Safety and efficacy of once weekly etanercept 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis

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Objectives. Etanercept, a recombinant TNF receptor fusion protein, has been approved for the treatment of resistant polyarticular course juvenile idiopathic arthritis at a dosage of 0.4 mg/kg twice weekly in children older than 4 years. In adult patients, efficacy and safety of etanercept 25 mg twice weekly was comparable with 50 mg once weekly. Therefore, safety and efficacy of etanercept once weekly 0.8 mg/kg up to 50 mg s.c. was evaluated in a 3 month open label trial.

Methods. Twenty patients 4 to 17 years old received 0.8 mg of etanercept per kilogram of body weight subcutaneously once weekly for 3 months in an open multicentre trial. Active polyarticular disease was defined by the presence of five or more active joints with swelling, alternatively with pain or tenderness combined with limitation of motion. Safety assessments were based on adverse events (AEs) reports. Efficacy was assessed using the PediACR30/50/70 criteria.

Results. At the start of treatment the patients showed high disease activity. A rapid reduction of all disease activity parameters was observed. A PediACR30/50/70 response was reached by 75%/35%/10% of patients after 4 weeks, 90%/75%/35% after 8 weeks and 95%/75%/75% after 12 weeks of treatment. There were 37 AEs, none of them serious, with injection site reactions and minor infections being the most frequent. There was no drop out. Long-term follow-up of the patients will be carried out in the German JIA Registry.

Conclusion. Treatment with etanercept once weekly using a double dosage leads to a significant improvement of disease activity in patients with active polyarticular course juvenile idiopathic arthritis and is well tolerated.

KEY WORDS: Etanercept, Once-weekly application, Juvenile idiopathic arthritis.

Introduction

With an incidence of 19.8/100,000 children below the age of 16 years, juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease in childhood and can lead to severe disability [1–4]. Conventional therapy consists of DMARDs with MTX as the most common first-line DMARD, corticosteroids and NSAIDs. Especially in patients with polyarticular and systemic subtypes this approach is not always successful [5–8]. Anti-TNF-α therapy with etanercept was tested in polyarticular JIA patients in a single randomized controlled study and it significantly improved JIA [9, 10].

In Germany, etanercept is licensed and recommended for children with polyarticular course JIA at a dosage of 0.4 mg/kg body weight twice weekly in children older than 4 years. In adult RA patients, double dose once weekly treatment has shown similar results to a twice weekly treatment [11].

The aim of the study was to evaluate the safety and efficacy of etanercept once weekly 0.8 mg/kg body weight up to 50 mg s.c. in a 3-month open label trial since some preliminary publications supported the usefulness of treatment with once weekly double dosage [12, 13].

Key words: Etanercept, Once-weekly application, Juvenile idiopathic arthritis.

Methods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the guideline of Good Clinical Practice and the International Conference on Homogenisation. The study was approved by the Ethical Committee of the Ärztekammer Nordrhein, Düsseldorf, Germany and by the respective ethical committees at every study site. Each patient’s parent gave written informed consent before the start of the study. In addition, children above the age of 12 years also had to give their consent. All elements of informed consent were explained to eligible patients and their parents.

Patients

Twenty patients from seven sites were enrolled into the study. Criteria for study eligibility were as follows: age 4–17 years and a diagnosis of JIA with active polyarticular course with ‘active’ polyarticular disease defined by the presence of five or more active joints. Joints were defined as active by the presence of swelling or, if no swelling was present, limitation of motion accompanied by pain, tenderness or both.

Before enrolment, patients had active disease despite treatment with NSAIDs and with MTX at doses of at least 10 mg/m² of body-surface area per week for at least 3 months. Pre-treatment with biologics was not allowed. Concomitant treatments had to be kept stable at least 3 months before and throughout the study. Prednisone equivalent of up to 10 mg or 0.2 mg/kg body weight, whichever was less, was allowed and had to be stable during the 4 weeks before and throughout the study. IA corticosteroid injections were not permitted within 4 weeks prior to study entry and during the trial.

Girls with childbearing potential did receive a pregnancy test and were required to use contraception throughout the study. Abstinence was considered as an acceptable form of contraception. Patients with major concurrent medical conditions as well as...
those with abnormal laboratory values indicating a situation in which the patient may carry an increased risk while participating in a study were excluded.

Patients with systemic onset JIA were excluded since former experience in this JIA subgroup revealed an inferior efficacy of etanercept treatment compared with other JIA subtypes [14, 15].

Assessments used

Efficacy was assessed with the PedACR30/50/70 criteria including the German Childhood Health Assessment Questionnaire (CHAQ) after 4, 8 and 12 weeks of therapy with reaching a PedACR30 as primary efficacy endpoint after 12 weeks [16–18]. These core set parameters consisted of (i) physician global assessment of disease activity, on a 10-cm visual analogue scale (VAS); (ii) parent/patient global assessment of overall well-being, on a 10-cm VAS; (iii) the CHAQ, a measure of physical function [17]; (iv) the number of joints with active arthritis, defined by the presence of swelling or, if no swelling was present, limitation of motion (LOM) accompanied by pain, tenderness or both; (v) the number of joints with limited range of motion; and (vi) the ESR. The PedACR30 was reached if there was an improvement of ≥30% in at least three of six core variables, with no more than one of the remaining variables worsened by ≥30% [16, 17]. Patients were also evaluated for ≥50 or ≥70% improvement in at least three of six core variables, with no more than one of the remaining variables worsened by ≥30% (PedACR50 and PedACR70). Other assessments not included in the PedACR score were the swollen and tender joint counts, duration of morning stiffness and serum CRP levels.

Similar to other trials, for the assessment of ‘inactive disease’ modified criteria proposed by Wallace et al. [19] have been used. ‘Inactive disease’ in this study was defined as no joint with active arthritis, ESR <20 mm/h and a physician global assessment of disease activity score of ≤10 mm on the 100 mm VAS.

For comparison of patients’ characteristics data from the German Etanercept Registry were used [15]. These patients received etanercept twice weekly 0.4 mg/kg body weight.

Safety analysis

Adverse events (AEs) were asked for at every visit performed after 4, 8 and 12 weeks. Serious AEs were defined as events that were fatal or life threatening or resulted in a persistent or significant disability or incapacity. The requirement or prolongation of hospitalization or congenital anomaly or birth defects was rated as serious AEs. All protocol deviations were collected and discussed between the investigator and the sponsor (G.H.).

Statistical analysis

Descriptive statistics were used for reporting demographics, clinical characteristics, efficacy variables and AEs. Single disease activity parameters at study entry and after 12 weeks were compared using the paired t-test.

The sample size was determined prospectively to discriminate a response rate of ≥80% from a balanced result of 50%. A population of 20 patients would be sufficient to detect this difference with a power of 1−β = 0.80 on the α-level of 0.05 (sign test). In the actual test situation, the odds ratio of responders to non-responder of 80%/20% would be calculated to be \( P = 0.0118 \), but 75%/25% would already be significant too (\( P = 0.0414 \)).

Results

Twenty patients 4 to 17 years old were included to receive 0.8 mg of etanercept per kilogram of body weight subcutaneously (max. 50 mg) once weekly for 3 months in an open multicentre trial (EudraCT No. 2007-000255-34).

Table 1. Baseline demographic and clinical characteristics of the JIA patients treated with etanercept 0.8 mg/kg (study cohort) or for comparison treated with 0.4 mg/kg from the German registry (registry cohort)

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>Registry cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Age, years</td>
<td>20</td>
</tr>
<tr>
<td>Female, %</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>4.1 ± 4.2</td>
</tr>
<tr>
<td>RF − polyarticular JIA, %</td>
<td>12 (60)</td>
</tr>
<tr>
<td>RF + polyarticular JIA, %</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Extended oligoarticular JIA, %</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis, %</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Unclassified JIA, %</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pre-treatment NSAIDs</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12 (60)</td>
</tr>
<tr>
<td>MTX</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>14 (70)</td>
</tr>
</tbody>
</table>

For comparison of patients’ characteristics data from the German Etanercept Registry were used [15]. These patients received etanercept twice weekly 0.4 mg/kg body weight.

There were 16 girls and 4 boys with a mean age of 12.9 years and disease duration until start of etanercept of 4.1 years. In the patient group, 12 had seronegative polyarticular JIA, 4 seropositive polyarticular JIA, 2 extended oligoarticular JIA, 1 enthesitis-related arthritis and 1 unclassified JIA. The patients received 0.80 ± 0.06 mg/kg etanercept once weekly. Concomitant treatments with disease-modifying drugs were kept stable at least 3 months before and throughout the study. All concomitant treatment consisted of NSAID (n = 20), low-dose prednisone (n = 4), MTX (n = 12), LEF (n = 1), mycophenolate mofetil (n = 1), AZA (n = 1) and SSZ (n = 1). The mean ± S.D. dosage of prednisone was 5.2 ± 3.2 mg/day, the mean ± S.D. dosage of MTX was 12.2 ± 1.5 mg/m²/week.

The patients’ characteristics, JIA subtype distribution, pre-study use of disease-modifying drugs and concomitant treatments are outlined in Table 1.

Efficacy

A rapid improvement was observed already at Week 4 (Fig. 1). A PedACR30/50/70 response was reached by 75%/35%/10% of patients after 4 weeks, 90%/75%/35% after 8 weeks and 95%/75%/75% after 12 weeks of treatment, respectively. These response rates were compared with those gained in patients followed by the German registry treated with 0.4 mg/kg body weight twice weekly. After 12 weeks of treatment, more patients in the study group had a PedACR70 response than those patients followed in the German registry (\( P = 0.01 \) for PedACR70).

At the start of treatment, our patients showed high disease activity (Table 2). A rapid reduction of all single disease activity parameters was observed. This decrease was significant except for the CHAQ and the CRP values. The majority of patients reached normal values of several single disease activity parameters at 12 weeks of treatment (Table 3). Inactive disease was observed in two patients after 8 weeks of treatment and in five patients after 12 weeks of treatment. There were no missing data.

Safety

There were 37 AEs, but no serious AEs. The AEs consisted of injection site reaction (n = 14), upper respiratory tract
TABLE 3. Disease activity parameters in patients with JIA treated with etanercept

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive disease^a</td>
<td>0^a</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Physician global (&lt;10 mm)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Patient global (&lt;10 mm)</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>No active joint</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>No joint with LOM</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>No tender joints</td>
<td>2</td>
<td>9</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>No swollen joints</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>CHAQ (0–3)</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>ESR (&gt;20 mm/h)</td>
<td>15</td>
<td>17</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>CRP (&lt;5 mg/dl)</td>
<td>13</td>
<td>17</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

LOM: limitation of motion. ^a Inactive disease according to the modified criteria proposed by Wallace et al. [19]. ^ Number of patients with parameter indicating inactive disease. Total patient number is 20.

**Discussion**

In this open uncontrolled study in 20 patients with JIA and polyarticular course, treatment with etanercept once weekly improved rapidly most disease activity indicators (morning stiffness, number of swollen or tender joints, number of joints with limited function) and disability. Improvement was noted as early as 4 weeks after start of etanercept. Improvement was achieved in nearly all JIA patients. Nineteen out of 20 patients (95%) showed a PedACR30 response at Week 12. Furthermore, major improvement was reached by 75% of patients fulfilling PedACR70 at Week 12.

There was only one patient who did not respond according to the PedACR30 criteria. However, in this patient morning stiffness disappeared completely, the patient’s assessment of global disease activity improved from 47 to 17 mm and her active joint count decreased from 7 to 4. The number of joints with limiting motion remained stable as well as the physician’s assessment of global disease activity. At the start of treatment, she already had a CHAQ of 0 and an ESR of 7 mm/h. So, although clinical improvement was likely this will not be documented in the formal assessment.

Five patients (20%) even attained inactive disease after 12 weeks of treatment.

Efficacy of etanercept once weekly resulted in a marked improvement that was comparable with standard treatment using etanercept 0.4 mg/kg twice weekly. Efficacy of standard treatment was shown in a randomized controlled trial as well as in the large JIA patient population followed by the German registry [9, 15, 21]. Direct comparison is limited by differences in the study design, patients’ characteristics and recruitment and other possibly relevant, but unknown differences in the study populations and comparison of the results of the studies remains questionable. However, comparison of our study population with that of the German registry and that of the 12-week open label inclusion cohort of the controlled study show that our patients did not differ in ways that might limit the interpretation of the results both for efficacy and safety.

The response rate of up to 95% of patients after 12 weeks of treatment was higher than in the German registry and in the inception cohort of the controlled study. This might be due in part to the exclusion of patients with systemic JIA. In addition, approximately half the patients were on combination therapy with etanercept and MTX or received other DMARDs in combination with etanercept. All our patients had received MTX for at least 12 weeks before entering the study but still had active disease. Combination therapy of etanercept and MTX has shown superior efficacy in randomized controlled trials in adult patients with RA. According to the data of the large German JIA Enbrel registry, combination therapy may also be more efficient in JIA patients and also might contribute to the high rate of responders [20, 21]. Due to this combination therapy, patients of the study cohort were not directly comparable with patients included in the pivotal randomized controlled trial [9].

Etanercept is generally safe and well-tolerated in children with JIA. In this small patient cohort studied for 12 weeks, there were no serious AEs. No patient discontinued treatment. Long-term evaluation of safety and efficacy will be done within the German JIA Enbrel registry [15, 21]. Fifteen patients were already transferred to the German Enbrel registry. Thirteen patients stayed on once weekly therapy. At last observation...
eight of them fulfilled the PedACR70 criteria, while the other five fulfilled the PedACR50 criteria. Sustained improvement in disease activity was documented for so far up to 15 months (mean ± s.d. 8.7 ± 3.4 months, median 7 months).

However, caution is warranted when drawing conclusions from these observations in a limited group of patients. The open character of our study leads to some limitations. However, a controlled study showing non-inferiority of once weekly double dosing of etanercept compared with twice weekly standard dosing might be difficult to perform due to the low incidence of polyarticular course JIA and the high number of patients needed for such a study. With these limitations in mind, we would like to emphasize that our study very much resembles the real-world setting in patients with polyarticular course JIA. At present, a biologic agent will be added to a suboptimal treatment with a combination of NSAIDs, low-dose prednisone and MTX or other DMARDs. In this situation, once weekly double dosing of etanercept may be preferred over standard treatment for both, sparing one injection per week and lowering the cost of treatment especially in younger children in whom the dosage given twice weekly is less than half a vial of etanercept.

Rheumatology key messages

- JIA patients can effectively be treated with etanercept once weekly 0.8 mg/kg.
- A total of 90%/75%/75% of the patients reached a PedACR30/50/70, respectively.
- During the short study period there were no serious AEs.

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References