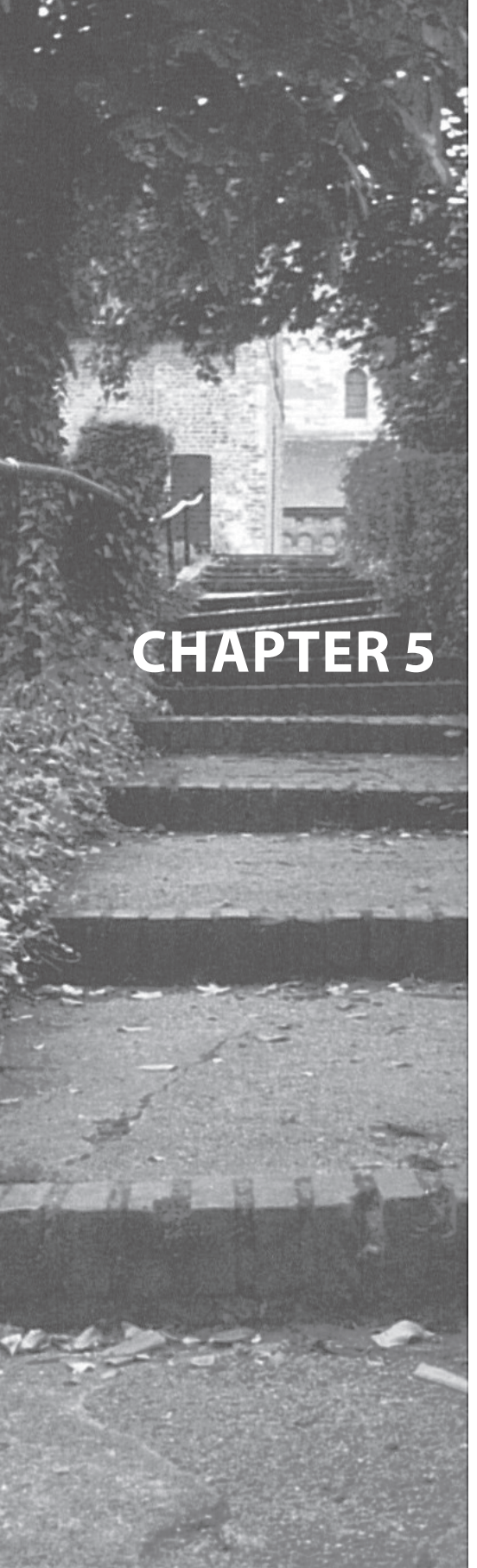

CHAPTER 5

Health related quality of life and functional ability in patients with early arthritis during remission steered treatment – results of the IMPROVED study

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ABSTRACT

Introduction

To investigate patient reported outcomes (PROs) of functional ability and health related quality of life (HRQoL) in patients with early (rheumatoid) arthritis during 1 year of remission steered treatment.

Methods

Six-hundred-ten patients with early rheumatoid (RA) or undifferentiated arthritis (UA) were treated with methotrexate (MTX) and tapered high dose of prednisone. Patients in early remission (Disease Activity Score (DAS) <1.6 after 4 months) tapered prednisone to zero and when in persistent remission, also tapered MTX. Patients not in early remission were randomized to either MTX+hydroxychloroquine+sulphasalazine+prednisone (arm 1) or to MTX+adalimumab (arm 2). Every 4 months, patients filled out the Health Assessment Questionnaire (HAQ) and the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR), the Short Form 36 (SF-36) and visual analogue scales (VAS). Change scores were compared between treatment groups. The association with achieving remission was analyzed using linear mixed models.

Results

During year 1, patients who achieved early remission had the most improvement in PROs with scores comparable to the general population. Patients in the randomization arms showed less improvement. Scores were comparable between the arms. There was a significant association between achieving remission and scores of HAQ, MACTAR and physical HRQoL.

Conclusions

In early arthritis, PROs of functional ability and HRQoL after 1 year remission steered treatment reach normal values in patients who achieved early remission. In patients not in early remission who were randomized to two strategy arms PROs improved less, with similar scores in both treatment arms.

INTRODUCTION

In rheumatoid arthritis (RA) treatment with disease modifying anti-rheumatic drugs (DMARDs) is targeted at achieving optimal suppression of disease activity. With that, clinical symptoms as well as radiological joint damage (progression) are prevented and patient reported outcomes (PROs) such as pain and health related quality of life (HRQoL), physical and mental wellbeing, improve.[1] Earlier studies have suggested that the better disease activity is suppressed, the better the outcomes of functioning and radiological joint damage progression.[2,3] Achieving clinical remission would ideally be associated with achieving PROs comparable to those in the general population.

In the IMPROVED study, anti-rheumatic treatment was targeted at remission. Patients with early (rheumatoid) arthritis were treated with initial combination therapy of methotrexate (MTX) and prednisone. If clinical remission (disease activity score (DAS) <1.6) was not achieved after 4 months, patients were randomized into two treatment arms: either starting with a combination of non-biologic DMARDs with low dose prednisone or with MTX and TNF-α inhibitor adalimumab. The aim of this sub-analysis was to measure change in functional ability and HRQoL during the first year of remission-steered treatment, to compare outcomes between the randomization arms and to compare study patients with the general population.

METHODS

Study design

The IMPROVED-study (acronym for Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) is a multicenter, randomized, single-blinded trial comparing two combination therapies in patients with recent onset arthritis aiming at clinical remission, defined as a DAS <1.6. The IMPROVED trial was designed and conducted by rheumatologists in the Foundation for Applied Rheumatology Research (FARR) and was registered in the ISRCTN Register (number 11916566) and the EudraCT (number 2006-006186-16).

Patients were recruited between March 2007 and September 2010 in 12 hospitals in the Western part of the Netherlands. The Medical Ethics Committee of each participating center approved the study protocol and all patients gave written informed consent. Patients with rheumatoid arthritis (RA) and patients with undifferentiated arthritis (UA) were included. RA was diagnosed according to the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria [4] with symptom duration of <2 years. UA was defined as 'arthritis' in at least one joint and one other painful joint in which no definitive diagnosis could be made, considered to have very early RA according to the

treating rheumatologist, regardless of symptom duration. All patients were ≥18 years old with a DAS ≥1.6. Detailed inclusion and exclusion criteria were previously described.[5]

All patients were initially treated for 4 months with MTX 25 mg/week and a tapered high dose of prednisone, starting with 60 mg/day, tapered to 7.5 mg/day in 7 weeks. Patients in early remission (DAS <1.6 after 4 months) tapered prednisone to 0 and when still in remission after 8 months, also tapered MTX to 0. Patients not in early remission (DAS ≥1.6) were randomized using variable block randomization stratified per centre to ensure numerical equality of the two treatment groups. Randomization sequence was obtained by computer. At the local centres, allocation was performed by drawing opaque envelopes from separate boxes for UA and RA. Patients were randomized to either a combination of either MTX 25 mg/week, hydroxychloroquine (HCQ) 400 mg/day, sulphasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or a combination of adalimumab 40 mg/2weeks and MTX 25 mg/week (arm 2). When patients did not achieve remission after 8 months, patients in arm 1 switched to MTX+ adalimumab and patients in arm 2 increased adalimumab to 40 mg/week. If patients achieved remission after 8 months, patients in both arms tapered to MTX monotherapy. Patients who did not achieve remission but were not randomized were analyzed in a separate group (outside of protocol (OP) group).[6]

Outcomes

Functional ability was assessed every 4 months with the Health Assessment Questionnaire (HAQ).[7] The HAQ score of a general (Finnish) population is 0.25.[8]

The McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR) also measures functional ability. Patients have to rank five activities that are impaired because of their arthritis. Over time, improvement or deterioration of these five activities can be measured. The MACTAR is sensitive to change and useful to detect small differences. Compared to the baseline score, a higher score denotes improvement and a lower score means deterioration. The MACTAR interview from Canada was translated into Dutch in collaboration with the author of the original MACTAR. The translation was first used in the COBRA study, validated and judged as highly responsive.[9-11]

HRQoL was assessed using the Short-Form 36 (SF-36) focusing on 8 domains of health; physical functioning, role limitations due to physical or due to emotional functioning, bodily pain, general health, vitality, social functioning, mental health. The total score ranges from 0 (worst) to 100 (best). Two summary components scores, the mental component score (MCS) and the physical component scores (PCS), can be calculated from the 8 domains. These component scores are standardized, based on the worldwide population norm, to a mean of 50 and a standard deviation of 10.[12,13] The minimum clinically important difference to assess improvement or deterioration is a 5-10 point difference from baseline for the subscales and 2.5-5 points for the component scores.[14]

Various visual analogue scales (VAS) were used and patients had to indicate on a scale from 0 to 100 millimeters (0 means none, 100 means the worst) their appreciation of global health (VASgl), pain (VASpain), disease activity (VASda) and morning stiffness (VASms).

Statistical analyses

All outcomes were calculated according to the intention-to-treat (ITT) principle. All mean outcomes after 4 months, 8 months and 1 year were tested between arms 1 and 2 using the students *t*-test and to test the difference in remission rates we used the χ^2-test.

HAQ- and MACTAR scores, MCS, PCS and VAS measurements were reported separately for patients who achieved early remission and those randomized, and were compared between the randomization arms. The results of the study population were compared with those in the general population, if available.

Mean change scores over time were tested between the randomization arms using an independent Student's *t*-test. Clinically relevant improvement or deterioration after 1 year in HRQoL was assessed per treatment group, using the minimum clinically important difference.

To assess the relationship between achieving remission and the PROs SF36-PCS, SF36-MCS, HAQ and MACTAR a linear mixed model (with an unstructured covariance structure) was used. The analyses were first performed with an interaction term for remission achievement and treatment (early remission, arm 1, arm 2, OP group) because the different treatment strategies might influence remission achievement (as fixed effects were entered into the model: time (study visit at 4 months, 8 months and 1 year) and mean baseline score of the assessed PRO) In case of a significant interaction term, the analyses were stratified for treatment. The association between remission and PROs was assessed with and without adjustment for baseline variables anti-citrullinated protein antibodies (ACPA) status (positive/negative), sex (male/female), DAS at baseline, Tender Joint Count and Swollen Joint count. We used these determinants because they were identified as predictors for achieving remission after the first 4 months of the study.[5] As fixed effects were entered into the model: time (study visit at 4 months, 8 months and 1 year), mean baseline score of the assessed PRO and the determinants for which the analyses were adjusted. After the initial analysis defining remission as a DAS <1.6 we re-analysed the association with remission defined according to the provisional Boolean based remission definition published by the ACR/EULAR with a 44 joint count.[15]

Statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, Ill).

RESULTS

In total, 610 patients were included. During the first year, 32 patients left the trial (23 withdrew consent, 3 discontinued because of a revised diagnosis, 6 because of co-morbidity).

After 4 months, 387 (63%) achieved early remission (DAS <1.6). Of the 221 patients who did not achieve early remission, 161 patients were randomized; 83 patients into arm 1 (poly-DMARD), 78 to arm 2 (MTX+ adalimumab). Fifty patients did not achieve remission but were not randomized (outside of protocol (OP) group).[6] Patients who achieved early remission had a lower mean baseline DAS, lower values of all DAS-components, a shorter median symptom duration and included fewer females and more ACPA positive patients.[5](table 1)

After 1 year, remission was most often achieved by patients in the early remission group (68%). Fewer patients randomized to arm 1 achieved remission after 1 year than patients randomized to arm 2 (respectively 25% and 40%, p=0.01) (table 2).

Functional ability

HAQ scores in the early remission group were lower, indicating better functional ability, than in the randomization arms, both at baseline and after 1 year.(figure 1) Functional ability

Table 1. Baseline characteristics per treatment group.

	Early remission	Arm 1	Arm 2	OP group
Baseline	n = 387	n = 83	n = 78	n = 50
Age (years), mean ± SD	52 ± 14	48 ± 14	51 ± 14	54 ± 14
Female, n (%)	239 (62)	63 (76)	64 (82)	42 (84)
Symptom duration (weeks)	17 (9-30)	22 (9-40)	21 (8-29)	18 (9-42)
ACPA positive, n (%)	225 (58)	40 (48)	36 (46)	25 (50)
RA2010, n (%)	297 (77)	66 (80)	64 (82)	40 (80)
Erosive disease, n (%)	63 (16)	10 (12)	13 (17)	3 (6)
DAS, mean ± SD	3.0 ± 0.9	3.6 ± 0.9	3.6 ± 1.0	3.6 ± 0.9
Tender Joint Count, median (IQR)	5 (2-9)	6 (3-10)	8 (4-12)	7 (3-13)
Swollen Joint Count, median (IQR)	5 (3-8)	8 (6-13)	9 (6-13)	8 (6-14)
HAQ, mean ± SD	1.0 ± 0.7	1.4 ± 0.6	1.4 ± 0.65	1.3 ± 0.7
MCS, mean ± SD	51.2 ± 10.2	46.1 ± 12.4	48.8 ± 11.5	46.5± 13.3
PCS, mean ± SD	37.6 ± 9.3	33.0 ± 8.8	32.9 ± 8.9	35.2± 8.5
MACTAR, mean ± SD	50.1 ± 4.5	47.7 ± 4.6	48.1 ± 4.6	47.7 ± 5.2
VAS global (mm) , mean ± SD	43 ± 24	54 ± 20	54 ± 22	51 ± 22
VAS disease activity (mm) , mean ± SD	56 ± 25	66 ± 19	67 ± 22	66 ± 20
VAS pain (mm) , mean ± SD	50 ± 24	63 ± 19	61 ± 20	60 ± 24
VAS morning stiffness (mm) , mean ± SD	56 ± 27	69 ± 21	62 ± 25	54 ± 30

* p-value between arm 1 and 2. Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%).
ACPA, anti-citrullinated protein antibody; DAS, disease activity score; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; OP group, outside of protocol group; PSC, Physical Component Score; RA2010, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; VAS, visual analogue scale.

Table 2. Patient reported outcomes during 1 year follow up per treatment group.

	Early remission	Arm 1	Arm 2	p*	OP group
	n=387	n=83	n=78		n=50
4 months follow up					
DAS	0.97 (0.40)	2.49 (0.63)	2.57 (0.68)	0.47	2.31 (0.63)
HAQ	0.23 (0.33)	0.86 (0.57)	0.88 (0.57)	0.77	0.73 (0.68)
MACTAR	58.2 (15.7)	52.8 (15.1)	48.9 (18.8)	0.14	51.6 (14.1)
MCS	52.4 (8.0)	48.8 (9.9)	50.7 (10.8)	0.26	49.8 (10.5)
PCS	51.7 (8.1)	39.4 (9.7)	38.1 (9.4)	0.44	42.5 (9.4)
VAS global (in mm)	14 (14)	37 (21)	39 (21)	0.61	28 (22)
VAS disease activity (in mm)	12 (15)	42 (24)	43 (24)	0.74	32 (25)
VAS pain (in mm)	10 (14)	39 (24)	38 (24)	0.79	27 (24)
VAS morning stiffness (in mm)	11 (17)	40 (27)	39 (27)	0.78	32 (30)
8 months follow up					
DAS	1.29 (0.69)	1.97 (0.87)	2.01 (0.91)	0.77	2.02 (0.84)
HAQ	0.35 (0.44)	0.74 (0.61)	0.81 (0.64)	0.51	0.68 (0.59)
MACTAR	56.4 (15.7)	55.8 (14.7)	54.5 (16.1)	0.60	48.9 (19.9)
MCS	52.9 (8.4)	46.6 (17.9)	48.7 (10.3)	0.85	48.5 (13.0)
PCS	48.9 (9.1)	42.8 (10.9)	42.5 (11.0)	0.26	43.7 (9.5)
VAS global (in mm)	20 (20)	33 (23)	34 (21)	0.75	30 (23)
VAS disease activity (in mm)	22 (23)	39 (26)	33 (24)	0.20	35 (25)
VAS pain (in mm)	19 (23)	35 (26)	31 (25)	0.36	32 (24)
VAS morning stiffness (in mm)	24 (26)	34 (29)	37 (28)	0.51	40 (27)
1 year follow up					
DAS	1.31 (0.78)	2.07 (0.89)	1.77 (0.90)	0.04	2.20 (0.83)
HAQ	0.38 (0.49)	0.87 (0.66)	0.81 (0.66)	0.60	0.77 (0.65)
MACTAR	63.0 (9.4)	59.2 (10.3)	60.4 (11.9)	0.54	59.7 (11.21)
MCS	53.1 (8.6)	50.5 (10.3)	50.5 (10.1)	0.97	50.4 (11.9)
PCS	48.6 (9.8)	39.9 (10.3)	43.0 (11.4)	0.10	42.6 (10.9)
VAS global (in mm)	20 (21)	33 (23)	27 (20)	0.10	33 (24)
VAS disease activity (in mm)	24 (26)	42 (29)	31 (26)	0.02	34 (27)
VAS pain (in mm)	21 (23)	38 (28)	28 (25)	0.02	28 (25)
VAS morning stiffness (in mm)	25 (26)	41 (31)	33 (27)	0.96	39 (30)
DAS-remission (DAS <1.6)	263 (68)	21 (25)	32 (41)	0.01	11 (22)

* p-value of the difference in mean scores and remission rates between arm 1 and 2. Data are presented as means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate.

ACPA, anti-citrullinated protein antibody; DAS, disease activity score; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; PSC, Physical Component Score; RA2010, rheumatoid arthritis according to the 2010 American College of Rheumatology classification criteria; VAS, visual analogue scale.

improved the most during the first 4 months in all patients.(figure 1) The mean improvement in HAQ during the first year was comparable between arm 1 and 2 (mean difference (95%CI) -0.005 (-0.3;0.2)). In the early remission group the mean HAQ score after 1 year of 0.38 was closest to the general population mean of 0.25 (compared to a mean HAQ of 0.87 in arm 1 and 0.88 in arm 2).(figure 1, table 2)

Functional ability as measured by the MACTAR, which is more sensitive to change than the HAQ, improved in all groups together with continuous improvements in mean DAS.(table 1, table 2) The mean change in MACTAR in year 1 was not significantly different between arm 1 and 2 (mean difference (95%CI) -1.1 (-5.2;3.1)). The outcomes of the OP group were comparable with those in arms 1 and 2.

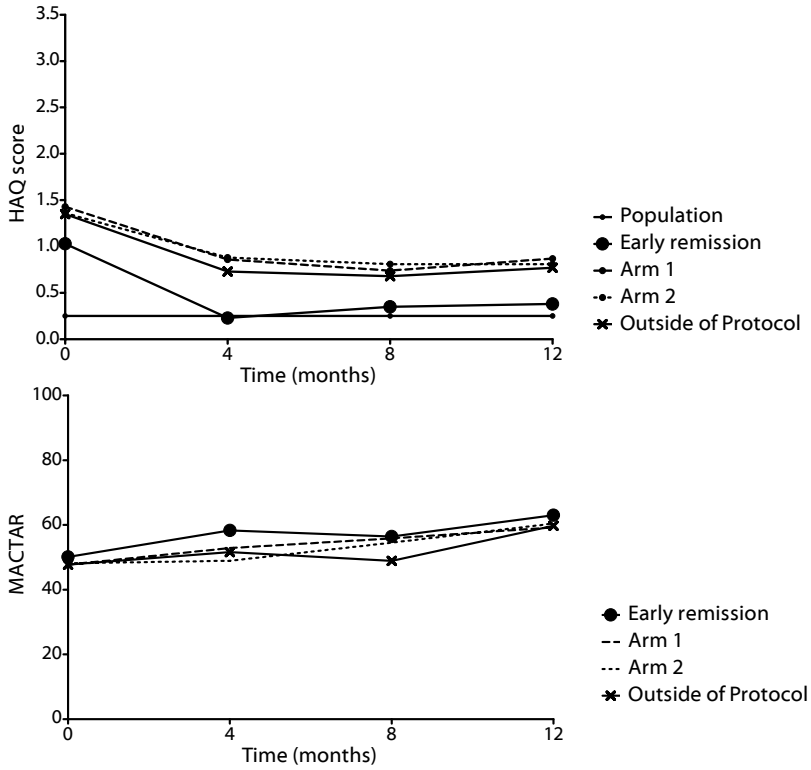

Figure 1. Functional ability as measured by the Health Assessment Questionnaire (HAQ) and the McMaster-Toronto Arthritis Patients Preference Questionnaire (MACTAR). Scores during the first year in the general population (only for HAQ), the early remission group, arm 1, arm 2 and the outside of protocol group.

Health Related Quality Of Life

At baseline, mental HRQoL measured with the mental component score (MCS) was higher than physical HRQoL measured by the physical component score (PCS) in all groups.(table

1, figure 2). Overall, the MCS at baseline was already close to the population average of 50, and improvement during the first year was minimal (table 1, figure 2), although clinically relevant in the randomization arms based on the minimal clinically important difference in component scores of 2.5-5 points (mean (SD) improvement arm 1: 3.8 (11.4), arm 2: 2.8 (10.0)). The mean improvement after 1 year was not significantly different between arm 1 and 2 (mean difference 1.0 (95%CI) -2.8;4.7). The domains in which most improvement was seen, were role emotional and social functioning.(figure 3)

For the PCS, baseline scores in all groups were below the population average of 50 (table 1, figure 2). The early remission group improved to the population average during the first 4 months of treatment and stabilized, whereas the randomization arms also improved during

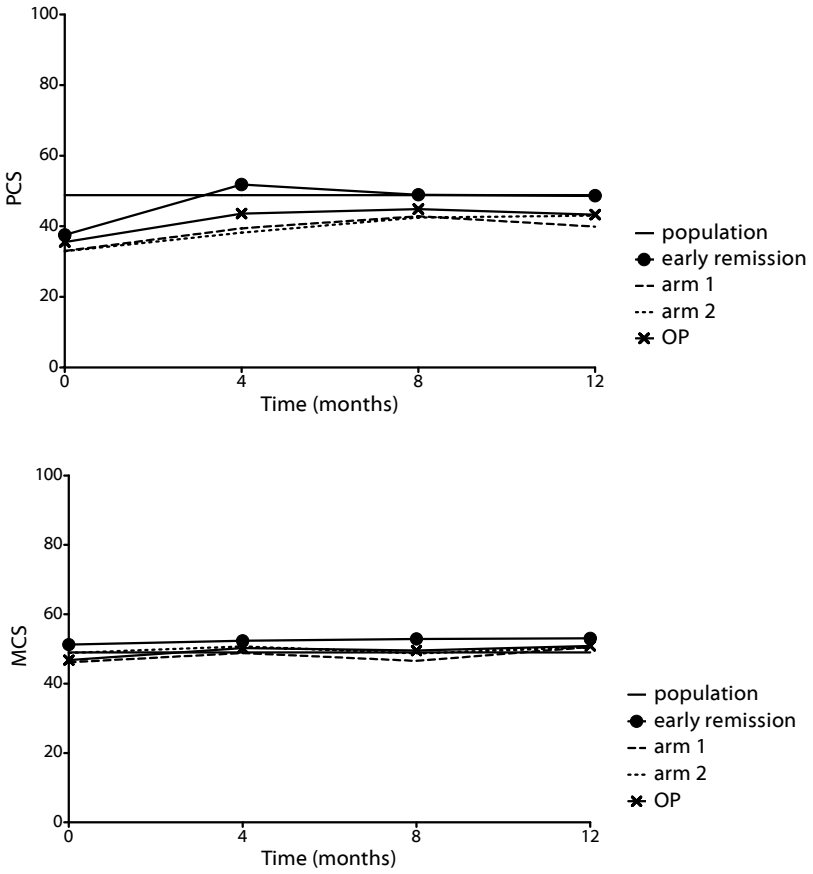

Figure 2. Summary components scores of health as measured by the Short-Form 36 (SF-36). Mental component scores (MCS) and physical component scores (PCS) are calculated from the 8 domains (physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health) of the SF-36. Scores during the first year in the general population, the early remission group, arm 1, arm 2 and the outside of protocol group.

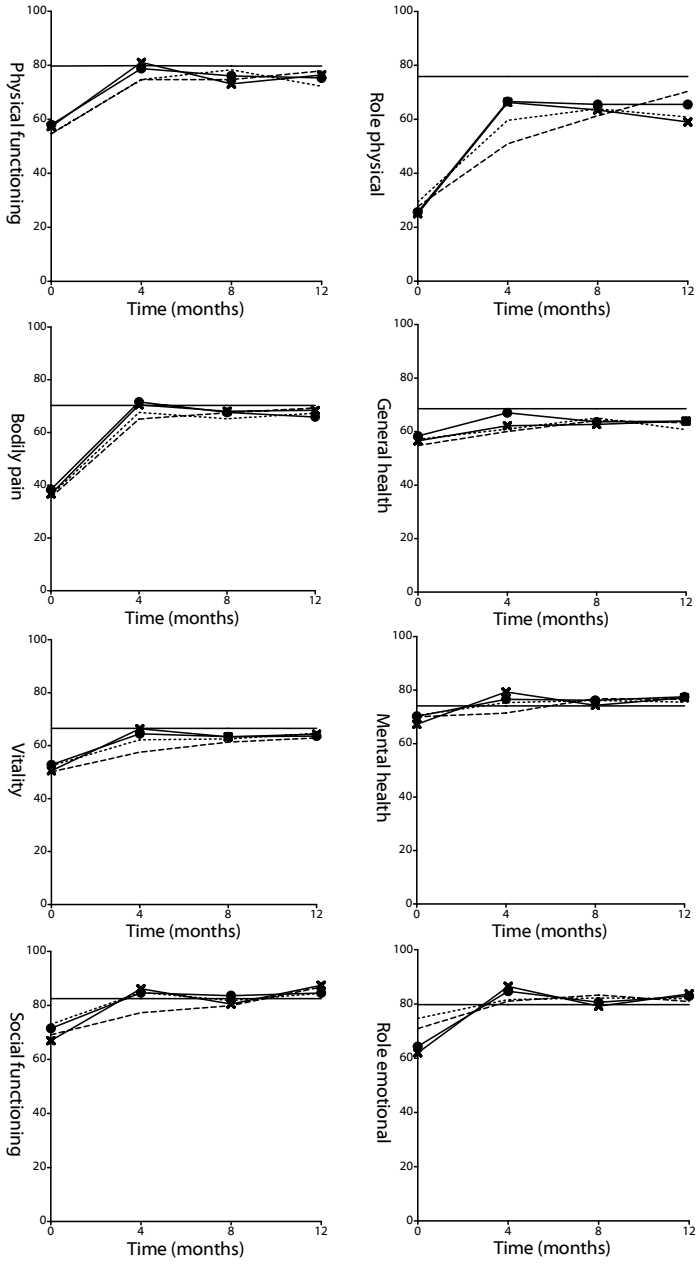

Figure 3. The 8 domains of health as measured by the Short-Form 36 (SF-36; physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning and mental health).
Scores range from 0 (worst) to 100 (best). Scores during the first year in the general population, the early remission group, arm 1, arm 2 and the outside of protocol group.

the first 4 months and stabilized, but below the population average (table 2, figure 2). The mean (SD) improvement in 1 year was clinically relevant in all groups based on the minimal clinically important difference of 2.5-5 points: in the early remission group 11.1 (11.7), in arm 1 8.0 (10.9) and in arm 2 10.1 (12.8). The mean improvement in 1 year between patients who did and did not achieve early remission was significantly higher in patients who achieved early remission (mean difference (95%CI) -2.7 (-4.9;0.5)). There was no significant difference between arm 1 and 2 (mean difference (95%CI) -2.1 (-6.3;2.1)). The domains in which most improvement was seen, were physical functioning, role limitations due to physical functioning and bodily pain.(figure 3) Again, MCS and PCS in the OP group were comparable with those in arms 1 and 2.

Visual analogue scales

Patients who achieved early remission had at baseline and after 1 year lower VAS scores (indicating better outcomes) than the randomization arms.(table 1, table 2) Patients in arm 2 reported lower VAS scores than patients in arm 1 after 1 year.(table 2) Only for VASda there

Table 3. Association between the patient reported outcomes and remission achievement during 1 year follow up for all patients and per treatment group.

	All	Early remission	Arm 1	Arm 2	OP group
Crude beta (95%CI)					
HAQ	-	-0.31 (-0.36;-0.26)	-0.43 (-0.57;-29)	-0.45 (-0.58;-0.32)	0.18 (-0.33;-0.02)
MACTAR	7.8 (6.9;8.9)	-	-	-	-
PCS	-	6.2 (5.1;7.4)	10.2 (7.5;12.9)	8.9 (5.8;12.0)	4.5 (0.6;8.4)
MCS	0.8 (0.01;1.6)	-	-	-	-
Adjusted beta* (95%CI)					
HAQ	-	-0.30 (-0.35;-0.25)	-0.43 (-0.57;-29)	-0.45 (-0.58;-0.32)	0.17 (-0.32;-0.01)
MACTAR	8.1 (7.0;9.2)	-	-	-	-
PCS	-	6.0 (4.9;7.2)	9.9 (7.1;12.7)	9.1 (6.1;12.1)	4.2 (0.2;8.1)
MCS	0.8 (-0.01;1.7)	-	-	-	-

*Adjusted for anti-citrullinated protein antibody (ACPA) status (positive/negative), sex (male/female), disease activity score (DAS) at baseline, Tender Joint Count and Swollen Joint count.
As fixed effects were entered: time (study visit at 4 months, 8 months and 1 year) and mean baseline score of the assessed patient reported outcome. HAQ and PCS were stratified for treatment group (early remission, arm1, arm 2, outside of protocol group) because of a significant interaction between treatment group and achieving remission.
CI, confidence interval; HAQ, Health Assessment Questionnaire; MACTAR, McMaster-Toronto Arthritis Patients Preference Questionnaire; MCS, Mental Component Score; OP, outside of protocol group; PCS, Physical Component Score.

was more improvement after 1 year in arm 2 than in arm 1 (mean difference (95%CI) 13 (2;23)) and for the other VAS scores the improvement was comparable between the randomization arms (mean difference (95%CI) VASgh 7 (-2;16), VASpain 9 (-1;19) and VASms 5 (7;16). The OP group showed similar results as patients in arm 1 and 2.

Association of PROs with achieving remission (DAS <1.6)

The analyses of the HAQ and the PCS were stratified for treatment group because there was an interaction between treatment group and achieving remission. The association between HAQ and achieving remission and between PCS and achieving remission was significant in all groups during the first year of the study.(table 3) The analyses for MACTAR and MCS were not stratified. In the total study group there was a significant association between MACTAR and achieving remission. There was also a significant association between MCS and achieving remission in the total study group, but after adjustment (for ACPA status (positive/negative), sex (male/female), DAS at baseline and Tender Joint Count and Swollen Joint count at baseline, this association was no longer found.(table 3) Results were the same when we used the ACR/EULAR provisional remission definition (data not shown).

DISCUSSION

We assessed patient reported outcomes (PROs) of functional ability and health related quality of life (HRQoL) in patients with UA and early RA who were treated with the aim to achieve remission (DAS <1.6). Patients who achieved early remission after 4 months had the best PROs from baseline through the first year of the study and only in these patients PROs reached levels comparable with those measured in the general population. Patients who did not achieve early remission and were randomized to multiple DMARDs with prednisone or a combination of methotrexate with adalimumab had lower, and between arms comparable, PRO scores during the first year.

At baseline, the IMPROVED population with a mean age of 52 years scored lower on all domains of the physical HRQoL compared to healthy individuals of the Dutch population aged >70 years [12] and therefore it seems that the disease burden of early arthritis is substantial. With treatment, the component score for physical HRQoL showed a clinically relevant improvement in all groups, with the most improvement in the early remission group during the first 4 months. The mental HRQoL remained stable around the population average during the first year of treatment, which suggests that the impact of early arthritis is mainly physical. This was also shown in previous published studies.[1,16] However, improvement of physical HRQoL and HAQ to the population average in the first year after diagnosis in a remission steered treatment protocol, was not earlier reported.[1,17]

It is generally accepted that remission is the optimal treatment target in rheumatoid arthritis. Ideally, this would result in patients having no radiological joint damage progression, and no symptoms and no limitations, in other words 'normality', with functional ability and quality of life comparable to the general population. More than disease activity scores, patient reported outcomes show whether such improvement can be achieved if treatment is steered at achieving remission. The current results indicate that scores comparable with the general population can indeed be achieved, but mainly in patients who were in early remission after 4 months of initial treatment. There is possibly a two-sided relationship between early remission and better PRO scores, since patients who achieved early remission had better PRO scores at baseline than patients who did not. This indicates that maybe a predisposition to achieve remission determines the outcomes. Our results indicate that patients with a milder disease or better predisposition to achieve remission benefit from remission steered treatment because this allows them to achieve normal levels of functional ability and quality of life, which may have a significant impact on their ability to work and personal and societal costs of having (rheumatoid) arthritis.[18,19] The magnitude of the association between remission and the various PROs is actually bigger in arms 1 and 2 than in the early remission group, which had better PROs after 1 year, but also already better PROs at baseline than patients in arms 1 and 2. This suggests that regardless of baseline score, achieving remission itself is associated with PRO improvement.

One may argue that also without treatment arthritis in these patients would have regressed, with function and quality of life restored. However, previously we showed that patients who achieved remission were in majority ACPA positive, which makes spontaneous remission less likely.[5]

Although after 1 year significantly more patients in arm 2 achieved remission than in arm 1, we found no significant differences in improvement of functional ability, HRQoL and VAS results between both arms. Only VAS disease activity, as estimated by the patient, improved more in arm 2 than in arm 1. Despite continued treatment adjustments targeted at remission, remission percentages in both arms remained lower than in the early remission group. Possibly as a consequence also functional ability and HRQoL in the physical domain did not achieve the same levels as the early remission group. In particular HAQ was higher in the randomization arms than in the early remission group and physical HRQoL did not reach levels found in the general population. Although we found that PROs were associated with achieving remission and significantly more patients in arm 2 achieved remission after 1 year than in arm 1, we found no significant differences in improvement of functional ability and HRQoL between both arms. Only improvement in VAS disease activity was significantly better in patients of arm 2 compared to patients in arm 1, which can be explained by a significantly lower mean DAS in arm 2 and it may also be related to higher patient expectations associated with earlier introduction of subcutaneous TNF-inhibitor, adalimumab, in this treatment arm.[20,21] Overall, disease activity was well suppressed in both arms which may explain why we

have found no differences in improvement in HAQ and HRQoL. The actual DAS, rather than having a score just above or below the threshold of remission, may be the main determinant of PROs. The patients in the OP group have similar results as patients in arm 1 and 2 which can be explained by the comparable response on initial treatment.

In conclusion, there is an association between achieving remission and having better functional ability and health related quality of life and other PROs in patients with early (rheumatoid) arthritis, which may in part be bidirectional. Patients who achieve early remission improve and remain at levels of the general population. This supports the idea that early remission steered treatment could result in complete suppression of symptoms with normal functioning and may prevent chronic deterioration also in patient reported outcomes.

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