A Pilot Trial of Rituximab in the Treatment of Patients With Dermatomyositis

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Background: Dermatomyositis is an autoimmune disease that primarily affects the muscles, skin, and lungs and is associated with considerable morbidity. Up to 32% of patients have an underlying malignancy.1 Treatments for DM include corticosteroids and immunosuppressive therapies, such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide.2 These therapies have considerable adverse effects and frequently fail to control the disease. Intra-venous immunoglobulin leads to clinical and histopathologic improvement in patients with DM,3 but tolerance often develops.

Evidence suggests that B lymphocytes play an important role in the pathogenesis of DM. Muscle biopsy specimens exhibit a predominance of perivascular B cells,4,5 and up to 40% of patients with DM have detectable myositis-specific autoantibodies.3 Microvascular deposition of the membrane attack complex occurs in both muscle and skin biopsy specimens, consistent with humoral activation of the complement system.6,8 Rituximab, which is a chimeric monoclonal antibody that is directed against the CD20 antigen on pre-B and mature B cells, has been used successfully in the treatment of various autoimmune diseases.9 Depletion of B cells with rituximab affects many functions of the immune system, including antibody production, cytokine release, and antigen presentation to T cells. Rituximab therapy has been reported to normalize muscle strength and creatine phosphokinase (CPK) levels in 2 patients with DM with refractory muscle disease and to improve recalcitrant skin disease in 3 patients.10-12 A preliminary open-label study of 6 patients with DM showed that rituximab therapy improved muscle strength, lung capacity, and skin disease; however, a standard scale to quantify cutaneous involvement was not used.13 The purpose of our study was to further evaluate the effects of rituximab therapy on the clinical signs and symptoms of patients with DM.

METHODS

STUDY DESIGN

We performed an open-label, single-arm trial of rituximab in 8 patients with DM at our institution. All procedures were reviewed and approved by the institutional review board, and all patients provided written informed consent before participation. The patients were enrolled from December 2004 through July 2005.

OBSERVATION

Depletion of peripheral B cells had modest effects on muscle disease and limited effects on skin disease in our cohort of patients with dermatomyositis.

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Patients were included if they were adults (age, >18 years) with a diagnosis of probable or definite DM according to the criteria of Bohan and Peter,14 with classic dermatologic features defined by Sontheimer,15 and at least 2 of the following criteria: symmetrical weakness, muscle biopsy features consistent with DM, elevation of muscle enzyme levels, and electromyographic evidence of muscle inflammation. All patients had skin biopsy findings consistent with DM. The patients had to have evidence of at least mild muscle disease with either a modified Medical Research Council Manual Muscle Test (MMT) score of less than 85 (scale, 0-90; individual muscle testing measure, 0-5) or elevation of CPK (>400 U/L) or aldolase (>8.0 U/L) levels. They were also required to have active skin disease defined as a Dermatomyositis Skin Severity Index (DSSI) score of greater than 2 (scale, 0-72). They had to have adequate renal, liver, and hematologic parameters. They were permitted to continue treatment with topical corticosteroids or immunomodulators, oral corticosteroids, antimalarial agents, or mycophenolate mofetil if the doses were stable for 4 weeks before screening. Methotrexate or azathioprine therapy was permitted if the doses were stable for 6 and 12 weeks, respectively. All patients underwent malignancy screening before enrollment as deemed appropriate by their primary care physicians. Patients with significant cardiac or pulmonary disease, active infection, or serologic tests that were positive for hepatitis B, hepatitis C, or human immunodeficiency virus were excluded, as were those with a known concurrent or previous malignancy.

INTERVENTIONS AND ASSESSMENTS

All patients received 2 doses of 1 g of rituximab 2 weeks apart (modeled after the dosing method used in rheumatoid arthritis studies).9 No peri-infusional steroids were administered. Clinical assessments were performed at baseline, day 15, and weeks 4, 8, 12, 16, 20, 24, 36, and 48. One of us (L.C.) performed the following evaluations for all patients at each visit: physical examination, MMT, photographs, and evaluation of skin disease. Skin involvement was quantified by the DSSI, a novel instrument based on the Psoriasis Area and Severity Index, which evaluates severity (erythema, induration, and scale) and extent of cutaneous disease (C. L. Carroll, MD, and J. L. Jorizzo, MD, unpublished data, 2002-2004). Based on physician and patient global assessments, a score of less than 2 is consistent with mild disease; 2 through 6, with moderate disease; and greater than 6, with severe disease. Subjective assessments included the modified Health Assessment Questionnaire16 and 3 visual analogue scales: patient and physician global assessments and patient assessment of pruritus. Laboratory evaluations included a complete blood cell count and determination of creatinine, albumin, alanine aminotransferase, CPK, and aldolase levels. CD19+ B cells were measured at baseline, day 15, and weeks 4, 12, 24, 36, and 48. Human antichimeric antibody levels were obtained at baseline and weeks 12, 24, 36, and 48.

OUTCOMES

The primary end point was the percentage of patients with a partial remission at week 24 defined as any of the following: at least 50% reduction in CPK levels if the baseline values were greater than 2 times the upper limit of normal; at least 50% reduction in muscle strength deficit (the difference between maximum possible MMT score of 90 and the patient’s baseline score) if the baseline MMT score was less than 85; or a 75% improvement in the DSSI score. Secondary end points included the mean percent change in subjective assessments at week 24 compared with baseline.

STATISTICAL ANALYSIS

Descriptive statistics were obtained using SAS software (Version 9.1; SAS Institute Inc, Cary, NC). For continuous variables, the paired t test was used to compare means at week 24 with those at baseline. Intention-to-treat analysis was used, and the last observations were carried forward for the patient who was lost to follow-up at week 16.

RESULTS

Ten patients with DM underwent screening (Figure 1). Two patients were excluded: one had progressive dysphagia requiring exclusionary therapies; the other had insufficient muscle disease according to the MMT score and determination of muscle enzyme levels. Eight patients (1 woman and 7 men; age range, 38-76 years) received 2 infusions of rituximab (Table). The median disease duration was 3.5 years (range, 1-24 years), and all patients were refractory to at least 1 systemic immunosuppressive agent (mean of 4 previous therapies). The median MMT score was 84.3, with 3 patients having scores greater than 85 at baseline. Median CPK and aldolase levels were 230 U/L and 9.9 U/L, respectively. All patients had significant skin disease (median DSSI score, 7.2). Patient 4 was able to taper the dosage of his corticosteroid therapy (from 16 to 12 mg of methylprednisolone) at week 8. Patient 7 was lost to follow-up after 16 weeks.

Figure 1. Disposition of patients.
OBJECTIVE ASSESSMENTS

B-Cell Levels

After the first infusion of rituximab, peripheral B cells were undetectable in all patients (Figure 2A). Circulating B cells remained depleted through week 24, and no human antichimeric antibodies were seen (data not shown).

Muscle Strength

Three patients (38%) achieved the primary end point of partial remission at week 24 by showing at least 50% reduction in muscle deficit (Figure 2B). Three other patients had improved muscle strength that did not meet criteria for partial remission, including patient 1, whose initial improvement reversed after week 16. This patient had self-discontinued methotrexate therapy at week 12 and had begun mycophenolate mofetil therapy at week 20.

Muscle Enzymes

Of the 4 patients with elevated baseline CPK levels, 3 had relatively stable values over the 24-week period (Figure 2C). Patient 7 experienced a progressive increase in CPK levels through 16 weeks of follow-up. Mean CPK and aldolase levels increased by 17.80% and 15.13% at week 24 compared with those at baseline (P = .60 and P = .36, respectively).

Skin Disease

Skin disease, as measured by the DSSI, was generally stable over time (Figure 2D). The mean percentage of change in DSSI was 9.5% (95% confidence interval, −35.8% to 16.7%) at week 24 compared with baseline, but this improvement did not reach statistical significance (P = .42). Photographs demonstrated that periungual telangiectasias were unchanged in all 8 subjects. Poikiloderma was present at baseline in 6 subjects and was unchanged at week 24 in half of the patients and slightly worse in the other 3. The heliotrope rash remained unchanged in 6 subjects, while 1 subject experienced improvement and 1 experienced worsening of the rash. Three subjects with Gottron papules at baseline had no change at week 24.

SUBJECTIVE ASSESSMENTS

None of the subjective assessments changed substantially when results at week 24 were compared with baseline (data not shown).

Table. Baseline Characteristics of 8 Patients With Dermatomyositis Treated With Rituximab

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Disease Duration, y</th>
<th>Baseline CPK Level, U/L</th>
<th>Baseline Aldolase Level, U/L</th>
<th>Baseline MMT Score (0-90)</th>
<th>Baseline DSSI Score (0-72)</th>
<th>Previous Treatments</th>
<th>Concomitant Treatments*</th>
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<tr>
<td>1/F/42</td>
<td>2</td>
<td>122</td>
<td>8.2</td>
<td>78</td>
<td>6.6</td>
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<td>2/M/76</td>
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<td>16</td>
<td>10</td>
<td>84.5</td>
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<td>Prednisone (40 mg/d)</td>
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<td>8</td>
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<td>4/M/54</td>
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<td>82</td>
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<td>Methotrexate and methylprednisolone (16 mg/d)</td>
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<tr>
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<tr>
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<td>15.5</td>
<td>90</td>
<td>10.4</td>
<td>Methotrexate, azathioprine, intravenous immunoglobulin, mycophenolate mofetil, and cyclosporine</td>
<td>Prednisone (25 mg/d) and methotrexate</td>
</tr>
<tr>
<td>8/M/46</td>
<td>11</td>
<td>360</td>
<td>8.5</td>
<td>82.5</td>
<td>9.2</td>
<td>Methotrexate and azathioprine</td>
<td>Prednisone (15 mg/d) and azathioprine</td>
</tr>
</tbody>
</table>

Abbreviations: CPK, creatine phosphokinase; DSSI, Dermatomyositis Skin Severity Index; MMT, Manual Muscle Test.

* Corticosteroid and mycophenolate mofetil doses were stable for 4 weeks before screening; methotrexate and azathioprine doses were stable for 6 and 12 weeks before screening, respectively.

† Topical therapies included moderate- to high-strength steroids and immunomodulators.
SAFETY

Rituximab therapy was well tolerated by all patients without peri-infusional steroids. During their first infusion, 3 patients experienced mild infusion reactions, including headache, transient hypertension, and congestion with facial flushing. One patient experienced a progressive increase in liver transaminase levels through week 20 that resolved with the discontinuation of azathioprine therapy. Infections were observed and included superficial skin infections (2 cases), bronchitis (3 cases), sinusitis (2 cases), urinary tract infection (1 case), and otitis media (1 case), but no serious infections were noted. One patient died of metastatic cancer with primary lesions in the lung and colon 9 months after his last infusion. This patient was 76 years old and had normal findings on computed tomographic scans of the chest, abdomen, and pelvis 4 months before enrollment and normal findings on magnetic resonance imaging of the brain as well as on radiography of the chest 1 month before enrollment.

COMMENT

We present a pilot study of rituximab treatment in 8 cases of DM. Rituximab infusions were well tolerated by all 8 patients. A 1-g dose of rituximab resulted in complete peripheral B-cell depletion, which was sustained through week 24 in all patients. Of the 8 subjects, 3 met pre-defined criteria for partial remission, showing improvement in muscle strength in each case. We did not observe significant changes in skin disease through 24 weeks of follow-up. Muscle enzyme levels fluctuated throughout the study and did not reflect muscle strength.

While our study did not show the same dramatic improvement as did a recently reported open-label study, several factors could explain this discrepancy. Our study population differed in that the patients were mostly male and, perhaps more importantly, had milder muscle disease. Although our patients were treatment refractory, the baseline strength of our patient population was only slightly decreased, and 3 of 8 subjects lacked sufficient baseline deficit in muscle strength to meet criteria for improvement. We measured muscle strength using the Medical Research Council MMT scale alone, whereas Levine also used myometry. Unfortunately, these measures of muscle strength are unable to differentiate active muscle inflammation from atrophy and damage related to chronic disease or long-term corticosteroid use. Thus, it could be possible that some of our patients had atrophy that might not be expected to respond to immunomodulation. Also, the rituximab dosing regimens in the 2 studies differed, ours being a fixed dose at 2 intervals rather than 4 weekly doses based on body mass index. Although peripheral B cells were undetectable following dosing, B-cell populations in other tissues may have perpetuated disease activity.

Several factors could explain the minimal effects of rituximab therapy on DM-related skin disease. The DSSI scale weights erythema, scale, and induration equally. Thus, small changes in erythema (which is the most dominant feature of skin disease in DM) may not have been adequately reflected in the DSSI score. Also, this scale
does not measure other skin findings in DM, such as periungual telangiectasias, cuticular overgrowth, poikiloderma, calcinosis cutis, lipoatrophy, and livedo reticularis. However, photographs do not support these possibilities. Alternatively, rituximab efficacy in DM skin disease might demonstrate selectivity in certain patients or certain cutaneous manifestations. Although not observed in our study, substantial improvement of Gottron papules, erythema in the V-neck distribution, heliotrope changes, and violaceous poikiloderma have been reported after rituximab therapy.10–12 Finally, a differential efficacy for skin and muscle disease may be explained by the fact that, unlike muscle disease, skin inflammation is characterized by a predominantly CD4+ T-cell rather than B-cell infiltrate.17,18

The tolerability of rituximab infusions is consistent with that observed in the previously published open-label study.13 Five patients (62%) experienced 9 infections requiring oral antibiotic therapy. This number was not unexpected, as 39% of patients treated in rheumatoid arthritis clinical trials developed infections (rituximab package insert). One patient died of metastatic cancer after rituximab infusions. He had several risk factors for cancer-associated DM: his age, disease duration of less than 2 years, severe skin disease, and dysphagia.19 Although the relationship between rituximab infusions and the onset of malignancy in this patient is unclear, it underscores the importance of cancer surveillance in patients with DM who are receiving immunomodulatory therapies.

The results of our study suggest that B-cell depletion may be useful in the treatment of muscle inflammation in certain patients with DM. The limited effect of rituximab on the skin suggests that the mechanism of skin disease may differ from that of muscle disease. Given our small sample size, the open-label nature of the study, and the mild muscle disease in our cohort, no definite conclusions can be made. A large placebo-controlled study is under way that may elucidate the appropriate patient population, dosing regimen, and efficacy of rituximab in the treatment of patients with DM.

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Author Contributions: David Fiorentino, the principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chung, Genovese, and Fiorentino. Acquisition of data: Chung, Genovese, and Fiorentino. Analysis and interpretation of data: Chung, Genovese, and Fiorentino. Drafting of the manuscript: Chung, Genovese, and Fiorentino. Critical revision of the manuscript for important intellectual content: Chung, Genovese, and Fiorentino. Statistical analysis: Chung. Obtained funding: Genovese and Fiorentino. Administrative, technical, and material support: Genovese. Study supervision: Genovese and Fiorentino.

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REFERENCES