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Early Targeted Combination Treatment With Conventional Synthetic Disease-Modifying Antirheumatic Drugs and Long-Term Outcomes in Rheumatoid Arthritis: Ten-Year Follow-Up Results of a Randomized Clinical Trial

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Objective. The short-term outcomes of remission-targeted treatments of rheumatoid arthritis (RA) are well-established, but the long-term success of such strategies is speculative, as is the role of early add-on biologics. We assessed the 10-year outcomes of patients with early RA treated with initial remission-targeted triple combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), 7.5-mg prednisolone, and additional infliximab (IFX) or placebo infusions.

Methods. Ninety-nine patients with early, DMARD-naive RA were treated with a triple combination of csDMARDs and prednisolone and randomized to double-blind receipt of infusions of either IFX (the Finnish Rheumatoid Arthritis Combination Therapy Trial [FIN-RACo] + IFX) or placebo (FIN-RACo + placebo) during the first 6 months. After 2 years, the treatment strategies became unrestricted, but the treatment goal was strict remission in the TNF-Blocking Therapy in Combination With Disease-Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis (NEO-RACo) study. At 10 years, the clinical and radiographic outcomes and the drug treatments used between 5 and 10 years were assessed.

Results. Ninety patients (91%) were followed after 2 years, 43 in the FIN-RACo + IFX and 47 in the FIN-RACo + placebo group. At 10 years, the respective proportions of patients in strict NEO-RACo remission and in Disease Activity Score using 28 joints remission in the FIN-RACo + IFX and FIN-RACo + placebo groups were 46% and 38% (P = 0.46) and 82% and 72% (P = 0.29), respectively. The mean total Sharp/van der Heijde score was 9.8 in the FIN-RACo + IFX and 7.3 in the FIN-RACo + placebo group (P = 0.34). During the 10-year follow-up, 26% of the FIN-RACo + IFX group and 30% of the FIN-RACo + placebo group had received biologics (P = 0.74).

Conclusion. In early RA, excellent results can be maintained up until 10 years in most patients treated with initial combination csDMARDs and remission-targeted strategy, regardless of initial IFX/placebo infusions.

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SIGNIFICANCE & INNOVATIONS

- In a 10-year follow-up, a majority of rheumatoid arthritis patients remains in remission or in very low disease activity, with well-preserved functional ability and minimal radiographic progression when initially treated actively with a triple combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and low-dose glucocorticoids.
- To maintain remission, one-third of the patients need continued combination csDMARD and low-dose glucocorticoid treatment and one-third need escalation to biologic DMARDs; in one-third of the patients the treatments can be tapered.

INTRODUCTION

Early and sustained remission is the current indisputable paradigm in the treatment of rheumatoid arthritis (RA) (1), and because of the modern treatment options, it has become reality to an increasing number of patients (2). However, because this chronic disease still cannot be cured, the answer to the question for how long the remission can be sustained, and by what means, remains unclear. There appears to be a very early window of opportunity, before any structural joint damage emerges, during which the initiation of treatment with disease-modifying antirheumatic drugs (DMARDs) results in an increased rate of remissions (3), but how long this early effect lasts is of interest. Further, because the definitions of remission vary, depending on their strictness, the pace of long-term structural damage progression as well as the functional capacity within each remission category that is reached may vary correspondingly (4).

There are few trials using the modern treat-to-target approach with truly long-term follow-ups (at least 10 years), or comprehensive follow-up coverage (5–7). Our previous analyses of the study TNF-Blocking Therapy in Combination With Disease-Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis (NEO-RACo) have shown that in early RA, an intensified initial combination treatment strategy (Finnish Rheumatoid Arthritis Combination Therapy Trial [FIN-RACo]) with methotrexate (MTX), sulfasalazine, hydroxychloroquine, and low-dose 7.5-mg prednisolone for 2 years, and free, active, remission-targeted DMARD treatment thereafter, resulted in very low disease activity in most patients at 2 and 5 years. This treatment also resulted in minimal to no radiographic joint damage progression in most patients, regardless of double-blind induction therapy with infliximab (IFX) or placebo for the first 6 months (8,9). In the current study we report the 10-year outcomes of these patients.

PATIENTS AND METHODS

Study design and patients. The NEO-RACo trial was a multicenter, investigator-initiated study that recruited 99 patients with early, active RA fulfilling the American College of Rheumatology (ACR) 1987 criteria (10). The patients were treated with an intensified FIN-RACo regimen for 2 years, as previously described, and in

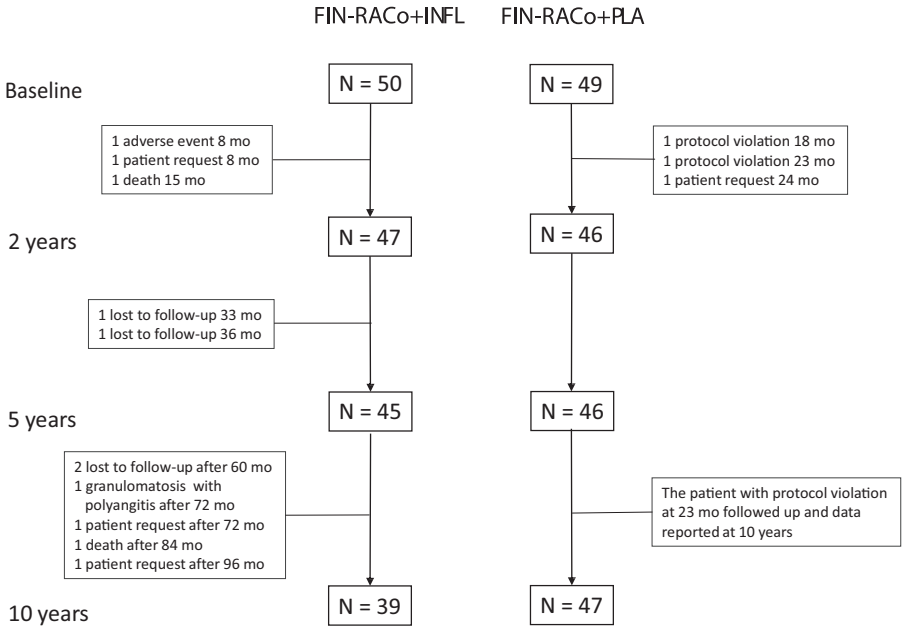

Figure 1. Flow-chart of the patients randomized to receive initial infliximab (the Finnish Rheumatoid Arthritis Combination Therapy Trial [FIN-RACo] + INFL) or placebo (FIN-RACo + PLA) for 6 months in addition to a combination of 3 conventional synthetic disease-modifying antirheumatic drugs and 7.5-mg prednisolone for 2 years and followed up for 10 years. After the 5-year visit, data were available for 43 patients in the FIN-RACo + INFL group, of which 4 patients dropped out by 10 years, and for 47 patients in the FIN-RACo + placebo group, all of which continued throughout the follow-up. mo = months.

addition were double-blind randomized to receive either IFX or placebo infusions at weeks 4, 6, 10, 18, and 26 (8). An active use of intraarticular glucocorticoid injections to all inflamed joints was part of the protocol throughout the follow-up. After the 2-year visit, if the patient was in remission by the strict NEO-RACo criteria (described below), prednisolone was gradually tapered off, followed by gradual reduction of conventional synthetic DMARDs (csDMARDs) as well. If remission was lost, the previous DMARD treatment/dosage was restored (9). If the patient was a nonresponder after dose and drug adjustments (less than a 50% improvement according to ACR criteria for improvement at maximal combination after individual substitutions) at 2 consecutive visits, the evaluation starting after week 26, the patient was regarded as failing treatment, and the therapy was open, including the possibility of using anti–tumor necrosis factor (anti-TNF) blocking agents (9).

After 5 years, study visits took place by protocol once a year, but clinical visits happened as often as needed. At all time points, the treatment was targeted to a strict NEO-RACo definition of remission, characterized as the presence of 5 of the 6 following criteria: morning stiffness <15 minutes, no fatigue, no joint pain, no tender joints (68 joint count), no swelling in joints (66 joint count) or tendons, and erythrocyte sedimentation rate (ESR) <30 mm/hour in women and <20 mm/hour in men. The therapies could be modified according to the judgment of the treating rheumatologist, with the use of all available csDMARDs, biologic DMARDs (bDMARDs), and glucocorticoids, orally as well as intraarticularly.

Outcomes and follow-up. The clinical assessments included evaluation of the number of swollen and tender joints (66 of 68 joints), patient's assessment of pain (10-cm visual analog scale [VAS]), patient's global assessment of disease activity (10-cm VAS), physician's global assessment of disease activity (10-cm VAS), patient's assessment of physical function according to the Health Assessment Questionnaire (HAQ), and acute-phase reactants (C-reactive protein level and ESR). The Disease Activity Score using 28 joints (DAS28) was also calculated. The medications used, the intraarticular glucocorticoid injections given, and the occurrence of adverse effects were carefully elucidated at each visit.

The small joints of the hands and feet were radiographed at 7 and 10 years and scored by an experienced radiologist (LL), who was aware of the chronology of the radiographs, according to the modified Sharp/van der Heijde (SHS) method. The primary outcome measures were the strict NEO-RACo remissions and the radiographic damage in hands and feet at 10 years. The secondary outcome measure was the DAS28 remission. In addition, we report the use of bDMARDs and adverse events.

Statistical analysis. Statistical comparisons between the groups were made using a *t*-test, bootstrap type *t*-test, Mann-Whitney test, chi-square test, or Fisher-Freeman-Halton exact test. The longitudinal remission data were analyzed with generalized estimating equations models with an unstructured correlation structure (binomial distribution with a log link). The bootstrap method (5,000 replications) was used when the theoretical distribution of the test statistics were unknown or in the case of violation of the assumptions (e.g., non-normality). The Kaplan-Meier method was used to estimate the cumulative use of bDMARDs and was compared between groups with the versatile weighted log-rank test. Clinical outcome variables were analyzed by the intent-to-treat principle, with the last observation carried forward. All analyses were performed using Stata software, version 14.1.

RESULTS

The flow chart of the patients is shown in Figure 1. One patient in the original FIN-RACo + placebo group was excluded from the 2- and the 5-year analyses due to a protocol viola-

Table 1. Demographic, clinical, and radiographic findings at baseline in patients randomized to receive initial infliximab (FIN-RACo + IFX) or initial placebo infusions (FIN-RACo + placebo) for 6 months in addition to a combination of 3 csDMARDs and 7.5-mg prednisolone for 2 years*

Finding	FIN-RACo + IFX (n = 43)	FIN-RACo + placebo (n = 47)	*P*
Demographic data at baseline			
Female, no. (%)	30 (70)	29 (62)	0.42
Age, years	48 ± 9	47 ± 11	0.32
Symptom duration, median (IQR) months	4 (2–6)	4 (2–6)	0.99
Rheumatoid factor present, no. (%)	33 (77)	34 (72)	0.63
Measures of disease activity at baseline			
Number of swollen joints (0–66)	15 ± 5	16 ± 8	0.38
Number of tender joints (0–68)	19 ± 10	21 ± 11	0.22
Erythrocyte sedimentation rate, mm/hour	34 ± 22	33 ± 22	0.93
Patient's global assessment (VAS, mm)	51 ± 24	48 ± 27	0.52
Pain (VAS, mm)	55 ± 27	53 ± 27	0.65
Physician's global assessment (VAS, mm)	49 ± 22	55 ± 20	0.17
DAS28	5.54 ± 1.00	5.60 ± 1.39	0.81
Physical function (HAQ)	1.09 ± 0.61	0.91 ± 0.71	0.22
Radiography at baseline			
Erosion score†	2.6 ± 7.2	1.3 ± 2.9	0.30
Narrowing score†	0.5 ± 1.6	0.3 ± 0.6	0.42
Total score†	3.1 ± 8.4	1.6 ± 3.2	0.29
Erosions in hand or foot radiographs, no. (%)	20 (47)	15 (32)	0.16

* Values are the mean ± SD unless indicated otherwise. FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy Trial; IFX = infliximab; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; IQR = interquartile range; VAS = visual analog scale; DAS28 = Disease Activity Score using 28 joints; HAQ = Health Assessment Questionnaire.
† Modified Sharp/van der Heijde method.

tion (bDMARD initiation despite an ACR response >50%) and subsequent treatment with a TNF inhibitor, but the patient was included in the 10-year analysis. One patient from the original FIN-RACo + placebo group withdrew consent at the 24-month visit and was included in the 2-year analysis but not after that. A slightly greater number of patients were lost from the original FIN-RACo + IFX group than from the FIN-RACo + placebo group during the 10-year follow-up period, but the baseline data of the dropouts were comparable to data from those patients who continued in the trial (data not shown). The baseline demographics and the measures of disease activity, function, and extent of structural joint damage at baseline are shown in Table 1.

The proportions of patients in NEO-RACo and in DAS28 remissions between 2 and 10 years are shown in Figures 2A and 2B. At 2 years, more patients in the FIN-RACo + IFX group had reached the very strict NEO-RACo remission, but after that, the differences leveled out. In addition, even though at 10 years a slightly higher proportion of patients in the FIN-RACo + IFX group reached the NEO-RACo remission, the difference was not statistically significant. Regarding the DAS28 remission, most of the patients in both groups reached this target throughout the follow-up (Figure 2B). The proportions of patients reaching various HAQ scores at 10 years are shown in Figure 2C. The HAQ score of 0 was reached by 66% of patients in the FIN-RACo + IFX group, and by 61% of patients

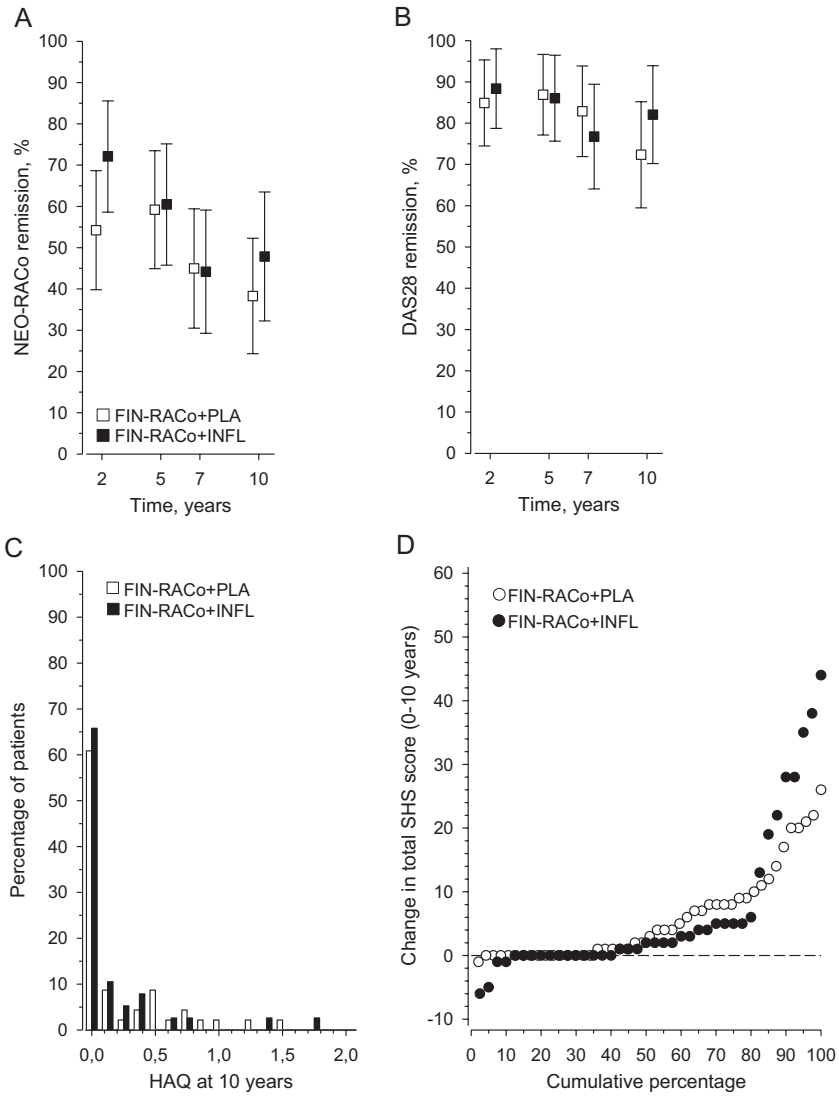

Figure 2. **A**, The proportions of patients in remission according to the TNF-Blocking Therapy in Combination With Disease-Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis study; **B**, The proportions of patients in remission according to the Disease Activity Score using 28 joints between 2–10 years; **C**, The proportions of patients reaching various Health Assessment Questionnaire scores at 10 years; and **D**, Probability plot of radiographic progression from baseline to 10 years in patients randomized to receive initial infliximab (the Finnish Rheumatoid Arthritis Combination Therapy Trial [FIN-RACo] + INFL) or placebo (FIN-RACo + PLA) for 6 months in addition to a combination of 3 conventional synthetic disease-modifying antirheumatic drugs and 7.5-mg prednisolone for 2 years. SHS = Sharp/van der Heijde.

Table 2. csDMARDs, bDMARDs, and prednisolone use at the 5–10-year check-up visits in both original treatment groups participating in the NEO-RACo trial and initially treated with an intensified FIN-RACo regimen for 2 years, then double-blind randomized to receive either infliximab (FIN-RACo + IFX) or placebo (FIN-RACo + placebo) infusions for 6 months*

	5 years		6 years		7 years		8 years		9 years		10 years	
Medications	+ IFX (n = 43)	+ Placebo (n = 47)	+ IFX (n = 43)	+ Placebo (n = 46)	+ IFX (n = 43)	+ Placebo (n = 46)	+ IFX (n = 41)	+ Placebo (n = 47)	+ IFX (n = 39)	+ Placebo (n = 47)	+ IFX (n = 39)	+ Placebo (n = 47)
No DMARD	1 (2.3)	0 (0.0)	2 (4.7)	0 (0.0)	2 (4.7)	2 (4.4)	3 (7.3)	3 (6.4)	1 (2.6)	4 (8.5)	5 (12.8)	4 (8.5)
Single csDMARD	1 (2.3)	1 (2.1)	1 (2.3)	3 (6.5)	3 (7.0)	7 (15.2)	4 (9.8)	7 (14.9)	6 (15.4)	8 (17.0)	6 (15.4)	9 (19.2)
Combination of csDMARDs	24 (55.8)	28 (59.6)	20 (46.5)	24 (52.2)	16 (37.2)	17 (37.0)	13 (31.7)	15 (31.9)	12 (30.8)	9 (19.2)	10 (25.6)	7 (14.9)
Prednisolone alone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (2.1)	1 (2.6)	0 (0.0)
Single or combination csDMARDs + prednisolone	17 (39.5)	13 (27.7)	17 (39.5)	14 (30.4)	17 (39.5)	16 (34.8)	13 (31.7)	15 (31.9)	11 (28.2)	15 (31.9)	10 (25.6)	18 (38.3)
Single or combination csDMARDs + bDMARD	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.2)	1 (2.3)	0 (0.0)	2 (4.9)	0 (0.0)	2 (5.1)	1 (2.1)	2 (5.1)	1 (2.1)
Prednisolone + bDMARD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (2.1)	1 (2.6)	1 (2.1)	1 (2.6)	2 (4.3)
Single or combination csDMARDs + prednisolone + bDMARD	0 (0.0)	4 (8.5)	3 (7.0)	4 (8.7)	4 (9.3)	3 (6.5)	6 (14.6)	6 (12.8)	5 (12.8)	8 (17.0)	4 (10.3)	6 (12.8)

* Values are the number (%). After the 2-year visit, if the patient was in strict remission, the medications could be tapered off, but reinstituted if remission was lost. No statistically significant differences between the groups in the frequencies of various treatment strategies at the check-up visits were found (Fisherman-Freeman-Halton test). csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDS = biologic DMARDS; NEO-RACo = TNF-Blocking Therapy in Combination With Disease-Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis; FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy Trial; IFX = infliximab.

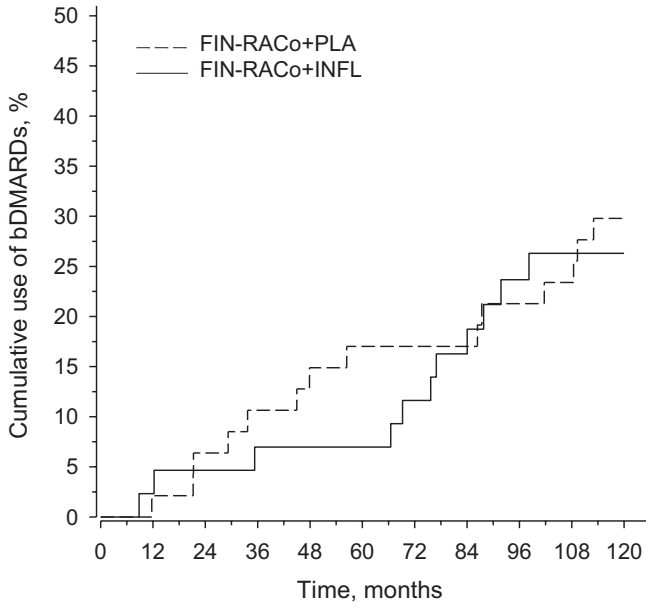

Figure 3. The cumulative use of biologic disease-modifying antirheumatic drugs (bDMARDs) in patients randomized to receive initial infliximab (the Finnish Rheumatoid Arthritis Combination Therapy Trial [FIN-RACo] + INFL) or placebo (FIN-RACo + PLA) for 6 months in addition to a combination of 3 conventional synthetic DMARDs and 7.5-mg prednisolone for 2 years and followed up for 10 years.

in the FIN-RACo + placebo group (P = 0.64). The mean ± SD HAQ score at 10 years was 0.17 ± 0.38 in the FIN-RACo + IFX group and 0.22 ± 0.37 in the FIN-RACo + placebo group (P = 0.59).

The details of radiographic damage scores at baseline are shown in Table 1 and the probability plot of radiographic progression is shown in Figure 2D. The radiographic joint damage progression remained slow in most of the patients up until 10 years, when the mean total SHS score was 9.8 in the FIN-RACo + IFX group and 7.3 in the FIN-RACo + placebo group (P = 0.34). The respective progression rates were 0.65 (95% confidence interval [95% CI] 0.31–1.1) and 0.58 (95% CI 0.39–0.79) units per year. Only 15% of all the patients had a total score higher than 20, and 20% had a total score of 0.

The DMARD and prednisolone treatments used by both patient groups after 5 years are shown in Table 2. There were no statistically significant differences between the groups in the treatment strategies throughout the follow-up. From 5 to 10 years, the use of combinations of csDMARDs was tapered down; the balance was shifted toward the use of single csDMARDs, and at 10 years, as many as 10.5% of the patients were using no DMARD. However, approximately one-third of the patients needed to use various combinations of csDMARDs with prednisolone throughout the follow-up. After 5 years, a total of 55.6% of the patients were at least sporadically using prednisolone. Among those patients using prednisolone for ≥1 period during the study, the mean ± SD daily dose of prednisolone during the study span was 1.8 ± 1.6 mg in the FIN-RACo + IFX group and 1.6 ± 1.4 mg in the FIN-RACo + placebo group (P = 0.65). After the 6-month blinded period, during the follow-up of 10 years, 26.3% (95% CI 15.5–42.5) of patients in the FIN-RACo + IFX group and 29.8% (95% CI 18.8–45.0) of patients in the FIN-RACo + placebo group had at some point been taking bDMARDs (P = 0.74) (Figure 3). After 6 months, the median (interquartile range) time using bDMARDs was 23 (2–63) months for patients in the FIN-RACo + placebo group and 11 (2–28) months for patients in the FIN-RACo + IFX group (P = 0.41). The number of bDMARDs used by the patients ranged between 1 and 3 in both groups; 1 bDMARD was sufficient for 50% of patients in the FIN-RACo + placebo group and for 58% of patients in the FIN-RACo + IFX group. At 10 years, 18.6% of all patients were currently using bDMARDs (Table 2).

Between 5 and 10 years, the occurrence of adverse events is shown in Table 3. There were 5 cases of malignancies (3 breast cancers, 1 metastatic adenomatous cancer, 1 unspecified malignancy) in the FIN-RACo + IFX group and none in the placebo group. Otherwise, the number of any adverse events, serious adverse events, or those adverse

Table 3. Adverse events (AEs) between 5 and 10 years in patients randomized to receive initial infliximab (FIN-RACo + IFX) or initial placebo infusions (FIN-RACo + placebo) for 6 months in addition to a combination of 3 csDMARDs and 7.5-mg prednisolone for 2 years*

AEs	FIN-RACo + IFX (n = 43)	FIN-RACo + placebo (n = 47)	*P*
Frequency of any AEs, no. (%)	34 (79)	29 (62)	0.073
Number of AEs/ patient	2.3 ± 1.8	2.2 ± 2.6	0.93
Frequency of moderate-serious AEs, no. (%)	28 (65)	26 (55)	0.34
No. of moderate-serious AEs/ patient	1.5 ± 1.6	1.4 ± 1.8	0.91
Malignancies, no. (%)	5 (12)	0 (0)	0.022
AEs leading to change of DMARD, no. (%)	19 (44)	15 (32)	0.23
No. of AEs leading to change of DMARD/patient	0.9 ± 1.2	0.6 ± 1.3	0.45
AEs related to DMARDs, no. (%)	18 (42)	20 (43)	0.95
No. of AEs related to DMARDs/ patient	0.8 ± 1.3	1.1 ± 1.8	0.42

* Values are the mean ± SD unless indicated otherwise. FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy Trial; IFX = infliximab; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.

events possibly related to the study medications did not differ between the groups.

DISCUSSION

This study shows that excellent clinical results achieved with early, remission-targeted treatment with a combination of csDMARDs and systemic (supplemented with intraarticular, if needed) glucocorticoid therapy in patients with recent-onset RA were sustained in most patients up until 10 years. At that time, approximately 40% of the patients had no RA symptoms, and 70% fulfilled the DAS28 criteria for remission, and the radiographic joint damage progression remained slow in the majority of patients. Furthermore, most of the patients preserved good functional capacity.

However, only 10% of the patients reached these goals without any DMARD at 10 years, and the majority needed active medications throughout the follow-up, with up to 25–30% of the patients in both groups requiring bDMARD treatment at some point in their disease course. This result is in accordance with real-life data (11) and agrees with the treatment protocol aiming at sustained remission. While the use of csDMARDs can be considered as self-evidently necessary, oral glucocorticoids raise contradictory opinions (12), and the use of bDMARDs is by no means straightforward and often confronts medical, social, and especially economic obstacles (13). Nevertheless, in different reports, approximately 50% of patients with established RA are currently treated with glucocorticoids, and depending on the patient population, 20–40% are treated with bDMARDs (14).

Earlier long-term studies have shown the course of RA with suboptimal treatment (15–17). As expected, the results of the current trial are far superior. To our knowledge, studies with an active, modern treat-to-target strategy and long follow-up times are sparse (5–7). The Dutch Behandel Strategieen (BeSt) trial compared 4 strategies guided by the DAS in 508 patients with early RA (7). In that trial, the mean HAQ score at 10 years was 0.57 and thus higher than in our study. Furthermore, 38% of the patients in the BeSt trial had dropped out from the 10-year follow-up, especially those with a higher baseline HAQ score. The remission rate evaluated by DAS (18) in the BeSt trial at 10 years was 53%, but the different definition of remission makes the comparison to our results difficult. In the BeSt trial, the drug-free remission was a treatment goal, unlike in our trial, and was reached by 14% of the patients participating at 10 years. Comparing the radiographic progression between these 2 trials is somewhat complicated, since more patients in the BeSt trial seem to have had erosive disease at baseline than in our trial. Furthermore, the duration of symptoms of the patients at entry in the BeSt trial was ≤2 years compared with ≤1 year in our study. Nevertheless, the total SHS score at 10 years was somewhat lower in the NEO-RACo patients than in the BeSt patients. Additionally, when comparing the probability plots showing the radiographic progression of each patient in these trials, the scale in the BeSt trial reaches up to 250 instead of 60 in our trial, and the highest outliers appear to have had considerably more progression than in the NEO-RACo trial. Comparison of medications used in these trials is basically impossible due to the heterogeneity of the strategies, and furthermore, approximately 20% of the patients in each group in the BeSt trial at 10 years were using medications outside the protocol. Still, the use of combination csDMARDs and low-dose prednisolone appeared to be more common in the NEO-RACo trial.

When comparing the NEO-RACo results to the long-term outcomes of the original FIN-RACo trial, the NEO-RACo remission rates in the current trial were surprisingly similar to the strict ACR remission rate in the original FIN-RACo combination therapy group at the 11-year visit (45–38% versus 38%, respectively). This result was despite the fact that only 11% of the FIN-RACo patients had been treated with bDMARDs (5). Comparing the radiographic joint damage progression between these 2 trials is complicated due to different methodologies (Larsen versus SHS score). However, evidently the more aggressive continuous treatment with higher doses of MTX and the earlier availability of bDMARDs in the NEO-RACo trial has led to less radiographic progression (mean 7.3–9.8 of a maximum of 448 with the SHS method) than noted in the FIN-RACo trial (mean 17 of a maximum 200 with the Larsen method) (6,19).

When comparing our results to real-life observational data, a Norwegian cross-sectional, observational study on RA patients with the disease duration of approximately 10 years showed that more recent cohorts had lower disease activity and better functional capacity than older ones (14). Nevertheless, compared to our patients, the percentage of patients in remission was lower, implying that the treatment in this real-life setting was not as efficient as in our trial, even though 26.0–34.9% of patients in all Norwegian year-cohorts had been taking bDMARDs.

Evidently, the main limitation of our study is the small size of the study population. The original population was calculated to have the power to demonstrate a 30% difference in the remission rates between the groups at 2 years. Smaller differences, therefore, may not be distinguished, especially at 10 years. Thus, this follow-up study functions best by showing the long-term evolution of this well-defined and actively treated population, regardless of the original randomization group, a strategy used even by larger randomized controlled trials with prolonged follow-ups. Another limitation of our study is that not all patients participated in all follow-up visits. However, the missing data were processed with the last observation carried forward method, and by the end of the trial only 13% of the patients were lost to follow-up, an excellent result considering the long follow-up period.

Even in the current treat-to-target era there appear to be different cultures of treating RA. One is based on the

fear of long-term overtreatment, having drug-free remissions as goals, even if those remissions turn out to be temporary, and then retreating the possible flares. The other strategy, employed also in this trial, tapers down the medications very conservatively and continues the csDMARD treatment even in patients in sustained remission if there are no adverse events. Further, a very strict sustained remission was required before any tapering of the DMARDs was allowed, making the feared overtreatment more likely, which would have made its potential harmful consequences visible in this trial. In spite of this possibility, there were no unexpected safety issues in all patients, and the rate of adverse events, especially serious adverse events, was not striking and was at least comparable to the data published from other long-term studies, mainly carried out on patients receiving biologic treatment (5,20,21). Nevertheless, there was a difference in the cancer incidence after 5 years between the groups. The incidences of lung cancer and lymphoma are known to be increased among RA patients, whereas for breast cancer there appears to be no increase in risk (22). Furthermore, there are several larger studies without signs of elevated risk of malignancies, even after or during long-term IFX treatment (23,24). Therefore, the finding of 5 malignancies in the NEO-RACo IFX group is somewhat unexpected, since the groups had received comparable treatments, including bDMARDs, after the initial double-blind randomized phase of IFX versus placebo infusions. Thus, the malignancies observed in our study population are unlikely to be related to the initial 6-month IFX treatment. Taken together, because the clinical outcomes remained very good, one could conclude that the earliest possible tapering of at least csDMARDs need not be a self-evident goal in treatment of RA.

Ample evidence has thus far shown that RA, as we diagnose it today, is an active and progressive disease requiring continuous and very often lifelong treatment. The current concept of a window of opportunity for early treatment allows us to start the medications before any structural joint damage has appeared. In a real-world setting, the prolonged combination csDMARD therapy has proven to be a cost-effective strategy to maintain remission in many patients (25). Our trial confirms the long-term efficacy of such a strategy in a well-defined follow-up.

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 submitted for publication. Dr. Rantalaiho 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.

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