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Clinical science

Long-term clinical outcomes in early rheumatoid arthritis that was treated-to-target in the BeSt and IMPROVED studies

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Abstract

Objectives: To assess disease outcomes after 20 and 12 years of patients with RA or undifferentiated arthritis (UA), treated-to-target in the BeSt and IMPROVED trials.

Methods: In BeSt (inclusion 2000–02, duration 10 years), 508 patients with early RA were randomized to: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial csDMARD combination therapy, 4. initial bDMARD/csDMARD combination therapy. The treatment target was low disease activity (DAS ≤ 2.4).
In IMPROVED (inclusion 2007–10, duration 5 years), 610 patients with early RA/UA started MTX with prednisone bridging. The treatment target was remission (DAS < 1.6). Patients not in early remission were randomized to 1. csDMARD combination therapy or 2. bDMARD/csDMARD combination therapy.
Between 2019 and 22, these patients were invited for long-term follow-up.

Results: One-hundred-fifty-three ex-Best and 282 ex-IMPROVED patients participated in the follow-up study after a median of 12 and 20 years since the study started.
In ex-BeSt and ex-IMPROVED patients, the rate of low disease activity was 91%, and 68% were in DAS remission. Median SHS was 14.0 in ex-BeSt (IQR 6.0–32.5; progression since end BeSt 6.0, IQR 2.0–12.5) and 8 in ex-IMPROVED participants (IQR 3–16; progression since end IMPROVED 4, IQR 2–9). Mean HAQ was 0.8 ± 0.6 in ex-BeSt (change since end BeSt: 0.3 ± 0.5) and 0.6 ± 0.6 in ex-IMPROVED participants (change since end IMPROVED: 0.06 ± 0.5).

Conclusion: At 12/20 years after treatment started, the majority of RA and UA patients who had been treated to target low DAS or DAS remission were in DAS remission and had limited functional disability. Radiographic damage progression was mild although not completely suppressed.

Keywords: rheumatoid arthritis, long-term follow-up, treat-to-target therapy.

Rheumatology key messages

- In a 12/20-year follow-up investigation, most patients with rheumatoid arthritis who had been treated-to-target were in clinical remission
- Relatively mild radiographic joint damage progression had occurred since the end of the trial phase of the studies
- Functional ability was relatively well preserved in the long-term, but was worse than in the general population

Introduction

With the introduction of early treat-to-target strategies, clinical outcomes in people with RA significantly improved [1, 2]. In trials, functional outcomes and quality of life improved when a strict treat-to-target regimen was used [3, 4]. Radiographic damage was also shown to be limited with early treat-to-target therapy [5, 6]. In the BeSt study, after 10 years, most patients with early RA who were treated with a treatment target of DAS ≤2.4 had little functional disability and limited radiographic damage [7]. After 5 years in the IMPROVED study, in which a stricter treatment target of drug-free remission (DAS < 1.6) was aimed, patients with RA and undifferentiated arthritis (UA) showed almost no radiographic damage and almost normal functional ability [8]. From the end of both studies, patients were followed up according to routine care. We recalled all patients for a long-term follow-up visit, with the aim to describe long-term clinical and radiological outcomes, 20 years after treatment start

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in BeSt (10 years since the end of the study) and 12 years after treatment start in IMPROVED (7 years since the end of the study). We hypothesized that the benefits of treat-to-target strategies had persisted in the long-term.

Methods

Patients

Between 2019 and 2022, patients from the treat-to-target BeSt and IMPROVED clinical trials were invited for a long-term follow-up visit (RECALL study) after a mean of 20 and 12 years respectively. Study information is provided in Table 1, Supplementary Table S1 and Supplementary Fig. S1, available at *Rheumatology* online and has been described previously [7–9]. After respectively 10 and 5 years of intervention, patients were treated according to daily practice.

To avoid sending invitations to deceased persons, death records were requested at the CBG (Centraal Bureau voor Genealogie) centre for family history. Additionally, to calculate the percentage of participation among non-deceased, vital status was assessed based on data from Statistics Netherlands (CBS). Results from comprehensive mortality analyses will be reported separately.

The RECALL study was approved by the Medical Ethics Committee (Commissie Medische Ethiek, P18.170). All participants gave written informed consent.

Outcomes

The primary outcomes were radiographic damage and functional ability. Radiographic damage was assessed with the Sharp-Van der Heijde score (SHS) based on radiographs of hands and feet at three time points: BeSt/IMPROVED baseline, BeSt/IMPROVED last visit and RECALL study visit. The SHS was only calculated if radiographs of both hands and both feet were available. One reader, who was unaware of patient identity, original treatment allocation and clinical outcomes, assessed the radiographs in chronological order (intrareader coefficient 0.98).

Functional ability was assessed with the health assessment questionnaire (HAQ, range 0–3) [10].

Disease activity, percentage in (drug-free) remission and health-related quality of life were secondary outcomes. Disease activity was measured with the three-component DAS (including number of swollen joints and tender joints and erythrocyte sedimentation rate (ESR), without patient global assessment because this was not assessed within one month after the follow-up visit in 39%). Remission was defined as DAS-remission (DAS < 1.6) [11]. The duration of remission was unknown. Medication use was self-reported.

Health-related quality of life was measured with the Short Form 36 (SF-36). We reported two summary component scores: physical health (PCS) and mental health (MCS), with scores ranging from 0 to 100 and higher scores indicating better health. The scores were standardized to a mean of 50 and SD of 10 in the age- and sex-matched Dutch reference population [12].

Statistical analyses

Mean/median SHS as well as the percentage of patients with detectable radiographic damage (SHS ≥ 1) and the percentage of patients with SHS > 30 (an arbitrarily chosen cut-off for considerable damage, corresponding with $>2/3$ of the joints with any detectable damage) was described. SHS at long-term follow-up was compared between treatment arms with a generalized linear model (GLM). If characteristics of BeSt/IMPROVED patients who participated in the follow-up study were not equally distributed between the treatment arms, the model was adjusted for these characteristics.

For BeSt, arm 4 (MTX/infliximab combination) was used as the reference category. Progression from end of the study

Table 1. Description of study details of BeSt and IMPROVED

	BeSt	IMPROVED
Patient population	Early RA (ACR 1987 criteria)	Early RA (ACR/EULAR 2010 criteria) or UA (not meeting 2010 criteria)
Inclusion period	2000–02	2007–10
Treatment target	DAS ≤ 2.4, assessed every three months	DAS < 1.6, assessed every four months
Treatment strategy	Randomization at baseline between: 1. sequential monotherapy starting with methotrexate (MTX), 2. step-up combination therapy starting with MTX, 3. Initial combination therapy starting with MTX, sulfasalazine and prednisone (with a tapering scheme) or 4. initial combination therapy starting with MTX and infliximab. Subsequent treatment steps in case of DAS > 2.4: Supplementary Table S1, available at *Rheumatology* online	Step 1: induction therapy with MTX with prednisone (tapered to low dose) Step 2: after 4 months, patients who were not in early remission (DAS < 1.6) were randomized between: 1. Addition of sulfasalazine and hydroxychloroquine, 2. Switching to MTX and adalimumab. Patients who achieved early remission, but subsequently flared (DAS ≥ 1.6), and had insufficient effect of reintroduction of prednisone, were also randomized between csDMARD combination therapy and adalimumab/MTX combination therapy. Subsequent treatment steps in case of DAS>=1.6: Supplementary Fig. S1, available at *Rheumatology* online
Tapering strategy	Tapering in case of DAS ≤ 2.4 for ≥ 6 months, next, in case of persistent DAS remission on low maintenance dose, stop the last remaining DMARD	Tapering to stop as soon as DAS < 1.6
Duration of trial period	10 years	5 years

was calculated from the last available study visit (BeSt: median 10 years, IMPROVED: median 5 years).

For IMPROVED, treatment arm 1 was compared with arm 2. Additionally, SHS was compared between patients who had or had not achieved early remission (at 4 months). This model was adjusted for potential confounders, based on previous research and clinical reasoning (baseline DAS, ACPA, BMI, sex, RA/UA diagnosis) [10, 13].

To assess radiographic progression since the BeSt/IMPROVED baseline, these models were additionally adjusted for baseline SHS.

HAQ was compared between treatment arms with a linear model, adjusted for baseline characteristics if necessary. IMPROVED patients with and without early remission were compared with a model adjusted for possible confounders (baseline DAS, ACPA, BMI, sex, RA/UA diagnosis) [14, 15].

The percentage of patients in remission was also compared between treatment arms with a GLM with a logit link function, if necessary adjusted for baseline differences between treatment arms. For the comparison between IMPROVED patients with and without early remission, the model was adjusted for possible confounders (baseline DAS, ACPA, sex, RA/UA diagnosis) [16].

At the follow-up visit, SHS was missing in 1.8%, DAS in 1.1% and HAQ in 5.5%. No methods to address missing data were used.

Results

BeSt

Of the 339 BeSt patients who were alive at the moment of invitation to the RECALL visit, 153 (45%) participated. They were on average 5 years younger than the 186 patients who did not attend follow-up (Table 2). The mean age of RECALL participants at follow-up was 66 ± 11 years. Slightly more patients who had originally been randomized to arm 4 (initial combination therapy with infliximab) participated in the RECALL study, compared with the other treatment arms (56% *vs* 39–45%). DAS at the last BeSt study visit was not different between participants and non-participants.

Although in the original BeSt population, this was not the case due to randomization, ACPA positivity and DAS at the BeSt baseline were statistically significantly different between RECALL participants of the different treatment arms (Supplementary Table S2, available at *Rheumatology* online).

At the mean 20-year follow-up, 141/152 (93%) patients with available radiographs had detectable radiographic joint damage (SHS ≥ 1) and 40/152 (26%) had SHS > 30. The mean SHS was 25.0 ± 34.8 (median 14.0, IQR 6.0–32.5), of which 16 points for joint space narrowing (10% of maximum joint space narrowing score) and 9 for erosions (3% of maximum erosions score). The SHS was mean 23.3 ± 33.8 (median 12, IQR 5–29.5) higher than at the BeSt baseline, and 10.2 ± 12.9 (median 6.0, IQR 2.0–12.5) higher than at the last study visit (at median 10 years after baseline). Mean SHS progression per year since baseline was 1.2 ± 1.7 (median 0.6, IQR 0.3–1.5).

Mean SHS was 35.2 ± 53.6 (median 17, IQR 8–38) in arm 1 (sequential monotherapy), 23.1 ± 33.7 (median 14, IQR 3–28) in arm 2 (step-up combination therapy), 29.0 ± 30.4 (median 19.5, IQR 7–41) in arm 3 (initial csDMARD combination therapy with prednisone) and 16.5 ± 17.7 (median 8.5, IQR 3–28) in arm 4 (initial bDMARD/csDMARD combination therapy). When adjusted for baseline differences in ACPA, DAS, smoking status and sex, arms 1 and 3 had statistically significantly more damage than arm 4 (Fig. 1A). This was the case both for erosions and for joint space narrowing (Supplementary Figs S2 and S3, available at *Rheumatology* online). Results for the progression of radiographic damage (adjustment of the model for baseline SHS) were similar (Fig. 1B). There were no statistically significant mutual differences in SHS between treatment arms 1, 2, and 3.

The mean HAQ at long-term follow-up was 0.8 ± 0.6 (median 0.8, IQR 0.3–1.3). This was 0.5 ± 0.7 lower than at the BeSt baseline but 0.3 ± 0.5 higher than at the last study visit. 54/144 (38%) of the participants had a HAQ of ≤0.5 (reflecting normal physical functioning) and 6/138 (4%) had a HAQ of ≥2 (severe disability). There was no statistically significant difference in HAQ between treatment arms (Fig. 1C).

Mean DAS at follow-up was 1.5 ± 0.6 with 91% (137/151) of participants with low disease activity and 68% (102/151) even in DAS remission. Of the 117 patients who met the study target of DAS ≤ 2.4 at their last BeSt study visit, 110 (94%) had DAS ≤ 2.4 at follow-up, compared with 27/34 (79%) who did not meet the target at the last study visit. Of the 70 patients who had been in DAS remission at the last

Table 2. BeSt baseline characteristics of patients who did and did not participate (deceased patients excluded) in the RECALL study

	RECALL participants ($n = 153$)	Non-participants ($n = 186$)	*P* value
Age (years), mean (SD)	46 (11)	51 (12)	<0.001
Symptom duration (weeks), median (IQR)	26 (14–55)	24 (14–56)	0.58
Sex (female), %	71	75	0.47
BMI, mean (SD)	25.6 (4)	26.4 (4)	0.08
Smoking, %	28	30	0.57
DAS, mean (SD)	4.3 (0.9)	4.5 (0.8)	0.06
BSE, mean (SD)	37 (25)	37 (24)	0.98
CRP, mean (SD)	32 (38)	35 (41)	0.42
HAQ, mean (SD)	1.3 (0.6)	1.4 (0.7)	0.37
Anti-citrullinated peptide antibodies (positive), %	64	57	0.14
Rheumatoid factor (positive), %	65	62	0.50
Arm 1 (sequential monotherapy), %	22	25	0.13
Arm 2 (step-up combination therapy), %	20	27	
Arm 3 (initial combination of MTX, sulfasalazine and prednisone), %	25	26	
Arm 4 (initial combination of MTX and infliximab), %	33	22	

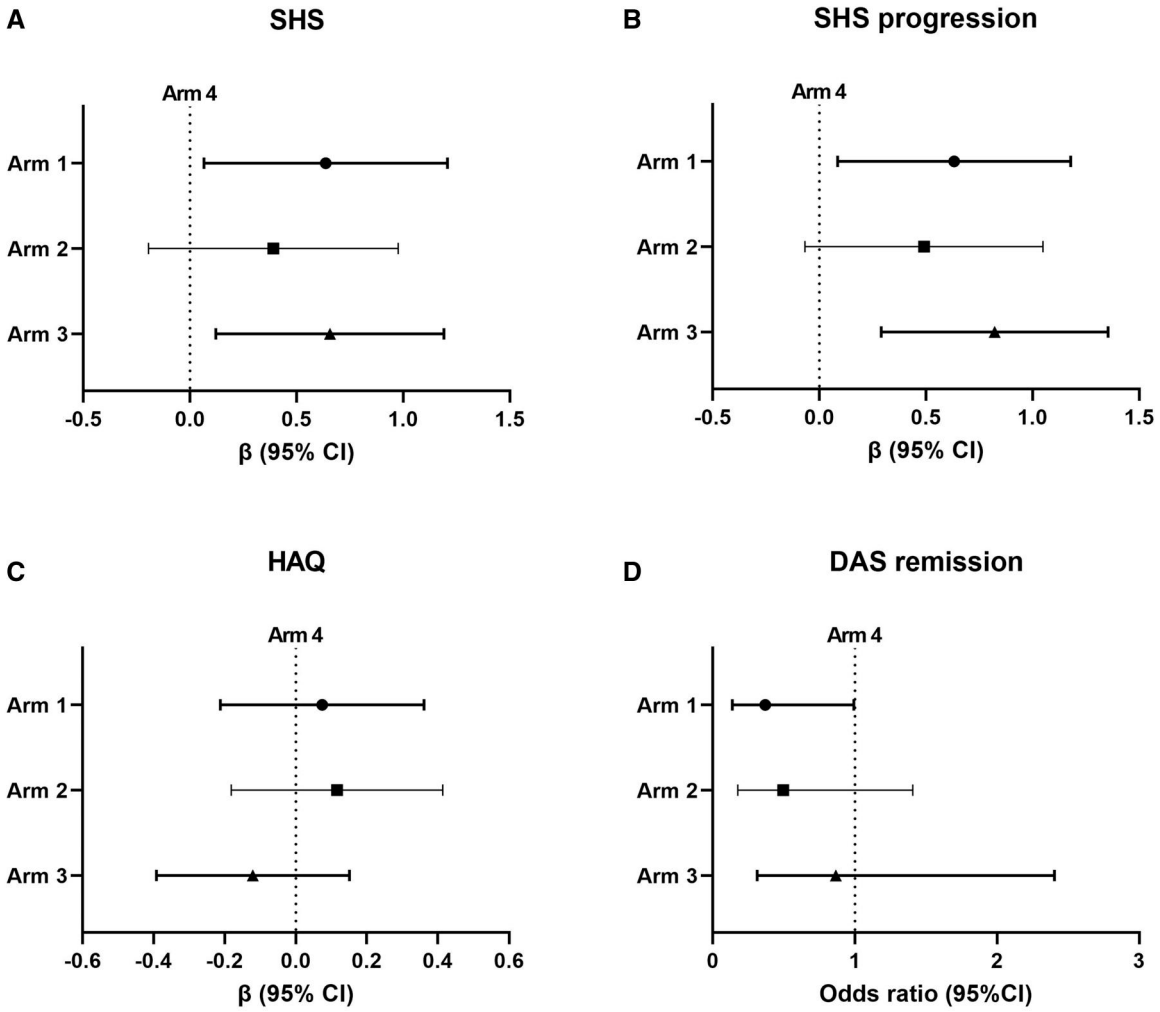

Figure 1. RECALL outcomes for BeSt treatment arms 1–3 compared with arm 4, adjusted for differences in patient characteristics. (**A**) SHS in arm 1 (sequential monotherapy; β 0.64, 95% CI 0.07–1.21), 2 (step-up combination therapy; β 0.39, 95% CI −0.19 to 0.98) and 3 (initial combination therapy with MTX, sulfasalazine and prednisone; β = 0.66, 95% CI 0.12–1.19), compared to arm 4 (initial combination therapy with MTX and infliximab). (**B**) SHS progression since BeSt baseline in arm 1 (β 0.63, 95% CI 0.09–1.18), arm 2 (β 0.49, 95% CI −0.07 to 1.05) and arm 3 (β 0.82, 95% CI 0.29–1.36). (**C**) HAQ in arm 1 (mean 0.9 ± 0.6, β 0.02, 95% CI −0.29 to 0.34), arm 2 (mean 1.0 ± 0.8, β −0.21, 95% CI −0.51 to 0.08), arm 3 (mean 0.7 ± 0.5, β −0.10, 95% CI −0.39 to 0.19) compared to arm 4 (mean 0.8 ± 0.6). (**D**) DAS remission in arm 1 (OR 0.4, 95% CI 0.1–0.99), arm 2 (OR 0.5, 95% CI 0.2–1.4), arm 3 (OR 0.9, 95% CI 0.3–2.4) compared to arm 4

study visit, 57 (81%) were in DAS remission at follow-up, compared with 45/81 (56%) who had not been in remission at the last study visit. At follow-up, significantly fewer patients who had been treated in BeSt arm 1 and numerically fewer from arm 2 were in DAS remission, compared with patients from arm 4 [arm 1: 17/32 (53%), arm 2: 18/31 (58%), arm 3: 28/38 (74%), arm 4: 39/50 (78%); Fig. 1D].

133 patients provided information on current medication. Of these, 16 (12%) were in drug-free DAS remission (arm 1: $n = 3$, arm 2: $n = 2$, arm 3: $n = 4$, arm 4: $n = 7$). Because of this small number, no further analyses were performed comparing initial treatment arms. Of the 23 patients who had been in drug-free remission at the last BeSt study visit, 11 (48%) were in drug-free remission at follow-up, compared with 5/110 (5%) who had not been in drug-free remission at the last study visit.

Most patients with self-reported medication use available, reported the use of either csDMARD monotherapy or bDMARD/csDMARD combination therapy (Table 3).

Physical quality of life was lower than that of the reference population: mean PCS of the SF-36 was 45.8 ± 9.7. Mental quality of life was comparable to the reference population with a mean MCS of 51.1 ± 8.4.

IMPROVED

Of the 523 patients who were alive at the moment of invitation for the RECALL, 282 (54%) participated. The 282 participants had on average been 2 years younger at baseline than the non-participants (Table 4). The mean age at follow-up was 61 ± 12 years. DAS at the last IMPROVED study visit was not different between participants and non-participants.

Fewer patients who currently participated had been in early remission compared within the original IMPROVED study (50% *vs* 63%), but differences in baseline characteristics between patients who had or had not achieved early remission were similar in the total IMPROVED population and the RECALL population. Patient characteristics at the IMPROVED baseline were comparable between arms 1 and

2 in the RECALL study (Supplementary Table S3, available at *Rheumatology* online).

At the mean 12-year follow-up, 254/275 (92%) patients with available radiographs had detectable radiographic joint damage and 26/275 (9%) had SHS > 30. The mean SHS was 12.7 ± 15.3 (median 8.0, IQR 3.0–16.0), of which 8 points for joint space narrowing (5% of maximum joint space narrowing score) and 5 for erosions (2% of maximum erosions score). The SHS was mean 10.9 ± 14.6 (median 6.0, IQR 3.0–13.0) higher than at the IMPROVED baseline and 7.3 ± 10.5 (median 2.0, IQR 2.0–9.0) higher than at the last IMPROVED study visit. Mean progression per year since baseline was 0.9 ± 1.2 (median 0.6, IQR 0.2–1.1).

Mean follow-up SHS was 13.5 ± 15.0 (median 10.0, IQR 4.0–17.0) in patients who had, and 11.5 ± 15.9 (median 6.0, IQR 2.0–15.0) in patients who had not been in early remission. This difference was not statistically significant (adjusted β for early remission: 0.17, 95% CI −0.15 to 0.48), also not if additionally adjusted for baseline damage (β 0.18, 95% CI −0.14 to 0.51). In the group that had not been in early remission, there was no significant difference in SHS between patients that had been randomized to arm 1 [mean SHS 10.4 ± 13.4 (median 6.5, IQR 2.0–15.0)] and arm 2 [mean SHS 13.3 ± 18.2 (median 6.0, IQR 3.0–16.0)] (adjusted β for arm 1 *vs* 2: −0.25, 95% CI −0.81 to 0.31). There was also no difference in joint damage progression between the two arms (β −0.44, 95% CI −0.98 to 0.11).

Erosions and joint space narrowing were both not statistically significantly different between patients who had and had not achieved early remission, and between the two treatment arms (Supplementary Tables S4 and S5, available at *Rheumatology* online).

The mean HAQ at long-term follow-up was 0.6 ± 0.6 (median 0.5, IQR 0.0–1.0). This was 0.6 ± 0.7 lower than at the IMPROVED baseline and 0.06 ± 0.5 higher than after 5 years of targeted treatment. HAQ score was <0.5 in 52% (140/267) and >2 in 2% (6/267) of the ex-IMPROVED participants. The mean HAQ in patients who had been in early remission was 0.5 ± 0.6, which was statistically significantly lower than in patients who had not been in early remission (mean HAQ: 0.8 ± 0.6): $\beta = -0.2$ (−0.4 to −0.1). There was no statistically significant difference in HAQ between randomization arms 1 and 2 (arm 1: mean HAQ 0.9 ± 0.5; arm 2: 0.8 ± 0.7; β arm 1 *vs* arm 2: −0.1 (95% CI −0.4 to 0.2).

Mean DAS at 12 years was 1.4 ± 0.7, with 91% (255/279) who had DAS ≤2.4 and 68% (189/279) even in DAS remission. Of the 170 patients who had been in DAS remission on the last IMPROVED study visit, 131 (77%) were in DAS remission at follow-up, compared with 58/109 (53%) who had not been in DAS remission on the last study visit. Of the 245 patients who had DAS ≤2.4 at the last study visit, 228 (93%) had DAS ≤2.4 at follow-up, compared with 27/34 (79%) who did not have DAS ≤2.4 at the last study visit.

Patients who had achieved early DAS remission were more often in DAS remission at the RECALL study visit than patients who had not achieved early DAS remission [77% (136/177) *vs* 51% (52/101); adjusted OR 2.3, 95% CI 1.3–4.2]. There was no difference between patients randomized to arms 1 and 2 [arm 1: 52% (23/44), arm 2: 52% (22/42), adjusted OR 1.0, 95% CI 0.4–2.3].

52 of the 248 patients (21%) with information available on medication use and DAS at follow-up were in drug-free

Table 3. Self-reported medication use from ex-BeSt RECALL participants with medication information available ($n = 135$)

	n	%
No antirheumatic medication	23	17
csDMARD monotherapy	38	28
csDMARD with prednisone	2	2
csDMARD combination therapy, with/without prednisone	10	7
bDMARD without csDMARD, with/without prednisone	19	14
bDMARD/csDMARD combination therapy, with/without prednisone	33	24
JAK inhibitor without csDMARD, with/without prednisone	3	2
JAK inhibitor with csDMARD, with/without prednisone	5	4
Prednisone monotherapy	2	2

JAK: Janus kinase.

Table 4. IMPROVED baseline characteristics of patients who did and did not participate (deceased patients excluded) in the RECALL study

	RECALL participants ($N = 282$)	Non-participants ($N = 241$)	*P* value
Age (years), mean (SD)	49 (12)	51 (15)	0.13
Symptom duration (weeks), median (IQR)	28 (27)	25 (26)	0.40
Sex (female), %	70	70	0.95
BMI, mean (SD)	26.0 (4.5)	25.6 (4.4)	0.30
Smoking, %	26	34	0.06
DAS, mean (SD)	3.2 (0.9)	3.2 (1.0)	0.41
BSE, mean (SD)	27 (22)	30 (25)	0.14
CRP, mean (SD)	20 (27)	23 (31)	0.32
HAQ, mean (SD)	1.2 (0.7)	1.1 (0.7)	0.20
Anti-citrullinated peptide antibodies (positive), %	60	52	0.09
Rheumatoid factor (positive), %	61	55	0.22
Early remission, %	63	67	0.13
Arm 1 (MTX, sulfasalazine, hydroxychloroquine, prednisone), %	16	15	
Arm 2 (MTX, adalimumab), %	15	9	
Out of protocol[a], %	6	9	
Diagnosis, % RA[b]	61	58	0.38

[a] Patients who had not achieved early remission, but were (erroneously) not randomized to arm 1 or 2.
[b] RA diagnosis based on ACR/EULAR 2010 criteria.

DAS remission. Of the 86 patients who had been in drug-free DAS remission at the last IMPROVED study visit, 39 (45%) were in drug-free DAS remission at follow-up, compared with 12/174 (7%) who had not been in drug-free DAS remission at the last study visit.

There was no statistically significant difference in drug-free remission at follow-up between patients who had achieved early remission and those who had not [23% (36/159) *vs* 18% (16/89); OR 1.7, 95% CI 0.8–3.6]. There was also no statistically significant difference in drug-free remission between arms 1 and 2 [14% (5/37) *vs* % 23 (9/39); OR 0.5, 95% CI 0.2–1.7].

Patients who reported to use antirheumatic drugs most often were on csDMARD monotherapy or bDMARD/csDMARD combination therapy (Table 5).

Physical quality of life was slightly lower than in the reference population (mean PCS 47.7 ± 9.2) and mental quality of life was similar (mean MCS 51.1 ± 8.5).

Discussion

At respectively 20 and 12 years after treatment initiation and subsequent treatment to target in the BeSt and IMPROVED studies and daily practice, patients with early RA/UA who returned for follow-up had improvement in functional ability compared with baseline, and the majority were in DAS remission. The mean HAQ was relatively low at 0.8 in ex-BeSt participants and 0.6 in ex-IMPROVED participants. After years of treatment aimed at low or very low DAS, the majority of patients who participated in this long-term follow-up study had developed radiographic damage, although this was relatively mild, with a median SHS of 13.5 in BeSt and 8.0 in IMPROVED participants (median progression since baseline 0.6 per year in both).

To our knowledge, this report describes the longest-term follow-up results after treat-to-target therapy in patients with newly diagnosed RA. Considering that RA is a lifelong, chronic disease, long-term follow-up results are needed to evaluate the effect of current treatment strategies. Previous early treat-to-target trials mainly assessed clinical outcomes up until 5 years [17, 18]. Only the FIN-RACo trial, in early RA patients treated to target aiming at remission, and the COBRA trial, in early RA patients treated without aiming at a formal treatment target, published 11-year results [3, 5, 19].

Table 5. Self-reported medication use from ex-IMPROVED RECALL participants with medication information available ($n = 252$)

	n	%
No antirheumatic medication	65	26
csDMARD monotherapy	79	31
csDMARD with prednisone	10	4
csDMARD combination therapy with/without prednisone	20	8
bDMARD without csDMARD, with/without prednisone	21	8
bDMARD/csDMARD combination therapy with/without prednisone	47	19
JAK inhibitor without csDMARD, with/without prednisone	3	1
JAK inhibitor with csDMARD, with/without prednisone	4	2
Prednisone monotherapy	3	1

Although in most patients there was joint damage progression 20 years after the start of BeSt and 12 years after the start of IMPROVED, median SHS scores were considerably lower than SHS scores after 11 years in the COBRA study [19]. Comparing our results to the 11-year results from the treat-to-target FIN-RACo study is difficult since different scores for joint damage were used. Using a percentage of the maximum score (SHS: 448; Larsen: 200), mean progression from baseline in the initial DMARD combination therapy arms was 5% (23/448) in BeSt after 20 years, 2% (11/448) in IMPROVED after 12 years and 9% (17/200) in FIN-RACo after 11 years. Compared with long-term results from old treatment strategies, radiographic outcomes have improved even more [20, 21]. The radiographic damage observed in our study was characterized more by joint space narrowing than by erosions. This might be an indication that age-related osteoarthritic features partially contributed to the observed changes.

We found less radiographic damage (both erosions and joint space narrowing) after initial combination therapy with infliximab (BeSt arm 4), but not after initial combination therapy with prednisone (arm 3), compared with other treatment arms. Previously, a so-called disconnect was described between disease activity and radiographic damage both with tumour necrosis factor inhibitors (TNFi) and with prednisone treatment [22–26]. Our results may support such a protective effect of TNFi on joint damage progression (although some joint damage still occurred, possibly after discontinuation of infliximab because of continued low DAS), but not of prednisone, indicating that early rapid disease activity suppression alone is not enough to prevent long-term damage progression. Based on our results, a causal (protective) effect of TNFi on joint damage progression cannot be proven.

We did not see better radiographic outcomes in patients who were randomized (after 4 months) to early TNFi in arm 2 of the IMPROVED study. This might have been a result of patient selection (adalimumab was only started in patients who did not achieve remission on MTX with prednisone), or shorter exposure to TNFi because of the fast tapering of adalimumab in IMPROVED after remission was achieved. It is also possible that differences between IMPROVED treatment arms were smaller because the treatment target was set lower than in BeSt (DAS <1.6 *vs* DAS ≤ 2.4).

Mean HAQ scores in our patients at follow-up (BeSt: 0.8 ± 0.6, IMPROVED: 0.6 ± 0.6) were lower than reported after 11 years in COBRA (1.0 ± 0.7 and 0.9 ± 0.7 in the two treatment arms), but higher than after 11 years in FIN-RACo (0.3 ± 0.5 and 0.4 ± 0.6 in the two treatment arms), who also had had lower HAQ scores at baseline [3, 19]. No direct comparison with a Dutch reference population without arthritis can be made, but among our participants, the percentage with HAQ > 0.5 was higher than in a cohort of Dutch citizens with a mean age of 70 years: 62%/48% *vs* 32% [27].

Compared with the Dutch reference population, the physical quality of life was slightly reduced in our participants. We did not find long-term results on health-related quality of life in other treat-to-target trials. However, an observational study from the ESPOIR cohort, in which patients with early RA, treated in daily practice since 2002 without predefined treatment strategies or treatment targets, reported slightly lower (that is, worse) PCS and MCS scores after 10 years: mean PCS 44.6 ± 9.2, MCS 46.7 ± 9.2 [28].

Mortality can be considered as another robust indicator of the effect of RA treatment. In a separate study, we assessed the mortality in the BeSt and IMPROVED population after a median of 20 and 13 years of follow-up. Although survival had improved compared with historical cohorts, we found excess mortality compared with the general Dutch population (standardized mortality ratio BeSt 1.32, 95% CI 1.14–1.53; IMPROVED 1.33, 95% CI 1.10–1.63) [29].

Besides providing unique long-term outcomes in a patient population who have been treated-to-target for a long time, the strengths of this study include the prospective nature of data collection, the use of standardized assessments, and the availability of mortality data, with which we could identify what selection of eligible patients participated.

However, the results should be interpreted with caution, since the patient population was selected, initially based on meeting the in- and exclusion criteria of BeSt and IMPROVED, and now based on their ability and motivation to visit the hospital for the long-term follow-up visit. Only 50% of former study participants still alive agreed to attend the 'RECALL' visit. This was also affected by the fact that the study took place mostly during the SARS-CoV-2 pandemic. However, even in this relatively young selection of participants, it was clear that some radiographic progression had occurred.

We do not know whether, after the last BeSt or IMPROVED study visit, patients continued to be treated aiming for the same treatment targets. Therefore, we cannot infer whether radiographic progression was caused by lower treatment intensity after the trial phase, or that it has occurred despite continued treat-to-target therapy. An additional limitation is that information on medication use was self-reported and therefore potentially less reliable. Subgroup analyses were adjusted for potential confounders, but residual bias cannot be ruled out. Finally, the results of this study might not be generalizable to patients that are treated-to-target in clinical practice, because of patient selection and since treatment was highly protocolized in BeSt and IMPROVED.

In conclusion, we found that patients with RA/UA who had been treated early and with treat-to-target strategies within the BeSt and IMPROVED trials, and attended long-term follow-ups, were mostly in low disease activity or even remission, had relatively mild radiological progression and had relatively preserved physical functioning. This was potentially the result of long-term treatment targeted at low disease activity or DAS remission. Patients who had started initial therapy with infliximab had the least radiographic damage progression. Our results imply the lasting benefit of early and prolonged treatment to target, but also show that there is still room for further improvement of treatment strategies to ensure better long-term outcomes in patients with RA/UA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available on reasonable request, except for mortality data. These results were based on calculations by Leiden University Medical Center using data from the BeSt and IMPROVED studies, and non-public microdata from Statistics Netherlands. Under certain conditions, these microdata are accessible for statistical and scientific research. For further information: microdata@cbs.nl.

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References

1. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360–72.
2. Matthijssen XME, Niemantsverdriet E, Huizinga TWJ, van der Helm-van Mil AHM. Enhanced treatment strategies and distinct disease outcomes among autoantibody-positive and -negative rheumatoid arthritis patients over 25 years: a longitudinal cohort study in the Netherlands. PLoS Med 2020;17:e1003296.
3. Rantalaiho V, Korpela M, Hannonen P *et al.*; FIN-RACo Trial Group. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum 2009;60:1222–31.
4. 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;364:263–9.
5. Rantalaiho V, Korpela M, Laasonen L *et al.*; FIN-RACo Trial Group. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.
6. Verstappen SMM, Jacobs JWG, van der Veen MJ *et al.*; Utrecht Rheumatoid Arthritis Cohort Study Group. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443–9.
7. Markusse IM, Akdemir G, Dirven L *et al.* Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment. Ann Intern Med 2016;164:523–31.
8. Akdemir G, Heimans L, Bergstra SA *et al.* Clinical and radiological outcomes of 5-year drug-free remission-steered treatment in patients with early arthritis: IMPROVED study. Ann Rheum Dis 2018;77:111–8.
9. Goekoop-Ruiterman YPM, 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; 52:3381–90.

10. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3:305–9.
11. Ferreira RJO, Welsing PMJ, Jacobs JWG *et al.* Revisiting the use of remission criteria for rheumatoid arthritis by excluding patient global assessment: an individual meta-analysis of 5792 patients. Ann Rheum Dis 2021;80:293–303.
12. Aaronson NK, Muller M, Cohen PD *et al.* Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055–68.
13. Mustila A, Korpela M, Haapala AM *et al.* Anti-citrullinated peptide antibodies and the progression of radiographic joint erosions in patients with early rheumatoid arthritis treated with FIN-RACo combination and single disease-modifying antirheumatic drug strategies. Clin Exp Rheumatol 2011;29:500–5.
14. Nikiphorou E, Norton S, Young A *et al.*; Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network. The association of obesity with disease activity, functional ability and quality of life in early rheumatoid arthritis: data from the Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network UK prospective cohorts. Rheumatology (Oxford) 2018; 57:1194–202.
15. Camacho EM, Verstappen SM, Lunt M, Bunn DK, Symmons DP. Influence of age and sex on functional outcome over time in a cohort of patients with recent-onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Care Res (Hoboken) 2011;63:1745–52.
16. Burmester GR, Ferraccioli G, Flipo R-M *et al.* Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum 2008;59:32–41.
17. Stouten V, Westhovens R, Pazmino S *et al.* Five-year treat-to-target outcomes after methotrexate induction therapy with or without other csDMARDs and temporary glucocorticoids for rheumatoid arthritis in the CareRA trial. Ann Rheum Dis 2021; 82:e163.
18. Verhoeven MMA, Tekstra J, Welsing PMJ *et al.* Effectiveness and safety over 3 years after the 2-year U-Act-Early trial of the strategies initiating tocilizumab and/or methotrexate. Rheumatology (Oxford) 2020;59:2325–33.
19. van Tuyl LHD, Boers M, Lems WF *et al.* Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis 2010; 69:807–12.
20. Drossaers-Bakker KW, Zwinderman AH, Vliet Vlieland TPM et al Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup. Arthritis Rheum 2002; 47:383–90.
21. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108–11.
22. Landewé R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum 2006;54:3119–25.
23. Smolen JS, Han C, Bala M *et al.*; ATTRACT Study Group. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52:1020–30.
24. Keystone E. Recent concepts in the inhibition of radiographic progression with biologics. Curr Opin Rheumatol 2009;21:231–7.
25. Klarenbeek NB, Güler-Yüksel M, van der Heijde DMFM *et al.* Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Ann Rheum Dis 2010;69:2107–13.
26. Boers M, van Tuyl L, van den Broek M, Kostense PJ, Allaart CF. Meta-analysis suggests that intensive non-biological combination therapy with step-down prednisolone (COBRA strategy) may also 'disconnect' disease activity and damage in rheumatoid arthritis. Ann Rheum Dis 2013;72:406–9.
27. Taş U, Verhagen AP, Bierma-Zeinstra SMA *et al.* Incidence and risk factors of disability in the elderly: the Rotterdam Study. Prev Med 2007;44:272–8.
28. Combe B, Rincheval N, Berenbaum F *et al.* Current favourable 10-year outcome of patients with early rheumatoid arthritis: data from the ESPOIR cohort. Rheumatology (Oxford) 2021; 60:5073–9.
29. Heckert SL, Maassen JM, le Cessie S *et al.* Long-term mortality in treated-to-target RA and UA: results of the BeSt and IMPROVED cohort. Ann Rheum Dis 2024;83:161–8.

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