Remission as the treatment goal – the FIN-RACo trial

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ABSTRACT
The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial was the first rheumatoid arthritis (RA) clinical trial in which remission served as the primary outcome measure. This chapter reviews the philosophical background, study design, and results of the FIN-RACo trial. The study showed that a third of patients with active early RA may achieve remission with a combination of methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and prednisolone.

Remission as the primary outcome measure
The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial was an investigator-initiated multi-center randomised controlled trial in which 18 Finnish rheumatology clinics participated (1). Between 1993 and 1995, 195 patients with early and active rheumatoid arthritis (RA) were enrolled in the study. The patients were randomised to two treatment arms for 2 years: 97 received a combination of methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and prednisolone, while 98 received mono-therapy with SSZ (with or without prednisolone), in which MTX was later substituted in 51 patients.

The primary outcome measure of the FIN-RACo study was remission, which was defined as no tender and no swollen joints, morning stiffness ≤ 15 minutes, no pain, and normal erythrocyte sedimentation rate. These remission criteria were those described by the American College of Rheumatology (ACR) (2), but did not include a requirement of no fatigue, as fatigue is regarded as not necessarily reflecting the inflammatory process of RA. However, all 5/5 criteria were required to be met for a patient to be regarded as in “remission,” rather than 5/6 in the ACR criteria (2). Therefore, the ACR remission criteria were effectively met by the FIN-RACo criteria.

The FIN-RACo trial was based on a long tradition of treating patients with RA that emphasised early and active care to improve long-term outcomes, as expressed by Luukkainen et al. in 1978: “...In our opinion gold treatment ought to be started in the early stages of RA, before the development of erosions. We are treating not only the actual inflammation of the joints but also the quality of the patient’s life for many decades in the future” (3). Clinical rheumatologists who designed the FIN-RACo trial believed that remission could be achieved in a large fraction of patients, although remission had not been used previously as an outcome measure in an RA clinical trial.

Why to aim for remission instead of percentage improvement or low disease activity?
The history of RA is that of a progressive disease with severe long-term outcomes (4) including joint damage, declines in functional capacity, work disability, and early death, which are associated with prior inflammatory activity. Early Finnish studies contributed to evidence that active treatment leads to improved long-term outcomes in many patients with RA. Minimal radiographic progression was observed in individual joints that did not show inflammation in serial clinical examinations (5). Sustained gold treatment was associated with reduced mortality rates in patients with RA (6).

Although it was known that remission was unusual in patients who sought care in rheumatology clinics, it was felt that remission is the optimal treatment goal in RA, analogous to “no evidence of disease” in cancer. Traditionally, RA clinical trials have been designed to identify statistically significant differences between the study treatment and a comparator, reflecting requirements of the United States Food and Drug Administration (FDA) to market a new
therapy. More recently criteria such as ACR 20% or 50% improvement criteria or disease activity score (DAS) have gone beyond mere statistical significance (7). The FIN-RACo trial was the first to incorporate the goal of remission in order to provide the best treatment to the patient whether she/he was randomised to a combination arm or the monotherapy arm.

High remission rates using combination of traditional DMARDs
After two years of treatment, remission was seen in 37% in the combination group and 18% in the monotherapy group (p = 0.003) according to the ACR-modified remission criteria (1). Thus, the combination of MTX, SSZ, HCQ, and prednisolone is “remission-inducing” in a third of patients with active early RA. This remission rate in the combination group appears remarkably high with a strict set of remission criteria – remission rates in clinical trials and clinical care are reviewed elsewhere in this Supplement.

It is noteworthy that the time interval from disease onset to institution of therapy was significant in the likelihood of remission in the FIN-RACo monotherapy group. Thirty-five percent of the patients with a short delay of < 4 months were in remission at 2 years in the monotherapy group, while only 11% of those with a long delay of > 4 months met remission criteria at 2 years (p = 0.021). In the combination group, the frequency of remission was similar in patients with short (0-4 months) or long delay (>4 months) of institution of the therapy (8).

Importance of remission as a treatment goal
Several studies show that although measures of inflammatory activity may be stable or somewhat improved over periods of 5 to 10 years, measures of damage may progress (7). Therefore, suppression of inflammation at a level of 20% or 50% appears unlikely to provide optimal long term suppression of disease progression in many patients. In the FIN-RACo study, 22% of patients who had ACR20% or 50% responses at 6 months and 54% of patients who did not have ACR20% responses, were receiving work disability payments at 5 years (Fig. 1) (9). By contrast, if inflammation was controlled to a level of remission at 6 months, 4.5 years later no patient was receiving work disability payments. Furthermore, loss of productivity was associated with lesser improvement of clinical status (10).

Patients who were in sustained remission assessed at 6, 12, and 24 months had practically no progression in radiographic damage in their hands, wrists, and feet, with no increase in mean Larsen score over the 2 years of observation. Patients who were not in sustained remission had an increase in mean Larsen score of 4 of 200 (11). These observations emphasize the importance of attempting to induce rapid and sustained remission in early RA. The data indicate that improvement rates of ACR20% or 50% are suboptimal goals of therapies for patients with early RA.

A combination of traditional DMARDs is effective in early RA
FIN-RACo patients were randomised to receive combination or monotherapy for 2 years. Subsequently, therapies were at physicians’ discretion. The 2-year results favoured early combination treatments, which continued at 5 years in analyses of radiographic progression and work disability. The 5-year median Larsen score was 11 in the initial combination group versus 24 in the monotherapy group (p < 0.01) (12). Patients in the initial combination group were more likely to maintain their capacity to continue in paid work over 5 years compared to the monotherapy group (13).

Did glucocorticoids drive remission in the FIN-RACo trial?
In the FIN-RACo trial, the combination therapy included prednisolone 5 mg daily, which could be tapered and discontinued at 9 months if patient remained in remission (1). In the monotherapy arm, prednisolone treatment was at physicians’ discretion, and was initiated in 27 (27%) patients at baseline and in another 36 patients at a median of 6 weeks after the onset of the study (14). At the end of the 2-year study, more patients in the monotherapy group than in the combination group were treated with prednisolone (50 vs 43 patients) and the cumulative number of intra-articular glucocorticoid injections was higher in the monotherapy group than in the combination group. These observations indicate that it appears unlikely that the more favourable results of the combination group in the FIN-RACo trial can be attributable to prednisolone. However, it may be that some individual patients gained considerable benefit from glucocorticoids, and the FIN-RACo trial does not speak against benefits of low-dose glucocorticoids in RA, which have been shown in other early RA
Nonresponders in the FIN-RACo trial

A proportion of patients with early RA do not improve with conventional treatments. In the FIN-RACo trial, 20% of patients in both the combination and monotherapy group did not meet ACR20% criteria at 6 months, and the percentages were 22% and 26% at 2 years, respectively (1). These patients with little to no response to active conventional therapies should be identified early in their rheumatology care, to consider institution of biologic agents.

Conclusions

Treatments for early RA should aim for remission as rapidly as possible to avoid severe “side effects” of RA (4). A combination of MTX, SSZ, HCQ, and prednisolone appears to be “remission-inducing” in a third of patients with active early RA, higher than remission rates seen in published reports involving biologic agents. It will be of interest to have results from another Finnish clinical trial in the near future, which investigates whether a biologic agent started with the FIN-RACo combination in early active RA increases remission rates and decreases the rate of nonresponders.

References