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IVIg in myasthenia gravis, Lambert Eaton myasthenic syndrome and inflammatory myopathies: current status

Abstract Intravenous immunoglobulin (IVIg) is an effective tool for the treatment of diseases with immune pathogenesis. This article reviews the current knowledge of the benefits of treating with IVIg patients with myasthenia gravis (MG), Lambert Eaton myasthenic syndrome (LEMS), dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM).

Myasthenia gravis Treatment of MG with IVIg was reported to be beneficial in a number of case series and two randomised controlled trials, in which efficacy was measured by clinical improvement using myasthenic muscle score and decrease in anti-acetylcholine receptor antibodies (AchRAb). According to the results, IVIg could be recommended for crisis and severe exacerbation. In many other clinical conditions, such as response to treatment of mild or moderate exacerbation, changes in steroid dosage and before thymectomy, IVIg has also been reported to be helpful, but no controlled trials to confirm its efficacy have been performed.

Lambert-Eaton myasthenic syndrome A placebo-controlled crossover study reported a significant clinical improvement in the amplitude of the resting CMAP following IVIg treatment. Further experience from case reports also indicates that IVIg is useful in patients with LEMS, both as a short- and long-term treatment, especially when immunosuppressive drugs are not fully effective.

Inflammatory myopathies/Dermatomyositis: In a double-blind placebo-controlled crossover trial in patients with DM resistant to other treatments, IVIg was shown to produce a significant increase of muscle strength as well as a marked improvement in immunopathological parameters in repeated muscle biopsies (before and after IVIg). Thus, IVIg is an important therapy in patients with DM resistant to other conventional therapies.

Polymyositis: No randomised trials have been undertaken. One study showed clinical improvement and a reduction in the need of prednisone in patients with chronic refractory PM.

Inclusion body myositis: Three controlled trials showed some muscle strength improvement, although the changes did not reach statistical significance. However improvement in swallowing was repeatedly observed, suggesting that some patients with severe dysphagia may derive a modest benefit from IVIg therapy.

Conclusion Controlled trials indicate that in MG, LEMS, and DM, IVIg at a total dose of 2 g/kg is a highly useful therapy. Uncontrolled trials and case reports indicate benefit in many different clinical situations, but further clinical investigation is required.

Key words IVIg · myasthenia · Lambert Eaton syndrome · inflammatory myopathies

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Introduction

The pathogenesis of the neuromuscular junction disorders myasthenia gravis (MG) [26, 42] and Lambert Eaton myasthenic syndrome (LEMS) [28, 33], as well as of the inflammatory myopathies (IM), dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM) [13] is considered to be autoimmune, either antibody or T cell mediated.

Different immunotherapies have been proven useful in the treatment of these neuromuscular diseases.

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Among the new therapies, intravenous immunoglobulin (IVIg) has been reported as effective in very different clinical situations, from myasthenia crisis to patients non-responsive as other immunosuppressive treatments. This article summarises the current knowledge in the use of IVIg in MG, LEMS and IM based on the different controlled or uncontrolled clinical trials. Furthermore, this review covers a number of published case series that have very few patients as the diseases are not prevalent.

Myasthenia gravis

MG is an autoimmune disease characterised by weakness and fatigability of the voluntary muscles [19]. The disease is clinically and immunologically heterogeneous. In 80–90 % of patients, IgG autoantibodies to nicotinic acetylcholine receptor (anti-AchRAb) are detectable in peripheral blood. These anti-AchRAb cause loss of functional receptors by different known mechanisms (complement-mediated lysis, cross-linking and block of the Ach receptor). Recently, antibodies to a second neuromuscular junction antigen, MuSK, have been identified in a group of previously "seronegative" MG patients [25, 41]. The action of the anti-MuSK antibodies is not fully understood, although it is thought that they reduce clustering of Ach receptors at the neuromuscular junction. Treatment of MG includes thymectomy, steroids, immunosuppressive agents and plasma exchange [20, 24, 31, 34].

In 1997, Gadjos et al. published the first randomised controlled trial of IVIg in patients with MG [22]. The study included 87 patients with clinical exacerbation of the MG and the authors compared the results of three courses of plasma exchange (PE) with the results obtained with IVIg given for 3 or 5 days at a total dose of 0.4 g/kg/day. The study demonstrated that both treatments were efficacious in a similar way, as measured by changes in MG muscle score or the antibody titre decrease. The rate of complications was lower in the IVIg group. In 1999, a retrospective multicentre chart review [36] compared PE and IVIg in the treatment of MG crisis. The authors reviewed 54 episodes and their conclusion was that PE (5–6 exchanges) was associated with a superior ventilatory status at 2 weeks and 1 month functional outcome than IVIg (0.4 g/kg/day/5 days). However, the complication rate was higher with PE compared with IVIg. Another controlled study compared IVIg versus PE in patients with chronic moderate to severe MG in a stable phase [38]. The study included 12 patients who were evaluated clinically using a quantified MG clinical score. The conclusion of the study was that both treatments had a clinical effect after 4 weeks, but the improvement was more rapid in this group of chronic MG patients after plasma exchange than after IVIg. Other publications of randomised, case series or open studies [3, 8, 21, 44] also indicate the usefulness of IVIg in different clinical situations, although none of these studies reached statistical significance. In 2001, it was reported [35] that there was a comparable efficacy between IVIg and plasmapheresis in the peri-operative period of MG. The study compared a prospective group of 33 patients treated with IVIg (2 g/kg) with a historical group of 38 patients treated with PE. As a final point, the efficacy of IVIg as a maintenance therapy has also been claimed [1] in 10 patients with severe generalised myasthenia and an acute deterioration, non-responsive to other immunosuppressive drugs.

In summary, according to published evidence, IVIg is recommended for patients with clinical exacerbation or crisis that is poorly controlled with other drugs. There is no sufficient placebo-controlled evidence for this recommendation in all the other different clinical situations [23], such as covering the initiation of corticosteroids treatment, sparing effect on steroid dosage or before thymectomy, amongst others. However, IVIg may be helpful on an individual basis, based on the findings of various uncontrolled studies and through my own personal experience.

In patients with seronegative MG and antibodies to MuSK, there are descriptions about the response to immunosuppressive agents [20, 37], but no specific studies about the response to IVIg in this particular group of MG patients. In fact, a negative antibody titre to AchR was an exclusion criteria in the published trials (reviewed above).

Lambert Eaton myasthenic syndrome

LEMS is an autoimmune disease mediated by antibodies to the presynaptic voltage-gated calcium channels at motor nerve terminals (VGCC). The antibodies are responsible for the physiological abnormality in LEMS, in which there is a decrease of the voltage-dependent influx of Ca^{++}, with a consequent reduction in quantal release that results in muscle weakness. In approximately 60 % of patients, the disease is paraneoplastic, most commonly small-cell carcinoma of the lung. The most common symptoms of patients with LEMS are proximal weakness, predominantly in the lower limbs, depressed tendon reflexes, autonomic dysfunction and extraocular muscle involvement [27]. Therapy for LEMS includes 3–4 diaminopyridine and immunosuppressive agents, such as prednisolone, azathioprine or cyclosporine [30, 39].

In 1992, the first report of clinical improvement after IVIg was published [5]. It was a single case. In 1996, Bain et al. [4] published a randomised double-blind placebo controlled crossover trial in 9 patients. Patients received either 1 g/kg/day of IVIg for 2 days, or albumin. There

was a significant improvement in the limb strength (myometric strength measures) with a peak at 2–4 weeks and a decline after 6 weeks. The clinical improvement was associated with a decline in serum VGCC antibodies. There are also other reports that have been published [32, 40] showing short- or long-term benefit from IVIg in LEMS patients.

The results of the single placebo-controlled study, plus a number of single cases published, demonstrate that IVIg is useful in the treatment of LEMS patients, especially as adjuvant therapy in patients with resistant muscle weakness to other therapies.

Inflammatory myopathies

The three main types of inflammatory myopathies, polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) are the largest group of the immune-mediated myopathies [9, 14]. They are characterised by proximal weakness and inflammation in the muscle biopsy. For an accurate diagnosis of this heterogeneous group of diseases, the muscle biopsy is essential, showing in PM and IBM endomysial infiltrates of $CD8^+$ T cells invading non-necrotic MHC-class I muscle fibres and in DM, perifascicular atrophy and a complement-mediated depletion of endomysial capillaries. These immunopathological findings lead to the hypothesis that different mechanisms are involved in these inflammatory myopathies. Whereas PM and IBM are due to an MHC-I restricted cytotoxic T cell response to non-identified muscle fibre antigens, DM is considered a humorally mediated microangiopathy. Based on the evidence that these diseases have an autoimmune origin, patients are treated with immunosuppressive agents or immunomodulation [12]. An antigen-specific immunotherapy would not be available until the antigenic targets for DM, PM and IBM are known. IVIg controlled trials have been done in DM and IBM, but not in PM [10].

Dermatomyositis

The clinical feature that characterises this entity is the presence of skin lesions that start with, or even precede, muscle weakness. In addition to a proximal and symmetric muscle weakness, patients develop a heliotrope-like colour rash in the upper eyelids, or a purple and erythematous discoloration on the face, upper trunk, knuckles and joints. The predominant immune response in DM appears to be humoral, directed against non-identified antigens in the muscle microvasculature, probably components of the vascular endothelium, as shown by light, electron microscopy and immunohistological studies. Immunocomplexes and deposits of C5b-9, the membranolytic attack complex (MAC) of the complement pathway, are detected on the endomysial capillaries early in the disease and before inflammatory changes in the muscle fibres take place. This stage is followed by necrosis of the capillaries, microvascular depletion, and impaired muscle perfusion. The noted perifascicular atrophy in DM is a reflection of the hypoperfusion [13].

IVIg therapy in patients with DM was demonstrated to produce a clinical and histopathological improvement in a double-blind placebo-controlled crossover trial [15]. The study was performed in 15 patients with DM resistant to other treatments. Patients received IVIg (2 g/kg) once a month for 3 months, or placebo. Clinical response was monitored by assessing the muscle strength and changes in the rash. Nine of twelve patients treated with IVIg had significant improvement, compared with none of the eleven patients in the placebo group. Changes in immune-mediated muscle abnormalities were determined by repeated muscle biopsies. The immunohistological parameters that normalised in the muscle biopsy of five patients whose strength improved were the following: a statistically significant increase in muscle-fibre diameter, an increase in the number and a decrease in the diameter of capillaries, and a resolution of complement deposits on capillaries, as well as a reduction in the expression of intercellular adhesion molecule 1 and major-histocompatibility-complex class I antigens [13]. IVIg is therefore an established therapy in patients with DM resistant to immunotherapies.

Other studies further confirm the efficacy of IVIg in DM, although they are not randomised. For instance, a retrospective study in a group of eighteen patients with juvenile DM showed that most steroid-dependent or -resistant patients were able to reduce the dose of corticosteroids with the addition of IVIg [2]. Another open study suggested that combined treatment of immunosuppressive drugs and IVIg is useful in patients with dermatomyositis and polymyositis [18].

Polymyositis

PM is possibly the most infrequent of the inflammatory myopathies. It is best defined as a myopathy occurring in patients who do not have any of the following: cutaneous involvement, family history of neuromuscular disease, signs of endocrinopathy, inclusion body myositis or history of exposure to myotoxic drugs and toxins. In PM, the muscle injury appears to be T-cell mediated and directed against unknown antigens expressed on the sarcolemma of the muscle fibres. This conclusion is supported by the immunohistochemical findings of $CD8^+$ T cells and macrophages surrounding and invading MHC-I class-expressing non-necrotic muscle fibres. No microangiopathy is detected in PM.

There are no randomised trials in PM. However, there are a number of publications that show efficacy in PM patients treated with IVIg [6, 29]. The largest study is an open prospective study that included 35 patients with chronic refractory PM. Patients were treated with 1 g/kg/2 days for 4–6 months and the study controlled clinical improvement, changes in a disability scale and improvement in oesophageal disorders. The study concluded that 25 out of 35 patients improved. The finding that the dose of prednisone could be reduced by more than 50% in all patients favours the use of IVIg in this small group of PM patients resistant to other therapies [7].

Inclusion body myositis

IBM is the most common cause of acquired myopathy in patients over 50 years. The aetiology is not known, but several mechanisms have been proposed. Autoimmunity may play a role in the disease, since $CD8^+$ T cells are found in the muscle biopsies, together with an increased expression of MHC class I. These cells must recognise muscle antigens that are unknown to date [13]. Histologically, IBM is differentiated from other inflammatory myopathies in many parameters, one of the more common characteristics being the presence of rimmed vacuoles in the muscle fibres. However, IBM does not respond to treatment with immunosuppressive drugs [16].

Three different placebo-controlled crossover trials were performed in patients with IBM. One of them [17] included nineteen patients who received IVIg (2 g/kg) once a month for 3 months, or placebo. Muscle strength scores showed some improvement and, although they did not reach statistical significance, there does appear to be greater improvement in the use of the swallowing muscles. A second study with 22 patients showed similar results [43]. Finally, another study designed to determine if a combination of IVIg and prednisone had a synergistic effect was published [16]. Thirty-six patients were included and the conclusion of the study was that IVIg combined with prednisone, for a 3-month period was not effective in IBM. In spite of the negative trials, it has been suggested [11], based on clinical impression, that some IBM patients may have a clinical improvement in activities of daily living and should justify a 2–3 month trial with IVIg.

Conclusions

IVIg is a useful tool in the treatment of neuromuscular junction and muscle disorders for which there is evidence of an autoimmune pathogenesis. Based on controlled clinical trials, IVIg is useful in the management of severe MG and in the treatment of patients with LEMS and DM resistant to other therapies. Furthermore, IVIg may produce a modest benefit in dysphagia in patients with IBM. New studies are needed to fully demonstrate if the benefit reported in different clinical conditions in uncontrolled studies is not anecdotal, but clinically relevant.

References

1. Achiron A, Barak Y, Miron S, Sarova-Pinhas I (2000) Immunoglobulin treatment in refractory Myasthenia gravis. Muscle Nerve 23:551–555
2. Al-Mayouf SM, Laxer RM, Schneider R, Silverman ED, Feldman BM (2000) Intravenous immunoglobulin therapy for juvenile dermatomyositis: efficacy and safety. J Rheumatol 27:2498–2503
3. Arsura EL, Bick A, Brunner NG, Grob D (1988) Effects of repeated doses of intravenous immunoglobulin in myasthenia gravis. Am J Med Sci 295:438–443
4. Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, Vincent A, Lang B (1996) Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology 47:678–683
5. Bird SJ (1992) Clinical and electrophysiologic improvement in Lambert-Eaton syndrome with intravenous immunoglobulin therapy. Neurology 42:1422–1423
6. Cherin P, Herson S, Wechsler B, Piette JC, Bletry O, Coutellier A, Ziza JM, Godeau P (1991) Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. Am J Med 91: 162–168
7. Cherin P, Pelletier S, Teixeira A, Laforet P, Genereau T, Simon A, Maisonobe T, Eymard B, Herson S (2002) Results and long-term follow-up of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis Rheum 46:467–474
8. Cosi V, Lombardi M, Piccolo G, Erbetta A (1991) Treatment of myasthenia gravis with high-dose intravenous immunoglobulin. Acta Neurol Scand 84:81–84
9. Dalakas MC (1991) Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med 325:1487–1498
10. Dalakas MC (1998) Controlled studies with high-dose intravenous immunoglobulin in the treatment of dermatomyositis, inclusion body myositis, and polymyositis. Neurology 51:S37–S45
11. Dalakas MC (1999) Intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: present status and practical therapeutic guidelines. Muscle Nerve 22:1479–1497
12. Dalakas MC (2003) Therapeutic approaches in patients with inflammatory myopathies. Semin Neurol 23: 199–206

13. Dalakas MC (2004) The molecular pathophysiology in inflammatory myopathies. Rev Med Interne 25(Suppl 1):S14–S16
14. Dalakas MC, Hohlfeld R (2003) Polymyositis and dermatomyositis. Lancet 362:971–982
15. Dalakas MC, Illa I, Dambrosia JM, Soueidan SA, Stein DP, Otero C, Dinsmore ST, McCrosky S (1993) A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 329:1993–2000
16. Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E (2001) A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology 56:323–327
17. Dalakas MC, Sonies B, Dambrosia J, Sekul E, Cupler E, Sivakumar K (1997) Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology 48: 712–716
18. Danieli MG, Malcangi G, Palmieri C, Logullo F, Salvi A, Piani M, Danieli G (2002) Cyclosporin A and intravenous immunoglobulin treatment in polymyositis/dermatomyositis. Ann Rheum Dis 61:37–41
19. Drachman DB (1994) Myasthenia gravis. N Engl J Med 330:1797–1810
20. Drachman DB, Jones RJ, Brodsky RA (2003) Treatment of refractory myasthenia: "rebooting" with high-dose cyclophosphamide. Ann Neurol 53: 29–34
21. Fateh-Moghadam A, Wick M, Besinger U, Geursen RG (1984) High-dose intravenous gammaglobulin for myasthenia gravis. Lancet 1:848–849
22. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C (1997) Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol 41:789–796
23. Gajdos P, Chevret S, Toyka K (2003) Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev:CD002277
24. Gronseth GS, Barohn RJ (2000) Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 55:7–15
25. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A (2001) Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 7:365–368
26. Hughes BW, Moro De Casillas ML, Kaminski HJ (2004) Pathophysiology of myasthenia gravis. Semin Neurol 24:21–30
27. Lang B, Newsom-Davis J, Wray D, Vincent A, Murray N (1981) Autoimmune aetiology for myasthenic (Eaton-Lambert) syndrome. Lancet 2:224–226
28. Mareska M, Gutmann L (2004) Lambert-Eaton myasthenic syndrome. Semin Neurol 24:149–153
29. Mastaglia FL, Phillips BA, Zilko PJ (1998) Immunoglobulin therapy in inflammatory myopathies. J Neurol Neurosurg Psychiatry 65:107–110
30. McEvoy KM, Windebank AJ, Daube JR, Low PA (1989) 3.4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. N Engl J Med 321:1567–1571
31. Meriggioli MN, Ciafaloni E, Al-Hayk KA, Rowin J, Tucker-Lipscomb B, Massey JM, Sanders DB (2003) Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. Neurology 61: 1438–1440
32. Muchnik S, Losavio AS, Vidal A, Cura L, Mazia C (1997) Long-term follow-up of Lambert-Eaton syndrome treated with intravenous immunoglobulin. Muscle Nerve 20:674–678
33. Newsom-Davis J (2004) Lambert-Eaton myasthenic syndrome. Rev Neurol (Paris) 160:177–180
34. Palace J, Newsom-Davis J, Lecky B (1998) A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology 50:1778–1783
35. Perez Nellar J, Dominguez AM, Llorens-Figueroa JA, Ferra-Betancourt A, Pardo A, Quiala M, Gali Z (2001) A comparative study of intravenous immunoglobulin and plasmapheresis preoperatively in myasthenia. Rev Neurol 33:413–416
36. Qureshi AI, Choudhry MA, Akbar MS, Mohammad Y, Chua HC, Yahia AM, Ulatowski JA, Krendel DA, Leshner RT (1999) Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. Neurology 52:629–632
37. Richman DP, Agius MA (2003) Treatment of autoimmune myasthenia gravis. Neurology 61:1652–1661
38. Ronager J, Ravnborg M, Hermansen I, Vorstrup S (2001) Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artif Organs 25:967–973
39. Sanders DB, Massey JM, Sanders LL, Edwards LJ (2000) A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. Neurology 54:603–607
40. Takano H, Tanaka M, Koike R, Nagai H, Arakawa M, Tsuji S (1994) Effect of intravenous immunoglobulin in Lambert-Eaton myasthenic syndrome with small-cell lung cancer: correlation with the titer of anti-voltage-gated calcium channel antibody. Muscle Nerve 17:1073–1075
41. Vincent A, Bowen J, Newsom-Davis J, McConville J (2003) Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. Lancet Neurol 2:99–106
42. Vincent A, McConville J, Farrugia ME, Bowen J, Plested P, Tang T, Evoli A, Matthews I, Sims G, Dalton P, Jacobson L, Polizzi A, Blaes F, Lang B, Beeson D, Willcox N, Newsom-Davis J, Hoch W (2003) Antibodies in myasthenia gravis and related disorders. Ann N Y Acad Sci 998:324–335
43. Walter MC, Lochmuller H, Toepfer M, Schlotter B, Reilich P, Schroder M, Muller-Felber W, Pongratz D (2000) High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol 247:22–28
44. Wolfe GI, Barohn RJ, Foster BM, Jackson CE, Kissel JT, Day JW, Thornton CA, Nations SP, Bryan WW, Amato AA, Freimer ML, Parry GJ (2002) Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. Muscle Nerve 26:549–552