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# Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis

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## ABSTRACT

**Objective:** To evaluate changes in health-related quality of life (HRQoL) in patients with refractory juvenile idiopathic arthritis (JIA) who are being treated with etanercept.

**Methods:** 53 patients with JIA from seven Dutch centres were included. HRQoL was measured by the Childhood Health Assessment Questionnaire (CHAQ), Child Health Questionnaire (CHQ) and Health Utilities Index mark 3 (HUI3) at the start and after 3, 15 and 27 months of treatment. At the same time points the following JIA disease activity variables were collected; physician's global assessment through the visual analogue scale (VAS), number of active and limited joints and erythrocyte sedimentation rate. A statistical method linear mixed models was used to assess outcomes over time.

**Results:** During etanercept treatment both disease-specific and generic HRQoL outcomes improved dramatically. Significant improvements were shown after 3 months and these improvements continued at least up to 27 months of treatment. The disease-specific CHAQ, including VAS pain and wellbeing, showed a significant improvement in all domains. The generic health-profile measure CHQ improved for all the health concepts except for "family cohesion", which was normal. The generic preference-based HUI3 showed impairment and, subsequently, significant improvement in the more specific domains ("pain", "ambulatory", "dexterity"). In accordance disease activity variables also improved significantly over time.

**Conclusion:** This study shows that the HRQoL of patients with refractory JIA can be substantially improved by the use of etanercept for all aspects impaired by JIA. Information on HRQoL is crucial to understand the complete impact of etanercept treatment on patients with JIA and their families.

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in childhood.[1 2] It frequently results in physical disabilities and chronic pain, influencing daily life.[3 4] Since its introduction, etanercept (a tumour necrosis factor α antagonist) has become an important treatment for patients with JIA who previously did not responded to other disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX).[5–10] Several studies have shown an impressive decline of disease activity expressed by the JIA core set of response variables, including the Childhood Health Assessment Questionnaire (CHAQ), during etanercept treatment.[8 9 11–16] Little is known about the changes in all aspects of health-related quality of life (HRQoL) in these patients.[17]

HRQoL can be defined as the physical, emotional and social aspects of the much broader concept quality of life, influenced by a person's disease and/or treatment and includes aspects of the patient's own perception of the effect.[18 19] Therefore HRQoL is an important outcome measure in understanding the total impact of a chronic illness and its treatment.[19 20]

The objective of this study was to describe changes in all domains of HRQoL during etanercept treatment in patients with previously refractory JIA.

## PATIENTS AND METHODS

### Patients and data collection

All Dutch patients with JIA treated with biological agents are included in the national Arthritis and Biologicals in Children (ABC) register to evaluate long-term effectiveness and safety.[9 21] For an extensive description of the patients and data collection see online supplementary files.

For complete evaluation of the HRQoL we prospectively collected additional data from patients who started etanercept treatment from 2003 until 2006. Seven of the nine Dutch paediatric rheumatology centres agreed to participate in this add-on study in the ABC project. Eligible patients of all ages and JIA subtypes were asked to complete three HRQoL questionnaires at the start and after 3, 15 and 27 months of treatment.

### Health-related quality of life (HRQoL) instruments

We used three HRQoL questionnaires all validated in Dutch.[18 22 23]

#### Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ, including visual analogue scale (VAS) for pain and wellbeing, is the "gold standard" for evaluating disease-specific HRQoL and is part of the JIA core set of response variables.[11 18 24] This 30-item disease-specific instrument measures disability and discomfort.[19 24 25] Functional status is part of HRQoL as it is an evaluation of the effect of a disease on the patient's ability to carry out activities of daily living. The CHAQ disability index (CHAQ DI) is divided into eight different domains (dressing, arising, eating, walking, hygiene, reach, grip and activities) and is scored

on a scale from 0 to 3 (0 best score). The need for help of others and the use of aids or devices is adjusted in the score. In addition, the patient's pain and overall wellbeing is rated on a VAS from 0 to 100 mm (0 best score). The CHAQ was completed by patient (from age 13 at moment of completion) or parent.[18]

### Child Health Questionnaire (CHQ)

The CHQ is a generic health-profile questionnaire which measures the physical and psychosocial wellbeing of children.[18 26] We applied the Dutch proxy version (CHQ-PF50) containing 50 items.[18] Answers score 13 different health concepts: physical functioning (PF); role functioning: emotional/behavioural limitations (REB), role functioning: physical limitations (RP); bodily pain/discomfort (BP); general behaviour perception (BE); mental health (MH); self-esteem (SE); general health perceptions (GH); change in health (CH); emotional impact on the parent (PE); impact on the parent's personal time (PT); limitations on family activities (FA) and family cohesion (FC). Concepts are rated on a scale from 0 to 100 with a higher score indicating a better health. All but three concepts (CH, FA, FC) are used for calculating the physical summary score (PhS) and the psychosocial summary score (PsS). Summary scores are transformed so that the mean is 50 and the standard deviation (SD) is 10.

### Health Utilities Index mark 3 (HUI3)

The HUI3 is a preference-based HRQoL measure that includes a classification system indicating the level of impairment in eight domains (attributes) based on information retrieved by a 15-item parent questionnaire. These eight single attributes are vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with each five or six levels representing the range of functioning from not impaired (1) to severely impaired (5 or 6). We applied formulas suggested by Feeny *et al* for estimating single-attribute and multiattribute utilities.[27] The latter are scored on a scale from 0 (dead) to 1 (perfect health). We used the proxy assessment.[23]

**Table 1** Patient and disease characteristics (n = 53)

| Characteristics | No (%) | IQR |
|---|---|---|
| Median age (years) at start etanercept | 11.9 | 8.1–14.9 |
| Sex | | |
| Male | 20 (38) | |
| Female | 33 (62) | |
| Onset subtype JIA | | |
| Systemic | 14 (26) | |
| Polyarticular rheumatoid factor positive | 5 (9) | |
| Polyarticular rheumatoid factor negative | 18 (34) | |
| Oligoarticular extended | 11 (21) | |
| Enthesitis-related arthritis | 2 (4) | |
| Juvenile psoriatic arthritis | 3 (6) | |
| Median disease duration JIA (years) at start of etanercept | 3.0 | 1.6–5.1 |
| History of antirheumatic drug use before start of etanercept | | |
| NSAID | 53 (100) | |
| Glucocorticoids systemic | 33 (62) | |
| Glucocorticoids local injection | 24 (45) | |
| MTX | 53 (100) | |
| Other DMARD | 28 (53) | |
| Concomitant drug use at start of etanercept | | |
| NSAID | 49 (92) | |
| Glucocorticoids systemic | 24 (45) | |
| MTX | 42 (79) | |
| Other DMARD | 5 (9) | |

DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug.

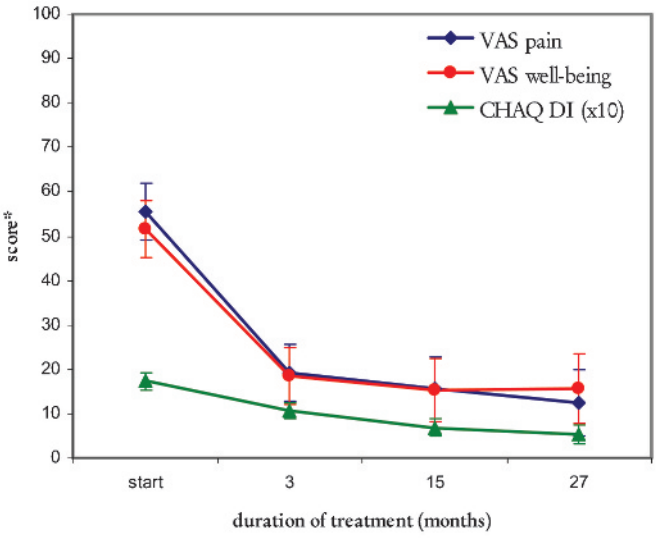


**Figure 1** Childhood Health Assessment Questionnaire (CHAQ). Changes in mean outcomes during treatment with etanercept of the CHAQ disability index (DI) (range 0–3), visual analogue scale (VAS) pain and VAS wellbeing (range 0–100) within 95% confidence limits (1.96×SEM). *Change over time: CHAQ DI $p<0.001$, VAS pain $p<0.001$, VAS wellbeing $p<0.001$.

### Statistical analysis

An extensive description of the statistics is given in the online supplementary files.

## RESULTS

### Patient and disease characteristics

During the study period 98 Dutch patients with JIA started treatment with etanercept, of whom 71 were treated in one of centres participating in the add-on study. Of these patients, 53 (75% response rate) completed the three HRQoL questionnaires (total 453 questionnaires, 29% missing) during treatment. Table 1 shows the patient and disease characteristics. No statistically significant differences were found when we compared the characteristics of this group with those of all 146 patients who were included in the ABC register until December 2006, and the 71 patients initially selected for this add-on study.[9]

Etanercept was given in the dose of 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly (9% started with once weekly, 34% switched to once weekly).[28 29]

### Changes in HRQoL

Detailed outcomes of the HRQoL questionnaires, as well as the JIA core set, are shown in the online supplementary table.

All JIA core set variables, including CHAQ, improved statistically significant over time ($p<0.001$, supplementary table; fig 1).

The 13 health concepts of the CHQ, which values were low at start compared with those of healthy children, improved significantly ($p<0.05$) in all but two (GH and FC, supplementary table; fig 2A). The PhS started 2.5 SD under the score of healthy children and improved 1.5 SD. The PsS improved from −0.5 SD up to the level of healthy children (supplementary table; fig 2B).

Statistically significant changes in single-attribute utility functions of the HUI3 were seen in domains "ambulatory" ($p = 0.02$), "dexterity" ($p = 0.02$) and "pain" ($p<0.001$, supplementary table;

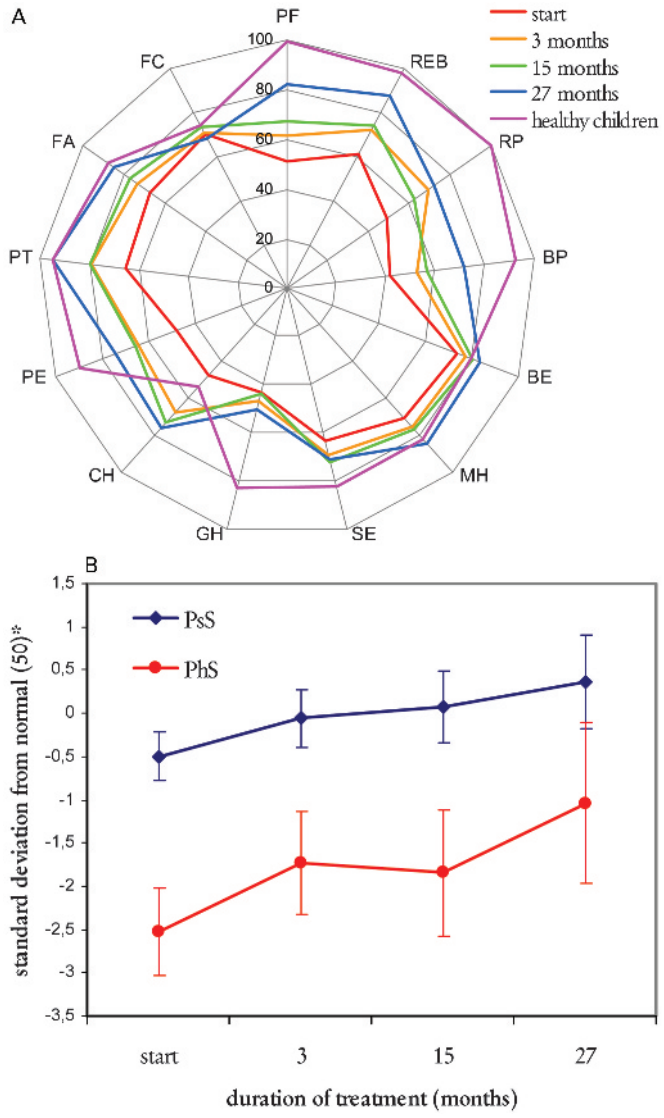


**Figure 2** Child Health Questionnaire (CHQ) (range 0–100); changes in mean outcomes during treatment with etanercept in all health concepts (A) compared with the outcomes in healthy children.[18] Changes in the physical summary score (PhS) and psychosocial summary score (PsS) (B) within 95% confidence limits (1.96×SEM). The PhS and PsS summary scores are expressed as standard deviation from the normal mean value of 50.[18] *Change over time: PhS p = 0.005, PsS p = 0.004. BE, general behaviour perception; BP, bodily pain/discomfort; CH, change in health; FA, limitations on family activities; FC, family cohesion; GH, general health perceptions; MH, mental health; PE, emotional impact on the parent; PF, physical functioning; PT, impact on the parent's personal time; REB, role functioning: emotional/behavioural limitations; RP, role functioning: physical limitations; SE, self-esteem.

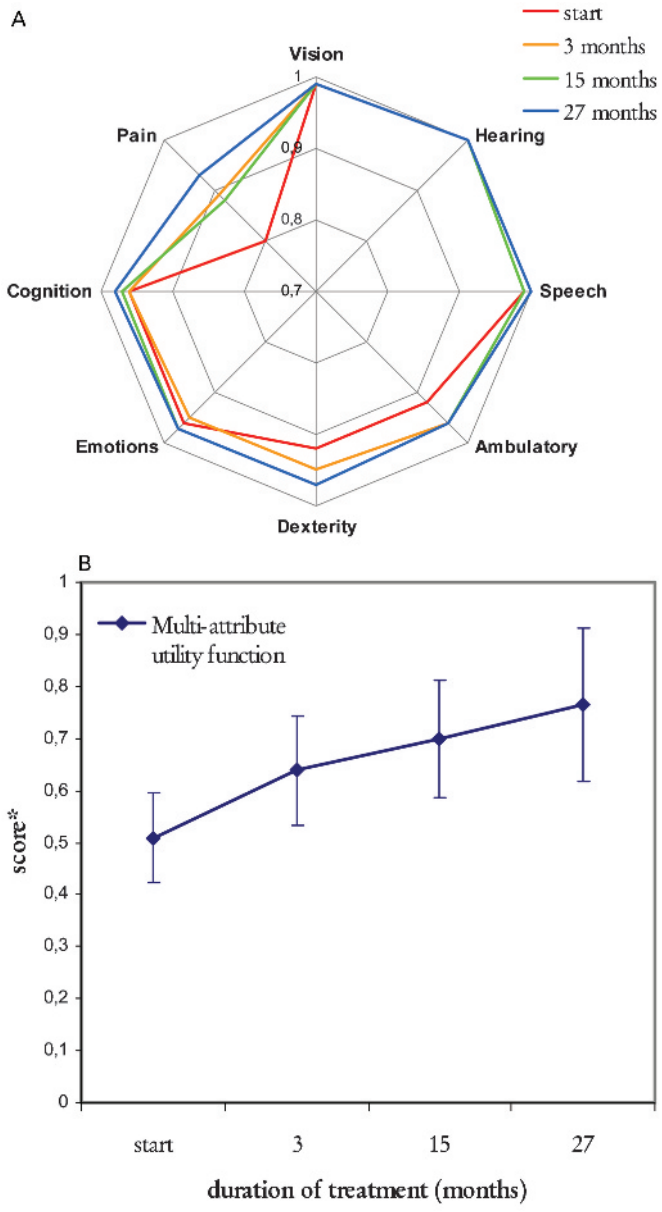


**Figure 3** Health Utilities Index mark 3 (HUI3); Changes during treatment with etanercept in the mean single-attribute (A) and multiattribute utility (B) function scores (range 0–1) on a death–health scale within 95% confidence limits (1.96×SEM). *Change over time: multiattribute utility function p = 0.001.

fig 3A). The multiattribute utility function improved significantly (p<0.001, supplementary table; fig 3B).

During the first 27 months of etanercept treatment, non-steroidal anti-inflammatory drugs were discontinued in 47%, glucocorticoids in 75% and MTX in 26% of all patients using these concomitant drugs at the start of etanercept treatment. All other DMARDs were discontinued. This resulted in 19 patients receiving monotherapy etanercept.

During the study period four patients (three systemic and one polyarticular rheumatoid factor positive JIA) discontinued etanercept because of inefficacy after a median use of 14.3 months (interquartile range (IQR) 3.3–26.7), two discontinued etanercept at 3 months. Response rates (percentages patients who reached ACR30, ACR50 and ACR70) from the 53 patients participating in this add-on study did not statistically significant differ from those of patients in the ABC register who did not participate.[11]

Eight patients had an adverse event (AE rate 0.08 per patient-year), one patient had a serious adverse event (SAE rate 0.010 per patient-year), but all continued etanercept treatment. All patients also continued to fill in the HRQoL questionnaires after experiencing the (S)AE.

## DISCUSSION

This is the first prospective long-term study of HRQoL changes in patients with JIA during etanercept treatment. The results show major improvement of HRQoL during 27 months of

etanercept treatment. This is highly relevant considering that these patients had a high disease activity and very poor HRQoL at the start of etanercept and previously had not responded to other DMARDs. For these children it is of great value to know, if a new treatment is likely to be successful in all aspects of health improvement.[30–32]

All JIA core set variables, including the CHAQ DI, VAS wellbeing and pain, dramatically declined after 3 months of etanercept use and improvement was sustained (supplementary table). The only exception is the VAS wellbeing which appears to be similar at 15 and 27 months. Several other studies have reported similar improvement of the CHAQ DI and VAS wellbeing during etanercept treatment; however, not all studies have evaluated the VAS pain score.[7 8 11 14 17 25 33 34] This is an important measurement since pain together with disability are the most important determinants of physical and psychosocial wellbeing.[30 35–37]

The dramatically low CHQ scores at the start of etanercept seem typical for patients with JIA with severe disease activity.[18 22 38] During treatment these HRQoL levels greatly improved, sometimes even to the same level as in healthy children.[18 22] The PsS score shows that although patients with JIA treated with etanercept still have some physical impairments, their overall psychosocial functioning improves to a score that is comparable to that of the general population. It is very reassuring that we not only found an increasing improvement of the PhS after 3 and 15 months of treatment, but also an additional strong improvement after 27 months. These findings, together with a decreasing number of active and limited joints, indicate that improvements in physical health can still occur after prolonged treatment with etanercept.

Of all the CHQ domains, only FC and GH did not change substantially. The finding that JIA has little impact on FC has already been reported in several other studies.[38 39] GH was low at the start and did not improve much during treatment. We suppose that the injections with etanercept might be a reason, among others, why patients (even though there is little or no disease activity) do not see themselves as healthy as their peers, which is also reflected in the further lack of improvement in VAS wellbeing after 15 months of treatment.

The multiattribute utility function of the HUI3 showed an impressive improvement over time. The poor baseline score (0.51) again indicates the serious impairments in health that these patients with JIA experience. We did not expect to find improvement in domains that are not likely to be affected by JIA such as "hearing" and "speech". The domains "ambulatory", "dexterity" and "pain" reflected a positive change; however, the domain "emotion" did not improve as much as expected. Possibly this HUI3 domain is not sensitive enough as relevant improvements are seen in CHQ scales related to emotions.

During etanercept treatment concomitant drug treatment was discontinued for a large proportion of the patients. This is likely to have had a positive influence on the HRQoL. However, this can also be attributable to the effect of etanercept, as previous treatments with other DMARDs, including MTX, were not sufficient in these patients.

The 53 patients are representative of the Dutch patients with JIA treated with etanercept, since we found no statistically significant differences in characteristics or disease course between patients from the ABC register participating in this add-on study and patients from the ABC register not participating. Although AE and SAE rates differed slightly from the data of all the 146 patients from the ABC register, findings were in line with safety data from other studies.[7–9 14 16 17]

The considerable number of patients with JIA, the long-term follow-up period and the use of three different questionnaires in combination with the high response rate make this study unique. The extremely low values at the start of treatment and the major improvements in the complete HRQoL assessment demonstrated in our study are important to understand the complete impact of etanercept treatment and balance the pros and cons. Therefore, it is advisable to include disease-specific and generic HRQoL assessments when evaluating the effectiveness of drug treatment in patients with JIA.[19 40]

In conclusion, the information on the HRQoL is an important addition to the information from the JIA core set presented in previous studies and is crucial for an understanding of the complete impact of etanercept treatment on patients with previously refractory JIA and their families.

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**Competing interests:** Wyeth International has financially supported the development and maintenance of the web-based ABC register since 2007.

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**Ethics approval:** Approval from the medical ethical committee of Erasmus MC, Rotterdam and the local medical ethical committee was given in every participating centre.

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## Notes