ORIGINAL ARTICLE

Etanercept Treatment for Children and Adolescents with Plaque Psoriasis

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ABSTRACT

BACKGROUND

Etanercept, a soluble tumor necrosis factor receptor, has been shown to lessen disease severity in adult patients with psoriasis. We assessed the efficacy and safety of etanercept in children and adolescents with moderate-to-severe plaque psoriasis.

METHODS

In this 48-week study, 211 patients with psoriasis (4 to 17 years of age) were initially randomly assigned to a double-blind trial of 12 once-weekly subcutaneous injections of placebo or 0.8 mg of etanercept per kilogram of body weight (to a maximum of 50 mg), followed by 24 weeks of once-weekly open-label etanercept. At week 36, 138 patients underwent a second randomization to placebo or etanercept to investigate the effects of withdrawal and retreatment. The primary end point was 75% or greater improvement from baseline in the psoriasis area-and-severity index (PASI 75) at week 12. Secondary end points included PASI 50, PASI 90, physician's global assessment of clear or almost clear of disease, and safety assessments.

RESULTS

At week 12, 57% of patients receiving etanercept achieved PASI 75, as compared with 11% of those receiving placebo (P<0.001). A significantly higher proportion of patients in the etanercept group than in the placebo group had PASI 50 (75% vs. 23%), PASI 90 (27% vs. 7%), and a physician's global assessment of clear or almost clear (53% vs. 13%) at week 12 (P<0.001). At week 36, after 24 weeks of open-label etanercept, rates of PASI 75 were 68% and 65% for patients initially assigned to etanercept and placebo, respectively. During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious adverse events (including three infections) occurred in three patients during treatment with open-label etanercept; all resolved without sequelae.

CONCLUSIONS

Etanercept significantly reduced disease severity in children and adolescents with moderate-to-severe plaque psoriasis. (ClinicalTrials.gov number, NCT00078819.)

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Psoriasis is a chronic, inflammatory, systemic disease characterized by scaly, erythematous plaques.[1] One third of adults report onset at or before 16 years of age,[2] usually as plaque psoriasis.[3] Psoriasis can be physically disfiguring and may lead to social stigmatization and psychological impairment.[4] Psoriasis has also been associated with other conditions, such as depression,[5] obesity,[6-8] myocardial infarction,[9] and the metabolic syndrome.[10-13] No systemic therapy for psoriasis in children and adolescents is currently approved by the Food and Drug Administration; phototherapy and systemic therapies have limited use because of low tolerability in children, cumulative adverse effects, and teratogenicity.[1,14-16]

Etanercept, a soluble tumor necrosis factor (TNF) receptor fusion protein that antagonizes the effects of endogenous TNF, is widely used to treat adult patients who have moderate-to-severe plaque psoriasis and is indicated for patients as young as 4 years of age with polyarticular juvenile rheumatoid arthritis.[17] Previous clinical trials of etanercept have shown significantly reduced disease severity, fatigue, and symptoms of depression, and significantly improved overall health-related quality of life in adult patients with psoriasis.[18-21] In this randomized, double-blind, placebo-controlled, phase 3 study, we assessed the efficacy and safety of etanercept in the treatment of children and adolescents with moderate-to-severe plaque psoriasis.

METHODS

STUDY PATIENTS

The inclusion criteria were age 4 to 17 years; stable, moderate-to-severe plaque psoriasis at screening, defined as a psoriasis area-and-severity index (PASI) score of at least 12 (PASI scores range from 0 to 72, with higher scores indicating worse condition[22]; PASI 50, PASI 75, and PASI 90 denote improvements in the PASI of 50%, 75%, and 90% over baseline, respectively), a static physician's global assessment of at least 3 (where 0 indicates clear and 5 severe psoriasis), and psoriasis involvement of at least 10% of the body-surface area; a history of psoriasis for at least 6 months; and previous or current treatment with phototherapy or systemic psoriasis therapy (e.g., methotrexate, cyclosporine, or retinoids) or psoriasis considered by the investigator as poorly controlled with topical therapy.

The exclusion criteria were pregnancy or lactation (sexually active patients were required to use contraception); guttate, erythrodermic, or pustular psoriasis; other skin conditions that would interfere with study evaluations; previous treatment with anti-TNF agents; major concurrent medical conditions; treatment with psoralen and ultraviolet A (PUVA), ultraviolet A, ultraviolet B, systemic psoriasis medications, oral or parenteral corticosteroids, topical corticosteroids, topical vitamin A or D analogue preparations, anthralin, or calcineurin inhibitor within a 14-day washout period before the study; and treatment with biologic agents within a 30-day washout period before the study. Patients could use low-to-moderate-potency topical steroids on the scalp, axillae, or groin.

The institutional review boards of the participating medical centers approved the protocol and amendments. Written informed consent was obtained from the parents or legal guardians of all patients, and assent was obtained from all appropriate patients as requested by the institutional review boards. An independent data and safety monitoring committee regularly reviewed all events. The study was designed by Immunex and members of the Etanercept Pediatric Psoriasis Study Group. Data were collected by the investigators, held by Amgen, and analyzed by Amgen. All authors contributed intellectually to the content of the manuscript, had full access to the data, and vouch for the completeness and accuracy of the data and data analyses. Amgen assisted with the writing of the manuscript.

STUDY DRUG

Etanercept (Enbrel, Immunex–Wyeth), at a dose of 0.8 mg per kilogram of body weight up to a maximum intended dose of 50 mg, or matching placebo was reconstituted at the study site or by local pharmacists and dispensed to the patients in syringes for once-weekly subcutaneous injections.

STUDY DESIGN

This 48-week study at 42 sites in the United States and Canada had three phases: an initial 12-week, double-blind, placebo-controlled treatment period (day 1 to week 12) aimed at establishing efficacy; a 24-week, open-label treatment period (weeks 13 to 36) to assess the efficacy of etanercept therapy in all patients; and a 12-week, randomized, double-blind, withdrawal–retreatment period (weeks 37 to 48) to examine the effects of

withdrawal of study drug and subsequent retreatment (Fig. 1A). Patient visits occurred at day 1, at weeks 2 and 4, and every 4 weeks thereafter.

The first patient was enrolled on September 8, 2004, and the last on November 29, 2005. On enrollment, patients underwent randomization at a 1:1 ratio by an interactive voice-response system.

During the initial double-blind period, the patients could enter an escape group and receive open-label etanercept until week 12 if, at or after week 4, their PASI score either increased by more than 50% over baseline and by a minimum of 4 points at one visit or increased by more than 25% and by a minimum of 4 points at each of two consecutive visits. During the second phase, all patients (including those who entered the escape group) received open-label etanercept. Patients who did not achieve PASI 50 at week 24 or PASI 75 at week 36 could discontinue the study or add topical standard-of-care therapy (low-to-moderate-potency topical corticosteroids) and continue to receive open-label etanercept until week 48. At week 36, patients with PASI 50 at week 24 or PASI 75 at week 36 were randomly assigned to placebo or etanercept. Patients in whom PASI 75 was lost resumed open-label etanercept through week 48.

END POINTS

The primary efficacy end point was PASI 75 at week 12. The secondary efficacy end points were PASI 50, PASI 90, a physician's global assessment of clear or almost clear (score of 0 or 1), and the Children's Dermatology Life Quality Index response (CDLQI)[23] at week 12 (range, 0 to 30; higher scores indicate worse outcomes). Other efficacy end points included these measures at weeks 2, 4, 8, and 16 and every 4 weeks thereafter, as well as the mean percentage improvement in PASI score at all time points.

The safety end points included adverse events, serious adverse events, infections, serious infections, injection-site reactions, cancers, laboratory values, serum concentrations of etanercept, and disease rebound during the withdrawal period (defined as worsening of PASI by more than 125% from baseline within 3 months after discontinuation of treatment). All adverse events and infections were coded according to the *Medical Dictionary for Regulatory Activities*. Adverse events and abnormal laboratory values were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

STATISTICAL ANALYSIS

Efficacy analyses at week 12 included all patients who underwent randomization (the intention-to-treat data set). The data were stratified according to the age of the patient at randomization (4 to 11 years and 12 to 17 years) and analyzed according to the patient's treatment group. This study had greater than 90% power to detect a 20% difference in PASI 75 rates between the etanercept and placebo groups at a significance level of 0.05.

Treatment comparisons were made for primary and secondary efficacy analyses at week 12 by the Cochran–Mantel–Haenszel test, with age group as the stratification factor for binary end points, and by the van Elteren stratified-rank test, with adjustment for age group for continuous end points.[24] All reported P values are two-sided. Analyses were performed with SAS software, version 8.2, on a Sun Solaris 2.6 operating system. The significance levels for primary and secondary efficacy end points were controlled at 0.05 with the use of a sequential testing scheme in this order: PASI 75, PASI 50, a physician's global assessment of clear or almost clear, percentage improvement from baseline in CDLQI, and PASI 90. For efficacy analyses at week 12, missing post-baseline data and all efficacy measurements taken after patients entered the escape group were imputed as nonresponses. For binary end points, missing data were imputed as nonresponses; for continuous end points, missing data were imputed to have the baseline values.

After week 12, efficacy measures were summarized separately for each treatment period with the use of statistical methods similar to those used for the week 12 final analysis; however, no statistical comparisons were made between the treatment groups. All categorical variables were summarized as numbers and percentages of patients, and all continuous variables were summarized as means, standard errors or standard deviations, medians, minimums, maximums, and numbers of patients. Only patients who entered the open-label period could be evaluated for efficacy analyses during the open-label period through week 36. Data from these patients were analyzed according to their original randomized treatment group. Missing post-baseline data were imputed as nonresponses. In addition to being included in the analysis, data collected from patients who might have received additional topical standard-of-care therapy in the incomplete-response group were

summarized separately. During the withdrawal period, only patients who underwent randomization at week 36 could be evaluated for efficacy analyses. Patients who received at least one dose of retreatment therapy after relapse of the disease could be evaluated for efficacy analyses during the retreatment period. During these periods, data were analyzed according to the treatment group to which the patients were assigned at their second randomization, and missing data were not imputed.

Long-term safety analyses were based on event incidence rates, adjusted for exposure, and included all patients who received at least one dose of study drug. In these analyses, the placebo group included only patients receiving placebo during the initial 12-week double-blind period. Events that occurred during exposure to placebo during the withdrawal–retreatment period were included in the etanercept group.

RESULTS

STUDY PATIENTS

The disposition of patients is shown in Figure 1B; 211 patients were randomly assigned to receive placebo or etanercept. The treatment groups were similar in demographic and disease characteristics at baseline, although slightly more patients in the placebo group than in the etanercept group (13% vs. 5%) had psoriatic arthritis, as determined historically by the question, "Does the patient have any indication of psoriatic arthritis?" (Table 1). Most patients (75%) were white, the median age was 13.0 years, and 36% were 11 years of age or younger at enrollment. At baseline, the median PASI score was 16.4 and the median body-surface area affected by psoriasis was 20.0%. The median height, weight, and body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) were 157.5 cm, 59.8 kg, and 23.2, respectively, corresponding to the 61st, 87th, and 87th percentiles, respectively, in comparison with an age- and sex-matched population.[25] The median BMI was 18.1 for children 4 to 11 years of age and 25.2 for adolescents 12 to 17 years of age, corresponding to the 81st and 92nd percentiles, respectively.

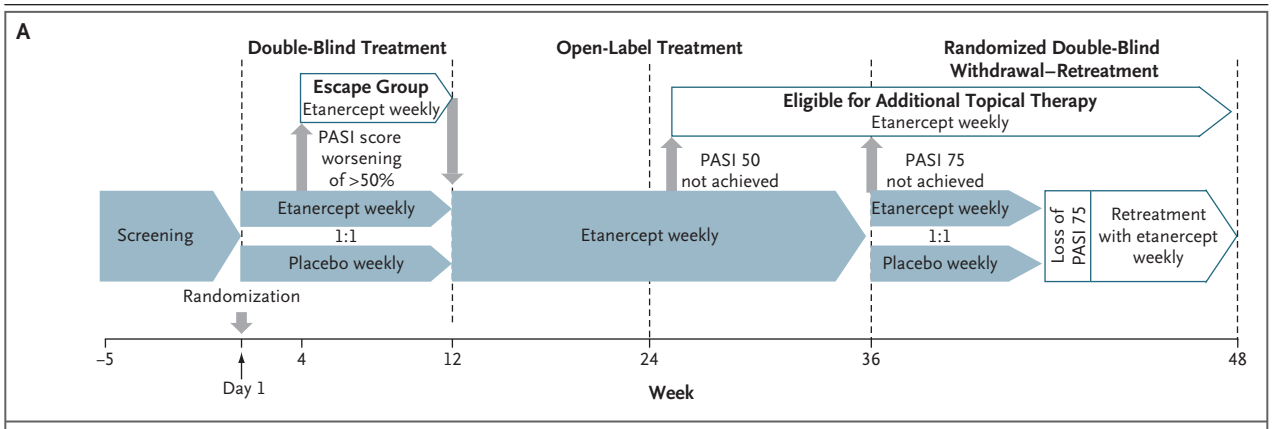
EFFICACY

At week 12, significantly more patients who received etanercept than those who received placebo achieved PASI 75 (57% [60 of 106] vs. 11% [12 of 105], P<0.001) (Fig. 2A); a significant difference was observed as early as week 4. The proportions of patients who achieved PASI 50 (75% [79 of 106] vs. 23% [24 of 105], P<0.001) and PASI 90 (27% [29 of 106] vs. 7% [7 of 105], P<0.001) were also significantly greater in the etanercept group than in the placebo group at week 12. At week 12, 64% of patients (38 of 59) receiving etanercept at a dosage of 0.8 mg per kilogram (37 children and 22 adolescents) achieved PASI 75, as compared with 47% of patients (22 of 47) receiving the maximum dose of 50 mg (1 child and 46 adolescents). In the etanercept group at week 12, the response rates of PASI 50, PASI 75, and PASI 90 were 76%, 58%, and 32%, respectively, in children and 74%, 56%, and 25%, respectively, in adolescents. Thirty-two patients entered the escape group, and their response rates were similar to response rates for patients in the etanercept group who were treated for 2 to 8 weeks in the initial double-blind period.

Figure 1 (facing page). Schematic Representation (Panel A) and Phases (Panel B) of the Study.
PASI denotes the psoriasis area-and-severity index. PASI 50 and PASI 75 denote improvements in the PASI of 50% and 75% over baseline, respectively.

During the open-label period, 62% of patients (64 of 103) in the original placebo group (i.e., those who received placebo first and then received etanercept during the open-label period) and 69% of patients (72 of 105) in the original etanercept group (i.e., those who received etanercept throughout) achieved PASI 75 at week 24. The PASI 75 response was maintained through week 36 (Fig. 3A). Two of 10 patients in the original placebo group and 5 of 16 patients in the original etanercept group who did not achieve PASI 50 at week 24, and who were given the option to receive topical standard-of-care therapy, achieved PASI 75 at week 36 and were included in this analysis. The proportions of patients who achieved PASI 50 and PASI 90 at weeks 24 and 36 increased in both groups (the original placebo group and the original etanercept group) as compared with the proportions of patients who achieved these end points at week 12.

The mean percentage improvement in PASI from baseline was significantly greater in the etanercept group than the placebo group from week 2 (22% vs. 5%, P<0.001) through week 12 (68% vs. 21%, P<0.001). At weeks 24 and 36, the mean percentage improvements were 71% and 76%, respectively, in the original placebo group and 77%



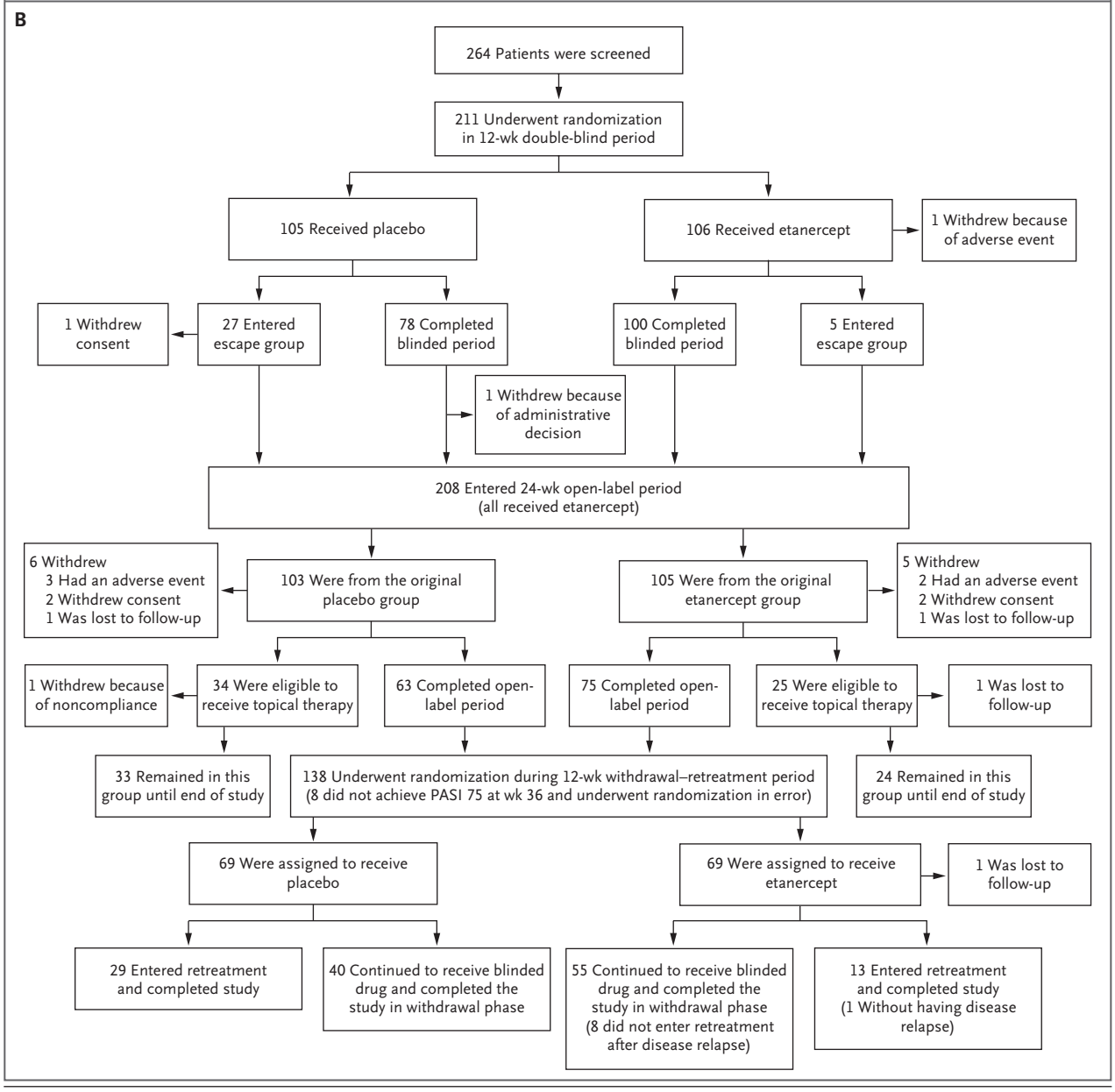


Table 1. Characteristics of the Patients.*

Characteristic	Baseline			Withdrawal–Retreatment Period (Second Randomized Treatment)		
	Etanercept (N=106)	Placebo (N=105)	All (N=211)	Etanercept (N=69)	Placebo (N=69)	All (N=138)
Age — yr						
Median	14.0	13.0	13.0	13.0	13.0	13.0
Range	4.0–17.0	4.0–17.0	4.0–17.0	5.0–17.0	4.0–17.0	4.0–17.0
Age group — no. (%)						
4–11 yr	38 (36)	38 (36)	76 (36)	24 (35)	25 (36)	49 (36)
12–17 yr	68 (64)	67 (64)	135 (64)	45 (65)	44 (64)	89 (64)
Female sex — no. (%)	51 (48)	52 (50)	103 (49)	37 (54)	33 (48)	70 (51)
Race or ethnic group — no. (%)†						
White	83 (78)	75 (71)	158 (75)	54 (78)	53 (77)	107 (78)
Black	3 (3)	8 (8)	11 (5)	6 (9)	4 (6)	10 (7)
Hispanic	8 (8)	14 (13)	22 (10)	5 (7)	8 (12)	13 (9)
Asian	9 (8)	6 (6)	15 (7)	4 (6)	2 (3)	6 (4)
Other	3 (3)	2 (2)	5 (2)	0	2 (3)	2 (1)
Weight — kg						
Median	59.6	59.8	59.8	60.0	54.1	57.6
Range	17.7–168.3	17.2–131.5	17.2–168.3	21.8–131.5	17.7–123.2	17.7–131.5
Height — cm						
Median	159.0	157.5	157.5	158.8	157.2	157.5
Range	104.2–188.0	104.0–190.5	104.0–190.5	112.0–188.0	110.0–188.0	110.0–188.0
Duration of psoriasis — yr						
Median	6.8	5.8	5.9	5.3	5.9	5.8
Range	0.3–17.9	0.3–15.8	0.3–17.9	0.3–15.8	0.5–17.9	0.3–17.9
Affected percentage of body-surface area						
Median	21.0	20.0	20.0	21.0	20.0	20.5
Range	10.0–90.0	10.0–95.0	10.0–95.0	10.0–83.7	10.0–90.0	10.0–90.0
PASI score‡						
Median	16.7	16.4	16.4	16.6	16.7	16.7
Range	12.0–51.6	12.0–56.7	12.0–56.7	12.0–42.3	12.2–51.6	12.0–51.6
Physician's global assessment of ≥3 — no. (%)§	105 (99)	104 (99)	209 (99)	67 (97)	69 (100)	136 (99)
Previous systemic therapy or phototherapy — no. (%)	58 (55)	62 (59)	120 (57)	42 (61)	36 (52)	78 (57)
Psoriatic arthritis — no. (%)	5 (5)	14 (13)	19 (9)	9 (13)	2 (3)	11 (8)

* Because of rounding, not all percentages add to 100.
† Race or ethnic group was determined by the investigator.
‡ PASI denotes the psoriasis area-and-severity index. Scores range from 0 to 72, with higher scores indicating worse condition.
§ Physician's global assessment scores range from 0 (clear) to 5 (severe psoriasis). A score of ≥3 indicates moderate-to-severe psoriasis.

and 77%, respectively, in the original etanercept group. Figure 4 shows a PASI 75 and a PASI 50 response in two patients.

Of the 138 patients who entered the withdrawal–retreatment phase and were randomly assigned at week 36 either to continue etanercept or to switch to placebo, 94% in each treatment group began this phase with a PASI 75 response.

Twenty-nine of the 69 patients assigned to placebo (42%) lost the response and were treated again with open-label etanercept. After 4 to 8 weeks of retreatment with etanercept, the response rates for these patients were similar to the response rates for patients originally treated with etanercept who had similar durations of etanercept treatment during the double-blind period. Thirty-four of the 40 patients who continued to receive placebo during the double-blind withdrawal–retreatment period maintained a PASI 75 response at week 48. Eighty percent of patients who were assigned to etanercept achieved a PASI 75 response at week 48. This percentage includes those patients who lost the PASI 75 response and received open-label etanercept during the retreatment period.

At baseline, 99% of patients had moderate-to-severe disease, according to the physician's global assessment (Table 1). At week 12, 13% of those in the placebo group (14 of 105) and 53% of those in the etanercept group (56 of 106) had a physician's global assessment of clear or almost clear (P<0.001), and significant differences were seen as early as week 4 (Fig. 2B). At both weeks 24 and 36, 56% of patients in the original placebo group (58 of 103) had a physician's global assessment of clear or almost clear. In the original etanercept group, the physician's global assessment was clear or almost clear in 57% of the patients (60 of 105) at week 24 and in 53% (56 of 105) at week 36 (Fig. 3B). The mean improvement in CDLQI from baseline was greater in the etanercept group than in the placebo group at week 12 (52% vs. 18%, P<0.001). At week 36, the mean improvements were 63% and 59% for the original etanercept group and the placebo group, respectively. The mean trough etanercept concentration at week 12 for etanercept-treated patients was 1614±828 ng per milliliter.

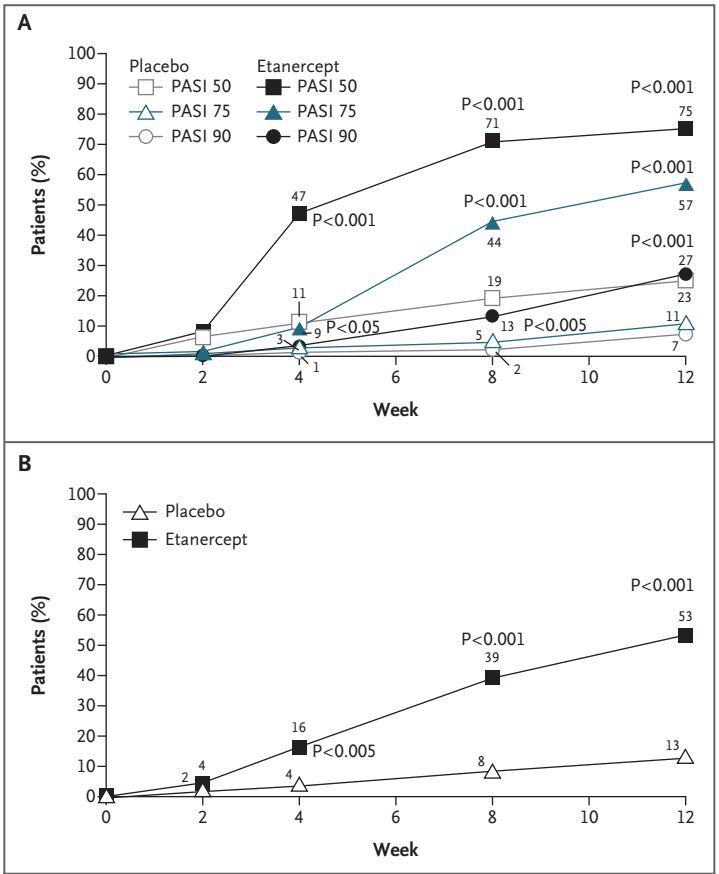


Figure 2. Responses through 12 Weeks.

Panel A shows the proportions of patients with improvements over baseline in the psoriasis area-and-severity index (PASI) of 50%, 75%, and 90% (PASI 50, PASI 75, and PASI 90, respectively). Panel B shows the proportions of patients with static physician's global assessment scores of clear or almost clear. Physician's global assessment scores range from 0 (clear) to 5 (severe). Missing data were imputed as nonresponses. All efficacy measurements taken after patients entered the escape group were also imputed as nonresponses. PASI 75 at week 12 was the primary efficacy end point of the study. P values are shown for the comparison of etanercept and placebo by the two-sided Cochran–Mantel–Haenszel test with data stratified according to age group.

SAFETY

Table 2 summarizes the exposure-adjusted rates of adverse events for which there were at least 10 events per 100 patient-years in the etanercept group. Since the patient-years of exposure differ substantially between the groups, comparisons must be made with caution. The rates of noninfectious adverse events (430.5 per 100 patient-years for placebo and 287.6 per 100 patient-years for etanercept) and of infections (308.3 per 100 patient-years for placebo and 229.3 per 100 patient-years for etanercept) were similar in the two groups, and all but 10 events (3 in the placebo group and 7 in the etanercept group) were of mild or moderate intensity. Injection-site reactions were mild to moderate and generally transient. There were no serious adverse events during the placebo-controlled period. During open-label treatment, one 14-year-old patient had a noninfectious serious adverse event, removal of an ovarian cyst (etanercept therapy was discontinued). In addition, a 9-year-old patient had concurrent serious episodes of gastroenteritis and gastroenteritis-associated dehydration, which were considered infectious by the

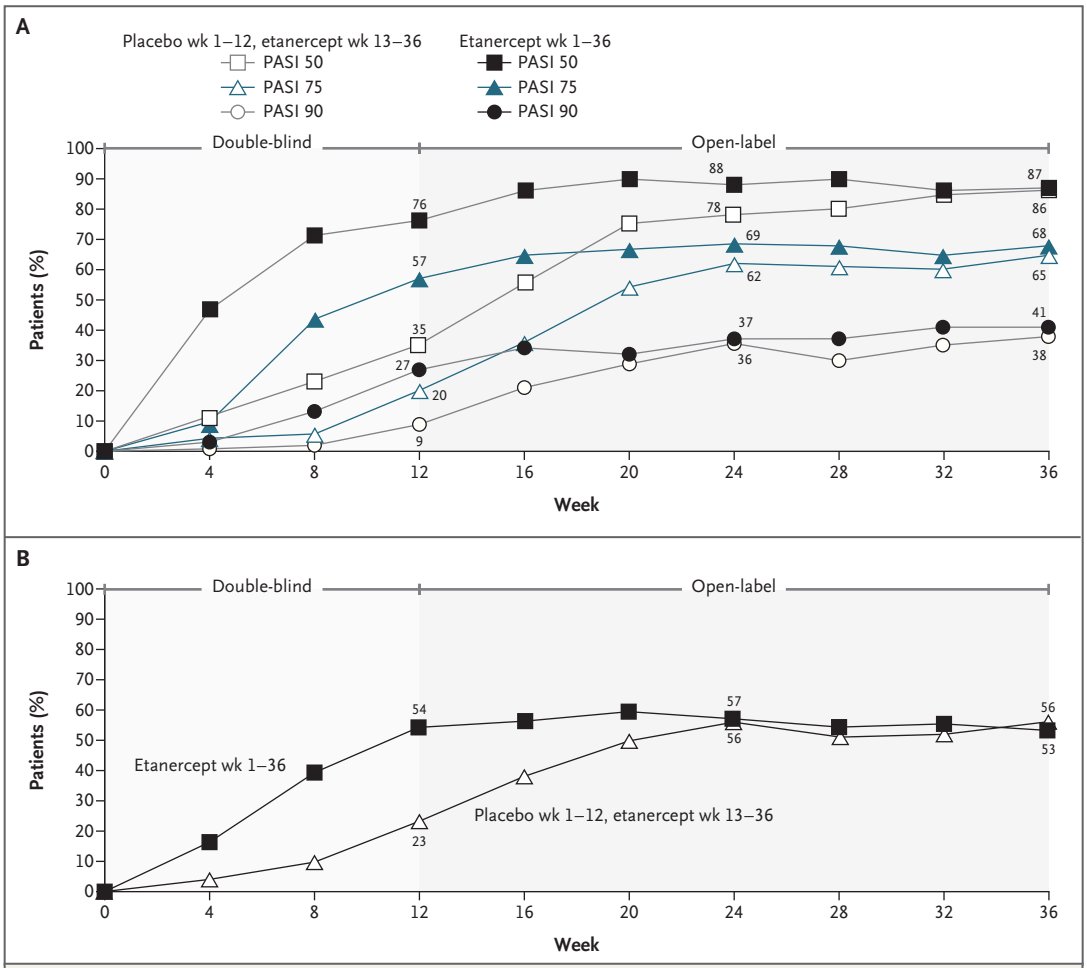


Figure 3. Responses through 36 Weeks.

Panel A shows the proportions of patients with improvements over baseline in the psoriasis area-and-severity index (PASI) of 50%, 75%, and 90% (PASI 50, PASI 75, and PASI 90, respectively). Panel B shows the proportions of patients with static physician's global assessment ratings of clear or almost clear. Missing data were imputed as nonresponses. Data from patients who entered the escape group were not imputed as nonresponses up to week 12. Therefore, the results through week 12 differ in Figures 2 and 3. The results after 24 weeks include patients who may have received topical therapy.

investigator and required hospitalization (etanercept was uninterrupted). A 7-year-old patient with a history of asthma had a serious infection of left basilar pneumonia that was treated with intravenous antibiotics (etanercept was discontinued). All serious noninfectious and infectious adverse events resolved without sequelae. No deaths, cancers, opportunistic infections, tuberculosis, or demyelination events were reported.

Three patients transiently had high hemoglobin concentrations (a grade 3 toxic effect), one before and two during etanercept therapy. No grade 4 toxic effects were seen in either group. During the withdrawal–retreatment period, no patient had psoriasis rebound or a change of psoriasis morphology (e.g., a change from plaque to guttate or pustular psoriasis); however, one patient withdrew during the open-label period because of worsening of psoriasis.

DISCUSSION

This multicenter, phase 3, randomized study demonstrated statistically significant and clinically meaningful reductions in disease severity as early as week 2 of weekly treatment with etanercept at

0.8 mg per kilogram (to a maximum of 50 mg) in children and adolescents with moderate-to-severe plaque psoriasis.

Fifty-seven percent of patients treated with etanercept in this study achieved PASI 75 at week 12; this rate is higher than the 12-week PASI 75 response reported for adult patients with psoriasis who were treated with 25 mg of etanercept twice weekly (response rates, 30 to 34%) but is consistent with rates reported in trials involving adults who received 50 mg of etanercept twice weekly (response rates, 47 to 49%).[18-21] The mean trough etanercept concentration at week 12 in our study was similar to that observed in adults receiving 25 mg twice weekly.[26] Thus, whereas the dosage in our study was equivalent to the 25-mg twice-weekly dosage used in adults, the clinical response was similar to that achieved with the 50-mg twice-weekly dosage.

In studies in adults, about 70% of patients were overweight (BMI >25),[27] as compared with 37% of the patients (32% of children and 41% of adolescents) in our study (BMI ≥95th percentile of age- and sex-matched population).[28] In addition, the disease severity at baseline was higher and the duration of disease was longer in the studies in adults than in our study. In our study, patients who received weight-based dosing had a better response than did patients who received the maximum dose. However, the disease characteristics at baseline were different as well, because the patients treated with the maximum dose of etanercept weighed more, were older, and had a longer history of psoriasis than those receiving smaller doses. All these factors can confound the analysis of any benefit of weight-based dosing in this study. After withdrawal of etanercept therapy, more than half of the patients maintained PASI 75 until the end of the study. Future studies should assess whether the frequency of administration could be decreased during remission with maintenance of control.

Four serious adverse events occurred in three patients: ovarian cyst removal in one patient, gastroenteritis and gastroenteritis-associated dehydration in one patient, and pneumonia in one patient (the latter three events were considered infectious). All occurred in patients receiving open-label treatment, and all resolved without sequelae. Longer-term data are needed to fully assess the safety profile of etanercept in this patient population.

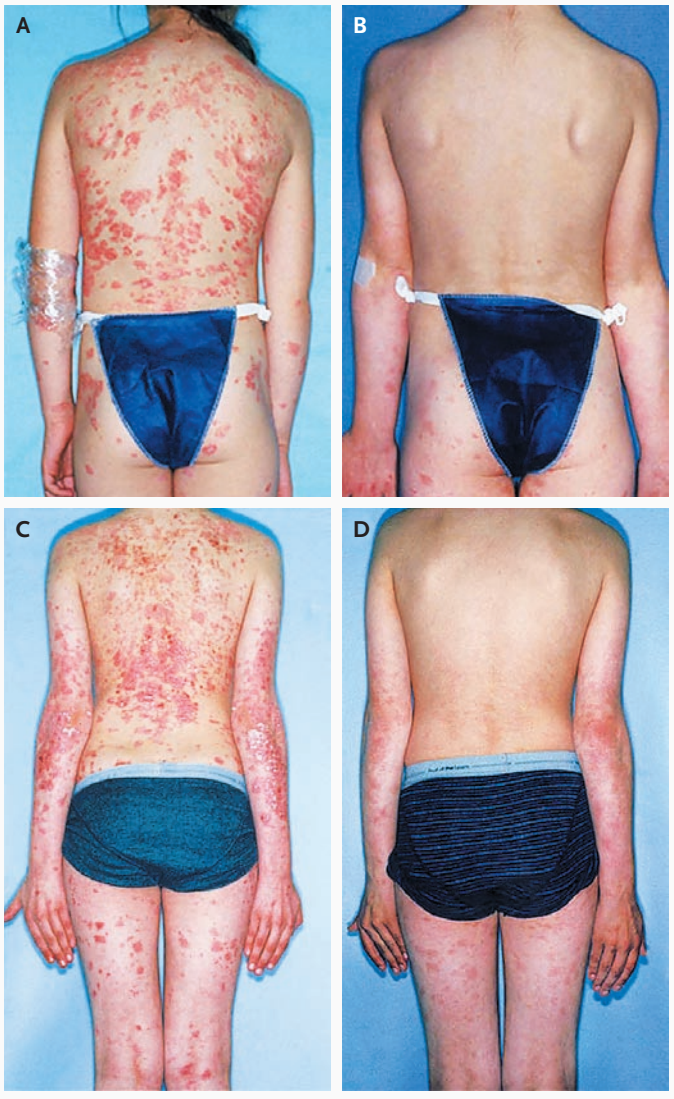


Figure 4. Photographs Showing Responses to Treatment.
Patient 1 (age, 6 years) is shown at baseline (psoriasis area-and-severity index [PASI] score, 21.6) in Panel A and at week 4 (PASI score, 7.6) in Panel B; Patient 2 (age, 10 years) is shown at baseline (PASI score, 35.2) in Panel C and at week 12 (PASI score, 1.0) in Panel D. PASI scores range from 0 to 72, with higher scores indicating worse condition.

In children and adolescents with polyarticular juvenile rheumatoid arthritis who received etanercept treatment (0.4 mg per kilogram twice weekly) for up to 8 years, the rates of serious adverse events did not increase with long-term exposure to etanercept.[29,30]

This randomized, placebo-controlled trial demonstrated that etanercept was effective in children

Table 2. Adverse Events Adjusted for Exposure to Etanercept or Placebo.*

Event	Etanercept (N=210)		Placebo (N=105)	
	No. of Adverse Events	Exposure-Adjusted Event Rate per 100 Patient-Years	No. of Adverse Events	Exposure-Adjusted Event Rate per 100 Patient-Years
Total no. of adverse events	914	554.5	144	765.4
Events with exposure-adjusted rates of ≥10 events/100 patient-yr				
Upper respiratory tract infection	90	54.6	13	69.1
Headache	54	32.8	18	95.7
Nasopharyngitis	52	31.5	10	53.2
Influenza	23	14.0	3	15.9
Streptococcal pharyngitis	22	13.3	1	5.3
Cough	20	12.1	2	10.6
Pharyngolaryngeal pain	20	12.1	6	31.9
Vomiting	20	12.1	2	10.6
Nasal congestion	17	10.3	3	15.9
Skin papilloma	16	9.7	0	0
Selected events through wk 48				
Adverse event leading to study withdrawal, excluding infections	4	2.4	0	0
Infection leading to study withdrawal	2	1.2	0	0
Severe adverse event, excluding infections	3	1.8	3	15.9
Severe infection	4	2.4	0	0
Serious adverse event, excluding infections	1	0.6	0	0
Serious infection	3	1.8	0	0
Adverse event, excluding infections	474	287.6	81	430.5
Infection	378	229.3	58	308.3
Injection-site reaction	62	37.6	5	26.6

* The placebo group includes patients who were exposed to placebo during the initial 12-week, double-blind period only; events that occurred during exposure to placebo in the randomized withdrawal–retreatment period are included in the group receiving 0.8 mg of etanercept per kilogram weekly. The total number of exposure-years was 18.8 for the placebo group and 164.8 for the etanercept group. The numbers of patients who underwent randomization and received at least one dose of study drug are given.

and adolescents with moderate-to-severe plaque psoriasis. The results of this study implicated TNF in the pathogenesis of pediatric psoriasis and demonstrated that etanercept significantly reduced disease severity.

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APPENDIX

The following members of the Etanercept Pediatric Psoriasis Study Group served as investigators at the clinical sites: B. Anderson — Hershey, PA; K. Bloom — Minneapolis; M. Boucier — Moncton, NB, Canada; L. Eichenfield — San Diego, CA; E. Frankel — Johnston, RI; I. Frieden — San Francisco; T. Hamilton — Alpharetta, GA; A. Hebert — Houston; R. Hornung — Seattle; T. Knoepp — Anderson, SC; N. Korman — Cleveland; C. Kovaleski — Panama City, FL; B. Krafchik — Toronto; A. Krol — Portland, OR; I. Landells — St. John's, NF, Canada; R. Langley — Halifax, NS, Canada; C. Leonardi — St. Louis; R. Loss — Rochester, NY; A. Lucky — Cincinnati; C. Lynde — Markham, ON, Canada; C. Maari — Laval, QC, Canada; M. Magliocco — New Brunswick, NJ; B. Miller — Portland, OR; S. Miller — San Antonio, TX; A. Moore — Arlington, TX; S. Mraz — Vallejo, CA: A. Nayak — Normal, IL; A. Nopper — Kansas City, MO; S. Orlow — New York; A. Paller — Chicago; K. Papp — Waterloo, ON, Canada; D. Pariser — Norfolk, VA; R. Parker — Little Rock, AR; E. Pope — Toronto; J. Prendiville — Vancouver, BC, Canada; Y. Poulin — Sainte-Foy, QC, Canada; E. Rafal — Stony Brook, NY; L. Rosoph — North Bay, ON, Canada; L. Schachner — Miami; E. Siegfried — St. Louis; A. Theos — Birmingham, AL; D. Toth — Windsor, ON, Canada.

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