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Improvement in Disease Activity in Refractory Juvenile Dermatomyositis Following Abatacept Therapy

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ABSTRACT

Objective. An open-label 24-week study was conducted to evaluate the safety and efficacy of abatacept in patients with refractory juvenile dermatomyositis (JDM).

Methods. Ten patients ≥7 years of age with moderate disease activity were enrolled in a 24-week study to examine the safety and treatment response of subcutaneous abatacept. The primary endpoint was the International Myositis Assessment and Clinical Studies Group (IMACS) Definition of Improvement (DOI). Secondary endpoints included safety, change in core set activity measures (CSMs) of IMACS and Pediatric Rheumatology International Trials Organization (PRINTO), and the ACR-EULAR response criteria for JDM. Blinded radiologists assessed thigh magnetic resonance imaging (MRI). Interferon gene score (IFNGS) was performed on whole-blood RNA by NanoString and cytokines were assessed by Luminex.

Results. Five patients achieved DOI at week 12, and nine achieved DOI at week 24, including two with minimal, four moderate, and three with major improvement by ACR-EULAR response criteria using IMACS CSMs. All CSMs improved from baseline at weeks 12 and 24, except muscle enzymes. Daily corticosteroid dose decreased from a mean of 16.7 mg at baseline to 10.2 mg at week 24 (p=0.002). Average MRI muscle edema score decreased from baseline 5.3 to 2.3 at week 24 (p=0.01). Six patients had down-trending IFNGS and galectin-9 at week 24. Decreases in IFNGS, IP-10, galectin-9 and IL-2 correlated with improvement in disease activity and in MRI muscle edema. Eleven Grade 2 or 3 treatment-emergent adverse events were observed.

Conclusions: This open-label study demonstrated abatacept may be beneficial for treatment-refractory JDM.

INTRODUCTION

Juvenile dermatomyositis (JDM) is a systemic autoimmune disease with chronic inflammation and microvasculopathy affecting muscle and skin, leading to symmetric proximal weakness and characteristic rashes (1). A large proportion of JDM patients are treatment resistant, requiring long term immunosuppressive therapy with glucocorticoids, methotrexate, and other medications (2). From uncontrolled data, both rituximab and anti-TNFα monoclonal antibody therapy may be effective in refractory JDM patients (3). In a randomized controlled trial, the majority of treatment-refractory JDM patients responded to rituximab; however, the primary endpoint was not achieved (4).

Abatacept, a recombinant fusion protein of CTLA4 that blocks CD80 and CD86 ligand binding to CD28, thereby inhibiting T cell activation, is FDA approved for the treatment of rheumatoid arthritis in adults and children (5). The rationale for use of abatacept in dermatomyositis (DM) includes the expression of CTLA4, CD28, CD86 and CD40 on the inflammatory cells of affected muscle tissue (6). In a small, randomized trial of intravenous abatacept in refractory adult DM and polymyositis (PM) patients, disease activity significantly improved, based on the 2016 ACR-EULAR myositis response criteria Total Improvement Score (TIS) (7). Improvement in disease activity has also been observed in several severe JDM patients treated with abatacept (8). We therefore conducted an open-label trial to evaluate the safety and efficacy of abatacept in children with refractory JDM.

METHODS

Patients. The study was conducted at the George Washington Myositis Center in an institutional review board approved protocol (GWU IRB111418, NCT02594735) in which enrollment began in September 2016 . Written informed consent and age-appropriate assent were obtained. Twenty-six candidates consented to screening, and ten patients with probable or definite JDM per Bohan and Peter criteria were enrolled (Supplementary Figure S1) (9). The most common reasons for screening failure included less than moderately active disease (4), recent medication change (3), and needle anxiety (2). Enrolled patients were ≥7 years of age with a body weight ≥25 kg and had at least moderately active disease (4), defined by Physician Global Activity of ≥2.5 out of 10 cm on the visual analog scale (VAS) and at least two other core set activity measures (CSMs) indicative of moderate disease activity: Patient/Parent Global Activity VAS ≥ 2.0 of 10 cm,

Extramuscular Global Activity VAS ≥2.0 of 10 cm, Manual Muscle Testing-8 (MMT-8) score ≤125/150, Child Health Assessment Questionnaire (C-HAQ) disability index ≥ 0.25 out of 3.0, or at least one of the muscle enzymes, including creatine kinase (CK), alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), and aldolase elevated ≥1.3 times the upper limit normal (ULN). Patients were also treatment refractory, defined as having an inadequate response or intolerance to prednisone and at least one other medication for at least 3 months duration (10). Patients receiving prednisone had a stable dose for at least four weeks and stable non-glucocorticoid medications at least six weeks prior to screening.

Study design. In an open-label study, patients received abatacept weekly for 24 weeks and were assessed every six weeks and contacted by telephone every two weeks, examining safety and treatment response. After screening and baseline assessment at week 0, participants were started on abatacept 125 mg subcutaneously (SQ) weekly for body weight ≥50 kg or 87.5 mg SQ weekly for body weight <50 kg. There was a dose escalation to 212.5 mg weekly or 137.5 mg weekly at week 12, respectively, for patients who did not improve by ≥5% in at least 3 core set activity measures (CSMs) (11). An extension of six months was offered to those who met improvement criteria at week 24. Corticosteroid tapering in the first 24 weeks followed a standardized dose reduction regimen starting at week 6 if the patient achieved the Definition of Improvement (DOI) and was rated at least moderately improved compared to the prior visit by the study physician (12).

Primary endpoint. The primary efficacy endpoint was the DOI at week 24, which includes improvement in at least three of any six International Myositis Assessment and Clinical Studies Group (IMACS) CSMs by ≥20%, with no more than two core set measures worsening by ≥25% (not including muscle strength in the assessment of worsening) (12).

Secondary endpoints. Secondary endpoints included minimal, moderate, and major improvement as defined by the Pediatric Rheumatology International Trials Organization (PRINTO), as well as the 2016 ACR-EULAR response criteria for JDM, using the Total Improvement Score (TIS) and thresholds for minimal, moderate and major improvement (13, 14, 15). Changes in IMACS and PRINTO disease activity CSMs were also examined at each visit (14). Skin evaluation included Cutaneous Dermatomyositis Area and Severity Index (CDASI) (range for activity 0-100, damage 0-32) (16), Cutaneous Activity Visual Analog Scales (VAS) by Myositis Disease Activity Assessment Tool (MDAAT), as well as Physician Global Skin Activity and Physician Global Skin Damage VAS. Physician Global Damage VAS and Myositis Damage Index (MDI) were obtained

at baseline and week 24 (15). Health-related quality of life was parent-assessed at each visit using the Child Health Questionnaire (CHQ-PF50), Dermatology Life Quality Index (DLQI), and Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue scale (17, 18).

Safety Analysis. Adverse events and serious adverse events (AEs and SAEs) were monitored every two weeks and reported in a standardized manner using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 was mild, Grade 2 moderate, Grade 3 severe, Grade 4 life threatening, and Grade 5 death. AEs were also coded by relationship to study drug (unrelated, unlikely related, possibly, probably, or definitely related). Adverse events were considered possibly related to study drug if there was a clinically plausible time sequence, biologically plausible mechanism, and/or attribution was unrelated to concurrent illness, other drugs, or procedures. Chemistries and blood counts were also monitored every six weeks. Autoantibodies were tested at LabCorp (Burlington, NC) at baseline and week 24, including ANA, ENA, and anti-thyroid autoantibody panels. Myositis autoantibody testing was performed by immunoprecipitation and immunoblotting by Oklahoma Medical Research Foundation (19). The data safety and monitoring board (DSMB) monitored overall safety.

Magnetic resonance imaging (MRI) and biomarkers. Axial STIR and T1 MRI images of bilateral thighs and pelvis were obtained at baseline and week 24. Images were coded and reviewed independently by two musculoskeletal radiologists who had comparable inter-observer variability and were blinded to subject data, including visit number. MRI scoring was performed utilizing a 4-point scale (0-normal, 1-mild, 2-moderate, 3-severe) for each of the following findings: muscle edema, muscle atrophy, fascial edema, and subcutaneous/soft tissue edema, for each of the muscle groups examined, i.e. gluteal, adductors, hamstrings, and quadriceps, resulting in an aggregate score between 0 to 12 (20, 21). MRI examinations were not available for clinician review during patient visits.

Whole blood RNA from weeks 0 and 24 and from age- and gender-matched control subjects from a National Institutes of Health natural history study (NCT00017914) was examined via NanoString Technologies (Seattle, WA) for a 28-gene interferon regulated gene score (IFNGS) calculated by geometric mean (22). Twenty serum cytokines and chemokines were examined in duplicate by Luminex assay (ThermoFisher Scientific, Waltham, MA).

Statistical analysis. Analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). Differences in mean scores of the CSMs between baseline and each follow-up visit were

evaluated for significance by paired t-tests ($p < 0.05$). Due to the small sample size, no adjustment was made for multiple comparisons. Nonparametric data, such as the IFNGS, cytokines/chemokines, and MRI scores, were tested for significance via Wilcoxon Signed Rank test ($p < 0.05$). Ranked differences in the total muscle edema scores in MRI readings from two raters were analyzed for concordance using Kendall's W statistic. Because concordance was excellent (Kendall's W 0.97), the two raters' scores were averaged (Supplementary Table S1). Analysis of IFNGS and cytokine/chemokine levels, including comparison to healthy controls, was by Wilcoxon signed-rank test, and an average of duplicate samples was used. Spearman correlations were calculated between the change in IFNGS or serum cytokines/chemokines and changes in ACR-EULAR JDM response criteria TIS and other disease activity measures. Strong correlations were considered Spearman $r_s \geq 0.7$.

RESULTS

Baseline demographic and clinical features of the ten enrolled JDM subjects are shown in Supplementary Table 1. Most of the patients were female (80%) and Caucasian (80%), with a mean age of 12 (range 7.1-17.0) years and mean disease duration of 2.7 years. At study entry, disease activity of all patients was moderate (mean Physician Global Activity VAS 5.0), and patients had moderate weakness and functional disability (mean MMT-8 122/150, Childhood Myositis Assessment Scale (CMAS) 34/52 and CHAQ 1.84/3.0), and moderately active skin disease (mean CDASI 21, range 0-100) (Table 1). Two patients had calcinosis and one patient had interstitial lung disease at study entry. The mean number prior of non-corticosteroid myositis medications was 4.7 (range 3-7) and at study entry, the mean number was 2.2 (range 1-3). Nine patients were receiving prednisone with a mean dose of 16.7 mg at baseline. Abatacept dosage was 125 mg subcutaneously weekly in six patients and 87.5 mg weekly in four patients. One patient had dose escalation from 125 mg to 212 mg at week 12 due to non-response.

Response to abatacept treatment. Among 10 patients studied**,** five met the DOI at week 12, and nine met the DOI at week 24, the primary study endpoint. Using PRINTO CSMs and the expanded PRINTO DOI, two patients met minimal improvement and two met moderate improvement at week 12, while four met minimal improvement and five met moderate improvement at week 24 (Table 2) (13).

Using IMACS and PRINTO CSMs, the mean ACR-EULAR JDM response criteria Total Improvement Score at week 12 was 40.8 ± 14.2 and 50.0 ± 15.2, respectively, and at week 24 was 53.8 ± 19.2 and 65.3 ± 25.9, respectively. Using IMACS CSMs, two patients attained minimal improvement, four moderate improvement, and three patients achieved major improvement at week 24 by the ACR-EULAR JDM response criteria (Table 2, Figure 1A). Using PRINTO CSMs, seven patients attained major improvement, one patient each achieved minimal and moderate improvement by the ACR-EULAR JDM response criteria (Table 2, Figure 1B).

All CSMs improved significantly from baseline to weeks 12 and 24, except for muscle enzymes (Table 1, Supplementary Table S2). Of the IMACS CSMs, most improved at week 12 (relative change 11-34%) and continue to improve through week 24 (relative change 13-57%). Of the Myositis Disease Activity Assessment Tool (MDAAT) organ system scores, the constitutional and cutaneous disease activity scores, which were also the most abnormal at baseline, improved significantly at week 24. The remaining organ system scores were unchanged (Supplementary Table S2). Among the additional PRINTO CSMs, improvement showed the same trend, with significant improvement at week 12 from baseline (relative change 17%-78%) and further improvement at week 24 (relative change 24%-108%).

Corticosteroid dosage significantly decreased from a mean of 16.7 ± 7.5 mg at baseline to 10.2 ± 5.4 mg at week 24, a decrease of 39% (Table 1). The weight-adjusted mean corticosteroid dosage was also significantly decreased by 50% at week 24. There was a significant decrease in the CDASI activity score from the baseline to week 12 and 24 by 27% and 35%, respectively (Supplementary Table S2, Supplementary Figures S3A-B). The CDASI damage score was unchanged. Physician global skin activity VAS decreased, but physician global skin damage VAS increased from baseline. There was also no detectable change in damage over the 24-week study period by the physician-assessed global damage and severity of damage and extent of damage scores from the MDI, although muscle damage trended lower through week 24 (by 53%) (Supplementary Table S2). The MRI total muscle edema score improved by 57% at week 24 (Table 2, Supplementary Figures S3C-D), but muscle atrophy, as well as fascial and subcutaneous edema were unchanged (Supplementary Table S2).

Many of the patient-reported outcome measures improved. CHQ-PF50 Physical Summary (PhS) scores increased over the 24-week study period (relative change 108%), along with improvements in specific subdomain scores of CHQ-PF50, but the Psychosocial Summary (PsS)

scores were unchanged (Table 2, Supplementary Table S3). Parent-reported fatigue improved by 27% on average using the PROMIS Pediatric Fatigue survey. Parent-reported skin quality of life improved by 59% on average using the DLQI. Parent-reported skin global activity trended toward improvement, while skin global damage and skin itch were unchanged.

Peripheral blood IFNGS and serum IP-10, galectin-9, IL-2, IL-4, and IL-6 were detectable in at least five of nine patients evaluated, and significantly increased above healthy controls at baseline, while serum IFN-α, IFN-γ, IL-7, IL-8, IL-10, and IL-18 were detectable, but not elevated above control values at baseline (Supplementary Table S4). Six of nine patients had a decrease in IFNGS (overall mean decrease of 43%) and galectin-9 (mean -19%) over the 24-week study period, although these were not significantly changed from baseline values. Four of nine patients had a decrease in serum IP-10 (overall mean decrease of 41%), IL-2 (mean -70%), and IL-4 (mean -81%) levels, and three of nine patients had a decrease in IL-6 levels (mean -61%).

Improvement in IFNGS at week 24 correlated with the improvement in Physician Global Activity (r_s=0.70) (Supplementary Table S5). Improvement in IP-10 correlated with improvement in CDASI activity (r_s=0.70) and improvement in muscle edema on MRI (r_s=0.81). Improvement in IL-2 also correlated with the improvement in MRI muscle edema (r_s=0.71).

Eight of nine patients opted to continue to the open-label extension phase and had a visit 41±4 weeks following week 0 (Table 1, Figures S1A-B). In the open label extension period, seven of the eight patients maintained at least minimal improvement based on the IMACS DOI, but one patient developed worsening in muscle strength and calcinosis at Week 40. By the ACR-EULAR JDM response criteria using IMACS CSMs, three patients attained moderate and four major improvement at the final evaluation, with an increase in improvement category in four patients. Using PRINTO CSMs, all eight patients had maintained improvement at the final evaluation, including two patients who achieved minimal, one moderate, and five major improvement. However, the patient with worsening strength and calcinosis changed from major to minimal improvement. There was no significant change in corticosteroid dosage and no change in other myositis medications in the extension phase.

Safety Analysis. Over the 24-week treatment period, abatacept was well tolerated, and nine of the ten patients completed the study. One patient was terminated at week 24 due to worsening of the pre-existing interstitial lung disease requiring hospitalization and treatment with IV cyclophosphamide. Study medication at Week 24 was withheld. There were three other Grade 3

treatment-emergent adverse events assessed as possibly related to abatacept treatment, including worsening calcinosis (2 events) and compression fracture (1 event). In one patient existing calcinosis worsened, and a second patient developed new calcinosis lesions (Table 3).

Seven Grade 2 treatment-emergent adverse events occurred, six of which were assessed as possibly related to abatacept. Events possibly related to abatacept treatment included worsening right knee contracture (1 event), focal lipoatrophy (1 event), febrile episodes (2 events), skin infection (1 event), and E. coli diarrhea (1 event). Three subjects developed a positive antinuclear antibody, with titers ranging from 1:80 to 1:160; one was transiently positive and turned negative at week 24. Two patients developed borderline positive anti-Ro autoantibodies, which were assessed as possibly related to abatacept (Table 3). Fifty-one Grade 1 adverse events occurred, assessed as unlikely related to abatacept. These were primarily laboratory abnormalities, including chemistry, hematologic, and renal test findings, as well as one episode of diarrhea thought to be unrelated to study drug and miscellaneous other adverse events (Supplementary Table S6).

DISCUSSION

In this 6-month, open-label, prospective clinical trial of abatacept in refractory and moderately active JDM patients there was a significant improvement in nearly all of the CSM that define disease activity in JDM, including muscle strength, physical function, skin activity, and fatigue. The primary endpoint, minimal clinical improvement by the IMACS DOI, was achieved by nine of the ten patients. Clinical response was observed early, beginning by week 12 in half of the patients, and continued to week 24 and through the extension period. Notably, 8 of 9 patients achieved moderate or major improvement by the ACR-EULAR response criteria using PRINTO CSMs, and 7 patients improved to this level using IMACS CSMs. A steroid-sparing benefit was also observed, as corticosteroid dose was significantly lower at trial end.

At week 24, seven patients achieved major clinical response when PRINTO CSMs were used as compared to three patients who achieved major improvement using IMACS CSMs. There was no difference in the frequency of minimal or moderate improvement in the ACR-EULAR response criteria with either set of CSMs. Since patients had a greater degree of improvement in the CMAS (30 % improvement at week 24) and CHQ-PF50 (108% improvement) which are part of the PRINTO CSMs but are not included in the IMACS CSMs, this generated a higher TIS or clinical response compared to the TIS derived from IMACS CSMs which uses MMT-8 (12% improvement at week 24) and muscle enzymes (not improved) instead. This is a pilot study of 10

patients, and additional examination of the responsiveness of PRINTO vs. IMACS CSMs and their use in the response criteria is needed.

The efficacy results in this open label study of JDM patients are similar to a small trial of 20 adult patients with refractory DM/PM receiving intravenous abatacept, in which clinical response was evident in the early treatment arm at month 3 compared to the delayed treatment arm. In that study, MMT-8 and muscle disease activity by the MDAAT both significantly improved after 6 months of treatment (7).

In the present trial in patients with JDM, the clinical improvement correlated with objective measures that were blinded to the clinical assessments, including the muscle edema score by MRI. The beneficial effect of abatacept on muscle performance (MMT-8, CMAS) was mirrored by a decrease in the amount of muscle edema, suggesting that abatacept ameliorated muscle inflammation in these patients with refractory disease.

The studies done on blood allowed us to explore the role of the IFN pathway and T cell activation. There has been convincing evidence that JDM immunopathogenesis involves a heightened activation of both the innate and adaptive immune systems and is associated with chronic endothelial changes (23). High levels of Type I and II IFN gene expression in the peripheral blood have correlated with greater disease activity in JDM (24). Moreover, peripheral blood levels of galectin-9 and IP-10 were found to be good biomarkers that differentiate varying levels of active disease in three large international cohorts of JDM patients (25). While several IFN-related and T cell serum cytokines trended lower from baseline, the primary findings here included a strong correlation of the improvement in IFN-related markers (IFNGS, IP-10, galectin-9) and in IL-2 with improvement in disease activity and in MRI muscle edema. These findings suggest that downregulation in IFN pathway and T cell signaling are at least partially related to the efficacy of abatacept in JDM. A Japanese study in patients with rheumatoid arthritis showed decreased blood IFN gene score levels in patients who responded to abatacept therapy as compared to non-responders (26). Although the effect of abatacept on Treg is still unknown, the higher expression of FOXP3 in the affected muscles of adult DM/PM patients after treatment with abatacept suggests downregulation of T cell activation (7).

Abatacept was well tolerated and there were no severe infections despite concomitant use of other immunosuppressive agents, including glucocorticoids. Three patients developed positive antinuclear antibodies, but none developed signs of another autoimmune disease. Seroconversion

has also uncommonly been reported in abatacept-treated patients with rheumatoid arthritis and juvenile idiopathic arthritis, also with no significant autoimmune symptoms (27, 28, 29). Though there were no safety signals in the present study, a full understanding of this requires larger datasets. Reassuringly, no safety signals were observed in previous trials of juvenile idiopathic arthritis and inflammatory myopathies using abatacept (7, 27, 28).

Worsening of interstitial lung disease was observed in one anti-MDA5 autoantibody-positive subject. This is in contrast with the ARTEMIS trial, where myositis-associated ILD remained stable in ten subjects. In patients with rheumatoid arthritis-associated ILD treated with abatacept, lung disease remained stable or improved following exposure to abatacept (30, 31, 32). An ongoing clinical trial (AttackMy-ILD, NCT03215927) is attempting to further investigate the efficacy of abatacept and its potential role in the treatment of ILD in myositis.

Calcinosis worsened in two anti-NXP2 autoantibody-positive patients who entered the trial with widespread calcinosis, despite their clinical improvement in disease activity, suggesting the multifactorial nature of this common chronic complication in refractory JDM. Other indices of chronicity, including the Myositis Damage Index and its subscales remained stable during the trial. Little is known about the pathogenesis of calcinosis, but several hypotheses have been proposed, including mitochondrial abnormalities, dysregulation of proteins that promote mineralization, upregulation of pro-inflammatory cells and cytokines at the site of calcification, and increased NET formation (33). It is possible that the pathogenesis of calcinosis may differ from the pathogenesis of muscle and skin inflammation in JDM. Abatacept may not be effective for this specific complication of JDM; further studies are needed.

Limitations of this study include the lack of a control group or randomization, and the small number of subjects, which limit the generalizability of the findings or ability to compare to other standard of care therapies. Given the rarity of the disease, the pediatric population, and lack of proven therapies, this was considered to be an acceptable design. The improvement in objective measures, including muscle MRI and serum cytokines/chemokines, which were blinded to the clinical evaluations, strengthens the importance of the clinical response demonstrated in this trial.

This small pilot study showed subcutaneous abatacept may be a beneficial and likely safe alternative for treatment refractory JDM. A larger controlled study is needed to confirm these findings.

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AUTHORS 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. Rider had full access to all of the data and the accuracy of data analysis.

Study conception and design. Curiel, Mamyrova, Ehrlich, Brindle, OY Jones, Rider.

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Table 1. Change in disease activity measures in the study patients following Abatacept treatment

Mean ± Standard Deviation	Baseline Week 0	Week 12	Difference in Means (%Δ*)	p-value	Week 24	Difference in Means (%Δ*)	p-value
IMACS Core Set Measures, (Range)							
Physician Global Activity, VAS (0-10 cm)†	5.0 ± 1.0	3.5 ± 1.2	-1.5 (-30.0%)	<0.001	2.6 ± 1.48	-2.4 (-48.0%)	<0.001
Patient/Parent Global Activity, VAS (0-10 cm)†	5.3 ± 1.2	3.5 ± 1.8	-1.7 (-34.0%)	0.009	2.3 ± 2.4	-3.0 (-56.6%)	0.004
MMT-8 (0-150)	121.8 ± 14.8	135.0 ± 11.0	13.2 (10.8%)	0.005	137.2 ± 10.7	15.4 (12.6%)	<0.001
CHAQ (0-3)†	1.84 ± 0.58	1.16 ± 0.5	-0.68 (37.0%)	<0.001	0.88 ± 0.6	-0.96 (-52.2%)	<0.001
Muscle Enzymes (Enzyme / Upper Limit Normal)‡	1.52 ± 0.66	1.3 ± 0.72	-0.22 (-13.3%)	0.193	1.52 ± 1.17	-0.0 (-0.0%)	0.375
Physician Extramuscular Activity, VAS (0-10 cm)	4.1 ± 1.5	2.8 ± 1.4	-1.3 (-31.7%)	0.015	2.4 ± 1.7	-1.7 (-41.5%)	<0.001
Additional PRINTO Core Set Measures, (Range)							
CMAS (0-52)†	33.9 ± 9.5	41.0 ± 6.9	7.1 (20.9%)	0.001	44.2 ± 5.7	10.3 (30.4%)	0.001
CHQ-PF50, PhS (0-100)†	17.9 ± 12.6	31.9 ± 12.9	14.0 (78.2%)	0.015	37.3 ± 12.7	19.4 (108.4%)	<0.001
DAS (0-20)†	14.0 ± 1.7	11.7 ± 2.1	-2.3 (-16.4%)	0.008	10.6 ± 2.8	-3.4 (-24.4%)	0.004
Other Outcome Measures, (Units or Range)							
Corticosteroid dosage (mg)	16.7 ± 7.5	15.9 ± 7.5	-0.8 (-4.9%)	0.195	10.2 ± 5.4	-6.5 (-38.9%)	0.002
Weight-adjusted corticosteroid dosage (mg/kg)	0.4 ± 0.3	0.3 ± 0.2	-0.1 (-25.0%)	0.009	0.2 ± 0.1	-0.2 (-50.0%)	0.008
CDASI Activity (0-100)	21.4 ± 11.0	15.6 ± 6.7	-5.8 (-27.1%)	0.044	14.0 ± 8.6	-7.4 (-34.6%)	0.044
MRI Total Muscle Edema (0-12)	5.3 ± 3.5	NA	NA	NA	2.3 ± 2.6	-3.0 (-56.6%)	0.01

*% Δ: Relative Percent Change

†Three IMACS Core Set Measures are included with PRINTO Core Set Measures.

‡Values shown were from muscle enzymes which were most abnormal, or different from healthy range (LDH 5 patients; ALT 3 patients; CK, 2 patients).

Abbreviations: IMACS, International Myositis Assessment and Clinical Studies Group; VAS, visual analog scale; MMT-8, Manual Muscle Testing; CHAQ, Childhood Health Assessment Questionnaire; PRINTO, Paediatric Rheumatology International Trials Organization; CMAS, Childhood Myositis Assessment Scale; CHQ-PF50, Child Health Questionnaire - Parent Form 50; PhS, Physical Summary Score; DAS, Disease Activity Score; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; MRI, Magnetic Resonance Imaging; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; CK, creatine kinase.

Table 2. Myositis response criteria over time in the study patients with Juvenile Dermatomyositis

	Definition of Improvement (DOI)					*ACR-EULAR response criteria*[‡]				
	IMACS[*]		PRINTO[†]							
Change in CSMs	No Improvement	At least Minimal Improvement	Minimal Improvement[†]	Moderate Improvement[†]	Major Improvement[†]	No Improvement	Minimal Improvement ≥30 to <45	Moderate Improvement ≥45 to <70	Major Improvement ≥70	Total Improvement Score Mean ± SD
Week 6										
IMACS CSMs	7	3				6	3	1	0	25.0 ± 14.3
PRINTO CSMs			3	0	0	5	4	1	0	31.0 ± 14.5
Week 12										
IMACS CSMs	5	5				3	3	4	0	40.8 ± 14.2
PRINTO CSMs			2	2	0	1	2	6	1	50.0 ± 15.2
Week 18										
IMACS CSMs	1	9				0	3	6	1	50.8 ± 13.7
PRINTO CSMs			6	3	0	0	3	3	4	59.3 ± 17.8
Week 24										
IMACS CSMs[*]	1	9				1	2	4	3	53.8 ± 19.2
PRINTO CSMs			4	5	0	1	1	1	7	65.3 ± 25.9
Extension Visit[§]										
IMACS CSMs	1	7				1	0	3	4	60.3 ± 17.8
PRINTO CSMs			2	5	1	0	2	1	5	67.8 ± 23.0

[*]IMACS Definition of Improvement: ≥ 3 of 6 CSMs improved by ≥ 20%, ≤ 2 of 6 CSMs worsened by ≥ 25% (cannot include MMT-8) (12). The IMACS Definition of Improvement at Week 24 was the primary endpoint.

[†]PRINTO Definition of Minimal Improvement: ≥ 3 of 6 CSMs improved by ≥ 20%, ≤ 1 of 6 CSMs worsened by ≥ 30% (cannot include CMAS), Moderate Improvement: ≥ 3 of 6 CSMs improved by ≥ 50%, ≤ 1 of 6 CSMs worsened by ≥ 30% (cannot include CMAS), Major Improvement: ≥ 3 of 6 CSMs improved by ≥ 70%, ≤ 1 of 6 CSMs worsened by ≥ 30% (cannot include CMAS) (13).

[‡]ACR-EULAR response criteria for JDM combines the absolute percentage change in each CSM to define a Total Improvement Score on a scale of 0-100 (14).

[§]8 of 10 patients had an optional extension visit 16.4 ± 4.0 weeks following week 24 and 40.6 ± 4.2 weeks following week 0.

Abbreviations: See Table 1; DOI, Definition of Improvement; ACR-EULAR, American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR); CSMs, Core Set Activity Measures; SD, Standard Deviation.

Table 3. Treatment-emergent adverse events assessed as possibly related to study drug*

Adverse Event	Number of events	Severity of event grade (0-5)†
Respiratory, thoracic, and mediastinal disorders		
Worsening of interstitial lung disease	1	3
Musculoskeletal disorders		
Compression fracture	1	3
Right knee contracture worsening	1	2
Skin and subcutaneous tissue disorders		
Calcinosis	2	3
Lipoatrophy, focal	1	2
Urticaria	1	1
Infections		
Febrile episodes	2	2
Skin-infection, organism not identified	1	2
E. coli diarrhea	1	2
Laboratory investigations		
Anti-thyroid peroxidase autoantibody and anti-thyroglobulin autoantibody titers increased	5	1
Lymphopenia	4	1
Hypergammaglobulinemia	4	1
ANA	3	1
Anti-Ro (SS-A) antibody	2	1

*Treatment-emergent adverse events are defined as events that were new or worsened after starting abatacept treatment and were determined to be at least possibly related to the abatacept treatment. All events were possibly related to study drug.

†Adverse event grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening consequences; 5, death related to adverse event (National Institutes of Health Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Abbreviations: E. coli, Escherichia coli; ANA, Antinuclear antibody; Anti-Ro (SS-A), Anti–Sjogren's-syndrome-related antigen A autoantibodies.