Inclusion body myositis : a nationwide study

Badrising, U.A.

VI

Comparison of weakness progression in inclusion body myositis during treatment with methotrexate or placebo

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ABSTRACT

We investigated whether 5 to 20 mg per week oral methotrexate (MTX) could slow down disease progression in 44 patients with inclusion body myositis in a randomized double-blind placebo-controlled study over 48 weeks. Mean change of quantitative muscle strength testing (QMT) sum scores was the primary study outcome measure. QMT sum scores declined in both treatment groups, -0.2% for MTX and -3.4% for placebo (95% confidence interval = -2.5% to $+9.1\%$ for difference). There were also no differences in manual muscle testing (MMT) sum scores, activity scale scores and patients' own assessments after 48 weeks of treatment. Serum creatine kinase (CK) activity decreased significantly in the MTX group. We conclude that oral MTX did not slow down progression of muscle weakness but decreased serum CK activity.

Introduction

Inclusion body myositis (IBM) is a progressive muscle disorder with unknown etiology. Muscle biopsy specimens show inflammation and depositions of proteins similar to those seen in degenerative disorders,[35,85,86] processes that do not seem to be closely related as they do not co-localize.[87]
Immunosuppressive therapies have yielded no or only short lasting improvement of muscle strength.[39,41,40,88,89] Whether immunosuppressive treatment can slow down disease progression has not been studied.
Oral methotrexate (MTX) is a widely used, effective and well-tolerated treatment in rheumatoid arthritis.[89-90] The weekly regimen facilitates compliance and MTX has low cost. In the present study, we compared the efficacy and tolerability of MTX and placebo in slowing down disease progression in IBM.

Patients & Methods

From April 1996 until December 2000, we conducted a nationwide, randomized, placebo-controlled, parallel-group, double-blind trial at the Leiden University Medical Center after approval of the protocol by the ethics review board. All patients gave informed consent. We included 44 patients fulfilling the diagnostic criteria[53,63] for definite (n = 42) or probable (n = 2) IBM according to a previously reported recruitment process.[63] Inclusion criteria included sufficient residual muscle strength to evaluate changes, absence of risk factors for MTX-induced toxicity, no use of immunosuppressive therapy for at least 6 weeks before the study, no previous use of MTX, no use of medication interfering with MTX pharmacokinetics or pharmacodynamics, and absence of severe dysphagia interfering with oral medication use.
Baseline studies were carried out 2 weeks before therapy initiation. Clinical evaluations comprised quantitative muscle power testing (QMT) by handheld myometry assessing the maximum voluntary contraction[69] and manual muscle testing (MMT) by the six-point Medical Research Council[68] (MRC) scale. Activity limitations were evaluated according to the Barthel index,[65] Brooke's Grading System[67] and the Rivermead Mobility Index.[66] Laboratory studies included serum creatine kinase (CK) activity levels.
One investigator (UB) tested baseline muscle strength. The mean scores of each of 14 muscle groups tested three times with QMT were added to a QMT sum score. MMT measurements resulting in a sum score were performed on 32 muscle groups.
Trial medication was distributed by the hospital pharmacy. Patients were randomly assigned, using a computer-generated schedule, to receive either MTX or an identical-appearing placebo. The randomization schedule used random numbers in permuted blocks of 4. The code was concealed by the pharmacy and broken after assessment of all patients.
A 48-week treatment period started with a dose of 5 mg per week, each six weeks increased by 5 mg up to 20 mg. To enhance blinding, all patients were requested to

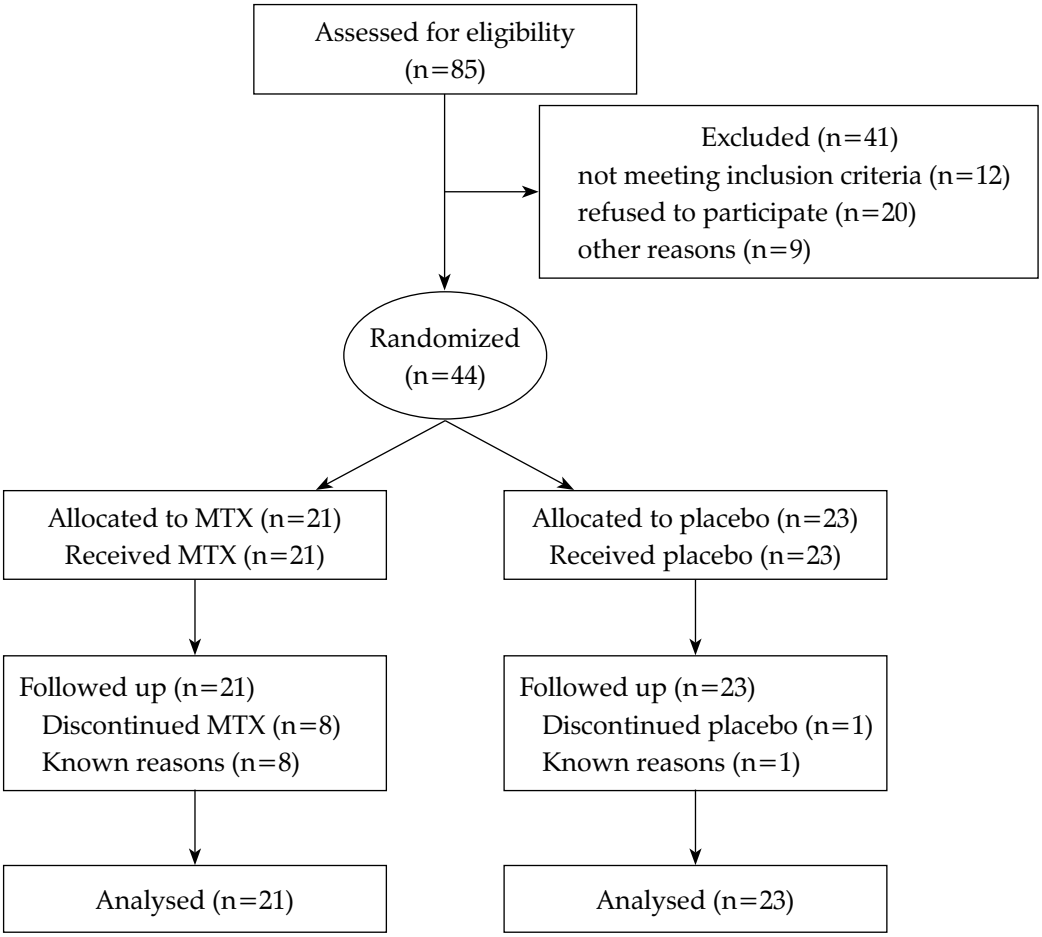
decrease their 20 mg dosage by 2.5 mg without explanation after routine laboratory evaluations for 3 months. After blood assessments, the dosage was restored to 20 mg per week.
A blinded assessor (JV) monitored patients with regard to treatment schedules, 3-month routine laboratory evaluations, including serum CK activity, and adverse events. Another blinded assessor (UB) evaluated the QMT and MMT measurements, and patients' opinion concerning the state of muscle weakness (scored as progression, stabilization or improvement) at 22 and 48 weeks after treatment initiation and activity limitations at 48 weeks. Patients who discontinued study treatment were immediately assessed.
The primary study outcome measure was the difference in mean change from baseline of the QMT sum scores between the two study groups. Secondary outcome measures were the differences in MMT sum scores, the three activity scales, the patient's subjective opinion of the muscle strength and the changes in serum CK activity levels.
To detect a difference of 100 Newtons (N) in mean changes or a clinically important stabilization 44 patients were required (power = 0.80; $\alpha = 0.05$) according to the following assumptions: an annual decline in muscle strength in IBM patients of 5%, a mean change in QMT sum score of 100 N over 48 weeks for placebo and zero for MTX with a standard deviation of 100 N and a dropout rate of 25%.
An intention-to-treat analysis with carry forward of last assessments in case of missing data was performed. Statistical tests were two-sided. The mean changes in muscle strength sum scores were compared by mixed-model analysis of variance, with the sum score as dependent variable, randomized treatment as factor, time as covariate and by treatment-time interaction, and by independent-samples *t*-test.

RESULTS

Twenty-one patients were allotted to MTX and 23 to placebo (Figure 1). Baseline characteristics were similar for the two groups (Table). Significantly more patients on MTX discontinued treatment (8 vs. 1 for placebo, p = 0.008, Fisher's exact test), mostly because of adverse events. The mean weekly dose of MTX was 14.0 mg in all treated patients and 14.6 mg in those who completed the entire study.

Primary outcome
Mean QMT sum scores declined both for MTX (−0.2%) and placebo (–3.4%). This difference was not significant (p = 0.3; 95% confidence interval [CI] −2.5% to +9.1% for difference). A per-protocol analysis including only those patients who fully completed the study also showed no difference: +0.9% for MTX and –2.7% for placebo (p = 0.3; 95% CI = –3.3% to +10.7%) (Figure 2).
Except for CK values, none of the other study parameters showed a significant difference between MTX and placebo. MMT sum scores decreased in both groups, −0.5% for MTX and −2.0% for placebo (p = 0.2; 95% CI = −1.0% to +3.9% for difference). In the per-protocol analysis MMT sum score changes were −2.2% for MTX and −3.8%

Figure 1 *Flow chart of assessed patients with IBM and progress during treatment with methotrexate (MTX) and placebo.*



for placebo (p = 0.4; 95% CI = −2.3% to +5.4%) (see Figure 2). The scores on activity scales did not change from baseline (see Table). Two patients had a subjective improvement in strength at 48 weeks, both from the placebo group. Twelve patients, 5 from the MTX group, noticed no change; others felt they had deteriorated. Serum CK values fell in both groups, but more so in the MTX group, notably in the first treatment period: from 676 to 274 U/l for MTX and from 725 to 690 U/l for placebo (p = 0.01; 95% CI = −732 to −102 for difference).

Table. *Characteristics of patients at baseline.*

Characteristic	Methotrexate (n = 21)	Placebo (n = 23)
Age	68 (±8)	69 (±7)
Female	6	5
Duration of symptoms (years)	9 (±5)	11 (±7)
Other autoimmune disorders	6	6
Discontinuation of immunosuppressive therapy prior to baseline studies	2	2
Sum score by hand-held dynamometry (N)	2533 (±800)	2492 (±844)
Sum score by MRC	255 (±34)	247 (±37)
Wheelchair bound	1	1
CK[a] (U/l)	676 (±830)	725 (±761)
Median	443	511
Minimum-maximum	121-3360	148-3035
Activity score		
Barthel index (0-20)	18 (±2)	18 (±3)
Rivermead mobility index (0-15)	12 (±2)	12 (±3)
Brooke's grading (3-22)	6 (±1)	6 (±3)

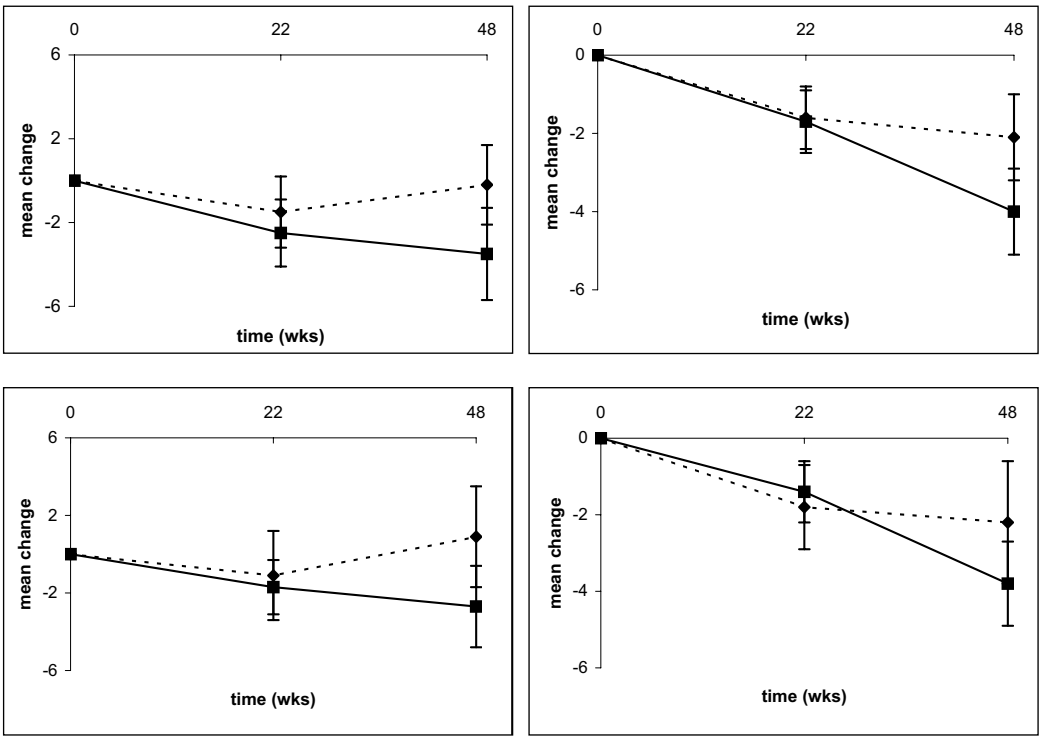
Mean ±SD
[a] Normal value < 200 U/l
CK = creatine kinase; MRC = Medical Research Council; N = Newton.

Adverse events
Four patients in the MTX group and 1 patient in the placebo group required dose reductions because of adverse events. One patient on placebo discontinued trial medication because of progressive muscle weakness. Seven patients on MTX discontinued trial medication because of nausea (n = 3), hair loss (n = 2), arthralgia (n = 2), and progressive muscle weakness (n = 1).

DISCUSSION

We investigated whether immunosuppression with MTX could slow down decline of muscle strength in IBM over a near-year treatment period. Randomization was adequate, as study groups were similar with regard to important baseline characteristics.
We failed to find a significant difference between MTX and placebo, possibly because of the lower than expected decline in the placebo group (3.4% in stead of 5%), a greater than anticipated variability in QMT results of patients (250 Newton in stead of 100 Newton), and a greater than expected dropout rate because of adverse events (8/21). As a result the

Figure 2 *Mean (±SE) changes in percent from baseline in quantitative muscle testing scores (left) and manual muscle testing scores (right) after 22 and 48 weeks of treatment with methotrexate (MTX) (solid diamonds) or placebo (solid quares) for intention to treat design (above) and per-protocol design (below).*



post hoc power of the study turned out to be only 23%. We had based our conservative estimation of disease progression on the only available data on the natural course of IBM showing a decline in muscle strength of 1.4% per month (range 0.5 to 2.8%).[44]

Muscle strength testing according to both the QMT and MMT sum scores showed a trend towards slowed decline of muscle weakness in the MTX group. Activity scales and patients' own assessments did not show a difference among treatment groups. The only statistically significant finding of predefined outcome measures was a decrease in serum CK activities in the MTX group.

Because of the low post hoc study power, as exemplified by the wide 95% confidence interval for treatment difference, we cannot completely rule out a clinically relevant effect of MTX, although this seems unlikely. To unequivocally demonstrate such a beneficial effect, 110 patients per treatment arm would be required over a 48 week-period or 28 patients per treatment arm over 2 years. The large patient groups necessary for the first option would require a multinational trial. The second option is obviously unattractive. Furthermore, the relatively high incidence of adverse events make MTX a less attractive treatment option in this disorder.

The decrease in serum CK activity levels during treatment with MTX suggests inhibition of inflammation and is in line with other findings showing a decrease of CK activity and of signs of inflammation in biopsies after treatment with intravenous immunoglobulin or prednisone.[91,92,92]
In conclusion, the findings of the present study do not support the use of MTX in IBM. The clinical course in the placebo group may provide a useful basis for future studies in this muscle disorder.