Treatment strategies in recent-onset rheumatoid arthritis : the best study

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Chapter 8

Cost-Utility analysis of treatment strategies in patients with early rheumatoid arthritis

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ABSTRACT

Objective: Evaluate societal costs and quality-adjusted life years (QALYs) of 4 treatment strategies for recent onset rheumatoid arthritis.

Methods: Patients (n=508) randomly received 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination therapy with prednisone, or 4. initial combination therapy with infliximab. Patients reported costs and utility measures. Productivity was valued using the friction-costs and the human-capital method.

Results: Average 2-year QALYs were 1.29, 1.31, 1.32 and 1.41 for the British EuroQol ($p \leq 0.05$ for group 4 vs 1-3); 1.41, 1.42, 1.44 and 1.52 for the Dutch EuroQol ($p \leq 0.05$ for 4 vs 1-3); and 1.38, 1.38, 1.39 and 1.44 for the Short Form 6D ($p \leq 0.05$ for 4 vs 1-3). The Time Trade-Off showed no significant differences. Using the friction-cost method, the cost-utility ratio for group 4 against the next best alternative was estimated at 121.000 euro per QALY (95% CI 34,000 to 1,660,000 euro per QALY). Using the human-capital method instead, the value of sustained productivity in group 4 largely compensated the extra medication costs.

Conclusion: Initial combination therapy with infliximab resulted in significantly better quality of life than the other strategies. Considering only healthcare costs, this improvement was obtained at costs that are generally considered too high, and initial combination therapy with prednisone would be preferred. Depending on the extent to which productivity is valued, infliximab costs could be largely compensated by savings on productivity. Since patterns of infliximab use had not yet stabilized after two years, longer follow-up may change the economic conclusions.

INTRODUCTION

In the last decade, treatment of patients with rheumatoid arthritis (RA) has improved considerably (1). The use of combinations of disease-modifying anti-rheumatic drugs (DMARDs), tumor necrosis factor (TNF) antagonists and tight disease control have led to less progression of joint damage and better physical function (2-15).

The BeSt study was designed to investigate whether combinations of DMARDS, corticosteroids or TNF antagonists should be the initial treatment in RA, or should be reserved for patients failing monotherapy (16;17). To this end, four treatment strategies were compared: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination therapy with prednisone; and 4. initial combination therapy with infliximab. The two-year study results (17) showed that, with tight disease control, initial combination therapy with either prednisone or infliximab (strategies 3 and 4) resulted in a more rapid improvement of functioning, less progression of radiological joint damage, and more rapid reduction of disease activity, without more side effects than sequential monotherapy and step-up combination therapy (strategies 1 and 2). However, progression was low in all groups, and after two years there were no statistically significant differences between groups in functional ability or in the percentage of patients in remission. These observations raise the question whether the higher costs of initial combination therapy and especially infliximab are justified.

Several studies have evaluated the economic consequences of different treatment strategies in patients with RA (18-25). However, these were all modeling studies, combining different types of data from different sources. Moreover, they all compared fixed medication therapies, whereas our study compared dynamic strategies, intensifying or tapering medication based on the patients' status. We will present here the full two-year societal cost-utility analysis of the BeSt study. Observed quality-adjusted life years (QALYs, i.e. the overall valuation of the patients' health) are compared to observed total costs to society, including not only the costs of medication, but also costs of other health care, costs incurred by the patients and productivity costs. Aim of the analysis is to show, from a societal perspective, which treatment strategy provides the best value for money.

METHODS

Between April 2000 and August 2002, 508 patients with recent onset RA were included in the study (ISRCTN32675862), from 20 medical centers from the Western part of the Netherlands. Patients fulfilled the American College of Rheumatology (ACR) 1987 RA criteria (26), were at least 18 years old, had a disease duration of at most 2 years, and had active disease with at least 6/66 swollen joints, at least 6/68 tender joints, and either an erythrocyte sedimentation rate ≥28 mm/hr or a global health score ≥20 mm on a visual analogue scale of 0-100 mm (0=best, 100=worst). Patients had not been previously treated with anti-rheumatic agents. Patient enrolment criteria have been described in detail

elsewhere (16). The Medical Ethics Committee at each participating center approved the study protocol and all patients gave written informed consent before inclusion.

Primary study endpoints were functional capacity measured by the Health Assessment Questionnaire (27) and progression of radiological damage measured by the Sharp/van der Heijde score (28). At least 117 patients per randomization group were required to obtain a power of 80% at 0.05 significance level.

Intervention

By variable block randomization, stratified by center, patients were allocated to 1 of 4 treatment strategies:

1. *sequential monotherapy:* starting with methotrexate (MTX), followed by sulphasalazine, leflunomide, methotrexate with infliximab, gold with methylprednisolone (intramuscular), methotrexate with cyclosporin A and prednisone, and finally azathioprine with prednisone.
2. *step-up combination therapy:* starting with MTX, followed by methotrexate with sulphasalazine, methotrexate with sulphasalazine and hydroxychloroquine, methotrexate with sulphasalazine, hydroxychloroquine and prednisone, methotrexate with infliximab, methotrexate with cyclosporin A and prednisone, leflunomide, and finally azathioprine with prednisone.
3. *initial combination therapy with prednisone:* beginning with a combination of MTX, sulphasalazine and 60 mg prednisone, cut back in to 7.5 mg/day in 6 weeks (2), followed by methotrexate with cyclosporin A and prednisone, methotrexate with infliximab, leflunomide, gold with methylprednisolone, and finally azathioprine with prednisone.
4. *initial combination therapy with infliximab:* beginning with a combination of MTX and infliximab 3mg/kg every 8 weeks, gradually increased to 10mg/kg every 8 weeks if necessary, followed by sulphasalazine, leflunomide, methotrexate with cyclosporin A and prednisone, gold with methylprednisolone, and finally azathioprine with prednisone.

Treatment was adapted based on the Disease Activity Score (29), which was determined every three months by a research nurse, unaware of the randomization group. Additional Disease Activity Scores were determined in all patients treated with infliximab, in the week prior to infusion. If the score was > 2.4, the next treatment step was started; if the score was ≤ 2.4, the present treatment was continued and after six months, the last added drug was tapered until one DMARD in a maintenance dose remained, tapering prednisone and infliximab before other DMARDS (16). Concomitant treatment with non steroidal anti-inflammatory drugs and intra-articular injections with corticosteroids was permitted. Other parenteral corticosteroids were not allowed. DMARDs or oral corticosteroids were only permitted as dictated by the treatment protocol. All patients received folic acid 1mg per day during MTX treatment.

Utilities and QALYs

Utility is the valuation of the patient's health (30), on a scale from 0 (as bad as death) to 1 (full health). Patients described their quality of life using the EQ5D and the Short Form 36 classification systems (31;32), from which the British and Dutch EQ5D utilities (EQ5D-UK, EQ5D-NL) and the Short Form 6D (SF6D) utilities were calculated (33-35). These utilities provide societal valuations, which is preferred for economic evaluations from a societal perspective. Valuations from the patients' perspective were obtained using the Time Trade-Off (TTO) method (36), in which they reported how many years in optimal health they would consider to be equivalent to their remaining life expectancy in their current health. The TTO utility score is then calculated as the ratio of both life times, thus obtaining lower TTO scores for patients who are willing to trade more years to obtain optimal health.

The EQ5D and SF6D were assessed every three months and the TTO at 0, 6, 12 and 24 months. For missing utility measurements of non-deceased patients (8%), the time and group specific average was imputed. Two-year quality-adjusted life years (QALYs) were calculated as the area under the utility curves.

Costs

Costs during the two-year follow-up period were assessed from the societal perspective. Costs were converted to price level 2005 euros using the general Dutch price index rate (www.cbs.nl). Euros can be converted to US dollars using the Dutch purchasing power parity index for 2005: 1 euro ≈ 1.09 USD (www.oecd.org). Because of the limited time horizon, costs were not discounted.

Costs of study medication were calculated from the dosage reporting in the patients' case records, priced according to the Pharmacotherapeutic Compass (37). Infliximab drug costs were 686 euro per month, for a standard dose of 3 mg/kg for eight weeks. Reported medication costs include fixed costs per prescription and VAT, startup doses, monitoring, co-medication and required daycare hospital admissions.

Patients filled out quarterly cost diaries, reporting on health care (consultations, admissions, medication, and home care), work (work time, absences, paid and unpaid work) and other societal costs (expenses from rheumatism, household help, and informal care). During each three-month checkup, the diary was returned to the research nurse. Data from missing diaries (12%) were imputed with the time and group specific average. Twenty-one patients (4%) did not return any diary and were excluded from the cost analysis.

Reported health and informal care, where possible, was valued at Dutch standard prices that were designed to reflect societal costs and to standardize economic evaluations (38;39). Expenses were valued as reported by the patients. Otherwise, published cost prices (40;41) or market prices were used. Reported health care costs include patient time and travel costs (39).

Time devoted to unpaid work (42), including, for example, household tasks and volunteer work, was compared with the age and sex-dependent average over the entire study population (corrected for household help and informal care) and the difference was valued at the value of informal care (41).

Paid work was valued at age and sex-dependent standard hourly costs (39), ranging from 16 to 39 euro per hour (which includes 80% production elasticity). In the base case analysis, the friction cost method was used to value paid work, so that a reduction of worked hours (= contract time minus absence) was counted as costs for a period of at most six months, i.e. the friction period organizations need to restore the initial production level (43). As sensitivity analysis, the human capital method was used, counting costs over the entire study period (the same way as unpaid work). Estimated productivity costs did not include costs associated with reduced productivity on the job or replacement costs.

Analysis

Outcomes were analyzed according to intention-to-treat. Groups were statistically compared using one-way ANOVA, with post-hoc least-significant-difference test. Confidence intervals (CI) for cost-utility ratios were calculated as those positive willingness-to-pay (WTP) values, for which the difference in net benefit (WTP × QALYs – costs) was not statistically significant (44). Cost-QALY pairs in different groups are called non-significantly different if their net benefit is not significantly different for any positive WTP value.

Table 1. Study flow and baseline characteristics

	Group 1 Sequential monotherapy	Group 2 Step-up combination therapy	Group 3 Initial combination with prednisone	Group 4 Initial combination with infliximab
Included (no, %)	126 (100%)	121 (100%)	133 (100%)	128 (100%)
1-year follow-up (no, %)	122 (97%)	115 (95%)	128 (96%)	126 (98%)
2-year follow-up (no, %)	120 (95%)	112 (93%)	125 (94%)	124 (97%)
Age (average, SD)	54 yr (13)	54 yr (13)	55 yr (14)	54 yr (14)
Female sex (no, %)	86 (68%)	87 (72%)	88 (66%)	85 (66%)
Paid work (no, %)	50 (40%)	40 (33%)	61 (46%)	59 (46%)
Working hours* (average, SD)	29.5 (13.8)	28.3 (10.6)	28.3 (12.0)	29.6 (13.6)
Time from diagnosis				
- Median	2 wk	2 wk	2 wk	3 wk
- Interquartile range	1-5 wk	1-4 wk	1-4 wk	1-5 wk
Symptom duration				
- Median	23 wk	26 wk	23 wk	23 wk
- Interquartile range	14-54 wk	14-56 wk	15-53 wk	13-46 wk
Rheumatoid factor positivity (no, %)	84 (67%)	77 (64%)	86 (65%)	82 (64%)
Disease Activity Score (average, SD)	4.5 (0.9)	4.5 (0.8)	4.4 (0.9)	4.3 (0.9)
Health Assessment Questionnaire (average, SD)	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.7)

* In patients with paid work

The base case analysis compared societal costs (using the friction cost method) to QALYs based on the EQ5D-UK. Sensitivity analyses were performed on the utility measure (EQ5D-NL, SF6D, TTO), on the inclusion of different cost categories (study medication only, health care only, societal costs using the human capital method), and on the price of infliximab.

RESULTS

A total of 126, 121, 133 and 128 patients were randomly assigned to treatment strategies 1, 2, 3 and 4, respectively. Over the two-year follow-up, the number of dropouts in the groups was not statistically significantly different (Table 1). Most baseline characteristics were balanced, except that more patients in groups 3 and 4 had paid work than in groups 1 and 2 (p=0.143).

Utilities and QALYs

The four utility measures all exhibited the same pattern: especially during the first half year, there was a strong improvement, which occurred most quickly in group 4, and relatively slowly in groups 1 and 2. After two years, utility values were comparable.

Table 2. Average QALYs (SD) for the four utility measures

	Group 1 Sequential monotherapy (N=126)	Group 2 Step-up combination therapy (N=121)	Group 3 Initial combination with prednisone (N=133)	Group 4 Initial combination with infliximab (N=128)	P-value	
EQ5D-UK						
- 1st Year	0.60 (0.20)	0.59 (0.20)	0.64 (0.18)	0.68 (0.17)	0.001	cde
- 2nd Year	0.68 (0.18)	0.72 (0.16)	0.69 (0.19)	0.74 (0.17)	0.050	df
- Together	1.29 (0.36)	1.31 (0.33)	1.32 (0.33)	1.41 (0.32)	0.014	def
EQ5D-NL						
- 1st Year	0.67 (0.18)	0.65 (0.19)	0.69 (0.16)	0.74 (0.15)	0.001	def
- 2nd Year	0.74 (0.15)	0.77 (0.14)	0.74 (0.16)	0.78 (0.15)	0.086	
- Together	1.41 (0.31)	1.42 (0.30)	1.44 (0.29)	1.52 (0.28)	0.019	def
SF6D						
- 1st Year	0.66 (0.09)	0.66 (0.09)	0.68 (0.09)	0.71 (0.09)	<0.001	def
- 2nd Year	0.72 (0.09)	0.72 (0.09)	0.71 (0.11)	0.73 (0.11)	0.267	
- Together	1.38 (0.17)	1.38 (0.16)	1.39 (0.18)	1.44 (0.19)	0.021	def
TTO						
- 1st Year	0.82 (0.21)	0.81 (0.19)	0.84 (0.18)	0.86 (0.16)	0.128	
- 2nd Year	0.89 (0.19)	0.88 (0.16)	0.89 (0.16)	0.90 (0.16)	0.773	
- Together	1.71 (0.36)	1.69 (0.32)	1.73 (0.31)	1.76 (0.29)	0.319	

[a] p≤0.05 for group 1 vs 2 [b] p≤0.05 for group 1 vs 3 [c] p≤0.05 for group 2 vs 3
[d] p≤0.05 for group 1 vs 4 [e] p≤0.05 for group 2 vs 4 [f] p≤0.05 for group 3 vs 4

Using the TTO, patients themselves provided considerably higher valuations for their health, but with smaller and non-statistically significant QALY differences between the strategies (Table 2). On the other QALY measures, group 4 was consistently better than the other groups. The difference was significant during the first year (except compared to group 3, according to the EQ5D-UK) and during both years together. During the first year, group 3 was significantly better than group 2 according to the EQ5D-UK.

Health care costs

Patients in all four dynamic strategies could eventually receive infliximab (Figure 1). Costs of study medication for patients using infliximab in a particular year, regardless of randomization group, averaged 13,341 euro (95% CI 12,510 to 14,172 euro), compared to only 482 euro (95% CI 383 to 580 euro) in patient years without infliximab. As a result, costs of study medication in the first year were relatively low in groups 1, 2 and 3, and significantly higher in group 4 (Table 3). In the second year, costs in groups 1 and 4 were comparable, and significantly higher than in groups 2 and 3.

Of the other categories of health care costs, the groups only differed significantly in terms of costs of non-study medication (Table 3). These were significantly lower in group 4 than the other group, but the magnitude of the difference was limited.

On total health care costs, all group differences were statistically significant, except for the difference between groups 2 and 3.

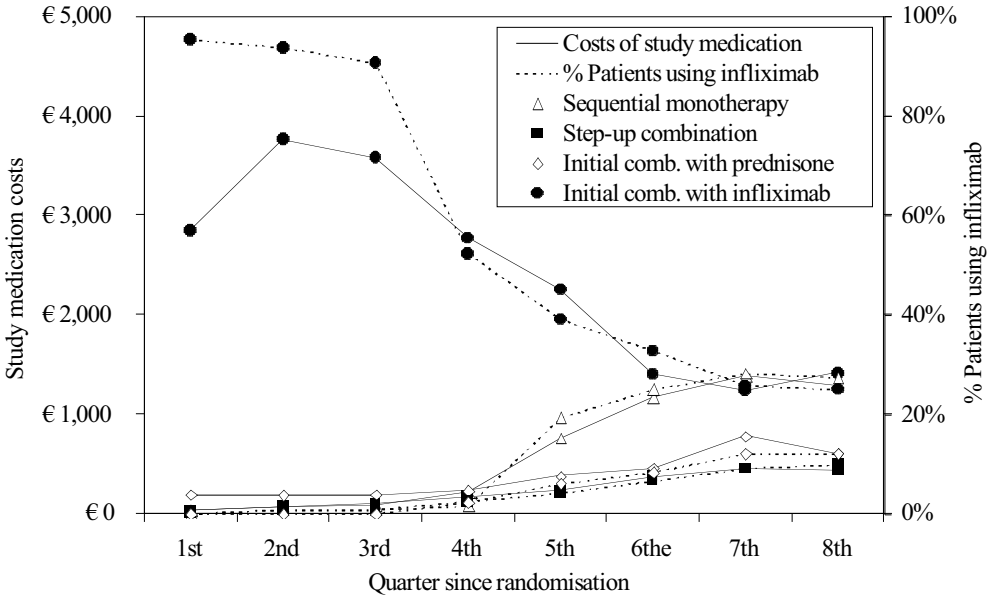

Figure 1. Costs of study mediation and percentage of patients using infliximab

Table 3. Average two-year health care costs (in euro)

	Group 1 Sequential monotherapy (N=121)		Group 2 Step-up combination therapy (N=114)		Group 3 Initial combination with prednisone (N=128)		Group 4 Initial combination with infliximab (N=124)		P-value	
	Volume*	Costs	Volume	Costs	Volume	Costs	Volume	Costs	Costs	
Patients using infliximab										
- 1st Year (no, %)	2 (2%)		3 (3%)		3 (2%)		118 (95%)		<0.001	def
- 2nd Year 2 (no, %)	38 (31%)		10 (9%)		18 (14%)		51 (41%)		<0.001	abf
Costs of study medication										
- 1st Year	411		396		804		13,014		<0.001	def
- 2nd Year	4,707		1,338		2,265		6,378		<0.001	abef
- Together (SD)	5,117 (7,872)		1,734 (4,410)		3,069 (5,226)		19,392 (13,244)		<0.001	adef
Rheumatologist	11.0	1,212	10.4	1,138	10.4	1,146	11.6	1,276	0.055	
Other specialists	2.3	198	2.9	258	3.0	247	1.9	158	0.147	
General practitioner	9.1	258	8.6	253	8.0	232	6.6	199	0.274	
Physical therapist	51.8	1,154	58.7	1,291	53.9	906	47.8	1,058	0.285	
Other paramedical	4.8	282	4.8	290	4.1	245	5.8	370	0.299	
Alternative	0.8	58	0.6	47	0.2	16	1.1	79	0.124	
Non-study medication		992		843		818		586	0.003	def
Hospital admission	43%	1,424	49%	1,258	46%	1,085	47%	624	0.338	
Nursing help	2.4 h	97	4.3 h	178	1.1 h	45	0.4 h	18	0.233	
Health care, excluding study medication (SD)	5,675 (6,713)		5,555 (4,943)		4,740 (4,489)		4,369 (4,021)		0.138	
Total health care costs	10,792 (10,724)		7,288 (6,995)		7,809 (7,046)		23,761 (13,484)		<0.001	abdef

* Percentage of patients, number of consultations or hours of care

[a] p≤0.05 for group 1 vs 2 [b] p≤0.05 for group 1 vs 3 [c] p≤0.05 for group 2 vs 3

[d] p≤0.05 for group 1 vs 4 [e] p≤0.05 for group 2 vs 4 [f] p≤0.05 for group 3 vs 4

Societal costs

Except for productivity costs, all other categories of non-health care costs did not show statistically significant differences between the treatment groups (Table 4). The weekly contract hours, absence and worked hours showed statistically significant overall differences, especially during the second year. Patients in group 4 reported less work absenteeism and more worked hours than patients in the other groups.

The employed evaluation method to value these productivity differences had a considerable effect on the results. According to the friction costs method, where a reduction of worked hours is counted as costs for at most a six-month period, the value of the worked hours in the four groups did not significantly differ. According to the human capital method, counting costs over the entire study period, the differences were large and statistically significant with higher productivity in group 4 compared to the other groups.

According to the friction cost method, due to the large difference in health care costs and the limited difference in productivity costs, the societal costs were significantly higher in group 4 than in groups 1, 2 and 3. According to the human capital method, however, the sustained productivity in group 4 largely compensated for the higher health care costs: estimated societal costs in group 3 and 4 were lower than in groups 1 and 2, but without statistically significant differences.

Costs-utility analysis

Figure 2 shows the estimated QALYs, based on the EQ5D-UK, and the estimated costs, depending on the extent to which different cost categories were included. In the base case analysis, with societal costs according to the friction cost method, the estimated QALYs and the costs for strategies 2 and 3 were both more favorable than for strategy 1, but their differences were not statistically significant ($p \geq 0.15$). Strategy 4 did result in significantly more QALYs than the other strategies, at significantly higher societal costs. The estimated costs-utility ratio of strategy 4 compared to strategy 3 was 121,000 euro per QALY (95% CI 34,000 to 1,660,000 euro per QALY).

Most sensitivity analyses showed the same picture as the base case analysis. For the other utility measures, EQ5D-NL, SF6D and TTO, the estimated QALY differences between strategies were smaller than for the EQ5D-UK. Strategies 2 and 3 remained (non-significantly) more favorable than strategy 1, and the cost-utility ratio of strategy 4 compared to strategy 3 increased to 130,000, 217,000 and 391,000 euro per QALY, respectively.

Restricting costs to health care or to study medication only, did lower the level of costs, but had little effect on the cost differences between the strategies (Figure 2). Strategies 2 and 3 remained (non-significantly) more favorable than strategy 1, and the cost-utility ratio of strategy 4 compared to strategy 3 increased to 179,000 and 183,000 euro per QALY, respectively.

The most crucial factor in the sensitivity analyses was the method used to value productivity costs. The friction cost method, used in the base case analysis, assigns relatively little value to differences in paid work. If productivity is valued according to

Table 4. Average two-year societal costs (in euro)

	Group 1 Sequential monotherapy (N=121)	Group 2 Step-up combination therapy (N=114)	Group 3 Initial combination with prednisone (N=128)	Group 4 Initial combination with infliximab (N=124)	P-value	
Household help	38.9 h (77.4)	76.2 h (159.3)	45.2 h (103.9)	53.8 h (100.7)	0.066	
Costs of household help	861 (1,714)	1,686 (3,526)	1,001 (2,300)	1,191 (2,230)	0.066	
Informal care	71.5 h (138.0)	80.2 h (236.4)	53.8 h (134.8)	46.1 h (124.3)	0.344	
Costs of informal care	729 (1,407)	819 (2,413)	549 (1,376)	470 (1,268)	0.344	
Out-of-pocket expenses	317 (1,189)	231 (935)	124 (354)	427 (2,126)	0.313	
Hours unpaid work, per wk						
- 1st Year (SD)	22.5 (13.4)	23.1 (17.5)	21.8 (14.2)	24.9 (17.5)	0.426	
- 2nd Year (SD)	23.9 (13.3)	21.6 (15.9)	20.9 (14.8)	24.4 (17.1)	0.212	
Contract hours paid work, per wk*						
- At baseline (SD)	14.4 (20.3)	14.8 (29.9)	13.8 (16.9)	16.5 (20.9)	0.789	
- 1st Year (SD)	12.1 (16.2)	11.4 (15.3)	14.4 (15.4)	16.6 (17.9)	0.059	
- 2nd Year (SD)	9.7 (13.7)	12.0 (14.9)	14.7 (14.8)	15.2 (15.9)	0.013	bd
Absent hours, per wk*						
- 1st Year (SD)	3.9 (8.2)	3.3 (8.6)	2.8 (5.6)	2.9 (7.6)	0.644	
- 2nd Year (SD)	1.8 (4.7)	0.7 (2.3)	2.0 (5.1)	1.0 (3.7)	0.034	ac
Worked hours, per wk*						
- 1st Year (SD)	8.2 (13.1)	8.1 (12.0)	11.6 (14.1)	13.6 (17.2)	0.005	de
- 2nd Year (SD)	7.9 (12.5)	11.3 (14.5)	12.7 (14.4)	14.2 (15.7)	0.005	bd
Costs of unpaid work† (SD)	108 (12,835)	1,069 (15,915)	1,454 (14,890)	-2,231 (17,535)	0.233	
Costs of paid work						
- Friction costs method (SD)	7,099 (12,741)	4,833 (8,291)	6,874 (9,756)	4,929 (6,892)	0.125	
- Human capital method* (SD)	11,267 (37,417)	3,227 (34,193)	-435 (37,999)	-12,111 (46,459)	<0.001	bdef
Societal costs						
- Friction costs method (SD)	19,905 (23,738)	15,926 (20,978)	17,810 (21,484)	28,547 (24,388)	<0.001	def
- Human capital method (SD)	24,073 (43,628)	14,320 (37,860)	10,501 (42,569)	11,508 (48,991)	0.06	

* In entire sample, including patients without paid work

† Negative costs are gains, because of worked hours above average

[a] p≤0.05 for group 1 vs 2 [b] p≤0.05 for group 1 vs 3 [c] p≤0.05 for group 2 vs 3

[d] p≤0.05 for group 1 vs 4 [e] p≤0.05 for group 2 vs 4 [f] p≤0.05 for group 3 vs 4

the human capital method, then strategy 4 is preferred over strategies 1 and 2 on both costs and QALYs (Figure 2). The cost-utility ratio of strategy 4 compared to strategy 3 decreases to 11,000 euro per QALY (95% CI 0 to 720,000 euro per QALY), which is usually considered highly acceptable.

In the base case analysis, medication costs for infliximab were assumed to be 686 euro per month, for a standard dose of 3 mg/kg for eight weeks. Halving these costs, the cost-utility ratio of strategy 4 compared to strategy 3 decreased to 36,000 euro per QALY (95% CI 0 to 670,000 euro per QALY), which is considered acceptable in most countries.

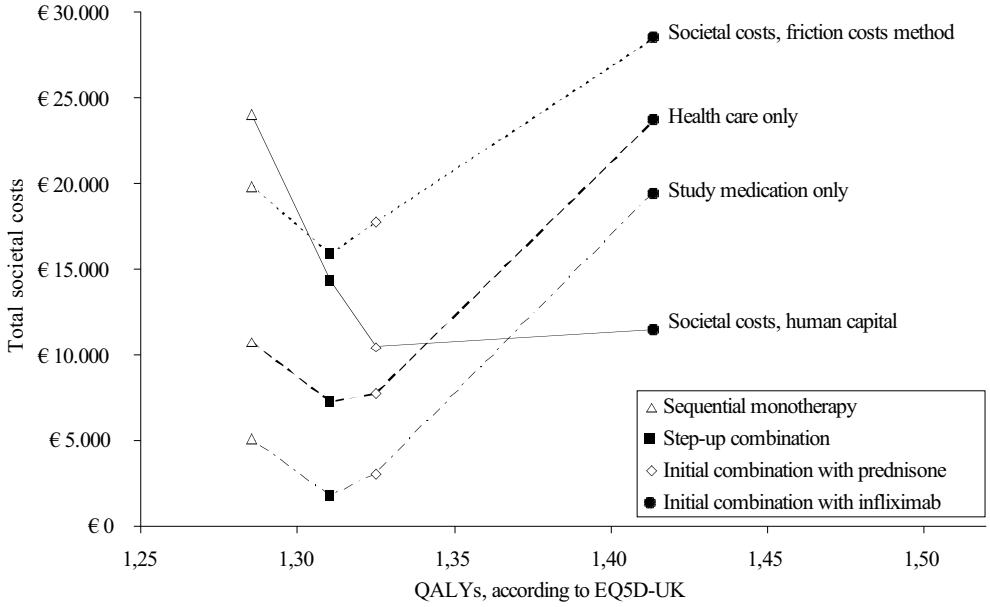

Figure 2. Costs and QALYs, depending on which costs are included in the analysis

DISCUSSION

The BeSt study (17) has shown that, in patients with recent onset rheumatoid arthritis, initial combination therapy with either prednisone or infliximab (strategies 3 and 4) results in a more rapid improvement of functional ability and in less progression of radiological joint damage than the other strategies. It was also demonstrated that regardless of the treatment strategy, tight disease control can achieve remarkable improvement in patients in all four treatment strategy groups, with after two years similar functional ability, disease control (Disease Activity Score ≤ 2.4 in 79% of all patients) and remission (Disease Activity Score < 1.6 in 42% of all patients). Use of infliximab varied over time: in groups 1-3, it increased to 27%, 7% and 13% after two years, respectively, whereas in group 4 tapering of medication resulted in a decrease of infliximab use, to 18%. In the current

analysis we found that initial combination therapy with infliximab (strategy 4) provided significantly better quality of life than the other strategies, with higher medication costs but also with sustained productivity.

We used the concept of quality-adjusted life years to analyze whether differences in effectiveness were attained at reasonable costs. QALYs cover both the advantages and disadvantages of interventions to the patients and can be evaluated for a wide range of diseases and treatments. As a result, they provide a means to establish the relative efficiency of interventions. Like the clinical outcome measures, also the QALY estimates showed a preference for initial combination therapy, and initial combination therapy with infliximab provided statistically significantly more QALYs than initial combination therapy with prednisone. In our base case analysis, the two-year difference between both strategies was estimated at 0.09 QALY, obtained with an estimated cost-utility ratio of 121,000 euro per QALY. Since cost-effectiveness is never the only criterion to choose one treatment over another, no strict thresholds exist for which cost-utility ratios are acceptable. Nevertheless, there is some consensus on the rule-of-thumb that costs are definitely acceptable below $ 20,000 per QALY, are acceptable up to $ 50,000 per QALY, and are possibly acceptable up to $ 100,000 per QALY (45). According to this rule, the costs for initial combination therapy with infliximab are too high. However, this conclusion strongly hinges on how productivity costs are valued, which is a matter of considerable debate among health economists (46). Although the major impact of rheumatic diseases on work disability is widely acknowledged (47), guidelines in different countries differ in whether the associated productivity costs should be included in health economic evaluations, and, if so, whether they should be valued according to the friction cost method or the human capital method (48). The main difference between both methods is the amount of lost working time that is counted as costs. The friction cost method takes the employer's perspective and only considers those hours as loss that fall in the period (set at six months) that the employer needs to adjust to the new situation, for example by hiring a new employee. The human capital method takes the patient's perspective and considers each hour not worked as loss. In our study, better quality of life was associated with more productivity: on average over the entire sample, a decrease of 0.1 on utility was accompanied be a decrease of 2 working hours per week (data not shown). Accordingly, productivity in group 4 was higher than in the other groups. Nevertheless, the friction cost method rendered results very similar to the analysis without productivity costs. Using the human capital method, the more favorable productivity costs almost completely compensated for the higher costs for the initial combination therapy with infliximab, making initial combination therapy with infliximab the preferred strategy. This finding is specific for patients with recent onset RA, since, with time, labor participation tends to decrease and patients will not easily be reincorporated into the workforce (22).

Comparing our observational result to the modeling results in the literature shows that, without taking productivity into account, our estimated cost-utility ratio for initial combination therapy with infliximab is higher than most previously reported ratios, which seems mostly due to our smaller estimated QALY gain. Our observed differences

between the treatment strategies were at most 0.12 QALYs, which is clinically relevant, but compares unfavorably to previous estimates (23;49). Our estimate was obtained using validated utility measures, estimating society's valuation for the health of the patients in our trial. Based on the Time Trade-Off valuations provided by the patients themselves, the QALY differences would have been even smaller. The discrepancy compared to the modeling studies may be due to a tendency of models driven by clinical parameters to overestimate the strength of their causal relationship with quality of life. Also, the tight disease control in all four strategies in our study may have made our comparator strategies more effective than comparator strategies in other studies. Finally, the gain in recent onset RA patients may be smaller than in patients with established disease, although also in our patients the baseline utility values were quite unfavorable. The majority of the modeling studies reported in the literature excluded productivity costs. Models that did include productivity costs did so by modeling their relationship with either the Health Assessment Questionnaire (18;20;21) or the health care costs (19), which ignores the mostly irreversible nature of productivity losses. Most models did include offsets in health care costs. Our study was unable to show the existence of such cost offsets, but may have been too small to do so.

Our study has a number of limitations. Firstly, the time horizon of the current analysis ended after two years of follow-up, when patterns of infliximab use had not yet stabilized. In strategies 1, 2 and 3, the patient could receive infliximab no sooner than after 4, 5 and 3 quarters, respectively, so quite a number of patients who fail on previous treatment may receive infliximab for the first time during the third year. The sustained working hours and suppressed progression of joint damage after initial combination therapy may have continued benefits beyond the second year. Therefore, longer follow-up may change the economic conclusions, most likely in favor of initial combination therapy with infliximab. Secondly, although the difference was not statistically significant, at baseline more patients in groups 3 and 4 had paid work, which may have increased the difference in productivity costs compared to groups 1 and 2. Thirdly, our specific Dutch setting may differ from other settings, among other things with respect to part-time work and labor legislation. In the Netherlands, working part-time is greatly accepted, which lightens the burden of labor and reduces the value of paid labor per year. Dutch labor legislation makes it relatively difficult to dismiss employees, which facilitates job retention. At the same time it may hinder finding a new job, because employers may be reluctant to hire an employee at risk of absenteeism. And, fourthly, both patients and physicians were aware of the allocated group, so the results may have been influenced by their treatment preference.

In conclusion, initial combination therapy with infliximab resulted in significantly better quality of life than the other treatment strategies. Considering only health care costs, this improvement is obtained at costs that are generally considered too high, and initial combination therapy with prednisone would be preferred. Depending on the extent to which productivity is valued, the costs of infliximab could be largely compensated by savings on productivity costs. Since patterns of infliximab use had not yet stabilized after two years, longer follow-up may change the economic conclusions.

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