CHAPTER 4

A TWO-STEP TREATMENT STRATEGY TRIAL IN PATIENTS WITH EARLY ARTHRITIS AIMED AT ACHIEVING REMISSION: THE IMPROVED-STUDY

Accepted for publication in Annals of the Rheumatic Diseases

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ABSTRACT

Objectives: To assess which treatment strategy is most effective in inducing remission in early (rheumatoid) arthritis.

Methods: 610 patients with early rheumatoid arthritis (RA 2010 criteria) or undifferentiated arthritis (UA) started treatment with methotrexate (MTX) and a tapered high dose of prednisone. Patients in early remission (Disease Activity Score <1.6 after 4 months) tapered prednisone to zero and those with persistent remission after 8 months, tapered and stopped MTX. Patients not in early remission were randomised to receive either MTX plus hydroxychloroquine plus sulfasalazine plus low-dose prednisone (arm 1) or to MTX plus adalimumab (ADA) (arm 2). If remission was present after 8 months both arms tapered to MTX monotherapy; if not, arm 1 changed to MTX plus ADA and arm 2 increased the dose of ADA. Remission rates and functional and radiological outcomes were compared between arms and between patients with RA and those with UA.

Results: 375/610 (61%) patients achieved early remission. After 1 year 68% of those were in remission and 32% in drug-free remission. Of the randomised patients, 25% in arm 1 and 41% in arm 2 achieved remission at year 1 ($p<0.01$). Outcomes were comparable between patients with RA and those with UA.

Conclusions: Initial MTX and prednisone resulted in early remission in 61% of patients with early (rheumatoid) arthritis. Of those, 68% were in remission and 32% were in drug-free remission after 1 year. In patients not in early remission, earlier introduction of ADA resulted in more remission at year 1 than first treating with disease-modifying antirheumatic drug combination therapy plus prednisone.

INTRODUCTION

The way in which patients with rheumatoid arthritis (RA) are treated has changed dramatically over recent decades. Early and tightly controlled treatment with disease-modifying antirheumatic drugs (DMARDs), targeted at low disease activity, suppresses inflammation better than previously, resulting in improved functional ability and minimised radiological joint damage.[1-6] Even remission can be achieved. Early combination therapy with synthetic DMARD treatment plus prednisone or a tumour necrosis factor (TNF) alpha inhibitor is effective in most patients.[7-9]

It is thought that there is a 'window of opportunity' during which initiation of effective treatment may prevent inflammatory symptoms from becoming chronic and damaging to bone and joint tissues. To enable earlier diagnosis and treatment initiation, classification criteria for rheumatoid arthritis (RA) were revised in 2010.[10] Starting antirheumatic treatment at the stage of undifferentiated arthritis (UA), when RA is still unclassifiable, might be useful.[7]

Treatment of patients with UA with methotrexate (MTX) was successful in postponing, but not preventing, progression to RA.[11] It is possible that, as in patients with RA, initial combination therapy with MTX and prednisone might be more effective.[8] If patients do not achieve remission with initial combination therapy, the best follow-up strategy needs to be determined: either expansion of DMARDs or switching to MTX with a TNF-alpha inhibitor; both proved effective in established RA.[6, 9]

We designed a two-step treatment strategy study (remission induction therapy followed by randomisation for patients who did not achieve remission) in patients with recent-onset RA or UA, to determine how often remission or even drug-free remission (DFR) can be achieved. Here we report clinical and radiological outcomes after 1 year.

METHODS

Study design and patients

The IMPROVED study (acronym for Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease, ISRCTN Register number 11916566 and EudraCT number 2006-006186-16) is a multicentre, randomised, single-blinded clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research. Patients were recruited between March 2007 and September 2010 in 12 hospitals in the western area of the Netherlands. Medical ethics committees of each participating centre approved the study protocol and all patients gave written informed consent.

Patients with both UA and early RA were included. Detailed inclusion and exclusion criteria have been previously published.[8] Recent-onset RA was defined according to the ACR/EULAR 2010 classification criteria,[10] with symptom duration ≤2 years. Patients with UA had at least one joint clinically assessed as 'arthritis' and at least one other tender joint, which the rheumatologist suspected to be early RA, but not fulfilling the 2010 ACR/EULAR criteria.

Intervention

The treatment target was clinical remission, defined as a Disease Activity Score (DAS)<1.6.[12] Four-monthly assessments of DAS were performed by trained nurses who were blinded to the allocated treatment. Patients and doctors were not blinded for practical reasons. All patients started with 4 months of open-label MTX 25 mg/week (dose escalated from 7.5 mg/week in 4 weeks) and prednisone tapered in 7 weeks from 60 mg/day to a stable dose of 7.5 mg/day. Patients in 'early DAS remission' (defined as DAS<1.6 at 4 months) tapered prednisone to zero in 3 weeks and when still in remission at 8 months, also tapered MTX to zero in 9 weeks. If DAS was ≥1.6 after stopping prednisone, it was restarted at 7.5 mg/day (figure 1).

Patients not in early remission at 4 months were randomised either to MTX 25 mg/wk plus hydroxychloroquine (HCQ) 400 mg/day, sulfasalazine (SSZ) 2000mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab (ADA) 40 mg/2 weeks (arm 2). If in remission at 8 months, patients in arm 1 started tapering prednisone and subsequently SSZ and HCQ to MTX monotherapy, patients in arm 2 tapered ADA to MTX monotherapy. If not in remission at 8 months, patients in arm 1 switched to MTX+ADA (40 mg/2 weeks), patients in arm 2 increased ADA to 40 mg/week (figure 1).

Patients who did not regain remission after restarting prednisone, were also randomised ('delayed randomisation') as described above.

Variable block randomisation stratified for each centre and diagnosis ensured the same number in the two randomisation arms. Randomisation sequence was obtained

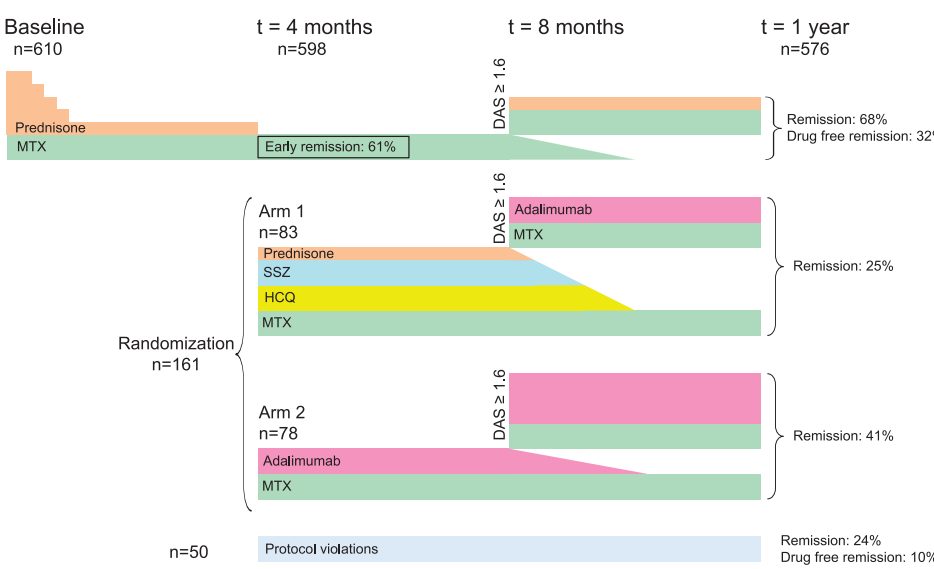

Figure 1. Study flow chart with percentages DAS-remission after the first study year. MTX: methotrexate, DAS: disease activity score, SSZ: sulfasalazine, HCQ: hydroxychloroquine, Remission: DAS≤1.6.

by computer. At the local centres, allocation was performed by the rheumatologists drawing opaque envelops.

Study outcomes and assessments

Primary outcomes after 1 year were percentages of clinical remission and DFR based on a DAS<1.6. A provisional Boolean-based remission definition, published by ACR/EULAR,[13] based on the 44-joint count was used to recalculate remission percentages at 4, 8 and 12 months. Secondary outcomes collected 4 monthly were DAS, functional ability measured with the Health Assessment Questionnaire (HAQ, ranging from 0 (best) to 3 (worst), ≥0.2 points' change is clinically relevant),[14] radiological damage progression measured with Sharp–van der Heijde score (SHS, ranging from 0 to 448, progression was defined as an increase in SHS≥0.5 point)[15] and toxicity. Radiographs of hands and feet, blinded for patient identity, were scored for the presence of erosions and joint space narrowing in time random order by two trained, independent readers (KW and LH). Since 88% of patients showed no progression, intraclass correlation coefficients were not suitable for measuring reliability.[16] In 83% of patients both readers scored the same progression. In 54 patients with inter-reader differences ≥2 (the median difference in progression score of patients for which both readers scored different progression) a consensus score was reached.

Outcomes were reported separately for patients who achieved early DAS remission and those randomised, and were compared between randomisation arms. Additional comparisons were made between patients with RA and those with UA. Patients who were not in early DAS remission and who were not randomised according to the protocol were analysed in the outside of protocol (OP) group. Reasons for protocol deviation were not inventoried.

Statistical analysis

With a power calculation we assessed the number of patients needed in each randomisation arm to detect differences between arms of at least 50% in remission rates and 0.2 points in HAQ with a power of 80%. Based on previous studies,[6, 9, 17] we estimated that 30% of the patients would achieve early remission. We needed 535 patients to randomise at least 100 patients in each arm. Because during the study early DAS remission rates were higher, the inclusion number was extended to 610 patients.

We performed intention-to-treat analyses. Outcomes were analysed using a Student's *t* test, Mann–Whitney U tests and χ^2 tests. DAS and HAQ were compared over time using linear mixed models, with treatment strategy (arms 1 and 2) and time (study visit) as fixed effects, in an unstructured covariance structure. Statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Study profile

In total 610 patients were included, 479 (79%) with RA and 122 (20%) with UA; nine patients could not be classified because of missing values. Over the year 23 patients withdrew consent, three discontinued because of a revised diagnosis and six because of comorbidity. Twelve of these patients dropped out during the first 4 months.

After 4 months, 375/610 patients (61%) had a DAS<1.6 (early DAS remission). Twelve other patients with a marginally high DAS at 4 months were by protocol reassessed after 1 month. All then had a DAS<1.6 and were included in the early remission group, bringing it to a total of 387 patients: 291/479 (61%) patients with RA and 79/122 (65%) patients with UA were in early remission (12 patients were lost to follow-up and five were not classifiable because of missing data). A total of 144/387 (37%) (114/291 (39%) with RA and 28/79 (35%) with UA, two had missing data) also fulfilled the proposed ACR/EULAR remission definition.

In total, 161/610 (26%) patients not in DAS remission were randomised, 83 patients into arm 1 and 78 to arm 2. None fulfilled the proposed ACR/EULAR remission definition. Two patients with a missing DAS at 4 months and 48 other patients with a DAS≥1.6 at 4 months who did not follow the protocol were analysed in the OP group. Thirty-three of these patients tapered prednisone and for 17 patients various other treatment decisions were made.

Clinical characteristics at baseline and 4 months

Patients who achieved early DAS remission had lower mean baseline DAS, HAQ and DAS components, were more often male and anti-citrullinated protein antibody (ACPA)-positive and had a shorter symptom duration than randomised patients.[8] Clinical characteristics at baseline and 4 months were comparable in arms 1 and 2 (table 1). After 4 months 12 patients were lost to follow-up and 598 patients were categorised a described in this table.

Outcomes after 1 year

After 1 year, 328/610 (54%) patients achieved DAS remission (253/479 (53%) patients with RA versus 71/122 (58%) patients with UA (p=0.10), four patients were not classifiable. Proposed ACR/EULAR remission was achieved in 144/610 (24%). DFR after 1 year was achieved in 130/610 (21%) patients (93/479 (19%) patients with RA versus 36/122 (30%) patients with UA, one patient was not classifiable). Patients most often achieved DAS remission in the group with early remission. Patients in arm 1 achieved DAS remission less often than patients in arm 2 (p=0.01) (table 1).

After 1 year, mean HAQ and DAS were lower in the group with early DAS remission than in arms 1 and 2. Over time, no significant difference in DAS and HAQ between arms 1 and 2 was found (mean DAS difference of 0.03 95% CI -0.16 to 0.22, mean HAQ difference 0.04, 95% CI 0.01 to 0.29).

Table 1. Baseline characteristics and clinical outcomes per treatment group.

	Early DAS remission	Randomization		Outside protocol treatment
		Arm 1	Arm 2	
Baseline characteristics	n = 387	n = 83	n = 78	n = 50
DAS, mean ± SD	3.0 ± 0.8	3.6 ± 0.9	3.6 ± 1.0	3.6 ± 0.9
HAQ, mean ± SD	1.0 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	1.3 ± 0.7
Swollen Joint Count, median (IQR)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Tender Joint Count, median (IQR)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
Age in years, mean ± SD	52 ± 14	49 ± 14	51 ± 14	54 ± 14
Female, n (%)	240 (62)	64 (77)	58 (74)	42 (84)
Symptom duration in weeks, median (IQR)	17 (9-30)	22 (9-41)	21 (8-31)	18 (9-42)
Symptom duration <12 weeks, n (%)	247 (64)	59 (71)	49 (63)	28 (56)
RF positive, n (%)	224 (58)	41 (49)	43 (55)	23 (46)
ACPA positive, n (%)	225 (58)	40 (48)	37 (47)	25 (50)
RA(2010), n (%)	298 (77)	66 (80)	66 (85)	40 (80)
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0)	0 (0-0)	0 (0-0)
Erosive, n (%)	63 (16)	10 (12)	13 (17)	3 (6)
Follow-up – 4 months				
DAS, mean ± SD	1.0 ± 0.4	2.5 ± 0.6	2.6 ± 0.7	2.3 ± 0.6
HAQ, mean ± SD	0.2 ± 0.3	0.9 ± 0.6	0.9 ± 0.6	0.8 ± 0.7
Swollen Joint Count, median (IQR)	0 (0-0)	1 (0-4)	2 (1-5)	0 (0-2)
Tender Joint Count, median (IQR)	0 (0-1)	4 (3-7)	5 (3-9)	4 (2-6)
ESR mm/hr, median (IQR)	6 (3-12)	13 (7-22)	11 (6-19)	15 (9-28)
VAS global health in mm, mean ± SD	14 ± 14	37 ± 21	38 ± 21	30 ± 21
Follow up – 1 year				
DAS, mean ± SD	1.3 ± 0.8	2.1 ± 0.9	1.8 ± 0.9	2.1 ± 0.8
HAQ, mean ± SD	0.4 ± 0.5	0.9 ± 0.6	0.8 ± 0.7	0.8 ± 0.6
Swollen Joint Count, median (IQR)	0 (0-1)	0 (0-3)	0 (0-1)	1 (0-2)
Tender Joint Count, median (IQR)	0 (0-2)	3 (1-7)	3 (0-6)	4 (1-8)
ESR mm/hr, median (IQR)	8 (4-15)	9 (5-18)	9 (4-16)	14 (7-31)
VAS global health in mm, mean ± SD	20 ± 21	33 ± 23	27 ± 20	33 ± 24
Total SHS, median (IQR)	0 (0-0.5)	0 (0-0.5)	0 (0-0)	0 (0-0)
Erosive, n (%)	65 (17)	12 (15)	12 (16)	2 (4)
DAS-Remission, n (%)	263 (68)	21 (25)	32 (41)*	12 (24)
Drug free remission, n (%)	124 (32)	1 (1)	0 (0)	5 (10)
ACR/EULAR remission, n (%)	122 (32)	9 (11)	13 (17)	4 (8)
SHS progression, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

After 4 months 12 patients were lost to follow up and 598 patients were categorized a described in this table. SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, RA(2010): rheumatoid arthritis according to the 2010 classification criteria, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, SHS: Sharp- van de Heijde Score, Progression: increase in SHS ≥0.5 points, DAS-remission: DAS<1.6[12], ACR/EULAR remission: provisional Boolean based remission definition published by the American College of Rheumatology and the European League Against Rheumatism based on a 44 joint count [13]. Erosive denotes the presence of at least 1 erosion on radiographs of hands and feet. *p-value <0.05 between arm 1 and arm 2.

Median (IQR) SHS progression score in all groups was 0 (0–0), with no difference between patients with UA and those with RA. Of the total study population, 33/610 (5%) had radiological progression defined as an increase in SHS≥0.5 point, 20/387 (5%) in the early remission group, 5/83 (6%) in arm 1, 6/78 (8%) in arm 2 and 2/50 (4%) in the OP group. Only one patient, in the early DAS remission group and losing remission at 8 months, had rapid radiological progression (defined as a progression score of≥5 points in 1 year) of 18 points.

Loss of early DAS remission after prednisone discontinuation

Fifteen of 387 patients who achieved early DAS remission did not taper and stop prednisone. Of the other 372 patients, 109 (29%) lost DAS remission at 8 months of whom, 67 restarted prednisone at 7.5 mg/day. In 40 patients the protocol was not followed and various other steps were taken. Two patients had missing data. After 1 year, 48/67 (72%) patients re-treated according to protocol and 22/40 (55%) treated otherwise had again achieved remission.

Results at 8 months

DAS remission at 8 months was achieved in 30/83 (36%) in arm 1 and 27/78 (35%) in arm 2 (p=0.99). In arm 1, 30 patients tapered to monotherapy, 33 switched to ADA and in 19 patients other steps were taken (one patient had missing data). In arm 2, 26 patients tapered to monotherapy, 28 increased ADA and in 21 patients other steps were taken (three patients had missing data). More patients in arm 2 who increased ADA achieved DAS remission after 1 year, than patients in arm 1 who switched to ADA (8/28 (29%) versus 6/33 (18%) (p=0.29)). In addition, more patients in arm 2 retained DAS remission after tapering to MTX monotherapy than in arm 1 (17/26 (65%) versus 11/30 (37%), respectively, p=0.02).

Subgroups

During the first year of the study 96/610 (16%) patients never achieved DAS remission, 462/610 (76%) achieved DAS remission at least once and 52 patients had one or more missing DAS values during the first year. Compared with those who achieved DAS remission at least once, patients who never achieved DAS remission had a higher mean baseline DAS (mean (SD) 3.7 (0.9) versus 3.1 (0.9), p<0.001), a longer median symptom duration (median (IQR) 24 (12–44) versus 17 (8–31) weeks, p=0.002), included more women (85/96 (89%) versus 291/462 (63%), p<0.001) and fewer were ACPA-positive (45/96 (47%) versus 265/462 (57%), p=0.047).

Adverse events

During the first 4 months there were 471 adverse events (AE) in 341/610 (56%) patients, including two deaths and 14 other serious adverse events (SAE) in 14 patients.[8]

From 4 months to 1 year, 346/610 (57%) patients reported 527 AE, 53% in the early DAS remission patients, 74% in arm 1, 68% in arm 2 (arm 1 versus arm 2, p=0.41) and 56% in the OP group. The most common AE in all groups were increased liver enzymes,

Table 2. Number of adverse events reported between 4 months and 1 year for patients in the early remission group, the randomization arms and the outside protocol group.

	Early remission n=387	Arm 1 n=83	Arm 2 n=78	Outside protocol n=50
Patients with AE*, no (%)	205/387 (53%)	61/83 (74%)	52/78 (68%)	28/50 (56%)
Total number of AE	298	101	88	40
Type of AE				
Cardiovascular	9	5	6	1
Pulmonary	11	-	2	1
Gastrointestinal	62	18	20	8
Nausea/emesis	15	6	5	2
Increased liver enzymes	33	5	9	3
Other	14	7	6	3
Neuropsychiatric	22	17	2	4
Headache	2	7	-	-
Dizzyness	10	1	-	2
Mood disorders	6	5	1	-
Other	4	4	1	2
Urogenital	5	2	2	1
Skin/mucous membranes	51	6	13	3
Rash	20	5	6	2
Hair thinning/loss	8	1	2	1
Sicca complaints	5	-	1	-
Stomatitis	4	-	-	-
Other	14	-	4	-
Infections	76	23	27	11
Upper airway tract	17	4	8	5
Gastro-intestinal	4	-	3	-
Skin/mucosa	11	2	1	1
Pneumonia / bronchitis	8	3	1	1
Urinary tract	9	6	5	1
Flu/unspecified fever	10	2	2	2
Other	17	6	7	1
Trauma/injury	15	3	-	2
Surgical procedures without hospitalization	9	3	2	2
Other	38	24	14	7

AE: adverse event. *One or more adverse events possible per patient.

nausea, upper airway and skin/mucosa infections and skin rashes (table 2). In 26/610 (4%) patients, SAE were reported. Three patients died: one of a squamous cell carcinoma of the tongue (early remission group), one of a cerebral tumour (arm 2, treated with ADA 40 mg/2 weeks for 4 months) and one patient of an ovarian carcinoma (OP group; in the 7 months before diagnosis the patient was treated with MTX and with prednisone

for 4 months). Three other malignancies were reported, all in the early remission group (breast carcinoma, basal cell carcinoma of the skin, malignant mesothelioma). Twenty-five hospital admissions were reported in 23/610 (4%) patients, 10 in the early remission group, seven in arm 1, six in arm 2 and two in the OP group. Reasons for admission to hospital were complications of malignancy (the three patients, described above), pneumonia (four patients; two in arm 1, one in arm 2 and one in the OP group), suspicion of septic arthritis (arm 1, cultures remained negative), cellulitis of the lower leg (two patients; early remission group and arm 1), percutaneous coronary intervention for cardiac ischaemia (two patients; early remission group and arm 2), cardiac arrhythmia (two patients in the early remission group), urosepsis (arm 1), myocardial infarction (early remission group), femoral fracture (early remission group), total hip replacement for osteoarthritis (arm 1), lower leg amputation for peripheral vascular disease due to diabetes mellitus (OP group), exacerbation of chronic obstructive pulmonary disease (arm 2), surgery for cervical spinal disc herniation (early remission group), cerebrovascular accident (arm 2), Nissen fundoplication (arm 2), femoral head necrosis (arm 2) and trauma due to a car accident (arm 1).

DISCUSSION

In patients with early arthritis, remission defined by Disease Activity Score can be achieved in 54% after 1 year with initial treatment with MTX and a tapered high dose of prednisone followed by remission-steered adjustments to treatment. Radiological damage progression was effectively suppressed in almost all patients. Of the 61% of patients who started tapering medication after being in remission after 4 months, 68% were in remission and 32% in drug-free remission (DFR) after 1 year. These results suggest that combination therapy with MTX and a tapered high dose of prednisone can halt the potentially chronic disease course of RA, prevent damage and induce DFR.

Remission is more difficult to achieve if the initial treatment was unsuccessful. For those patients who did not achieve early remission, an early switch to a combination of MTX with ADA resulted in more remission (41% versus 25%) than treatment expansion with SSZ and HCQ, reserving ADA as possible next step. Functional ability, radiological damage progression and toxicity were similar.

This study is the first to steer according to remission in patients with early RA, and taper and stop medication as soon and as long as this is achieved. The overall remission rate of 54% after 1 year is high. Few other studies have reported similar percentages, and in those studies treatment was continued for longer and none tapered medication or achieved early DFR.[17-20]

A possible explanation for the high (drug-free) remission rates and the minimal radiological damage progression is that we included patients in a relatively early, and possibly reversible, disease stage, which may represent the 'window of opportunity'.[21] Perhaps in this stage, chronicity and damage can be prevented or reversed. It is also

possible that some patients with UA or even classified as RA might have had a self-limiting type of arthritis.[22] A second explanation might be that we included patients with relatively low disease activity, who will more easily achieve the target of a DAS<1.6.[8, 23] The final explanation might be the treatment chosen, initially with a rapidly built up high dose of MTX and a high dose of prednisone tapered to 7.5 mg/day -a combination which has been proved to be better than DMARD monotherapy in patients with RA[6,24,25]- followed after randomisation by progressive treatments either with multiple DMARDs or with a TNF inhibitor, which proved to be effective both in early and established RA.[26-28]

We used the DAS criteria to define remission. These criteria are less stringent than the provisional remission criteria proposed by ACR and EULAR. Nonetheless, we have shown that our patients in DAS remission have good functional ability and virtually no progression of damage.

After 1 year significantly more patients in arm 2 had achieved DAS remission than in arm 1, although after 8 months the remission rates were similar. The 1-year difference is explained by more patients losing remission after tapering low-dose prednisone and poly-DMARDs to MTX monotherapy and fewer patients achieving remission after switching from poly-DMARDs and prednisone to ADA (both in arm 1). This suggests that if remission is not achieved with initial combination therapy, it is better to introduce ADA early. It appears that patients for whom prednisone and poly-DMARDs fail, may respond less well to any other treatment, as was previously shown in a comparison of initial or delayed treatment with infliximab in patients with recent-onset RA (1987 classification criteria).[29]

Although prednisone in the initial treatment combination appears to be very effective, it may also have several side effects and therefore our results may come at a price. Fourteen SAE (infections, cardiovascular disease, femoral head necrosis, diabetic complications) might be related to the use of prednisone. Thirty-six per cent of our patients did not achieve DAS remission with the initial treatment, and 16% did not achieve DAS remission with any treatment. Other (biological) treatments may be more effective and less toxic.

In this trial, which integrated treatment adjustments by protocol with daily practice, the treating rheumatologist sometimes disagreed with required treatment steps based on DAS evaluations by nurses who were blinded to treatment. In some cases the patients refused to take the next treatment step. Despite the protocol deviations that ensued, in general, treatment remained steered according to DAS remission or clinical remission, and follow-up visits continued as before. Because we included all data in our analyses, no information was lost.

In conclusion, most patients with early RA can achieve remission with initial combination therapy followed by treatment targeted at remission early in the disease course. Of the 61% of patients who achieve remission with the initial treatment and start tapering medication, 68% are in remission and 32% are in DFR after 1 year. For patients not in early remission, combination therapy including ADA resulted in significantly more remission after 1 year than combination therapy with poly-DMARDs. Overall, in all

patients functional ability was preserved and radiographic damage progression was minimal. This study suggests that, if diagnosed and treated early, RA may not progress to the chronic and destructive autoimmune disease as we knew it.

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