Indirect and Total Costs of Early Rheumatoid Arthritis: a Randomized Comparison of Combined Step-down Prednisolone, Methotrexate, and Sulfasalazine with Sulfasalazine Alone

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ABSTRACT. ***Objective.*** To describe the effect of indirect costs for patients with early rheumatoid arthritis (RA) within the COBRA trial (Combinatietherapie Bij Reumatoide Artritis) on the cost-effectiveness of both therapies. Analyses of the efficacy and direct costs of the treatments have already been reported.
Methods. Patients with early RA selected for the 56-week trial were randomly assigned to prednisolone, methotrexate, and sulfasalazine (the COBRA combination) (n = 76, tapered after 28 weeks) or to sulfasalazine (SSZ; n = 79, of which 78 patients were evaluable) alone. The main efficacy outcomes were a pooled index and radiographic damage score in hands and feet, and utilities. Direct and indirect costs were measured (from a societal perspective) by means of cost diaries and interviews completed by patients during the intervention phase and the followup phase, each lasting 28 weeks. Differences in mean costs between groups and cost-utility ratios were evaluated by applying nonparametric bootstrapping techniques.
Results. In the first 28 weeks, indirect costs per patient totaled US $2,578 and US $3,638 for COBRA and SSZ therapy, respectively ($p = 0.09$). The total costs were $5,931 and $7,853, respectively ($p < 0.05$). These differences were lost in the second 28 weeks. For the total period the mean total costs per patient were $10,262 and $12,788, respectively ($p = 0.11$). Sensitivity analyses showed robustness of the data. The point estimate of the cost per quality-adjusted life-year based on the rating scale was negative at $–385, suggesting dominance of COBRA (more effect at lower cost).
Conclusion. COBRA therapy adds additional disease control (improvements in disease activity, physical function, and rate of damage progression) at lower or equal cost compared to SSZ in early RA. (J Rheumatol 2004;31:1709–16)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DRUG THERAPY SULFASALAZINE
COST-EFFECTIVENESS ECONOMIC

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Over the past 15 years, several studies have shown that rheumatoid arthritis (RA) is associated with major consumption of health care resources and substantial work disability[1]. Patients with RA suffer from pain, stiffness and impaired function in daily life and at work, increased dependence on family and friends, and decreased participation in leisure activities. Between one-third and two-thirds of previously employed patients with RA have reduced work capacity[2]. Many patients will eventually have to stop working and will not be able to perform their normal daily activities due to their disease. Consequently, direct and indirect costs associated with RA are high due to increased use of outpatient medical services, increased hospital rates, and high rates of work disability in the course of this chronic disease.

In the field of musculoskeletal disorders indirect costs are often substantial compared to direct costs; including these costs in an evaluation can therefore strongly influence

the cost-effectiveness of a treatment[3-6]. Because of the costs to society associated with sick leave and disability due to RA, there is a need to determine cost-effective interventions. Information from an economic evaluation can be used to support decision-making to determine the allocation of scarce resources and to achieve the maximum health outcome obtainable[7,8].

The aim of the COBRA (Combinatietherapie Bij Reumatoide Artritis) trial was to compare the clinical effectiveness and the cost-effectiveness of a combined drug regimen in early RA to standard treatment with sulfasalazine (SSZ).

This report completes the economic evaluation (including direct as well as indirect costs) performed alongside the COBRA trial. An evaluation of the clinical effects of these methods of treatment and the cost-effectiveness and cost-utility results comprising only the direct costs have been reported[9,10].

MATERIALS AND METHODS

Subjects. The COBRA trial was performed in the period May 1993 to May 1996. Patients between 18 and 70 years of age with active early RA (American College of Rheumatology criteria[11]) were recruited at 9 medical centers in The Netherlands and one in Belgium. No prior treatment with second-line antirheumatic medication apart from antimalarials was allowed. Research and medical ethics committees in all the participating hospitals had approved the study protocol. All patients had given written informed consent before entering the trial.

Treatments. The patients with early RA selected for the trial were randomly assigned to the combination of SSZ (2 g/day), methotrexate (MTX, 7.5 mg/week), and prednisolone (PRED, 60 mg/day initially, tapered to 7.5 mg/day in 6 weekly steps) (COBRA) or to SSZ alone. PRED and MTX were tapered and stopped after 28 and 40 weeks, respectively. All patients were prescribed calcium supplementation (1 g/day) for as long as they used PRED and folic acid (1 mg/day) for as long as they used MTX. If any side effects occurred, the treatment was modified according to the protocol. Patients were followed for 56 weeks after randomization.

Efficacy measures. The primary clinical outcome was a pooled index, a weighted mean that reflected each patient's clinical improvement[9]. The pooled index consisted of the patients' improvements in erythrocyte sedimentation rate, grip strength, tender joint count, the observers' global assessment, and the patients' improvement in functional ability. In addition the Sharp/van der Heijde scale measured radiographic damage in hands and feet. All clinical effects were measured and evaluated by independent blind researchers at baseline and after 16, 28, 40, and 56 weeks; radiographs were taken and evaluated only at baseline, 28, 56, and 80 weeks[9].

Utilities were measured at baseline and after 28 and 56 weeks. The Maastricht Utility Measurement Questionnaire (range 0, death, to 1, indicating perfect health), comprising rating scale and standard gamble techniques, was used to define the utilities[12,13]. The questionnaire was administered as an interview by trained assessors not involved in the treatment of patients. Calculating the area under the curve for the Maastricht Utility Measurement Questionnaire resulted in quality-adjusted life-years (QALY) for each treatment group. The time horizon was not extended beyond the trial duration (one year).

Costs. As the costs were observed from a societal perspective, both direct and indirect costs were included.

The use of the terms direct and indirect costs is not consistent across studies, which sometimes causes confusion. We use the following definitions.

Direct costs refer to the use of resources attributable to the intervention or treatment regimen. Direct costs include the value of all the goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current or future consequences linked to the intervention. Thus direct healthcare costs include the costs of the intervention itself but also its economic consequences, i.e., changes in healthcare utilization, costs of additional therapies, drug use, periods of hospitalization, and visits to health care providers. The direct healthcare costs in this trial were divided into costs of the intervention protocol drugs and monitoring, costs of nonprotocol drugs, other costs of outpatient care, and costs of inpatient care. Costs strictly related to the execution of the trial such as costs of outcome assessment and trial clinic visits were not included in the total direct costs[10]. Direct non-healthcare costs include out-of-pocket expenses, costs of paid and unpaid help (e.g., time family members or volunteers spent on home care), and the time a patient needs to visit healthcare providers. Relevant time costs for patients include travel and waiting time as well as the length of time of treatment[8]. Indirect costs refer to production losses due to RA for both paid and unpaid labor[7,8]. Indirect costs can be calculated in 2 different ways. The Human Capital Method estimates the value of potential production loss during the entire period of work absenteeism. The potential loss of productivity is quantified in terms of foregone income, assuming full productivity. An alternative approach is the Friction Cost Method, which assumes that the amount of production lost, and/or the costs to maintain production due to disease, depend on the time-span organizations need to restore the initial level of production and costs. Sick employees can be replaced after a period necessary for adaptation: the friction period[14-16]. In this trial the friction period was set at 3 months, but the period can be varied for different education levels. In the main analysis, indirect costs for both paid and unpaid labor will be estimated by the Human Capital Method (time horizon: one year).

Data on resource use was collected by weekly patients' diaries specifically developed for this study, the biannual interviews, and hospital records. Patients were asked to complete the weekly diaries for 56 weeks. The diaries were collected at every study visit. The patients' diaries comprised questions about the medical consumption of a patient during one week. Patients were asked to report each healthcare utilization and inability to perform paid or unpaid labor regardless of whether it was related to RA. The symptoms and signs as well as the side effects of treatment in RA are very heterogeneous and possibly unknown to the patients, which means it is very difficult for patients to distinguish whether a certain condition was caused by RA or by a different disease. In the patients' diaries, only patients with a paid job had to fill out the question about work absenteeism (i.e., How many days did you miss a work day in the past 3 months?; Have you performed paid work in the last 3 months?). The information from the patients' diaries about work absenteeism was clustered together, resulting in a total number of work-loss days for the first semester (0–28 weeks) and second semester (29–56 weeks).

In the biannual interviews, all patients, including the patients without a paid job, were asked about their work absenteeism or inability to perform their normal tasks during 6 months prior to the interviews. Information from the biannual interviews was used to estimate the number of days patients without a job were unable to perform normal daily activities. For patients with a paid job the biannual questionnaires did not distinguish between the number of days the patients were unable to perform their normal daily activities or the total number of work-loss days.

Cost prices were expressed in Dutch guilders and subsequently converted into US dollars ($) at the 1994 Purchasing Power Parities rate of 2.143:1[10]. To evaluate indirect costs patients were divided into 4 different groups: (1) patients with a paid job, (2) patients with a disability pension, (3) retired patients, and (4) remaining patients (mostly homemakers). We considered patients to have a paid job if they were employed for at least 8 hours per week. To value (the loss of) production, the mean income of all patients with a paid job was used: $93/day. The number of days retired patients and homeworkers were unable to perform normal daily activities

was valued at $56, i.e., 80% of the wage for a qualified homemaker ($70)[10]. Patients with a disability pension have a different position in society compared to patients with short work absenteeism. After a certain period of work absenteeism, patients in The Netherlands can be declared unfit to work and to have a certain percentage of disability. For example, 100% fit to work indicates that someone is able to work 5 days a week. Disabled for 100% indicates that someone is unable to work at all. So if a patient had been declared 40% disabled, this patient has a reduction of 40% in the capacity to earn his salary, i.e., as having 2 days of absence per week. In the main analysis, indirect costs for patients with a disability pension were calculated on the basis of the official percentage of disability pension expressed as number of days patients were declared unfit to work. These days were also valued at $56. The status of a patient at the beginning of each 6-month period determined the group to which a patient was allocated.

Statistical analysis. Main outcomes in this analysis were indirect and total costs. To compare costs between groups, bootstrapped confidence intervals were computed. The mean of the costs in a group is the most informative measure irrespective of eventual skewed distributions, since it is directly related to the total costs. Thus, to compare costs between groups any test statistic should be based on the mean[17]; in this trial Student's t-test would be appropriate. However, Student's t-test statistics are biased if the cost variable is irregularly distributed (skewed, bimodal, or presence of outliers). As this was the case, bootstrapping was used for comparison of mean costs between groups[18]. Confidence intervals for mean differences in costs were obtained by bias-corrected and accelerated (BCa) bootstrapping, choosing 500 for the number of replications. Cost-utility ratios were calculated by dividing the difference between treatment groups in mean costs by the difference between groups in the gain in QALY, resulting in costs per QALY[19-21]. Cost-utility ratios were also calculated with bootstrapping (5000 replications) according to the bias-corrected percentile method[21] (software to perform these calculations developed in-house is available as shareware from H.J. Adèr, E-mail: hj.ader.biostat@med.vu.nl). All differences in costs were tested per semester because a priori maximum contrast was expected in the first semester, considering the withdrawal of COBRA after 28 weeks. All analyses were performed on an intention-to-treat basis. As the timeframe of followup in this report is only a little over one year, no discounting of future costs or benefits back to current value was carried out. A 2-sided p value below 0.05 was considered significant. No correction for multiple testing was applied.

Sensitivity analysis. In a sensitivity analysis, the robustness of the methods used for calculating costs of disability and paid employment were evaluated univariately. In the main analysis, indirect costs for patients with a disability pension were calculated using the official percentage of disability pension, expressed as number of days patients were declared unfit to work. In the sensitivity analysis, for patients with a disability pension the self-reported number of days patients were unable to perform their normal tasks was used to calculate the indirect costs. In the main analysis, as described above, we used a combination of information available from the weekly diaries and the biannual interviews to get the most reliable information on the days absent from work or inability to perform normal daily activities. In the sensitivity analysis we have calculated the differences in indirect costs for patients with a paid job > 8 hours/week using the information of the weekly diaries and the information of the biannual interviews separately, in order to determine if there was a difference in the reported number of days absent from work. The indirect costs according to the friction cost method are also calculated in the sensitivity analysis.

RESULTS

Subjects. A total of 155 patients were included in the trial. One patient from the SSZ group dropped out in Week 2 due to adverse effects (rash), and consequently only baseline data were available for this patient. Of the remaining 154 patients, 76 received COBRA and 78 received SSZ alone. Eight patients (all in the SSZ group) were lost to followup and only incomplete cost data were available for these patients. Occasional missing cost values (3%) were substituted by group means.

The 2 therapy groups were similar at baseline in terms of disease activity, radiographic damage, and demographic and other prognostic variables (Table 1)[9]. Although patients had been randomly assigned to treatment, there were also some baseline differences. There were more women in the COBRA group than in the SSZ group. There were also slightly more retired patients in the COBRA group than in the SSZ group and fewer patients with a disability pension at the beginning of the trial. For the patients with a disability pension it was often difficult to establish whether disability was caused by incipient RA or another disease.

Efficacy measures. The clinical and radiological results have been published previously. Briefly, within a few weeks COBRA greatly reduced disease activity (pooled index) in most patients. The difference in clinical efficacy between the treatment groups decreased and was no longer significant after the withdrawal of PRED, and there were no further changes when MTX was withdrawn[9].

At baseline both therapy groups were balanced in terms of radiographic damage at baseline. The median increase in total score in the SSZ group was 3 times higher than in the COBRA at 28, 56, and 80 weeks[9].

Utility assessments including baseline and 2 followup assessments were available for 67 (88%) patients in the COBRA group and 75 (95%) in the SSZ group. At 56 weeks most of the between-group difference seen after the first semester was lost. Mean improvement at 56 weeks by rating scale was 0.18 in COBRA group versus 0.16 in the SSZ group and 0.07 in both groups by the standard gamble method. In the COBRA group the area under the curve of the rating scale utility (yielding QALY) was 0.06 greater

Table 1. Baseline characteristics of the study patients according to treatment group.

	COBRA, n = 76	Sulfasalazine, n = 78
Age, yrs, mean (SD)	49 (12)	49 (12)
Female, n (%)	50 (66)	40 (51)
Married, n (%)	63 (83)	59 (76)
Educational years, mean (SD)	10 (3)	10 (3)
RA Disease duration, months, median (range)	4 (1–24)	4 (1–23)
Health Assessment Questionnaire score, mean (SD)	1.5 (0.7)	1.4 (0.7)
Employment status		
Patients with a paid job (> 8 hours per week), n (%)	33 (43)	32 (41)
Patients with a disability pension, n (%)	5 (7)	9 (12)
Retired patients, n (%)	16 (21)	9 (12)
Remaining patients (mostly homemakers), n (%)	22 (29)	28 (36)

than in the SSZ group (p = 0.01). The standard gamble utility area under the curve was 0.02 higher (p = 0.33)[10].

Indirect costs and total costs (Human Capital Method). Before disease onset, 79 out of 154 (51%) patients reported having a paid job of more than 8 hours/week; 12 patients already received a disability pension and 24 patients were retired. The 39 remaining patients were unemployed; most were homemakers. At the start of the trial (baseline) the number of patients with a paid job had decreased to 65, 14 patients had a disability pension, 25 patients were retired (Table 2A). The number of remaining (unemployed) patients had increased to 50. During the trial, most changes in work status were seen in the patients with a paid job at baseline and the patients in the "remaining" category. There were no clear differences between the treatment groups. After 28 weeks, 45 of the initial 65 patients still had a paid job. Of the other 20 patients, 4 started on a disability pension, 4 retired, and 12 were unable to continue their paid job due to different circumstances. Of the "remaining" group of 50 patients at baseline, 6 started a paid job, 4 previously unemployed patients started on a disability pension, and 2 were retired. After 56 weeks the net number of patients with a job had decreased to 44. The number of patients with a disability pension had doubled from 14 at baseline to 29 (Table 2A). Almost all (90%) were classified as fully disabled (disability pension for 100%).

If we look at the mean number of days patients reported not being able to work or perform daily activities, i.e., regardless of gainful employment, the effect of COBRA is more evident (Table 2B). At 28 weeks, the COBRA group reported mean 24 days (SEM 5) compared to SSZ, 38 days (SEM 5; p = 0.04). In the second half-year the SSZ group improved to the level of the combined group, and differences were no longer apparent.

Table 3 shows the direct and indirect costs for both therapy groups. During the first semester the mean indirect costs of COBRA were $1,059 lower than those of SSZ (p = 0.09, 95% CI $–156, $2,333; Table 3A). Patients with a disability pension incurred the highest costs. As the direct costs were also lower, the difference of $1,921 in total costs was significant (p = 0.04, 95% CI $237, $3,727). During the second semester the mean indirect costs of all patients were much lower and the differences between the groups were very small and not statistically significant. Again, the patients with a disability pension had the highest indirect costs (Table 3B). Over the whole year (Table 3C), the difference in indirect costs was $1,534 (p = 0.10, 95% CI $–480, $3,611); the difference in total costs was $2,526 (p = 0.11, 95% CI $–518, $5,576). In the category of "remaining" patients, the difference in indirect costs between the groups was significant both in the first semester and overall (p = 0.03).

Sensitivity analysis. In the sensitivity analysis the indirect costs for patients with a disability pension were calculated based on the self-reported number of days patients were unable to perform their normal tasks. The indirect costs of patients with a disability pension in COBRA group were lower than the indirect costs of patients with a disability pension for SSZ therapy for the total year ($2,730 and $4,511), contrasting with the main analysis ($15,287 and $16,006).

Table 4 shows the sensitivity analysis of indirect costs of

Table 2A. Occupational status of patients during the trial per treatment per subgroup.

	COBRA			Sulfasalazine			Total		
	Baseline	28 Wks	56 Wks	Baseline	28 Wks	56 Wks	Baseline	28 Wks	56 Wks
Patients with a paid job (> 8 h/week)	33	26	23	32	25	21	65	51	44
Patients with a disability pension	5	10	13	9	12	16	14	22	29
Retired patients	16	18	18	9	13	16	25	31	34
Remaining patients (mostly homemakers)	22	22	22	28	28	25	50	50	47
Total	76	76	76	78	78	78	154	154	154

Table 2B. Mean number (SEM) of self-reported days of absence or unable to perform daily activities per treatment group per subgroup.

	0–28 Weeks		28–56 Weeks	
	COBRA	SSZ	COBRA	SSZ
Patients with a paid job (> 8 h/week)	42 (8)	46 (9)	24 (7)	28 (9)
Patients with a disability pension	3 (1)	34 (14)	27 (14)	25 (11)
Retired patients	8 (6)	12 (11)	11 (7)	3 (2)
Remaining patients (mostly homemakers)	13 (7)*	37 (8)*	13 (7)	18 (7)
Total	24 (5)*	38 (5)*	18 (4)	20 (4)

* p < 0.05. SSZ: sulfasalazine.

Table 3. Mean total costs per patient with early RA by treatment.

A. Mean total costs per patient with early RA by treatment in US $ for the period 0–28 weeks.

	COBRA Mean (SEM)	SSZ Mean (SEM)	D	95% CI
Direct costs[10]	3,355 (383), n = 76	4,218 (638), n = 78	863	–250, 2,250
Indirect costs				
Patients with a paid job	3,942 (771), n = 33	4,108 (801), n = 32	165	–1,702, 2,461
Patients with a disability pension	7,643 (720), n = 5	7,839 (648), n = 9	196	–2,040, 2,432
Retired patients	525 (391), n = 16	1,045 (722), n = 9	520	–1,388, 1,893
Remaining patients	875 (471), n = 22	2,584 (550), n = 28	1,709*	147, 3,369
Total indirect costs	2,578 (439), n = 76	3,638 (445), n = 78	1,059	–156, 2,333
Total costs	5,931 (600), n = 76	7,853 (748), n = 78	1,921*	237, 3,727

B. Mean total costs per patient with early RA by treatment in US $ for the period 29–56 weeks.

	COBRA Mean (SEM)	SSZ Mean (SEM)	D	95% CI
Direct costs[10]	2,163 (393), n = 76	2,293 (345), n = 78	130	–1074, 1,117
Indirect costs				
Patients with a paid job	2,208 (635), n = 26	2,650 (855), n = 25	443	–1,933, 2,245
Patients with a disability pension	7,350 (903), n = 10	8,329 (490), n = 12	980	–1,763, 2,468
Retired patients	778 (477), n = 18	279 (150), n = 13	–499	–1,332, 556
Remaining patients	907 (468), n = 22	1,300 (457), n = 28	394	–1,188, 1,756
Total indirect costs	2,169 (385), n = 76	2,644 (436), n = 78	475	–588, 1,567
Total costs	4,330 (620), n = 76	4,935 (600), n = 78	604	–1,197, 2,396

C. Mean total costs per patient with early RA by treatment in US $ for the period 0–56 weeks.

	COBRA Mean (SEM)	SSZ Mean (SEM)	D	95% CI
Direct costs[10]	5,519 (714), n = 76	6,511 (858), n = 78	992	–1,010, 3,098
Indirect costs				
Patients with a paid job	6,024 (1,176), n = 33	6,206 (1,302), n = 32	182	–3,343, 3,420
Patients with a disability pension	15,287 (1,440), n = 5	16,006 (1,186), n = 9	719	–3,474, 4,911
Retired patients	1,400 (617), n = 16	1,278 (703), n = 9	–122	–1,789, 1,794
Remaining patients	1,555 (596), n = 22	3,983 (877), n = 28	2,428*	356, 4,485
Total indirect costs	4,747 (730), n = 76	6,282 (799), n = 78	1,534	–480, 3,611
Total costs	10,262 (1,086), n = 76	12,788 (1,176), n = 78	2,526	–518, 5,576

Intention to treat analysis. SEM: standard error of the mean; D: difference of the means, SSZ – COBRA. * $p < 0.05$

patients with early RA. The indirect costs for patients with a paid job based only on the biannual interviews were $5,897 for the COBRA group and $5,787 for the SSZ group. The indirect costs calculated using the weekly diaries were higher: $5,922 for COBRA and $6,262 for SSZ (Table 4C). The use of different resources to calculate the indirect costs for patients with a paid job did not result in any change in the indirect costs as presented in the main analysis.

By limiting the effect of long absenteeism to a fixed maximum, this method lowers the indirect costs for patients with a paid job in both groups. However, the decrease was greater in the SSZ group because there the duration of work absenteeism was longer. As a consequence, the difference in indirect costs between the groups disappeared. Indeed, indirect costs were now slightly higher in the COBRA group compared to the SSZ group ($4,208 and $3,949, respectively), in contrast to the results of the Human Capital Method ($6,024 and $6,206, respectively).

Cost-utility ratio. The cost-utility ratio (dividing the incremental costs by incremental effects expressed as utility) for the rating scale technique was $–385 cost per QALY. The cost-utility ratio using the standard gamble technique was $–1,134.

DISCUSSION

COBRA was more effective in restoring functional ability expressed as days unable to perform normal activities (regardless of employment). Together with direct cost savings this resulted in the difference in total costs becoming statistically significant. After tapering of the combination, these differences compared to SSZ were lost in the second semester, in parallel with the clinical findings.

Table 4. Sensitivity analysis.

A. Indirect costs (US $) of patients with a paid job at baseline during 0–28 weeks (reference case, friction cost method, weekly diary, interview).

	COBRA, n = 33 Mean (SEM)	SSZ, n = 32 Mean (SEM)	D	95% CI
Reference case*	3,942 (771)	4,108 (801)	165	–1,702, 2,461
Friction cost	2,820 (484)	2,946 (489)	126	–1,360, 1,360
Weekly diary	3,943 (771)	4,325 (818)	383	–2,400, 2,629
Interview	3,620 (727)	4,149 (725)	529	–1,579, 2,674

B. Indirect costs (US $) of patients with a paid job at baseline during 29–56 weeks (reference case, friction cost method, weekly diary, interview)

	COBRA, n = 26 Mean (SEM)	SSZ, n = 25 Mean (SEM)	D	95% CI
Reference case*	2,208 (635)	2,650 (855)	443	–1,933, 2,245
Friction cost	1,813 (452)	1,762 (528)	–51	–705, 518
Weekly diary	2,208 (635)	2,650 (855)	443	–1,800, 2,448
Interview	2,405 (730)	1,873 (672)	–532	–2,645, 1, 184

C. Indirect costs (US $) of patients with a paid job at baseline during 0–56 weeks (reference case, friction cost method, weekly diary, interview)

	COBRA, n = 33 Mean (SEM)	SSZ, n = 32 Mean (SEM)	D	95% CI
Reference case*	6,024 (1,176)	6,206 (1,302)	182	–3,343, 3,420
Friction cost	4,208 (732)	3,949 (737)	–259	–1,391, 1,323
Weekly diary	5,922 (1,206)	6,262 (1,330)	340	–3,412, 3,975
Interview	5,897 (1,031)	5,787 (1,025)	–110	–3,106, 2,663

Intention to treat analysis. SEM: standard error of the mean; D: difference of the means, SSZ–COBRA. * Reference case: costs are calculated using the Human Capital Method.

Nevertheless, recently published 5-year followup data indicate that the rate of yearly radiographic progression remained lower in the COBRA group despite similar treatment and disease activity levels[22]. It is likely that without this tapering, the contrast between the groups in clinical efficacy and costs would have remained.

Full economic analyses of RA treatment are scarce[23-28]. However, awareness is growing about the importance of also including indirect costs in an economic evaluation. Our finding that about half of the total costs of RA were indirect costs supports this. To be relevant for policy decisions, the estimates of indirect costs need to reflect the real economic impact of disease[14]. Indirect costs play an important role if short-term absenteeism from work is affected considerably and if a significant proportion of the target population is employed at the moment they benefit from the program[14]. In this trial more than 40% of the patients had a paid job at baseline. If health care programs have a considerable influence on disability and mortality, estimates of indirect costs according to the Human Capital Method only illustrate the program's potential economic effect. This may overestimate the true economic consequences considerably[14].

Economic evaluations should preferably also include the indirect costs, not only for paid labor but also unpaid labor. However, data on work absenteeism and disability related to unpaid labor are scarce. To value the days patients were unable to perform normal daily activities is very difficult. Posnett and Jan[29] described that the most common approach is to value housework at the replacement-cost relevant wage for comparable services provided in the market, and on the basis of opportunity costs (measured by earnings foregone) of leisure. In this trial there was a statistically significant difference in days unable to perform normal daily activities in favor of COBRA for the remaining patients.

On the other hand, there are some objections against including indirect costs in economic evaluations. Inclusion may favor healthcare interventions directed to well-paid workers, which may conflict with equity considerations, especially when the results of economic studies are used to support decisions at the level of individual patient treatment. This objection could be countered by specifying a standard income for all patients in a trial for the cost-effectiveness analysis. We applied this method in our trial. A mean income for all patients formed the basis for calculations, instead of

the real income for each individual patient. Despite the same level of education at baseline, patients in the COBRA group received a higher salary than those in the SSZ group. Calculations with the real income would have resulted in inappropriately higher indirect costs in the COBRA group, even though the mean number of days of work loss in the COBRA was equal to or lower than that in the SSZ group.

In a study by Merkesdal, *et al*[30] the indirect costs for patients with early RA were estimated to be US $11,750 per person-year, for gainfully employed patients. Our trial included not only patients with a paid job but also patients with a disability pension, retired patients, and homemakers. This resulted in much lower indirect costs during the period of the trial for both therapy groups. The valuation of lost productivity has an enormous influence on the results. In the sensitivity analysis, Merkesdal, *et al*[30] found that using individual earnings instead of standardized valuation resulted in 24% lower costs per patient. Thus it is important to describe the number of days of work absenteeism and the valuation of these days in order to put the indirect costs into perspective.

In our trial 2 methods of data collection were used. Patients with a paid job had to fill out weekly diaries reporting the number of self-reported work-loss days. We anticipated that patients without a paid job would probably have difficulty accounting for the number of days they were not able to perform their normal daily activities. Therefore these patients were asked in the biannual interview to give an estimate of the total number of days they had been unable to perform normal daily activities. The sensitivity analysis showed that the indirect costs based on the biannual interview and weekly diaries were almost equal. Thus, in the future the weekly diaries can perhaps be clustered to a longer period without loss of valuable information. It must be kept in mind that some patients with a paid job may have shown up at work unable to perform to their previous capability. This aspect is difficult to measure and even more difficult to interpret. In this trial we focused only on the number of days absent from work.

In this study we divided patients into subcategories by their working status. Although we acknowledge that the number of patients in each study group was limited, we believe it is important to understand the impact of RA on the change in working status of the patients for each different subgroup.

In sensitivity analyses, the study results proved robust for the use of different resources to calculate indirect costs for patient with a paid job, but were sensitive to the use of self-reported number of days for patients with a disability pension, resulting in a difference in total costs during the first semester that was no longer statistically significant. The difference in costs between the Human Capital Method and the Friction Cost Method is limited due to the followup of one year. Costs that will be undertaken in the future are not taken into account in this trial. With a followup longer than one year the human capital costs will increase more than the friction costs.

It is well known that trials are usually underpowered to demonstrate cost differences with sufficient (statistical) confidence. Despite the considerable difficulties of assessing indirect costs adequately, the first-semester results of this study show that where such costs play an important role, power may actually be gained by including these costs in the analysis.

This study confirms that COBRA therapy is more effective compared to sulfasalazine in patients with early RA: i.e., better disease control at equal or lower total costs. However, these advantages were no longer significant when prednisolone and MTX were stopped. We suggest both validity and discrimination can increase when indirect costs are included in economic studies in RA.

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