

Impact of Initial Aggressive Drug Treatment With a Combination of Disease-Modifying Antirheumatic Drugs on the Development of Work Disability in Early Rheumatoid Arthritis

A Five-Year Randomized Followup Trial

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Objective. To compare the efficacy of therapy with a combination of disease-modifying antirheumatic drugs (DMARDs) versus therapy with a single DMARD in the prevention of work disability in patients with early rheumatoid arthritis (RA).

Methods. In the Finnish Rheumatoid Arthritis Combination Therapy trial, 195 patients with recent-onset RA were randomly assigned to receive either combination therapy with DMARDs (sulfasalazine, methotrexate, hydroxychloroquine) plus prednisolone or single therapy with a DMARD with or without prednisolone. After 2 years, the drug treatment strategy was no longer restricted. At baseline, 162 patients (80 in the combination-treatment group and 82 in the single-treatment group) were still working or at least available

for work. After 5 years of followup, data on all sick leave and retirement were obtained from social insurance registers or case records. The main outcome for each patient was the cumulative duration of all sick leaves and RA-related disability pensions, divided by the observation period during which the patient was not retired because of another disease or because of age.

Results. The cumulative duration of work disability per patient-observation year was significantly lower in those randomized to combination therapy than in those randomized to single therapy: median 12.4 days (interquartile range [IQR] 0–54) versus 32.2 days (IQR 6–293) ($P = 0.008$, sex- and age-adjusted $P = 0.009$). This was mainly due to the difference in sick leaves (i.e., work disability periods ≤ 300 days): median 11.7 days (IQR 0–44) per patient-observation year in those treated with combination therapy and 30.0 days (IQR 6–68) in those treated with single therapy ($P = 0.002$). No statistically significant difference was seen in RA-related disability pensions.

Conclusion. Aggressive initial treatment of RA with a combination of DMARDs improves 5-year outcome in terms of lost productivity in patients with RA of recent onset.

Loss of ability to work is a frequent and serious outcome of rheumatoid arthritis (RA) (1–14), accounting for a large proportion of the costs of this disease (15,16). Cessation of working life results from interactions between various physiologic variables, social conditions, and work-related factors. Several studies have indicated that physically demanding jobs, lower educa-

Supported by the medical research foundations of Lappeenranta Central Hospital and the Rheumatism Foundation Hospital.

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Submitted for publication October 21, 2002; accepted in revised form September 17, 2003.

tion levels, older age, and longer duration of disease as well as disease severity (e.g., higher clinical disease activity, more extensive structural joint damage, lower functional capacity) enhance the risk of loss of employment (1–6,8,10–14). Few studies, however, have focused on the impact of clinical management, especially drug treatment, on the patient's ability to work. A lower risk of work disability was associated with early control of RA in a longitudinal study in the US (8). A comparison of 2 historical cohorts from the Norfolk Arthritis Register failed to show improvement in work disability rates (5). To our knowledge, only 2 prospective clinical trials have included as an outcome measure the ability to work. The results reported by Borg et al (17) suggest that early institution of disease-modifying antirheumatic drug (DMARD) treatment (auranofin) is protective against work disability. In the RAPOLO study, a longitudinal observational study that has been published as an abstract (18), Yelin et al concluded that longer-term treatment with etanercept results in increased hours of employment.

In 1999, we reported the 2-year clinical results of the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial, an open, randomized, followup trial comparing the efficacy and safety of therapy with a combination of DMARDs versus therapy with a single DMARD in 195 patients with early RA (19). A total of 178 patients completed the 2-year followup. At the 2-year followup visit, 36 of the 97 patients who were receiving combination therapy (37%) and 18 of the 98 patients who were receiving single-drug therapy (18%) ($P = 0.03$) had achieved clinical remission (20). Progression of radiologic joint damage was also lower in the combination-therapy group than in the single-therapy group, with median increases in the Larsen score (21) of 1.5 (interquartile range [IQR] 0–10.5) and 7.0 (IQR 1.0–16.0), respectively ($P < 0.001$).

After 2 years, the drug-treatment strategy was no longer restricted, and the patients who had had an inadequate response to single-drug therapy were allowed to switch to combination therapy. The patients have now been followed up for 5 years. In the present 5-year followup study, we evaluated the effectiveness of the 2 treatment strategies on maintenance of the patient's ability to work.

PATIENTS AND METHODS

Selection of patients and study design. From April 1993 to May 1995, a total of 199 patients with RA of recent onset (<2 years; median disease duration 6 months) who had

never received DMARDs were enrolled in a multicenter, parallel-group, randomized study comparing the efficacy and tolerability of therapy with a combination of DMARDs (simultaneous sulfasalazine, methotrexate, and hydroxychloroquine plus prednisolone) with the efficacy and tolerability of therapy with a single DMARD, with or without prednisolone. Combination therapy was started with sulfasalazine 500 mg twice a day, methotrexate 7.5 mg/week, hydroxychloroquine 300 mg/day, and prednisolone 5 mg/day, but the protocol allowed flexibility in dosage adjustments to mimic clinical practice. In the group receiving single-drug therapy, sulfasalazine (2–3 gm/day) served as the initial DMARD, but if the clinical response was <25% at 6 months, the protocol required that sulfasalazine be replaced with methotrexate (7.5–15 mg/week). Low-dose oral prednisolone was prescribed for 63 of the 98 patients (according to the clinicians' decisions). The study has been described in detail previously (19).

Patient selection criteria were as follows: fulfillment of the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 revised criteria for RA (22), age 18–65 years, symptom duration <2 years, and presence of active disease, as indicated by ≥ 3 swollen joints and at least 3 of the following 4 features: either an erythrocyte sedimentation rate ≥ 28 mm/hour or a C-reactive protein level of >19 mg/liter, morning stiffness >29 minutes' duration, >5 swollen joints, and >10 tender joints.

Of the 195 patients who started treatment, 97 received combination therapy and 98 received single-drug therapy. Patients were assessed clinically at the beginning of the study and at 1, 3, 4, 5, 6, 9, 12, 18, and 24 months. After 2 years, the treatment strategy was no longer restricted, and 48 of the patients receiving single-drug therapy switched to combination therapy (simultaneous treatment with at least 2 DMARDs). During followup, all patients randomized to combination therapy as well as 63 and 62 patients randomized to single-drug therapy received methotrexate and prednisolone, respectively. The median number of DMARDs was 4 (IQR 3–4) in the combination-therapy group and 3 (IQR 2–4) in the single-therapy group. The patients were reassessed clinically at 30, 36, 42, 48, 54, and 60 months. Radiographs of the hands and feet were scored by the method described by Larsen et al (21).

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and the ethics committees in all 18 participating hospitals. All patients gave written informed consent.

The Finnish social security system. Finland has a statutory national health insurance system. If a resident of Finland becomes temporarily unable to perform his or her regular job or another similar job because of an illness, he or she is entitled to a sickness allowance as compensation for lost income. This is payable to persons between the ages of 16 and 64 years and can be awarded to both employed and self-employed persons, as well as to persons who are involuntarily unemployed. Self-employment may also take the form of household work or studies. Sickness allowance is paid after completion of a waiting period consisting of the first day of work incapacity and the following 9 weekdays (from Monday through Saturday). However, the waiting period is waived if incapacity due to the same illness recurs before 30 days have elapsed since the end of the previous payment. The amount of

Table 1. Demographic, clinical, and radiographic characteristics of the rheumatoid arthritis patients at baseline, by treatment group*

	Treatment group	
	Combination (n = 80)	Single (n = 82)
Demographic features		
No. of females/no. of males	45/35	56/26
Married, %	73	77
Age, mean \pm SD years	45 \pm 9	46 \pm 10
Duration of education, mean \pm SD years	11 \pm 4	11 \pm 3
No. with physically demanding job/no. with light-duty job	41/39	42/40
Professional/managerial job, no. (%)	18 (23)	14 (17)
Disease duration, median (range) months	6 (2–22)	7 (2–24)
Rheumatoid factor present, no. (%)	59 (74)	57 (70)
Measures of disease activity		
ESR, mean \pm SD mm/hour	37 \pm 24	38 \pm 20
No. of swollen joints, mean \pm SD	14 \pm 6	14 \pm 7
No. of tender joints, mean \pm SD	18 \pm 8	20 \pm 10
Physical function, mean \pm SD HAQ score	0.8 \pm 0.6	0.9 \pm 0.6
Radiographic features		
No. of patients with available radiographs	77	79
Larsen score, median (IQR)	2 (0–4)	2 (0–7)
Erosion on hand or foot radiographs, no. (%)	39 (51)	43 (54)

* ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; IQR = interquartile range.

sickness allowance is calculated on the basis of the most recent earnings assessed by the tax authorities. The allowance is paid for weekdays (including Saturday) for up to 300 days (~1 year). The claim for sickness allowance must be accompanied by a certificate issued by a doctor or a hospital documenting the claimant's incapacity for work.

If work incapacity persists at least for 1 year and prevents a person from engaging in gainful employment or from working in his or her own household, he or she can apply for a disability pension. When a claim for this pension is filed, the claimant's ability to work is examined on the basis of a doctor's statement. The pension can be permanent or of a defined duration. The 2 complementary pension systems in Finland are national pensions linked to residence in Finland and employment pensions linked to past employment. All employees and self-employed persons are covered under statutory employment pension insurance. The Social Insurance Institution is responsible for sickness allowances and national pensions and maintains a register of all benefits awarded. The Central Pension Security Institute maintains a register of employment contracts and employment pensions. From the age of 65 years, all Finns are entitled to a retirement pension; this can be awarded as a reduced early old-age pension from the age of 60 years.

Data collection. At the 5-year followup visit, a registered specialist nurse assisted the patients in completing a questionnaire. Employment status since study entry was determined, including any changes in the number of hours at work, the job title, and the nature of work. The patients were classified into 2 groups based on job title (physically demanding work or physically light work). Those with professional/managerial jobs were recorded separately. The patients were

asked for permission to access their sick leave and pension data as recorded in the social insurance registers. Patients who were lost to followup were contacted by letter. At study entry, 162 patients were not retired. Of these, 146 gave their written permission to access the data. Of the remaining 16 patients (11 in the single-treatment arm and 5 in the combination-treatment arm), 13 were lost to followup, and the other 3 withheld their permission at the 5-year visit. However, based on their informed consent given at baseline, information about sick leave and retirement was obtained from case records, including duplicate copies of doctors' statements with diagnoses.

The population of the present study comprised all 162 patients (82 receiving single-drug therapy, 80 receiving combination therapy) who were potentially employable (i.e., were not retired for any reason) at the beginning of the trial. The treatment groups were comparable with regard to most demographic and clinical variables (Table 1). More women, however, were receiving single-drug therapy ($P = 0.11$), and slightly more patients with professional/managerial jobs were receiving combination therapy ($P = 0.39$).

At entry, a total of 67 patients receiving single-drug therapy (82%) and 71 receiving combination therapy (89%) were employed for pay; 1 patient in each group worked part-time. Equal proportions of patients in the 2 groups were on sick leave because of RA: 25 receiving single-drug therapy (30%) and 25 receiving combination therapy (31%). Other diseases led to sick leave for 2 patients in the single-therapy group. Ten patients receiving single-drug therapy (12%) versus 4 patients receiving combination therapy (5%) were unemployed job-seekers. However, during the followup, a total of 18 and 14 patients, respectively, were unemployed for some

period; the median duration of unemployment was 13 months in the single-therapy group and 14 months in the combination-therapy group. One person in each group was in vocational training at study entry. At that time, 4 patients in each group were doing housework. However, all of these patients had completed professional training and, with the exception of 2 patients receiving single-drug therapy and 1 receiving combination therapy, they did not work at least for some period during the followup.

During the followup, 10 patients in each group changed employment, and a further 12 patients in the single-therapy group and 11 in the combination-therapy group experienced a change in their work conditions. Five patients receiving single-drug therapy and 2 receiving combination-therapy retired because of age. Two other patients receiving combination therapy retired early because of a nonrheumatic disease (myeloma, coronary heart disease). Two patients receiving single-drug therapy died during the study: one died of myelodysplastic syndrome, and the other died of alcohol intoxication.

At 5 years, data on labor-force participation was available for 158 patients: 78 in the single-treatment arm and 80 in the combination-treatment arm. We failed to contact 4 patients randomized to single-drug therapy who had discontinued followup. Five patients in each study group (6%) were unemployed. Three patients in the single-treatment arm and 1 patient in the combination-treatment arm were doing housework. Three patients in the single-therapy group and 1 patient in the combination-therapy group were employed part-time.

Definition of work disability. We defined work disability as the period of time during which a patient was on sick leave, receiving a sickness allowance from the Social Insurance Institution, or receiving a disability pension because of RA. RA was identified in the pension register by the code 714 in the International Classification of Diseases, Ninth Revision (ICD-9) system and M05 or M06 in the ICD-10 system. The sickness allowance register does not contain information on diagnosis codes, which means that the sickness allowances may also be initiated by diseases other than RA.

The cumulative duration of sick leaves and RA-related disability pensions was calculated for each patient. The duration of a pension was divided by 2 if a person was receiving a disability pension for part-time work. The number of work disability days for each patient was divided by the number of years during which the patient was potentially employable (without taking RA into account). Accordingly, if a patient left the labor market due to retirement on an old-age pension or on a disability pension due to causes other than RA, the date of retirement defined the end of his or her observation period. If a patient was lost to followup or died, the date of the last data received for that patient defined the end of his or her observation period. The period of time during which the patients were known to be potentially employable ranged from 0.5 years to 5 years (mean 4.7 years).

The social insurance data included allowances and pensions paid. Sums were adjusted to correspond to their value in euros in 2001. The mean benefit per day for these 146 patients was used to estimate the allowances and pensions of the 16 patients whose work disability data came from case records.

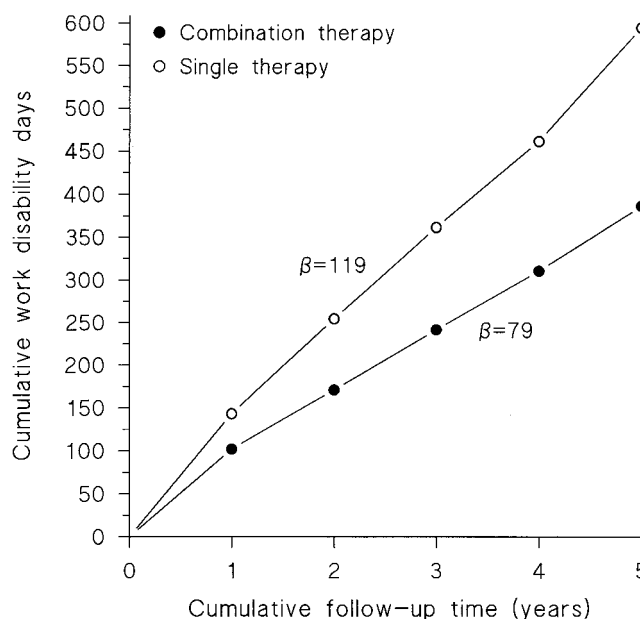


Figure 1. Cumulative work disability days per patient-observation year, by treatment group. β = annual regression coefficient.

Statistical analysis. The results are expressed as the mean \pm SD and as medians with IQRs and 95% confidence intervals (95% CIs). Statistical comparison between groups was performed with the Mann-Whitney test and the Hodges-Lehmann estimation of the shift of medians. Median regression, also known as least absolute value models, served to estimate adjusted medians. Normality of variables was evaluated by Shapiro-Wilk statistics. Retirement analysis was based on product-limit estimation; the Mantel-Cox test served to identify any differences. The Cox proportional hazards regression model with robust estimate of variance was used to estimate adjusted risks for retirement.

RESULTS

Figure 1 illustrates the group sums of work disability days per patient-observation year for each year during followup. There was an almost linear relationship between work disability time and followup in each group: the absolute difference increased over time. In 5 years, the median cumulative duration of work disability per patient-observation year was 32.2 days (IQR 6–293) in the single-therapy group and 12.4 days (IQR 0–54) in the combination-therapy group ($P = 0.008$). The sex- and age-adjusted medians were 37 days (95% CI 24–50) and 18 days (95% CI 5–31), respectively ($P = 0.009$, and $P = 0.02$ adjusted for baseline difference in unemployment status). The Hodges-Lehmann estimate of the shift in median days was 11 (95% CI 1–27). The mean

duration of work disability per patient-observation year was 128 days for the single-therapy group and 78 days for the combination-therapy group.

The superiority of combination therapy was primarily related to the difference in the cumulative duration of sick leaves (i.e., work disability with a maximum length of 300 weekdays) between the groups: the median number of days receiving sick allowance per patient-observation year was 30.0 (IQR 6–68) in the single-therapy group and 11.7 (IQR 0–44) in the combination-therapy group ($P = 0.002$). The respective means were 48 days and 23 days. There was no significant difference in the median number of days on RA-related disability pension per patient-observation year between the 2 study groups: 0 days (IQR 0–138) in the single-therapy group and 0 days (IQR 0–0) in the combination-therapy group ($P = 0.23$). The means were 78 days and 55 days, respectively.

RA-related permanent work disability. During the 5-year followup, 24 patients randomized to single-drug therapy (29%) and 16 patients randomized to combination therapy (20%) retired prematurely on a permanent disability pension because of RA. One of these patients was working part-time, and another patient died during followup; both were in the single-therapy group. The product-limit estimate of the rate of patients receiving a permanent disability pension because of RA during the 5-year followup period was 30% (95% CI 20–40) in the single-therapy group and 20% (95% CI 11–29) in the combination-therapy group ($P = 0.16$); the sex- and age-adjusted hazard ratio was 1.27 (95% CI 0.66–2.44) (Figure 2). After controlling for the baseline difference in unemployment status, the hazard ratio was 1.25 (95% CI 0.65–2.41).

During the study, 4 patients randomized to single-drug therapy and 1 randomized to combination therapy retired on an RA-related disability pension of defined duration but later returned to the active work force. Thus, the number of patients with any RA-related disability pension was 28 (34%) in the single-therapy group and 17 (21%) in the combination-therapy group. A considerable proportion of our patients (18 [22%] in the single-therapy group and 11 [14%] in the combination-therapy group) were continuously and eventually permanently unable to work beginning the first month of followup.

Gainfully employed patients. Because several studies of RA-related work disability have included only gainfully employed patients and to facilitate comparison between studies, we also analyzed this subset of our patients. Thus, we excluded patients who were unemployed, were doing household work, or were in voca-

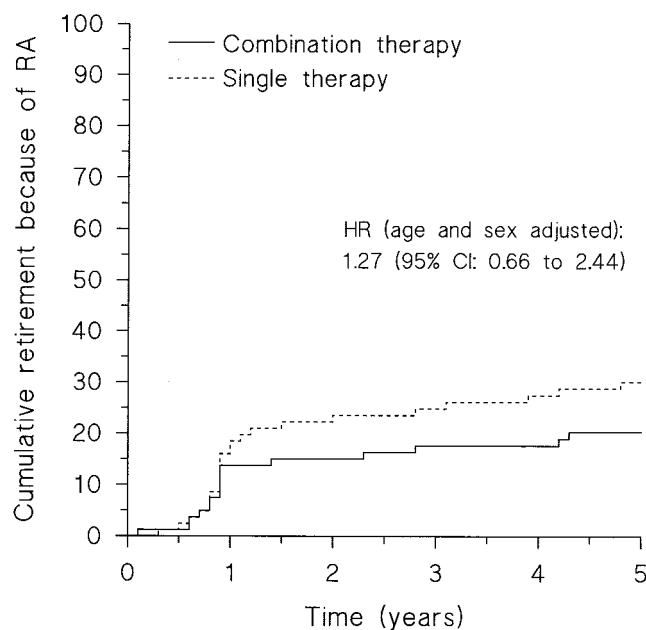


Figure 2. Five-year cumulative proportion of patients retiring for rheumatoid arthritis (RA)-related reasons, by treatment group, based on the product-limit estimate. HR = hazard ratio; 95% CI = 95% confidence interval.

tional training at baseline, leaving 67 patients in the single-therapy group (82% of the nonretired) and 71 patients in the combination-therapy group (89%) who were gainfully employed.

In this population, the median cumulative duration of sex- and age-adjusted work disability per patient-observation year was 29 days (95% CI 18–39) in the single-therapy group and 15 days (95% CI 5–24) in the combination-therapy group ($P = 0.03$). The sex- and age-adjusted hazard ratio for permanent RA-related work disability in the single-therapy group compared with the combination-therapy group was 1.05 (95% CI 0.53–2.07). When those who were gainfully employed at baseline ($n = 138$) were compared with the rest of the study patients ($n = 24$), we found no statistically significant difference in the number of work disability days per patient-observation year (median 19 days versus 57 days; $P = 0.25$), in the job types (50% versus 58% of the patients had a physically demanding occupation; $P = 0.45$), or in the duration of formal education (mean 11 years versus 12 years; $P = 0.23$).

Unemployed patients. At baseline, there were more unemployed job-seekers in the single-therapy group than in the combination-therapy group (10 versus 4 patients). The 14 unemployed patients had more work

disability days than did the remaining 148 patients, with a median of 120 days versus 18 days per patient-observation year ($P = 0.02$). However, there was also a difference in job types: 86% of the unemployed had a physically demanding job versus 48% of the remaining patients ($P = 0.007$). The unemployed patients were not as well educated as the employed patients: the mean duration of formal education was 9.5 years versus 11 years ($P = 0.16$).

Early old-age pension. The Finnish social insurance system offers the possibility of an early, but financially reduced, old-age pension that can be awarded independently of ability to work. It is, of course, probable that people with impaired ability to work are more likely to claim this type of pension than are persons who are healthy and fit. Our social insurance data showed that 4 patients randomized to single-drug therapy and 3 randomized to combination therapy had retired early, and 1 patient in each group had semiretired to part-time work. Adding these data to the sick leave and RA-related disability pension data resulted in a median cumulative number of lost work days per patient-observation year of 38 (IQR 6–328) for the single-therapy group and 15 (IQR 0–118) for the combination-therapy group ($P = 0.02$). The respective means were 136 days and 85 days.

Work disability benefits. The median work disability benefit (i.e., the sum of sick allowances and RA-related disability pensions) paid by the social insurance system per patient-observation year was €897 (IQR 99–6,863) for the single-therapy group and €305 (IQR 0–1617) for the combination-therapy group ($P = 0.008$, sex- and age-adjusted $P = 0.009$). The mean benefits were €3,610 and €2,077, respectively. The overall difference between the groups during the 5 years was €467,000, which is approximately the same value in US dollars.

DISCUSSION

In this 5-year prospective controlled study, we found that treatment of early RA with a combination of DMARDs, as compared with single-DMARD therapy, curtailed the number of days of sick leave and disability pension. Several previous studies, including ours, have indicated that early and aggressive therapy with conventional DMARDs improves the long-term outcome of RA, including retardation of radiographic damage and improvement in physical function (19,23–25). To our knowledge, this is the first demonstration that aggressive drug treatment reduces work disability as well.

Most studies of RA-related work disability have used early retirement on a permanent disability pension as their definition of work disability (1,6,7,10,11,14). Permanent work disability, however, represents only a portion of the impact of this disease on work capacity. Furthermore, a patient's ability to work sometimes improves even after a long period of disability, and he or she can return to gainful employment; this occurred in 5 of our patients. Thus, counting the number of days a patient is work-disabled because of RA during a given period of time appears to us to be a more sensitive and appropriate indicator of work disability. We recommend this measure as the standard method for studying disease-related work disability. Actually, we found no statistically significant difference in the rate of permanent disability pensions related to RA between the 2 treatment arms.

Accumulation of work disability days per patient-observation year was most rapid during the first year (Figure 1). After that, it continued almost steadily, but at different rates, in both treatment arms for the entire followup period. No deviation occurred in the single-therapy arm after 2 years, although drug treatment was no longer restricted at that time. The efficacy of the initial treatment therefore seems to be of utmost importance.

The social insurance data for Finland do not include causes of sick leave (i.e., diagnosis codes). This means that some of the sick leave may have been due to diseases other than RA. It seems unlikely, however, that other diseases could have caused significant bias in sick leaves between the 2 groups. First, the patients were randomly assigned to the treatment groups. Furthermore, with few exceptions, all our patients were followed up strictly according to the study protocol, with documentation of all adverse events as well as concomitant diseases. By the end of the first 2 years, drug-related adverse events in both treatment arms were parallel (19). At study entry, only 2 patients (both in the single-therapy group) were on sick leave due to causes other than RA. During followup, an equal proportion of patients in each group (6 per group) experienced severe adverse events, and only 2 patients (both in the combination-therapy group) retired early on a disability pension because of a disease other than RA. The medical records of all these patients (8 in each group) were reviewed in depth, and only sick leaves due to RA were included in the analysis.

Our definition of work disability does not capture all "sick days." Very short sick leaves were not registered and were therefore not included in our study, because of

the waiting period of 10 weekdays (including Saturdays) for sickness allowance. Sick leaves because of, for example, most ordinary infections were not included. Because the waiting period is waived if incapacity due to the same illness recurs before 30 days have elapsed since the end of the previous payment, sick leaves caused by longer-lasting conditions, such as RA, were more likely to be included after the first waiting period without further waiting periods. Considering this fact and the aforementioned review of case records, it therefore seems unlikely that other diseases and conditions caused bias in our outcome measure.

In Finland, the proportion of women who are employed outside the home is one of the highest in the world. In fact, not one of our patients was a housewife in the traditional sense. Furthermore, in the Finnish social security system, persons doing housework are also entitled to work disability benefits; the same is true for students and for those who are involuntarily unemployed. Since all these groups could develop the outcome of interest, we chose to include them in our study. During the followup, the dynamics of working life caused both entry to and exit from the labor force as well as changes in work conditions. When the entire followup period is considered, basic participation in the active labor force did not differ between treatment arms.

There was imbalance in the number of unemployed job-seekers at baseline, although the difference almost disappeared during the followup period. The patients who were unemployed at baseline had more work disability days than did the other patients. It is likely, however, that this is due to the observed differences in job titles, because work disability in the Finnish social security system is defined as the inability to perform one's regular job or another similar job. Furthermore, unemployed persons were not as well educated as the other patients. After controlling for baseline differences in unemployment status, there was still a statistically significant difference between treatment arms. Likewise, in an analysis of only the patients who were gainfully employed at baseline, there was a difference in favor of the combination-therapy group; the smaller *P* value is likely to be due to the small sample size. Clinical variables in the unemployed patients were comparable to those in the other patients, which means that unemployment was unlikely to be due to more severe disease.

We had no social insurance register data for 16 of the patients. It is possible that their medical records did not include data on all their sick leaves. However, since there were more single-therapy patients in this group,

the situation cannot cause bias in favor of the combination-therapy group.

Our work disability study was open, but the FIN-RACo Trial group was not informed of it until 1998, when the first patients had been followed up for almost 5 years. At least for most of the followup, it is very unlikely that the clinicians would have dealt differently with the treatment groups when assessing a patient's ability to work. Furthermore, all decisions concerning longer sickness allowances and disability pensions were made by the medical examiners of social insurance institutions outside the FIN-RACo Trial group.

The aim of our study was to compare the outcomes of 2 treatment strategies. The principle in both treatment arms was to target remission by adjusting drug dosages and by changing the prescribed DMARDs if response was inadequate. In the single-therapy strategy, the patients continuously received 1 DMARD (and prednisolone, if clinically indicated); in the combination-therapy strategy, patients simultaneously received at least 2 DMARDs plus prednisolone for the first 2 years, after which time the treatment was no longer restricted. This kind of study design does not allow comparison of the influence of separate DMARDs on the ability to work.

It is difficult, and may even be misleading, to compare studies conducted in different settings and environments. Some studies of RA-related work disability have been cross-sectional (2,13). In contrast, comparison of longitudinal studies (1,5–8,10–12,14) is impeded by disparities in study populations with regard to age, disease severity, and occupation profile, as well as by differences in social security systems between countries. Although our study included only patients with early and, according to accepted criteria, active RA, the cumulative probability of receiving a permanent disability pension because of RA over a period of 5 years was lower in the combination-therapy group and comparable in the single-therapy group with that in the study by Sokka et al (6), who studied Finnish patients treated according to the "sawtooth" strategy. In a recent British study (1), 29% of patients with early RA stopped working because of the disease over a period of 5 years.

Consistent with previous prospective studies of early RA, our results show that the work capacity of patients with RA is threatened from the very start of the disease (1,5–8). Almost one-fifth of our patients were permanently work-disabled from the first month of the study, a value that is lower, however, than that in a Swedish study (10). Nevertheless, the proportion is still

far too large, and therapies that are more effective are urgently needed. Studies exploring risk factors for this unfavorable outcome are obviously indicated.

Savings in work disability benefits (i.e., costs to the social insurance system) were considerable: on average, €7,500 per patient treated with combination therapy for 5 years. Compensation for lost income, however, represents only a portion of lost productivity, the value of which can be far higher. Consequently, the actual savings for society may be much higher.

In summary, these results show that RA-related work disability should be measured by counting the number of days that patients are unable to work, instead of merely the number of permanent disability pensions. Aggressive treatment of early RA with a combination of DMARDs leads to improved ability to work and fewer days off work than does therapy with a single DMARD. Since lost productivity causes a considerable portion, if not most, of the economic burden of RA, our results suggest that early aggressive therapy for RA saves substantial costs to society.

ACKNOWLEDGMENTS

Acknowledgements are due to the other members of the FIN-RACo Trial group, as follows: Martti Nissilä, MD, PhD, Kirsti Ilva, MD, Urpo Yli-Kerttula, MD, PhD, Pentti Järvinen, MD, PhD, Mikko Hakola, MD, Heikki Piirainen, MD, PhD, Jari Ahonen, MD, Ilppo Pälvimäki, MD, Sinikka Forsberg, MD, Kalevi Koota, MD, PhD, Claes Friman, MD, PhD, Oili Kaipainen-Seppänen, MD, PhD, Per Franzen, MD, Tapani Helve, MD, PhD, Juhani Koski, MD, PhD, Marianne Gripenberg-Gahmberg, MD, PhD, Riitta Luosujärvi, MD, PhD, and Anna Karjalainen, MD.

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