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ORIGINAL ARTICLE

Sustained Beneficial Effects of a Protocolized Treat-to-Target Strategy in Very Early Rheumatoid Arthritis: Three-Year Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort

M. VERMEER,[1] H. H. KUPER,[2] H. J. BERNELOT MOENS,[3] K. W. DROSSAERS-BAKKER,[2] A. E. VAN DER BIJL,[4] P. L. C. M. VAN RIEL,[5] AND M. A. F. J. VAN DE LAAR[1]

Objective. **Treat-to-target (T2T) leads to improved clinical outcomes in early rheumatoid arthritis (RA). The question is whether these results sustain in the long term. Our objective was to investigate the 3-year results of a protocolized T2T strategy in daily clinical practice.**

Methods. **In the Dutch Rheumatoid Arthritis Monitoring remission induction cohort, patients newly diagnosed with RA were treated according to a T2T strategy aimed at remission (Disease Activity Score in 28 joints [DAS28] <2.6). Patients were treated with methotrexate, followed by the addition of sulfasalazine, and exchange of sulfasalazine with anti–tumor necrosis factor α agents in case of failure. Primary outcomes were disease activity, Health Assessment Questionnaire (HAQ) score, Short Form 36 physical component summary (PCS) and mental component summary (MCS) scores, and the Sharp/van der Heijde score (SHS) after 3 years. Secondary outcomes were sustained DAS28 remission (≥6 months) and remission according to the provisional American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition.**

Results. **After 3 years (n = 342), 61.7% of patients were in DAS28 remission and 25.3% met the provisional ACR/EULAR definition of remission. Sustained remission was experienced by 70.5%, which in the majority was achieved with conventional disease-modifying antirheumatic drugs only. The median scores were 0.4 (interquartile range [IQR] 0.0–1.0) for the HAQ, 45.0 (IQR 38.4–53.2) for the PCS, 53.1 (IQR 43.2–60.8) for the MCS, and 6.0 (IQR 3.0–13.0) for the total SHS.**

Conclusion. **In very early RA, T2T leads to high (sustained) remission rates, improved physical function and health-related quality of life, and limited radiographic damage after 3 years in daily clinical practice.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can have a major impact on the patient's physical and psychological health. When insufficiently treated, RA may lead to serious radiographic damage, functional disability (1–3), and reduced quality of life (4). The main therapeutic goal in RA is to suppress disease activity as early in the disease process as possible, thereby preferably achieving (sustained) remission, in order to prevent radiographic damage and disability (5). Indeed, remission is associated with a lower chance of deterioration of radiographic progression and function in the long term compared with not achieving a state of remission (6).

Intensified treatment including biologic agents has

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[1]M. Vermeer, MSc, M. A. F. J. van de Laar, MD, PhD: University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands; [2]H. H. Kuper, MD, PhD, K. W. Drossaers-Bakker, MD, PhD: Medisch Spectrum Twente, Enschede, The Netherlands; [3]H. J. Bernelot Moens, MD, PhD: Ziekenhuisgroep Twente, Almelo, The Netherlands; [4]A. E. van der Bijl, MD, PhD: Isala Klinieken, Zwolle, The Netherlands; [5]P. L. C. M. van Riel, MD, PhD: Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

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Address correspondence to H. H. Kuper, MD, PhD, Medisch Spectrum Twente, Department of Rheumatology and Clinical Immunology, PO Box 50 000, 7500 KA Enschede, The Netherlands. E-mail: h.kuper@mst.nl.

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Significance & Innovations

- This study shows data on the long-term outcomes of a treat-to-target (T2T) strategy aiming at remission in early rheumatoid arthritis (RA) daily clinical practice, which were scarce until now.
- The beneficial outcomes of a protocolized T2T strategy aiming at remission in very early RA in daily clinical practice were sustained over 3 years.
- The T2T strategy resulted in low disease activity, improvement of physical function and health-related quality of life, and a favorable radiographic outcome after 3 years of followup.

proven to be effective in achieving remission in patients with recent-onset RA (7). Clinical trials, e.g., the BeSt (Behandelstrategieën voor Reumatoide Artritis) study (8) and CAMERA (Computer-Assisted Management in Early Rheumatoid Arthritis) study (9), have demonstrated that intensive therapy including combination therapy and biologic agents or corticosteroids results in more beneficial clinical outcomes than initial monotherapy with disease-modifying antirheumatic drugs (DMARDs).

Furthermore, treat-to-target (T2T) is considered an important concept in the induction of remission in the treatment of RA (10). T2T entails a treatment strategy tailored to the disease activity of the individual RA patient with the aim of achieving a predefined level of low disease activity or remission. The Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort demonstrated that remission is a realistic goal in daily clinical practice with the application of a T2T strategy aimed at remission according to the Disease Activity Score in 28 joints (DAS28) (11), with early and intensive treatment leading to high remission rates (12) and limited radiographic progression after 1 year of followup (13). The question is whether these beneficial results sustain in the long term. Until now, data on the long-term outcomes of T2T in daily clinical practice have been scarce.

The aim of the present study was to investigate the 3-year effects of the implementation of a protocolized T2T strategy in the treatment of very early RA patients with respect to the achievement of (sustained) remission, radiographic progression, physical function, and health-related quality of life.

PATIENTS AND METHODS

Patients. Between January 2006 and March 2012, newly diagnosed RA patients were invited to participate in the DREAM remission induction cohort, and data collection is still ongoing. Patients with a clinical diagnosis of RA (made at the discretion of the attending rheumatologist) were included if they were age ≥18 years, had a symptom duration (defined as the time from the first reported symptom to the diagnosis of RA) of ≤1 year, had a DAS28 ≥2.6, and did not receive DMARDs and/or prednisolone previously.

The rheumatology clinics of 6 hospitals in The Netherlands collaborated in this study. This observational study on data from protocol-based daily clinical practice was approved by the hospitals' ethics committees. The patients were fully informed and informed consent was obtained.

Treatment. Patients were treated according to a T2T strategy including 4–12 weekly followup visits and protocolized treatment adjustments aiming at remission (DAS28 <2.6). Patients started treatment with methotrexate (MTX) 15 mg/week upon diagnosis. In the case of inefficacy, the consecutive intensification steps with DMARD medication were: at week 8, increase in MTX dosage to 25 mg/week; at week 12, addition of sulfasalazine (SSZ) 2,000 mg/day; and at week 20, increase in SSZ dose to 3,000 mg. In accordance with the Dutch guidelines, anti–tumor necrosis factor α (anti-TNFα) treatment was prescribed for patients whose DAS28 remained ≥3.2. These subsequent steps included: at week 24, adalimumab 40 mg every 2 weeks; at week 36, frequency increase of adalimumab to every week; at week 52, exchange of adalimumab for etanercept 50 mg/week; after 1 year and 3 months, infliximab 3 mg/kg of body weight every 8 weeks; and after 1 year and 6 months, frequency increase of infliximab to every 4 weeks. If the target of DAS28 <2.6 was met, medication was not changed. In the case of sustained remission (≥6 months), medication was gradually reduced and eventually discontinued. In the case of a disease flare (DAS28 ≥2.6), the most recently effective medication or medication dose was restarted and treatment could be subsequently intensified. In individual patients with contraindications for specific medication, deviations from the protocol were allowed. In patients with an allergy to sulfa drugs (sulfonamides), SSZ was replaced by oral hydroxychloroquine at a dosage of 400 mg/day. Concomitant treatment with nonsteroidal antiinflammatory drugs, prednisolone at a dosage of ≤10 mg/day, and intraarticular corticosteroid injections was allowed at the discretion of the attending rheumatologist. Further details of the study protocol were reported elsewhere (13).

Assessments. The following variables were collected at baseline: age, sex, symptom duration, fulfillment of the American College of Rheumatology (ACR) 1987 criteria for the classification of RA (14), rheumatoid factor positivity, and anti–cyclic citrullinated peptide (anti-CCP) antibody positivity. Assessments at baseline and at every followup visit (week 8, 12, 20, 24, 36, and 52, and every 3 months thereafter) consisted of the DAS28 (including the 28 tender joint count [TJC28], 28 swollen joint count [SJC28], erythrocyte sedimentation rate [ESR], and patient rating for general health on a 100-mm visual analog scale [VAS; where 0 = best and 100 = worst]), C-reactive protein (CRP) level, and patient rating for pain on a 100-mm VAS. The DAS28 was assessed by trained rheumatology nurses.

The Dutch version of the Health Assessment Questionnaire (HAQ) (15,16) and the Short Form 36 (SF-36) health survey (17) were administered every 3 months. The HAQ

disability index ranges from 0–3, with higher scores indicating more disability. The SF-36 generates a physical component summary (PCS) and mental component summary (MCS) score ranging from 0–100, with higher scores indicating better health.

Radiographs of the hands and feet were obtained at baseline, after 6 and 12 months, and then annually. Radiographs were evaluated in chronological order by 2 pairs of observers (MV and HHK/HJBM/KWD-B), according to the original methodology developed and published as the "modified Sharp/van der Heijde method" (18), and a consensus score was obtained. A patient was classified as having erosive disease if the erosion score was ≥1. An expert panel judged the minimum clinically important difference in the total Sharp/van der Heijde score (SHS) at an increase of ≥5 (19).

Study outcomes. The primary outcomes after 3 years of followup were disease activity according to the DAS28, the median scores of the HAQ and SF-36 (PCS and MCS), and radiographic outcome according to the SHS. Secondary outcomes included sustained DAS28 remission, time to achieve as well as the duration of sustained DAS28 remission, the number of disease flares, and remission according to the provisional ACR/European League Against Rheumatism (EULAR) definition of remission in RA (20).

Sustained remission was defined as a DAS28 <2.6 during ≥6 consecutive months, and could be classified as drug free or biologic free when remission was sustained (≥6 consecutive months) without any antirheumatic drugs or after withdrawal of anti-TNF therapy, respectively. The Boolean-based definition of the provisional ACR/EULAR definition of remission in RA required a TJC28 ≤1, SJC28 ≤1, CRP level ≤1 mg/dl, and patient global assessment (PGA) ≤1 (on a 0–10 scale) (20). In a previous study, we demonstrated that many patients did not meet the PGA criterion despite a good clinical disease state (21). Therefore, we also assessed the provisional ACR/EULAR definition of remission without the PGA criterion.

Statistical analyses. Since we were interested in the 3-year outcomes, only patients enrolled in the cohort between January 2006 and March 2009 were selected for the present study. In the case of missing values of the DAS28, HAQ, SF-36, and SHS scores, imputation using the trapezoid method was used, conditional on the data being missing at random.

A completer analysis as well as an intent-to-treat analysis were performed on the primary study variables after 3 years of followup. For the completer analysis, we used only the data of patients in whom data on the 3 years of followup visits were available. In the intent-to-treat analysis, the last observation was carried forward, i.e., if data were missing at the 3-year followup visit, then the data from the most proximal prior visit were used.

Kaplan-Meier survival analysis was performed to assess the time to achieve sustained DAS28 remission. *P* values less than 0.05 were considered significant. Statistical analyses were performed using SPSS software, version 18.0.

Table 1. Baseline characteristics of the patients (n = 409)*

	Value
Female sex, no. (%)	254 (62.1)
Age, mean ± SD years	58.4 ± 14.0
Symptom duration, weeks	14.0 (8.0–26.0)
Fulfillment of ACR 1987 criteria for RA, no./total (%)	334/398 (83.9)
RF positive, no./total (%)	246/406 (60.6)
Anti-CCP positive, no./total (%)	219/376 (58.2)
Erosive disease, no./total (%)	169/369 (45.8)
Total SHS	2.0 (0.0–5.0)
ESR, mm/hour	30.0 (17.0–44.0)
CRP level, mg/liter	15.0 (5.0–34.0)
No. of tender joints (28 assessed)	5.0 (2.0–9.0)
No. of swollen joints (28 assessed)	8.0 (5.0–12.0)
DAS28, mean ± SD	5.0 ± 1.1
Patient's assessment of pain (0–100 VAS)	50.0 (36.0–70.0)
Patient's assessment of general health (0–100 VAS)	50.0 (37.0–70.0)
HAQ score	1.0 (0.5–1.4)
SF-36 PCS score	35.6 (29.9–42.4)
SF-36 MCS score	48.0 (38.5–58.2)

* Values are the median (interquartile range) unless otherwise indicated. ACR = American College of Rheumatology; RA = rheumatoid arthritis; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; SHS = Sharp/van der Heijde score; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; SF-36 = Short Form 36 health survey; PCS = physical component summary; MCS = mental component summary.

RESULTS

Baseline characteristics. A total of 409 patients were eligible for the present study. The baseline characteristics of the patients are shown in Table 1. The mean ± SD age at baseline was 58.4 ± 14.0 years and 62.1% of the patients (254 of 409) were women. Patients were included at the moment of diagnosis and, therefore, disease duration was, per the definition, 0 weeks. The patients had on average a high level of disease activity as shown by the mean ± SD DAS28 of 5.0 ± 1.1. Erosive disease was already present in 45.8% of the patients (169 of 369) and the median total SHS was 2.0 (interquartile range [IQR] 0.0–5.0).

Three-year followup data were available for 342 patients (83.6%). In total, 67 patients were lost to followup or did not have 3 years of data for various reasons, including: death (n = 9), moving out of the area (n = 14), comorbidity (n = 7), other diagnosis (n = 1), patient wish (n = 22), other (n = 5), and no 3-year followup visit yet (n = 9). These patients were older (mean ± SD age 64.2 ± 13.3 years versus 57.3 ± 13.9 years; $P < 0.001$), had a higher ESR (median 36.0 [IQR 24.0–53.0] mm/hour versus 28.0 [IQR 16.0–42.0] mm/hour; $P = 0.007$) and CRP level (median 24.0 [IQR 9.3–39.0] mg/liter versus 13.0 [IQR 5.0–31.3] mg/liter; $P = 0.03$), and were more often anti-CCP positive (56.1% versus 39.2%; $P = 0.017$), but they did not

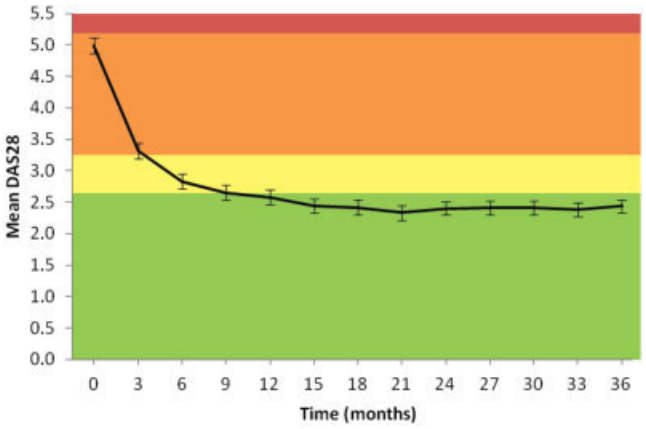

Figure 1. The mean (SEM) of the Disease Activity Score in 28 joints (DAS28) over 3 years of followup. Background coloring shows the levels of disease activity: green = remission (DAS28 <2.6); yellow = low (2.6 ≤ DAS28 ≤ 3.2); orange = moderate (3.2 < DAS28 ≤ 5.1); red = high (DAS28 >5.1).

differ significantly from the completers with respect to the distribution of sex and other clinical variables at baseline.

Both an analysis on the completers (n = 342) and an intent-to-treat analysis on the total cohort (n = 409) were performed. The results of both analyses did not differ; therefore, we show only the results of the completer analysis.

Disease activity. After 3 years, the mean ± SD DAS28 decreased to 2.4 ± 1.0. Figure 1 shows the course of the DAS28 over time. The largest improvement in the DAS28 was observed in the first 6 months of treatment, with a mean ± SD change in the DAS28 of −2.1 ± 1.4 points ($P <$ 0.001).

The remission percentages at 4 time points during the study are shown in Table 2. After 3 years, 61.7% of the patients (211 of 342) were in DAS28 remission. The provisional ACR/EULAR remission definition was met in 25.3% (74 of 293) and the adapted ACR/EULAR remission definition was met in 60.9% (179 of 294). The percentages of DAS28 remission and remission according to the adapted ACR/EULAR remission definition increased significantly during the first year (all $P <$ 0.01). The 1-year remission percentages remained consistent over followup except for the percentage of adapted ACR/EULAR remission, which increased significantly from 1 to 2 years ($P <$ 0.01).

Sustained remission. In 70.5% of the patients (241 of 342), sustained DAS28 remission (≥6 months) was observed at least once during the first 3 years of followup; of these, in 74.7% (180 of 241), remission was sustained for >1 year. At the 3-year followup visit, sustained remission was present in 42.7% of patients (146 of 342).

The Kaplan-Meier estimate of the median time to the achievement of the first sustained remission was 1.2 years (IQR 1.0–1.4 years). Obviously, not all patients reaching remission stayed in remission. The median duration of the first sustained remission was 1.5 years (IQR 0.9–2.3 years). In 51.0% of the patients (123 of 241) who experienced sustained remission, the disease did not flare. Almost one-quarter of the patients (28 of 118) who experienced a disease flare experienced a second sustained remission.

In the majority of cases (206 [85.5%] of 241), sustained remission was achieved with conventional DMARDs only. Sustained remission was induced by adjuvant therapy with anti-TNF agents in 12.0% (29 of 241), and in 2.5% (6 of 241), sustained remission was observed without antirheumatic medication. After achieving sustained remission, medication was tapered in 65.6% of patients (158 of 241), discontinued in 18.7% (45 of 241), unchanged in 9.1% (22 of 241), and switched to another antirheumatic drug in 6.6% (16 of 241) because of other reasons. Of the 29 patients who achieved sustained remission while receiving an adjuvant anti-TNF agent, biologic-free sustained remission was achieved in 24.1% of the patients (7 of 29). Sustained drug-free remission was observed in 14.9% (51 of 342).

Physical function. At 3 years, the HAQ score was available for 286 patients (83.6%). The box plots of the HAQ scores during followup are shown in Figure 2A. At 3 years, the median HAQ score was 0.4 (IQR 0.0–1.0). The HAQ score strongly improved during the first 6 months of treatment, and this improvement was maintained during followup.

Table 2. Levels of disease activity over 3 years of followup (n = 342)*

	6 months	1 year	2 years	3 years
DAS28 level				
Remission (DAS28 <2.6)	160 (46.8)	198 (57.9)	217 (63.5)	211 (61.7)
Low (2.6 ≤ DAS28 ≤ 3.2)	67 (19.6)	49 (14.3)	64 (18.7)	66 (19.3)
Moderate (3.2 < DAS28 ≤ 5.1)	101 (29.5)	86 (25.1)	54 (15.8)	57 (16.7)
High (DAS28 >5.1)	14 (4.1)	9 (2.6)	7 (2.0)	8 (2.3)
Provisional ACR/EULAR remission, no./total (%)	57/335 (17.0)	67/318 (21.1)	79/309 (25.6)	74/293 (25.3)
Adapted provisional ACR/EULAR remission, no./total (%)†	116/334 (34.7)	157/319 (49.2)	189/307 (61.6)	179/294 (60.9)

* Values are the number (percentage) unless otherwise indicated. Provisional American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission could not be evaluated in all patients due to missing values for C-reactive protein level and/or patient global assessment (PGA). DAS28 = Disease Activity Score in 28 joints.
† The provisional ACR/EULAR definition of remission without the PGA criterion.

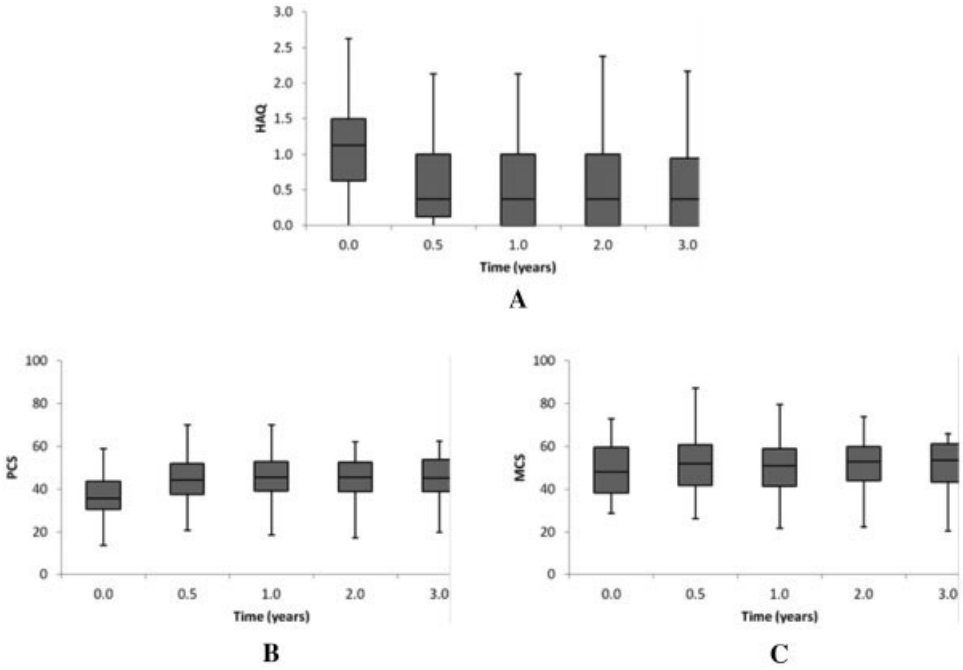

Figure 2. Box plots of **A**, the Health Assessment Questionnaire (HAQ) score, **B**, the Short Form 36 (SF-36) health survey physical component summary (PCS) score, and **C**, the SF-36 mental component summary (MCS) score over 3 years of followup.

Health-related quality of life. Three-year data on the SF-36 were available for 284 patients (83.0%). Figures 2B and C show the box plots of the SF-36 PCS and MCS scores during followup, respectively. The median scores of the PCS and MCS after 3 years were 45.0 (IQR 38.4–53.2) and 53.1 (IQR 43.2–60.8), respectively. After 6 months of followup, significant improvements in the PCS and MCS scores were observed, and the SF-36 scores remained stable hereafter.

Radiographic progression. Three-year radiographic data were available for 325 patients (95.0%). The radiographic outcomes at 4 points during 3 years of followup are shown in Table 3. After 3 years, 76.3% of the patients (248 of 325) had erosive disease. The percentage of patients with erosive disease significantly increased between baseline and 1 year of followup (44.9% versus 70.5%; $P < 0.001$). Figure 3 shows the course of the SHS over time. From baseline to 3 years, the median annual total SHS progression rates were as follows: 2.0 (IQR 1.0–4.0), 1.0 (IQR 0.0–2.0), and 0.0 (IQR 0.0–2.0), respectively. After 3 years, the median total SHS was 6.0 (IQR 3.0–13.0) and clinically relevant progression was observed in 43.4% of the patients (141 of 325).

Medication. In the remission group (n = 211), the actual medication use at the 3-year followup visit was as follows: 43.1% of the patients (91 of 211) were being treated with MTX monotherapy, 6.2% (13 of 211) received MTX and SSZ, 9.0% (19 of 211) received other DMARD medication, 16.6% (35 of 211) received MTX in combination with a biologic agent (12.3% adalimumab, 3.8% etanercept, and 0.5% infliximab), and 25.1% (53 of 211) were medication free. Low-dosage prednisolone (≤10 mg/day) was added to the medication in 6.2% (13 of 211).

In the nonremission group (n = 131), the actual medication use at the 3-year followup visit was as follows: 43.5% of the patients (57 of 131) received MTX monotherapy, 5.3% (7 of 131) received MTX with SSZ, 16.8% (22 of 131) were given other DMARD therapy, 20.6% (27 of 131) received MTX with a biologic agent (12.2% adalimumab, 4.6% etanercept, and 3.8% infliximab), and 13.7% (18 of 131) were medication free (mainly due to

Table 3 Radiographic outcomes over 3 years of followup (n = 325)*

	6 months	1 year	2 years	3 years
Erosive disease, no. (%)	204 (62.8)	229 (70.5)	242 (74.5)	248 (76.3)
Erosion score	1.0 (0.0–3.0)	2.0 (0.0–4.0)	2.0 (0.0–5.0)	2.0 (1.0–6.0)
Joint space narrowing score	2.0 (0.0–4.0)	2.0 (0.0–5.0)	2.0 (1.0–6.0)	3.0 (1.0–7.0)
Total SHS	3.0 (1.0–7.0)	4.0 (2.0–9.0)	5.0 (2.0–11.0)	6.0 (3.0–13.0)

* Values are the median (interquartile range) unless otherwise indicated. SHS = Sharp/van der Heijde score.

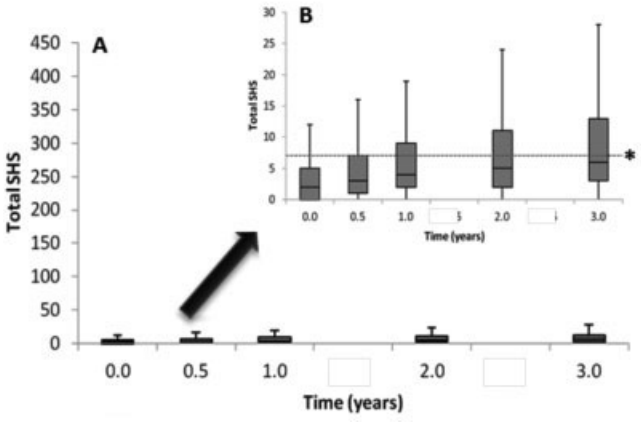

Figure 3. Box plots of the Sharp/van der Heijde score (SHS) over 3 years of followup **A**, shown on the full range of the score (0–448), and **B**, zoomed into the range of the observed scores. * = the dotted line (SHS 7) shows the clinically important difference in SHS (i.e., 5) from the baseline median SHS score (i.e., 2).

medication side effects). Prednisolone was taken in 13.0% of patients (17 of 131).

DISCUSSION

This long-term followup study demonstrated that the early beneficial outcomes of a protocolized T2T strategy aiming at remission in very early RA in daily clinical practice are sustained over 3 years. T2T resulted in high remission percentages, improvement of physical function and health-related quality of life, and a favorable radiographic outcome after 3 years of followup.

High remission percentages were observed during followup and remission (≥6 months) was sustained in the majority of patients (71%). Remission was maintained for more than 1 year in 53% of patients. These results are notable, since previous studies have suggested that sustained remission is uncommon in daily clinical practice (22–25). In the majority of our patients, sustained remission was achieved with conventional DMARDs (monotherapy or combination therapy). This is in line with other studies showing that optimal use of MTX early in the disease course leads to considerable improvements in disease activity (9,26). Moreover, a shorter time to remission has been shown to be related to sustainability of remission, supporting the importance of early intervention with effective therapy to achieve early remission (27). In spite of achieving sustained remission, it is important to continue to frequently and strictly monitor disease activity because a proportion of the patients may experience a disease flare. In line with the favorable results on disease activity, physical function (i.e., the HAQ) and health-related quality of life (i.e., the SF-36) over the 3-year followup period demonstrated significant and clinically meaningful improvements.

Although the baseline radiologic damage scores were low, 76% of patients proved to have erosive disease during observation. However, the total SHS and the progression in SHS were extremely low after 3 years of followup. It must be mentioned that we used the original methodology for the SHS, so all radiographs of a single patient are evaluated in chronological order and therefore only progression can be scored. This is in contrast with some recent radiologic studies suggesting healing of erosions (28–30). We have observed the same phenomenon in individuals in our cohort, but due to the original SHS methodology, this cannot be seen in the data. Several studies have shown a strong relationship between progression of radiographic damage and functional disability at the end of the followup period (3,31,32). Radiographic damage, which already occurs early in the course of RA, accounts for a substantial proportion of the disability in established RA. This targeted treatment strategy is able to decrease clinically relevant progression of joint damage and, therefore, it may lead to better joint function and outcome in the longer term.

Among the major strengths of this study are the large size of the cohort, the long followup period, and the fact that it concerns prospectively observed real-life data of newly diagnosed RA patients in clinics that implemented T2T in combination with protocolized treatment. Therefore, the results of this study in daily clinical practice can be generalized to the general RA population. Data collection of the cohort is still ongoing, which is critical for examining whether sustained drug-free remission is an achievable goal in daily clinical practice.

This study has some limitations. First, the target of this treatment strategy was remission according to the DAS28, which has some shortcomings. Although the DAS28 requires a complex calculation and its remission cutoff point has been debated (33–35), it is widely implemented, especially in Europe. Moreover, we have shown that all remission definitions are strongly related. In our opinion, our data underline the importance of treating RA to the target of remission, where remission can be assessed by any of the available definitions. Second, it is inevitable that a percentage of the patients become lost to followup in cohort studies. Therefore, a completer analysis as well as an intent-to-treat analysis were performed. Since both analyses led to comparable results, the fact that some patients were lost to followup did not affect our outcomes. Third, our results reflect the effects of only one medication strategy; no comparator was included. Recently, we compared the short-term results of our cohort with a comparable cohort in which usual care treatment was applied, demonstrating that T2T had superiority (12).

T2T has emerged as a new paradigm for the treatment of early RA. However, T2T has not been fully implemented in all rheumatology clinics yet. The DREAM remission induction cohort demonstrated that a DAS28-driven T2T strategy is feasible in early RA daily clinical practice, and herewith achieving and sustaining remission becomes a realistic treatment goal.

In conclusion, the present study showed that in daily clinical practice, a protocolized T2T strategy for very early RA leads to low disease activity and high (sustained) remission rates, improved physical function, better health-related quality of life, and limited radiographic damage, which sustain over 3 years.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kuper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Vermeer, Kuper, van Riel, van de Laar.

Acquisition of data. Vermeer, Kuper, Bernelot Moens, Drossaers-Bakker, van der Bijl, van Riel, van de Laar.

Analysis and interpretation of data. Vermeer, Kuper.

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