

Comparison of the Clinical Efficacy and Safety of Subcutaneous Versus Oral Administration of Methotrexate in Patients With Active Rheumatoid Arthritis

Results of a Six-Month, Multicenter, Randomized, Double-Blind, Controlled, Phase IV Trial

J. Braun,¹ P. Kästner,² P. Flaxenberg,³ J. Währisch,³ P. Hanke,⁴ W. Demary,⁵ U. von Hinüber,⁵ K. Rockwitz,⁶ W. Heitz,⁷ U. Pichlmeier,⁸ C. Guimbal-Scholck,⁸ and A. Brandt,⁸ for the MC-MTX.6/RH Study Group

Objective. To compare the efficacy and safety of subcutaneous (SC) versus oral administration of methotrexate (MTX) in patients with active rheumatoid arthritis (RA).

Methods. MTX-naïve patients with active RA (Disease Activity Score in 28 joints ≥ 4) were eligible for the study if they had not previously taken biologic agents and had not taken disease-modifying antirheumatic drugs for 2 weeks prior to randomization. Patients were randomly assigned to receive 15 mg/week of MTX either orally (2 7.5-mg tablets plus a dummy prefilled syringe; n = 187 patients) or SC (prefilled syringe containing 10 mg/ml plus 2 dummy tablets; n = 188 patients) for 24 weeks. At week 16, patients who did not meet the American College of Rheumatology criteria for 20% improvement (ACR20) were switched from 15 mg of oral MTX to 15 mg of SC MTX and from 15 mg of SC MTX to 20 mg of SC MTX for the remaining 8 weeks, still in a blinded manner. The primary outcome was an ACR20 response at 24 weeks.

Results. At week 24, significantly more patients

treated with SC MTX than with oral MTX showed ACR20 (78% versus 70%) and ACR70 (41% versus 33%) responses. Patients with a disease duration ≥ 12 months had even higher ACR20 response rates (89% for SC administration and 63% for oral). In 52 of the ACR20 nonresponders (14%), treatment was switched at week 16. Changing from oral to SC MTX and from 15 mg to 20 mg of SC MTX resulted in 30% and 23% ACR20 response rates, respectively, in these patients. MTX was well tolerated. The rate of adverse events was similar in all groups.

Conclusion. This 6-month prospective, randomized, controlled trial is the first to examine oral versus SC administration of MTX. We found that SC administration was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability.

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with a prevalence of ~0.5–1% and an incidence of 25–50 cases/100,000 population, as recently reported (1–6). The burden of the disease is significant (7). After 5 years, one-half of RA patients have developed clinically important changes in health status (3). Thus, the socioeconomic costs of RA are quite high (8).

A variety of disease-modifying antirheumatic drugs (DMARDs) are used to control the clinical activity of RA (9). Methotrexate (MTX), a derivative of folic acid and aminopterin, is the most commonly used and most commonly recommended DMARD for the treatment of RA (10,11). Because of its favorable efficacy to

Supported by medac GmbH.

¹J. Braun, MD: Rheumazentrum Ruhrgebiet, Herne, Germany; ²P. Kästner, MD: Erfurt, Germany; ³P. Flaxenberg, MD, J. Währisch, MD: Essen, Germany; ⁴P. Hanke, MD: Halle, Germany; ⁵W. Demary, MD, U. von Hinüber, MD: Hildesheim, Germany; ⁶K. Rockwitz, MD: Goslar, Germany; ⁷W. Heitz, MD: Cologne, Germany; ⁸U. Pichlmeier, PhD, C. Guimbal-Scholck, PhD, A. Brandt, PhD: medac GmbH, Wedel, Germany.

Address correspondence and reprint requests to J. Braun, MD, Rheumazentrum Ruhrgebiet, Landgrafenstrasse 15, 44652 Herne, Germany. E-mail: J.Braun@rheumazentrum-ruhrgebiet.de.

Submitted for publication January 30, 2007; accepted in revised form September 28, 2007.

toxicity ratio, MTX is currently prescribed to at least 500,000 RA patients worldwide. The efficacy of MTX monotherapy is not much different from that of monotherapy with the tumor necrosis factor (TNF) blockers etanercept (12) and adalimumab (13) in clinical studies.

MTX was originally developed as a folate antagonist for the treatment of cancer. The mechanism of action of low-dose MTX in RA is still unknown. Several mechanisms have been proposed (14), including inhibition of T cell proliferation due to the effects of MTX on purine and pyrimidine metabolism, inhibition of transmethylation reactions required for the prevention of T cell cytotoxicity, interference with glutathione metabolism leading to alterations in recruitment of monocytes and other cells to the inflamed joint, and promotion of the release of the endogenous antiinflammatory mediator adenosine (14). Among several genetic polymorphisms that possibly predict response to MTX, the most frequently studied are those of methylenetetrahydrofolate reductase (MTHFR) and thymidylate synthase genes (14). Thus, the MTHFR 1298AA and 677CC alleles were associated with greater clinical improvement in patients taking MTX therapy, whereas only the MTHFR 1298C allele was associated with toxicity (15).

The pharmacokinetics of MTX has been studied extensively (16–21). Serum and synovial fluid concentrations of MTX are approximately equal (19). Food intake reduces the peak concentration and slightly increases the time to peak concentration of MTX (20). The bioavailability of higher oral doses of MTX in adult patients with RA is highly variable and, on average, is two-thirds that of subcutaneous (SC) or intramuscular (IM) administration (16–20). Although it is known that parenteral administration of MTX results in better and reliable bioavailability, it remains unclear whether this results in superior clinical efficacy and safety (21). Some studies, however, have suggested that IM MTX showed improved clinical efficacy with fewer side effects compared with oral MTX (22–24). In 1 study, 16% of patients experienced a relapse of RA after switching from parenteral to oral MTX treatment (22). RA manifestations were reported to be improved and side effects reduced by switching from oral to parenteral administration in most patients (23–27). The possibility of self injection is a potential advantage of SC versus IM administration of MTX. The excellent tolerability of SC injection of MTX has recently been demonstrated (medac, Wedel, Germany: unpublished observations).

Some patients cannot tolerate MTX (28); this can be explained by interference of the drug with folate and homocysteine metabolism (29). Low-dose folic acid supplementation has been shown to prevent or diminish the

influence of MTX on folate status and has demonstrated a protective effect on MTX-induced liver toxicity (30,31). However, there is limited evidence that the addition of folic acid decreases the efficacy of MTX (32,33). It has recently been proposed that 5 mg of folic acid, to be taken orally on the day following MTX administration, should routinely be prescribed for all patients receiving this drug for the treatment of RA (31), but this approach has not necessarily been adopted worldwide.

Taken together, there is strong evidence that MTX is the standard DMARD therapy for patients with RA. However, it is not clear which route of administration is the best. The aim of the present study was to directly compare the clinical efficacy and safety of SC versus oral administration of MTX in patients with active RA.

PATIENTS AND METHODS

Patients. Patients with RA diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria (34) were enrolled at 29 centers in Germany between November 20, 2003 and July 28, 2005. Patients were eligible for enrollment if they were 18–75 years of age and presented with active disease, as defined by a Disease Activity Score in 28 joints (DAS28) ≥ 4 (35) at baseline and had never been treated with MTX prior to randomization. Treatment with biologic agents was not allowed before or during the study. Treatment with other DMARDs had to be discontinued for ≥ 2 weeks prior to randomization (leflunomide ≥ 4 weeks) and during the study period. Systemic corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) were permitted if the dosages were stable for at least 2 weeks before randomization and until the end of the study and if the corticosteroid dosage did not exceed 10 mg/day.

Intraarticular injections of corticosteroids and prophylaxis against possible adverse events (AEs) (i.e., antiemesis) were not allowed during the study. Other exclusion criteria were impaired renal function or hematopoiesis; history of severe liver disease or elevated transaminase levels; known clinically relevant pulmonary disease; severe, acute, or chronic infectious diseases, such as hepatitis B or C virus, tuberculosis, or human immunodeficiency virus; and ulcers of the oral cavity and known ulcers of the gastrointestinal tract within 6 months prior to randomization. Patients with current or recent alcohol or drug abuse, extensive consumption of caffeine, and women who were pregnant or breastfeeding were also excluded from the study.

Familiarity with self-administration of SC medicine was ensured by confirmed training of the patients with the use of placebo syringes before randomization into the study.

The study was performed in accordance with the Declaration of Helsinki. All participating centers received approval from their ethics committees, and all patients provided written informed consent.

Study protocol. This was a 6-month, multicenter, randomized, double-blind, controlled, 2-arm, phase IV trial. Permuted block randomization stratified by study center was

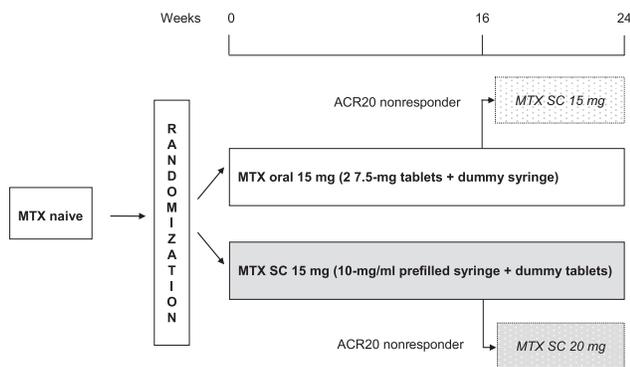


Figure 1. Design of the 6-month, multicenter, randomized, double-blind, controlled clinical trial evaluating the efficacy of subcutaneous (SC) administration of methotrexate (MTX) compared with oral administration of MTX in the treatment of patients with active rheumatoid arthritis. The primary efficacy end point was achievement of a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) at 24 weeks. At week 16, patients who did not meet the ACR20 criteria were switched from 15 mg of oral MTX to 15 mg of SC MTX and from 15 mg of SC MTX to 20 mg of SC MTX for the remaining 8 weeks of study.

applied to randomize patients in a 1:1 ratio to 1 of 2 treatment groups: 15 mg of SC MTX (1 prefilled syringe containing 15 mg of MTX [10-mg/ml preparation] plus 2 placebo tablets) or 15 mg of oral MTX (2 7.5-mg tablets of MTX plus 1 prefilled syringe containing placebo) to be taken once a week. Both groups received 5 mg of folic acid 24 hours after the MTX dose.

At week 16, patients who did not meet the ACR criteria for 20% improvement (ACR20) (36) were switched from their initial treatment to the following: from 15 mg of oral MTX to 15 mg of SC MTX, and from 15 mg of SC MTX to 20 mg of SC MTX. This regimen was continued for the remaining 8 weeks, and study blinding was maintained (Figure 1).

Clinical and safety assessments (ACR disease activity measures and recording of AEs) were performed at baseline, at week 4, then every 2 weeks through week 12, and at week 16 and week 24. Additional safety assessments were performed at weeks 1, 2, 3, and 20.

Observation bias was avoided by study randomization and blinding. Neither the patients, the investigators, nor the persons responsible for randomization, data monitoring, or statistical analyses knew the assignment of the patient to the 2 treatment arms until the official unblinding. Because of the different modes of application, the so-called double-dummy technique was used. The dummy tablets were visually indistinguishable from the MTX tablets. But, for technical reasons, the dummy prefilled syringes could not be made visually indistinguishable from the MTX prefilled syringes. In order to make the color difference between the placebo and the MTX solutions less apparent, a large transparent yellow label was applied to the body of the syringe. Nevertheless, it was assumed that since the patients were MTX-naïve, this would not influence their study blinding. To ensure blinding of the investigators and monitors, these persons were prevented from seeing or having contact with the prefilled syringes during

the course of the study. At each study center, a designated person who was independent of the study investigator was responsible for management of the trial medication (receipt, dispensing, documentation, and return) as well as contact with the patients concerning matters related to the trial medication. Moreover, the syringes were sealed into white cartons, and patients were given cartons with unbroken seals. To ensure blinding of the trial monitor, drug accountability data were checked onsite by a different person.

With the above-mentioned exception for ACR20 nonresponders at week 16, no other dosage modifications of the study medication were permitted during the study. Drugs causing folate deficiency (e.g., sulfonamides) were prohibited during the study.

Assessment of efficacy. The primary end point was the percentage of patients with an ACR20 response at week 24, defined as at least 20% improvement from baseline values in the swollen joint count and the tender joint count, as well as the other 5 disease activity measures that constitute the ACR improvement criteria (36): the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, the physician's global assessment of disease activity (using a 0–100-mm visual analog scale, where 0 = no disease activity and 100 = greatest disease activity imaginable), the patient's global assessment of disease activity (using a 0–100-mm visual analog scale, where 0 = no disease activity and 100 = greatest disease activity imaginable), the patient's assessment of pain (0–100-mm visual analog scale, where 0 = no pain and 100 = greatest pain imaginable), and the patient's assessment of disability (using the disability index of the Health Assessment Questionnaire [HAQ]). Secondary end points included ACR50 and ACR70 responses (50% and 70% improvement from baseline according to ACR criteria, respectively).

Assessment of safety. A secondary objective of the trial was to compare the tolerability of SC versus oral MTX administration during the 6 months of treatment. All patients who received at least 1 dose of study medication (safety analysis set) were evaluated for the occurrence of AEs, serious AEs (SAEs), discontinuations due to AEs, and clinical laboratory test abnormalities.

Statistical analysis. Sample size estimation was based on the expectation of detecting a difference in the percentage of patients with an ACR20 response in the SC MTX and in the oral MTX groups. The test statistics for evaluating the primary target criterion was the chi-square test. The 2-tailed significance level was set at 5%. The power of the statistical test was fixed at 80%. Based on these assumptions, 180 patients were to be enrolled in each treatment arm. Assuming that ~5% of the patients would not fulfill the criteria for the full analysis set, we planned for a total of 380 patients to be randomized. Efficacy analyses were performed in the full analysis set, which comprised all randomized patients who received at least 1 dose of study treatment and had at least 1 documented efficacy evaluation at least 2 weeks after randomization. The patients in the full analysis set were analyzed according to the intent-to-treat principle in their initial randomization group.

The confirmatory statistical analysis of the primary efficacy criterion (ACR20 response) consisted of comparing the proportions of successful responses between the treatment arms, applying the Cochran-Mantel-Haenszel chi-square test, with adjustment for study centers. Mantel-Haenszel estimates

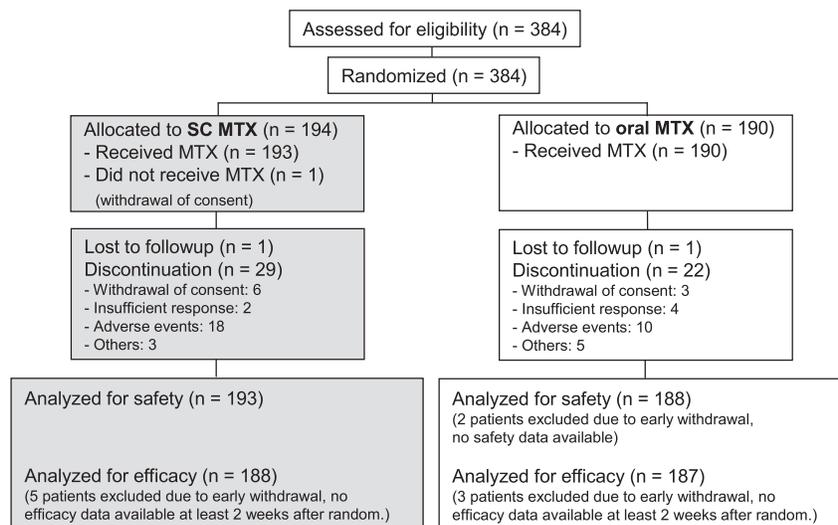


Figure 2. Disposition of the study patients from randomization to week 24. Patients with rheumatoid arthritis were randomized to receive 15 mg of methotrexate (MTX), which was administered either subcutaneously (SC) or orally.

of common relative risks and their associated 95% confidence intervals were calculated for nonparametric assessment of the overall treatment effect, with adjustment for study centers. For statistical analysis of ACR50 and ACR70 response rates, the statistical methods were the same as those used for the primary efficacy criterion.

For patients who withdrew prematurely from the study, the last value recorded for the associated efficacy parameter was carried forward for statistical analysis (i.e., the last observation carried forward method); that is, missing data were replaced with the value for the last available measurement obtained prior to the missing value. Only postbaseline values were allowed to be carried forward. Because of the specific feature of the study design requiring a switch of treatment in ACR20 nonresponders at the week 16 visit, the efficacy results at 16 weeks in these patients were carried forward in order to guarantee unbiased estimation of the overall treatment effect at 24 weeks after randomization. Statistical analyses were performed using the SAS statistical software package (SAS Institute, Cary, NC).

RESULTS

Characteristics of the study patients. A total of 384 patients were enrolled in the study: 194 in the subcutaneous MTX group and 190 in the oral group (Figure 2). Nine patients (6 taking SC and 3 taking oral MTX) were excluded from the efficacy analysis. One of these 9 patients was not exposed to study drug. The other 8 patients received the study drug at least once, but discontinued the study very early, at least 2 weeks after the start of therapy, without any documented efficacy assessments. Reasons for discontinuation were

patient request in 4, protocol deviation in 2, and lost to followup in 2. Thus, 188 patients in the SC group and 187 in the oral group were included in the analysis of clinical efficacy, and 193 and 188 patients, respectively, were included in the analysis of safety.

There were no clinically relevant differences in demographic and clinical characteristics at baseline between the treatment groups (Table 1). The median age of all subjects was 59 years. Approximately 75% of patients were women, and the median time between the diagnosis of RA according to the ACR criteria and randomization into the study was 2.1–2.5 months, indicating that the majority of patients were a population with very early RA. Corresponding to the short interval between diagnosis and start of the trial, most patients (75%) had not received any DMARD treatment prior to the study, but instead received NSAIDs or/and steroids. Approximately 20% of the population had failed to respond to treatment with 1 DMARD, and 5% had failed to respond to 2 or more DMARDs. Sulfasalazine was the DMARD most often prescribed (~14% of the patient population). Hydroxychloroquine had been prescribed for 8% of the patients before the study, and leflunomide had been prescribed for 6% of the patients in the SC MTX group and 2% in the oral MTX group. The median DAS28 was 6.1 and 6.3, respectively, indicating high levels of disease activity in both groups of patients. The majority of patients (62%) were rheumatoid factor positive at baseline.

Table 1. Baseline characteristics of the study patients, by treatment group*

	SC MTX (n = 188)	Oral MTX (n = 187)
Demographic characteristics		
Sex, % female	79	74
Age, median (range) years	58 (20–75)	59 (22–75)
Body weight, median (range) kg	73 (45–126)	75 (47–147)
Time since RA diagnosis, median (range) months	2.5 (0–535)	2.1 (0–293)
% taking concomitant steroids	71	67
% taking concomitant NSAIDs	62	64
No. of previous DMARDs taken, median (range)	0 (0–4)	0 (0–3)
% receiving no previous DMARDs	75	75
% receiving only 1 previous DMARD	18	20
% RF positive	66	59
Clinical characteristics		
Tender joint count (68 assessed), median (range)	23 (4–68)	24 (3–68)
Swollen joint count (66 assessed), median (range)	14 (1–58)	16 (2–58)
DAS28, median (range)	6.1 (3.9–8.8)	6.3 (4.0–8.7)
HAQ score, median (range)	1.25 (0–2.88)	1.38 (0–2.88)
CRP, median (range) mg/liter	8.6 (0–126)	11.6 (0–260)
ESR, median (range) mm/hour	24 (1–120)	28 (2–103)
Patient’s assessment of disease activity, median (range)	58 (6–92)	62 (2–100)
Patient’s assessment of pain, median (range)	63 (0–98)	66 (2–100)
Physician’s assessment of disease activity, median (range)	57 (19–97)	60 (12–95)

* Rheumatoid arthritis (RA) patients were randomized to receive subcutaneous (SC) or oral methotrexate (MTX) therapy. A 0–100-mm visual analog scale was used for the patient’s assessment of disease activity and pain and for the physician’s assessment of disease activity. NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire (disability index); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Clinical efficacy of SC versus oral administration of MTX. At 24 weeks, the percentage of patients with an ACR20 response was significantly higher in the group receiving SC MTX (78%) than in the group receiving oral MTX (70%) ($P < 0.05$) (Figure 3). ACR20 response rates over time showed a statistically significant separation between SC and oral therapy beginning as early as week 16 (85% of those receiving SC MTX versus 77% of those receiving oral MTX; $P < 0.05$).

The percentage of patients achieving an ACR70 response at week 24 was also higher in patients receiving SC MTX than in those receiving oral MTX (41% versus 33%; $P < 0.05$) (Figure 3). No statistically significant difference was found between the proportion of patients achieving an ACR50 response at week 24 (62% of the SC group versus 59% of the oral group).

At week 24, the number of swollen joints was lower in the SC group than in the oral group (2 versus 3; $P = 0.04$), as was the number of tender joints (3.5 versus 6; $P = 0.08$). The median HAQ score was slightly lower in the SC group compared with the oral group at week 24 (0.4 versus 0.5), but the difference was not significant. The median DAS28 was also lower in the SC group than in the oral group (3.3 versus 3.7) after 24 weeks.

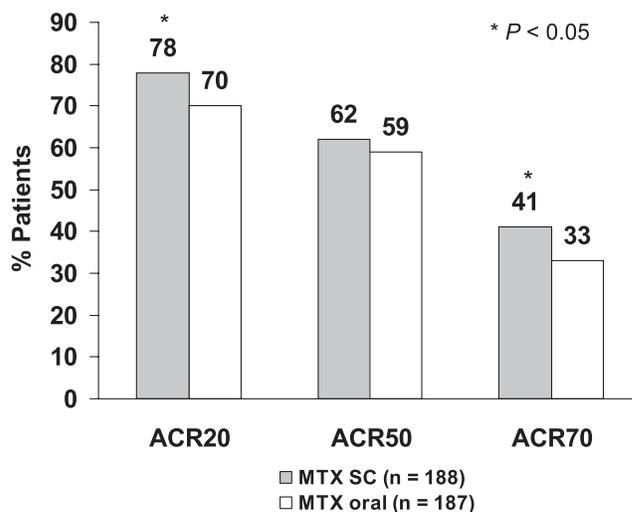


Figure 3. Percentages of patients achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70) at week 24 (full analysis set). The ACR20 and ACR70 responses in patients taking subcutaneous (SC) methotrexate (MTX) were significantly different from those in patients taking oral MTX. Numbers across the tops of the bars are the percentages represented by the bars.

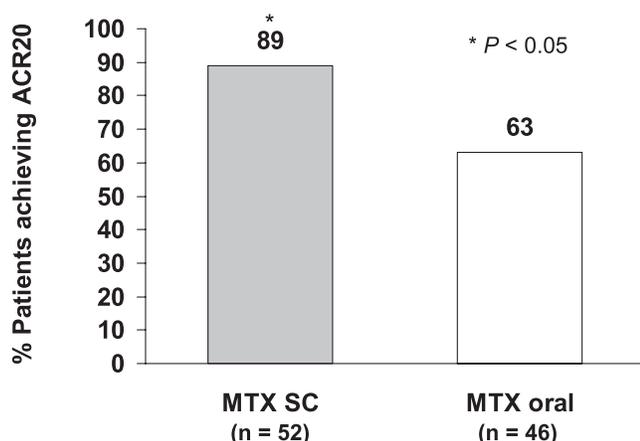


Figure 4. Percentages of patients with a time between diagnosis and study entry of ≥ 1 year who achieved a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) at week 24 (full analysis set). The ACR20 response in patients taking subcutaneous (SC) methotrexate (MTX) was significantly different from that in patients taking oral MTX. Numbers across the tops of the bars are the percentages represented by the bars.

The percentage of ACR20 responders was stratified by disease duration. The largest subgroup analyzed ($n = 206$) included patients with disease duration of < 3 months at study entry, which reflects the trend for German rheumatologists to treat RA patients early. Patients with a disease duration of 3–6 months and 6–12 months at study entry each represented $\sim 10\%$ of the study patients.

Another subgroup we analyzed consisted of patients with a time between diagnosis and study entry of ≥ 1 year who had received prior DMARDs or steroids ($n = 98$). In this subgroup, the difference in the percentage of ACR20 responders in the oral (63%) and SC (89%) MTX groups was even greater than in the entire study population ($P < 0.05$) (Figure 4). Furthermore, in this group of patients, the time to achieve an ACR20 response tended to be 2 weeks shorter in those receiving SC MTX (4 weeks) than in those receiving oral MTX (6 weeks) ($P = 0.067$).

At week 16, only 52 patients (14%) were classified as ACR20 nonresponders, and their medication was consequently switched according to the study protocol. Changing the MTX route of administration from 15 mg orally to 15 mg SC was associated with an ACR20 response in another 30% of the patients, and changing the dosage of SC MTX from 15 mg to 20 mg was associated with an ACR20 response in another 23% of the patients (Figure 5).

Safety of SC versus oral administration of MTX.

Overall, 66% of SC MTX-treated patients reported an adverse event during the study, as compared with 62% of

oral MTX-treated patients (Table 2). The percentage of patients reporting an at least moderate AE was identical in the 2 treatment groups (41%). The majority of AEs was rated by the investigator as being possibly related to the study drug (53% for SC MTX versus 48% for oral MTX). Similar percentages of patients in the 2 groups had SAEs (5.7% in the SC group versus 4.3% in the oral group). With the exception of 1 case of pneumonitis (reported as being possibly a study drug-related SAE) in the group taking SC MTX, all other SAEs were rated as being unrelated to the study medication. No life-threatening AEs and no deaths occurred during the study. More patients in the SC MTX group than in the oral MTX group withdrew because of AEs.

The frequencies of moderate or severe AEs reported at a $\geq 3\%$ incidence were higher in patients treated with oral MTX (Table 2). Diarrhea was also reported more often in patients treated with oral MTX (6.9% versus 2.6% for SC MTX), while the frequency of reported loss of appetite was higher in the SC MTX group (7.3% versus 3.2% for oral MTX).

DISCUSSION

This trial is the first to systematically investigate the optimal administration of MTX in patients with active RA. It should be emphasized that in this trial, the

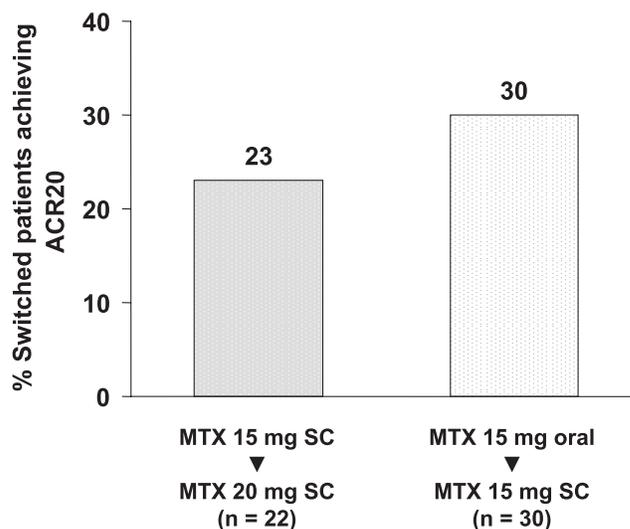


Figure 5. Percentages of patients achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) at week 24 who had been ACR20 nonresponders at week 16. Patients who did not meet the ACR20 criteria at week 16 were switched from 15 mg of oral methotrexate (MTX) to 15 mg of subcutaneous (SC) MTX and from 15 mg of SC MTX to 20 mg of SC MTX for the remaining 8 weeks of study (full analysis set). Numbers across the tops of the bars are the percentages represented by the bars.

Table 2. Summary of adverse events during the study (safety analysis set)*

	No. (%) of patients receiving SC MTX (n = 193)	No. (%) of patients receiving oral MTX (n = 188)
Adverse events		
Any adverse event	128 (66)	116 (62)
At least a moderate adverse event	79 (41)	77 (41)
Adverse event possibly related to study drug	102 (53)	90 (48)
Serious adverse event	11 (5.7)	8 (4.3)
Adverse event leading to withdrawal	18 (9.3)	8 (4.3)
At least moderate adverse events reported at a $\geq 3\%$ incidence		
Gastrointestinal		
Abdominal pain	17 (8.8)	20 (10.6)
Diarrhea	5 (2.6)	13 (6.9)
Dyspepsia	13 (6.7)	11 (5.9)
Loss of appetite	14 (7.3)	6 (3.2)
Nausea	32 (16.6)	23 (12.2)
Stomatitis	6 (3.1)	7 (3.7)
Vomiting	7 (3.6)	6 (3.2)
Increased alanine aminotransferase	3 (1.6)	8 (4.3)
Bronchitis	4 (2.1)	7 (3.7)
Headache	4 (2.1)	8 (4.3)
Nasopharyngitis	9 (4.7)	10 (5.3)

* Methotrexate (MTX) was administered subcutaneously (SC) or orally.

rate of response to MTX in patients with a rather early stage of disease, irrespective of the route of administration, was impressive. Therefore, although the response rate was not optimal (i.e., 100% remission was not achieved), MTX is largely considered to be the drug of first choice in RA. Recent studies directly comparing MTX with TNF blockers as monotherapy (12,13) have even more strongly established MTX as the gold standard of RA therapy.

Against that background, our main reason for conducting the present study was to determine whether the known differences in bioavailability of oral versus parenteral MTX therapy are clinically relevant. A study of the pharmacokinetics of MTX showed that the bioavailability of oral MTX is lower than that of SC MTX (area under the curve [0–48 hours] 2,466 hours \cdot $\mu\text{g/liter}$ versus 3,786 hours \cdot $\mu\text{g/liter}$) but is associated with higher variability (calculated coefficient of variation 32% versus 23%) (18).

Our data indicate that SC administration is indeed associated with a larger proportion of patients achieving an ACR response. This may suggest that SC administration is especially useful in patients with active disease (DAS28 ≥ 4), as in our study population. We found that when SC MTX therapy was begun at the widely used starting dosage of 15 mg/week, ACR20 response rates as high as 80% were achievable. In addition, exploratory analyses showed that in patients with a somewhat longer disease duration, and thus, early but more established disease, this rate was even higher (nearly 90%). Whether this can be explained by similar

mechanisms, as in a previous study of very early RA and undifferentiated arthritis (37), is unclear.

Our observations suggest that initiation of MTX therapy by the SC route, using a possible dosage of 15 mg/week for a period of at least 24 weeks (including a possible dosage increase), is superior to initiation of MTX therapy by the oral route, since the ACR20 response rate of 60%, which is typically obtained with oral MTX (12,13), was increased to 78% in patients taking SC MTX. One possible explanation for this difference is that the ethnic background of the populations in the other studies (12,13) was more heterogeneous.

Previous studies have already suggested that in patients with poor compliance, inadequate effectiveness, and/or gastrointestinal side effects of MTX, a switch from the oral route of administration to IM or SC administration should be considered (22–25). Juvenile patients in whom oral MTX has failed, either because of inefficacy or toxicity, were found to have a high likelihood of success with the use of SC MTX, with >70% of patients achieving clinically significant improvement while taking SC MTX (38). In contrast, switching from parenteral to oral MTX led to a loss of response or a decline in the response in a large proportion of patients in another study (22). A second course of MTX via the parenteral route in these patients resulted in a lower response rate as compared with the first course of parenteral MTX. Thus, a switch from parenteral to oral MTX and then back to parenteral MTX seems to result in a loss of efficacy (22). In our study, the switch from oral to SC MTX and the switch from a lower dosage of

SC MTX to a higher dosage of SC MTX were both effective in 30% and 23% of patients, respectively. Switching from oral to SC administration and increasing the SC dosage led to an increase in the percentage of patients who achieved an ACR20 response.

Investigators in Canada and the UK have shown that changing from oral to parenteral administration of MTX in patients with an inadequate response is also advantageous for cost-effectiveness reasons, since subsequent therapy with biologic agents can be avoided or delayed (23,38,39). Nevertheless, patients who are unresponsive to MTX are suitable candidates for therapy with biologic agents (40). The cost of oral versus SC administration of MTX differs from country to country, and no direct socioeconomic comparison has yet been published.

The superior clinical efficacy of SC administration of MTX in this study was not accompanied by a significantly higher rate of AEs, although withdrawal of study medication was seen more often in the SC MTX group than in the oral MTX group. Overall, even the gastrointestinal AEs were similar between the 2 routes of MTX administration. This was rather unexpected, since in other studies, patients have been shown to benefit from parenteral administration of MTX, particularly with regard to the number of gastrointestinal AEs (24,37,41–45). Nevertheless, the increased efficacy with SC MTX that was seen in our study was not counterbalanced by an increased rate of AEs.

Our findings from the present study showed that SC administration of MTX is significantly more effective than oral administration of MTX at the same dosage, with no increase in side effects. The results of our study support the use of MTX as monotherapy in patients with RA, being the best of the currently available monotherapies for this condition.

ACKNOWLEDGMENTS

The authors wish to thank all of the patients who participated in the trial and all of the rheumatologists and nursing staffs of the participating centers who enrolled at least 1 patient in the study: P. Kästner (Erfurt), P. Flaxenberg and J. Währisch (Essen), P. Hanke (Halle), W. Demary and U. von Hinüber (Hildesheim), K. Rockwitz (Goslar), W. Heitz (Cologne), R. Alten (Berlin), J. Braun (Herne), G. Fliedner and G. Gauler (Osnabrück), L. Meier (Hofheim/Taunus), G. Kramer (Remscheid), G. Wessel (Erfurt), O. Ditrich and U. Mauß-Etzler (Karlsruhe), J. Wollenhaupt (Hamburg), E. Edelmann (Bad Aibling), F. Mielke (Berlin), K. Babinsky (Halle), K. Krüger (Munich), A. Gause and H. Körber (Elms-horn), I. Gao (Heidelberg), T. Schewe (Munich), A. Krause (Berlin), H. Lang (Plauen), T. Linde (Halle), S. Jacki (Tübingen), E. Röther (Villingen-Schwenningen), C. Specker

(Essen), W.-D. Wörth (Wiesbaden), and T. Schuart (Winsen). The authors also wish to thank Sonja Böhm, PhD (medac GmbH), for excellent monitoring of the study.

AUTHOR CONTRIBUTIONS

Dr. Braun had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Braun, Pichlmeier, Guimbal-Schmolck, Brandt.

Acquisition of data. Braun, Kästner, Flaxenberg, Währisch, Hanke, Demary, von Hinüber, Rockwitz, Heitz.

Analysis and interpretation of data. Braun, Pichlmeier, Guimbal-Schmolck, Brandt.

Manuscript preparation. Braun, Pichlmeier, Guimbal-Schmolck, Brandt.

Statistical analysis. Braun, Pichlmeier.

ROLE OF THE STUDY SPONSOR

The study was sponsored by medac Gesellschaft für klinische Spezialpräparate mbH; medac was involved in the design of the study and was responsible for data collection and statistical analysis.

REFERENCES

1. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk arthritis register. *Br J Rheumatol* 1994; 33:735–9.
2. Kvien TK, Glennas A, Knudrod OG, Smedstad LM, Mowinckel P, Forre O. The prevalence and severity of rheumatoid arthritis in Oslo: results from a county register and a population survey. *Scand J Rheumatol* 1997;26:412–8.
3. Uhlig T, Kvien TK, Glennas A, Smedstad LM, Forre O. The incidence and severity of rheumatoid arthritis: results from a county register in Oslo, Norway. *J Rheumatol* 1998;25:1078–84.
4. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778–99.
5. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27:269–81.
6. Savolainen E, Kaipiainen-Seppänen O, Kroger L, Luosujarvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. *J Rheumatol* 2003;30:2460–8.
7. Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A, for the German Collaborative Arthritis Centres. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. *Ann Rheum Dis* 2006;65:1175–83.
8. Zink A, Braun J, Listing J, Wollenhaupt J, and the German Collaborative Arthritis Centres. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis—results from the German rheumatological database. *J Rheumatol* 2000;27:613–22.
9. Zink A, Listing J, Niewerth M, Zeidler H, for the German Collaborative Arthritis Centres. The national database of the German Collaborative Arthritis Centres. II. Treatment of patients with rheumatoid arthritis. *Ann Rheum Dis* 2001;60:207–13.
10. Rau R, Herborn G. Benefit and risk of methotrexate treatment in rheumatoid arthritis. *Clin Exp Rheumatol* 2004;22 Suppl 35: S83–94.
11. Pavy S, Constantin A, Pham T, Gossec L, Maillefert JF, Cantagrel A, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine* 2006;73:388–95.

12. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443–50.
13. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.
14. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. *Pharmacol Rev* 2005;57:163–72.
15. Wessels JA, de Vries-Bouwstra JK, Heijmans BT, Slagboom PE, Goekoop-Ruiterman YP, Allaart CF, et al. Efficacy and toxicity of methotrexate in early rheumatoid arthritis are associated with single-nucleotide polymorphisms in genes coding for folate pathway enzymes. *Arthritis Rheum* 2006;54:1087–95.
16. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol* 1993;20:1845–9.
17. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. *Br J Rheumatol* 1997;36:86–90.
18. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol* 2004;31:645–8.
19. Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. *J Pharm Sci* 1989;78:165–71.
20. Oguey D, Kolliker F, Gerber NJ, Reichen J. Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 1992;35:611–4.
21. Lafforgue P, Monjanel-Mouterde S, Durand A, Catalin J, Acquaviva PC. Lack of correlation between pharmacokinetics and efficacy of low dose methotrexate in patients with rheumatoid arthritis. *J Rheumatol* 1995;22:844–9.
22. Rozin A, Schapira D, Balbir-Gurman A, Braun-Moscovici Y, Markovits D, Militianu D, et al. Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate. *Ann Rheum Dis* 2002;61:756–7.
23. Bingham SJ, Buch MH, Lindsay S, Pollard A, White J, Emery P. Parenteral methotrexate should be given before biological therapy. *Rheumatology (Oxford)* 2003;42:1009–10.
24. Wegrzyn J, Adeleine P, Miossec P. Better efficacy of methotrexate given by intramuscular injection than orally in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004;63:1232–4.
25. Breslin A, Owen C. Improving tolerance and bioavailability of methotrexate by switching from oral to subcutaneous route of administration [abstract]. *Rheumatology (Oxford)* 2005;44 Suppl 1:i150.
26. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose escalation of parenteral methotrexate in active rheumatoid arthritis that has been unresponsive to conventional doses of methotrexate: a randomized, controlled trial. *Arthritis Rheum* 2004;50:364–71.
27. Linde L, Hetland ML, Ostergaard M. Drug survival and reasons for discontinuation of intramuscular methotrexate: a study of 212 consecutive patients switching from oral methotrexate. *Scand J Rheumatol* 2006;35:102–6.
28. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. *Rheumatology (Oxford)* 2005;44:61–6.
29. Hornung N, Ellingsen T, Stengaard-Pedersen K, Poulsen JH. Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. *J Rheumatol* 2004;31:2374–81.
30. Van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001;44:1515–24.
31. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004;43:267–71.
32. Bressolle F, Kinowski JM, Morel J, Pouly B, Sany J, Combe B. Folic acid alters methotrexate availability in patients with rheumatoid arthritis. *J Rheumatol* 2000;27:2110–4.
33. Khanna D, Park GS, Paulus HE, Simpson KM, Elashoff D, Cohen SB, et al. Reduction of the efficacy of methotrexate by the use of folic acid: post hoc analysis from two randomized controlled studies. *Arthritis Rheum* 2005;52:3030–8.
34. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
35. Prevo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
36. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
37. Van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2007;56:1424–32.
38. Alsfuyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol* 2004;31:179–82.
39. Lindsay K, Shiela S, Lesley H, Sarah M. Subcutaneous methotrexate is an effective alternative to biologic agents: results of a review of service provided [abstract]. *Rheumatology (Oxford)* 2006;45 Suppl 1:i124.
40. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Emery P, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2006. *Ann Rheum Dis* 2006;65 Suppl 3:iii2–15.
41. Robbins L, Maclary S, Ostrov B, Ferriss J. Methotrexate use in rheumatic diseases: comparison of efficacy and tolerance of oral, intramuscular and subcutaneous methods of administration [abstract]. *Arthritis Rheum* 1997;40 Suppl 9:S230.
42. McKendry RJ. The remarkable spectrum of methotrexate toxicities. *Rheum Dis Clin North Am* 1997;23:939–54.
43. Ostrov B, Robbins L, Ferriss JA, Newman E, Maclary S, Ayoub W, et al. Improved tolerance and cost-effectiveness of subcutaneous versus oral methotrexate in rheumatoid arthritis (RA) and juvenile rheumatoid arthritis (JRA) [abstract]. *Arthritis Rheum* 1998;41 Suppl 9:S75.
44. Russo RA, Katsicas MM. Tolerance of parenteral, higher dose methotrexate in children with juvenile chronic arthritis [letter]. *Clin Exp Rheumatol* 2000;18:425.
45. Mardsen CH. A preliminary survey of patients views in relation to the use of subcutaneous methotrexate in the management of inflammatory arthritis [abstract]. *Ann Rheum Dis* 2005;64 Suppl III:411–2.