OBSERVE-5 interim analysis: An observational postmarketing safety registry of etanercept for the treatment of psoriasis

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Background: Etanercept is approved for the treatment of chronic moderate to severe plaque psoriasis in adults.

Objective: We sought to evaluate the long-term safety of etanercept in a real-world clinical setting. Assessment of etanercept efficacy was a secondary objective.

Methods: OBSERVE-5 is a 5-year observational safety registry initiated in May 2006 at multiple sites in the United States and Canada. Data collection includes the number of serious adverse events, serious infectious events, and prespecified events of medical interest. Efficacy data include body surface area assessments, physician and patient global assessments of psoriasis, and the Dermatology Life Quality Index. This interim analysis presents data from the first 3 years of the follow-up period.

Results: A total of 2511 patients were enrolled. Of 1890 patients continuing in the registry after 3 years, 113 were inactive for 1 to 2 years, and 115 were inactive for longer than 2 years. The 3-year incidence proportions of serious adverse events and serious infectious events based on Kaplan-Meier methodology were 0.14 and 0.04, respectively. The observed numbers of patients experiencing lymphoma, serious infectious events requiring hospitalization, nonmelanoma skin cancer, and malignancies excluding

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nonmelanoma skin cancer were not higher than the expected number of cases estimated from a large US administrative health claims database.

Limitations: The registry lacks a control group, and the study is too small to measure the frequency of rare events.

Conclusion: Etanercept demonstrated good tolerability in patients with plaque psoriasis in the clinical setting in this interim analysis. No new or unexpected safety concerns were observed. (J Am Acad Dermatol 2013;68:756-64.)

Key words: etanercept; infections; lymphoma; nonmelanoma skin cancer; psoriasis; registry; safety.

CAPSULE SUMMARY

- Previous data from randomized, controlled clinical trials have demonstrated that etanercept is safe and effective in patients with moderate to severe plaque psoriasis.
- This postmarketing safety registry provides data on the first 3 years of a 5-year observational study on real-world use of etanercept in this patient population.
- No new or unexpected safety signals were observed with the use of etanercept in this interim observational analysis.

Psoriasis is a chronic, potentially debilitating, inflammatory skin disease that affects approximately 2% to 3% of individuals in the United States.[1,2] Health-related quality of life is often reduced in patients with active psoriasis, and approximately one quarter of patients with psoriasis report that the disease presents a large problem in their daily lives.[2]

Psoriasis treatments include topical therapy, phototherapy, nonbiologic systemic agents, and biologic therapy.[3] Etanercept is a fully human, soluble tumor necrosis factor (TNF) receptor fusion protein approved in the United States for treating adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[4] Etanercept has demonstrated clinical efficacy and good tolerability in short- and long-term (up to 2.5 years) clinical trials in patients with moderate to severe plaque psoriasis.[5-11]

Observational registries are useful in that they accumulate long-term data from a more heterogeneous real-world cohort of patients with respect to baseline demographics, disease severity, and comorbid conditions, as compared with clinical trials. Such registries also facilitate detection of long-term effects and other risks that may affect the risk-benefit profile for a specific group of patients. OBSERVE-5 is a prospective 5-year observational safety registry designed to gather data on the long-term safety of etanercept in a large population of patients with plaque psoriasis. This report presents interim 3-year data for OBSERVE-5.

METHODS

Study design

This postmarketing phase IV cohort study (clinical trial registry NCT00322439) was initiated at 375 sites (338 in the United States, 37 in Canada) in May 2006 and is continuing at 286 sites (257 in the United States, 29 in Canada). The planned duration of follow-up is 5 years. This prespecified interim report includes 3-year data available from study start through January 20, 2011. The primary objective of this registry was to assess the long-term safety of etanercept in patients with plaque psoriasis, as determined by evaluating the incidence proportions of serious adverse events (including serious infectious events). A key secondary objective was to assess etanercept safety by evaluating incidence proportions of prespecified events of medical interest.

Patients with plaque psoriasis for whom etanercept was indicated per prescribing information were eligible for inclusion in the registry. Patients were excluded if they had been treated with any other TNF inhibitor, had been treated with etanercept before April 2004 in the United States or before December 2005 in Canada (approval dates for etanercept for the psoriasis indication), had participated in a previous etanercept clinical trial, or had contraindications to etanercept treatment according to prescribing information (ie, sepsis).

The etanercept dose and dosing regimen was determined by the study investigator. During the follow-up period, patients may have discontinued etanercept treatment, switched to another antipsoriatic treatment, used etanercept in combination with other antipsoriatic treatments, or discontinued all antipsoriatic treatments. Patients were evaluated at least twice yearly (at approximately 6-month intervals).

Serious adverse events (including serious infectious events) were assessed as the primary study

Abbreviations used:

BSA:	body surface area
CI:	confidence interval
NMSC:	nonmelanoma skin cancer
TNF:	tumor necrosis factor

objective. A serious adverse event was defined as one that suggests a significant hazard or adverse event. This included, but was not limited to, any event that was fatal, was life threatening, required overnight inpatient hospitalization or prolongation of hospitalization, was a persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or other significant medical hazard. Prespecified events of medical interest (key secondary study objective) were defined as serious and nonserious adverse events of malignancies, tuberculosis, opportunistic infections treated with intravenous therapy, histoplasmosis or coccidioidomycosis treated with oral antibiotics, central nervous system demyelinating disorders, lupus, coronary artery disease, and worsening psoriasis (defined by change in psoriasis morphology and withdrawal of therapy due to worsening of psoriasis). Such events were coded according to the *Medical Dictionary for Regulatory Activities* preferred terms. Also included were any adverse events or laboratory abnormalities that, in the investigator's opinion, were events of medical significance.

Retention efforts included encouragement of sites to conduct telephone reminders of approaching visits, distribution of retention packages containing visit reminder cards to the investigator sites, and reimbursement of sites for efforts to remind patients. In the event of patient relocation, patient transfer to another investigative site was permitted. Telephone visits, where adverse event information was obtained from patients via telephone, even in the absence of a direct physical examination, were permitted. The sponsor company did not provide study drug to the participants.

Incidence proportions for serious adverse events, serious infectious events, and events of medical interest were calculated using Kaplan-Meier methodology to adjust for varying exposure as a result of dropouts. The incidence proportions represent the probability that an event occurs within a given time period. Because the study does not include an internal comparison group, rates of specific events of interest (malignancies, lymphoma, nonmelanoma skin cancer [NMSC], infections requiring hospitalization) were assessed against background rates from an external database.

Outcomes data were also collected to assess treatment efficacy, impact on health-related quality of life, and health care resource use. Key outcomes measures presented here are the change in body surface area (BSA) affected by psoriasis and the patient and physician global assessments (using a 6-point Likert scale, 0-5; 0 or 1 represents clear or almost-clear status in the physician global assessment), with higher scores indicating more severe psoriasis. For these analyses, no imputation was performed for missing data. The study is being conducted in compliance with the Declaration of Helsinki. The study protocol and informed consent forms were approved by all institutional review boards, and all patients provided written consent before starting study-specific procedures.[12]

Data analysis

The primary analysis set was all patients who received at least 1 dose of etanercept. For the primary analysis, incidence proportions of serious adverse events and serious infections were calculated using Kaplan-Meier methodology. Follow-up for each patient began on the date of the first dose of etanercept during the study and time at risk continued until the occurrence of the first event or until the end of the study.

In addition to the Kaplan-Meier analyses of incidence proportions, incidence rates based on patient-years of exposure and patient-years of observation were calculated. This methodology was used to align to that used in the calculation of expected incidence rates derived from the external database. This analysis provided context for the observational safety results obtained from the study. For calculations of incidence rates per patient-years of exposure, all events that occurred during etanercept exposure were included. Exposure was calculated as the duration of time on etanercept, including a 30-day risk window after each dosing period. For calculations of incidence rates per patient-years of observation, all events that occurred during the registry were included and observation was calculated as the duration of time on the study (including breaks in etanercept use, if any). Follow-up time was truncated at the first occurrence of the event for each subject or at the end of the study. All events were included in the analysis. For those events where no date was available (n = 10), the unknown start dates for the event were estimated for each subject as the baseline registry date plus one half of the total observed duration that the subject was in the study (ie, the middle of the exposure period).

For the external comparator analysis, the incidence rates of the following events were estimated

using data from a large US administrative health claims database (Market-Scan, Truven Health Analytics Inc, Ann Arbor, MI): malignancies (all cancers combined including lymphoma, but excluding NMSC [basal cell carcinoma and squamous cell carcinoma]), lymphoma, NMSC, and serious infections requiring hospitalization.[13] A psoriasis cohort was selected based on evidence of having more than 1 inpatient or more than 2 outpatient claims with the *International Classification of Diseases, Ninth Revision, Clinical Modification* code for psoriasis (696.1) and the specific treatment cohorts were selected based on first medication prescribed. Among 48,136 patients with a diagnosis of psoriasis in the database, 7.6% were prescribed nonbiologic systemic therapies, 4.1% other TNF blocker therapies, 10.7% etanercept, and 8.0% were undergoing phototherapy.[14] The primary comparator group was a cohort of patients with psoriasis prescribed methotrexate or cyclosporine (nonbiologic systemic therapies). They had a mean (SD) of 2.1 (1.0) years of enrollment and a mean (SD) duration of therapy of 0.7 (0.8) years. This group was selected as the comparator group because they were more likely to have psoriasis disease severity that was comparable with a group given etanercept.

Because of the longer latency of cancers, the primary comparison for all cancers (excluding NMSC), lymphoma, and NMSC was performed using patient-years of observation. For hospitalized infections, which have a more acute effect, the primary comparison was made using patient-years of exposure. Incidence rates, which were age- and sex-standardized to the OBSERVE-5 population, for these 4 types of events were estimated for a psoriasis population prescribed methotrexate or cyclosporine (nonbiologic systemic therapies) based on the first medication prescribed. A standardized incidence ratio and 95% confidence intervals (CI) were calculated to compare the number of observed patients experiencing events in the registry with the number of expected patients from the comparator group in the administrative health claims database.

RESULTS

Of 2511 patients initially enrolled in the registry, 1890 (75%) were still participating at the time of this interim analysis. Of these ongoing patients, 1662 (66.2%) patients had been evaluated in the past year, 113 had not been evaluated for 1 to 2 years, and 115 had not been evaluated for more than 2 years. The most common reason for discontinuation from the study was withdrawn consent; all of the reasons given for discontinuation are listed in Table I.

Table I. Patient attributes

	Prior etanercept*	Etanercept naive†	Total
Enrolled, n	664	1847	2511
Received ≥1 etanercept dose, n	664	1847	2511
Patients continuing in study, n (%)	509 (76.7)	1381 (74.8)	1890 (75.3)
Last visit within 1 y	456 (68.7)	1206 (65.3)	1662 (66.2)
No visits for 1-2 y	21 (3.2)	92 (5.0)	113 (4.5)
No visits for >2 y	32 (4.8)	83 (4.5)	115 (4.6)
Patients discontinued from study, n (%)	155 (23.3)	466 (25.2)	621 (24.7)
Consent withdrawn	52 (7.8)	250 (13.5)	302 (12.0)
Administrative decision	24 (3.6)	57 (3.1)	81 (3.2)
Ineligibility determined	56 (8.4)	11 (0.6)	67 (2.7)
Lost to follow-up	4 (0.6)	57 (3.1)	61 (2.4)
Disease progression	3 (0.5)	32 (1.7)	35 (1.4)
Death	9 (1.4)	21 (1.1)	30 (1.2)
Adverse event (other than death)	4 (0.6)	14 (0.8)	18 (0.7)
Noncompliance	2 (0.3)	12 (0.6)	14 (0.6)
Protocol deviation	1 (0.2)	6 (0.3)	7 (0.3)
Pregnancy	0 (0)	1 (0.1)	1 (<0.1)
Other	0 (0)	5 (0.3)	5 (0.2)

*Includes patients with etanercept exposure before registry.
†Includes patients with no etanercept exposure before registry who initiated etanercept for first time at baseline.

At 3 years, 272 (10.8%) patients were considered discontinued without resumption of therapy.

The majority of patients were white and younger than 65 years, with approximately equal numbers of men and women enrolled (Table II). There were 664 patients with etanercept exposure before the registry (ie, prior etanercept group) and 1847 patients with no etanercept exposure before the registry who initiated etanercept for the first time at baseline (ie, etanercept-naive group). The mean ± SD duration of psoriasis at screening was 18.4 ± 12.9 years in the prior etanercept group and 14.7 ± 12.5 years in the etanercept-naive group. In the prior etanercept group, approximately 25% of patients had baseline percentages of BSA affected by psoriasis of less than 2%. In the etanercept-naive population, approximately 25% of patients had baseline percentages of BSA affected by psoriasis of less than 10%. The most common comorbid conditions at screening among all 2511 patients were arterial hypertension (28.5%), hypercholesterolemia/hyperlipidemia (18.7%), psoriatic arthritis (18.5%), and type 1 or type 2 diabetes (10.5%). The demographic characteristics of the patients with previous exposure to etanercept (n = 664)

Table II. Patient demographics and clinical characteristics

	Prior etanercept* (n = 664)	Etanercept naive† (n = 1847)	Total (n = 2511)
Sex, n (%)			
Men	378 (56.9)	939 (50.8)	1317 (52.4)
Women	286 (43.1)	908 (49.2)	1194 (47.6)
Age, y			
Mean ± SD	48.5 ± 12.6	45.6 ± 13.9	46.3 ± 13.6
Range	19-86	11-92	11-92
Age group, n (%)			
<65 y	601 (90.5)	1697 (91.9)	2298 (91.5)
≥65 y	63 (9.5)	150 (8.1)	213 (8.5)
Race, n (%)			
White	546 (82.2)	1507 (81.6)	2053 (81.8)
Black	29 (4.4)	79 (4.3)	108 (4.3)
Hispanic or Latino	35 (5.3)	129 (7.0)	164 (6.5)
Asian	31 (4.7)	85 (4.6)	116 (4.6)
Other	23 (3.5)	47 (2.5)	70 (2.8)
Highest level of school completed, n (%)			
Grade 8	7 (1.1)	41 (2.2)	48 (1.9)
Grade 12 or GED	206 (31.0)	609 (33.0)	815 (32.5)
Technical school	26 (3.9)	61 (3.3)	87 (3.5)
Some college	138 (20.8)	401 (21.7)	539 (21.5)
College	204 (30.7)	544 (29.5)	748 (29.8)
Postgraduate	83 (12.5)	189 (10.2)	272 (10.8)
Unknown	0 (0.0)	2 (0.1)	2 (0.1)
Present employment status, n (%)			
Full time (≥35 h/wk)	466 (70.2)	1216 (65.8)	1682 (67.0)
Part time (<35 h/wk)	38 (5.7)	139 (7.5)	177 (7.0)
Temporarily employed	1 (0.2)	3 (0.2)	4 (0.2)
Disabled	25 (3.8)	67 (3.6)	92 (3.7)
Retired	83 (12.5)	218 (11.8)	301 (12.0)
Unemployed	31 (4.7)	164 (8.9)	195 (7.8)
Other	20 (3.0)	40 (2.2)	60 (2.4)
Duration of psoriasis, y			
Mean ± SD	18.4 ± 12.9	14.7 ± 12.5	15.7 ± 12.7
Median	16.6	11.1	12.6
Range	0-69.7	0-78.6	0-78.6
Baseline body surface area affected by psoriasis, %			
Mean ± SD	11.7 ± 14.5	24.5 ± 20.3	21.1 ± 19.8
Median (IQR)	6.0 (2-15)	17.0 (10-34)	15.0 (8-30)
Range	0-96.0	0-100.0	0-100.0

GED, General equivalency diploma; *IQR*, interquartile range.
*Includes patients with etanercept exposure before registry.
†Includes patients with no etanercept exposure before registry who initiated etanercept for first time at baseline.

and those with no prior etanercept exposure (n = 1847) were similar.

During the follow-up period, mean ± SD duration of etanercept exposure was 1.7 ± 1.1 years and 1.6 ± 1.1 years in the prior etanercept and etanercept-naive groups, respectively. In total, 846 (33.7%) patients were receiving etanercept at 3 years, 291 of whom had no gaps in treatment, and 1509 patients discontinued etanercept or changed doses at least once. The median number of etanercept discontinuations or dose changes per patient was 1.0 (range, 1-10). The most common reasons for initial discontinuation of etanercept were other (n = 272), alternative psoriasis therapy prescribed (n = 205), nonserious adverse event (n = 180), subject request (n = 164), insurance change (n = 149), and disease progression (n = 138).

Safety

A total of 145 patients discontinued etanercept because of 1 or more adverse events; the most common of these events were cellulitis (n = 8), pneumonia (n = 8), hypoesthesia (n = 6), paresthesia (n = 5), dyspnea (n = 4), and worsening psoriasis (n = 4). Thirty patients died during the follow-up period, and these fatal adverse events are summarized in Table III. Three of these deaths (idiopathic pulmonary fibrosis, osteomyelitis and sepsis, and cardiac failure) were judged by the investigator to be related to etanercept. However, the relationship of these deaths to etanercept was confounded by pre-existing conditions in 2 of the 3 patients and by the period of time not receiving etanercept in the third patient. One of these patients was a 77-year-old man with a history of acute bronchitis, chronic obstructive pulmonary disease, and pulmonary fibrosis. He developed interstitial pneumonia (idiopathic pulmonary fibrosis) and was hospitalized on the same date (September 5, 2010). Etanercept was discontinued (date of first and last dose not specified). The patient subsequently died of interstitial pneumonia on October 7, 2010; the investigator thought there was a reasonable possibility that this pneumonia was related to etanercept. The other patient with confounding pre-existing conditions was a 64-year-old man on dialysis with a history of insulin-dependent diabetes mellitus, myocardial infarction, bypass graft, angioplasty, foot amputation, diverticulosis, and multiple back surgeries. Approximately 70 days after initiation of etanercept treatment, he developed pain and fever in an unspecified location, was hospitalized 6 days later with sepsis and osteomyelitis, underwent unspecified back surgery for the sepsis, and died approximately 1 week later. The investigator thought that the initial pain was

Table III. Fatal adverse events occurring during follow-up period

	Patients, n
Total No. of patients with fatal adverse events	30
Unknown cause of death	6
Myocardial infarction	4
Cardiac failure	2
Completed suicide	2
Pneumonia	2
Sepsis	2
Abdominal pain	1
Alcoholic pancreatitis	1
Asphyxia	1
Chronic obstructive pulmonary disease	1
Crushing injury of trunk	1
Drug toxicity	1
Generalized edema	1
Hepatic cirrhosis	1
Hepatic encephalopathy	1
Idiopathic pulmonary fibrosis	1
Large-cell carcinoma of respiratory tract	1
Lung cancer, metastatic	1
Lung neoplasm, malignant	1
Multiorgan failure	1
Myelodysplastic syndrome	1
Neoplasm, malignant	1
Bladder cancer	1
Osteomyelitis	1
Pancreatic carcinoma	1
Renal failure, chronic	1
Respiratory failure	1
Road traffic accident	1

Not all patients were receiving etanercept throughout follow-up period. Six patients had >1 reported fatal events.

unrelated to etanercept, but that the fatal sepsis and osteomyelitis were possibly related to etanercept. The third death occurred in a 72-year-old woman with a history of osteoporosis, small-cell carcinoma of the lung, and squamous cell carcinoma of the labia, who had discontinued etanercept in October 2009, after 2 years and 4 months of treatment. She subsequently discontinued all medications, became comatose, and died in March 2010, with no cause of death initially reported. The investigator judged there was a reasonable possibility that her death was related to etanercept. The cause of death was later confirmed to have been heart failure.

A total of 290 patients had 1 or more serious adverse events, including 82 patients with 1 or more serious infectious events and 61 patients with 1 or more serious infectious events requiring hospitalization. Events occurring in 5 or more patients are listed in Table IV. The Kaplan-Meier estimated 3-year incidence proportion for serious adverse events was 0.14 (0.13-0.16) (Table V). The incidence rate

Table IV. Serious adverse events, serious infectious events, serious infectious events requiring hospitalization, and events of medical interest occurring in 5 or more patients during follow-up period

	Patients, n
Patients enrolled, total	2511*
Serious adverse events, total	290
Cellulitis	17
Pneumonia	17
Myocardial infarction	13
Coronary artery disease	9
Dyspnea	8
Osteoarthritis	7
Angina pectoris	6
Atrial fibrillation	6
Cholecystitis	6
Diverticulitis	6
Intervertebral disk protrusion	6
Nephrolithiasis	6
Staphylococcal infection	6
Death	6
Chronic obstructive pulmonary disease	5
Dehydration	5
Pancreatitis	5
Serious infectious events, total†	82
Cellulitis	17
Pneumonia	17
Diverticulitis	6
Staphylococcal infection	6
Serious infectious events requiring hospitalization, total†	61
Pneumonia	16
Cellulitis	15
Events of medical interest, total	459
Other‡	359
Malignancy	87
Coronary artery disease	33
Worsening psoriasis	7
Central nervous system demyelinating disorders	6

*No. of patients who received at least 1 registry dose of etanercept. Not all patients were receiving etanercept throughout evaluation period.

†Serious infectious events are subset of serious adverse events, and serious infectious events requiring hospitalization are subset of serious infectious events.

‡Includes any event or laboratory abnormality that, in investigator's opinion, represents event of medical significance. Events in this category reported in ≥5 patients included sinusitis (n = 24); upper respiratory tract infection (n = 16); pneumonia (n = 15); positive tuberculin test result (n = 14); bronchitis (n = 13); hypertension (n = 12); cellulitis, diabetes mellitus, paresthesia (n = 11 each); hypoesthesia, type 2 diabetes mellitus (n = 9 each); psoriasis (n = 8); urinary tract infection (n = 7); arthralgia, hepatic steatosis, nephrolithiasis (n = 6 each); and cough, fatigue, gastroesophageal reflux disease, herpes zoster, injection site erythema, rash (n = 5 each).

Table V. Kaplan-Meier analysis and exposure-adjusted incidence of serious adverse events and serious infectious events during follow-up period

	No. of patients with event	Incremental yearly incidence proportion (95% CI)	Cumulative incidence proportion (95% CI)
Serious adverse events			
Kaplan-Meier method			
Year 1	141	0.0605 (0.0508-0.0703)	0.0605 (0.0508-0.0703)
Year 2	98	0.0488 (0.0394-0.0583)	0.1094 (0.0962-0.1225)
Year 3	51	0.0318 (0.0231-0.0405)	0.1412 (0.1258-0.1565)
Incidence rate per 100 person-years of exposure (95% CI)	213	5.18 (4.51-5.93)	
Incidence per 100 person-years of observation (95% CI)	290	5.58 (4.96-6.27)	
Serious infectious events			
Kaplan-Meier method			
Year 1	44	0.0188 (0.0133-0.0243)	0.0188 (0.0133-0.0243)
Year 2	24	0.0120 (0.0072-0.0168)	0.0308 (0.0236-0.0381)
Year 3	14	0.0088 (0.0042-0.0134)	0.0396 (0.0311-0.0482)
Incidence rate per 100 person-years of exposure (95% CI)	62	1.46 (1.12-1.87)	
Incidence rate per 100 person-years of observation (95% CI)	82	1.51 (1.20-1.87)	

No. of patients at risk is adjusted over time to account for dropouts, deaths, and patients who have already had an event.
CI, Confidence interval.

per 100 patient-years of exposure was 5.18 (95% CI, 4.51-5.93) and per 100 patient-years of observation was 5.58 (95% CI, 4.96-6.27). For serious infectious events, the Kaplan-Meier estimated 3-year incidence proportion was 0.04 (95% CI, 0.03-0.05) (Table V). The incidence rate per 100 patient-years of exposure was 1.46 (95% CI, 1.12-1.87) and per 100 patient-years of observation was 1.51 (95% CI, 1.20-1.87). A total of 459 patients had 1 or more events of medical interest; events occurring in 5 or more patients are listed in Table IV. The number of events of NMSC, lymphoma, and all cancers combined excluding NMSC (based on patient-years of observation) and serious infectious events requiring hospitalization (based on patient-years of exposure, because these events would be expected to be effects of treatment, rather than delayed effects, eg, cancer) in this registry was not higher than that expected for patients with psoriasis using nonbiologic systemic therapies based on data from a large administrative health claims database (Table VI).

Efficacy

The mean and median percentages of BSA affected by psoriasis were similar in the prior etanercept and etanercept-naive groups by 6 months (mean: 7.9% and 8.3%, respectively; median: 4.0% and 4.0%, respectively). The numbers of patients included in this 6-month time point were 538 and 1538 for prior etanercept and etanercept-naive, respectively, out of 2494 total patients evaluated for efficacy. In addition, approximately half of patients in both groups achieved a score of 0 or 1 (clear/almost-clear status in physician global assessment) in the physician and patient global assessment by 6 months. For physician global assessment score, 48.6% of patients achieved a score of 0 or 1 in the prior etanercept group (n = 539), as did 51.7% in the etanercept-naive group (n = 1537). For patient global assessment score, 47.4% of patients achieved a score of 0 or 1 in the prior etanercept group (n = 529), versus 50.0% in the etanercept-naive group (n = 1508). A limitation of the efficacy results is that not all patients were receiving etanercept throughout the evaluation period. At month 6, there were 290 patients who temporarily or permanently discontinued etanercept despite being evaluated for efficacy, including patients who may have discontinued etanercept, switched to another antipsoriatic treatment, or discontinued all antipsoriatic treatments. Indeed, some patients who dropped out of the study were not included in these numbers because of insufficient available information. The responses are likely biased upward as a result of missing values.

DISCUSSION

These interim analysis results from the first 3 years of this 5-year etanercept observational safety registry

Table VI. Standardized incidence ratio analysis for events of medical interest using expected rates from psoriasis population using nonbiologic systemic therapies

	Observed No. of patients	Patient-years*	Expected No. of patients†	SIR (95% CI)
Malignancies, excluding NMSC	39	5537.8	40.1	0.97 (0.69-1.33)
Lymphoma	2	5565.6	2.3	0.88 (0.11-3.17)
NMSC‡	48	5489.6	68.3	0.70 (0.52-0.93)
Serious infectious events requiring hospitalization	45	4267.2	86.1	0.52 (0.38-0.70)

CI, Confidence interval; *NMSC*, nonmelanoma skin cancer; *SIR*, standardized incidence ratio.
*Based on patient-years of observation data for malignancies (excluding NMSC), lymphoma, and NMSC. For serious infectious events requiring hospitalization, patient-years of exposure data were used. Nonbiologic systemic therapies include methotrexate and cyclosporine.
†Estimated data from large US administrative health claims database of patients with psoriasis (external comparator) age- and gender-standardized to OBSERVE-5 study population.
‡Incident cases of NMSC only.

present Kaplan-Meier estimates for the incidence proportions of serious adverse events and serious infectious events during the follow-up period. The number of deaths during the 3-year period was 30. There were 3 deaths judged by the investigator to be related to etanercept; however, the relationship of each of these deaths to etanercept was confounded by pre-existing conditions or time off from etanercept.

The number of serious infections requiring hospitalization (per patient-years of exposure), lymphomas, NMSC, and all cancers excluding NMSC (per patient-years of observation) in this study was not higher than that expected based on age- and sex-standardized incidence rates for patients with psoriasis treated with nonbiologic systemic therapies (eg, methotrexate, cyclosporine). Although the comparator database analysis provides a context for the event rates in OBSERVE-5, the case identification methods differ, and often patients who enroll and continue participation in prospective observational studies are healthier than those in the general population.[15,16] Therefore, the results should be carefully interpreted in this context.

Results from this observational registry paralleled those from an integrated safety analysis by Pariser et al[17] in 2012 of data from 7 clinical trials of up to 2 years' duration (total N = 5806). In the analysis of Pariser et al,[17] the rates of serious noninfectious adverse events were low and generally remained stable or declined over the long term, with no dose-related increases in serious infectious events. The results of our current analysis are also in line with a recent integrated safety report for etanercept across approved indications, including psoriasis, which found generally similar rates of overall serious infections and malignancies between etanercept and control groups, along with low overall rates of opportunistic infections and tuberculosis.[18]

The use of a large registry in the current analysis offers several advantages. Data from such a registry represent real-world long-term use of etanercept in a large population of patients with plaque psoriasis. It has the potential to provide data from a broader patient population than those enrolled in randomized controlled clinical trials,[12] although the profiles of enrolled patients were not dissimilar from the study populations in terms of basic demographic data. Limitations inherent to a single-agent registry include the lack of an internal control group to help interpret event rates and a lack of power to detect rare events.[12] We used a comparator group that was based on a database analysis. Within this database, we identified a disease population that was likely to have a similar disease severity as the OBSERVE-5 population given that the incidence of some of the outcomes is known to be higher in those with more severe psoriasis. Although patients with psoriasis prescribed other anti-TNF therapies should have the most comparable disease severity, that group might not be the most appropriate comparator group given that there might be similar safety issues for the entire class. Interpretation of registry data is also constrained by patients lost to follow-up, in part because of the long duration of the study and the fact that study drug was not provided to patients. The registry also does not provide data on phenotypic and genetic components of psoriasis and their relationship to treatment response, adverse events, and disease severity. Further, there is potential observation bias by investigators who assessed patients more than twice yearly, and for recall bias by patients when reporting adverse events. The retrospective nature of event capture may have led to recall bias. Finally, the efficacy estimates do not account for the patients who discontinue etanercept or use other therapeutic agents and may thus overestimate efficacy.

CONCLUSIONS

In summary, this analysis found that no new or unexpected safety concerns were observed in the

first 3 years of this 5-year etanercept observational postmarketing registry. Data will continue to be collected and final results will be reported at study end.

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REFERENCES

1. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the US population. J Am Acad Dermatol 2004;51:704-8.
2. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol 2009;60:218-24.
3. American Academy of Dermatology Work Group; Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis, section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011;65:137-74.
4. Enbrel (etanercept) [full prescribing information]. Thousand Oaks, CA: Immunex Corp; 2011.
5. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014-22.
6. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152:1304-12.
7. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomized phase III trial. Lancet 2006;367:29-35.
8. Gordon KB, Gottlieb AB, Leonardi CL, Elewski BE, Wang A, Jahreis A, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. J Dermatolog Treat 2006;17:9-17.
9. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139:1627-32.
10. Leonardi C, Strober B, Gottlieb AB, Elewski BE, Ortonne JP, van de Kerkhof P, et al. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. J Drugs Dermatol 2010;9:928-37.
11. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol 2007;143:719-26.
12. Kimball AB, Pariser D, Yamauchi PS, Menter A, Teller CF, Shi Y, et al. OBSERVE-5, an observational post-marketing safety surveillance registry of etanercept for the treatment of psoriasis: a model for studying new psoriasis therapies. Psoriasis Forum 2010;16:3-7.
13. Yong M, Schenfeld J, Creamer K, Shi Y, Aras G, Anthony M. External comparator data for the observational post-marketing safety surveillance registry of Enbrel (etanercept) for the treatment of psoriasis—a single-arm registry study [abstract]. Pharmacoepidemiol Drug Saf 2011;20(Suppl S1):S228.
14. Yong M, Schenfeld J, Anthony M, Kimball AB. Incidence rates of malignancies and hospitalized infectious events in psoriasis patients with or without treatment and a general population in the US: 2005-2009. Accepted poster presented at: American Academy of Dermatology 70th Annual Meeting; March 16-20, 2012; San Diego, CA.
15. Lindsted KD, Fraser GE, Steinkohl M, Beeson WL. Healthy volunteer effect in a cohort study: temporal resolution in the Adventist Health Study. J Clin Epidemiol 1996;49:783-90.
16. Pinsky PF, Miller A, Kramer BS, Church T, Reding D, Prorok P, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol 2007;165:874-81.
17. Pariser DM, Leonardi CL, Gordon K, Gottlieb AB, Tyring S, Papp KA, et al. Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. J Am Acad Dermatol 2012;67:245-56.
18. Aletaha D, Alasti F, Smolen JS. Rheumatoid arthritis near remission: clinical rather than laboratory inflammation is associated with radiographic progression. Ann Rheum Dis 2011;70:1975-80.