Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 47, No. 5, October 15, 2002, pp 459–467
DOI 10.1002/art.10658

ORIGINAL ARTICLE

Cost Effectiveness of Combined Spa–Exercise Therapy in Ankylosing Spondylitis: A Randomized Controlled Trial

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Objective. **To evaluate the cost effectiveness and cost utility of a 3-week course of combined spa therapy and exercise therapy in addition to standard treatment consisting of antiinflammatory drugs and weekly group physical therapy in ankylosing spondylitis (AS) patients.**

Methods. **A total of 120 Dutch outpatients with AS were randomly allocated into 3 groups of 40 patients each. Group 1 was treated in a spa resort in Bad Hofgastein, Austria; group 2 in a spa resort in Arcen, The Netherlands. The control group stayed at home and continued their usual activities and standard treatment during the intervention weeks. After the intervention, all patients followed weekly group physical therapy. The total study period was 40 weeks. Effectiveness of the intervention was assessed by functional ability using the Bath Ankylosing Spondylitis Function Index (BASFI). Utilities were measured with the EuroQoL (EQ-5D$_{utility}$). A time-integrated summary score defined the clinical effects (BASFI-area under the curve [AUC]) and utilities (EQ-5D$_{utility}$-AUC) over time. Both direct (health care and non-health care) and indirect costs were included. Resource utilization and absence from work were registered weekly by the patients in a diary. All costs were calculated from a societal perspective.**

Results. **A total of 111 patients completed the diary. The between-group difference for the BASFI-AUC was 1.0 (95% confidence interval [95% CI] 0.4–1.6; $P = 0.001$) for group 1 versus controls, and 0.6 (95% CI 0.1–1.1; $P = 0.020$) for group 2 versus controls. The between-group difference for EQ-5D$_{utility}$-AUC was 0.17 (95% CI 0.09–0.25; $P < 0.001$) for group 1 versus controls, and 0.08 (95% CI 0.00–0.15; $P = 0.04$) for group 2 versus controls. The mean total costs per patient (including costs for spa therapy) in Euros (€) during the study period were €3,023 for group 1, €3,240 for group 2, and €1,754 for the control group. The incremental cost-effectiveness ratio per unit effect gained in functional ability (0–10 scale) was €1,269 (95% CI 497–3,316) for group 1, and €2,477 (95% CI 601–12,098) for group 2. The costs per quality-adjusted life year gained were €7,465 (95% CI 3,294–14,686) for group 1, and €18,575 (95% CI 3,678–114,257) for group 2.**

Conclusion. **Combined spa–exercise therapy besides standard treatment with drugs and weekly group physical therapy is more effective and shows favorable cost-effectiveness and cost-utility ratios compared with standard treatment alone in patients with AS.**

KEY WORDS. Cost-effectiveness analysis; Cost-utility analysis; Randomized clinical trial; Ankylosing spondylitis; Spa therapy.

INTRODUCTION

Treatment of ankylosing spondylitis (AS) is aimed at reducing symptoms and preventing, or at least minimizing, spinal deformity and disability. Standard treatment of active AS consists of nonsteroidal antiinflammatory drugs (NSAIDs), which reduce pain and stiffness, and physical therapy, which prevents deformity and improves or maintains mobility, fitness, and strength (1). Patients are advised to exercise daily and to follow weekly group physi-

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Submitted for publication May 9, 2001; accepted in revised form January 19, 2002.

cal therapy. In addition, patients may annually take courses of spa therapy in a spa resort. Spa therapy has a longstanding history, but apart from the opinions of participants, its value is largely unknown. It is usually considered expensive, and reimbursement by insurance companies is inconsistent.

Recently in a randomized controlled trial in patients with AS, we have demonstrated considerable and persistent improvements in a variety of clinical outcomes after a 3-week course of spa therapy in combination with physical exercises in addition to standard treatment with NSAIDs and weekly group physical therapy compared with standard treatment alone (2). In this article we present the results of incremental cost-effectiveness and cost-utility analyses of combined spa therapy and exercise therapy in patients with AS.

PATIENTS AND METHODS

Design. This economic evaluation, performed from a societal perspective, was designed alongside a randomized, controlled trial on the efficacy of combined spa–exercise therapy in AS. The methodology of this trial has been published elsewhere (2). In brief, 120 Dutch patients with active AS were recruited and randomly allocated to 3 groups of 40 patients each. Group 1 received spa therapy at a spa resort in Bad Hofgastein, Austria. Group 2 received spa therapy at a spa resort in Arcen, The Netherlands. The control group stayed at home and continued their usual activities and drug treatment, and followed weekly group physical therapy during the 3 intervention weeks. Spa–exercise therapy was standardized and consisted of group physical exercises, walking, postural correction therapy (lying supine on bed), hydrotherapy, sports, and thermal treatment by visits to either the so-called Heilstollen (Austria) or the sauna (The Netherlands). After the intervention period, all patients from the 3 groups continued weekly group physical therapy for another 37 weeks, consisting of 1 hour of physical exercises, 1 hour of sports, and 1 hour of hydrotherapy. During the intervention and the followup period, all patients continued their usual drug treatment, but were allowed to change this, if needed.

Spa–exercise therapy took place from T_{0w} (start of spa therapy) to T_{3w} (3 weeks after start of spa therapy). Assessments, consisting of questionnaires, were performed at baseline (2 weeks prior to spa therapy), and at 4 weeks, 16 weeks, 28 weeks, and 40 weeks after the start of spa–exercise therapy.

Assessments, consisting of questionnaires were performed at baseline (2 weeks before spa therapy; T_{-2w}), and at 4 weeks (T_{4w}), 16 weeks (T_{16w}), 28 weeks (T_{28w}), and 40 weeks (T_{40w}) after the start of spa–exercise therapy.

Effectiveness measurement. The primary outcomes of the study were functional ability assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) (3), pain assessed by a 10-cm visual analog scale (VAS), global well-being assessed by a 10-cm VAS, and duration of morning stiffness in minutes. The BASFI contains 10 questions concerning activities of daily living, scored on a 10-cm VAS with anchors "easy" and "impossible" at either end. The mean of the items defines the final score, ranging from 0 (best) to 10 (worst). The BASFI has been shown to be a valid, reliable, and responsive instrument for measuring function in AS (3–7). The results on the BASFI are used here to express effectiveness of the intervention and to calculate the cost-effectiveness ratio. The scores on the pain and global question range from 0 (best) to 10 (worst).

Utility measurement. Utilities refer to preferences individuals or society may have for any particular health state (8). For the present study, the EuroQol (EQ-5D$_{utility}$) was chosen to assess utility from a societal perspective (9). The EQ-5D$_{utility}$ measures quality of life in 5 dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be divided into 3 levels of severity: "no problems," "some problems," and "severe problems." The levels for each dimension are combined into one health state. For each of the possible health states, a utility is attributed from a societal point of view, based on a large population survey using the time-trade-off procedure (10,11). The final utility score ranges from 0 (representing death) to 1 (full health). The results of a cost-utility analysis are expressed as quality-adjusted life years (QALYs). A QALY is a composite index that includes effects in terms of both quality of life (utility) and the duration of time in such a health state (8).

Costs. In this incremental cost-effectiveness and cost-utility analysis, the recommendations proposed by the Dutch Guidelines for Pharmaco-Economic Analyses were followed as closely as possible (12). Direct (health care and non-health care) as well as indirect (non-health care) costs were included. Only costs related to AS were considered, including predefined AS-related disorders such as uveitis, inflammatory bowel disease, and psoriasis. The time horizon to measure costs was limited to the duration of the study (40 weeks).

Direct and indirect costs. All direct and indirect costs included are presented in Table 1. Acquisition of aids and appliances or adaptations to house or car were excluded, because they were considered not to be influenced by the intervention. For transport costs, only transport to and from the spa resort was considered (incorporated in the overall costs for spa–exercise therapy). Costs of informal (unpaid) help and patients' reported loss of time due to AS were not included in the base-case analysis. We assumed that the time spent on informal help was done in leisure time, i.e., not creating productivity loss of the helping person. Similarly, inactivity was also considered as taking place in leisure time, otherwise, this would have been registered as days of illness-related absence from work.

Resources. All resource utilization and number of days of illness-related absence from work were measured during the entire study period in a cost diary adapted from Goossens et al (13). Data from the day the intervention groups left for spa–exercise therapy up to 40 weeks afterwards were used for analysis. Patients made the determination as to whether the costs were related to AS or not.

Table 1. Categories, methods, and sources for valuation of unit costs*

Category costs	Method of valuation	Source of costs	Euro per unit
Direct health care			
Spa therapy in Bad Hofgastein, Austria	Market price	Spa resort Bad Hofgastein, Austria	1739
Spa therapy in Arcen, Netherlands	Market price	Spa resort Arcen, The Netherlands	1515
Weekly group physical therapy	Market price	Ankylosing spondylitis patient society	306
Visit to general practitioner	Cost per visit based on true cost calculations	DGEE	16.59
Outpatient visit to specialist in university hospital	Cost per visit based on true cost calculations	DGEE	40.84
Outpatient visit to specialist in non-university hospital	Cost per visit based on true cost calculations	DGEE	72.60
Alternative health care	Price per session or medication as registered by patient	Cost diary	
Physiotherapy	Cost per session based on true cost calculations	DGEE	18.15
Medication	Reimbursable price per prescription augmented with an extra contribution (€5.26) or price paid by patient in case of OTC medication	TAXE	
Additional diagnostic tests	Tariff	COTG	
Admission to university hospital	Day-price based on true cost calculations	DGEE	331.72
Admission to non-university hospital	Day-price based on true cost calculations	DGEE	235.97
Visit to emergency department	Integral (true) costs	Financial department hospital in question	199.66
Day care in rehabilitation center	Cost per hour based on true cost calculations	DGEE	79.87
Direct non-health care			
Formal help in household	Cost per hour as stated by patient or based on true cost calculations	Cost diary or DGEE	As stated or 8.53
Personal allowance	Integral (true) costs	Cost diary	
Indirect non-health care			
Workday lost because of illness	Production value of working day based on gross earnings of patient	Cost diary	

* OTC = over-the-counter; DGEE = Dutch Guidelines for Economic Evaluations; TAXE = official price list of the Royal Dutch Society of Pharmacists; COTG = Dutch official organization for tariffs in health care.

Valuation of costs. For the valuation of the health care costs, opportunity costs (representing market prices) are preferred from a theoretical point of view (12). In this comparative study they are reflected best by integral (i.e., true) costs. In The Netherlands, integral costs are not available for all resources (14). In these cases, tariffs were used (prices negotiated by health insurance companies). In Table 1, the method of valuation and source of all cost categories are presented and, if applicable, costs specified. The market price was used for the total cost of the spa–exercise therapy (see Table 2) and weekly group physical therapy (consisting of the honorarium of the physiotherapists, rent of sports and swimming accommodation, materials, and administrative costs). For the costs due to loss of productivity attributable to AS or related disorders, the friction cost method was used (15,16). In this method, the period of production loss due to illness is limited to the time needed to replace a sick worker or to reorganize the production process (4 months). The production value of this friction period was based on the reported gross earnings of the patients, corrected for part-time work and, if applicable, for the percentage of disability benefits.

All costs were calculated in Euros (€). Costs for 1999 were used and if not available for 1999, they were adapted using the Dutch health-specific price index (14).

Statistical analysis. The clinical trial was designed as an intent-to-treat analysis and the sample size was based on clinical outcomes (2). Between-group differences in clinical outcomes and utilities were analyzed by Student's *t*-tests for unpaired observations. Not normally distributed data were analyzed by Mann-Whitney U test. A time-integrated summary score, the area under the curve (AUC),

Table 2. Market price for spa therapy at the 2 spa resorts*

	Group 1 Spa therapy Austria	Group 2 Spa therapy The Netherlands
Travel costs from home to spa resort	102	11
Hotel accommodation (all meals included) and attendant	842	1040
Travel costs from hotel to spa resort during treatment period	29	89
Therapy costs and medical treatment	766	375
Total costs	1739	1515

* Costs per patient in Euros.

defined the effects and utilities over time. The AUC of the change from baseline was calculated with the trapezium rule standardized by the study duration (17,18).

Resource utilization and costs are reported as arithmetic means (±SD) per patient per group (19). The differences in volumes of resource utilization were analyzed by Mann-Whitney U test. The 95% confidence interval (95% CI) around the mean total costs per patient and the between-group differences in mean total costs were estimated with bootstrapping, repeating the analysis 10,000 times (20).

The incremental cost-effectiveness ratio was calculated by dividing the extra costs for the intervention group by the extra effects derived from it. The incremental cost-utility ratio was calculated by dividing the extra costs for the intervention group by the extra utilities derived from it, and expressed as costs per QALY gained. The 95% CIs of the ratios were estimated with bootstrapping. Because the time horizon of this study was <1 year, neither costs nor effects were discounted.

Sensitivity analysis. Four one-way sensitivity analyses were performed: 1) Costs of informal (unpaid) help were added to the base-case analysis. The costs per hour were based on a shadow price of €7.94. 2) Costs of patient-reported inactivity were added to the base-case analysis. In the cost diary, only the number of days lost due to inactivity was registered. Therefore, 2 analyses were performed considering a day of inactivity being either 4 or 8 hours. The costs per hour were based on a shadow price of €7.94. 3) The number of days of sick leave during spa-exercise therapy was varied. Only a few patients from the intervention groups reported sick leave during the 3 intervention weeks; most patients had voluntarily taken days off from work. The mean total costs and costs per QALY were recalculated first assuming that all patients would be on sick leave during the 3 intervention weeks, and second assuming that all patients would need to voluntarily take days off from work. 4) The outcome measures "global well-being" and "pain" were used as measures of effectiveness of the intervention in the incremental cost-effectiveness ratio. Morning stiffness was not investigated in a sensitivity analysis because it has a different scale (0 to infinite) compared with the other outcome measures (0 to 10), which could be misleading in cost-effectiveness ratios. In addition, morning stiffness is not sensitive to change.

RESULTS

Of the 120 participating patients, 9 did not complete the cost diary (2 from group 1, 4 from group 2, 3 from the

Table 3. Baseline characteristics of the 111 patients who completed the diary*

	Group 1 Spa therapy Austria (n = 38)	Group 2 Spa therapy The Netherlands (n = 36)	Control group physical therapy, home (n = 37)
Male/female	24/14	24/12	31/6
Age† (years)	47 (10) (range 29–68)	48 (9) (range 25–66)	48 (10) (range 29–63)
Disease duration† (years)	11 (6)	12 (5)	10 (6)
Inflammatory bowel disease (yes/no)	7/31	5/31	9/28
Uveitis (yes/no)	10/28	15/21	18/19
Psoriasis (yes/no)	4/34	4/32	4/33
Education† (years)	12 (4)	12 (4)	13 (4)
Manual/nonmanual profession	15/20	6/27	16/20
Paid work (yes/no)	21/17	17/19	23/14
Reasons no work‡			
Household	3	3	1
(Early) retirement	2	4	2
Work disability	13	12	12
Unemployment	0	1	0
Own choice	0	4	0

* Absolute number of patients.
† Mean (SD).
‡ Multiple answers were allowed.

Table 4. Clinical outcomes of 111 patients*

Measure (range)	Baseline value T_{-2w}	Change from baseline				Mean AUC of change during study period
		T_{4w}	T_{16w}	T_{28w}	T_{40w}	
BASFI (0–10)						
Group 1	4.9 (1.8)	1.1 (1.5)‡	1.0 (1.6)†	0.7 (1.5)†	0.4 (1.3)	1.0 (1.3)‡
Group 2	4.2 (2.0)	0.8 (1.2)‡	0.5 (1.1)	0.0 (1.2)	0.0 (1.1)	0.6 (1.0)†
Controls	4.2 (2.1)	0.0 (1.1)	0.0 (1.7)	−0.1 (1.7)	−0.1 (1.3)	0.0 (1.1)
Global wellbeing (0–10)						
Group 1	5.2 (2.0)	1.3 (2.8)	2.3 (2.4)†	1.4 (2.6)	1.1 (2.6)	1.5 (2.1)†
Group 2	5.3 (2.4)	1.8 (2.6)†	1.3 (3.0)	1.0 (2.9)	0.4 (2.6)	1.5 (2.5)
Controls	4.8 (2.4)	0.3 (3.0)	0.6 (3.1)	0.4 (2.8)	0.4 (2.8)	0.4 (2.6)
Pain (0–10)						
Group 1	4.6 (2.5)	0.7 (2.4)	1.4 (2.7)	0.8 (2.8)	0.1 (2.4)	1.0 (2.0)†
Group 2	4.6 (2.5)	1.4 (2.6)†	1.1 (2.7)	−0.3 (3.0)	−0.4 (2.8)	1.1 (2.3)
Controls	4.6 (2.7)	0.1 (2.3)	0.4 (2.8)	0.0 (2.8)	−0.2 (2.1)	0.1 (2.1)
Morning stiffness (min)§						
Group 1	30 (10;60)	3 (0;21)	3 (0;17)	0 (−6;15)	0 (−9;11)	8.9 (21.0)
Group 2	30 (15;60)	0 (0;18)	0 (−5;15)	0 (−6;14)	0 (−15;12)	3.1 (24.5)
Controls	30 (10;56)	5 (0;10)	4 (−5;15)	0 (−13;10)	0 (−5;15)	−3.4 (30.4)
$EQ\text{-}5D_{utility}$ (0–1)						
Group 1	0.64 (0.22)	0.10 (0.24)‡	0.12 (0.24)‡	0.10 (0.21)‡	0.03 (0.23)	0.11 (0.20)‡
Group 2	0.65 (0.22)	0.02 (0.20)†	0.04 (0.21)†	−0.03 (0.23)	−0.01 (0.27)	0.02 (0.17)†
Controls	0.72 (0.10)	−0.06 (0.18)	−0.04 (0.19)	−0.08 (0.28)	−0.03 (0.19)	−0.06 (0.14)

* Data are presented as mean (SD) at baseline, and as mean change (SD_{change}) from baseline. Group 1 (n = 38) spa therapy, Austria, group 2 (n = 36) spa therapy, The Netherlands, Controls (n = 37) home. Positive changes imply improvement.
† $P < 0.05$.
‡ $P < 0.01$ between intervention group and control group.
§ Skewed data are presented as median (interquartile range) and median change (interquartile range). Positive changes imply improvement.

control group), but they did not differ from the patient groups with respect to sex, age, work, or education. All analyses are based on the 111 (93%) patients who completed the cost diary. The baseline characteristics of the groups are presented in Table 3. All characteristics, except sex, were well balanced among the groups. Relatively fewer women were randomly allocated to the control group compared with both intervention groups.

Clinical outcomes and utilities. The clinical outcomes and utilities of the 111 patients are listed in Table 4. Improvements in all primary outcomes, except for morning stiffness, were found in both intervention groups after spa–exercise therapy. The between-group differences in the AUC for the BASFI of 1.0 (95% CI 0.4–1.6) for group 1 versus controls and of 0.6 (95% CI 0.1–1.1) for group 2 versus controls were both statistically significant (P = 0.001, P = 0.020, respectively). After adjustment for the score of the control group, the mean improvement over the entire study period in BASFI was 20% compared with baseline for group 1, and 14% for group 2.

The between-group difference in the AUC of the EQ-

Table 5. Volumes of health care and non-health care utilization during study period (40 weeks)*

	Group 1 Spa therapy Austria (n = 38)	Group 2 Spa therapy The Netherlands (n = 36)	Control group home (n = 37)
Visits to general practitioner	1.6 (2.5)	1.3 (2.0)	1.7 (2.1)
Visits to specialists (outpatient)	2.0 (2.0)	1.9 (2.3)	2.5 (2.9)
Physiotherapy sessions	17.0 (20.9)	14.9 (21.9)	21.5 (24.3)
Prescribed and OTC medication	4.3 (6.0)‡	4.5 (4.8)†	6.1 (4.5)
Prescribed and OTC alternative medication	0.5 (1.8)	0.2 (0.7)	0.1 (0.7)
Visits to alternative practitioner	0.4 (1.7)	0.3 (1.2)	0.8 (2.7)
Formal help in household (hours)	17.3 (45.0)	12.7 (31.7)	11.5 (34.8)

* Values are number (SD) per patient. OTC = over-the-counter.
† $P < 0.05$.
‡ $P < 0.01$ compared to the control group (Mann-Whitney U test).

Table 6. Results of costs during study period (40 weeks) of 111 patients*

	Group 1 Spa therapy Austria (n = 38)	Group 2 Spa therapy The Netherlands (n = 36)	Control group home (n = 37)
Direct costs			
Health care costs			
Spa therapy	1739 (0)	1515 (0)	—
Group physical therapy	306 (0)	306 (0)	306 (0)
Health care professionals (GP and specialist)	112 (109)	107 (142)	163 (168)
Physiotherapy	308 (379)	271 (398)	391 (440)
Medications (prescription and OTC)	153 (239)	182 (234)	206 (177)
Additional diagnostic tests	38 (72)	24 (80)	23 (39)
Hospitalization and day care rehabilitation	24 (174)	26 (157)	86 (525)
Alternative health care	24 (89)	3 (12)	35 (106)
Sum direct health care costs (excluding spa therapy)	*964 (744)*	*919 (625)*	*1210 (785)*
Sum direct health care costs (including spa therapy)	*2703 (744)*	*2434 (625)*	*1210 (785)*
Non-health care costs			
Formal help in household	106 (275)	100 (256)	72 (220)
Personal allowance	2 (10)	14 (83)	11 (67)
Indirect costs			
Absenteeism from work	211 (549)	693 (2864)	461 (1204)
Sum direct and indirect costs (excluding spa therapy)	*1284 (1009)*	*1725 (2988)*	*1754 (1772)*
Sum direct and indirect costs (including spa therapy)	*3023 (1009)*	*3240 (2988)*	*1754 (1772)*

* Values are mean (SD) costs per patient in Euro. GP = general practitioner; OTC = over-the-counter.

$5D_{utility}$ was 0.17 (95% CI 0.09–0.25, $P < 0.001$) for group 1 versus controls, and 0.08 (95% CI 0.00–0.15, $P = 0.04$) for group 2 versus controls.

Health resource utilization and costs. The volumes of health care and non-health care utilization during the followup period are listed in Table 5. The number of prescribed and over-the-counter medications was significantly lower in both intervention groups compared with controls ($P = 0.006$ group 1 versus controls; $P = 0.032$ group 2 versus controls). The number of hours and costs of formal help in household were higher in both intervention groups compared with the control group, but the differences were not statistically significant.

Of the patients with a paid job, 7 from group 1 (33%), 4 from group 2 (24%), and 9 from the control group (39%) reported AS-related absence from work during the study period, including 3 patients from group 1 and 4 patients from group 2 who reported sick leave during the spa therapy period. The mean number of days (±SD) of illness due to AS was 2.5 (±6.5) for group 1, 6.4 (±26.4) for group 2, and 6.1 (±15.8) for the control group.

Direct and indirect costs per patient for each category are listed in Table 6. Mean total costs were €3,023 (95% CI 2,728–3,359) for group 1, €3,240 (95% CI 2,553–4,391) for group 2, and €1,754 (95% CI 1,268–2,402) for the control group. The mean total incremental costs were €1,269 (95% CI 565–1,867) for group 1 and €1,486 (95% CI 501–2,707) for group 2.

Cost effectiveness and cost utility. The incremental cost-effectiveness ratio per unit effect gained in function ability on a 0–10 scale (based on the AUC of the BASFI) was €1,269/1.0 = €1,269 (95% CI 497–3,316) for group 1, and €1,486/0.6 = €2,477 (95% CI 601–12,098) for group 2.

Assuming that the difference in AUC of the $EQ\text{-}5D_{utility}$ will be equal to 0 during the last 3 months of the year after a 3-week course of spa–exercise therapy, and that the costs will be equal in all 3 groups (because no extended effect of the intervention is expected, the cost will presumably equal the costs of the control group), the cost per QALY gained would be €1,269/0.17 = €7,465 (95% CI 3,294–14,686) for group 1, and €1,486/0.08 = €18,575 (95% CI 3,678–114,257) for group 2.

Sensitivity analysis. In Table 7 the mean total costs per patient per group and the mean costs per QALY gained are shown for each of the additional costs or alternatives calculated in the sensitivity analysis.

Informal help. The mean (±SD) number of hours of informal help was 22.9 (±67.7) in group 1, 25.4 (±76.4) in group 2, and 19.9 (±76.6) in the control group. Additional costs for informal help would be €182 (±537) for group 1, €202 (±607) for group 2, and €158 (±608) for the control group. The costs per QALY gained would slightly increase (Table 7.)

Inactivity. The mean (±SD) number of days of inactivity was 7.3 (±19.1) in group 1, 4.6 (±12.5) in group 2, and 7.8 (±21.3) in the control group. Applying 4 hours per day as

Table 7. One-way sensitivity analyses*

	Mean total costs			Incremental costs per QALY gained		Incremental costs per unit of effect gained on a 0–10 scale	
	Group 1	Group 2	Controls	Group 1	Group 2	Group 1	Group 2
Base-case analysis (with BASFI)	3,023	3,240	1,754	7,465	18,575	1,269	2,477
Sensitivity analysis							
Informal help in household	3,205	3,442	1,912	7,606	19,125	1,293	2,550
Inactivity 4 hours/day	3,256	3,386	2,003	7,371	17,288	1,253	2,305
Inactivity 8 hours/day	3,488	3,533	2,252	7,271	16,013	1,236	2,135
Absenteeism work during spa therapy	3,523	3,690	1,754	10,406	24,200	1,769	3,227
Voluntary days off during spa therapy	2,965	3,047	1,754	7,124	16,163	1,211	2,155
CEA with global well-being as outcome measure	3,023	3,240	1,754	7,465	18,575	1,154	1,351
CEA with pain as outcome measure	3,023	3,240	1,754	7,465	18,575	1,410	1,486

* Mean costs per patient in Euro. Group 1 = spa therapy Austria; group 2 = spa therapy The Netherlands. BASFI = Bath Anklylosing Spondylitis Functional Index; CEA = cost-effectiveness analysis.

the mean number of hours of inactivity, the additional costs would be €233 (±606) for group 1, €146 (±398) for group 2, and €249 (±678) for the control group. In case a day of inactivity would represent 8 hours, the additional costs would be €465 (±1,212) for group 1, €293 (±795) for group 2, and €498 (±1,356) for the control group. Due to higher reported inactivity in the control group, the costs per QALY gained would decrease for both intervention groups (Table 7).

Absenteeism from work. If all patients who work were on sick leave during spa therapy, the mean (±SD) number of days of illness would be 7.5 (±9.2) in group 1, and 10.9 (±26.3) in group 2, both significantly more than the control group ($P = 0.020$ group 1 versus controls, $P = 0.032$ group 2 versus controls). The costs per QALY gained would increase to €10,406 for group 1, and €24,200 for group 2. If all patients voluntarily took days off to follow spa therapy, the mean number of days of illness would decrease to 1.9 (±5.7) for group 1 and 4.7 (±23.8) for group 2. The costs per QALY gained would decrease to €7,124 for group 1, and €16,163 for group 2.

Cost effectiveness. When "global well-being" and "pain" are used as outcome measures in the cost-effectiveness study, the incremental costs per unit of effect gained are more or less similar for both intervention groups. Compared with the base-case analysis, group 2 showed considerably fewer incremental costs per unit of effect gained (Table 7).

DISCUSSION

This economic evaluation shows that a 3-week course of spa–exercise therapy in addition to standard treatment has favorable cost-effectiveness and cost-utility ratios compared with standard treatment alone in patients with AS. Cost savings were found for both intervention groups compared with the control group with respect to visits to health care professionals, physiotherapy, and use of medication. In the sensitivity analyses, the results were robust to variation in several cost categories, but were sensitive to variation in indirect costs. The incremental cost ratios would considerably increase for both intervention groups if all patients with a paid job were on sick leave during spa–exercise therapy instead of considering the treatment period as regular holidays.

Only one cost analysis of spa therapy could be found in the English literature (21). The study evaluated the cost effectiveness of (undefined) spa therapy for a variety of rheumatic diseases, measured from a health insurance company's perspective. Effectiveness was assessed indirectly through determination of health care utilization before and after the intervention, based on reimbursement claims. No decrease in health care utilization was found in the groups that received spa therapy compared with controls. However, some concerns have been raised about the methodology of the study with respect to patient recruitment, lack of baseline description of the groups, the randomization procedure, and inadequate statistical procedures (22). Therefore, no reasonable comparison with the present study can be made.

Expressing the effects of an intervention in terms of "cost per QALY gained" has become increasingly popular in recent years. The primary argument was to facilitate the allocation of health care resources by decision makers, because the QALY concept allows comparison among different interventions in different diseases (23). Incremental cost-utility ratios can be listed in league tables, in which the costs per QALY gained for each study are visible at a glance. There are, however, a number of disadvantages in using league tables (24). League tables suggest homogeneity in, and comparability among, study designs. However, studies included in league tables might have been conducted in different years with consequently different technologies and relative prices. The approaches to measuring utilities differ greatly among studies; some studies include only direct costs, whereas others also report indirect costs, and not all studies apply discounting, if necessary. In addition, the amount of costs per QALY gained is dependent on the alternative program. An intervention will show fewer costs per QALY gained if compared with "doing nothing" instead of with the "best alternative treatment."

The incremental costs per QALY gained for each of the intervention groups (€7,465 for group 1; €18,575 for group 2) are relatively high compared with the rather low prevalent costs for patients with AS (€1,754). This probably reflects the absence of effective (curative) treatment for AS. Drug treatment is mostly limited to NSAIDs. Also, the costs for weekly group physical therapy are relatively low (25). These low prevalent costs contrast with the important impact the disease has with respect to pain, well-being, and work ability (26,27). The latest developments in the treatment of AS include the administration of tumor necrosis factor α (TNFα) inhibiting drugs, which have been reported to yield dramatic improvements (28,29). Due to the huge costs of anti-TNFα treatment (approximately €11,000 per patient per year) it is not to be expected that cost-utility analyses with respect to these new drugs will reveal costs per QALY gained that are lower than demonstrated by us. It is probable that these studies might show even larger discrepancies between the costs per QALY gained for the intervention groups, compared with the prevalent costs of the control group.

A few methodologic issues should be considered. First, the data as reported by the patients in the diaries were not ascertained by consulting other data sources. It is conceivable that patients might have had different opinions as to what is related to AS. Second, there were no data available on non-health care expenditures and days of illness-related absence from work during the pretrial period. Therefore, no comparison with the previous year can be made, and preexisting differences in non-health care utilization between the groups cannot be excluded. Third, the generalizability of the study findings is restricted to Dutch patients with active AS who follow weekly group physical therapy and have a disease duration of $<$20 years. The results might differ when other spa resorts are visited or different programs are provided. Similarly, the costs are likely to be different for other countries with other health care systems.

In The Netherlands, reimbursement for spa therapy is provided by a few insurance companies for a limited number of diseases (usually rheumatoid arthritis and AS only), with a maximum reimbursement level. It is estimated that 0.1% of the Dutch population has AS ($\sim$16,000 patients) (30). Approximately 20% of them follow weekly group physical therapy. If reimbursement for spa therapy would be limited to these 3,200 patients, who have adhered to treatment by following weekly group physical therapy, then the incremental societal costs for providing spa therapy would be €4,408,000 annually. In exchange for these costs, a large, although temporary, improvement in functional outcome and quality of life will be gained in a group of patients for whom no curative treatment is yet available.

In conclusion, a 3-week course of combined spa–exercise therapy in addition to standard treatment with NSAIDs and weekly group physical therapy provides beneficial effects compared with standard treatment alone, and can be regarded as cost effective in patients with AS.

ACKNOWLEDGMENTS

We thank the participating patients, D. Martens and B. van Albada from the Dutch league of associations of patients with rheumatic disorders, J. Daanen from Thermaalbad Arcen, M. Schafflinger from Kurzentrum Thermentempel Bad Hofgastein, F. Hartlieb and A. Falkenbach from the Gasteiner Heilstollen, M. Asscher, N. Wolter, E. Genth, H. Goei Thè, J. Thomassen, and all others who have contributed to the successful completion of this study.

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