Etanercept Treatment Improves Longitudinal Growth in Prepubertal Children with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** Anti-tumor necrosis factor (TNF) therapy is known to decrease disease activity of juvenile idiopathic arthritis (JIA), but its effect on longitudinal growth in relation to puberty is not clear. We studied longitudinal growth in response to etanercept treatment in prepubertal and pubertal patients with JIA.

Methods. Out of 52 children treated with etanercept, we studied 20 prepubertal and 11 early/midpubertal patients adherent to treatment for at least 1 year. We collected data on growth and glucocorticoid medication and calculated each patient's height standard deviation score (SDS) in relation to the midparental height, the change of this value (ΔhSDS) from –1 to 0 and 0 to 1 year of treatment, and the change between the ΔhSDS values to assess growth improvement.

Results. In the prepubertal group, the relative height SDS (mean ± standard error of the mean) was –1.8 ± 0.2, –2.1 ± 0.3, and –1.9 ± 0.3, and in the pubertal group –1.1 ± 0.4, –1.3 ± 0.3, and –1.1 ± 0.3 at –1, 0, and +1 year of treatment, respectively. The ΔhSDS before etanercept was –0.3 ± 0.1 in prepubertal and –0.2 ± 0.2 in pubertal patients. Over the first year with etanercept, ΔhSDS was +0.2 ± 0.1 in prepubertal ($p = 0.001$ vs before etanercept; paired Student t-test) and +0.2 ± 0.1 in pubertal patients ($p = 0.071$). Nevertheless, most prepubertal (17/20) and pubertal (8/11) patients had improved growth (ΔhSDS) in response to etanercept treatment when analyzed individually. The need for intraarticular glucocorticoid injections was negatively correlated to the improved growth ($p = 0.001$).

Conclusion. TNF inhibition with etanercept improved growth in a majority of patients with JIA. Our data demonstrate that growth improvement with etanercept was independent of the pubertal growth spurt. (First Release Nov 15 2007; J Rheumatol 2007;34:2481–5)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS ETANERCEPT GROWTH PUBERTY

The introduction of anti-tumor necrosis factor (TNF) agents has revolutionized the treatment of rheumatoid arthritis (RA) in children and adults. Anti-TNF treatment leads to a significant decrease in disease activity in adult RA[1,2] and also in juvenile idiopathic arthritis (JIA)[3], with sustained improvement and few side effects after 4 years' followup[4]. In patients with RA undergoing anti-TNF treatment it has been shown that bone erosions are halted[5], especially when the treatment is combined with methotrexate[6] (MTX). Etanercept is a recombinant fusion protein based on the p75-receptor for TNF and the Fc part of human immunoglobulin. It acts as a soluble receptor through competitive inhibition of the TNF-receptor on the cell surface, thereby diminishing TNF-driven inflammation that plays a key role in the arthritic process.

Children who are affected by chronic inflammatory diseases may have stunted linear growth[7,8]. Data in rats suggest that TNF-α acts in synergy with interleukin 1ß to inhibit linear bone growth[9]. In a small mixed population (n = 7) of prepubertal and pubertal patients with refractory JIA and growth retardation, the institution of anti-TNF therapy was reported to be associated with growth reconstitution[10]. A recent study, in a larger (n = 71) population of prepubertal/pubertal patients with JIA, showed similar results of anti-TNF treatment on growth[11]. Our aim was to confirm these positive effects on growth in patients with JIA treated with etanercept, analyzing the responses for prepubertal and pubertal patients separately.

MATERIALS AND METHODS

Study patients. Between 1999 and 2004, treatment with Enbrel™ (etanercept) was initiated in 52 of our patients with JIA (Pediatric Rheumatology Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden). These patients had previously shown an unsatisfactory response to treatment with nonsteroidal antiinflammatory drugs, intraarticular corticosteroid injections, and MTX, and/or developed intolerable side effects to MTX.

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Six patients were excluded as the treatment was stopped within the first year due to insufficient clinical improvement (n = 4) or adverse events (n = 2; anaphylactic reaction, herpes zoster). In addition, 1 patient with myelomeningocele and lower limb contractures, 5 patients concomitantly treated with growth hormone, 8 patients in advanced puberty (girls older than 13.6 years and growth velocity < 5 cm/yr the year before start of etanercept treatment), and 1 patient with missing data before etanercept treatment were excluded from the study. Among the remaining 31 patients, 2 groups were identified, the "prepubertal" patients (n = 20), who started etanercept treatment at least 1 year before pubertal onset, and the "pubertal" patients (n = 11), which included adolescents in early/midpuberty (girls and boys younger than 13.3 and 13.6 yrs, respectively; with pubertal signs and growth velocities ≥ 5 cm/yr at start of etanercept treatment). These 2 groups were selected for growth evaluation before and during etanercept treatment. The clinical characteristics of the 31 patients are summarized in Table 1.

Our study was approved by the human ethical committee at the Karolinska University Hospital.

Data collection. Height and weight before and during etanercept therapy were recorded at every clinic visit. Information about the parents' self-reported heights were collected in order to calculate the mid-parental target height. In a few patients, the pubertal status was unclear and in those subjects historical information about pubertal signs (breast development in girls and penile/scrotal enlargement and/or presence of pubic hair in boys) was collected from the parents. Data regarding the administration of oral and intraarticular corticosteroids before and during etanercept therapy were collected in a retrospective manner based on notes in the hospital records.

Data analysis. The height standard deviation score (SDS) for each of the 31 subjects was calculated using the NordiNet® database (version 2.3; Novo Nordisk A/S, Bagsvaerd, Denmark) based on the Karlberg 1976 SDS height standards[12] and by use of piecewise linear regression (per 1-yr intervals). To correct for genetic causes of abnormal growth, the height SDS was subtracted by the mid-parental target (the sum of the father's and mother's height plus 13 cm in a boy or minus 13 cm in a girl, all divided by 2) height SDS for each individual patient. To evaluate how growth was affected by etanercept, ΔhSDS (i.e., the change in height SDS) was calculated the year before (from timepoint –1 yr to 0) and the first year after (timepoint 0 to +1 yr) the treatment was initiated.

Response definition. For each individual patient, we aimed to determine if the treatment with etanercept had a positive influence on longitudinal growth. To achieve this, the ΔhSDS the first year after etanercept was started was subtracted with the ΔhSDS the year before the onset of treatment. We defined "responders" as the patients who improved their ΔhSDS after etanercept treatment was initiated (i.e., positive difference) and "nonresponders" as patients who did not (i.e., negative or no difference). In this way, even the patient who loses height SDS, but to a lesser extent than before etanercept, would be considered a responder. On the other hand, a patient who continues to gain height SDS, but less than before etanercept, is considered a nonresponder.

Statistical analysis. The relative height SDS of the prepubertal and pubertal groups is expressed as mean ± standard error of the mean. Comparison of relative height SDS between 1 year before and 1 year after treatment was carried out by use of paired Student t-test. Correlation analyses were carried out by Pearson correlation. A value of $p < 0.05$ (5%) was considered as significant. All statistical analyses were conducted using the SAS statistical software package (version 8.1; SAS Institute Inc.).

Table 1. Clinical characteristics of the 31 included patients with JIA.

	Prepubertal	Pubertal
No. of patients	20	11
Girls/boys	14/6	8/3
Subgroups[16]		
Polyarticular	8	4
Extended oligoarticular	6	2
Systemic	4	1
Polyarticular (RF+)	0	3
JAS	1	0
Psoriatic	0	1
Other (IBD)	1	0
Uveitis	4*	2
ANA-positive (pretreatment)	10	5
DMARD (with etanercept)		
Methotrexate	17	8
Sulfasalazine	1	2
Methotrexate dose†	9.3 (0–20)	8.0 (0–15)
Age at diagnosis††	3:5 (1:0–8:6)	5:10 (1:6–9:0)
Age when etanercept treatment was started††	8:2 (2:11–12:8)	11:10 (10:2–13:7)

JIA: juvenile idiopathic arthritis; ANA: antinuclear antibodies; DMARD: disease modifying antirheumatic drugs. Systemic: systemic onset; RF+: rheumatoid factor-positive; JAS: juvenile ankylosing spondylitis/enthesopathy associated JIA; Psoriatic: psoriasis arthropathy; IBD: inflammatory bowel disease. * 3 cases of uveitis with onset after starting etanercept treatment. † Mean dose: mg/wk (range); †† age (yrs:mos) = mean (range).

RESULTS

Growth response to etanercept treatment. For the group of 20 prepubertal patients, the mean height SDS (corrected for mid-parental target height, see Methods) was –1.8 ± 0.2 SDS 1 year before, –2.1 ± 0.3 SDS at start of, and –1.9 ± 0.3 SDS 1 year after the initiation of etanercept treatment. For the group of 11 pubertal patients, the mean relative height SDS was –1.1 ± 0.4 SDS 1 year before, –1.3 ± 0.3 SDS at start of, and –1.1 ± 0.3 SDS 1 year after the start of etanercept treatment. To analyze the growth response to etanercept, ΔhSDS was calculated. ΔhSDS from timepoint –1 year to the day of initiation of etanercept treatment was –0.3 ± 0.1 in prepubertal and –0.2 ± 0.2 in pubertal patients. When calculated over the first year of etanercept treatment, the ΔhSDS in prepubertal patients (n = 20) was +0.2 ± 0.1 ($p = 0.001$ vs the year before etanercept) and in pubertal patients (n = 11) it was +0.2 ± 0.1 ($p = 0.071$ vs the year before etanercept). The difference between before and after treatment was 0.5 SDS [95% confidence interval (CI) 0.3–0.8] for prepubertal and 0.4 SDS (95% CI 0.0–0.8) for pubertal patients.

After analyzing the growth response in each individual patient (Table 2), we found that 17 of 20 prepubertal children and 8 of 11 pubertal children had a positive difference between the ΔhSDS 1 year after and 1 year before the onset of etanercept treatment (Figure 1, "Responders"). However, it is important to point out that from this group, 5 prepubertals (Patients 4, 11, 14, 16, and 20) and 1 pubertal patient (Patient 25) still lost height SDS the first year after etanercept treatment was initiated, although to a lesser extent than the year before the treatment. In contrast, among "Nonresponders" we found 2 prepubertals (Patients 1 and 8) and 1 pubertal (Patient 31) who gained height SDS the first year after etanercept treatment was initiated, although to a lesser or same extent as the year prior to the initiation of the treatment.

When etanercept treatment was initiated, 8 prepubertal

Table 2. Changes in height SDS and glucocorticoid medication in response to etanercept treatment.

Patient	Age* (y:m)	Sex	Target Height SDS	Adjusted Parental Height SDS			Δ Height SDS		Change in Δ Height SDS	Oral GC, mg/day		Local GC Injections (no./year)	
				–1 yr	0 yr	1 yr	–1 to 0 yr	0 to 1 yr		0 yr	1 yr	–1 to 0 yr	0 to 1 yr
Prepubertal													
1	2:11	F	1.29	–1.6	–0.9	–0.4	0.7	0.5	–0.14	0.0	0.0	15	0
2	3:10	M	1.27	–0.8	–0.5	–0.5	0.3	0.0	–0.36	3.8	0.0	0	0
3	4:2	F	1.45	–1.5	–1.7	–1.4	–0.2	0.3	0.52	0.0	0.0	21	11
4	4:7	F	0.41	–1.9	–3.3	–3.6	–1.4	–0.3	1.05	10.0	5.0	61	40
5	6:0	F	1.21	–3.2	–3.9	–2.5	–0.7	1.4	2.06	1.3	0.0	58	0
6	6:7	F	1.13	–1.2	–1.4	–0.8	–0.1	0.6	0.76	0.0	0.0	15	0
7	7:1	F	0.18	–1.2	–1.2	–0.7	–0.1	0.5	0.57	5.0	0.0	1	1
8	7:3	F	0.3	–1.6	–1.5	–1.3	0.1	0.1	0.00	5.0	0.0	5	4
9	7:8	F	1.05	–2.4	–2.5	–2.4	–0.2	0.1	0.31	7.5	0.0	8	0
10	8:4	F	1.05	–3.0	–2.9	–2.7	0.2	0.2	0.03	0.0	0.0	22	1
11	8:6	F	1.13	–3.5	–3.8	–4.0	–0.3	–0.2	0.09	0.0	0.0	64	46
12	8:10	F	1.85	–1.8	–1.5	–1.1	0.3	0.5	0.17	0.0	0.0	7	0
13	8:10	F	2.01	–1.5	–1.7	–1.1	–0.2	0.6	0.78	0.0	0.0	0	0
14	9:5	F	1.05	–0.3	–0.8	–1.0	–0.5	–0.2	0.33	0.0	0.0	12	0
15	10:1	M	0.1	–1.8	–2.5	–2.0	–0.7	0.5	1.23	12.5	0.0	8	0
16	10:2	F	2.25	–3.2	–4.0	–4.5	–0.8	–0.6	0.18	0.0	0.0	19	24
17	10:5	M	–0.39	–1.0	–1.6	–1.1	–0.6	0.5	1.11	0.0	0.0	62	0
18	12:0	M	2.23	–3.8	–4.0	–3.8	–0.2	0.2	0.41	2.5	0.0	15	0
19	12:7	M	0.65	–0.7	–1.4	–1.4	–0.7	0.0	0.67	0.0	0.0	26	7
20	12:9	M	0.85	–0.4	–1.2	–1.6	–0.8	–0.4	0.47	0.0	0.0	26	3
Pubertal													
21	10:3	F	–0.30	–1.0	–1.5	–1.2	–0.5	0.3	0.80	0.0	0.0	45	18
22	10:5	M	1.37	1.3	0.9	1.2	–0.4	0.3	0.68	0.0	0.0	20	0
23	10:9	F	0.97	–2.6	–2.5	–1.9	0.1	0.6	0.58	2.5	2.5	47	20
24	11:5	F	–0.54	0.5	–0.3	–0.2	–0.8	0.2	0.97	5.0	0.0	18	6
25	11:8	F	1.37	–2.1	–2.6	–2.7	–0.5	–0.1	0.41	7.5	0.0	29	8
26	11:10	M	–0.32	–0.5	–0.9	–0.2	–0.4	0.7	1.03	NA	0.6	13	0
27	11:11	F	1.61	–1.2	–1.6	–1.1	–0.4	0.4	0.83	0.0	0.0	70	1
28	12:2	F	0.18	–1.4	–1.6	–1.4	–0.2	0.2	0.41	5.0	1.3	0	0
29	12:11	F	1.05	–1.2	–1.1	–1.3	0.1	–0.1	–0.21	10.0	NA	10	12
30	13:3	F	0.73	–2.1	–1.9	–2.1	0.2	–0.2	–0.36	5.0	3.8	3	2
31	13:7	M	0.85	–1.9	–0.9	–0.8	1.0	0.1	–0.94	0.0	0.0	1	0

* Age at start of treatment (years:months). GC: glucocorticoid; SDS: standard deviation score; NA: data not available.

(Patients 4, 5, 9, 10, 11, 15, 16, and 18) and 2 pubertal patients (Patients 23 and 25) had a height > 2 SDS below their individual mid-parental target height (see Methods) and could therefore be considered growth-retarded. After 1 year of treatment with etanercept, almost the same number of patients (7 prepubertal: Patients 4, 5, 9, 10, 11, 16, 18; and 2 pubertal: Patients 25 and 30) were still considered growth-retarded. Interestingly, all these growth-retarded/short subjects were "Responders," because etanercept treatment either halted further loss of height SDS or induced partial catchup growth.

Effect of etanercept on glucocorticoid treatment. In general, glucocorticoid treatment decreased after etanercept was started (Table 2). To get an idea of any potential correlation between the growth response and the oral and intraarticular glucocorticoid treatments, bivariate correlation analysis (Pearson) was done. We found a significant negative correlation between the growth response and the number of intraarticular glucocorticoid injections when comparing the changes between 1 year before and 1 year after the timepoint for start of etanercept treatment ($p = 0.001$).

DISCUSSION

We observed that a majority of prepubertal and pubertal patients with JIA who did not respond to conventional therapy do grow better when treated with the TNF-antagonist etanercept, although the growth improvement in the pubertal group did not reach statistical significance. The improvement in growth was negatively correlated with the need of intraarticular glucocorticoids.

Our study separately analyzes the growth response to etanercept treatment in prepubertal and pubertal children with JIA. A previous study in a combined population of prepubertal and pubertal patients with JIA showed improved growth when the inflammatory disease was treated with the TNF-antagonist

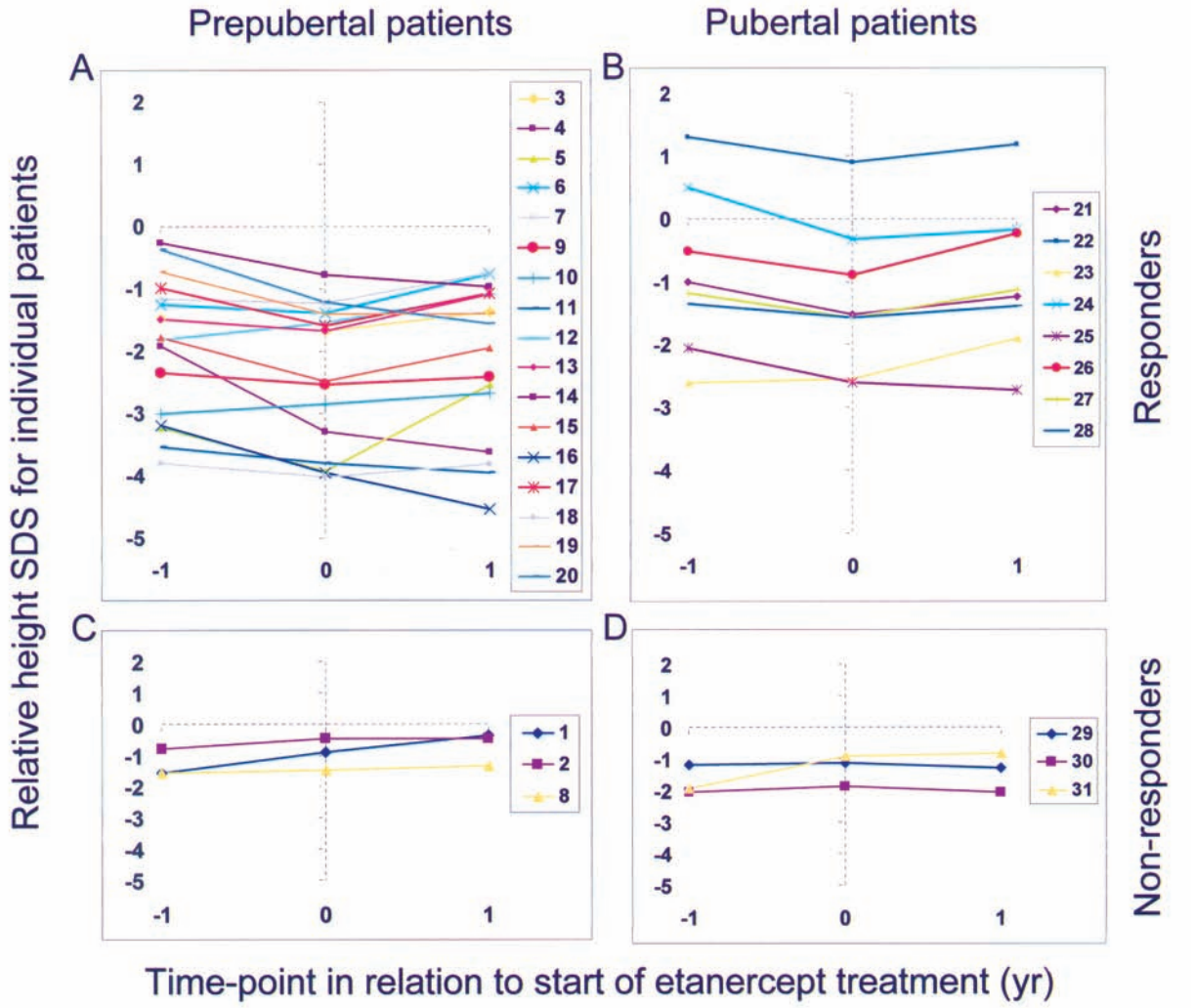

Figure 1. Individual relative height SDS before and during etanercept treatment. Height SDS in relation to target for individual prepubertal (A, C) and pubertal (B, D) patients 1 year before (–1), at start (0, vertical line), and 1 year after (+1) start of etanercept treatment. Patients were grouped according to their individual growth responses into Responders (A, B) and Nonresponders (C, D). Responders are the patients who improved their ΔhSDS after etanercept treatment was initiated and nonresponders those who did not. A patient who loses height velocity but to a lesser extent than before etanercept would be considered a responder. A patient who continues to gain height velocity, but less than before etanercept, is considered a nonresponder.

etanercept[10]. Unfortunately, the authors mixed data for prepubertal and pubertal patients in their analysis, which limits the conclusions that can be made, as the growth rate normally is almost doubled during puberty. The importance of avoiding this confounding factor impelled us to analyze the prepubertal group separately. Further, height SDS scores were calculated for each individual patient, which allowed us to minimize the confounding effects of the pubertal growth spurt. Our data confirm the previous findings that the growth promotion is independent of the pubertal growth spurt[11]. Although the growth improvement in the pubertal group did not reach statistical significance, the majority of those patients improved their ΔhSDS after etanercept treatment. The nonsignificant result might reflect the great variability and low number of patients in the pubertal group.

To further improve the accuracy of our analyses, we collected information about the genetic growth potential. The mid-parental target height SDS was calculated for each patient and this value was compensated for in all analyses (see Methods). Despite this adjustment, we found that most (21/31) of our patients with JIA were not growth-retarded (height less than –2 SDS). However, the reason that the prepubertal patients showed relative height SDS lower than those of the pubertal subjects is unclear.

Our finding that almost 20% of prepubertal and pubertal patients did not grow better when treated with etanercept is in agreement with a previous study reporting that about 25% of JIA patients treated with etanercept did not respond with decreased disease activity[3].

It is important to point out that this is a retrospective study with the limitation of missing data for disease activity. However, the information about the number of joint injections

is complete and may serve as a marker for disease activity. We found that the need for intraarticular glucocorticoid injections decreased significantly after the initiation of etanercept treatment. Therefore, the observed improvement in growth may be explained by less exposure to glucocorticosteroids, well known to inhibit longitudinal growth[13]. Our knowledge about TNF effects on human growth-plate cartilage is not complete, although animal data have shown that TNF-α inhibits bone growth by acting locally on the growth plate[9]. In addition, it is likely that the decrease in systemic inflammation contributes to the improvement of linear growth observed in a majority of patients treated with etanercept. One study of patients with JIA treated before the anti-TNF era demonstrated improved growth when the disease was brought under inflammatory control[14].

Although growth hormone (GH) treatment has been shown to restore linear growth in some patients with JIA[15], it is not known whether GH is capable of rescuing growth in those patients with JIA who do not respond to anti-TNF medication. Given that the average change in ΔhSDS was just 0.5 and 0.4 for the prepubertal and pubertal groups, respectively, other treatment strategies to further improve the effect of etanercept on growth may be considered.

Etanercept was able to improve linear growth and reduce the need for intraarticular glucocorticoid injections in a majority of prepubertal and pubertal patients with JIA not responding to conventional therapy. The minority of patients with JIA who do not respond to anti-TNF treatment may be candidates for therapeutic agents that target other proinflammatory cytokines and also for growth hormone intervention.

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