Rituximab as Therapy for Refractory Polymyositis and Dermatomyositis

ERIKA H. NOSS, DOROTA L. HAUSNER-SYPEK, and MICHAEL E. WEINBLATT

ABSTRACT. We describe response to rituximab treatment of refractory inflammatory myopathy. Three patients with long-standing polymyositis (PM) or dermatomyositis (DM) poorly responsive to prednisone combined with several immunosuppressants were given intravenous rituximab 1000 mg on Days 0 and 14. Prior to rituximab, each had significant proximal weakness with creatine phosphokinase (CPK) elevation to > 3 times the normal upper limit (range 789–3123 U/l). Patients were receiving prednisone plus methotrexate (MTX) or azathioprine. CPK decrease was observed 1 month post-infusion, with normalization of levels averaging 4.6 months (range 2.6–7.7 mo). Muscle strength improved in all, with strength returning to normal in 2. Average daily prednisone dose decreased from 16.7 mg (range 10–20 mg) to 4 mg (range 0–7 mg) after infusion. MTX dose was tapered by 50% in 2 patients. The third patient eventually discontinued all additional therapies. Percentage of CD19+ cells in each were suppressed at 0–1% 5 to 6 months after infusion (normal 5–21%). Elevated CPK with return of clinical symptoms occurred in 2 patients 6 and 10 months post-infusion, requiring rituximab retreatment. CD19+ cells remained suppressed at 1% in one patient, but were almost normal at 4% in the other. The third patient remains disease-free 12 months after initial treatment, even though her CD19+ cells are now normal at 8%. Thus, short-term beneficial effects with rituximab were observed in patients with DM and PM. However, the need for retreatment did not correlate with levels of CD19+ cells.

Key Indexing Terms:
MYOSITIS       DERMATOMYOSITIS      POLYMYOSITIS      ANTIBODIES     MONOCLONAL

Inflammatory myopathies are idiopathic autoimmune disorders leading to chronic muscle inflammation. Corticosteroids have been the cornerstone of therapy1-3. However, a substantial number of patients respond incompletely or relapse with corticosteroids alone. The choice of additional immunosuppressive agents has remained largely empirical. A small number of controlled trials have shown treatment efficacy with intravenous immunoglobulin (IVIG), azathioprine, and methotrexate (MTX)4-7. A larger number of case series and reports have suggested that medications such as cyclosporine, tacrolimus, cyclophosphamide, infliximab, etanercept, and mycophenolate mofetil may be useful in patients with aggressive disease8-15. Despite immunosuppressive treatment, polymyositis (PM) and dermatomyositis (DM) cause significant morbidity and mortality, both from the disease itself and from treatment-related complications8,16,17.

Rituximab is a human/murine chimeric monoclonal antibody directed against CD20+ B cells that has shown promising results in the treatment of a broad array of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and IgM-mediated neuropathies18-23. A recent study reported improvement in muscle inflammation and strength after rituximab infusion in an open trial of 7 patients with DM24. An additional case report25 suggested that rituximab may be effective in PM. We describe 3 patients with long-standing, treatment-refractory PM and DM who also had striking clinical and biochemical responses after treatment with rituximab.

CASE REPORTS
Demographic information for each patient is summarized in Table 1, with case histories given below. Two patients had PM, one patient had DM. The patients had long-standing disease (average 9.1 yrs, range 3.2–12.8 yrs), were anti-histidy-l-aminoacyl-tRNA synthetase (Jo-1 antibody)-negative, and had failed to respond to multiple immunosuppressive therapies (range 5–7) prior to rituximab therapy.

Patient 1. A 54-year-old woman was diagnosed in summer 1992 with PM after 6 months of progressive, painless, proximal muscle weakness and elevated creatine phosphokinase (CPK) of 1040 U/l. Electromyography (EMG) showed marked myopathic changes. Left deltoid biopsy showed multiple small inflammatory infiltrates with myofiber degeneration with necrosis and phagocytosis of individual fibers, consistent with inflammatory myopathy.
Despite treatment with 60 mg prednisone daily and IVIG monthly, her strength declined to the point where she had difficulty climbing stairs. She developed recurrent episodes of atrial flutter, ultimately requiring radiofrequency ablation with insertion of a permanent pacemaker. Eventually, her strength and CPK improved with high-dose MTX (up to 70 mg subcutaneous, SQ, weekly), allowing her to lower her prednisone dose to as little as 5 mg daily (Figure 1A). Over the next 4 years, further attempts to taper her medications resulted in worsening disease. By 1998, her exercise intolerance worsened and her CPK rose despite increased doses of MTX and prednisone. Over the next 4 years, she was treated with multiple immunosuppressive combinations, including MTX/azathioprine, MTX/azathioprine/etanercept, and MTX/infliximab. She received prednisone throughout at low to moderate doses. With each combination, she initially responded, often with CPK normalization. However, within one to 2 years, she would experience flare, with further loss of muscle strength. By August 2004, she was wheelchair-bound with a rapidly rising CPK at 789 U/l while receiving MTX 40 mg weekly and infliximab 10 mg/kg every 6 weeks. At this point, infliximab was stopped, and she received 2 doses of rituximab IV 1000 mg on Days 0 and 14, with methylprednisolone IV 80 mg as infusion premedication. One month after rituximab infusion, her CPK had started to decrease. By 3 months, it had fallen 30%. At this point, she was started on low-dose mycophenolate mofetil (500 mg twice daily) to achieve better disease control and to potentially prevent development of human antichimeric antibodies. Eight months after initial infusion, her CPK was normal. She is now 12 months post-rituximab, with normal CPK and muscle strength after self-discontinuing mycophenolate mofetil despite recovery of CPK.

<table>
<thead>
<tr>
<th>Current age/sex</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>PM</td>
<td>PM</td>
<td>DM</td>
</tr>
<tr>
<td>Duration, yrs</td>
<td>12.8</td>
<td>11.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Initial CPK, U/l</td>
<td>1040</td>
<td>5840</td>
<td>4819</td>
</tr>
</tbody>
</table>

**Table 1.** Patient demographic information, immunosuppressive therapies, and CPK levels before and after rituximab therapy.

<table>
<thead>
<tr>
<th>Pred-rituximab</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPK (U/l)</td>
<td>789</td>
<td>3123</td>
<td>949</td>
</tr>
<tr>
<td>Medications</td>
<td>MTX 40 mg/</td>
<td>Pred 20 mg</td>
<td>MTX 50 mg/</td>
</tr>
<tr>
<td></td>
<td>Pred 10 mg</td>
<td></td>
<td>Pred 20 mg</td>
</tr>
<tr>
<td>Post-rituximab (time of maximal improvement)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months</td>
<td>9*</td>
<td>10</td>
<td>5*</td>
</tr>
<tr>
<td>CPK (U/l)</td>
<td>119</td>
<td>84</td>
<td>103</td>
</tr>
<tr>
<td>Medications</td>
<td>MTX 20 mg/</td>
<td>MFM 500 mg</td>
<td>MTX 25 mg/</td>
</tr>
<tr>
<td></td>
<td>Pred 5 mg</td>
<td></td>
<td>Pred 7 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BID (self-discontinued at 12 mo)</td>
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</tr>
</tbody>
</table>

| Percentage CD19-positive** | 3 | 8 | 1 |

* Receiving a second dose of rituximab. ** Normal 5–21%. EMG: electromyography; ANA: antinuclear antibody; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; MFM: mycophenolate mofetil; Pred: prednisone.

**Patient 2.** A 53-year-old woman was diagnosed in winter 1994 with PM after 4 months of palpitations and progressive proximal weakness. Presenting CPK was 5840 U/l, and EMG confirmed widespread myopathic changes. Right quadriceps biopsy showed necrosis, myophagocytosis, and regenerating fibers, indicating active myopathy. A focus of interstitial inflammation consistent with PM was noted. She was also diagnosed with new-onset atrial flutter. Response to prednisone 60 mg daily was partial, and her strength declined to the point where she needed assistance getting out of a chair or getting dressed. Eventually, her CPK and strength returned to normal on a combination of IVIG, MTX, and prednisone (Figure 1B). Stopping IVIG led to a return of disease activity, but she developed fevers and shortness of breath when challenged with this medication. Her disease was again brought under control, this time with high-dose MTX (50 mg weekly), and prednisone was tapered for a period of several months. Three years after presentation, her muscle disease again returned. She was switched to combination prednisone/MTX/azathioprine and then azathioprine alone after she developed gastrointestinal intolerance to MTX, with further good control for over 2 years before once again developing quadriceps weakness. Leflunomide was briefly started but then discontinued due to an allergic rash. Her CPK rose to greater than 3000 U/l, and etanercept and prednisone were added to the azathioprine. Her CPK fell markedly on this therapy over the course of one year, but then rapidly rose again after etanercept was stopped due to the national etanercept shortage. CPK rise was accompanied by worsening weakness and atrial fibrillation complicated by frequent runs of ventricular ectopy. Resumption of etanercept did not control her disease, so she was switched to infliximab with significant improvement, eventually discontinuing prednisone and azathioprine. However, in fall 2003, infliximab was stopped during a hospital admission for acute cholecystitis, congestive heart failure, and sustained wide-complex tachycardia requiring defibrillator implantation. Prednisone treatment was resumed to control her PM. By spring 2004, infliximab was restarted due to rising CPK concentrations and worsening cardiac arrhythmias. However, she developed New York Heart Association Class III failure, and infliximab was again discontinued. An attempt was made to restart azathioprine, but dosing was limited by gastrointestinal side effects. By this point, her strength had declined to where she required a cane to ambulate, and her CPK was 3123 U/l. In August 2004, she was treated with 2 doses of rituximab IV 1000 mg on Days 0 and 14, with methylprednisolone IV 80 mg as infusion premedication. One month after rituximab infusion, her CPK had started to decrease. By 3 months, it had fallen 30%. At this point, she was started on low-dose mycophenolate mofetil (500 mg twice daily) to achieve better disease control and to potentially prevent development of human antichimeric antibodies. Eight months after initial infusion, her CPK was normal. She is now 12 months post-rituximab, with normal CPK and muscle strength after self-discontinuing mycophenolate mofetil despite recovery of CD19+ cell counts to the normal range at 8% (Table 1).
his DM flared after 4 months when prednisone was tapered to 13 mg daily. Despite increasing adalimumab to 40 mg weekly and raising his prednisone dose to as high as 55 mg daily, his CPK remained elevated. His CPK plateaued around 1000 U/l for several months on this therapy, with continued fatigue and myalgias. In November 2004, his CPK was 949 U/l. Adalimumab was discontinued, and 2 doses of rituximab 1000 mg IV at Days 0 and 14 were given. Methylprednisolone 80 to 100 mg IV was given prior to each dose to prevent transfusion reactions. After one month, his CPK began to fall. By 3 months post-infusion, his CPK and proximal muscle strength were entirely normal. He resumed regular exercise and the erythema on his hands improved. At 6 months post-rituximab, he reported mild fatigue, but no myalgias or muscle weakness. His rash was limited to mild periungual and facial erythema. He had reduced his MTX dose by 50% and his steroid dose by greater than 60% (Table 1). The next month (Month 7 after initial infusion), his myalgias and fevers returned, and his CPK rose above the normal range to 328 U/l. Magnetic resonance imaging of his thighs was consistent with active myositis. Two weeks prior to the documented increase in CPK, CD19+ cell counts remained suppressed at 1%. He has subsequently received a repeat course of rituximab and again normalized his CPK.

As shown in Figure 1, disease activity was improved or controlled in each patient, often for months to years, with a variety of immunosuppressive agents, including IVIG, high-dose MTX, azathioprine, tumor necrosis factor

Rituximab-mediated B cell depletion as an effective treatment for DM is consistent with proposed models of disease pathogenesis. Several lines of evidence, especially histopathologic studies, have suggested a strong role for both CD4+ T cells and B cells in mediating disease activity. Perifascicular endothelium immunoglobulin and complement deposition are believed to lead to muscle ischemia and atrophy, indicating the importance of humoral immunity. This model is supported by the activity of rituximab against DM now in 2 studies.

On the other hand, our study and a recent case report document the effectiveness of rituximab in treatment of PM, which seems to contradict proposed models of disease pathogenesis. Although subsets of patients with both PM and DM have myositis-specific antibodies, the pathogenic role of these antibodies is not clear. PM has been viewed as a predominantly CD8+ cytotoxic T lymphocyte-mediated attack on muscle fibers, manifested by a predominantly endomyesial infiltration. Therefore, it is somewhat surprising that B cell depletion had such a striking response in patients with 3 months post-rituximab to prevent the development of human antichimeric antibodies. This patient’s initial response to rituximab was less robust, and a contribution of mycophenolate mofetil to her eventual improvement cannot be excluded. However, her CPK level had already fallen by 30% by the time that mycophenolate was begun, the mycophenolate dose remained less than standard treatment doses, and she successfully stopped the medication, arguing that rituximab had a significant role in her improvement.

Our observations add to those recently published. Levine reported effectiveness of rituximab in treating 6 patients with DM, most with refractory disease. Unlike this study, we also found effectiveness of rituximab against PM, similar to a recent case report. Our experience, like Levine’s, showed disease improvement as early as 4 weeks after infusion. Time to maximal response was also similar between this and Levine’s series (2.6–8 and 3–9 months, respectively). Four patients in that report had return of symptoms by 6 to 9 months, coinciding with return of CD19+ B cells. The other 2 had sustained improvement one year after rituximab infusion, despite the return of circulating CD19+ cells in one. In our series, 2 patients had return of symptoms, even though CD19+ cells remained suppressed in the patient with DM. In contrast, one PM patient continued to be free of disease activity 10 months after rituximab, despite evidence for the reemergence of her CD19+ cells. It remains to be seen whether this increase in circulating CD19+ cells heralds a return of disease activity or suggests a more sustained remission such as that seen in one patient in the report by Levine. Although return of CD19+ cells is a marker for decreasing activity of the rituximab monoclonal antibody, it is possible that rituximab treatment alters the immune response in ways independent of the CD19 cell count, accounting for this discrepancy between CD19+ cell counts and disease activity post-infusion in some patients.

Rituximab-mediated B cell depletion as an effective treatment for PM seems to contradict proposed models of disease pathogenesis. Although subsets of patients with both PM and DM have myositis-specific antibodies, the pathogenic role of these antibodies is not clear. PM has been viewed as a predominantly CD8+ cytotoxic T lymphocyte-mediated attack on muscle fibers, manifested by a predominantly endomyesial infiltration. Therefore, it is somewhat surprising that B cell depletion had such a striking response in patients with
of chronic lymphocytic leukemia. Neither a fall in serum levels nor an increase in infectious complications was observed with this sustained therapy. However, the optimal dosing regimen, duration of therapy, and safety profile of rituximab therapy in treatment of autoimmune diseases remains to be elucidated.

Our case series supports an earlier study showing rituximab as a promising new therapy in DM, and for the first time shows its efficacy against PM. The effect of rituximab in PM supports a role for B cells in disease pathogenesis. Our observations highlight the need for further controlled trials in the treatment of inflammatory myopathies to investigate the efficacy of rituximab and to delineate its role in treatment compared to other immunosuppressive therapies. Randomized trials to test the effectiveness of rituximab in treatment of inflammatory myopathies are warranted.

REFERENCES


