Retrospective IVIg (2 g/kg on 5 days) vs PE (5–6 PE, 25–45 ml/kg each session)	54 (26)	55 (16–86)	Crisis with respiratory impairment	NG	NG	P+AZA (29)	38% of IVIg-treated patients extubated at 1 week (significantly worse than PE) and 62% without disability at 1 mo (similar to PE)		
Achiron	Open 0.4 g/kg day x 5 days + 0.4 g/kg once every 6 weeks for 1 year	10 (30)	44 (25–70)	Acute refractory	24–96	T (1), H (2)	P (5), P+AZA (4), AZA (1)	10 (100)	6 (4–12)	>30
Selcen	Open 2 mg/kg on 3–5 infusions	10 (40)	13 (2–18)	Acute II (2), III (4), IV (4)	33 (1–180)	H (5)	P (1), PE (2), P+PE (4) P+PE+AZA (1)	9 (90)	4 (1–7)	25 (21–30)

PE, plasma exchange; *NG*, not given; *P*, prednisone; *AZA*, azathioprine; *CYCLO*, cyclophosphamide; *T*, thymoma; *H*, hyperplasia

[a] Mean (range)

[b] Osserman's classification

[c] In parentheses, numbers of patients

[d] After PE

receiving therapeutic PE (three courses of PE performed once every 2 days). The IVIg group had two arms, according to IVIg total dose administered (0.4 g/kg for 3 or 5 days). The endpoint was an improvement in muscle strength by day 15. This study showed that IVIg is as effective as PE to counteract acute MG exacerbations, but with fewer side effects. Criticisms of the study include the lack of an untreated control arm and the nonblinding of the PE-treated group.

IVIg efficacy in MG patients can also be deduced by the reduction in circulating levels of anticholinesterase or immunosuppressant drugs often seen after IVIg treatment. Bulbar involvement disappears in about 50% of treated patients within two weeks after starting IVIg, and anticholinesterase doses are reduced in 50% of patients from 4 to 9 weeks after starting IVIg. Some authors [45, 46] have noted a transient early clinical deterioration (beginning 3 days after starting IVIg) in about 20%–25% of treated patients, but this feature was not reported by other authors. Some conclusions can be drawn from these studies:

(a) The majority (50%–90%) of patients demonstrated some improvement after IVIg infusions, even if the degree of improvement varied, never achieving a complete remission;
(b) The clinical efficacy of IVIg treatment is similar between patients who started IVIg in an acute or relapsing phase and those who received IVIg in a stationary phase [47];
(c) Clinical improvement begins during the first week of therapy for most patients;
(d) The improvement usually lasts less than 3 months in most courses of treatment, although improvement for as long as 6 months was noted in some patients treated concurrently with immunosuppressive drugs or in patients treated in stationary phase [47], perhaps due to less spontaneous clinical fluctuation in these two groups of patients;
(e) The most common IVIg dose administered was 0.4 g/kg day for five days, but the amount of IVIg necessary to produce improvement has not been fully addressed (in the only study in which no patient improved, only 10 g immunolobulin daily for 5 days was administered [48]);
(f) IVIg is a well tolerated therapy, with very few and generally slight side effects (usually in less than 10% of treated patients).

Because of these few side effects and its clinical efficacy, IVIg therapy has been also used in transient neonatal MG [49] and in juvenile MG (usually at 2 mg/kg in 3–5 daily administrations) with encouraging results [50–53].

In some of the studies reported in Table 1, anti-AChR antibody level before and after IVIg therapy were determined to tentatively explain clinical improvement. A decrease in anti-AChR antibody levels after therapy was found by some authors [32, 43, 46, 54–56] and not by others [47, 48, 57–60]. However, when observed, the decrease in anti-AChR antibody level was found in different percentages (20%–80%) of patients, usually between 15 and 30 days after starting IVIg, without a constant correlation with the observed clinical improvement.

IVIg doses in therapy for MG

IVIg are composed of intact IgG with a distribution of subclasses corresponding to that of normal serum (according to the requirements of the World Health Organization [6]) and a half-life of approximately 18-32 days, which is similar to that of native immunoglobulin. On the basis of kinetic studies, after intravenous infusion of 2 g/kg IVIg, serum IgG level increases about 4- to 5-fold, and then decreases by 50% over 3 days (due to an extravascular redistribution) and returns to the pretreatment level within 4 weeks [62]. IVIg can reach every tissue compartment including muscles and cerebrospinal fluid (CSF), but with different kinetics from serum (for example, during the first 48 hours of infusion, when the IgG serum level is four times normal value, the concentration of IgG in the CSF increases about two-fold, returning to normal values within one week).

Several paradigms of IVIg infusion have been reported in the literature. In the first clinical report of immunomodulation by IVIg [63], a dose of 0.4 g/kg body weight was administered over five consecutive days, for a total of 2 g/kg. Other authors have used a total of 50 g [48] or 120-180 g over 3 weeks [42]. The 0.4 g/kg day for 5 days protocol has been the most frequently used paradigm of IVIg infusion in MG patients, and it is thus considered to be the "standard" protocol. Although the total dose of IVIg for infusion (2 g/kg) is usually divided into five daily doses of 0.4 g/kg each, the preference now is to divide the total dose into two daily doses of 1 g/kg each, with no increase in side effects if the infusion rate is kept lower than 200 ml/h. Considering the rapid drug diffusion into the extravascular space, achieving a high serum concentration of IgG within 2 days may enhance its efficacy, as demonstrated by clinical studies on children with Kawasaki's syndrome [64], neuromuscular disease [65, 66] and in vitro experimental studies [67, 68]. For chronic diseases (including MG) there is no consensus about maintenance therapy, but probably the regimen has to be adjusted individually [69]. Because of the possibility of adverse reactions, it is recommended to start the infusion at approximately 30 ml/h for the first 15 min and increase the flow slowly up to 120-150 ml/h after 30 min. In case of adverse reactions, it is usually sufficient to stop the infusion or to reduce the infusion rate and wait until the reaction subsides. The infusion may then be restarted at a lower rate.

Precautions for use and side effects of IVIg in MG treatment

The increasing interest for this form of treatment is, without any doubt, greatly sustained by the almost total absence of significant side effects, unusual feature for an effective immunosuppressive therapy. Improved chemical procedures have abolished the severe anaphylactic reactions observed

before the 1970s after intravenous use [70, 71], and the only serious side effect reported was the transmission of non-A, non-B hepatitis in 12 of 24 agammaglobulinemic patients all treated with the same IVIg preparation [72]. Other IVIg preparations currently available have not been associated with transmission of HIV, hepatitis B (HBV) or non-A, non-B hepatitis [73], but careful monitoring of recipients is recommended. It is of interest (and not explained) that there were some episodes of hepatitis B contamination, but no confirmed reports of hepatitis C (HCV) transmission by intramuscular immunoglobulin administration. Actually, three methods are used for ensuring safety from infections: the restrictive choice of donor, the precise introductory screening of every individual blood or plasma donation, and the additional virus inactivation procedures (treatment with solvents, detergents or enzymes, incubation at low pH, and pasteurization) that surpass the virus elimination of the Cohn-fractionation method. While the elimination rates of HIV and HBV appear to be sufficient, the reduction in HCV is distinctly lower. Still some patients showed a transient rise in serum alanine transferase followed by an increase of total serum IgM [74]. This evidence could be related to contaminating viruses in IVIg, although HIV, HCV, HBV and hepatitis A virus (HAV) markers were not found.

The most important recommendation for the safe use of IVIg therapy in MG patients is to screen for IgA deficiency in all patients. IgA in deficiency is common, particularly in association with autoimmune diseases; these patients are at risk of developing IgA autoantibodies if exposed to IgA and may have severe anaphylactic reactions subsequently [75, 76]. A slow rate of infusion is advisable in MG patients with congestive heart failure to avoid acute pulmonary edema.

In general, side effects from IVIg therapy occur in about 5%–10% of MG patients and are similar to those reported in other autoimmune disorders. Most of these reactions are mild and self-limited. Probably the most frequent side effect is headache, usually responding to acetaminophen or codeine. This side effect can be usually of two types. The first has been described as an aseptic meningitis, because of the moderate lymphocytosis found in CSF of some of these patients; this headache is self-limited, resolves after several days, is presumed to be the result of a hypersensitivity to plasma-derived protein products and appears unrelated to infusion rate or to the proprietary product [62]. Other patients, with a history of migraine, may develop severe migraine headache associated with IVIg infusions; this headache usually is not associated with CSF pleocytosis and begins 72 hours after starting IVIg but may be seen during or immediately after the infusion in patients who receive a single 1 g/kg infusion [77]. Other more frequently described benign side effects are: flu-like syndrome and/or fever, nausea and vomiting, flushing, pallor and malaise, worsening of preexisting pedal edema or hypertension, mild dyspnea, chills, myalgia and chest discomfort which usually respond to stopping the infusion for 30 minutes and resuming it at a slower rate [14, 17, 23, 28, 45, 70, 73, 78]. These side effects occur within 12–24 hours after infusion and are mild and transient, lasting a few hours [73]. Activation of complement by aggregated IgG molecules or various stabilizing agent used in the IVIg preparation has been implicated in these side effects [79]. More rare side effects are skin reactions (urticaria, lichenoid cutaneous lesions, petechiae and alopecia), developing 2–5 day after starting the infusion and lasting up to 1 month [33]. Furthermore IVIg therapy causes an increase in serum viscosity, especially in patients with already elevated serum viscosity, such as those with cryoglobulinemia, hypercholesterolemia or hypergammaglobulinemia: the higher the serum viscosity, the greater the risk for thromboembolic events, such as stroke and pulmonary embolism anecdotally reported after IVIg treatment [80, 81]. Acute renal tubular necrosis occurs rarely with IVIg therapy in patients who have pre-existing kidney disease and/or volume depletion, especially the elderly and those with diabetes or poor hydration [82, 83]. IVIg-related nephropathy is usually associated with marked increase in serum creatinine. This complication was associated with a high concentration of sucrose in one proprietary IVIg product [84]. Diluting the IVIg preparation and slowing the rate of infusion minimize the risk.

Allergic reactions toward some plasma-derived protein products or some stabilizing agents used in the IVIg preparation are rare. In cases of known hypersensitivity reactions, it is recommended to administer 1–2 mg/kg hydrocortisone intravenously approximately 30 min before IVIg infusion [85]. Finally, it must be noted that, because of the glucose contained in some IVIg preparations, blood sugar should be measured in diabetic patients [86].

The only major drawback of IVIg use (but approximately comparable to that occurring with PE) is the high cost of purified IgG (about € 3.00–3.50 per treatment, at 0.4 g/kg for a 70-kg person), associated to the short-lasting effect. The high cost may induce hospital pharmacies to choose the cheapest IVIg preparation without consultation with the clinician caring for patients. Products vary substantially in content of immunoglobulins and complement activating properties, and in the rate of generating minor adverse reactions [71]. Clinicians ought to have the possibility of choosing the best products.

Mechanisms of action of IVIg in MG

In neurological diseases, the beneficial effect of IVIg has been ascribed to a wide variety of effects on the immune system. Such mechanisms often act synergistically and some of them may prevail for an individual disease, according to the underlying immunopathological process. The most impor-

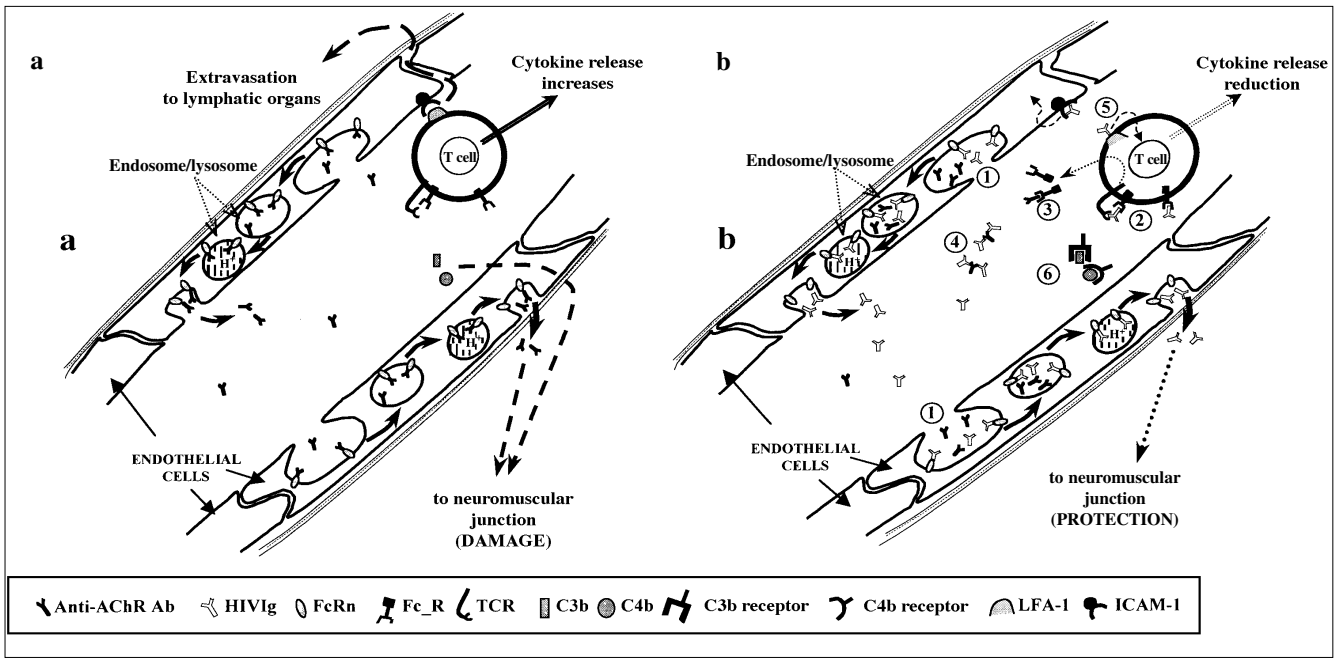

Fig. 2a, b *Mechanisms of action of IVIg operating at the vascular level in MG*. **a** Situation prior to therapy. **b** Therapeutic action of IVIg. *1*, Endothelial FcRn saturation by IVIg increases the FcRn-unbound anti-AChR antibody lysosomic catabolic pathway and IVIg extravasation; *2*, Specific (by TCR) or aspecific (by FcγR alone) interactions of IVIg with FcγR of T cells reduce cytokine secretion and B cell activation; *3*, Aspecific (by FcγR alone) interaction of IVIg with FcγR of T cells increases secretion of soluble FcγR that block anti-AChR antibodies; *4*, Idiotypic-anti-idiotypic interaction-dependent immune complex formation between anti-AChR antibodies and IVIg increases anti-AChR antibody clearance; *5*, IVIg-dependent ICAM-1/LFA-1 downregulation reduces extravasation of autoreactive lymphocytes to their target organs; *6*, Specific C3b/C4b receptors present in IVIg block complement activated molecules, reducing their levels at the neuromuscular junction

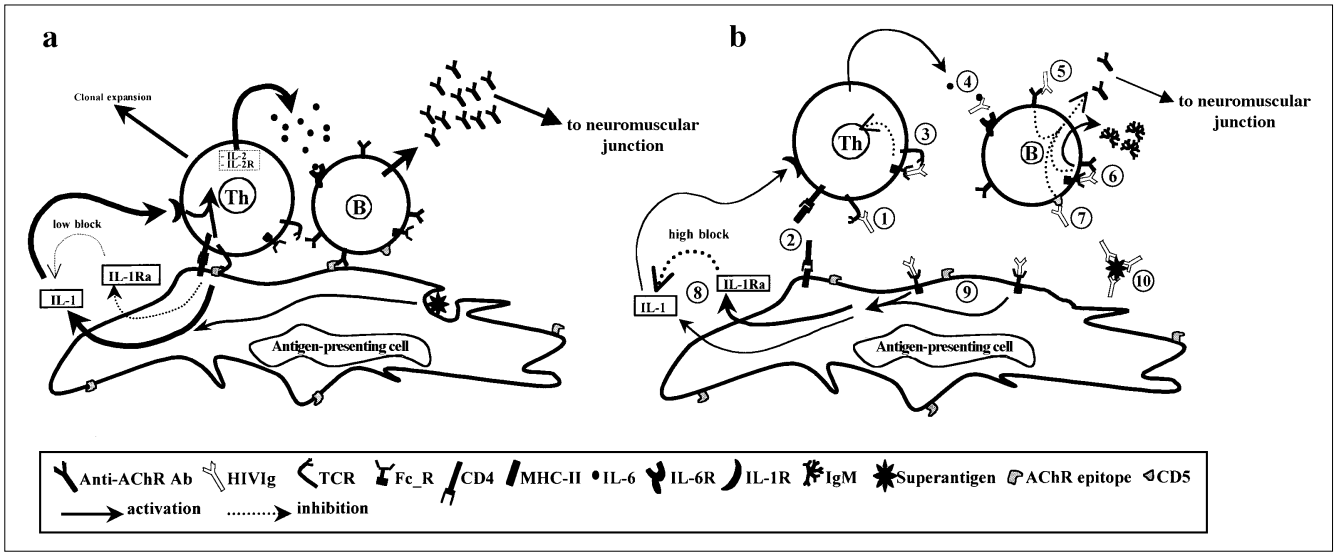

Fig. 3a, b *Mechanisms of action of IVIg operating at the lymphatic organ level in MG.* **a** Situation prior to therapy. **b** Therapeutic action of IVIg. *1*, Exogenous anti-idiotypic IgG interact with TCR, decreasing the antigen-dependent autoreactive T cell activation; *2*, Blockade of CD4 or of MHC-II by, respectively, soluble MHC-II or CD4 molecules in IVIg decreases T cell activation; *3*, Anti-idiotypic interaction of IVIg with TCR and FcγR of T cells reduces the ability of autoreactive T cells to produce IL-6; *4*, Anti-IL-6 antibodies in IVIg block IL-6/IL-6R binding, reducing the activity of a most important costimulating factor for B cells; *5*, Exogenous anti-idiotypic IgG interact with surface anti-AChR antibodies on B cells, decreasing autoantibody production; *6*, Anti-idiotypic interactions of IVIg with FcγR of B cells decrease anti-AChR antibody production and increase polyclonal IgM secretion; *7*, Anti-CD5 antibodies in IVIg reduce the activity of autoantibody-producing CD20 subset of B cells; *8*, Anti-IL-1 antibodies in IVIg and the increase in APC-dependent IL-1Ra secretion reduce the costimulating IL-1 activity for T cells; *9*, Aspecific (by FcγR alone) interactions of IVIg with FcγR of APC reduce IL-1 and increase IL-1Ra secretion; *10*, Anti-superantigen antibodies in IVIg intercept superantigen presentation to APC, decreasing aspecific T cell activation

tant effects of IVIg therapy in MG can schematically be divided into mechanisms principally working just at the neuromuscular junction level (Fig. 1) and those working extrajunctionally (at intravascular and lymphatic organ levels, Figs. 2, 3). In addition, many of the immunological effects of IVIg simultaneously work both at junctional and extrajunctional levels.

Mechanisms operating at the neuromuscular junction level

Anti-AChR antibody activity decrease by idiotypic-anti-idiotypic interactions

The F(ab') portion of immunoglobulin contains, on its hypervariable domains, many antigenic determinants (idiotopes): the entire repertoire of these idiotopes defines the idiotype [87, 88], detectable using monoclonal anti-idiotypic antibodies. Analogous idiotypic determinants are also expressed on T and B cells [89], and autoantibodies specifically reacting with several idiotypes have been demonstrated in sera of normal people. According to this evidence, Jerne [90] in 1974 proposed that lymphocytes and their immunoglobulin products are in a dynamic equilibrium regulated by a network of idiotypes and anti-idiotypes. In addition to this regulatory effect on antibody synthesis, anti-idiotypic antibodies may specifically reduce antibody activity through a direct F(ab')-mediated interaction with idiotopes of circulating immunoglobulins, disturbing antigen-antibody links with a rapid decrease in the avidity of binding or with the inhibition of binding [91]. In fact, IVIg treatment can neutralize circulating pathogenic antibodies in vivo [15, 92]. This effect has been also demonstrated in vitro for systemic lupus erythematosus patients in whom anti-idiotypic antibodies specifically suppress the binding of anti-DNA antibodies to DNA [93]. For these reasons, one of the most important functions of anti-idiotypic antibodies seems to be the peripheral immune surveillance with control of autoantibodies activity and of autoreactive lymphocyte clones.

Because anti-idiotypic antibodies are a natural component of human serum, IVIg preparations, derived from a large pool of human donors, contain a wide range of antibodies and anti-idiotypic antibodies against the naturally occurring proteins and their autoantibodies (for example, anti-AChR antibodies). These idiotypic-anti-idiotypic antibodies, in contrast to the monomeric IgG from a single donor, can form complexes of dimeric pairs. In fact, electron microscopy has shown that IVIg preparations contain 40% dimers formed by double-arm or single-arm binding between the $F(ab')_2$ domains of the IgG molecules [94]: the larger the pool of donors, the higher the number of these dimers and the wider the expected spectrum of idiotypic-anti-idiotypic specificities [95].

The presence of such anti-idiotypic IgG against autoantibodies has been suggested in pseudohemophilic patients with autoantibodies to factor VIIIc [13] and in patients with chronic inflammatory demyelinating polyneuropathy with antibodies to a neuroblastoma cell line [96]. In both cases in vitro incubation of purified IgG or $F(ab')_2$ fragment obtained from the IVIg preparation with purified IgG or $F(ab')_2$ fragment obtained from patients' serum resulted in similar inhibition of the pathologic activity of their autoantibodies, suggesting a direct F(ab')-mediated IgG interaction, i.e. an idiotypic interaction. Moreover, the rapid decrease of autoantibody activity demonstrated in vivo in these cases is also in agreement with the quite instantaneous idiotypic-anti-idiotypic interaction. This interaction has been then directly demonstrated by the evidence that autoantibodies were specifically retained on affinity chromatography columns of IVIg or of their F(ab') fragments [97]. These indirect and direct interactions between IVIg treatment and autoantibodies, supposed or demonstrated for some autoimmune diseases, are probably operating in several antibody-mediated autoimmune diseases (such as MG, Lambert-Eaton myasthenic syndrome, and some neuropathies with antibodies against MAG, glycolipid, or GM_1) [33], because the anti-idiotypic antibodies, cooperating with the immune surveillance, are directed against widely diffused public regulatory idiotopes, making IVIg-unresponsive patients quite rare. An analogy can be made between the recovery from autoimmune diseases due to IVIg treatment and the spontaneous remission from autoimmune diseases which occurs in association with the generation of auto-anti-idiotypic antibodies against prerecovery autoantibodies. Anti-idiotypic antibodies against autoantibodies have been found in remission sera of patients with myasthenia gravis [98], Guillain-Barré syndrome [18], systemic ANCA-positive vasculitis [99], systemic lupus erythematosus [100] and anti-factor VIII autoimmune disease [101].

When IVIg therapy is administered MG patients, anti-idiotypic antibodies against anti-AChR antibodies, present in exogenous IgG, bind by dimerization to idiotopes of circulating pathogenic anti-AChR autoAb, neutralize their functional activity, and prevent their interaction with the AChR at the end-plates, leading to an increase in AChR number [31, 56]. On the other hand, in an in vitro study of 30 samples of MG serum, IVIg interacted with AChR antibodies, inhibiting their activity in a dose-dependent manner up to 30% of the preincubation level [102].

We have recently studied 27 MG patients treated with IVIg (0.4 g/kg day for 5 days) (unpublished observations). We observed a significant clinical improvement in 22 patients, starting in about 18% of patients between 3 and 5 days and in another 62% of patients between 6 and 15 days after IVIg. To verify the hypothesis that clinical improvement was related to a decrease in avidity of anti-AChR antibodies for to AChR, we analyzed the binding kinetics of these antibodies at baseline and after IVIg therapy. A modified anti-AChR antibody assay (using a standard calibration curve and *Staphylococcus aureus* protein A as immunoprecipitating agent because its short incubation time) was indispensable in performing these kinetic studies [103, 104]. We extrapolated from these binding curves the $T_{1/2}$ value, an indirect measure of binding avidity [103] (unpublished observations). $T_{1/2}$ corresponds to the incubation time necessary for half of the total amount of antibodies to complex

with antigen; the lower the $T_{1/2}$ value, the higher the binding avidity. We found in IVIg-responding MG patients a significant early increase of anti-AChR antibody $T_{1/2}$ (i.e. a significant decrease of avidity) 5 and 10 days after starting therapy: this early decrease in avidity was related to the rapid initial clinical improvement. On the other hand, in patients who did not improve after IVIg therapy, there was no significant decrease of anti-AChR antibody avidity.

ACh-AChR interaction increase
Antibodies directed against the acetylcholine binding site on the AChR have been observed, at varying concentrations, in the serum of patients with MG. It is therefore possible that some anti-idiotypic IgG present in IVIg can bind to this anti-AChR blocking antibody, increase the binding of acetylcholine to its receptor and, thereby, stimulate neuromuscular transmission [60].

Reduction of complement binding to post-synaptic neuromuscular membrane
The decrease in binding affinity of anti-AChR antibodies to the receptor, related to anti-idiotypic antibodies present in IVIg, reduces this interaction at the neuromuscular junction and, thereby reduces C1 fixation at the post-synaptic membrane. Subsequently, the generation of C3b/C4b and of membranolytic attack complexes (MAC) is markedly reduced, as is complement-dependent damage of post-synaptic folds while AChR density at the neuromuscular junction increases. Moreover, IVIg forms covalent and non-covalent complexes between C3b/C4b molecules and specific antibodies or receptors in the infused IgG molecules [104], preventing the incorporation of C3 fragments into the C5 convertase assembly (up to 90% after two IVIg infusions) and promoting the dissociation of circulating immune complexes [67]. This IVIg effect on complement is probably relevant in diseases in which the complement pathway has an important pathogenic action, such as dermatomyositis, Guillain-Barré syndrome and MG. In MG pathogenesis, anti-AChR antibodies can fix complement, and MAC are present at the motor end-plates [105], suggesting that there is complement-mediated damage of postsynaptic membranes, with reduction of active AChR number. Complement seric levels have been investigated with variable results (Table 1). Many authors revealed a C3 increase in serum 3 weeks after starting IVIg [47] and a more rapid decrement of C3b and C4b [104, 106]; this evidence is in agreement with a probable reduction of complement consumption by IVIg. Even if a correlation between serum complement molecule levels and clinical improvement has never been demonstrated, there is evidence suggesting a "dramatic" clinical improvement in MG associated with a marked reduction of complement-activated molecules [106]. On the other hand, one paper reported no changes in antigenic concentrations of individual complement components or regulators just after IVIg infusion [107]. Moreover, the soluble Fc receptor for IgG, increased after IVIg infusion, can block the C1q site, reducing the fixation of C4 molecules to target membranes and, then, the complement cascade activation [108].

Reduction of antibody-dependent phagocytosis
During IVIg therapy, Fc receptors (FcγR) of inflamatory cells (e.g. macrophages) can become saturated and blocked from binding AChR antibodies present on postsynaptic membranes, reducing Fc-mediated phagocytosis of AChR-bearing end-plates. This mechanism of action of IVIg, demonstrated in some disease such as Guillain-Barré syndrome, is not likely to occur in MG because macrophages have been never found in the end-plate region [109].

Mechanisms operating at intravascular and lymphatic organ levels

Reduction of anti-AChR antibody synthesis
The antibody-mediated immune response usually depends on cooperation among antigen-presenting cells (APC), usually monocytes/macrophages, T helper lymphocytes (Th cells) and B lymphocytes (B cells). Schematically, Th cells recognize (via the T cell receptor, TCR), an antigen only presented by an APC in the context of major histocompatibility complex (MHC) class II products (MHC-II). Th cells, stimulated by this antigen-APC complex and by interleukin-1 (IL-1) released by APC, increase IL-2 receptor (IL-2R) expression and IL-2 release, which drives antigen-activated Th cells into proliferation and secretion of some interleukin molecules (according to Th1 or Th2 profile). B cells, clonally restricted to the same antigen recognized by Th cells, bind, via cell surface Ig, the APC-presented antigen. This binding and the T-cell-released interleukins are the specific stimuli that transform B cells into plasma cells, increasing their specific idiotype Ig secretion. On the other hand, the antibody-mediated immune response can be decreased by T suppressor lymphocytes (Ts cells), able to recognize, using the TCR-CD8 complex, an antigen presented by APC in the context of MHC class I products (MHC-I).

As described before, lymphocytes and their immunoglobulin products are in a dynamic equilibrium regulated by a network of idiotypes and anti-idiotypes. Serum antibodies plays a role in the regulation of the normal antibody response: IgG synthesis may terminate both IgM and IgG synthesis itself [110–112]. Both primary and secondary immune responses may be suppressed by large quantities of passively transferred antibodies [113]: in vivo inhibition of autoantibody production [114] and in vitro inhibition of pokeweed mitogen-stimulated antibody production [115–117] have been observed. This immune response suppression is highly specific (i.e. the immune response is downregulated only by a corresponding antigen), indicating a specific interaction between the $F(ab')_2$

of anti-idiotypic antibodies with the idiotype of surface Ig (for B cells) or TCR (for T cells), and an aspecific interaction between the Fc of anti-idiotypic antibodies with cell-surface FcR [111]. In fact, both Fc and $F(ab')_2$ fragments bring about effective suppression, while monovalent F(ab') fragments do not. This slow inhibition of anti-idiotype-mediated antibody synthesis has been postulated because serum autoantibody activity after IVIg therapy remains low, in certain patients, for a time longer than that expected from the clearance time of exogenous IgG [13]. Actually, antibody synthesis suppression by anti-idiotype does not always affect the overall level of antibodies despite the fact that the idiotype itself is largely inhibited [118]. Lymphocyte clones, not bearing that idiotype, expand to replace the idiotype-positive clones which are suppressed. In addition, anti-idiotypic antibodies may also have a stimulatory effect on B and T helper lymphocytes [119], with an increase in serum polyclonal IgM levels after IVIg infusion [77]. The latter effect and the high degree of specificity of the idiotypic interaction may explain why the clinical response to IVIg is not constant in all patients and probably varies from one IVIg preparation to another: IVIg preparations have variable anti-idiotypic compositions and may not always contain inhibitory cross-reacting antibodies.

Although the inhibition of anti-idiotypic antibody synthesis is theoretically well explained and supported by some experimental evidence, there are conflicting reports regarding anti-AChR antibody changes in sera of IVIg-treated MG patients. A decrease in anti-AChR antibody levels after IVIg treatment has been found by some authors [42, 46, 54–56], but not by others [32, 45, 47, 57, 120], perhaps, in part, dependent on the anti-AChR antibody assay used. In fact, the use of the "standard" amount of immunoprecipitating agent may be insufficient to precipitate all IgG, since the IgG level in IVIg-treated patients may be 3- to 4-times greater than normal [48]. The decrease in anti-AChR antibodies is generally seen between 15 and 30 day after the initiation of therapy, when total IgG level has already returned to baseline values [46]. In the 27 MG patients treated with IVIg [7], a significant decrement of anti-AChR antibodies from baseline level was observed at days 15–30, well correlating with more late clinical improvement of the patients. Although several reports demonstrated that clinical improvement is not related to circulating anti-AChR antibody level, it must be outlined that serum anti-AChR antibody level in MG does not reflect the intensity of the immune attack against the neuromuscular junction.

IVIg also contains antibodies to CD5 molecules, normally expressed on the autoantibody-producing CD20 subset of B cells, contributing to their functional inactivation and maintenance of self-tolerance [121], and explaining the peripheral anergy of autoreactive T lymphocytes after IVIg infusion [122]. In addition, IVIg therapy induces transient lymphopenia [123] and downregulates the expression of lymphocyte function-associated antigen-1 (LFA-1) on activated T cells and of intercellular adhesion molecules (such as ICAM-1) on endothelial cells [124], reducing lymphocyte extravasation towards their target organ.

Modification of serum complement level

As reported before, specific receptor sites in IgG molecules can form complexes with serum C3b and C4b, reducing seric complement activities [104] and increasing seric levels of intact complement molecules, such as C3. Moreover, the binding of infused IgG to lymphomonocytic FcγR increases the release of soluble FcγR (sFcγR), which is able to neutralize autoantibodies or immune complexes by preventing their binding to membranes [108].

Suppression of pathogenic cytokines

IVIg preparations contain specific, high-affinity antibodies against interleukins (IL-la and IL-6) and tumor necrosis factor (TNF-α) able to neutralize these circulating cytokines and to increase their clearances, reducing or suppressing the immune response (even if an increase in IL-6 after IVIg was reported in idiopathic thrombocytopenic purpura) [66]. Moreover, in vivo and in vitro studies showed that IVIg produces a dose-dependent decrease of synthesis and release of TNF-α and IL-1β, and an increase of IL-1 receptor antagonist (IL-1Ra) release [125] from monocytes (explaining the acute anti-inflammatory effect of IVIg therapy). These effects are probably related to an anti-idiotypic anti-cytokine or anti-cytokine-receptor activity.

Reduction of superantigen-induced immune system activation

Superantigens may be responsible for disrupting self-tolerance and for triggering the activation and polyclonal expansion of cytotoxic T cells. In Kawasaki's disease, antibodies in IVIg preparations neutralized epitopes of superantigens able to counteract their pathologic activity [126]. This mechanism of action may also be important in MG patients, because superantigen is able to trigger a MG crisis, such as the relapses seen after infections. Anti-superantigen antibodies present in IVIg antagonizing superantigen presentation to APC can inhibit T cell activation and decrease the aspecific activation of the immune system, including anti-AChR specific Th and B cell subsets.

Competition for antigen recognition

The glycoproteins CD4 and CD8, expressed on helper and suppressor/cytotoxic T cells, are the physiological ligands for MHC-II and MHC-I molecules, respectively. Some IVIg preparations contain high levels of soluble CD4 and MHC-II molecules [127]. In MG patients, soluble CD4 molecules present in IVIg can interfere with the MHC-II system on the surface of APC, reducing the activity of anti-AChR autoimmune T and B cells. The same disturbing effect on CD4-MHC-II interaction can result for soluble MHC-II molecules present in IVIg.

Inhibition of suppressor T cell function

IVIg preparations contain antibodies against a conserved region of MHC-I [128]. These infused antibodies may interfere with MHC-I-CD8 interactions and, thereby, inhibit suppressor T cell function. Such effect can aspecifically and rapidly increase immune system activity and, subsequently, the anti-AChR antibody level, as described in some reports during the first days of IVIg therapy [45, 46].

Modulation of IgG Fc-related cell functions

The interactions between Fc fragment of exogenous IgG and FcγR can be specific or aspecific, and can involve APC (usually monocytes/macrophages), lymphocytes, or endothelial cells.

The modulatory effects of IVIg may depend on the specific binding with circulating IgG or antigen receptors on lymphocytes through variable regions (a specific idiotype-anti-idiotype interaction) and FcγR, as discussed before.

IVIg preparations can also act as immunomodulating agents, interacting with inflammatory cells and lymphocytes through their FcγR alone (an aspecific interaction). This interaction leads to the crosslinking of receptors, with an increase in IgG endocytosis, antigen presentation, phagocytosis, and antibody-dependent cellular cytotoxicity (ADCC) [129]. This aspecific IVIg-dependent blockade of FcγR on inflammatory cells is a possible mechanism for ameliorating the cytopenia of idiopathic thrombocytopenic purpura and the destruction of myelin in Guillain-Barré syndrome [130], but it is unlikely to explain its rapid effect in other autoimmune disease such as MG, in which the IgG-dependent damage of post-synaptic folds is independent of FcγR-bearing effector cells.

The aspecific IVIg-dependent blockade of FcγR on lymphocytes can be an important mechanism in MG by the negative feedback of Th-cell-dependent cytokine release and B-cell-dependent antibody secretion [131]. This aspecific lymphomonocyte IgG-FcγR link has been demonstrated to increase cellular secretion of soluble FcγR (sFcγR), which blocks in vitro IgG production, downregulating local autoantibody production [108]. Three major classes of leukocyte FcγR (differing in molecular size, cell distribution, and IgG affinity) have been recognized: the exclusive distribution of high affinity FcγR (FcγR type I, CD64) on monocytes and macrophages can explain why the aspecific FcR-dependent mechanism of action of IVIg principally involves these cells; this can be the most important mechanism when monocytes or macrophages form the pathogenetic basis of the disease, as in idiopathic thrombocytopenic purpura (ITP) and Guillain-Barré syndrome (GBS). The action via this aspecific macrophagic Fc-mediated pathogenic mechanism can explain a more pronounced efficacy of this therapy in some diseases (such as ITP and GBS) than in others less dependent on a macrophagic Fc-mediated pathogenic mechanism (such as MG).

In in vivo and in vitro studies, acceleration of the catabolic pathway of IgG contributed to the beneficial action of IVIg in antibody-mediated autoimmune disorders. One of the most important IgG catabolic pathways involves a specialized intracellular Fc receptor, FcRn, found in many adult tissues, mainly in vascular endothelial cells, suggesting that these cells are a major site of IgG catabolism [132]. The function of FcRn is to bind pinocytosed IgGs only in the acidic environment of the endosome, preventing IgG transfer to lysosomes and subsequent degradation. The FcRn (so called from "FcR of the neonate", where it was initially identified) has a beta2-microglobulin molecule as a critical subunit. For this reason, mutant mice lacking beta2-microglobulin have low serum IgG levels. The saturation of FcRn in states of endogenous or exogenous (i.e. during IVIg therapy) hypergammaglobulinemia accelerates IgG catabolism, also including IgG autoantibodies whenever detectable in serum. Glucocorticoids, downregulating the expression of FcRn messenger RNA [133], increase the clearance of autoatibodies. This may explain the positive synergic effect of IVIg-corticosteroid combined therapy [47].

Guidelines for the correct use of IVIg in MG

IVIg is a safe and effective adjunctive treatment for MG, but there are no established guidelines for the use of IVIg in MG, due to the lack of controlled randomized trials assessing its efficacy in a homogeneous group of MG patients. The main advantages of IVIg are the rapid onset of the effect, the lack of long-term toxicity, and the possibility to reduce the required doses of immunosuppressive drugs.

IVIg appears to have a role as an acute treatment in rapidly progressive MG weakness (as a bridging treatment in the period before the effects of corticosteroid or azathioprine become apparent) and in the treatment of acutely worsening disease for which rapid improvement in strength is necessary to minimize the risk for bulbar or respiratory failure (for example, before thymectomy), particularly in situations in which therapeutic apheresis is not feasible. IVIg therapy induces a lower clinical response than PE, but it is more easily administered and does not require specialized personnel and equipment. For these advantages IVIg therapy can be more easily and rapidly started. Furthermore, since the placement of a central venous catheter is not necessary, no plasma proteins or administered drugs are removed, and the blood volume is not reduced, IVIg is safer than PE in patients with hypotension or autonomic instability, in children, in elderly patients (>65 years), and in those suffering from sepsis. For these reasons, at the present, IVIg therapy is recommended during MG crises in older patients when PE is contraindicated or not feasible.

IVIg can be also used as a chronic maintenance therapy when other immunosuppressive treatments have failed or cannot be used. Periodic administration of IVIg on a bimonthly or monthly basis may stabilize chronically nonresponding patients.

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