

# Rituximab for Refractory Polymyositis: An Open-label Prospective Study

CHI CHIU MOK, LING YIN HO, and CHI HUNG TO

**ABSTRACT.** *Objective.* To report the efficacy and toxicity of rituximab in the treatment of refractory polymyositis. *Methods.* Adult patients with active polymyositis as evidenced by persistent proximal muscle weakness, elevated creatine kinase (CK) level, and features of active myositis on electromyography who were refractory to corticosteroids and at least 2 other immunosuppressive agents were recruited. While immunosuppressive agents were continued, rituximab (375 mg/m<sup>2</sup>) was given by intravenous infusion weekly for 4 consecutive weeks. Patients were followed up 4-weekly for serial assessment of muscle power, serum muscle enzymes, physician's and patient's global impression of disease activity, disability, and quality of life scores. *Results.* Four patients (3 women, 1 man) were studied. The mean age was 53 ± 11 years and the mean duration of polymyositis was 4.8 ± 3.3 years. All had persistently active myositis for at least 2 years. At Week 28, significant improvement in the mean proximal muscle power scores and reduction in CK levels in comparison to baseline were observed. Two patients had return of full muscle power with significant drop in CK level. There was a trend of improvement in disability scores and both the mental and physical components of the Medical Outcomes Study Short Form-36 Health Survey scores. Rituximab was well tolerated. *Conclusion.* Rituximab is an option to be considered in refractory polymyositis, but further controlled trials are necessary to confirm its efficacy. (First Release August 15 2007; J Rheumatol 2007;34:1864-8)

*Key Indexing Terms:*

INFLAMMATORY MYOPATHIES      RITUXIMAB      RESISTANT      B CELL DEPLETION

Polymyositis (PM) is a chronic idiopathic autoimmune inflammatory muscle disorder that is associated with significant morbidity and mortality<sup>1</sup>. The mainstay of treatment is corticosteroids. However, a substantial proportion of patients with PM are either partially responsive or refractory to corticosteroid treatment. Uncontrolled and small controlled trials have demonstrated that azathioprine (AZA), methotrexate (MTX), cyclosporine A (CSA), and intravenous immunoglobulin (IVIG) are effective in inflammatory myopathies that included polymyositis<sup>2</sup>. A number of agents such as IVIG, cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus, CSA, etanercept, and infliximab have also been used anecdotally with success in refractory polymyositis<sup>3</sup>.

Rituximab is a chimeric monoclonal antibody that directs against the CD20 antigen on the surface of B cells. Administration of rituximab leads to selective depletion of the CD20+ B cells, leaving the stem cells and plasma cells unaffected. A randomized controlled trial has shown that rituximab is effective in rheumatoid arthritis that is refractory to MTX<sup>4</sup>.

Uncontrolled open-label trials have also demonstrated efficacy of rituximab in the treatment of a variety of autoimmune diseases such as refractory systemic lupus erythematosus, immune thrombocytopenic purpura, autoimmune hemolytic anemia, IgM associated polyneuropathies, and systemic vasculitides<sup>5</sup>. A recent open-label study demonstrated efficacy of rituximab in the treatment of 6 patients with dermatomyositis<sup>6</sup>. Several other case reports have described benefits of rituximab in the management of refractory polymyositis<sup>7-9</sup>. However, formal assessment of disability and quality of life is not available in these reports. We conducted an open-label prospective study of the efficacy of rituximab in 4 patients with polymyositis who were refractory to conventional therapies.

## MATERIALS AND METHODS

*Patient recruitment.* Four patients who fulfilled the following criteria were included for this study: (1) age ≥ 18 years; (2) met the Bohan and Peter criteria for definite or probable diagnosis of polymyositis<sup>10</sup>; (3) investigations did not reveal other underlying autoimmune diseases or malignancies; (4) active myositis as evidenced by persistent proximal muscle weakness, elevated creatine kinase (CK), and features of active myositis on electromyography (EMG) for at least 4 months; (5) refractory to corticosteroids and at least 2 other immunosuppressive agents. Exclusion criteria were: (1) major surgery within 8 weeks prior to study; (2) immunization with a live/attenuated vaccine within 4 weeks prior to study; (3) active current bacterial, viral, fungal, mycobacterial, or other infections; (4) pregnant women or lactating mothers.

*Treatment protocol.* Informed consent was obtained from all patients. While immunosuppressive agents at study entry were allowed to be continued, their dosages could not be altered throughout the study period. In addition, rituximab (375 mg/m<sup>2</sup>) was given by IV infusion weekly for 4 consecutive weeks.

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Paracetamol (1000 mg) alone was routinely given as a premedication before infusion of rituximab. Antihistamines and corticosteroids were not routinely given as premedications, but were reserved for patients who developed allergic reactions to rituximab infusion.

**Clinical assessment.** Patients were followed up at baseline and then 4-weekly until the 20th week. The following assessment was serially performed: (1) manual muscle strength testing of the proximal (shoulder adductors and abductors, biceps, triceps, hip flexors and extensors, hip adductors and abductors, knee flexors and extensors) and axial muscles (neck and trunk muscles) as assessed on a 0–10 point scale<sup>11</sup>; (2) serum muscle enzymes [CK, lactate dehydrogenase, serum glutamic-oxaloacetic transaminase (SGOT)]; (3) physician's global assessment of disease activity [visual analog scale (VAS) 0–10]; (4) patient's global assessment of disease activity (VAS 0–10); (5) disability scores [Health Assessment Questionnaire (HAQ)] (baseline, Week 12 and 20); (6) quality of life [Medical Outcomes Study Short Form-36 Health Survey (SF-36) questionnaire] (baseline, Week 12 and 20); (7) complete blood counts, lymphocyte counts, liver and renal function tests; and (8) adverse events related to rituximab infusion. The same physician (CHT), who was blinded for the medical records, laboratory results, drug treatment, and visit week number of patients, was responsible for assessing the muscle power and physician's global scores of the activity of myositis throughout the study visits. A research nurse was responsible for obtaining the self-reported questionnaire results before clinical assessment.

After completion of Week 20 assessment, we continued to follow our patients up 4-weekly for another 2 visits for clinical muscle power and serum muscle enzyme levels.

**Statistical analyses.** Unless otherwise specified, values were expressed as mean  $\pm$  standard deviation (SD). The paired Student's *t*-test was used to compare continuous data between baseline and various time intervals after rituximab infusion. Statistical significance was defined as *p* values  $< 0.05$ , 2-tailed. All statistical analyses were performed by the SPSS program (version 11.5 for Windows XP; SPSS, Chicago, IL, USA).

## RESULTS

Four patients (3 women, 1 man) were studied. The mean age was  $53 \pm 11$  years and the mean duration of polymyositis was  $4.8 \pm 3.3$  years. Previous ineffective therapies included high dose corticosteroids ( $n = 4$ ), IV pulse methylprednisolone ( $n = 2$ ), AZA ( $n = 4$ ), MTX ( $n = 1$ ), MMF ( $n = 4$ ), CSA ( $n = 3$ ), tacrolimus ( $n = 1$ ), and IVIG ( $n = 3$ ). All of them had active myositis at study entry as evidenced by persistent muscle weakness and elevation of the muscle enzymes for at least 4 months, with documentation by EMG. Muscle biopsy was performed in all patients at the time of diagnosis and 2 of them showed histological features compatible with polymyositis. In the other 2 patients, special staining of the muscle fibers for glycogen was negative and their lipid content was not increased. Examination by electron microscopy did not reveal any inclusion or tubuloreticular bodies. Table 1 shows the clinical characteristics and histological findings of the 4 patients studied. Anti-Jo-1 antibody was present in Patient 2 but absent in the other patients.

**Changes in muscle power and muscle enzyme levels.** Figures 1 and 2 show the serial changes in proximal muscle power (mean score of the proximal muscles tested) and serum CK levels of our patients. There was a significant improvement in proximal muscle power at Week 28 compared to baseline ( $5.3 \pm 3.8$  to  $7.3 \pm 3.8$ , respectively;  $p = 0.002$ ). The drop in CK levels also reached significance ( $2632 \pm 1583$  to  $661 \pm 359$

U/l;  $p = 0.05$ ). The treatment response of individual patients is also summarized in Table 1. Two patients had return of full muscle power with a significant drop in muscle enzymes (Patients 2 and 3). The clinical improvement in these 2 patients was significant and meaningful. The other 2 patients had reduction in muscle enzyme level, but clinical improvement in muscle power was only modest (Patients 1 and 4).

**Changes in disability and quality of life.** Figures 3 to 5 show the serial changes in global assessment, quality of life, and disability scores in our patients from baseline to Week 20. A trend of reduction in global assessment scores and HAQ scores and improvement in both the mental and physical components of the SF-36 scores was observed.

**Changes in total lymphocyte counts.** Figure 6 shows the serial changes in mean total lymphocyte counts of our patients before and after rituximab infusion. A drop in the lymphocyte counts occurred at Week 4, followed by a gradual return of the counts to pretreatment levels at Week 16.

**Adverse events.** Despite the fact that corticosteroids were not used as premedication prior to rituximab infusion, none of our patients experienced allergic or infusion reactions. No infective episodes or other adverse events were reported throughout the study period.

## DISCUSSION

This is a prospective study of the efficacy of rituximab in 4 patients with refractory polymyositis. Significant improvement in the mean proximal muscle power scores and serum CK levels was observed at 28 weeks as compared to baseline. Two patients had clinically meaningful improvement in muscle power with a significant drop in CK level. Moreover, there was a trend of improvement in disability scores and quality of life at 20 weeks after rituximab treatment. Although a control group is lacking, the clinical improvement is unlikely to be spontaneous because all patients had persistently active myositis and elevated CK levels for at least 4 months before rituximab infusion. Indeed, all patients had active myositis refractory to multiple treatment modalities for at least 2 years before study entry. One additional observation is that the clinical response of myositis to rituximab may be delayed. Obvious improvement in clinical muscle power and reduction in CK level was not observed until Week 20 after treatment. Nevertheless, rituximab was well tolerated.

Our results are in accord with those recently reported by several independent groups<sup>6–9</sup>. Levine described improvement in muscle strength, muscle enzymes, and skin lesions after rituximab treatment (4-weekly infusions of 100 mg/m<sup>2</sup> in 3 patients and 375 mg/m<sup>2</sup> in the other 3) in 6 patients with refractory dermatomyositis<sup>6</sup>. Maximum improvement in muscle power only occurred at 12 to 36 weeks after treatment. Noss, *et al*<sup>7</sup> described successful use of rituximab (2 doses of 1000 mg at 2-week interval) in 3 patients with refractory polymyositis. Decrease in muscle enzymes was observed 1

Table 1. Clinical characteristics and treatment response of individual patients.

Patient	Age, Sex yrs	Disease Duration, yrs	Muscle Histological Findings	Previous Ineffective Therapies	Therapies within 3 Months of Study Entry	Treatment Response
1	46 F	4	Muscle fibers vary in diameter, atrophic and regenerative fibers present, minimal inflammatory cellular infiltration. Glycogen stain negative, lipid content normal, EM examination for tubuloreticular and inclusion bodies negative	Pred, pulse MP, AZA, CSA, MMF, IVIG	Pred 5 mg/day, MMF 1.5 g/day	Drop in CK level with mild improvement in proximal muscle power
2	51 F	5	Variation in fiber diameter, atrophic and regenerating fibers present, mononuclear cellular infiltration, glycogen stain negative, lipid content not increased, no fiber necrosis	Pred, AZA, CSA, MTX, MMF, tacrolimus, IVIG	Pred 7.5 mg/day, tacrolimus 4 mg/day	Normalization of muscle power and CK
3	69 M	2	Muscle fibers vary in diameter, angular atrophic fibers of random distribution and sporadic regenerating fibers present, endomysial mononuclear cellular infiltration, glycogen stain negative, lipid content not increased	Pred, AZA, MMF	Pred 2.5 mg/day, MMF 2 g/day	Normalization of muscle power and significant drop in CK level
4	47 F	8	Necrotic and atrophic fibers present, with regenerating fibers at various stages, mononuclear cellular infiltrate in endomysium and within muscle fibers, glycogen stain negative, EM examination for tubuloreticular and inclusion bodies negative	Pred, pulse MP, AZA, CSA, CYC, IVIG, MMF	Pred 20 mg/day, MMF 2 g/day	Significant drop in CK level but minimal improvement in muscle power

Pred: prednisolone; MP: methylprednisolone; AZA: azathioprine; CSA: cyclosporine A; MMF: mycophenolate mofetil; IVIG: intravenous immunoglobulin; MTX: methotrexate; CK: creatine kinase.

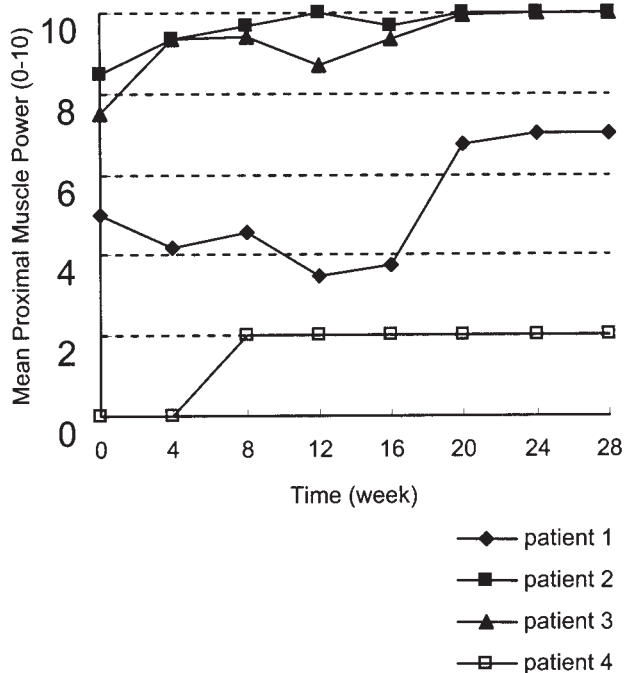


Figure 1. Serial change in mean proximal muscle power.

month postinfusion, with normalization of levels ranging from 2.6 to 7.7 months. Muscle strength improved in all, with strength returning to normal in 2 patients. Two other case reports also described efficacy of rituximab in the treatment of refractory dermatomyositis and polymyositis<sup>8,9</sup>.

There are limitations to our study. The sample size is small and may have contributed to the insignificant changes of disability and quality of life scores by statistical analyses. The adoption of the Bohan and Peter criteria for the diagnosis of polymyositis may have led to the inclusion of patients with inclusion body myositis in our study. Although muscle biopsy examination did not reveal inclusion bodies in our patients, we cannot totally exclude this possibility, especially in the 2 patients who had suboptimal response to rituximab, because evidence of inclusion body myositis may still be missed in biopsy samples as a result of sampling error. Finally, we did not evaluate the CD20+ B cell count and the human anti-chimeric antibodies in our patients, which may be factors influencing the clinical efficacy of rituximab.

Because of publication bias, the efficacy of rituximab in inflammatory myopathies might have been overemphasized in the literature. Therefore, further controlled trials are needed to confirm the clinical efficacy of the drug. However, rituximab is generally well tolerated and is an option to be con-

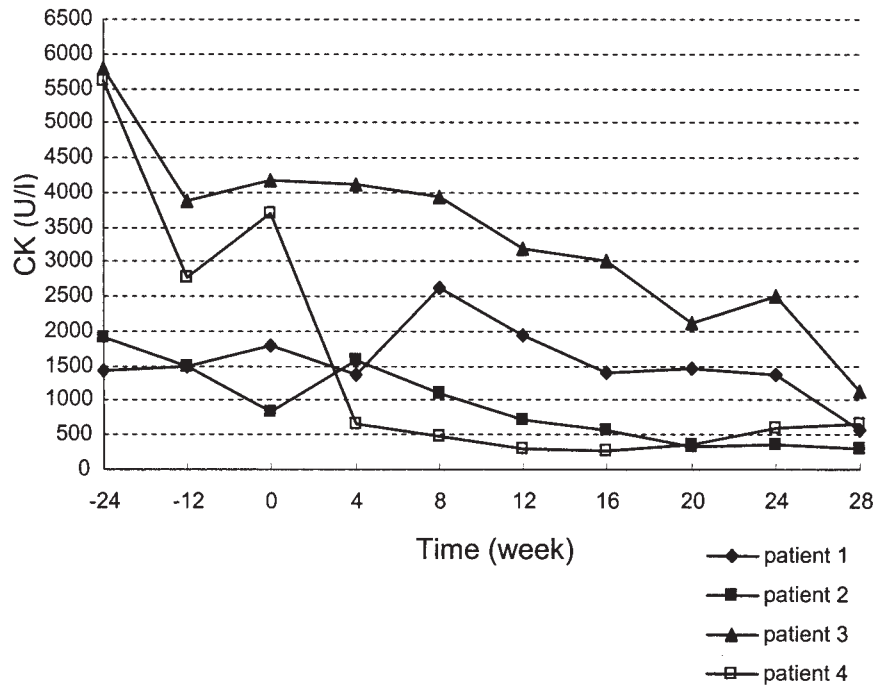


Figure 2. Serial change in creatine kinase (CK) level.

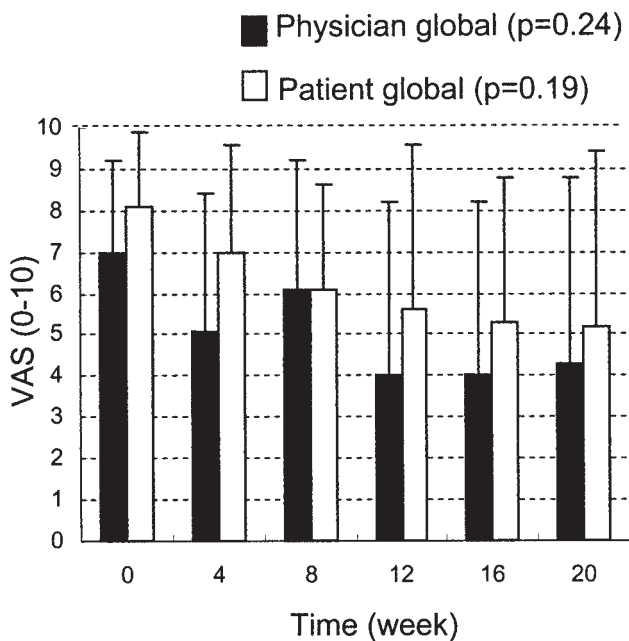


Figure 3. Change in global assessment scores (higher scores indicated more serious disease). p values refer to change from baseline to Week 20. VAS: visual analog scale.

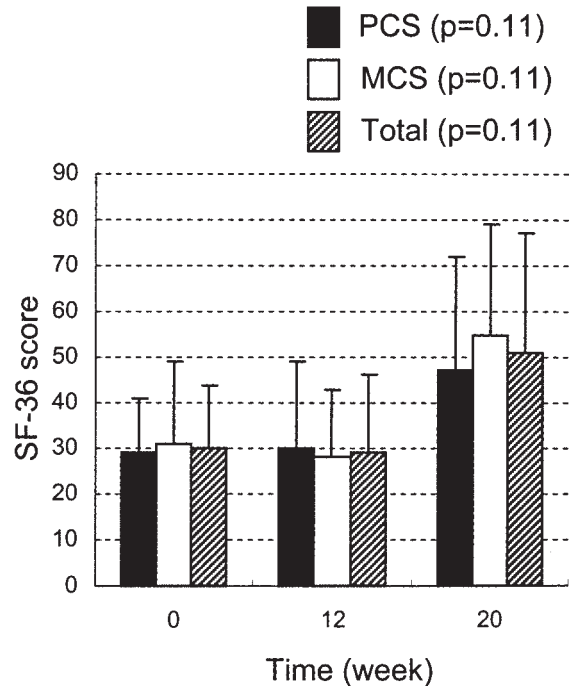


Figure 4. Change in quality of life scores. p values refer to change from baseline to Week 20. PCS: physical component score; MCS: mental component score; Total: total SF-36 score.

sidered in patients with inflammatory myopathies who are refractory to multiple conventional therapeutic modalities. A caution of the use of rituximab is the rare occurrence of fulminant chronic hepatitis B reactivation<sup>12</sup> and progressive multifocal leukoencephalopathy, probably caused by reactivation

of JC virus recently reported by the US Food and Drug Administration<sup>13</sup>.

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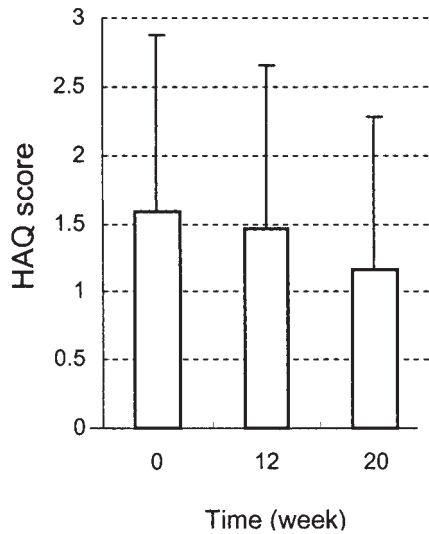


Figure 5. Change in disability scores.  $p = 0.29$ ; i.e., change from baseline to Week 20. HAQ: Health Assessment Questionnaire.

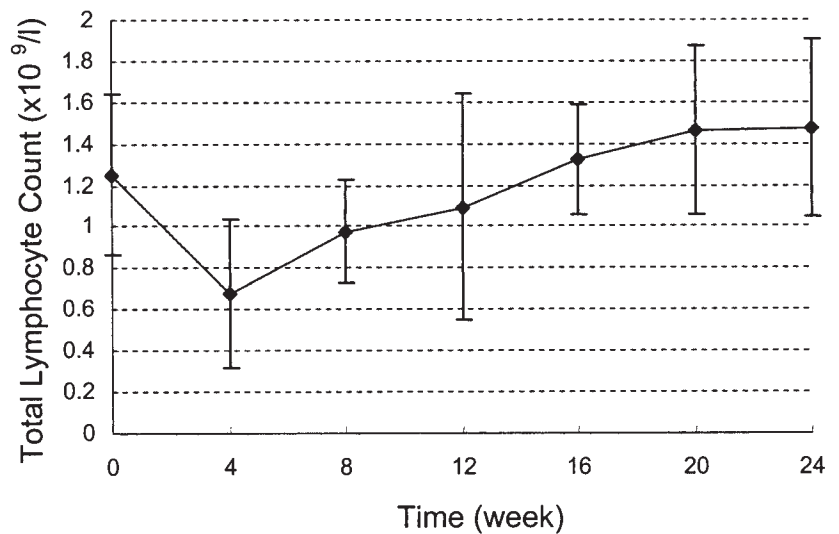


Figure 6. Serial change in total lymphocyte counts.

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