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COMPARISON OF METHOTREXATE WITH PLACEBO IN THE TREATMENT OF SYSTEMIC SCLEROSIS: A 24 WEEK RANDOMIZED DOUBLE-BLIND TRIAL, FOLLOWED BY A 24 WEEK OBSERVATIONAL TRIAL

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SUMMARY

In this study, methotrexate (MTX) was compared with placebo in the treatment of systemic sclerosis (scleroderma, SSc) in a 24 week randomized double-blind trial, followed by an observational trial of 24 weeks duration. Twenty-nine scleroderma patients were allocated to receive weekly injections of either 15 mg MTX or placebo. Patients who responded favourably after 24 weeks continued with the same regimen for a further 24 weeks; those who showed a poor response on placebo were allocated to further treatment with 15 mg MTX weekly, and those who responded poorly to treatment with 15 mg MTX weekly had their doses increased to 25 mg. A favourable response was defined as an improvement of total skin score (TSS) by $\geq 30\%$, of single breath diffusion capacity (DL_{CO}) by $\geq 15\%$, or of the score on a visual analogue scale of general well-being (VAS) by $\geq 30\%$, provided that such improvements were not accompanied by persistent digital ulcerations or worsening of $DL_{CO} \geq 15\%$. Seventeen patients were allocated to MTX treatment and 12 to treatment with placebo. After 24 weeks, a significantly larger number of patients receiving MTX ($n = 8$, 53%) who completed the first 24 weeks of the study had responded favourably compared to patients receiving placebo ($n = 1$, 10%, $P = 0.03$). Comparison of separate variables between the two treatment groups by intention-to-treat analysis at week 24 showed improvement in the MTX group of TSS ($P = 0.06$) and creatinine clearance ($P = 0.07$). At week 48, 13 patients received MTX from the start of the study and nine during 24 weeks. From these 22 patients, 15 (68%) responded favourably and compared with the start of the study they showed significant improvement of TSS ($P = 0.04$), VAS ($P = 0.02$), grip strength of the right hand ($P = 0.02$) and ESR ($P = 0.01$). Although the number of patients enrolled in this study is small, these results suggest that in a group of patients with active systemic sclerosis, low-dose MTX seems to be more effective than placebo according to pre-defined response criteria.

KEY WORDS: Systemic sclerosis, Methotrexate, Double-blind placebo-controlled treatment, Side-effects.

SYSTEMIC sclerosis (SSc) or scleroderma is a multisystemic disease characterized by excessive deposition of collagen and other extracellular matrix components by fibroblasts, damage to the endothelium of small vessels, resulting in intimal hyperplasia and tissue ischaemia, and activation of the immune system. These phenomena may lead to progressive fibrosis of the skin, muscles, joints and internal organs, accounting for many of the clinical manifestations [1, 2]. The natural course of the disease may vary: a few patients experience spontaneous remission; the majority undergo progression of skin and internal organ involvement, resulting in considerable morbidity and ultimately in death. Several studies have given estimates of 5 yr cumulative survival rates ranging from 34 to 73% [3]. Involvement of heart, lung or kidney, the presence of antitopoisomerase-I autoantibodies and diffuse skin involvement adversely affect outcome [4–6]. SSc is a rare disease, with an estimated annual incidence rate of 20 new cases per million [7]. Its pathogenesis is unclear, but evidence suggests an autoimmune or vascular aetiology [8]. No treatment has proven convincingly to be effective. Several studies have reported favourable effects of certain drugs, but most of them consist of case reports, uncontrolled trials or studies with historical controls [9–15]. Placebo-controlled, double-blind trials in SSc are scarce, and have given negative or inconclusive results [16–22].

Methotrexate (MTX) is an antifolate drug. In low dosages it has shown favourable effects in the treatment of autoimmune diseases such as rheumatoid arthritis (RA) [23–27] and dermato- and polymyositis [28, 29]. We recently reported the results of a 1 yr pilot study in SSc patients treated with low-dose MTX. In the majority of the patients, cutaneous symptoms improved within 6 months and no further internal organ deterioration was detected [30]. Similar encouraging observations have been reported in the meantime [31, 32]. To obtain more data about the role of MTX in the treatment of SSc, we conducted a double-blind trial comparing MTX and placebo, focusing on the efficacy and toxicity of these treatments, and on the differences between responders and non-responders on MTX treatment.

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PATIENTS AND METHODS

Patients

The inclusion criteria for the trial consisted of the preliminary criteria for the classification of SSc of the American Rheumatism Association [33] and the requirement that disease duration from the first signs of skin thickening was <3 yr. Patients with longer disease duration were also included if they had experienced a progression of skin thickening, persistent digital ulcerations, or a deterioration in pulmonary function, during the last 6 months. All patients voluntarily signed an informed consent form; the study protocol was approved by the institution's ethical committee.

We applied the following exclusion criteria: age <16 yr; the presence of another connective tissue disease or SSc-like illness related to exposure or ingestion; the presence of acute or chronic infection; pregnancy or childbearing potential without an acceptable means of contraception; the presence of liver disease, defined as a value exceeding twice the upper limit of normal for a hepatic function test or the presence of a known liver disease; serum creatinine level >130 μmol/l or a creatinine clearance rate <50 ml/min as estimated by the method of Cockcroft and Gault [34]; total lung capacity (TLC), vital lung capacity (VC) or single breath diffusion capacity for carbon monoxide (DL_{CO}) <50% of its predicted value; a leucocyte count of $<3.5 \times 10^9$/l or a platelet count $<150 \times 10^9$/l; the presence of a concurrent neoplastic disease; the presence of insulin-dependent diabetes mellitus; alcohol abuse (>4 oz/day); the use of an antifolate drug other than MTX, such as sulphonamide derivates, allopurinol or probenecid; and the presence of active peptic ulcer disease.

Study design

The study was set up as a multicentre single-observer trial. The study protocol was reviewed and approved by institutional viewboards at each participating clinical centre. Patients were randomly allocated to treatment with either MTX (Ledertrexate, Lederle Nederland bv, The Netherlands) or placebo, both of which were administered weekly by i.m. injection. The two groups were balanced for disease duration (time between onset of skin thickening and entry to the trial) and extent of skin involvement, known prognostic factors for SSc. The weekly dose of MTX was initially 15 mg. Potentially disease-modifying drugs, such as D-penicillamine and colchicine, were discontinued at least 3 months prior to study entry.

Since there is no consensus concerning the outcome measures to be used in assessing disease activity and, hence, response to treatment in SSc, we set up our own criteria by which response can be evaluated. We based them arbitrarily on data from previous studies and on our own experience. They employ the following variables: total skin score (TSS), which is the sum of scores of 0–4 obtained manually at 26 anatomic locations, described by Steen *et al.* [9]; visual analogue scale (VAS) of general well-being, as determined by the patient on a 100 mm scale on which 100 mm represents optimal general well-being; lung diffusion capacity as reflected by DL_{CO}; and presence or absence of digital ulcerations. Response to treatment was defined as favourable if TSS or VAS improved by ≥30% or if DL_{CO} improved by ≥15%. However, when digital ulcerations developed or persisted, or when DL_{CO} decreased by ≥15%, despite improvement of VAS or TSS, the response was defined as unfavourable. Evaluation of response criteria was performed double blind at weeks 24 and 48. Patients with favourable response after 24 weeks of treatment continued the same regimen for another 24 weeks. Non-responders on placebo after 24 weeks were started on MTX 15 mg weekly; non-responders on 15 mg MTX weekly received an increased dose of 25 mg weekly for the remaining 24 weeks of the trial. The clinical examiner and the patients were blind regarding the changes in treatment; the treatment code was broken only after all patients had completed the 48 week study. All subjects were out-patients at the time of enrolment and were admitted to hospital during the course of the study only in the event that severe complications occurred.

Clinical assessment

At study entry, a detailed medical history was taken and the patient was given a thorough physical examination. Each patient was evaluated monthly during the trial year by the same investigator (FHJvdH). The evaluations consisted of a detailed clinical examination and the determination of TSS, VAS, extension indices for both hands, grip strength in both hands and maximal oral opening. An extension index is the distance between the tip of the third finger and the distal palmar crease with the hand fully extended. Grip strength was measured by a sphygmanometer (Tonometer, von Recklinghausen, Germany) with a range of 0–300 mmHg; the value recorded was the maximum of three consecutive measurements. At study entry, and after 24 and 48 weeks of treatment, pulmonary function tests, including those for TLC, VC and DL_{CO}, were performed, barium swallow of the oesophagus was measured, an electrocardiogram (ECG) was recorded and a radiological examination of the chest was performed.

Laboratory assessment

Haemoglobin level, white blood cell (WBC) and platelet counts, and hepatic and renal functions were evaluated weekly during the first month of treatment and then every 4 weeks for the remainder of the study. Hepatic function tests consisted of the assessment of alkaline phosphatase, serum aspartate aminotransferase (AST) and serum alkaline aminotransferase (ALT) levels; renal function tests consisted of the assessment of serum creatinine and creatinine clearance rate according to the method of Cockcroft and Gault [34]. Other laboratory variables measured once every 4 weeks from the beginning of therapy were erythrocyte

sedimentation rate (ESR) according to Westergren, serum levels of IgA, IgM, IgG, C3, C4 and circulating immune complexes, and urinalysis. At study entry, patients were tested for antinuclear antibodies, by immunoblotting and counterimmunoelectrophoresis, and for rheumatoid factor by the latex fixation test. All laboratory tests, except the hepatic and renal function tests and those for ESR and blood cell counts, were performed at the University Hospital Nijmegen, to ensure that uniform methods were used.

Organ involvement

Pulmonary dysfunction was defined as a VC and TLC $\leqslant 80\%$ or $DL_{CO} \leqslant 70\%$ of predicted normal values, or chronic interstitial changes on chest roentgenograms; oesophageal dysfunction, as diminished motility as determined by barium swallow; cardiac dysfunction, as conduction disturbances on an ECG or cardiomegaly on a chest X-ray; renal dysfunction, as serum creatinine level $> 130\ \mu mol/l$ or a creatinine clearance rate of < 50 ml/min as estimated according to the method of Cockcroft and Gault [34]. SSc was considered diffuse if sclerotic skin changes were present proximal to the elbows or knees; SSc was considered limited if skin changes were present distal to the elbows or periorally with other areas being unaffected.

Concurrent medication

Concurrent treatment with corticosteroids at dosages not exceeding 10 mg/day, non-steroidal anti-inflammatory drugs, analgesics, nifedipene, ketanserine, cimetidine or omeprazole were permitted. No changes in dosages were permitted from at least 8 weeks before study entry until the end of the trial.

Adverse reactions and withdrawals from the study

At each visit, patients were routinely questioned about symptoms related to MTX toxicity. The trial medication was temporarily withheld if the WBC count was $< 3.0 \times 10^9/l$, if the platelet count was $< 150 \times 10^9/l$, if liver enzyme levels exceeded three times the upper limit of normal or if serum creatinine levels exceeded $160\ \mu mol/l$, for two consecutive measurements. Treatment was resumed once the values had normalized. If the same abnormality reoccurred a second time, after recovery the patients received a dose reduced by 50%. A third occurrence resulted in the patient being permanently withdrawn from the study. Patients who failed to keep scheduled appointments at the clinic or whose clinical conditions deteriorated to such an extent as to necessitate other therapy were also permanently withdrawn.

Statistical analysis

Categorical variables were compared with Fisher's exact test. The Wilcoxon test was used to compare the changes in the variables over time in the MTX group with those in the placebo group. Differences were calculated by intention-to-treat analysis (i.e. all patients were analysed in the group to which they were assigned) and by same drug treatment analysis. Ninety-five per cent confidence intervals were calculated. For changes within the MTX group, the sign rank test was used. P values of 0.05 or less were considered significant.

RESULTS

Patient characteristics

Fifty-seven patients were referred to participate in this trial. Twenty-eight of these patients either did not fulfil the inclusion criteria or were not included because of the exclusion criteria, thus leaving 29 patients who were enrolled in the study. Seventeen were allocated to MTX treatment and 12 to placebo treatment. This difference in numbers resulted from the fact that by mistake two patients in the MTX group were initially recorded as belonging to the placebo group. The error was discovered after breaking the code at the end of the study. Owing to this error, the number of patients with diffuse and limited cutaneous involvement is also different, although not statistically significant, in both groups. Tables I and II give the initial demographic, clinical and laboratory data of the two groups. The

TABLE I
Patient characteristics at study entry*

Variable	Methotrexate group ($n = 17$)	Placebo group ($n = 12$)
Age, mean ± S.D. yr (range)	52 ± 12 (32–75)	56 ± 11 (39–72)
Duration of cutaneous SSc, mean ± S.D. yr (range)	3.2 ± 6.3 (0.1–27)	3.2 ± 3.4 (0.6–12)
Sclerodematous skin distribution		
Diffuse	5 (29)	6 (50)
Limited	12 (71)	6 (50)
Male	7 (41)	2 (17)†
Raynaud's phenomenon	17 (100)	11 (92)
Duration of Raynaud's phenomenon mean ± S.D. yr (range)	3.5 ± 7.0 (0.4–30)	5.6 ± 9.5 (0.9–34)
Digital ulcers/scars	12 (70)	5 (42)
Autoantibodies		
ANA	15 (88)	11 (91)
Anti-TOPO	9 (53)	7 (58)
Anti-centromere	0	1 (9)
Anti-RNP	1 (6)	0
Rheumatoid factor	5 (29)	3 (25)
Prevalence of organ involvement		
Pulmonary	9 (53)	6 (50)
Cardiac	3 (18)	4 (33)
Renal	0	0
Oesophageal	15 (88)	10 (83)
Previous treatments		
Penicillamine	6 (35)	4 (33)
Prednisone	3 (18)	4 (33)
NSAIDs	5 (29)	1 (8)
Colchicine	1 (6)	0

SSc = systemic sclerosis; ANA = antinuclear autoantibodies; RF = rheumatoid factor; anti-TOPO = antitopoisomerase-I antibodies; anti-centromere = anticentromere antibodies; anti-RNP = antiribonucleoprotease antibodies.

*Values given are the number of patients and values in parentheses are percentages, unless otherwise indicated.

†$P = 0.32$ for differences between groups.

TABLE II
Clinical and laboratory variables: mean ± S.D. values at study entry

Variable	Baseline	
	MTX group ($n = 17$)	Placebo group ($n = 12$)
Total skin score	20.2 ± 11.0	20.7 ± 11.4
Extension index right (mm)	95.0 ± 12.2	88.4 ± 20.2
Extension index left (mm)	97.1 ± 15.0	95.1 ± 13.8
Grip strength right (mmHg)	88.7 ± 70.4	116.2 ± 56.0
Grip strength left (mmHg)	99.5 ± 77.1	121.8 ± 68.7
Oral opening (mm)	41.9 ± 9.3	38.7 ± 6.5
General health (0–100 mm VAS)	54.1 ± 18.0	56.1 ± 17.3
Organ involvement		
Lung		
Fibrosis (*N*, %)	5 (29)	5 (42)
TLC (% predicted)	87.2 ± 12.7	82.3 ± 16.9
VS (% predicted)	92.7 ± 18.0	86.1 ± 20.3
DL_{CO}	1.42 ± 0.25	1.45 ± 0.37
Cardiac (*N*, %)	3 (18)	4 (33)
Renal (*N*)	0	0
Creatinine clearance rate (ml/min)	77.9 ± 18.3	75.4 ± 13.5
Oesophageal (*N*, %)	15 (88)	10 (83)
Creatine phosphokinase (U/ml)	132.7 ± 135.4	53.5 ± 37.6†
ESR (Westergren, mm/h)	29.0 ± 20.1	22.4 ± 12.5
Haemoglobin (mmol/l)	8.1 ± 0.9	8.1 ± 0.6
WBC ($\times 10^9$/l)	8.4 ± 2.6	7.6 ± 1.0
Thrombocytes ($\times 10^9$/l)	349 ± 135	335 ± 66
IgA (g/l)	3.57 ± 1.81	2.74 ± 1.31
IgM (g/l)	1.46 ± 0.46	1.75 ± 0.97
IgG (g/l)	16.44 ± 4.35	14.66 ± 3.95
C3 (mg/l)	1227 ± 308	1328 ± 300
C4 (mg/l)	264 ± 91	263 ± 74
Circulating immune complexes (%)	3.1 ± 2.4	3.4 ± 2.8

MTX = methotrexate; VAS = visual analogue scale; TLC = total lung capacity; VS = vital capacity; DL_{CO} = diffusion capacity for carbon monoxide. See the text for definitions of organ involvement.
†$P = 0.04$ between methotexate- and placebo-treated patients.

duration of cutaneous involvement and the prevalence of Raynaud's phenomenon in the two groups were similar. Disease duration was < 1 yr for seven patients (41%) in the MTX group and four (33%) in the placebo group. Five patients receiving MTX (29%) and six patients receiving placebo (50%) were classified as having diffuse SSc. Digital ulcerations or pitting scars were present in 12 patients (70%) in the MTX group and in five (42%) in the placebo group. No autoantibodies other than antitopoisomerase-I, anticentromere and anti-RNP antibodies and rheumatoid factor could be detected. CPK values were significantly higher ($P = 0.04$) in the MTX group (Table II). There were no significant differences between the two groups with regard to internal organ involvement or previous treatment.

Response to treatment

Eight (53%) of the 15 patients in the MTX group who had completed the first 24 weeks had responded favourably after 24 weeks, whereas nine (90%) of the patients receiving placebo and completing the first 24 weeks did not respond favourably (Fig. 1). This difference is significant ($P = 0.03$). The power for this difference between the ratio of responders was 0.67. Power measurements for the mean difference in those numeric variables that were part of the response criterion were < 0.30 in each variable measured. The favourable response among the patients receiving MTX was due to improvement in TSS in three cases, to improvement in VAS in four and to improvement in both in one case. One patient whose VAS improved ⩾30% was classified as a non-responder, owing to a ⩾15% decrease in DL_{CO}. The patient who responded while undergoing placebo treatment had a ⩾30% reduction in TSS.

During the first 24 weeks of treatment, two patients in each treatment group had to be withdrawn from the study (see further). Two further patients, both of whom had been started on an increased dose of 25 mg MTX weekly, had to be withdrawn between weeks 24 and 48 (see further), leaving 23 patients to complete the trial. At week 48, of the nine patients who had been transferred from placebo to MTX treatment after the first 24 weeks, five had responded favourably with ⩾30% improvement in TSS. Two patients who had not responded to 15 mg MTX weekly during the first 24 weeks responded favourably to the increased dose of 25 mg with an improvement of ⩾30% in VAS. Thus, at week 48, of the 22 patients who had completed the trial and had been treated with MTX for at least 24 weeks, 15 (68%) responded favourably according to the pre-determined criteria.

Comparison of variables between groups after 24 weeks

The differences between the initial and week 24 values of the clinical and laboratory variables are shown in Table III for both groups. As there were no differences between the intention-to-treat analysis and same drug treatment analysis, only the results of the intention-to-treat analysis will be discussed. The following differences in improvement of clinical variables between the MTX- and placebo-treated patients were found: (a) TSS decreased in the MTX group and increased in the placebo group ($P = 0.06$); (b) VAS tended to improve in the MTX group and remained approximately the same in the placebo group ($P = 0.19$); (c) the creatinine clearance rate increased in the MTX group and decreased in the placebo group ($P = 0.07$). Differences between the groups with respect to laboratory variables consisted of a greater decrease of haemoglobin level in the placebo group ($P = 0.06$) and WBC count in the MTX group ($P = 0.003$). IgM and IgG concentrations also decreased more in the MTX group ($P = 0.06$ and $P = 0.09$, respectively).

Comparison of variables after 48 weeks of methotrexate treatment

The week 48 values were compared with the initial values of the patients treated with MTX throughout the trial. Improvements were found in VAS ($P = 0.08$) and grip strength of the right hand ($P = 0.04$, Table IV), which was dominant in all patients. The creatinine clearance rate tended to improve ($P = 0.06$). Other parameters concerning internal organs showed no change. Laboratory analysis demonstrated significant reductions in haemoglobin concentration ($P = 0.03$), WBC count ($P = 0.04$), thrombocyte count ($P = 0.02$), and concentrations of IgG ($P = 0.0002$) and C3 ($P = 0.02$).

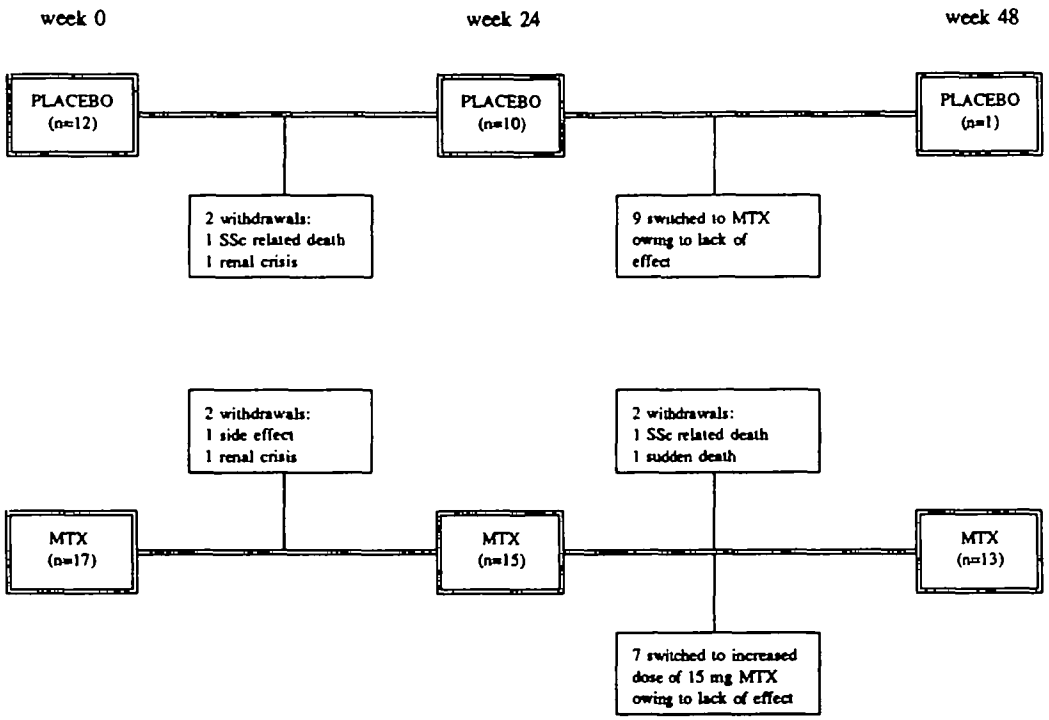

FIG. 1.—Course of the trial.

TABLE III

Clinical and laboratory variables: differences after 24 weeks of treatment between methotrexate- and placebo-treated groups, by intention-to-treat analysis

	MTX group (n = 17)	Placebo group (n = 12)	P, MTX *vs* placebo
Total skin score	−0.7 (−3.4, 2.1)*	1.2 (−1.2, 3.5)	0.06
Extension index right (mm)	−2.1 (−5.1, 0.1)	−1.2 (−2.8, 0.5)	0.43
Extension index left (mm)	−0.8 (−3.4, 1.7)	−0.3 (−2.6, 1.9)	0.44
Grip strength right (mmHg)	18.8 (−4.1, 41.7)	12.9 (−13.6, 39.4)	0.40
Grip strength left (mmHg)	−0.5 (−18.4, 17.5)	−2.8 (−15.5, 9.8)	0.37
Oral opening (mm)	−0.7 (−1.7, 0.4)	−0.2 (−2.1, 1.8)	0.34
General health (0–100 mm VAS)	4.5 (−7.1, 16.0)	−1.0 (−7.9, 5.9)	0.19
Organ involvement			
Lung			
Fibrosis (N, %)	5 (17)	4 (33)	0.50
TLC (% predicted)	−1.1 (−3.4, 1.3)	−0.5 (−2.2, 1.2)	0.43
VC (% predicted	−2.7 (−6.7, 1.4)	−1.7 (−4.9, 1.6)	0.37
DL_{CO}	−0.03 (−0.07, 0.00)	−0.01 (−0.08, 0.08)	0.48
Cardiac (N, %)	4 (15)	3 (25)	1.0
Renal (N)	0	0	
Creatinine clearance rate (ml/min)	4.0 (−0.6, 8.6)	−3.0 (−8.7, 2.7)	0.07
Oesophageal (N, %)	13 (77)	8 (67)	1.0
Creatine phosphokinase (U/ml)	−8.4 (−57.9, 41.1)	1.7 (−6.6, 9.9)	0.24
ESR (Westergren, mm/h)	−0.71 (−9.5, 8.1)	2.2 (−6.3, 10.7)	0.28
Haemoglobin (mmol/l)	−0.2 (−0.4, 0.1)	−0.4 (−0.8, −0.1)	0.06
White blood cell count ($\times 10^9$/l)	−1.2 (−2.1, −0.2)	1.0 (−0.3, 2.4)	< 0.01
Thrombocytes ($\times 10^9$/l)	−53 (−116, 10)	4.5 (−27, 36)	0.09
IgA (g/l)	−0.08 (−0.5, 0.3)	0.08 (−0.21, 0.37)	0.15
IgM (g/l)	−0.12 (−0.41, 0.17)	−0.05 (−0.23, 0.13)	0.06
IgG (g/l)	−1.40 (−2.40, −0.40)	−0.48 (−1.51, 0.55)	0.09
C3 (mg/l)	−122 (−245, 2)	−110 (−293, 74)	0.46
C4 (mg/l)	−0.7 (−44, 43)	13 (−19, 45)	0.42
Circulatory immune complexes (%)	0.07 (−1.43, 1.57)	0 (−1.47, 1.47)	0.44

MTX = methotrexate; VAS = visual analogue scale; TLC = total lung capacity; VC = vital capacity; DL_{CO} = diffusion capacity for carbon monoxide. See the text for definitions of organ involvement.

*Values in parentheses are 95% confidence intervals.

TABLE IV
Clinical and laboratory variables: differences with entry values after 48 weeks of methotrexate treatment, by intention-to-treat analysis

	MTX treatment ($n = 17$)	P, 48 week *vs* entry
Total skin score	−1.12 (−4.21, 1.97)*	0.22
Extension index right (mm)	−1.29 (−5.33, 2.74)	0.25
Extension index left (mm)	−0.77 (−4.08, 2.55)	0.31
Grip strength right (mmHg)	20.35 (−3.89, 44.60)	0.04
Grip strength left (mmHg)	6.00 (−15.25, 27.25)	0.28
Oral opening (mm)	−0.18 (−1.70, 1.35)	0.40
General health (0–100 mm VAS)	9.88 (−4.25, 24.02)	0.08
Organ involvement		
Lung		
TLC (% predicted)	−1.88 (−4.18, 0.43)	0.95
VC (% predicted)	−3.00 (−7.35, 1.35)	0.42
DL_{CO}	−0.03 (−0.11, 0.05)	0.29
Creatinine clearance rate (ml/min)	3.18 (−0.89, 7.25)	0.06
Creatine phosphokinase (U/ml)	−43.77 (−107.42, 19.89)	0.08
ESR (Westergren, mm/h)	−1.41 (−11.21, 8.38)	0.38
Haemoglobin (mmol/l)	−0.23 (−0.47, 0.01)	0.03
WBC ($\times 10^9$/l)	−0.97 (−2.13, 0.18)	0.04
Thrombocytes ($\times 10^9$/l)	−69.77 (−131.61, −7.92)	0.02
IgA (g/l)	0.04 (−0.41, 0.49)	0.43
IgM (g/l)	−0.16 (−0.39, 0.07)	0.08
IgG (g/l)	−1.76 (−2.70, −0.81)	< 0.01
C3 (mg/l)	−146 (−287, −5)	0.02
C4 (mg/l)	−10.06 (−50.02, 29.90)	0.30
Circulating immune complexes (%)	1.21 (−0.48, 2.91)	0.43

MTX = methotrexate; VAS = visual analogue scale; TLC = total lung capacity; VC = vital capacity; DL_{CO} = diffusion capacity for carbon monoxide. See the text for definitions of organ involvement.
*Values in parentheses are 95% confidence intervals.

Responders versus non-responders

Of the 15 patients who could be classified as responders at the end of the trial, eight achieved a ⩾30% improvement in TSS, six a ⩾30% improvement in VAS and one a ⩾30% improvement in both. The initial values and the differences between the week 48 values and the initial values of clinical and laboratory variables of responders compared with those of non-responders are shown in Table V. The difference between the two groups regarding disease duration was due to the presence of two patients with longstanding disease among the responders, but was not significant. Significantly more women than men responded favourably ($P = 0.05$). Antitopoisomerase-I antibodies seemed to be identified more frequently in the non-responders ($P = 0.06$). There were no further differences between responders and non-responders with respect to any of the other variables that were tested at study entry.

TABLE V
Characteristics of responders ($n = 15$) and non-responders ($n = 7$) to methotrexate therapy at study entry

	Responders	Non-responders
Age (yr, S.D.)	48.6 ± 8.2	53.5 ± 12.3
Disease duration (yr, S.D.)	2.4 ± 5.7	0.5 ± 0.5
Males (n, %)	2 (15)	5 (71)*
Diffuse (n, %)	6 (40)	2 (29)
Limited (n, %)	9 (60)	5 (71)
Antitopoisomerase-I antibodies	5 (33)	6 (86)†
Total skin score	18.6 ± 6.5	18.4 ± 9.0

For a definition of responders and non-responders, see the text.
*$P = 0.05$ and †$P = 0.06$ between responders and non-responders.

Diffuse and limited skin involvement, short and long disease duration

There were no significant differences between the changes that occurred among patients with diffuse skin involvement and those that occurred among patients with limited skin involvement, or between the changes that occurred among patients with disease duration of > 1 yr and those that occurred among patients with disease duration of < 1 yr (data not shown).

Withdrawals and adverse reactions

Withdrawals and adverse reactions are summarized in Table VI. One patient from the placebo group experienced a severe progression of cardiopulmonary and gastrointestinal manifestations of SSc, eventually accompanied by a renal crisis of which she died in week 10. Another patient receiving placebo had to be withdrawn in week 12, owing to renal failure due to scleroderma renal crisis. Two patients from the MTX group were also withdrawn: one in week 10 because of renal failure due to scleroderma renal crisis, which was successfully treated in the acute phase, but which left the patient with chronic renal failure; another because she suffered from persistent, severe headache after each injection. Two patients died between weeks 24 and 48: one patient died because of cardiorespiratory insufficiency caused by progressive pulmonary fibrosis; the other died suddenly, presumably because of acute myocardial infarction. Both patients had been receiving an increased dose of 25 mg MTX weekly. The patient who died of cardiorespiratory insufficiency had suffered shortly before from a pancytopenia. This pancytopenia had completely recovered after temporarily withholding MTX. Six patients receiving MTX experienced liver enzyme abnormalities characterized by elevated levels of AST and ALT. These normalized in 2–4 weeks after the trial medication had been withheld. None of these patients experienced reoccurrences of hepatic function abnormalities after resuming MTX. None of the patients in the placebo group experienced any adverse reaction that could be ascribed to the injections.

DISCUSSION

This study is the first double-blind, placebo-controlled study concerning MTX treatment in SSc. The design of this study was largely determined by the

TABLE VI
Adverse reactions, withdrawals and deaths during the study period

Patient	Sex	Age	Disease duration	Week	MTX		Placebo	Side-effects		Death
					15 mg	25 mg		Temporary withdrawal	Permanent withdrawal	
HH	F	48	2.9	12	x			liver		
NH	F	50	0.1	16	x			liver		
BM	F	55	5.1	36	x			liver		
LG	F	32	2.4	20	x			liver		
DA	M	68	0.6	36	x			liver		
RA	F	41	30.0	44	x			liver		
WE	M	63	0.4	26		x		pancytopenia		
TA	F	75	2.3	5	x				headache	
SC	M	52	0.8	10	x				renal crisis	
MO	F	71	12.4	16			x		renal crisis	
HP	F	67	0.9	36		x				sudden death
WE	M	63	0.4	28		x				SSc-related*
EL	F	68	0.8	6			x			SSc-related*

*SSc-related death, death caused by SSc-related cardiopulmonary and/or renal involvement.

findings of our pilot study [30], in which skin thickening was reversed within 6 months of the beginning of MTX therapy, and no further internal organ deterioration occurred. It was therefore felt that, because of the seriousness of SSc, a potentially beneficial treatment could not be withheld from patients in a placebo group for more than 6 months. Therefore an evaluation was made after 24 weeks, using response criteria that were defined prior to the start of the study. On the basis of this evaluation, patients remained either on the same drug regimen, changed from placebo to 15 mg MTX per week or had the MTX dosage increased from 15 to 25 mg weekly. Although these changes in therapy were blinded to the clinical investigator, it appeared at the end of the study, when the treatment code was broken, that only one patient had responded to placebo. Because of this fact, the initial set-up of this study as a 48-week double-blind placebo-controlled trial could not be fulfilled; the placebo-controlled double-blind part of this study therefore lasted 24 weeks, making the period between week 24 and 48 an observational study.

The rarity of SSc limits the number of patients available for trials, unless multicentre trials with multiobserver examinations are undertaken. However, multiobserver examinations are liable to diminish the reliability of TSS, which is the most important marker of disease progress. We chose one observer in this multicentre trial as TSS is at least as reliable in SSc as joint count is in rheumatoid arthritis, provided that it is evaluated serially by a single investigator [35].

The paucity of suitable disease variables makes it difficult to evaluate therapies for SSc. It was necessary to develop criteria for separating responders and non-responders. These employed a combination of TSS, VAS, DL_{CO} and the presence or absence of digital ulcers. The choice was based on findings reported in the literature and our own experience. Pope and Bellamy [36] recently reviewed the literature dealing with outcome measurements for treatments of scleroderma patients in clinical trials. They too concluded that skin score measurements and global assessment are the best primary outcome measures for clinical trials; good secondary measures include variables of internal organ involvement, mortality, functional assessment, and physical parameters such as grip strength and extension index. Although the number of patients included in this study was small, we found that significantly more patients responded favourably to MTX treatment than placebo after 24 weeks. Analysis of results at week 48 between the two groups could not be carried out since at week 24 all placebo-treated patients, except one, were switched to MTX treatment according to the study protocol. Analysis of MTX-treated patients at week 48, who completed the study, showed that 68% of the patients in the present study benefited from MTX treatment.

Low-dose MTX is suspected of impairing renal function, principally glomerular and tubular function, especially when it is used in combination with other nephrotoxic drugs [37, 38]. We found no reduction in renal function, as measured by creatinine clearance rate, as we observed in the pilot study. This may have been because only a few patients in the present study used potentially nephrotoxic drugs (non-steroidal anti-inflammatory drugs or cimetidine at a constant dose).

Only one patient had to be permanently withdrawn from the study because of side-effects (severe headache) attributable to MTX. MTX would therefore appear to be reasonably well tolerated and safe in low, weekly, i.m. dosages. The number of adverse reactions was relatively high, but in general minor and manageable. The occurrence of transient hepatic function disturbances in six patients and pancytopenia in one emphasizes the necessity of closely monitoring hepatic function tests and blood cell counts.

More patients whose serum was positive for antitopoisomerase-I antibodies and significantly more patients of male gender failed to respond to MTX therapy. The presence of antitopoisomerase-I anti-

bodies is also known to be associated with an unfavourable prognosis in SSc.

The dosage of 15 mg MTX weekly seemed to be sufficient for the majority of patients who responded favourably. A higher dose of 25 mg may be necessary in those cases in which it is not.

In spite of the small number of patients enrolled in this study, we could demonstrate that after 24 weeks a significantly larger number of SSc patients responded favourably to MTX compared to placebo treatment. Moreover, of all patients who received MTX for at least 24 weeks and completed the trial, 68% responded favourably to MTX therapy with reductions in skin thickness or improvements in general well-being and without further damage to internal organs after 48 weeks. Owing to the small number of patients involved in this study and the limited period of follow-up, long-term prospective trials examining efficacy and toxicity and randomized trials comparing MTX with, for example, D-penicillamine or cyclosporin, will determine the position of MTX therapy in the treatment of scleroderma.

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