Efficacy and safety of adalimumab in patients with plaque psoriasis who have shown an unsatisfactory response to etanercept

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Background: The safety and efficacy of adalimumab in patients who have shown an unsatisfactory response to etanercept are unknown.

Objective: We sought to evaluate the safety and efficacy of adalimumab in patients who failed to show a satisfactory response or lost their satisfactory response to etanercept.

Methods: This multicenter study enrolled patients who either failed to reach a physician global assessment (PGA) score of 0 or 1 after 12 weeks of etanercept (group A; 50 patients) or who lost their PGA score of 0 or 1 at any time after etanercept dose decrease from 50 mg twice a week to 50 mg every week (group B; 35 patients). Patients received adalimumab 40 mg every other week without loading dose for 12 weeks followed by 40 mg every week for an additional 12 weeks if they did not reach a PGA score of 0 or 1.

Results: After 12 weeks of adalimumab, 34.0% (n = 17; 95% confidence interval [CI] 20.4-47.6) and 31.4% (n = 11; 95% CI 15.2-47.6) of patients from groups A and B, respectively, reached a PGA score of 0 or 1. A total of 46.0% (n = 23; 95% CI 31.7-60.3) and 45.7% (n = 16; 95% CI 28.4-63.1) of patients from group A and B, respectively, achieved a PGA score of 0 or 1 after 24 weeks of adalimumab. Adalimumab was well tolerated and no serious adverse events were reported.

Limitations: This was an open-label uncontrolled study.

Conclusions: Adalimumab should be considered as an alternative in patients with psoriasis who have not shown an adequate response or who lost their response to etanercept after a dose decrease. (J Am Acad Dermatol 2010;63:228-34.)

Key words: adalimumab; anti-tumor necrosis factor-alfa; etanercept; psoriasis.
Etanercept is a fusion protein binding to soluble tumor necrosis factor (TNF)-alpha. It is one of the most widely used systemic treatments for moderate to severe psoriasis. After 12 weeks of etanercept at 50 mg twice a week, 49% of patients reached Psoriasis Area and Severity Index (PASI) 75, and 57% achieved a physician global assessment (PGA) score of clear or almost clear. When the dose was decreased to 50 mg once a week most patients maintained their reduction in PASI of 75% or more (PASI 75). Some patients who did not reach PASI 75 after 12 weeks of etanercept at 50 mg twice a week did reach PASI 75 after an additional 12 weeks of etanercept at 50 mg once a week. However, studies have also shown that 23% of patients lost their PASI 75 response when the etanercept dose was lowered to 50 mg once a week after 12 weeks of etanercept at 50 mg twice a week.

The best treatment strategy for patients who have shown an unsatisfactory response to etanercept or who have lost their response after dose reduction is currently unknown. Should the clinician favor non–TNF-alfa antagonist as these patients had an unsatisfactory response to etanercept or will these patients still respond to another TNF-alfa antagonist?

Adalimumab is another anti–TNF-alfa agent that was approved in 2008 in Canada and the United States for the treatment of moderate to severe chronic psoriasis. After a loading dose of 80 mg and a second dose of 40 mg 1 week later followed by 40 mg every other week (EOW), the phase III study showed that PASI 75 response was 71% after 16 weeks of treatment.

The objective of the current study was to evaluate the safety and efficacy of adalimumab in patients who have shown an unsatisfactory or loss of response to etanercept.

**METHODS**

**Patients**

To be eligible, patients had to be between 18 and 80 years of age and have plaque psoriasis at screening that was severe enough for a systemic therapy. Patients with poorly controlled medical conditions such as uncontrolled diabetes; patients with symptoms of demyelinating diseases, a history of cancer, listeriosis, tuberculosis, persistent chronic infections, or immunodeficiency; or patients who had taken live attenuated vaccine within 28 days of baseline were excluded from the study.

All patients were required to have a PGA score of 3 or more at baseline. Documentation of an unsatisfactory response to etanercept as defined by failure to reach a PGA score of clear or almost clear after at least 3 months of etanercept at 50 mg twice a week without dose reduction (group A) or by achieving a PGA score of clear or almost after at least 3 months of etanercept at 50 mg twice a week followed by a loss of a PGA score of clear or almost clear after dose reduction to 50 mg weekly (group B) was also required. Unsatisfactory response or loss of response to etanercept could have occurred at any time before study enrollment as long as this was documented in the patient’s clinical chart. Washout periods were 30 days for phototherapy, 14 days for topical therapy, and 90 days for biologics (apart from etanercept). Etanercept had to be stopped before initiation of adalimumab but a washout period was not required. Patients who used topical therapy during the 4 weeks preceding documentation of the unsatisfactory response or loss of response to etanercept had to use the same topical therapy at the same frequency for 2 weeks before baseline and throughout the study.

**Study design**

The study was approved by an institutional review board and informed consent was obtained from each patient. This was an unblinded, open-label study conducted at 12 centers in Canada. All patients received adalimumab, 40 mg EOW, for the first 12 weeks without the usual loading dose of 80 mg. Patients who had a PGA score of 0 or 1 at week 12 were continued on adalimumab at 40 mg EOW for an additional 12 weeks. Patients who had a PGA score of 2 or more at week 12 had an increase in adalimumab to 40 mg every week (EW) for an additional 12 weeks. Patients were seen every 4 weeks for a total of 24 weeks with an additional telephone call to inquire about serious adverse events (AEs) 4 weeks later.

**CAPSULE SUMMARY**

- In all, 46% of patients with psoriasis who showed an unsatisfactory response to etanercept or who lost their satisfactory response after dose reduction had a satisfactory response, as defined by a physician global assessment score of 0 or 1, to adalimumab treatment for 24 weeks.
- The safety profile of adalimumab was similar to phase III studies even if an etanercept washout was not required.
- Adalimumab should be considered a treatment option in patients who have shown an unsatisfactory response to etanercept.
Efficacy evaluations

A PGA score corresponding to the degree of overall lesion severity using a scale of 0 to 5 (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) was performed at each visit. Body surface area (BSA) covered with psoriasis and PASI were also performed at each visit. The primary end point was the percentage of patients with a PGA score of 0 or 1 at week 12 for group B. Secondary end points included the percentage of patients with a PGA score of 0 or 1 at week 12 for group A and the percentage of patients with a PGA score of 0 or 1 at week 24 for each group in patients who had a dose increase to 40 mg EW at week 12. A similar subanalysis of the percentage of patients reaching PGA score of 0 or 1 at weeks 12 and 24 was also performed for patients who started adalimumab less than 2 weeks after stopping etanercept. Mean BSA and PASI score were also calculated over time. The percentage of patients who presented a PGA score of clear or almost clear at weeks 12 and 24 was likewise calculated.

Safety evaluations

Screening procedures included hepatitis B and C serology, routine chemistry and hematology, physical examination, vital signs, purified protein derivative of tuberculosis, chest radiograph, and recording of medical history. Safety was evaluated at each visit by vital sign recording, routine chemistry and hematology tests, and AE reporting.

Statistical analysis

Sample size was calculated on the assumption of a 10% response rate (PGA score of clear or almost clear) if adalimumab did not provide any additional efficacy benefits and a 25% response rate if adalimumab increased the percentage of patients reaching a score of clear or almost clear. A sample size of 50 patients in each group had a lower limit of the confidence interval (CI) of 12 (in absolute percentage point response rate), which enabled the detection of a difference between the predicted response rate of 25% and a 10% response rate if no benefit was derived from treating with adalimumab patients who showed an unsatisfactory response to etanercept. Based on these assumptions, if the response rate is 25%, the 95% CI would be between 13 and 37 (the lower limit of the 95% CI would therefore be higher than the assumed 10% response rate if adalimumab did not provide additional benefits).

For PGA, an intent-to-treat analysis with non-responder imputation was used for patients who missed the week 12 and/or week 24 visits. For PASI and BSA evaluations, an intent-to-treat analysis with last observation carried forward was used. PGA results of clear or almost clear at weeks 12 and 24 are presented as percentage with 95% CI. An analysis of variance for repeated measures was used to analyze BSA and PASI score from day 0 to week 12.

RESULTS

Demographics and patient disposition

A total of 85 patients were included in this study (50 patients in group A and 35 patients in group B). The original plan was to include 50 patients in both groups. However, recruitment of patients who presented a PGA score of 0 or 1 after 12 weeks of etanercept followed by an increase in PGA score to 2 or higher upon etanercept dose reduction was more difficult than anticipated. As recruitment was not progressing, it was decided to stop enrollment during the spring of 2008. Demographics of patients for both groups are provided in Table I. Patient disposition is provided in Fig 1. Of the 85 patients, 75 completed the study.

According to the protocol, patients who for any reason missed 2 or more consecutive doses or more than 3 doses of adalimumab were to be discontinued.
from the study. This occurred for 5 patients; however, 4 of these patients were not discontinued as the noncompliance was only noted by the site or by the monitor after they completed the study.

**Efficacy**

**Group A.** A total of 34.0% (95% CI 20.4-47.6) of patients who had an unsatisfactory response to at least 3 months of etanercept at 50 mg twice a week without dose reduction achieved a PGA score of clear or almost clear after 12 weeks of adalimumab at 40 mg EOW. Of those patients in group A who did not achieve a PGA score of clear or almost clear at week 12, 32.3% (95% CI 14.8-49.7) achieved a PGA score of clear or almost clear at week 24, 12 weeks after adalimumab dose increase to 40 mg EW. At week 24 a total of 46.0% (95% CI 31.7-60.3) of patients in group A achieved a PGA score of 0 or 1 with adalimumab at either 40 mg EOW or EW.

There was a significant improvement over time in mean BSA (Fig 2) \( (P < .001) \) and mean PASI score from day 0 to week 12 (Fig 3) \( (P < .001) \). The mean BSA was reduced by 42.2% at week 12. After 12 weeks of adalimumab at 40 mg EOW, 40.0% of patients reached PASI 75. Of the patients who had a dose increase at week 12, mean BSA was reduced by 40.8% at week 24 as compared with day 0. A total of 48.4% of patients who had a dose increase at week 12 reached PASI 75 at week 24. For all patients at week 24, the reduction in mean BSA and percentage of patients who reached PASI 75 was 53.0% and 52.0%, respectively.

**Group B.** For patients who had a PGA score of clear or almost clear after at least 3 months of etanercept at 50 mg twice a week followed by a loss of this PGA response after a dose reduction to 50 mg once a week, a total of 31.4% (95% CI 15.2-47.6) of patients achieved a PGA score of clear or almost clear after 12 weeks of adalimumab at 40 mg EOW. Of those patients in group B who did not achieve a PGA score of clear or almost clear at week 12, 30.4% (95% CI 10.1-50.8) achieved a PGA score of clear or almost clear at week 24, 12 weeks after adalimumab dose increase to 40 mg EW. At week 24 a total of 45.7% (95% CI 28.4-63.1) of patients in group B achieved a PGA score of 0 or 1 with either adalimumab 40 mg EOW or EW.

There was a significant decrease over time in mean BSA (Fig 4) \( (P < .001) \) and mean PASI score from day 0 to week 12 (Fig 5) \( (P < .001) \).
BSA was reduced by 60.7% at week 12 and 31.4% of patients reached PASI 75 after 12 weeks of adalimumab at 40 mg EOW. Of the patients who had a dose increase at week 12, a reduction in mean BSA from baseline of 39.0% was attained at week 24. A total of 52.2% of patients who had a dose increase at week 12 reached PASI 75 at week 24. For all patients at week 24, the reduction in average BSA and the percentage of patients who reached PASI 75 was 59.3% and 62.9%, respectively.

Safety

There were no serious AEs during this study. There were no AEs of cancer, tuberculosis, congestive heart failure, or demyelination. A summary of AEs is presented in Table II. The patient with an AE of allergic reaction had a contact dermatitis to a moisturizing cream and not a reaction to adalimumab. No patients were withdrawn from the study because of AEs. Viral, bacterial, and fungal infections were all coded under the term infectious AE. The most frequent infectious AEs were: upper respiratory tract infections, common cold, urinary tract infection, sinusitis, gastroenteritis, and bronchitis.

A total of 10 patients did not complete the study. Two patients withdrew before week 12 because of lack of efficacy. Five more patients withdrew after week 12 because of lack of efficacy. One withdrew at week 16, two more at week 20, and two at week 24. Before week 20, one patient was withdrawn as he received a vaccination with a live virus (yellow fever). This patient did not have any AEs after this vaccination. One patient was lost to follow-up at week 24 and another withdrew from the study after week 12 without providing a specific reason.

DISCUSSION

Treatment of patients with moderate to severe psoriasis has changed dramatically since the
approval of biological agents. In addition to topical therapy, phototherapy, and the oral systemic agents, there are, at the time of this writing, 5 biologics approved in various countries for the treatment of psoriasis with at least one more pending approval.7,8 Choosing the best treatment for moderate to severe psoriasis becomes more complex both for patients and clinicians. Biologics targeting TNF-alfa are among the most frequently prescribed systemic treatments for psoriasis in the United States and Canada. Even if many of these biologics are very effective, there are always patients who do not respond well or who will eventually lose their response. Under these circumstances it is not always easy for the clinician to choose which agent should be used next. This is especially difficult in the case of a failure responding to an anti–TNF-alfa agent. Should the clinician propose an agent from a different class (T-cell agent or anti-interleukin12/23) or should the clinician also consider another anti–TNF-alfa agent? Another option for patients who lost their response to etanercept after a dose decrease to 50 mg once a week would be to go back to 50 mg twice a week and keep this dose. There is currently a paucity of data in the literature on the efficacy and safety of one anti–TNF-alfa for the treatment of plaque psoriasis in patients who showed an unsatisfactory or a loss of response to another anti–TNF-alfa agent. Information on previous lack of response to systemic agents was collected in some phase III studies with biological agents but this was not always confirmed by documentation from the patient’s medical records. To be eligible for the current trial, patients had to have documentation in their dermatology records of a nonsatisfactory response or loss of a satisfactory response based on PGA.

The current study showed that 34% of patients from group A and 31% of patients from group B reached a PGA score of clear to almost clear after 12 weeks of adalimumab. The two phase III controlled studies with adalimumab showed that 60% and 67% of patients reached a PGA score of 0 or 1 at week 12.9,10 The percentages of patients reaching PGA score of 0 or 1 in the current study are lower than results from phase III studies; however, the current study only enrolled patients with documented unsatisfactory or loss of response to etanercept. Another important difference between the current trial and phase II and III studies conducted with adalimumab for the treatment of psoriasis is the absence of a loading dose. The approved adalimumab dosage for psoriasis includes a loading dose of 80 mg followed by 40 mg 1 week later and 40 mg EOW. Patients in the current trial were started with 40 mg EOW as there was no washout period between the last dose of etanercept and initiation of adalimumab. It should be emphasized that the 31% and 34% of patients who reached a PGA response of 0 or 1 do not represent all patients who improved or all patients who showed significant benefits from adalimumab. Other patients had significant improvement, sometimes more than 75% improvement in PASI score or BSA, but did not reach PGA score of 0 or 1.

Haitz and Kalb11 reported on 19 patients treated with infliximab and previously treated with etanercept. Reasons for stopping etanercept in this retrospective study included loss of response, lack of response, and insurance issues. They did not use a specific criterion to define lack or loss of response and patients were allowed to use concomitant phototherapy, topical therapy, systemic therapy, or a combination of these while being treated with infliximab. A total of 37% of patients reached a PGA score of 0 or 1 with infliximab but most patients required an increase in dosing interval from every 8 weeks to every 6 weeks. Papoutsaki et al12 published an open-label study of 30 patients who failed biologics (including etanercept) and systemic therapy. They defined failure to respond as failure to have a reduction in PASI by 50% or more after at least 12 weeks of etanercept. All patients received adalimumab at 40 mg EW. They reported that 87% of patients reached PASI 75 at week 12. However, patients had to go through at least a 2-month washout period before starting adalimumab. This washout period combined with the fact that all patients received adalimumab at 40 mg EW could explain in part the higher PASI 75 response they observed as compared with the current study.

The current study showed that adalimumab was well tolerated by patients who either failed to reach a PGA score of 0 or 1 after 12 weeks of etanercept or who lost their PGA response after etanercept dose decrease. There were no allergic reactions to adalimumab, no serious infections, and no serious AEs reported despite the fact that 22 (26%) patients started adalimumab less than 2 weeks after stopping etanercept. The total number of AEs or infectious AEs per patient-year in the current study was 4.1 and 1.22, respectively. This was very similar to what was reported in the phase III placebo-controlled study (4.62 and 1.26, respectively, for total AE and infectious AE/patient-year).5 This is important information as washout periods for biologics in clinical trials tend to be as long as 2 to 6 months. In addition, many phase III protocols exclude patients who have used a biologic that has a mechanism of action similar to the one being investigated. Transition from one biologic to another can sometimes be problematic as seen by
reports of erythrodermic psoriasis in patients transitioned from efalizumab to etanercept. In the current trial, transition from etanercept to adalimumab was well tolerated by all patients.

In conclusion this study showed that adalimumab is safe and effective in patients who have shown an unsatisfactory or loss of response to etanercept. Adalimumab should be considered as a treatment alternative in patients with psoriasis who have not shown an adequate response to etanercept or who lost their response after a dose decrease to 50 mg once a week.

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