ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 8, August 2015, pp 2240–2249
DOI 10.1002/art.39145

Efficacy and Safety of Etanercept in Patients With the Enthesitis-Related Arthritis Category of Juvenile Idiopathic Arthritis

Results From a Phase III Randomized, Double-Blind Study

Gerd Horneff,[1] Ivan Foeldvari,[2] Kirsten Minden,[3] Ralf Trauzeddel,[4] Jasmin B. Kümmerle-Deschner,[5] Klaus Tenbrock,[6] Gerd Ganser,[7] and Hans-Iko Huppertz[8]

Objective. **To evaluate the efficacy and safety of etanercept in patients with enthesitis-related arthritis (ERA) in juvenile idiopathic arthritis (JIA).**

Methods. **This was a 2-phase study in JIA patients with active, refractory ERA. Phase I was an open-label, uncontrolled 24-week study period in which all patients were administered etanercept. Patients considered to be treatment responders at week 24 according to the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) criteria for improvement in juvenile arthritis entered the second phase, a 24-week randomized, double-blind, placebo-controlled withdrawal study, for an additional 24 weeks, for evaluation of the primary end point, occurrence of a disease flare from week 24 to week 48, based on the ACR preliminary definition of disease flare in juvenile arthritis.**

Results. **Forty-one patients were enrolled. At week 24, treatment with etanercept resulted in response rates of 93%, 93%, 80%, 56%, and 54% based on the ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 criteria, respectively. In addition, a marked decrease in all disease activity measures was observed. The mean number of tender joints, swollen joints, and joints with active arthritis decreased by 91%, 97%, and 94%, respectively. Physician's global assessment of disease activity, parent's assessment of patient's overall well-being, and the Childhood Health Assessment Questionnaire disability index improved by 91%, 80%, and 86%, respectively. The number of tender enthesis sites and total scores for back pain, nocturnal pain, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, and Juvenile Arthritis Disease Activity Score based on 10-joint counts (JADAS10) decreased by 75%, 72%, 81%, 72%, 85%, and 87%, respectively. In phase II, 38 patients were randomly assigned to receive placebo (n = 18) or to continue receiving etanercept (n = 20). Up to week 48, 12 disease flares occurred, in 9 patients receiving placebo and 3 patients receiving etanercept (odds ratio 6.0, $P = 0.02$). There were no serious infections, malignancies, or deaths.**

EudraCT database no. 2010-020423-51.

Supported by an unrestricted grant from Pfizer Pharma, Germany. Pfizer also supplied the study medication.

[1]Gerd Horneff, MD: Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany; [2]Ivan Foeldvari, MD: Hamburg Center for Pediatric Rheumatology, Hamburg, Germany; [3]Kirsten Minden, MD: Charité University Hospital Berlin, Berlin, Germany; [4]Ralf Trauzeddel, Dipl-Med: HELIOS Clinic Berlin-Buch, Berlin, Germany; [5]Jasmin B. Kümmerle-Deschner, MD: University Children's Hospital Tuebingen, Tuebingen, Germany; [6]Klaus Tenbrock, MD: RWTH Aachen University, Aachen, Germany; [7]Gerd Ganser, MD: St. Josef-Stift Sendenhorst Hospital, Sendenhorst, Germany; [8]Hans-Iko Huppertz, MD: Prof.-Hess Children's Hospital and Gesundheit Nord Klinikverbund Bremen, Bremen, Germany.

Dr. Horneff has received honoraria for advisory board service from Abbott, Pfizer, Novartis, Roche/Chugai, Genzyme, UCB, and Bristol-Myers Squibb (less than $10,000 each), as well as clinical trial funding from these companies. Dr. Minden has received consulting fees, speaking fees, and/or honoraria from Pfizer, AbbVie, Roche/Chugai, Medac, and Pharm-Allergan (less than $10,000 each) and research grants from Pfizer and AbbVie. Dr. Trauzeddel has received consulting fees, speaking fees, and/or honoraria for advisory board service from Pfizer (less than $10,000) and honoraria from Novartis (less than $10,000). Dr. Tenbrock has received speaking fees and honoraria for advisory board service from Pfizer (less than $10,000), speaking fees from Novartis and Abbott (less than $10,000 each), and research funding from the Novartis Foundation. Dr. Huppertz has received speaking fees and/or honoraria for advisory board service from Abbott, Pfizer, Roche/Chugai, Novartis, and Swedish Orphan Biovitrum (less than $10,000 each).

Address correspondence to Gerd Horneff, MD, Department of General Pediatrics and Adolescent Medicine, Asklepios Clinic Sankt Augustin, Arnold Janssen Street 29, 53757 Sankt Augustin, Germany. E-mail: g.horneff@asklepios.com.

Submitted for publication January 4, 2015; accepted in revised form March 31, 2015.

Conclusion. **In this study of patients with the ERA category of JIA, etanercept proved effective, as indicated by high ACR Pedi response rates and JADAS10 response rates at week 24. Patients who continued treatment with etanercept had significantly fewer flares than those who received placebo, although 50% of patients in the placebo group did not experience a flare. Treatment suspension may be a consideration for patients with the ERA category of JIA who achieve remission.**

Juvenile idiopathic arthritis (JIA) describes a heterogeneous group of diseases with chronic arthritis of at least 6 weeks' duration and onset before the age of 16 years. The International League of Associations for Rheumatology (ILAR) defines 7 categories of JIA, each of which varies in its signs, symptoms, and prevalence (1). Enthesitis-related arthritis (ERA) is one well-defined JIA category, which presents with arthritis and/or enthesitis but can also involve the axial skeleton during the course of the disease (2). Most JIA patients with ERA (herein after referred to as patients with ERA) may also be classified as having juvenile-onset spondyloarthritis (SpA), but often children with ERA do not fulfill the criteria for ankylosing spondylitis (AS) because axial involvement is absent or limited during childhood (3,4). Disease activity and structural change can adversely affect the long-term physical function and quality of life of patients with ERA (2–7).

Compared to treatments for AS or other SpA in adults, there is limited evidence for the efficacy of most treatments for these diseases in children (8). In addition to nonsteroidal antiinflammatory drugs (NSAIDs), patients with ERA are often treated with sulfasalazine (SSZ), methotrexate (MTX), and glucocorticoids (9). Several open-label studies with tumor necrosis factor (TNF) inhibitors administered to patients with either ERA or juvenile SpA demonstrated an improvement in the symptoms of the disease (10–15). Only 2 studies used a controlled design. In one study, patients classified as having juvenile-onset SpA were treated with infliximab, a chimeric monoclonal anti-TNF antibody. In a second, placebo-controlled trial, patients with juvenile AS were treated with the human anti-TNF antibody adalimumab (16,17).

The safety and efficacy of etanercept, a human TNF receptor fusion protein, have been demonstrated in a double-blind, placebo-controlled trial in children ages 4–17 years with polyarticular JIA, and in an open-label trial of etanercept in children ages 2–17 years with other categories of JIA, including the ERA category (18,19). In these studies, etanercept was shown to improve the signs and symptoms of ERA and, with prolonged treatment, a number of patients achieved remission.

In 1997, the criteria for improvement in juvenile arthritis (referred to as the American College of Rheumatology [ACR] preliminary definition of improvement in juvenile arthritis, or ACR Pediatric [ACR Pedi] criteria [20]) were evaluated, and since then these criteria have been widely used in trials involving children with JIA, including those with ERA. When these criteria were used in an analysis of JIA patients in the German Biologics in Paediatric Rheumatology (BIKER) registry, JIA patients with the ERA category showed a remarkably high rate of response to treatment with etanercept (21). When compared to all other JIA categories, including the most frequent form, polyarticular JIA, patients with ERA have shown a higher rate of remission while being treated with etanercept, with remission being defined as the absence of any clinical disease activity indicators (10,12,22,23).

Patients with the ERA category of JIA often exhibit only an oligoarticular joint pattern (fewer than 5 affected joints), with a preference for the involvement of large joints. Accordingly, until recently in Germany, no approved (systemic) disease-modifying antirheumatic drug (DMARD) had been available, and patients had to be treated off-label. In the past year, 2 biologic TNF inhibitors (etanercept and adalimumab) were approved for the treatment of ERA following an open-label trial in the case of etanercept, and a double-blind, placebo-controlled study in the case of adalimumab (19,24).

The present study is the first clinical trial to evaluate the efficacy and safety of etanercept, compared to placebo, in children and adolescents with the ERA category of JIA. As a second primary outcome criterion, we also evaluated the stability of disease remission after discontinuation of etanercept.

PATIENTS AND METHODS

Participants and study design. This was a multicenter, randomized, placebo-controlled, double-blind, investigator-initiated study that began in May 2011 and involved 8 sites in Germany. The study was conducted in accordance with the protocol of the International Conference on Harmonisation Guidelines for Good Clinical Practice, regulations governing clinical study conduct, and the Declaration of Helsinki ethics principles (1996 revision and 2000 revision with subsequent clarifications). Before the study was initiated, the study protocol, the informed consent form, and each subject's information were submitted to the responsible independent ethics committee of the North Rhine Medical Association (Duesseldorf, Germany) for review and approval. Voluntary written informed consent was obtained from either the patient and his or her parent(s) or the patient and his or her legal guardian(s) at the screening visit prior to participation in any study procedures.

Key inclusion criteria consisted of the following: 1) a diagnosis of the ERA category of JIA, as determined by the

ILAR criteria (1); 2) presence of active disease, defined as the presence of each of the following features: a minimum of 3 joints with active arthritis, characterized by either swelling not due to deformity or, if no swelling is present, limited range of motion and pain, or pain on movement, a numeric rating scale (NRS) score of at least 3 (scale 0–10) on the physician's global assessment of disease severity, and an NRS score of at least 3 (scale 0–10) on the parent's global assessment of patient's overall well-being; 3) ages 6 years to <18 years at baseline; 4) a history of inadequate response or intolerance to at least one NSAID and at least one DMARD, either SSZ or MTX; 5) current treatment with a DMARD or, if the patient is being treated with SSZ and treatment is planned to be continued throughout the study period, a stable dose of SSZ must have been given for at least 4 weeks; and 6) treatment with a stable dose of NSAIDs for at least 4 weeks before baseline, a stable dose of corticosteroids (≤0.2 mg of prednisone per kg per day, up to a maximum of 10 mg/day) for at least 4 weeks before baseline, or both.

Key exclusion criteria consisted of the following: 1) treatment with DMARDs other than SSZ during the last 28 days before baseline; 2) diagnosis of any JIA category other than ERA (based on the ILAR criteria), acute inflammatory joint disease not associated with ERA, presence of IgM rheumatoid factor, history of inflammatory bowel disease, or psoriasis; 3) previous treatment with biologic therapy, including anti-TNF therapy; and 4) previously received intravenous, intramuscular, intraarticular, or soft tissue injections of corticosteroids within 4 weeks before the first administration of study medication.

An open-label, uncontrolled study (phase I) with etanercept treatment (0.8 mg/kg body weight, maximum dosage 50 mg/week) for 24 weeks was followed by a randomized, double-blind, placebo-controlled, parallel-group treatment-withdrawal study (phase II) for an additional 24 weeks. Patients who demonstrated a treatment response of at least 30% improvement on the ACR Pedi criteria (ACR Pedi 30) were randomized into 2 groups. The primary end point of the phase II study was the achievement of an ACR Pedi 30 response. The ACR Pedi 50, Pedi 70, Pedi 90, and Pedi 100 response rates and the rate of patients achieving remission according to the Juvenile Arthritis Disease Activity Score based on 10-joint counts (JADAS10) (25,26) were secondary outcome criteria. Only patients who had achieved at least an ACR Pedi 30 response were eligible to enter the phase II study. Patients who did not achieve an ACR Pedi 30 response at week 24 of the phase I study but were willing to continue with the current treatment were offered treatment with open-label etanercept for up to an additional 24 weeks.

In the phase II study, group 1 continued treatment with etanercept for a maximum of 24 weeks, while group 2 received placebo. The primary efficacy end point of the phase II study was the proportion of patients who developed a disease flare from week 24 to week 48, defined according to the ACR preliminary definition of disease flare in juvenile rheumatoid arthritis (27).

End points. Secondary efficacy end points were changes from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores (each using the German versions) (28,29), the number and percentage of responders with 50% improvement in the BASDAI (BASDAI50), reduction in the number of tender enthesis sites (range 0–35) (30), and the patient's assessments of total back pain and nocturnal back pain and parent's assessment of the patient's pain (each on 0–10 NRS).

Patients were withdrawn from the phase II study in the event of a disease flare or at week 48, whichever occurred earlier. After a flare, patients received open-label etanercept until week 48.

Clinical assessments, performed at baseline and weeks 4, 8, 16, 24, 28, 32, 40, and 48, included assessment of the core set of outcome variables in JIA. These variables included the number of joints with active arthritis, number of joints with limited range of motion, physician's global assessment of disease activity, and parent's or patient's global assessments of overall well-being, total back pain, and nocturnal back pain (each using 0–10 NRS, with higher scores indicating more active or worsening severity of disease), assessment of physical function using the German version of the Childhood Health Assessment Questionnaire (C-HAQ) disability index (DI) (score range 0–3, with higher scores indicating more disability), C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

The total entheseal assessment was performed by a pediatric physician who assessed the presence (score of 1) or absence (score of 0) of enthesitis at 27 different sites on the body. On each side of the body, the physician assessed tenderness of the entheses at the first costochondral joint, seventh costochondral joint, anterior superior iliac spine, iliac crest, greater trochanter, quadriceps insertion into the superior border of the patella, patellar ligament insertion into the inferior pole of the patella or tibial tubercle, first supraspinatus insertion into the greater tuberosity of the humerus, lateral epicondyle of the humerus, medial epicondyle of the humerus, posterior superior iliac spine, proximal insertion of the Achilles tendon, calcaneal insertion of the plantar fascia, and the fifth lumbar spinous process.

Concomitant treatment with NSAIDs, low-dose corticosteroids (up to a maximum of 0.2 mg/kg body weight or 10 mg/day, whichever was less), and SSZ was allowed. During phase I, a decrease in dosage, as well as a discontinuation of concomitant medication, was allowed at the discretion of the principal investigator. No change to the concomitant treatment was allowed in phase II.

Adverse events (AEs) were documented throughout the study and for 70 days after each patient received the last dose of the study medication.

Statistical analysis. The efficacy analyses were performed in an intent-to-treat (ITT) population. The ITT population is defined as all subjects who were randomized and received at least one administration of the study drug and at least one postdose efficacy assessment.

For sample size calculation, efficacy data from the German BIKER registry were extrapolated. Eighty percent of placebo-treated patients were expected to develop a disease flare within 24 weeks, compared to a maximum of 20% of those receiving continuous treatment with etanercept. With a power of 80% and a significance level of $P < 0.05$, 13 patients per group would be considered a sufficient sample size to show a significant difference in efficacy between the groups (sample size calculation at $P < 0.05$ by 2-sided test).

The safety population consisted of all patients who received at least one dose of the study medication. Safety results represent data collected through week 48 or up to

Table 1. Baseline demographic and disease characteristics of the patients*

	Placebo (n = 18)	Etanercept (n = 20)
Age at baseline, mean ± SD years	14.1 ± 1.9	12.6 ± 2.8
Disease duration, mean ± SD years	3.2 ± 3.5	2.4 ± 2.1
Male, no. (%)	14 (77.7)	14 (70)
HLA–B27 positive, no./total (%)	14/18 (77.8)	11/19 (57.9)
Weight, mean ± SD kg	57.4 ± 20.4	50.8 ± 16.3
Height, mean ± SD cm	167.3 ± 15.1	157.1 ± 17.4
DMARDs		
Previous use, no. (%)	14 (77.7)	12 (60)
Total number taken	17	14
Joints with active arthritis, mean ± SD	5 ± 2.6	5.7 ± 2.6
Joints with limited range of motion, mean ± SD	5.3 ± 2.7	5.2 ± 2.8
Tender joints, mean ± SD	6.6 ± 5.2	7.1 ± 3.9
Swollen joints, mean ± SD	3.1 ± 2.7	3.6 ± 3.4
Physician's global assessment of disease activity NRS score, mean ± SD	5.2 ± 1.8	5.2 ± 1.9
Parent's assessment of patient's overall well-being NRS score, mean ± SD	5.5 ± 2	6.1 ± 2.3
CRP, mean ± SD mg/liter	1.6 ± 0.7	1.6 ± 0.7
ESR, mean ± SD mm/hour	27 ± 30	25 ± 23
C-HAQ DI, mean ± SD	0.6 ± 0.5	0.8 ± 0.8
Back pain NRS score, mean ± SD	4.8 ± 2.3	5.3 ± 2.4
Nocturnal back pain NRS score, mean ± SD	2.8 ± 2.8	2.7 ± 2.8
JADAS10, mean ± SD	15.6 ± 4.2	16.2 ± 4.7
BASFI, mean ± SD	2.4 ± 2.1	2.7 ± 2.5
BASDAI, mean ± SD	4.3 ± 1.7	4.4 ± 2.1
Enthesitis score, mean ± SD	1.5 ± 2.2	2.0 ± 1.6

* DMARDs = disease-modifying antirheumatic drugs; NRS = numeric rating scale (scale 0–10); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; C-HAQ DI = Childhood Health Assessment Questionnaire disability index (scale 0–3); JADAS10 = Juvenile Arthritis Disease Activity Score based on 10-joint counts (scale 0–40); BASFI = Bath Ankylosing Spondylitis Functional Index (scale 0–10); BASDAI = Bath Ankylosing Spondylitis Disease Activity Index (scale 0–10).

70 days following the last study dose of etanercept for patients who discontinued the study drug prior to week 48. AEs were summarized as the number and percentage of patients experiencing AEs, as defined by the Medical Dictionary for Regulatory Activities (version 15.1).

RESULTS

Patient disposition and baseline characteristics. Forty-four patients were screened and 41 patients were included in the trial. Two patients were excluded during phase I of the study: 1 because of a self-remitting allergic skin reaction, and 1 because of a major protocol deviation (rheumatoid factor positivity and concomitant treatment with MTX). Thirty-nine patients remained in the study until week 24. One patient did not achieve an ACR Pedi 30 response and was not randomized, but was offered treatment with etanercept for an additional 24 weeks. All other patients were randomized, 18 to the placebo group and 20 to the etanercept group. All of the randomized patients remained in the study until week 48. No patients dropped out of the study during the double-blind phase (phase II).

The demographic and disease characteristics of the randomized patients are shown in Table 1. As expected, the majority of patients were male. Patients had a moderate-to-high level of disease activity, as demonstrated by the number of joints with active arthritis and the scores on the parent's and physician's global assessments of disease activity. Before inclusion in the study, all patients had previously been treated with NSAIDs, 6 (14.6%) had received cyclooxygenase 2 inhibitors, 14 (34%) had been treated with oral corticosteroids, 17 (41.5%) had received intraarticular corticosteroids at least once, 17 (41.5%) had received MTX, 15 (36.6%) had received SSZ, and 1 (2.4%) had received cyclosporin A. At baseline, 36 patients (88%), 14 patients (34%), and 20 patients (49%) were receiving concomitant treatment with NSAIDs, oral corticosteroids, and SSZ, respectively. One patient who had been treated with oral MTX withdrew from the study because of a protocol deviation. At week 24, among the 39 patients, 22 (56%), 5 (13%), and 7 (18%) were still receiving concomitant treatment with NSAIDs, oral corticosteroids, and SSZ, respectively. There were no

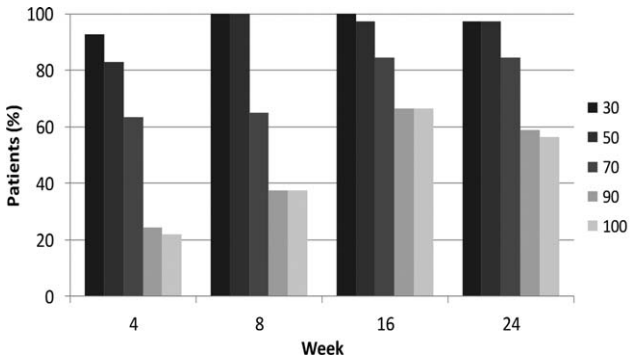

Figure 1. Treatment response rates determined in the intent-to-treat population (n = 41) at each visit through week 24 in phase I of the study, according to the American College of Rheumatology (ACR) Pediatric (Pedi) response criteria for improvement in juvenile arthritis, at ACR Pedi improvement levels of 30%, 50%, 70%, 90%, and 100%.

meaningful differences in disease characteristics at baseline between patients in the total patient cohort and those in the cohorts randomized to receive placebo or etanercept after week 24 (Table 1).

Efficacy in phase I (open-label). Two patients withdrew prematurely from the study: 1 withdrew because of intolerance to treatment, and the other was withdrawn at the discretion of the principal investigator due to the presence of rheumatoid factor, which was an exclusion criterion. One patient treated for 24 weeks did not achieve an ACR Pedi 30 response, and therefore this patient was not randomized for phase II of the study. Instead, this patient received open-label etanercept treatment for 48 weeks.

Patients receiving etanercept responded rapidly to the treatment, as determined by the ACR Pedi criteria. This was already evident at week 4 and increased in strength with continuous treatment (Figure 1). The ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 response rates at week 24 were 93%, 93%, 80%, 56%, and 54%, respectively, in the ITT population. The primary outcome measure of the open-label phase I study was the ACR Pedi 30 response at week 24, which was achieved in 38 patients. Furthermore, there was a marked decrease in all disease activity measures, with findings ranging from a 31% reduction in the CRP level to a 97% reduction in the number of swollen joints (Table 2). Active arthritis was an inclusion criterion for the study, but some of the patients did not have an elevated CRP level or elevated ESR at baseline, and therefore the laboratory markers of inflammation in these patients could not show improvement.

During the open-label period, improvements in the ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 response rates at week 24 were numerically and relatively similar later in both groups of patients (those receiving placebo and those receiving etanercept). More than 90% of patients achieved the ACR Pedi 30 response, which was defined as the minimal response. All 38 randomized patients achieved an ACR Pedi 50 response by at least week 8.

As shown in Table 2, a marked decrease in all disease activity markers was observed. The mean number of tender joints, swollen joints, joints with active arthritis, and joints with limited range of motion decreased by 91%, 97%, 94%, and 76%, respectively. The mean NRS score for physician's assessment of global disease activity decreased by 91%, and the parent's assessment of patient's overall well-being improved, with an 80% decrease in the mean NRS score. The total number of tender enthesis sites decreased by 75%, the total BASDAI score decreased by 72%, the total back pain score decreased by 72%, the nocturnal back pain score decreased by 81%, the patients' BASFI scores decreased by 85%, and the JADAS10 score decreased by 87%; moreover, marked improvements were noted for indicators of spinal involvement as well. Eleven patients (27%) fulfilled the criteria for a BASDAI50 response. Furthermore, there was a decrease in the C-HAQ DI, which demonstrated functional improvement.

The JADAS10 also demonstrated a marked reduction in disease activity. Twenty-three patients (59%) treated for 24 weeks achieved remission and 69% achieved minimal disease activity, as determined by the JADAS10 criteria (Figure 2). At the end of the open-label phase I study, 31 patients (79%) had no joints with active disease, 35 (90%) had no swollen joints, 31 (79%) had no tender joints, and 25 (64%) had a physician global VAS of 0. Twenty-one patients (54%) had a patient global VAS of 0, 37 (95%) had a normal ESR (≤20 mm/hour), and 36 (92%) had a normal CRP level (≤6 mg/liter).

Efficacy in phase II (double-blind, withdrawal). In phase II of the study, 12 disease flares (defined according to the ACR criteria for flare in JIA) were documented. A flare occurred in 9 patients in the placebo cohort (on days 15, 25, 28, 31, 43, 53, 56, 151, and 168 [end of study]) and in 3 patients in the etanercept cohort (on days 31, 37, and 168). The study met its primary end point at week 48, with a significantly higher proportion of placebo-treated patients experiencing a flare compared to etanercept-treated patients; thus, significantly more patients treated with placebo after week 24 developed a flare compared to those who continued treatment with etanercept (odds ratio for flare in the placebo group versus etanercept group 6.0, 95%

Table 2. Mean change from baseline in clinical end points and responder status according to the American College of Rheumatology Pediatric response criteria at week 24*

	Baseline	Week 24	Change from baseline	
			Absolute decrease	Relative decrease, %
Physician's global assessment of disease activity NRS score, mean	5.17	0.49	−4.68	−90.6
Parent's assessment of patient's overall well-being NRS score, mean	5.83	1.15	−4.68	−80.2
Joints with active arthritis, mean	5.32	0.31	−5.01	−94.2
Tender joints, mean	7.05	0.62	−6.43	−91.3
Swollen joints, mean	3.24	0.10	−3.14	−96.8
Joints with limited range of motion, mean	5.15	1.26	−3.89	−75.6
CRP, mean mg/liter	1.61	1.11	−0.50	−31.3
ESR, mean mm/hour	1.56	1.03	−0.54	−34.3
CHAQ DI, mean	0.80	0.11	−0.69	−86.5
Back pain NRS score, mean	5.20	1.46	−3.73	−71.9
Nocturnal back pain NRS score, mean	2.88	0.54	−2.34	−81.3
BASDAI, mean	4.42	1.25	−3.17	−71.6
BASFI, mean	2.69	0.41	−2.28	−84.8
Spinal inflammation	3.24	0.58	−2.66	−82.1
Tender entheses				
Mean enthesitis score	1.80	0.40	−1.40	−77.8
Total number of tender enthesis sites	72	18	−54	−75.0
JADAS10, mean	15.90	2.03	−13.87	−87.3

* NRS = numeric rating scale (scale 0–10); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; C-HAQ DI = Childhood Health Assessment Questionnaire disability index (scale 0–3); BASDAI = Bath Ankylosing Spondylitis Disease Activity Index (scale 0–10); BASFI = Bath Ankylosing Spondylitis Functional Index (scale 0–10); JADAS10 = Juvenile Arthritis Disease Activity Score in 10 joints (scale 0–40).

confidence interval 1.1–37, $P = 0.02$ by chi-square test). The probability of remaining flare-free was higher in the etanercept-treated patients than in the placebo-treated patients in phase II, with a 35% reduction in the risk of a flare in the etanercept cohort compared to the placebo cohort (Figure 3).

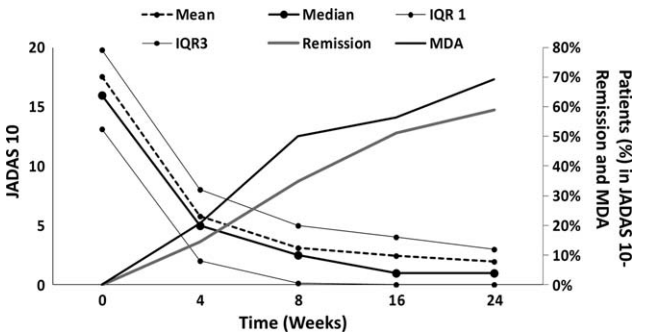

Figure 2. Rates of disease remission and minimal disease activity (MDA) determined at each visit through week 24 in phase I of the study, according to the Juvenile Arthritis Disease Activity Score based on 10-joint counts (JADAS10). The JADAS10 scores are shown as the mean and median values (with interquartile range 25th [IQR1] and 75th [IQR3] percentile values) at each visit. Remission was defined as a JADAS10 score of ≤1. MDA was defined as a JADAS10 score of ≤2 in patients with oligoarthritis or JADAS10 score of ≤3.8 in patients with polyarthritis.

Of interest, 7 flares occurred in placebo-treated patients between week 26 and week 32 of the study; during a pharmacokinetically meaningful time period after discontinuation of etanercept at week 24, only 2 flares occurred in etanercept-treated patients. Three additional flares were noted later: 1 at week 44, and 2 at the final patient visit (in 1 patient receiving etanercept and 2 receiving placebo). Twenty-six patients reached week 48 without a flare (17 patients receiving etanercept [85%] compared to 9 patients receiving placebo [50%]).

Of the 11 patients (55%) receiving continuous etanercept treatment who achieved remission (defined by the JADAS10 criteria) at week 24, 9 remained in remission until week 48, whereas 2 did not. Two other patients who did not show signs of JADAS10-defined remission at week 24 achieved remission at week 48. One of 11 patients whose disease was in remission at week 24 developed a flare (i.e., fulfilled the ACR flare criteria) on day 168 during the double-blind phase II study, while being continuously treated with etanercept.

Twelve (66%) of 18 patients assigned to receive placebo subsequently achieved JADAS10-defined remission upon treatment with etanercept at week 24, of whom 5 (42%) remained in remission while receiving placebo. One patient (of 6 total) whose disease was not in remission at week 24 achieved JADAS10-defined

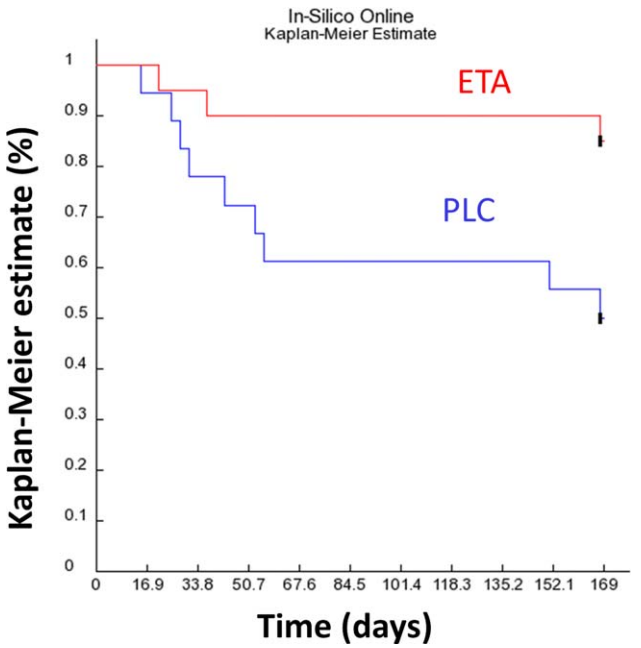

Figure 3. Rates of disease flare determined in phase II of the study (weeks 24–48), according to the American College of Rheumatology (ACR) preliminary definition of disease flare in juvenile arthritis. Results are Kaplan-Meier estimates of the probability of staying flare-free in etanercept (ETA)– and placebo (PLC)–treated patients in phase II. A disease flare (meeting the ACR flare criteria) occurred in 3 (13.5%) of 20 patients treated with etanercept and in 9 (50%) of 18 patients treated with placebo, leading to a 35% reduction in the risk of flare in the etanercept cohort compared to the placebo cohort (hazard ratio 0.242, 95% confidence interval 0.065–0.898, $P = 0.0211$).

remission at week 48 while being treated with placebo. Nine patients in the placebo group fulfilled the ACR flare criteria between week 24 and week 48. Seven of these patients were in remission at week 24.

Seven patients in the placebo cohort who developed a disease flare before week 48 switched to open-label etanercept treatment after the flare. Five of these patients achieved JADAS10-defined remission.

Safety. The total observation time was 35.6 patient-years, including 21.5 patient-years of exposure to open-label etanercept treatment, 8.4 patient-years of exposure to double-blind etanercept treatment, and 5.7 patient-years of exposure to placebo treatment. The most frequently reported AEs were adverse drug reactions, gastrointestinal infections, and upper respiratory tract infections (Table 3). In 1 patient, an allergic skin reaction resulted in withdrawal from the study during the open-label phase II study. Two serious AEs were reported: a posttraumatic fracture and a renal hemorrhage.

During the double-blind phase II study, rates of AEs were similar in the 2 treatment groups. No malignancies and no serious or opportunistic infections, tuberculosis, lupus-like syndrome, demyelinating disease, or deaths were reported through week 48. Thus, no new safety signals regarding treatment with etanercept emerged from this study.

DISCUSSION

This is the first double-blind study in which the efficacy of etanercept was demonstrated for treatment of patients with the ERA category of JIA. In addition to being approved for the treatment of additional JIA categories, etanercept has been approved for children with ERA who are older than age 12 years based on the results of an open-label study (the Clinical Benefit and Long-Term Safety of Etanercept in Children and Adolescents With Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Psoriatic Arthritis [CLIPPER] study), which involved an historical control cohort of etanercept-treated patients exposed to placebo, and an historical cohort of patients with polyarticular JIA who were exposed to etanercept (19). The present patient population, in whom ERA was diagnosed according to the ILAR classification criteria, ranged in age from 6 years to 17 years, while the CLIPPER study was conducted in patients with ERA ages 12–17 years.

During the first 24-week wash-in period, treatment with etanercept resulted in meaningful improvement in a very high number of patients, with values exceeding the rate of improvement observed in clinical practice as documented in the BIKER registry (21,31). Patients included in this study had to have a more severe phenotype, having higher levels of disease activity than those documented in the BIKER registry (31). High disease activity as an inclusion criterion was chosen for this study to avoid including children who might not need treatment; at study baseline, etanercept had not been approved for the treatment of ERA JIA.

Safety results were similar to the findings obtained in etanercept trials in polyarticular JIA, the experiences gained from registries, and the findings in adults with rheumatoid arthritis and patients with SpA (18,21,31–33). No AEs unique to patients with ERA were identified, such as the development of chronic inflammatory bowel disease, a condition that had been previously observed in the CLIPPER trial cohort as well as in the much larger BIKER registry cohort, which had a much longer followup period (19,31). Infections also commonly observed in the general population were the most frequently reported AEs. No events of special interest identified as potential risks of anti-TNF therapy,

Table 3. Adverse events (AEs) and serious AEs (SAEs) from the first dose (week 0) through week 24 and week 48*

	All patients		Phase II randomization (weeks 24–48)		
	Phase I (weeks 0–24) (n = 41)	Phase II (weeks 24–48) (n = 38)	Placebo (n = 18)	Etanercept (n = 20)	All-exposure safety group (n = 41)†
Patient-years of exposure	18.2	14.1	5.7	8.4	35.6
AEs					
Total no. of events	101	49	15	34	162
Rate per year (95% CI)	5.5 (4.5–6.7)	3.4 (2.6–4.5)	2.6 (1.5–4.3)	4 (2.8–5.6)	4.5 (3.9–5.3)
Patients with at least 1 AE	32 (78.0)	25 (65.7)	11 (61.1)	14 (70.0)	37 (94.9)
Type of event‡					
Abdominal pain	5 (12.1)	2 (5.2)	0	2 (10.0)	7 (17.0)
Adverse drug reaction	18 (43.9)	1 (2.6)	0	1 (5.0)	19 (46.3)
Back pain	3 (7.3)	3 (7.8)	0	3 (15.0)	6 (14.6)
Bronchitis	3 (7.3)	0	0	0	3 (7.3)
Diarrhea	2 (4.8)	1 (2.6)	0	1 (5.0)	3 (7.3)
Fatigue	0	3 (7.8)	1 (5.5)	2 (10.0)	4 (9.7)
Fever	2 (4.8)	1 (2.6)	0	1 (5.0)	3 (7.3)
Gastrointestinal infection	8 (19.5)	7 (18.4)	3 (16.6)	4 (20.0)	16 (39.0)
Headache	4 (9.7)	3 (7.8)	2 (11.1)	1 (5.0)	7 (17.0)
Knee pain	0	3 (7.8)	0	3 (15.0)	3 (7.3)
Upper respiratory tract infection	13 (31.7)	8 (21.0)	1 (5.5)	7 (35.0)	25 (60.9)
SAEs					
Total no. of events	1	1	0	1	2
Rate per year (95% CI)	0.05 (0.01–0.39)	0.07 (0.01–0.5)	–	0.1 (0.02–0.8)	0.05 (0.01–0.2)
Patients with at least 1 SAE	1 (2.4)	1 (2.6)	0	1 (5.0)	2 (4.8)
Type of event	0	1 (2.6)	0	1 (5.0)	1 (2.4)
Fracture					
Renal hemorrhage	1 (2.4)	0	0	0	1 (2.4)

* Except where indicated otherwise, values are the number (%) of patients. 95% CI = 95% confidence interval.
† Events occurring in patients during phase I, phase II, and open-label treatments (weeks 0–48).
‡ Events occurring in ≥2 patients and listed according to lower-level Medical Dictionary of Regulatory Activities terms.

such as serious infections, tuberculosis, malignancies, or deaths, were observed.

One of the limitations of this study was the small number of patients available for study enrollment, which could be attributed to the rarity of the disease; however, the number of patients was sufficiently high to evaluate the primary outcome criterion, even in the double-blind phase II study. Not all patients had elevated levels of markers of inflammation at baseline, even in the context of active disease, which limits the use of the 6-item ACR Pedi response criteria. Moreover, since laboratory parameters are also included in the 4-item JADAS, the value of the JADAS is also limited. Nevertheless, the consistency in improvement across all disease activity indicators represents strong evidence to support the efficacy of this treatment. Furthermore, a high number of patients achieved ACR Pedi 90 or ACR Pedi 100 responses, and more than 50% of patients achieved JADAS10-defined remission after 24 weeks of open-label treatment.

It is interesting to note that in most cases, the state of remission was stable during the period of continuous treatment with etanercept throughout week 48, but it is even more interesting that approximately one-half of the patients who switched to placebo in phase II did not develop a disease flare (defined by the ACR flare criteria), and a number of these patients remained in JADAS10-defined remission as well. The study data are insufficient with regard to further factors that might influence the recurrence of the disease after discontinuation of etanercept treatment. Those patients who experienced a flare and were thereafter treated with etanercept on an open-label basis also achieved a favorable treatment response. This observation may lead to the suggestion that patients with ERA who respond well to 24 weeks of treatment with etanercept may discontinue medication, with close clinical monitoring.

Another limitation of this study is the lack of imaging to demonstrate the influence of the treatment on structural damage or axial involvement. The marked improvements observed with regard to the extent of back pain, the BASDAI, and the BASFI suggest that axial involvement was present in these patients and showed improvement upon TNF inhibition with etanercept. In a study involving patients with juvenile AS, significant short-term improvement was observed in those treated

with adalimumab compared to those receiving placebo. Patients with juvenile AS will often fulfill the criteria for the ERA category of JIA, whereas not all children with ERA will have predominant axial involvement and, therefore, may not qualify for the juvenile AS diagnosis (17).

In summary, 24 weeks of etanercept treatment reduced the signs and symptoms of ERA, with marked improvement and a high number of patients achieving JADAS10-defined remission. Improvement was sustained through week 48 in those patients who continued etanercept treatment, which, in the double-blind phase II study, showed significant superiority over placebo. The safety profile of etanercept observed in patients with ERA was consistent with that observed in children ages $\geq$2 years who had been treated for polyarticular JIA.

ACKNOWLEDGMENTS

We thank Monika Szemkus (Sankt Augustin Center for Pediatric Rheumatology, Cologne, Germany) and Ingrid Becker (Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Germany) for help with data management, statistical analyses, and adverse event reporting.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Horneff had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Horneff, Kümmerle-Deschner, Huppertz.

Acquisition of data. Horneff, Foeldvari, Minden, Trauzeddel, Kümmerle-Deschner, Tenbrock, Ganser, Huppertz.

Analysis and interpretation of data. Horneff, Kümmerle-Deschner.

ROLE OF THE STUDY SPONSOR

Pfizer, Germany funded this study and provided the study medication. Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

REFERENCES

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
2. Flato B, Hoffmann-Vold AM, Reiff A, Forre O, Lien G, Vinje O. Long-term outcome and prognostic factors in enthesitis-related arthritis: a case–control study. Arthritis Rheum 2006;54:3573–82.
3. Burgos-Vargas R, Pacheco-Tena C, Vazquez-Mellado J. Juvenile-onset spondyloarthropathies. Rheum Dis Clin North Am 1997;23:569–98.
4. Garcia-Morteo O, Maldonado-Cocco JA, Suarez-Almazor ME, Garay E. Ankylosing spondylitis of juvenile onset: comparison with adult onset disease. Scand J Rheumatol 1983;12:246–8.
5. Sarma PK, Misra R, Aggarwal A. Outcome in patients with enthesitis-related arthritis (ERA): juvenile arthritis damage index (JADI) and functional status. Pediatr Rheumatol Online J 2008;6:18.
6. Stone M, Warren RW, Bruckel J, Cooper D, Cortinovis D, Inman RD. Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. Arthritis Rheum 2005;53:445–51.
7. Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schontube M, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392–401.
8. Tse SM, Burgos-Vargas R, Colbert RA. Juvenile spondyloarthritis treatment recommendations. Am J Med Sci 2012;343:367–70.
9. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double-blind, placebo-controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. Ann Rheum Dis 2002;61:941–2.
10. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol 2004;31:2055–61.
11. Tse SM, Burgos-Vargas R, Laxer RM. Anti–tumor necrosis factor α blockade in the treatment of juvenile spondylarthropathy. Arthritis Rheum 2005;52:2103–8.
12. Tse SM, Laxer RM, Babyn PS, Doria AS. Radiologic improvement of juvenile idiopathic arthritis-enthesitis-related arthritis following anti-tumor necrosis factor-α blockade with etanercept. J Rheumatol 2006;33:1186–8.
13. Sulpice M, Deslandre CJ, Quartier P. Efficacy and safety of TNFα antagonist therapy in patients with juvenile spondyloarthropathies. Joint Bone Spine 2009;76:24–7.
14. Schmeling H, Horneff G. Infliximab in two patients with juvenile ankylosing spondylitis. Rheumatol Int 2004;24:173–6.
15. Otten MH, Prince FH, Twilt M, ten Cate R, Armbrust W, Hoppenreijs EP, et al. Tumor necrosis factor-blocking agents for children with enthesitis-related arthritis—data from the Dutch Arthritis and Biologicals in Children Register, 1999–2010. J Rheumatol 2011;38:2258–63.
16. Burgos-Vargas R, Casasola-Vargas J, Gutierrez-Suarez R. A 3-month, double-blind, placebo-controlled, randomized trial of infliximab in juvenile-onset spondyloarthritis (SpA) and a 52-week open extension [poster]. Clin Exp Rheumatol 2008;26:745.
17. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther 2012;14:R230.
18. Lovell DJ, Giannini EH, Reiff A. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Eng J Med 2000;342:763–9.
19. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. for the Paediatric Rheumatology International Trials Organisation (PRINTO). Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: phase 1 (week 12) of the CLIPPER study. Ann Rheum Dis 2014;73:1114–22.
20. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202–9.
21. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA registry. Ann Rheum Dis 2009;68:519–25.
22. Papsdorf V. Horneff G. Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis [published erratum appears in Rheumatology (Oxford) 2011;50:814]. Rheumatology (Oxford) 2011;50:214–21.

23. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290–4.
24. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A double-blind, placebo-controlled, multicenter study of the efficacy and safety of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res (Hoboken). In press.
25. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. for the Paediatric Rheumatology International Trials Organisation. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658–66.
26. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, et al, for the Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the Juvenile Arthritis Disease Activity Score. Arthritis Rheum 2012;64:2366–74.
27. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002;29:1058–64.
28. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
29. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
30. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127–32.
31. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol 2015;34:61–9.
32. Van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, et al, for the ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136–46.
33. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72:815–22.