Towards improved treatment of undifferentiated and rheumatoid arthritis

Visser, K.

Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis

A double-blind, randomized, placebo-controlled trial

Arthritis Rheum 2007;56(5):1424-1432

2

H. van Dongen, J. van Aken, L.R. Lard, K. Visser,
H.K. Ronday, H.M.J. Hulsmans, I. Speyer,
M.L. Westedt, A.J. Peeters, C.F. Allaart,
R.E.M. Toes, F.C. Breedveld, T.W.J. Huizinga

Abstract

Objective

To determine whether patients with undifferentiated arthritis (UA; inflammatory, nontraumatic arthritis that cannot be diagnosed using current classification criteria) benefit from treatment with methotrexate (MTX).

Methods

The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study was a double-blind, placebo-controlled, randomized, multicenter trial involving 110 patients with UA who fulfilled the American College of Rheumatology (ACR) 1958 criteria for probable RA. Treatment started with MTX (15 mg/week) or placebo tablets, and every 3 months the dosage was increased if the Disease Activity Score was >2.4. After 12 months, the study medication was tapered and discontinued. Patients were followed up for 30 months. When a patient fulfilled the ACR criteria for RA (primary end point), the study medication was changed to MTX. Joint damage was scored on radiographs of the hands and feet.

Results

In 22 of the 55 patients (40%) in the MTX group, UA progressed to RA compared with 29 of 55 patients (53%) in the placebo group. However, in the MTX group, patients fulfilled the ACR criteria for RA at a later time point than in the placebo group (P=0.04), and fewer patients showed radiographic progression over 18 months (P=0.046).

Conclusion

This study provides evidence for the efficacy of MTX treatment in postponing the diagnosis of RA, as defined by the ACR 1987 criteria, and retarding radiographic joint damage in UA patients.

INTRODUCTION

For a number of autoimmune diseases, such as diabetes mellitus, it has been suggested that a critical period exists during which intervention may reverse the disease process.[1] For rheumatoid arthritis (RA), such a window of opportunity may also exist, because laboratory abnormalities, such as antibodies against cyclic citrullinated peptide (anti-CCP), can occur years before disease onset.[2] In previous studies of patients with undifferentiated arthritis (UA), defined as an inflammatory arthritis in which no definitive diagnosis can be made[3], it was observed that the presence of anti-CCP, with an odds ratio of 38, is an important predictor of the development of RA.[4] Of all the patients who present with UA, depending on the study population, 6–55% develop RA within 1 year.[5] Current treatment of UA patients mainly consists of non-steroidal antiinflammatory drugs (NSAIDs), and treatment with disease-modifying antirheumatic drugs (DMARDs) is not initiated until the disease has progressed to RA.[3] Once patients fulfill the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA[6], early initiation of DMARD treatment results in less disease activity, reduction of radiographic joint damage, and maintenance of function, as compared with delayed treatment.[7-9] Consequently, it is hypothesized that DMARD treatment that is started as early as possible in UA patients may alter disease progression and may prevent the development of RA.

Therefore, we designed a double-blind, placebo-controlled, randomized clinical trial to compare 2 treatment strategies. The immediate treatment strategy consisted of methotrexate (MTX) for a course of 1 year followed by tapering the amount of treatment if UA had not evolved into RA (as defined by fulfillment of the ACR classification criteria). The control group received conventional treatment with NSAIDs, and MTX therapy was initiated only if the patients fulfilled the ACR criteria for RA (the primary end point). The primary outcomes of the PRObable RA: Methotrexate versus Placebo Treatment (PROMPT) study were diagnosis at the end of the study and progression of radiographic joint damage.

PATIENTS AND METHODS

Study setting and design

The PROMPT study was a prospective double-blind, randomized, placebo-controlled, multicenter trial involving 110 patients. Randomization was performed by the pharmacist. The study was conducted between March 2001 and January 2006 in 4 hospitals in Leiden, The Hague, and Delft, The Netherlands. The study was approved by the medical ethics committee of the participating hospitals. Patients started with 6 tablets, each containing either 2.5 mg MTX or placebo. Every 3 months, the medication was increased by 2 tablets if the Disease Activity Score (DAS) was >2.4[10], to a maximum of 12 tablets or 30 mg of MTX (Figure 1). The DAS was calculated using a tender joint count (Ritchie Articular Index; RAI), the erythrocyte sedimentation rate (ESR), and a visual analog scale (VAS) for general health status, according to the following formula:

$$DAS = 0.54 \times \sqrt{(RAI)} + 0.065 \times (\text{swollen joint count}) + 0.33 \times \ln(ESR) + 0.0072 \times (\text{VAS general health})$$

Trained research nurses calculated the tender and swollen joint scores. To minimize the side effects of MTX, all patients, including those in the placebo group, received folic acid daily (1 mg) or weekly (5 mg). In both groups, patients were allowed to take NSAIDs, but no other immunosuppressive therapies, including steroids, were allowed. In cases of side effects that might be related to MTX, the treatment was adjusted.
If a patient reached the primary end point during follow-up, defined as fulfilling the ACR 1987 RA classification criteria, it was considered unethical to continue with study medication (possibly placebo), and the treatment was initially continued by building up open-label MTX to the same amount as in the study medication scheme. After 12 months, the study medication was decreased by 2 tablets every 4 weeks until it reached a level of 0 in the patients who did not reach the primary end point. At study inclusion and at 3, 6, 9, 12, and 18 months thereafter, a tender and swollen joint count, a Health Assessment Questionnaire, and a VAS for general health were obtained.[11,12] Every 6 months, radiographs of hands and feet were obtained. At 30 months, the diagnosis was recorded.

Participants

Eligible patients attended the rheumatology outpatient clinic of the participating hospitals, had symptoms of arthritis that did not exceed 2 years in duration, were 18 years of age or older, and were diagnosed as having UA (i.e., did not fulfill classification criteria for any rheumatologic disorder). Given the lack of criteria for UA, patients had to fulfill the ACR 1958 criteria for probable RA.[13] One patient with psoriasis was also included because the small joints of the hands and feet were involved. Exclusion criteria were RA (according to the ACR 1987 criteria), impaired kidney or liver function, alcoholism, bone marrow insufficiency, pregnancy or the desire to become pregnant within 21 months from inclusion in the study, and DMARD use in the past. All patients provided written informed consent.

Outcome

The diagnosis at the end of the study and the radiographic progression were prespecified primary outcomes. After 30 months, a diagnosis of RA, UA, remission, or other was recorded. Remission was defined as no clinical symptoms of arthritis according to the patient's rheumatologists and no DMARD use in the preceding year. Radiographic damage was graded by 2 experienced readers (JvA and HvD) using the Sharp/van der Heijde scoring method (SHS), with the radiographs in chronological order and patient identity masked.[14,15] The interobserver intraclass correlation coefficient (ICC) was 0.898. The intraobserver ICCs for both readers were 0.990 and 0.993, as measured in 20 patients. The smallest detectable change (SDC) was 3.02.[16] Prespecified secondary outcomes were changes in disease activity represented by the ESR and the DAS. For a post hoc analysis of the outcomes according to anti-CCP status, the presence of anti-CCP was measured at the end of the study in baseline serum samples from all patients, before decoding the treatment arms.

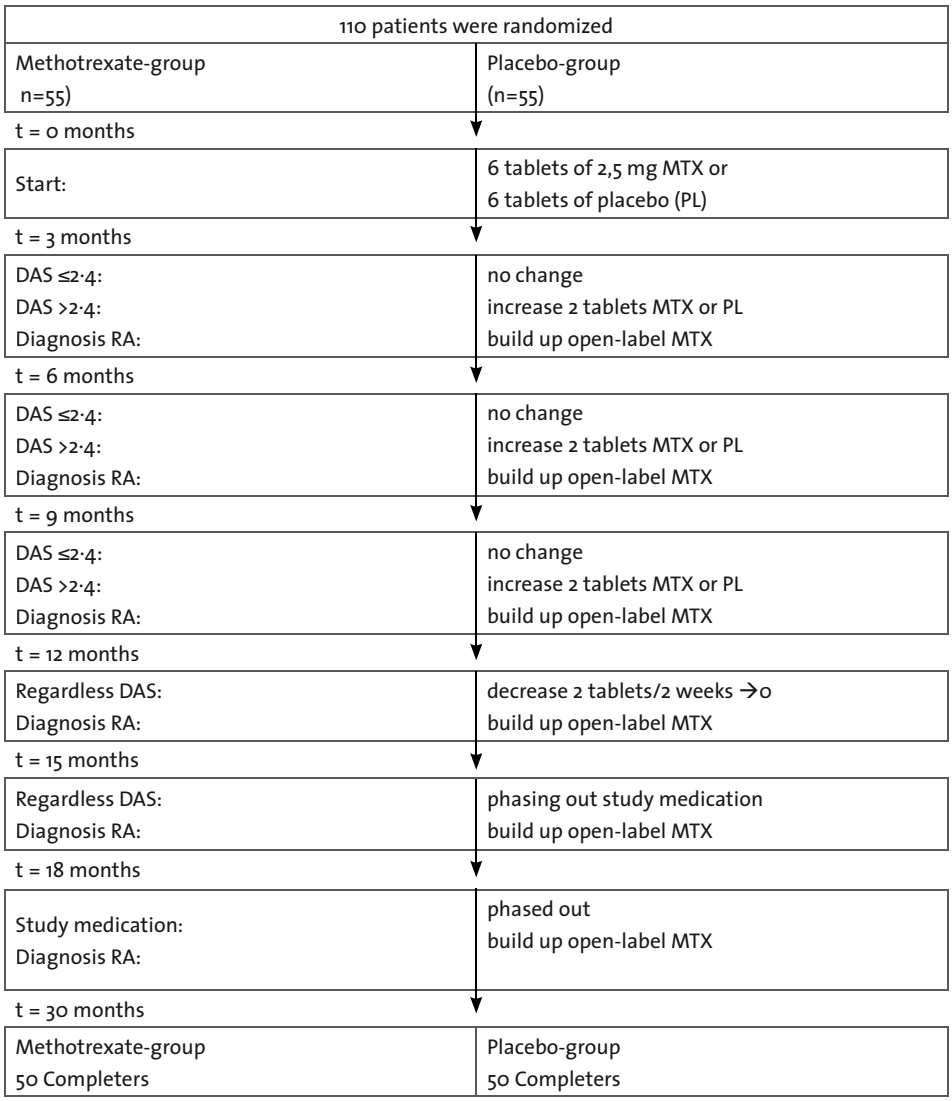

Figure 1. Overview of treatment strategy. Patients received open-label methotrexate (MTX) if rheumatoid arthritis (RA; n=49) or psoriatic arthritis with erosive disease (n=2) was diagnosed. PL=placebo; DAS=Disease Activity Score.

Statistical analysis

Using historical data from the Leiden Early Arthritis Clinic (EAC), 40% of the patients with UA were expected to develop RA within 1 year.[4] It was estimated that immediate treatment with MTX would result in 20% of the patients with UA developing RA. A sample size of 46 patients per treatment group was required in order to attain a power of

80% to detect a significant difference between groups with a P value of 0.05. To allow for dropouts, 110 patients were included in the study.
Demographic and baseline characteristics, changes in the DAS and ESR, and radiographic progression in the 2 treatment groups were compared using the chi-square test, Student's 2-tailed t-test, or the Mann-Whitney U test. Because MTX reduces radiographic joint damage in RA and the SHS method does not allow for healing, radiographic progression was tested 1-sided.[15,17] Differences in the development of RA during the study were determined using a Kaplan- Meier curve with a log rank test. The Cox proportional hazards model yielded the hazard ratios and 95% confidence intervals. P values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of the study patients

The demographic and clinical characteristics of the patients at baseline are shown in Table 1. To allow for assessment of the external validity of this trial, the baseline characteristics of the total group of patients in the PROMPT study were compared with a control group of UA patients who were included in the Leiden EAC study between 1993 and 1999.[3] In the PROMPT study group, the duration of symptoms was longer and the proportion of patients who were rheumatoid factor (RF)–positive was higher than in the EAC group. The ESR and C-reactive protein (CRP) levels were lower in the PROMPT group than in the EAC group.

Table 1. Demographic and clinical characteristics at baseline of members of the PROMPT study and of the UA patients in the Leiden EAC study.

	MTX group (n=55)	Placebo group (n=55)	EAC group (n=330)
Age, years	51 (42–60)	51 (42–56)	48 (36–61)
Female, no. (%)	35 (64)	38 (69)	177 (54)†
Duration of symptoms at first visit, days	312 (195–507)	263 (169–432)	92 (31–186)†
Duration of morning stiffness, minutes	30 (10–60)	30 (10–60)	30 (0–60)
No. of swollen joints	3 (2–5)	2 (2–4)	2 (1–4)†
3-variable DAS score	2.7 (2.1–3.1)	2.4 (2.0–3.0)	2.5 (2.0–3.1)
4-variable DAS score	2.7 (2.2–2.7)	2.5 (2.0–3.0)	–
RF positive, no. (%)	20 (36)	19 (35)	66 (21)†
Anti-CCP positive, no. (%)	12 (22)	15 (27)	55 (20)
ESR, mm/hour	12 (5–24)	11 (5–25)	22 (10–40)†
CRP, mg/liter	5 (3–11)	5 (3–9)	11 (5–31)†
HAQ score	0.75 (0.38–1.13)	0.75 (0.25–1.13)	0.62 (0.25–1.12)
Patients with erosive disease, no. (%)	2 (4)	3 (6)	37 (16)†
Sharp/van der Heijde score	0.5 (0–2.5)	1 (0–3.0)	0 (0–1.0)†

Except where indicated otherwise, values are the median (interquartile range). PROMPT=PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment; UA=undifferentiated arthritis; EAC=Early Arthritis Clinic; MTX=methotrexate; DAS=Disease Activity Score; RF=rheumatoid factor; anti-CCP=anti–cyclic citrullinated peptide antibody; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; HAQ=Health Assessement Questionnaire. † P≤0.05 versus the PROMPT group.

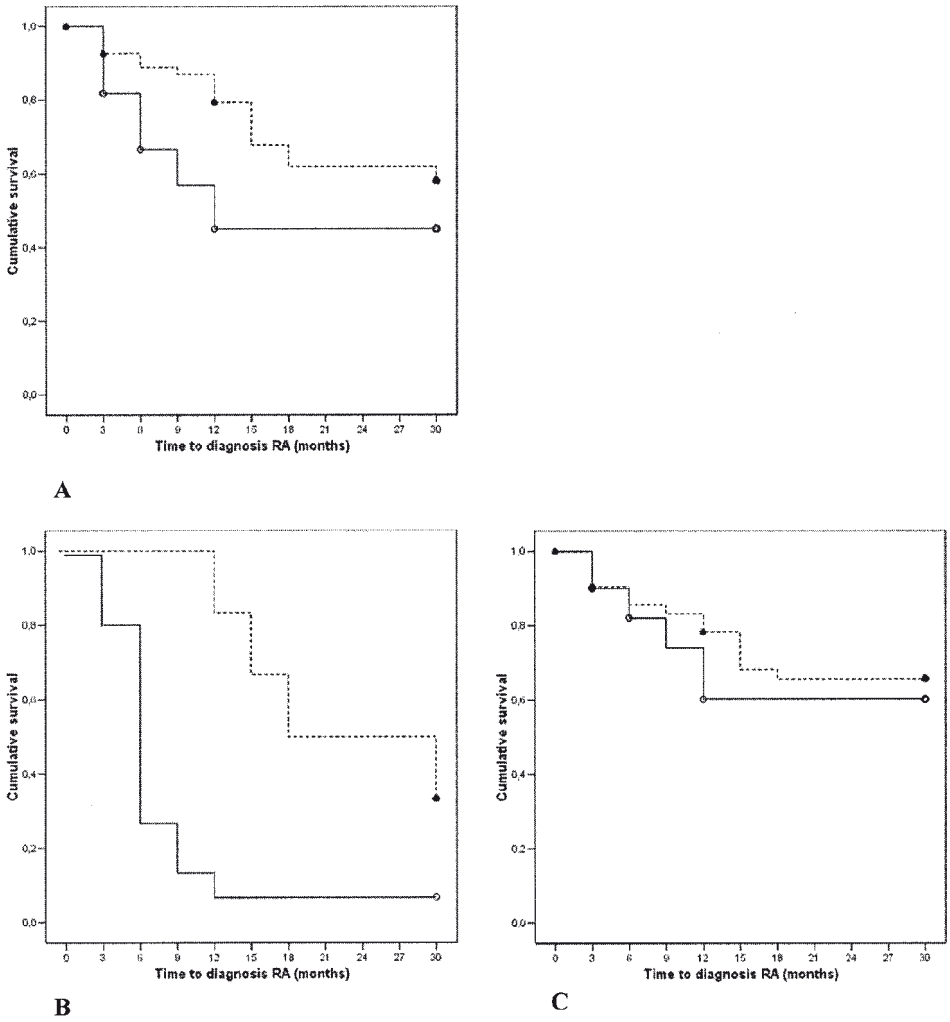

Figure 2. Kaplan-Meier survival analysis for the diagnosis of rheumatoid arthritis (RA). The methotrexate (MTX) group is indicated by the broken line, the placebo group is indicated by the solid line, and dropouts are indicated by circles. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) indicate the risk of developing RA during the study in the placebo group versus the MTX group. A, Total group (n=110) (HR 1.7 [95% CI 0.99–3.01], P=0.04). B, Members of the subgroup positive for antibodies against cyclic citrullinated peptide (anti-CCP) (n=27) (HR 4.9 [95% CI 1.88–12.79], P<0.001). C, Members of the subgroup negative for anti-CCP (n=83) (HR 1.3 [95% CI 0.61–2.63], P=0.51).

Diagnosis at the end of the study

Figure 1 shows the randomization and treatment strategy. After 30 months, in 22 of 55 of the patients in the MTX group (40%) versus 29 of 55 in the placebo group (53%) UA had eventually progressed to RA. However, in the placebo group, all patients whose disease had progressed to RA fulfilled the ACR criteria within 1 year, versus only one-half of the RA patients in the MTX group (P=0.04) (Figure 2A). The other half of the RA patients in the MTX group reached the diagnosis during or after tapering of the study medication. After 30 months, a similar number of patients achieved remission in both treatment groups: 15 in the MTX group and 13 in the placebo group (Table 2).

Radiographic progression

The distribution of the radiographic progression over 18 months is shown in Figure 3A. In both groups, 51 patients had completed radiographic follow-up. After 18 months, the majority of patients had no radiographic progression at all: 73% in the placebo group and 88% in the MTX group. However, 6 patients in the MTX group versus 14 patients in the placebo group showed radiographic progression above the SDC (P=0.046). Individual progression measured only in patients with erosions was significantly lower in the MTX group versus the placebo group (P=0.035).

Table 2. Diagnosis at 30 months, by subgroup.

Group (n)	RA	UA	UA in Remission	Other	Lost to follow-up
Total					
MTX (55)	22	10	15	3 (2 osteoarthritis, 1 autoimmune hepatitis)	5
Placebo (55)	29	4	13	4 (3 osteoarthritis, 1 diabetic arthropathy)	5
Anti-CCP–positive					
MTX (12)	8	2	2	0	0
Placebo (15)	14	0	1	0	0
Anti-CCP–negative					
MTX (43)	14	8	13	3 (2 osteoarthritis, 1 autoimmune hepatitis)	5
Placebo (40)	15	4	12	4 (3 osteoarthritis, 1 diabetic arthropathy)	5

RA=rheumatoid arthritis; UA=undifferentiated arthritis; MTX=methotrexate; anti-CCP=anti–cyclic citrullinated peptide antibody.

Subgroup analysis

In the anti-CCP–positive subgroup treated with placebo, UA in 14 of the 15 patients (93%) progressed to RA and did so at an earlier time point than that in 8 of the 12 patients (67%) in the MTX group (P<0.001) (Table 2 and Figure 2B). In contrast, in the anti-CCP–negative subgroup no differences in outcome at 30 months were seen (Figure 2C). Similar effects on radiographic progression were observed (Figures 3B and C). In the anti-CCP–negative group, no MTX effect could be detected, whereas in the anti-CCP–positive group, the progression was slowed down significantly (P=0.03).

Subgroup analysis for the presence of RF showed considerable overlap with the presence

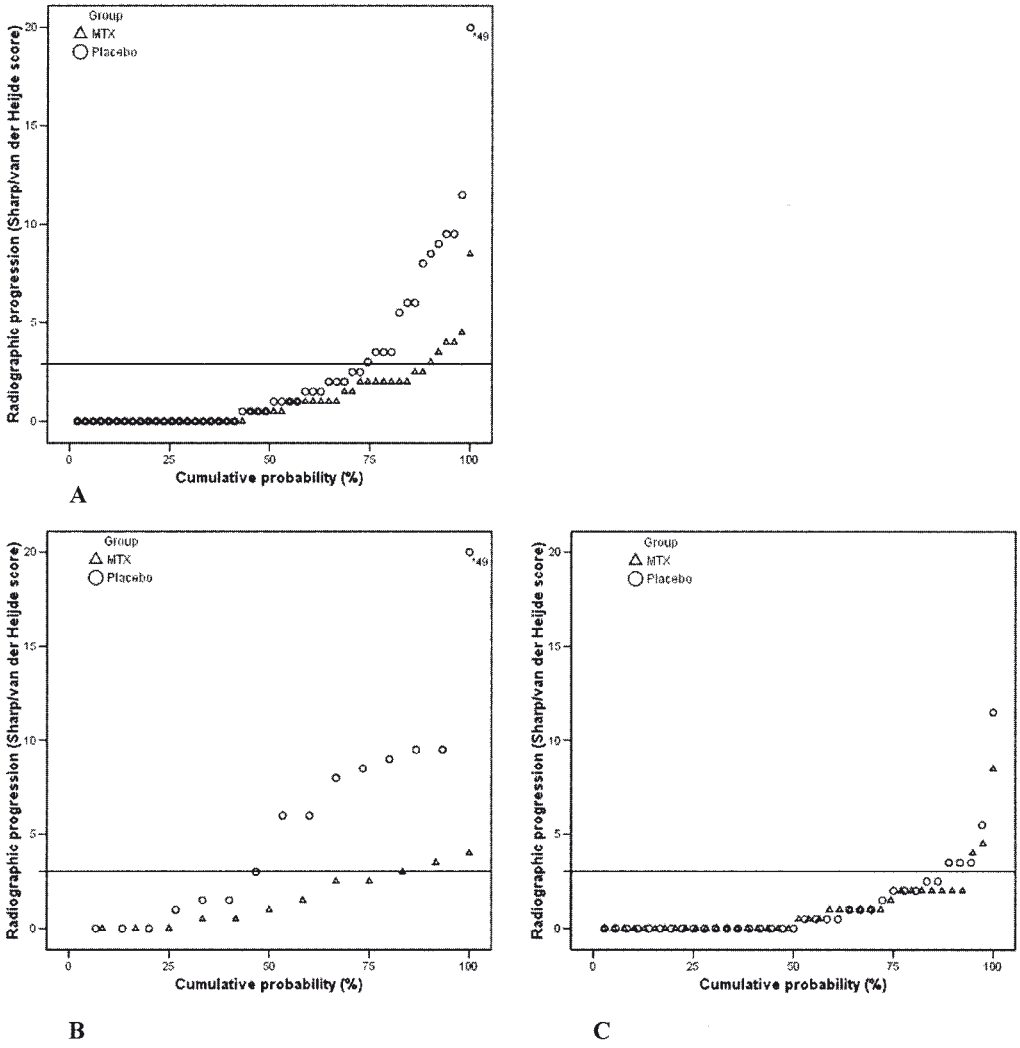

Figure 3. Occurrence of radiographic progression. The presence or absence of radiographic progression (Sharp/van der Heijde score) at 18 months in 102 patients who completed radiographic follow-up was calculated. Each symbol represents 1 patient. Horizontal lines represent the smallest detectable difference (indicating radiographic progression). A, Total group (n=102). B, Patients positive for antibodies against cyclic citrullinated peptide (anti-CCP) (n=27). C, Patients negative for anti-CCP (n=75). For methotrexate (MTX)–treated versus placebo-treated patients, P=0.15 in the total group, P=0.03 in the anti-CCP–positive patients, and P=0.46 in anti-CCP–negative patients.

of anti-CCP: 26 of 39 RF-positive patients (67%) were anti-CCP positive, whereas 60 of 61 RF-negative patients (98%) were anti-CCP negative. In the placebo group, UA in 13 of the 19 RF-positive patients (68%) progressed to RA and did so at an earlier time point than did 11 of the 20 RF-positive patients (55%) in the MTX group (P=0.036). In contrast, in the RF-negative subgroup, no differences in outcome at 30 months were seen (P=0.403). With regard to radiographic progression, RF-positive patients in the placebo group showed a trend for more radiographic progression than those in the MTX group (data not shown).
Subgroup analysis of the development of RA over time for autoantibody-positive (anti-CCP–positive or RF-positive) patients weakened the significance as compared with analysis of the anti-CCP–positive patients alone (P=0.024). Of the 27 anti-CCP–positive patients, only 1 was RF-negative. This patient received placebo and was diagnosed as having RA 6 months after study inclusion. The outcome of the 26 patients who were anti-CCP–positive and RF-positive is shown in Table 2.

Cross-sectional follow-up

At the time of submission of this article, further follow-up data were not available for all patients due to different follow-up periods. However, we can report on 5 of 27 patients in the anti-CCP–positive subgroup (18%) who did not develop RA after 30 months (Table 2). The 3 patients who were in remission at 30 months (1 in the placebo group and 2 in the MTX group) were still in remission without DMARD treatment 4 years after study inclusion. However, the 2 patients with persistent UA (both from the MTX group) restarted MTX treatment after 30 months, 1 because of recurrent symptoms and, ultimately, arthritis shortly after withdrawal of study medication and 1 because of recurrent arthritis after a 6-month remission period. The patients continued to receive MTX at the time of submission of this article. As a result, although only 1 fulfilled the ACR criteria for RA, it can be argued that they both have RA, given the recurrent arthritis symptoms that require DMARDs. Taking these data into account, 10 of 12 anti-CCP–positive patients (83%) in the MTX group eventually developed RA and 2 of 12 patients (17%) achieved sustained remission, emphasizing that MTX postponed, but did not prevent, RA.

Disease activity

After 3 months, the mean decrease in DAS (from 2.7 to 2.3) and ESR (from 17 mm/hour to 13 mm/hour) values in the MTX group differed significantly from the mean change in DAS (from 2.5 to 2.5) and ESR (from 15 mm/hour to 16 mm/hour) in the placebo group (P=0.01 and P=0.02, respectively). However, subgroup analysis showed that in the anti-CCP–positive patients, the mean DAS decreased (from 2.8 to 1.9) in the MTX group and increased in the placebo group (from 2.6 to 3.1) (P<0.001). However, in the anti-CCP–negative patients, the mean DAS decreased irrespective of treatment group (from 2.7 to 2.4 versus from 2.5 to 2.3 in the MTX and placebo groups, respectively; P=0.62).
After 12 months, study medication was decreased regardless of the DAS. In the MTX group, 8 of 40 patients who still received study medication had a DAS>2.4 at 12 months and started phasing out the study medication; the UA in 2 of these 8 patients later progressed to RA. Of the 32 patients with a DAS≤2.4, the UA in 9 of them progressed to RA.

Of the anti-CCP–positive patients in the MTX group, only 1 of the 10 who still received study medication at 12 months had a DAS>2.4 and later developed RA. Of the 9 patients with a DAS≤2.4, 5 developed RA, 2 had UA without fulfilling the ACR criteria for RA at 30 months, and 2 went into remission.

Toxicity

Adverse events were recorded during the first 18 months, the intervention period of the study. Of the patients who were taking study medication, 26 of 55 patients (47%) in the MTX group and 18 of 55 patients (33%) in the placebo group experienced ≥1 (serious) adverse event (P=0.173). While taking the study medication, a total of 44 adverse events and 5 serious adverse events occurred in the MTX group versus a total of 25 adverse events and 4 serious adverse events in the placebo group (Table 3).

When patients fulfilled the ACR 1987 RA classification criteria during follow-up, they were switched to open-label MTX. If MTX produced undesirable adverse events or was ineffective, other DMARDs were prescribed. The 20 patients who developed RA in the former MTX group in the first 18 months were subsequently treated with MTX (19 patients), sulfasalazine (1 patient), hydroxychloroquine (3 patients), and/or leflunomide (1 patient). Adverse events (12 adverse events and 3 serious adverse events) were reported in 7 of 20 patients while they were treated with these DMARDs. In the former placebo group, the 29 patients who developed RA in the first 18 months were treated with MTX (29 patients), sulfasalazine (2 patients), hydroxychloroquine (5 patients), leflunomide (1 patient), infliximab (2 patients), etanercept (1 patient), and/or adalimumab (2 patients). Adverse events (39 adverse events and 3 serious adverse events) were reported in 18 of 29 patients while they were treated with these DMARDs.

DISCUSSION

This study indicates that MTX treatment of patients with UA can postpone progression to RA, as defined by fulfillment of the ACR 1987 criteria, and can retard radiographic joint damage. However, the results do not suggest that a 1-year course of MTX treatment can prevent the development of RA from UA. Although these findings must be confirmed in future trials, the PROMPT study provided the first evidence of the efficacy of MTX treatment in UA patients.

Data from the current study showed that initiation of MTX treatment in UA patients in the stage before they fulfilled the ACR criteria for RA resulted in postponement of the diagnosis of RA. During the first year, the incidence of RA was lower in the MTX group than in the placebo group, but after 12 months, the opposite was seen. Furthermore, the results suggest that MTX did not induce more remission, but prolonged the period of persistent UA. Interestingly, the benefit of this effect seemed to be the retardation of radiographic progression. The majority (62%) of the 29 RA patients in the placebo group had already fulfilled the ACR criteria and started taking open-label MTX within 6 months. Nevertheless, the results still show a more favorable outcome in the group that immediately received MTX after study inclusion.

Table 3. Adverse events and serious adverse events during the use of the study medication and during the use of DMARDs after RA diagnosis, by treatment group.

	During use of study medication		During use of DMARDs after RA diagnosis	
	MTX	Placebo	Former MTX	Former Placebo
All adverse events				
Gastrointestinal	11	6	1	12
Dermal/mucosal	9	7	2	5
Neurologic	3	5	5	4
Cardiologic	3	–	–	2
Pulmonary	3	1	3	1
Hematologic	1	1	–	–
Ophthalmologic	3	–	1	2
Elevated serum liver enzyme levels	6	1	–	4
Other				
Tiredness	1	1	–	2
Giant cell tumor	1	–	–	–
Rhinitis	1	–	–	–
Not feeling well	2	–	–	1
Fracture	–	1	–	–
Hair loss	–	1	–	3
Synovectomy	–	1	–	1
Arthroplastic surgery	–	–	–	1
Weight gain and edema	–	–	–	1
Total	44	25	12	39
Serious adverse events				
Necessitating discontinuation of study medication				
Gastrointestinal	1	1	NA	NA
Erythema annulare centrifugum	1	–	NA	NA
General unwellness	–	1	NA	NA
Dyspnea, insomnia, weight gain	–	1	NA	NA
Necessitating hospital admission				
Pancreatitis	1	–	–	–
Knee replacement surgery	1	–	–	–
Erosive arthritis	1	–	2	3
Meningitis	–	1	–	–
Venous thrombosis	–	–	1	–
Total	5	4	3	3

Values are the number of events. DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; MTX = methotrexate; NA = not available.

This is the first double-blind, randomized, placebo-controlled trial that addresses early DMARD treatment in patients with UA before they fulfill the ACR criteria for established RA. Although these criteria are currently under debate for use in clinical practice, for research purposes they are regarded as the standard for objectively describing the RA phenotype and have been widely used as inclusion criteria for trials. Moreover, results from many randomized controlled trials have shown that in patients who fulfill the ACR criteria for RA, DMARDs improve the outcome.[18,19] Thus, for ethical reasons, a placebo-controlled trial in UA patients could not be extended once the patients fulfilled the criteria. Therefore, the primary outcome of the study, the diagnosis of RA as defined by fulfillment of the ACR 1987 classification criteria, seems a reasonable end point.

Patients with UA included in this study are not completely representative of the average UA patient. This was illustrated by comparing the data from the patients in the PROMPT study with controls from the Leiden EAC.[3] Longer symptom duration and lower ESR and CRP levels were seen in the patients in the PROMPT study. This indicates that the UA patients were no longer in the earliest and most active disease state by the time they were included in the current study. The best explanation for this observation seems to be that physicians at the 4 centers were reluctant to expose patients with UA to a 1-year course of MTX treatment, given the high spontaneous remission rate and the risk of unnecessary toxicity.[3,20] Also, the use of the ACR 1958 criteria for RA as inclusion criteria could have resulted in a selection of UA patients. Despite the fact that UA patients already had longer disease duration, a 1-year course of MTX treatment was still able to provide beneficial effects on disease and joint damage progression.

The existence of a therapeutic window of opportunity in UA patients, defined as a period of time in which the disease process can be reversed, might not be demonstrated in this study. However, it is possible that with a different design and a different medication scheme, such a therapeutic window can be addressed. First, the incidence of RA increased during tapering of the study medication in the MTX group. This raises the question of what would have happened if MTX had not been tapered. Second, MTX as monotherapy could not have been sufficient, since in the MTX group, half of the RA patients still developed RA while taking study medication, and 6 patients still showed progression of joint damage. Trials in RA patients have shown that treatment with combination therapy and/or biologic agents is more effective in preventing radiographic joint damage.[18,19,21] Finally, dosages of study medication were altered according to the DAS because rheumatologists are generally satisfied and do not intensify therapy when the DAS is <2.4 in RA patients.[22-23] It is possible that treatment in UA patients should aim at remission or a lower cutoff value of the DAS.

In this study, 53% of the patients in the placebo group developed RA and 24% achieved spontaneous remission, demonstrating that MTX treatment is overtreatment in a considerable proportion of UA patients. Because it is undesirable to start a potentially harmful drug in UA patients who will remit spontaneously, there is a need to identify those UA patients who will most likely develop RA and who will benefit the most from DMARD treatment. In previous studies and in a recently published prediction model that calculates the UA patients' risk of developing RA based on clinical variables, the presence of anti-CCP emerged as one of the strongest predictors of RA.[2,4,24] Moreover,

applying the model to our study, theoretically initiating treatment in patients with a prediction score ≥8 and withholding treatment in patients with a prediction score ≤6, only 6% of the patients would have been inaccurately withheld from treatment, and no patients would have been inaccurately treated.

In the current study, subgroup analysis revealed that the beneficial outcomes were most pronounced in patients with anti-CCP. In striking contrast, in the anti-CCP–negative subgroup, the effect of MTX on the development of RA, the radiographic progression, and even on the signs and symptoms, was not demonstrable. The same observations were made for patients who were or were not RF-positive, although this could reflect the overlap with anti-CCP. Although the current groups are small, this post-hoc analysis suggests that only anti-CCP– positive UA patients, who have the highest risk of developing RA, benefit from early MTX treatment. It also supports the growing evidence that anti-CCP– positive and anti-CCP–negative UA are different disease entities that should be approached differently.

We conclude that treatment with MTX benefits patients with UA by reducing signs and symptoms, by postponing the progression to RA as defined by the ACR 1987 criteria, and by retarding radiographic joint damage. Furthermore, with the guidance of a prediction model and the antibody status, it seems feasible to identify a subset of UA patients who are most in need of and who will benefit the most from initiation of MTX therapy, thereby avoiding unnecessary toxic treatment. Although these findings have to be confirmed, and the optimal duration and intensity of treatment still have to be determined, the PROMPT study provides evidence for the efficacy of MTX treatment in UA patients.

References

1. Majka DS, Holers VM. Can we accurately predict the development of rheumatoid arthritis in the preclinical phase? [review]. Arthritis Rheum 2003;48:2701–5.
2. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380–6.
3. Van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. Ann Rheum Dis 2006;65:20–5.
4. Van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum 2004;50:709–15.
5. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis: disease course assessed in several inception cohorts [review]. Clin Exp Rheumatol 2004;22(5 Suppl 35):S12–7.
6. 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.
7. Lard LR, Visser H, Speyer I, van der Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446–51.
8. Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs: a randomized, controlled trial. Ann Intern Med 1996;124:699–707.
9. Hannonen P, Mottonen T, Hakola M, Oka M. Sulfasalazine in early rheumatoid arthritis: a 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum 1993;36:1501–9.
10. Van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
11. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
12. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3:305–9.
13. Ropes MW, Bennett GA, Cobb S, Jacox R, Jessar RA. 1958 revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9:175–6.
14. Van der Heijde DM. Plain x-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10:435–453.
15. Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method [corrected and republished in J Rheumatol 2000;27:261–3]. J Rheumatol 1999;26:743–5.
16. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change [review]. Ann Rheum Dis 2005;64:179–82.
17. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: update after a mean of 90 months. Arthritis Rheum 1992;35:138–45.
18. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
19. Goekoop-Ruiterman Y, De Vries-Bouwstra J,

Van Zeben D, Kerstens J, Hazes J, Zwinderman A, et al. Comparison of treatment strategies in early rheumatoid arthritis. Ann Intern Med. 2007; 146(6): 406-15.
20. Weinblatt ME, Kaplan H, Germain BF, Block S, Solomon SD, Merriman RC, et al. Methotrexate in rheumatoid arthritis: a five-year prospective multicenter study. Arthritis Rheum 1994;37: 1492–8.
21. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347–56.
22. Van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579–81.
23. Van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/ International League Against Rheumatism criteria. Arthritis Rheum 1996;39:34–40.
24. Van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56: 433–40.