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ORIGINAL ARTICLE

First-Line Treatment of Pulmonary Sarcoidosis with Prednisone or Methotrexate

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ABSTRACT

BACKGROUND

Prednisone is currently recommended as the first-line treatment for pulmonary sarcoidosis but is associated with many side effects. Methotrexate, which is recommended as a second-line treatment, appears to have fewer side effects than prednisone but a slower onset of action. Data are needed on the efficacy and side-effect profile of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis.

METHODS

In this multicenter, open-label, noninferiority trial involving patients with pulmonary sarcoidosis who had not previously received treatment, we randomly assigned patients, in a 1:1 ratio, to receive prednisone or methotrexate according to a prespecified treatment schedule. The primary end point was the mean change from baseline to week 24 in the percentage of the predicted forced vital capacity (FVC), as estimated with the use of mixed models for repeated measures. The noninferiority margin for the primary end point was 5 percentage points.

RESULTS

Of the 138 patients who underwent randomization, 70 were assigned to receive prednisone and 68 to receive methotrexate. The unadjusted mean change from baseline to week 24 in the percentage of the predicted FVC was 6.75 percentage points (95% confidence interval [CI], 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group. Methotrexate was noninferior to prednisone with regard to the primary end point, with an adjusted between-group difference of −1.17 percentage points (95% CI, −4.27 to 1.93). Adverse events occurred in a similar percentage of patients in the two trial groups. Weight gain, insomnia, and increased appetite were the most common adverse events with prednisone, and nausea, fatigue, and any abnormal liver-function test were among the most common adverse events with methotrexate.

CONCLUSIONS

In patients with pulmonary sarcoidosis, initial treatment with methotrexate was noninferior to that with prednisone with regard to the change from baseline to week 24 in the percentage of the predicted FVC. Differences in the side-effect profile between methotrexate and prednisone may inform shared decision making by providers and patients about the appropriate treatment approach. (Funded by the Dutch Lung Foundation; PREDMETH ClinicalTrials.gov number, NCT04314193.)

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*A complete list of the PREDMETH collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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Sarcoidosis is a systemic inflammatory disease characterized by the development of granulomas, which can occur in almost any organ. The lungs are most often affected, and involvement of the lungs is the leading cause of worsened health and death among persons with sarcoidosis.[1-3] Treatment is aimed at decreasing morbidity and mortality and improving quality of life.[2-4]

International guidelines recommend prednisone as the first-line treatment for pulmonary sarcoidosis.[4,5] However, this recommendation is based on low-quality evidence in the absence of well-designed trials.[4] Prednisone may lead to short-term improvement of pulmonary function, decreased symptoms, and decreased radiologic abnormalities.[6-8] However, prednisone often causes side effects such as weight gain, sleep problems, hypertension, and diabetes, which may reduce quality of life and could lead to long-term adverse effects on health.[9,10] In patients with pulmonary sarcoidosis, an urgent need exists for better evidence-based treatment strategies with fewer toxic effects.

Methotrexate is recommended as a second-line treatment for sarcoidosis and may have fewer side effects than prednisone.[11] The most frequent side effects of methotrexate treatment include gastrointestinal events, general malaise, and infections.[11-13] Methotrexate is thought to have a slower onset of action than prednisone, but studies substantiating this view are lacking. Observational and interventional studies have suggested that the use of methotrexate as second-line treatment can lead to substantial tapering of glucocorticoids and improvement in pulmonary function.[13-16] In an observational study in which methotrexate was administered to patients with a contraindication to glucocorticoid therapy, the efficacy and safety profile of methotrexate appeared to be similar to that of prednisone; however, the results should be interpreted with caution owing to the observational design of the study and the lack of well-defined end points.[17]

Prospective randomized trials investigating first-line treatments in patients with pulmonary sarcoidosis are lacking. Therefore, we conducted the PREDMETH trial to investigate the efficacy and side-effect profile of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis.

Methods

Trial Design and Oversight

The PREDMETH trial was an open-label, randomized, noninferiority trial conducted at 17 hospitals in the Netherlands. The trial was designed by clinicians, researchers, and patients from the Dutch Sarcoidosis Patient Association and was conducted in accordance with the trial protocol (available with the full text of this article at NEJM.org) and with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Council for Harmonisation.[18] Approval was obtained from the medical ethics committee at the Erasmus Medical Center and the local ethics committee at each trial site. Written informed consent was obtained from all the patients. All the authors gathered the data.

An independent statistician who was unaware of the treatment assignments before the database lock performed the primary analyses. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adult patients with pulmonary sarcoidosis (as defined by the American Thoracic Society, European Respiratory Society [ERS], and World Association for Sarcoidosis and Other Granulomatous Disorders[19]) who had not previously received treatment were eligible for inclusion. The inclusion criteria were a pulmonary indication to initiate treatment (defined as moderate or severe symptoms and pulmonary sarcoidosis associated with a risk of worsened health or death), in line with the current ERS guideline recommendations[4]; a forced vital capacity (FVC) of less than 90% of the predicted value, a diffusing capacity of the lungs for carbon monoxide (DLCO) of less than 70% of the predicted value, a decrease of at least 5 percentage points in the predicted FVC, or a decrease of at least 10 percentage points in the predicted DLCO in the previous 12 months; and parenchymal abnormalities as determined by investigators at the local trial sites. Exclusion criteria are provided in Table S1 in the Supplementary Appendix (available at NEJM.org).

Patients were randomly assigned in a 1:1 ratio to receive prednisone or methotrexate for 24 weeks

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according to a prespecified treatment schedule (Fig. S1). Randomization was performed with the use of a centralized electronic system. Oral prednisone treatment was initiated at a dose of 40 mg per day and was tapered every 4 weeks until a maintenance dose of 10 mg per day was established at week 16. Oral methotrexate treatment was initiated at a dose of 15 mg per week and was increased by 5 mg per week every 4 weeks to a maximum dose of 25 mg per week if the side-effect profile was acceptable. If side effects occurred, adjustments to the dose of prednisone or methotrexate or to the route of methotrexate administration could be made according to a prespecified plan. If unacceptable side effects persisted, patients could switch to the other treatment group. In case of insufficient efficacy, which was defined as a decrease from baseline of at least 10 percentage points in the percentage of the predicted FVC, the other treatment was added to the current treatment. All the patients were asked to attend every trial visit, regardless of whether they had discontinued the trial treatment.

END POINTS AND ASSESSMENTS

The primary end point was the mean change from baseline to week 24 in the percentage of the predicted FVC. The secondary end points were the change in the FVC, measured in liters, at week 24; an increase of at least 5 percentage points in the percentage of the predicted FVC at week 24; a decrease of at least 5 percentage points in the percentage of the predicted FVC at week 24; the change in the percentage of the predicted DLCO at week 24; an increase of at least 10 percentage points in the percentage of the predicted DLCO at week 24; a decrease of at least 10 percentage points in the percentage of the predicted DLCO at week 24; and the changes in the King's Sarcoidosis Questionnaire (KSQ) health status domain and lung domain scores,[20-22] the Fatigue Assessment Scale (FAS) score,[23,24] and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire descriptive health index score and visual analogue scale (VAS) score,[25] all at week 24.

The KSQ general health status domain score ranges from 0 to 100, with higher scores indicating better health status; the KSQ lung domain score ranges from 0 to 100, with higher scores indicating fewer symptoms.[20] The minimal clinically important difference is 8 points for the general health status domain and 4 points for the lung domain.[21] The FAS is used to assess fatigue; scores range from 10 to 50, with higher scores indicating worse fatigue. The minimal clinically important difference is 4 points.[23,24] The EQ-5D-5L is used to assess health outcomes. Scores on the descriptive health index range from 0 (death) to 1 (full health); scores on the VAS range from 0 to 100, with higher scores indicating better health status. The minimal clinically important differences for the descriptive health index and the VAS are unknown in patients with sarcoidosis and 0.065 and 6.9 points, respectively, in patients with chronic obstructive pulmonary disease.[26]

We administered the Patient Experiences and Satisfaction with Medications (PESaM) questionnaire at week 24. The PESaM is used to assess medications with regard to experiences, satisfaction, and importance as reported by the patient. A Likert scale is used to assess experiences and importance (scores range from 0 to 4, with higher scores indicating more positive experiences and greater importance), and a Likert-type scale is used to assess satisfaction (scores range from −5 to 5, with lower scores indicating greater dissatisfaction and higher scores greater satisfaction). The minimal clinically important difference for each score on the PESaM is not known in patients with sarcoidosis (Table S2).[27]

Levels of soluble interleukin-2 receptor in serum were measured with the use of enzyme immunoassays, in accordance with the instructions of the manufacturer (IBL International, part of the Tecan Group). Safety was assessed by the recording of adverse events and the monitoring of clinical status. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 27.1.

Pulmonary function, patient-reported outcomes, and adverse events were assessed at baseline and at weeks 4, 16, and 24. The first database lock was performed after the last patient completed the week 24 visit.

STATISTICAL ANALYSIS

The trial was designed to assess the noninferiority of methotrexate as compared with prednisone regarding the difference in the mean change from baseline to week 24 in the percentage of the predicted FVC (primary end point). We determined that a sample size of 110 patients would provide

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Table 1. Baseline Characteristics of the Patients (Modified Intention-to-Treat Population).*

Characteristic	Prednisone (N=69)	Methotrexate (N=68)	Total (N=137)
Male sex — no. (%)	54 (78)	47 (69)	101 (74)
Age — yr	48.5±10.6	44.7±12.8	46.6±11.9
Smoking history — no. (%)			
Never smoked	46 (67)	37 (54)	83 (61)
Current smoker	4 (6)	7 (10)	11 (8)
Former smoker	19 (28)	24 (35)	43 (31)
Race — no. (%)†			
White	58 (84)	59 (87)	117 (85)
Black	5 (7)	5 (7)	10 (7)
Other	6 (9)	4 (6)	10 (7)
Scadding stage — no./total no. (%)‡			
Stage 2	35/44 (80)	34/48 (71)	69/92 (75)
Stage 3	1/44 (2)	9/48 (19)	10/92 (11)
Stage 4	8/44 (18)	5/48 (10)	13/92 (14)
Pattern on chest CT — no./total no. (%)			
Parenchymal abnormalities with lymphadenopathy	53/63 (84)	49/63 (78)	102/126 (81)
Parenchymal abnormalities without lymphadenopathy	1/63 (2)	8/63 (13)	9/126 (7)
Pulmonary fibrosis	9/63 (14)	6/63 (10)	15/126 (12)
Time since diagnosis — yr	2.0±3.5	1.5±4.4	1.7±4.0
Disease duration — no. (%)			
<2 yr	51 (74)	58 (85)	109 (80)
2–5 yr	10 (14)	7 (10)	17 (12)
>5 yr	8 (12)	3 (4)	11 (8)
Body composition§			
Weight — kg	81.7± 15.9	84.9±18.8	83.3±17.4
Waist circumference — cm	95.1±12.1	96.6±15.8	95.8±14.0
Body-mass index	26.1±4.5	26.6±5.9	26.4±5.2
FVC			
Mean — liters	3.7±0.9	3.7±1.1	3.7±1.0
Percentage of predicted value	79.8±15.4	74.8±12.7	77.3±14.3
FEV_1			
Mean — liters	2.64±0.64	2.67±0.78	2.66±0.71
Percentage of predicted value	71.4±16.2	68.3±13.4	69.9±14.9
Ratio of FEV_1 to FVC	0.71±0.09	0.73±0.11	0.72±0.10
DLco¶			
Mean — mmol/min/kPa	6.7±1.6	6.9±2.1	6.8±1.9
Percentage of predicted value	69.8±13.8	69.3±15.7	69.6±14.8
King's Sarcoidosis Questionnaire scores‖			
General health status domain	63.3±13.2	59.4±13.5	61.3±13.5
Lung domain	60.5±14.5	59.4±15.1	59.9±14.7

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Table 1. (Continued.)

Characteristic	Prednisone (N=69)	Methotrexate (N=68)	Total (N=137)
Fatigue Assessment Scale score**	25.1±8.1	25.9±8.2	25.5±8.2
EQ-5D-5L questionnaire scores††			
Descriptive health index	0.8±0.2	0.7±0.2	0.8±0.2
Visual analogue scale	65.1±21.8	60.6±20.2	62.8±21.0
Soluble interleukin-2 receptor level — U/ml‡‡	164.4±106.2	176.8±94.4	170.6±100.3

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Patient-reported outcomes were assessed no more than 7 days after baseline. CT denotes computed tomography, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.
† Race was reported by the patient.
‡ The Scadding criteria for staging pulmonary sarcoidosis are defined by findings on chest radiography, with stage 0 indicating normal findings, stage 1 hilar lymphadenopathy, stage 2 bilateral hilar lymphadenopathy and pulmonary infiltrates, stage 3 pulmonary infiltrates without bilateral hilar lymphadenopathy, and stage 4 pulmonary fibrosis. Data were from chest radiographs obtained within the previous 3 months and were available in 92 patients.
§ Data on weight and body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 1 patient in the methotrexate group. Data on waist circumference were missing for 4 patients in the methotrexate group.
¶ Values of the diffusing capacity of the lungs for carbon monoxide (DLco) were corrected for hemoglobin level.
‖ Scores on the King's Sarcoidosis Questionnaire general health status domain (range, 0 to 100; higher scores indicate better health status) and lung domain (range, 0 to 100; higher scores indicate fewer symptoms) were missing for 10 patients in the prednisone group and for 7 patients in the methotrexate group.
** Scores on the Fatigue Assessment Scale (range, 10 to 50; higher scores indicate worse fatigue) were missing for 10 patients in the prednisone group and for 7 patients in the methotrexate group.
†† Scores on the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire descriptive health index (range, 0 [death] to 1 [full health]) and visual analogue scale (range, 0 to 100; higher scores indicate better health status) were missing for 10 patients in the prednisone group and for 8 patients in the methotrexate group.
‡‡ Normal values are less than 44 U per milliliter. Data were missing for 5 patients in the prednisone group and for 4 patients in the methotrexate group.

the trial with 80% power to assess noninferiority at a two-sided significance level of 0.05, with a noninferiority margin of 5 percentage points. The sample-size calculation assumed a standard deviation of 10.5 percentage points for the primary end point[28] in both groups and no difference between the groups in the percentage of the predicted FVC at week 24. Accounting for an estimated loss to follow-up or withdrawal of 20%, we aimed to include 138 patients.

The primary analysis was conducted in the modified intention-to-treat population, defined as all the patients who underwent randomization and received at least one dose of prednisone or methotrexate. In the primary analysis, the difference between methotrexate and prednisone regarding the mean change in the percentage of the predicted FVC (with its 95% confidence interval) at week 24 was estimated with the use of mixed models for repeated measures that included the percentage of the predicted FVC at each visit as dependent variables; treatment, visit, and treatment-by-visit interaction as factors; and the percentage of the predicted FVC at baseline as a covariate. Noninferiority was confirmed if the lower limit of the 95% confidence interval for the between-group difference in the mean change at week 24 was greater than –5 percentage points (noninferiority margin).

Mixed models for repeated measures that were similar to those used in the primary analysis were used to assess between-group changes in the percentage of the predicted FVC at week 24 in the per-protocol population, which included all the patients who received prednisone or methotrexate according to the prespecified treatment schedule at least 80% of the time. Similar mixed models for repeated measures were also used to calculate changes in the FVC (measured in liters), the percentage of the predicted DLco, the KSQ general health status and lung domain scores, the FAS score, the EQ-5D-5L scores, and the soluble interleukin-2 receptor level.

The Cochran–Mantel–Haenszel test was used to evaluate between-group differences in the percentage of patients with an increase or decrease of at least 5 percentage points in the percentage of the predicted FVC or an increase or decrease

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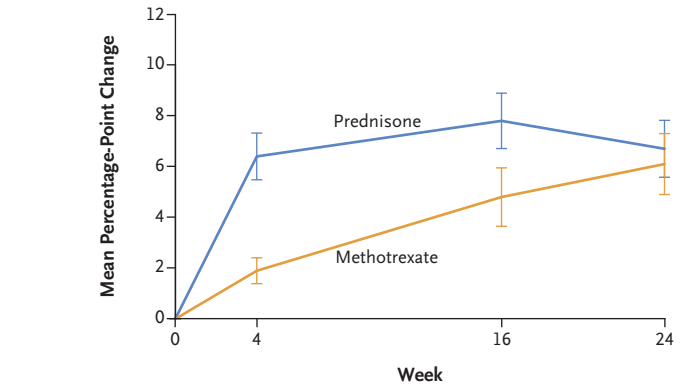

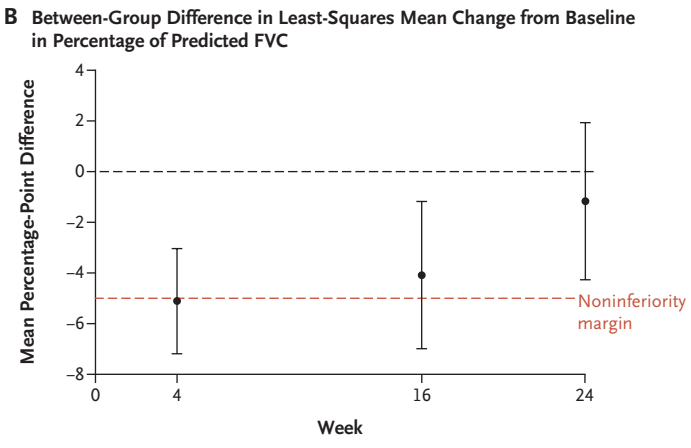

Figure 1. Change in Percentage of Predicted Forced Vital Capacity (Modified Intention-to-Treat Analysis).

Panel A shows the unadjusted mean change in the percentage of the predicted forced vital capacity (FVC) in the prednisone and methotrexate groups between baseline and weeks 4, 16, and 24. The unadjusted mean change at week 24 (primary end point) was 6.75 percentage points (95% CI, 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group. Panel B shows the between-group difference in the least-squares mean change in the percentage of the predicted FVC between baseline and weeks 4, 16, and 24. The between-group difference at week 24 was –1.17 percentage points (95% CI, –4.27 to 1.93), which indicated that methotrexate was noninferior to prednisone. Point estimates and 95% confidence intervals were calculated with the use of mixed models for repeated measures that included treatment, visit, and treatment-by-visit interaction as factors and the percentage of the predicted FVC at baseline as the covariate. I bars indicate 95% confidence intervals.

of at least 10 percentage points in the percentage of the predicted DLCO at week 24. PESaM data were tabulated according to treatment group. Adverse events that started before the week 24 visit and adverse events that were ongoing at the week 24 visit were tabulated according to treatment group. A post hoc analysis of the change at week 24 in the percentage of the predicted forced expiratory volume in 1 second (FEV_1) was conducted.

Secondary end points were not controlled for multiplicity. Results are reported as point estimates and 95% confidence intervals, and the widths of these confidence intervals should not be used to infer definitive treatment effects.

RESULTS

PATIENTS

From July 17, 2020, through February 22, 2024, we enrolled 138 patients; 70 were randomly assigned to receive prednisone and 68 to receive methotrexate (Fig. S2). One patient in the prednisone group was excluded because of an alternative diagnosis (silicosis). Baseline characteristics appeared to be generally balanced between the two groups (Table 1). The patients were generally representative of the population with pulmonary sarcoidosis, although the trial included a higher percentage of men (Table S3).

EFFICACY

The mean (±SD) daily dose of the assigned medication up to week 24 was 21.1±2.1 mg in the prednisone group and 20.1±3.0 mg in the methotrexate group (Table S5.1). The primary end-point analysis was conducted in the modified intention-to-treat population, which included 135 patients. The unadjusted mean change from baseline in the percentage of the predicted FVC at week 24 was 6.75 percentage points (95% confidence interval [CI], 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group (Fig. 1A and Table S4.1). The between-group difference in the least-squares mean change at week 24 was –1.17 percentage points (95% CI, –4.27 to 1.93), which indicated that methotrexate was noninferior to prednisone (Fig. 1B). The per-protocol analysis, which included 112 patients, also showed that methotrexate was noninferior to prednisone at week 24, with a between-group difference in the least-squares mean change of –1.40 percentage points (95% CI, –4.85 to 2.05) (Table S4.2).

SECONDARY END POINTS

Secondary end points related to pulmonary function are shown in Table 2. An increase of at least

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Table 2. Secondary End Points at Week 24.*

End Point	Prednisone (N=69)	Methotrexate (N=68)	Difference (95% CI)†
Pulmonary function			
Change in FVC — liters‡	0.34±0.05	0.25±0.07	−0.08 (−0.25 to 0.09)
Increase of ≥5 percentage points in percentage of predicted FVC — no./total no. (%)	37/68 (54)	34/67 (51)	—
Decrease of ≥5 percentage points in percentage of predicted FVC — no./total no. (%)	6/68 (9)	2/67 (3)	—
Change in percentage of predicted DLco§	4.26±1.11	3.72±1.22	−0.43 (−3.43 to 2.57)
Increase of ≥10 percentage points in percentage of predicted DLco — no./total no. (%)	17/65 (26)	15/66 (23)	—
Decrease of ≥10 percentage points in percentage of predicted DLco — no./total no. (%)	3/65 (5)	3/66 (5)	—
Patient-reported outcomes			
Change in King's Sarcoidosis Questionnaire score¶			
General health status domain	4.80±1.63	8.18±1.67	2.50 (−1.88 to 6.88)
Lung domain	7.32±1.64	9.77±2.29	2.88 (−2.20 to 7.97)
Change in Fatigue Assessment Scale score‖	−2.62±0.75	−1.57±0.99	1.41 (−0.79 to 3.61)
Change in EQ-5D-5L questionnaire score‖			
Descriptive health index	0.06±0.02	0.04±0.02	0.01 (−0.05 to 0.06)
Visual analogue scale	2.70±3.03	7.16±3.06	−1.49 (−8.66 to 5.68)
Biomarkers			
Soluble interleukin-2 receptor level — U/ml**	−82.7±12.80	−81.1±12.98	10.90 (−8.91 to 30.72)

* Plus–minus values are means ±standard error. Shown are changes at week 24 as compared with baseline.
† Differences (methotrexate group minus prednisone group) and 95% confidence intervals were calculated with the use of mixed models for repeated measures that included treatment, visit, and treatment-by-visit interaction as factors and the percentage of the predicted FVC at baseline as a covariate. Secondary end points were not controlled for multiplicity; therefore, the confidence intervals should not be used to infer definitive treatment effects.
‡ Data were missing for 1 patient in the prednisone group and for 1 patient in the methotrexate group.
§ Data were missing for 4 patients in the prednisone group and for 2 patients in the methotrexate group.
¶ Data were missing for 22 patients in the prednisone group and for 21 patients in the methotrexate group.
‖ Data were missing for 23 patients in the prednisone group and for 21 patients in the methotrexate group.
** Normal values are less than 44 U per milliliter. Data were missing for 12 patients in the prednisone group and for 10 patients in the methotrexate group.

5 percentage points in the percentage of the predicted FVC between baseline and week 24 occurred in 37 patients (54%) in the prednisone group and in 34 patients (51%) in the methotrexate group.

In a post hoc analysis, the change in the percentage of the predicted FEV_1 at week 24 was 6.24 percentage points (95% CI, 3.94 to 8.55) in the prednisone group and 5.73 percentage points (95% CI, 3.55 to 7.92) in the methotrexate group. Changes through week 24 in the KSQ lung domain score and general health status domain score, EQ-5D-5L VAS score, FAS score, and soluble interleukin-2 receptor level are shown in Figure 2 and Tables S6.1 through S6.5. PESaM scores at week 24 were generally similar in the prednisone and methotrexate groups (Table S7).

SAFETY

A summary of the most common adverse events is provided in Table 3. A total of 308 adverse events occurred in the prednisone group, and 283 adverse events occurred in the methotrexate group. At least one adverse event occurred in 96% of the patients in the prednisone group and in 94% of those in the methotrexate group. Serious adverse events occurred in 3 patients (4%) and 7 patients (10%), respectively. A total of 165 adverse events (54%) in the prednisone group and 104 (37%) of those in the methotrexate group

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were ongoing at week 24. Adverse events that led to the discontinuation of treatment or a switch to the other treatment group occurred in 10 patients (14%) in the prednisone group and in 9 patients (13%) in the methotrexate group (Table 3 and Table S8). The most frequently reported adverse events included weight gain, insomnia, increased appetite, and mood swings with prednisone and nausea, fatigue, any abnormal liver-function tests, and abdominal pain with methotrexate.

The mean change in weight was 5.0±5.1 kg in the prednisone group and 1.1±4.0 kg in the methotrexate group. The mean change in waist circumference was 4.4±6.6 cm in the prednisone group and 0.5±4.9 cm in the methotrexate group.

DISCUSSION

This multicenter, randomized trial assessed the efficacy of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis. Methotrexate was noninferior to prednisone regarding the change in the percentage of the predicted FVC between baseline and week 24.

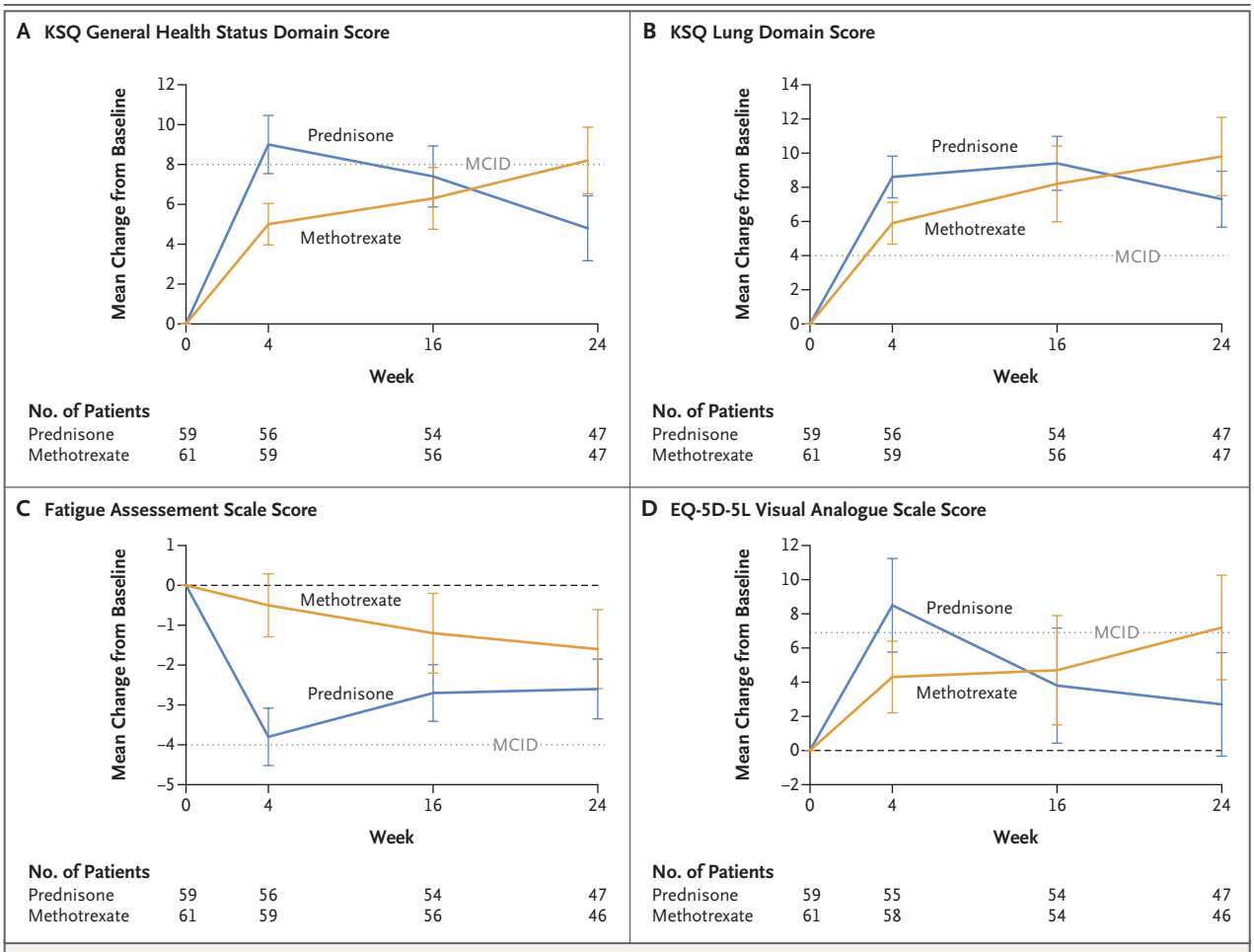

Figure 2. Change in Patient-Reported Outcomes (Modified Intention-to-Treat Analysis).

Shown are the mean changes from baseline in the King's Sarcoidosis Questionnaire (KSQ) general health status domain score (range, 0 to 100; higher scores indicate better health status) (Panel A), the KSQ lung domain score (range, 0 to 100; higher scores indicate fewer symptoms) (Panel B), the Fatigue Assessment Scale score (range, 10 to 50; higher scores indicate worse fatigue) (Panel C), and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale score (range, 0 to 100; higher scores indicate better health status) (Panel D). Because the minimal clinically important difference (MCID) for sarcoidosis as assessed with the EQ-5D-5L visual analogue scale is unknown, the minimal clinically important difference for chronic obstructive pulmonary disease is shown. I bars indicate 95% confidence intervals.

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Table 3. Adverse Events in the Overall Population.*

Event	Prednisone (N=69)		Methotrexate (N=68)	
	All Adverse Events	Ongoing Adverse Events at Wk 24	All Adverse Events	Ongoing Adverse Events at Wk 24
≥1 Adverse event — no. of patients (%)	65 (96)	—	65 (94)	—
Total no. of adverse events	308	165	283	104
Serious adverse events — no. of patients (%)†	3 (4)	NA	7 (10)	NA
Adverse events that led to treatment discontinuation or switch in treatment group — no. of patients (%)	10 (14)	NA	9 (13)	NA
Most common adverse events — no. of patients (%)‡				
Endocrine disorders				
Cushingoid appearance	10 (14)	6 (9)	2 (3)	2 (3)
Gastrointestinal disorders				
Abdominal pain	2 (3)	1 (1)	11 (16)	2 (3)
Diarrhea	4 (6)	1 (1)	10 (15)	2 (3)
Reflux	8 (12)	2 (3)	4 (6)	1 (1)
Nausea	6 (9)	0	25 (37)	9 (13)
General disorders				
Fatigue	7 (10)	5 (7)	18 (26)	10 (15)
Increased appetite	13 (19)	9 (13)	3 (4)	2 (3)
Malaise	3 (4)	1 (1)	10 (15)	1 (1)
Infections				
Respiratory tract infection	1 (1)	0	10 (15)	1 (1)
Investigations				
Abnormal liver-function tests				
Any test	2 (3)	2 (3)	17 (25)	8 (12)
Aspartate aminotransferase test: >3× ULN	1 (1)	0	2 (3)	1 (1)
Alanine aminotransferase test: >3× ULN	0	0	6 (9)	1 (1)
Weight gain	30 (43)	27 (39)	5 (7)	5 (7)
Musculoskeletal and connective-tissue disorders				
Myalgia	10 (14)	5 (7)	7 (10)	3 (4)
Nervous system disorders				
Headache	8 (12)	3 (4)	10 (15)	2 (3)
Psychiatric disorders				
Insomnia	29 (42)	11 (16)	4 (6)	2 (3)
Mood swings	9 (13)	5 (7)	5 (7)	4 (6)
Nervousness	8 (12)	2 (3)	1 (1)	1 (1)
Respiratory disorders				
Productive cough	9 (13)	5 (7)	8 (12)	4 (6)
Skin and subcutaneous tissue disorders				
Rash	7 (10)	3 (4)	13 (19)	4 (6)

* NA denotes not applicable, and ULN upper limit of the normal range.
† The following serious adverse events were reported in the prednisone group: diabetes mellitus (assessed by the investigator as being related to treatment), pulmonary embolism (unrelated to treatment), and elective ureteral stent insertion (unrelated to treatment). The following serious adverse events were reported in the methotrexate group: arrhythmia supraventricular, dyspnea, multiple traumatic fractures, and afferent loop syndrome (all unrelated to treatment) and coronavirus disease 2019, respiratory tract infection, and gastroenteritis (all possibly related to treatment).
‡ Shown are adverse events reported in more than 10% of patients in either treatment group. Events were coded according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 27.1.

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The need for alternative first-line treatment options for pulmonary sarcoidosis has been recognized for many years; however, evidence from randomized, controlled trials of alternative treatments was lacking. In the current trial, we have shown that methotrexate may be an alternative to prednisone as first-line treatment in patients with pulmonary sarcoidosis. In our trial, prednisone led to a rapid increase in the percentage of the predicted FVC within 4 weeks, after which this value remained stable through week 24. This finding is in line with results of previous trials, in which major improvement in pulmonary function was found to occur within 1 month after starting prednisone.[28-30] The improvement from baseline in the percentage of the predicted FVC was more gradual with methotrexate than with prednisone, but the change between baseline and week 24 was similar in the two groups. In both treatment groups, the changes at week 24 in the KSQ lung domain score and general health status domain score, EQ-5D-5L VAS score, and FAS score showed a pattern generally similar to that of the changes at week 24 in the percentage of the predicted FVC (Fig. 2).

The current trial included patients with a wide range of disease severity (34% to 125% of the predicted FVC). We did not observe a substantial difference between the prednisone and methotrexate groups in the percentages of patients who had treatment failure, needed rescue therapy, or withdrew from the trial. The lack of a difference in these percentages is reassuring because one of the hesitations for the use of methotrexate as first-line treatment has been an onset of action that is slower than that for prednisone.[31] The recently published SARCORT trial showed that 45% of patients who received 6 months of prednisone treatment for pulmonary sarcoidosis had disease relapse between 12 and 18 months after the cessation of therapy.[32] Thus, long-term treatment of sarcoidosis is likely to be needed in order to adequately suppress granulomatous inflammation, which means that the side-effect profile and patient preference are key issues for adherence.[32] In patients with severe symptoms or impaired pulmonary function, methotrexate combined with short-term use of prednisone could be considered as initial treatment, but such an approach warrants further study.

The total number of adverse events was similar in the trial groups, but the adverse-event profiles of prednisone and methotrexate were clearly different. The percentage of adverse events that were transient (i.e., not ongoing at week 24) was higher in the methotrexate group than in the prednisone group (63% vs. 46%). One of the reasons for this finding could be that changes in the route of methotrexate administration or the methotrexate dose were successful in alleviating adverse events.

Elevated liver-enzyme levels were seen in 25% of the patients treated with methotrexate, with the alanine aminotransferase level being more than three times the upper limit of the normal range in 9% of the patients and leading to treatment discontinuation in two patients. This aligns with findings from methotrexate studies involving patients with rheumatoid arthritis.[33,34] Long-term use of methotrexate in patients with rheumatoid arthritis is also associated with increased liver-enzyme levels and toxic effects; data in previous studies on the risk of liver fibrosis and cirrhosis are inconsistent.[34]

Increases of 5.0 kg in weight and 4.4 cm in waist circumference were observed at week 24 in the prednisone group and persisted after the prednisone dose was tapered; these findings are similar to those in previous trials.[10,32] Long-term use of prednisone is associated with a high risk of chronic conditions, such as hypertension and diabetes mellitus, with waist circumference and body-mass index as direct risk factors.[35-38]

Three treatment-related serious adverse events were reported in the methotrexate group as compared with one in the prednisone group. The small number of events precludes definitive conclusions about the clinical implications of this finding. Differences between methotrexate and prednisone regarding the onset of action and adverse-event profile provide important information to guide shared decision making between patients and providers in choosing the most appropriate treatment.

The current trial was designed before the most recent treatment guidelines for sarcoidosis were published.[4] As a result, in our trial the initial prednisone dose of 40 mg per day differs from the current guideline-recommended dose of 20 to 40 mg per day, and the initial methotrexate dose of 15 mg per week (which was increased to 25 mg per week if the side-effect profile was acceptable) differs from the current guideline-recommended dose of 10 to 15 mg per

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week.[4] However, the current guideline recommendations are based on low to very low quality of evidence, and future studies are needed to clarify the best dose and frequency of administration.[4] The SARCORT trial showed that the effects of medium-dose prednisone (20 mg per day) were similar to those of high-dose prednisone (40 mg per day); nevertheless, the medium dose did not lead to a lower incidence of adverse events than the high dose.[32] Methotrexate has been extensively investigated in patients with rheumatoid arthritis, and the appropriate dose is considered to be 20 to 25 mg per week.[39] In patients with sarcoidosis, the appropriate methotrexate dose remains to be elucidated; a previous prospective study showed that a lack of methotrexate efficacy was mainly associated with a dose of 10 mg per week, a finding that appears to indicate the need for a dose of at least 15 mg per week.[17]

Our trial has several limitations. Although this trial was larger than other randomized, controlled trials of first-line treatment in sarcoidosis, it still was small and was conducted in a single country. The number of patients screened for inclusion in the trial was not consistently reported in all centers, and the effect that this may have had on the generalizability of the results is unknown. Nonadherence to the treatment schedule (i.e., crossover to the other treatment group) could have biased the results of the modified intention-to-treat analysis toward noninferiority; however, our per-protocol analysis also showed noninferiority of methotrexate. Limitations in funding and the need for treatment schedules for two drugs, including schedules for dose increases and decreases, precluded blinding.

In patients with pulmonary sarcoidosis, initial treatment with methotrexate was noninferior to that with prednisone regarding the change from baseline to week 24 in the percentage of the predicted FVC. Differences in the side-effect profile and time to onset of action between prednisone and methotrexate may inform shared decision making by patients and providers about the appropriate treatment approach.

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