Mod Rheumatol (2008) 18:34–44
DOI 10.1007/s10165-007-0013-0

ORIGINAL ARTICLE

Efficacy of high-dose intravenous immunoglobulin therapy in Japanese patients with steroid-resistant polymyositis and dermatomyositis

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Received: 4 July 2007 / Accepted: 26 September 2007 / Published online: 25 January 2008

Abstract Intravenous immunoglobulin (IVIG) therapy was administered to 15 patients who were refractory to traditional steroid therapy [eight with polymyosis (PM), seven with dermamyosis (DM)] to evaluate its efficacy. Serum creatine kinase (CK) significantly decreased from week 1, and manual muscle test scores (MMT) and activities of daily living (ADL) significantly increased from week 2. Efficacy rates were 93.3% (14/15 patients) as assessed using the MMT score, 80.0% (12/15 patients) using the ADL score, and 100% (15/15 patients) using the serum CK level. When changes in the serum CK level over two four-week periods, one before IVIG therapy (from week −4 to week 0) and one after IVIG therapy (from week 0 to week 4), were transformed to natural logarithms, the four-week change after IVIG therapy was significantly greater than that before IVIG therapy. The estimated duration of the serum CK level remaining normal in 50% of the patients after IVIG therapy was 334.5 days. Adverse reactions were observed in seven of 16 patients (43.8%) during the study period, but none of the adverse reactions were considered to be serious or required emergency treatment. In conclusion, the present study indicates that IVIG therapy is effective for steroid-resistant PM/DM.

Keywords Dermatomyositis · Intravenous immunoglobulin · Polymyositis steroid resistance · Serum creatine kinase level

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Introduction

Steroids have traditionally been used as a first-line treatment of subjects with polymyositis (PM) and dermatomyositis (DM), and about 80% of patients exhibit a good response, while the remainder show either no or an incomplete response [1]. For the latter patients, other therapies such as steroid pulse therapy combined with immunosuppressive drugs can be used but are not always effective [2]. In addition, long-term administration of high doses of steroids and immunosuppressive drugs may cause infections, such as bacterial or fungal pneumonia and sepsis. This necessitates the development of a new drug which is effective in the treatment of PM/DM but has minimum risk of infection.

There is still much to be resolved about the precise mechanism of action of intravenous immunoglobulin (IVIG) therapy; however, various studies have reported that the therapy might have some actions on PM/DM which are related to the specific recognition of antigens [3, 4], to an impact on the cytokine network or adhesion factors [5, 6, 7] or to an impact on the proliferation, turnover or maturation of immunocompetent cells. This suggests that IVIG therapy is a promising treatment for PM/DM.

Since the use of immunoglobulin for the treatment of PM was first reported in a clinical study by Roifman et al. [8] in 1987, the effectiveness of IVIG therapy for PM/DM and juvenile DM refractory to available therapies has been reported in many studies [9–28]. In 1993, Dalakas et al. [29] reported the results of a double-blind, placebo-controlled crossover study in DM patients resistant to available therapies, and the effectiveness of IVIG therapy was established. However, with the exception of the study by Dalakas et al. [29], there have been few comparative studies done to investigate the efficacy of IVIG therapy for steroid-resistant PM/DM. Most were retrospective studies on a small number of patients.

In this study we examined the efficacy and safety of IVIG therapy in 15 Japanese patients with steroid-resistant PM/DM.

Materials and methods

Patients

Patients with PM/DM (all Japanese living in Japan) aged from 16 to 64 years who fulfilled the diagnostic criteria of Bohan and Peter [30] as "definite" PM/DM sufferers, and who had previously been treated with high-dose steroid therapy at a prednisolone equivalent dose of ≥50 mg/day or ≥1 mg/kg/day, were tentatively enrolled in the study. The present study excluded patients with malignancies, acute interstitial pneumonia, or immunoglobulin A (IgA) deficiency; those with severe liver, kidney, or cardiac disorders; and pregnant subjects. When the patients exhibited incomplete or no responses after four weeks of high-dose steroid therapy (observation period) after the tentative registration, they were determined to be steroid resistant and were formally enrolled in the IVIG therapy study except where their total score was 81 points or more in the manual muscle test (MMT) (normal score is 90 points; see the subsection on "Efficacy assessment"). No response or an incomplete response was determined when the MMT score assessed at the time of formal registration showed an improvement of four points or less. Written informed consent was obtained from all tentatively registered patients.

Study design

The present study was performed as a research project in 20 medical institutions specializing in the treatment of rheumatic diseases in Japan, and the study protocol was approved by the Institutional Review Board of each participating institution. Table 1 shows the study schedule with regard to assessment of MMT and activities of daily living (ADL) scores, and laboratory tests including the serum creatine kinase (CK) level. IVIG therapy was administered by intravenous infusion of GB-0998 (Benesis Corporation, Osaka, Japan), a polyethylene glycol-treated human normal immunoglobulin, for five consecutive days at a dose of 0.4 g/kg/day, followed by a follow-up study period of 12 weeks. Treatment with steroids was continued during and after IVIG therapy, but increases in

Table 1 Study schedule: timing of observations and assessments

Weeks after the initiation of IVIG therapy	−4	0	1	2	4	8	12
	Observation period*		Follow-up period†				
Consent obtained	○						
Tentative registration	○						
Formal registration		○					
IVIG therapy		↑↑↑↑↑‡					
Manual muscle test (MMT)	○	○		○	○	○	○
Activities of daily living (ADL)	○	○		○	○	○	○
Laboratory tests		○	○	○	○	○	○

* The period for confirming steroid therapy resistance (monotherapy with high-dose steroid administration)

† The period for confirming the efficacy of IVIG therapy (the steroid dose was maintained or reduced according to the degree of symptoms)

‡ GB-0998: 0.4 g/kg/day × 5 days

the steroid dose, even for steroid pulse therapy, were not allowed during the period from the tentative registration to completion of the follow-up study. When the dose of steroid was reduced, a decrease of ≤10% over two weeks was recommended. Concurrent use of other immunosuppressive drugs and plasma exchange therapy were prohibited.

In addition, after the 12-week follow-up study, serum CK levels and all treatments administered to patients were monitored for all patients who had been tentatively registered for up to 757 days.

Throughout this manuscript, the timing was defined as follows: the week initiating on the first day of the five consecutive days of infusion is defined as week 0. The subsequent weeks are then defined as week 1, week 2 and so on. Thus, "week −4" is the fourth week before week 0, the start of infusion. This timing terminology will be used throughout the text.

Efficacy assessment

The clinical efficacy of IVIG therapy was assessed by monitoring changes in the following parameters. The most common symptom of PM/DM is muscle weakness, and since therapeutic efficacy can be assessed by observing the degree of restoration of weakened muscle strength [10, 15, 16, 20, 28, 29], changes in MMT scores were determined. The MMT was done on 18 proximal muscles as follows: the neck flexors and neck extensors as well as the right and left deltoids, biceps brachii, brachioradialis, triceps brachii, iliopsoas, gluteus maximus, quadriceps femoris, and hamstring muscles. Each muscle was graded from zero to five points (normal score: 90 points). The assessment of each patient was carried out by the same rheumatologist throughout the study period. Improvement was determined by comparing the score at week 12 or at study discontinuation with the score at the initiation of IVIG therapy (week 0). An assessment of "markedly improved" was made if the score increased by ten points or more, "improved" if the score increased by 5–9 points, "unchanged" if the score changed by −4 to 4 points, and "worsened" if the score decreased by five points or more.

Changes in ADL scores were also assessed for the following 15 activities: raising the arms, taking off outer clothes, turning on a water tap, combing hair, fastening buttons, getting out of bed, lifting up the feet, standing up from a chair, climbing stairs, walking on a flat surface, turning over in bed, holding up the head, sitting down on a bed, having a conversation, and swallowing. Each activity was graded from zero to three points as follows: 0: unable to do, 1: can do with much difficulty, 2: with some difficulty, and 3: without any difficulty (normal score: 45 points). Improvement was determined by comparing the ADL score at week 12 or at study discontinuation with the score at the initiation of IVIG therapy (week 0). An assessment of "markedly improved" was made if the score increased by ten points or more, "improved" if the score increased by 5–9 points, "unchanged" if the score changed by −4 to 4 points, and "worsened" if the score decreased by five points or more.

Changes in the serum CK levels were assessed. Improvement was determined by comparing the serum CK level at week 12 or at study discontinuation with that at the initiation of IVIG therapy (week 0). An assessment of "markedly improved" was made if the level decreased by ≥50%, "improved" if the level decreased by 30 to <50% or was normalized, "unchanged" if the level changed by −30 to 30% (decreased by < 30% or increased by <30%) and was not normalized, and "worsened" if the level increased by ≥30%.

Statistical analysis

The mean and standard deviation (SD) were calculated based on MMT and ADL scores and serum CK levels at each assessment point, and changes from baseline values at the initiation of IVIG therapy were analyzed using the one-sample *t*-test. The significance level was set at 5% (two-sided), and the confidence coefficient was set at 95% (two-sided).

In evaluating the effect of IVIG therapy on the change in serum CK levels, a correction by logarithmic transformation (to natural logarithms) was made [31] for the serum CK level since the scattering of values of the CK level increased exponentially, depending on the degree of disease severity in each patient. The change over four weeks before the initiation of IVIG therapy (from week −4 to week 0) and the change after the initiation of IVIG therapy (from week 0 to week 4) were compared by the one-sample *t*-test.

A Kaplan–Meier life table analysis was made to estimate the duration of IVIG therapy. The event was defined as the time when the serum CK level re-elevated beyond the upper normal limit after it had normalized following IVIG therapy.

Results

Patient profile

Of 25 tentatively registered patients, 16 were formally registered, and all were given IVIG therapy (Table 2). The

Table 2 Summary of data on study patients administered IVIG

Patient	Diagnosis	Age (years)	Sex	Disease duration (years)	Previous treatment before initial registration	MMT score					ADL score					Serum CK (IU/L)				
						Weeks after the initiation of IVIG therapy					Weeks after the initiation of IVIG therapy					Weeks after the initiation of IVIG therapy				
						−4	0	4	8	12	−4	0	4	8	12	−4	0	4	8	12
1	PM	39	F	1.58	CS, MTX, CYA	65	59	85	87	90	24	26	40	43	44	3613	4565	1570	1640	1719
2	PM	64	F	0.08	CS, pulses MPS	58	53	65	68	73	12	14	20	24	28	4162	554	82	23	39
3	PM	46	F	0.92	CS, pulses MPS	72	62	74	73	79	34	31	36	33	35	598	366	83	34	42
4	PM	64	F	0.67	CS	70	74	89	89	86	20	26	34	40	43	1789	973	147	52	33
5	PM	42	F	0.58	CS	78	76	81	83	86	27	29	29	35	37	4557	2871	1141	908	586
6	PM	42	F	0.17	CS, pulses MPS	57	61	73	78	81	15	13	22	35	38	941	275	35	33	70
7	PM	31	F	0.08	CS	72	69	88	89	90	24	24	35	42	42	3629	1107	164	42	30
8	PM	50	F	1.42	CS, pulses MPS, CPA, MTX	38	41	45	48	48	11	11	13	19	22	755	487	199	84	99
9	DM	58	F	2.67	CS, CYA	72	64	83	83	88	30	23	31	38	38	1862	282	34	28	48
10	DM	60	M	1.17	CS, pulses MPS, MTX, γ-globulin	58	46	67	69	72	9	7	23	25	27	525	183	51	91	61
11	DM	59	M	0.33	CS	77	59	67	74	79	29	15	21	29	36	3455	2482	255	71	46
12	DM	50	F	0.75	CS, AZP	73	68	75	76	87	33	36	41	39	37	3068	581	65	52	51
13	DM	55	F	0.33	CS	58	42	68	75	86	13	12	27	39	40	7180	2023	159	89	73
14	DM	55	M	0.25	CS	45	27	33	47	55	15	3	6	8	15	5922	2005	418	229	173
15[a]	DM	64	F	0.17	CS	70	60	63	54 (5w)		14	14	13	5 (5w)		1400	143	73	39 (5w)	
16[b]	DM	58	F	5.42	CS	72	75				34	37				312	83			
Mean		52.3		1.04		64.7	58.5	70.4	72.9	78.6	21.5	20.1	26.1	30.3	34.4	2735.5	1186.3	298.4	227.7	219.3
SD		10.0		1.36		11.4	13.7	15.4	13.8	12.9	8. 9	10.3	10.4	11.9	8.4	2055.4	1271.3	448.2	449.6	455.0
Mean[c]		51.9		0.74		64.2	57.4	70.4	72.9	78.6	20.7	18.9	26.1	30.3	34.4	2897.1	1259.8	298.4	227.7	219.3
SD[c]		10.2		0.72		11.7	13.5	15.4	13.8	12.9	8.5	9.6	10.4	11.9	8.4	2019.6	1280.2	448.2	449.6	455.0

PM polymyositis; *DM* dermatomyositis; *SD* standard deviation; *CS* corticosteroid; *MPS* methylprednisolone; *MTX* methotrexate; *AZP* azathioprine; *CYA* cyclosporin; *CPA* cyclophosphamide

[a] The study was discontinued at 35 days after the initiation of IVIG therapy, as a prohibited concomitant drug had to be administered to the patient due to a worsening of DM

[b] The patient developed bronchial asthma on the second day of IVIG therapy, therefore the study was discontinued for this patient on the third day (this patient was excluded from the efficacy analysis)

[c] Calculated excluding patient no. 16

remaining nine were excluded from formal registration and did not receive IVIG therapy for the following reasons: steroid monotherapy was effective in five patients, one patient withdrew from treatment, BUN was extremely elevated in one patient, and two patients were found to have contravened the study protocol. The follow-up study after IVIG therapy was discontinued in two patients, because it was necessary to administer a prohibited concomitant drug (cyclosporine) to one patient due to aggravation of DM 35 days after the initiation of IVIG therapy (patient no. 15), and because of the occurrence of an adverse reaction (bronchial asthma) two days after the initiation of IVIG therapy in one patient (patient no. 16). Of the two, patient no. 16 was excluded from the efficacy analysis, as IVIG therapy was administered for only two days.

Consequently, the efficacy evaluation was performed for 15 patients (eight patients with PM, seven patients with DM; three men and 12 women). The patients ages at the time of tentative registration ranged from 31 to 64 years (mean: 51.9 years, SD: 10.2 years), and disease duration ranged from 0.08 to 2.67 years (mean: 0.74 years, SD: 0.72 years). A safety evaluation was performed for all 16 patients administered IVIG therapy.

Changes in muscle strength, ADL scores and serum CK levels

Changes in MMT scores, ADL scores, and serum CK levels from week −4 to week 12 or at study discontinuation are shown in Fig. 1a–c. The MMT score at four weeks before IVIG therapy was 64.2 ± 11.7 points and it was 57.4 ± 13.5 points at the initiation of IVIG therapy. The score significantly increased by week 2 and reached 78.6 ± 12.9 points by week 12. The ADL score at week −4 was 20.7 ± 8.5 points and it was 18.9 ± 9.6 points at the initiation of IVIG therapy. The score had significantly increased by week 2 and reached 34.4 ± 8.4 points by week 12. The serum CK level at week −4 was 2897.1 ± 2019.6 IU/L; it was 1259.8 ± 1280.2 IU/L at the initiation of IVIG therapy and had significantly decreased by week 1 and reached 219.3 ± 445.0 IU/L by week 12.

The response rate (percentage of patients for whom an assessment of "markedly improved" or "improved" was made) was 93.3% (14/15 patients) for the MMT score, 80.0% for the ADL score (12/15 patients), and 100% (15/15 patients) for the serum CK level. There were two patients who did not show an improvement in the ADL score despite an improvement in the MMT score. One patient had acute lower back pain (strained back) 45 days after the initiation of IVIG therapy (patient no. 3), and the other patient developed a lumbar compression fracture 28 days after the initiation of IVIG therapy (patient no. 12), which restricted their activities of daily living.

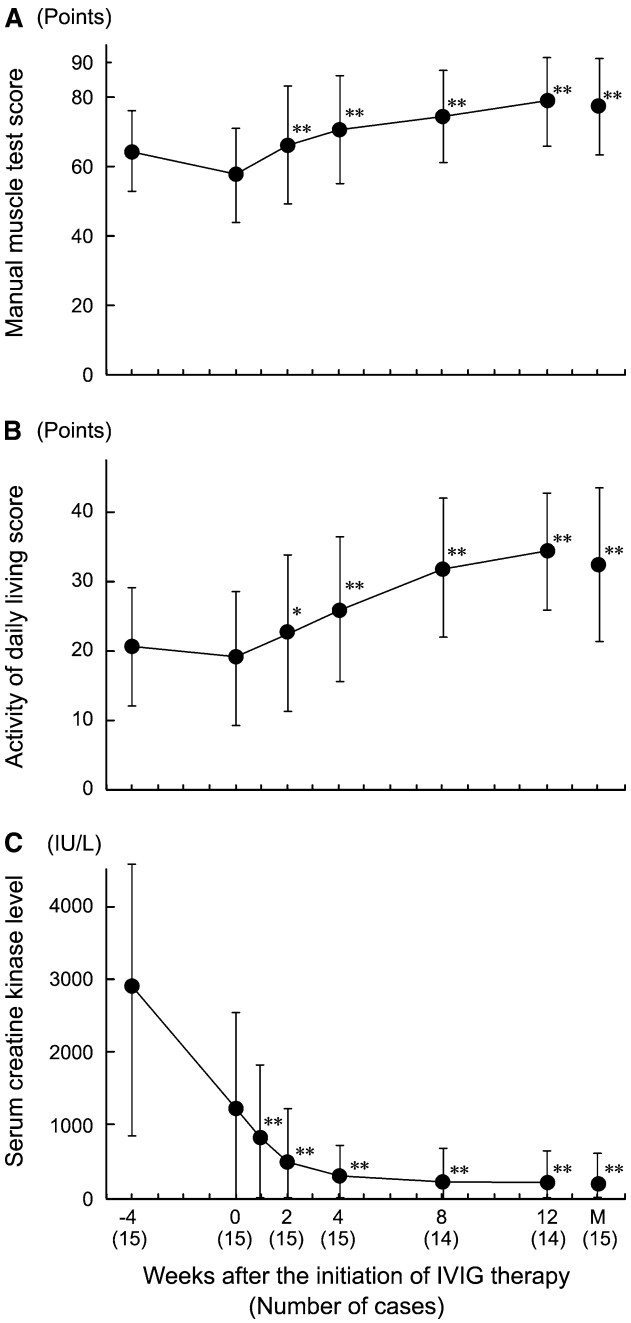

Fig. 1 Improvements in muscle strength (**a**), activities of daily living (**b**), and serum CK level (**c**) in 15 patients with PM/DM on IVIG therapy, who were included in the efficacy analysis. *Bars* represent mean ± SD. Values in parentheses represent the number of patients. Note that in (**c**) the number of patients at one week after the initiation of IVIG therapy is 15. The letter *M* on the *horizontal axis* indicates 12 weeks after the initiation of IVIG therapy or the time at treatment discontinuation. The one-sample t-tests were performed for changes in the values of the muscle strength, activity of daily living, and serum CK level from those at the initiation of IVIG therapy. *: $P < 0.01$, **: $P < 0.05$

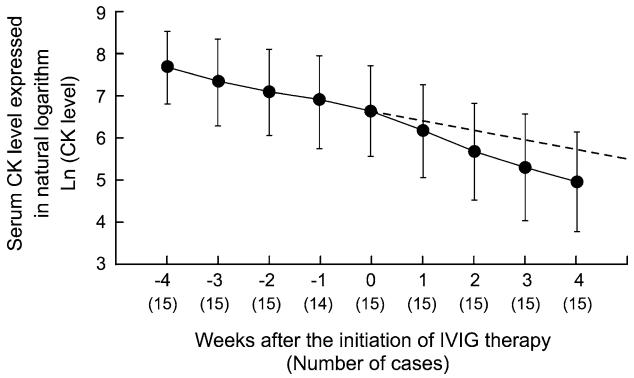

Fig. 2 Four-week changes in serum CK levels before and after the initiation of IVIG therapy in 15 patients with PM/DM on IVIG therapy who were included in the efficacy analysis (values are transformed to natural logarithms). *Dotted lines* represent estimated values for cases where steroid treatment would be continued (the formula for estimation: $y = -0.25602x + 6.60394$, where x and y represent the horizontal and vertical axes, respectively). *Bars* represent mean ± SD. Values in parentheses represent the number of patients

Changes in serum CK levels before and after IVIG therapy

Figure 2 shows four-week changes in serum levels CK before and after IVIG therapy transformed to natural logarithms. Changes from week 4 to therapy initiation and from therapy initiation to week 4 were compared; the results show that the four-week change after IVIG therapy was significantly greater than the four-week change before IVIG therapy ($P = 0.0122$; Table 3).

Duration over which the serum CK level remained normal after IVIG therapy

Table 4 shows the occurrence or non-occurrence and timing of the normalization of the serum CK level, and the duration over which it remained within normal limits for the study patients. For the 13 patients for whom serum CK levels were normalized after IVIG therapy, by defining the time of re-elevation (beyond the upper normal limit) as the event, the duration over which the level remained within normal limits is presented using the Kaplan–Meier method (Fig. 3). The results showed that the estimated duration over which the serum CK level remained normal in 50% of the patients was 334.5 days.

Safety

Adverse reactions for which a causal relationship with IVIG therapy could not be ruled out were observed in seven of 16 patients (43.8%; Table 5). None of the adverse reactions required emergency treatment. Abnormalities in liver function were observed in patient no. 3 seven days after the initiation of IVIG therapy, but as these abnormalities developed shortly after the initiation of IVIG therapy, the causal relationship with IVIG therapy was judged as "probably related." The causal relationship of other adverse reactions to IVIG therapy was unknown but could not be ruled out, so was judged as "could not be determined." Furthermore, electrocardiography performed on patient no. 12 seven days after the initiation of IVIG therapy showed ST-segment depression, and, although no particular clinical symptoms were present, a diagnosis of subendocardial ischemia was made. Following administration of enteric-coated aspirin and isosorbide dinitrate, electrocardiography performed 28 days after the initiation of IVIG therapy showed no abnormality. In addition, no infections were observed during the course of the study.

Discussion

The present study was performed to investigate the efficacy and safety of IVIG therapy for subjects with steroid-resistant PM/DM. Except for the study by Dalakas et al. [29], most previous studies to investigate the efficacy of IVIG for PM/DM were retrospective studies and used only a small number of patients. The present study, however, enrolled a relatively large number of 15 patients and prospectively examined the efficacy of IVIG therapy for steroid-resistant PM/DM under a strict protocol. The parameters evaluated were MMT scores, ADL scores, and serum CK levels. The serum CK level was followed up for as long as possible, and the duration of the effect of IVIG therapy was also examined.

Table 3 Four-week changes in the serum CK levels before and after IVIG therapy (values are transformed to natural logarithms)

	Patients on IVIG therapy (mean ± SD)
n	15
Change over 4 weeks pre-therapy (week −4 to week 0)	1.051 ± 0.708
Change over 4 weeks post-therapy (week 0 to week 4)	1.652 ± 0.575
Difference between the changes (4 weeks post-therapy −4 weeks pre-therapy)	0.601 ± 0.809
Paired *t*-test	$t = 2.877$ $P = 0.0122$

Table 4 Presence or absence of and timing of normalization of the serum CK level, and duration for which the serum CK level remained within normal limits

Patient	Diagnosis	Steroid dose at the start of the study (mg)	Steroid dose at the last observation (mg)	Duration of monitoring period for the serum CK level (days)	Timing of normalization of the serum CK level[a] (days)	Timing of re-elevation of the serum CK level[b] (days)	Duration of the period over which the serum CK level remained within normal limits (days)	Comments
1	PM	41	20	409	–	–	–	Not normalized
2	PM	70	35	279	25	–	>254	Monitoring discontinued
3	PM	55	25	510	19	390	371	Re-elevated
4	PM	40	27.5	472	24	–	>448	Monitoring discontinued
5	PM	50	30	374	–	–	–	Not normalized
6	PM	45	22.5	615	9	139	130	Re-elevated
7	PM	55	27.5	444	35	–	>409	Monitoring discontinued
8	PM	50	35	714	38	137	99	Re-elevated
9	DM	45	20	487	15	438	423	Re-elevated
10	DM	55	32.5	136	12	96	84	Re-elevated
11	DM	60	17	729	35	255	220	Re-elevated
12	DM	55	28	757	21	400	379	Re-elevated
13	DM	50	20	628	34	–	>594	Monitoring discontinued
14	DM	55	15	511	49	180	131	Re-elevated
15	DM	40		59	7	–	>52	Monitoring discontinued

PM polymyositis; *DM* dermatomyositis

[a] The time at which the serum CK level dropped to within normal limits after IVIG therapy

[b] The time at which the serum CK level re-elevated above the upper normal limit after IVIG therapy

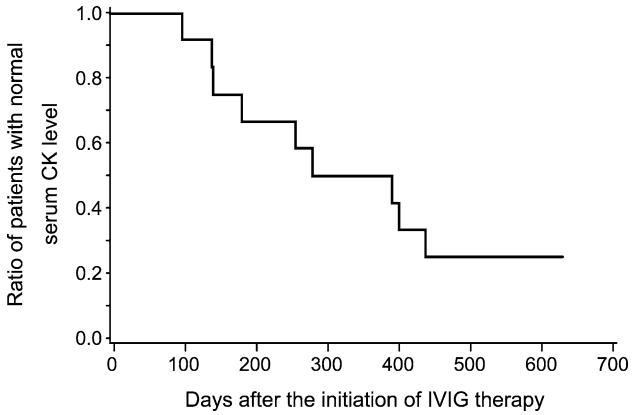

Fig. 3 The Kaplan–Meier representation of the 13 patients with PM/DM whose serum CK levels were normalized after the initiation of IVIG therapy. The time of re-elevation of serum CK levels was taken as the event in the representation. It was estimated that the 50% effective duration (the duration of the period for which serum CK levels remained normal in 50% of the patients after the initiation of IVIG therapy) was 334.5 days, and the mean effective duration of the IVIG therapy was 302.3 ± 40.0 days (mean ± SD)

With regard to efficacy, IVIG therapy resulted in a significant improvement in MMT and ADL scores. The efficacy of IVIG therapy was assessed to be 93.3% (14/15 patients) using the MMT score and 88.0% (12/15 patients) using the ADL score; this was because two patients for whom an assessment of "unchanged" was made were restricted in their activities of daily living due to the occurrence of acute lower back pain and a lumbar compression fracture. The improvement in MMT and ADL scores after IVIG therapy were significant when compared with changes in MMT and ADL scores before IVIG therapy. Considering that the study patients were resistant to high-dose steroid treatment, these results suggest that IVIG therapy is a promising treatment modality that is highly effective in treating refractory PM/DM. Improvements due to IVIG therapy were apparent by week 2 and persisted until week 12. Although the efficacy rate using the serum CK level was 100% (15/15 patients), the assessment of the effect of IVIG therapy on the serum CK level needs to be considered carefully, because the serum CK level had significantly decreased even before IVIG therapy. When changes in the serum CK level over two four-week periods (one before and one after IVIG therapy) were taken into consideration, we clearly demonstrated that IVIG therapy significantly accelerated the decrease in the serum CK level.

The present study appears to be the only study which prospectively evaluated the effect of IVIG therapy on myositis except for the previous study reported by Dalakas et al. [29]. In their study, they clearly demonstrated the efficacy of IVIG therapy in patients with DM. Although they stated that their study had enrolled treatment-resistant DM patients, there was no precise description of the therapies administered before IVIG administration. Actually, the mean daily dose of prednisolone at the time of IVIG therapy was 25 mg, and this is not considered to be a high dose of steroids.

In the present study, we strictly defined the condition of steroid resistance, and all patients were treated with more than 40 mg of prednisolone at the time of the start of IVIG therapy. In addition, there was no consideration or analysis of serum CK levels in the Dalakas study. Serum CK levels are considered to be an objective measure when evaluating the condition of myositis and so it is very important to clarify the effect of IVIG therapy on the serum CK level. In the present study we clearly demonstrated a significant positive effect of IVIG therapy on serum CK levels.

In the Dalakas study they demonstrated the efficacy of IVIG therapy for DM patients only. In the present study,

Table 5 Details of adverse reactions

Patient	Diagnosis	Age (years)	Sex	Adverse reactions
3	PM	46	F	Abnormalities in liver function (elevated LDH, elevated AST, elevated ALT, elevated Aldorase, elevated γ-GTP, elevated Al-p)
8	PM	50	F	Elevation of blood pressure, elevated AST, elevated ALT, elevated γ-GTP
9	DM	58	F	Elevated γ-GTP, elevated ALP, elevated IgA, elevated IgM
10	DM	60	M	Dizziness, back pain, swelling of eyelid, elevation of tumor marker levels[a]
11	DM	59	M	Skin eruption, itchy feeling
12	DM	51	F	Hypertension, nose bleed, subendocardial ischemia, elevated γ-GTP
16	DM	58	F	Bronchial asthma

PM polymyositis; *DM* dermatomyositis; *LDH* lactic acid dehydrogenase; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase; *γ-GTP* γ-glutamyl transpeptidase; *ALP* alkaline phosphatase; *IgA* immunoglobulin A; *IgM* immunoglobulin M

[a] CA19-9 and DUPAN-II elevated to 133 and 1,200, respectively, after IVIG therapy, but further examinations found no malignant tumor, and thus no definite diagnosis was given

we showed that IVIG therapy was effective for both PM and DM patients based on the prospective study protocol.

In addition, the present study enrolled eight patients with DM, including five patients who had cutaneous symptoms at the time of registration as follows: heliotrope rash (in three patients), Gottron's sign (in three patients), and Reynaud's phenomenon (in one patient). After a minimum of two weeks post-therapy, heliotrope rash disappeared in two patients (from positive to negative in one patient, and from false-positive to negative in one patient), while Gottron's sign disappeared in one patient (from positive to negative). Reynaud's phenomenon remained positive until 12 weeks post-therapy.

There are few studies that have examined the duration of the therapeutic effect after a single course of IVIG therapy. In the present study, the estimated duration of the period over which the serum CK level remained normal in 50% of patients was 334.5 days. Moriguchi et al. [19] reported that two patients with DM had no recurrence for 19 months and 23 months, respectively, after a single course of IVIG therapy. In contrast, Dalakas et al. [29] reported that responders needed to receive IVIG therapy every six weeks. Also, in their study, most of the patients receiving IVIG therapy once a month for three months exhibited restored muscle strength, which worsened again when a placebo was given during a subsequent three-month period in a crossover study. Therefore, the patients in the study of Dalakas et al. appear to have had a shorter duration of treatment efficacy when compared with our patients. The reason for this difference is unclear, but it might be due to racial differences or differences in concurrently administered therapies. In the present study, even in patients who failed to respond to conventional high-dose steroid therapy, the effectiveness of IVIG therapy persisted for a relatively long period, suggesting the importance of follow-up treatment including steroids after IVIG therapy. It is possible that once an improvement in PM/DM symptoms occurs with IVIG therapy, subsequent steroid therapy, the effect of which was not evident before IVIG therapy, may have a relapse-preventing effect. Due to the limited number of subjects, no clear relationship was observed between the steroid dose at the time of the last observation and the duration over which the serum CK level remained normal. In any case, even when the serum CK level is normalized, re-elevation may occur over time. Thus, patients should be carefully followed up, and it is necessary for patients showing a tendency to relapse to receive intensive treatment with anti-immune therapy or repeat IVIG therapy.

With regard to safety, no adverse reactions requiring emergency treatment or infections such as pneumonia or sepsis caused by microorganisms were observed in the study. We therefore consider that IVIG therapy has a good safety profile with minimum risk of infection. However, a total of four patients experienced adverse reactions relating to liver function abnormalities. The possibility that this was caused by a concomitantly used steroid could not be ruled out, but it is recommended that a thorough examination of liver function be made after IVIG therapy. In addition, it is important to address the possibility of blood flow disturbance associated with elevated blood viscosity due to IVIG therapy. In the present study, one patient was diagnosed with subendocardial ischemia. It has been reported that elderly patients are at a high risk for vascular dysfunction in coronary or cerebral arteries, possibly resulting from blood flow disturbance associated with an elevated blood viscosity due to IVIG therapy [32–35]. Therefore, IVIG therapy should be administered with caution to patients with risk factors for thromboembolism.

Currently, even more rigorous evaluation is required to prove efficacy of drug therapy in accordance with the need for evidence-based medicine. For evaluation of a therapy, a study is ranked as high quality when it is conducted in a double-blind, controlled manner. However, in the case of PM/DM, conducting a double-blind, controlled study is not only difficult because the patient population is small but it is also ethically problematic under the current treatment protocols for refractory PM and DM, which are very serious illnesses. The present study was not a double-blind, controlled study, but was a prospective study with a relatively large number of patients, which conformed to a well-reviewed protocol with precise evaluation criteria. Moreover, as the present study showed concrete efficacy, we consider that the present data could provide strong evidence for the efficacy of IVIG therapy for PM/DM.

A number of hypotheses have been proposed with regard to the mechanism of action of IVIG therapy, but none have been proven. Recently, it has been established that PM and DM have various differences in pathology. It is likely that T cell-mediated muscle fiber injury (type IV) plays a major role in PM, while immunocomplex deposition in the muscular microvessels (endothelial injury) (type III) is of primary importance in DM. Therefore, there is the possibility that IVIG therapy acts on different sites in the specific pathology of PM and DM. The potential mechanisms of IVIG therapy reported include: for PM, (1) inhibition of macrophage function mediated by binding to FcR [36, 37], (2) direct inhibition of cytotoxic T cells [38], and (3) effects on cytotoxic factors such as perforin and granzyme β; for DM, (1) mechanism mediated by the complement receptor (inhibition of Membrane Attack Complex formation) [5, 29, 39, 40], (2) elution of tissue-precipitated immune complexes, (3) inhibition of tissue TGFβ1 [26, 41], and (4) decreases in serum IL-2R [25]. However, in the present study, the therapy was clearly effective for both PM and DM, so sites for immune reaction common to PM and DM are probable targets. Thus, the

therapeutic effect may be related to specific antigen recognition (inhibition of maturation and function of antigen presenting cells [3], an effect on lymphocyte antigen-receptor [4], inhibition of expression of Class I MHC), an effect on the cytokine network or adhesion factors [5, 6, 7], or an effect on the proliferation, turnover or maturation of immunocompetent cells.

The present study indicates that IVIG therapy is an effective treatment modality for steroid-resistant PM/DM and is beneficial when carried out appropriately.

Acknowledgments We would like to express our gratitude to the members of the GB-0998 Study Group who are not listed as authors but have provided valuable advice and data for the present study. This work was supported by Mitsubishi Pharma Corporation.

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