# Treatment of early rheumatoid and undifferentiated arthritis

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# CHAPTER 2

## FIVE YEAR OUTCOMES OF PROBABLE RHEUMATOID ARTHRITIS TREATED WITH METHOTREXATE OR PLACEBO DURING THE FIRST YEAR (THE PROMPT STUDY)

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## ABSTRACT

**Objective:** To assess long-term disease outcome of undifferentiated arthritis (UA) after initial treatment with methotrexate (MTX) or placebo.

**Methods:** 110 patients with UA were randomised to receive MTX (n=55) or placebo (n=55) for 1 year. After 5 years the outcomes for diagnosis (rheumatoid arthritis, 1987 criteria (RA (1987)), UA or UA in remission) and radiographic progression were compared between treatment arms and anti-citrullinated protein antibody (ACPA)-positive and -negative patients. Outcomes were recalculated for patients who, with hindsight, might have been classified at baseline as having RA according to the 2010 criteria (RA (2010)).

**Results:** 25 patients in the MTX group and 29 in the placebo group progressed to RA (1987) (p=0.45). MTX delayed progression from UA to RA (1987) but only in ACPA-positive patients. Drug-free remission was achieved in 35 patients, 20 of whom were initially treated with MTX, and 32 were ACPA-negative. ACPA-positive patients had more radiographic progression, regardless of treatment. Forty-three patients (39%) could be reclassified as having had RA (2010) at baseline, 6/24 (25%) of whom achieved remission after placebo treatment.

**Conclusions:** After 5 years there is no lasting benefit of a 1 year initial course of MTX for patients with undifferentiated arthritis, compared with initial placebo. Progression to classifiable RA was not suppressed, drug-free remission not induced and the progression of radiological damage was similar in both groups. Reclassification at baseline with the 2010 criteria showed that 25% of patients with RA (2010) achieved spontaneous drug-free remission.

# INTRODUCTION

Patients with inflammatory arthritis may present with undifferentiated arthritis (UA) not fulfilling any classification criteria.[1] Although UA may be a self-limiting disease, a considerable proportion of patients with UA has an early manifestation of rheumatoid arthritis (RA). For patients with recent-onset RA, a timely start of treatment with disease-modifying antirheumatic drugs (DMARDs) has proved to be crucial for achieving better clinical and radiographic outcomes. Therefore starting antirheumatic treatment already in UA might result in even more sustained benefits and potentially a chance for cure.[2, 3]

In the PROMPT study, we showed that treatment with methotrexate (MTX) compared with placebo for 1 year did not prevent, but (in anti-citrullinated protein antibody (ACPA)-positive patients at least) delayed, the development of UA into RA.[4] MTX reduced signs and symptoms at 12 months and radiographic progression at 18 months—again, particularly in ACPA-positive patients with UA. It remains to be determined whether this very early introduction of MTX has benefits in the long term.

In this study, the effect of early MTX treatment on clinical and radiological outcomes was assessed after 5 years. In addition, we identified predictors for disease progression to classifiable RA and for persistent remission in patients with UA. Finally, we re-evaluated current and previous study results using the 2010 classification criteria for RA to see whether MTX monotherapy in patients who fulfil the 2010 criteria and have relatively low disease activity is sufficient to achieve remission.[5]

# PATIENTS AND METHODS

## Study setting and design

The PROMPT study is a prospective double-blind, randomised, placebo-controlled multicentre trial evaluating the effect of 1 year MTX versus placebo treatment.[4] All 110 patients fulfilled the 1958 classification criteria for probable RA[6], were DMARD-naïve and had a symptom duration of <2 years.

Patients started treatment with MTX 15 mg/week (6 tablets of 2.5 mg) or the equivalent number of placebo tablets. No other DMARDs or steroids were allowed during the first year of treatment. Every 3 months, medication was increased by 5 mg MTX or two tablets placebo to a maximum of 30 mg or 12 tablets placebo a week as long as the Disease Activity Score (DAS) was >2.4. As soon as a patient fulfilled the 1987 ACR classification criteria for RA[7] (RA (1987)) during the first year, medication was switched to open-label MTX. After 12 months, the study drug was tapered and discontinued in the patients who had not developed RA (1987). IgM rheumatoid factor (RF) and ACPA were measured retrospectively in serum samples taken at baseline using commercial kits (Euro-Diagnostica, Arnhem, The Netherlands). ACPA levels >25 U/ml and RF levels >5 IU/ml were considered positive. Further details of the study and results of the primary outcomes have been published elsewhere.

To substantiate the PROMPT study results, the patients were reclassified at baseline according to the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR)/EULAR criteria for RA.

### Outcomes

At 3, 6, 9, 12, 30 and 60 months the diagnosis was recorded as classifiable RA (1987)[7] or UA (UA not fulfilling the 1987 ACR criteria), drug-free remission (DFR) without progression to RA (1987) or other (lost to follow-up or other diagnosis). Remission was defined as a DAS≤1.6[8] or the absence of synovitis or self-reported absence of symptoms without use of DMARDs. Radiographs of the hands and feet were obtained at inclusion and at 6, 12, 18, 30 and 60 months. Radiographic progression was scored by two independent readers using the Sharp–van der Heijde scoring (SHS) method[9] with radiographs blinded for patient identity, treatment group and time order.

### Statistical analysis

Baseline and disease characteristics were compared between the two treatment arms, between ACPA-positive and ACPA-negative patients and between patients with RA (1987) and patients in DFR using the $\chi^2$ test, Student's *t* test and the Mann–Whitney U test. To assess differences in time to reach one of the endpoints (RA (1987) or DFR), Kaplan–Meier curves with a log rank test were used.

In a large proportion of patients the readers independently scored no radiological damage progression (71% and 73%, respectively). Consequently, interobserver and intraobserver intraclass correlation coefficients were not suitable for measuring reliability.[10] In 71% of patients both readers scored the same progression. A consensus score was reached for the radiographs with inter-reader differences ≥1, based on a median (IQR) difference in progression score between readers of 0 (0–2). The mean score of the readers was used for the analyses. We performed a completers' analysis, then repeated the analyses with imputed values according to last observation carried forward, for incomplete series.

Univariate logistic regression analysis was used to identify potential predictors for fulfilling the criteria of RA (1987) after 60 months and for DFR, including age, sex, symptom duration, baseline SHS, baseline erosion score, baseline DAS, baseline Health Assessment Questionnaire, ACPA status and RF status. The univariate predictors that reached statistical significance ($p \leq 0.1$) were entered stepwise in a multivariate model. Age and gender, as known predictors, were forced into the model. To avoid problems of colinearity, separate analyses were done with either ACPA or RF.

## RESULTS

After 5 years, seven patients were lost to follow-up because they had either moved away or had died. Radiographs after 5 years were obtained for 67 patients.

Baseline and disease characteristics of the 110 patients with UA (55 receiving MTX, 55 placebo) are shown in table 1.





## Diagnosis at 60 months

### *1987 RA criteria*

After 60 months 54/110 patients (49%) had disease progression and fulfilled the 1987 RA classification criteria. In the MTX group 25/55 patients (45%) progressed to RA (1987), in the placebo group 29/55 (53%) patients (p=0.45) (table 2). All the 29 patients in the placebo group who progressed to RA (1987) did so within 1 year, compared with 11/25 in the MTX group. Yet, possibly owing to small numbers, Kaplan–Meier analyses showed no significant difference in time to progression to RA between the treatment groups (p=0.11) (figure 1A). Of the patients who progressed to RA (1987), the 25 patients in the MTX group used a median of 1 (1–2) DMARDs in 5 years, compared with a median of 2 (1–3) DMARDs in the 29 patients of the placebo group. ACPA-positive patients progressed significantly faster to RA (1987) than ACPA-negative patients (p<0.001). Initial MTX treatment delayed progression to RA (1987) in the ACPA-positive group but not in the ACPA-negative group (p<0.001) (figure 1B,C).

### *Drug-free remission and persistent UA*

In the MTX group 25/55 patients (45%) did not progress to RA (1987). At 5 years, of those 25 patients, 19 were in persistent DFR since 1 year, and one was in DFR after using hydroxychloroquine for 35 months. Five were still diagnosed as having active UA (table 2). In the placebo group 17/55 (31%) patients did not progress to RA (1987) and 15 were in DFR after 60 months, two still had arthritis (table 2). None of these 15 patients had used DMARDs since 1 year. Of the total group, 35/110 patients (32%) were

**Table 1.** Baseline and disease characteristics for both randomization groups.

| | MTX (n=55) | Placebo (n=55) | p |
|---|---|---|---|
| Age in years | 51 (42-60) | 51.3 (42-56) | 0.39 |
| Female | 35 (64) | 38 (69) | 0.55 |
| Symptom duration in days | 312 (195-507) | 263 (169-432) | 0.29 |
| Morning stiffness in minutes | 30 (10-60) | 30 (10-60) | 0.95 |
| RF positive | 20 (36) | 19 (35) | 0.96 |
| ACPA positive | 12 (22) | 15 (27) | 0.51 |
| DAS | 2.72 (0.78) | 2.52 (0.76) | 0.19 |
| HAQ | 0.79 (0.51) | 0.78 (0.58) | 0.90 |
| Sharp-van der Heijde score | 0 (0-2) | 0 (0-2) | 0.93 |
| Fulfilled ACR-EULAR 2010 RA criteria | 19 (35) | 24 (44) | 0.33 |

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, HAQ: Health Assessment Questionnaire, DAS: disease activity score, SHS: Sharp-van der Heijde score, RA: Rheumatoid Arthritis.

in DFR at 60 months. The survival analysis did not show a difference in time to achieve DFR between the MTX and the placebo group (p=0.34) (figure 1D). Most patients who achieved DFR were ACPA negative (32/35), and achieved DFR significantly earlier than the three ACPA-positive patients (p=0.008).

*2010 RA criteria*

Based on signs and symptoms, 43/110 patients with UA (39%) fulfilled the 2010 ACR/EULAR classification criteria for RA (RA (2010)) at baseline (table 1). Nineteen of these patients were randomised to the MTX group. Of these patients, 12/19 (63%) had disease progression to fulfilling the 1987 classification criteria, 5/19 (26%) achieved DFR. Of the 24 RA (2010) patients randomised to the placebo group, 17/24 (71%) progressed to RA (1987) and 6/24 (25%) achieved DFR.

## Predictors of drug-free remission and fulfilling the criteria for RA

The univariate predictors for fulfilling the 1987 classification for RA after 60 months were, separately tested, ACPA positivity (OR=9.7, 95% CI 3.1 to 30.5) and RF positivity (OR=3.0, 95% CI 1.3 to 6.8). Multivariate analyses including ACPA or RF, age, gender, SHS and DAS at baseline, showed ACPA (OR=8.9 95% CI 2.7 to 29.1), SHS at baseline (OR=1.3,

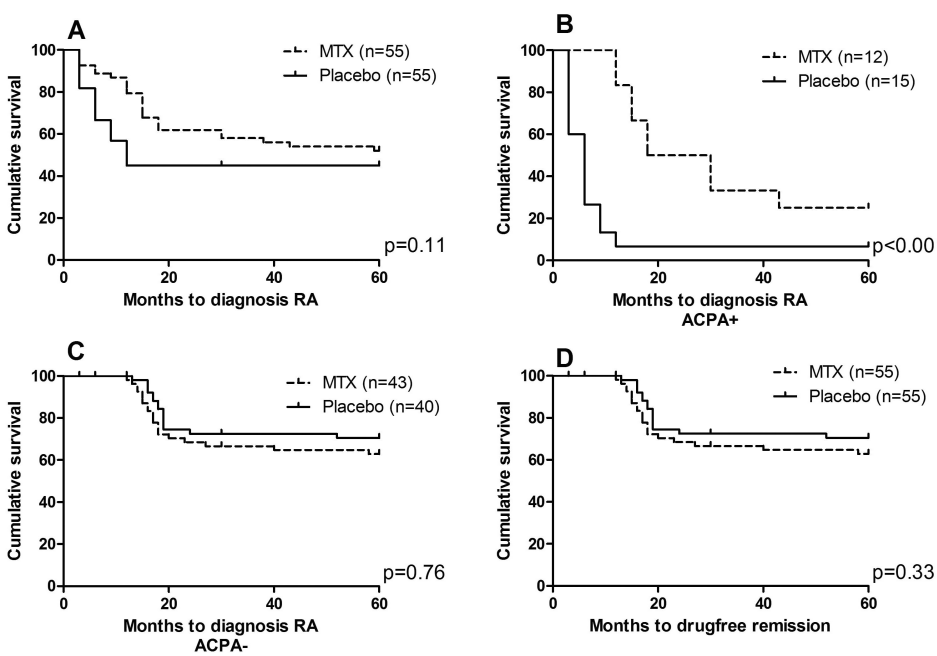


**Figure 1.** Kaplan-Meier survival analysis for (A) the time to diagnosis of rheumatoid arthritis in the total group, (B) in ACPA (anti-citrullinated protein antibody)-positive patients, (C) in ACPA-negative patients, (D) the time to drug free remission in the total group. MTX: methotrexate, ACPA: anti-citrullinated protein antibody.

**Table 2.** Diagnosis after 30 and 60 months follow up in patients initially treated with 1 year MTX or 1 year placebo.

| | 30 months | | 60 months | |
|---|---|---|---|---|
| **Diagnosis** | **MTX** | **Placebo** | **MTX** | **Placebo** |
| RA (1987 criteria) | 22 | 29 | 25 | 29 |
| UA (active arthritis) | 10 | 4 | 5 | 2 |
| Drug free remission | 15 | 13 | 20 | 15 |
| Other diagnosis | 3* | 4** | 3* | 4** |
| Lost to follow up | 5 | 5 | 2 | 5 |
| Total | 55 | 55 | 55 | 55 |

Values indicate the number of patients.
* 2 osteoarthritis, 1 autoimmune hepatitis. ** 3 osteoarthritis and 1 diabetic arthropathy. RA: rheumatoid arthritis, UA: undifferentiated arthritis, DFR: patients in drug free remission without progression to RA.

95% CI 1.01 to 1.6) and RF (OR=2.9, 95% CI 1.2 to 7.1) as independent predictors for progression to RA (1987).

Absence of ACPA (OR=5.0, 95% CI 1.4 to 18.0) was identified as the only independent predictor for DFR (OR=5.1, 95% CI 1.4 to 18.5, in the multivariate analysis including ACPA, age and gender).

## Radiographic damage

### *Completers*

After 60 months, 67 patients had completed the radiographic follow-up. Patients who completed follow-up were more often ACPA positive (36% versus 7% in non-completers) and more had progressed to RA (1987) (66% versus 23% in non-completers). In 39/67 patients (58%) there was no radiological progression at all. Radiological damage progression was comparable in patients who had progressed to RA (1987) and those who were in DFR after 5 years (p=0.08). There was significantly more damage progression in the ACPA-positive than in the ACPA-negative patients (median (IQR) 1.8 (0–6) versus 0 (0–0.5); p=0.001).

### *Total group*

Imputation of missing values by last observation carried forward was done in 107 patients (no imputation in three patients with only baseline scores). In 73/110 (66%) patients were estimated to have no progression. In the 34 patients who showed progression, median progression was 2 (1–7). The median (IQR) progression of patients initially treated with MTX was 0 (0–1) and in the placebo group 0 (0–1) (p=0.78). After 5 years, patients who progressed to RA (1987) had more progression than patients in DFR (respectively 0 (0–2) versus 0 (0–0); p=0.02). Again, ACPA-positive patients showed more radiological progression than ACPA-negative patients (1.5 (0–3) points progression in SHS versus 0 (0–0), p<0.001), regardless of initial treatment (figure 2). Two ACPA-positive patients who initially received placebo showed rapid radiological progression, defined

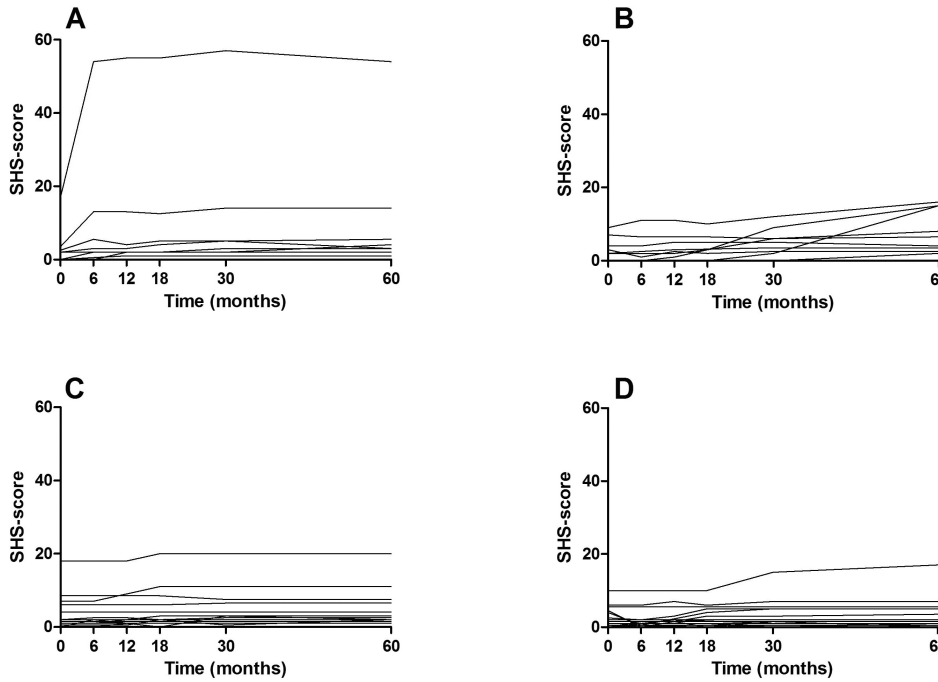


**Figure 2.** Sharp- van der Heijde Score at every time point for individual patients who were either A) anti-citrullinated protein antibody (ACPA) positive and treated with placebo (n=15), B) ACPA positive and treated with MTX (n=12), C) ACPA negative and treated with placebo (n=40), or D) ACPA negative and treated with MTX (n=43). SHS: Sharp-van der Heijde Score, MTX: methotrexate, ACPA: anti-citrullinated protein antibody.

as an increase in SHS of ≥5 points in year 1 (figure 2A).[77, 78] None of the other patients showed rapid radiological progression.

## DISCUSSION

The PROMPT study, a randomised clinical trial in patients with UA, was set up to establish whether very early treatment with MTX could induce drug-free remission or prevent progression to RA (1987). Early study results showed that MTX can postpone progression from UA to RA and suppresses radiological damage progression, in particular in ACPA-positive patients.[4] In this study we have found that after 5 years there is little lasting benefit of early MTX treatment. Overall, patients with UA treated with MTX did not achieve more DFR, did not progress less often to RA (1987) and had comparable damage progression compared with patients with UA who initially were treated with placebo. Only in ACPA-positive patients did initial MTX postpone progression to RA (1987). These results indicate that early treatment with MTX is ineffective in altering the disease course of UA. This may be owing to inefficacy of the drug, duration of treatment, characteristics of the targeted illness, inadequate timing of treatment, or all of the above.

MTX may be seen as the cornerstone of antirheumatic treatment,[13, 14] yet MTX monotherapy as initial treatment in patients with RA is often inferior to initial combination treatment with corticosteroids or biological DMARDs.[15-18] It may be that such initial combination treatment in our population would have been more successful in altering the disease course than MTX monotherapy. It is also possible that discontinuation of MTX after 1 year was too soon, but longer treatment cannot be seen as induction therapy, which was the target of the PROMPT study.

The finding that initial treatment with MTX delayed progression to 1987 classifiable RA only in ACPA-positive patients suggests that the effect of treatment may depend on the type of illness presenting as UA. We found that ACPA and RF are independent predictors for disease progression to RA (1987) after 60 months. Time to progress to RA (1987) was significantly shorter in ACPA-positive patients than in the ACPA-negative patients. Absence of ACPA was the only independent predictor of drug-free remission after 5 years. ACPA-positive patients showed more radiographic progression, despite the fact that having progressed to classifiable RA many started treatment with open-label MTX, after which damage progression was suppressed. Overall, we found no difference in radiographic progression between the MTX- or placebo-treated groups. These results suggest that ACPA-positive and ACPA-negative early arthritis are different disease entities, which may require different treatments. In addition, the persistence of remission in the majority of ACPA-negative patients (also those treated with placebo) suggests that these had a temporary disease, which could not be identified at presentation, by symptom duration or characteristics other than ACPA status.

It might be that we started initial treatment with MTX too late. We included and treated patients who were at the time considered to have UA, but who now would be classified as RA, based on the 2010 classification criteria for RA.[5] In retrospect, 43 patients (39%) of the patients included as UA fulfilled the 2010 ACR/EULAR criteria at baseline, 23 of whom were ACPA positive. It is possible that for these patients the opportunity to achieve a change in the disease course by whatever treatment, might already have been lost. On the other hand, the new criteria may also misclassify some patients as having RA, and lead to overtreatment. Twenty-four of the 43 patients fulfilling the 2010 criteria were randomised to initial placebo treatment, and six of those 24 achieved clinical remission. This means that, had we started MTX in all patients who fulfilled the 2010 criteria, we would have overtreated these six patients (25%). We also started MTX treatment in 36 patients who in retrospect did not fulfil the 2010 classification criteria, which may also qualify as overtreatment. Of these patients, 13 did progress to RA (1987), which more effective treatment might have prevented.

In summary, in this randomised clinical trial comparing the outcomes after 5 years of initial MTX treatment and placebo in patients with UA, there is no lasting effect of MTX treatment given in the first year. A positive ACPA status and radiological damage at baseline are independent predictors for progression to RA and a negative ACPA status is a predictor for DFR. The observed rate of spontaneous remission, particularly in the ACPA-negative

patients, demonstrates that initiation of MTX treatment in all patients who fulfil the 2010 ACR/EULAR criteria would constitute overtreatment in 25% of patients. On the other hand, mostly in ACPA-positive patients, initial MTX monotherapy is insufficient to prevent disease progression. Further research should focus on early and correct recognition of RA, as well as identifying a treatment that might truly alter the disease process.

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