Indications for intravenous gammaglobulin therapy in inflammatory myopathies

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Polymyositis (PM) and dermatomyositis (DM) are inflammatory muscular diseases of unknown cause. An immune mechanism may cause these inflammatory myopathies.\(^1\) The mainstay of therapy in inflammatory myopathies is corticosteroids.\(^3\) In patients who are resistant to corticosteroids, many therapies are available: immunosuppressive drugs, plasmapheresis, or total body irradiation.\(^7\) These therapies are not always effective and may be responsible for certain serious side effects.

Immunomodulatory therapy with intravenous immunoglobulins (IVIg) has been shown to be useful in a number of diseases featuring disordered immunoregulation.\(^5\) Consequently, we first administered IVIg to patients with chronic refractory inflammatory myopathies in an uncontrolled trial\(^7\) with favourable results. We describe our experience of IVIg in PM/DM.

**IVIg therapy in chronic refractory polymyositis and dermatomyositis**

Between August 1987 and December 1991, 35 adult white patients (25 women, 10 men) with PM or DM were included in the study. According to the diagnostic criteria described by Bohan and Peter,\(^6\) all patients had at least three of the following four features: proximal muscle weakness, elevated serum muscle enzymes, myopathic changes on electromyography and muscle biopsy changes. Twenty two patients had PM, 10 had DM, and three had PM associated with connective tissue disease (two with progressive systemic sclerosis, and one with cutaneous chronic lupus erythematosus). The mean (SD) age of the subjects was 42.5 (16-3) years. Sixteen patients had an oesophageal disorder (proximal dysphagia or uncoordinated peristalsis from striated muscle dysfunction). Raynaud's phenomenon was noted in five cases and calcinosis universalis in one. Visceral involvement included five cases of pulmonary fibrosis, two renal attacks with proteinuria and two cardiomyopathies (one dilated cardiomyopathy and one tachyarrhythmia).

The average (SD) duration of PM before IVIg was 3-6 years (4-8 years, with a range of six months to 26 years). Consecutive patients with PM/DM refractory to prednisone and an immunosuppressive drug were included (with the exception of one patient with contra-indication to steroids, who did not respond to azathioprine and plasma exchange). The 35 patients had not responded to standard therapies. These standard therapies were: prednisone (1 to 1.5 mg/Kg/day) (34 cases), methotrexate (0.5 to 0.8 mg/kg/week intramuscular) (17 patients), azathioprine (2 to 3 mg/Kg/day with oral administration) (13 cases), cyclophosphamide (boluses of 0.75 g/m² monthly for intravenous administration) (six cases), cyclosporin (5 to 7 mg/Kg/day with monitoring of plasma cyclosporin levels) (four cases), chlorambucil (one case), plasma exchange (11 patients), lymphopheresis (one case) and total body irradiation (one case).

During the study, IVIg was added to other treatments in 30 of the 35 cases. These therapies had been introduced at least two months before the beginning of the IVIg infusions. Steroids were administered in 29 cases, methotrexate in eight cases, azathioprine in three cases and plasma exchange in one case. There were no treatment changes in the two months before the introduction of IVIg and no increases in dose during gammaglobulin therapy. The mean disease duration between the last modification of treatment and the beginning of IVIg infusions was 3-5 months. Despite these treatments, the disease was still clinically active: muscle strength and serum muscle enzyme levels were stable or deteriorating before initiation of IVIg treatment. The failure of these treatments led us to introduce a new therapy to control the disease.

**Methods**

**Therapeutic protocols**

We used preparations of polyvalent human intravenous gammaglobulins with an elevated proportion of intact plasma IgG. IVIg was administered monthly in one of two ways: 1 g/kg/day during two days for 26 patients and 0.4 g/kg/day during five days for nine subjects. The mean course of treatment was four months.

**Clinical assessment**

Clinical evaluation was performed before each or every two IVIg infusions. Muscle power was gauged using a simple modification of the British Medical Research Council grading system\(^7\) which assigns numbers to muscle power from 0 to 5. For increased precision, each number was subdivided into an intermediate score, resulting in a possible score from 0 to 11. The intensity of the muscular deficit was determined from the total quotation of eight muscles: neck flexors,
trapezius, deltoid, biceps, psoas, maximus and medius gluteus, and quadriceps. As muscle weakness is symmetric, only one side was tested. The theoretical maximum score was 88 points. Each patient was tested by only one examiner. IVIg treatment was considered successful if a clinical improvement of 18 points or greater from initial power was obtained.

BIOCHEMICAL ASSESSMENT
Biochemical assessment was performed by measuring serum levels of the muscle enzymes, creatine kinase (CK) and aldolase, before each IVIg infusion. All the samples were obtained at the same laboratory using constant techniques (normal CK values <110 U/l). Biochemical results were considered "good" (or "moderate improvement") if CK levels dropped between 30 and 50 per cent and "very good" (or "major improvement") over 50 per cent. Below 30 per cent, the therapy was considered as biologically ineffective.

STATISTICAL METHODS
Mean muscle strength assessment for the 35 patients before and after IVIg therapy, was examined using the Student's t test. The mean CK values obtained after each IVIg infusion, and the mean steroid dose reduction before and after IVIg therapy were compared using paired Student's t tests. Significance was assessed at p = 0·05.

Results
CLINICAL ANALYSIS
No patient discontinued therapy because of side effects. A worsening of clinical status was observed in one patient. An absence of clinical improvement was noted in 10 patients despite three or four IVIg infusions. Clinical improvement was observed in 24 patients (70%), with a gain on the initial muscular testing of 18 points for 11 patients, 26 points for six and 36 points or greater for the last seven patients. The mean clinical assessment as gauged by the muscle power score before therapy and after three IVIg infusions showed a statistically significant improvement [mean (SD) initial muscle power for the 35 patients: 46·5 (11·5) points, mean (SD) muscle power after IVIg therapy for the 35 patients: 67·1 (15·4) points, p < 0·01] (fig 1). Clinical improvement was usually noted within the first two IVIg infusions. Because of improvement, steroid doses could be significantly reduced in 20 of the 29 patients who received steroids from the second or the third IVIg infusion [mean (SD) initial steroid doses before IVIg therapy: 38·7 (22·1) mg/day, mean (SD) steroid doses after three IVIg infusions: 24·9 (19·5) mg/day; p < 0·05]. In the same way, immunosuppressive treatment was discontinued in three patients, and plasma exchange in another.

BIOCHEMICAL ANALYSIS
Serum CK levels were initially normal in three patients and remained unchanged during IVIg infusions. Among the 32 patients with initially elevated CK levels, 28 patients showed biochemical improvement. Twenty-two patients had major biochemical improvement and six subjects had moderate biochemical improvement. CK levels usually dropped within two months after the first IVIg infusion.

The development of mean CK levels for the 35 patients during the immunoglobulin therapeutic period showed a statistically significant decrease [mean (SD) initial CK levels for the 35 patients: 1540 (1700) U/l, mean CK levels after IVIg therapy: 710 (1270) U/l, p < 0·01] (fig 2). The recorded improvement reached a maximum at the fourth perfusion and remained stable afterwards.

In our patients, general tolerance was excellent in 29 subjects. Minor side effects were observed in six others (headaches, fever, shivering and sweating). These adverse reactions disappeared spontaneously after infusion discontinuation and did not re-occur during further IVIg infusions.

Discussion
Although the aetiology of inflammatory myopathies has not been identified, there is considerable evidence that both cellular and humoral autoimmune mechanisms play an important role in their pathogenesis with a difference between polymyositis and dermomyositis. In childhood dermatomyositis, the necrotic areas and the inflammatory infiltrates have a perivascular distribution.

Figure 1 Clinical evaluation of the 35 chronic refractory PM/DM with IVIg. MS: muscle strength (SD) (Theoretical maximum score of 88 points).

Figure 2 Mean (SD) creatine kinase levels of the 35 chronic refractory PM/DM with IVIg.
Microvascular deposits of IgG, IgM, complement C3 and above all C5b-C9 membrane attack complex have been found in muscle capillary. The inflammatory infiltrates contain especially B and T CD4 lymphocytes. Other authors have confirmed vascular, and especially capillary injury in dermatomyositis, suggesting a resultant ischaemic mechanism mediated by a humoral autoimmune process.10

In polymyositis, the necrotic areas and the inflammatory infiltrates have no perivascular distribution. The muscle inflammatory infiltrates contain mainly monocytes and lymphocytes, especially activated cytotoxic T CD8 cells, natural killer (NK) cells and macrophages, with a perinecrotic distribution. There are few B lymphocytes and T CD4 lymphocytes, and no microvascular deposits. The target of cellular autoimmune reactions in polymyositis might be the myofibril.10

Treatment of polymyositis and dermatomyositis remains empirical. Corticosteroids are generally used initially, resulting in an improved prognosis and life style in more than 50 per cent of cases. Patients who are resistant or intolerant to corticosteroids are treated with immunosuppressive agents,11 12 or more recently cyclosporin,13 plasma exchange14 or total body irradiation.15

IVIg have proved their efficacy or at least their interest in various immune disorders: idiopathic thrombocytopenic purpura16 and HIV-1 associated thrombocytopenia,17 Kawasaki disease,18 autoimmune haemolytic anaemia,19 myasthenia gravis,20 diabetes mellitus,21 membrano-proliferative glomerulonephritis,22 rheumatoid arthritis,23 Guillaum-Barré syndrome,24 chronic inflammatory demyelinating polyneuropathy25 and other polyneuropathies.26 In 1987, Roifman et al described the case of IVIg in a young girl with PM who had failed to respond to conventional therapies.27 Consequently, we initially administered IVIg to patients with chronic refractory inflammatory myopathies in the first published open trial,4 7 with favourable results. Since this study, other authors have reported similar benefits of IVIg in single case-reports of inflammatory myopathies.28-31

Our results suggest a role for IVIg in the treatment of refractory PM/DM. In our experience, IVIg is of benefit in 70% (24/35) of chronic inflammatory myopathies refractory to standard therapy.

Despite these therapies, the PM or DM remained clinically active, justifying the introduction of a new therapy. The mean disease duration between the last modification in traditional therapy and IVIg infusions enabled us to exclude the effect of conventional therapies in the patients' improvement.

There was no relationship between disease duration and response to IVIg therapy. The mean (SD) disease duration of improved patients was 3:95 (5:7) years. One patient with a 26 year history of PM showed a dramatic response with IVIg infusions. The patients who did not respond to IVIg therapy had a mean (SD) disease duration of 2-8 (1-7) years.

Clinical and biochemical improvement always occurred after the first two infusions in chronic refractory myopathy (see figures) and persisted until the following infusion. Improvement reached a maximum at the fourth perfusion. The duration of efficacy varied. There was no standardised follow up treatment. Mean (SD) follow up was 22 (7-6) months in the 24 patients clinically improved with IVIg infusions. Ten of these 24 patients relapsed, with a mean (SD) duration of stable improvement after discontinuation of gammaglobulin without further therapy, of 8-3 (3-9) months. Four of these relapsed patients responded to a further IVIg treatment. The six remaining patients required the introduction of immunosuppressive drugs. Fourteen patients remained stable with IVIg therapy with a mean (SD) follow up of 17-3 (4-3) months. Eleven of these fourteen patients required monthly or bimonthly IVIg infusions and remained stable without any supplementary therapy.

The two protocols of monthly administration of IVIg (1 g/kg/day during two days and 0-4 g/kg/day during five days) show no differences in efficacy. No significant difference was found between PM and DM responses to IVIg. Sixteen of the 25 patients with PM treated with IVIg had improved (65%), compared with eight of the 10 DM treated (80%).

No significant correlation was observed between biochemical and clinical improvement. However, all patients with clinical improvement, improved biochemically or had normal initial CK serum levels. For some patients who had intermediate clinical and biochemical assessment, an initial drop in the CK serum levels preceded clinical improvement. However, all patients who improved with IVIg were effective in the treatment of chronic refractory PM/DM, allowing decreased use of immunosuppressive drugs and their potentially major side effects, and allowing steroid-sparing.

Surprisingly, IVIg therapy seems less effective as a first line treatment in patients with PM/DM.4 14 Corticosteroids are generally proposed for this purpose in inflammatory myopathy. However, corticosteroids are responsible for frequent side-effects, especially steroid myopathy with chronic treatment. Steroid myopathy worsens disability, and may hinder the assessment of disease activity. To avoid steroid side effects, and steroid myopathy in patients chronically treated, we evaluated the efficacy of IVIg as first line therapy in patients with PM or DM.4 14 Eleven adult white patients with active recent inflammatory myopathy, were treated with high doses of IVIg as first choice, using the same protocol as in chronic PM/DM refractory to standard treatment. Only three of the 11 patients treated with IVIg dramatically improved with a gain of 18 points or more in our muscular testing of 88 points. Moreover, two of the three improved patients
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had a characteristic myopathy. One patient developed PM after acute cossacke B virus infection, and another improved patient developed DM after penicillamine therapy. IVlg seems less effective as first therapy in patients with inflammatory myopathy, and should be considered in viral or drug-induced myopathy or in patients with contra-indication to steroids.

A recent controlled study on IVlg in 15 cases of DM was recently published and is the first controlled trial on IVlg in inflammatory myopathies. The authors in this study considered the improvement to be major when the total Medical Research Council (MRC) modified scores increased by five or more grades, and to be mild when they increased by two to four grades. The maximal MRC modified score was 90 points. This definition of improvement is hardly justifiable. In our studies, with a similar modified MRC scores (maximum 88 points), a significant improvement was fixed at 18 points and over, since the intra-observer variability for such a muscular scale lies in this range of values of two to five grades. The design of the study was described as a cross over trial. The first phase of the cross over was appropriately analysed. Unfortunately, the analysis of the second phase was inappropriate, neglecting the significantly different level of the scores between the two groups at the start of phase two of the study. Moreover, three of the seven patients of the placebo group did not receive IVlg in phase 2. This study, however, underlines the fact that in the IVlg group, the lower the initial scores, the more important their increase. In view of the high cost of IVlg, it does not sound reasonable to use IVlg therapy on patients presenting with initial scores above 80. In our opinion, this treatment should be reserved for inflammatory myopathies refractory either to high dose prednisone or to other immunosuppressive drugs, and presenting with significantly reduced scores. These studies, and their difficulties of interpretation, justify the development of international muscular scales specific to inflammatory myopathies.

The exact mechanism of action of IVlg in autoimmune disorders remains unclear. Intravenous immune serum globulin is derived from large pools of serum or human placental tissue from thousands of donors. A pooled IVlg preparation might be effective in providing a source of anti-idiotypic antibodies. IVlg may also provide a large range of antibodies that could potentially neutralise a causative agent as yet unknown. Other mechanisms of action of IVlg in dystimmune diseases such as elimination of circulating immune complexes, locking of Fc receptors from phagocyte-cells, Fc dependent modulation of T-lymphocytes CD4 and CD8, protection of muscle cells against antimuscle antibodies, or neutralisation of a causative agent have been described. In addition to the masking of antigens, IVlg can suppress antibody formation, T-cell proliferation, the activity of natural killer cells and some cytokines in animals and in vitro studies. The lack of difference of efficacy between PM, a predominant cellular immune disease, and DM, a predominant humoral immune disease, suggests several different mechanisms of actions of IVlg in inflammatory myopathies.

The low success rate obtained with IVlg as first choice treatment of recent PM/DM compared with their benefit when used in association with steroids in chronic refractory PM/DM suggests a synergistic action of these two drugs in inflammatory myopathies. Steroids have a mainly cellular immune action, inhibiting the production of interleukin-2 and gamma interferon of CD4 cells and of cytokines from macrophages, but also reducing the humoral response when used in high doses. Steroids have a possible complementary action with IVlg, necessitating their combined use for maximum effect.

To appreciate the real place of IVlg in the treatment of inflammatory myopathies, we have recently initiated an international randomised study. It is a multicentre prospective open trial, comparing the effectiveness of IVlg versus immunosuppressive agents in adults suffering from active PM or DM resistant to steroids. The main assessment, based on the evaluation of muscle function, is the improvement of muscular strength, consisting of a functional muscular scale, muscular strength testing, and muscle enzyme levels. The criterion of eligibility for the trial is a MRC modified score below 72. We retained a stringent criterion for defining improvement, that is, above 18 grades. A stratification between PM and DM has been used.


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