Towards improved treatment of undifferentiated and rheumatoid arthritis

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Disease activity, joint damage and functional disability and the effect of methotrexate treatment in patients with undifferentiated arthritis with or without anti-citrullinated protein antibodies

A rationale for early treatment of undifferentiated arthritis

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Abstract

Objectives

To investigate the relationships between disease activity, joint damage and functional disability, and the effect of methotrexate (MTX) therapy, in patients with undifferentiated arthritis (UA) with or without anti-citrullinated protein antibodies (ACPA).

Methods

In the PROMPT study, 110 UA patients were randomized to one year MTX or placebo therapy. The disease activity score (DAS), health assessment questionnaire (HAQ) and patient-reported symptoms on a VAS were measured 3-monthly. Joint damage was scored on 6-monthly radiographs using the Sharp-van der Heijde score (SHS). The longitudinal relationships between DAS-HAQ, DAS-SHS and SHS-HAQ, and the effect of MTX treatment on all outcomes were analyzed via generalized estimating equations (GEE) regression. Differential associations for ACPA-positive and ACPA-negative patients were explored via interaction terms.

Results

A change in DAS was related to a change in HAQ (beta=0.15, 95%CI 0.08-0.21) and a change in SHS (beta=0.24, 95%CI 0.03-0.44), for both ACPA-positive and ACPA-negative UA patients. The still low SHS was not associated with the HAQ. Compared with placebo, MTX treatment was associated with lower DAS (beta=-1.0, 95%CI -1.4;-0.6), less symptoms, and lower SHS (beta=-5.1, 95%CI -7.9;-2.3) in ACPA-positive, but not in ACPA-negative patients. HAQ decreased significantly only in ACPA-positive patients (beta=-0.03, 95%CI -0.05;-0.01).

Conclusion

Similar to RA, in UA, disease activity is related to functional disability and joint damage, irrespective of ACPA, providing a rationale for early intensive treatment of UA. MTX therapy improves symptoms, function and damage progression only in ACPA-positive UA, indicating that effective therapy for ACPA-negative UA needs yet to be found.

INTRODUCTION

Traditionally, for rheumatoid arthritis (RA) a relationship between disease activity and joint damage has been established as well as an association of both of them with functional disability.[1-5] This forms an important part of the rationale behind current RA treatment: aiming at minimal disease activity and inhibition of radiographic progression in order to maintain functional ability. As a result, early start of disease-modifying anti-rheumatic drugs (DMARDs), combination therapies, biologicals, and tight control strategies, have significantly improved the outcome of RA.[6-8]

It has been suggested to start treatment even earlier, in patients with undifferentiated arthritis (UA), aiming at a 'window of opportunity' for remission induction or even cure.[9] This is in part based on the observation that in 40% of UA patients the disease progresses to RA within three years and joint damage and functional impairment can already be present.[10-12] If relationships between inflammation, joint damage and function can be shown to exist in UA as in RA, this would give more insight into the entity of undifferentiated arthritis and provide an additional argument for early intensive treatment in UA.

In the PROMPT study, we recently showed that one year methotrexate (MTX) therapy in UA delayed, but not prevented, the diagnosis of RA and reduced radiographic progression compared with a delayed start of DMARD treatment, in anti-citrullinated protein antibody (ACPA)-positive but not in ACPA-negative patients.[13] This observation fits with the growing evidence that ACPA-positive and ACPA-negative arthritis represent two different disease entities, which might need a different therapeutic approach.[14-16] However, the use of fulfilling the 1987 ACR criteria for RA as primary outcome in the PROMPT study has been questioned.[17] If the effect of MTX treatment on more validated outcome measures as disease activity, functional ability and patient-reported symptoms would also be different for ACPA-positive and ACPA-negative patients, this would strengthen our previous findings and have implications for future trials investigating treatment strategies for UA.

Therefore, in the current paper, we set out to investigate i) whether in UA a relationship exists between disease activity and functional disability, disease activity and radiographic damage, and between joint damage and disability, ii) whether MTX treatment in UA is beneficial with regard to disease activity, functional ability and patient-reported symptoms, and iii) whether the results for i) and ii) are different for ACPA-positive or ACPA-negative UA patients.

PATIENTS AND METHODS

Patient population

The study group comprised 110 patients with UA (DMARD-naive, symptoms <2 years), randomized in the PROMPT study to one year MTX or placebo therapy.[13] All patients fulfilled the 1958 ACR criteria for probable RA, and did not fulfill any other rheumatologic classification criteria.[18] Treatment started with 15 mg MTX or 6 placebo tablets and

every three months the dose was increased by 5 mg (2 tablets) to a maximum of 30 mg (12 tablets) in order to achieve a disease activity score (DAS) <= 2.4.[19] If during the trial a patient progressed to fulfilling the 1987 ACR criteria for RA, medication was switched to open-label MTX.[17] Thus, the study was a delayed-design trial, and the real difference between MTX and placebo is underestimated. Further details on the study and results on the primary outcomes diagnosis and radiographic progression have been published elsewhere.[13]

Outcomes

At study inclusion and at 3, 6, 9 and 12 months the DAS was scored, functional ability was measured via the health assessment questionnaire (HAQ) and patients reported symptoms of disease activity, pain, morning stiffness and fatigue on a 100 mm visual analog scale (VAS).[19,20] The DAS consisted of a 44 swollen joint count (SJC), the Ritchie articular index (RAI), the erythrocyte sedimentation rate (ESR) and a VAS for general health status. C-reactive protein (CRP) was also measured. Radiographs of hands and feet obtained at baseline, 6, 12 and 18 months were available in 102 patients (93%). Radiographic damage was scored according to the Sharp-van der Heijde score (SHS) in chronological order by two independent readers blinded for patient identity and treatment allocation.[21] The interobserver correlation coefficient for the change scores was 0.90 and the intraobserver coefficients were both 0.99. Radiographic progression was defined as an increase in SHS >3, according to the smallest detectable change (SDC) which was 3.02 in this study.[22] The presence of IgM rheumatoid factor (RF) and ACPA was determined in baseline sera with commercial kits (Euro-Diagnostica, Arnhem, The Netherlands). ACPA levels >25 IU/ml and RF levels >5 IU/ml were considered positive.

Statistical analysis

Generalized estimating equations (GEE)

We explored the longitudinal relationships between disease activity, radiographic damage and functional disability across 12 months time using longitudinal regression analysis with generalized estimating equations (GEE).[23] The advantage of GEE above ordinary regression techniques is that it takes into account the whole pattern of repeated measurements over time, corrects for the fact that these are correlated within individual patients, and is robust against violation of normality. To correct for the within-patient correlation, we chose an 'unstructured working correlation matrix', which would impose the least restriction on the models and best fitted our data. The Identity link and the linear model were applied. SPSS version 16.0 software (SPSS, Chicago, IL) was used.

Relationships DAS-HAQ, DAS-SHS, SHS-HAQ

To investigate the relations between DAS-HAQ, DAS-SHS and SHS-HAQ, three GEE models were built following a multistep approach. For each model, in the first step the outcome variable (3-monthly HAQ scores or 6-monthly SHS) was modeled with the covariate time (in months) to describe the course of the variable in time. In the second

step the explanatory variable of interest (DAS or SHS) was added to the model. In the third step potential baseline predictors were introduced to investigate their contributory or confounding effect on the relationship of interest. Finally, we investigated whether the identified associations were different for ACPA-positive or ACPA-negative patients by introducing interaction terms.

Autoregressive GEE

Because we were particularly interested in the longitudinal relationships (meaning for example, in patients whose mean DAS increases/decreases, the HAQ simultaneously increases/decreases) rather than the cross-sectional relationships (patients with a high DAS have on average a high HAQ), we used first order autoregression, correcting each value of the outcome variable for the value one time point earlier, which can be interpreted as modeling change.[24] For the relation DAS-HAQ for example, we related the consecutive 3-months mean interval DAS (DAS_{t-1} + DAS_t)/2 with the HAQ at the end of each time interval, corrected for the previous HAQ. This resulted in the following regression equation: HAQ_t = constant + $ß_1$time + $ß_2DAS_{mean\ interval}$ + $ß_3HAQ_{t-1}$ + [corr] + error, in which the ß's are the regression coefficients and [corr] the correction for the working correlation structure.

Effect of MTX treatment

The effect of MTX versus placebo treatment on the DAS, its separate components, the HAQ, patient-reported VAS scores and SHS during the one year treatment period, was investigated in two ways. Time-integrated means were calculated for the outcome variables as areas-under-the-curve divided by the total time. The time-integrated means were compared between MTX and placebo treatment via student t-test or Mann-Whitney test for the total group and stratified for ACPA status. Secondly, we used GEE analysis to be able to correct for the within-patient correlation and potential confounders. For each outcome the 3-monthly (for SHS 6-monthly) scores were modeled with time, adjusted for the baseline value. In a stepwise manner, the effect of treatment group, ACPA, potential modifying baseline variables and the interaction between ACPA and treatment was investigated. For example, the final regression equation for the outcome DAS was: DAS_t = constant + $ß_1$time + $ß_2$DASbaseline + $ß_3$treatment + $ß_4$ACPA + $ß_5$treatment*ACPA + $ß_6$confounder + [corr] + error.

RESULTS

At baseline, all UA patients had active disease, but ACPA-positive patients had significantly higher ESR and CRP levels, were more often RF-positive and already displayed more joint damage than ACPA-negative UA patients (table 1).

Relationships DAS-SHS-HAQ

A total number of 531 (419 mean interval) DAS scores, 526 HAQ scores and 423 (313 mean interval) SHS scores were available for the GEE analyses.

Table 1. Baseline characteristics of 110 UA patients included in the PROMPT study, stratified by ACPA status.

Baseline characteristics	ACPA-positive (n=27)	ACPA-negative (n=83)	p-value
Age, mean ± SD	50.8 (10.6)	51.6 (14.0)	0.788
% Females	17 (63%)	56 (68%)	0.667
Symptom duration, median (IQR) weeks	40 (29-67)	42 (25-68)	0.962
DAS, mean ± SD	2.72 (0.72)	2.59 (0.79)	0.442
RAI, median (IQR)	5.0 (2.0-9.0)	6.0 (3.0-10.0)	0.851
SJC, median (IQR)	2.0 (1.0-4.0)	3.0 (2.0-5.0)	0.042
CRP, median (IQR) mg/L	7 (4-16)	3 (2-9)	0.013
ESR, median (IQR) mm/hr	25 (7-32)	9 (4-21)	<0.001
HAQ, mean ± SD	0.77 (0.60)	0.79 (0.53)	0.884
VAS global health, mean ± SD mm	40 (24)	39 (23)	0.897
% RF positive	26 (96%)	13 (18%)	<0.001
SHS, median (IQR)	1.5 (0-4.0)	0 (0-2.0)	0.015
% Erosions >=1	15 (56%)	11 (13%)	0.000

ACPA=anti-citrullinated protein antibodies; SD=standard deviation; IQR=interquatile range; DAS= disease activity score; RAI=Ritchie articular index; SJC=swollen joint count; CRP=C-reactive protein; ESR= erythrocyte sedimentation rate; HAQ=health assessment questionnaire; VAS=visual analogue scale; RF=rheumatoid factor; SHS=Sharp/van der Heijde score

DAS-HAQ

The GEE model for the relation DAS-HAQ showed that on average the HAQ decreased in time in the total patient group (table 2A, model 1). In addition, the mean interval DAS was significantly longitudinally related to the HAQ (beta=0.15) (table 2A, model 2). This relationship was not modified by age, gender, ACPA status or treatment arm (table 2A, model 3). As the HAQ scores were corrected for the previous HAQ (first order autoregression), the results can be interpreted longitudinally: UA patients who have a change in mean interval DAS of 1 point, have a corresponding change in HAQ of 0.15 points, compared to the previous time interval. This relation was present in both ACPA-positive and ACPA-negative patients (beta=0.17 and 0.14, respectively) (table 2A, model 4), and the interaction term DAS*ACPA was not significant (beta=0.027, 95%CI -0.10;0.15, p=0.672). Of the individual components of the DAS, the RAI and the SJC, but not the ESR were significantly longitudinally associated with the HAQ (data not shown).

DAS-SHS

The GEE model for the relation DAS-SHS showed that on average the SHS increased in time (table 2B, model 1). In addition, the mean interval DAS was significantly longitudinally related to the SHS (beta=0.24), adjusted for the previous SHS (table 2B, model 2).

Table 2. Building the GEE model for the longitudinal relationship between A. disease activity (DAS) and functional disability (HAQ) in UA patients, and B. between disease activity (DAS) and joint damage (SHS).

A	Model 1	Model 2	Model 3	Model 4
Time (months)	-0. 01* (-0.02;-0.01)	0.004 (-0.01;0.01)	0.004 (-0.01;0.01)	0.004 (-0.01;0.01)
HAQ previous	-	0.93* (0.90;0.96)	0.93* (0.90;0.96)	0.93* (0.90;0.96)
DAS mean interval	-	0.15* (0.08;0.21)	0.15* (0.09;0.21)	-
In ACPA pos.				0.17* (0.07;0.27)
In ACPA neg.				0.14* (0.06;0.21)

B	Model 1	Model 2	Model 3	Model 4
Time (months)	0.10* (0.06;0.14)	-0.06* (-0.12;-0.01)	-0.05* (-0.10;0.004)	0.004 (-0.01;0.01)
SHS previous		1.34* (1.25;1.44)	1.32* (1.22;1.41)	0.93* (0.90;0.96)
DAS mean interval		0.24* (0.03;0.44)	0.28* (0.04;0.52)	-
In ACPA pos.				0.61* (0.03;1.18)
In ACPA neg.				0.17# (-0.004;0.34)

Values are the regression coefficients (95% confidence intervals) for the dependent variable functional disability as measured by the HAQ (A) or joint damage as measured by the SHS (B). Model 1 describes the course of the HAQ/SHS over time. Model 2 describes the longitudinal relationship between disease activity and functional disability/joint damage in time, with correction for the previous HAQ/SHS score (autoregression). In model 3 potential confounders were added to the model to investigate their influence on the relationship between disease activity and functional disability (gender, age, ACPA, treatment arm, all not significant) or joint damage (gender, baseline CRP*, ACPA, treatment arm*). In model 4 the interaction between DAS and ACPA was investigated to see whether the relation between disease activity and functional ability/damage was different for ACPA-positive or ACPA-negative patients. *p<0.05, #p=0.056. For abbreviations see table 1.

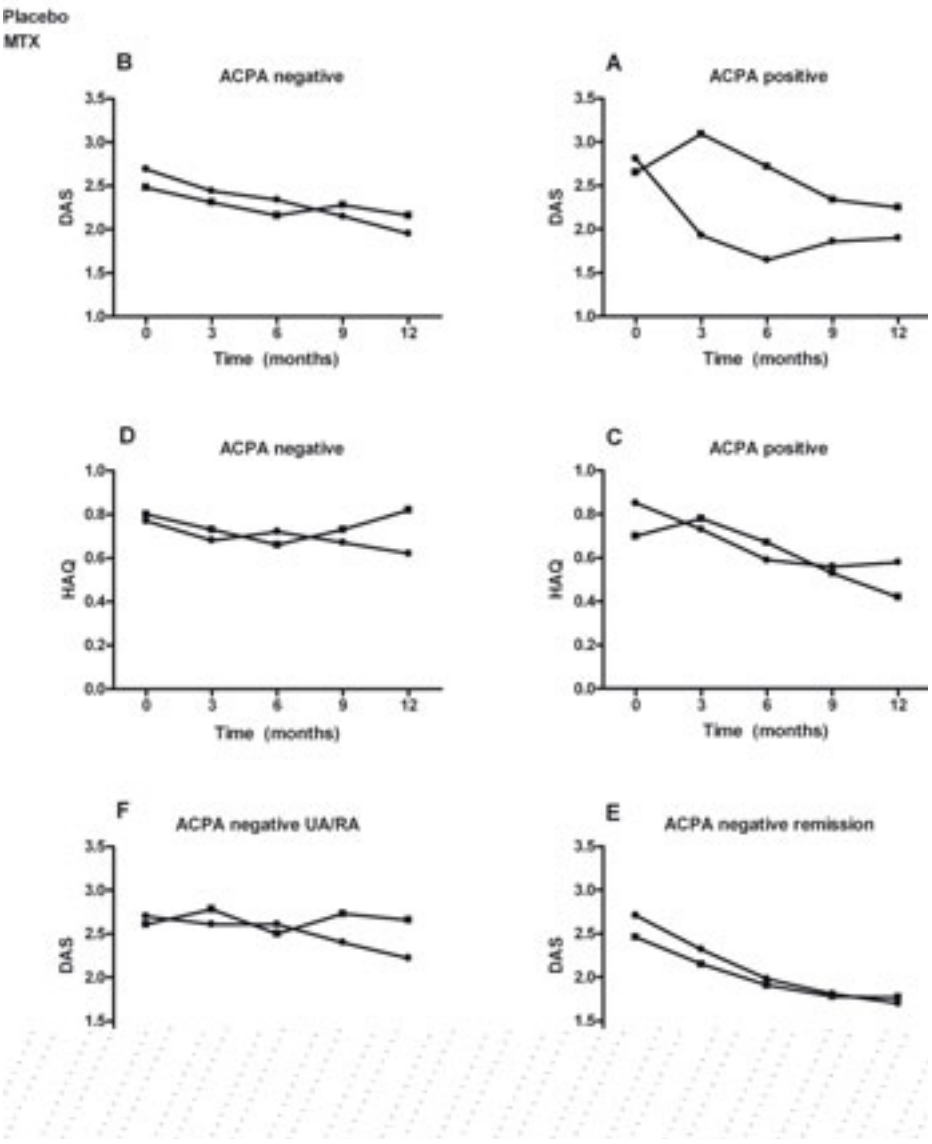

Figure 1. The development of the mean DAS (A,B) and HAQ (C,D) during 12 months of MTX or placebo treatment in the PROMPT study, stratified for ACPA-positive (n=27) and ACPA-negative (n=83) UA patients. E and F show the subanalysis of DAS in ACPA-negative patients who achieved remission or had persistent UA/RA. For abbreviations see table 1.

This implies that a change in disease activity over time results in a corresponding change in radiographic damage. Although only 8 (11%) ACPA-negative patients compared to 12 (44%) ACPA-positive patients experienced damage progression above the SDC, the relation between DAS and SHS was found for both patient subsets. Although the magnitude of the relation appeared larger in ACPA-positive patients (beta=0.61) than in ACPA-negative patients (beta=0.17), the interaction term did not reach significance (beta=0.44, 95%CI-0.11;0.99, p=0.115). Confirming our previous findings, MTX treatment was a significant determinant of (less) joint damage over time (beta=-0.56, 95%CI -1.0; -0.13, p=0.012), but it did not influence the relation between DAS and SHS.[14] Trends for a longitudinal relation with joint damage were found for the RAI and the SJC, but not for the ESR (data not shown).

SHS-HAQ

The mean interval SHS was not longitudinally associated with the HAQ in the GEE analysis (beta=-0.02, 95%CI -0.04;0.001), neither for ACPA-positive nor ACPA-negative UA patients separately (data not shown).

Table 3. Time-integrated means of disease activity parameters, functional disability and patient-reported symptoms over 12 months time, compared between MTX or placebo treatment stratified for ACPA status via Mann-Whitney or t-tests.

	ACPA-positive			ACPA-negative		
Parameter (AUC)	MTX (n=12)	Placebo (n=15)	p-value	MTX (n=43)	Placebo (n=40)	p-value
DAS	2.0 (1.0)	2.7 (0.5)	0.044	2.4 (0.8)	2.3 (1.0)	0.889
Ritchie, median (IQR)	2 (1-6)	5 (4-8)	0.064	6 (3-9)	4 (2-11)	0.652
SJC, median (IQR)	1 (1-2)	2 (2-5)	0.048	2 (1-3)	2 (1-4)	0.531
ESR, median (IQR)	12 (8-22)	23 (10-27)	0.130	10 (5-16)	9 (4-19)	0.766
CRP, median (IQR)	3 (2-5)	12 (2-20)	0.121	5 (3-9)	4 (2-6)	0.201
HAQ, median (IQR)	0.4 (0.1-1.3)	0.6 (0.1-1.0)	0.979	0.8 (0.2-1.1)	0.7 (0.3-1.2)	0.604
VAS disease activity	26 (18)	41 (17)	0.043	39 (16)	39 (18)	0.961
VAS pain	26 (19)	38 (16)	0.069	39 (15)	37 (18)	0.545
VAS morning stiffness	28 (18)	37 (20)	0.248	35 (19)	34 (22)	0.779
VAS general health	26 (20)	34 (20)	0.329	39 (17)	36 (16)	0.388
VAS fatigue	34 (26)	37 (26)	0.809	48 (24)	42 (23)	0.252
SHS, median (IQR)	0.5 (0.4-2.6)	3.0 (1.0-6.5)	0.050	0 (0-1.0)	0 (0-1.5)	0.867

Mean (standard deviations) are given except where indicated otherwise. AUC=area under the curve; MTX=methotrexate. For further abbreviations see table 1.

Table 4. The overall effect of MTX versus placebo treatment on DAS during 12 months and the differential effect in ACPA-positive and ACPA-negative UA patients, results from the GEE analysis.

	Model 1	Model 2	Model 3	Model 4	Model 5
Time (months)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.06;-0.03)	-0.05* (-0.07;-0.03)
Baseline DAS	0.85* (0.69;1.01)	0.88* (0.729;1.03)	0.85* (0.69;1.01)	0.71* (0.53;0.88)	0.71* (0.55;0.87)
ACPA pos	-	-	0.01 (-0.31;0.33)	0.002 (-0.26;0.27)	-
MTX therapy	-	-0.33* (-0.58;-0.09)	-	-0.27* (-0.49;-0.04)	-
In ACPA pos					-1.00* (-1.4;-0.6)
In ACPA neg					-0.04 (-0.3;0.2)

Values are the regression coefficients (95% confidence intervals) for the dependent variable disease activity as measured by the DAS. Model 1 describes the course of the DAS over time, corrected for the baseline DAS. Model 2 describes the effect of MTX treatment on DAS under the correction of time. Model 3 describes the effect of ACPA on DAS under correction of time. In model 4 known predictive factors (gender*, age*, baseline HAQ) were added to the model to investigate their influence on the effect of MTX therapy on DAS. In model 5 the interaction between MTX and ACPA was investigated to see whether the effect of MTX was different for ACPA-positive and ACPA-negative patients. *p<0.05. MTX=methotrexate; GEE=generalized estimating equations. For further abbreviations see table 1.

Effect of MTX on disease activity, patient-reported symptoms, function and damage

In figure 1 (A,B) the development of the mean DAS during 12 months of MTX or placebo treatment is depicted for the ACPA-positive and ACPA-negative patients. The ACPA-positive patients treated with MTX showed a large initial decrease in DAS compared to the patients treated with placebo. For ACPA-negative patients, the DAS decreased less and irrespective of the treatment group. However, 32/83 (39%) ACPA-negative patients achieved (spontaneous) remission during the study, and this might have influenced the results. After stratification, in the 41 (49%) of the ACPA-negative patients who continued to have UA or progressed to RA still no treatment effect emerged and DAS scores remained elevated (figure 1E,F). This suggests that the ACPA-negative UA patients with the propensity to have persistent/progressive arthritis, seem to have less benefit from MTX therapy than ACPA-positive UA patients.

This was further investigated by comparing the 12 months time-integrated mean DAS, RAI, SJC, ESR, CRP, VAS scores, HAQ and SHS between the MTX and placebo group, separate for ACPA-positive and negative patients (table 3). For ACPA-negative patients the time-integrated means of all parameters were similar for both treatment groups. However, for ACPA-positive patients, the time-integrated means of DAS, SJC, VAS disease

Table 5. The differential effects of MTX versus placebo treatment on disease activity parameters, patient-reported symptoms and functional disability during 12 months in ACPA-positive and negative UA patients.

	in ACPA-positives (n=27)			in ACPA-negatives (n=83)		
Effect of MTX on parameter	Beta	95% CI	p-value	Beta	95% CI	p-value
DAS	-1.00	-1.4 ; -0.6	<0.001	-0.04	-0.3 ; 0.2	0.763
SJC	-1.88	-3.9 ; 0.1	0.065	-0.41	-1.2 ; 0.4	0.310
TJC	-4.15	-6.1 ; -2.2	<0.001	-0.68	-2.3 ; 1.0	0.421
ESR	-7.54	-11.5 ; -3.6	<0.001	-1.45	-4.1 ; 1.2	0.284
CRP	-4.97	-9.3 ; -0.6	0.025	0.58	-2.1 ; 3.3	0.670
VAS						
disease activity	-12.43	-22.5 ; -2.4	0.015	-2.17	-4.6 ; 9.0	0.532
pain	-10.82	-21.1 ; -0.5	0.039	3.15	-3.1 ; 9.4	0.322
morning stiffness	-8.80	-21.1 ; 3.5	0.160	2.59	-3.9 ; 9.1	0.435
general health	-6.34	-16.2 ; 3.5	0.207	2.44	-3.6 ; 8.5	0.430
fatigue	-3.08	-14.4 ; 8.2	0.593	2.36	-5.1 ; 9.8	0.533
HAQ	-0.05	-0.32 ; 0.21	0.702	-0.04	-0.16 ; 0.09	0.567
SHS	-5.11	-7.9 ; -2.3	<0.001	0.12	-0.7 ; 1.0	0.781

Each row represents a separate GEE analysis from which the effect of MTX therapy (beta) is reported. MTX=methotrexate; CI= confidence interval. For further abbreviations see table 1.

activity and SHS were significantly lower in the MTX group than in the placebo group and there were trends for lower RAI, ESR, CRP and VAS pain.

This was confirmed in the subsequent GEE analysis. MTX treatment was significantly associated with a 0.27 point lower DAS over time (table 4, model 4), but the effect was different for ACPA-positive and ACPA-negative patients according to the interaction term treatment*ACPA (beta=-0.96, 95%CI -1.45;0.47, p<0.001). ACPA-positive patients treated with MTX had on average a 1.0 point lower DAS than patients treated with placebo, while for ACPA-negative patients there was virtually no treatment effect (table 4, model 5). Similar results were found for the effect of MTX treatment on the SJC, RAI, ESR, CRP, VAS scores for pain and disease activity and SHS in ACPA-positive patients (table 5). In contrast, MTX did not significantly reduce the VAS for morning stiffness, general health or fatigue compared with placebo therapy.

For the outcome HAQ, there appeared to be no effect of MTX versus placebo therapy,

neither in the total group, nor for ACPA-positive and negative patients separately (figure 1C,D; table 3 and 5). However, the interaction term ACPA*time revealed that the HAQ improved significantly over time in the ACPA-positive patients (beta=-0.03, 95%CI -0.05;-0.01, p=0.002), but not in the ACPA-negative patients (beta=-0.003, 95%CI -0.01;0.01, p=0.515). This might still reflect an effect of MTX treatment in ACPA-positive patients, since 14 out of 15 ACPA-positive patients in the placebo group switched to open-label MTX during the first 12 months of the study, as their UA progressed to RA.

DISCUSSION

We have demonstrated that in patients with undifferentiated arthritis (UA) disease activity is closely related to functional disability and radiographic joint damage, irrespective of the ACPA status, providing a rationale for early intensive treatment. In addition, we showed that MTX therapy improved disease activity, symptoms and function, but only in ACPA-positive UA patients, indicating that effective therapy for ACPA-negative UA needs yet to be found.

We showed that in UA, similar to in RA, changes in disease activity, measured by the 3-month mean interval DAS, were significantly related to changes in physical function, measured by the HAQ.[1,2,5] Using autoregressive GEE, we found that the HAQ was predominantly determined by the previous HAQ, and further by changes in disease activity, with for every 1 point change in DAS a corresponding 0.15 point change in HAQ. This can be regarded as a clinically relevant effect, as the minimal important difference for the HAQ varies around 0.10 and 0.20 in clinical practice and clinical trials, respectively.[25,26] Furthermore, the relation DAS-HAQ existed for both ACPA-positive and ACPA-negative UA patients in comparable strength. Not only the composite measure DAS, but also the separate parameters RAI and SJC were associated with the HAQ, which strengthens the results. These findings suggest that in UA, similar to in RA, keeping disease activity as low as possible will maintain functional ability.

Fluctuations in disease activity also precede changes in radiological progression in RA.[24,27] Correspondingly, for UA, we found that for every 1 point increase in DAS radiographic damage increased with 0.3 SHS points. The effect was not large, probably reflecting the overall minimal joint damage (progression) in this population, but it was present in both ACPA-positive and ACPA-negative UA patients. Interestingly, the effect appeared more pronounced in ACPA-positive patients, similar to what has been reported for RF-positive RA patients.[24] These results combined suggest that already in this early stage of arthritis it is important to rapidly lower disease activity to prevent damage progression. Furthermore, the resemblance to RA adds to the view that UA (ACPA-positive and negative) is likely to be an early stage of RA.

We were not able to find a relationship between joint damage and functional disability in UA. Due to the large proportion of patients without radiographic damage in our study population (80%), we might have lacked power to detect any association. On the other hand, our results fit with the observation that also in RA this relationship is more pronounced later in the disease course.[1,5,28,29] As UA is an even earlier phase of arthritis, the amount of joint damage in UA might be too little to result in difficulties in daily

physical functioning. Also, the HAQ might not be sensitive enough to pick up subtle changes in joint damage in UA, especially since the HAQ is strongly influenced by disease-aspecific factors such as pain, depression and comorbidity as well.[30-32]

Previously we showed that early versus delayed MTX treatment in UA postponed, but not prevented, the progression to RA and reduced radiographic damage, but only in ACPA-positive patients.[13] However, the use of the 1987 ACR criteria as primary outcome in that study has been questioned, since these were neither designed nor validated for that purpose. We now showed that MTX rapidly improved the DAS, SJC, RAI, ESR, CRP, and VAS scores for pain and disease activity, again only in ACPA-positive patients. Finding similar effects in multiple outcome measures, both physician- and patient-oriented, with two types of analyses (AUC and GEE), adds to the robustness of our results. Given the delayed-design of the PROMPT study, a considerable number of ACPA-positive patients switched from placebo to open-label MTX during the first 12 months. Therefore, the reported effects and differences between MTX and placebo are even underestimated and will probably be larger in reality.

We have shown that MTX therapy does not appear to have a positive effect in ACPA-negative UA, neither by postponing RA nor reducing signs and symptoms.[13] One could argue that ACPA-negative patients, with lower disease activity at baseline, could improve less than ACPA-positive patients. This was indeed true regarding the ESR and CRP levels, but not for the DAS, RAI or VAS scores. As ACPA-negative UA is a heterogeneous patient population, including patients who will not progress to RA, or who will remit spontaneously, this might also have diluted any treatment effect. Therefore, we performed a subanalysis leaving out the ACPA-negative patients who achieved spontaneous remission, but for the remaining ACPA-negative UA patients who had persistent arthritis, still no treatment effect emerged. Not even a trend for improvement was observed. A type 2 error cannot be ruled out, but would not explain why significant effects were found in the smallest patient subset (n=27 ACPA-positives) and not in the largest population (n=83 ACPA-negatives). Therefore, in light of the growing evidence that ACPA-positive and ACPA-negative arthritis represent different disease entities, it is conceivable that ACPA-negative UA may need a different therapeutic approach than ACPA-positive UA.[14-16,33]

In light of the recently published new 2010 ACR criteria for RA, this has even further implications, as these criteria aim to identify UA patients with a sufficient risk of persistence to be considered for DMARD therapy.[34] However, when the disease entity RA is redefined by these new criteria, existing data on available therapies will have less relevance, as these come from trials in which a different patient population was included, namely patients fulfilling the 1987 ACR criteria for RA. Moreover, our observation that MTX appears ineffective in a subset of patients in an earlier phase of arthritis (58% of the PROMPT population fulfilled the new ACR criteria at baseline), indicates that it can not be assumed that existing therapeutic strategies in 'old criteria RA' will perform the same in patients fulfilling the new criteria for RA. Therefore, not only our findings, but also other strategies need to be (re)investigated and validated before clear treatment recommendations for UA can be given.

In summary, we have provided a rationale for starting early intensive treatment in UA since disease activity is closely related to functional disability and radiographic damage, irrespective of the ACPA status. MTX monotherapy improves symptoms, function and damage progression, but only in ACPA-positive patients, and it is not sufficient to prevent progression to RA. This implicates that for both ACPA-positive and negative UA better treatment strategies are needed.

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