Case Report

Rituximab as Therapy for Refractory Polymyositis and Dermatomyositis

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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. (First Release Mar 15 2006; J Rheumatol 2006;33:1021-6)

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 therapy[1-3]. However, a substantial number of patients respond incompletely or relapse with corticosteroids alone. The choice of additional immunosuppressive agents has remained largely empiric. 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 disease[8-15]. Despite immunosuppressive therapy, polymyositis (PM) and dermatomyositis (DM) cause significant morbidity and mortality, both from the disease itself and from treatment-related complications[2,16,17].

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 neuropathies[18-23]. A recent study reported improvement in muscle inflammation and strength after rituximab infusion in an open trial of 7 patients with DM[24]. An additional case report[25] 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.

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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-histidyl-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.

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

	Patient 1	Patient 2	Patient 3
Current age/sex	54 F	54 F	48 M
Diagnosis	PM	PM	DM
Duration, yrs	12.8	11.4	3.2
Initial CPK, U/l	1040	5840	4819
EMG	+	+	–
Consistent biopsy	+	+	+
ANA	NA	–	–
Jo-1	–	–	–
Arrhythmias	+	+	–
Lung disease	–	–	Transient infiltrates
No. DMARD	5	7	5
Pre-rituximab			
CPK (U/l)	789	3123	949
Medications	MTX 40 mg/ Pred 10 mg	Pred 20 mg	MTX 50 mg/ Pred 20 mg
Post-rituximab (time of maximal improvement)			
Months	9*	10	5*
CPK (U/l)	119	84	103
Medications	MTX 20 mg/ Pred 5 mg	MMF 500 mg BID (self-discontinued at 12 mo)	MTX 25 mg/ Pred 7 mg
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; MMF: mycophenolate mofetil; Pred: prednisone.

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 1000 mg IV on Days 0 and 14 with methylprednisolone 100 mg IV as premedication prior to infusion. One month later, her CPK began to fall, and by 3.5 months post-infusion, was completely normal. Nine months after infusion, her strength improved to allow ambulation with a walker, and her CPK remained in the normal range. Her other immunosuppressive medications were tapered by 50%, down to MTX 20 mg weekly and prednisone 5 mg daily (Table 1). At this point, screening of lymphocyte subsets suggested some recovery of her CD19+ cells, increasing to 3% from 1% 4 months earlier. The following month, 10 months after her initial infusion, her CPK increased to 348 U/l and her CD19+ B cells climbed to 4%. She then received a second course of rituximab, with repeat normalization of her CPK.

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 rechallenged 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 defribrillator 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).

Patient 3. A 47-year-old man was diagnosed with DM in March 2002 after 6 weeks of severe myalgias, progressive proximal weakness, fevers, and Gottron's papules. His presenting CPK was 4819 U/l. Although EMG did not show myopathic changes, right quadriceps muscle biopsy showed myopathic changes consistent with DM, with a predominantly perifascicular distribution with focal perifascicular, and to a lesser extent, endomysial inflammatory infiltrates. Chest computed tomography (CT) showed small subpleural and bibasilar infiltrates, which along with a decreased diffusing capacity (carbon monoxide, DLCO) suggested possible interstitial lung disease. His strength and CPK only partially improved on high-dose prednisone (60 mg daily), so monthly IVIG in combination with MTX (up to 42.5 mg weekly) was added (Figure 1C). On this therapy, he had significant improvement in clinical symptoms, near normalization of his CPK, and resolution of his pulmonary infiltrates. As his prednisone was tapered, his disease returned with fevers and myalgias. IVIG was discontinued after 5 doses, and infliximab begun. He had marked improvement on infliximab (5 mg/kg) and MTX, allowing reduction of prednisone to 20 mg daily. However, infliximab was discontinued after post-infusion hypotension and back spasms. Initially, etanercept was tried, but myalgias and fevers returned. Then adalimumab 40 mg every other week was added to MTX and prednisone, with near normalization of his CPK. However,

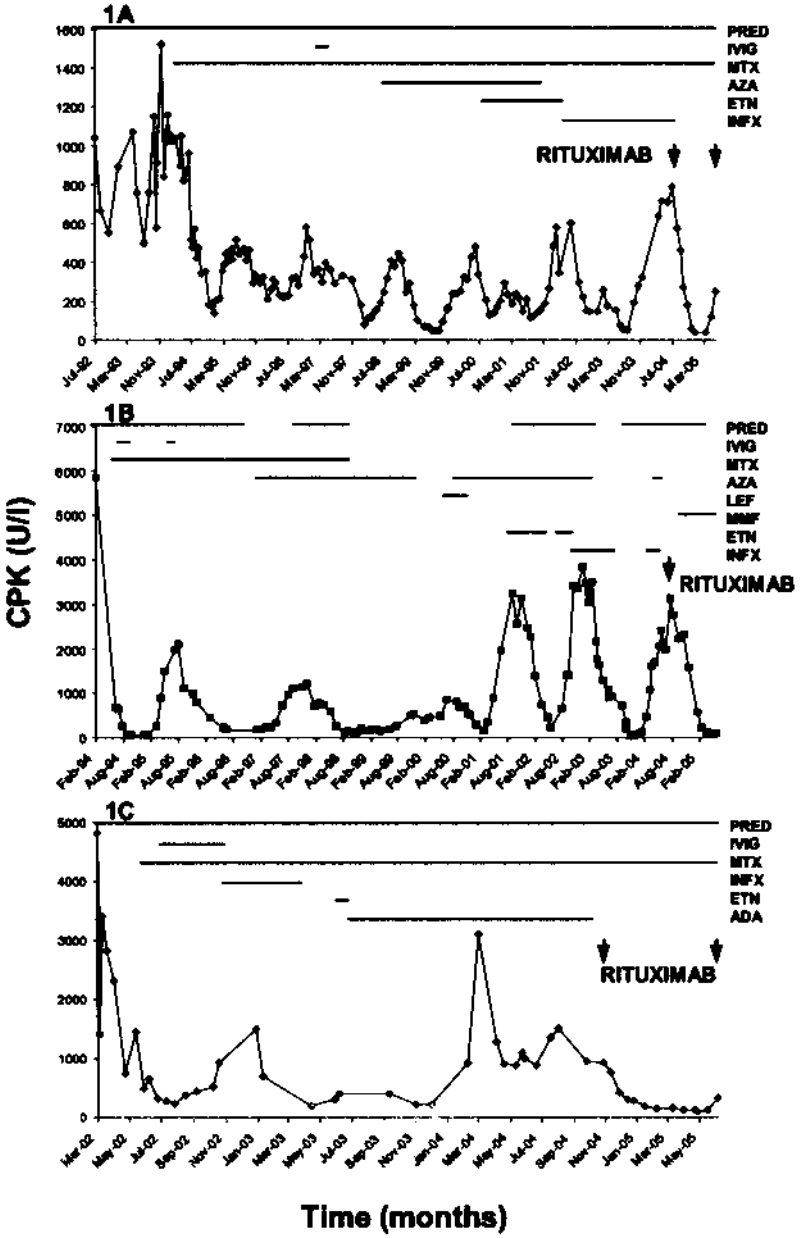

Figure 1. Disease activity documented by patients' CPK over time, with correlating immunosuppressive therapies. Timing of rituximab infusions shown by arrows in each graph. Patients 1 and 3 have now received 2 doses of rituximab. A: Patient 1. B: Patient 2. C: Patient 3. PRED: prednisone, MTX: methotrexate, AZA: azathioprine, LEF: leflunomide, MMF: mycophenolate mofetil, INFX: infliximab, ETN: etanercept, ADA: adalimumab.

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

(TNF) inhibitors, or combinations of these agents. However, in each case, their effect was limited by side effects or return of disease activity. By the time rituximab was given, each patient had both elevated CPK (Table 1) and significant clinical symptoms. Patient 1 was wheelchair-bound, Patient 2 ambulated with a cane and suffered from congestive heart failure with recurrent cardiac ventricular arrhythmias, and Patient 3 reported myalgias and subjective weakness. Within one month of the infusion, each patient's CPK had fallen. CPK concentrations were normal by an average of 4.8 months (range 2.6 to 8 mo), with significant improvement in clinical symptoms. In all patients, prednisone dose was reduced from an average of 16.7 mg (range 10 to 20 mg) to 4 mg (range 0 to 7 mg). Patients 1 and 3 were both able to taper their weekly MTX dose, from 40 and 50 mg to 20 and 25 mg, respectively. Mycophenolate mofetil was started 3 months after rituximab infusion in Patient 2, for persistent symptoms and to prevent the development of human antichimeric antibodies. By this time, her CPK level had already decreased by 30%.

To date, 2 patients have had a return of symptoms and associated increased CPK, 6 to 9 months after initial infusion. Interestingly, return of disease activity did not appear to correlate with levels of B cells, as monitored by the percentage of CD19+ cells on a lymphocyte panel. Percentage of CD19+ (%CD19+) cells is used as a B cell marker, as %CD20+ cells cannot be measured accurately by flow cytometry due to interference from rituximab present in patient serum. One patient did have an increase in her %CD19+ cells when disease activity returned (Patient 1, 4% at 10 months post-infusion). However, the other patient's %CD19+ cells remained suppressed when checked just 2 weeks prior to documented CPK increase (Patient 3). The final patient, who remains disease-free, also has had recovery of her %CD19+ cells to normal levels (Patient 2, Table 1). Serum immunoglobulin levels were not significantly decreased by rituximab in any of these patients, and no infectious complications or infusion reactions have been noted to date.

DISCUSSION

Our case series illustrates a remarkable short-term response to rituximab in 3 patients with treatment-refractory inflammatory myopathy. These patients had at least a partial response to commonly used immunosuppressive therapies after corticosteroids alone did not control their disease. As suggested by previous trials[1-3], IVIG, MTX, azathioprine, or combinations of these therapies were all initially effective, often giving a sustained response. However, each patient's disease activity returned, despite high-dose treatment. This recurrence of disease is consistent with previously reported initial responses with IVIG followed by return of disease activity despite continued dosing of this medication[26]. Once each patient had failed these more conventional therapies, TNF inhibitors were added to baseline MTX or azathioprine. Although, as described in many case reports[9,15,27-32], each patient did have an initial marked response to TNF inhibitors, this response was ultimately not sustained or was limited by medication side effects.

Rapid response was observed after rituximab infusion, with decline in CPK starting within one month. Although each patient did receive a single dose of IV methylprednisolone prior to each infusion, the addition of high-dose steroids seems unlikely to explain the disease response, as each patient had failed high-dose steroid treatment in the past. In 2 patients, response seemed solely due to the addition of rituximab, as this medication was added to stable doses of MTX and prednisone, which were subsequently tapered. However, in one patient (Patient 2), mycophenolate mofetil was started 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[24]. Unlike this study, we also found effectiveness of rituximab against PM, similar to a recent case report[25]. 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 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[33-37]. 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[25] 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[33,36,38]. PM has been viewed as a predominantly CD8+ cytotoxic T lymphocyte-mediated attack on muscle fibers, manifested by a predominantly endomysial infiltration[33-36]. Therefore, it is somewhat surprising that B cell depletion had such a striking response in patients with

PM, especially as both patients were at least negative for the most common myositis-specific antibody, Jo-1. This result suggests a stronger role for B cells in PM disease pathogenesis than may have been previously recognized, perhaps in a costimulatory or antigen presentation function.

Rituximab therapy is an attractive treatment option for several reasons. Its onset of action seems to be relatively rapid and its short-term safety profile is favorable. Experience from the lymphoma literature suggests a low incidence of adverse effects with the medication, mostly related to infusion reactions after the first dose[39,40]. One study described repeated rituximab infusions every 6 months for 2 years for the treatment of chronic lymphocytic leukemia[41]. Neither a fall in serum immunoglobulin 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.

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