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ORIGINAL ARTICLE

Safety and efficacy of once-weekly application of Etanercept in children with juvenile idiopathic arthritis

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Abstract Etanercept—a recombinant TNF receptor fusion protein—has been approved for the treatment of resistant polyarticular juvenile idiopathic arthritis. In children with JIA, 0.4 mg/kg is given subcutaneously twice weekly. In adult patients efficacy and safety of etanercept, 25 mg twice weekly was comparable to 50 mg once weekly. In the German paediatric Etanercept registry six patients with JIA were identified, who received Etanercept once weekly primarily and six patients who received Etanercept initially twice weekly and later once weekly with increased dose per injection. In both groups, treatment was efficacious and well tolerated. In patients switching from twice to once weekly administration, there was no loss of efficacy and no increase in toxicity. At last observation 10/12 patients achieved an ACR-JRA 30 and 8/12 achieved an ACR-JRA70 response. These data indicate that once weekly application of etanercept is safe and efficacous in children.

Keywords Etanercept · Once-weekly application · Juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is a relatively rare disease with an incidence of 10–20/100,000 children. However JIA is one of the most common autoimmune diseases in childhood and a major cause of disability [1].

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Although the overall prognosis for most children with chronic arthritis is good, in 5–10% of children, especially those with the systemic and polyarticular onset forms, the disease is refractory to conventional therapies, consisting of a combination of non-steroidal anti-inflammatory drugs (NSAID) and immunosuppressive drugs such as methotrexate (MTX) and corticosteroids [2, 3].

In such cases, patients can develop severe joint destruction, growth retardation and various adverse effects from long-term treatment with immunosuppressive drugs. The introduction of anti-Tumour-Necrosis-Factor (TNF) therapy appeared to have a major impact on outcome of children with polyarticular JIA who were unresponsive to methotrexate, with a persistent response of up to 80% [4].

Etanercept is a recombinant TNF receptor fusion protein that acts competitively to inhibit the binding of TNF and lymphotoxin-α to their cell surface receptor. Etanercept has been approved and licensed for the treatment of active resistant polyarticular juvenile idiopathic arthritis in patients aged at least 4 years following a randomised controlled study [5].

The standard dose regimen in children with JIA is 0.4 mg/kg bodyweight given subcutaneously twice weekly with a maximum dosage of 25 mg per injection. In adult patients with rheumatoid arthritis comparative efficacy and safety has been shown, when the standard dosing of 25 mg twice weekly was compared to once weekly application of 50 mg. Thereafter, once weekly administration of Etanercept has been licensed for treatment of adult patients with rheumatoid arthritis [6].

Aim of the study

To describe efficacy and safety of etanercept in once weekly application at a dosage of 0.8 mg/kg in children with JIA.

Patients and methods

Study design and patient search

In the German paediatric Etanercept registry, six patients with JIA refractory to conventional therapy were identified, who received Etanercept once weekly primarily and six patients who received Etanercept initially twice weekly and later once weekly with increased dose per injection.

Informed consent was obtained from these patients and their parents for evaluation of clinical data and laboratory parameters.

A prospective analysis was performed to assess the efficacy and safety of etanercept in once weekly application in children with JIA.

Patients demographics, clinical data and follow-up

Patients characteristics including sex, age, diagnosis, duration oft JIA, previous therapy, ANA and RF were determined. At each visit all systems were reviewed. A complete physical examination assessed all organ systems. Treatment protocols, changes in medication dosing, adverse events and intolerance to treatment were documented. Study follow-up assessments were recorded at months 0, 3 and 6.

Diagnosis

Based on the clinical symptoms at disease onset, diagnosis of JIA was made according to the ILAR criteria [7].

Laboratory test results

Standardized laboratory testing at each visit included: (a) Renal function: serum creatinine, urea, and urinalysis including dipstick for blood and albumin, (b) Inflammatory markers and hematology tests: ESR,CRP, CBC/differential, hemoglobin, platelet count, (c) Liver function: AST, ALT; AP and GGT .

Abnormal test results were documented. Infections were determined.

Safety analysis

Serious adverse events (SAEs) were defined as events that were fatal or life threatening. SAE reports were collected during the study.

Efficacy analysis

Efficacy was assessed using the ACR Pediatric 30, 50, and 70 criteria, as well as the JIACRP 30, 50 and 70. Patient´s global assessment (visual analogue scale), CHAQ score, total number of joints with active disease, limitation of motion (LOM), swollen joints, tender/painful joints and the duration of morning stiffness were also included [8].

Safety and efficacy parameters after 6 months of once weekly therapy were prospectively gained.

Statistics

Statistical analysis was performed by comparison between the screening visit and the follow up time-point after 6 months. The mean decrease of efficacy parameters at last observation upon treatment was calculated.

Results

Patients characteristics and concomitant medications

The demographics characteristics are presented in Table 1.

The age ranged from 5–17 years. The JIA subtype included in group 1, who received etanercept therapy once weekly primarily: one patient with systemic onset JIA, two patients with seronegative polyarticular JIA, one patient with extended oligoarthritis and two patients with psoriatic arthritis. In group 2, who received etanercept once weekly after twice weekly therapy, the JIA subtypes included: one patient with systemic onset JIA, three patients with seronegative polyarticular JIA, one patient with extended oligoarthritis and one patient.

5/6 patients who received etanercept once weekly primarily were ANA positive and 5/6 patients who received etanercept once weekly after twice weekly were also ANA positive. In all patients treatment with methotrexate has been performed before institution of etanercept therapy. The majority (5/6) in each group received MTX concomitantly to etanercept therapy as well as NSAIDs and 1/ 6 in the group of patients who received etanercept once weekly primarily and 3/6 in the group the group who received etanercept once weekly after twice weekly, were treated with steroids as outlined in Table 1.

Safety

In patients with primary once weekly administration of etanercept, treatment was well tolerated. No SAEs or serious infections were noted. In patients switching from twice to once weekly administration, no increase in toxicity was noted, when administration was changed to the higher single dose.

However, one single adverse event occurred in one patient of the latter group upon regular treatment with twice weekly etanercept: a viral infection with rash and transient elevation of serum transaminases was noted. No action was taken.

Table 1 Demographic characteristics, disease history and previous therapy

	Patients who received etanercept once weekly primarily ($n = 6$)	Patients who received etanercept once weekly after twice weekly ($n = 6$)
Age range	5–13 years	6–17 years
Gender		
Female	3	5
Male	3	1
JIA onset type[a]		
JIA systemic onset	1 (16)	1 (16)
JIA seronegative polyarticular	2 (33)	3 (50)
JIA extended oligoarthritis	1 (16)	1 (16)
JIA psoriatic arthritis	2 (33)	1 (16)
Mean duration of JIA (range)	53 months (10–84)	89 months (15–132)
ANA positive	5 (83)	4 (66)
Rheumatoid factor positive	0	0
Concomitant therapy at enrollment[a]		
NSAID	5 (83)	6 (100)
Corticosteroids	1 (16)	3 (50)
Methotrexate	5 (83)	5 (83)

JIA juvenile idiopathic arthritis, *ANA* antinuclear antibodies, *NSAID* nonsteroidal anti-inflammatory drugs, *n* number

[a] Values are *n* (%)

Efficacy

All but two patients responded well to treatment. One patient with seronegative polyarticular JIA discontinued treatment because of inefficacy in the primarily once weekly group.

In patients switching from twice to once weekly administration, there was no loss of efficacy. One patient with psoriasis-associated JIA discontinued treatment because of inefficacy.

At last observation 10/12 patients achieved an ACR-JRA 30 and 8/12 achieved an ACR-JRA 70 response (Table 2).

Table 2 Scores und clinical status in once weekly etanercept therapy

	Once weekly therapy primarily ($n = 6$)	Once weekly therapy after twice weekly ($n = 6$)
Age	5–13 years	6–17 years
JRA-ACR Criteria[a]	ACR30 5/6	ACR30 5/6
	ACR50 4/6	ACR50 5/6
	ACR70 4/6	ACR70 3/6
JIACRP Criteria[a]	30% 5/6	30% 5/6
	50% 4/6	50% 5/6
	70% 3/6	70% 3/6
Serious adverse events	None	None
Clinical signs of disease activity	None 5/6	None 5/6
	Flare 1/6	Flare 1/6
Therapy discontinued	1/6 (Inefficacy)	1/6 (Inefficacy)

[a] Efficacy values of last observation upon therapy are given

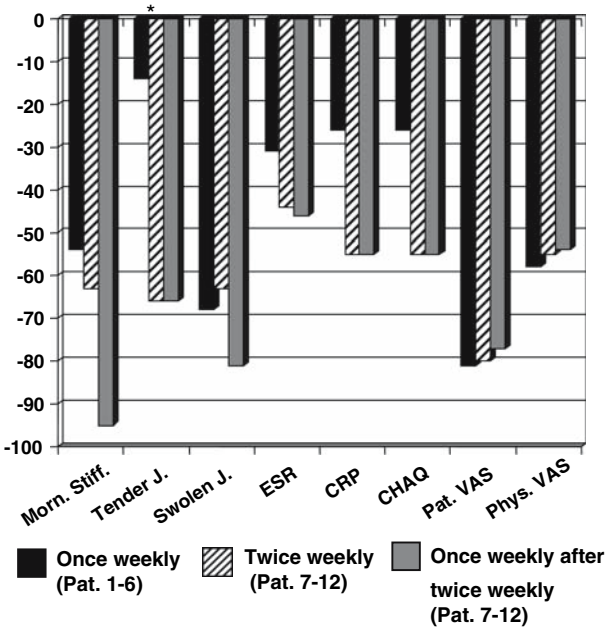

Fig. 1 Mean decrease (%) of efficacy parameters at last observation upon treatment. *At last observation four of the six patients treated primarily with etanercept once weekly had a tender joint count of 0 (therefore the reduction was 100%). In one patient the number of tender joints decreased from 28 to 8 (71% reduction) and in the sixth patient the tender joint count increased from 2 to 34

Patient´s global assessment (visual analogue scale), CHAQ score, total joints with active disease, LOM, swollen joints, tender/painful joints and the duration of morning stiffness improved after 6 months (Fig. 1).

Discussion

This prospective pilot study examined the safety and efficacy of once weekly application of etanercept. To our knowledge this is the first report, in which the once-weekly application of etanercept is examined in children.

Subcutaneous application remains a drawback in this otherwise very valuable new treatment option for patients with refractory JIA [9]. The possibility to reduce the frequency of application is therefore highly welcomed particularly in younger children. The results from this preliminary observation are very promising.

The rate of SAEs did not increase and there were no serious infections noticed. Neither in the group, who started primarily once weekly, nor in the group who switched from twice to once weekly application.

The majority of the patients with polyarticular JIA showed sustained improvement in disease activity in the group with primary once weekly application as well as in the group which switched from twice weekly to once weekly. ACR 30 scores were observed in 10/12 patients. 2 patients (one of each group) discontinued because of inefficacy. ACR 70 was achieved in 6/12 patients (one of each group).

When comparing efficacy parameters in patients who received primarily once weekly application to those who received primarily twice weekly application the reduction of single clinical and laboratory efficacy parameters seems more prominent in the twice weekly group (Fig. 1). However the strong effect of twice weekly application was not lost when application was switched to a once weekly regimen. Therefore twice weekly application might be the regimen of choice for the initiation of etanercept treatment. After some time application can be reduced to once weekly without loss of efficacy.

However caution is warranted when drawing conclusions from these observations in a limited group of patients. We therefore would recommend a trial with sufficient power to provide more reliable data on this relevant subject.

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