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

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Abstract

Background—OBSERVE-5 was a 5-year FDA-mandated surveillance registry of psoriasis patients.

Objective—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 (SAEs), serious infectious events (SIEs), events of medical interest, psoriasis-affected body surface area, physician global assessment, and Dermatology Life Quality Index. Safety outcomes were assessed relative to data from the MarketScan database.

Results—For 2,510 patients, 5-year cumulative incidence (95% confidence interval [CI]) was 22.2% (20.3%, 24.2%) for SAEs; 6.5% (5.4%, 7.7%) for SIEs; 3.2% (2.3%, 4.1%) for malignancies excluding nonmelanoma skin cancer (NMSC); 3.6% (2.7%, 4.5%) for NMSC; 2.8% (2.0%, 3.6%) for coronary artery disease; 0.7% (0.3%, 1.2%) for psoriasis worsening; 0.2% (0.0%, 0.4%) for CNS demyelinating disorder; 0.1% (0.0%, 0.3%) for lymphoma and for tuberculosis; 0.1% (0.0%, 0.2%) for opportunistic infection and for lupus; 55 fatal events were reported. Rates of malignancies, lymphomas, NMSC, 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.

Keywords

etanercept; plaque psoriasis; surveillance registry; safety; adverse events; infections; malignancy

INTRODUCTION

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 (RA), 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 two phase 3 clinical trials showed a favorable safety profile, with no cumulative toxicity noted for up to 4 years of treatment.[2]

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 2,510 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 4, 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 US or December 2005 in Canada (when etanercept was approved for 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, life-threatening, required hospitalization, resulted in disability/ incapacity, was a congenital anomaly/birth defect, or other 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 (CNS) 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),[5] and Dermatology Life Quality Index (DLQI).[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 ≥18 and ≤90 years of age, met the qualifying criteria between 1/1/2006 and 12/31/2006 (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 2,500 patients was required by the FDA. No statistical hypothesis was tested in this observational study. Descriptive statistics are provided for baseline characteristics and outcome measures. The primary analysis of safety endpoints 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 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 US). A total of 2,511 patients enrolled in OBSERVE-5 of which 2,510 received ≥1 dose of etanercept; 1,326 enrolled after the amendment allowing prior etanercept exposure. Six hundred sixty-four (26%) patients had prior etanercept exposure before enrolling in OBSERVE-5 and 1,846 (74%) patients were etanercept-naïve on enrollment. Baseline characteristics have been previously

described.[4] Of all patients, 1,455 (58.0%) continued in the study until the end of follow-up, 1,042 (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% of patients who continued on study also continued on etanercept (Figure 1). A total of 164 patients received etanercept continuously without interruption throughout the study, 182 received etanercept throughout the study with 1–30 day gaps (mean 16 total gap days) in etanercept therapy, and 63 received etanercept throughout the study with 31–60 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.

SAEs

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) and coronary artery disease (0.6%), and osteoarthritis (0.6%) and the most common SIEs were pneumonia (1.2%) and cellulitis (0.9%). Fifty-five 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 (95% CI) of SAEs based on observation time was 22.2% (20.3%, 24.2%) and the incremental yearly incidence (data not shown) decreased during the study (Table II).

SIEs

A total of 120 patients reported ≥1 SIE and 94 patients reported an SIE leading to hospitalization (Table I). The 5-year Kaplan-Meier cumulative incidence (95% CI) for SIEs based on observation time was 6.5% (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 (95% CI) for SIEs requiring hospitalization was 5.2% (4.1%, 6.2%).

EMIs

A total of 604 patients had ≥1 EMI (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 (95% CI) based on observation time were 0.1% (0.0%, 0.3%) for tuberculosis (n=2); 0.2% (0.0%, 0.4%) for CNS demyelinating disorder (n=3); 0.1% (0.0%, 0.2%) for lupus disease and for opportunistic infections (n=1 each); 2.8% (2.0%, 3.6%) for coronary artery disease (n=46); and 0.7% (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 (95% CI) based on observation time were 3.21% (2.34%, 4.08%) for malignancy excluding NMSC; 3.60% (2.69%, 4.50%) for NMSC; and 0.12% (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 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 (Figure 2A). 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 (Figure 2B). Mean (standard deviation [SD]) DLQI scores at baseline were 6.1 (6.3) and 12.5 (6.9) for patients who had received prior etanercept and etanercept-naïve patients, respectively. The mean (SD) score for all patients at baseline was 10.8 (7.3), which improved to 4.4 (5.1) at month 6 and remained stable throughout 5 years (Figure 2C).

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 DLQI 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%–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 dose-related increases in these events were observed in both short- and long-term analyses. Additionally, cumulative event rates for SIEs did not differ importantly across dose groups and over time. In an analysis of 49 clinical trials across etanercept indications, rates of SIEs were similar between patients receiving etanercept and controls. In that analysis, 49 SIEs were reported in 4,361 psoriasis patients for 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 psoriasis patients) reported an odds ratio (OR) of 0.78 (95% CI: 0.38, 1.58) for serious

infections in psoriasis patients treated with a TNF blocker vs placebo and an OR (95% CI) of 1.14 (0.92, 1.40) for overall infections in patients treated with etanercept vs 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 psoriasis patients, 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 to placebo in psoriasis patients 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 psoriasis patients compared with Surveillance Epidemiology and End Results (SEER) data.[9] Additionally, psoriasis patients 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 3 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. Additionally, 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 vs an administrative claims database compiled for billing purposes. Interpretation of safety and effectiveness-related outcomes should take into account the 42% drop-out 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.

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ABBREVIATIONS

BSA	body surface area
CI	confidence interval
CNS	central nervous system
DLQI	Dermatology Life Quality Index
EMI	event of medical interest
FDA	Food & Drug Administration
NMSC	nonmelanoma skin cancer
OR	odds ratio
PGA	physician global assessment
RA	rheumatoid arthritis
SAE	serious adverse event
SD	standard deviation
SEER	Surveillance Epidemiology and End Results
SIE	serious infectious event
SIR	standardized incidence ratio
TNF	tumor necrosis factor

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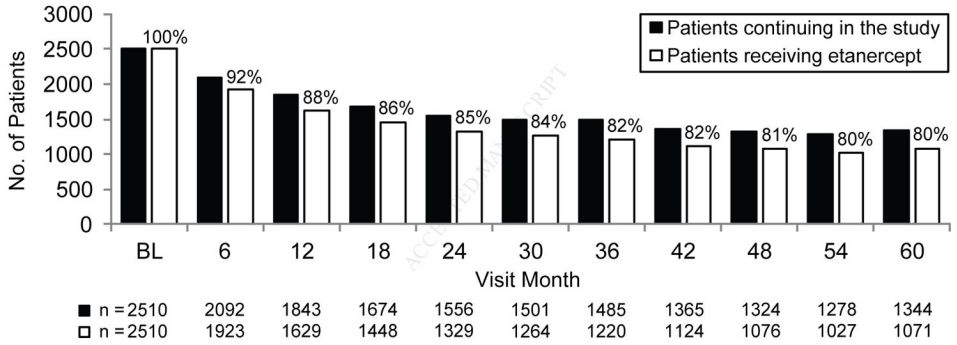

Figure 1.

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.

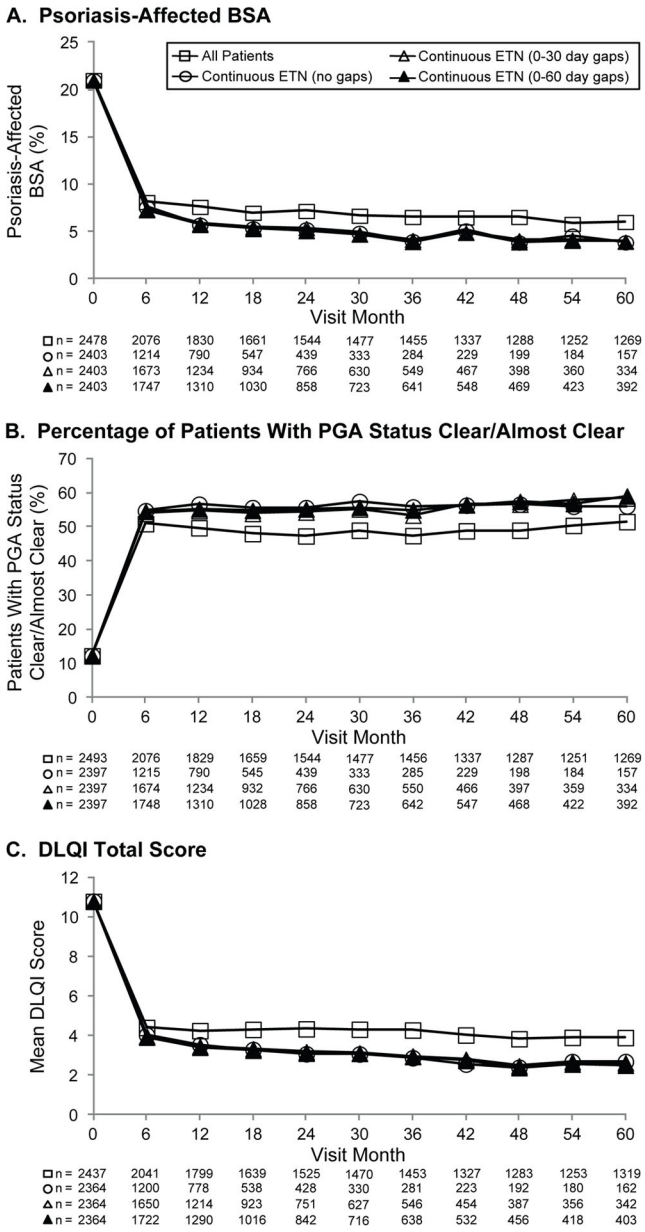

Figure 2.

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

Table I

Summary of SAEs, SIEs, and EMIs[*†]

	All Patients (N = 2510)
SAEs, patients reporting event (%)	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)

	All Patients (N = 2510)
Opportunistic infection	1 (< 0.1)
Coccidioidomycosis	0
Histoplasmosis	0

* Includes events counted beyond year 5 due to left truncation adjustment in Kaplan-Meier analyses.

† Includes patients on and off etanercept

SAEs, serious adverse events; SIEs, serious infectious events; EMIs, events of medical interest; NMSC, nonmelanoma skin cancer; CNS, central nervous system.

Table II

Kaplan-Meier incidence proportions of SAEs and SIEs

	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)

*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.

SAEs, serious adverse events; SIEs, serious infectious events; CI, confidence interval.

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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.

† 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.

NMSC, nonmelanoma skin cancer; CI, confidence interval.

Table IV

SIRs 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.

†Analysis based on patient-years of observation.

‡Analysis based on patient-years of exposure.

§The general MarketScan population comprised all insured individuals who met the eligibility criteria.

SIRs, standardized incidence ratios; CI, confidence interval; NMSC, nonmelanoma skin cancer; NA, not applicable.

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