Improving targeted treatment in early rheumatoid and undifferentiated arthritis

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Chapter 4

REMISSION INDUCTION THERAPY FOLLOWED BY TWO TREATMENT STRATEGIES AIMED AT DRUG-FREE REMISSION IN PATIENTS WITH EARLY ARTHRITIS: FIVE YEAR RESULTS OF A MULTICENTRE, RANDOMISED SINGLE-BLIND CLINICAL TRIAL (THE IMPROVED-STUDY)

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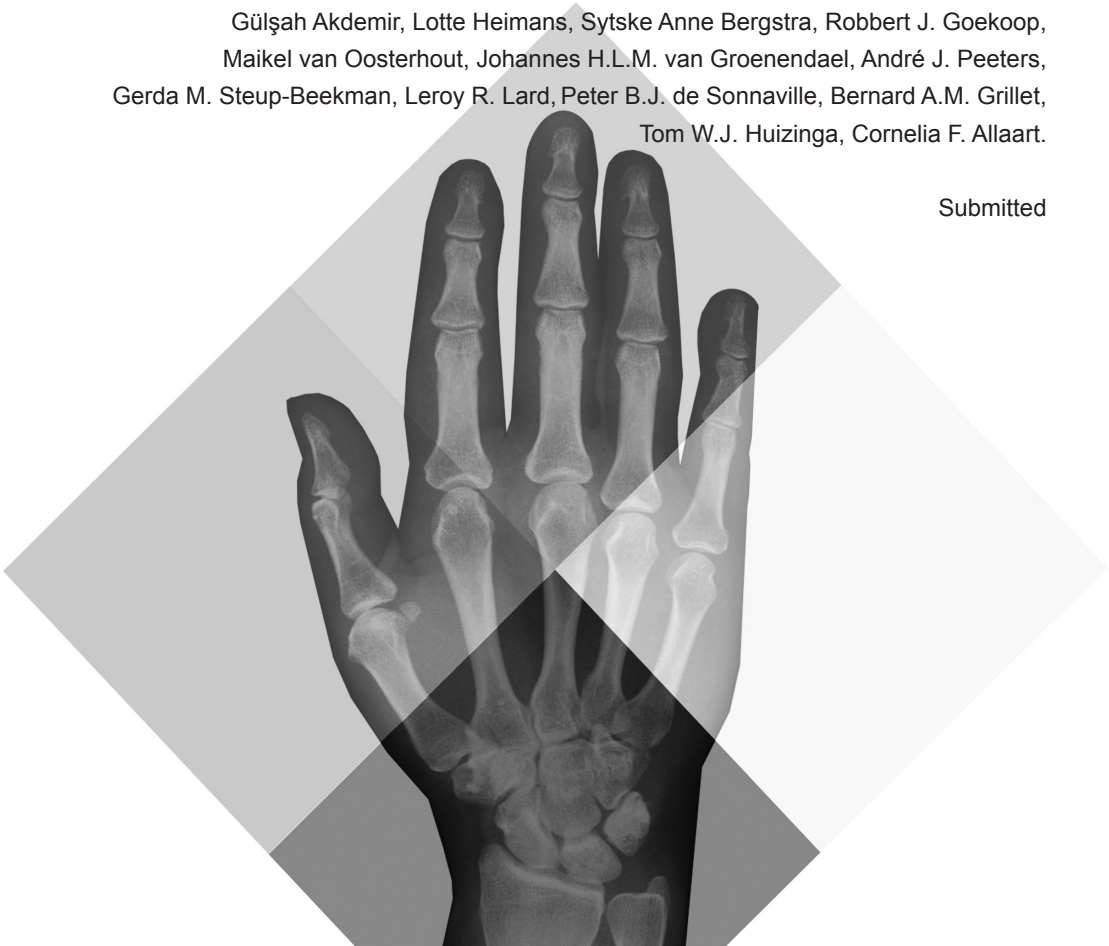

SUMMARY

Background
Early treatment start and earlier introduction of biologic therapies in rheumatoid arthritis (RA) may ensure that early sustained drug-free remission (DFR) can be achieved.

Methods
In 12 hospitals, 610 early (<2 years) RA or undifferentiated arthritis (UA) patients were included in a randomised, single-blinded clinical trial. All patients started methotrexate (MTX) 25mg/week and prednisone (60mg/day tapered to 7.5mg/day). Patients **not** in early DAS-remission (Disease Activity Score <1.6 after 4 months) were randomized to arm 1: adding hydroxychloroquine 400mg/day and sulphasalazine 2000mg/day, or arm 2 switching to MTX plus adalimumab 40mg/2weeks. Treatment adjustments over time aimed at DFR. Outcomes were DAS-remission percentages, functional ability, toxicity and radiologic damage progression after five years.

Results
After four months, 387 patients were in early DAS-remission, 83 were randomised to arm 1 and 78 to arm 2. After five years, 295/610 (48%) patients were in DAS-remission, 26% in sustained (≥ 1 year) DFR. In the early DAS-remission group 220/387 (57%) were in DAS-remission and 135/387 (35%) in sustained DFR. Between the randomization arms clinical outcomes were comparable, (50% in DAS-remission, 12% in sustained DFR). Overall, mean HAQ was 0.6 (SD 0.5)), and damage progression was low (median progression 0.5 (0-2.7) Sharp/vanderHeijde points).

Conclusions
Five years of DFR steered treatment in early arthritis patients results in almost normal functional ability without clinically relevant joint damage across treatment groups. Patients in early DAS-remission had the best clinical outcomes. There were no differences between the randomization arms. Sustained DFR is a realistic treatment goal.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by inflammation of synovial joints.[1] Uncontrolled inflammation can lead to destruction of affected joints, which can occur before symptoms meet the classification criteria (undifferentiated arthritis, UA), and vasculitis with organ damage.[1-3] In the last decades the therapeutic approach of RA has changed drastically, starting with Disease Modifying Antirheumatic Drugs (DMARD) as soon as possible, in particular in combination with a course of corticosteroids or a biologic DMARD, and intensifying or changing medication as long as a predefined target of disease activity has not yet been achieved.[4-13] Achievement of remission (disease activity score (DAS)<1.6) appears to be a realistic goal in these patients and even drug-free remission is feasible.[4, 8] Sustained drug-free remission can be used as an analogue for cure, although a disease flare may occur which warrants restart of medication. There is evidence that the chance of a flare is reduced if treatment is started very early, possibly before the disease characteristics meet classification criteria.[12]

In the IMPROVED-study we aimed at early drug-free remission in early RA and UA patients. All patients started with induction therapy with methotrexate (MTX) and a tapered high dose of prednisone. As long as DAS-remission was not achieved, every four months the medication was intensified according to two randomisation arms with variations in the order of use of DMARDs. Drug tapering was required when DAS-remission was achieved, but medication was increased or restarted when DAS-remission was lost. Here we report five years clinical and radiological outcomes of induction therapy followed by DAS-remission steered treatment in the two randomisation arms as well as in the total group.

METHODS

Study design

The IMPROVED-study (acronym for Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease) is a multicentre, two-step randomised, single-blinded, clinical trial designed by Dutch rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). The general aim was to achieve clinical remission (Disease Activity Score <1.6) as early as possible, with initial combination therapy, followed, for patients not in DAS-remission at four months, by two strategies of medication use, either switching immediately to a biologic DMARD or first trying additional synthetic DMARDs. All patients were required to taper and stop medication if and as long as DAS-remission was achieved. The study was conducted in 12 hospitals in the Western part of the Netherlands. The study protocol was approved by the Medical Ethics Committee of each participating centre.

Patients

Eligible patients were ≥18 years, with early RA fulfilling the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria[5] with a symptom duration ≤2 years, or UA suspected to be early RA according to the rheumatologist, regardless of symptom duration, with a DAS≥1.6, who had not been treated with prednisone and/or DMARDs. Exclusion criteria were pregnancy or wish to become pregnant during the study, malignancy within the last five years, bone marrow hypoplasia, aspartate transaminase (AST) and/or alanine transaminase (ALT) >3 times normal value, serum creatinine level >150umol/l or estimated creatinine clearance <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (New York Heart Association class III/IV), alcohol or drug abuse, serious infections in the previous three months or chronic infectious disease, active or latent hepatitis B infection, known HIV infection, lymphoproliferative disease and multiple sclerosis.[7, 13] Patients with active tuberculosis (TB) and UA patients with latent TB were excluded. RA patients with latent TB could be enrolled if they started adequate antituberculous therapy prior to initiation of high dose prednisone, according to local recommendations. All patients gave written informed consent.

Intervention

During the first four months all patients were treated with MTX 7.5 mg/week increased to 25 mg/week in 5 weeks (or highest tolerated dose, oral or subcutaneous at the discretion of the rheumatologist) and prednisone tapered in seven weeks from 60 mg/day to 7.5 mg/day. The DAS (based on an evaluation of 53 joints for tenderness and 44 joints for swelling, ESR and patient's assessment of global health on a 100 mm Visual Analogue Scale)[11] was assessed every four months. A DAS<1.6 was considered to denote DAS-remission.[9] For all patients over five years, if the DAS was ≥1.6, dose intensification or a drug change or restart of last discontinued medication was required, and medication was tapered to 0 as soon as and as long as DAS was <1.6, until drug-free remission was achieved.

Patients who were in DAS-remission after four months (early DAS-remission) tapered and after three weeks stopped prednisone, then, if DAS-remission continued at eight months, over ten weeks tapered and stopped MTX, thus achieving drug-free remission at year one (supplementary figure 1). If, at eight months, DAS had increased to ≥1.6 prednisone was restarted at 7.5 mg/day. With regained DAS-remission, this could be tapered and stopped again, but with persistent or recurrent DAS≥1.6, 'delayed randomisation' (in the arms as below) was required. They, as patients not in early DAS-remission, continued treatment according to one of two randomisation arms:

In arm 1 patients were treated with MTX (25 mg/week or highest tolerated dose), sulphasalazine (SSZ) 2000 mg/day, hydroxychloroquine (HCQ) 400 mg/day and prednisone 7.5 mg/day. If DAS-remission was achieved, first prednisone, then SSZ, then HCQ were tapered and

stopped, followed by tapering and discontinuation of MTX if DAS-remission remained four months later. Medication was restarted if DAS-remission was lost. If DAS-remission was not achieved, medication was changed to MTX and adalimumab 40 mg/2 weeks, which subsequent treatment steps as in arm 2. Patients in arm 2 received adalimumab at four months, tapering and stopping prednisone in three weeks and continuing MTX. In both arm 1 and arm 2, if DAS-remission was not achieved on adalimumab plus MTX, adalimumab was increased to 40 mg/week. If DAS-remission was still not achieved, subsequent treatment steps were left to shared decision making by rheumatologist and patient.
Fifty patients who did not achieve DAS-remission at four months who were incorrectly not randomised (protocol violation) were followed in the Outside of Protocol (OP) group.

Primary and secondary outcomes

Data of all centres were centrally assessed. Primary outcomes after five years were percentages of DAS-remission and drug-free remission based on a DAS<1.6, or on the proposed DAS-remission definition published by the ACR/EULAR in 2011 (Boolean).[6] 'Sustained drug-free remission was defined by drug-free remission during ≥1 year, starting at any time point. 'Early sustained drug-free remission' was defined by a subsequent period of ≥1 year of drug-free remission beginning at the first possibility to achieve drug-free remission at t=12 months, which was only possible in the early DAS-remission patients.
Secondary outcomes were mean DAS, mean functional ability assessed by the Dutch version of the Health Assessment Questionnaire (HAQ),[10] radiological damage progression of the joints in hands and feet, and toxicity. Baseline and annual radiographs of hands and feet, blinded for patient identity and treatment allocation, were scored for the presence of erosions and joint space narrowing using the Sharp-van der Heijde score (SHS)[214], by two trained, independent readers (GA and SB) in chronological order. The mean of both readers' score was used, unless there was disagreement >2 points, in which case the radiographs were rescored in consensus (n=82 patients). Progression ≥0.5 or ≥5 points[15] was reported and compared between groups. Prior to scoring the IMPROVED radiographs, a sample of 35 patients from the BeSt-study[16] with baseline and five year annual radiographs of hands and feet were scored in chronological order blinded for patient identity and treatment allocation, and an intra-class correlation coefficient ICC[17] calculated to measure reliability between the readers: this was 0.97. Due to the small number of patients with damage progression, ICC in the IMPROVED-study could not be determined.
In patients with available baseline and five year radiographs the progression score over five years was calculated. Missing values for annual erosion and narrowing scores of hands and feet were imputed by multiple imputation, after first log-transformation because of skewed data, with age, gender, symptom duration, body mass idex (BMI), smoking status, diagnosis, autoantibody status (rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA)

and anti-carbamylated protein antibodies (anti-CarP)), baseline DAS and HAQ, as well as allocated treatment strategy, annual DAS and HAQ and log-transformed annual erosion and joint space narrowing scores of hands and feet added in the imputation model.
Signs and symptoms of adverse events were recorded through unstructured open end questioning by the research nurses at each four-monthly visit in the first two years and afterwards annually, and/or by the treating physician, and coded by the trial physician. Serious adverse events were reported to the study centre within 24 hours of occurrence. (Serious) Adverse events were reported per 100 patient years.

Statistical analysis

The target sample size was calculated with a power calculation to detect differences between randomisation arms of at least 50% in DAS-remission rates and 0.2 points in HAQ with a power of 80%. Based on an estimated 30% of the patients achieving early DAS-remission we would need 535 patients to randomise 100 patients in each arm. During the study more patients achieved early DAS-remission and the target sample size was recalculated and increased to 610 patients. Comparisons in outcomes were made between the randomisation arms. In addition, outcomes were compared across the whole cohort in relation to drug-free remission steered treatment, for baseline characteristics such as disease activity, autoantibody status and symptom duration.
Outcomes were compared 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 a Toeplitz heterogenous covariance structure (DAS), and unstructured covariance structure (HAQ). We performed intention-to-treat analyses. All statistical analyses were conducted with SPSS for Windows version 23·0.
The study is registered with the **ISRCTN Register, number** 11916566 and EudraCT number 2006-006186-16.

RESULTS

Between March 13, 2007 and September 24, 2010, we assessed 730 patients, of which 120 were ineligible and 610 were included in the study (figure 1). Of the 610 patients, 479 (79%) had classifiable RA and 131 (21%) UA (including nine patients who could not be classified because of missing information on symptom duration and/or ACPA/RF status). During five years of the study 152/610 (25%) patients (112 with RA, 40 with UA) were lost to follow-up: 17 patients died, 13 left the study due to comorbidity, 12 had a revised diagnosis and 110 withdrew consent. Twelve patients left the study before the first assessment at four months. Of 610 patients, 387 (63%) achieved early DAS-remission, 375 (61%) at four months, 12

(2%) more after a reassessment 4-6 weeks later (per protocol because the rheumatologists disagreed with the DAS at four months). One-hundred-sixty-one of 610 patients (26%) were randomised; 83 patients to arm 1, and 78 to arm 2. Fifty patients not in early DAS-remission were not randomised (protocol violation) and were analysed in the OP group. Baseline characteristics were well balanced between the randomisation arms.

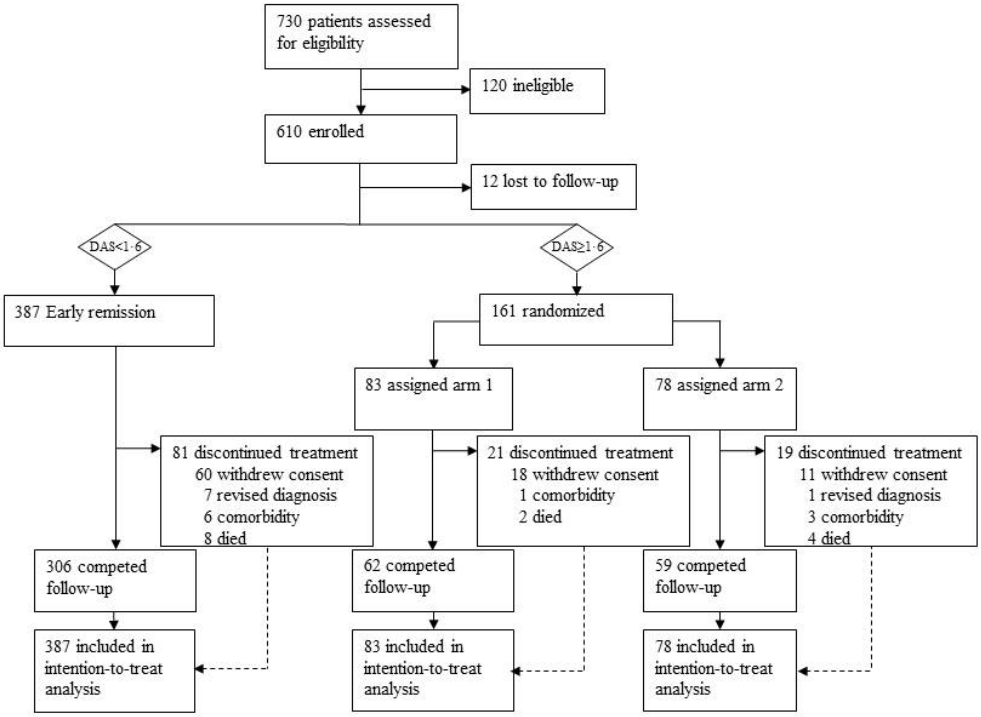

Figure 1. Trial profile IMPROVED-study
First DAS evaluation was at four months. Fifty patients who were not in DAS-remission at four months but were not randomized according to the protocol, were treated outside of protocol (OP group). Of those, nineteen discontinued treatment before five years and 31 patients were included in the intention-to-treat analysis.

General outcomes of the whole group

Baseline characteristics of all patients in the study are shown in table 1. Six patients never achieved DAS-remission during five years follow-up. All others achieved DAS-remission at least once. Over five years, 295/610 patients (48%) were in DAS-remission and 137/610 (22%) were in ACR/EULAR Boolean remission. Of those 295 in DAS-remission, 159 (26% of 610) were in sustained (≥1 year) drug-free remission. Of those 159, 58 had achieved drug-free remission from year one (i.e. early sustained drug-free remission), and of those 58, 24

(4% of 610) were still in drug-free remission at five years. Twenty-six had lost DAS-remission and restarted medication, and eight had left the study early, while still in drug-free remission. Patients in or not in DAS-remission had clinically relevant differences [13] in functional ability: mean difference in HAQ was -0.4 (95% confidence interval -0.5;-0.3) and mean difference in DAS -0.4 (-0.6;-0.3) between patients in or not in DAS-remission at five years.

After five years, radiographs at baseline and five years were available in 362/610 patients (362/458 of patients still in the study after five years). SHS progression ≥0.5 points was seen in 180/458 (39%) of completers, with a median SHS progression (interquartile range) of 0 (0-3) points. 58/458 (13%) had progression ≥5. Mean yearly progression rates were 0.43 points/year, in all completers.

During five years of follow-up 555 (91%) patients had in total 2897 adverse events (AE) (21.4 AE per 100 patient years (supplementary table 2)). The most common AE were upper airway infections, increased liver enzymes and skin rash. 148 (24%) patients reported 242 serious (S)AEs (5.7 SAE per 100 patient years).

Table 1. Baseline characteristics of the IMPROVED-study population.

	Total population
	n = 610
DAS, mean ± SD	3.2 ± 0.9
HAQ, mean ± SD	1.2 ± 0.7
Age in years, mean ± SD	52 ± 14
Female, n (%)	414 (68)
Symptom duration (weeks), median (IQR)	18 (9-32)
RF positive, n (%)	339 (56)
ACPA positive, n (%)	333 (55)
Anti-CarP positive, n (%)	172 (28)
Fulfilled RA(2010) classification criteria, n (%)	479 (79)
Swollen Joint Count, median (IQR)	5 (3-10)
Tender Joint Count, median (IQR)	6 (4-9)
ESR mm/hr, median (IQR)	25 (11-39)
VAS global health (mm), mean ± SD	46 ± 23
Total SHS, median (IQR) (observed)	0 (0-3)
Total SHS, median (IQR) (after imputation)	0.5 (0-3)
Erosive, n (%) (observed)	73 (12)
Erosive, n (%) (after imputation)	79 (13)

DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; RA: rheumatoid arthritis; Anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; n: number.

Comparisons between patients in and not in early DAS-remission

Patients who achieved early DAS-remission had at baseline lower DAS (mean (SD) 3.0 (0.8) compared to 3.6 (0.9) in patients who were not in early DAS-remission and HAQ (1.0 (0.7)

compared to 1.4 (0.6) (supplementary table 1), which may explain why the DAS-threshold of 1.6 was more readily achieved. Still, HAQ improvement over time was similar as in the other patients (-0.6 (0.7) in the early DAS-remission group and -0.5 (0.8) in the other patients (figure 2A), resulting in mean HAQ over time over 0.4 (0.4) and 0.9 (0.5), respectively. Also, symptom duration was slightly less in the early DAS-remission group, and fewer patients in the early DAS-remission group were female. On the other hand, slightly less fulfilled the classification criteria for RA, however more were positive for autoantibodies, and more had erosions on radiographs at baseline. (supplementary table 1).

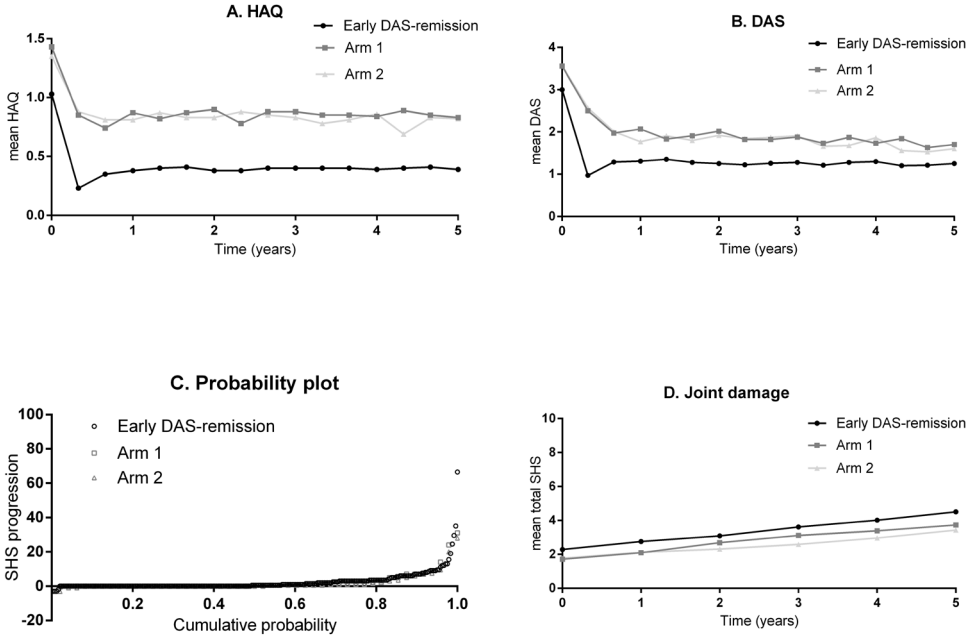

Figure 2A. HAQ over time, B. DAS over time, C. Probability plot after 5 years, D. total SHS over time after imputation.
A. Mean HAQ over time. B. mean DAS over time. C. Probability plot SHS progression in completers. D. mean total SHS over time after imputation.
HAQ: health assessment questionnaire; DAS: disease activity score; SHS: Sharp-van der Heijde score.

In general, patients who achieved early DAS-remission had better outcomes than patients in the randomisation arms or out of protocol group. Over five years, sustained drug-free remission was achieved by 135/387 (35%) in the early DAS-remission group, compared to 11% (9+10+5/83+78+50) in the other patients. At five years, 220/387 (57%) in the early DAS-remission group patients were in DAS-remission, and 111/387 (29%) in ACR/EULAR Boolean remission, compared to 75/211 (36%) and 26/211 (12%), respectively, in the other patients (supplementary table 1 and figure 3D). After imputation, radiologic damage progression

was similar in the early DAS-remission group and the other patients. Figure 2C shows the probability plot for SHS progression at five years, and figure 2D the mean total SHS after imputation at year five. More patients in the early DAS-remission group than the other patients had erosion progression.

In the early DAS-remission group use of medication initially decreased, then remained stable over time (figure 3A). In particular, the percentage of patients that were treated with prednisone dropped steeply, then remained low. MTX use also dropped and remained stable from year three. During five years 55/387 (14%) patients initially in early DAS-remission after DAS-increase were randomised in arm 1, of whom 30 later switched to adalimumab and 68 (17%) were randomised in arm 2. Up to 18% at five years switched to medication according to the rheumatologists' decision, of whom 38% used a biologic DMARD.

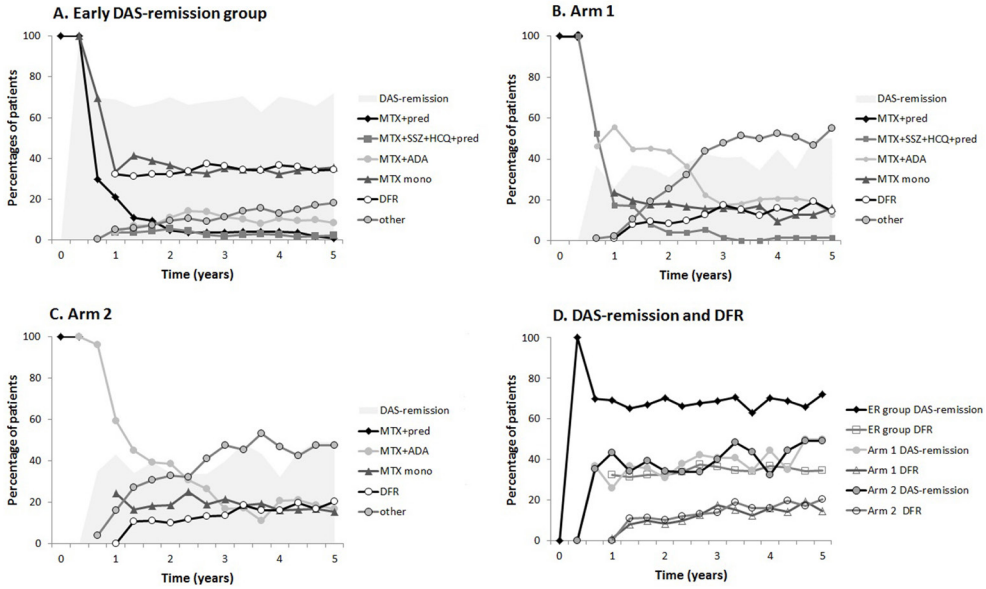

Figure 3: Treatment during 5 years in A. Early DAS-remission group, B. Arm 1, C. Arm 2, in percentage of completers per treatment group. D. Percentages in DAS-remission and percentages in drug-free remission per treatment group.

4A. Early DAS-remission group; 4B. Arm 1; 4C. Arm 2. Lines are approximations of the proportions of patients discontinuing medications (according to tapering strategies or due to side effects), or starting medications according to DAS-remission steered escalation strategies, across various treatment steps per arm, during 5 years. Percentages are calculated for completers per time point. The category 'Other' includes medications that were prescribed per protocol in the 'treatment according to rheumatologist' step after failure on methotrexate plus adalimumab, as well as medications prescribed outside of the protocol but still maintaining a DAS-remission targeted strategy. Shaded areas denote patient proportions in DAS-remission during five years.

4D. Proportions of patients in DAS-remission and drug-free DAS-remission per strategy over time.

Abbreviations: MTX: methotrexate; pred: prednisone; SSZ: sulphasalazine; HCQ: hydroxychloroquine; ADA: adalimumab; mono: monotherapy; DFR: drug-free (DAS-) remission; ER: Early DAS-remission.

Comparison between randomization arms

At five years, 31/83 (37%) in arm 1 and 29/78 (37%), p=0.768 in arm 2 were in DAS-remission, 9/83 (11%) in arm 1 and 12/78 (15%), p=0.374 in arm 2 were in drug-free remission (table 2), and 8/83 (10%) in arm 1 and 13/78 (17%), p=0.186 in arm 2 were in ACR/EULAR Boolean remission.[6] Over five years, sustained drug-free remission was achieved by 9/83 (11%) in arm 1 and 10/78 (13%) in arm 2, p=0.698. Mean (SD) HAQ improvement from baseline to five years was -0·6 (0·7) in arm 1 and -0.6 (0.8) in arm 2 (figure 2A), mean HAQ over time and mean DAS over time were the same in both arms (HAQ 0.9 (0.5), DAS 2.1 (0.6)) (figure 2A and 3B). At five years, 21/83 (25%) in arm 1 and 19/78 (24%) in arm 2 had a HAQ <0.5, approaching normal daily functioning. After five years, radiographs at baseline and five years were available in 362/610 patients (362/458 of patients still in the study after five years). After imputation, radiologic progression was similar in both arms (figure 2D).

Table 2: Outcomes at time of randomisation and after 5 years in the randomisation arms.

4 months	**Arm 1 n=83**	**Arm 2 n=78**	
DAS, mean ± SD	2.5 ± 0.6	2.6 ± 0.7	
HAQ, mean ± SD	0.9 ± 0.6	1.7 ± 0.7	
Swollen Joint Count, median (IQR)	1 (0-4)	2 (1-5)	
Tender Joint Count, median (IQR)	4 (3-7)	5 (3-9)	
ESR mm/hr, median (IQR)	13 (7-22)	11 (6-19)	
VAS global health (mm), mean ± SD	1.7 ± 0.7	1.7 ± 0.7	
5 years	**n = 62**	**n = 59**	**p-value**
DAS, mean ± SD	1.7 ± 0.7	1.6 ± 0.8	0.469
HAQ, mean ± SD	0.8 ± 0.7	0.8 ± 0.6	0.936
Swollen Joint Count, median (IQR)	0 (0-1)	0 (0-2)	0.200
Tender Joint Count, median (IQR)	1 (0-3)	1 (0-4)	0.818
ESR mm/hr, median (IQR)	11 (7-23)	12 (6-19)	0.517
VAS global health (mm), mean ± SD	31 ± 22	27 ± 23	0.369
Total SHS, median (IQR) (observed)	1 (0-4.9)	1.7 (0-4.1)	0.816
Total SHS, median (IQR) (after imputation)	1.3 (0.2-4)	1.9 (0-4)	0.340
Erosive, n (%) (observed)	13 (21)	13 (22)	0.828
Erosive, n (%) (after imputation)	19 (23)	16 (21)	0.753
SHS progression, median (IQR) (observed)	0 (0-1)	0 (0-1)	0.818
SHS progression, median (IQR) (after imputation)	0.5 (0-1.7)	0.3 (0-1.5)	0.115
SHS progression ≥0.5, n (%) (observed)	23 (37)	23 (39)	1.000
SHS progression ≥0.5, n (%) (after imputation)	46 (55)	37 (47)	0.327
SHS progression ≥5, n (%) (observed)	9 (15)	7 (12)	0.710
SHS progression ≥5, n (%) (after imputation)	11 (13)	9 (12)	0.653
SHS progression ≥10, n (%) (observed)	3 (5)	2 (3)	0.968
SHS progression ≥10, n (%) (after imputation)	4 (5)	2 (3)	0.712
In DAS-remission, n (%)	31 (50)	29 (49)	0.768
In drug-free remission, n (%)	9 (15)	12 (20)	0.374
In ACR/EULAR Boolean remission, n (%)	8 (13)	13 (22)	0.186

DAS: disease activity score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; n: number.

In arm 1 up to 75% (62/83) of patients over time switched to MTX+adalimumab because DAS-remission was not (re)achieved, and of these, 66% had increased adalimumab to 40mg/week. Treatment with adalimumab decreased to 13% of initial users at five years (figure 3B), either after successful tapering, or because DAS-remission was not achieved. At five years, 55% of patients use 'other medication', in 41% of cases another biologic DMARD.
In arm 2, 45/78 (58%) of patients who started on adalimumab increased the dose to once weekly. At five years, 17% of patients still/again used adalimumab, and 48% of patients had proceeded to 'other medication', in 39% of cases another biologic DMARD (figure 3C).
During five years of follow-up 95% in arm 1 and 96% in arm 2 had at least one adverse event, 22 per 100 patient years per arm. Serious adverse events occurred in 5.3 per 100 patient years in arm 1 and 7.6 per 100 patients years in arm 2 (p=0.140) (supplementary table 2). Two patients in arm 1 died (1 of haemorrhagic cerebrovascular accident and 1 of metastatic pancreatic carcinoma), 4 in arm 2 (1 of cerebral tumour, 1 of pneumococcal sepsis, 1 of pulmonary embolism and 1 of colon carcinoma).

Other comparisons between patients

At five years, 234/479 RA patients (49%) and 61/131 (47%), p=0.366 UA patients were in DAS-remission. More UA (41/131 (31%)) than RA patients (93/479 (19%), p<0.001 were in drug-free remission at five years. Over five years, sustained drug-free remission was achieved by more UA patients 49/131 (37%) than RA patients 110/479 (23%), p=0.001. These results in part overlap with the findings that at five years more RF-negative patients (69/245, 28%) than RF-positive patients (58/339, 17%, p<0.001), and more ACPA-negative (81/262, 31%) than ACPA-positive patients (50/332, 15%, p<0.001) were in drug-free remission. However DAS-remission rates were similar in RF-positive and RF-negative patients (171/339 (50%) versus 111/245 (45%), p=0.611) and in ACPA-positive and ACPA-negative patients (172/332 (52%) versus 120/262 (46%), p=0.887). DAS-remission rates and drug-free remission rates at five years were similar in anti-CarP-positive and anti-CarP-negative patients (88/172 (51%) vs 163/350 (47%), p=0.374 for DAS-remission and 33/172 (19%) vs 82/350 (23%), p=0.139 for drug-free remission). Over five years, sustained drug-free remission was achieved by more RF negative patients 79/245 (32%) compared to RF positive 74/339 (22%), p=0.005. Sustained drug-free remission was also achieved by more ACPA negative patients 96/262 (37%) than ACPA positive patients 60/332 (18%), p<0.001. Also, more anti-CarP negative patients (106/350 (30%)) were in sustained drug-free remission over time compared to anti-CarP positive patients (35/172 (20%), p=0.016). Mean DAS and HAQ over time were similar in autoantibody (RF, ACPA and anti-CarP) positive and negative patients. Only HAQ over time was significantly different between anti-CarP positive (0.6 (0.5)) and anti-CarP negative (0.7 (0.5), p=0.031) patients. Mean HAQ over time was similar in RA and UA patients and mean DAS over time was significantly lower in UA patients 1.5 (0.6) compared to RA patients

1.7 (0.7), p=0.003. DAS-remission rates at five years were similar in patients with baseline symptom duration <12 weeks (95/204, 47%) or ≥12 weeks (196/397, 49%) (p=0.740), and 51/204 (25%) of patients with symptom duration<12 weeks were in drug-free remission compared to 82/397 (21%) of patients with symptom duration ≥12 weeks (p=0.071).
More ACPA positive patients compared to ACPA negative patients had SHS progression (193/333 (58%) ≥0.5 SHS after 5 years versus 117/255 (46%), p<0.001, 54/333 (16%) ≥5 SHS versus 22/255 (9%), p<0.001), with a higher median progression score (0.8 (0-3) versus 0.3 (0-1.8), p<0.001). Also erosive disease was seen in more ACPA positive patients (119/333 (36%, was 17% at baseline)) than in ACPA negative patients (41/255 (16%, was 9% at baseline), p<0.001 for comparison at five years). More RA than UA patients had SHS progression (257/479 (54%) versus 60/131 (46%), p<0.001) with a higher median (0.5 (0-3) versus 0.4 (0-1.9), p=0.024).

DISCUSSION

This study shows for the first time that sustained (≥1 year) drug-free remission can be achieved in about a quarter of early rheumatoid or undifferentiated arthritis patients. Irrespective of DMARD use, after five years 48% of patients were in DAS-remission. Functional ability approached normality in these patients, and radiologic damage progression was generally well suppressed. In the whole cohort, UA patients, overlapping with patients who were negative for autoantibodies, achieved more drug-free remission than RA patients and autoantibody positive patients, but overall showed similar disease activity and functional ability over time, and similarly little radiologic damage progression. In general, patients who were in DAS-remission after four months treatment had better outcomes than patients who were not, despite continuous drug-free remission steered treatment adjustments in all patients. We found no differences in outcomes between two treatment strategy arms in the patients who did not achieve early DAS-remission on the initial treatment of methotrexate and a tapered high dose of prednisone. Initially, as reported earlier, patients randomised to switch immediately to adalimumab achieved more DAS-remission at year one than patients who first expanded the initial treatment with other synthetic antirheumatic medications.[7] However, after five years there are no lasting clinical nor radiological benefits, with reasonably good functional ability and little damage progression in both arms. Toxicity over time was similar and generally as expected.
Our study shows that MTX with a tapered high dose of prednisone is effective as DAS-remission induction therapy in 63% of patients and that these patients continue to have better outcomes during long term follow-up compared to patients who do not achieve early DAS-remission. These patients already had lower DAS and HAQ at baseline, placing the DAS-

target within closer reach. In previous cohorts, presence of ACPA was associated with worse outcomes in patients with UA and RA.[18, 19] A previous sub-analysis in the current IMPROVED-study showed that presence of ACPA, baseline DAS, HAQ, symptom duration, male gender and BMI were associated with achieving early DAS-remission.[13] After one year, presence or absence of ACPA was not associated with achieving drug-free remission in the early DAS-remission group.[7] However, in the next four months, ACPA positive patients were more at risk than ACPA negative patients to lose drug-free remission, having to restart medication,[20] a trend which is now confirmed with finding fewer ACPA positive patients than ACPA negative patients achieving sustained drug-free remission. In addition, absence of autoantibodies and not fulfilling the ACR/EULAR 2010 classification criteria for RA (which rest heavily on the presence of ACPA) were associated with being in drug-free remission after five years. Total damage progression after five years was similar in patients who were or were not in early DAS-remission, but we saw slightly more erosive joint damage progression in patients in the early DAS-remission group. It may be that due to more drug tapering to drug-free remission, and less use of anti-TNF therapy compared to the other treatment groups, there may have been subclinical inflammation. On the other hand, more patients in the early DAS-remission group already had erosions at baseline, which is associated with more erosion progression.[21] Previous studies aiming at low DAS (≤2.4)[22, 23] or even stricter remission definitions than DAS-remission,[24, 25] despite reporting similar or higher remission rates, reported more radiological damage progression than in our study, possibly due to inclusion of patients with more severe and/or advanced disease. Compared to the other studies, radiologic damage progression may even be relatively overestimated, as we scored subsequent radiographs in chronologic order, whereas in the other studies the time order was random. The used scoring method is aimed to detect small changes, which may have limited clinical relevance. We reported progression <0.5 points as absolute negative of 'no progression', and >5 points as positive, as this was considered by experts to be clinically relevant, albeit *per year*,[15] which would expand to 25 points during the course of this study. Only five of our patients had progression >25 points.

This study is the first to aim for relatively rapid tapering of medication aiming at sustained drug-free remission, which we felt is the outcome closest approaching cure. Therefore we aimed to include and treat patients in an early phase of RA (even if classification criteria were not yet met), as it appears that earlier treatment may result in better and long-lasting suppression of inflammatory processes, which at that time may be reversible. During this so-called 'window of opportunity', estimated to encompass around 12 weeks from symptom onset,[12] chronicity of inflammation may be prevented and potentially prolonged remission may be induced.[26-28] However, we found few differences in DAS-remission rates and only a trend for more drug-free remission in patients with symptom duration <12 weeks compared to ≥12 weeks. As this time window is based on studies with slow acting DMARDs, thanks to drug tapering strategies the use of prednisone over time was low. Also, in the early DAS-remission

group, use of adalimumab and other biologic DMARDs (as option in case of failure to achieve DAS-remission on adalimumab) was low. Most patients were on MTX monotherapy or in drug-free remission. In the randomisation arms, use of adalimumab stabilized at twice the level of use as in the early DAS-remission group and also use of other biologic DMARDs was higher, which implies that treatment costs in both arms were higher than in the early DAS-remission group. Toxicity in the early DAS-remission group and the randomisation arms was roughly comparable.

There are several limitations to the study design. First, we cannot claim that the good clinical and radiologic outcomes are the result of the initial treatment, subsequent medications, or the DAS-remission steered treatment adjustments, as there is no arm in which we did not adapt the treatment strategy to induce early remission, nor did we include an arm where a spontaneously disease course could be observed. We may have temporarily over-treated patients who would have achieved spontaneous remission. This was part of the reason why we chose to taper and discontinue medication early. We chose the MTX and prednisone doses for induction therapy based on the results of the COBRA[29] and BeSt-study. More recent studies[30, 31] have shown that lower dosages of prednisone may be equally effective. The four-monthly evaluation time points may not have provided sufficiently tight control in combination with targeted treatment. This, together with more rapid tapering strategies than were previously introduced in the BeSt-study, may have resulted in fewer patients achieving sustained (drug-free) DAS-remission than we hoped. Our treatment target of DAS-remission may be insufficiently stringent, even though we used the original DAS and not the DAS28 which is based on the evaluation of fewer joints. More patients might have achieved drug-free remission if we had aimed at a more strict remission definition, but also it would have risked higher use of costly medications in patients who would not achieve this threshold. All definitions of remission may be influenced by non-inflammatory pain.[32] Finally, early study termination in the various patient groups may have influenced the results.

In conclusion, after five years of DAS-remission steered treatment, 48% of early RA and UA patients were in DAS-remission and 26% in sustained in drug-free remission. HAQ results indicate almost normal functional ability over time and radiological damage progression was generally well suppressed in all groups. Patients with milder disease activity at baseline who achieve more often early DAS-remission continue to do better than other patients while using less antirheumatic medication. Most results were similar for RA and UA patients, autoantibody positive or negative patients, but more UA patients and autoantibody negative patients achieved drug-free remission at five years. If DAS-remission is not achieved after four months, immediate introduction of adalimumab has limited benefits over first expanding treatment with synthetic DMARDs.

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SUPPLEMENTARY FILE

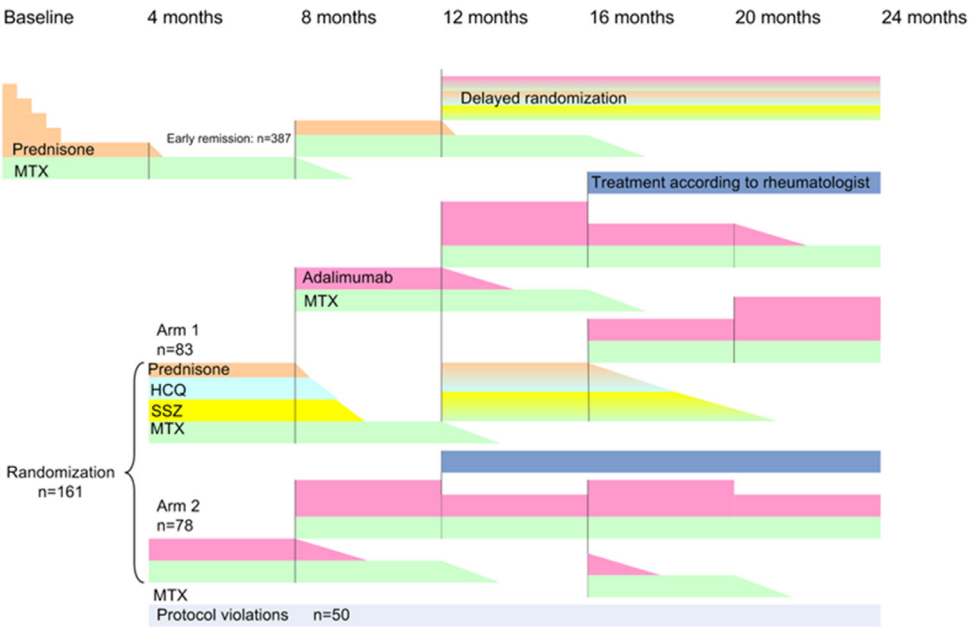

Figure S1: Study flow chart IMPROVED-study
DFR: drug-free DAS-remission, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulphasalazine. Colours: orange=prednisone, green=MTX, dark blue=treatment according to opinion rheumatologist (TAR), aqua=HCQ, yellow=SSZ, purple=adalimumab biweekly, double thickness purple=adalimumab weekly, grey=protocol not followed as required but remained in follow up (outside of protocol, OP).

Table S1: (Serious) adverse events per 100 patient years during 5 years according to the different treatment groups.

	Total population	Early DAS-remission	No early DAS-remission		
	n=610	n=387	Arm 1 n=83	Arm 2 n=78	OP n= 50
AE per 100 patient years	21.4	20.8	22.2	22.0	24.3
Type of AE					
Cardiovascular	4.5	4.0	4.5	6.8	5.0
Pulmonary	3.1	3.0	3.4	2.4	4.4
Gastrointestinal	11.2	10.8	11.5	13.2	9.9
Neuropsychiatric	6.4	6.0	8.2	6.8	6.6
Metabolic	1.5	1.3	1.4	2.7	1.7
Hematological	0.8	0.8	1.4	0.9	-
Urogenital	1.8	1.9	1.7	1.8	1.1
Skin/mucous membranes	8.3	8.3	8.2	7.9	9.4
Infections	12.9	12.4	11.8	15.9	14.9
Auto-immune	0.2	0.1	0.6	-	-
Malignancy	0.4	0.3	0.3	0.9	0.6
Trauma/injury	3.2	3.1	3.7	2.4	4.4
Infusion reaction	0.3	0.2	0.6	0.3	-
Malaise	2.5	2.3	3.9	2.4	1.7
Surgical procedures without hospitalization	2.7	2.4	3.4	3.5	2.8
Other	9.6	8.8	12.9	10.0	10.5
SAE per 100 patient years	5.7#	4.9	5.3	7.6	8.3
Hospital admissions per 100 patient years	4.8#	4.2	4.5	7.1	6.1
Malignancies, n	39#	25	4	6	3
Deaths, n	17#	8	2	4	1
Causes of death	1 infection, 1 CVD#	4 malignancies, 4 CVD	1 malignancy, 1 CVD	2 malignancies, 1 infections, 1 CVD	1 malignancy

OP: outside of protocol, AE: adverse event, SAE: serious adverse event, CVD: cardiovascular disease; n: number; # 4 patients had SAE's after baseline and left the study before the assessment at 4 months.

Table S2: Baseline characteristics and 4 month outcomes of patients who did or did not achieve early DAS-remission.

	Early DAS-remission	No early DAS-remission
Baseline	**n = 387**	**n = 211**
DAS, mean ± SD	3·0 ± 0·8	3·6 ± 0·9
HAQ, mean ± SD	1·0 ± 0·7	1·4 ± 0·6
Age in years, mean ± SD	52 ± 14	51 ± 14
Female, n (%)	240 (62)	164 (78)
Symptom duration (weeks), median (IQR)	17 (9-30)	21 (9-38)
RF positive, n (%)	224 (58)	107 (51)
ACPA positive, n (%)	225 (58)	102 (48)
Anti-CarP positive, n (%)	118 (30)	51 (24)
Fulfilled RA(2010) classification criteria, n (%)	298 (77)	172 (82)
Swollen Joint Count, median (IQR)	5 (2-9)	7 (3-12)
Tender Joint Count, median (IQR)	5 (3-8)	9 (6-13)
ESR mm/hr, median (IQR)	23 (8-38)	26 (13-41)
VAS global health (mm), mean ± SD	43 ± 24	52 ± 21
Total SHS, median (IQR) (observed)	0·5 (0-3)	0 (0-2·5)
Total SHS, median (IQR) (after imputation)	0·5 (0-3)	0 (0-2·9)
Erosive, n (%) (observed)	55 (14)	18 (9)
Erosive, n (%) (after imputation)	59 (15)	20 (9)
4 months		
DAS, mean ± SD	1·0 ± 0·4	2·5 ± 0·7
HAQ, mean ± SD	0·2 ± 0·3	0·8 ± 0·6
Swollen Joint Count, median (IQR)	0 (0-0)	1 (0-4)
Tender Joint Count, median (IQR)	0 (0-1)	5 (3-8)
ESR mm/hr, median (IQR)	6 (3-12)	12 (6-22)
VAS global health (mm), mean + SD	14 ± 14	36 ± 21

DAS: disease activity score; HAQ: health assessment questionnaire; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; RA: rheumatoid arthritis; Anti-CarP: anti-carbamylated protein antibodies; ESR: erythrocyte sedimentation rate; VAS: visual analogue scale; SHS: Sharp-van der Heijde score; Erosive: ≥1 erosions; n: number.