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Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

A Randomized, Placebo-Phase Trial

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Objective. **To assess the safety and efficacy of rituximab in a randomized, double-blind, placebo-phase trial in adult and pediatric myositis patients.**

Methods. **Adults with refractory polymyositis (PM) and adults and children with refractory dermatomyositis (DM) were enrolled. Entry criteria included muscle weakness and ≥2 additional abnormal values on core set measures (CSMs) for adults. Juvenile DM patients required ≥3 abnormal CSMs, with or without muscle weakness. Patients were randomized to receive either rituximab early or rituximab late, and glucocorticoid or immunosuppressive therapy was allowed at study entry. The primary end point compared the time to achieve the International Myositis Assessment and Clinical Studies Group preliminary definition of improvement (DOI) between the 2 groups. The secondary end points were the time to achieve ≥20% improvement in muscle strength and the proportions of patients in the early and late rituximab groups achieving the DOI at week 8.**

Results. **Among 200 randomized patients (76 with PM, 76 with DM, and 48 with juvenile DM), 195 showed no difference in the time to achieving the DOI between the rituximab late (n = 102) and rituximab early (n = 93) groups ($P = 0.74$ by log rank test), with a median time to achieving a DOI of 20.2 weeks and 20.0 weeks, respectively. The secondary end points also did not significantly differ between the 2 treatment groups. However, 161 (83%) of the randomized patients met the DOI, and individual CSMs improved in both groups throughout the 44-week trial.**

Conclusion. **Although there were no significant differences in the 2 treatment arms for the primary and secondary end points, 83% of adult and juvenile myosi-**

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tis patients with refractory disease met the DOI. The role of B cell–depleting therapies in myositis warrants further study, with consideration for a different trial design.

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired disorders characterized by chronic inflammation of striated muscle, leading to predominantly proximal muscle weakness. The most common subsets of IIM include adult polymyositis (PM), adult and juvenile dermatomyositis (DM), myositis in overlap with cancer or another connective tissue disease, and inclusion-body myositis (IBM). The IIMs are frequently associated with constitutional symptoms and commonly involve other organ systems, including the skin, joints, lungs, gastrointestinal tract, and heart. They are rare, with an estimated incidence of 4–10 cases/million population per year, and a bimodal incidence pattern reflecting childhood onset of juvenile DM and a later peak in adulthood (1). Although the precise pathogenesis is unknown, IIMs likely result from immune-mediated processes initiated by environmental factors in genetically susceptible individuals (2). Factors that strongly support their autoimmune basis include the association of myositis with other autoimmune diseases, such as Hashimoto thyroiditis, Grave's disease, and various connective tissue diseases, the high frequency of circulating serum autoantibodies, and their response to therapy with immunosuppressive or immunomodulatory agents.

The treatment of IIM is challenging, complicated by its rarity and heterogeneity as well as the lack of controlled trials with only partially validated outcome measures. Most studies involve single referral centers using cross-sectional and retrospective analyses of small numbers of patients with treatment-refractory disease observed for relatively short time periods. In addition, widely disparate inclusion criteria have complicated the assessment of treatment response, since disease damage and the inclusion of misdiagnosed patients contribute to suboptimal therapeutic outcomes. Although glucocorticoids have not been formally tested in controlled trials, expert consensus is that they are the primary therapy, to be followed by a variety of immunosuppressive or immunomodulatory agents either alone or in combination (2).

Rituximab, a B cell–depleting agent long recognized to be an effective therapy for B cell lymphomas, has gained increased favor in the treatment of many autoimmune diseases and has been approved by the Food and Drug Administration for use in rheumatoid arthritis (3) as well as in granulomatosis with polyangiitis and microscopic polyangiitis (4). The effectiveness of rituximab in PM and DM has been suggested by case reports and case series in adult and pediatric patients with refractory disease (5–9). B cells play a critical role in the initiation and propagation of the immune response, and they have been implicated in the pathogenesis of myositis. They localize to the perivascular region of DM muscle and are found in the inflammatory infiltrates from both PM and DM patients (10). In addition to functioning as the precursor of autoantibody-producing plasma cells, B cells present antigen to T cells and secrete proinflammatory cytokines (10). Therefore, based on the autoimmune characteristics of myositis and the aforementioned immunopathogenic role of B cells, the Rituximab in Myositis (RIM) trial assessed the effectiveness of rituximab in refractory adult PM and adult and juvenile DM, using validated measures of myositis disease activity and damage, a consensus-driven definition of improvement (11–13), and a unique randomized placebo-phase trial design (14,15).

PATIENTS AND METHODS

Study population. This study was conducted at 31 sites (20 adult centers and 11 pediatric centers), and the protocol was approved by the Institutional Review Board at each location. Written informed consent was obtained from each study subject.

Eligible patients included adults with a diagnosis of definite or probable DM or PM and patients at least 5 years of age or older with definite or probable juvenile DM according to the criteria of Bohan and Peter (16). In an effort to exclude IBM and other myositis mimics (17), the medical records and muscle biopsy results (if available) of adults with PM were reviewed by a 3-member Adjudication Committee before enrollment. Refractory myositis was defined by the intolerance, or an inadequate response, to glucocorticoids *and* at least 1 other immunosuppressive or immunomodulatory agent (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, leflunomide, or intravenous immunoglobulin [IVIG]). An "adequate" glucocorticoid regimen was defined as 60 mg/day of prednisone in adults and 1.0 mg/kg/day of prednisone in pediatric patients, for a duration of at least 1 month in both groups. An adequate immunosuppressive regimen was 3 months of the agent at a known effective dose.

Adult patients had demonstrable muscle weakness, and manual muscle testing was assessed using a validated measure, the Manual Muscle Testing 8 (MMT-8) (18), a core set measure (CSM) with a maximum score of 150 when tested bilaterally. The examination for the MMT-8 was generally completed by trained physical therapists. RIM Study investigators and physical therapists were trained and certified by one of us (MOH-L) to complete the MMT-8 during the RIM Study investigators meeting. Christopher Bise (University of Pitts-

burgh, Pittsburgh, PA), Joseph Shrader (National Institutes of Health [NIH], Bethesda, MD), and Mina Jain (NIH) assisted in the training of the RIM Study investigators, who are listed in Appendix A. Enrollment of adult subjects required a score of <125 (of 150) on the MMT-8 in conjunction with 2 other abnormal CSMs. Juvenile DM patients could enter the study according to the same criteria, but if the MMT-8 score was >125 (of 150), a third abnormal CSM was necessary. The other CSM needed to qualify for study entry in this trial consisted of 1 of the following 5 measures (19): 1) patient's/parent's global assessment of disease activity by visual analog scale (VAS) with a minimum score of 2.0 cm; 2) physician's global assessment of disease activity by VAS with a minimum score of 2.0 cm; 3) Health Assessment Questionnaire (HAQ) (20) or Childhood HAQ (C-HAQ) (21) disability index with a minimum value of 0.25; 4) elevated level of at least 1 (locally measured) muscle enzyme (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, or aspartate aminotransferase AST) to a minimum of 1.3 times the upper limit of normal, with the most abnormal muscle enzyme value selected as the target enzyme to be followed during the trial; and 5) global extramuscular disease activity score with a minimum value of 1.0 cm (based on the investigator's composite assessment of disease activity on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool [MDAAT]) (13). All visual analog scales were 10 cm, anchored at the ends and the midpoint.

Patients had been receiving a stable dosage of prednisone for 4 weeks prior to screening (preferably <1 mg/kg/day), and at least 1 nonglucocorticoid immunosuppressive agent was required (with stipulated exceptions) at a stable dose for 6 weeks prior to screening. A 4-week washout for methotrexate and an 8-week washout for any other immunosuppressive agent discontinued prior to screening were required. No live vaccines, creatine dietary supplements, IVIG (in adults), or the initiation of colchicine was permitted during the study.

To minimize confounding, patients with the following conditions were excluded: drug-induced myositis, juvenile PM, IBM, cancer-associated myositis (myositis diagnosed within 2 years of a diagnosis of cancer), myositis in overlap with another connective tissue disease, or any concomitant illness that precluded an accurate treatment response during the trial or posed an added risk for participants. Patients were excluded if they had previously received rituximab. Juvenile DM patients with baseline IgG or IgM levels below the age-adjusted lower limit of normal and adults with IgM levels >30% below the lower limit of normal were also excluded.

Patients were allowed to continue an exercise program that had been initiated before the 4-week screening period, and a stretching program was permitted at any time. An active muscle-strengthening program could not be initiated during the study.

Study definitions. The definition of improvement (DOI) chosen for this trial was based on the International Myositis Assessment and Clinical Studies (IMACS) Group preliminary, validated, top-ranked response criterion (11) of ≥20% improvement in 3 of any 6 CSMs, with no more than 2 worsening by ≥25%. Of note, the MMT-8 could not be one of the worsening measures. To meet the DOI, patients had to satisfy criteria on 2 consecutive monthly visits; the time to achieve the DOI was designated at the second time point of these consecutive visits. The definition of worsening included 1) physician's global assessment of worsening of ≥2 cm on the VAS *and* worsening of ≥20% on the MMT-8 score, or 2) global extramuscular activity worsening of ≥2 cm on the MDAAT VAS, or 3) any 3 of 6 CSMs worsening by ≥30% on 2 consecutive visits.

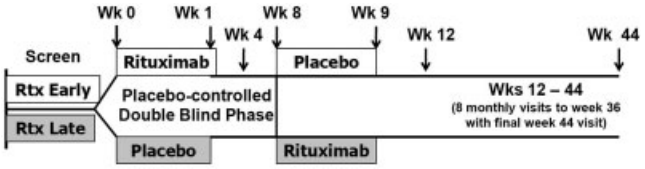

Figure 1. Schematic diagram of the design of the Rituximab in Myositis Study, demonstrating the randomized, placebo-phase design. Patients were randomly assigned to the rituximab (Rtx) early or rituximab late arm. Open boxes indicate the rituximab early arm, during which active drug was administered at weeks 0 and 1 and placebo at weeks 8 and 9. Shaded boxes indicate the rituximab late arm, during which placebo infusions were administered at weeks 0 and 1 and rituximab at weeks 8 and 9. The measurement at week 8 can be regarded as the final end point of an 8-week parallel group, randomized, placebo-controlled clinical trial. At each of the 14 visits over 44 weeks, core set measures and adverse events were assessed and biologic specimens were obtained for analysis.

Design overview. The RIM Study used a randomized, placebo-phase design (RPPD) (15) in which a computer-generated hidden-allocation system was used in a double-blind manner to randomly assign patients to a rituximab early or rituximab late treatment arm. An equal number of adult PM, adult DM, and juvenile DM patients received the active drug either at the beginning of the trial or 8 weeks later; this duration for the placebo phase was agreed upon by consensus of the Steering Committee. Figure 1 outlines the trial design. Week 8 is the time point at which the trial was a randomized placebo-controlled trial, since the rituximab late group had not yet received the active study drug.

Rituximab dosing was based on the patient's body surface area (BSA); children with a BSA ≤1.5 m^2 received 575 mg/m^2 at each infusion, and adults and children with a BSA >1.5 m^2 received 750 mg/m^2 up to 1 gm per infusion. Study drug was kindly provided by Genentech. Patients in the rituximab early arm received the drug at weeks 0 and 1, and placebo infusions were given at weeks 8 and 9. Patients in the rituximab late arm received placebo infusions at weeks 0 and 1, and rituximab was given at weeks 8 and 9. The glucocorticoid dosage was held constant, without reduction, until week 16, and intravenous glucocorticoids were not allowed at the time of any study medication infusion. If patients met the DOI (or experienced complications), a reduction in the glucocorticoid dosage was begun at no more than 20% of the existing dose every 4 weeks.

Other trial features included 14 visits spread over 44 weeks during which laboratory specimens were obtained and safety and CSMs were assessed. It was recommended that the same investigator assess the CSMs throughout the trial period, except for the MMT-8, which was done by the physical therapist. Patients meeting the DOI who then met the defined

criteria for worsening by week 36 were offered re-treatment with rituximab.

The Data and Safety Monitoring Board monitored overall safety independently of the participating institutions.

Outcomes: primary and secondary end points. The primary end point was the time to achieve the DOI, which was compared between the rituximab early and rituximab late groups. There were 2 secondary end points. The first compared the time to achieving 20% improvement in the MMT-8 on 2 consecutive visits between the 2 groups. This end point was chosen since the MMT-8 is quantitative and represents a key CSM in a myositis trial assessing muscle weakness as an important clinical outcome. The other secondary end point compared the response rates, or the proportion of patients achieving the DOI, at week 8 in the early versus late treatment groups, since this time point defines the parallel-groups randomized placebo-controlled phase of this trial.

B cell determination by flow cytometry. Whole blood samples were collected in cell preparation tubes (Becton Dickinson), and peripheral blood mononuclear cells (PBMCs) were isolated, aliquotted, and stained with a panel of conjugated antibodies recognizing the leukocyte cell surface markers CD45RA/CD45RO as well as the B cell–specific surface molecules CD19 and CD20. This combination permitted calculation of the percentage of B cells among the CD45+ leukocyte population. An automated complete blood cell count (CBC) that included a total white blood cell count was performed at each study visit. The percentages of lymphocytes and monocytes in the CBC and the fraction of CD19/CD20+ cells among the CD45+ cells in the PBMC preparations were then used to estimate the number of B cells/μl of whole blood.

Adverse events (AEs). The clinical site investigator determined which AEs were associated with the study drug. An AE or serious AE (SAE) was regarded as possibly related to the study drug if the investigator believed 1) there was a clinically plausible time sequence between onset of the AE and the administration of rituximab, and/or 2) there was a biologically plausible mechanism by which rituximab could cause or contribute to the AE, and 3) the AE could not be attributed solely to the concurrent/underlying illness, other drugs, or procedures. The RIM Study investigator coded each AE and SAE as one of the following: definitely related, probably related, possibly related, unlikely to be related, or unrelated. For purposes of analysis, only AEs and SAEs deemed to have a definite, probable, or possible relationship to the study drug were considered to be related.

Statistical analysis. Randomization was done within disease subsets (adult PM, adult DM, juvenile DM) for each institution. A minimization procedure was used to control overall balance in the 2 treatments. Assuming a daily hazard of 0.0023 in the 8-week placebo phase of the control group, a daily hazard of 0.017 while receiving rituximab (16), and an alpha level of 0.05 by 2-sided test, there was statistical power of 0.82 to detect a difference in treatment arms in each of the 2 adult disease groups (PM and DM). The study was not designed to have sufficient power to detect such a difference in the juvenile DM group. All of the analyses were based on the intent-to-treat principle and were performed using 2-sided tests. Analyses of the primary outcome and the time to achieving a $\geq$20% reduction in baseline MMT-8 score were done using a log rank test, and the proportion showing improvement at 8 weeks was analyzed using logistic regression. For the primary outcome, analysis was repeated, adjusting for CSMs and potential confounders using a proportional hazards model. As specified a priori in the protocol, comparison of the treatment arms was done within each of the disease subgroups (adult PM, adult DM, and juvenile DM).

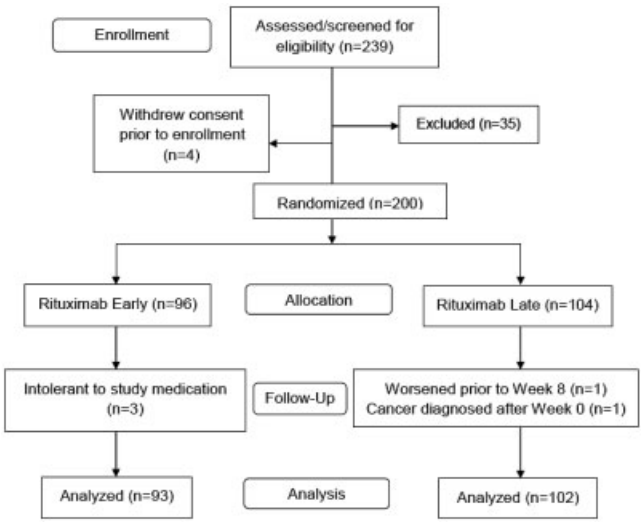

Figure 2. Flow diagram of participants in the Rituximab in Myositis Study. After adjudicating all polymyositis patients (see Patients and Methods for details), 239 patients were screened, and 200 were randomized. Most of the excluded patients either did not meet the criteria for muscle weakness or had immunoglobulin levels that were too low. Of the 200 randomized patients, 195 were included in the final analysis. Thirty-five patients were excluded for the following reasons: definite diagnosis not met in 1, other form of myositis in 1, prednisone dose stable <4 weeks in 1, Manual Muscle Testing 8 score >125 in 10, IgG or IgM level below the lower limit of normal in 11, hematologic abnormality in 2, concomitant illness in 2, and prior central nervous system toxoplasmosis, muscle atrophy and damage, chronic lymphocytic leukemia, hypercholesterolemia, hypercalcemia/high hemoglobin, current use of adalimumab, and disease flare in 1 patient each.

RESULTS

Baseline characteristics and core set measures. Of the 236 patients who were screened, 200 were randomized (Figure 2). Prior to screening, diagnostic accuracy was adjudicated in all PM patients, leading to 86 muscle biopsy reviews and 44 subsequent exclusions (14 for IBM, 29 for undetermined myopathy but not PM or DM, and 1 for excessive muscle damage). Targeted accrual goals were met for adult PM and DM (76 each), while 48 juvenile DM patients (of 50 expected) were enrolled. The quality of the data was excellent, with only 1.2% missing values. There was very low patient drop-

Table 1. Baseline demographic and clinical characteristics and core set measures, by treatment group*

Characteristic	Rituximab early (n = 96)	Rituximab late (n = 104)
No. (%) Caucasian	62 (65)	81 (78)
Age, mean ± SD years	43 ± 18.2	40 ± 18.4
No. (%) female	68 (71)	78 (75)
IIM subset		
PM	37	39
DM	36	40
Juvenile DM	23	25
Disease duration, mean ± SD years	5.2 ± 6.5	5.4 ± 6.0
Prednisone dosage, mean ± SD mg/day	19.7 ± 12.1	21.4 ± 14.4
No. (%) taking noncorticosteroid immunosuppressive agents	84 (88)	89 (86)
Myositis autoantibody, no. (%) positive		
Antisynthetase	16 (18)	16 (16)
Anti–signal recognition particle	13 (14)	12 (12)
DM-associated†	33 (37)	38 (38)
Other autoantibody‡	8 (9)	16 (16)
None of the above	20 (22)	19 (19)
No. with undefined autoantibody§	6	3
Mean MMT-8 ratio¶	71	71.7
Mean global assessment, by VAS (0–100 mm scale)		
Physician's	51.4	49.2
Patient's/parent's	65.4	65.6
Mean HAQ/C-HAQ disability index (range 0–3)	1.55	1.53
Muscle enzyme, mean ± SD ×ULN#	9.5 ± 14.9	5.5 ± 9.0
Mean extramuscular score, by VAS (0–100 mm scale)	27.4	30.7

* Visual analog scale (VAS) scores were based on a 10-cm scale, but were standardized to a 100-point scale to account for printing differences across clinical centers. IIM = idiopathic inflammatory myopathy; PM = polymyositis; HAQ = Health Assessment Questionnaire; C-HAQ = Childhood HAQ.

† Dermatomyositis (DM)–associated autoantibodies consisted of positivity for 1 of the following 3 autoantibodies: anti–transcription intermediary factor 1γ, anti-MJ, or anti–Mi-2.

‡ Other autoantibodies were those associated with connective tissue disease (CTD) overlap syndromes or other CTDs (e.g., anti–PM-Scl, anti–U1 RNP, or others).

§ Undefined autoantibodies were those that could not be definitively identified by immunoprecipitation.

¶ The Manual Muscle Testing 8 (MMT-8) ratio was calculated as the recorded MMT-8 score divided by the total possible score for the muscles tested (maximum 150; less if some muscle groups were not assessed).

Elevation of at least 1 (locally measured) muscle enzyme value (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, or aspartate aminotransferase) to a minimum level of 1.3 times the upper limit of normal (ULN). The muscle enzyme with the most abnormal value was selected as the target enzyme that was mentioned during the trial. The difference between rituximab early and rituximab late groups was significant ($P = 0.03$).

out, with only 5 patients having a baseline visit and no subsequent measures.

Table 1 summarizes the baseline demographic features of the 2 treatment groups. In general, the demographic characteristics were well balanced; however, there was a greater percentage of Caucasians in the late rituximab group. This cohort with refractory myositis consisted of patients in whom therapy with glucocorticoids and a mean of 3.1 immunosuppressive agents had failed. At study entry, the prednisone dosage averaged 20.8 mg/day, and almost 90% of the patients were taking additional immunosuppressive agents, either alone or in combination. Most patients were Caucasian (70%) and female (73%), with a mean disease duration exceeding 5 years. Their disease was active, as evidenced by a physician's global assessment of disease activity VAS score >5.0 cm at study entry and an average baseline VAS muscle activity score of 4.8 cm on the MDAAT (not shown in Table 1). Autoantibody subsets were well represented, with 80% of the cohort possessing at least 1 myositis-specific autoantibody, as determined by immunoprecipitation (22). Specifically, 17% had antisynthetase antibodies (primarily anti–Jo-1), 13% had anti–signal recognition particle (anti-SRP) antibodies, and 37% had DM-associated autoantibodies (either anti–Mi-2, probable anti–transcription intermediary factor 1γ [23], or probable anti-MJ [24,25]).

The values for the CSMs at baseline were similar between the early and late rituximab groups except for the baseline muscle enzyme value, which was statistically higher in the early rituximab arm. Patients were weak, as evidenced by the low baseline MMT-8 scores, with a mean of 105 in adult DM patients, 103 in adult PM patients, and 116 in juvenile DM patients. Patients generally rated their overall disease activity higher (by VAS) than did the investigators. Extramuscular manifestations appeared mild to moderate, with mean VAS scores of 34.1 and 33.1 in adult DM and juvenile DM patients, respectively, and 21.6 in adult PM patients, the higher scores reflecting cutaneous involvement in the DM subsets. In 48% of patients, the same investigator assessed the CSMs throughout the trial, while 92% of patients had assessments by ≤2 investigators. If the MMT-8 was not done by trained physical therapists, it was completed by the principal investigator at the site, who was also trained and certified at the RIM Study investigator meeting.

B cell depletion. Peripheral blood B cell depletion was complete and appropriate for the timing of rituximab, with the lowest B cell counts occurring 4 weeks after rituximab infusion (Figure 3). There were no differences in the median nadir B cell counts between the early and late rituximab groups. Seven of 200 patients receiving active drug did not experience depletion to <5 B cells/μl of blood; these patients were

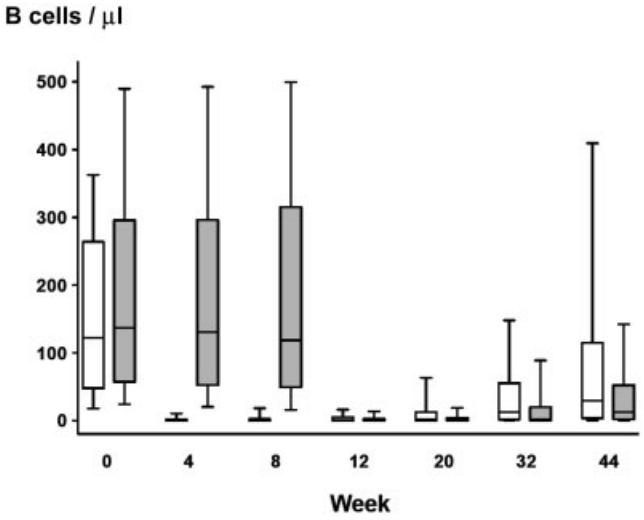

Figure 3. Peripheral blood B cell numbers prior to and following rituximab treatment of patients with idiopathic inflammatory myopathies (IIMs) in the Rituximab in Myositis Study. Peripheral blood samples were obtained at baseline (week 0) and at weeks 4, 8, 12, 20, 32, and 44 following the baseline visit. Whole blood white blood cell counts and a differential cell counts were obtained at each visit and used in conjunction with flow cytometry to estimate the number of B cells/μl of blood at each time point (see Patients and Methods for details). Data are shown as box plots. Each box represents the 25th to 75th percentiles of each sample set. Lines inside the boxes represent the median. Whiskers represent the 10th and 90th percentiles. Patients treated at weeks 0 and 1 with rituximab (n = 85) are represented by open boxes; patients treated with rituximab at weeks 8 and 9 (n = 98) are represented by shaded boxes. Because of either technical reasons or performance of flow cytometry locally at European sites, the total number of patients represented (n = 183) does not match the total number analyzed (n = 195).

equally distributed among the myositis subsets and between the early and late rituximab groups. There were no differences in the median B cell numbers at each time point following rituximab infusion, with a return of median B cell numbers to $>5/\mu$l at ~32–36 weeks after rituximab infusion in both groups (Figure 3).

Primary outcome. Five patients had a baseline visit, but no subsequent measurements were performed because they dropped out of the study. Of the remaining 195 randomized patients included in the analysis of the primary outcome, 161 (83%) met the predetermined DOI by the week 44 evaluation. The primary outcome in the RIM Study compared the *time to achieving the DOI* between the 2 patient groups (early versus late rituximab therapy) as shown in the Kaplan-Meier analysis, plotting failure to meet the DOI versus time (Figure 4). Unlike most survival plots, the occurrence of the primary event (achieving the DOI) represents a favorable outcome; therefore, the lower curve of patients failing to meet the DOI signifies superior treatment.

The early treatment arm had 93 analyzable (assessed through week 8) patients, with a median time from randomization to achieving the DOI of 20.0 weeks, while the late rituximab arm had 102 analyzable patients, with a median time from randomization to achieving the DOI of 20.2 weeks ($P = 0.74$ by log rank test, indicating no statistical difference in the time to achieving the DOI between the early and late rituximab groups). Adjustment for the individual CSMs or the 6 combined CSMs at baseline did not result in statistical significance for the test of the primary hypothesis. Conducting the analysis with a requirement of only a single time point of improvement in order to meet the DOI (rather than the predetermined 2 consecutive time points) also revealed no statistically significant differences in the time to achieving the DOI between the 2 treatment arms.

Also included in Figure 4 are separate Kaplan-Meier plots comparing the time to achieving the DOI in the adult PM, adult DM, and juvenile DM subsets, each without evidence of a statistically significant difference in the time to achieving the DOI. Although the juvenile DM plot shows an 8-week difference in the median time to achieving the DOI and a clear separation in the early and late rituximab arms, this difference was not statistically significant. Since the test for interaction of treatment and disease category was not statistically significant ($P = 0.42$), there is no justification to conclude that the treatment effect differs in the disease subgroups. Only 7 patients treated with rituximab did not experience depletion of B cells to $<5/\mu$l, but 6 of these patients still met the DOI.

Secondary outcomes. The time to achieve a 20% improvement in the MMT-8 on 2 consecutive visits was a secondary end point. Comparison of this end point for the 2 treatment arms indicated no statistically significant difference ($P > 0.90$) (data not shown). The other secondary end point compared the response rates, or the proportion of patients achieving the DOI, in the early versus late treatment groups at week 8. Fifteen percent of patients in the rituximab-treated group met the DOI, while 20.6% in the placebo-treated group met the DOI at this 8-week time point, with no statistically significant difference between the 2 groups. Since there was a significant difference in the baseline values for the muscle enzyme CSM (Table 1), we tested the difference in the proportions of patients meeting the DOI in the 2 treatment groups, adjusting for these baseline values, but the results remained nonsignificant. When comparing the proportion of patients showing improvement at

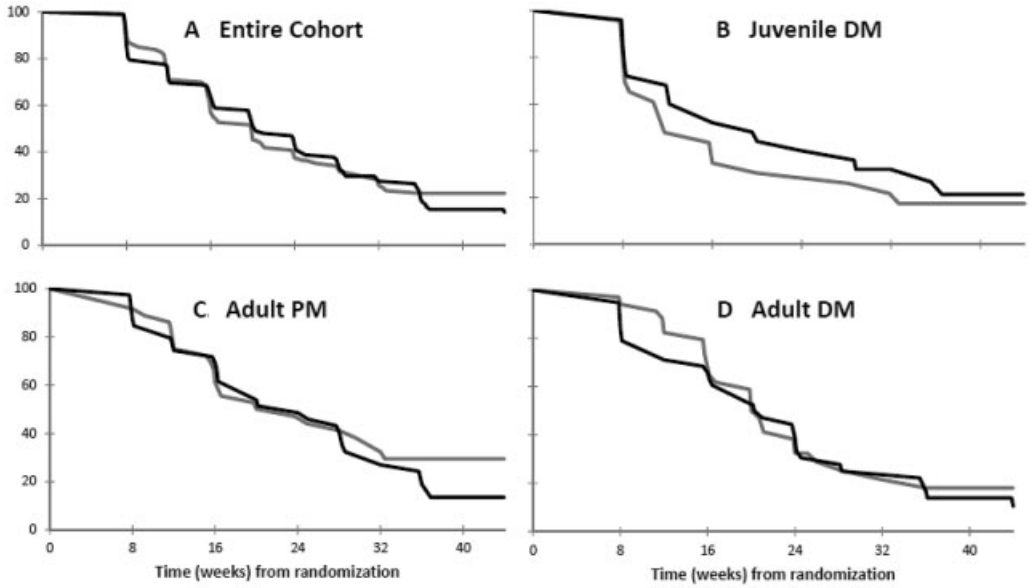

Figure 4. Kaplan-Meier curves plotting failure to meet the definition of improvement (DOI) versus time from randomization in the entire study cohort and in the 3 myositis subsets. Graphs depict the probability of DOI-free survival in the rituximab late (black line) and rituximab early (gray line) groups. The percentage of patients who did not meet the DOI is indicated on the y-axis. Values for the entire cohort (**A**) are as follows: for the rituximab late group, 87 met the DOI and 17 censored at a median of 20.2 weeks and for the rituximab early group, 74 met the DOI and 22 censored at a median of 20.0 weeks ($P = 0.74$). Values for the juvenile dermatomyositis (DM) subset (**B**) are as follows: for the rituximab late group, 20 met the DOI and 5 censored at a median of 19.6 weeks and for the rituximab early group, 20 met the DOI and 3 censored at a median of 11.7 weeks ($P = 0.32$). Values for the adult polymyositis (PM) subset (**C**) are as follows: for the rituximab late group, 33 met the DOI and 6 censored at a median of 24.0 weeks and for the rituximab early group, 26 met the DOI and 11 censored at a median of 21.9 weeks ($P = 0.43$). Values for the adult DM subset (**D**) are as follows: for the rituximab late group, 34 met the DOI and 6 censored at a median of 20.3 weeks and for the rituximab early group, 28 met the DOI and 8 censored at a median of 20.4 weeks ($P = 0.70$).

either the 4-week or the 8-week visit, 38% in the early treatment group met the criteria, compared to 35% in the late treatment group ($P = 0.73$).

Core set measures as outcomes. We also conducted analyses comparing the 2 treatment arms with regard to a ≥20% reduction from baseline in individual CSMs at 2 consecutive visits. None of these comparisons revealed statistically significant differences. However, the mean/median CSM values indicated improvement throughout the entire 44-week trial in both groups (data not shown). Therefore, we also conducted a longitudinal analysis adjusting for baseline level to compare the change over time in the 2 treatment groups. Again, however, these results did not consistently favor one treatment arm over the other.

Additional treatment effect results. The mean prednisone dosage at baseline in the 160 patients taking glucocorticoids was 20.8 mg/day. This dropped to 14.4 mg/day, based on the 153 patients who were taking steroids at their last visit and the 7 patients who were able to completely discontinue prednisone ($P < 0.001$ by paired comparison). Four patients were taking steroids at their last visit, but not at baseline. There was no significant difference in the steroid taper rate between the early and late treatment groups.

Seventeen patients met the criteria for re-treatment with rituximab (by first meeting the DOI and then fulfilling the criteria for definition of worsening). Seven were ineligible for re-treatment (had low immunoglobulin levels, did not consent to re-treatment, or were outside the window of eligibility), and 9 of the remaining 10 were re-treated and evaluable (4 in the early rituximab and 5 in the late rituximab arms). Their mean time to *initial* achievement of the DOI was 12.4 weeks, with increased disease activity occurring a mean of 16.5 weeks later. Eight of the 9 patients who were re-treated met the DOI again after a mean of 19.9 weeks.

Several potential confounders, if imbalanced at baseline between the 2 treatment arms, could have affected the results of the trial. When analysis of the primary outcome was repeated, adjusting for global disease damage measured by a validated index (26), for disease duration, and for myositis autoantibody status,

Table 2. Common drug-related adverse events (frequency >2) and all drug-related infectious adverse events

Adverse event	No. of events
Common adverse events	
Headache	21
Nausea/vomiting	19
Diarrhea	11
Rash	10
Cough and cold	10
Pruritus	8
Fatigue/malaise	8
Leukopenia	7
Nasal congestion	5
Dizziness/vertigo	5
Chills	4
Sweats	4
Hypertension	3
Hypotension	3
Bronchospasm	3
Joint pain/swelling	3
Flushing	3
Hypogammaglobulinemia	3
Hypersensitivity reactions	3
Infectious adverse events	
Urinary tract infection	30
Sinus/ear infection	20
Upper respiratory tract infection	18
Pneumonia/lower respiratory tract infection	18
Cellulitis	14
Herpesvirus infection	11
Febrile episodes	10
Fungal infection	4
Eye infection	3
Bacteremia	3
Joint infection	2
Soft tissue infection	2
Viral syndrome	1

the results remained essentially unchanged. Similarly, 14 patients received add-on therapy during the trial outside of the study protocol, but adjustment for these also did not affect our overall conclusions.

Findings of the safety analysis. AEs and SAEs along with infusion reactions were monitored and reported in a standardized manner throughout the study period, using the Common Terminology Criteria of the National Cancer Institute, with clinical site investigators determining their relatedness to the study drug. During the 44-week trial period, only 1 patient (in the late rituximab group) withdrew early due to an AE. A total of 67 SAEs occurred in 64 patients, 26 of which were related to the study drug. Infections were the most common of these SAEs, with pneumonia in 6, cellulitis in 6, urosepsis in 2, herpes zoster in 2, and septic arthritis, histoplasmosis, urinary tract infection, respiratory failure, heart failure, dysrhythmia, venous thrombosis, syncope, rash, and neurologic symptoms (without evidence of progressive multifocal leukoencephalopathy) occurring in 1 patient each. There was no difference in AEs at week 8, the randomized placebo-controlled time point. Table 2 summarizes the adverse events. There was 1 death during the trial, occurring in a 74-year-old woman who developed a lung mass that was suspected to be a malignancy, followed by a stroke that led to a dense hemiparesis.

Infusion reactions were specifically tracked, since no glucocorticoids were administered at the time of infusion of the study medication. There were significantly more infusion reactions with rituximab (15.4% [60 of 389 events]) than with placebo (5.3% [21 of 393 events]; $P < 0.01$), but no difference was seen between the first and second rituximab infusions. Most reactions (88% [53 of 60]) were related to the study drug; 4 of them were severe, 24 moderate, and 32 mild. Two events required hospitalization, and most patients (53 of 60 infusion reactions) were able to receive the full dose of rituximab after resolution of the infusion reaction.

DISCUSSION

The RIM Study is the first prospective, randomized, double-blind trial in myositis enrolling both pediatric and adult patients and is the largest clinical trial ever performed in the inflammatory myopathies. It represents the first collaboration of pediatric and adult rheumatologists and neurologists to study an autoimmune illness affecting children and adults. This trial used a unique design, the RPPD (15) or delayed-start design (14,27), and was the first study to implement recently validated myositis disease activity and damage measures (11,13,26). This trial was also the first to test a consensus-driven definition of improvement that has been proposed for juvenile and adult IIM clinical trials (11,12,28). Although the study did not provide sufficient evidence to reject the null hypothesis of no treatment effect in the primary and secondary outcomes, 83% of the enrolled patients met the DOI by the end of the trial. It is important to note that these patients represented a cohort of patients with refractory myositis in whom therapy with glucocorticoids and, on average, more than 3 additional immunosuppressive agents had failed over the course of their disease. The addition of rituximab provided a significant steroid-sparing effect between the start and conclusion of this trial, and 8 of 9 patients meeting criteria for the definition of worsening after an initial response improved again after re-treatment with rituximab.

Rituximab was generally well tolerated in a trial

in which preinfusion glucocorticoids were not routinely administered. There were significantly more infusion reactions associated with rituximab administration, but 88% of the patients with infusion reactions still received the full dose of rituximab. Infectious complications comprised the majority of severe adverse events, with a frequency similar to that in a recently reported trial of rituximab in vasculitis (4).

There were several factors that decreased the probability of detecting an effect of rituximab. First, the power calculations to detect differences in the 2 treatment groups were based on the premise that rituximab had an earlier effect as a therapeutic agent. Based on the existing literature for rituximab use in IIM at the time of study design (6), the steering committee postulated that >50% of patients would respond to rituximab by 8 weeks. In fact, one-half of the patients responded by ~20 weeks, indicating a lower than expected potency, for which this study was not adequately powered. Compounding this problem, the anticipated placebo rate was underestimated in the original power calculations, meaning that the response during the 2 months of placebo therapy was greater than would be expected for the assumed hazard when the trial was designed. In essence, there was an overestimate of the rapidity of the response to rituximab and an underestimate of the DOI in those receiving placebo.

When assessing the results in the individual myositis disease subsets, the juvenile DM cohort response reflected what was originally hypothesized. That is, the early rituximab group among those with juvenile DM had a median time to achieving the DOI that was nearly 8 weeks sooner than that in the late rituximab group, mirroring the duration of the placebo phase. However, the trial was not powered for assessing response in individual myositis subsets at the observed potency.

A second factor leading to the statistical failure of the trial relates to the RPPD study design and the selection of the "placebo-phase" duration of 8 weeks chosen by the RIM Steering Committee. There are several reasons for this: 1) the enrollment of children precluded a traditional parallel-groups randomized controlled trial in which only one-half of the patients would receive active drug, 2) international consensus guidelines for the conduct of clinical trials in myositis suggested that the ethical median duration for placebo administration or background therapy in a clinical trial should be 8 weeks for adult myositis patients and 6 weeks for childhood myositis patients (28), and 3) the expected mean response to rituximab was assumed to be 8 weeks. Ultimately, the slower onset of action of rituximab in our cohort with refractory myositis (reflected by the longer than expected time to improvement) coupled with the short 8-week placebo phase made it difficult to distinguish the response in the 2 treatment arms. Similar delayed-start trial designs have been used in other chronic diseases, with favorable results (28). Although this design has regulatory support (29), its limitations, such as the duration of the placebo phase and the statistical approach to data analysis, have been discussed elsewhere (14). Nevertheless, the use of the delayed-start design with appropriate attention to stipulated details has been encouraged in chronic rheumatic diseases (14). It is conceivable that the RPPD, or delayed-start design, may still be appropriate for agents with a shorter time to effect.

Finally, although the CSMs and the DOI used in this study have been partially validated and agreed upon by myositis experts (11,13,18,26), there were no recent prospective clinical trials that used these measures before the RIM Study. Several of the CSMs that contributed to the DOI are subjective, including the physician's/patient's global assessments of disease activity VAS scores, HAQ scores, and extramuscular disease activity indices. The MMT-8, although quantitative and fully blinded with regard to treatment group, may be subject to patient effort (30). Moreover, muscle enzyme levels may not correlate with either clinical improvement or increased disease activity. Finally, myositis is heterogeneous, as evidenced by the long disease duration (Table 1) and the range of autoantibody subsets in our cohort (28% positivity for an antisynthetase or anti-SRP autoantibody [9,31,32]) that resulted in wide variance around the time to achieving the DOI in both treatment groups. Nevertheless, these CSMs have been carefully studied and scrutinized by experts from many disciplines who provide care for both adult and pediatric myositis patients under the auspices of international myositis collaborative groups (11,18,19,33). In the future, it will be necessary to use the prospective data collected from the RIM Study, the largest trial ever performed in adult and juvenile myositis, and other prospective myositis trials, to reexamine the CSMs and DOI in order to develop more robust measures of disease activity and improvement for use in future clinical trials.

While the trial itself showed no statistical difference between treatment groups, the overall response rate in a group of patients with refractory myositis, the ability to taper glucocorticoid therapy, and the responses to re-treatment suggest that the agent had an effect but that certain aspects of the study design made identification of such an effect difficult. The information gleaned

from the RIM Study will clearly be enhanced by subsequent immunologic analyses to address the mechanisms of disease response in this cohort of patients with inflammatory myopathy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Oddis 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 conception and design. Oddis, Reed, Rider, Ascherman, Barohn, Feldman, Harris-Love, Pryber, Miller, Rockette.

Acquisition of data. Oddis, Reed, Aggarwal, Rider, Ascherman, Levesque, Barohn, Feldman, Koontz, Fertig, Kelley, Pryber, Miller.

Analysis and interpretation of data. Oddis, Reed, Aggarwal, Rider, Ascherman, Levesque, Barohn, Feldman, Koontz, Fertig, Kelley, Miller, Rockette.

REFERENCES

1. Oddis CV, Conte CG, Steen VD, Medsger TA Jr. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. J Rheumatol 1990;17:1329–34.
2. Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA 2011;305:183–90.
3. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572–81.
4. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
5. Bader-Meunier B, Decaluwe H, Barnerias C, Gherardi R, Quartier P, Faye A, et al, for the Club Rhumatismes et Inflammation. Safety and efficacy of rituximab in severe juvenile dermatomyositis: results from 9 patients from the French Autoimmunity and Rituximab registry. J Rheumatol 2011;38:1436–40.
6. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum 2005;52:601–7.
7. Mahler EA, Blom B, Voermans NC, van Engelen BG, van Riel PL, Vonk MC. Rituximab treatment in patients with refractory inflammatory myopathies. Rheumatology (Oxford) 2011;50:2206–13.
8. Rios Fernandez R. Rituximab in the treatment of dermatomyositis and other inflammatory myopathies: a report of 4 cases and review of the literature. Clin Exp Rheumatol 2009;27:1009–16.
9. Valiyil R, Casciola-Rosen L, Hong G, Mammen A, Christopher-Stine L. Rituximab therapy for myopathy associated with anti–signal recognition particle antibodies: a case series. Arthritis Care Res (Hoboken) 2010;62:1328–34.
10. Chiu YE, Co DO. Juvenile dermatomyositis: immunopathogenesis, role of myositis-specific autoantibodies, and review of rituximab use [published erratum appears in Pediatr Dermatol 2011; 28:627]. Pediatr Dermatol 2011;28:357–67.
11. Rider LG, Giannini EH, Brunner HI, Ruperto N, James-Newton L, Reed AM, et al, for the International Myositis Assessment and Clinical Studies Group. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum 2004;50:2281–90.
12. Rider LG, Giannini EH, Harris-Love M, Galen J, Isenberg D, Pilkington CA, et al. Defining clinical improvement in adult and juvenile myositis. J Rheumatol 2003;30:603–17.
13. Sultan SM, Allen E, Oddis CV, Kiely P, Cooper RG, Lundberg IE, et al. Reliability and validity of the Myositis Disease Activity Assessment Tool. Arthritis Rheum 2008;58:3593–9.
14. D'Agostino RB Sr. The delayed-start study design. N Engl J Med 2009;361:1304–6.
15. Feldman BM, Wang E, Willan A, Szalai JP. The randomized placebo-phase design for clinical trials. J Clin Epidemiol 2001;54: 550–7.
16. Bohan A, Peter JB, Bowman RL, Pearson CM. A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine (Baltimore) 1977;56:255–86.
17. Van der Meulen MF, Bronner IM, Hoogendijk JE, Burger H, van Venrooj WJ, Voskuyl AE, et al. Polymyositis: an overdiagnosed entity. Neurology 2003;61:316–21.
18. Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. Arthritis Care Res (Hoboken) 2010;62: 465–72.
19. Miller FW, Rider LG, Chung YL, Cooper R, Danko K, Farewell V, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford) 2001;40:1262–73.
20. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
21. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761–9.
22. Targoff IN. Laboratory testing in the diagnosis and management of idiopathic inflammatory myopathies. Rheum Dis Clin North Am 2002;28:859–90, viii.
23. Targoff IN, Mamyrova G, Trieu EP, Perurena O, Koneru B,

O'Hanlon TP, et al, for the Childhood Myositis Heterogeneity and International Myositis Collaborative Study Groups. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. Arthritis Rheum 2006;54:3682–9.
24. Espada G, Maldonado Cocco JA, Fertig N, Oddis CV. Clinical and serologic characterization of an Argentine pediatric myositis cohort: identification of a novel autoantibody (anti-MJ) to a 142-kDa protein. J Rheumatol 2009;36:2547–51.
25. Gunawardena H, Wedderburn LR, Chinoy H, Betteridge ZE, North J, Ollier WE, et al, for the Juvenile Dermatomyositis Research Group, UK and Ireland. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. Arthritis Rheum 2009;60:1807–14.
26. Rider LG, Lachenbruch PA, Monroe JB, Ravelli A, Cabalar I, Feldman BM, et al, for the IMACS Group. Damage extent and predictors in adult and juvenile dermatomyositis and polymyositis as determined with the Myositis Damage Index. Arthritis Rheum 2009;60:3425–35.
27. Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009;361:1268–78.
28. Oddis CV, Rider LG, Reed AM, Ruperto N, Brunner HI, Koneru B, et al, for the International Myositis Assessment and Clinical Studies Group. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum 2005;52:2607–15.
29. Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: a regulatory viewpoint. Stat Med 2004;23: 305–14.
30. Agarwal S, Kiely PD. Two simple, reliable and valid tests of proximal muscle function, and their application to the management of idiopathic inflammatory myositis. Rheumatology (Oxford) 2006;45:874–9.
31. Kao AH, Lacomis D, Lucas M, Fertig N, Oddis CV. Anti–signal recognition particle autoantibody in patients with and patients without idiopathic inflammatory myopathy. Arthritis Rheum 2004; 50:209–15.
32. Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore) 1991;70:360–74.
33. Ruperto N, Ravelli A, Pistorio A, Ferrianni V, Calvo I, Ganser G, et al, for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Paediatric Rheumatology Collaborative Study Group (PRCSG). The provisional Paediatric Rheumatology International Trials Organisation/American College of Rheumatology/European League Against Rheumatism Disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. Arthritis Rheum 2008;59:4–13.

APPENDIX A: RIM STUDY GROUP MEMBERS

Members of the RIM Study Group (countries, principal investigators, and centers) are as follows. In Canada (pediatric sites): Brian Feldman (Hospital for Sick Children, Toronto, Ontario) and Adam Huber (IWK Health Centre, Halifax, Nova Scotia). In the Czech Republic (adult site): Jiří Vencovský and Herman Mann (Institute of Rheumatology, Prague). In Sweden (adult site): Ingrid E. Lundberg (Karolinska Institutet, Stockholm). In the US (adult sites): Richard Barohn, Mazen Dimachkie, and Kevin Latinis (University of Kansas Medical Center, Kansas City), Lorinda Chung and David Fiorentino (Stanford University, Palo Alto), Leslie Crofford (University of Kentucky, Lexington), Mary Cronin (Medical College of Wisconsin, Milwaukee), Stephen DiMartino (Hospital for Special Surgery, New York), Barri Fessler (University of Alabama at Birmingham), Michael Harris-Love (Washington DC Veterans Affairs Medical Center), Sharon Kolasinski (University of Pennsylvania, Philadelphia), Todd Levine (Phoenix Neurological Associates), Galina Marder (North Shore–LIJ, New York), Richard Martin and Aaron Eggebeen (adult and pediatric site: Michigan State University, Grand Rapids), Frederick Miller (National Institute of Environmental Health Sciences, NIH, Bethesda), Pushpa Narayanaswami and Seward B. Rutkove (Beth Israel Deaconess Medical Center/Harvard Medical School, New York), Chester Oddis, Dana Ascherman, Rohit Aggarwal, David Lacomis, and Christopher Bise (University of Pittsburgh), Nancy Olsen and Andreas Reimold (University of Texas Southwestern Medical Center at Dallas), Elena Schiopu, Kristine Phillips, and James Seibold (University of Michigan, Ann Arbor), Khema Sharma (University of Miami), Swamy Venturupalli and Michael Weisman (Cedars-Sinai Medical Center, University of California at Los Angeles), and Steven Ytterberg (Mayo Clinic, Rochester). In the US (pediatric sites): Susan Kim (Children's Hospital of Boston), Tzielan Lee (Stanford University, Palo Alto), Daniel Lovell (Cincinnati Children's Hospital), C. Egla Rabinovich (Duke University Medical Center, Durham), Ann Reed (Mayo Clinic, Rochester), Lisa Rider (National Institute of Environmental Health Sciences, NIH, Bethesda), Rafael Rivas-Chacon (Miami Children's Hospital), and David Sherry (The Children's Hospital of Philadelphia).

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EDITORIAL

The Efficacy of Rituximab in Refractory Myositis: The Jury Is Still Out

Marianne de Visser

Over the last decade, there has been a paradigm shift in the classification of the idiopathic inflammatory myopathies (IIMs). Bohan and Peter established diagnostic criteria for polymyositis (PM) and dermatomyositis (DM) in 1975 that are still widely used (1). However, those criteria have low specificity and therefore fail to distinguish IIMs from sporadic inclusion-body myositis (IBM) and noninflammatory myopathies, including limb muscular dystrophies with a similar distribution of weakness (e.g., dysferlinopathies) that may be associated with cellular infiltrates (2).

A different approach was taken in the 1980s. Classification was based on the results of elegant (immuno)histopathologic studies (3). It was noted that in both PM and sporadic IBM, non-necrotic muscle fibers are injured by autoinvasive CD8+ T cells that act in concert with CD4+ T lymphocytes, plasmacytoid dendritic cells, and macrophages, whereas in DM, infiltration of B lymphocytes, CD4 helper T cells, and macrophages can be found in perimysial areas of muscle fascicles and around small blood vessels (3).

The existence of PM as defined by Arahata and Engel was recently challenged (4,5). In these studies, PM was found to be rare among the Dutch and French Canadian population and instead, another disease entity was recognized and labeled as nonspecific myositis (4) or overlap myositis (5). This myositis variant had the clinical characteristics of PM, but lacked the canonical histologic features described by Arahata and Engel. In contrast, nonspecific/overlap myositis had a histologic picture resembling DM. As in DM, patients with nonspecific/overlap myositis were frequently found to have an associated connective tissue disorder (CTD) or myositis-specific antibodies (4,5). In addition, another IIM was recognized: necrotizing autoimmune myopathy (4,6,7), characterized by subacute or insidious onset, progressive symmetric proximal weakness, no skin abnormalities, and a grossly elevated serum creatine kinase value. Necrotizing autoimmune myopathy is distinguished from the other inflammatory myopathies by the absence of prominent inflammatory infiltrates and with macrophages rather than T cells being the effector cells (8). Necrotizing autoimmune myopathy has been found to be associated with CTD, cancer, and the use of statins. Because of the potential of necrotizing autoimmune myopathy to be amenable to treatment, it is important to distinguish it from other causes of muscle necrosis, such as rhabdomyolysis, muscular dystrophies, endocrinopathies, medications, and toxins.

There is a clear need for a new perspective on the treatment of the IIMs. The prognosis is not well known, since long-term outcome and prognostic factors vary widely. Favorable long-term outcome ranges from 18% to 90%. Predictors of poor outcome are the duration at disease onset, the presence of cancer (9,10), and possibly also male sex (9), dysphagia, longstanding symptoms prior to diagnosis or start of therapy, subset of myositis, skin ulcers, delay in diagnosis or in start of therapy, various types of myositis, pulmonary (especially interstitial lung disease) and cardiac involvement, the presence of low total protein and albumin levels, and antisynthetase or anti–signal recognition particle autoantibodies (10).

A monocyclic disease course was seen in 15–48% of patients (9,10). Over the long term, myositis has a chronic continuous or polycyclic disease course, with major effects on perceived disability and quality of life, despite regained muscle strength (9), although other investigators have reported that after a median of 7.5 years of followup, most patients (86%) had no disease activity, and 83% had no disability (10). It is of note that all these outcome studies were performed using the conventional classification criteria for PM and DM.

Despite the lack of a randomized controlled trial (RCT), high-dose steroids are considered first-line treatment in PM and DM. However, in a RCT comparing 2

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regimens of steroids (daily oral high-dose prednisone versus 4 weekly cycles of high-dose oral dexamethasone) in adult patients with newly diagnosed myositis, a substantial proportion of the patients (~55%) had to discontinue either type of steroid treatment early because of a lack of improvement and/or severe side effects (11).

In clinical practice, many immunosuppressants are added to the prednisone regimen, particularly if the patients do not respond adequately. However, a Cochrane review on treatment of DM and PM concluded that there was insufficient evidence from the available RCTs to confirm the value of immunosuppressants (other than prednisone) in myositis. This conclusion appears to contradict the experience of many clinicians (12). Novel therapies, such as biologic agents in the form of monoclonal antibodies or fusion proteins, are emerging. To date, these have not been investigated for use in patients with IIM in an adequate RCT, and results of case studies have been disappointing, showing only moderate improvement.

For example, in a 52-week pilot RCT of etanercept compared to placebo in patients with newly diagnosed DM and in those with refractory DM, no statistically significant differences between treatment groups were found with regard to muscle strength and motor functions, but there was a possible steroid-sparing effect in the etanercept-treated patients (13). Rituximab, a B cell–depleting agent, has been used in small series of patients with refractory myositis with reportedly favorable outcomes (14,15). Encouraged by these results and based on the critical role of B cells in the initiation and propagation of the immune response in the pathogenesis of myositis, Oddis et al (16) initiated a multicenter, randomized, double-blind, placebo-phase trial in adult and pediatric myositis to assess the safety and efficacy of rituximab, the Rituximab in Myositis (RIM) study. Their findings are presented in this issue of *Arthritis & Rheumatism.*

Eligible patients included adults with a diagnosis of definite or probable refractory DM or PM and patients at least 5 years of age or older with definite or probable juvenile DM according to specific criteria. The definition of improvement chosen for this trial was based on the International Myositis Assessment and Clinical Studies Group (IMACS) preliminary validated top-ranked response criterion of a ≥20% improvement in 3 of any 6 core set measures with no more than 2 worsening by ≥25%. A definition of worsening was also specified.

Patients were randomly assigned to a rituximab early (active drug at weeks 0 and 1, with placebo at weeks 8 and 9) or rituximab late (placebo at weeks 0 and 1, with active drug at weeks 8 and 9) arm. An equal number of adult PM, adult DM, and juvenile DM patients received drug either at the beginning of the trial or 8 weeks later (placebo-phase duration agreed upon by consensus of the Steering Committee). Week 8 represented the end point of the placebo-controlled trial since the rituximab late group had not yet received study drug. The corticosteroid dosage was held constant until week 16; if patients met the definition of improvement (or experienced complications), a dosage reduction was begun at no more than 20% of the existing dose every 4 weeks. The primary end point was the time to achieving the definition of improvement, which was compared between the rituximab early and rituximab late groups. Secondary end points were the time to achieving a 20% improvement in manual muscle testing scores on 2 consecutive visits, as compared between the 2 groups, and the proportion of patients achieving the definition of improvement at week 8. Of 236 patients screened, 200 were randomized. Prior to screening, diagnostic accuracy was adjudicated in all PM patients (86 muscle biopsy samples reviewed; 44 subsequent exclusions, 14 for IBM, 29 for undetermined myopathy but not PM or DM, and 1 for excessive muscle damage).

Eighty-three percent of the patients met the definition of improvement by week 44, with no between-group difference in the time to achieving the definition of improvement. Results for the 2 secondary outcomes were also similar. There was a nonsignificant difference between the early and late rituximab arms in the juvenile DM group. A prednisone-sparing effect was not a defined outcome measure, but most of the patients were able to reduce their prednisone dosage irrespective of being in the early or late rituximab group. Rituximab was tolerated rather well. There were 67 serious adverse events in 64 patients, 26 of which were drug-related, and the majority were of infectious origin. No difference in adverse events was observed at week 8, the randomized placebo-controlled time point.

The authors are to be commended for performing a large clinical trial encompassing 200 patients with a rare disease such as myositis. The RIM Study is the first prospective, randomized double-blind trial in myositis to enroll both pediatric and adult patients and is the largest trial ever performed in patients with IIMs. It represents the first collaboration between adult and pediatric rheumatologists and neurologists for the study of myositis, showing that both specialist groups were able "to share the same planet" (17), and this holds promise for future collaborative trials. The investigators

showed that improvement was measurable, albeit after 20 weeks, in both treatment groups in adult myositis patients, that adding rituximab led to a steroid-sparing effect, and that the drug was relatively safe.

Several reasons may explain why the RIM Study failed to achieve its primary efficacy end point. The investigators mention the following issues: the power calculation based on the postulated effect of rituximab by 8 weeks, the selection of a placebo phase of 8 weeks, and the core set of measures and the definition of improvement.

The Steering Committee had assumed an effect of rituximab at week 8 in more than half of the patients based on data reported in the literature, but this was seen at week 20 in the adult myositis group, similar to another reported observation in patients with adult myositis who were treated with rituximab (15). This led to underestimation of the anticipated placebo rate. The choice of an 8-week placebo phase was mainly determined based on ethical considerations. The core set of measures was partially validated and agreed upon by consensus, but has not recently been used in a prospective clinical trial such as the RIM Study.

Another important issue is to identify which patients with PM and DM would be the most likely to benefit from receiving treatment with rituximab or any other of the novel therapies. Selection of the patients should be based on the most recent classification criteria (18). The authors ruled out myositis patients who had an overlap with connective tissue disorders and those with concomitant cancer, thus excluding patients with nonspecific myositis and necrotizing autoimmune myopathy, both of which are known to be amenable to treatment. Since not all muscle biopsy samples were available for review, it is still possible that cases were misdiagnosed as "true PM" when in fact they were IBM. Whether the reviewers of the muscle biopsies adhered to strict histopathologic criteria for the diagnosis of IBM, requiring the presence of rimmed vacuoles, is not explicitly mentioned. It could well be that this led to the inclusion of patients who may not to be responsive to treatment. The juvenile DM group, in which diagnosis is rather straightforward, did show a trend toward a difference between both treatment arms, but the sample size was too small to draw solid conclusions.

Finally, muscle imaging and, in particular, magnetic resonance imaging may be helpful in further selection of suitable myositis patients. Muscle edema indicating active inflammation can be demonstrated by showing areas of high signal intensity on STIR and fat-suppressed T2-weighted sequences, even in clinically asymptomatic muscles, and on T1-weighted sequences, replacement of skeletal muscle by fat can be assessed (19). These analyses may help select the patient subgroups that should be included in future clinical trials.

In conclusion, Oddis et al have proved that large treatment trials are possible in this difficult disease. Future trials will benefit from the experience obtained in the RIM Study.

AUTHOR CONTRIBUTIONS

Dr. de Visser drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.
2. Confalonieri P, Oliva L, Andreetta F, Lorenzoni R, Dassi P, Mariani E, et al. Muscle inflammation and MHC class I upregulation in muscular dystrophy with lack of dysferlin: an immunopathological study. J Neuroimmunol 2003;142:130–6.
3. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies. I. Quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T cells. Ann Neurol 1984;16:193–208.
4. Van der Meulen MF, Bronner IM, Hoogendijk JE, Burger H, van Venrooij WJ, Voskuyl AE, et al. Polymyositis: an overdiagnosed entity. Neurology 2003;61:316–21.
5. Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senecal JL. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. Medicine (Baltimore) 2005;84:231–49.
6. Bronner IM, Hoogendijk JE, Wintzen AR, van der Meulen MF, Linssen WH, Wokke JH, et al. Necrotising myopathy, an unusual presentation of a steroid-responsive myopathy. J Neurol 2003;250:480–5.
7. Grable-Esposito P, Katzberg HD, Greenberg SA, Srinivasan J, Katz J, Amato AA. Immune-mediated necrotizing myopathy associated with statins. Muscle Nerve 2010;41:185–90.
8. Liang C, Needham M. Necrotizing autoimmune myopathy. Curr Opin Rheumatol 2011;23:612–9.
9. Bronner IM, van der Meulen MF, de Visser M, Kalmijn S, van Venrooij WJ, Voskuyl AE, et al. Long-term outcome in polymyositis and dermatomyositis. Ann Rheum Dis 2006;65:1456–61.
10. Shu XM, Lu X, Xie Y, Wang GC. Clinical characteristics and favorable long-term outcomes for patients with idiopathic inflammatory myopathies: a retrospective single center study in China. BMC Neurol 2011;11:143.
11. Van de Vlekkert J, Hoogendijk JE, de Haan RJ, Algra A, van der Tweel I, van der Pol WL, et al. Oral dexamethasone pulse therapy versus daily prednisolone in sub-acute onset myositis, a randomised clinical trial. Neuromuscul Disord 2010;20:382–9.
12. Gordon PA, Winer JB, Hoogendijk JE, Choy EH. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. Cochrane Database Syst Rev 2012:CD003643.
13. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol 2011;70:427–36.
14. Bader-Meunier B, Decaluwe H, Barnerias C, Gherardi R, Quartier P, Faye A, et al, for the Club Rhumatismes et Inflam-

mation. Safety and efficacy of rituximab in severe juvenile dermatomyositis: results from 9 patients from the French Autoimmunity and Rituximab registry. J Rheumatol 2011;38:1436–40.
15. Mahler EA, Blom M, Voermans NC, van Engelen BG, van Riel PL, Vonk MC. Rituximab treatment in patients with refractory inflammatory myopathies. Rheumatology (Oxford) 2011;50: 2206–13.
16. Oddis CV, Reed AM, Aggarwal R, Rider LG, Ascherman DP, Levesque MC, et al, and the RIM Study Group. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013;65:314–24.
17. Christopher-Stine L. Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies. Curr Opin Rheumatol 2010; 22:623–6.
18. Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, Rose MR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands. Neuromuscul Disord 2004;14:337–45.
19. Tomasova Studynkova J, Charvat F, Jarosova K, Vencovsky J. The role of MRI in the assessment of polymyositis and dermatomyositis. Rheumatology (Oxford) 2007;46:1174–9.