Delayed Clinical Response in Patients with Juvenile Idiopathic Arthritis Treated with Etanercept

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ABSTRACT. ***Objective.*** To evaluate response in patients with juvenile idiopathic arthritis (JIA) who failed to meet response criteria after 3 months of etanercept treatment.

Methods. This was a prospective ongoing multicenter observational study of all Dutch patients with JIA using etanercept. Response according to American College of Rheumatology Pediatric 30 criteria was assessed at study start and at 3 and 15 months.

Results. In total we studied 179 patients of median age 5.8 years at disease onset; 70% were female. Thirty-four patients did not respond after 3 months, of which 20 continued etanercept and 11 achieved response thereafter.

Conclusion. The delayed clinically relevant response in a substantial proportion of patients who initially did not respond justifies the consideration of continuing therapy to at least 6 months. (First Release Jan 15 2010; J Rheumatol 2010;37:665–7; doi:10.3899/jrheum.090550)

Key Indexing Terms:
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For patients with juvenile idiopathic arthritis (JIA) resistant to conventional agents, treatment with biological therapies such as etanercept is a valuable option. Studies showed rapid improvements achieved with etanercept, but the optimal duration of therapy to evaluate effectiveness in JIA is still unknown[1-4]. Improvement should be expected before 3 months of treatment for rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) and for both RA and JIA according to the 2007 consensus group findings[5,6]. The British Pediatric Rheumatology Group advises withdrawal of biological agents in the event of lack of response after 6 months of treatment[7]. Due to the guidelines and to the coverage regulations for health insurance, response in The Netherlands is evaluated at 3 months.

Several studies in adults show that a substantial proportion of patients with RA who failed to reach the response criteria at 3 months, and continued treatment, achieved response at 6 months, indicating a time lag in clinical efficacy[8-10]. JIA patients in whom a delayed response was seen at 6 months are mentioned by Lovell, *et al*, although no details were given[11]. Our objective was to evaluate clinical response to etanercept in patients with JIA who failed to meet the response criteria at 3 months.

MATERIALS AND METHODS

This study was embedded in the Arthritis and Biologicals in Children project, a prospective, continuing, multicenter observational study that includes all Dutch JIA patients using etanercept since its introduction in 1999[3]. Since 2008 a Web-based register has been used[12]. The study protocol was approved by the Medical Ethics Committee of Erasmus MC, Rotterdam, and participating hospitals. In The Netherlands, patients with polyarticular-

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course JIA are eligible for treatment if the disease is active despite maximum (tolerated) dose of methotrexate (MTX). The decision to continue the reimbursement is based on objective signs of improvement, taking into account other arguments from the treating physician such as phasing out comedication. In the register, patient and disease characteristics are collected at baseline. Data regarding the course of the disease are retrieved at start of therapy, at 3 months, and yearly thereafter, including variables of the JIA disease activity score: physician's global assessment of disease activity by visual analog scale (VAS; range 0–100 mm, 0 = best score); Childhood Health Assessment Questionnaire (range 0–3, 0 = best score) by patients/parents, including global assessment of well-being by VAS; number of active and limited joints; and erythrocyte sedimentation rate. Patients with a followup of at least 15 months were selected up until November 2008. Response was assessed using the ACR Pediatric 30, 50, and 70 criteria (ACRpedi30, 50, 70), defined as at least 30% (50%, 70%) improvement from baseline in 3 variables of the JIA core set, with no more than one of the remaining variables worsening by > 30%[13]. We used the definition of inactive disease according to Wallace, *et al*[14].

We defined initial nonresponders as patients not achieving ACRpedi30 response after 3 months' treatment and secondary responders as initial nonresponders who continued treatment, and achieved an ACRpedi30 response later during followup.

RESULTS

There were 179 patients eligible for inclusion, 70% female, with median age at onset of JIA 5.8 years (interquartile range 3.0–10.0 yrs) with subtypes as summarized in Table 1.

The disease course of the included patients is shown in Figure 1. Initial nonresponders were 5 patients in whom etanercept was withdrawn before 3 months of therapy, because of progression of the disease or serious adverse events, and 29 patients who did not meet the ACRpedi30 criteria at 3 months of treatment. In 20 of those 29 patients, the decision was made by the treating physician to continue etanercept and 11 responded thereafter. Of these 11 patients, 91% showed ACRpedi50 and 73% showed ACRpedi70 response; 36% achieved inactive disease at 15 months. None started or raised the dosage of MTX or systemic prednisone during etanercept treatment, and in the majority comedication was discontinued (MTX in 75% and prednisone in 67% of the patients who used it). Seven percent of all responders were secondary responders.

For the initial 145 responders, efficacy analysis according to intention to treat resulted in the following responses at 3 and 15 months, respectively: ACRpedi30 in 100% and 92%, ACRpedi50 in 86% and 90%, ACRpedi70 in 66% and 77%, and inactive disease in 22% and 38%. Ten patients stopped etanercept between 3 and 15 months due to remission (n = 1), inefficacy (n = 6), or (serious) adverse events (n = 3).

Characteristics of initial responders, secondary responders, and nonresponders as well as association of initial responses with subtypes are shown in Table 1. The number of secondary responders was too small to allow analysis of relations.

DISCUSSION

Our study shows that in patients with JIA a substantial proportion (55%) of nonresponders at 3 months of treatment who nevertheless continued etanercept achieved a response thereafter. In adults this time lag in clinical efficacy is also seen, with a "delayed" response of up to 57% at 6 months in patients that continue treatment despite insufficient initial response[8-10].

That the delayed responders achieved relevant improvement is shown by high percentages of ACRpedi50 and ACRpedi70 responses and even inactive disease in 36%, and by the fact that comedication was phased out in the majority of the patients. These results are similar to those of the initial responders at 15 months.

From data available in our register, we examined improvement at 3 and 15 months of treatment. However, the majority of the secondary responders will have achieved response before 15 months. We recently decided to add an evaluation to our register protocol at 6 months for a better analysis. The decision to continue etanercept despite failure

Table 1. Characteristics of initial responders, secondary responders, and nonresponders. Response according to the American College of Rheumatology Pediatric 30 response criteria (ACRpedi30).

Feature	Initial Responders, N = 145	Secondary Responders, N = 11	Nonresponders, N = 23
Total n = 179, F:M	101:44	5:6	20:3
Median age onset of JIA, yrs (IQR)	6.3 (3.1–10.0)	5.6 (3.4–10.0)	4.7 (2.7–5.3)
Median duration from diagnosis to start of etanercept, yrs (IQR)	3.5 (1.7–7.8)	4.0 (3.3–6.6)	3.1 (1.9–8.7)
JIA subtype (%)			
Systemic JIA, n = 42	26 (62)*	2 (5)	14 (33)
Polyarticular RF–, n = 71	63 (89)**	3 (4)	5 (7)
Polyarticular RF+, n = 13	11 (85)	0 (0)	2 (15)
Oligoarticular extended, n = 37	31 (84)	4 (11)	2 (5)
Psoriatic arthritis, n = 10	9 (90)	1 (10)	0 (0)
Enthesitis related arthritis, n = 6	5 (83)	1 (17)	0 (0)

* More systemic JIA patients are nonresponders at 3 months compared to other subgroups ($p < 0.001$, chi-square). ** More polyarticular JIA RF– patients are initial responders compared to other subgroups ($p = 0.03$, chi-square). RF: rheumatoid factor; IQR: interquartile range.

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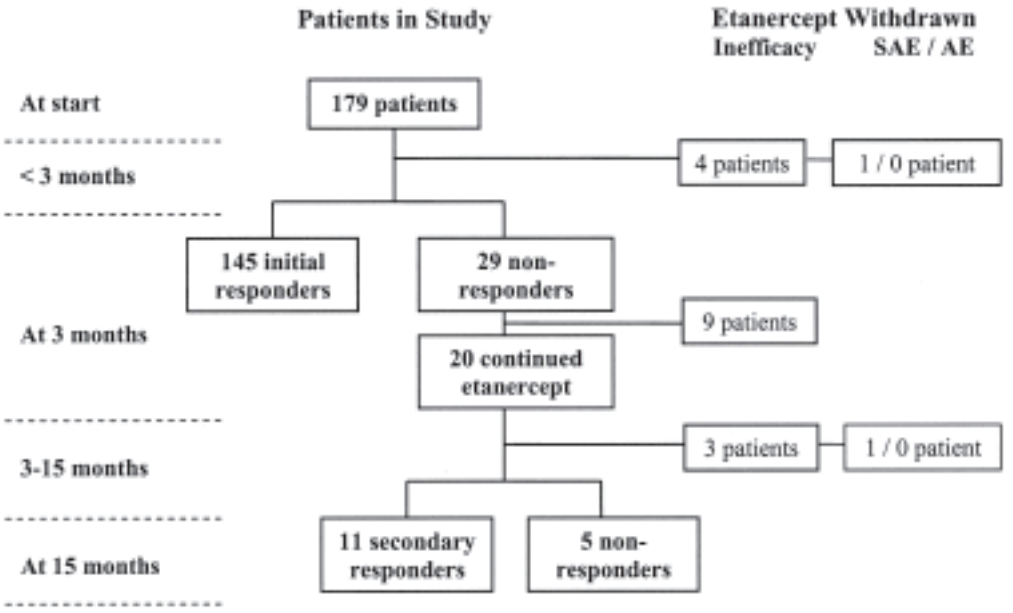

Figure 1. Disease course of patients in the study. SAE: serious adverse event.

to achieve an ACRpedi30 response will have been made with supporting arguments from the treating physician. The initially nonresponding patients who continued etanercept are therefore likely to have shown at least some improvement at 3 months.

European and American guidelines limit the duration of biological agents in case of nonresponse because of possible (serious) adverse events, unknown longterm effects, and high costs, although recent data on the longterm safety of etanercept show a low rate of serious adverse events[2-4]. However, etanercept is a valuable option for patients previously not responding to other second-line agents, including MTX. The increase in response observed in our study is therefore important.

In patients with JIA a substantial proportion of nonresponders at 3 months who continue etanercept eventually show a clinically relevant improvement; especially in patients with a partial initial response we advise consideration of continuation of treatment to at least 6 months. Recommendations in the current guidelines should be adapted accordingly.

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