The effect of intravenous immunoglobulin (IVIG) treatment on patients with dermatomyositis: a 4-year follow-up study

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Abstract

Objectives

The aim of this study is to evaluate the short- and long-term outcome of patients with dermatomyositis treated with IVIG.

Methods

Forty-two dermatomyositis patients (43±19 yrs, 40.5% males) were studied; 24 of them received IVIG as an add-on treatment, while the rest received conventional immunosupression. The first follow-up point was 6 months following the initiation of treatment. Muscular and cutaneous involvement, as well as demographical and baseline data of the IVIG treated patients, were documented for a median period of 76 months (1st, 3rd quartiles 48, 108).

Results

Muscular remission rate was higher for IVIG treated patients at 6 months after the onset of treatment (p=0.007). During long-term follow-up, IVIG treated patients presented with low muscular and cutaneous involvement, as well as low percentages of muscular relapses. The total number of muscular relapses was inversely associated with the number of pulses (p=0.03).

Conclusion

This study is a retrospective one, consisting of a small patient sample, and both muscle and skin involvement scores were developed on the basis of the clinical data provided in the patients' records. Nevertheless, it manages to demonstrate that IVIG may improve the short-term prognosis of dermatomyositis patients as compared to the classical therapies. During long-term follow-up, IVIG treated patients experienced relapses, but their muscular and cutaneous involvement scores were significantly better than their pre-treatment ones. A larger number of IVIG infusions could maintain disease remission for a longer period of time, reducing the total number of muscular relapses.

Key words

dermatomyositis, intravenous immunoglobulins, therapy

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Introduction

Dermatomyositis is a clinically distinct inflammatory muscle disease characterised by complement-mediated microangiopathy affecting both skin and muscle. The disease generally responds to steroids or immunosuppressive drugs; however, a number of patients are non-responsive or partially responsive to these therapies leading to severe physical disability (1). Intravenous immunoglobulin (IVIG) is an adjunct treatment for such cases (2, 3), and has proven to be very effective in improving both muscle strength and cutaneous lesions in a controlled study. However, its efficacy is short-lived, and repeated treatments may be needed for long-term benefit (4). Little is known about the long-term outcome of IVIG therapy (2), and no data are available comparing the long-term outcome of IVIG to other treatment modalities.

The aim of this work is to evaluate the short- and long-term outcome of patients with dermatomyositis treated with IVIG, and to compare the short-term outcome of the IVIG treated patients with that of patients who received other treatments.

Materials and methods

Patient population

We retrospectively analysed a cohort of 42 dermatomyositis patients (mean age 43±19 yrs, 40.5% males) that were treated in our clinic between 1994 and 2005. Among those, 24 patients received IVIG as adjunct treatment, depending on the physicians' judgement, while the rest received only conventional therapies (Table I). All patients had a definite diagnosis of dermatomyositis, as attested by clinical and laboratory picture, electromyographic findings and/or muscle biopsy (5, 6), and they all presented with at least one of the classic dermatomyositis rashes. The National Ethics Committees approved the study and informed consent in writing was received from the living patients.

Measurements

IVIG treatment was considered adequate if patients had received at least four monthly doses of 2 g/kg of body weight for two consecutive days. After IVIG treatment, patients continued receiving conventional therapies, including corticosteroids, methotrexate, azathioprine and hydroxychloroquine. The first follow-up visit that was included in this study was at six months following the onset of treatment, for both groups of patients. Thereafter, we focused on the IVIG treated patients and documented their annual clinical findings, based on the follow-up visits performed on a regular basis in our institution. The median follow-up period for the IVIG treated patients was 76 months (1st, 3rd quartiles 48, 108), with a range of 36–192 months.

We evaluated the Medical Research Council (MRC) strength score of proximal muscles of both upper and lower extremities of the patients, with the slight modification used in the article by Dalakas *et al*. (4). The total MRC score for each patient was calculated as the sum of the mean MRC score of the proximal muscles of the upper extremities (range 0–5) and of the lower extremities (range 0–5). The total range of the score was 0–10.

Cutaneous involvement was evaluated by the use of a slight modification of the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) (7), a validated score which has proven to be superior to other cutaneous scores in a recent study (8). The total CDASI score ranges from 0 to 148 with an activity sub-score ranging from 0 to 116 and a damage sub-score ranging from 0 to 32. Both muscular and cutaneous scores were deduced retrospectively after each visit of the patient, following the clinical information provided in the patient's record. All patients' muscular strength was reported in the files as an MRC score of the upper and lower extremities. Concerning skin involvement, our department's physicians had to list in each visit the total number of areas with skin involvement, the colour and texture of the lesions, as well as any comments about the amelioration or deterioration of the involvement.

Patients with muscle strength equal or greater than 9 and minimal or no skin lesions at all (CDASI ≤2) were considered to be in remission. Relapse was defined as a reduction in MRC score of

≥3 points, or reappearance of skin rash (CDASI ≥3). CPK levels weren't taken into consideration, since the clinical picture was of primary importance (4) and CPK levels have proven inconsistent with the clinical course of patients (9).

Data analysis

Continuous variables are presented as mean ± SD when normally distributed, or median and quartiles when they are skewed. Categorical variables are presented as frequencies. Student's *t*-test was used for mean comparisons between groups of study; while the assumption of normality was graphically tested using P-P plots. In the case of not-normally distributed variables the Mann-Whitney U-test was used. The chi-square test was applied to evaluate associations between categorical variables. Analysis of variance was applied to test mean differences between subcategories of the IVIG treated group. The log rank test was used to evaluate the effect of maintenance or non-maintenance of the IVIG therapy on relapse-free survival. SPSS statistical software (version 14) was used for all the statistical analyses (SPSS Hellas Inc., Athens, Greece).

Results

Demographic data and therapies (other than IVIG) were not different between the IVIG treated and non-IVIG treated patients. However, at disease onset, muscular involvement was worse for IVIG treated patients indicating that the IVIG treated group had more severe disease (Table I). IVIG treated patients received a median number of 6 monthly doses (1st, 3rd quartile 5.25, 6) with a range of 4–18 doses; 6 patients received 4–5 monthly doses, while the majority (n=13 patients) received 6 doses and 5 patients received between 7–18 IVIG doses (7, 8, 11, 17 and 18 pulses, respectively). Patients that did not achieve remission received additional IVIG treatment cycles (25%). Side effects were observed in 16.7% of the patients, and were in most cases mild (headache and migraine). Two patients experienced severe side effects (aseptic meningitis and allergic reaction), and were forced to temporarily discontinue treatment.

Table I. Baseline characteristics of dermatomyositis patients (n=42).

	IVIG treated patients (n=24)	Non-IVIG treated patients (n=18)	*p*-value
Age at disease onset (years)	41 ± 21	46 ± 16	0.40
Male sex, n (%)	9 (37.5%)	8 (44.4%)	0.65
Duration between disease onset and the onset of follow-up (months)	15, 11–21	14, 11–15	0.07
MRC at diagnosis [0- 10]	6.71 ± 1.60	7.89 ± 1.41	0.01
CPK at diagnosis (U/ L)	849, 124–3170	181, 60–626	0.04
CDASI score at diagnosis [0, 148]	7.5 ± 6.3	7.1 ± 6.6	0.84
Cancer, n (%)	2 (8.3%)	4 (22.2%)	0.20
Calcifications, n (%)	4 (16.7%)	2 (11.1%)	0.61
Lung involvement, n (%)	9 (37.5%)	6 (33.3%)	0.78
Corticosteroids*, n (%)	23 (95.8%)	16 (88.9%)	0.38
Methotrexate*, n (%)	19 (79.2%)	10 (55.6%)	0.10
Azathioprine*, n (%)	5 (20.8%)	4 (22.2%)	0.91
Hydroxychloroquine*, n (%)	1 (0.04%)	1 (0.06%)	0.83

¥Continued variables are presented as mean ± SD or median and quartiles (if they are skewed).
*Drug administration during the first 6 months following the onset of treatment.

IVIG patients' immediate response to treatment, as well as long-term maintenance of remission, was documented in the chart. Six months after treatment onset, 91.7% of the IVIG treated patients presented with muscular disease remission as compared to 55.6% for the non-IVIG treated group (p=0.007). However, complete remission and remission of the cutaneous involvement did not statistically differ between the IVIG treated patients and patients receiving other medications. Complete remission rates were 50% *vs*. 33.3% for IVIG and non-IVIG treated patients (p=0.28) and cutaneous disease remission rates were 54.2% *vs*. 44.4% for the same groups of patients (p=0.53). When patients who suffered from cancer were excluded from the analysis, there were no differences in the statistical significance of the results (p=0.01, p=0.27, p=0.79 for muscular, complete and cutaneous remission rates, respectively). Steroid treatment did not statistically differ between the two groups of patients at six months following the onset of treatment.

Thereafter, we documented the clinical characteristics of the IVIG treated group, at 12, 24 and 48 months of follow-up. Patients who had received IVIG therapy were treated with varying doses of corticosteroids (methylprednisolone doses ranging from 4 to 84 mg or prednisolone doses ranging from 5 to 60 mg), methotrexate (ranging from 10 to 22.5 mg), azathioprine (ranging from 50 to 150 mg) and hydroxychloroquine (200 mg), after the completion of the IVIG treatment. 54.2% of the IVIG treated patients relapsed throughout a 4-year follow-up period, and the mean relapse-free period was 38.5±34.3 months. However, only 16.7% of the patients presented with muscular relapses (mean relapse-free period, 62.1±43.5 months), while the rest of the events concerned cutaneous involvement. Overall survival was 95.8% for the IVIG treated patients; one deceased patient belonged to the IVIG treated group and died of cardiovascular problems irrelevant to his underlying condition. The only patient whose death was attributed to the disease (interstitial lung disease complicated by fungal infection) did not belong to the IVIG treated group.

MRC score and cutaneous involvement score significantly improved after 6 months of IVIG treatment. MRC score was 9.54±1.02 and CDASI score was 2.96±3.64 at 6 months after IVIG treatment *vs*. 6.71±1.6 and 7.46±6.26, respectively, for the pre-treatment period (p<0.001). Thereafter, patients had a satisfying course throughout the 4-year follow-up period, since the patients' overall MRC score was 9.56±0.66 and their overall CDASI score was 1.95±1.72, which significantly differed from their pre-treatment scores (p<0.001).

In order to evaluate the long term course of patients who maintained on

IVIG therapy *versus* those who did not, we compared patients who received ≤6 or >6 IVIG pulses. No difference was found neither in the number of patients who experienced remission at the initial follow-up point, nor in the relapse rate at 38 months of follow-up (p>0.10). However, the total number of muscular relapses experienced during a 35-month period was lower for those patients who received more IVIG pulses (p=0.03) (Fig. 1).

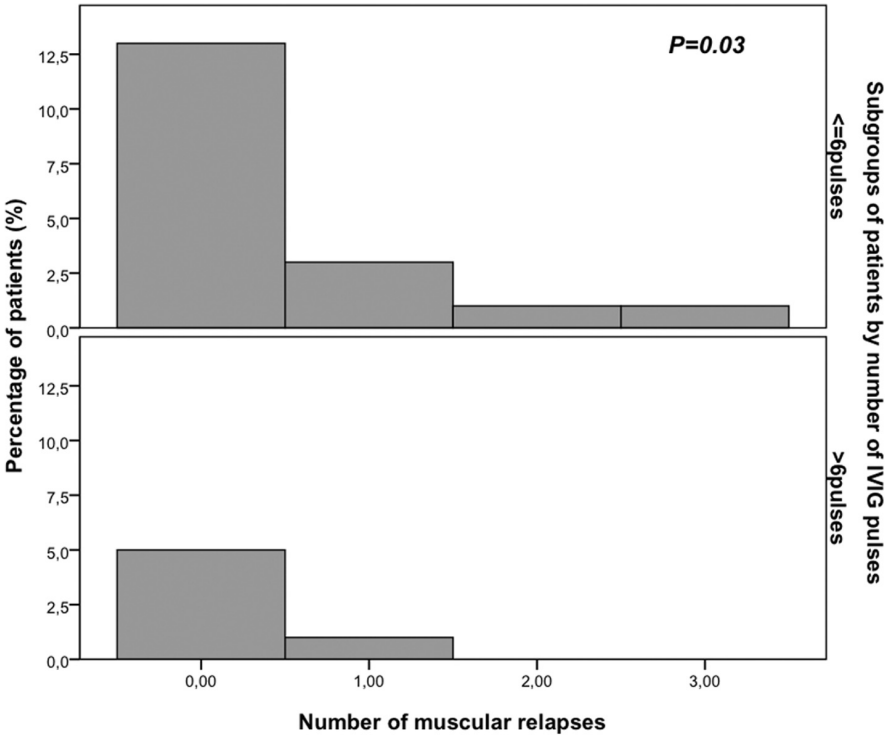

Fig. 1. Number of muscular relapses of IVIG treated patients (n=24), by number of IVIG pulses. Each sub-diagram refers to the respective subgroup of patients, by number of pulses. Each column represents the total number of muscular relapses the patients experienced (range 0–3), while the Y axes displays the percentage (%) of patients that presented with the respective number of relapses.

Discussion

In this study, we investigated the effect of IVIG treatment on immediate outcome of dermatomyositis patients, in comparison to other common treatments. We documented clinical and laboratory characteristics of the IVIG treated cohort for a 4-year period. IVIG treated patients had a better muscular outcome compared to non IVIG treated patients at 6 months following treatment initiation. During long-term follow-up, IVIG treated cohort presented low muscular and cutaneous involvement, as well as low percentages of muscular relapses. Finally, a larger number of IVIG infusions seemed to maintain remission for a longer period of time, reducing the number of muscular relapses.

Many therapies are used for dermatomyositis treatment, with steroids remaining the first-line therapy (1, 10, 11), even though their use is empirical (11). In cases of steroid refractory patients or complications due to steroid use, second-line treatments, alone or in combination, can be instituted. These include immunosuppressants such as azathioprine, methotrexate, mycophenolate mophetil and cyclosporine. Trials conducted to address the effectiveness of the above medications have demonstrated almost equal results (12-15). Cyclophosphamide is reserved for severe cases, due to its side effects (10, 11), and hydroxychloroquine can be used as an alternative for cutaneous lesions (16). Finally, newer agents include anti-CD20, which appears to be effective in small series of patients (17), as well as tacrolimus and rapamycin (11). In the present study, patients received corticosteroids, methotrexate, azathioprine and hydroxychloroquine as main treatments, apart from the IVIG therapy.

IVIG treatment was first found to be beneficial for toxin mediated diseases and immunodeficiencies (18). Since then, it has been used for multiple autoimmune and neurological diseases, such as Kawasaki syndrome, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, Guillain-Barré syndrome and paraneoplastic neurological syndromes (19, 20). As far as the inflammatory myopathies are concerned, the efficacy of IVIG in dermatomyositis has been documented in a double-blind placebo-controlled trial (4), as opposed to IBM (21). Although encouraging results are available for polymyositis (PM), these consist of series with limited number of patients (2, 11).

The efficacy of IVIG was first documented in an open study with severe refractory PM and DM (22), and was followed by a prospective study of 20 patients with PM and DM who were refractory to other treatments (9). The patients received 3–12 IVIG infusions, and 15 of them presented clinical improvement, a result that agrees with our study. The relapse rate of the patients was larger than that of our study, since 6 out of 15 patients (40%) relapsed in 11.3 months, while the relapse rate in the present study was 16.7% at 12 months of follow-up. The above results were confirmed in 1993 by a double-blind placebo-controlled study conducted by Dalakas *et al*. (4). Out of 15 dermatomyositis patients, 8 were given IVIG and 7 placebo together with prednisone, for 3 months. The difference between baseline and end of treatment scores among IVIG and placebo-treated patients was significant, in accordance to our study, where percentages of muscular remission were higher for IVIG treated patients (p=0.007). Finally, after crossover, of 12 patients treated with IVIG, 9 had a major improvement in their condition, whereas of 11 patients given placebo, 3 had a mild improvement in their condition, 3 had no change, and 5 worsened. The efficacy of IVIG was short-lived (mean duration 6 weeks), and repeated treatments were needed to achieve long-term benefit. Accordingly, at the present study, IVIG maintenance led to a smaller number of muscular relapses.

This study is not a randomised clinical trial, but a prospective historical one; thus it shares the limitations of its observational design. The patient sample was small and treatments were not allocated on a random basis, thus leading to differences at the baseline characteristics of the 2 groups. More specifically, the IVIG treated patients presented with a more severe clinical picture at disease onset. However, all the demographic and the remaining clinical data were equally distributed between the 2 groups. Due to the retrospective collection of the clinical data, the total MRC score (range 0–10) was arbitrary developed. Other articles also include sums of individual muscles which are separately evaluated by the use of the MRC scale (4, 23). Furthermore, the CDASI score that was used for the cutaneous evaluation of the patients is a validated score, but not in retrospective studies. However, the patients' records included sufficient information to allow the reliable calculation of MRC and CDASI scores, and both scores were identically applied to both groups of patients, leading to the elimination of possible defects.

To conclude, the immediate outcome of IVIG is significantly better than that of conventional medications. During long-term follow-up, IVIG treated patients experienced relatively few muscular relapses, and had a less severe course of the disease. It finally seems that a larger number of IVIG infusions could maintain remission for a longer period of time, reducing the number of muscular relapses. Further prospective studies, including larger patient populations, are needed to confirm these findings and to compare long-term results between groups of patients that maintain on same types and doses of drugs.

Authors' contributions

E.I. Kampylafka collected and co-analysed patients' data, and drafted the manuscript. M.L. Kosmidis examined patients and contributed to the correct documentation of clinical data. D.B. Panagiotakos performed the statistical analysis of the data and revised the manuscript. M. Dalakas co-supervised the study and revised the manuscript. H.M. Moutsopoulos co-supervised the study and revised the manuscript. A.G. Tzioufas conceived the study, revised the manuscript and had the overall supervision of this work.

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