ORIGINAL ARTICLE

OBSERVE-5: Observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results

Alexa B. Kimball, MD,[a] Kenneth J. Rothman, DrPH,[b] Gregory Kricorian, MD,[c] David Pariser, MD,[d] Paul S. Yamauchi, MD, PhD,[e] Alan Menter, MD,[f] Craig F. Teller, MD,[g] Girish Aras, PhD,[c] Neil A. Accortt, PhD,[c] Michele Hooper, MD,[c] Kara Creamer Rice, MS,[c] and Joel M. Gelfand, MD, MSCE[h]

Boston, Massachusetts; Research Triangle Park, North Carolina; Thousand Oaks and Santa Monica, California; Norfolk, Virginia; Dallas and Bellaire, Texas; and Philadelphia, Pennsylvania

Background: OBSERVE-5 was a 5-year Food and Drug Administration—mandated surveillance registry of patients with psoriasis.

Objective: We sought to assess long-term etanercept safety and effectiveness.

Methods: Patients with moderate to severe psoriasis enrolled; a single baseline dose of etanercept was required. Key outcome measures included serious adverse events, serious infectious events, events of medical interest, psoriasis-affected body surface area, physician global assessment score, and Dermatology Life Quality Index score. Safety outcomes were assessed relative to data from the MarketScan database.

From Massachusetts General Hospital[a]; RTI Health Solutions, RTI International, Research Triangle Park[b]; Amgen Inc, Thousand Oaks[c]; Eastern Virginia Medical School and Virginia Clinical Research Inc[d]; Dermatology Institute and Skin Care Center, Santa Monica[e]; Baylor Research Institute, Dallas[f]; Bellaire Dermatology Associates[g]; and University of Pennsylvania Perelman School of Medicine.[h]

Funded by Immunex, a wholly owned subsidiary of Amgen Inc, and by Wyeth, which was acquired by Pfizer Inc in October 2009.

Disclosures: Dr Kimball is a consultant for AbbVie Inc, Amgen Inc, Merck & Co Inc, Janssen-Ortho Inc, and Pfizer Inc; is an investigator for Janssen-Ortho Inc; and serves on an advisory board for Vascular Biogenics. Dr Rothman is an employee of RTI International, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies. Drs Kricorian, Aras, Accortt, and Hooper, and Ms Rice are employees and shareholders of Amgen Inc. Dr Pariser is a consultant for Abbott Laboratories, Amgen Inc, Astellas Pharma US Inc, Bickel Biotechnology, Celgene Corp, Dermira, DUSA Pharmaceuticals Inc, LEO Pharma Inc, MelaSciences, Novartis Pharmaceuticals Corp, Procter & Gamble Co, and Valeant Pharmaceuticals International; is an investigator for Abbott Laboratories, Amgen Inc, Astellas Pharma US Inc, Asubio Pharmaceuticals Inc, Basliea, Celgene Corp, Eli Lilly and Co, Galderma Laboratories LP, Graceway Pharmaceuticals LLC, Intendis Inc, Johnson & Johnson Consumer Products Co, LEO Pharma Inc, Novartis Pharmaceuticals Corp, Novo Nordisk A/S, Ortho Dermatologics, Peplin Inc, Pfizer Inc, Photocure ASA, Stiefel a GSK Company, and Valeant Pharmaceuticals International; and serves on advisory boards for Galderma Laboratories LP, Genentech Inc, Janssen-Ortho Inc, Medicis Pharmaceutical Corp, Ortho Dermatologics, Pfizer Inc, and Stiefel a GSK Company. Dr Yamauchi is a consultant for AbbVie Inc, Amgen Inc, Baxter Healthcare Corp, Janssen-Ortho Inc, Novartis Pharmaceuticals Corp, and Pfizer Inc; is an investigator for Amgen Inc, Celgene Corp, Galderma USA, Janssen-Ortho Inc, LEO Pharma Inc, Lilly ICOS LLC, and Pfizer Inc; serves on speakers bureaus for AbbVie Inc, Amgen Inc, Galderma USA, Janssen-Ortho Inc, LEO Pharma Inc, and Novartis Pharmaceuticals Corp; and serves on an advisory board for Lilly ICOS LLC. Dr Menter serves on advisory boards for AbbVie Inc, Allergan Inc, Amgen Inc, Boehringer Ingelheim GmbH, Genentech Inc, Janssen Pharmaceuticals Inc, LEO Pharma Inc, and Pfizer Inc; is a consultant for AbbVie Inc, Allergan Inc, Amgen Inc, Convoy Therapeutics Inc, Eli Lilly and Co, Janssen Pharmaceuticals Inc, LEO Pharma Inc, Novartis AG, Pfizer Inc, Syntrix Biosystems Inc, Wyeth, and XenoPort Inc; is an investigator for AbbVie Inc, Allergan Inc, Amgen Inc, ApoPharma Inc, Boehringer Ingelheim GmbH, Celgene Corp, Convoy Therapeutics Inc, Eli Lilly and Co, Genentech Inc, Janssen Pharmaceuticals Inc, LEO Pharma Inc, Merck & Co Inc, Novartis AG, Pfizer Inc, SymBio Pharmaceuticals/

Maruho Co Ltd, Syntrix Biosystems Inc, and Wyeth; and serves on speakers bureaus for AbbVie Inc, Amgen Inc, Janssen Pharmaceuticals Inc, LEO Pharma Inc, and Wyeth. Dr Teller is a consultant for Amgen Inc, AbbVie Inc, Janssen Pharmaceuticals Inc, and Celgene, and is an investigator for Amgen Inc. Dr Gelfand is a consultant for Pfizer Inc, Janssen Pharmaceuticals Inc, and Merck & Co Inc, and a consultant and investigator for Amgen Inc, Eli Lilly and Co, and AbbVie Inc.

Data from this study were presented at the Fall Dermatology Conference in Las Vegas, Nevada, on October 17-20, 2013, and the 72nd Annual Meeting of the American Academy of Dermatology in Denver, Colorado, on March 21-25, 2014.

Accepted for publication August 26, 2014.

Reprint requests: Alexa B. Kimball, MD, Department of Dermatology, Massachusetts General Hospital, 50 Staniford St, #240, Boston, MA 02114. E-mail: harvardskinstudies@partners.org.

Published online September 25, 2014.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.08.050

Results: For 2510 patients, 5-year cumulative incidence was 22.2% (95% confidence interval [CI] 20.3%-24.2%) for serious adverse events; 6.5% (95% CI 5.4%-7.7%) for serious infectious events; 3.2% (95% CI 2.3%-4.1%) for malignancies excluding nonmelanoma skin cancer; 3.6% (95% CI 2.7%-4.5%) for nonmelanoma skin cancer; 2.8% (95% CI 2.0%-3.6%) for coronary artery disease; 0.7% (95% CI 0.3%-1.2%) for psoriasis worsening; 0.2% (95% CI 0.0%-0.4%) for central nervous system demyelinating disorder; 0.1% (95% CI 0.0%-0.3%) for lymphoma and for tuberculosis; and 0.1% (95% CI 0.0%-0.2%) for opportunistic infection and for lupus; 55 fatal events were reported. Rates of malignancies, lymphomas, nonmelanoma skin cancer, and hospitalization-associated infections were not higher than expected relative to administrative claims data. The percentage of patients rated as clear/almost clear was 12% at baseline, which increased to 51% at month 6 and remained relatively stable throughout 5 years.

Limitations: No internal comparator group was included; rare events may not have been detected.

Conclusion: No new safety signals were observed with long-term, real-world etanercept use. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.08.050.)

Key words: adverse events; etanercept; infections; malignancy; plaque psoriasis; registry; safety; surveillance.

Etanercept is a tumor necrosis factor (TNF) blocker indicated for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, and for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis.[1] An analysis of long-term safety in 506 patients with psoriasis who initiated etanercept in 2 phase-III clinical trials showed a favorable safety profile, with no cumulative toxicity noted for up to 4 years of treatment.[2]

CAPSULE SUMMARY

- OBSERVE-5 evaluated long-term safety of etanercept in 2510 patients.
- Rates of malignancies, lymphomas, nonmelanoma skin cancer, and hospitalization-associated infections were not higher than expected relative to claims data (standardized incidence ratios < 1.0).
- No new/unexpected safety signals were noted for up to 5 years of real-world use of etanercept.

Although short-term clinical trials provide important information on the efficacy and safety of a drug, long-term registry studies are also needed to detect rare adverse events in a broader patient population. OBSERVE-5 was a 5-year observational registry that enrolled 2510 patients with plaque psoriasis who received etanercept.[3] We now report the final analysis of OBSERVE-5 data representing long-term, real-world experience with etanercept therapy.

METHODS

Study design

OBSERVE-5 was a phase-IV, prospective, multicenter, observational, surveillance registry and has been previously described.[4] Briefly, etanercept was self-administered at the dose and regimen determined by the investigator and patients were evaluated at 6-month intervals for up to 5 years. Patients could have discontinued etanercept, switched to another antipsoriatic therapy, used etanercept in combination with other antipsoriatic therapies, or discontinued any or all antipsoriatic treatments during the study. The study was approved by institutional review boards at all study sites. Written informed consent was provided by all patients before initiation of any study-related procedures. This study was registered under ClinicalTrials.gov identifier NCT00322439.

Patients

As previously described,[4] patients with plaque psoriasis for whom etanercept therapy was indicated per prescribing information and for whom the treating physician decided to initiate, reinitiate, or continue etanercept therapy according to usual care were eligible. Initially, patients were etanercept-naïve but a protocol amendment allowed patients with prior etanercept exposure to enroll (capped at 50%). Patients were ineligible if they were contraindicated for etanercept treatment according to the prescribing information,[1] had been treated with other TNF blockers or with commercial etanercept before April 2004 in the United States or December 2005 in Canada (when etanercept was approved for

Abbreviations used:

BSA:	body surface area
CI:	confidence interval
EMI:	event of medical interest
NMSC:	nonmelanoma skin cancer
PGA:	physician global assessment
SAE:	serious adverse event
SIE:	serious infectious event
SIR:	standardized incidence ratio
TNF:	tumor necrosis factor

psoriasis), or had participated in previous etanercept clinical studies.

Outcome measures

Serious adverse events (SAEs); serious infectious events (SIEs), which included infectious events requiring hospitalization; and events of medical interest (EMIs) were reported and assessed throughout the study and for 30 days after the study. An event was considered to be an SAE if it was fatal, was life-threatening, required hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect, or was a significant medical hazard. EMIs included malignancies (including basal cell and squamous cell carcinomas); tuberculosis; opportunistic infections treated with intravenous therapy; histoplasmosis and coccidioidomycosis infections treated with oral antibiotics; central nervous system demyelinating disorders; lupus disease; coronary artery disease; and worsening of psoriasis (change in psoriasis morphology and withdrawal of therapy). An EMI was considered to be an SAE if additional criteria such as death or hospitalization occurred. Effectiveness outcomes included changes in psoriasis-affected body surface area (BSA), physician global assessment (PGA) score,[5] and Dermatology Life Quality Index score.[6]

External context analysis

Incidence rates of all malignancies (excluding nonmelanoma skin cancer [NMSC]), lymphoma, NMSC, and infectious events leading to hospitalization were assessed in relation to corresponding rates from the Truven Health MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental databases using incidence rates based on person-time of observation for malignancy outcomes and person-time of exposure for the hospitalized infections. MarketScan databases collect enrollment data, medical claims, and laboratory and prescription data. For this analysis, MarketScan patients were aged 18 years or older and 90 years or younger; met the qualifying criteria between January 1, 2006, and December 31, 2006 (enrollment window); and had 12 months of continuous enrollment before their index date to describe their medical and treatment history (baseline period). The primary comparator analysis was with patients in MarketScan who received nonbiologic systemic therapies (methotrexate, cyclosporine); additional analyses were conducted with patients receiving etanercept, phototherapy, other biologic therapies, methotrexate only, all patients with psoriasis, and the general population. Incidence rates from MarketScan were calculated and age- and sex-standardized to the OBSERVE-5 population for each outcome of interest. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated using MarketScan rates as the reference.

Statistical considerations

A study size of 2500 patients was required by the Food and Drug Administration. No statistical hypothesis was tested in this observational study. Descriptive statistics are provided for baseline characteristics and outcome measures. The primary analysis of safety end points was performed using Kaplan-Meier methodology. Cumulative incidences were calculated using 2 methods: first, by including all time from first dose of etanercept to start date of the first event occurrence, regardless of the pattern of etanercept exposure (observation time); and second, by excluding time intervals and corresponding events when the patient was not on etanercept (exposure time). For EMIs, survival estimates were adjusted using left truncation methodology to address potential survival bias introduced by the inclusion of patients with prior etanercept exposure. It was assumed that patients with prior etanercept exposure who had experienced rare events or malignancies would have permanently discontinued treatment and would not have qualified to enter the study. The left truncation technique accounts for this conditional sampling. For example, a patient with 2 years of prior exposure before entering the registry would begin follow-up in his or her third year since becoming exposed; for such a patient, an event in the second year of being followed up in the registry would be counted as an event in the fourth year since starting exposure.

RESULTS

Patients

This study was conducted at 375 sites (37 Canada, 338 United States). A total of 2511 patients enrolled in OBSERVE-5 of whom 2510 received 1 or more doses of etanercept; 1326 enrolled after the amendment allowing prior etanercept exposure. In all, 664 (26%)

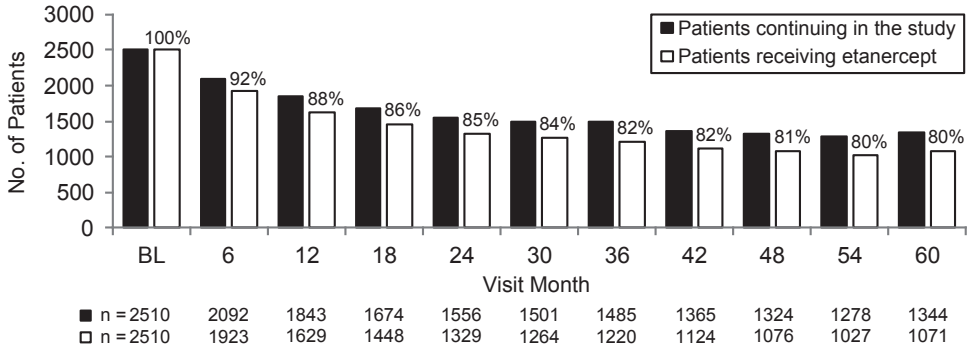

Fig 1. Plaque psoriasis. Etanercept status by visit. The number of patients remaining in the study (*black bars*) and those who remained on etanercept therapy (*white bars*) throughout the 5-year study is shown. *BL*, Baseline.

patients had prior etanercept exposure before enrolling in OBSERVE-5 and 1846 (74%) patients were etanercept-naïve on enrollment. Baseline characteristics have been previously described.[4] Of all patients, 1455 (58.0%) continued in the study until the end of follow-up, 1042 (41.5%) discontinued before the end of follow-up, and 13 patients did not have discontinuation status because of early site closure. At each study visit, 80% or more of patients who continued on study also continued on etanercept (Fig 1). A total of 164 patients received etanercept continuously without interruption throughout the study, 182 received etanercept throughout the study with 1- to 30-day gaps (mean 16 total gap days) in etanercept therapy, and 63 received etanercept throughout the study with 31- to 60-day gaps (mean 58 total gap days) in etanercept therapy. Of the patients who experienced gaps in etanercept therapy, most had only 1 or 2 treatment gaps.

Serious adverse events

A total of 418 patients, on and off etanercept, reported an SAE during the study (Table I). The most commonly reported noninfectious SAEs were myocardial infarction (0.7% of patients), coronary artery disease (0.6%), and osteoarthritis (0.6%) and the most common SIEs were pneumonia (1.2%) and cellulitis (0.9%). In all, 55 patients had a fatal event; of these, 17 were of unknown cause. Four deaths were considered by the investigator to be related to etanercept: brain cancer and lung cancer, heart failure, osteomyelitis and sepsis, and idiopathic pulmonary fibrosis. The 5-year Kaplan-Meier cumulative incidence of SAEs based on observation time was 22.2% (95% CI 20.3%-24.2%) and the incremental yearly incidence (data not shown) decreased during the study (Table II).

Serious infectious events

A total of 120 patients reported 1 or more SIEs and 94 patients reported an SIE leading to hospitalization (Table I). The 5-year Kaplan-Meier cumulative incidence for SIEs based on observation time was 6.5% (95% CI 5.4%-7.7%) and the incremental yearly incidence (data not shown) generally decreased over time (Table II). The 5-year Kaplan-Meier cumulative incidence for SIEs requiring hospitalization was 5.2% (95% CI 4.1%-6.2%).

Events of medical interest

A total of 604 patients had 1 or more EMIs (Table I), including 159 patients with an EMI that was considered by the investigator to be related to etanercept. The 5-year Kaplan-Meier cumulative incidences based on observation time were 0.1% (95% CI 0.0%-0.3%) for tuberculosis (n = 2); 0.2% (95% CI 0.0%-0.4%) for central nervous system demyelinating disorder (n = 3); 0.1% (95% CI 0.0%-0.2%) for lupus disease and for opportunistic infections (n = 1 each); 2.8% (95% CI 2.0%-3.6%) for coronary artery disease (n = 46); and 0.7% (95% CI 0.3%-1.2%) for worsening of psoriasis (n = 12). No case of histoplasmosis or coccidioidomycosis was reported. The 5-year Kaplan-Meier cumulative incidences based on observation time were 3.21% (95% CI 2.34%-4.08%) for malignancy excluding NMSC; 3.60% (95% CI 2.69%-4.50%) for NMSC; and 0.12% (95% CI 0.0%-0.29%) for lymphoma (Table III).

External context

For the outcomes of malignancies excluding NMSC, lymphoma, and NMSC, incidence rates for registry patients were not higher than the rates of the psoriasis population using nonbiologic systemic therapies (primary comparator) or those receiving etanercept in the MarketScan database (Table IV). Incidence rates of SIEs requiring hospitalization in OBSERVE-5

Table I. Summary of serious adverse events, serious infectious events, and event of medical interest

	All patients (N = 2510)
SAEs, patients reporting event, n (%)	418 (16.7)
Most common treatment-emergent SAEs, n (%)	
Pneumonia	30 (1.2)
Cellulitis	22 (0.9)
Myocardial infarction	17 (0.7)
Coronary artery disease	14 (0.6)
Osteoarthritis	14 (0.6)
Diverticulitis	11 (0.4)
Most common treatment-related SAEs, n (%)	
Pneumonia	8 (0.3)
Cellulitis	8 (0.3)
SIEs, patients reporting event, n (%)	120 (4.8)
Most common treatment-emergent SIEs, n (%)	
Pneumonia	30 (1.2)
Cellulitis	22 (0.9)
Diverticulitis	11 (0.4)
Staphylococcal infection	7 (0.3)
Sepsis	5 (0.2)
Appendicitis	4 (0.2)
Bronchitis	4 (0.2)
Herpes zoster	4 (0.2)
SIEs leading to hospitalization, n (%)	94 (3.7)
Pneumonia	28 (1.1)
Cellulitis	19 (0.8)
Diverticulitis	8 (0.3)
Sepsis	5 (0.2)
Appendicitis	4 (0.2)
Gastroenteritis	3 (0.1)
Staphylococcal infection	3 (0.1)
EMIs, patients reporting event, n (%)	604 (24.1)
Select EMIs, n (%)	
Malignancy	122 (4.9)
NMSC	66 (2.6)
Coronary artery disease	49 (2.0)
Worsening of psoriasis	13 (0.5)
CNS demyelinating disorder	3 (0.1)
Lymphoma	2 (0.1)
Tuberculosis	2 (0.1)
Lupus disease	1 (< 0.1)
Opportunistic infection	1 (< 0.1)
Coccidioidomycosis	0
Histoplasmosis	0

Includes events counted beyond year 5 because of left truncation adjustment in Kaplan-Meier analyses.
Includes patients on and off etanercept.
CNS, Central nervous system; *EMIs*, events of medical interest; *NMSC*, nonmelanoma skin cancer; *SAEs*, serious adverse events; *SIEs*, serious infectious events.

were not higher than the rates from the primary external comparator group based on patient-years of etanercept exposure (SIR 0.34; 95% CI 0.26-0.43).

Effectiveness outcomes

Mean baseline psoriasis-affected BSA was 12% and 24% for patients receiving prior etanercept and etanercept-naïve patients, respectively. Mean psoriasis-affected BSA improved from 21% at baseline to 8% at month 6, and remained stable throughout 5 years (Fig 2, *A*). At baseline, 37% and 3% of patients who had received prior etanercept and etanercept-naïve patients, respectively, had PGA status of clear/almost clear (score of 0 or 1). The percentage of all patients with PGA status of clear/almost clear was 12% at baseline, which increased to 51% at month 6 and remained relatively stable throughout 5 years (Fig 2, *B*). Mean Dermatology Life Quality Index scores at baseline were 6.1 (SD 6.3) and 12.5 (SD 6.9) for patients who had received prior etanercept and etanercept-naïve patients, respectively. The mean score for all patients at baseline was 10.8 (SD 7.3), which improved to 4.4 (SD 5.1) at month 6 and remained stable throughout 5 years (Fig 2, *C*).

DISCUSSION

This assessment of long-term safety of etanercept in patients with plaque psoriasis found that Kaplan-Meier cumulative incidences of SAEs, SIEs, and SIEs requiring hospitalization were low and incremental yearly incidences decreased during the 5 years of the registry. Using MarketScan data to provide age- and sex-standardized expected incidence rates, observed rates of malignancies, lymphomas, NMSC, and infections requiring hospitalization in OBSERVE-5 were not higher than expected. Patients who had received prior etanercept had generally better baseline mean scores for BSA, PGA, and Dermatology Life Quality Index assessments compared with patients who were etanercept-naïve at study entry. Both groups had improvements from baseline in these assessments, and by month 6, the 2 groups were similar. The proportion of patients with PGA status of clear/almost clear after month 6 was approximately 45% to 50% in patients with and without prior etanercept exposure, which was higher than the rate seen with etanercept monotherapy in a large, real-world, cross-sectional study (34%).[7] Patients with up to 60-day gaps in etanercept therapy demonstrated similar effectiveness as patients who remained on continuous etanercept therapy.

The results for SAEs and SIEs in OBSERVE-5 were similar to those reported in an integrated analysis of safety, which examined data from 7 clinical trials that lasted up to 2 years.[8] In that analysis, rates of SAEs and SIEs were comparable between placebo and etanercept groups in short-term studies, and no

Table II. Kaplan-Meier incidence proportions of serious adverse events and serious infectious events

	Based on observation time*		Based on exposure time†	
Registry year	**Patients with event, n**	**Cumulative incidence, Q (95% CI)**	**Patients with event, n**	**Cumulative incidence, Q (95% CI)**
SAEs				
First year	139	0.0633 (0.0531-0.0735)	121	0.0581 (0.0480-0.0682)
Second year	103	0.1163 (0.1024-0.1301)	75	0.1070 (0.0926-0.1215)
Third year	70	0.1557 (0.1397-0.1718)	37	0.1386 (0.1215-0.1558)
Fourth year	53	0.1878 (0.1703-0.2054)	35	0.1771 (0.1565-0.1977)
Fifth year	51	0.2224 (0.2031-0.2417)	19	0.2029 (0.1799-0.2260)
SIEs				
First year	45	0.0204 (0.0145-0.0263)	39	0.0184 (0.0127-0.0242)
Second year	25	0.0334 (0.0257-0.0411)	18	0.0301 (0.0222-0.0379)
Third year	17	0.0432 (0.0343-0.0521)	12	0.0408 (0.0310-0.0506)
Fourth year	13	0.0514 (0.0415-0.0613)	5	0.0467 (0.0356-0.0577)
Fifth year	20	0.0650 (0.0536-0.0765)	8	0.0581 (0.0447-0.0716)

CI, Confidence interval; *SAEs*, serious adverse events; *SIEs*, serious infectious events.
*Includes all events and exposure days that occurred since the first day of treatment with etanercept.
†Includes only events that occurred during etanercept exposure plus a 30-day risk window after each dosing interval.

Table III. Kaplan-Meier incidence proportions of malignancies

	Based on observation time*		Based on exposure time†	
Registry year	**Patients with event, n**	**Cumulative incidence, Q (95% CI)**	**Patients with event, n**	**Cumulative incidence, Q (95% CI)**
All malignancies excluding NMSC				
First year	7	0.0041 (0.0011-0.0072)	7	0.0033 (0.0004-0.0061)
Second year	12	0.0115 (0.0064-0.0167)	8	0.0090 (0.0039-0.0141)
Third year	15	0.0208 (0.0139-0.0277)	10	0.0156 (0.0085-0.0226)
Fourth year	6	0.0244 (0.0169-0.0319)	7	0.0230 (0.0142-0.0319)
Fifth year	11	0.0321 (0.0234-0.0408)	5	0.0304 (0.0195-0.0413)
Sixth year	7	0.0475 (0.0332-0.0617)	0	0.0304 (0.0195-0.0413)
Seventh year	1	0.0509 (0.0352-0.0666)	0	0.0304 (0.0195-0.0413)
Eighth year	1	0.0574 (0.0373-0.0775)	0	0.0304 (0.0195-0.0413)
Lymphoma				
First year	1	0.0006 (0.0000-0.0018)	1	0.0007 (0.0000-0.0020)
Second year	0	0.0006 (0.0000-0.0018)	0	0.0007 (0.0000-0.0020)
Third year	1	0.0012 (0.0000-0.0029)	1	0.0016 (0.0000-0.0040)
Fourth year	0	0.0012 (0.0000-0.0029)	0	0.0016 (0.0000-0.0040)
Fifth year	0	0.0012 (0.0000-0.0029)	0	0.0016 (0.0000-0.0040)
Sixth year	0	0.0012 (0.0000-0.0029)	0	0.0016 (0.0000-0.0040)
Seventh year	0	0.0012 (0.0000-0.0029)	0	0.0016 (0.0000-0.0040)
NMSC				
First year	13	0.0075 (0.0035-0.0116)	20	0.0069 (0.0028-0.0109)
Second year	14	0.0162 (0.0101-0.0222)	15	0.0158 (0.0092-0.0223)
Third year	10	0.0223 (0.0152-0.0295)	12	0.0254 (0.0165-0.0342)
Fourth year	18	0.0333 (0.0246-0.0419)	9	0.0352 (0.0244-0.0460)
Fifth year	4	0.0360 (0.0269-0.0450)	0	0.0352 (0.0244-0.0460)
Sixth year	4	0.0447 (0.0321-0.0573)	0	0.0352 (0.0244-0.0460)
Seventh year	3	0.0551 (0.0380-0.0723)	0	0.0352 (0.0244-0.0460)

Kaplan-Meier analyses of malignancies included left truncation adjustment for patients with prior etanercept exposure and therefore include follow-up time from etanercept exposure before the registry.
CI, Confidence interval; *NMSC*, nonmelanoma skin cancer.
*Includes all events and exposure days that occurred since the first day of treatment with etanercept.
†Includes only events that occurred during etanercept exposure plus a 30-day risk window after each dosing interval.

dose-related increases in these events were observed in either short- and long-term analyses. In addition, cumulative event rates for SIEs did not differ importantly across dose groups or over time. In an analysis of 49 clinical trials across etanercept indications, rates of SIEs were similar between patients receiving etanercept and control subjects. In that analysis, 49 SIEs were reported in 4361 patients with psoriasis for

Table IV. Standardized incidence ratios based on observed rates from OBSERVE-5 and expected rates from MarketScan

MarketScan comparator group, SIR (95% CI)	Malignancy excluding NMSC*	Lymphoma*	NMSC*	Infectious event requiring hospitalization†
Patients receiving nonbiologic systemic therapies	0.78 (0.59-1.00)	0.26 (0.03-0.95)	0.54 (0.42-0.69)	0.34 (0.26-0.43)
Patients receiving etanercept	0.89 (0.68-1.15)	0.50 (0.06-1.80)	0.58 (0.45-0.74)	0.51 (0.39-0.66)
Patients receiving phototherapy	0.74 (0.57-0.96)	0.14 (0.02-0.52)	0.54 (0.42-0.69)	0.41 (0.32-0.53)
Patients receiving other biologic therapies	0.97 (0.74-1.25)	0.36 (0.04-1.29)	0.46 (0.36-0.58)	0.29 (0.22-0.37)
Patients receiving methotrexate	0.78 (0.60-1.00)	0.28 (0.03-1.00)	0.55 (0.43-0.70)	0.36 (0.27-0.46)
Patients with psoriasis	0.81 (0.61-1.04)	0.28 (0.03-1.02)	0.62 (0.48-0.79)	NA
General MarketScan population‡	0.95 (0.72-1.22)	0.46 (0.06-1.67)	0.95 (0.73-1.20)	NA

Incidence rates from MarketScan were age- and sex-standardized to the OBSERVE-5 population.
CI, Confidence interval; *NA*, not applicable; *NMSC*, nonmelanoma skin cancer; *SIRs*, standardized incidence ratios.
*Analysis based on patient-years of observation.
†Analysis based on patient-years of exposure.
‡Comprised all insured individuals who met the eligibility criteria.

an exposure-adjusted rate of 1.24 events per 100 patient-years.[9] A meta-analysis of 20 randomized, controlled trials in patients with psoriatic diseases (including 14 trials in patients with psoriasis) reported an odds ratio of 0.78 (95% CI 0.38-1.58) for serious infections in patients with psoriasis treated with a TNF blocker versus placebo and an odds ratio of 1.14 (95% CI 0.92-1.40) for overall infections in patients treated with etanercept versus control.[10] In the 3-year interim analysis of OBSERVE-5[4] and the final 5-year results reported here, greater etanercept exposure was not associated with increased rates of SAEs or SIEs. Although SIEs are rare events in patients with psoriasis, physicians should screen patients for infections before initiating etanercept and monitor them during therapy.[11]

Prior studies have suggested that patients with psoriasis may be at increased risk of malignancy,[12] particularly NMSC[12] and lymphoma,[13] although the overall risk remains low and the magnitude of association is modest.[13] Psoriasis severity is proportional to the risk of developing NMSC.[12] In an integrated analysis of safety of 7 clinical trials of etanercept, there was no increase in overall malignancies with etanercept therapy compared with the psoriasis population.[8] In an analysis of 49 clinical trials across indications, the rate ratio for NMSC comparing etanercept with placebo in patients with psoriasis was 2.77 (95% CI 0.59-25.97).[9] The SIR for lymphoma in these trials was 2.01 (95% CI 0.24-7.27) in patients with psoriasis compared with Surveillance Epidemiology and End Results data.[9] In addition, patients with psoriasis who received etanercept appeared to have higher risk of squamous cell carcinomas.[9] The meta-analysis of randomized, controlled trials in patients with psoriasis or psoriatic arthritis receiving TNF blockers showed no increased risk of malignancy.[10] In OBSERVE-5, rates of malignancies, NMSCs, and lymphomas were not higher than expected relative to data from MarketScan.

In contrast to previous phase-III studies, which had stringent eligibility criteria and excluded patients with medically significant underlying diseases and/or were concomitantly taking certain antipsoriatic medications, enrollment in OBSERVE-5 was based on the clinical decision by investigators to continue, initiate, or resume treatment with etanercept. Therefore, this surveillance registry did not exclude patients for comorbidities or concomitant medications, representing real-world use of etanercept.

A limitation of the study was lack of an internal comparator. In the absence of a placebo arm, conclusions about efficacy are less reliable; however, in large placebo-controlled clinical studies of similar populations, usually less than 10% of subjects achieve a status of clear or almost clear with placebo alone. In addition, the size and duration of the study may not have been sufficient to detect extremely rare adverse events that may be related to treatment. Interpretation of SIRs should consider differences in data collection methods, sampling designs, and study populations in a prospective registry versus an administrative claims database compiled for billing purposes. Interpretation of safety and

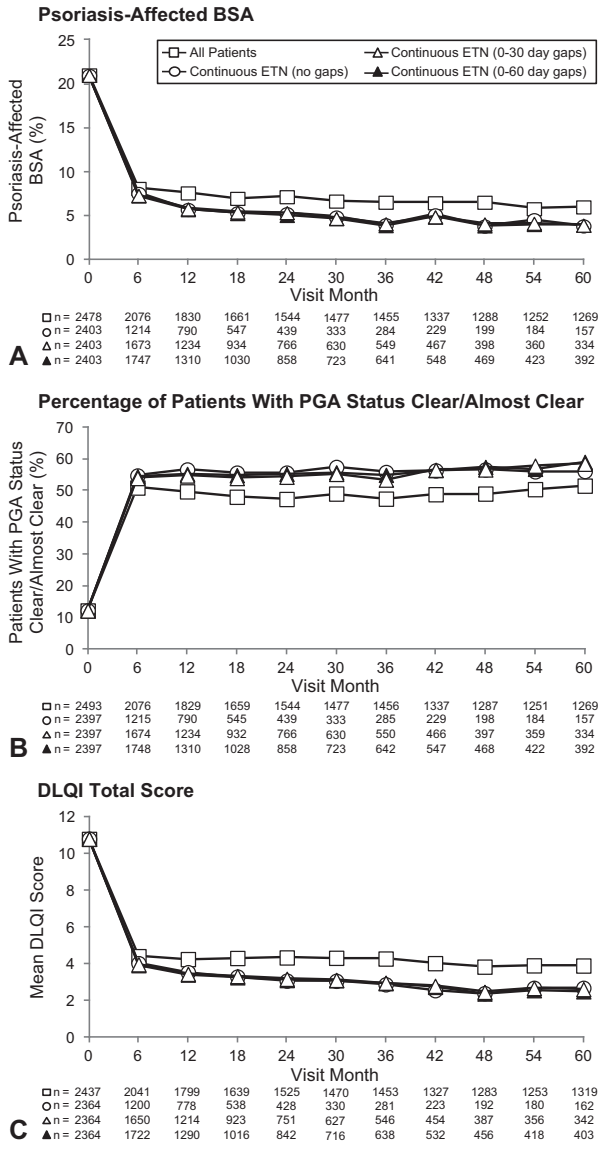

Fig 2. Plaque psoriasis. Effectiveness outcomes. The percentage of psoriasis-affected body surface area (*BSA*) (**A**); percentage of patients with physician global assessment (*PGA*) status of clear/almost clear (score 0/1) (**B**); and mean Dermatology Life Quality Index (*DLQI*) total score (**C**) for all patients (*squares*), patients on continuous etanercept (*ETN*) (*circles*), and patients on ETN who had a 0- to 30-day (*open triangles*) or 0- to 60-day (*closed triangles*) gap in therapy. Data are presented as observed without imputation for missing data.

effectiveness-related outcomes should take into account the 42% dropout rate, which may lead to an underestimation of safety events and an overestimation of effectiveness if discontinuation was related to these outcomes.

In summary, no new or unexpected safety signal was observed in this 5-year observational study. Rates of malignancies, lymphomas, NMSC, and infections requiring hospitalization in OBSERVE-5 were not higher than expected relative to data from MarketScan.

Julia R. Gage, PhD (on behalf of Amgen Inc), and Dikran Toroser, PhD (Amgen Inc), assisted with writing and editing the manuscript.

REFERENCES

1. Enbrel (etanercept) [prescribing information]. Thousand Oaks, CA: Immunex Corp; 2013.
2. Papp KA, Poulin Y, Bissonnette R, Bourcier M, Toth D, Rosoph L, et al. Assessment of the long-term safety and effectiveness of etanercept for the treatment of psoriasis in an adult population. J Am Acad Dermatol 2012;66:e33-45.
3. 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 simple model for studying new psoriasis therapies. Psoriasis Forum 2010;16:3-7.
4. Kimball AB, Pariser D, Yamauchi PS, Menter A, Teller CF, Shi Y, et al. OBSERVE-5 interim analysis: an observational postmarketing safety registry of etanercept for the treatment of psoriasis. J Am Acad Dermatol 2013;68:756-64.
5. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005;64(Suppl):ii65-8.
6. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
7. Gelfand JM, Wan J, Callis Duffin K, Krueger GG, Kalb RE, Weisman JD, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol 2012;148:487-94.
8. 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.
9. Gottlieb AB, Gordon K, Giannini EH, Mease P, Li J, Chon Y, et al. Clinical trial safety and mortality analyses in patients receiving etanercept across approved indications. J Drugs Dermatol 2011;10:289-300.
10. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011;64:1035-50.
11. Papp KA, Dekoven J, Parsons L, Pirzada S, Robern M, Robertson L, et al. Biologic therapy in psoriasis: perspectives on associated risks and patient management. J Cutan Med Surg 2012;16:153-68.
12. Margolis D, Bilker W, Hennessy S, Vittorio C, Santanna J, Strom BL. The risk of malignancy associated with psoriasis. Arch Dermatol 2001;137:778-83.
13. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol 2006;126:2194-201.