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## High-dose intravenous immunoglobulin in inflammatory myopathies: experience based on controlled clinical trials

**Abstract** Controlled clinical trials with high-dose intravenous immunoglobulin (IVIg) have been conducted in patients with DM and IBM, but not PM. A double-blind placebo-controlled study in DM patients, resistant or partially responsive to conventional therapies, showed that IVIg is very effective in improving both the muscle strength and the skin rash. The clinical benefit, which was impressive in patients with early disease, was associated with improvement in the muscle cytoarchitecture. Quantitative histological studies in repeated muscle biopsies showed a statistically significant increase in the size of muscle fibers and the number of capillaries with normalization of the capillary diameter. Resolution of the aberrant immunopathological parameters including interception of complement activation products and downregulation of T cells, ICAM-I, VCAM, TGF- $\beta$  and MHC-I molecules was also noted. In IBM, IVIg showed marginal, and non statistically significant, improvements in muscle strength. Up to 20% of patients however, demonstrated clinical improvement with increased activities of daily living while certain muscle groups, such as the muscles of swallowing, showed significant improvements compared to placebo implying mild regional benefits. In PM, small uncontrolled series have shown improvements in muscle strength in up to 70% of the IVIg-treated patients. Because PM, as a stand-alone clinical entity, is a very rare disease, completion of controlled trials will be very difficult.

### Introduction

The inflammatory myopathies are divided into three major and distinct subsets: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) [1–5]. Although their cause is unknown, autoimmune mechanisms are implicated as supported by their association with other putative or definite autoimmune diseases or viruses, the evidence for a T cell-mediated myocytotoxicity or complement-mediated microangiopathy, and the presence of various autoantibodies [1–5]. This is also true for IBM, in spite of the co-existence of various degenerative features in these patients' muscle biopsies [1–5].

Clinical experience suggests that patients with PM and DM respond to prednisone to some degree and for a period of time [1–5]. In some patients the response may be dramatic and, if prudently used, prednisone may have a long-lasting effect with minimal side effects [1–5]. In others, however, the response is mild to moderate, and in still others, the steroid-induced side effects are severe, necessitating the need for other immunosuppressive drugs. Azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate are commonly used immunosuppressants which offer a mild, or at the very best, a modest benefit but with considerable toxicity after long-term use. Plasmapheresis is ineffective. IBM is almost always unresponsive to steroids or other immunosuppressants. The need for more effective therapies and the encouraging results from pilot or uncontrolled studies have prompted the need to perform controlled studies to examine the therapeutic efficacy of high-dose intravenous immune globulin (IVIg), an immunomodulating drug with prohibitive cost but minimal toxicity. I will review the evidence-based data on the effect of IVIg in DM, PM, and IBM.

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### IVIg in DM

DM affects the skeletal muscles, resulting in proximal muscle weakness, and the skin, causing a characteristic viola-

ceous rash on the face, chest, knees, back, and the knuckles of the fingers [1–5]. Dilated or infarcted capillaries at the base of the fingernails are frequently present. The muscle biopsy shows endomysial inflammation which is predominantly perivascular or in the interfascicular septae and around, rather than within, the fascicles. The earliest lesion that precedes inflammation or structural changes in the muscle fibers is the deposition of the complement c5b-9 membranolytic attack complex (MAC) on the intramuscular capillaries [1–4]. This is followed by necrosis and marked reduction in the number of capillaries per muscle fiber, especially in the perifascicular regions, resulting in ischemia and muscle fiber destruction that often resembles microinfarcts. Cytokines and adhesion molecules participate in the trafficking of sensitized lymphocytes and macrophages from the intramuscular blood vessels to the muscle fibers [1–5].

In the first double-blind, placebo-controlled study we conducted, a total of 15 patients (aged 18–55 years) with biopsy-proven, treatment-resistant DM were randomly assigned to receive IVIg (a total of 2 g/kg per day) or placebo, every month for 3 months, with the option of crossing over to the alternative therapy for 3 more months after a wash-out period of 1 month [6]. The patients continued to receive prednisone (mean daily dose, 25 mg) that remained unchanged for 3 months before and after therapy. Clinical response was gauged by assessing changes in: (a) muscle strength, using a modified MRC scale, a well-validated scale in the treatment of neuromuscular disorders; (b) scores of neuromuscular symptoms that provide a picture of daily living activities; and (c) the rash, using photography under the same lighting conditions. Corroboration of the clinical response was further established by searching for changes in the histological and immunopathological profile of repeated muscle biopsies.

Of the 15 patients, eight were assigned to IVIg and seven to placebo. Their scores at randomization and the mean disease duration in years were similar in both groups (Table 1) [6, 7]. The patients randomized to IVIg showed a significant improvement in the scores of muscle strength,

from a mean of 76.6±5.7 to 84.6±4.6, and in the neuromuscular symptoms scores, from a mean of 44±8.2 to 51.4±6. In contrast, the scores in the seven patients assigned to placebo did not change and remained the same from 78.6±6.3 to 78.6±8.2 and from 45.9 to 45.7±11.3, respectively (Table 1). The differences in scores between baseline and end of treatment among IVIg and placebo-treated patients was significant ( $p<0.018$  for the muscle strength and  $p<0.035$  for the neuromuscular symptoms). With crossovers, a total of 12 patients received IVIg; of those nine with severe disabilities had dramatically improved, with a mean change in muscle-strength scores from 74.5±4.9 to 84.7±4.5 and in neuromuscular symptoms from 38.6±5.9 to 51±8.0 (19); two others had a clear but less impressive improvement and one other, who had chronic disease, did not improve. These statistically significant improvements in muscle strength were functionally impressive for individual patients, some of whom were wheel-chair bound before therapy and walked independently or regained full strength after 3 months of IVIg [6–8]. Of 11 placebo-treated patients, none showed major improvement, and five worsened.

In addition to the muscle strength, the skin changes also improved. In eight patients the active violaceous rash or the chronic scaly eruptions on their knuckles improved markedly, which often preceded or coincided with the improvement of muscle strength. Serum creatine kinase levels, elevated up to tenfold in seven of the IVIg-treated patients, fell by 50% after the first infusion and decreased further or normalized by the second infusion.

In subsequent open-labeled infusions, the benefit of IVIg was also documented in more than 30 patients treated by us or under our supervision in several institutions and documented with objective measurements of muscle strength. Although the improvement in strength is usually short-lived, not lasting more than 4–8 weeks, a number of patients experience long-lasting remissions. Most of them, however, require IVIg every 4–8 weeks to maintain their benefit. In several patients, the prednisone dose can be lowered but, after a period of time, others may require the addition of another immunosuppressant.

**Table 1** Response to intravenous immune globulin (IVIg) in a placebo-controlled study of patients with dermatomyositis. Values are mean manual muscle strength (MRC) scores and mean neuromuscular symptom (NS) scores

Mean duration of disease	Therapy (years)	Pre-treatment		Post-treatment <sup>a</sup>	
		MRC	NS	MRC	NS
IVIg (n=8)	3.9	76.6±5.7	44.1±8.2	84.6±4.6 <sup>†</sup>	51.4±6.0 <sup>‡</sup>
Placebo (n=7)	3.8	78.6±6.3	45.9±9.0	78.6±8.2	45.7±11.3

<sup>†</sup>  $p=0.018$  (Wilcoxon) for comparison with placebo value

<sup>‡</sup>  $p=0.035$  (Wilcoxon) for comparison with placebo value

<sup>a</sup> Response to IVIg or placebo was measured after 3 months of treatment and before cross-over to the alternative therapy

### Repeated biopsies

In patients who showed major improvement, repeat open muscle biopsies showed a marked improvement in muscle histology. The mean number of muscle fibers counted in five regions decreased due to an increase in the muscle fiber diameter, from a mean of  $54.0 \pm 11 \mu\text{m}$  to  $71.0 \pm 15 \mu\text{m}$  ( $p < 0.04$ ); the mean number of capillaries increased and their mean diameter decreased from  $11.0 \pm 3$  to  $7.4 \pm 2$  (normal,  $6.5 \pm 0.1$ ) ( $p < 0.01$ ) while the mean ratio of muscle fiber to capillaries decreased from 3.4 to 1.5 (normal, 1.2) or normalized. Among the main immunological markers on the repeated biopsy there was downregulation of MHC-I and ICAM-I expression on the surface of muscle fibers and endomysial blood vessels and reduction of the TGF- $\beta$  expression on the connective tissue along with reduction of TGF- $\beta$  mRNA [6, 9]. Further, IVIg intercepted the formation and intramuscular deposition of the MAC, the lytic component of the complement pathway [10]. The C3bNEO (neoantigen), which is immune-complex specific, and the MAC could not no longer be detected in the endomysial capillaries of the repeated biopsies [7, 10, 11]. Further, in an in vitro assay system of sensitized erythrocytes, the consumption of C3 uptake by the patients' sera was suppressed after IVIg compared to the pretreatment sera [10]. On this basis, we have concluded that IVIg inhibits the incorporation of C3 into the C5 convertase assembly, thereby preventing the formation of C3bNEO and intercepting the formation and deposition of MAC on the endomysial capillaries. Such an effect of IVIg in intercepting the formation and deposition of MAC in target tissues is relevant to other IVIg-responsive diseases in which tissue damage is mediated by complement activation and MAC deposition such as Guillain-Barré syndrome, CIDP, and myasthenia gravis [11].

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### IVIg in IBM

IBM is the most common acquired inflammatory myopathy in patients above the age of 50 years [1–5]. The condition presents with selective atrophy of forearm flexor muscles, frequent falls, atrophy of the quadriceps muscles, and dysphagia. There is prominent endomysial inflammation in a pattern identical to that seen in PM with upregulation of MHC-I expression on muscle fibers invaded by CD8+ T cells, clonal expansion of these cells, and upregulation of cytokines or costimulatory molecules [12]. In contrast to PM, however, the IBM muscle contains vacuoles and amyloid deposition and is poorly responsive to steroids.

In an open pilot trial that we conducted, IVIg seemed to be helpful in some patients with IBM [13]. Although the improvement was not dramatic and not confirmed by others

[14], these results prompted us to perform a controlled, double blind study [15]. The study, a 3-month, randomized, crossover trial, was designed similarly to the one described earlier for DM. Efficacy was assessed by quantitative muscle strength testing and quantification of swallowing function, which is commonly affected in IBM patients. No statistically significant differences were noted in the strength of the limb muscles between placebo and IVIg. However, significant regional differences were observed in the IVIg-randomized patients, especially in the muscles of swallowing, as measured objectively by the ultrasound technique [15]. Although in the limb muscles the study did not overall establish efficacy of IVIg, six of 19 IBM patients (28%) showed a mild improvement in muscle strength that was functionally important for their daily activities. To further substantiate these findings, we conducted a larger study, this time combining IVIg with prednisone [16]. This was a double-blind, placebo-controlled study involving 37 patients, 17 of whom were randomized to IVIg plus high-dose steroids and 16 to placebo plus high-dose steroids [16]. The changes in muscle strength were assessed with quantitative muscle strength testing and MRC scale. After 3 months of treatment, there was no clear benefit in any of the two groups. Of interest, subjective improvements were noted in 10 of the 17 patients randomized to IVIg compared to 1 of 16 randomized to placebo [16]. Similar results were obtained by another controlled study [17].

In spite of these two negative trials, we had the impression that, clinically, a few patients with IBM showed transient signs of improvement, which are minor and difficult to capture with the methods used, but can be clinically significant for the patients' activities and life styles, at least for a period of time. Whether such a mild improvement in a small number of IBM patients justifies a 2- to 3-month trial with IVIg, remains a matter of clinical judgment and should be viewed on a case by case basis [17]. The noted statistical improvement in the swallowing muscles may be a factor for considering IVIg in selected patients with significant dysphagia. Safety, age, economics, and the reminder that nothing else (including steroids) offers even minor clinical improvement to IBM patients, should be also taken into account.

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### IVIg in PM

In uncontrolled studies, IVIg has been shown to be effective in PM [18–21]. However, controlled studies using quantitative muscle strength testing and documentation of the disease with muscle biopsies prior to therapy have not been conducted because PM is a rare disease. From the very few PM patients we have treated, we have the impression that, clinically, IVIg appears to be helpful in up to 70% of carefully selected patients. It is extremely difficult to conduct a controlled study in PM because it is a very rare disease, as recently emphasized [22].

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