British Journal of Rheumatology 1998;**37:**1102–1109

COST-EFFECTIVENESS AND COST-UTILITY OF COMBINATION THERAPY IN EARLY RHEUMATOID ARTHRITIS: RANDOMIZED COMPARISON OF COMBINED STEP-DOWN PREDNISOLONE, METHOTREXATE AND SULPHASALAZINE WITH SULPHASALAZINE ALONE

A. C. VERHOEVEN, J. C. BIBO, M. BOERS,* G. L. ENGEL and Sj VAN DER LINDEN for the COBRA TRIAL GROUP

*Department of Internal Medicine and Rheumatology, Maastricht University Hospital, Maastricht and *Department of Clinical Epidemiology, University Hospital 'de Vrije Universiteit', Amsterdam, The Netherlands*

SUMMARY

Objective. Assessment of the cost-effectiveness and cost-utility of early intervention in rheumatoid arthritis (RA) patients, with combined step-down prednisolone, methotrexate and sulphasalazine, compared to sulphasalazine alone.

Methods. Multicentre 56 week randomized double-blind trial with full economic analysis of direct costs and utility analysis with rating scale and standard gamble measurement techniques.

Results. The combined-treatment group included 76 patients and the sulphasalazine group 78 patients. The mean total costs per patient in the first 56 weeks of follow-up were $5519 for combined treatment and $6511 for treatment with sulphasalazine alone ($P = 0.37$). Out-patient care, in-patient care and non-health care each contributed about one-third to the total costs. The combined-treatment group appeared to generate savings in the length of hospital stay for RA, non-protocol drugs and costs of home help, but comparisons were not statistically significant. Protocol drugs and monitoring were slightly more expensive in the combined-treatment group. Clinical, radiographic and functional outcomes significantly favoured combined treatment at week 28 (radiography also at week 56). Utility scores also favoured combined treatment.

Conclusion. Combined treatment is cost-effective due to enhanced efficacy at lower or equal direct costs.

KEY WORDS: Early rheumatoid arthritis, Cost-effectiveness, Cost–utility analysis, Combined treatment, DMARDs, Glucocorticoids, Prednisolone, Methotrexate, Sulphasalazine, Randomized double-blind trial.

RHEUMATOID arthritis (RA) is a systemic disease with symmetrical inflammation of joints in the upper and lower extremities as the most important feature. Patients suffer from pain, stiffness, impaired function in daily life and at work, increased dependence on family and friends, and decreased participation in leisure activities. RA is associated with morbidity, worsening of quality of life and mortality [1, 2].

The monetary cost of RA is high due to increased use of out-patient medical services, increased hospitalization rates and major work disability in the course of the disease [3]. Intervention studies that include an economic evaluation in RA are rare [4] and, to our knowledge, non-existent in early RA.

A combination therapy regimen of step-down prednisolone, methotrexate and sulphasalazine, tested against sulphasalazine alone in early RA patients, demonstrated excellent clinical response, low toxicity and slowing of radiographic progression [5] (COBRA trial; COmbinatietherapie Bij Reumatoïde Artritis). The current full economic analysis addresses the question of whether this combined treatment is also cost-effective.

Submitted 15 December 1997; revised version accepted 2 June 1998.

Correspondence to: M. Boers, Department of Clinical Epidemiology VE9-78, VU University Hospital, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

PATIENTS AND METHODS

Study design

The methods of the COBRA study have been reported extensively [5]. Briefly, in a 1 yr double-blind randomized clinical trial, 156 RA patients (ACR criteria [6]), aged 18–70 yr, were randomly assigned to two treatment groups. All patients had early, active disease. No prior treatment with second-line anti-rheumatic medication, apart from antimalarials, was allowed. One group was treated with a combination of sulphasalazine, methotrexate and prednisolone; the other group was treated with sulphasalazine and double placebo. Prednisolone and methotrexate (or the placebos) were tapered and stopped after week 28 and week 40, respectively, while sulphasalazine was continued. All patients had calcium supplementation (1 g/day) prescribed for as long as they used prednisolone, and folic acid (1 mg/day) for as long as they used methotrexate. The primary clinical outcome was a pooled index [7]; a composite measure that reflects each patient's clinical improvement. This measure is suited for the comparison of clinical benefits between groups. In this report, the benefits are also expressed in terms of improved physical function and utility. All utility assessments were performed by trained independent assessors who contacted the patients only at baseline and four times thereafter. This way, the assessors stayed blind for effects of high-dose prednisolone during the first 6 weeks of the protocol. The study protocol was approved by research and medical ethics committees in all participating hospitals (nine

clinical centres in The Netherlands and one in Belgium). All patients gave informed consent in writing before they entered the study protocol between May 1993 and May 1995.

Costs

Costs were elicited from a societal perspective. To evaluate the economic consequences of combined treatment, only direct costs were considered. Direct costs are costs that are directly related to the intervention. These are detailed below in five parts: (1) costs of the intervention (protocol drugs and monitoring); (2) costs of non-protocol drugs; (3) other costs of out-patient care; (4) costs of in-patient care; (5) direct non-medical costs. The period of follow-up comprised 56 weeks in all patients.

Costs were primarily expressed in 1995 Dutch guilders and subsequently converted into US dollars ($) at the 1994 Purchasing Power Parities rate of 2.143:1 [8]. Where possible, specific cost prices were derived from cost research performed in the University Hospital Maastricht (Financial Control Group internal report, February 1996). These cost prices were generalized to all participating clinical centres. Data on health care utilization were obtained from patient diaries specifically developed for this study. Patients were asked to complete forms for 56 weeks; these weekly forms were collected at every control visit. Additional data were collected from hospital records and biannual structured interviews. In the case of doubt, the hospital record was decisive (e.g. to determine the exact duration of hospitalization). Patients were asked to report every health care utilization, regardless of whether it was related to their disease, because the symptoms and signs as well as the side-effects of treatment in RA are very heterogeneous, and possibly unknown [9].

Total intervention costs comprise costs of the therapeutic intervention itself and costs related to the necessary monitoring of adverse effects. The costs of protocol medication were calculated per patient by multiplying prices (1995 Dutch pharmacy standards, handling costs included) by the volume of protocol medication in the first 56 weeks. The costs of calcium and folic acid supplements were only attributed to the combined-treatment group, although patients in both treatment groups had these prescribed. The costs of monitoring were based on a post hoc consensus among the trial rheumatologists who were knowledgeable on the prevalence of toxicity that had occurred during the trial. They set the frequency of out-patient rheumatology consultation at seven in the first year for either treatment, the frequency of laboratory monitoring for sulphasalazine treatment at seven and that for combined treatment at eight. With respect to the extensiveness of laboratory monitoring, we referred to the programme that was used during the trial. This is open to discussion, and will be dealt with in the sensitivity analysis. Annual radiography of hands and feet to assess joint damage was considered to be part of normal clinical practice in patients with early RA and the integral monitoring schedule of both treatment groups. These costs were included. In addition, bone density measurement and thorax radiography were considered mandatory in patients before starting combined treatment to assess pre-existing osteopenia and to exclude pulmonary tuberculosis; these costs were attributed to combined-treatment only. Remaining costs strictly related to the execution of the trial were not included, e.g. costs of outcome assessments and extra visits.

Costs of non-protocol medication (prescription and 'over-the-counter' drugs) were assessed by records from the diaries. Four different classes of medication were distinguished: non-steroidal anti-inflammatory drugs (NSAIDs) and analgetics, gastroprotective agents, disease-modifying anti-rheumatic drugs (DMARDs) (apart from protocol medication) and miscellaneous.

Apart from medication, health care utilization included visits to the general practitioner, specialists, physiotherapists, and any diagnostic and all therapeutic procedures ordered as a consequence of these visits. The costs of consultation of a general practitioner ($15) or physiotherapist ($16) were based on charges. The costs of out-patient department specialist consultations (ranging from $22 to $55 per consultation) were based on records of 26 (17%) trial patients in the University Hospital Maastricht and generalized per treatment group to patients from other participating clinical centres. Although registered, costs for any aids (prostheses and ortheses) and adjustments to the patients' homes are not reported here (the volume of different aids and adjustments is relatively small, and the reimbursement systems both in The Netherlands and Belgium vary substantially by municipality).

Costs of hospitalization were priced at $400/day in a university or non-university hospital (based on cost research) and $110/day in a rehabilitation centre (charge derived from the literature [10]).

The direct non-medical costs comprise costs for professional or non-professional help at home, costs related to loss of leisure time of the patient and an accompanying person where necessary, transportation costs, and out-of-pocket expenses for disease-related activities and purchases. Costs of paid and unpaid help were derived from the time estimates registered in the weekly patient diary. The price for qualified housekeeping was set at $11. Unpaid help was valued at 80% of the price for professional help. Loss of leisure time due to visiting health care-providing institutes was valued at $2.12/hour, a price derived from a literature survey [10]. Travel costs were calculated from the number of visits (excluding those for trial purposes only) and costs per visit. Kilometre distances were gathered from a route-planning computer package that uses postal area codes. The kilometre price was set at $0.27, an amount also in use for reimbursement purposes. Out-of-pocket expenses include such costs as swimming in extra heated pools and costs of alternative health care (calculated from patients' reports in the biannual interviews).

As the time frame of follow-up in this report is only a little over 1 yr, no discounting of future costs (or benefits) back to current value was carried through.

Arthritis-related indirect costs, such as sick leave or occupational disability, are not reported here, but will be elucidated in a separate article with a follow-up period of >1 yr.

Efficacy measures: clinical effects

The primarily clinical outcome was a pooled index. This composite measure comprised each patient's standardized improvement in erythrocyte sedimentation rate (ESR), grip strength, tender joint count, observer's global assessment and improvement in functional ability (scored from the MacMaster Toronto Arthritis patient preference interview [11]). A secondary endpoint was radiographic damage of joints in hands and feet, expressed in a quantitative score for erosions and joint space narrowing [12]. Many clinicians feel that this type of radiological damage score represents cumulative disease activity [13]. Radiographs were read by two trained independent observers unaware of treatment allocation. Physical function was evaluated by a validated Dutch version of the Health Assessment Questionnaire [14, 15] filled out by the patients at baseline, and weeks 16, 28, 40 and 56.

Interpolation of each patient's scores at five time points yielded a time-integrated score reflecting average clinical benefit and disability during the 56 week follow-up period. Direct costs in both treatment groups were related to the clinical benefits; between-group differences in time-integrated units of the pooled index, progression of radiographic damage and time-integrated functional disability scores may be used in cost-effectiveness ratios.

Efficacy measures: utilities

In addition to traditional measures of efficacy, utilities by standard gamble and rating scale methods were measured at baseline, and weeks 28 and 56. A utility is a single comprehensive outcome measure that reflects the value or preference that respondents assign to a particular health state. This value is expressed on a scale ranging from 1 (perfect health) to 0 (death), and takes into account both the positive treatment effects and the negative side-effects. We elicited utilities from patients participating in the trial by means of the Maastricht Utility Measurement Questionnaire, a reliable and validated adaptation in Dutch of the MacMaster Utility Measurement Questionnaire [16, 17]. It is administered as an interview. Utility measurement using this questionnaire comprises the rating scale and the standard gamble methods. The rating scale measures utilities directly by asking the patients to place health states on a thermometer scale (i.e. vertical visual analogue scale). The standard gamble method derives utilities from the patients' responses to decision situations under risk. A chance board with a probability wheel was used as a visual aid to facilitate the standard gamble questions.

The quality adjusted life year (QALY) is a measure that expresses effects in terms of both quality of life and survival. A calculation of the area under the curve of the baseline and biannual assessments of utility yielded an approximation of QALY gained in each treatment group. We restricted our time window to the first 56 weeks of the protocol in every patient, i.e. we did not extrapolate by multiplying the result with a life expectancy approximation. Direct costs in both treatment groups were related to the gained QALYs to yield cost–utility ratios.

Sensitivity analysis

Sensitivity analysis tested the robustness of the cost estimates obtained. Volumes, as well as prices, especially those solely based on assumptions, were varied to evaluate the resulting change in the costs. The focus was on the influence of set prices of hospital admissions and help at home, as in this study other volumes were based on empirical data. Each of these two prices were varied by adding and subtracting 25%. The relative price for help by non-professionals was also reduced from the original 80 to 0% of professional charges. Monitoring costs were set at a fixed level in the primary analysis. The monitoring schedule is the consensus of the trial rheumatologists achieved in completion of the study. The economic consequences of different monitoring schedules (i.e. a 25% increase) were considered, as not only the frequency, but also the extensiveness, of the monitoring schedule for combined treatment is open to discussion. The monitoring costs for treatment with sulphasalazine alone were derived from a published ACR recommendation [18]. Here, we did not change the frequency of laboratory checks as our protocol agreed with this standard.

Statistical analysis

To analyse the difference in costs between the combined-treatment and sulphasalazine group, costs per patient-year (of 56 weeks) were calculated and expressed as means per patient per group. As costs are cumulative, the mean is a useful statistic because of its direct relationship to the sum. Although the distribution of costs was skewed, the number of patients in our trial permitted parametric (Student's t) testing for between-group differences in mean aggregate costs (central limit theorem). In the secondary analyses on the differences in volumes, non-parametric Mann-Whitney tests were preferred. All differences in volume were tested per semester because a priori maximal contrast was expected in the first semester considering the withdrawal of combined treatment after week 28. No adjustments were made for multiple testing. All analyses were performed on an intention-to-treat basis.

RESULTS

In one patient (randomized to combined treatment), protocol medication was stopped within 1 week because his disease was in remission at baseline. Another patient (randomized to sulphasalazine treatment) dropped out in week 2 due to adverse effects (skin rash) and was lost to follow-up for most cost parameters. Data from these two patients were excluded from the analysis. Consequently, the

combined-treatment group included 76 patients and the sulphasalazine group 78 patients. Data on costs were complete for all these patients. Both groups were balanced in most important demographic and prognostic variables (Table I).

The mean total costs per patient in the first 56 weeks of follow-up were \$5519 for combined treatment and \$6511 for treatment with sulphasalazine alone ($P = 0.37$; Table II). Out-patient care, in-patient care and non-health care each contributed about one-third to the total costs. In the first semester, total costs were almost twice those in the second semester. By definition, combined treatment (protocol drug cost) was more expensive than sulphasalazine: \$326 *vs* \$181 per patient. Likewise, the monitoring schedules cost \$839 per year in the combined-treatment group *vs* \$559 in the sulphasalazine group (Table III). The costs of drugs outside the protocol were significantly lower in the combined-treatment group (\$237 *vs* \$329; $P < 0.001$). This was mainly due to lower use of NSAIDS, analgetics and gastroprotective drugs in the combined-treatment group, especially during the first semester.

Apart from the intervention under study and non-protocol drugs, the costs of ambulant care were slightly lower in the combined-treatment group. Patients in the combined-treatment group consulted their general practitioners more often, but paid less visits to physio- and ergotherapists (Table IV). Taken together, the effect of protocol treatment predominated to make combined treatment \$219 more expensive than sulphasalazine in out-patient costs ($P = 0.007$).

Costs of in-patient care were a mean \$917 lower for combined treatment compared to sulphasalazine ($P = 0.27$). This was mainly due to a significantly lower number of in-hospital days in admitted patients during the first semester: 515 *vs* 190 days ($P = 0.05$). In the first semester, the number of hospital admissions was 18 in the combined-treatment group *vs* 24 in the sulphasalazine group; in the second semester, there were seven admissions in both groups. Admissions were shorter in the combined-treatment group; mean 11.6 *vs* 20.1 days.

Total direct non-medical costs were a mean \$1840 for patients in the combined-treatment group and \$2133 in the sulphasalazine group ($P = 0.54$). Home help accounted for 94%. Not all of these costs were really spent, as not only professional but also voluntary help by spouse, family or friends was appraised. The demand decreased slightly in the second semester. Patients in the combined-treatment group reported less help than patients in the sulphasalazine group, but this difference was not significant.

The clinical effects have been fully reported elsewhere [5]. Briefly, at week 28, the mean improvement in terms of the pooled index was 1.4 for the combined-treatment group and 0.8 for the sulphasalazine group ($P < 0.0001$). At week 56, these values were 1.1 *vs* 0.9. Comparison of time-integrated indices (with four follow-up measurements and baseline by definition equal to zero) shows mean improvement of 1.1 *vs* 0.7 ($P = 0.0001$). Radiographic damage scores of both groups were comparable at baseline. At this time, 23% of the patients in the combined-treatment group and 19% in the sulphasalazine group showed no damage. After 56 weeks, the median progression in the radiographic damage score was two points in the combined-treatment group *vs* six in the sulphasalazine group ($P = 0.004$). Baseline and follow-up data on disability of 154 patients were available (76 combined-treatment and 78 sulphasalazine). Baseline scores of both groups were comparable. At week 28, the improvement in the disability score was 1.1 for the combined-treatment group and 0.6 for the sulphasalazine group ($P < 0.0001$). At week 56, improvement compared to baseline was 0.8 *vs* 0.6 ($P = 0.06$). Comparison of 56 weeks time-integrated scores showed mean improvement scores of 0.83 *vs* 0.50 ($P = 0.0003$).

Utility assessments including baseline and two follow-up assessments were available for 67 patients in the combined-treatment group and 75 in the sulphasalazine group. Baseline utility assessment resulted in similar scores for both treatment groups; scores with the rating scale method were 0.55 (S.D. 0.18) and 0.55 (0.20) for the combined-treatment and sulphasalazine group, respectively; scores with standard gamble were 0.78 (0.16) and 0.76 (0.19). At week 28, rating scale utility scores increased by 0.24 (S.E.M. 0.02) in the combined-treatment and 0.15 (0.02) in the sulphasalazine group ($P = 0.006$). Standard gamble utility scores increased by 0.10 (0.02) in the combined-treatment and 0.06 (0.02) in the sulphasalazine group ($P = 0.05$). At week 56, most of the between-group contrast seen after the first semester was lost: mean improvement

TABLE I
Baseline characteristics of the study patients, according to treatment group*

	Combined treatment ($n = 76$)	Sulphasalazine ($n = 78$)
Age (yr)	49 ± 12	49 ± 12
Female	50 (66%)	40 (51%)
Educational years	10 ± 3	10 ± 3
Married	69 (91%)	71 (91%)
Professional occupation >2 days/week	25 (33%)	26 (33%)
Disease duration (months)	4 (1–24)	4 (1–23)
Previous treatment with antimalarials	16 (21%)	19 (24%)
Hospitalized for RA at baseline	9 (12%)	11 (14%)
Positive IgM rheumatoid factor	59 (78%)	57 (72%)
Erosions on hand or foot radiographs†	55 (74%)	59 (79%)
Number of tender joints (0–68)	25 ± 14	24 ± 14
Grip strength (kPa)	24 ± 15	29 ± 20
Erythrocyte sedimentation rate (mm/h)	57 ± 34	53 ± 32
Global assessment observer (mm; 0–100)	53 ± 24	51 ± 22
MACTAR functional ability questionnaire	24 ± 4	24 ± 4
Health Assessment Questionnaire (0–3)	1.5 ± 0.7	1.4 ± 0.7

*Mean ± S.D., count and percentages, or median (minimum–maximum).

†Patients with available baseline radiographs; combined treatment group $n = 74$, sulphasalazine group $n = 75$.

TABLE II
Direct costs of treatment in 56 weeks of follow-up*

Direct costs (US$)	1st semester (week 0–28) COBRA Mean (S.E.M.)	SSZ Mean (S.E.M.)	Difference†	95% CI	P	2nd semester (week 29–56) COBRA Mean (S.E.M.)	SSZ Mean (S.E.M.)	Difference†	95% CI	P
Health care										
Intervention										
Protocol drug(s)	190	88	102		‡	137	93	44		‡
Monitoring	652	409	243		‡	187	150	37		‡
Non-protocol drugs	130	186	−56		0.003	108	143	−35		0.06
Other	364	444	−80		0.08	378	414	−36		0.03
Total out-patient care	1336 (39)	1127 (34)	208	113; 303	<0.001	810 (25)	800 (32)	10	−70; 91	0.79
Total in-patient care	1002 (478)	1868 (390)	−866	−2076; 343	0.16	532 (304)	582 (286)	−50	−874; 772	0.90
Non-health care	1018 (205)	1223 (178)	−205	−739; 329	0.45	821 (182)	911 (134)	−90	−534; 356	0.69
Total	3356 (600)	4218 (457)	−863	−2343; 617	0.25	2163 (407)	2293 (330)	−130	−1161; 902	0.80

Direct costs (US$)	1st year (week 0–56) COBRA Mean	COBRA Min–max	SSZ Mean	SSZ Min–max	Difference†	95% CI	P
Health care							
Intervention							
Protocol drug(s)	326		181		146		‡
Monitoring	839		559		280		‡
Non-protocol drugs	237		329		−92		<0.001
Other	742		858		−116		0.38
Total out-patient care	2146	1514–4284	1927	1140–3536	219	62; 375	0.007
Total in-patient care	1534	0–26 690	2451	0–25 934	−917	−2573; 739	0.27
Non-health care	1840	15–12 885	2133	6–16 773	−293	−1232; 645	0.54
Total	5519	1562–43 860	6511	1190–35 387	−992	−3204; 1220	0.37

*COBRA, combined treatment of step-down prednisolone, methotrexate and sulphasalazine. SSZ, sulphasalazine. Intention-to-treat analysis; combined treatment: $n = 76$; sulphasalazine: $n = 78$.
†Positive values indicate higher costs for the group with combined treatment.
‡Costs fixed per protocol.

TABLE III
Costs of possible monitoring schedules during the first 56 weeks of treatment

For combined treatment (post hoc consensus rheumatologists, see Patients and methods):	
8 × : laboratory tests:	
ESR, haemoglobin, haematocrit, white blood cell count (WBC) including differentiation, platelet count and mean corpuscular volume, ALAT, ASAT, bilirubin, alkaline phosphatase, glucose, creatinine, sodium, potassium, phosphate, calcium, albumin and total protein, urinalysis (albumin and glucose)	US$292
1 × : hands and feet radiographs	US$124
1 × : thorax radiographs	US$ 36
1 × : bone densitometry lumbar spine and one hip	US$207
7 × : consultation rheumatologist	US$180
	Total US$839
For sulphasalazine treatment (post hoc consensus rheumatologists):	
7 × : laboratory tests (see above)	US$256
1 × : hands and feet radiographs	US$124
7 × : consultation rheumatologist	US$180
	Total US$559
For sulphasalazine treatment according to ACR recommendations [18]:	
7 × : laboratory tests:	
haemoglobin, WBC including differentiation and platelet count	US$ 53
1 × : hands and feet radiographs	US$124
7 × : consultation rheumatologist	US$180
	Total US$357

TABLE IV
Volumes of out-patient care. Number of visits to health care professionals*

	1st semester (week 0–28)		2nd semester (week 29–56)		1st year (week 0–56)	
	COBRA	SSZ	COBRA	SSZ	COBRA	SSZ
General practitioner	104	76	108	97	212	173
Physiotherapists	428	706	318	407	746	1113
Ergotherapists	31	85	11	48	42	133

*COBRA, combined treatment of step-down prednisolone, methotrexate and sulphasalazine. SSZ, sulphasalazine. Intention-to-treat analysis; COBRA: $n = 76$; SSZ: $n = 78$.

with rating scale 0.18 (0.03) in the combined-treatment group *vs* 0.16 (0.02) in the sulphasalazine group, and with standard gamble 0.07 (0.02) *vs* 0.07 (0.02). The area under the curve calculation of the utility scores demonstrated a significantly better gain of 0.06 QALY assessed by rating scale ($P = 0.01$; 95% CI: 0.02; 0.10). Assessed by standard gamble, the difference is 0.02 gained QALY ($P = 0.33$; -0.02; 0.06).

The efficacy of the combined treatment in clinical outcomes is superior to sulphasalazine alone. The total costs are slightly lower, although not significantly so in the combined group. Accordingly, relative cost-efficacy favours combined treatment; it will be cost-effective when implemented in patients comparable to those included in this COBRA trial. Likewise, significantly better utility scores and equal costs result in better cost–utility ratios in the combined-treatment group.

No extra toxicity due to the extra medication in the combined-treatment group occurred. On the contrary, significantly fewer patients in the combined-treatment group stopped protocol medication due to adverse events or lack of therapy effect; 6 *vs* 23 in the sulphasalazine group ($P = 0.0008$). The drop-outs in the combined-treatment group also occurred later. Loss of bone mineral density in spine and hips was modest, and not significantly different in both groups; in the combined-treatment group, bone density in the lumbar spine decreased by a mean of 1.3% in 56 weeks.

In the sensitivity analysis, when the price of hospitalization was reduced by 25%, the mean total cost remained $849 lower in the combined-treatment group. The same adjustment in the charge for help at home resulted in a smaller between-group contrast of $900. When the price for help at home by non-professionals was set at zero, mean total costs of combined-treatment remained $443 lower than costs of treatment with sulphasalazine. Finally, the consequences of adjustments to the monitoring schedule were tested (Table III). The adjusted monitoring costs were $1049 (+25%) and $357 (−36%) for combined treatment and sulphasalazine, respectively; this still resulted in $580 lower total costs for combined treatment.

DISCUSSION

In the setting of a randomized trial, this full economic analysis revealed combined treatment with step-down prednisolone, methotrexate and sulphasalazine to be more effective than sulphasalazine alone at equal or lower costs. The combined-treatment group had lower expenses for non-protocol medication and in-patient care, and lower costs outside the health care

system that offset the higher costs for protocol medication and monitoring.

The efficacy of the combined treatment in clinical as well as radiological outcomes is superior to sulphasalazine alone. As the total direct costs in the combined-treatment group were equal or lower, relative cost-efficacy favours combined treatment. Utility scores, as a generic measure of therapy benefits, also favoured combined treatment. Concordant with other reported studies, the scores derived with the standard gamble method were at an absolute higher level and least responsive to change. This has been attributed to the risk-aversive attitude of patients with a putatively non-fatal or chronic disease like RA [19].

The time frame of this study is long compared to most other studies, but still relatively short for a chronic disease like RA, and definitely too short to evaluate the incidence of late effects. Continuing follow-up of the included patients will provide important answers on costs and outcomes in the long run. Prednisolone might have induced modest (non-significant, mean $<1\%$) and partially reversible bone loss, but this did not result in symptomatic fractures or complaints in any of the patients.

Like most clinical trials, this trial was primarily designed to study clinical benefits and thus probably underpowered to prove cost benefits. A post hoc power calculation reveals minimum group sizes of 374 necessary for the between-group difference found to reach the level of significance ($P < 0.05$, two-sided). The only significant difference in cost found favoured the sulphasalazine group, i.e. $219 lower costs for outpatient care. However, this can be largely attributed to the per protocol (fixed) difference in intervention costs.

Sensitivity analysis showed the robustness of the conclusions in the economic analysis. The direct costs of combined treatment are not significantly lower (and must thus be presumed to be similar to the costs of treatment with sulphasalazine alone). On the other hand, calculations with considerable alternations in the assumptions of charges and extensiveness of monitoring schedules consistently showed lower costs for combined treatment. As the primary analysis of the trial showed significantly less drop-out due to therapy failure and adverse events in the combined-treatment group, a less frequent and extensive monitoring schedule than that performed during the trial might be appropriate in normal clinical practice. Also, the necessity of initial bone densitometry—in this analysis still regarded as mandatory for combined treatment—is questionable with regard to the observed modest effects on bone.

The generalizability of our findings is principally restricted to the health care systems in The Netherlands and Belgium. The health care system in these countries is characterized by universal access and equal facilities for all inhabitants, and small distances between patients' homes and clinical centres. From a North American perspective, patients were frequently hospitalized [20]. Notably, at baseline, all included patients had active disease, and restrictions to the number or duration of hospitalizations would most likely have worsened the outcomes in the more frequently hospitalized sulphasalazine group [21]. Moreover, the costs of health care found in this study do not seem to be 'out of range' in comparison with figures from an American health care setting [9, 20].

In comparison with sulphasalazine, combined treatment is the dominant therapeutic option, due to equal or lower costs and enhanced efficacy. This full economic analysis confirms that combined treatment with step-down prednisolone, methotrexate and sulphasalazine may be a rational choice in early and active RA.

Acknowledgements

The COBRA trial was funded by grant 92-045 Ontwikkelingsgeneeskunde, Ziekenfondsraad, The Netherlands, of which ACV was a research fellow. We thank Pharmacia and Upjohn, Sweden, for providing sulphasalazine free of charge, and are grateful to Mrs Carla Bakker for her contribution in the development of the utility interview, to Mrs Marjolein Braeken for trial management and to Mrs Lily Heusschen-Houben for data entry. The COBRA trial group comprised the following centres and rheumatologists: Daniël den Hoed Kliniek, Rotterdam, H. M. Markusse; Medisch Spectrum Twente and Twenteborg Hospital, Enschede and Almelo, M. A. F. J. van de Laar; University Hospital, Maastricht, M. Boers; Pellenberg Hospital, Catholic University, Leuven, Belgium, R. Westhovens; Jan van Breemen Instituut, Amsterdam, J. C. van Denderen; Bronovo Hospital, The Hague, D. van Zeben; University Hospital, Leiden, B. A. C. Dijkmans; Reinier de Graaf Gasthuis, Delft, A. J. Peeters; Sint Laurentius Hospital, Roermond, P. Jacobs; Medisch Centrum, Alkmaar, H. R. van den Brink.

References

1. Gordon DA, Hastings DE. Rheumatoid arthritis. Clinical features: early, progressive and late disease. In: Klippel JH, Dieppe PA, eds. Rheumatology. St Louis: Mosby, 1994:1–14.
2. Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. J Rheumatol 1991;18:1290–7.
3. McIntosh E. The cost of rheumatoid arthritis. Br J Rheumatol 1996;3:781–90.
4. Bosi Ferraz M, Maetzel A, Bombardier C. Critical appraisal of economic evaluation published in the field of rheumatology and related disciplines. Arthritis Rheum 1997;40:1587–93.
5. Boers M, Verhoeven AC, Markusse HM *et al.* Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
6. Arnett FC, Edworthy SM, Bloch DA *et al.* The American Rheumatism Association revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
7. Smythe HA, Helewa A, Goldsmith CH. 'Independent assessor' and 'pooled index' as techniques for measuring

treatment effects in rheumatoid arthritis. J Rheumatol 1977;4:144–52.
8. Centraal Economisch Plan. The Hague: SDU, 1996.
9. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. J Rheumatol 1997;24:719–25.
10. Rutten FFH, van Ineveld BM, van Ommen R, van Hout BA, Huijsman R. Directe kosten binnen de gezondheidszorg. In: Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk. Utrecht: van Arkel, 1993.
11. Tugwell P, Bombardier C, Buchanan WW, Goldsmith CH, Grace E, Hanna B. The MACTAR patient preference disability questionnaire: an individualized functional priority approach for assessing improvement in physical disability in clinical trials in rheumatoid arthritis. J Rheumatol 1987;14:446–51.
12. van der Heijde DMFM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LBA. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;i:1036–8.
13. van Leeuwen MA, van der Heijde DMFM, van Rijs wijk MH *et al.* Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol 1994;21:425–9.
14. Fries JF, Spitz PW, Young DY. The dimensions of health outcome: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol 1982;9:789–93.
15. Siegert CEH, Vleming LJ, Vanderbroucke JP, Cats A. Measurement of disability in Dutch rheumatoid arthritis patients. Clin Rheumatol 1984;3:305–9.
16. Bennett K, Torrance GR, Tugwell P. Methodological challenges in the development of utility measure of health-related quality of life in rheumatoid arthritis. Control Clin Trials 1991;12 (suppl.):118–28.
17. Bakker CH, Rutten-van Mölken MPMH, van Doorslaer EKA, Bennet K, van der Linden S. Health related utility assessment by rating scale and standard gamble in patients with ankylosing spondylitis or fibromyalgia. Patient Educ Counsel 1993;20:145–52.
18. American College of Rheumatology ad hoc committee on clinical guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:723–31.
19. Goossens MEJB, Rutten-van Mölken MPMH, Leidl RMJ, Bos SGPM, Vlaeyen JWS, Teeken-Gruben NJG. Cognitive-educational treatment of fibromyalgia: Randomized clinical trial. II Economic evaluation. J Rheumatol 1996;23:1246–54.
20. Lanes SF, Lanza LL, Radensky PW *et al.* Resource utilization and cost of care for rheumatoid arthritis and osteoarthritis in a managed care setting. The importance of drug and surgery costs. Arthritis Rheum 1997;40: 1475–81.
21. Vliet Vlieland TPM, Zwinderman AH, Vandenbroucke JP, Breedveld FC, Hazes JMW. A randomised clinical trial of in-patient multidisciplinary treatment versus routine outpatient care in active rheumatoid arthritis. Br J Rheumatol 1996;35:475–82.