

Etanercept Does Not Essentially Increase the Total Costs of the Treatment of Refractory Juvenile Idiopathic Arthritis

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ABSTRACT. *Objective.* To assess the costs of adding etanercept to the prevailing drug therapy for a one-year period in a group of 31 children with juvenile idiopathic arthritis (JIA) whose disease was refractory to conventional disease modifying antirheumatic drugs.

Methods. The changes in total costs were retrospectively collected from medical records and by interviewing parents 6 months before the initiation of etanercept treatment and during a 12-month followup divided into 3-month periods.

Results. Direct median costs increased during the first 3 months after the introduction of etanercept, but decreased later during the followup. The estimated median direct costs per patient increased by US \$4200 per year, and the indirect costs were reduced by 50%, i.e., \$1700. The estimated median total cost per patient was increased by about \$2700 per year (10%).

Conclusion. After combining etanercept with the prevailing treatment, the total costs of refractory JIA calculated per year were only slightly higher than those of traditional therapy. This finding must be evaluated in light of the reduced inflammatory activity of the joint disease and the probable reduction of lifetime pain and disability produced by the disease. (*J Rheumatol* 2004;31:2286–9)

Key Indexing Terms:

ETANERCEPT
REFRACTORY

TREATMENT COSTS
JUVENILE IDIOPATHIC ARTHRITIS

Longterm disability is the main cause of the burden imposed by musculoskeletal diseases. Although the prevalence of juvenile idiopathic arthritis (JIA) is low, patients will suffer from the disease throughout their adult life¹. Thus, in the most severe cases, the impact of the disease on both the individual and society is considerable¹. There are recent reports about improvement of the outcome of JIA^{2,3}, including our own experience². This can be attributed to the increasing use of cytostatic drugs and intraarticular treatments. Currently there is a consensus to treat JIA aggressively with methotrexate (MTX) as the gold standard⁴, with satisfactory results in 60–80% of patients⁵. According to the results of recent randomized controlled trials, higher doses (up to a dose of 15–20 mg/m² body surface area weekly) of MTX than those conventionally used (8–12.5 mg/m²) improve efficacy^{6,7}. However, there are still cases whose disease cannot be controlled with conventional disease modifying antirheumatic drugs (DMARD). In such instances, which made up our present series, etanercept is the drug of choice⁸.

A positive effect of etanercept (Enbrel[®]), a recombinant tumor necrosis factor receptor, on the disease activity of

patients with JIA was reported in one randomized controlled trial^{9,10}. In addition, a few observational studies have documented substantial efficacy of etanercept when combined with DMARD^{11–14}; only 2 of the series included followup for one year or longer^{13,14}. There are no studies on the health-economic aspect of etanercept therapy in JIA¹⁰.

We have reported retrospective one-year data on the clinical effect of etanercept in 31 patients with JIA whose disease was refractory to conventional DMARD therapy¹⁴. In conclusion, after combining etanercept with the prevailing therapy, a positive treatment effect was documented in the form of statistically significant reductions in the laboratory indicators of inflammation, in the dose of oral corticosteroids, in the number of intraarticular steroid injections needed, and in the number of inpatient days.

We now report the total costs of this treatment schedule of JIA during a one-year period from this same series and compare them with the total costs of an average of 3 months from a 6-month pretreatment period.

MATERIALS AND METHODS

According to statistics from the Finnish Social Insurance Institute, the total number of children with JIA is roughly 1200 in the population of about one million children in Finland. The care of patients with JIA in Finland has been strongly centralized to the Rheumatism Foundation Hospital (RFH), which means that almost all severe cases of JIA in the country are under our supervision. It has been possible to use etanercept medication in Finland since the spring of 1999. At that time, the first children with the most severe JIA were chosen for treatment. Altogether 31 patients with JIA started etanercept between April 1999 and September 2000 in our hospital.

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Demographic data and disease characteristics of the 31 patients have been reported¹⁴. Briefly, 6 had extended oligoarthritis, 22 had polyarthritis, and 3 systemic onset JIA. The patients' mean age was 10 years (range 3–15) and mean disease duration 6 years (range 1–14). At the time of starting etanercept, 28 (90%) patients were receiving a combination of 2 or more DMARD and 3 patients one DMARD. All except one patient had systemic corticosteroid therapy, with a mean (range) dose of prednisolone 16.3 (0–45) mg every 2nd day. All patients continued their earlier treatment until inflammatory activity was strongly reduced or remission was attained. The followup was organized by the Paediatric Department of RFH. Routine clinical and laboratory tests were used to monitor the safety of the drug, and patients' physiotherapy programs were continued, as determined earlier, during the observation period. Intraarticular corticosteroid injections were given (often under general anesthesia) whenever inflamed joints were detected.

Cost data collection. Direct and indirect costs were retrospectively collected from medical records and complemented by parental inquiry, and they are expressed as medians.

Direct costs. The data for economic evaluation were collected over an 18-month period, including a 6-month pretreatment period and a 12-month treatment period with etanercept. The average 3-month costs were calculated for the 6 months' pretreatment period, and these were used as reference costs. After the initiation of etanercept, 3-month sequencing was used to even out the effect of variation in disease activity and treatment on the costs. Table 1 shows the unit costs used for the calculation of direct costs. Only costs considered to be directly related to arthritis were included.

Of pharmaceutical expenditures other than the cost of etanercept, only the costs of DMARD were considered. For these drugs, pharmacy prices were used, taking package size into account. The costs of nonsteroidal anti-inflammatory drug (NSAID) use were not included in the analysis because the retrospective study design and the use of these drugs "as necessary" would have made the calculations unreliable. For the intraarticular corticosteroid injections, only costs related to general anesthesia were taken into account; other costs, such as those due to laboratory testing and physiotherapy, were included in the hospital fee. The costs due to the latter procedures outside RFH are also shown in Table 1.

Indirect costs. Travel expenses related to arthritis were calculated on the basis of the medical certificates addressed to the Social Insurance Institution, where the need for special transportation is documented. Reimbursement of \$0.35 per kilometer was calculated for using one's own car. For transportation by taxi, train, bus, and plane, the price excluding tax was calculated as the cost. The costs related to transportation to school by taxi based on the medical certificate were also considered. Indirect costs mainly consisted of computational losses of work by the children's parents, which were calculated using the weighted gross earnings of men and women plus the employer's non-wage costs, taking into account the unemployment rate of men and women and their employment. The calculated daily price was \$137 in 1999 and \$142 in 2000 (all costs US dollars). The costs of losses of work input due to children's hospitalization were considered only for the days on which parental presence was necessary for treat-

Table 1. Computational unit costs of treatment of JIA.

Treatment and examination services	Price, \$
Inpatient ward therapy (one day)	405
Visit at outpatient department	20
General anesthesia for joint injections	235
Physiotherapy ¹⁶	
Therapy at health center	42
Therapist's visit at home	101
Laboratory visit ¹⁶	10
Visit to a nurse ¹⁶ (administration of methotrexate-etanercept injections)	13

ment. Parents' accommodation costs were not taken into account. Parents' losses of work time due to visits to the laboratory and physiotherapy were not considered, because they could mainly be organized outside the parents' profitable working hours. The computations give average prices for each cost heading (median cost) per patient in periods of 3 months.

Etanercept therapy. Etanercept was administered subcutaneously twice weekly. The wholesale price excluding tax for 4 injections of the preparation, \$640, was taken as the price. Calculation of costs of administering etanercept injections was based on the assumption that the injection was given by the school nurse or a nurse in the nearest health center, and it was considered as an additional cost of \$13.

Statistical methods. Due to their skewed distribution, cost data are presented as medians with an interquartile range (IQR). No sensitivity analysis was done, because the expenses considered were not based on assumptions. Assessment of the effect of etanercept treatment on the costs was based on the comparison of median costs of a 3-month pretreatment period (estimated from 6 months before etanercept treatment) and those of the last 3 months of the treatment period. These data were projected for one year, respectively, to have an annual change of costs during etanercept treatment. The significance of the change was determined by permutation tests with general scores with Monte Carlo p values. Bonferroni adjustments were used to correct significance levels for multiple testing.

RESULTS

The total costs per patient estimated for a 3-month period before the initiation of etanercept therapy and during the one-year followup are presented in Table 2. When the costs due to etanercept are excluded, the change in the median direct costs was -54% (approximately -\$10,000 per patient on an annual basis), which was mainly due to the reduction of treatment days and use of DMARD. Estimated on an annual level, the total direct costs rose by \$4220 per patient ($p = 0.006$). Indirect costs dropped by 50% during the followup period ($p = 0.005$), i.e., \$1688 per child in one year. This means a saving of about 10–14 work days per escorting parent per year. The total median costs rose by \$2716 (+10%) estimated on an annual basis ($p = 0.09$).

DISCUSSION

The main aim of the treatment of JIA is to suppress inflammation and to prevent longterm disability. If this target cannot be reached, chronic arthritis inevitably leads to joint destruction and a loss of function and disability. JIA is associated with growth inhibition, loss of vision (as a result of uveitis), and a significant risk of premature death due to infections, myocarditis, or the side effects of drugs and, in certain populations, amyloidosis¹. Alleviation of inflammation by optimal treatment, if it could be developed, would inhibit these manifestations. Economic benefits would be obtained by preventing life-long disability and incapacity.

To our knowledge, this is the first cost-consequence analysis of etanercept therapy in JIA. Assessment of health economics is important in a real clinical setting, such as ours. The rise of overall median costs during etanercept therapy per child per year in this patient series consisting of the most severe forms of juvenile rheumatoid arthritis was only about \$2700 (a rise of 10%). The major part of the drop in direct costs was caused by the reduced need for treatment

Table 2. Costs of treatment of juvenile rheumatoid arthritis during one-year therapy with etanercept (Enbrel). Costs (\$) are given as medians (interquartile range).

Costs	Etanercept Therapy				
	Before start (/3mo)	0–3 mo	3–6 mo	6–9 mo	9–12 mo
Direct					
Treatment*	3448 (2243, 4252)	3046 (1640, 3850)	1841 (1439, 3046)	1607 (804, 2644)	1439 (804, 2644)
Medication	417 (187, 693)	265 (93, 689)	139 (65, 237)	122 (65, 210)	81 (65, 236)
Etanercept therapy	0	3804	3804	3804	3804
Physiotherapy	1000 (1000, 1000)	1000 (1000, 1000)	1000 (875, 1000)	1000 (875, 1000)	1000 (875, 1000)
Laboratory**	39 (10, 39)	29 (19, 48)	19 (17, 48)	19 (15, 29)	19 (19, 27)
Other †	724 (407, 1122)	764 (492, 1067)	649 (465, 1087)	598 (448, 936)	590 (465, 872)
Indirect					
Transportation to school	0 (0, 42)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Loss of working time	696 (557, 1253)	557 (278, 1113)	348 (278, 731)	418 (278, 696)	348 (278, 418)
Subtotal					
Direct	6284 (4671, 7245)	9056 (7573, 9962)	7320 (6873, 9476)	7204 (6730, 8854)	7339 (6099, 8340)
Indirect	840 (696, 1253)	557 (278, 1113)	487 (278, 772)	554 (278, 721)	418 (278, 645)
Total	7053 (5545, 8459)	9807 (7795, 10908)	7740 (7116, 10260)	7892 (7078, 9606)	7732 (6377, 8955)

* Inpatient ward, outpatient clinic, and general anesthesia related to injection costs. ** Visits for safety laboratory tests when at home. Does not concern the inpatient period or visits to the outpatient clinic. † Includes travel costs and costs related to the administration of injections (methotrexate and etanercept).

days, which was reflected positively in the costs of the parents' work input, implying savings of 10–14 work days per child per year.

In our series, costs were calculated only when they could be unambiguously attributed to the treatment of JIA. Other costs, especially indirect ones, were intentionally excluded. Costs were calculated over a period of 12 months, which can be considered long enough in view of the clinical outcome and the cost calculations. It is plausible that the greatest cost reductions would continue after that.

This study included the therapeutic introduction of a new drug in Finland. That made the monitoring costs higher at the beginning of the treatment. It should be noted that the costs of etanercept therapy are lower today than they were when this study was conducted. With increasing clinical experience, the treatment can be given at home today.

Conventional drugs, especially MTX, have recently yielded fairly good therapeutic results, most patients with JIA being able to live almost without restrictions. In a few patients, however, the disease is refractory and development of disability cannot be prevented. The need for new drugs is greatest in these unresponsive patients. About 2.5% of children with JIA in Finland were actively recruited into this series. They represent the individuals most severely affected by JIA, and all had also been treated with MTX and different drug combinations. The number of children to be treated was mainly restricted by the availability of etanercept. According to the latest information¹⁵, roughly 15% of all those with JIA will die or become disabled for work, which means about 180 children in Finland. This would

apparently be the maximum number of patients who could be treated with the new biological medicines in line with current principles. It is possible that the principles of treatment of JIA will change in such a way that even more patients will be able to receive biological antiinflammatory drugs at an even earlier stage of the disease course. The problem remains how to predict the patients with a poor prognosis early enough.

This study was done in Finland, where therapeutic approaches to JIA may be different compared to other parts of the world, including North America. Our protocol includes active use of DMARD and intraarticular corticosteroids, and NSAID are used only as necessary, in contrast to the practice of using NSAID as the cornerstone of therapy. In addition, our practice of hospitalizing patients, first to facilitate proper multidisciplinary care and second due to long distances, may not be relevant in other parts of the world such as North America. Although our series represents the cases with the most severe JIA in Finland at the time of study, the center-specific treatment approaches and patient selection criteria may have influenced the results of the study, with an influence on its external validity. Therefore, as in any economic analysis, the results may not be generalizable to other healthcare systems.

It can be concluded that the addition of etanercept to the prevailing treatment did not increase the overall costs compared to conventional therapy. This must be viewed against the background of the reduced inflammatory activity and the probable reduction of lifetime pain and disability produced by the disease.

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