CHAPTER 5

OUTCOMES OF TWO YEARS REMISSION STEERED TREATMENT IN EARLY ARTHRITIS PATIENTS – THE IMPROVED-STUDY

Submitted

L. Heimans, K.V.C. Wevers-de Boer, G. Akdemir,
Y.P. Goekoop-Ruiterman, E.T. Molenaar, J.B. Harbers,
A.J. Peeters, G.M. Steup-Beekman, L.R. Lard, M.P.D.M. de Buck,
P.B.J. de Sonnaville, B.A.M. Grillet, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Background: To assess 2-year clinical and radiological outcomes of remission steered treatment in patients with early arthritis.

Methods: 610 patients with early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (disease activity score (DAS44<1.6) after 4 months tapered and stopped medication. Patients who did not achieve early DAS-remission were randomized to either MTX, hydroxychloroquine, sulphasalazine and low dose prednisone (arm 1) or to MTX and adalimumab (arm 2). During follow-up, medication was increased, switched or restarted in case of no remission and tapered and stopped in case of remission. Proportions of (drug free) remission (DFR) were analyzed separately for the treatment strategies and patients with RA and UA.

Results: After 2 years, 301/610 (49%) of the patients were in DAS-remission and 131/610 (21%) in DFR. In the early remission group 241/387 patients (62%) achieved DAS-remission and 111/387 (29%) DFR. In arm 1 22/83 (27%) achieved remission and 7/83 (8%) DRF. In arm 2 24/78 (31%) achieved remission and 7/78 (9%) DFR. Patients with RA and with UA achieved DAS-remission in comparable percentages (RA: 234/479 (49%), UA: 64/122 (52%), p=0.25). UA patients more often achieved DFR (42/122 (34%)) than RA patients (88/479 (18%), p<0.001). Median (IQR) radiological progression in all groups was 0 (0-0).

Conclusions: After 2 years remission steered treatment, patients in the early remission group more often achieved (drug) free remission than patients who needed additional treatment steps in the randomization arms. Radiologic damage progression remained well suppressed.

INTRODUCTION

In rheumatoid and undifferentiated arthritis (RA and UA) it is preferable to initiate treatment early after onset of symptoms to induce early remission and maybe reverse the disease process.[1-3]

In the IMPROVED-study we have shown that it is possible for 61% of the RA patients and 65% of the UA patients to achieve early remission (Disease Activity Score DAS<1.6) after 4 months treatment with methotrexate (MTX) and tapered high dose of prednisone.[4] In case of early remission, medication was tapered until drug free remission (DFR) was achieved. Those patients who did not achieve early remission were randomized. In all patients, treatment adjustments, including drug tapering, were made every 4 months aiming at a DAS<1.6. Here, the clinical and radiological outcomes after 2 year follow-up are presented.

METHODS

Study design and patients

The IMPROVED-study (ISRCTN Register number 11916566 and EudraCT number 2006-006186-16) is a multicenter, randomized, single-blinded clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). Patients were recruited between March 2007 and September 2010 in 12 hospitals in the Western part of the Netherlands. The study protocol was approved by the Medical Ethics Committee of each participating center, all patients gave written informed consent.

Patients were ≥18 years, with recent onset RA or UA, a DAS≥1.6 and no previous antirheumatic therapy. RA was defined as fulfilling the 2010 the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria [5] with a symptom duration ≤2 years. UA was defined as at least one joint with clinical synovitis and one other painful joint, clinically suspected for early RA, regardless of symptom duration. Exclusion criteria were published previously.[4, 6]

Intervention

All patients started with 4 months of MTX 25 mg/week and prednisone 60 mg/day which was tapered to 7.5 mg/day in 7 weeks. Every 4 months the DAS was assessed by a trained research nurse, blinded for treatment allocation. The treatment target of the study was a DAS<1.6 which was considered to denote remission (figure 1).[7]

Patients in early remission after 4 months tapered prednisone to 0. When still in remission after 8 months, MTX was also tapered to 0. In case of a DAS≥1.6 after 8 months, prednisone was restarted at 7.5 mg/day.

Patients with a DAS≥1.6 after 4 months were randomized, either hydroxychloroquine (HCQ) 400mg/day and sulphasalazine (SSZ) 2000mg/day were added to MTX and prednisone (arm 1) or they switched to MTX 25mg/week plus adalimumab (ADA) 40mg/2weeks (arm 2). Patients who had achieved early remission and discontinued prednisone, then lost

remission and restarted prednisone without achieving remission, were also randomized ('delayed randomization') (figure 1). In arm 1, if remission after 8 months was achieved, prednisone, SSZ and then HCQ were stopped. MTX was stopped if remission remained 4 months later. If remission was not achieved at 8 months, patients switched to MTX+ADA (40mg/2weeks, increased to 40 mg/week if DAS remained ≥1.6). Patients in arm 2 tapered ADA in case of remission after 8 months and increased ADA to 40mg/week in case of no remission. In both arms, if patients did not achieve remission on a combination of MTX+ADA 40mg/week, further treatment decisions were left to the opinion of the rheumatologist (figure 1). A detailed description of the randomization procedure was published previously.[6]

Primary and secondary outcomes

Primary outcomes were percentages of patients in remission and DFR based on a DAS<1.6 or on the proposed remission definition published by the ACR/EULAR in 2011.[8]

Secondary outcomes were mean DAS, mean functional ability as measured by the Dutch version of the Health Assessment Questionnaire (HAQ [9]), toxicity and radiological damage progression of the joints in hands and feet (defined as an increase of ≥0.5 point in Sharp-van der Heijde score (SHS) [10]).

Baseline and yearly radiographs of hands and feet were blinded for patient identity and scored in time random order for the presence of erosions and joint space narrowing by 2

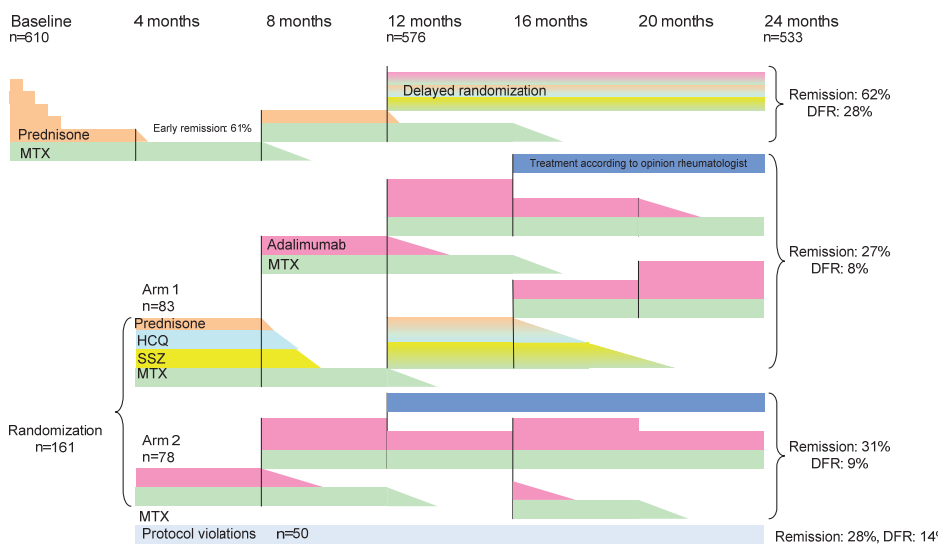

Figure 1. Study flow chart with percentages DAS- and drug free remission after the second study year. DFR: drug free remission, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment left to decision of rheumatologist, aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow up.

trained, independent readers (LH and GA). Only 8% of the patients showed progression and therefore intra-class correlation coefficients were not suitable for measuring reliability.[11] In 443 of 496 patients who had radiographs taken after 2 years follow-up, there was an inter-reader difference of <2 between the progression scores of both readers. For the other 53 a consensus score was reached.

Outcomes were reported separately for patients who achieved early DAS-remission and those randomized and were compared between the randomization arms, as well as between patients with RA and patients with UA and between patients in or not in remission after 2 years.

Statistical analysis

We performed intention-to-treat analyses. Outcomes were analyzed using students *t*-tests, Mann Whitney U tests and χ^2 tests. DAS and HAQ over time were compared using linear mixed models, with treatment strategy (arm 1 and 2) and time (study visit) as fixed effects, in an unstructured covariance structure. All statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Study population

Of the 610 patients included in the IMPROVED-study, 479 (79%) had classifiable RA and 122 (20%) UA (9 patients could not be classified because of missing data). During the first 2 years 79 patients were lost to follow-up; 54 withdrew consent, 9 discontinued because of a revised diagnosis and 8 because of co-morbidity. Eight patients died,[4, 6] 3 of those in the second year of the study (supplementary table S1).

Of 610 patients, 387 (63%) achieved early remission, 375 (61%) at 4 months, 12 (2%) more after a reassessment 4-6 weeks later (if the rheumatologists disagreed with the DAS after 4 months). One-hundred-sixty-one of 610 patients (26%) were randomized; 83 patients into arm 1 and 78 to arm 2. Fifty patients with a DAS≥1.6 after 4 months were not randomized as the protocol required and were analyzed in the outside of protocol (OP) group. Twelve patients left the study before the assessment at 4 months (table 1).

Remission and drug free remission

In 50/610 patients (8%) remission had never been achieved during 2 years follow-up. Most patients at least once achieved remission which was lost again and medication was reintroduced. At the next evaluation, remission had been achieved again in >70% of those patients. Fifty-five patients (9%) (37 with RA, 17 with UA, p=0.01. One patient was unclassifiable because of missing data) were in sustained remission from 4 months through to 2 years (and therefore in DFR from 8 months to 2 years). After 2 years follow up, 301/610 (49%) patients were in remission and 131/610 (21%) were in DFR. In the early remission group, 241/387 (62%) were in remission and 111/387 (29%) in DFR after

Table 1. Baseline characteristics of the IMPROVED study population.

	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	OP 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
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 (weeks), median (IQR)	17 (9-30)	22 (9-41)	21 (8-31)	18 (9-42)
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)
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)
ESR mm/hr, median (IQR)	23 (8-38)	28 (13-41)	22 (11-41)	29 (16-42)
VAS global health in mm, mean ± SD	43 ± 24	53 ± 20	54 ± 22	49 ± 23
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)

After 4 months 12 patients were lost to follow up and 598 patients were categorized as described in this table. OP outside of protocol, 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, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, SHS: Sharp- van de Heijde Score, Erosive: at least 1 erosion. Arm 1: randomized at 4 months to methotrexate, sulphasalazine, hydroxychloroquine and low dose prednisone. Arm 2: randomized at 4 months to methotrexate and adalimumab.

2 years. In arm 1, 22/83 (27%) were in remission compared to 24/78 (31%) in arm 2 (p=0.76). DFR was achieved by 7/83 patients in arm 1 (8%) and in 7/78 patients in arm 2 (9%) (p=0.90). Remission defined according to the proposed ACR/EULAR remission criteria was achieved in 138/610 (23%) patients; 117/387 (30%) in the early remission group, 2/83 (2%) in arm 1 and 14/78 (18%) in arm 2 (arm 1 versus arm 2: p=0.001).

After 2 years, comparable percentages of ACPA positive and ACPA negative patients were in remission (ACPA positive: 172/333 (52%), ACPA negative: 125/262 (48%), p=0.68) but more ACPA negative patients achieved DFR than ACPA positive patients: 74/262 (28%) versus 54/333 (16%), p<0.001. Comparable percentages of patients with UA or with RA achieved remission after 2 years (UA: 64/122 (52%) and RA: 234/479 (49%), p=0.25) but significantly more patients with UA, of whom 94% were ACPA-negative, achieved DFR (41/122 (34%) compared to 89/479 (19%) in RA patients, p<0.001).

Patients who were not in remission at 2 years, had a higher tender joint count than patients who were in remission (median (IQR) 4 (2-6) versus 0 (0-1) p<0.001) and also higher scores on the visual analogue scale (VAS) for pain (mean (SD) 41 (24) versus 11 (16) p<0.001), higher ESR (13 (9-22) versus 6 (3-13) p<0.001) and a higher swollen joint count (1 (0-3) versus 0 (0-0), p<0.001). Except for ESR and swollen joint count, the statistical significant differences between these patients were already present at baseline.

Remission rates were comparable between patients who at baseline had <12 weeks symptom duration and patients who had symptoms for ≥12 weeks, 106/204 (52%) versus 192/397 (50%) (p=0.31), as were DFR rates 50/204 (25%) versus 80/397 (20%) (p=0.19).

DAS and HAQ after 2 years

At 2 years, mean (SD) DAS was 1.25 (0.77) in the early remission group, 2.02 (0.70) in arm 1 and 1.92 (0.85) in arm 2 (arm 1 versus arm 2: p=0.45). Patients treated outside the protocol had a mean DAS of 1.9 (0.7) (table 2). Mean (SD) HAQ at 2 years was 0.38 (0.48) in the early remission group, 0.90 (0.66) in arm 1 and 0.83 (0.67) in arm 2 (arm 1 versus arm 2: p=0.55) (table 2). Compared to baseline, in all groups improvement in mean HAQ was >0.20 and therefore clinically relevant.[9] Mean (SD) HAQ in patients who were in remission at 2 years was 0.29 (0.39) compared to 0.94 (0.63) in patients who were not in remission (p<0.001). Mean (SD) HAQ at 2 years of patients in ACR/EULAR remission was 0.14 (0.28).

Over time, DAS or HAQ were not significantly different between arm 1 and 2 (mean difference (95%CI) LMM for DAS 0.01 (-0.2;0.2) and for HAQ 0.1 (-0.1;0.2)).

Radiological joint damage

Of the total study population, 50/610 (8%) patients showed radiological progression defined as an increase in SHS of ≥0.5; in the early remission group 33/387 (9%) patients showed progression, in arm 1 9/83 (11%), in arm 2 5/78 (6%) (arm 1 versus arm 2: p=0.31) and in the OP-group 3/50 (6%). Median SHS progression in all groups was 0 (range 0-22). There was no significant difference in progression scores between patients who at 2 years were in DAS-remission and patients who were not. Eight patients (1%) after 2 years had radiological damage progression of ≥5 points which represents the minimal clinically important difference.[12] Seven of these 8 patients had achieved early remission and one patient was in persistent remission from 4 months.

Compared to the results after 1 year we found less erosions after 2 years, probably due to differences in interpretation of the minimal changes on radiographs. The differences were found across the scores of both readers, one of whom had also scored year 1 while the new reader used the same scoring method and had received the same training. In the early remission group 39/387 (10%) showed erosions after 2 years compared to 65 (17%) after year 1, in arm 1 2/83 (2%) after 2 years compared to 12 (15%) after year 1, in arm 2 8/10 (6%) after 2 years and 12 (16%) after year 1 and in the OP-group 1/50 (2%) after 2 years and 2 (4%) after year 1.

Therapy

Of the 400 patients not in DFR at 2 years, 196 patients were on DMARD monotherapy, 12 used a combination of multiple non-biologic DMARDs, 37 a combination of non-biologic DMARDs with prednisone, 79 with adalimumab and 18 with another biologic

Table 2. Outcomes in the IMPROVED-study population after 2 years.

	Early remission n = 387	Arm 1 n = 83	Arm 2 n = 78	p arm 1 vs 2	OP group n = 50
DAS, mean ± SD	1.3 ± 0.8	2.0 ± 0.7	1.9 ± 0.9	0.45	1.9 ± 0.7
HAQ, mean ± SD	0.4 ± 0.5	0.9 ± 0.7	0.8 ± 0.7	0.55	0.8 ± 0.7
Swollen Joint Count, median (IQR)	0 (0-1)	1 (0-2)	0 (0-2)	0.25	0 (0-2)
Tender Joint Count, median (IQR)	0 (0-2)	3 (2-5)	3 (1-6)	0.84	2 (1-4)
ESR mm/hr, median (IQR)	8 (4-16)	11 (6-20)	9 (6-17)	0.19	14 (7-25)
VAS global health in mm, mean ± SD	18 ± 21	30 ± 21	28 ± 24	0.61	32 ± 22
Total SHS, median (IQR)	0 (0-0.5)	0 (0-1.1)	0 (0-0)	0.12	0 (0-0.3)
Erosive, n (%)	39 (10)	2 (2)	8 (10)	0.04	1 (2)
SHS progression, n (%)	33 (9)	9 (11)	5 (6)	0.31	3 (6)
DAS-remission, n (%)	241 (62)	22 (27)	24 (31)	0.76	15 (28)
Drug free remission, n (%)	111 (28)	6 (7)	7 (9)	0.73	7 (14)
ACR/EULAR remission, n (%)	117 (30)	2 (2)	14 (18)	0.001	5 (10)

After 4 months 12 patients were lost to follow up and 598 patients were categorized.
OP: outside of protocol, SD: standard deviation, IQR: interquartile ranges, n: number, DAS: disease activity score, HAQ: Health Assessment Questionnaire, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, SHS: Sharp- van de Heijde Score, Erosive: at least 1 erosion, Progression: increase in SHS ≥0.5 points, DAS-remission: DAS<1.6[7], 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].
Arm 1: randomized after 4 months to methotrexate, sulphasalazine, hydroxychloroquine and low dose prednisone. Arm 2: randomized after 4 months to methotrexate and adalimumab.

agent. In 16 patients therapy at 2 years was unknown because of missing data and 42 patients were drug free but not in remission.

During 2 years follow-up, 43/83 (52%) of the patients in arm 1 switched to ADA+MTX and after 2 years 28 patients still used ADA+MTX.

Toxicity

During the second year of the study, 337/610 (55%) patients reported 704 adverse events (AE): 53% of the patients in the early remission group, 64% in arm 1, 67% in arm 2 (arm 1 versus arm 2: p=0.71) and 54% in the OP-group. The most common AE were gastro-intestinal complaints, upper airway infections and skin rashes (table 3). Twenty-five serious adverse events (SAE) were reported in the early remission group, 5 in arm 1, 8 in arm 2 and 3 in the OP group (table S1).

DISCUSSION

Two years after initial therapy with MTX and a tapered high dose of prednisone, followed by remission steered treatment including drug tapering and discontinuation, 49% of the patients with early RA or UA were in remission and 21% were in DFR. Patients

Table 3. Number of adverse events reported between 1 year and 2 years.

	Early remission n=387	Arm 1 n=83	Arm 2 n=78	Outside protocol n=50
Patients with AE, no (%)	205/387 (53%)	53/83 (64%)	52/78 (67%)	27/50 (54%)
Total number of AE	408	129	109	58
Cardiovascular	25	5	8	4
Pulmonary	17	5	2	2
Gastrointestinal	67	16	14	12
GI complaints	8	2	2	-
Nausea/emesis	23	2	4	4
Increased liver enzymes	15	7	3	4
Other	21	5	5	4
Neuro-psychiatric	37	5	7	3
Headache	14	-	4	1
Dizziness	7	1	-	1
Mood disorders	4	-	-	1
Other	12	4	3	-
Urogenital	7	3	2	3
Skin/mucous membranes	45	18	15	3
Rash	19	8	5	-
Hair loss/thinning	4	1	1	1
Sicca complaints	3	-	-	1
Eczema	3	1	-	-
Other	16	8	9	1
Infections	106	38	41	18
Upper airway tract	29	11	16	10
Gastro-intestinal	4	1	-	2
Skin/mucosa	14	2	4	2
Pneumonia/bronchitis	9	1	1	1
Urinary tract	15	7	5	1
Flu/unspecified fever	25	10	6	1
Other	10	6	9	1
Trauma/injury	13	5	2	3
Infusion reaction	3	1	-	-
Malaise	9	5	1	1
Surgical procedures without hospitalization	13	5	4	1
Other	65	23	12	8

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

who achieved early remission after 4 months more often achieved remission (62%) and DFR (29%) at 2 years than patients who did not (29% remission and 9% DFR, without differences between the two treatment strategies). Radiological damage progression was seen in only 8% of the patients and functional ability improved up to the normal range in those who achieved remission.

The radiological results are better than previously reported in patients with early RA.[14-17] For example, 7-33% of the patients in the BeSt study showed progression after 1 year and 20-47% of the patients in the NEO-RACo study showed progression after 2 years.[14, 18] Still, the overall remission rates in the IMPROVED-study are only slightly higher than what we observed in the BeSt study.[14, 19] At baseline, those patients had active RA (1987 criteria[20]) with high disease activity, were more often ACPA positive patients and had longer symptom duration.

Furthermore, only half of the BeSt study population received initial combination therapy and the target of treatment was low disease activity (DAS≤2.4) instead of remission (DAS<1.6). That only half of the patients achieved remission in the IMPROVED-study may in part be explained by rapid tapering and discontinuation of drugs as soon as DAS<1.6 was achieved. There were only 55 patients who had been in remission from 4 months onwards. Together with the exception of 50 patients who never achieved remission, all others had achieved but lost remission at least once. It is possible that steering at a treatment target of remission defined by DAS<1.6 is hampered by some patients reporting pain and joint tenderness where no joint swelling was found. One may argue that using DAS<1.6 as the treatment target is unrealistic, as with a DAS just above the threshold of 1.6 inflammation is equally well suppressed, resulting in equally well prevented joint damage. Still, patients not in remission had a mean HAQ approaching 1 whereas patients in remission had near-normal functional ability. This, however, may have come at the cost of relatively high usage of medications with potential side effects and high costs.

We found the highest remission and DFR rates in patients who had achieved early remission. It may be that patients who fail to achieve remission on initial combination treatment are a selected group with less responsive disease. After 1 year follow-up we have reported there was a statistically significant difference in remission rates between the randomization arms.[6] After 2 years, the remission rates were comparable and this is probably due to remission steered treatment adjustments in both arms and due to treatment overlap in the treatment strategies during follow-up.

Remission rates were comparable between patients with RA and UA. This could either indicate that we missed the 'window of opportunity' and therefore the opportunity to alter the disease course. However, the outcomes between patients with <12 weeks symptom duration and those with ≥12 weeks symptom duration are comparable. It could also indicate that early RA and UA, when effectively treated, result in comparable outcomes. On the other hand, UA patients more often achieved DFR than RA patients. This may suggest that, although it is possible to achieve remission in RA and UA in comparable percentages, the possibility to taper and stop medication when remission is achieved, is not. These same arguments probably also explain the higher DFR rates in ACPA negative patients, compared to ACPA positive patients.

We found less erosive joint damage after 2 years than after 1 year. Our data suggest that this is not due to repair, which has been shown to occur more often in damaged joints.[21] Joint damage, in general, was minimal and therefore normal variations were difficult to distinguish

from early abnormalities. Furthermore, the radiographs taken at baseline, after 1 year and after 2 years, were scored in random order. It has been demonstrated that chronological scoring is more sensitive to change and may lead to an increased detection of clinically relevant progression.[22, 23] Since the overall progression rates are so low and for most patients below the minimal clinically important difference, it is unlikely that the small difference between the erosion scores after 1 and 2 years affect the main radiological outcomes.

In conclusion, in patients with recent onset RA or UA, 2 years of remission targeted treatment results in 49% of the patients being in remission and 21% in DFR and virtually no radiological damage progression. Patients who achieved early remission also achieved more remission and DFR after 2 years than the patients who had not achieved early remission and were randomized to 2 treatment strategies, between which no differences in outcomes were found. These results suggest that initial treatment with MTX and prednisone followed by remission steered treatment is effective in suppressing disease activity and in particular in suppressing joint damage progression.

REFERENCE LIST

1. van Tuyl LH, Lems WF, Voskuyl AE et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 2008;67(11):1574-1577.
2. Puolakka K, Kautiainen H, Mottonen T et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005;52(1):36-41.
3. Grigor C, Capell H, Stirling A et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-269.
4. Wevers-de Boer K, Visser K, Heimans L et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis 2012;71(9):1472-1477.
5. 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(9):1580-1588.
6. Heimans L, Wevers-de Boer KV, Visser K et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013.
7. Prevoo ML, van Gestel AM, van 't Hof M, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35(11):1101-1105.
8. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63(3):573-586.
9. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3(3):305-309.
10. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26(3):743-745.
11. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420-428.
12. Bruynesteyn K, van der Heijde D, Boers M et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46(4):913-920.
13. Felson DT, Smolen JS, Wells G et al. American College of Rheumatology/European League

against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70(3):404-413.

14. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52(11):3381-3390.
15. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54(1):26-37.
16. Bakker MF, Jacobs JW, Welsing PM et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 2012 Mar 6;156(5):329-39.
17. O'Dell JR, Mikuls TR, Taylor TH et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013 Jul 25;369(4):307-18.
18. Leirisalo-Repo M, Kautiainen H, Laasonen L et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013 Jun;72(6):851-7.
19. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70(6):1039-1046.
20. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-324.
21. van der Linden MP, Boja R, Klarenbeek NB, Huizinga TW, van der Heijde DM, van der Helm-van Mil AH. Repair of joint erosions in rheumatoid arthritis: prevalence and patient characteristics in a large inception cohort. Ann Rheum Dis 2010 Apr;69(4):727-9.
22. Bruynesteyn K, van der Heijde D, Boers M et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. J Rheumatol 2002;29(11):2306-2312.
23. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001 Sep;60(9):817-27

Table S1. Serious adverse events during the second year of the IMPROVED-study

	Early remission n=387	**Arm 1 n=83**	**Arm 2 n=78**	**Outside protocol n=50**
Patients with SAE, no (%)	18/387 (5%)	4/83 (5%)	7/78 (9%)	3/50 (6%)
Total number of SAE	25	5	8	3
Died	Cardiac arrest after pericarditis Kidney failure during sepsis as complications of multiple myeloma	-	Pneumococcal sepsis	-
Malignancies	Multiple myeloma Sigmoid colon carcinoma Metastases of an unknown primary tumour	Non-melanoma skin cancer, twice in 1 patient	B-cell non-Hodgkin lymphoma	-
Hospital admissions	Resection sigmoid colon carcinoma, acute coronary syndrome, aortic root replacement, 2 myocardial infarctions, diarrhoea with dehydration, respiratory distress suspected to be due to pulmonary embolism and infection, haemolytic anaemia, pulmonary embolism, 2 total knee replacements, pyelonephritis, epileptic seizure, PCI for cardiac ischemia, surgery for spinal disc herniation, 3 admissions for constipation (in 1 patient), multiple sclerosis, motorbike accident.	PCI for cardiac ischemia, interstitial lung disease, total shoulder replacement.	Pulmonary embolism, total knee replacement, pneumonia, fever with high blood pressure and abdominal lymphadenopathy (unknown cause), stroke, surgery for a fractured ankle.	Polymyalgia rheumatica, septic arthritis of the left knee, bilateral extirpation of the adnexes (cyst).

SAE: serious adverse event, PCI: percutaneous coronary intervention.