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Implementation of a Treat-to-Target Strategy in Very Early Rheumatoid Arthritis

Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort Study

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Objective. **Clinical remission is the ultimate therapeutic goal in rheumatoid arthritis (RA). Although clinical trials have proven this to be a realistic goal, the concept of targeting at remission has not yet been implemented. The objective of this study was to develop, implement, and evaluate a treat-to-target strategy aimed at achieving remission in very early RA in daily clinical practice.**

Methods. **Five hundred thirty-four patients with a clinical diagnosis of very early RA were included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Treatment adjustments were based on the Disease Activity Score in 28 joints (DAS28), aiming at a DAS28 of <2.6 (methotrexate, followed by the addition of sulfasalazine, and exchange of sulfasalazine with biologic agents in case of persistent disease activity). The primary outcome was disease activity after 6 months and 12 months of followup, according to the DAS28, the European League Against Rheumatism (EULAR) response criteria, and the modified American College of Rheumatology (ACR) remission criteria. Secondary outcomes were time to first DAS28 remission and outcome of radiography.**

Results. **Six-month and 12-month followup data were available for 491 and 389 patients, respectively. At 6 months, 47.0% of patients achieved DAS28 remission, 57.6% had a good EULAR response, and 32.0% satisfied the ACR remission criteria. At 12 months, 58.1% of patients achieved DAS28 remission, 67.9% had a good EULAR response, and 46.4% achieved ACR remission. The median time to first remission was 25.3 weeks (interquartile range 13.0–52.0). The majority of patients did not have clinically relevant radiographic progression after 1 year.**

Conclusion. **The successful implementation of this treat-to-target strategy aiming at remission demonstrated that achieving remission in daily clinical practice is a realistic goal.**

Clinical remission has proven to be an achievable therapeutic goal in patients with rheumatoid arthritis (RA) in the setting of randomized controlled trials. Ultimately, remission should be achieved in daily clinical practice as well, and, therefore, it has been proposed as the primary target of treatment in recent guidelines and recommendations for RA (1–3). Nevertheless, the concept of targeting at remission has not yet been implemented in all rheumatology units.

Remission of RA is associated with strongly

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reduced radiographic progression and improved functional ability (4). This emphasizes the importance of inducing rapid and sustained remission in RA. Keys to successful remission-inducing treatment are an early diagnosis, prompt therapeutic intervention, and intensive treatment. Shortly after the onset of symptoms, the differential diagnosis of arthritis can be difficult to make. RA develops in some patients, whereas in others the arthritis remits spontaneously, remains undifferentiated, or develops into other rheumatic diseases (5). However, early recognition of RA is important, because it is now widely accepted that patients in whom RA is destined to develop should begin receiving therapy as soon as possible.

Various findings support the importance of early intervention. First, it is consistent with the "therapeutic window of opportunity" hypothesis. Processes generating joint destruction appear to have been triggered in the early stages of the disease (6). In this phase, treatment has the potential to alter the disease process before irreversible damage is caused, thereby improving long-term outcomes in radiographic damage and functional ability (6,7). Second, many patients respond well to conventional disease-modifying antirheumatic drugs (DMARDs) in an early stage of the disease (8,9); such therapy approaches or even exceeds the level of effectiveness obtained with biologic agents (7). Third, there is an indication that after an excellent early response has been achieved, combination therapy can be successfully withdrawn without causing disease relapse (10–12).

Besides the use of combination therapy with DMARDs and biologic agents, a novel approach to intensive management of RA has been advocated: tight treatment to target (or tight control) (3). It has been consistently demonstrated that monitoring disease activity and subsequent adjustment of medication following a fixed protocol aiming at a predefined treatment goal is more beneficial than conventional treatment (13–15). Inspiring examples of strategy studies applying tight control are the Finnish Rheumatoid Arthritis Combination Therapy study (16,17), the TICORA (Tight Control of Rheumatoid Arthritis) study (18), the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study (9), the BeSt (Behandel Strategieën) study (11,19), and a pilot trial of an intensified Combinatietherapie Bij Reumatoïde Artritis (COBRA) strategy (20). However, these studies were performed in the setting of a randomized controlled trial, with strict inclusion and exclusion criteria, per-protocol treatment, and trial-dependent monitoring.

Until now, data on achieving disease remission in daily clinical practice are scarce (21). Therefore, the question is whether the promising results of randomized controlled trials can be generalized to the general population of patients with RA. Development and implementation of strategies to achieve remission in clinical care are warranted. Therefore, we conducted the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study. The objective of this study was to develop, implement, and evaluate a treat-to-target regimen aiming at disease remission in very early RA. Here, we report the 1-year clinical results.

PATIENTS AND METHODS

Patients. Since January 2006, consecutive patients (ages ≥18 years) with newly diagnosed RA were invited to participate in the DREAM remission induction cohort study. Inclusion criteria were a clinical diagnosis of RA made at the discretion of the attending experienced rheumatologist, symptom duration (defined as time from the first reported symptom to the diagnosis of RA by a rheumatologist) of 1 year or less, a Disease Activity Score in 28 joints (DAS28; calculated using the erythrocyte sedimentation rate [ESR]) ≥2.6 (22), and no previous treatment with DMARDs and/or prednisolone. Patients were included in the study at the moment of diagnosis. The rheumatology clinics of 5 hospitals in The Netherlands collaborated in this study. The study protocol was submitted to the ethics committee of each participating hospital. Because the study contains data from daily clinical practice, the ethics committees determined, in accordance with Dutch law, that no approval was required. Nonetheless, patients were fully informed, and informed consent was obtained.

Treatment. Patients were evaluated at weeks 0, 8, 12, 20, 24, 36, and 52 and every 3 months thereafter. At every visit, disease activity was assessed with the DAS28. Therapy adjustments were protocolized and based on the DAS28, with intensification of treatment if the predefined targets (i.e., DAS28 <2.6 for treatment with conventional DMARDs and DAS28 <3.2 for treatment with anti–tumor necrosis factor α [anti-TNFα]) were not met.

At baseline, we prescribed all patients methotrexate (MTX) at an initial dosage of 15 mg per week (given orally). In case of an insufficient response, consecutive intensification steps with DMARDs included an increase in the dosage of oral MTX to 25 mg/week, the addition of oral sulfasalazine at a dosage of 2,000 mg/day, and an increase in the dose of sulfasalazine to 3,000 mg. In accordance with the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti-TNFα therapy was prescribed for patients whose DAS28 remained ≥3.2. These subsequent steps included subcutaneous administration of adalimumab at a dosage of 40 mg every 2 weeks; an increase in the frequency of administration of adalimumab to every week in case of a DAS28 ≥2.6 and a decrease in the DAS28 of >1.2; exchange of adalimumab for subcutaneous etanercept at a dosage of 50 mg/week; exchange of etanercept for intravenous infliximab at a dosage of 3 mg/kg every 8 weeks after a loading dose at weeks 0, 2, and 6; and an increase in the frequency of administration

Table 1. Treatment protocol*

Followup	DAS28	Medication
Week 0	≥2.6	MTX 15 mg/week
Week 8	≥2.6	MTX 25 mg/week
Week 12	≥2.6	MTX 25 mg/week + SSZ 2,000 mg/day
Week 20	≥2.6	MTX 25 mg/week + SSZ 3,000 mg/day
Week 24	≥3.2†	MTX 25 mg/week + ADA 40 mg every 2 weeks
Week 36	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + ADA 40 mg/week
Week 52	≥3.2†	MTX 25 mg/week + etan. 50 mg/week
1 year + 3 months	≥3.2†	MTX 25 mg/week + inflix. 3 mg/kg every 8 weeks (after a loading dose at weeks 0, 2, and 6)
1 year + 6 months	≥2.6 and decrease of >1.2‡	MTX 25 mg/week + inflix. 3 mg/kg every 4 weeks

* The goal of treatment was remission (Disease Activity Score in 28 joints [DAS28] <2.6). Treatment was intensified when this target was not met. In case of remission, medication was not changed. SSZ = sulfasalazine; ADA = adalimumab; etan. = etanercept; inflix. = infliximab.
† Following the guidelines of the Dutch Society of Rheumatology and Dutch reimbursement regulations, anti–tumor necrosis factor α (anti-TNFα) therapy could be prescribed to patients with at least moderate disease activity (DAS28 ≥3.2) and in whom treatment with at least 2 disease-modifying antirheumatic drugs had failed (including methotrexate [MTX] 25 mg/week).
‡ Anti-TNFα therapy could be continued only if the DAS28 had decreased by >1.2 after 3 months.

of infliximab to every 4 weeks in case of a DAS28 ≥2.6 and decrease in the DAS28 of >1.2 (all in addition to MTX at a dosage of 25 mg/week). The full medication protocol is shown in Table 1. If the target of a DAS28 <2.6 was met, medication was not changed. If the DAS28 was <2.6 for at least 6 months, medication was gradually stepped down and eventually discontinued. In case of a disease flare (DAS28 ≥2.6), the most recently effective medication or medication dosage 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), sulfasalazine was replaced by oral hydroxychloroquine at a dosage of 400 mg/day. Nonsteroidal antiinflammatory drugs, prednisolone at a dosage of ≤10 mg/day, and intraarticular corticosteroid injections were allowed at the discretion of the attending rheumatologist.

Assessments. Baseline characteristics of the patients were collected, including age, sex, symptom duration, fulfillment of the American College of Rheumatology (ACR) 1987 criteria for the classification of RA (23), rheumatoid factor status, and anti–cyclic citrullinated peptide antibody status. Patients were assessed at the time of study entry and at every followup visit. Assessments included the tender joint count in 28 joints, the swollen joint count in 28 joints, the ESR, the C-reactive protein level, and the duration of morning stiffness. Patient-reported outcomes included global assessments of pain and general health on a 100-mm visual analog scale (VAS; 0 = best and 100 = worst); the disability index of the Dutch version of the Health Assessment Questionnaire, ranging from 0 to 3 (with high scores indicating more disability) (24,25); and component summary scores for physical and mental health on the 36-item Short Form Health Survey, ranging from 0 to 100 (with high scores indicating better health) (26). Data collection, including assessing the DAS28, was performed by well-trained rheumatology nurses.

Radiographs of the hands and feet were obtained at baseline and then annually. Radiographs were evaluated in chronologic order by 2 observers (MV and HHK), according to the modified Sharp/van der Heijde score (SHS) (27), and a consensus score was obtained. A patient was classified as having erosive disease if the erosion score was ≥1. Clinically relevant radiographic progression after 1 year was defined as an increase in the total SHS greater than the smallest detectable change, calculated as 4.3 points in the first year of followup (28).

Study outcomes. The primary outcome was disease activity after 6 months and 12 months of followup. For the evaluation of disease activity, we used 3 sets of criteria: the DAS28, the European League Against Rheumatism (EULAR) response criteria (29), and the ACR preliminary criteria for clinical remission in RA (30). Disease activity according to the DAS28 was interpreted as remission (DAS28 <2.6), low (2.6 ≤ DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), and high (DAS28 >5.1). The EULAR response criteria classify patients as good responders, moderate responders, or nonresponders, depending on the extent of change and the level of DAS28-defined disease activity reached. In this study, patients were followed up every 4–12 weeks, and fatigue was not assessed. Therefore, a modification of the ACR remission criteria was used, requiring 4 of the following 5 criteria: morning stiffness lasting ≤15 minutes, patient's global assessment of pain ≤10 mm on a VAS, no tender joints (28-joint count), no swollen joints (28-joint count), and normal ESR (<20 mm/hour in men and <30 mm/hour in women).

The secondary outcomes were time to the first moment of DAS28 remission and the radiographic outcome after 12 months of followup. A description of the medication being used at 12 months of followup was given.

Statistical analysis. Baseline characteristics of the patients are reported as the mean ± SD for normally distributed variables or as numbers with corresponding percentages for categorical variables. If variables were not normally distributed, values are reported as the median with the corresponding interquartile range (IQR). To test differences in baseline characteristics between subsets of patients, we used independent *t*-tests for normally distributed variables, chi-square tests for categorical variables, and Mann-Whitney U tests for non-normally distributed variables. *P* values less than 0.05 were considered significant.

Kaplan-Meier survival analysis was performed to assess time to the first moment of DAS28 remission. To ensure

accuracy of the results, data from all followup visits were included in the Kaplan-Meier analysis. Statistical analyses were performed using SPSS version 17.0 software.

RESULTS

From January 2006 to January 2010, a total of 534 patients were included in the cohort. The baseline characteristics of these patients are presented in Table 2. Patients were included at the moment of diagnosis. Therefore, disease duration was, per definition, 0 weeks. The study population consisted of patients with very early RA; the median duration of symptoms was 14.0 weeks (IQR 8.0–26.0 weeks). All patients had active disease with a mean ± SD DAS28 of 5.0 ± 1.1. Disease activity according to the DAS28 criteria was low in 6.4% of patients, moderate in 48.1% of patients, and high in 45.5% of patients.

Six-month data were available for 491 patients (91.9%), and 12-month data were available for 389 patients (72.8%) (Figure 1). Baseline characteristics of the patients included in the analyses of the 6-month and 12-month data were comparable with the characteristics of the total cohort population. In total, 17 patients were lost to followup for various reasons: death (n = 1), moving out of the area (n = 4), comorbidity (n = 9), and other (n = 3).

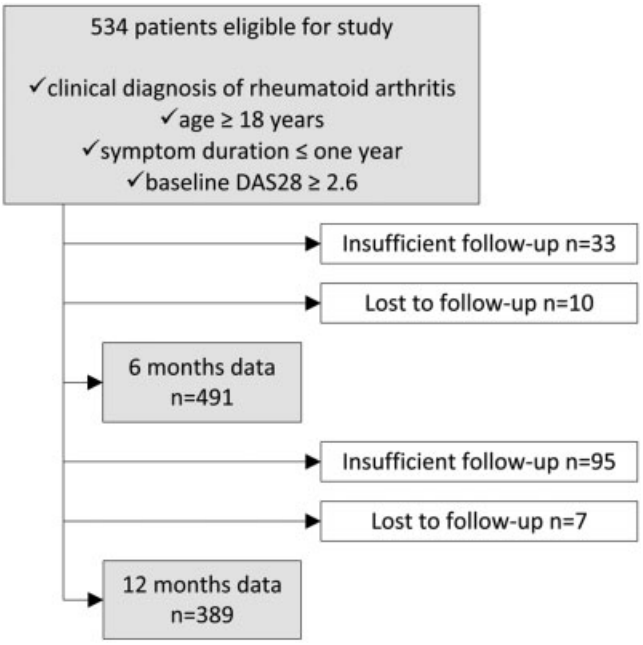

Figure 1. Study flow chart showing the number of patients included in the analyses for clinical outcomes after 6 months and 12 months and the number of patients lost to followup at different points in time. DAS28 = Disease Activity Score in 28 joints.

Table 2. Baseline characteristics of the patients (n = 534)*

Female sex	333 (62.4)
Age, mean ± SD years	58.6 ± 14.1
Symptom duration, median (IQR) weeks	14.0 (8.0–26.0)
Fulfillment of ACR 1987 criteria for RA	416/507 (82.1)
RF positive	318/524 (60.7)
Anti-CCP positive	281/488 (57.6)
RF negative and anti-CCP negative	158/498 (31.7)
ESR, median (IQR) mm/hour	28.5 (16.0–43.0)
CRP, median (IQR) mg/liter	13.0 (5.0–30.0)
No. of tender joints (28 assessed), median (IQR)	5.0 (2.0–9.0)
No. of swollen joints (28 assessed), median (IQR)	8.0 (4.0–12.0)
DAS28, mean ± SD	5.0 ± 1.1
Patient's assessment of pain, median (IQR) (0–100 VAS)	50.0 (36.0–70.0)
Patient's assessment of general health, median (IQR) (0–100 VAS)	50.0 (35.0–70.0)
HAQ score, median (IQR)	0.9 (0.5–1.4)
SF-36 PCS score, median (IQR)	35.8 (29.9–42.9)
SF-36 MCS score, median (IQR)	48.4 (38.5–58.3)

* Except where indicated otherwise, values are the number of patients/number of patients assessed (%). IQR = interquartile range; ACR = American College of Rheumatology; RA = rheumatoid arthritis; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; 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.

DAS28. After 6 months of treatment to target, 47.0% of patients achieved the predefined goal of DAS28 remission (DAS28 <2.6). Low, moderate, and high disease activity was observed in 19.4%, 29.1%, and 4.5% of the patients, respectively. At the 12-month followup, 58.1% of patients had achieved DAS28 remission. Disease activity was low in 14.7%, moderate in 24.9%, and high in 2.3% of patients (Table 3).

EULAR response. After 6 months, a good EULAR response was observed in 57.6% of patients, response was moderate in 28.3%, and no response was observed in 14.1% of the patients. After 12 months, good, moderate, and no responses were observed in 67.9%, 23.9%, and 8.2% of the patients (Table 3).

ACR remission. ACR remission could be analyzed in 384 of 491 patients after 6 months and in 321 of 389 patients after 12 months (due to missing values for morning stiffness). After 6 months, 32.0% of these patients had achieved ACR remission. After 12 months, ACR remission had been achieved in 46.4% of these patients (Table 3).

Time to remission. The time to the first occurrence of DAS28 remission was analyzed by Kaplan-

Table 3. Clinical outcomes in the patients after 6 months and 12 months of followup*

	6 months (n = 491)	12 months (n = 389)
DAS28 level		
Remission (DAS28 <2.6)	231 (47.0)	226 (58.1)
Low (2.6 ≤ DAS28 ≤ 3.2)	95 (19.4)	57 (14.7)
Moderate (3.2 < DAS28 ≤ 5.1)	143 (29.1)	97 (24.9)
High (DAS28 >5.1)	22 (4.5)	9 (2.3)
EULAR response		
Good	283 (57.6)	264 (67.9)
Moderate	139 (28.3)	93 (23.9)
None	69 (14.1)	32 (8.2)
ACR remission	123/384 (32.0)	149/321 (46.4)

* Values are the number (%). American College of Rheumatology (ACR) remission could not be evaluated in all patients due to missing values for morning stiffness. DAS28 = Disease Activity Score in 28 joints; EULAR = European League Against Rheumatism.

Meier survival analysis. The estimate of the median time to this first moment of remission was 25.3 weeks (IQR 13.0–52.0 weeks).

Radiographic outcome. Radiographic data were available for a limited but random number of patients; radiographs at baseline and after 12 months were evaluated in 186 of the 389 patients with 1-year followup. At baseline, 48.4% of the patients had erosive disease, and the median total SHS was 2.0 (IQR 0.0–5.0). After 12 months, the median total SHS was 5.0 (IQR 2.0–10.0), and the median progression in the total SHS from baseline was 2.5 (IQR 1.0–5.0). Clinically relevant progression was observed in 26.9% of the patients. The percentage of patients without radiographic progression was different, although not yet reaching statistical significance, between the remission (n = 117) and non-remission (n = 69) groups (76.1% and 68.1%, respectively; $P = 0.237$).

Medication. Figure 2 presents actual medication use at the 12-month followup, stratified for remission state. In the remission group (n = 226), 59.3% of the patients were being treated with MTX monotherapy. MTX in combination with sulfasalazine was given to 22.6% of the patients, MTX with a biologic agent was given to 5.7% (5.3% received adalimumab, and 0.4% received infliximab), and other DMARD medication was prescribed in 8.0% of the patients. Low-dose prednisolone (≤10 mg/day) was added to the medication regimen in 8.4% of the patients, and 4.4% of the patients were medication-free.

In the non-remission group (n = 163), 32.5% of the patients received MTX monotherapy, 28.8% received MTX with sulfasalazine, 18.4% received MTX with a biologic agent (17.2% received adalimumab, and

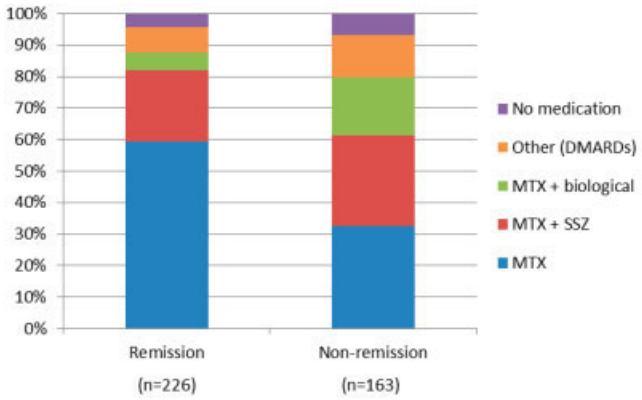

Figure 2. Actual medication use, stratified for the presence or absence of remission (defined as a Disease Activity Score in 28 joints of <2.6) after 12 months of followup. Other (disease-modifying antirheumatic drugs [DMARDs]) treatment consisted mainly of either monotherapy or combination therapy with methotrexate (MTX), hydroxychloroquine, or sulfasalazine (SSZ).

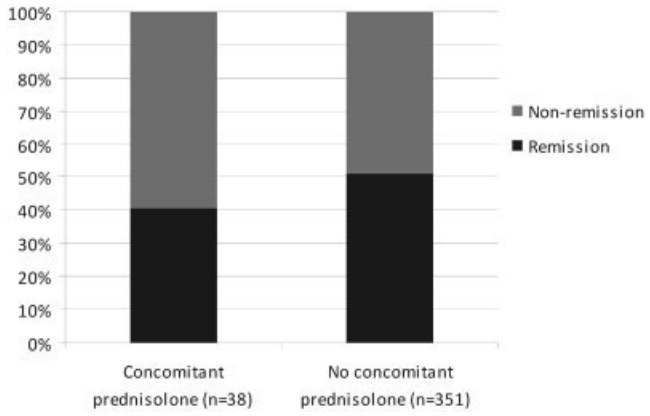

Figure 3. Remission (defined as a Disease Activity Score in 28 joints of <2.6), stratified for concomitant prednisolone treatment or no concomitant prednisolone, after 12 months of followup.

1.2% received etanercept), and 13.5% were given other DMARD therapy. Prednisolone was added to the medication in 11.7% of the patients. Almost 7% of the patients were medication-free (mainly due to medication side effects).

In those patients who received prednisolone in addition to their other medication, prednisolone was mostly prescribed as bridging treatment. The most frequently used dosage was 5–10 mg/day. Figure 3 shows the influence of concomitant prednisolone therapy on achievement of remission. During the first year of followup, approximately one-fourth of patients received at least one intraarticular injection of corticosteroids.

DISCUSSION

The results of the current study show that achieving remission in very early RA in daily clinical practice using a treat-to-target strategy is a realistic goal. After 6 months and 12 months of followup, remission rates according to the DAS28 as well as the ACR criteria were high, and a good EULAR response rate was observed frequently. Moreover, remission was achieved rapidly. Preliminary results on radiographic outcome showed that the majority of patients did not have clinically relevant radiographic progression in the first year of followup. Therefore, targeting at remission should be adopted in clinical practice.

Remission has become an important outcome in clinical trials. However, there is little information about achieving remission in early RA under routine care conditions. It is assumed that the efficacy achieved in clinical trials is hardly ever achieved in clinical practice (31–33). This assumption can be explained by, among other factors, the restrictive inclusion criteria of clinical trials, as a result of which trials reflect only a minor proportion of the patients seen in clinical practice (34,35). In our cohort, in contrast, no stringent inclusion or exclusion criteria were used. As such, this study reflects the population of adults with very early RA as seen in daily clinical practice, irrespective of age, comorbidities, and disease activity. This study shows that treatment to target in combination with per-protocol treatment is feasible and successful in daily clinical practice. The implementation of such a treatment strategy depends on logistical and practical issues.

Treatment protocols aiming at remission evidently depend on national guidelines and local reimbursement regulations. Our study shows that MTX (monotherapy followed by combined treatment with other DMARDs when indicated) is highly successful in achieving this treatment goal. It is noteworthy that during the first year, anti-TNFα agents were prescribed for only ~10% of the patients. Concomitant prednisolone therapy did not contribute to the achievement of remission. Previously, the CAMERA study also showed that optimal use of MTX in a tight control setting leads to considerable improvement in disease activity in early RA (9).

This study has some limitations. First, the DAS28 has been subject to criticism, because joints in the feet are not included in measuring disease activity, and the DAS28 remission criterion is less stringent than that of, for example, the original DAS (36,37) and ACR remission criteria (38). To support the outcomes of disease activity measured with the DAS28, we presented additional outcomes such as the EULAR response criteria and ACR remission. Although the ACR remission criteria were slightly less frequently met, remission results according to the different definitions were comparably favorable. Second, the data used in this study are limited to a followup of 1 year. Long-term followup of the DREAM remission induction cohort is ongoing, which is critical for examining whether remission is sustained and for evaluating the long-term effects on radiographic progression and functional ability. Third, our results reflect the effects of only one medication strategy; no comparator was included. Other strategies will be evaluated in forthcoming cohorts.

The strengths of our study lie in the setting and design. First, the results of this study in daily clinical practice can be easily generalized to the entire population of patients with RA. Second, this cohort consists of a large number of patients with RA. Third, this study investigates a treatment strategy reflecting clinical practice. These are advantages of cohort data compared with those from clinical trials, in which generalizability of results is often limited, smaller numbers of patients are included, and the efficacy of only one drug is investigated. Fourth, our results appear robust and independent from definitions of remission. These first results of the DREAM remission induction cohort demonstrate, in contrast to previous clinical trials showing the efficacy of antirheumatic drugs, the effectiveness of a contemporary treatment strategy in rheumatology.

We defined very early RA as a duration of symptoms of $\leq$1 year in combination with immediate treatment at the moment of diagnosis. To our knowledge, this is the first study of very early RA. Other studies in early RA used durations as long as 1–2 years after the diagnosis to define early disease. However, this definition is not equivalent to the duration of disease,

which extends back to the onset of symptoms. Our results underscore the importance of immediate treatment after diagnosis. Moreover, the excellent results observed in this very early phase of disease support the window-of-opportunity theory.

In conclusion, we successfully implemented a treat-to-target and per-protocol treatment strategy aiming at remission in very early RA and demonstrated that achieving disease remission is a realistic goal in daily clinical practice. When remission is accepted as the therapeutic goal of RA, it is evident that disease management should include monitoring of disease activity and adjustment of therapy accordingly. We suggest a change in the current clinical approach to treating very early RA and believe that rheumatologists should make disease remission the mission for all patients.

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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. Ms Vermeer 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.
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Analysis and interpretation of data. Vermeer, Kuper, van de Laar.

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