Towards improved treatment of undifferentiated and rheumatoid arthritis

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Drug-free remission, relapse or persistent disease after discontinuation of methotrexate or placebo therapy in patients with undifferentiated arthritis

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Abstract

Objectives

To investigate (predictors for) drug-free remission, relapse or persistent disease after discontinuation of methotrexate (MTX) or placebo therapy in undifferentiated arthritis (UA).

Methods

In the PROMPT study, 110 UA patients were randomized to one year MTX or placebo therapy. If a patient fulfilled the 1987 ACR criteria for rheumatoid arthritis (RA), open-label MTX was started. In all other patients, after 12 months, study medication was discontinued. Predictors for drug-free remission after 30 months were identified via logistic regression. Focusing on the patients who discontinued MTX, clinical and radiographic outcome and predictors for 'non-remission' (recurrent, persistent or progressive arthritis) were assessed.

Results

After 30 months, 18 (33%) patients achieved drug-free remission after MTX therapy, compared with 17 (31%) after placebo therapy. Drug-free remission was associated with the absence of APCA, little baseline joint damage, age>65 and low continued disease activity, regardless of treatment. Thirty-nine (71%) UA patients who during MTX treatment did not progress to RA discontinued MTX, followed by an increase in mean DAS from 1.67 (SD 0.77) to 1.96 (SD 0.71) and continued radiographic progression, predominantly in the ACPA-positive patients. After stopping MTX, arthritis recurred, persisted or progressed in 21/39 (54%), predicted by the presence of ACPA, joint damage and age<65, while 18/39 (46%) achieved drug-free remission.

Conclusions

In UA, drug-free remission is not induced by MTX therapy, but determined by self-limiting disease. Non-remission after stopping MTX is common and associated with ACPA, joint damage and age<65. Better remission-induction therapies and safer discontinuation strategies in UA are needed.

INTRODUCTION

Patients with inflammatory arthritis may present with undifferentiated arthritis (UA) not yet fulfilling any classification criteria.[1] Although up to 50% of UA patients have self-limiting disease, a considerable proportion has an early and/or mild manifestation of rheumatoid arthritis (RA). To identify the latter patients, recently, new classification criteria for RA have been published.[2] Still, some early arthritis patients may not meet these criteria and remain 'UA'. Since for patients with recent-onset RA, a timely start of disease-modifying antirheumatic therapy (DMARDs) has proven crucial for achieving better clinical and radiographic outcomes[3], starting antirheumatic therapy already in UA might result in even more sustained benefits and potentially a chance for cure.
In the PROMPT study, we recently showed that one year methotrexate (MTX) therapy compared with placebo therapy effectively delayed, but not prevented, the development of UA into RA, and reduced radiographic progression in patients with anti-citrullinated protein antibody (ACPA)-positive UA.[4] ACPA-negative UA patients, however, did not benefit from MTX therapy. These results provided first evidence for the efficacy of MTX treatment in a subset of UA patients and have encouraged rheumatologists to start treatment earlier.
To assess whether MTX could induce prolonged drug-free remission, after one year of treatment in the PROMPT-study, study medication was tapered and discontinued in all patients whose UA had not progressed to RA. In addition, given that continuing treatment might be overtreatment in some patients, we assessed which UA patients did not progress to RA after stopping MTX, and which patients were at risk for further disease progression.
To investigate these two questions, we compared the rate and predictors of drug-free remission after one year MTX versus placebo therapy. In addition, we focused on the subgroup of UA patients who did not develop RA under MTX therapy and assessed the clinical and radiographic outcome of stopping MTX, as well as predictors for 'non-remission', defined as recurrent, persistent or progressive arthritis.

PATIENTS AND METHODS

Patient population and treatment

The study group comprised 110 patients with UA (not meeting the then available American College of Rheumatology (ACR) 1987 criteria for RA) who participated in the PROMPT study.[4] Since no classification criteria for UA exist, all patients fulfilled the 1958 ACR criteria for probable RA and were DMARD-naive with symptoms less than two years.[5] Patients 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.[6] Steroids were not allowed. If a patient progressed to fulfilling the 1987 ACR criteria for RA, medication was switched to open-label MTX.[7] After 12 months, the study medication was tapered by 2 tablets every 4 weeks and ultimately discontinued in all patients who had not developed RA, regardless of the DAS right before tapering (12 months). If, after stopping treatment, arthritis

recurred, persisted or progressed to RA, the decision to (re)start treatment and the choice of DMARD was up to the rheumatologist.

Outcomes

After 30 months the diagnosis was recorded by the rheumatologist as UA (not meeting the ACR 1987 criteria), RA (meeting the ACR 1987 criteria) or drug-free remission. Drug-free remission was defined as the continued absence of clinical synovitis by routine joint examinations, after discontinuation of MTX or placebo, until the 30 months time point. In the 'non-remission' patients, arthritis (UA) had recurred (signs of synovitis assessed by the rheumatologist), persisted or progressed to RA (meeting the 1987 ACR criteria) after discontinuation of study medication. As reported previously, seven patients were ultimately diagnosed with osteoarthritis (n=5), diabetic arthropathy (n=1) or vasculitis (n=1).[4] For the current analyses, these patients were included as drug-free remission patients, since they satisfied the above definition. However, sensitivity analyses were performed leaving out these 7 patients as well as the 10 patients who were lost to follow-up. At baseline and at 3, 6, 9, 12 and 18 months the DAS was measured.[6] Radiographs of hands and feet obtained at baseline (for n=110), 18 months (for n=102) and 30 months (for n=89) were available, and scored according to the Sharp-van der Heijde score (SHS) in chronological order by two independent readers blinded for patient identity and treatment allocation.[8] Mean scores were used for the analyses. The interobserver correlation coefficient was 0.80 and the intraobserver coefficients were 0.91 and 0.75.

Statistical analysis

The characteristics of patients achieving drug-free remission were compared via Mann-Whitney or Chi-square tests, for the MTX and placebo therapy group separately. In the total group (n=110) possible predictors for drug-free remission, including treatment, were investigated via univariate logistic regression analysis. Predictors which had previously been reported and variables with a p-value <0.10 in univariate analysis were taken along in a multivariate analysis with a backward selection procedure (removal criterion <0.05). To avoid colinearity with the variable ACPA, baseline SHS and RF were not introduced simultaneously with but in stead of ACPA in separate models. To determine whether identified predictors were different in the context of MTX or placebo therapy, interaction terms were explored.

Next, we focused on the patients in the MTX group whose UA did not progress to RA during therapy, and thus who started tapering MTX at 12 months (n=39). The individual DAS scores just before (12 months) and right after stopping MTX (18 months) were depicted in probability plots, stratified for the patients who achieved drug-free remission or non-remission. Similarly, the cumulative SHS under MTX therapy (0-18 months) and after MTX had been stopped (0-30 months) were plotted. Potential predictors for non-remission (recurrent, persistent or progressive arthritis) after stopping MTX were explored via univariate and multivariate logistic regression analysis. P-values <0.010 were considered associative, p-values <0.05 were considered statistically significant. SPSS version 16.0 software (SPSS, Chicago, IL) was used.

RESULTS

Drug-free remission rate

Baseline characteristics of the 110 UA patients in the PROMPT study can be found elsewhere.[4] Of the 55 patients randomized to the placebo group, 29 (53%) developed RA meeting the ACR 1987 criteria during the first year and switched to open-label DMARD treatment, 5 patients dropped out and thus 21 (38%) could discontinue placebo (figure 1). After 30 months, 17 (31%) were in drug-free, spontaneous, remission. Of the 55 UA patients in the MTX group, 11 (20%) had progressed to RA within 12 months, 5 patients dropped out and thus 39 (71%) patients discontinued MTX. After 30 months, 18 (33%, p=0.838 compared with placebo treated patients) were in drug-free remission, but in 21 patients arthritis had recurred, persisted or progressed, indicating non-remission (figure 1).

Table 1. Baseline characteristics of UA patients achieving remission or non-remission after 30 months of MTX or placebo therapy.

Baseline characteristics	MTX (n=55)		Placebo (n=55)	
	Remission (n=18)	Non-remission (n=37)	Remission (n=17)	Non-remission (n=38)
Age, mean ± SD (years)	58 (15)	50 (13)	52 (15)	49 (11)
No. Females	12 (67%)	23 (62%)	10 (59%)	28 (74%)
Symptom duration (months)	8 (4-14)	12 (6-17)	9 (6-15)	8 (5-13)
DAS, mean ± SD	2.70 (0.62)	2.73 (0.85)	2.50 (0.84)	2.53 (0.74)
RAI	8 (6-10)	6 (3-11)	6 (2-9)	5 (3-9)
SJC	3 (1-4)	3 (2-6)	3 (2-6)	2 (1-3)
CRP (mg/L)	6 (3-11)	5 (3-13)	4 (3-11)	5 (3-8)
ESR (mm/hr)	13 (5-22)	11 (5-24)	12 (6-25)	8 (4-26)
HAQ, mean ± SD	0.77 (0.46)	0.79 (0.54)	0.77 (0.46)	0.78 (0.63)
No. ACPA positive	2 (11%)	10 (27%)	1 (6%)	14 (37%)
No. RF positive	6 (33%)	14 (38%)	5 (29%)	14 (37%)
SHS	0 (0-1)	0 (0-2)	0 (0-1)	1 (0-2)
No. Erosive (>=1)	3 (17%)	7 (19%)	4 (24%)	12 (32%)

Values are medians (interquartile range) unless otherwise specified. ACPA=anti-citrullinated protein antibodies; SD=standard deviation; DAS=disease activity score; RAI=Ritchie articular index; SJC=swollen joint count; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; HAQ=health assessment questionnaire; RF=rheumatoid factor; SHS=Sharp/van der Heijde score; MTX=methotrexate.

Predictors of drug-free remission in the total group

Baseline characteristics of the patients who achieved drug-free remission or non-remission are shown in table 1, separately for both treatment groups. Baseline characteristics of the patients who achieved drug-free remission after MTX or placebo therapy were

Table 2. Independent predictors for A. achieving drug-free remission after 30 months of MTX or placebo therapy in UA patients (n=110) and for B. 'non-remission' after discontinuation of one year MTX therapy in the patients with UA which had not evolved into RA (n=39).

A. Predictors for **drug-free remission** in UA, regardless of MTX or placebo	OR	95% confidence interval	p-value
ACPA negative	4.8	1.3-17.4	0.018
Age, years > 65	3.1	0.96-10.3	0.059
AUC DAS 0-12 months	0.5	0.3-0.9	0.021
B. Predictors for non-remission after stopping MTX therapy in UA	**OR**	**95% confidence interval**	**p-value**
ACPA positive	6.4	0.9-47	0.069
Age, years < 65	9.6	0.9-98	0.057
AUC DAS 0-12 months	3.2	0.7-14.9	0.146

ACPA=anti-citrullinated protein antibodies; AUC=area under the curve; DAS=disease activity score; OR= odds ratio; MTX=methotrexate.

not significantly different. Therefore, we investigated predictors for drug-free remission in the total group and identified age (OR 1.03, 95%CI 1.0-1.1, p=0.050) and the absence of ACPA (OR 5.0, 95%CI 1.4-18, p=0.013) as significant univariate predictors. Explored as a categorical variable, age >65 years was the strongest predictor for drug-free remission (OR=3.4, 95%CI 1.1-10.7, p=0.036). MTX compared with placebo therapy was not associated with more drug-free remission (OR 1.09, 95% CI 0.49-2.43, p=0.838). The multivariate analysis including ACPA, age, gender, symptom duration and treatment group, revealed absence of ACPA and age >65 as independent predictors (table 2A). Baseline SHS was also associated with drug-free remission if put in the model without ACPA (OR 0.77, 95%CI 0.56-1.05, p=0.097), but absence of RF was not. In addition, a higher area under the curve (AUC) DAS during the first 12 months of treatment was inversely associated with drug-free remission (table 2A). The effects of ACPA and age did not depend on placebo or MTX therapy (as interaction terms were not significant), suggesting that the predictors of drug-free remission reflected intrinsic characteristics of self-limiting disease and not treatment effects. The sensitivity analysis excluding the patients with osteoarthritis and those lost to follow-up yielded comparable results.

Outcome of UA patients who discontinued MTX

Of the 39 patients who discontinued MTX (10 ACPA-positive, 29 ACPA-negative), 18 were in drug-free remission after 30 months, while in 21 patients arthritis recurred, persisted or progressed to RA, all defined as non-remission (figure 1). Thus the chance for achieving drug-free remission after having received MTX therapy for one year without progressing to RA, was 46% and the chance for non-remission 54%. Non-remission was more frequent in ACPA-positive patients (figure 1).

At 12 months, right before tapering, the mean DAS in these 39 patients was 1.67 (SD

0.77). More specifically, the DAS was <1.6 in 45%, between 1.6 and 2.4 in 37% and >2.4 in 18% of the patients. At 18 months, right after tapering and stopping MTX, the mean DAS had increased to 1.96 (SD 0.71), of which 28% was <1.6, 50% between 1.6 and 2.4, and 22% >2.4, respectively. Figure 2A and 2C show per patient the DAS just before and right after discontinuation, separately for patients who achieved drug-free remission (2A) or non-remission (2C).

Joint damage progression was evaluated at 18 months, i.e. the time point where MTX was fully tapered and discontinued, and at 30 months. From baseline to 18 months, 17% of patients had damage progression ≥ 1 SHS, but this increased to 26% during the period without MTX therapy until 30 months. Patients in drug-free remission suffered no joint damage progression, but 45% of patients in non-remission did (figure 2B,D, respectively). Damage progression in ACPA-negative patients was nil, both until 18 months (median: 0, IQR: 0-0; mean: 0.3, SD: 0.9) and after 30 months (median 0, IQR: 0-0; mean 0.6, SD: 1.5), in contrast to ACPA-positive patients who suffered ongoing damage progression the first 18 months (median: 0.5, IQR: 0-2.0; mean 0.9, SD: 1.1) and after 30 months (median: 1.5, IQR: 0-5.0; mean 2.7, SD: 3.3).

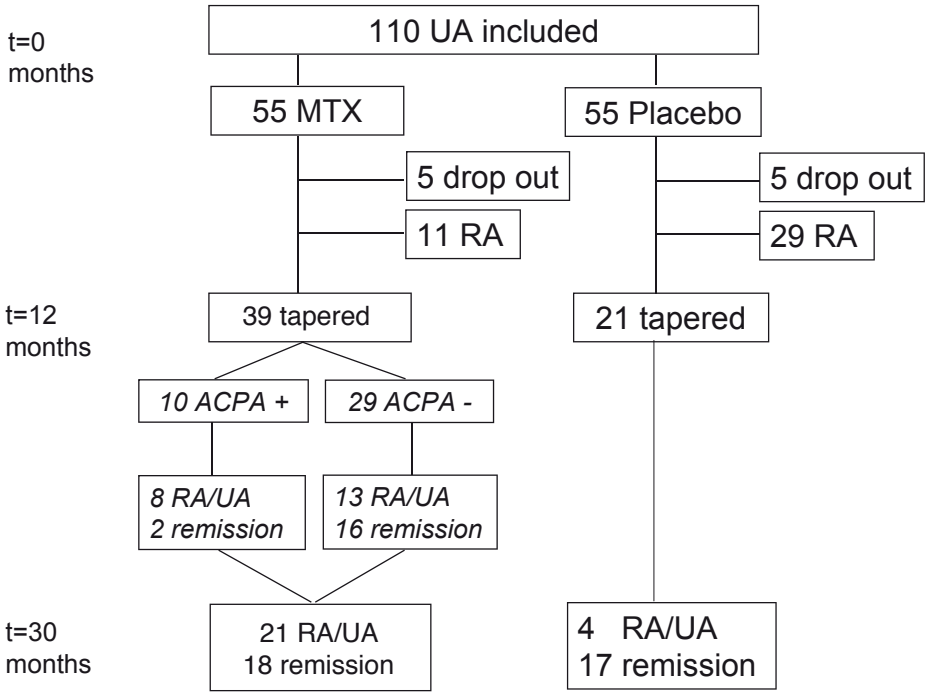

Figure 1. Flowchart of the course of UA and the final diagnosis after 30 months in 110 patients randomized to 12 months MTX or placebo therapy.

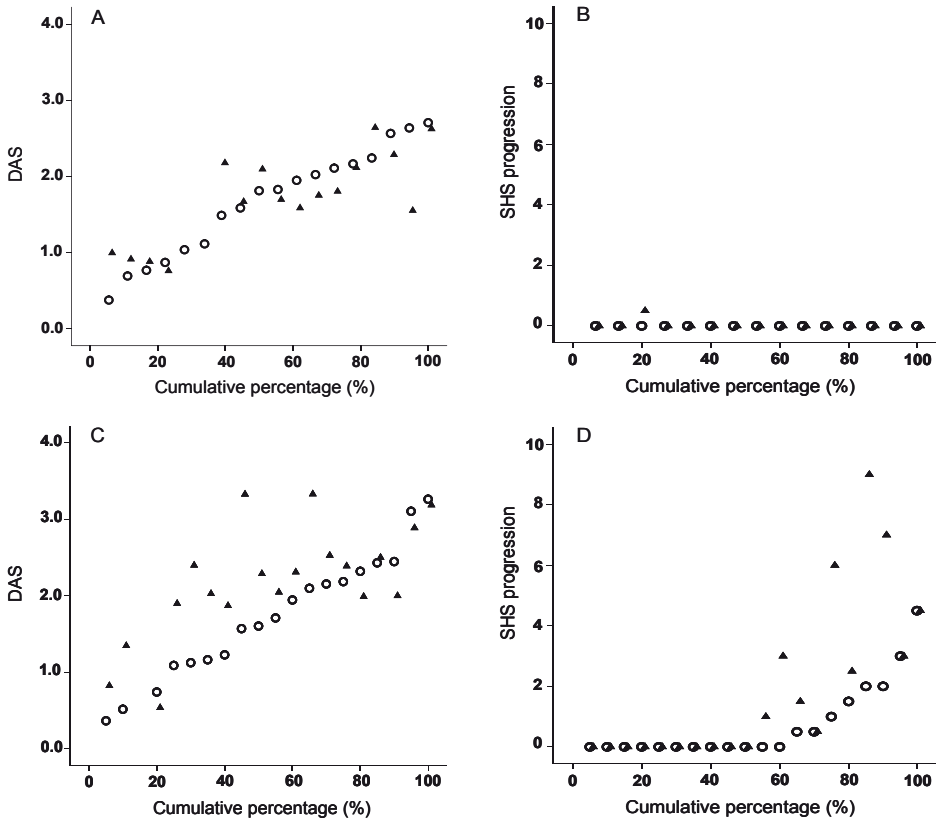

Figure 2. Individual DAS and cumulative SHS progression before and after discontinuation of MTX in 39 UA patients, stratified for patients who achieved drug-free remission or 'non-remission'. A+C. DAS just before tapering MTX at 12 months (circles) and right after discontinuation at 18 months (triangles) in patients who achieved drug-free remission (A) or non-remission (C). B+D. Cumulative SHS progression under MTX therapy (0-18 months) (circles) and after 30 months (triangles) in patients who achieved drug-free remission (B) or non-remission (D). Vertically, a circle and triangle correspond to the same patient. DAS=disease activity score; SHS=Sharp/van der Heijde score.

Predictors for non-remission after stopping MTX

We investigated the characteristics of the UA patients who could successfully discontinue MTX or who suffered further disease progression. Univariate predictors for non-remission after stopping MTX were the presence of ACPA (OR 4.9, 95%CI 0.9-27, p=0.068) and age <65 years (OR 10, 95%CI 1.1-93, p=0.043). The multivariate analysis, including ACPA, age, gender and symptom duration, revealed the presence of ACPA and age <65 years as independently associated with non-remission (table 2B). Baseline SHS in stead of ACPA showed a trend towards more non-remission (OR 1.9, 95% CI 0.9-4.0, p=0.104). A higher AUC DAS during 12 months MTX therapy was weakly associated with non-remission after stopping MTX, while an incidental DAS >1.6 just before tapering was not

predictive. The sensitivity analysis leaving out the patients with osteoarthritis and those lost to follow-up did not change the tenor of the results.

Influence of new RA classification criteria on PROMPT outcomes

With the publication of the new EULAR/ACR classification criteria for RA, some of the UA patients included in the PROMPT study would now be classified as RA. We went back to the inclusion data and found that 64 out of the 110 patients (58%) included as UA fulfilled the 2010 RA criteria at baseline. These patients included all 27 ACPA-positive patients and 37 out of 83 ACPA-negative patients. Of the 64 patients who fulfilled the 2010 criteria, 33 were treated with MTX therapy and 31 received placebo therapy. After 30 months, in the MTX group, 4 patients dropped out, 19 (58%) patients had developed RA meeting the 1987 criteria or had persistent arthritis, and 10 (30%) patients achieved drug-free remission. In the placebo group, 1 patient dropped out, 20 (65%) patients met the 1987 criteria and 10 (32%) were in drug-free spontaneous remission after 30 months. Thus, compared to the total PROMPT population, in this selection of patients fulfilling the 2010 criteria, comparable remission rates were found and still no effect of MTX emerged with respect to the number of patients achieving the outcome drug-free remission.

DISCUSSION

Starting DMARD treatment in patients with UA ideally should prevent the progression to RA and alter the disease course towards sustained remission or cure. In the PROMPT study the first effect was addressed when we showed that MTX monotherapy postponed, but did not prevent RA, then defined by fulfilling the 1987 ACR classification criteria.[4] In this paper we focused on disease course alteration and sustained drug-free remission and found that this was not induced by MTX therapy, but rather reflected self-limiting disease. Furthermore, we showed that after stopping MTX in UA, non-remission, defined as recurrence, persistence or worsening of arthritis, was common and associated with the presence of ACPA or baseline joint damage, age <65 years, and possibly with a high DAS during therapy. Our results indicate that more potent remission-induction therapies and safer discontinuation strategies for UA are needed. The essence of these observations was not altered when we narrowed down our UA population to those who fulfilled the new EULAR/ACR classification criteria for RA at baseline.

We observed a spontaneous remission rate of 31% in UA patients fulfilling the criteria for probable RA.[5] Spontaneous remission was reported in 13% to 55% of patients in previous studies, depending on how UA was defined according to various baseline characteristics.[9,10,11] The findings that the rate and the predictors of drug-free remission were similar in the MTX-treated group and in the placebo group, and that MTX was not a predictor for drug-free remission in the total group, indicate that the capacity to achieve drug-free remission depends more on an internal predisposition than on the efficacy of MTX. The identified predictors for drug-free remission, ACPA-negativity, no or low joint damage and age above 65 years, thus appear intrinsic characteristics of self-limiting disease.[12,11]

MTX was effective in reducing signs and symptoms, delaying radiographic progression and postponing the diagnosis of RA in ACPA-positive UA patients.[4] We now showed that after discontinuation of MTX recurrence, persistence or worsening of arthritis was common, with worsening of the DAS, ongoing radiographic progression, and eventually still fulfilling the 1987 criteria for RA. These results again suggest that, although MTX temporarily suppressed the disease, it is not potent enough to fundamentally alter the disease course. Moreover, these results proclaim that, once started, MTX should better not be discontinued, especially in ACPA-positive UA, although this would need to be confirmed in a randomized controlled fashion.

ACPA-negative UA did not benefit from MTX therapy in terms of delaying RA or reducing symptoms.[4] Although the a priori risk of developing RA is not as high as in ACPA-positive patients, still 35% of the ACPA-negative UA patients fulfilled the 1987 criteria for RA during this study and 14% had persistent UA, indicating a high level of morbidity. When reassessed with the new 2010 EULAR/ACR classification criteria, 37 of the 83 ACPA-negative UA patients would have been classified as RA at baseline, and of those 41% fulfilled the 1987 criteria during the study or had persistent arthritis. We suggest that also (a subset of) ACPA-negative patients would benefit from early therapy, but which therapy is yet unclear. On the other hand, attempts to taper and stop initial treatment might be relatively safe, as radiographic progression appears to be milder than in APCA-positive patients.

An important clinical question is whether we can identify those UA patients who started on MTX therapy, who might be eligible for a trial of MTX withdrawal without the risk of further disease progression. In our study, non-remission after discontinuation of MTX was predicted by the presence of ACPA or baseline joint damage and age under 65. The ACPA-positive patients also had most erosions, confirming the unfavorable prognostic value and interrelationship of these persistency factors.[12] A incidental DAS<1.6 just before tapering MTX was not associated with drug-free remission afterwards, but a continued low DAS during treatment showed a trend towards more drug-free remission. The small numbers in this study, however, might have led to type 2 errors. Nevertheless, tapering treatment in UA has hardly been studied, and our results should be seen as encouraging first clues.

One might have expected a higher rate of persistent arthritis, less remission and possibly a higher efficacy of MTX versus placebo therapy in the patients who fulfill the new 2010 criteria at baseline. However, both the observed remission rates and the incidence of fulfilling the 1987 criteria for RA were comparable to those in the total group of UA patients included in the PROMPT study. On the one hand, these observations strengthen our view that MTX monotherapy in this early inflammatory arthritis population is not the therapy to rely on. On the other hand, one might also conclude that, in this particular study population, the 2010 criteria conferred low predictive value to distinguish between UA patients with the tendency to have persistent or self-limiting disease.

Few other randomized short-term intervention studies have tried to alter the course of early undifferentiated (oligo- or poly-) arthritis, but results are disappointing. In the STIVEA trial, a course of intramuscular methylprednisolone in inflammatory polyarthritis of <10 weeks duration postponed the need for DMARDs and resulted in more

resolved disease after 12 months, but longer follow-up was not available.[13] In the larger SAVE study in a similar patient population, 120 mg intramuscular methylprednisolone was not effective in inducing remission or delaying development of RA.[14] In two, although underpowered, studies in mostly antibody-positive, poor prognosis UA patients a short course of infliximab or abatacept also did not prevent the progression to RA.[15,16] Together, these data call for more randomized controlled trials with sufficient power and follow-up, to tackle the challenge of finding an effective strategy or therapy that can really halt the progression to RA.

In summary, in patients with UA, MTX did not induce drug-free remission. Drug-free remission was mainly determined by self-limiting disease, characterized by the absence of ACPA, low joint damage, age >65 and lower continued disease activity. Recurrent, persistent or progressive arthritis after stopping MTX in UA was common and associated with the presence of ACPA or joint damage and age <65. Therefore, more potent remission-induction therapies and safer discontinuation strategies for UA need to be investigated.

References

1. Schumacher HR. Early arthritis clinics. Much early arthritis is unclassified. J Rheumatol 2002;29:2258-60.
2. Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
3. Finckh A, Liang MH, van Herckenrode CM et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55:864-72.
4. van Dongen H, van Aken J, Lard LR, 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.
5. Ropes MW, Bennett GA, Cobb S. 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9(4):175-6.
6. van der Heijde DM, van 't Hoff M, van Riel PL et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20: 579-81.
7. Arnett FC, Edworthy SM, Bloch DF et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.
8. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-3.
9. Harrison BJ, Symmons DP, Brennan P et al. Natural remission in inflammatory polyarthritis: issues of definition and prediction. Br J Rheumatol 1996;35:1096-100.
10. Quinn MA, Green MJ, Marzo-Ortega H et al. Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. Arthritis Rheum 2003;48:3039-45.
11. Wolfe F, Ross K, Hawley DJ et al. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. J Rheumatol 1993;20:2005-9.
12. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ 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.
13. Verstappen SM, McCoy MJ, Roberts C et al. The beneficial effects of a 3 week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. Ann Rheum Dis 2010;69(3):473-5.
14. Machold KP, Landewe R, Smolen JS et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Ann Rheum Dis 2010;69:495-502.
15. Saleem B, Mackie S, Quinn M et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? Ann Rheum Dis 2008;67:1178-80.
16. Emery P, Durez P, Dougados M et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis 2010;69:510-6.