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ORIGINAL ARTICLE

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Prospective study of high-dose intravenous immunoglobulin for the treatment of steroid-resistant polymyositis and dermatomyositis

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Abstract High-dose intravenous immunoglobulin (IVIG) therapy has been effective in treating many autoimmune and systemic inflammatory diseases. In the present prospective study, we evaluated the efficacy of IVIG for patients with polymyositis (PM) and dermatomyositis (DM) refractory to treatment with high-dose corticosteroids. PM/DM was defined as steroid-resistant when the muscle strength of a patient did not improve despite the administration of more than 50 mg prednisolone per day for more than 4 weeks. A total of 12 patients with biopsy-proven, steroid-resistant PM/DM received one infusion of polyethylene glycol-treated human IgG at a dose of 0.4 g per kg per day for five successive days. Three of the patients received a second infusion. All patients were followed for up to 3 months after the infusion. Finally, 8 patients (6 PM and 2 DM; 5 men and 3 women) aged 29–67 years (mean 48 years) were analyzed. Their clinical response was assessed by changes in (a) subjective signs, i.e., fatigue (visual analog scale, VAS), muscle pain (VAS), activities of daily living (ADL), (b) objective signs, i.e., manual muscle strength (MMT) and serum level of creatine kinase (CK). At 12 weeks after the infusion, the patients showed significant improvement in their scores of muscle strength (from a mean of 67.0 to 81.0) and their ADL scores (from a mean of 27.1 to 39.1). The mean serum CK level decreased significantly from 1287.4 to 612.6 IU/l. In addition, the mean VAS of fatigue decreased significantly from 5.5 to 1.3 cm. The physicians' assessment showed that 87.5% of patients had improved. The average reduced dose of prednisolone was 47.1 mg/day at 12 weeks after infusion in 7 patients who exhibited improvement. Adverse effects, i.e., asymptomatic myocardial infarction and increased blood urea nitrogen (BUN), were noted with two of the 15 infusion (13%). Overall, IVIG was found to be safe and effective for refractory PM and DM.

Key words Dermatomyositis (DM) · High-dose intravenous immunoglobulin (IVIG) · Polymyositis (PM)

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Introduction

Polymyositis (PM) and dermatomyositis (DM) are distinctive inflammatory myopathies. Although their triggering agents are unknown, autoimmune mechanisms are implicated in the etiology of these conditions, as supported by evidence for T-cell-mediated myocytotoxicity[1–6] or complement-mediated microangiopathy,[7–10] and the presence of various autoantibodies.[11,12] The underlying immunopathogenesis has been the basis for treating the inflammatory myopathies with immunosuppressive drugs. Clinical experience suggests that patients with PM and DM respond to some degree to corticosteroids. However, in some patients, the response is not sufficient, resulting in severe physical disabilities, and in others steroid-induced side-effects are severe, necessitating the use of other treatments.

In case reports and uncontrolled series, high-dose intravenous immunoglobulin (IVIG), used as an immunomodulating drug, is emerging as a promising therapy for patients with inflammatory myopathies.[13–24] In 1993, Dalakas et al.[25] reported the efficacy of IVIG in a double-blind, placebo-controlled study for DM. We conducted a prospective study to assess the efficacy of IVIG for steroid-resistant PM/DM in Japan.

Materials and methods

Patients

All patients met the criteria of Bohan and Peter[26] for polymyositis and dermatomyositis, and were 16–65 years of age. The patients had active disease characterized by progressive muscle weakness and impaired ability fully to perform activities of daily living. Patients whose total scores on manual muscle testing were less than 80 points (normal 90 points), and who had responded incompletely to high-dose steroid therapy of more than 50 mg/day prednisolone for 4 weeks, including steroid pulse therapy, were selected. An incomplete response was defined as an improvement of fewer than 4 points or worsening. A total of 12 patients (aged 25–67) with biopsy-proven, steroid-resistant PM/DM were randomly assigned to receive IVIG. The study protocol shown below was approved by the Ethics Committee of each institution. Informed consent was obtained from all patients.

Study design

The protocol specified the administration of one infusion of immunoglobulin, polyethylene glycol-treated human IgG, GB-0998 (Mitsubishi Pharma, Osaka, Japan) at a dose of 0.4 g per kg per day for five consecutive days. All patients were followed for up to 3 months after completion of the infusions.

The patients continued to receive prednisolone, the dose of which could be reduced within 10% every 2 weeks. Increasing the dose of steroids was not permitted in principle. Other immunosuppressive drugs were not permitted from 4 weeks before and during the trial.

Before and after each infusion and weekly thereafter, routine blood chemical values, serum muscle enzymes, complete blood count, and an immunological profile were determined. ECG (0, 2, 4, and 12 weeks), echocardiography, chest X-ray, and respiratory function testing (0 and 12 weeks) were also assessed.

Assessment

The clinical response was gauged by assessing changes in subjective signs, i.e., fatigue (visual analog scale, VAS), muscle pain (VAS), and activities of daily living (ADL). Each of 15 ADL areas was graded on a weighted three-component scale. The maximum possible ADL score was 45, and the objective signs were serum level of creatine kinase (CK), and manual muscle strength (MMT) using a modified MRC scale,[25] which is a well-validated scale in the treatment of neuro-muscular disorders (normal score 90). Standard manual muscle testing was performed on 18 proximal muscle groups: the right and left deltoid, biceps brachii, brachioradialis, triceps brachii, iliopsoas, gluteus maximus, quadriceps femoris and hamstring muscles, as well as the neck flexors and neck extensors. Each patient was evaluated throughout the study by the same rheumatologist.

Changes in MMT and ADL were classified as follows: an increase of 10 points or more was registered as a marked improvement; an increase of between 5 and 9 points was an improvement; a change between −4 and +4 points was unchanged; a decrease of 5 or more points was worse.

A decrease in the serum level of CK of more than 50% of the basal level was considered to be a marked improvement, and one of 30%–50% was considered as an improvement. Values considered to be unchanged were decreases of less than 30%, or an increase from basal CK, or not normalized. An increase of more than 30% in basal CK was considered to be a worsening. The final global assessment of efficacy and safety, which was a subjective assessment, was graded as markedly improved, moderately improved, slightly improved, unchanged, or worse.

Statistical analysis

Dunnett's *t*-test and Wilcoxon's rank sum test were used to document the differences between the means of each value. A P value of less than 0.05 was considered to indicate statistical significance.

Results

Patient profile (Table 1)

Twelve patients took part in this study, and three of them received a second infusion. Safety was evaluated for the 12 patients and the 15 infusions. Cases 9 and 10 were excluded from the analyses because of a low dose of prednisolone during the 4-week period preceding the infusion. Cases 11 and 12 received a steroid-pulse after the infusion and then improved, so they could not be evaluated for the efficacy of IVIG. Case 8, who got worse after the infusion although the dosage of prednisolone was increased, was included for evaluation.

Therefore 8 patients, including 6 PM and 2 DM, 5 men and 3 women, aged 25–67 years (mean 48 years), were analyzed to evaluate the effect of IVIG infusion. Their disease durations were 0.3–3.2 years (mean 1.25 years).

Their MMT scores before IVIG ranged from 40 to 80 (mean 67), while their ADL scores ranged from 10 to 39 (mean 27.1). The level of serum CK was elevated in all patients to between 248 and 2690 IU/l (mean 1287 IU/l).

Table 1. Patient profile

Number	Subset	Age (years)	Sex	Disease duration (years)	MMT score	ADL score	Serum CK	No. of infusions
1	PM	56	M	1.5	68	27	895	1
2	DM	67	F	0.3	40	10	1017	1
3	PM	48	M	3.2	67	30	2690	1
4	PM	25	F	0.5	65	30	248	1
5	PM	53	M	0.4	71	23	1962	2
6	PM	44	M	0.3	73	39	1483	2
7	DM	29	F	1.2	80	32	930	1
8	PM	62	M	2.6	72	26	1074	2
9[a]	PM	61	F	2.1	46	17	666	1
10[a]	DM	25	M	5.0	70	–	671	1
11[a]	PM	58	F	0.6	72	39	289	1
12[a]	PM	44	F	3.5	67	43	398	1

[a] Excluded from the efficacy analysis
Five cases were investigated at Toho University,[27] two cases at Juntendo University, and one case each at Tokyo Medical and Dental University, Tokyo Women's Medical University, Keio University, Hokkaido University, and St. Marianna Medical University
PM, polymyositis; DM, dermatomyositis

Table 2. Effect of IVIG on each parameter measured 12 weeks after the infusion

	Marked improvement	Improvement	Unchanged	Worse	Total
Muscle strength	7 (87.5%)	0 (0%) 87.5%	0 (0%)	1 (12.5%)	8
Activities of daily living	4 (50.0%)	3 (37.5%) 87.5%	0 (0%)	1 (12.5%)	8
Serum CK level	5 (62.5%)	2 (25.0%) 87.5%	0 (0%)	1 (12.5%)	8

CK, creatine kinase

Table 3. Changes in clinical parameters after IVIG therapy (mean ± SE)

Week(s) after the infusion	MMT	ADL	Serum CK level	Fatigue
0	67.0 ± 4.2	27.1 ± 3.0	1287.4 ± 265.3	5.5 ± 1.1
1	70.1 ± 3.4	28.9 ± 2.6	1018.9 ± 197.1	3.8 ± 1.1
2	74.3 ± 1.9	31.1 ± 2.4	814.4 ± 212.1*	3.0 ± 0.8*
3	75.5 ± 1.9*	31.8 ± 2.4	550.8 ± 154.6**	2.9 ± 0.8**
4	76.9 ± 1.5**	33.3 ± 2.4*	494.1 ± 182.8**	2.1 ± 0.7**
6	78.3 ± 1.6**	36.0 ± 2.2**	424.5 ± 159.7**	1.9 ± 0.7**
8	80.1 ± 2.1**	36.8 ± 2.4**	535.3 ± 218.2**	1.4 ± 0.9**
12	81.0 ± 3.6**	39.1 ± 2.7**	612.6 ± 264.7**	1.3 ± 0.7**

Dunnett's *t*-test: * $P < 0.05$ versus week 0; ** $P < 0.01$ versus week 0
MMT, manual muscle strength; ADL, activities of daily living

Changes in muscle strength, ADL, and serum CK level

MMT, ADL, and serum CK level gradually improved after IVIG. Twelve weeks after the infusion, 7/8 (87.5%) patients showed a marked improvement in MMT, and the other one was worse. In ADL, 4/8 patients showed a marked improvement, 3 had improved, and 1 was worse. For serum CK level, 5/8 had a marked improvement, 2 had improved, and 1 was worse (Table 2).

Table 3 shows the changes in the scores for each value as mean ± SE. The mean MMT score of eight patients was significantly improved 3 weeks after the infusion, and the mean ADL score was significantly improved 4 weeks after the infusion. The serum CK levels and fatigue as indicated by VAS at 2 weeks after the infusion showed continuing improvement. The differences in MMT score during the 4 weeks before the infusion, while steroid treatment was being given, were not significant (mean 69.0–67.0, data not shown). The percentage decrease in serum CK levels at 4 weeks after the infusion was significantly different from that during the 4 weeks before the infusion ($P = 0.012$, data not shown).

At 12 weeks after the infusion, the patients showed a significant improvement in their scores for muscle strength,

from a mean of 67.0 to 81.0, and for ADL, from a mean of 27.1 to 39.1. The mean serum CK level decreased significantly from 1287.4 to 612.6 IU/l. In addition, the mean VAS of fatigue decreased significantly from 5.5 to 1.3 cm.

Assessment by patients and physicians

Of the 37.5% of patients who assessed themselves as being markedly improved at 1 week after the infusion, 75% agreed with that assessment at the end of the trial, 12 weeks after the infusion. The physicians involved assessed 25% of patients as improved at 1 week after the infusion, and 87.5% of patients as improved at 12 weeks.

Final global assessment of efficacy, safety, and usefulness

Of 8 patients treated with IVIG, 4 showed a marked improvement, 3 showed an improvement, and 1 had worsened. Adverse effects were noted in two of 15 infusions (13%). In one patient, asymptomatic inferior myocardial infarction was found on ECG at 3 weeks after the infusion, but whether the time of onset was before or after the infusion could not be specified. The same patient exhibited an increased CK isozyme. MB from the day of the infusion to 1 week after the infusion, and this was considered to be a possible side-effect. This patient exhibited an improvement after 12 weeks. One patient exhibited increased blood urea nitrogen (BUN) (from 17 to 30 mg/ml) after the infusion. Whether this was related to the IVIG was not clear, but could not be ruled out. This case was assessed almost safety. Consequently, the usefulness of the IVIG treatment was assessed as 88%.

Steroid-sparing effect (Table 4)

Seven patients who showed an improvement were evaluated on the decreased dosage of their steroids during 12 weeks after the infusion. Five patients exhibited a more than 31% steroid-sparing effect. The average reduced dose of prednisolone was 47.1 mg/day at 12 weeks after the infusion.

Long-term efficacy

All patients continue to maintain their improvement with the use of steroids. In several patients, we were able to decrease their prednisolone dose by more than 31%, and they continue on a low maintenance dose only.

After the 12-week study period, three of seven patients who had an improvement in their condition received a second infusion because of a worsening of the disease, the first just after the 12-week study period, the second 5 months after, and the third 8 months after the first infusion. The one patient who had got worse and the three recurrent cases had no common characteristic features except that they were all males with PM.

Excluding the first patient, the serum CK levels of six patients were monitored for 9 months. The mean (SE) levels of serum CK are plotted in Fig. 1. The mean CK level had decreased significantly at 6 months after the first infusion, and this effect of IVIG was sustained until 6 months after the infusion. The second infusion significantly decreased the serum CK level and increased the MMT score of all three patients. The steroid dose was also decreased for these patients.

Discussion

Although our study was an open-labeled, uncontrolled trial, we ascertained the efficacy of IVIG for the myositis in PM as well as DM using precise evaluation criteria such as quantitative muscle strength tests, ADL, serum CK level, and a prospective documentation of disease.

In our study, an improvement became noticeable 2 or 3 weeks after IVIG therapy, and was sustained for 12 weeks in both PM and DM cases. Patients tolerated this therapy well, and overall, IVIG was assessed as being safe and effective for refractory PM and DM.

In case reports and uncontrolled series, IVIG has been reported to be effective in up to 60%–70% of patients with PM and DM.[13–24] In 1993, Dalakas et al.[25] reported the results of a well-designed, double-blind, placebo-controlled study of IVIG for DM. Their patients were randomly assigned to receive IVIG (a total of 2 g/kg body weight divided into two daily infusions of 1 g per kg per day) or placebo every month for 3 months, with the option of

Table 4. Steroid-sparing effect of IVIG therapy

Number	Average dose		Rate of reduction of steroid dose (%)
	During 2 weeks before the infusion (mg/day)	From 11 to 12 weeks after the infusion (mg/day)	
1	100.0	17.5	82.5
2	60.0	42.3	29.5
3	80.0	60.0	25.0
4	60.0	21.3	64.5
5	37.1	25.0	32.6
6	45.0	24.5	45.6
7	50.0	25.0	50.0

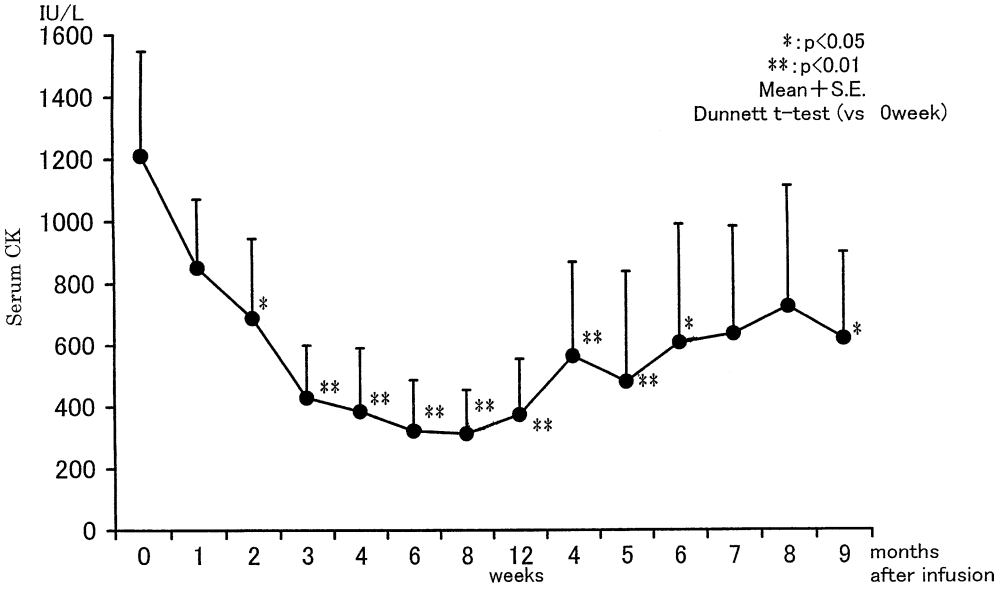

Fig. 1. Long-term efficacy. Except for the patient who received a second infusion at just after 12 weeks, all of the 6 patients who had an improvement in their condition were followed for 9 months after the infusion. Excluding a patient who received a second infusion at 5 months and 9 months, the mean (SE) levels of serum creatine kinase (CK) were plotted

crossing over to the alternative therapy for 3 more months after a wash-out period of 1 month. They confirmed a significant improvement in muscle strength and ADL, and the disappearance of any rash, and as well as a marked improvement or resolution of histological and immunopathological findings on repeated muscle biopsies.[28]

Both experimental and clinical data suggest that PM and DM result from different pathophysiological mechanisms. In DM, the specific pathological target is thought to be the capillaries. The disease process may begin with the binding of antibodies to microvascular components, and the activation of the classic complement pathway, resulting in the sequential loss of capillaries and ischemia-induced damage of muscle fibers with inflammatory infiltrates.[7–10] In PM, T cell-mediated and MHC class I-restricted antigen-directed cytotoxic processes on muscle cells may play major roles. This is supported by the presence of CD8+ T cells, which, along with macrophages, surround muscle fibers expressing MHC class I antigen and eventually invade and destroy such fibers.[1–6]

The benefits of IVIG have been reported in many other immunologically related diseases such as idiopathic thrombocytopenic purpura (ITP),[29,30] Guillain–Barre syndrome,[31] chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, multiple sclerosis, Lamber–Eaton myasthenic syndrome,[32–34] myasthenia gravis,[35] anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis,[36] and Kawasaki disease[37,38] in controlled studies, and antiphospholipid syndrome,[39] livedo vasculitis, Miller Fisher syndrome, acute disseminated encephalomyelitis (ADEM), Still disease,[40] systemic lupus erythematosus, and systemic sclerosis[41,42] in uncontrolled studies. In Japan, IVIG is approved for the treatment of ITP, Kawasaki disease, and CIDP by the Ministry of Welfare and Labor.

After considering the immunopathogenesis of those diseases, and the results obtained with animal models and in vitro experiments,[43–60] the mechanisms of action of IVIG are thought to be as follows:

1. the Fc portion of IgG exerts partial blockade of the Fc receptors when expressed on blood vessels and capillaries, and activated macrophages;
2. the F(ab′)2 fragment has antiidiotype antibody activity against autoantibodies and blocks their binding to autoantigens;
3. IgG contains neutralizing antibodies to various cytokines, including IL-1, IL-2, IL-6, and TNF-α, and also antibodies against T cell receptor β chain, CD5, CD4, and MHC-class I and II antigens.

On repeated muscle biopsies, Basta and Dalakas[61] found that after IVIG, deposits of the membrane attack complex disappeared from the capillaries and necrotic muscle fibers. There was a restoration of the capillary network, a reduction in the number of regenerating muscle fibers and lymphocytic infiltrates, an increase in the size of the perifascicular muscle fibers, and a reduced expression of MHC class 1 and intercellular adhesion molecule-1 (ICAM-1) on the surface of muscle fibers and blood vessels.

Wada et al.[62] produced an experimental autoimmune myositis model in SJL/J mice by immunization with rabbit myosin B fraction. The administration of IVIG dose-dependently reduced the incidence of necrotic and inflammatory changes in the skeletal muscle, and decreased the deposition of IgG and C3 in muscle fibers, as well as the elevation of antimyosin B antibody level.

In this study, we observed a case of asymptomatic inferior myocardial infarction, and a case of elevated serum level of BUN, for which a relationship with IVIG could not be ruled out.

A 67-year-old female DM patient exhibited an ECG change 3 weeks after the infusion. Her serum level of CK-MB had already increased on the day of the infusion, and it then decreased to a normal level at 2 weeks after the infu-

sion, before the ECG change was noticed. The physician in charge could not identify the day of onset of the cardiac event, and could not deny the possibility of the involvement of the IVIG, her steroid dose, or her myositis itself. A high dose of immunoglobulin could increase the blood viscosity, and the steroid given together with the IVIG could increase the coagulability. Therefore, IVIG therapy should be considered carefully before it is given to patients who are at risk of cardiovascular involvement, such as those with atherosclerosis or hyperlipidemia, or the very old.

IVIG therapy has been reported to have relatively few side-effects. In Japan, it has been used in 325 cases of Kawasaki disease or ITP, and side-effects have been reported in 5% of cases. These included tremor, cyanosis, eruption, hypertension, nausea, fever, and chills (reported by the Mitsubishi Pharma Co. in postmarketing research). The reported adverse effects[63,64] of IVIG in patients with autoimmune diseases and neurological diseases are commonly vasomotor symptoms, such as headache, fever, and shortness of breath, which were usually mild and transient. Serious complications are congestive heart failure, acute renal failure, deep vein thrombosis in patients with heart disease, renal insufficiency, and a bed-ridden state.

There are reports of hepatitis C transmission[65] and potential concerns over the transmission of viruses with the use of immunoglobulin. The current progress in the technology for virus inactivation, and verification tests to exclude HIV, HCV, or HBV in raw blood plasma, mean that the final products are safer than ever before. The GB-0098 used in this study is inactivated by heating, and any viruses are removed by nanofiltration during the manufacturing process. Virus transmission in relation to the use of immunoglobulin has not been reported during this study.

It has been reported that IVIG eventually ceases to work effectively. This can occur from 2 months to 2 years after treatment. In our study, three of eight patients were treated twice when their disease recurred. Although the long-term efficacy and benefits of continued IVIG treatment have not been documented, the short-term benefits have been established. Because of the expense and relative scarcity of large amounts of purified, pooled normal IgG, IVIG should be used only for selected illness for which other treatment is ineffective.

The benefits of therapies for myositis are difficult to determine clearly because of the lack of controlled and long-term studies that include large numbers of patients. There is thus a continuing need for large-scale controlled trials to evaluate IVIG therapy.

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