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Early Targeted Combination Treatment with csDMARDs Sustains Excellent Long-term Outcomes in Rheumatoid Arthritis.

The 10-year Follow-up Results of a Randomized Clinical Trial, the NEO-RACo Trial.

Running head: NEO-RACo 10-year outcomes

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Abstract

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 (PRD) and additional infliximab or placebo infusions.

Methods: Ninety-nine patients with early, DMARD-naïve RA were treated with a triple combination of csDMARDs and PRD, and randomized to double-blindly receive either infliximab (FIN-RACo+INFL) or placebo (FIN-RACo+PLA) infusions during the first 6 months. After 2 years, the treatment strategies became unrestricted, but the treatment goal was strict NEO-RACo remission. At 10 years, the clinical and radiographic outcomes and the drug treatments used between 5-10 years were assessed.

Results: Ninety patients (91%) were followed after 2 years, 43 in the FIN-RACo+INFL and 47 in the FIN-RACo+PLA group. At 10 years, the respective proportions of patients in strict NEO-RACo and in DAS28 remissions in the FIN-RACo+INFL and FIN-RACo+PLA groups were 46% and 38% (p=0.46), and 82% and 72% (p=0.29). The mean total Sharp van der Heijde score was 9.8 in the FIN-RACo+INFL and 7.3 in the FIN-RACo+PLA group (p=0.34). During the 10-year follow-up 26% of the FIN-RACo+INFL group and 30% of the FIN-RACo+PLA group patients had received biologics (p=0.74).

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

Significance and Innovations

- In a 10-year follow-up, majority of RA 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 csDMARDs and low dose glucocorticoids.
- To maintain remission, one third of the patients needs continued combination csDMARD and low dose glucocorticoid treatment, one third needs escalation to biologic DMARDs; in one third 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, as 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 emerge, during which the initiation of disease-modifying antirheumatic-drugs (DMARD) treatment results in increased rate of remissions (3), but for how long this early effect lasts, is of interest. Further, as 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 reached remission category may vary correspondingly (4).

There are few trials using the modern treat to target (T2T) approach with truly long-term follow-ups (at least 10 years), or comprehensive follow-up coverage (5-7). Our previous analyses of the NEO-RACo study have shown that in early RA, an intensified initial Finnish Rheumatoid Arthritis combination treatment strategy (FIN-RACo) with methotrexate (MTX), sulfasalazine (SASP), hydroxychloroquine (HCQ) and low dose (7.5 mg) prednisolone (PRD) for 2 years, and free, active, remission-targeted DMARD treatment thereafter, resulted in very low disease activity in most patients at 2 and at 5 years, and minimal to no radiographic joint damage progression in most patients, regardless of the double-blindly given induction therapy with infliximab (INFL) or placebo (PLA) for the first 6 months (8,9). In the present 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, which recruited 99 patients with early, active RA fulfilling the ACR 1987 criteria (10). The patients were treated with an intensified FIN-RACo regimen for two years, as previously described, and, in addition, double blindly randomized to receive either INFL or PLA infusions at weeks 4, 6, 10, 18 and 26 (8). An active use of intra-articular glucocorticoid (GC) 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 (vide infra), PRD was gradually tapered off, followed by gradual reduction of csDMARDs, too. If remission was lost, the previous DMARD treatment/dosage was restored (9). If,

after dose and drug adjustments, the patient was a non-responder (<ACR50% at maximal combination after individual substitutions) at 2 consecutive visits, the evaluation starting after week 26, the patient was regarded as a treatment failure, and the therapy was open, including the possibility to use anti-TNF blocking agents (9).

After 5 years, the study visits took place by protocol once a year, but clinical visits as often as needed. At all time points, the treatment was targeted to a strict NEO-RACo remission, defined as the presence of 5 out of the 6 following criteria: (1) morning stiffness < 15 min, (2) no fatigue, (3) no joint pain, (4) no tender joints (68 joint count), (5) no swelling in joints (66 joint count) or tendons, and (6) the erythrocyte sedimentation rate (ESR) < 30 mm/h in women and < 20 mm/h in men. The therapies could be modified according to the judgement of the treating rheumatologist, with the use of all available conventional synthetic (cs) and biological (b) DMARDs, and GCs orally as well as intra-articularly.

Outcomes and follow-up

The clinical assessments included the evaluation of the number of swollen and tender joints (out of 66/68 joints), patient's assessment of pain (10 cm visual analogue 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 [CRP], ESR). The DAS according to the state of 28 joints was calculated. The medications used, the intra-articular GC 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), aware of the chronology of the radiographs, according to the modified Sharp/van der Heijde method (SHS). 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 (AEs).

Statistical methods

Statistical comparisons between the groups were made by using t test, bootstrap type t test, Mann-Whitney test, $\chi 2$ test or Fisher-Freeman-Halton test. The longitudinal remission data was analysed with generalised estimating equations models with unstructured correlation structure (binomial distribution with a log link). The bootstrap method (5000 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). Kaplan-Meier method was used to estimate the cumulative use of bDMARDs and compared between groups with the Versatile weighted log-rank test. Clinical outcome variables were analysed by the intention-to-treat principle with the last observation carried forward (LOCF). All analyses were performed using STATA 14.1 (StataCorp LP, College Station, TX).

Results

The flow chart of the patients is presented in Figure 1. One patient in the original FIN-RACo +PLA group had been excluded from the 2- and the 5-year analyses due to a protocol violation (bDMARD initiation despite the ACR response > 50%) and subsequent treatment with a TNF-inhibitor, but was included in the 10-year analysis. One patient from the original FIN-RACo+PLA group withdrew

consent at the 24-month visit and was included in the 2-year analysis, but not after that. Somewhat more patients were lost from the original FIN-RACo+INFL group than from the FIN-RACo+PLA group during the 10-year follow-up period, but the baseline data of the drop-outs were comparable to those who continued in the trial (data not shown). The baseline demographics, 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 2–10 years are presented in figure 2A and 2B. At 2 years, more patients in the FIN-RACo+INFL group had reached the very strict NEO-RACo remission, but after that, the differences leveled out. In addition, even though at ten years a slightly higher proportion of patients in the FIN-RACo+INFL 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 the FIN-RACo+INFL group patients, and by 61% of the FIN-RACo+PLA group patients (p=0.64). The mean (SD) HAQ score at 10 years was 0.17 (0.38) in the FIN-RACo+INFL group patients and 0.22 (0.37) in the FIN-RACo+PLA group patients (p=0.59).

The details of radiographic damage scores at baseline are presented 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 till 10 years, where the mean (SD) total SHS was 9.8 in the FIN-RACo+INFL and 7.3 in the FIN-RACo+PLA group (p=0.34). The respective progression rates were 0.65 (95% CI: 0.31 to 1.1) and 0.58 (95% CI: 0.39 to 0.79) units per year. Only 15% of all the patients had the total score higher than 20, and 20% had the total score of 0.

The DMARD and PRD treatments used by both patient groups after 5 years are described 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 were tapered down; the balance was shifted towards 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 PRD throughout the follow-up. After 5 years, altogether 55.6% of the patients were at least sporadically using PRD. Amongst those using PRD at least for one or several periods during the study, the mean (SD) daily dose of PRD during the study span was 1.8 (1.6) mg in the FIN-RACo+INFL group and 1.6 (1.4) mg in the FIN-RACo+PLA group (p=0.65). After the 6 months' blinded period, by 10 years, 26.3% (CI 15.5 to 42.5) of the FIN-RACo+INFL group patients and 29.8% (CI 18.8 to 45.0) of the FIN-RACo+PLA group patients had at some point been on bDMARDs (p=0.74) (Figure 3). After 6 months, the median (IQR) time on bDMARDs was 23 (2 to 63) months in the FIN-RACo+PLA group patients and 11 (2 to 28) months in the FIN-RACo+INFL group patients having used bDMARDs (p=0.41). The number of bDMARDs used by the patients ranged between 1-3 in both groups, one bDMARD was sufficient for 50% of the FIN-RACo+PLA group patients and 58% of the FIN-RACo+INFL group patients on bDMARDs. 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 presented in Table 3. There were five cases of malignancies (three breast cancers, one metastatic adenomatous cancer, one unspecified malignancy) in the FIN-RACo+INFL group and none in the placebo group. Otherwise, the number of any adverse effects, serious adverse events, or those 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 intra-articular, if needed) GC therapy in patients with recent-onset RA can be sustained in most patients up till 10 years. At that time, approximately 40% of the patients have no RA symptoms, and 70% fulfill the DAS28 criterion

for remission, and the radiographic joint damage progression remains slow in the majority of patients. Further, most of the patients had 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 having required bDMARD treatment at some point of their disease course. This is in accordance with the real life data (11), and agrees with the treatment protocol aiming at sustained remission. While the use of csDMARDs can be considered self-evident, oral GCs raise contradictory opinions (12), and the use of bDMARDs is by no means straightforward, but confront often medical, social and especially economical obstacles (13). Yet, in different reports, approximately 50% of patients with established RA are currently treated with GCs, and depending on the patient population, 20-40% with bDMARDs (14).

Earlier long-term studies have shown the course of RA with suboptimal treatment (15, 16, 17). As expected, the results of the current trial are far superior. To our knowledge, studies with active, modern T2T strategy and long follow-up times are sparse (5-7). The BeSt Trial compared four DAS-steered strategies in 508 patients with early RA (7). In that trial, the mean HAQ at 10 years was 0.57, thus higher than in our study. Further, 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 two 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. Also, 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 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, further, 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 PRD in appeared to be more common in the NEO-RACo trial.

When comparing the 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% vs. 38%, respectively), despite that only 11% of the FIN-RACo patients had been treated with bDMARDs (5). Comparing the radiographic joint damage progression between these two trials is complicated due to different methodologies (Larsen vs. SHS). 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 lesser radiographic progression here (mean 7.3-9.8 out of max 448 with the SHS method) than noted in the FIN-RACo trial (mean 17 out of max 200 with the Larsen method) (6, 19).

When comparing our results to real life observational data, a Norwegian cross-sectional, observational study on real life 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). Still, 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 on bDMARDs.

Evidently, the main limitation of our study is the small study population size. The original population was calculated to have the power to demonstrate a 30% difference in the remission rates between the groups at 2 years. Therefore, it is clear that smaller differences may not be distinguished,

especially at 10 years. Thus, this follow-up study functions best by describing the long-term evolution of this well-defined and actively treated population, regardless of the original randomization group, a strategy used even by larger RCTs with prolonged follow-ups. Another limitation of our study is that not all patients participated in all follow-up visits. However, the missing data was 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 T2T era there appears 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 they 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 rather 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 liable, which would have made its potential harmful consequences visible in this trial. Yet there were no unexpected safety issues in all patients, and the rate of adverse events, and especially serious adverse events, was not striking and 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. It is known that the incidences of lung cancer and lymphoma are increased among RA patients, whereas for breast cancer there appears to be no increase in risk (22). Furthermore, there are several larger studies without no signs of elevated risk of malignancies even after/during long-term infliximab treatment (23, 24). Therefore, the finding of five malignancies in the NEO-RACo-INFL group is somewhat unexpected since the groups had received comparable treatments, including bDMARDs, after the initial double-blind randomized phase of infliximab vs. placebo infusions. Thus, it is unlikely that the malignancies observed in our study population are related to the initial 6-month infliximab

treatment. Taken together, since the clinical outcomes remained very good, one could conclude that the earliest possible tapering of at least csDMARDs needs not to be a self-evident goal in 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 window of opportunity of 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 strategy in a well-defined follow-up material.

References

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.

2. Rannio T, Asikainen J, Kokko A, Hannonen P, Sokka T. Early Remission Is a Realistic Target in a Majority of Patients with DMARD-naive Rheumatoid Arthritis. J Rheumatol 2016;43:699-706.

3. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis 2014;73:861-70.

4. Mäkinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. Clin Exp Rheumatol 2006;24(6 Suppl 43):S-22-8.

5. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Järvenpää S, Leirisalo-Repo M, et al. 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.

6. Rantalaiho V, Korpela M, Laasonen L, Kautiainen H, Järvenpää S, Hannonen P, et al. 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.

7. Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YP, van Groenendael JH, Han KH, Molenaar TH, Le Cessie S, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. Ann Intern Med 2016;164:523-31.

8. Leirisalo-Repo M, Kautiainen H, Laasonen L, Korpela M, Kauppi MJ, Kaipiainen-Seppänen O, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013;72:851-7.

9. Rantalaiho V, Kautiainen H, Korpela M, Hannonen P, Kaipiainen-Seppänen O, Möttönen T, et al. Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomised clinical trial, the NEO-RACo trial. Ann Rheum Dis 2014;73:1954-61.

10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.

11. Schmajuk G, Solomon DH, Yazdany J. Patterns of disease-modifying antirheumatic drug use in rheumatoid arthritis patients after 2002: a systematic review. Arthritis Care Res (Hoboken) 2013;65:1927-35.

12. Buttgereit F, Bijlsma JWJ, Strehl C. Will we ever have better glucocorticoids?. Clin Immunol 2018;186:64-6.

13. Yelin E, Tonner C, Kim SC, Katz JN, Ayanian JZ, Brookhart MA, et al. Sociodemographic, disease, health system, and contextual factors affecting the initiation of biologic agents in rheumatoid arthritis: a longitudinal study. Arthritis Care Res 2014;66:980-9.

14. Haugeberg G, Hansen IJ, Soldal DM, Sokka T. Ten years of change in clinical disease status and treatment in rheumatoid arthritis: results based on standardized monitoring of patients in an ordinary outpatient clinic in southern Norway. Arthritis Res Ther 2015;17:219.

15. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611-6.

16. Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2008;10:R106.

17. Svensson B, Andersson MLE, Forslind K, Ajeganova S, Hafström I, et al. Persistently active disease is common in patients with rheumatoid arthritis, particularly in women: a long-term inception cohort study. Scand J Rheumatol 2016;45:448-55.

18. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.

19. Levitsky A, Wick MC, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, et al. Early treatment intensification induces favourable radiographic outcomes according to predicted versus observed radiographic progression in early rheumatoid arthritis: a subanalysis of the randomised FIN-RACo and NEO-RACo trials. Clin Exp Rheumatol 2016;34:1065-71.

20. Keystone EC, Breedveld FC, van der Heijde D, Landewe R, Florentinus S, Arulmani U, et al. Longterm effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. J Rheumatol 2014;41:5-14.

21. Furst DE, Kavanaugh A, Florentinus S, Kupper H, Karunaratne M, Birbara CA. Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy. Rheumatology 2015;54:2188-97.

22. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther 2015;17:9.

23. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA 2012;308:898-908.

24. Wadström H, Frisell T, Askling J, for the Anti-Rheumatic Therapy in Sweden (ARTIS) Study, Group. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: A nationwide cohort study from sweden. JAMA Intern Med 2017;177:1605-12.

25. Sokka T, Haugeberg G, Asikainen J, Widding Hansen IJ, Kokko A, Rannio T, et al. Similar clinical outcomes in rheumatoid arthritis with more versus less expensive treatment strategies. Observational data from two rheumatology clinics. Clin Exp Rheumatol 2013;31:409-14.

Tables

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

Characteristic	**The initial randomization group**		
	FIN-RACo+INFL N=43	**FIN-RACo+PLA** N=47	**P value**
Demographic data at baseline			
Female, n (%)	30 (70)	29 (62)	0.42
Age (years), mean (SD) years	48 (9)	47 (11)	0.32
Duration of symptoms (months), median (IQR)	4 (2 , 6)	4 (2 , 6)	0.99
Rheumatoid factor present, n (%)	33 (77)	34 (72)	0.63
Measures of disease activity at baseline			
Number of swollen joints (0-66), mean (SD)	15 (5)	16 (8)	0.38
Number of tender joints (0-68), mean (SD)	19 (10)	21 (11)	0.22
Erythrocyte sedimentation rate (mm/h), mean (SD)	34 (22)	33 (22)	0.93
Patient's global assessment (VAS, mm), mean (SD)	51 (24)	48 (27)	0.52
Pain (VAS, mm), mean (SD)	55 (27)	53 (27)	0.65
Physician's global assessment (VAS, mm), mean (SD)	49 (22)	55 (20)	0.17
DAS28, mean (SD)	5.54 (1.00)	5.60 (1.39)	0.81
Physical function (HAQ), mean (SD)	1.09 (0.61)	0.91 (0.71)	0.22
Radiography at baseline			
Erosion score, mean (SD) *	2.6 (7.2)	1.3 (2.9)	0.30
Narrowing score, mean (SD) *	0.5 (1.6)	0.3 (0.6)	0.42
Total score, mean (SD) *	3.1 (8.4)	1.6 (3.2)	0.29
Erosions in hand or foot radiographs, n (%)	20 (47)	15 (32)	0.16

*SHS, modified Sharp/van der Heijde method

Table 2

Conventional synthetic (cs) and biological (b) disease-modifying antirheumatig-drug (DMARD) and prednisolone (PRD) 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 two years, and, in addition, double blindly randomized to receive either infliximab (FIN-RACo+INFL) or placebo (FIN-RACo+PLA) infusions for 6 months. 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).

Medications	**5 years**		**6years**		**7 years**		**8 years**		**9 years**		**10 years**	
	FIN-RACo +INFL n=43	FIN-RACo +PLA n=47	FIN-RACo +INFL n=43	FIN-RACo +PLA n=46	FIN-RACo +INFL n=43	FIN-RACo +PLA n=46	FIN-RACo +INFL n=41	FIN-RACo +PLA n=47	FIN-RACo +INFL n=39	FIN-RACo +PLA n=47	FIN-RACo +INFL n=39	FIN-RACo +PLA 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%)
PRD 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 + PRD	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%)
PRD + 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 + PRD+ 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%)

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

	FIN-RACo+INFL N=43	**FIN-RACo+PLA** N=47	**P-value**
The frequency of any AEs, n (%)	34 (79)	29 (62)	0.073
Number of AEs/patient, mean (SD)	2.3 (1.8)	2.2 (2.6)	0.93
The frequency of moderate-serious AEs, n (%)	28 (65)	26 (55)	0.34
Number of moderate-serious AEs/patient, mean (SD)	1.5 (1.6)	1.4 (1.8)	0.91
Malignancies, n (%)	5 (12)	0 (0)	0.022
AEs leading to change of DMARDs, n (%)	19 (44)	15 (32)	0.23
Number of AEs leading to change of DMARDs/patient, mean (SD)	0.9 (1.2)	0.6 (1.3)	0.45
AEs related to DMARDs, n (%)	18 (42)	20 (43)	0.95
Number of AEs related to DMARDs/patient (SD)	0.8 (1.3)	1.1 (1.8)	0.42

Figure legends

Figure 1.

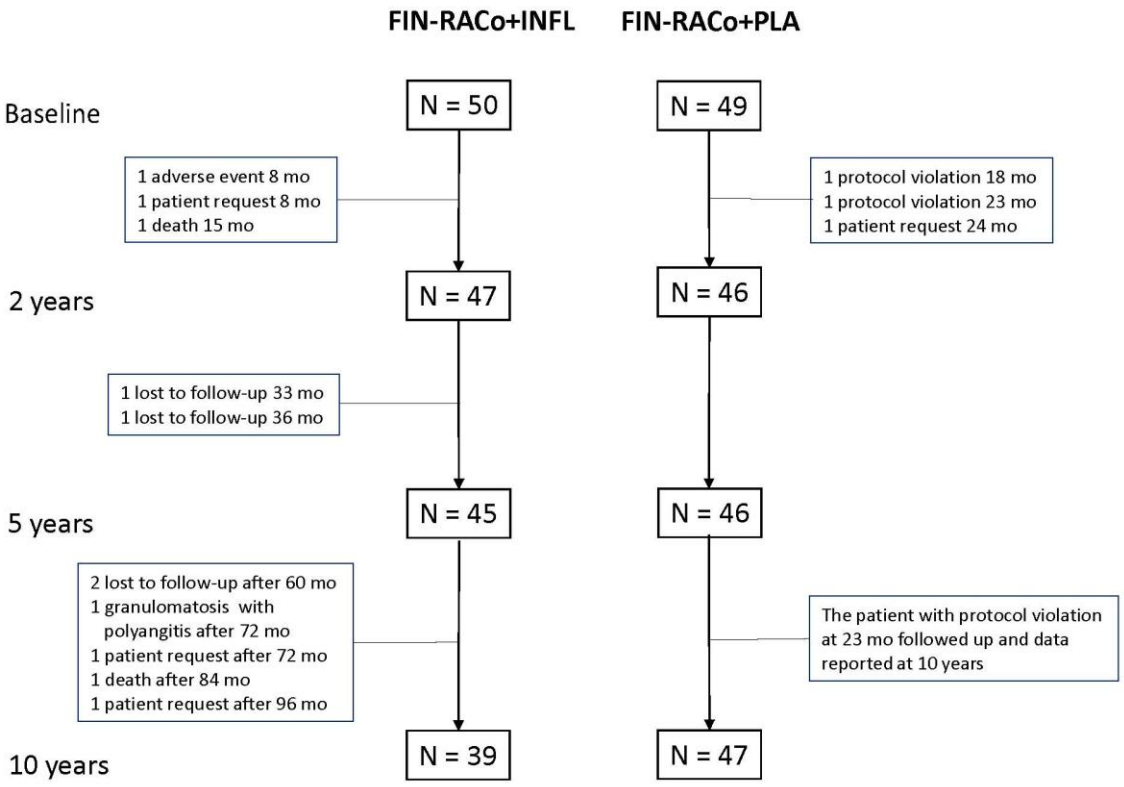
Flow-chart of the patients randomized to receive initial infliximab (FIN-RACo+INFL) or initial placebo infusions (FIN-RACo+PLA) for 6 months in addition to a combination of three csDMARDs and 7.5mg prednisolone for 2 years and followed up for 10 years. Thus, after the 5-year visit, data was available for 43 patients in the FIN-RACo+INFL group, of which 4 dropped out by 10 years, and for 47 patients in the FIN-RACo+PLA group, all of which continued throughout the follow-up.

Figure 2.

The proportions of patients in NEO-RACo remission (2A), and in DAS28 remission (2B) between 2–10 years, the proportions of patients reaching various HAQ scores at 10 years (2C), and the probability plot of radiographic progression from baseline to 10 years (2D) in patients randomized to receive initial infliximab (FIN-RACo+INFL) or initial placebo infusions (FIN-RACo+PLA) for 6 months in addition to a combination of three csDMARDs and 7.5mg prednisolone for 2 years.

Figure 3.

The cumulative use of bDMARDs in patients randomized to receive initial infliximab (FIN-RACo+INFL) or initial placebo infusions (FIN-RACo+PLA) for 6 months in addition to a combination of three csDMARDs and 7.5mg prednisolone for 2 years and followed up for 10 years.



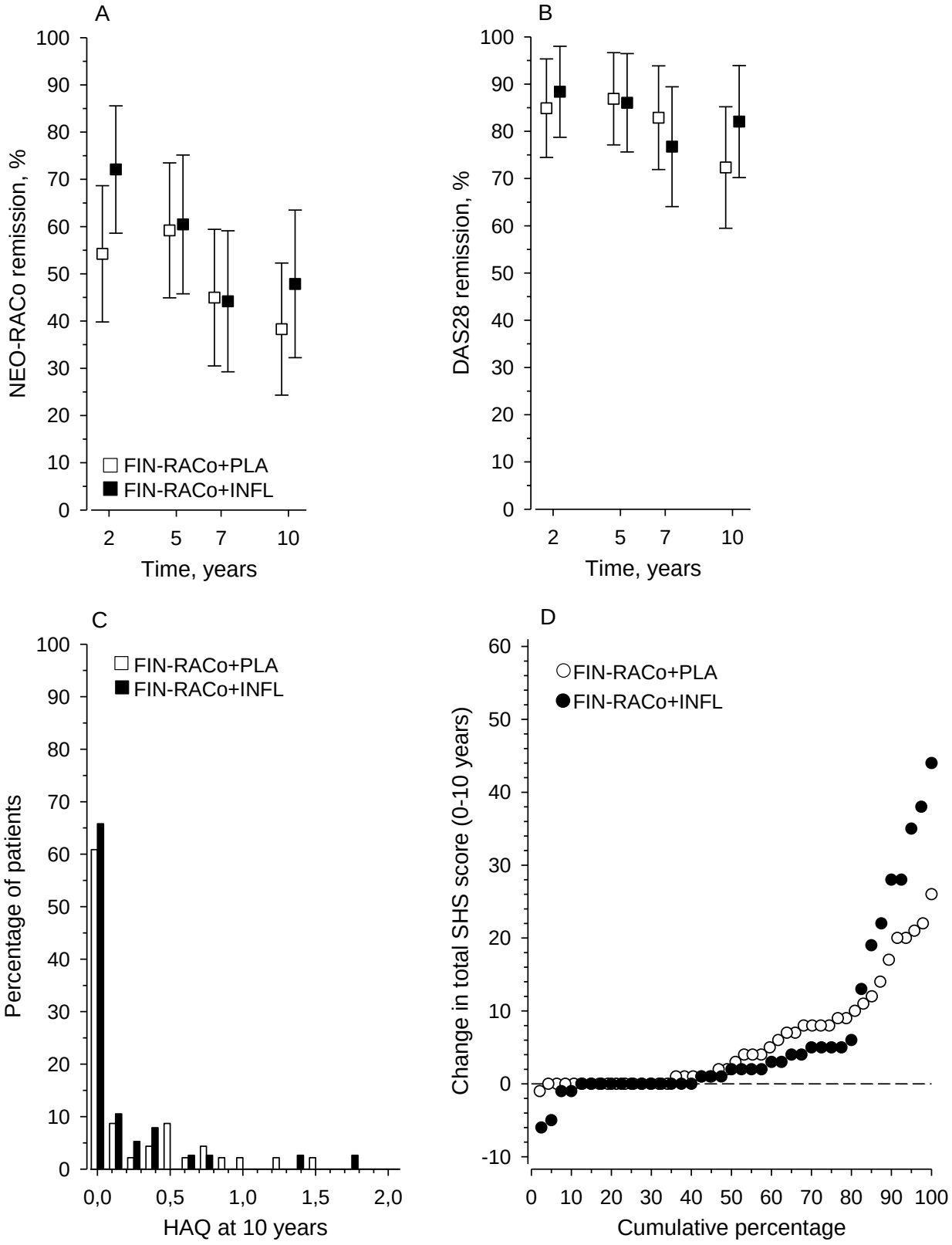


Figure 2

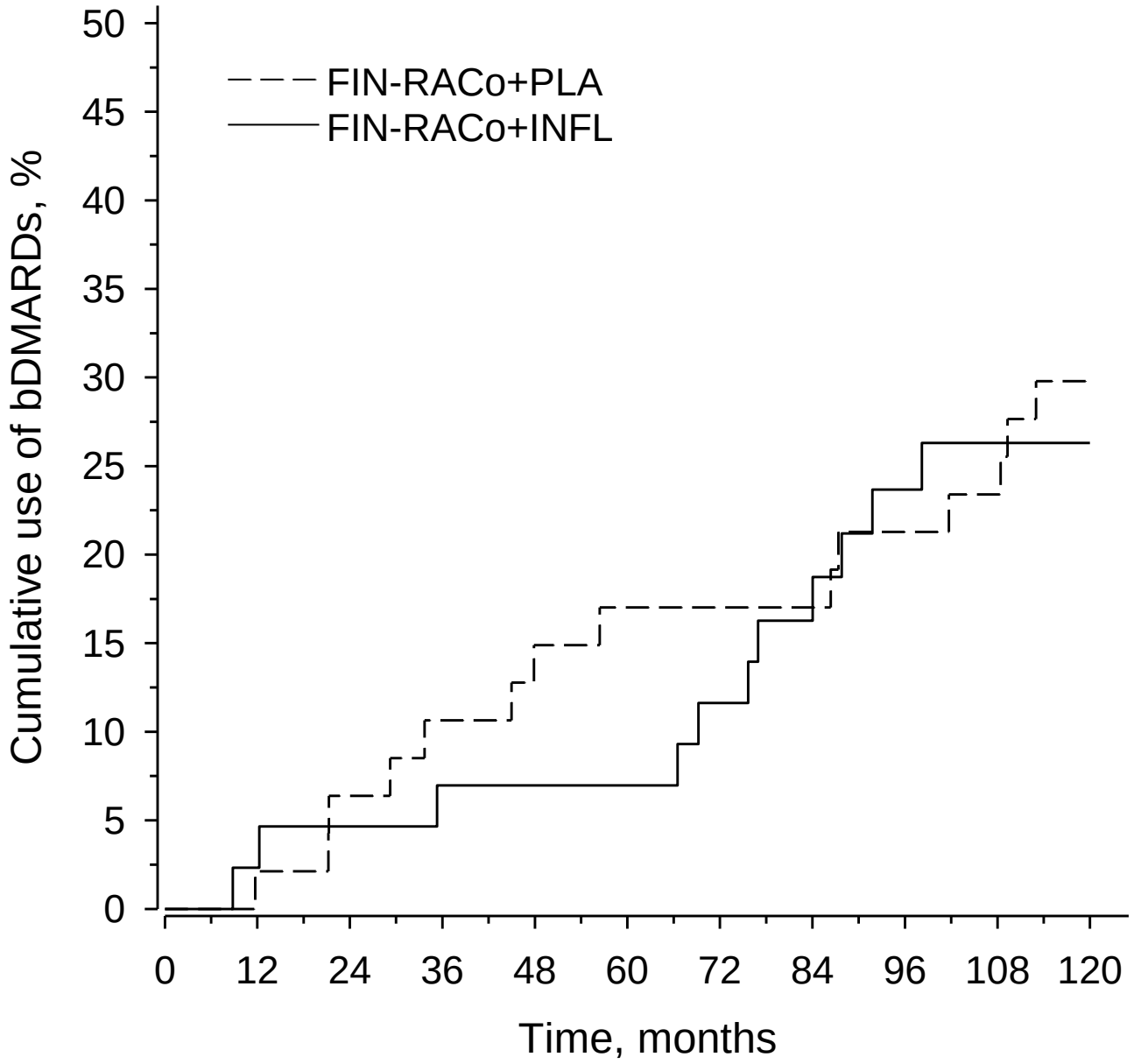


Figure 3