A Randomized, Pilot Trial of Etanercept in Dermatomyositis

The Muscle Study Group

Objective: The aims of this pilot study were to assess (1) the safety and tolerability of etanercept in dermatomyositis (DM); (2) the feasibility and safety of a forced prednisone taper; and (3) outcome measures, including those recommended by the International Myositis Assessment Clinical Study (IMACS) group.
Methods: We conducted a randomized, double-blind, placebo-controlled trial of etanercept (50mg subcutaneously weekly) for 52 weeks in DM subjects. Subjects were tapered off prednisone in a standardized schedule as tolerated over the initial 24 weeks of the study. Principal outcomes included adverse events, time from randomization to treatment failure (inability to wean off prednisone on schedule), and average prednisone dosage after week 24.
Results: Sixteen subjects were randomized, 11 to etanercept and 5 to placebo. There were no significant differences in adverse event rates between the treatment groups, although 5 etanercept-treated and 1 placebo-treated subjects developed worsening rash. All 5 subjects receiving placebo were treatment failures (median time to treatment failure 148 days). In contrast, 5 of 11 subjects in the etanercept arm were successfully weaned off prednisone; the median time to treatment failure in this group was 358 days ($p = 0.0002$). The median of the average prednisone dosage after week 24 was 29.2mg/day in the placebo group and 1.2mg/day in the etanercept group ($p = 0.02$). IMACS and other outcome measures demonstrated excellent test–retest reliability (intraclass correlation coefficients 0.79–0.99). There was no significant treatment effect on functional outcome.
Interpretation: The findings of no major safety concerns and a steroid-sparing effect in our study suggest that further investigation of etanercept as a treatment for DM is warranted.

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Dermatomyositis (DM) is a subtype of inflammatory myopathy; prednisone is the initial treatment of choice.[1] Because many patients have disabling weakness despite treatment, and because of the long-term side effects of prednisone and of second-line immunosuppressive agents, better treatment options are needed. Tumor necrosis factor (TNF)-α may play a role in the pathogenesis of DM.[2–8] Etanercept is a soluble TNF-α receptor fusion protein that inactivates TNF-α and is effective in rheumatoid arthritis,[9] ankylosing spondylitis,[10] and psoriatic arthritis.[11] Small uncontrolled series of DM patients treated with various TNF-α blockers have had mixed results; some suggested a possible benefit,[12–17] whereas others found no improvement or worsening of the myositis.[18–21] Side effects of etanercept include infection, malignancies, and induction of systemic lupus erythematosus (SLE), the risks of which might be increased in patients with DM.[22–26]

An obstacle in designing therapeutic studies is the need to establish reliable and responsive outcome measures. IMACS proposed a core set of measures for disease outcome assessment and preliminary definitions of improvement (DOIs) to be used in clinical trials in myositis.[27–29]

The objectives of this pilot study were: (1) obtain preliminary data regarding the safety and tolerability of etanercept in DM; (2) assess the feasibility and safety of a forced prednisone withdrawal study design; and (3) evaluate different outcome measures.

Patients and Methods

Study Design

This was a randomized, double-blind, placebo-controlled trial of etanercept (50mg subcutaneously weekly) in subjects with DM. The study was approved by the ethics committees at each site.

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See the Appendix on page 434 for all participants and their roles in the study.

Clinicaltrials.gov registry # NCT00282880.

Additional supporting information can be found in the online version of this article.

Subjects

Eligible subjects were 18 to 65 years old and had active DM defined by (1) symmetric proximal weakness, (2) characteristic rash, and (3) laboratory evidence of active DM with elevated serum creatine kinase (CK), electromyography demonstrating myopathic features, abnormal skeletal muscle magnetic resonance imaging, or a muscle biopsy demonstrating perifascicular atrophy and perivascular inflammation. Exclusion criteria included juvenile DM, uncontrolled diabetes mellitus, symptomatic cardiovascular or pulmonary disease, SLE, cancer, tuberculosis, active infection, chronic hepatitis B or C, other autoimmune neurological disorders, any prior or concurrent cyclophosphamide therapy or concurrent use of azathioprine or mycophenolate, or recent use of a live vaccine.

We initially planned to enroll 40 newly diagnosed DM subjects who were either treatment naive or had been treated only with prednisone for <2 months. Due to slow recruitment, the protocol was modified in the last year to allow enrollment of refractory subjects on prednisone for >2 months, a stable dosage of methotrexate for at least 1 month, or intravenous immunoglobulin for at least 3 months. Recruitment began in March 2006 and ended in May 2009 after enrollment of the 16th subject.

Screening

The screening period could be up to 2 months to perform the necessary studies prior to initiating study drug. The following studies were obtained: complete blood count, basic metabolic profile, CK, aldolase, thyroid function tests, 25-hydroxyvitamin D levels, urinalysis, antinuclear antibodies (ANAs), anti–double-stranded DNA, SSA, SSB, U1RNP, PM-Scl, Scl-70, and Jo-1 antibodies (see Supplemental Methods), tuberculosis skin test (purified protein derivative), electrocardiogram (EKG), pulmonary function tests (PFTs), and dual energy x-ray absorptiometry (DEXA) for bone density. A workup for underlying cancer was done, if not already performed within the past 6 months; this included a chest X-ray, mammogram, abdominal computed tomography (CT) scan, pelvic CT scan or ultrasound in women, and a colonoscopy in patients aged >50 years.

During screening, newly diagnosed or treatment-naive subjects (new DM) were placed on prednisone 60mg/day. If they were already on prednisone for <2 months or on a different dosage, their prednisone dosage was adjusted to 60mg/day. Subjects with refractory DM, who were on prednisone for >2 months, stayed on their current dosage or had the dosage increased to up to 60mg/day at the discretion of the treating physician. All subjects were treated with vitamin D 800IU daily and calcium 1,500mg daily. Unless contraindicated, alendronate was started.

Randomization and Treatment Protocol

After treatment with prednisone for 2 months and completion of screening evaluations, subjects underwent baseline evaluation over 2 consecutive days to ascertain test–retest reliability of outcome measures. Afterward, subjects were randomly assigned (3:1 allocation; stratified by DM status: new vs refractory) to receive either etanercept 50mg or placebo once weekly by subcutaneous injection (see Supplementary Methods). The dosage formulation for the placebo prefilled liquid syringes consisted of 25mM Na phosphate, 25mM L-arginine-HCI, 100mM NaCI, 1% sucrose per syringe, pH 6.3.

After starting the study drug, the prednisone dosage was tapered over the next 24 weeks in newly diagnosed DM subjects by 5mg/day every 2 weeks (eg, dosage reduced to 55mg/day starting week 3, 50mg/day starting week 5, etc). Refractory DM subjects remained on their baseline dosage of prednisone in keeping with the taper schedule for new DM subjects. For example, if they were on prednisone 60mg daily or higher, they would take prednisone 60mg/day for 2 weeks before initiating taper. If refractory DM subjects were on prednisone 40mg/day, they would remain on this dosage for 10 weeks before initiating taper. Thus, by week 25 all subjects (new DM and refractory DM) would be off of prednisone if they were able to tolerate the prednisone taper. Subjects were seen every 4 weeks to obtain study drug and assess clinical response, adverse events, and compliance (counting syringes and review of medication diaries).

Outcome Measures

The principal outcome measures were adverse events, time from randomization to treatment failure, and average prednisone dosage after week 24. Adverse events and compliance with study medication and prednisone dosing were ascertained at each visit.

Muscle strength was assessed by manual muscle testing (MMT) and quantitative myometry utilizing maximum voluntary isometric contraction testing (MVICT).[30,31] MMT was performed on 26 muscle groups: neck flexors and extensors; bilateral shoulder abductors; elbow flexors and extensors; wrist flexors and extensors; hip flexors, extensors, and abductors; knee flexors and extensors; and ankle dorsiflexors and plantar flexors. Muscle strength of each muscle group was graded utilizing a modified Medical Research Council score that was converted to a 13-point scale (grade 0 = 0, 1=1, 2− = 1.67, 2 = 2, 2+ = 2.33, 3− = 2.67, 3 = 3, 3+ = 3.33, 4− = 3.67, 4 = 4, 4+ = 4.37, 5− = 4.67, 5 = 5), and the cumulative and average MMT scores were calculated. MVICT was performed on 5 muscle groups bilaterally: shoulder abductors, elbow flexors and extensors, and knee flexors and extensors. Composite MVICT scores were derived by averaging the standardized (normalized) scores across the individual muscles. Other outcome assessments included measurements of disease activity by the Myositis Intention to Treat Activity Index (MITAX) and Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT) (see Supplementary Methods), subject and physician assessments of global disease activity utilizing Likert and visual analog scales (VAS), objective functional testing (time to arise from a chair and time to walk 30 feet), and subjective functional abilities utilizing the Health Assessment Questionnaire (HAQ).[27,28] Dermatological manifestations were graded using a modified cutaneous disease activity score index,[32] patient VAS for pruritis, and relevant components of the

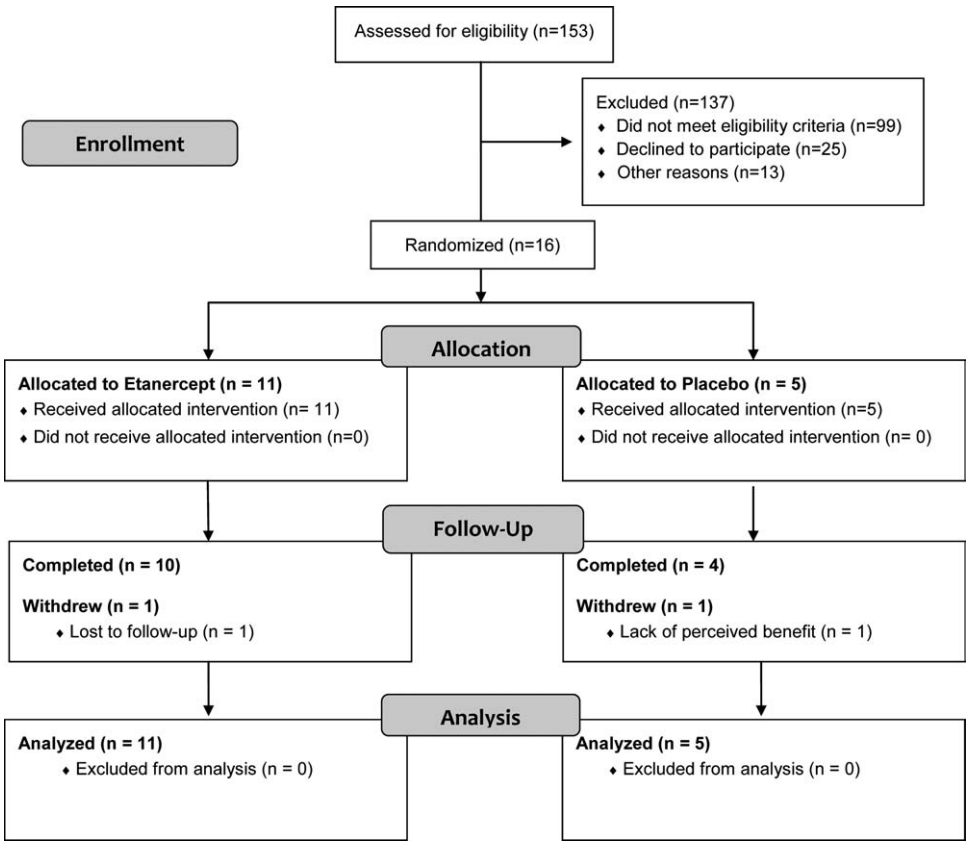

FIGURE 1: Participant flow is shown. Sixteen subjects were randomized; 5 were new, and 11 were refractory dermatomyositis (DM) patients. Most of the prescreen failures were patients with well-controlled DM (8 patients) or refractory patients on prednisone or other second-line agents prior to our modifying the protocol (71 patients). The main reason eligible patients did not participate was that they or their referring physicians wanted them to first try other treatments.

MYOACT and MITAX. Quality of life was assessed utilizing the Short Form-36 General Health Survey (SF-36) and the Individualized Neuromuscular Quality of Life questionnaire.[33] We assessed these outcome measures at baseline, 1 day apart, to assess their intrarater reliability.

Laboratory assessment included measurements of muscle enzymes, antinuclear antibodies, complete blood counts, complete metabolic profile, DEXA, EKG, and PFTs. We also evaluated International Myositis Assessment Clinical Study (IMACS)-recommended DOIs.[29]

Treatment failure was defined as 1 of the following: (1) worsening of the Physician Global Disease Activity Assessment by $\geq$2cm on a VAS; (2) worsening of the manual muscle testing composite score by $\geq$20%; (3) progression of weakness of orophayrngeal muscles sufficient to impair nutrition or pose a risk of aspiration; (4) 20% worsening of forced vital capacity or diffusion capacity; or (5) no improvement in muscle strength after 12 weeks. The study physicians also had latitude to slow the taper or increase the dosage of prednisone or add an alternative agent if they deemed it necessary at any point during the study even if subjects did not meet any of the above criteria.

In treatment failures, the prednisone dosage was doubled (up to 60mg/day). If the subject was not on prednisone at the time, the subject was placed on a dosage that previously provided optimal control of the disease in the judgment of the treating physician. The subject remained on this dosage until improvement was demonstrated, and then the taper was resumed but at a slower rate (every 4 weeks). If the subject had no improvement, the subject could be started on a second-line agent (eg, intravenous immunoglobulin [IVIG], methotrexate), and prednisone dosage was adjusted per the treating physician.

Statistical Analysis

Descriptive statistics were used to summarize subject disposition, adverse events, and abnormal laboratory values by treatment group. Kaplan-Meier curves were used to describe the distribution of the time from randomization to treatment failure by treatment group, and a log-rank test was used to compare these distributions between the groups. The distributions of prednisone dosage after week 24 were compared between the treatment groups using a Wilcoxon rank sum test. Repeated measures analysis of covariance models was used to compare the treatment groups over time with respect to mean responses in continuous outcome variables. The models included treatment group, week (categorical), the interaction between treatment group and week, and the baseline value of the outcome variable as a covariate. A heterogeneous autoregressive structure

TABLE 1: Baseline Characteristics

Characteristic	Etanercept, n = 11	Placebo, n = 5
F/M, No.	6/5	4/1
New/refractory DM, No.	3/8	2/3
Age, yr	43.4 ± 14.8	44.2 ± 11.1
Duration, yr	1.1 ± 0.8	2.2 ± 3.4
Baseline dosage of prednisone, mg/day	45.0 ± 18.0	39.0 ± 16.7
Physician Global Activity Assessment	4.0 ± 1.8	4.2 ± 2.3
Patient Global Activity Assessment	5.4 ± 2.3	6.1 ± 2.2
Average MMT score	4.5 ±0.5	4.3 ± 0.5
Average standardized MVICT score	−4.2± 2.1	−4.5 ± 1.6
Average percentage of predicted normal MVICT score	50.7 ± 19.5	45.1 ± 12.5
MYOACT, total	0.13 ± 0.07	0.11 ± 0.03
MYOACT, Muscle Disease Activity	3.2 ± 1.8	2.9 ± 1.2
MYOACT, Cutaneous Disease Activity	4.0 ± 2.2	2.4 ± 1.9
MYOACT, Extramuscular Global Assessment	2.9 ± 2.2	1.9 ± 1.8
CDASI	11.9 ± 6.1	8.4 ± 7.7
HAQ	1.2 ± 1.0	1.2 ± 1.0
INQoL, Overall Quality of Life score	58.1 ± 23.9	62.3 ± 13.5
INQoL, Weakness Score	64.6 ± 24.4	65.3 ± 37.1
SF-36, Physical Component Summary	32.0 ± 8.6	29.7 ± 12.0
SF-36, Mental Component Summary	42.2 ± 10.5	47.0 ± 15.0
Creatine kinase, U/l	821 ± 2069	1098 ± 929
Aldolase, U/l	16.1 ± 22.3	18.4 ± 10.0
Bone density, lumbar spine *Z* score	−0.3 ± 1.2	−0.2 ± 1.5

Values are mean ± standard deviation unless otherwise indicated.
CDASI = Cutaneous Disease Activity Score Index; DM = dermatomyositis; HAQ = Health Assessment Questionnaire; INQoL = Individualized Neuromuscular Quality of Life; MMT = manual muscle testing; MVICT = maximum voluntary isometric contraction testing; MYOACT = Myositis Disease Activity Assessment Visual Analogue Scales; SF-26 = Short Form-36 General Health Survey.

was assumed for the covariance matrix of the repeated measurements.[34] The model parameters were estimated using restricted maximum likelihood, and a missing at random assumption was used for the missing data mechanism. All analyses were performed according to the intention-to-treat principle and included data from all randomized subjects.

Intrarater reliability of the outcomes measured was assessed using intraclass correlation coefficients (ICCs), calculated using 1-way random effects analysis of variance models. Ninety-five percent lower confidence bounds were computed for the ICCs. Responsiveness of outcome variables was quantified at the week 24 and week 52 visits using the effect size (mean change divided by the baseline standard deviation)[35] and the standardized response mean (mean change divided by the standard deviation of the change).[36] No imputation was performed for missing data in the computation of these responsiveness statistics.

Results

Characteristics of Subjects

We prescreened 153 patients and randomized 16 subjects (10 women and 6 men) (Fig 1). Eleven subjects were randomized to receive etanercept (3 new, 8 refractory) and 5 subjects to placebo (2 new, 3 refractory). Subjects ranged in age from 21 to 61 years (mean, 43.64 years). Mean baseline prednisone dosage was 45mg/day in the etanercept group and 39mg/day in the placebo group. Other key features were similar between the 2 groups at baseline (Table 1 and Supplementary Table 1).

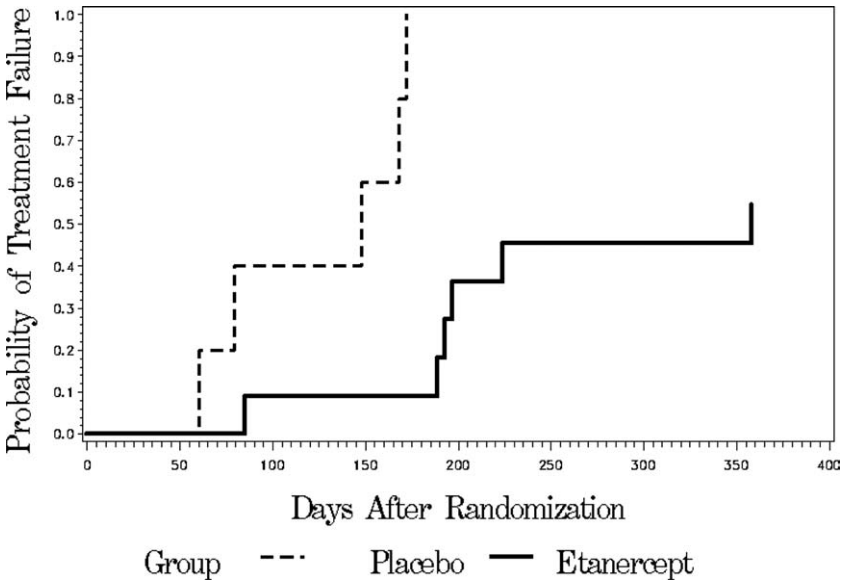

FIGURE 2: Kaplan-Meier curves display the time from randomization to the first occurrence of treatment failure. There was a significant difference between the treatment groups favoring etanercept ($p = 0.0002$, log-rank test)

Safety

There were no significant differences in adverse event rates between the treatment groups (Supplementary Table 2). In the etanercept group, 6 serious adverse events (SAEs) were reported. One subject's girlfriend became pregnant and miscarried; another subject was hospitalized twice (once for a urinary tract infection and once for fever of unknown origin). A third subject was hospitalized 3× (once for postherpetic neuralgia and twice for psychosis). In the placebo group, 3 SAEs were reported. One subject was hospitalized for gastroenteritis, 1 for IVIG treatment of a DM flare because she could not receive it as an outpatient, and 1 for ovarian cancer discovered at the end of the study.

No placebo-treated subjects had an ANA at baseline, but 1 developed an ANA at the end of the study (the subject with the ovarian malignancy). In the etanercept group, 2 had ANAs at both baseline and week 52, whereas 2 developed ANAs at week 52. None developed antibodies to double-stranded DNA or an SLE-like illness.

Treatment Failures and Prednisone Dosage

All 5 subjects receiving placebo were treatment failures (median time to treatment failure was 148 days). In contrast, 5 of 11 subjects in the etanercept arm were successfully weaned off prednisone (median time to treatment failure was 358 days, $p = 0.0002$) (Fig 2). The average time to treatment failure in the placebo group was 125 days, whereas the average time to failure in the 6 etanercept subjects who failed was 208 days. Three of the 6 treatment failures in the etanercept group and 1 of the 5 failures in the placebo group did not meet our research criteria for treatment failure, but the study physician felt the need to adjust treatment.

In the etanercept group, 5 of the 6 (83%) treatment failures were in previously refractory subjects. Two required an increase in prednisone dosage and the subsequent addition of second-line agents (methotrexate in 1 and IVIG and methotrexate in the other), and 1 had a worse skin rash treated with topical medication. In the placebo group, 3 of the 5 (60%) treatment failures were previously refractory subjects. Two of the 5 were treated by increasing the prednisone dosage. Three subjects also required the addition of another agent (1 received IVIG; 2 were treated with IVIG and methotrexate).

Prednisone dosage from weeks 25 to 52 in the placebo group (median, 29.2mg/day; range, 9.9–62.6mg/day) was significantly higher than that in the etanercept group (median, 1.2mg/day; range, 0.0-31.1mg/day) ($p = 0.02$). Compliance with study medication was excellent in both treatment groups (mean, 99.7%; range, 96–100% in the etanercept group; mean, 96.7%; range, 87–100% in the placebo group), as was compliance with prednisone (mean, 92.6%; range, 58–100% in the etanercept group; mean, 97.6%; range, 88–100% in the placebo group).

Clinical Outcome Measures

IMACS and other outcome measures demonstrated excellent test–retest reliability at the baseline visit (intraclass correlation coefficients, 0.79 to 0.99) (Supplementary Table 3). There were significant improvements during the study, and moderate to large responsiveness was observed for various outcome measures with all subjects

TABLE 2: Mean Changes from Baseline to Weeks 24 and 52 and Responsiveness Statistics

Outcome Variable	Etanercept	Placebo	Overall	p^a	ES	SRM
Week 24						
Average MMT score	0.22 (0.05)	0.27 (0.09)	0.24 (0.05)	<0.0001	0.46	0.87
Average standardized MVICT score	1.58 (0.40)	0.59 (0.62)	1.09 (0.37)	0.006	0.67	0.80
Average % of predicted normal MVICT score	12.1 (3.7)	4.4 (5.7)	8.2 (3.4)	0.02	0.58	0.84
Time to walk 30 feet, s	−3.1 (1.4)	−1.9 (2.3)	−2.5 (1.4)	0.07	−0.17	−0.42
Physician Global Activity Assessment	−2.0 (0.7)	−1.0 (1.1)	−1.5 (0.7)	0.03	−0.90	−0.80
Patient Global Activity Assessment	−1.7 (0.9)	−2.1 (1.4)	−1.9 (0.9)	0.03	−0.73	−0.53
MYOACT overall score	−0.029 (0.023)	−0.009 (0.036)	−0.019 (0.021)	0.37	−0.35	−0.26
MYOACT muscle disease activity score	−1.14 (0.68)	−0.59 (1.04)	−0.87 (0.62)	0.17	−0.56	−0.43
MYOACT cutaneous disease activity score	−0.84 (0.50)	0.07 (0.77)	−0.39 (0.45)	0.40	−0.29	−0.27
CDASI score	−4.9 (1.5)	1.5 (2.4)	−1.7 (1.4)	0.23	−0.41	−0.40
HAQ score	−0.44 (0.19)	−0.34 (0.29)	−0.39 (0.18)	0.03	−0.42	−0.66
SF-36 Physical Component Summary score	7.0 (2.9)	5.7 (4.6)	6.3 (2.7)	0.02	0.65	0.66
SF-36 Mental Component Summary score	−7.6 (4.6)	−1.5 (7.2)	−4.5 (4.3)	0.30	−0.42	−0.31
INQoL overall quality of life score	0.5 (4.9)	0.4 (7.3)	0.4 (4.4)	0.92	−0.01	−0.01
Log [creatine kinase], U/l	−0.10 (0.28)	0.16 (0.43)	0.03 (0.26)	0.91	−0.05	−0.11
Week 52						
Average MMT score	0.27 (0.06)	0.21 (0.09)	0.24 (0.06)	<0.0001	0.52	0.97
Average standardized MVICT score	1.71 (0.41)	0.47 (0.67)	1.09 (0.39)	0.009	0.70	0.68
Average % of predicted normal MVICT score	13.0 (4.2)	5.3 (7.0)	9.1 (4.0)	0.03	0.62	0.70
Time to walk 30 feet, s	−1.2 (2.1)	−2.3 (3.3)	−1.7 (2.0)	0.37	−0.10	−0.43
Physician global activity assessment	−2.4 (0.6)	−1.3 (0.9)	−1.8 (0.5)	0.0008	−1.09	−0.95
Patient global activity assessment	−2.4 (0.8)	−0.2 (1.3)	−1.3 (0.8)	0.09	−0.80	−0.60
MYOACT overall score	−0.054 (0.025)	−0.003 (0.039)	−0.029 (0.023)	0.22	−0.63	−0.41
MYOACT muscle disease activity score	−2.20 (0.58)	−0.79 (0.89)	−1.50 (0.53)	0.007	−1.07	−0.76
MYOACT cutaneous disease activity score	−1.15 (0.68)	−0.71 (1.07)	−0.93 (0.63)	0.15	−0.48	−0.39
CDASI score	−3.1 (1.4)	−0.5 (2.2)	−1.8 (1.3)	0.17	−0.34	−0.47
HAQ score	−0.34 (0.14)	−0.32 (0.23)	−0.33 (0.14)	0.02	−0.36	−0.67
SF-36 Physical Component Summary score	7.5 (2.6)	1.1 (4.2)	4.3 (2.5)	0.09	0.59	0.67
SF-36 Mental Component Summary score	0.5 (3.0)	−0.8 (4.7)	−0.2 (2.8)	0.95	0.02	0.02
INQoL overall quality of life score	−4.0 (5.9)	1.4 (9.2)	−1.3 (5.5)	0.81	−0.08	−0.10
Log [creatine kinase], U/l	−0.11 (0.32)	−0.95 (0.51)	−0.53 (0.30)	0.08	−0.21	−0.30

Values for etanercept, placebo, and overall are mean (standard error) of changes from baseline to week 24 or week 52, estimated using a repeated measures analysis of covariance model (see text for details).
Values of ± 0.20, 0.50, and 0.80 or greater represent small, moderate, and large responsiveness, respectively for the ES and SRM.[35–37]
[a] p value is for a test of the null hypothesis of zero mean change overall.
CDASI = Cutaneous Disease Activity Score Index; ES = effect size (mean change from baseline divided by the baseline standard deviation); HAQ = Health Assessment Questionnaire; INQoL = Individualized Neuromuscular Quality of Life; MMT = manual muscle testing; MVICT = maximum voluntary isometric contraction testing; MYOACT = Myositis Disease Activity Assessment Visual Analogue Scales; SF-36 = Short Form-36 General Health Survey; SRM = standardized response mean (mean change from baseline divided by the standard deviation of the change).

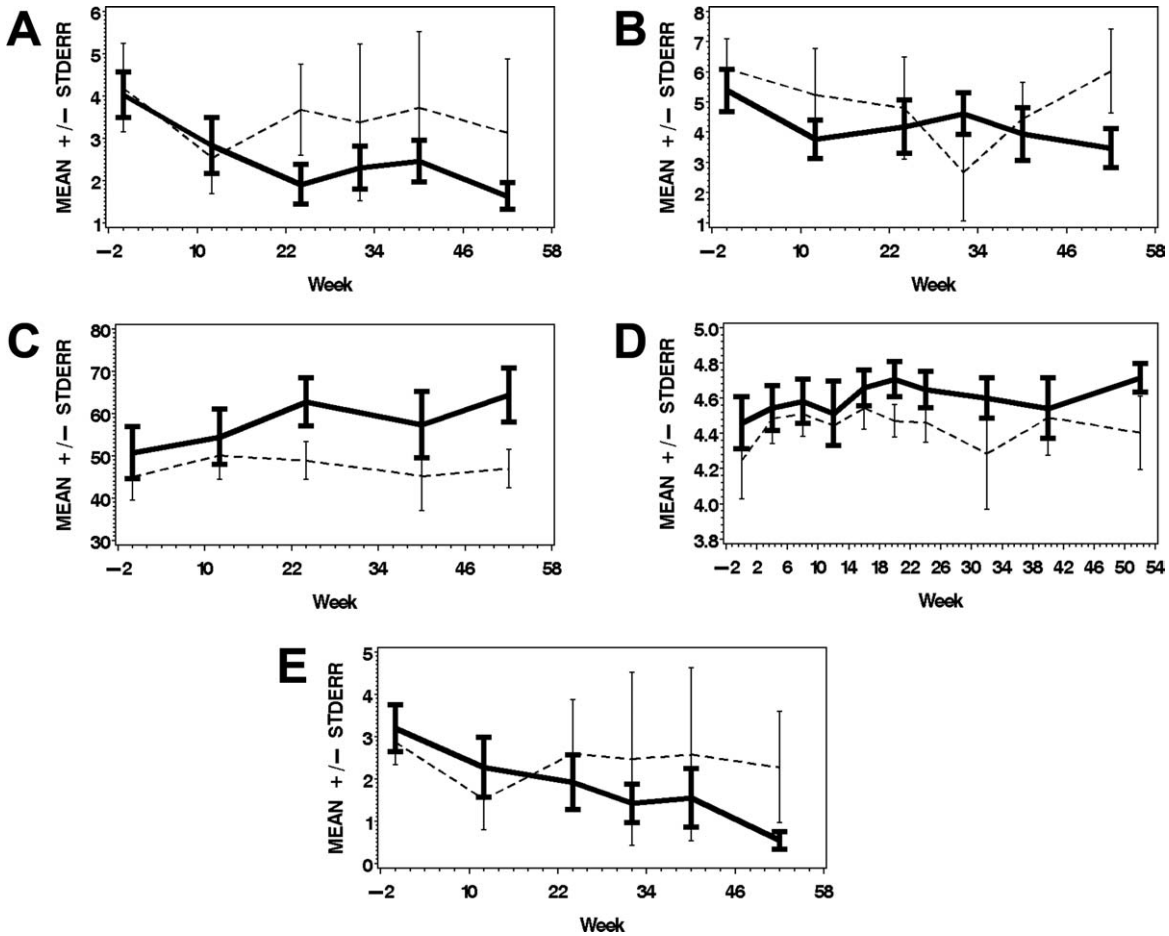

FIGURE 3: Means and standard errors (STDERR) of (A) Physician Global Activity Assessment score, (B) Patient Global Activity Assessment score, (C) average percentage of predicted normal maximum voluntary contraction testing score, (D) average manual muscle testing score, and (E) Myositis Disease Activity Assessment Visual Analogue Scales-Muscle Disease Activity score are plotted over time by treatment group. There were statistically significant improvements from baseline in each of these outcomes (see Table 2), but no significant differences between the treatment groups.

combined (Table 2). There were no significant treatment group differences in mean response during the course of the study. Those outcome measures with consistently moderate to large responsiveness included the Physician Global Activity, Patient Global Activity, average MMT, average MVICT, and SF-36–Physical Component Summary scores. Mean responses over time for selected outcome measures are shown in Figure 3.

IMACS DOIs

The top scoring IMACS DOI by consensus criteria was A1 (improvement in 3 of 6 core set measures by 20% or more, with no more than 2 worsening by at least 25%), leading to the recommendation that this be assessed in any clinical trial.[28,29] We looked at all 6 suggested DOIs (Supplementary Table 4). At week 24, 9 subjects (82%) in the etanercept group met A1 criteria. Eight of 9 were successfully weaned off prednisone; the remaining subject required IVIG at week 12. In contrast, only 2 of 5 (40%) placebo-treated subjects met A1 criteria, and only 1 was able to be weaned off prednisone during this time.

At the end of the study, 6 subjects in the etanercept group met A1 criteria. Of these, 4 remained off prednisone and had no additional treatment. One subject was weaned off prednisone and received no other treatment, but he did not meet any DOIs. The 5 etanercept subjects who were successfully weaned off prednisone had the following improvements in core set outcome measures: Physician Global Activity (mean, 54.3%), Patient Global Activity (mean, 55.3%), average MMT score (mean, 5.2%), percentage of predicted normal MVICT (mean, 39.2%), MYOACT Extramuscular (mean, 56.9%), and HAQ (mean, 40.3%). Three placebo-treated subjects met A1 criteria at week 52, but each required increased prednisone, and 2 also needed the addition of second-line agents (IVIG in 1 and IVIG and methotrexate in the other). In summary, at week 52, 4 of 11 etanercept-treated subjects were receiving only the study drug and

met IMACS DOI criteria, in contrast to none of the placebo-treated subjects.

Discussion

Etanercept was safe and well-tolerated over 1 year in our study. Two of the 11 etanercept-treated subjects developed newly elevated ANAs in the course of the study. None developed SLE, although rash worsened in 5 etanercept-treated subjects. The rash was initially attributed to worsening DM, although in 1 subject the rash improved at the end of the study upon discontinuing etanercept while he was on no other medications. This could have represented a lupus-like reaction related to etanercept. The 1 subject who developed cancer was on placebo.

There were valuable lessons learned from this study, especially in regard to the unanticipated difficulty recruiting subjects. Although the investigators felt that there was equipoise regarding the risk–benefit ratio of starting a second-line immunosuppressive agent along with corticosteroids at the time of initial diagnosis and treatment, many clinicians in our referral areas disagreed and felt that patients should be given both prednisone and methotrexate initially. These clinicians referred patients only after they failed both treatments. Many potential subjects also wanted to try at least prednisone before enrolling in the study. This hampered recruitment of newly diagnosed, treatment-naive patients. The study design utilizing a forced prednisone taper may be useful in subsequent studies of myositis and other immune-mediated disorders, because we found a significant steroid-sparing effect of etanercept despite the small sample size.

Another objective of this study was to assess various outcome measures for myositis trials. We assessed the IMACS-recommended core set of measures and other measures; most demonstrated excellent intrarater reliability and responsiveness in our hands, particularly strength and global disease activity outcomes. Patients' global assessments of their disease activity were usually worse than those of the physicians' assessments. We looked at the performance of IMACS preliminary DOIs, although our study was not designed to validate these definitions. It is important to validate the efficacy outcomes used here and the IMACS DOIs and definitions of worsening prior to embarking on larger efficacy trials. The small sample size of our pilot trial and the allowance of rescue treatment limited our ability to detect effects of etanercept on efficacy outcomes not related to steroid-sparing and also limits the conclusions that can be drawn regarding the safety of etanercept. The findings of no major safety concerns and a steroid-sparing effect in our study suggest that further investigation of etanercept as a treatment for DM is warranted.

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Potential Conflicts of Interest

Anthony Amato: medical advisory board and consulting fees, MedImmune; royalties, Up to Date, McGraw-Hill. Grant Anhalt: consultancy, Dyax Corp., Biogen Idec, Pfizer. Christine Annis: grant, subcontract with Brigham and Women's University; travel support, Brigham and Women's University. Richard Barohn: speaking fees, Talecris. Hannah Briemberg: speaking fees, American Academy of Neurology, British Columbia Rheumatology Association; royalties, Up to Date. Michael Weiss: consultancy, Athena Diagnostics, Washington state Labor and Industries, Genzyme Corporation; speaking fees, Athena Diagnostics, Talecris Biotherapeutics. Jan Dutz: speaking fees, payment for development of educational presentations, Amgen. John Kissel: Abbott Laboratories supplied drug for a clinical study. Michael McDermott: consultancy, Boehringer-Ingelheim Pharmaceuticals, Teva Pharmaceutical Industries, Pfizer, Smith and Nephew, Synosia, Impax Pharmaceuticals; grants/grants pending, Medivation, NeuroSearch Sweden AB, Boehringer-Ingelheim Pharmaceuticals, Pfizer. Sharon Nations: medication, Amgen. Kathryn Wagner: grant, subcontract with Brigham and Women's Hospital; consultancy, Solae, GLG; grants/grants pending, Cytokinetics, Charlie's Fund; speaking fees, Athena Diagnostics. Gil Wolfe, consultancy, Talecris.

Appendix

Muscle Study Group Participants

Principal Investigator: Anthony A. Amato, MD
Steering Committee: Rabi Tawil, MD, John Kissel, MD, Richard Barohn, MD, Michael P. McDermott, PhD, Shree Pandya, DPT, MS, Wendy King, RPT

Study Coordinators: Alexis Smirnow, MPH, Christine Annis, BS, Kristen Roe, BA

MUSCLE STUDY GROUP COORDINATION AND BIOSTATISTICS CENTER. Director: Rabi Tawil, MD; Biostatistician: Michael P. McDermott, PhD; Programmer/Analyst: Joanne Janciuras, AS; Data Managers: Nuran Dilek, MS and William B. Martens, BA; Information Analyst: Eileen Eastwood, AS

Individual Study Site Participants

BRIGHAM AND WOMEN'S HOSPITAL (3 SUBJECTS). Investigators: Anthony Amato, MD, Thomas Cochrane, MD; Clinical Evaluators: Merideth Donlan, DPT, Samantha Chused, MSPT; Study Coordinator: Kristen Roe, BS

UNIVERSITY OF KANSAS MEDICAL CENTER (3 SUBJECTS). Investigators: Richard Barohn, MD, Mazen Dimachkie, MD, Daniel J. Aires, MD, Kevin M. Latinis, MD, PhD; Clinical Evaluator: Laura Herbelin, BS; Study Coordinator: Hiwot Michaels, BS

OREGON HEALTH AND SCIENCE CENTER (3 SUBJECTS). Investigators: Edward Cupler, MD, Atul Deodhar, MD, Eric Simpson, MD, Prinyarat Burusnukul, MD, Eric Edgar, MD; Clinical Evaluator: Andrea Serdar, PT; Study Coordinators: Thomas Brennan, BS and Kathryn Gance, MA

THE OHIO STATE UNIVERSITY (2 SUBJECTS). Investigators: John Kissel, MD, Miriam L. Freimer, MD, Kevin V. Hackshaw, MD, Victoria Lawson, MS, MD; Clinical Evaluator: Wendy M. King, BA, PT; Study Coordinator: Amy Bartlett, BA

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER (2 SUBJECTS). Investigators: Gil Wolfe MD, Sharon Nations, MD; Clinical Evaluator: Rhonda McLin; Study Coordinator: Nina Gorham, CCRP

UNIVERSITY OF BRITISH COLUMBIA (1 SUBJECT). Investigators: Hannah Briemberg, MD, Kristine M. Chapman, MD, Jan P. Dutz, MD; Study Coordinator: Judy Wilson, RN; Clinical Evaluator: Franca Varelas, BSc (PT)

JOHNS HOPKINS MEDICAL CENTER (1 SUBJECT). Investigators: Kathryn Wagner, MD, Lisa Christopher Stine, MD, MPH, Grant James Anhalt, MD, Jon H. Meyerle, MD; Clinical Evaluator: Jennifer O. Swain, MS; Study Coordinator: Regina Brock-Simmons, BA

UNIVERSITY OF WASHINGTON (1 SUBJECT). Investigators and Evaluators: Michael Weiss, MD, PhD, B. Jane Distad, MD; Study Coordinators: John Lin, Joanna A. Haug, MS, MPH, Sharon Downing, RN

References

1. Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. J Neurol Neurosurg Psychiatry 2009;80:1060–1068.
2. DeBleeker JL, Meire VI, Declercq W, Van Aken EH. Immunolocalization of tumor necrosis factor-alpha and its receptors in inflammatory myopathies. Neuromusc Dis 1999;9:239–246.
3. DeBleeker JL, Engel AG. Expression of cell adhesion molecules in inflammatory myopathies and Duchenne dystrophy. J Neuropathol Exp Neurol 1994;53:369–376.
4. Fedcyyna TO, Lutz J, Pachman LM. Expression of TNFα by muscle fibers in biopsies from children with untreated juvenile dermatomyositis: association with the TNF-α allele. Clin Immunol 2001; 100:236–239.
5. Kuru S, Inukai A, Liang Y, et al. Tumor necrosis factor-α expression in muscles of polymyositis and dermatomyositis. Acta Neuropathol (Berl) 2000;99:585–588.
6. Pachman LM, Liotta-Davis MR, Hong DK, et al. TNF alpha-308A allele in juvenile dermatomyositis: association with increased production of tumor necrosis factor alpha, disease duration, and pathologic calcifications. Arthritis Rheum 2000;43:2368–2377.
7. De Bleeker JL, De Paepe B, Vanwalleghem IE, Schroder JM. Differential expression of chemokines in inflammatory myopathies. Neurology 2002;58:1779–1785.
8. Tezak Z, Hoffman EP, Pachman LM. Expression profiling in untreated juvenile dermatomyositis. J Immunol 2002;168: 4145–4163.
9. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50:353–356.
10. Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346:1349–1356.
11. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349: 2014–2022.
12. Hengstman GJ, van den Hoogen FH, Barrera P, et al. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations. Eur Neurol 2003; 50:10–15.
13. Hengstman GJD, van den Hoogen FHJ, van Engelen BGM. Treatment of dermatomyositis and polymyositis with anti-tumor necrosis factor-alpha: long-term follow-up. Eur Neurol 2004;52:61–63.
14. Sprott H, Glatzel M, Michel BA. Treatment of myositis with etanercept (Enbrel), a recombinant human soluble fusion protein of TNF-αlpha type II receptor and IgG1. Rheumatology (Oxford) 2004;43:524–526.
15. Korkmaz C, Temiz G, Cetinibas F, Bukukkidan B. Case report: successful treatment of alveolar hypoventilation due to DM with anti-tumor necrosis factor-alpha. Rheumatology (Oxford) 2004:43: 937–938.
16. Labioche I, Liozon E, Weschler B, et al. Refractory polymyositis responding to infliximab: extended follow-up. Rheumatology (Oxford) 2004;3:531–532.
17. Constanine K, Saadeh A. Etanercept is effective in the treatment of polymyositis/DM which is refractor to conventional therapy including steroids and other disease modifying agents [Abstract]. Arthritis Rheum 2000;43:S193.
18. Hengstman GJ, De Bleecker JL, Feist E, et al. Open-label trial of anti-TNF-alpha in dermato- and polymyositis treated concomitantly with methotrexate. Eur Neurol 2008;59:159–163.
19. Klein R, Rosenbach M, Kim EJ, et al. Tumor necrosis factor inhibitor-associated dermatomyositis. Arch Dermatol 2010;146: 780–784.

20. Iannone F, Scioscia C, Falappone PC, et al. Use of etanercept in the treatment of dermatomyositis: a case series. J Rheumatol 2006;33:1802–1804.

21. Dastmalchi M, Grundtman C, Alexanderson H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. Ann Rheum Dis 2008;67:1670–1677.

22. Fleischmann R, Iqbal I, Naneswar P, Quiceno A. Safety and efficacy of disease-modifying antirheumatic agents: focus on the benefits and risks of etanercept. Drug Safety 2002;25:173–197.

23. Debrandt M, Vittecoq O, Descamps V, et al. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol 2003;22:56–61.

24. Carlson E, Rothfield N. Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis. Arthritis Rheum 2003;48:1165–1166.

25. Cairns AP, Duncan MK, Hinder AE, Taggart AJ. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis 2002;61:1031.

26. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet 2002;359:579–580.

27. Miller FW, Rider LG, Chung Y-L, et al. Proposed preliminary core measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology 2001;40: 1262–1273.

28. Oddis CV, Rider LG, Reed AM, et al. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum 2005;52:2607–2615.

29. Rider LG, Giannini EH, Brunner HI, et al;International Myositis Assessment and Clinical Studies Group. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum 2004;50:2281–2290.

30. Muscle Study Group. A randomized trial of βINF1a (Avonex) in patients with inclusion body myositis (IBM). Neurology 2001;57: 1566–1570.

31. Muscle Study Group. Randomized pilot trial of high dose βINF1a in patients with inclusion body myositis. Neurology 2004;63: 718–720.

32. Klein RQ, Bangert CA, Costner M, et al. Comparison of the reliability and validity of outcome instruments for cutaneous dermatomyositis. Br J Dermatol 2008;159:887–894.

33. Vincent KA, Carr AJ, Walburn J, et al. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL). Neurology 2007;68:1051–1057.

34. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken, NJ: John Wiley and Sons, 2002.

35. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27(suppl 3):S178–S189.

36. Liang MH, Larson MG, Cullen KE, Schwartz JA. Comparative measurement efficiency and sensitivity of five health status instruments for arthritis research. Arthritis Rheum 1985;28:542–547.

37. Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000;53:459–468.