

Rituximab for the Treatment of Juvenile Dermatomyositis

A Report of Four Pediatric Patients

Megan A. Cooper, Donna L. Willingham, Diane E. Brown, Anthony R. French,
Fei F. Shih, and Andrew J. White

Objective. Juvenile dermatomyositis (DM) is a chronic inflammatory myopathy of childhood primarily affecting the muscles and skin. Treatment for juvenile DM is often difficult, and conventional therapies include corticosteroids and other immune suppressants. We reviewed the records of 4 patients with juvenile DM who received the B cell–depleting anti-CD20 monoclonal antibody rituximab to determine whether this therapy resulted in improved control of their juvenile DM.

Methods. This is a retrospective review of 4 pediatric patients ages 10–17 years with juvenile DM who were treated with rituximab. All patients were tested for myositis autoantibodies and received weekly rituximab infusions for a total of 4 doses. Two patients received repeat courses of rituximab 1 year after their first dose. Patients were followed up between 12 and 24 months after their first course of rituximab, and their strength, muscle enzymes, and rash were reviewed.

Results. One patient was positive for a myositis-specific antibody, anti-Mi-2, and demonstrated striking reductions in her muscle enzyme levels for 1 year after rituximab therapy. Following a second course of rituximab, this patient remained disease free for 14 months before requiring a third course of rituximab. Two myositis antibody–negative patients showed clinical improvement and tolerated lower doses of corticosteroids

following treatment with rituximab. Finally, 1 patient had worsening of her disease following rituximab.

Conclusion. These cases highlight the potential for anti-B cell therapies in the treatment of juvenile DM in both myositis-specific autoantibody–positive and –negative patients.

Juvenile dermatomyositis (DM) is a chronic inflammatory disease affecting the muscles and skin (1). While juvenile DM is relatively rare, with an incidence of 2.5–4.1 cases per million children in the US (2), it is the most common inflammatory myopathy of childhood. This disease is characterized by proximal muscle weakness and pathognomonic rashes, including a scaly rash over the dorsal aspect of the finger joints (Gottron's papules) and heliotrope discoloration of the eyelids. The course of juvenile DM is variable, and patients can have multiorgan system involvement with clinical manifestations including fatigue, calcinosis, visceral vasculitis, and lipodystrophy.

The use of corticosteroids over the last 40 years has dramatically reduced the morbidity and mortality of juvenile DM (for review, see ref. 3); however, long-term use of corticosteroids is associated with multiple complications. Therefore, steroid-sparing agents are needed for the long-term management of juvenile DM. While there have been no randomized controlled studies of other immunosuppressive agents for the treatment of juvenile DM, retrospective reports have indicated that methotrexate (MTX) and intravenous immunoglobulin (IVIG) may be beneficial for decreasing the dosage of corticosteroids needed to control disease, and a variety of other therapies, such as cyclosporine and cyclophosphamide, have been used with mixed results in children with refractory disease (for review, see ref. 4).

Megan A. Cooper, MD, PhD, Donna L. Willingham, RN, MSN, PNP, Diane E. Brown, MD, PhD, Anthony R. French, MD, PhD, Fei F. Shih, MD, PhD, Andrew J. White, MD: St. Louis Children's Hospital, and Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to Andrew J. White, MD, Director, Division of Pediatric Rheumatology and Immunology, St. Louis Children's Hospital, Box 8116, 1 Children's Place, St. Louis, MO 63110. E-mail: White_a@kids.wustl.edu.

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The pathogenesis of juvenile DM remains unclear, although an increasing role of humoral immunity has been suggested by the association of myositis-specific and myositis-associated antibodies with myopathies, including juvenile DM and adult DM (5). While the majority of adults with DM have circulating myositis autoantibodies, <10% of children with juvenile DM have these autoantibodies, and their significance with regard to clinical diagnosis and disease course is unclear (1,6). A recent open trial by Levine (7) and 3 case reports (8–10) of adults with DM have shown a potential benefit with the B cell-depleting anti-CD20 monoclonal antibody rituximab, with improvement of muscle strength and/or skin manifestations following therapy. The only pediatric patient described was a 16-year-old girl with juvenile DM treated with rituximab for persistent cutaneous disease (10) who experienced remission of her skin disease following therapy.

Here we review our experience treating 4 pediatric juvenile DM patients ages 10–17 years with rituximab. One patient was positive for the myositis-specific autoantibody anti-Mi-2 and demonstrated dramatic normalization of her muscle enzyme levels and clinical improvement of her strength and rash following each of 2 courses of rituximab 1 year apart. Two myositis antibody-negative patients demonstrated improvement in strength and rash. The final patient had progression of her disease after rituximab.

PATIENTS AND METHODS

We retrospectively reviewed the records of patients at our institution with a diagnosis of juvenile DM alone, without an overlap syndrome, who received rituximab. A summary of the patient demographics, therapies, and immunologic parameters is shown in Table 1. All patients were diagnosed as having juvenile DM based on the presence of characteristic rash (heliotrope discoloration around the eyes and/or Gottron's papules), proximal muscle weakness, and elevated muscle enzyme levels. Myositis antibody profiles (Oklahoma Medical Research Facility, Oklahoma City, OK) were performed on all patients to assay for myositis-specific and myositis-associated autoantibodies specific for the following antigens: Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, signal recognition particle, PM-Scl, Ku, U1 RNP, U2 RNP, and Ro. All patients received 375 mg/m² of rituximab weekly by IV infusion for a total of 4 weeks (cumulative dose 1,500 mg/m²). Patients were pretreated with hydrocortisone (0.7–2 mg/kg) or dexamethasone (0.25 mg/kg in patient 1, first course) with each infusion. This study was conducted in accordance with the guidelines for case studies from the Human Resources Research Protection Office at Washington University, and informed consent was obtained from the patients for inclusion in this study.

RESULTS

All patients tolerated rituximab well, with no hospitalizations for serious infections in the 6 months after treatment. Only patient 1, who was positive for the myositis-specific antibody anti-Mi-2, had positive results

Table 1. Demographic characteristics, prior and concurrent therapies, myositis antibody panel results, CD19 B lymphocyte count, and daily prednisone doses in 4 patients with juvenile dermatomyositis treated with rituximab*

Patient/sex, age at rituximab treatment†	Disease duration	Prior therapies‡	Concurrent therapies	Myositis panel	CD19 cells/ mm ³ §		Prednisone, mg/day¶		
					Pre	Post	At start	At 6 months	
1/F	10 years 10 months 11 years 10 months	27 months 39 months	Pred., MTX, IVIG, MP Pred., MTX, IVIG, MP, CYC	MTX, IVIG MTX	Anti-Mi-2 positive ND	634 475	0 0	None None	None None
2/M	14 years 11 months	5 weeks	Pred., MTX, HCQ	Pred., MTX, MP	Negative	1,289	0	40	15
3/F	14 years 1 month 15 years 2 months	4 months 17 months	Pred., MTX, IVIG, MP Pred., MTX, IVIG, MP, HCQ	Pred., MTX, IVIG, MP Pred., MTX, IVIG, MP	Negative ND	NA 14	11 0	20 3	11 1
4/F	17 years 9 months	1.5 months	Pred., MTX	Pred., MTX, MP	Negative	88	0	30	20

* Pred. = prednisone; MTX = methotrexate; IVIG = intravenous immunoglobulin; MP = intravenous methylprednisolone; CYC = cyclophosphamide; ND = not determined; HCQ = hydroxychloroquine; NA = not available.

† Patients 1 and 3 had two courses of treatment.

‡ Any medications given from diagnosis until treatment with rituximab.

§ Pre = CD19 count measured at the start of rituximab infusions; post = CD19 count measured at the fourth dose of rituximab, with the exception of the first course in patient 3 (measured 3 months after rituximab) and patient 4 (measured 5 weeks after rituximab).

¶ At the start of rituximab infusions and 6 months later.

of the myositis panel. Patients 1, 2, and 4 had full depletion of their B cells, and patient 3 had depletion of B cells after her second course of rituximab (Table 1). All patients who were receiving daily prednisone at the start of rituximab treatment tolerated a lower dose after 6 months (Table 1). Three patients (patients 1–3) had clinical improvement of their juvenile DM and/or laboratory parameters after treatment with rituximab, while patient 4 had progression of her disease, as described below.

A summary of the treatment course and muscle enzyme levels in patient 1 is shown in Figure 1. The patient presented at age 8.5 years with globally elevated muscle enzyme levels, profound proximal muscle weakness, and Gottron's papules on her hands. Prior to receiving rituximab, her disease was controlled with IV methylprednisolone, oral prednisone, monthly high-dose (2 gm/kg) IVIG, and weekly MTX (Table 1). Two years after diagnosis, she had a relapse of her juvenile DM, with increasing muscle enzyme levels (time 0 in Figure 1), proximal muscle weakness with strength of 3/5 in her upper extremities and 4/5 in her lower extremities, and increased rash. She could not tolerate daily corticosteroid therapy due to osteopenia and vertebral compression fractures. Rituximab was started, and she also received IV methylprednisolone and 3 months of cyclophosphamide (Figure 1) due to profound muscle weakness and muscle enzyme elevation. However, she did not receive any further corticosteroids 2 months after starting rituximab (Figure 1).

The patient's muscle enzyme levels began to decrease 1 month after starting rituximab (Figure 1), and her strength and rash started to improve 2 months after completing rituximab. Her muscle enzyme levels normalized after 6 months (Figure 1), and she regained 4+ to 5/5 strength throughout, with resolution of her rash. However, after 9 months while maintained on treatment with MTX alone, her muscle enzyme levels began to rise (Figure 1) while she maintained normal strength. By 12 months, she had significant elevation of all of her muscle enzyme levels (Figure 1), 4/5 proximal muscle strength in her upper and lower extremities, increasing erythema of her Gottron's papules, and recovery of her B cells (Table 1). She subsequently received a second 4-week course of rituximab. She again began to have improvement of her muscle enzyme levels 1 month after restarting rituximab, and her muscle strength improved after 2.5 months. Ten months after her second course of rituximab, she had normalization of all of her muscle enzyme levels (Figure 1) and normal strength. At her last followup visit, 14 months after her

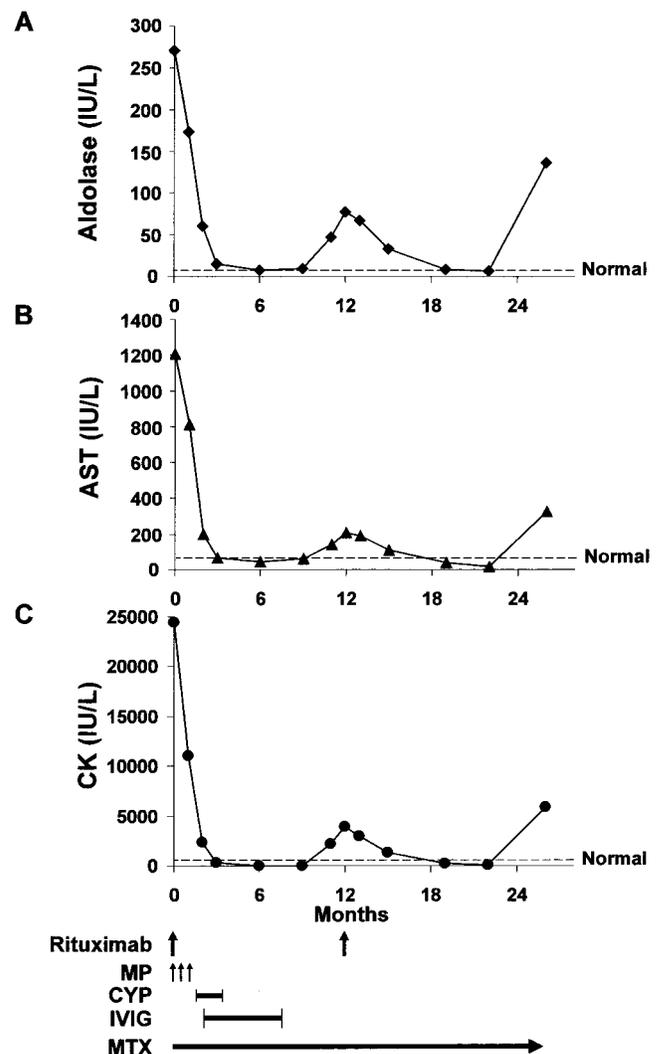


Figure 1. Muscle enzyme levels and treatment course with rituximab in patient 1. Time 0 represents initiation of the first course of rituximab, with a second course given at 12 months. Intravenous methylprednisolone (MP) was given with the first (500 mg twice daily for 5 doses) and third (500 mg for 1 dose) rituximab infusions and 1 month after rituximab (500 mg for 6 doses). Cyclophosphamide (CYP) was given monthly for a total of 3 doses (750–875 mg/m²). Shown are levels of aldolase (reference range 0–8 IU/liter) (A), aspartate aminotransferase (AST) (reference range 10–60 IU/liter) (B), and creatine kinase (CK) (reference range 0–300 IU/liter) (C). IVIG = intravenous immunoglobulin; MTX = methotrexate.

second course of rituximab, she had normal strength on examination but worsening rash and significantly elevated muscle enzyme levels (Figure 1). Her CD19 count was 564 cells/mm³, and she is starting a third course of rituximab. She has continued receiving weekly MTX and

has not received any other therapies for her juvenile DM since starting her second course of rituximab.

Patients 2 and 3 had normal muscle enzyme levels at the time of treatment with rituximab but demonstrated clinical responses. Patient 2 started rituximab 5 weeks after diagnosis due to worsening weakness and rash (heliotrope rash, Gottron's papules, and shawl rash) despite therapy with 1 mg/kg/day of oral corticosteroids and weekly MTX. He received IV methylprednisolone (250 mg for 7 doses) with his first infusion. After starting rituximab, he continued taking prednisone 20 mg twice daily and MTX, but he received no further methylprednisolone. Two months after starting rituximab, he had improved proximal muscle strength of 4/5 in his upper and lower extremities and decreased rash. Six months after starting rituximab, he had normal proximal muscle strength and his prednisone was decreased to 10 mg daily (Table 1). Twelve months after starting rituximab, he had full strength with fading Gottron's papules and faint heliotrope discoloration around his eyes, and all medications were stopped.

Patient 3 received 2 courses of rituximab 1 year apart (Table 1). She was treated with her first course of rituximab 4 months after diagnosis due to persistent fatigue and proximal muscle weakness (4/5 upper extremity strength) with normal muscle enzyme levels after therapy with weekly MTX, prednisone, IV methylprednisolone, and 3 months of high-dose IVIG (2 gm/kg/month). IV methylprednisolone was given with her first and fourth doses of rituximab (500 mg for 3 doses and 500 mg for 1 dose, respectively). One month after completing rituximab, she continued to receive MTX, prednisone, and monthly IVIG with subjective improvement of her fatigue, normal proximal muscle strength, and improving Gottron's papules and heliotrope rash. Six months after completing rituximab, she was maintained on a lower dose of prednisone (Table 1), weekly MTX, monthly IVIG, and hydroxychloroquine, with normal strength and trace rash.

Approximately 1 year after completing rituximab, the patient had increased fatigue and rash and subjective decreased strength with normal muscle enzyme levels. She received a second course of rituximab and IV methylprednisolone with her first, second, and fourth doses of rituximab (2 500-mg doses with each infusion). One month after her second course of rituximab, her weakness and fatigue had subjectively improved. By 6 months, she had resumed competitive sports and was maintained on monthly IVIG, MTX, and prednisone (1 mg daily). At her last followup visit, 1 year after her

second course of rituximab, she is no longer taking prednisone.

Patient 4 had progression of her disease after receiving rituximab. She was started on rituximab 1.5 months after diagnosis and received 1 course of IV methylprednisolone (250 mg for 3 doses) with her first infusion. Two months after starting rituximab, her strength improved to 4/5–5/5, but she had persistent rash, weakness, and fatigue and an elevated lactate dehydrogenase level, and monthly IVIG (2 gm/kg) was started. One year after diagnosis (10.5 months after the start of rituximab), cyclosporine was started due to increased rash and fatigue. Now, 14 months following her diagnosis, she has developed vasculitic skin lesions and interstitial lung disease and is receiving cyclophosphamide.

DISCUSSION

Juvenile DM is a multisystem inflammatory disorder that is often difficult to treat, and traditional therapies including corticosteroids and immunosuppressive agents often have unacceptable side effects (1,3,4). To the best of our knowledge, this case series represents the first report of the use of the B cell-depleting anti-CD20 monoclonal antibody rituximab for the treatment of the muscle and skin manifestations of juvenile DM in children. All of the patients described in this report tolerated rituximab infusions well, with good depletion of their peripheral blood B cells after a 4-week course of rituximab (Table 1), and we observed no treatment-related infections. Three of 4 patients described in this report had clinical improvement following rituximab, while the fourth patient had progression of her disease requiring escalation of her immunosuppressive therapy.

Patient 1 had perhaps the most significant clinical symptoms and treatment-refractory juvenile DM and also had the most notable response following rituximab. While she did receive additional immunosuppressive therapies concurrent with her first course of rituximab (Figure 1), she had no additional medications aside from her baseline MTX during or after her second course of rituximab, when she had a clear clinical and laboratory response for 14 months (Figure 1), implicating rituximab as playing a role in remission of her disease. One possible explanation for her dramatic response may be the presence of the myositis-specific autoantibody anti-Mi-2, suggesting a strong B cell-driven component to her disease. This hypothesis is supported by the recurrence of disease coincident with recovery of her

peripheral blood B cells 12 months after her first course of rituximab and 14 months after her second course.

While the significance of myositis autoantibodies in pediatric patients remains unclear, these antibodies can be useful for classifying disease and predicting outcome in adults with myositis (5,6). Two of the 3 myositis autoantibody-negative patients also had clinical improvement. We hypothesize that these patients may have had unidentified autoantibodies that were depleted and/or that eliminating B cells may have altered the activity of other immune cells, as has been suggested by a recent report of altered macrophage function in adult rheumatoid arthritis patients receiving rituximab (11). However, B cell dysfunction alone is unlikely to fully explain the pathogenesis of juvenile DM, as demonstrated by patient 3, who had relatively low numbers of circulating B cells at the time of relapse of her disease, and as demonstrated by patient 4, who had progression of her disease despite B cell depletion. Larger studies will be required to see whether the presence of myositis autoantibodies predicts a better response to anti-B cell therapies and to determine the mechanism of rituximab-induced remission in juvenile DM. A recently opened phase II trial of rituximab for the treatment of refractory juvenile DM, adult DM, and polymyositis (ClinicalTrials.gov identifier NCT00106184) may help to address some of these questions.

All of the patients presented here who had clinical responses showed improved strength and decreased rash within 2 months after completing rituximab. Furthermore, their remissions persisted for 12 months or longer. Two patients (patients 1 and 3) received a second course of rituximab after 1 year due to disease relapse, while the third patient (patient 2) continues to do well 12 months after rituximab and has discontinued all medications for his juvenile DM. These observations of remission for up to 1 year are consistent with Levine's open-label pilot study of rituximab in adults with DM, in which 2 of the 6 evaluable patients had clinical responses for at least 1 year after rituximab (7). Since rituximab therapy may not induce a durable cure for juvenile DM, it remains to be determined whether there is an optimal treatment schedule for administering repeated courses based on recurrence of clinical symptoms, periodic monitoring of B cell num-

bers, or predetermined intervals, or a combination thereof.

The case series presented here supports the further investigation of anti-B cell therapies such as rituximab for the treatment of pediatric patients with juvenile DM through clinical trials. Such therapies may be particularly beneficial for pediatric patients with myositis-specific autoantibodies, although the favorable clinical responses of 2 antibody-negative patients suggest that rituximab may ultimately be considered for all patients with refractory juvenile DM.

AUTHOR CONTRIBUTIONS

Dr. White had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Cooper, Brown, French, Shih, White.

Acquisition of data. Cooper, Willingham, Brown, French, Shih, White.

Analysis and interpretation of data. Cooper, White.

Manuscript preparation. Cooper, Brown, French, Shih, White.

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