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Disease Course and Therapeutic Approach in Dermatomyositis: A Four-Center Retrospective Study of 100 Patients

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Abstract

Dermatomyositis is a life-altering inflammatory disorder of skin and muscle. Details regarding the natural course of this disorder, the effects of specific therapies on its progression, and the optimal therapeutic dosage and duration of prednisone are limited. We performed a retrospective medical record review of dermatomyositis patients at four medical centers. All patients were over the age of 21 and had a clinical diagnosis of dermatomyositis with pathological confirmation. We reviewed average muscle strength, corticosteroid use, creatine kinase levels, and supplemental immunosuppressant use during the 36-month period following each patient's initial assessment. 100 patients participated with an average age of 50.1 years. Average muscle strength improved and prednisone requirements lessened six months after initial assessment. There was no difference in the mean change in muscle strength or cumulative corticosteroid use over 36 months among those initially treated with methotrexate, mycophenolate mofetil, pulse IVIG, or azathioprine. There was a 5% mortality rate in dermatomyositis patients due to infections. Treated

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dermatomyositis patients demonstrate the most significant improvement in strength during the first six-to-twelve months following their initial clinical assessment. Additional prospective studies are needed to determine the relative benefit of select immunosuppressant agents in preserving strength and reducing corticosteroid use in dermatomyositis.

Search Terms

Dermatomyositis; comparative effectiveness; immunosuppression; inflammatory myopathies

1. Introduction

Dermatomyositis is a rare inflammatory myopathy that affects skin, muscle, and connective tissue. The estimated prevalence of dermatomyositis is 21.4 per 100,000 persons with an overall incidence of 9.6 per 1 million persons-years [1–3].

Clinically, patients frequently present with proximal muscle weakness and a characteristic skin rash [4]. The low prevalence of dermatomyositis in the general population has limited the implementation of large-scale prospective studies of disease progression. While some studies have retrospectively evaluated the relapse rate in juvenile and adult forms of dermatomyositis, these studies have not extensively detailed overall disease progression in either of these populations [5,6]. To date, it is unknown how dermatomyositis symptoms change over extended periods of time and in response to corticosteroids. In addition, while several immunotherapies have been proposed as therapy in dermatomyositis, it is not known which agent (if any) provides the greatest long term gain of function [7–12]. Furthermore, while corticosteroids are frequently used as a first-line treatment for dermatomyositis, the optimal daily dosages of these medications are not known.

The current study retrospectively evaluates the disease course of dermatomyositis patients over time in the context of treatment with corticosteroids and other immunosuppressant agents at four tertiary centers.

2. Methods

2.1 Patients

Dermatomyositis patients were identified from the clinical and research neuromuscular databases at the University of Rochester, The Ohio State University, University of Kansas Medical Center, and Brigham and Women's Hospital between the years 1990 and 2011. All aspects of this study were conducted with institutional review board approval.

All patients had a pathological diagnosis of either inflammatory myopathy or dermatomyositis based on skin or muscle biopsy [5]. In addition, all participants were required to: 1) be 21 years or older at the time of initial assessment; 2) have both muscle weakness and a skin rash characteristic of dermatomyositis; and 3) have had at least two subsequent clinical visits after the baseline visit performed by a specialist with either neurology or rheumatology training.

2.2 Data Collection

Baseline clinical data were recorded for each participant using outpatient records. The baseline visit was defined as the first outpatient visit for dermatomyositis at the tertiary center. Subsequent clinical data for each participant were recorded at 6–12 months, 12–18 months, 18–24 months, 24–30 months, and 30–36 months after the baseline assessment. Clinical data from the first outpatient visit during each interval were utilized.

2.3 Outcome Variables

At each outpatient assessment we documented: 1) the patient's corticosteroid dosage and use of secondary immunosuppressants; 2) strength as determined by manual muscle testing (MMT); 3) creatine kinase (CK) levels; and 4) any adverse reactions attributed to immunosuppressant use. For each visit, the patient's corticosteroid dosage was recorded in daily prednisone-equivalent mg dosing.

Recorded manual muscle tests included shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, hip flexion, knee flexion, knee extension, ankle dorsiflexion, and ankle plantar flexion. Individual MMT grades were converted to numerical scores using a 13-point scale (grade 0 = 0, 1 = 1, 2– = 1.67, 2 = 2, 2+ = 2.33, 3– = 2.67, 3 = 3, 3+ = 3.33, 4– = 3.67, 4 = 4, 4+ = 4.33, 5– = 4.67, 5 = 5) and then averaged across muscles to form a composite score [13]. Given the proximal nature of dermatomyositis weakness, a proximal MMT score was calculated that included only proximal muscles (shoulder abduction, elbow flexion, elbow extension, hip flexion, knee flexion, and knee extension).

Adverse events were extracted from the progress notes in the chart. Events were included if the physician attributed symptoms or events (e.g., infections) to the medication on record. If multiple steroid-sparing agents were used, then the event was attributed to all listed agents.

2.4 Statistical Methods

Composite MMT scores, proximal MMT scores, corticosteroid dosages, and treatment regimens were summarized descriptively over time. For subject-visits that had an MMT score recorded for at least one muscle but fewer than 10 muscles, multiple imputation was used to accommodate missing data [14,15]. Specifically, a Markov chain Monte Carlo procedure [16] was used to impute the missing MMT values. The imputations were performed 100 times, resulting in 100 complete data sets. All analyses (descriptive and inferential) were performed separately for each of the 100 complete data sets, and the results were combined across data sets using standard combining rules [15,17]. This method of imputation appropriately reflects the uncertainty associated with the imputed values and is valid under the standard missing at random assumption.

A formal analysis was performed to compare the mean change in composite MMT and proximal MMT scores from the visit immediately preceding the introduction of immunosuppressive treatment (other than prednisone) to the 6–12 month and 12–18 month visits among the following initial treatments: methotrexate, azathioprine, mycophenolate mofetil, and IVIG. A standard analysis of variance model was used in conjunction with multiple imputation as described above to accommodate missing data. Pairwise comparisons

among the four groups were performed, with results reported as group differences in mean response along with associated 95% confidence intervals (CIs) and p-values. Paired t-tests were performed to evaluate the significance of the mean changes in composite MMT and proximal MMT scores from baseline to 6–12 months as well as from 18–24 to 24–30 months. Associated 95% CIs and p-values were also reported.

Additionally, a quadratic regression analysis was performed to relate the change in muscle strength over all combined 6–12 month intervals to prednisone dosage (that the patient was taking coming into their interval visit), irrespective of a patient's immunosuppressant use. An overall F-test was used to evaluate the significance of this association.

3. Results

One hundred dermatomyositis patients were identified for this study. Characteristics of the sample are provided in Table 1. Of the 100 patients, the last visit was in the 6–12 month assessment for 10% of patients, in the 12–18 month assessment for 9% of patients, in the 18–24 month visit for 5% of patients, in the 24–30 month visit for 13% of patients, in the 30–36 month visit for 8% of patients, and was greater than 36 months for 54% of patients. The average increase in the composite MMT score between baseline and the 6–12 month assessment was 0.22 (95% confidence interval –0.34 to 0.78), although this change was not statistically significant ($p=0.44$, eFigure 1a). For the proximal MMT score, the average increase between baseline and the 6–12 month assessment was 0.30 (95% CI-0.62 to 1.22, $p=0.52$) (Figure 1a). This increase in strength remained stable throughout subsequent visits. Over the same period of time, the average prednisone dosage declined (Figure 1b).

The initial prednisone dosage varied substantially among patients (Table 1). By the 6–12 month follow-up period, all groups (regardless of initial prednisone dose) demonstrated improvements in both composite and proximal MMT scores (Figure 2a, eFigure 1b). During this same time interval, only groups of patients receiving an initial average daily dosage of prednisone of 10 mg or less did not have their prednisone dose reduced (Figure 2b).

Evaluation of the association between change in muscle strength (measured by proximal MMT) and prednisone dose revealed a non-significant quadratic relationship between clinic visits separated by 6 to 12 months. A daily average prednisone dosage of 36 mg (using proximal MMT scores) and 34 mg (using composite MMT scores) was associated with maximum improvement of muscle strength over this time period (Figure 2c, efigure 1c).

Compared to other centers, the patients evaluated at the University of Kansas had a higher average reported strength at their initial visit. At subsequent visits there were no differences in strength among patients seen at the different centers (eFigure 2a). There were no differences in mean prednisone dosage among patients seen at different centers (eFigure 2b).

Mean CK level did not correlate with MMT but did drop over the first 6–12 months (Figure 3a, Figure 3b).

Patients received the following immunosuppressant agents commonly: methotrexate, azathioprine, mycophenolate mofetil, and IVIG. Several immunosuppressant regimens (e.g.,

rituximab and cyclophosphamide) were used uncommonly and therefore excluded. No immunosuppressant agent was shown to provide a superior benefit over the other agents in terms of improving average composite or proximal MMT scores or prednisone requirement at 6–12 months or 12–18 months after the initiation of the secondary agent (Table 2).

Adverse events were recorded in patients taking secondary immunosuppressant agents. Of the 22 patients receiving pulse-IVIG, 2 reported headaches, 1 had an infusion reaction, and 1 had an anaphylactic reaction. Two of 17 patients on mycophenolate mofetil had recurrent infections. One of 29 patients using methotrexate developed pneumonitis and 2 patients stopped methotrexate for hepatotoxicity. One of 17 patients taking azathioprine stopped this medication for gastrointestinal side effects, while others taking this medication stopped it for pancreatitis (n=1), recurrent infections (n=1), recurrent malignancies (n=1), or leukopenia (n=1).

Of the 100 patients, there were 6 documented deaths. Five of these patients died of infections. These included two patients taking mycophenolate mofetil, one patient taking IVIG and prednisone, one patient taking methotrexate, and one patient taking azathioprine. One patient taking prednisone died of lung cancer.

4. Discussion

This retrospective study provides data regarding the disease course of dermatomyositis patients treated at tertiary centers. Our study demonstrates that the greatest improvement in strength in dermatomyositis patients appears to occur over the first 6–12 months following the patient's initial assessment. This improvement is associated with lower required use of corticosteroid immunosuppression and remains relatively constant over the subsequent 36-month period.

Our data highlight the equipoise associated with immunosuppression selection for dermatomyositis patients. Although most of our patients received prednisone as a first-line agent, the selection of secondary immunosuppressant agents was not uniform with pulse IVIG, methotrexate, mycophenolate, and azathioprine all being selected for use.

Of particular interest is the dosage selection of prednisone for dermatomyositis patients. The appropriate therapeutic dosage of prednisone has long been a source of discussion among neuromuscular specialists. Prednisone is not only used for dermatomyositis, but also for other neuromuscular autoimmune disorders including myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, and polymyositis. While higher dosages are thought to provide more extensive immunosuppression, these dosages can also theoretically raise the risk of a steroid induced myopathy [18]. In such instances, it is possible that a higher dosage of steroids could further reduce patient strength. To this end we hypothesized a quadratic relationship between prednisone dosage and strength improvement over an interval of time. We were unable to detect such a relationship. Aside from a true absence of a dosage-responsive relationship, one possible explanation is the limited amount of dermatomyositis participants available to make this determination. This analysis may also have been affected by the possibility that rapidly deteriorating patients may have been placed on higher dosages of prednisone during their clinical descent. The prednisone dosage

that was correlated to the participant's change in strength over the 6–12 month period was the dosage that the participant was on coming into their interval visit. While this prednisone dosage represents an estimation of the prednisone dosage that the patient was on in the preceding 6–12 months, it is unknown how compliant the participant was with the prednisone during the time period or if the participant's clinician made any prednisone dosage modifications between clinical visits.

Prospective randomized clinical trials would be required to definitively determine the optimal dosing strategy for prednisone in dermatomyositis, a difficult task given the rarity of the condition.

A superior secondary immunotherapeutic agent was not identified through this study. No agent appeared to be superior in increasing strength in the 6 to 18 months after initiating the agent nor did any agent allow for significantly more prednisone sparing compared to alternatives. A large multicenter comparative effectiveness trial would be required to determine which secondary agent, if any, is superior. Given the rarity of dermatomyositis, such a study would need to draw upon many tertiary referral centers over an extended period of time.

Of note, most of the deaths in the study were the result of infections, presumably in part related to immunosuppression. Given these risks, clinicians should monitor immunosuppressed patients closely and aggressively treat infections when appropriate.

Limitations of this research are inherent to the retrospective nature of the study design. No patient was on a predefined prednisone starting dosage or taper schedule, nor were any rules in place for the addition, subtraction, or selection of secondary agents or their dosages at the four centers. We recognize that the decisions regarding immunotherapy are largely shaped by both patient clinical status and the practice behaviors of selected physicians at each of the participating sites. In addition, some variation in MMT scoring may have occurred due to the variety of physicians performing this testing across time. In some instances, physicians were trained neurologists; in other instances board-certified rheumatologists performed the assessments. In no cases was the selection of immunosuppressive agents controlled or the assessment of benefit blinded. This study also excluded dermatomyositis patients without pathological confirmation and those not seen and managed through a tertiary center. Given limitations in documentation extra-muscular manifestations and ambulation status were not analyzed. Specifically, skin findings were not widely or consistently documented and therefore not analyzed. Finally, we did not control for known prognostic factors, including older age, male gender, non-caucasian ethnicity, interstitial lung disease, cardiac involvement, cancer, or serum myositis-specific antibodies [19–22].

Overall, this study suggests that most patients with dermatomyositis improve over time. In addition, initiation of a moderate dosage of prednisone may provide an optimal benefit. Future multicenter clinical trials may be challenging but could further evaluate these agents and confirm an optimal therapeutic prednisone dosage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Overall, many patients improved in strength over time and corticosteroid use was reduced.
- No difference was found between typically used immunosuppressants in dermatomyositis.
- There is a 5% mortality rate in dermatomyositis due to infections.

Figure 1. Mean values for strength and corticosteroid dosage over time

1a. Mean strength over time, as measured by proximal manual muscle testing (MMT) score.
1b. Mean corticosteroid dosage (mg/day) over time. Bars indicate one standard error of the mean.

Figure 2. Association between initial corticosteroid dosage and strength

2a. Mean strength over time, as measured by proximal manual muscle testing (MMT) score, stratified by initial corticosteroid dosage (mg/day). 2b. Mean corticosteroid dosage (mg/day) over time, stratified by initial corticosteroid dosage. 2c. The association between corticosteroid dosage and change in strength (proximal MMT score) over all 6–12 month intervals; the corticosteroid dosage associated with the maximum mean improvement in proximal MMT score was 36 mg/day. Bars indicate one standard error of the mean.

Figure 3. Mean creatine kinase (CK) over time

3a. Mean CK level (U/mL) over time. 3b. Relationship of the mean baseline CK to the mean baseline proximal MMT score at baseline. Bars indicate one standard error of the mean.

Table 1

Patient Characteristics

Characteristic	Value
Female gender (n, %)	65 (65%)
Age at initial evaluation	50.1 ± 15.7
Initial prednisone dosage (mg/day)	36.7 ± 33.6
Initial prednisone dosage (mg/day) (n, %)	
0	33 (33%)
1 to 10	20 (20%)
11 to 30	17 (17%)
31 to 60	21 (21%)
> 60	9 (9%)
Initial baseline composite MMT score	4.50 ± 0.44
Baseline CK	3329 ± 5101
Median baseline CK (IQR)	920 (3721)
Able to walk at initial assessment (n, %)	78 (92%)
Able to stand at initial assessment (n, %)	50 (79%)
Initial secondary agents (n, %)	
IVIG	22 (26%)
Azathioprine	17 (20%)
Mycophenolate	17 (20%)
Methotrexate	28 (33%)
Center (n, %)	
University of Rochester	38 (38%)
Ohio State University	42 (42%)
University of Kansas	7 (7%)
Brigham and Women's Hospital	13 (13%)

Values are mean ± standard deviation unless otherwise indicated

MMT = Manual muscle testing; CK = creatine phosphokinase; IVIG = Intravenous immunoglobulin

Table 2

Comparisons of mean changes in composite Manual Muscle Testing (MMT) score and proximal MMT score among immunosuppressant agents, where changes were between initiation of the agent and the subsequent visits 6–12 and 12–18 months later.

Comparison	Difference between agents in mean change at the 6–12 month visit [/]	95% Confidence Interval	p-value	Difference between agents in mean change at the 12–18 month visit [/]	95% Confidence Interval	p-value
Composite MMT score						
Azathioprine and IVIG	0.004	(-0.45, 0.46)	0.99	-0.20	(-0.73, 0.32)	0.43
Azathioprine and Mycophenylate	0.11	(-0.35, 0.57)	0.63	-0.06	(-0.63, 0.51)	0.84
Azathioprine and Methotrexate	-0.11	(-0.58, 0.36)	0.63	-0.10	(-0.65, 0.45)	0.72
Mycophenylate and IVIG	-0.11	(-0.48, 0.27)	0.57	-0.15	(-0.61, 0.32)	0.53
Mycophenylate and Methotrexate	-0.22	(-0.64, 0.19)	0.28	-0.04	(-0.53, 0.45)	0.87
Methotrexate and IVIG	0.12	(-0.29, 0.52)	0.57	-0.11	(-0.52, 0.31)	0.61
Proximal MMT score						
Azathioprine and IVIG	0.16	(-0.53, 0.85)	0.65	-0.10	(-0.85, 0.65)	0.78
Azathioprine and Mycophenylate	0.25	(-0.44, 0.95)	0.47	0.05	(-0.77, 0.88)	0.90
Azathioprine and Methotrexate	-0.003	(-0.73, 0.72)	0.99	0.05	(-0.76, 0.85)	0.90
Mycophenylate and IVIG	-0.10	(-0.63, 0.44)	0.72	-0.16	(-0.79, 0.48)	0.62
Mycophenylate and Methotrexate	-0.26	(-0.88, 0.37)	0.41	-0.004	(-0.71, 0.70)	0.99
Methotrexate and IVIG	0.16	(-0.46, 0.78)	0.60	-0.15	(-0.72, 0.41)	0.59

[/] Positive numbers favor the first listed agent.