Long-term results of the FIN-RACo trial; treatment with a combination of traditional disease-modifying anti-rheumatic drugs is an excellent option in early rheumatoid arthritis

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ABSTRACT

The Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo) started in 1993, in an era of disappointing results in the treatment of rheumatoid arthritis (RA). The FIN-RACo was the first trial aiming at remission and comparing two different treatment strategies: initially triple therapy with compulsory prednisolone (FIN-RACo strategy), or monotherapy with optional prednisolone (SINGLE strategy). The results at 2, 5 and at 11 years are in favour of the initial FIN-RACo strategy without an increase in adversities. Nevertheless, with targeted treatment, even the SINGLE strategy group patients show low disease activity and moderate radiographic progression.

Most leading Finnish rheumatologists participated in the FIN-RACo trial and have become convinced of the excellent results, good safety, and feasible administration of the FIN-RACo strategy. They have thus adopted it in real life and tutored the next generation to do the same. This has undoubtedly affected the Finnish approach to treating early RA; the Finnish Current Care Guideline recommends the FIN-RACo combination as the first treatment choice in early, active RA. As a consequence, the use of biologics in early RA is less frequent in Finland compared to many countries. Simultaneously, however, at least one hard outcome of RA, work disability, has decreased.

Why and how the FIN-RACo trial was started?

Since the early 1950s the drug treatment strategy of rheumatoid arthritis (RA) in Finland has been to start a disease-modifying anti-rheumatic drug (DMARD) (either aurothiomalate or an antimalarial) early, before the development of erosions (1). From the early 1980s sulfasalazine (SASP), and later methotrexate (MTX) were added to the drug armamentarium. Additionally, low dose systemic and intra-articular glucocorticoids (GC) were applied to switch off inflammation. Nevertheless, the results of this "saw-tooth" strategy with single DMARDs remained disappointing; remissions were rare, and the rheumatologists frustrated in daily practice.

The paper by Wilske and Healy in 1989 (2) inspired a group of Finnish rheumatologists to design a study comparing the "saw-tooth" DMARD therapy to a therapy with three simultaneously administered DMARDs in early and active RA. The combination of MTX, SASP, hydroxychloroquine (HCQ) and low dose prednisolone (PRD) was considered feasible, although at that time nothing was known of the effectiveness or tolerability of the combination. Nevertheless, the primary endpoint of all study patients was designated aggressively to be nothing less than clinical remission.

The protocol was presented and discussed with Finnish rheumatologists during national meetings, and 18 rheumatology clinics agreed to participate in the investigator-initiated Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) Trial.

Main principles of the FIN-RACo trial protocol

To aim for the most favourable outcome for the patients, clinical remission (no signs of inflammation) was defined as the primary outcome for the first time in any RA clinical trial. (Most trials to this day do not specify remission as a primary outcome). Further, we wanted the treatment protocol to be practical with flexible dose adjustments, guided by the clinical response.

As an intimate part of the Finnish rheumatology clinical practise, liberal use of intra-articular GCs was allowed. Thus, in the 1990s, the FIN-RACo trial was designed to compare two different treatment strategies, both of which were using tight control and targeting remission. As, at that time, the safety of such strategies was unknown, to avoid excessive dropouts, the study approach was not a double-blind one.

FIN-RACo: patients and methods

Between April 1993 and May 1995, 199 DMARD-naïve patients with a recent onset RA were enrolled. The patients fulfilled the ACR 1987 revised criteria for RA (3), were aged 18–65 years, had less than 2 years' symptom duration, and had an active disease (4). The patients were randomised to receive either FIN-RACo or SINGLE strategy.

The FIN-RACo strategy included an initial combination of three DMARDs started with MTX 7.5 mg/week, SASP 500 mg twice daily, HCQ 300 mg/day, and PRD 5 mg/day. It was obligatory to adjust the drug doses to achieve remission, but the highest doses allowed were 15 mg/week for MTX, 2 gm/day for SASP, and 10 mg/day for PRD. If any of these drugs had to be discontinued, it was replaced by another DMARD so that a combination of three DMARDs was used at all times. The SINGLE, "saw-tooth", strategy was initiated by using SASP (2 g/day) as the first drug for all patients. The dose could be increased to 3 g/day, and the simultaneous use of PRD up to 10 mg/day was allowed. If the clinical response was insufficient or if an adverse event occurred, SASP was replaced with MTX, and if needed, further with another single DMARD (4).

After 2 years, the use of DMARDs became unrestricted. However, in both groups the treatment remained to aim at maintaining or achieve remission. Therefore, regardless of the original randomisation group, patients with an insufficient response could be treated liberally with increased doses of DMARDs and with DMARD combinations. Once available to market, biologic agents could be used. On the other hand, for patients in long-term remission, the drug doses were tapered off, beginning with PRD. (For furher details see Korpela *et al*. 2004 (5)).

In addition to remission, other outcome measures of the FIN-RACo study included function (HAQ), ACR treatment responses (ACR20, ACR50, ACR70), modified minimal disease activity (MDA), radiographic damage in hands and feet (6), selected large joints and cervical spine, working ability, need for joint replacement, serious adverse events, and mortality. During the first 2 years, study visits occurred every 1-3 months, between 2–5 years at least every 6 months and after that at least once a year. The main prospective results are analysed and reported concerning the two, five and 11 year's follow-up data (4, 5, 7-11).

Main results at 2 and at 5 years

After 2 years (195 patients), strict ACR remission and ACR50 treatment responses were more common in the FIN-RACo than in the SINGLE groups (37% *vs*. 18%, p=0.003; 71% *vs*. 58%, p=0.058, respectively). FIN-RACo strategy was the only significant variable predicting remission at two years (4). A delay of a few months from the symptoms of RA to the institution of therapy decreased the ability of the SINGLE strategy to induce remission (12). At two years, DAS28 remission (<2.6) was observed in 68% and 41% and it was sustained in 51% and 16% of the patients in the FIN-RACO and SINGLE groups, respectively (13).

At two years, radiographic progression was slower in the FIN-RACo than the SINGLE group patients (4). Evidently, sustained remission protected against radiographic joint damage (13).

At 5 years (160 patients), the difference in the ACR remissions rates between the FIN-RACo and SINGLE groups was not significant (28% *vs*. 22%), but the mean time-weighted DAS28 area under curve (AUC) from baseline up to five years was significantly lower in the FIN-RACo than in the SINGLE group (5). RA patients in the FIN-RACo group had less radiographic damage at 2 and 5 years radiographs than those in the SINGLE group. The Larsen score at five years was predicted by the SINGLE strategy (5), as well as by the presence of rheumatoid factor, and ESR at baseline, a finding in accordance with others (14). ACPA (anti-citrullinated peptide antibodies) positivity was significantly related to radiographic progression even in patients initially treated with the FIN-RACo strategy, whereas ACPA negativity and FIN-RACo treatment were related to slow radiographic progression (15). Less cervical atlantoaxial subluxations were observed in RA patients in the FIN-RACo than in the SINGLE group at two (16) and at five years (17).

The FIN-RACo was the first trial to show that effective treatment of RA really matters in the maintenance of work ability. The FIN-RACo patients experienced less work disability days (sick leave and RA-related disability pension periods altogether) throughout the first 5 years than those in SINGLE group (8). The 6-month treatment response was crucial for the later work ability. Regardless of the treatment strategy, none of the patients achieving remission at 6 months became work disabled during 5 years (7). Of the patients divided in groups according to 6-month ACR response (ACR50, ACR20 or less than ACR20), 23%, 21%, and 56%, respectively, became permanently work disabled by 5 years (Fig. 1). This result translated in respective extensive differences in indirect cost of RA (9).

Results at 11 years

At 11 years (138 patients) the indices of clinical disease activity were low in both treatment groups (Table I) (10). Further, the function of most patients remained excellent; at 11 years 56% of the patients of the FIN-RACo group and 43% of the SINGLE group had a HAQ score of 0, and HAQ scores >1 were present in only 10% and 9% of the patients, respectively. Still, more patients met the strict ACR remission criteria in the FIN-RACo than in the SINGLE group (Table I).

The radiographic progression in small joints was moderate in both groups (Table I) (11), approximately half of that of some historical cohorts (18-20). Only RF-positivity and SINGLE strategy predicted the progression of joint

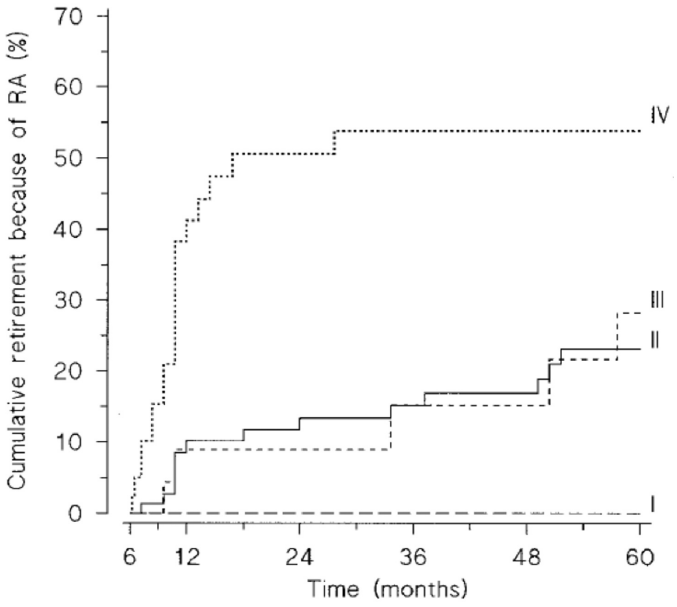

Fig. 1. Age, sex, job type, and education level adjusted risk for RA-related permanent disability pension, by response group at 6 months: group I = clinical remission; group II = ACR50 response but no remission; group III = ACR20 but not ACR 50 response; group IV = less than ACR20 response. Adapted from ref (7) with permission from John Wiley and Sons.

Table I. Measures of disease activity and damage at the 11-year visit, as well as treatments after 2 years in the patients participating in the FIN-RACo study.

	Randomisation group for the 2 initial years		*p*-value
	FIN-RACo (n=68)	SINGLE (n=70)	
Erythrocyte sedimentation rate (mm/h), median (IQR)	10 (6–21)	13 (6–20)	NS
Number of swollen joints, median (IQR)	0 (0–3)	2 (0–4)	NS
Number of tender joints, median (IQR)	1 (0–5)	2 (0–5)	NS
Patient's global assessment (VAS, mm), median (IQR)	16 (3–35)	19 (5–36)	NS
Pain (VAS, mm), median (IQR)	15 (3–30)	16 (5–34)	NS
Physician's global assessment (VAS, mm), median (IQR)	5 (1–14)	12 (3–19)	0.016
DAS28, mean (SD)	2.48 ± 1.22	2.73 ± 1.23	NS
Physical function (HAQ, range 0-3), mean ± SD	0.34 ± 0.54	0.38 ± 0.58	NS
In ACR remission, percentage (95% CI)	37% (26 to 49)	19% (11 to 29)	0.017
Change in Larsen score 2-11 years, mean (SD)	17 (12 to 26)	27 (22 to 33)	0.037
No damaged large joints, percentage (95% CI)	87% (74 to 94)	72% (58 to 84)	NS
On combi-DMARD strategy 2-11 years, median (IQR) percentage of treatment time	79% (43–100)	54% (3–94)	0.0043
On oral prednisolone at 11 years, percentage	32%	47%	NS
On biological agent at 11 years, percentage	12%	7%	NS

ACR: American College of Rheumatology; CI: confidence interval; DAS28: disease activity score assessing 28 joints; DMARD: disease-modifying anti-rheumatic drug; HAQ: health assessment questionnare; IQR: Interquartile range; SD: standard deviation; VAS: visual analogue scale.

damage at 11 years. Regardless of the randomisation group, the patients who had been in remission at 1 year had less radiographic progression than those not in remission. Moreover, the large joints of the patients in both groups were well preserved; damage to any large joint was present only in 13% of the FIN-RACo and 28% of the SINGLE patients, and the need for total joint replacement was rare (10).

Between 2-11 years the patients in the FIN-RACo group had used DMARD combinations more frequently than the patients in the SINGLE group (Table I), but the difference had levelled by 11 years, when 47% and 46% of the patients, respectively, were using DMARD combinations. However, the more frequent use of combination DMARDs between 2-11 years did not explain the proportion of patients having minimal disease activity (10) or low radiographic progression (11) at 11 years. Quite the contrary, the patients with the most radiologic progression after 2 years had used the longest periods of combination DMARDs after 2 years, and the same was true also regarding the biologic treatments; of the 14 patients having received biologics (Table I), 8 belonged to the tertile of the highest radiologic progression, and only one to the lowest tertile (11). This reflects the concept of the early "window of opportunity"; damage once arisen cannot later be undone.

Throughout the follow-up, the number of serious adverse events, the occurrence of all malignancies (10), or the occurrence of comorbidities, such as hypertension, osteoporosis, cardiovascular diseases, or diabetes mellitus (21), did not differ between the groups. Also the mortality was similar between the groups, and more importantly, not elevated compared to the general population (10). Thus, the initial combination strategy proved to be as safe but more effective than the initial single strategy, even over long periods.

The impact of the FIN-RACo Trial

The targeted treatment resulted in low disease activity, well-preserved function, and moderate radiographic progression in most patients. However, the patients treated with the original FIN-RACo strategy for 2 years had more frequent remissions at 2 and at 11 years and less radiographic progression throughout the follow-up than the patients treated with the original SINGLE strategy; all this without an excess of adverse events or mortality.

The importance of strict remission as the primary treatment target was emphasised by the follow-up results. Early remission proved to predict consequent remission (21), halted joint damage (11), as well as preserved working ability (7). Thus, the FIN-RACo trial, launched 15 years before the rest of the world's rheumatologists reached a consensus on treating RA to target (22), has given invaluable and accurate information on the results reached by such protocol in long-term.

Today, the FIN-RACO protocol may be criticised for starting the initial single-DMARD treatment with SASP. How-

ever, in 1993, when the trial begun, the clinical use of MTX in RA was far less common than today, and there were no studies showing its superiority compared to other DMARDs. Moreover, the SINGLE strategy was not tied to SASP but to a strategy of using one DMARD at a time. Consequently, during the first 2 years, 52% of the SINGLE group patients were switched to MTX, and some of these even further to another DMARD (4). Also, recently, in a direct comparison, the combination of MTX, SASP, and HCQ has been proven superior to single MTX in early RA (23).

Another point for criticism is the use of glucocorticoids (GCs), which retard radiological progression in early RA (24), and have successfully been included in the treatment protocols of several studies (25-27). Still, even though oral PRD was obligatory in the FIN-RACo group and discretionary in the SINGLE group, most SINGLE patients used PRD from the very beginning, and by 2 years more SINGLE group patients used systemic GCs and had a higher cumulative dose of intra-articular GCs than the FIN-RACo group patients (4). Thus, even though complicating the inclusion of the FIN-RACo trial into meta-analyses, the protocol complexities hardly explain the observed superiority of the FIN-RACo strategy.

However, the MTX dose in the original FIN-RACo trial was small, and more patients may had reached remission with higher MTX doses. With this in mind, the Finnish rheumatologists launched in 2003 the NEO-RACo Trial (28), where 99 early RA patients were treated with an intensified FIN-RACo protocol with intra-articular GCs, and randomised to receive either infliximab (INFL) or placebo (PLA) infusions for the first 6 months. At 2 years the remission rates were even higher than in the FIN-RACo trial (ACR remissions FIN-RACo+PLA 53% *vs*. FIN-RACo+INFL 66%, DAS28 remissions 82% *vs*. 82%), and radiographic progression marginal (change in SHS 1.4 *vs*. -0.2, respectively). PRD 7.5mg/day was part of the NEO-RACo protocol, and in general, including PRD into the initial treatment strategy appears to guarantee superior results (27, 29). Further, aiming for remission appears to be the right choice; targeting low disease activity seldom produces an excess of remissions into the bargain. This may explain why not all trials have found initial combination treatment to better induce remissions than stepping up to it (30).

Finnish rheumatologists have had a tradition of treating RA intensively (31, 32), already from the 1970s (1). The FIN-RACo Trial has further promoted the introduction of this strategy into everyday practice. The Finnish Current Care Guideline (33) recommends the FIN-RACo combination as the first treatment of early, active RA. Consequently, due to satisfactory treatment results, the use of biologics is less frequent than in most other countries (34-36). Further, the long-term work disability due to RA in Finland is declining, even though a direct protective effect of the intensified treatment strategies is hard to prove (37). Nevertheless, the implementation of the FIN-RACo strategy into real life may have vast financial consequences: each remission reached with traditional DMARDs decreases the need for expensive biologics and reduces both direct and indirect costs caused by RA. Therefore we encourage our colleagues worldwide for a broad-minded use of the FIN-RACo strategy, and even suggest that all new treatments should be tested against it.

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