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# The Utrecht experience with different treatment strategies in early rheumatoid arthritis

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on behalf of the Utrecht Rheumatoid Arthritis Cohort study group

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*Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S165-S168.

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**Key words:** Rheumatoid arthritis, treatment, efficacy, toxicity, pyramid strategy.

## ABSTRACT

Since 1990 the Utrecht Rheumatoid Arthritis Cohort study group has performed several clinical trials on different treatment strategies in early rheumatoid arthritis (RA) patients.

From 1990 till 1994, patients were randomly assigned to the pyramid strategy group or the early DMARD group. Patients in the early DMARD group were allocated to one of the three following treatment strategies: strategy I, starting with hydroxychloroquine (HCQ); strategy II, starting with intramuscular gold (iAU); or strategy III, starting with oral methotrexate (MTX). After one year, statistically significant advantages for the early DMARD group compared with the pyramid group were found for disability, pain, joint score, and ESR. The increase in radiological damage did not differ significantly between the two strategy groups. These first year results proved that early introduction of DMARDs is more beneficial than a delayed introduction. After 5 years, however, no prolongation of the clinical advantages in favor of the early DMARD group, as observed after one year, was found. It was found that patients assigned to the pyramid group received more intra-articular injections during the first two years; at the end of this period 75% of them used DMARDs, especially the more aggressive DMARDs.

Based on the first year results, all patients were randomly assigned to one of the three treatment strategies in the early DMARD group between 1994 and 1998. Patients who started with MTX or iAU as the first DMARD demonstrated better results regarding clinical efficacy and radiological damage after 2 years. However, more patients who received iAU therapy had to discontinue their therapy compared with patients who took MTX. We there-

fore conclude that MTX is the DMARD of first choice and that treatment should be tailored to the individual patient.

## Introduction

Since 1990 the Utrecht Rheumatoid Arthritis Cohort study group has performed several trials on different treatment strategies in early rheumatoid arthritis (RA) patients. From 1990 till 1994 we performed a randomized controlled trial in early RA patients (< 1 year) in which two therapeutic strategies were compared, i.e. the pyramid approach versus the early DMARD approach. In the past, the pyramid approach was the traditional treatment paradigm for RA. In the pyramid approach, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) were the initial drugs administered to control inflammation and especially pain. Drugs that are more effective, such as disease modifying anti-rheumatic drugs (DMARDs), but were considered to be more toxic, were added relatively late in the course of the disease. However, the beneficial effects of the pyramid strategy have been questioned because the long-term outcome continued to be disappointing. For this reason, we started a randomized controlled trial. Patients were randomly assigned to the early DMARD group (n = 182) or the pyramid group (n = 56) (1).

## Early DMARD treatment versus the pyramid strategy

Patients in the pyramid group were treated with NSAIDs, and the administration of DMARDs was started only if NSAIDs alone were clinically ineffective. The early DMARD strategy comprised three different therapeutic strategies to which patients were randomly assigned. Strategy I was less aggressive with an expected long lag time until

**Table I.** Number of patients whose first assigned treatment was discontinued during 5 year follow-up, and the reasons for discontinuation.

Treatment at start	Period in years	Patients who discontinued the first treatment	Pts. who continued to use the first treatment for 5 years	Reasons for discontinuation		
				Ineffective-ness	Adverse events	Other
No DMARD (n = 44)	0-1	13		13	0	0
	1-2	21		20	0	1
	2-3	1		1	0	0
	3-4	3		3	0	0
	4-5	0	6	0	0	0
Intramuscular gold (n = 47)	0-1	8		3	3	2
	1-2	25		17	3	5
	2-3	5		2	0	3
	3-4	3		2	1	0
	4-5	1	5	1	0	0
Methotrexate (n = 56)	0-1	7		2	3	2
	1-2	17		8	1	8
	2-3	10		0	2	8
	3-4	3		1	0	2
	4-5	2	17	0	1	1
Hydroxychloroquine (n = 42)	0-1	7		1	2	4
	1-2	20		11	0	9
	2-3	4		2	0	2
	3-4	1		0	0	1
	4-5	2	8	1	0	1

Evaluation of patients who discontinued the first assigned treatment included only those patients who had been followed for five years (i.e., n = 44 in the pyramid group and n = 145 in the early DMARD group).

Number (n) of patients assigned to each treatment at study start.

treatment effect: treatment was started with hydroxychloroquine (HCQ) and if necessary replaced by auranofin (oAU). Strategy II was more aggressive and with an expected long lag time: treatment with intramuscular gold (iAU) and if necessary replaced by D-penicillamine (dPa). Strategy III was more aggressive and relatively fast acting: oral methotrexate (MTX) and if necessary replaced by sulfasalazine (SSZ). Patients in the early DMARD group were treated with the initial DMARD during the first year of the study unless adverse reactions necessitated discontinuation. The efficacy and toxicity of this randomized trial were evaluated at 1 year (1) and 5 years (2) after the study start.

Table I shows the number of patients who discontinued the first assigned treatment and their reasons for discontinuation; in addition, the number of patients who continued the first allocated treatment for 5 years is given. Among patients assigned to the pyramid group at the study start, 86% began to use DMARDs during the 5-year fol-

low-up since NSAIDs alone were ineffective. The mean lag time until prescription of the first DMARD ( $\pm$  SD) was 14 ( $\pm$  9) months. Of those patients who started to take DMARDs, these were most often more aggressive DMARDs (MTX, dPa, iAU, SSZ, or combinations of DMARDs). Thirty patients in the early DMARD group continued to use their initially assigned DMARD for five years (2).

#### *Efficacy*

After one year, statistically significant advantages for the early DMARD group compared to the pyramid group were found for disability, pain, the joint score, and the erythrocyte sedimentation rate (ESR). The increase in radiological damage did not differ significantly between the two strategies. The percentage of patients showing clinical improvement (33%) from baseline varied from 28 (for disability) to 57 (for the joint score) in the pyramid group and from 54 (disability) to 78 (joint score) in the early DMARD group. (1) These first year results proved that the

early introduction of DMARDs is more beneficial than a delayed introduction of DMARDs.

After 5 years, we evaluated the clinical and radiological outcomes again for those patients who remained in the study (n=44 patients in the pyramid group and n=145 patients in the early DMARD group). In this population which was followed for 5 years, no prolongation of the clinical advantages in favor of the early DMARD group, as observed after the first year, was found (2).

The clinical results in favor of the early DMARD group, as observed after the first year, were not as evident after 5 years. However, during the first 2 years patients assigned to the pyramid group received more intra-articular injections, and at the end of this period 75% of them were using DMARDs, especially the more aggressive DMARDs. Although in our study DMARDs were given immediately after inclusion, therapeutic strategies prevalent at that time are now thought to be too conservative (eg. SSZ 2-3 g/day or MTX 7.5-15 mg/

**Table II.** Number of patients who discontinued the DMARD strategy and their reasons for discontinuation.

Strategy	Period	Patients who discontinued the first treatment	Reasons for discontinuation			
			Adverse reaction	Ineffective-ness	Adverse reaction & ineffectiveness	Other
Strategy I (n = 107)	0-1	12	0	12	0	0
	1-2	17	5	10	2	0
Strategy II (n = 101)	0-1	4	1	2	0	1
	1-2	26	15	9	1	1
Strategy III (n = 105)	0-1	11	4	4	1	2
	1-2	10	3	7	0	0

Strategy I: mild slow DMARD drug with an expected long lag time: hydroxychloroquine or auranofin.

Strategy II: potent DMARD with an expected long lag time: intramuscular gold or D-penicillamine.

Strategy III: potent DMARD with relatively short lag time: methotrexate or sulfasalazine.

Discontinuation rates were not significantly different between the three strategies.

week). At present at least 20 mg MTX/wk or 3 g SSZ per day are used.

### Toxicity

After the first year, 16 (28%) patients in the pyramid group reported serious gastrointestinal symptoms. In the early DMARD group, major adverse reactions leading to discontinuation of the DMARD therapy primarily consisted of gastrointestinal symptoms (9 patients) and skin reactions (7 patients). Mild toxicity, which did not lead to dis-

continuation of therapy, was frequent and was primarily evident as gastrointestinal symptoms (64 patients, in 37 of whom this was due to the use of NSAIDs), skin reactions (17 patients), and headache or dizziness (15 patients, in 4 patients due to use of NSAIDs) (1). Although the results show that there is a potential risk for toxicity when treating patients with DMARDs, it is increasingly apparent that these adverse effects outweigh the negative effects of the disease in established RA.

### Different early DMARD strategies

From 1994 until 1998, all patients with early RA were randomly allocated to one of the three DMARD strategies (I, HCQ if necessary oAU; II, i.m. gold if necessary dPa; III, MTX if necessary SSZ). The efficacy and toxicity of the three different strategies were compared after one and two years of follow-up (total study population = 313) (3).

At one year, 86% of the patients was still being treated with the initial allocated DMARD (hydroxychloroquine, intra-muscular gold, methotrexate) and after 2 years this percentage was 47%. Eighty patients (26%) discontinued the strategy, i.e. they started to use other DMARDs than the two DMARDs defined in the protocol for each strategy. Table II shows the number of patients that discontinued the strategy and reasons for discontinuation.

### Efficacy

Table III shows the clinical and radiographic changes from baseline after two years. Changes from baseline were significant for all clinical outcomes in each strategy. Improvement seemed slightly less in strategy I than in the other strategies. Although no significant differences in clinical variables were observed between the three strategies, radiological progression was significantly worse for strategy I compared to strategy II or III.

Analysis for repeated measurements showed that disability over time was favorable in strategy III compared with strategy I. No significant difference was found between the three strategies for pain and joint score. The ESR over time was significantly higher in strategy I than in II. Remission rates at one year were higher in strategy II (31%) and III (24%) than strategy I (16%), but no obvious differences were seen at two years.

Early treatment according to the three different treatment strategies reduced disease activity over two years. Overall, introduction of MTX (second SSZ) or iAU (second dPa) as the first DMARD demonstrated better results regarding clinical efficacy and radiological progression.

**Table III.** Changes from baseline after 2 years in the clinical variables and radiological damage.

	Strategy I n = 107	Change from baseline Strategy II n = 101	Strategy III n = 105
Disability score, HAQ	-0.3 (-0.5, -0.2)	-0.4 (-0.6, -0.2)	-0.3 (-0.4, -0.2)
Pain score, VAS	-22 (-27, -16)	-25 (-31, -19)	-21 (-27, -16)
Joint score, Thompson	-89 (-111, -67)	-104 (-128, -80)	-86 (-106, -66)
ESR, mm/1st hr	-19 (-24, -14)	-21 (-27, -16)	-20 (-24, -15)
Wellbeing score, mm	-17 (-23, -11)	-24 (-30, -17)	-18 (-24, -12)
Grip strength, kPa	12 (8, 15)	13 (8, 17)	15 (11, 20)
Morning stiffness, min., median (10-90 centiles)	-45 (-309, 36)	-45 (-150, 30)	-30 (-216, 45)
Radiological damage, median (10-90 centiles) †	12 (0, 48)	9 (0, 28)	8 (0, 37)

Values are the mean change from baseline and the 95% CI for the mean, or the median change and 10-90 centiles, where appropriate.

Negative values indicate improvement for all variables, except for grip strength and radiological damage.

Strategy I: mild slow DMARD drug with an expected long lag time: hydroxychloroquine or auranofin.

Strategy II: potent DMARD with an expected long lag time: intramuscular gold or D-penicillamine.

Strategy III: potent DMARD with relatively short lag time: methotrexate or sulfasalazine.

† Significantly different between the three different strategy groups.

### Toxicity

In strategy I most events were subjective gastrointestinal complaints (52 patients), followed by anaemia (21), and rash (17). Mucocutaneous reactions occurred most commonly in strategy II (62); subjective gastrointestinal complaints and hepatotoxicity were most commonly seen in strategy III, and renal toxicity was more commonly seen in strategy II (24) and III (17) than in strategy I (11). Most patients (99%) also took NSAIDs, and part of the results might have been a consequence of NSAID use.

Since the toxicity profiles of DMARDs and NSAIDs might be similar, we investigated the relation between drug use and adverse events in more detail (4). The relation between drug use and adverse events was defined as definitely, probably, possibly or doubtfully attributable to a drug treatment. In this study, 232 of the 419 patients (55%) suffered 391 adverse events. The association between the adverse effect and a DMARD use was as follows: definite, 0 cases; probable, 60 cases; possible, 292 cases; doubtful, 5 cases. Thirty-four adverse events were unrelated to DMARDs because only NSAIDs were taken during that period. Of those 60 events that were classified as probable,

the lowest incidence was found for HCQ therapy (6 per 100p-yr) compared with 15 per 100 p-yr for MTX and 16 per 100 p-yr for iAU. The NSAID related toxicity was similar in the three DMARD groups. Among the three treatment strategies, treatment with iAU resulted in the highest percentage (25%) of discontinuation of this treatment due to adverse events. The mean period until the first adverse event was longer for the MTX group (39 weeks) than the HCQ group (27 weeks).

When both studies (3, 4) were taken into consideration, adverse events were most common during iAU therapy which resulted more frequently in discontinuation of the therapy when compared to MTX or HCQ therapy.

### Conclusion

In this report we described the experience of the Utrecht Rheumatoid Arthritis Cohort study group with different treatment strategies in early rheumatoid arthritis. Taking both efficacy and toxicity into consideration, the results implicate that early and prolonged treatment tailored to the individual patient with aggressive DMARDs (e.g. MTX) is necessary for continuation of the beneficial results found after the first year.

### Acknowledgements

The authors would like to thank all of the other participants in the Utrecht Rheumatoid Arthritis Cohort study group: G.A. van Albada-Kuipers, A.A. M. Blaauw, C. van Booma-Frankfort, E.J. ter Borg, H.C.M. Haanen, A.H.M. Heurkens, D.M. Hofman, A.A. Kruize, Y. Schenk, M.J. van der Veen, and C.M. Verhoef.

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