# Biologic Safety in Psoriasis

## Review of Long-Term Safety Data

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**ABSTRACT**

The development of targeted biologic agents has revolutionized the treatment of psoriasis. In this review, the authors focus on the published long-term (≥ one year) safety data for the use of tumor necrosis factor-α antagonists etanercept, infliximab, and adalimumab, as well as the IL-12/IL-23 antagonist ustekinumab, in adult patients with moderate-to-severe psoriasis. The efficacy of these currently available biologic therapies has been demonstrated in several studies, and their safety profiles are also reassuring. (*J Clin Aesthet Dermatol.* 2015;8(2):30–42.)

Psoriasis is a chronic immune-mediated inflammatory disorder with a prevalence of one to three percent of the world population.[1–3] Up to 40 percent also have joint involvement,[4] and an association with cardiovascular disease is increasingly recognized.[5] Conventional systemic treatments, such as methotrexate, cyclosporine A, acitretin, and fumaric acid esters (mostly used in Germany) can be associated with loss of efficacy, side effects, and organ-specific toxicity.[6]

Over the last decade, the introduction of biologic therapies targeting selective key immune pathways has revolutionized the management of patients with moderate-to-severe disease, and these newer drugs are now the mainstay of systemic treatment for psoriasis. These biologic agents have demonstrated high efficacy and a favorable safety profile without evidence of cumulative organ-specific toxicity. Biologic treatments currently approved for the management of moderate-to-severe psoriasis in the United States and Europe can be classified into the following two main categories: the tumor necrosis factor (TNF)-α inhibitors etanercept, infliximab, and adalimumab, and the interleukin (IL)-12/23p40 inhibitor ustekinumab.

TNF-α inhibitors are potent immunosuppressants and can potentially increase the risk of infections and malignancy, particularly in patients with rheumatoid arthritis and inflammatory bowel disease. In a systematic review of available data in patients with psoriasis, Dommasch et al[7] concluded that there is a small increased risk of overall infections, but no evidence of an increased risk of serious infections or malignancy in this group of patients. Reactivation of latent tuberculosis (TB) is a known risk factor of TNF-α inhibitor therapy, as TNF-α is an important cytokine in preventing TB infection and in keeping latent TB infection from becoming active disease.[8] A review of five Phase 3 trials of ustekinumab did not identify any cases of latent TB reactivation in patients receiving concomitant prophylaxis for latent TB.[9]

Rare adverse events include lupus-like syndrome from autoantibody formation and exacerbation of demyelinating disorders. Over the past few years, it has become increasingly evident that chronic inflammatory diseases, such as rheumatoid arthritis and psoriasis, may be associated with an increased risk of cardiovascular disease.

Studies suggest that TNF-α inhibitors may reduce this risk. However, the exact mechanism and whether this risk is reduced significantly, remain unclear. There is further epidemiological evidence that systemic treatment of psoriasis and subsequent decrease in inflammation can reduce the risk of cardiovascular events.[10]

It is possible that they may prevent plaque rupture and improve endothelial function. The majority of available safety data from TNF-α inhibitors originates from clinical trials in rheumatology, since these agents were first approved for the treatment of rheumatological disease. Overall, studies of their effects on cardiovascular risk show mixed results.

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In a review of 22 randomized controlled trials (RCT) involving more than 10,000 patients, there was no significant difference in the rate of major adverse cardiac events—a composite endpoint of myocardial infarction (MI), stroke, or cardiovascular (CV) death (MACEs) observed in patients receiving anti–TNF-α treatments, anti–IL-12/IL-23 antibodies, or placebo.[11] In another recent review of the literature, the authors concluded that anti–TNF-α treatments may indeed reduce cardiovascular events in psoriatic patients, while IL-12/23 inhibitors appear to be neutral.[12]

This review focuses on the published safety data of randomized controlled studies and extension studies in which adult patients with moderate-to-severe plaque psoriasis were exposed to etanercept, adalimumab, infliximab, or ustekinumab for a minimum of one year.

## METHODS

A PubMed database search was conducted for English language publications from January 2007 to April 2014. The search strategy used MeSH and keyword headings, using the search string "psoriasis" AND ("biologics" OR "etanercept" OR "adalimumab" OR "infliximab" OR "ustekinumab") AND ("safety" OR "adverse events" OR "side effects"). Abstracts were then screened to identify relevant publications. Only studies in which adult subjects received a biologic agent for at least one year were included, and those studies in which subjects were treated with a combination of a biologic therapy and another systemic agent were excluded from this review. No statistical analysis or evidence grading was performed.

To allow comparison between the various studies, the incidence rates presented are based on patient years (PY) of exposure or observation (Igarashi et al #3 ustekinumab study). For calculations of incidence rates per patient-years of exposure/observation, all events that were reported during drug exposure/observation in the studies were included.

## LIMITATIONS

This review relies solely on the strict analysis and the results provided in the presented papers without any significant adjustments. The following describes the key limitations of the review:

- The data provided is inconsistent between the studies. In particular, differences exist in the doses and frequencies of drug administration.
- Certain studies were performed over a shorter period of time and using a relatively small sample size and therefore rare adverse events would not be captured.
- Not all studies made statistical adjustments of the data to address dropout events, missing data, etc., and thus their rates for adverse events (AEs) may be underestimated.
- Some authors do not describe their definitions used to classify AEs into severe versus non-severe, etc.
- Selected studies assess the significance of AE rates by comparison to expected rates in the general population, whereas others compare rates to those in other populations. Some results in the studies are not assessed for their statistical significance.
- The objectives of the studies ranged from efficacy and safety to comparison between biologic-naïve and non-naïve patients.

## PRESENTATION OF THE STUDIES

### Etanercept

Six studies were included covering patients from the United States, Canada, and Europe with the following key characteristics:

- The average age was consistently 46 years.
- Between 52 and 68 percent of subjects in the studies were men.
- The majority of subjects were Caucasian (82–96%).
- The number of participants in the studies varied between 230 to 2,511.
- Duration of these studies varied between 52 and 208 weeks.

**Detailed review.** Based on the average results:

- AE rates ranged from 57 to 274 per 100 PY.
- Serious adverse event (SAE) rates ranged from 7 to 9 per 100 PY.
- Serious infectious event rates ranged from 0.9 to 1.6 per 100 PY.
- Death occurred at a rate of 0.1 to 0.5 per 100 PY.
- Nonmelanoma skin cancer (NMSC) occurred at rates of 0.5 to 1.3 per 100 PY.
- TB occurred in one study only.
- There were no reported cases of demyelination in these studies.

**Study 1.** In a post-authorization, prospective, multicenter study at 59 dermatology units in Spain, 444 patients were treated with etanercept and were followed up for 12 months.[13] Of the 444 patients, 21.6 percent received the drug as a continuous regimen for 12 months and 79.4 percent as an intermittent regimen; 79.7 percent of patients completed the study period of 12 months.

Exposure-adjusted AE rates, expressed as the number of AEs per 100 PY of treatment (events/100 PY) were 56.8 for AEs and 7.0 for SAEs. Infectious events were seen in 15.1 per 100 patient years. The most common infections involved the respiratory tract (7.4 per 100 PY) and urinary tract (1.6 per 100 PY).

Exposure-adjusted rates were 1.4 per 100 PY for malignancies, 0.5 per 100 PY for NMSC, and 0.1 per 100 PY for non-skin malignancies. Melanoma and lymphoma were seen in 0.2 per 100 PY. No opportunistic infections, tuberculosis, or demyelinating diseases were detected. The exposure-adjusted event rates for cardiovascular events and serious cardiovascular events were 0.5 per 100 PY and 0.2 per 100 PY, respectively. There were two deaths during the study (0.5 per 100 PY).

**Study 2.** Interim results of the first three years of a five-year observational Phase 4 cohort study (OBSERVE-5) at 375 sites in the United States and Canada showed that 1,890 (75%) of 2,511 patients enrolled continued in the registry

after three years.[14]

Exposure-adjusted rates for SAEs and serious infectious events were 5.2 per 100 PY and 1.46 per 100 PY, respectively. The most common serious infections were cellulitis and pneumonia, followed by diverticulitis and staphylococcal infection. Exposure-adjusted rates were 1.6 per 100 PY for malignancies and 0.6 per 100 PY for NMSC. Rates for tuberculosis and lymphoma were 0.2 and 0.1 per 100 PY, respectively. Demyelinating disease occurred in 0.8 per 100 PY. Exposure-adjusted rates for cardiovascular events were 0.4/PY, and death occurred at a rate of 0.4/100 PY.

**Study 3.** In another one-year, multicenter, open-label study of 230 patients in Canada, the exposure-adjusted event rate for all AEs was 186.5 per 100 PY.[15] The most common AEs were nasopharyngitis (9.7 per 100 PY), headache (9.2 per 100 PY), and upper respiratory tract infection (11.5 per 100 PY). Exposure-adjusted event rates for infectious AEs were 54.8 per 100 PY.

Exposure-adjusted rates were 8.3 per 100 PY for SAEs and 1.8 per 100 PY for malignancies. One death occurred during the study (0.4 per 100 PY), and due to lack of data, a causal relationship for this death could not be established. Malignancy rates were 1.8 per 100 PY, with 0.9 per 100 PY for NMSC. There were no reports of tuberculosis, lymphoma, or demyelinating disease.

**Study 4.** A prospective analysis of two Phase 3 trials and open-label extensions has allowed assessment of the safety profile of up to four years of etanercept treatment.[16] A total of 506 patients entered a Phase 3 trial; 208 of these were in a double-blind study and were randomized to receive either etanercept (25 or 50mg) or placebo twice weekly (BIW) for the first 12 weeks, followed by etanercept 25mg BIW for further 12 weeks.

Exposure-adjusted AE rates were 243.5 for AEs and 7.8 for SAEs. Infectious events were seen in 96.9/100 PY. The most common infections were nasopharyngitis (26.1 events/100 PY) and upper respiratory tract infection (14.9 events/100 PY).

Exposure-adjusted rates were 1.5 per 100 PY for malignancies, 0.6 per 100 PY for NMSC and 0.3 per 100 PY for non-skin malignancies. No cases of malignant melanoma, opportunistic infections, TB, or lymphoma were detected. The exposure-adjusted event rates for serious cardiovascular events were 1.7 per 100 PY. There were three deaths during the study (0.1 per 100 PY).

**Study 5.** Patients who had participated in one of two Phase 3, randomized, placebo-controlled studies of etanercept in the United States, Canada, and Europe were eligible to enter an open-label extension study. For the first 12 weeks, all patients received open-label etanercept 50mg once weekly (QW). Patients could then continue 50mg QW or increase the dose to BIW for 9 to 18 months.[17]

Exposure-adjusted event rates were 235.7/100 PY for AEs and 7.2/100 PY for SAEs. Infectious events were seen in 95.2/100 PY and serious infectious events in 1.6/100 PY.

Exposure-adjusted rates were 1.5/100 PY for malignancies, 0.8/100PY for NMSC and 0.3/100 PY for non-skin malignancies. Melanoma rates were 0.2/100 PY. No lymphoma, opportunistic infections, tuberculosis, or demyelinating diseases were detected. There was one death during the study (0.1/100PY).

**Study 6.** In another Phase 3 double-blind study with an open-label extension, patients were randomized to either 50mg of etanercept or placebo BIW for the first 12 weeks, and then 50mg etanercept BIW for both groups for a further 84 weeks.[18] A total of 618 patients were recruited at 39 medical centers in the United States and Canada. Of the 618 subjects, 598 received etanercept and were included in the safety analysis. Exposure-adjusted AE rates were 274.1 for AEs and 8.9 per 100 PY for serious SAEs. Infectious events were seen in 103.9 per 100 patient years and serious infectious events in 1.2 per 100 PY. The most common infections involved the upper respiratory tract (20.2 per 100 PY). Exposure-adjusted rates were 2.1/100 PY for malignancies, 1.3 per 100 PY for NMSCs and 0.8 per 100 PY for non-skin malignancies. Rates for lymphoma were 0.2 per 100 PY. No cases of melanoma, opportunistic infections, TB, or demyelinating disease were detected. There were two deaths during the study (0.2 per 100 PY).

Based on these data of up to four years of therapy, etanercept appears to be a well-tolerated treatment for patients with moderate-to-severe plaque psoriasis, with low AE rates as well as serious infectious events and lymphoma. While reactivation of TB is known to be associated with TNF antagonists, it appears to occur infrequently with etanercept.

**Adalimumab**

Three studies were included covering patients from the United States, Canada, and Netherlands with the following key characteristics:

- The average age was 44 to 49 years.
- Between 56 and 67 percent of subjects in the studies were men.
- The majority of subjects were Caucasian (91–93%).
- The number of participants in the studies ranged from 85 to 1,212.
- Duration of these studies varied between 1 to 3 years.

**Detailed review.** Based on the average results:

- AE rates ranged from 245 to 399 per 100 PY.
- SAE rates ranged from 6 to 23 per 100 PY.
- Serious infectious event rates ranged from 1.5 to 2 per 100 PY.
- Death occurred at a rate of 1 to 2 per 100 PY.
- NMSC occurred at rates of 0.8 to 1.9 per 100 PY.
- Rates of TB ranged from 0.1 to 0.2 per 100 PY.
- There were no reported cases of demyelination or lymphoma in these studies.

**Study 1.** In a prospective cohort study, 85 patients received a loading dose of 80mg adalimumab subcutaneously, then 40mg every other week starting one week after the loading dose.[19] If the treating dermatologist assessed the response as insufficient, the dose could be increased to 40mg weekly. Nineteen percent of patients were biologic-naïve and 81 percent had previously been

treated with at least one TNF-α-blocker. Fifty-four patients (64%) completed one year of adalimumab treatment, 25 patients (29%) completed two years, and one patient (1%) completed three years.

Exposure-adjusted AE rates were 23/100 PY for SAE and 1.9 for serious infectious events. One death occurred during the study, with a rate of 0.9/100 PY. NMSC occurred at 1.9/100 PY. The authors did not discuss the occurrence of TB, demyelination, or lymphoma.

**Study 2.** The efficacy and safety of adalimumab were evaluated in a Phase 3 randomized, controlled evaluation every other week dosing in moderate-to-severe psoriasis (REVEAL).[20,21] A total of 1,212 patients were randomized to adalimumab treatment consisting of 80mg loading dose followed by 40mg every other week starting one week after the first dose, or placebo, beginning at Week 1 through Week 15. At Week 16, patients who had achieved at least a Psoriasis Area and Severity Index (PASI) 75 response were switched to placebo if they had started on adalimumab or to 80mg adalimumab if they had started on placebo. Starting Week 17 and continuing until Week 31, all patients received open-label adalimumab (40mg every other week). Those patients who achieved PASI 75 at Week 33 and had been given the active drug at study initiation were randomized to receive either placebo or adalimumab 40mg every other week (eow) until Week 52. Exposure-adjusted event rates were 399/100 PY for AE and 6/100 PY for SAE. Infectious events occurred at a rate of 120/100 PY with serious infections at 2/100 PY. Rates for malignancies were 0.4/100 PY, including 1.3/100 PY for NMSC. TB occurred in 0.2/100 PY. There were no cases of demyelination, melanoma, or lymphoma.

**Study 3.** Patients enrolled in REVEAL later had the option to continue receiving adalimumab in an open-label extension study and receive 40mg adalimumab eow for a minimum of 108 weeks.[22] The rate of AEs was lower than in REVEAL and declined over time. The rate of serious infections was similar to REVEAL, while the rate of AEs leading to discontinuation was lower.

Exposure-adjusted event rates were 245.1/100 PY for all AE, 7.3/100 PY for SAEs, and 1.5/100 PY for serious infectious events. Rates for malignancies were 1.5/100 PY, including rates for NMSC at 0.8/100 PY. Two deaths occurred during the study (0.1/100 PY). Rates for TB and opportunistic infections were <0.1 per 100 PY and 0.2/100 PY, respectively. There were no reports of demyelinating disease, melanoma, or lymphoma.

These data suggest that adalimumab is generally well tolerated in patients with plaque psoriasis. However, there appears to be an increased risk of NMSCs requiring appropriate evaluation for these patients, and the rates for total AEs, infectious, and serious infectious events were higher in the adalimumab studies compared to the other biologic agents.

### Infliximab

Two studies were included covering patients from various countries with the following key characteristics:

- The average age in both studies was 46 years.
- 68 percent of subjects in both studies were men.
- The majority of subjects were Caucasian (77–98%).
- The number of participants in these studies were 441 and 660.
- The duration of one of the studies was 50 weeks for the treatment phase. While some patients continued for a total of 98 weeks, our review only includes data from the first study phase, as the number of subjects who completed the second phase was much lower. The second study was terminated early due to AEs.

**Detailed review.** Based on the average results:

- AE rates ranged from 29.8 to 37.9 per 100 PY.
- SAE rates ranged from 4.4 to 7.9 per 100 PY.
- Serious infectious event rates ranged from 1.8 to 2.4 per 100 PY.
- While there were no reported deaths in one study, death occurred at a rate of 0.6 per 100 PY in the second study.
- NMSC occurred at rates of 0.2 to 0.3 per 100 PY.
- Rates of TB ranged from 0 to 0.5 per 100 PY.
- There were no reported cases of demyelination or lymphoma in these studies.

**Study 1.** In a prospective, observational, open-label study, 659 patients received infliximab for plaque-type psoriasis at one of multiple centers in 14 countries (real-world assessment of long-term infliximab therapy for psoriasis [REALITY]).[23] Infliximab 5mg/kg was administered at Weeks 0, 2, and 6, followed by maintenance infusions every eight weeks for 50 weeks, and those achieving ≥25 percent PASI improvement from baseline to the end of the 50-week treatment phase were able to continue into an extended treatment phase. The results from the treatment phase (Weeks 0–52) showed exposure-adjusted event rates of 37.9/100 PY for all AE, 7.9/100 PY for SAE, and 2.4/100 PY for serious infectious events. The most common AEs in this phase were nasopharyngitis, pharyngitis, and upper respiratory tract infections.

Rates for malignancies were 0.6/100 PY, including NMSC at 0.3/100 PY. There were no reported cases of melanoma, lymphoma, or demyelination. Four deaths occurred during the study period, with a rate of 0.6/100 PY. Infusion-related reactions occurred at a rate of 7.7/100 PY.

**Study 2.** In RESTORE2, patients who had received infliximab for 26 weeks and achieved PASI75 in a comparison study of methotrexate and infliximab (RESTORE1) were randomized to continuous infliximab (5mg/kg every 8 weeks) or intermittent treatment (no infliximab until >50% loss of PASI improvement).[24] Two hundred twenty-two patients received continuous and 219 patients received intermittent therapy. The overall incidence and type of AEs were similar in both groups, with the exception of infusion-related reactions and serious infections. Infusion-related reactions were more common in the intermittent group (15 vs. 9%) with greater numbers of serious infusion-related reactions in that group (4 vs. 1%), leading the sponsor to terminate the study early. Data provided include calculations up to Week 100, as sample

| TABLE 1. Summary of studies | | |
|---|---|---|
| **TREATMENT** | **PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS** | **SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n)** |
| **Etanercept** | | |
| **Study 1**<br>Etanercept<br>Puig et al[13]<br>(Spain) | **Male:** 66%<br>**Mean age:** 46 y<br>**PASI at baseline:** 22<br>**PGA at time 0:** 3.2<br>**Mean duration of psoriasis:** 20.1 y | **Adverse events:** 56.8<br>**Serious adverse events:** 7.0<br>**Infectious events:** 15.1<br>**Serious infectious events:** not given<br>**Malignancies:** 1.4<br>**NMSC:** 0.5<br>**Death:** 0.5 (2)<br>**TB:** 0<br>**Opportunistic infections:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0.2 |
| **Study 2**<br>Etanercept<br>Kimball et al[14]<br>OBSERVE-5<br>(US, Canada) | **Male:** 52%<br>**Mean age:** 46 y<br>**Caucasian:** 82%<br>**BSA:** 20%<br>**PGA at time 0:** Moderate or worse<br>**Mean duration of psoriasis:** 16 y | **Adverse events:** 0.2<br>**Serious adverse events:** 5.2<br>**Serious infectious events:** 1.5<br>**Malignancies:** 1.6<br>**Deaths:** 0.4 (30)<br>**TB:** 0.2<br>**Demyelinating disease:** 0.8<br>**Lymphoma:** 0.1 |
| **Study 3**<br>Etanercept<br>Vender et al[15]<br>(Canada) | **Male:** 59 %<br>**Mean age:** 46 y<br>**Caucasian:** 93%<br>**Mean baseline BSA:** 27.6%<br>**PGA at time 0:**<br>**Mean duration of psoriasis:** 11.6 y | **Adverse events:** 186.5<br>**Serious adverse events:** 8.3<br>**Infectious events:** 54.8<br>**Serious infectious events:** 0.9<br>**Malignancies:** 1.8<br>**NMSC:** 0.9<br>**Deaths:** 0.4 (1)<br>**TB:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |

| TABLE 1 continued. Summary of studies | | |
|---|---|---|
| **TREATMENT** | **PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS** | **SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n)** |
| **Etanercept continued** | | |
| **Study 4**<br>Etanercept<br>Papp et al[16]<br>(Canada) | **Male:** 67%<br>**Mean age:** 46 y<br>**Caucasian:** 96%<br>**BSA:** 26%<br>**PGA at time 0:** (average 3.2 on a score from 0 to 5): Mild (13%), moderate (56%), marked (28%), severe (2%)<br>**Mean duration of psoriasis:** 21 y | **Adverse events:** 243.5<br>**Serious adverse events:** 7.8<br>**Serious infectious events:** 0.9<br>**Malignancies:** 1.5<br>**NMSC:** 0.5<br>**Death:** 0.1 (3)<br>**TB:** 0<br>**Demyelinating disease:** not mentioned<br>**Lymphoma:** 0 |
| **Study 5**<br>Etanercept<br>Leonardi et al[17]<br>US, Canada, Europe | **Male:** 68%<br>**Mean age:** 46 y<br>**Caucasian:** 88%<br>**Mean PASI at baseline:** 19<br>**PGA marked or severe:** 26%<br>**Mean duration of psoriasis:** 20 y | **Adverse events:** 235.7<br>**Serious adverse events:** 7.2<br>**Infectious events:** 95.2<br>**Serious infectious events:** 1.6<br>**Malignancies:** 1.5<br>**NMSC:** 0.8<br>**MM:** 0.2<br>**Death:** 0.1 (1)<br>**TB:** 0<br>**Opportunistic infection:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |

sizes were small for Weeks 100 to 128.

Serious infections were observed more frequently in the continuous group (5%) than in the intermittent group (1%). These included pneumonia, diverticulitis, disseminated TB, pulmonary TB, tonsillitis, influenza, gastrointestinal infection, and jaw abscess. For patients in the continuous group, exposure-adjusted event rates were 38.2/100 PY for all AEs, 5.6/100 PY for SAEs, and 2.3/100 PY for serious infectious events. Malignancies occurred at a rate of 0.5/100PY, with 0.2/100PY for NMSC. Infusion-related reactions occurred at a rate of 4.9/100 PY. There were no reports of TB, demyelinating disorders, or death during the study period.

These findings were in contrast to those in the EXPRESS II trial, in which serious infusion reactions were not more frequent in the as-needed group.[25] This may be partly explained by the different timings of infusions in the intermittent groups in both studies. In RESTORE2, patients received a full re-induction course of therapy at relapse, while in EXPRESS II, treatments were single infusions.

These studies suggest that while infliximab can be a well-tolerated treatment for patients with moderate-to-severe plaque-type psoriasis, intermittent therapy should be avoided due to the higher incidence of serious infusion-related reactions and serious infections in this group.

| TABLE 1 continued. Summary of studies | | |
|---|---|---|
| **TREATMENT** | **PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS** | **SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n)** |
| **Etanercept continued** | | |
| **Study 6**<br>Etanercept<br>Tyring & Gordon[18]<br>(US and Canada) | **Male:** 68 %<br>**Mean age:** 46 y<br>**White:** 89%<br>**Mean PASI at baseline:** 27.2<br>**PGA at time 0:**<br>**Mean duration of psoriasis:** 19.9 y | **Adverse events:** 274.1<br>**Serious adverse events:** 8.9<br>**Infectious events:** 103.9<br>**Serious infectious events:** 1.2<br>**Malignancies:** 2.1<br>**NMSC:** 1.3<br>**Deaths:** 0.2 (2)<br>**TB:** 0<br>**Opportunistic infections:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0.2 |
| **Infliximab** | | |
| **Study 1**<br>Infliximab<br>Shear et al[23]<br>REALITY<br>(14 countries) | **Male:** 68%<br>**Caucasian:** 77%<br>**Mean age:** 46 y<br>**PGA at time 0:** Moderate or worse<br>**PASI score:** 19 | **Adverse events:** 37.9<br>**Serious adverse events:** 7.9<br>**Serious infectious events:** 2.4<br>**Malignancies:** 0.6<br>**NMSC:** 0.3<br>**Death:** 0.6 (4)<br>**TB:** 0.5<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0<br>**Infusion-related reactions:** 8.1 |

**Ustekinumab**

Four studies were included covering patients from Europe, North America, and Japan with the following key characteristics:

- The average age in all four studies was 46 years.
- 68 to 80 percent of subjects were men.
- Only one study reported the number of Caucasian subjects (92%).
- The number of participants in these studies ranged from 154 to 3,117.
- The duration of the studies ranged from one to five years

**Detailed review.** Based on the average results:

- AE rates ranged from 70 to 232.6 per 100 PY.
- SAE rates ranged from 4 to 7.1 per 100 PY.
- Serious infectious event rates ranged from 0.8 to 1.1 per 100 PY.
- Reported death rates ranged from 0.2 to 0.3 per 100 PY.
- NMSC occurred in up to 0.5 per 100 PY.
- There were no reported cases of TB or demyelination.
- While there we no reports of lymphoma in three of the studies, one study reported a rate of 0.1 per 100 PY.

**Study 1.** In a 76-week Phase 3 study (PHOENIX 1), 766

**TABLE 1 continued. Summary of studies**

| TREATMENT | PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS | SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n) |
|---|---|---|
| **Infliximab continued** | | |
| **Study 2**<br>Reich et al[24]<br>RESTORE2<br>Infliximab<br>(Europe) | **Male:** 68%<br>**Mean age:** 46 y<br>**Caucasian:** 98%<br>**PASI:** 1.7 | **Adverse events:** 38.2<br>**Serious adverse events:** 5.6<br>**Serious infectious events:** 2.3<br>**Malignancies:** 0.5<br>**NMSC:** 0.2<br>**Death:** 0<br>**TB:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0<br>**Infusion-related reactions:** 4.9 per 100 PY |
| **Adalimumab** | | |
| **Study 1**<br>van Luemig et al[19]<br>Adalimumab<br>(The Netherlands) | **Male:** 56%<br>**Mean age:** 49 y<br>**Baseline PASI:** 15<br>**Mean duration of psoriasis:** 23 y | **Serious adverse events:** 23<br>**Infectious events:** not mentioned<br>**Serious infectious events:** 1.9<br>**Malignancies:** only NMSC mentioned<br>**NMSC:** 1.9<br>**Deaths:** 0.9 (1)<br>**TB:** not mentioned<br>**Demyelinating disease:** not mentioned<br>**Lymphoma:** not mentioned |
| **Study 2**<br>Menter et al[20]<br>REVEAL<br>Adalimumab<br>(US and Canada) | **Male:** 67%<br>**Mean age:** 44 y<br>**Caucasian:** 91%<br>**Mean baseline BSA:** 26<br>**PGA at time 0:** moderate (51%), severe (43%), very severe (6%)<br>**Mean baseline PASI Score:** 19<br>**Mean duration of psoriasis:** 18 y | **Adverse events:** 399<br>**Serious adverse events:** 6<br>**Infectious events:** 120<br>**Serious infectious events:** 2<br>**Malignancies:** 0.4<br>**NMSC:** 1.3<br>**Death:** not mentioned<br>**TB:** 0.2<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |

**TABLE 1 continued. Summary of studies**

| TREATMENT | PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS | SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n) |
|---|---|---|
| **Adalimumab continued** | | |
| **Study 3**<br>Gordon et al[22]<br>Open label extension of REVEAL<br>Adalimumab<br>(US and Canada) | **Male:** 65%<br>**Mean age:** 45 y<br>**Caucasian:** 93%<br>**Average BSA:** 25<br>**Average PGA:** moderate (54%), severe (42%), very severe (5%)<br>**Average PASI Score:** 19<br>**Mean duration of psoriasis:** 18 y | **Adverse events:** 245.1<br>**Serious adverse events:** 7.3<br>**Serious infectious events:** 1.5<br>**Malignancies:** 1.5<br>**NMSC:** 0.8<br>**Deaths:** 0.1 (2)<br>**TB:** <0.1<br>**Opportunistic infection:** 0.2<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |
| **Ustekinumab** | | |
| **Study 1**<br>Leonardi et al[26]<br>PHOENIX 1<br>Ustekinumab<br>(US, Canada, Belgium) | **Male:** 68%<br>**Mean age:** 46 y<br>**BSA:** 26%<br>**PGA:** 44% marked or severe<br>**Mean baseline PASI:** 20<br>**Mean duration of psoriasis:** 20 y<br>**Mean duration of psoriasis:** not mentioned | **Adverse events:** 129.4<br>**Serious adverse events:** 4.0<br>**Infectious events:** 76.4<br>**Serious infectious events:** 0.8<br>**Malignancies:** 1.3<br>**MM:** 0.1<br>**Death:** not mentioned<br>**Cardiovascular events:** 5.8<br>**TB:** 0<br>**Salmonella:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |

patients with moderate-to-severe psoriasis were randomized to ustekinumab (45 or 90mg) at Weeks 0 and 4 and then every 12 weeks, or placebo at Weeks 0 and 4 with crossover to ustekinumab (45 or 90mg) at Week 12.[26] Twenty-six patients who had initially received ustekinumab and achieved at least PASI 75 at Weeks 28 and 40 were re-randomized at Week 40 to maintenance ustekinumab or were withdrawn from active treatment until loss of response, defined as loss of at least 50 percent of PASI improvement. Patients achieving less than PASI 50 response at Week 28 were discharged and those achieving PASI 50 to <75 were administered ustekinumab every eight weeks instead. The study duration was 76 weeks.

Exposure-adjusted event rates were 129.4/100 PY for all AEs and 4.0/100 PY for SAEs. The most common AEs in patients on ustekinumab therapy were upper respiratory infection (13.7%), nasopharyngitis (9.9%), headache (3.7%), and arthralgia (1.9%). Rates for infectious and serious infectious events were 76.4 and 0.8 per 100 PY, respectively. Malignancies occurred at a rate of 1.3/100PY

**TABLE 1 continued. Summary of studies**

| TREATMENT | PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS | SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n) |
|---|---|---|
| **Ustekinumab continued** | | |
| **Study 2**<br>Papp et al[27]<br>PHOENIX 2<br>Ustekinumab<br>(Europe and North America) | **Male:** 68%<br>**Mean age:** 46 y<br>**BSA:** 26%<br>**PGA:** 40% marked or severe<br>**Mean baseline PASI:** 19<br>**Mean duration of psoriasis:** 20 y | **Adverse events:** 176.1<br>**Serious adverse events:** 6.5<br>**Infectious events:** 104.7<br>**Serious infectious events:** 0.8<br>**Malignancies:** 1.4<br>**Cutaneous malignancies:** 1.1<br>**Death:** 0.3 (2)<br>**Cardiovascular events:** 0.2<br>**TB:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |
| **Study 3**<br>Igarashi et al[28]<br>Ustekinumab<br>(Japan) | **Male:** 80%<br>**Mean age:** 46 y<br>**BSA:** 47%<br>**Mean baseline PASI:** 29<br>**Mean duration of psoriasis:** 16 y | **Adverse events:** 70.3<br>**Serious adverse events:** 6.1<br>**Infectious events:** 62.8<br>**Serious infectious events:** 1.4<br>**Malignancies:** 1.4<br>**NMSC:** 0<br>**Death:** not mentioned<br>**Cardiovascular events:** 0.5<br>**TB:** 0<br>**Salmonella:** 0<br>**Demyelinating disease:** 0<br>**Lymphoma:** 0 |

with melanoma at 0.1/100 PY. Cardiovascular event rates were 5.8/100 PY. There were no reported cases of TB, salmonella, lymphoma, or demyelinating disease.

AE rates were similar in patients receiving maintenance ustekinumab and those on interrupted therapy. Rates of AEs, SAEs, and events leading to discontinuation of therapy were similar in patients receiving ustekinumab and those receiving placebo with no dose-response noted.

**Study 2.** In a second Phase 3 trial (PHOENIX 2), patients were randomized to ustekinumab (45 or 90mg) or placebo for the first 28 weeks.[27] Partial responders (PASI improvement >50% but <75%) were then re-randomized to continue 12-week dosing or 8-week dosing up to 52 weeks. Results were similar to those reported in PHOENIX 1. AEs were generally mild and did not require treatment adjustment. The most common AEs in patients receiving ustekinumab were infections (0.7%) and cardiac disorders (0.7%).

Exposure-adjusted event rates were 176.1/100 PY for all AEs and 6.5/100 PY for SAEs. Rates for infectious and

| TABLE 1 continued. Summary of studies | | |
|---|---|---|
| **TREATMENT** | **PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS** | **SAFETY: EVENT RATES GIVEN PER 100 PATIENT YEARS DEATH RATES ALSO GIVEN AS (n)** |
| **Ustekinumab continued** | | |
| **Study 4**<br><br>PAPP et al[29]<br>Pooled safety data from 4 studies<br><br>Ustekinumab | **Male:** 68%<br><br>**Caucasian:** 92%<br><br>**Mean age:** 46 y<br><br>**BSA:** 26%<br><br>**Mean baseline PASI:** 20<br><br>**Mean duration of psoriasis:** not mentioned | **Adverse events:** 232.6<br><br>**Serious adverse events:** 7.1<br><br>**Infectious events:** 86.5<br><br>**Serious infectious events:** 1.1<br><br>**Malignancies:** 1.1<br><br>**NMSC:** 0.5<br><br>**Death:** 0.29 (20)<br><br>**MACE:** 0.44<br><br>**TB:** 0<br><br>**Salmonella:** 0<br><br>**Demyelinating disease:** not mentioned<br><br>**Lymphoma:** 0.01 |

serious infectious events were 104.7 and 0.8/100 PY, respectively. Malignancies occurred at a rate of 1.4/100 PY, with cutaneous malignancies at 1.1/100 PY. The death rate during the study period was 0.3/100 PY, and cardiovascular events occurred at a rate of 0.2/100 PY. There were no reported cases of TB, lymphoma, or demyelinating disease.

**Study 3.** A Japanese group performed a Phase 2/3 study in 158 patients with moderate-to-severe psoriasis.[28] The study design included an initial placebo-controlled phase of 12 weeks duration, followed by an active treatment phase (Weeks 12–64). Safety data were collected through Week 72, and rates of events are thus presented as incidence per patient years of observation.

AEs were generally mild and rates were similar in ustekinumab-treated patients and placebo-controlled patients. The most common AEs were nasopharyngitis, increased blood triglycerides, and creatine phosphokinase, and seasonal allergies.

Exposure-adjusted event rates were 70.3/100 PY for all AEs and 6.1/100 PY for SAEs. Rates for infections and serious infections were 62.8/100 PY and 4/100 PY, respectively. Malignancies occurred at a rate of 1.4/100 PY. There were no reports of NMSC. Cardiovascular events occurred at a rate of 0.5/100 PY. There were no cases of TB, salmonella infection, lymphoma, or demyelinating disease.

The safety data from various studies, including PHOENIX 1 and PHOENIX 2, were pooled by Papp et al[29] to evaluate the safety of ustekinumab in patients with moderate-to-severe psoriasis treated for up to five years.[29] A total of 3,117 patients received at least one dose of ustekinumab.

The exposure-adjusted event rates were 232.6/100 PY for all AEs, and 7.1/100 PY for SAEs. The most common AEs were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Rates for infections and serious infections were 86.5/100 PY and 1.1/100 PY, respectively. There were no reports of TB or salmonella infection during the study. Cases of lymphoma occurred at a rate of 0.1/100 PY. Twenty deaths were reported through Year 5, with rates of 0.29/100 PY. The mortality rate among patients treated with ustekinumab was consistent with that expected in the general US population. Overall AE rates, rates of AEs leading to discontinuation, and rates of overall infections decreased over time from Year 1 to Year 5. Malignancies occurred at a rate of 1.1/100 PY, with NMSC at 0.52/100 PY. The rates of NMSC were comparable for the 45mg and the 90mg ustekinumab groups. A higher incidence of NMSC was observed among patients with prior psoralen plus ultraviolet A (PUVA) exposure. The observed rate of malignancies other than NMSC was comparable with that expected in the general US population. The BCC:SCC ratio observed in immunocompetent patients is 4:1,[30] and the same ratio has been seen in ustekinumab studies.[29] While this ratio is reversed in immune-suppressed patients, a reversal of the BCC:SCC ratio has not been observed in ustekinumab-treated patients, and no increased risk of malignancy has been reported in patients treated with the drug for up to five years.

The overall rates of MACEs were 0.44/100 PY. These were comparable between the 45mg (0.56/100 PY) and 90mg

(0.36/100 PY) groups. There was year-to-year variability, but rates of MACE did not increase over time. Studies have suggested an increased risk of cardiovascular events in patients with psoriasis.[31,32]

The data from the five-year analysis of ustekinumab-treated patients did not identify an increased risk of MACE,[29] and results of various ustekinumab studies performed to date do not establish a clear relationship between the drug and CV risk.[33] The power of the studies has however been limited due to the short duration of controlled periods (<6 months).

These studies suggest that ustekinumab is generally a safe treatment for patients with moderate-to-severe plaque-type psoriasis for up to five years. Available data suggest that long-term safety outcomes are unaffected by the dose of ustekinumab or the cumulative exposure to the drug.[29] Rates of both infectious and noninfectious AEs are low. There were no cases of TB or demyelination in the studies reviewed.

## DISCUSSION

Since the growing understanding of the pathogenesis of psoriasis and the introduction of more targeted biologic therapies for patients suffering from this disease, their use has increased markedly, and these newer drugs have become part of the psoriasis armamentarium. Conventional systemic therapies can be associated with severe adverse drug reactions, such as hepatotoxicity, bone marrow suppression, and gastrointestinal ulcerations in the case of methotrexate, nephrotoxicity, increase in blood pressure, an increased risk of malignancies in the case of cyclosporine, and hepatotoxicity and teratogenicity in the case of acitretin.[6]

Nevertheless, methotrexate remains the most commonly prescribed drug worldwide,[34] and current European and British treatment guidelines still recommend the use of biologic agents as third-line treatment.[6,35] Etanercept and adalimumab are recommended above infliximab as first-line biologic therapy,[35] as clinical trials under 12 months duration showed a lower rate of AEs compared with infliximab.[36,37]

The studies that we reviewed have shown lower total AE rates for infliximab compared to the other agents (Table 1). However, sample sizes were lower, and study duration was shorter compared to the other biologics. Rates for serious AEs and serious infectious events were higher. The lower rate of malignancies in the infliximab studies is likely related to the shorter study duration, which cannot capture less common AEs.

Ustekinumab was introduced later than the TNF antagonists, and has therefore been recommended as second-line biologic therapy for psoriasis by the British Association of Dermatologists.[35] However, the data presented in our review suggests that ustekinumab may be associated with lower SAE rates, and lower infectious and serious infectious event rates compared to the TNF antagonists. Furthermore, there were no reports of TB or demyelination in these studies. Rheumatoid arthritis registry data suggest that etanercept may be associated with a lower risk of TB than adalimumab and infliximab,[37] and this was further seen in the studies reviewed here.

While more long-term safety data on current biologic therapies continues to emerge, new therapeutic agents for psoriasis will be launched.[38] While some of these newer drugs may be promising in terms of higher efficacy for psoriasis patients, it remains to be seen if these agents will prove to be both more efficacious and safe.

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