No Evidence for Increased Risk of Cutaneous Squamous Cell Carcinoma in Patients With Rheumatoid Arthritis Receiving Etanercept for Up to 5 Years

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Objective: To determine the incidence of cutaneous squamous cell carcinoma (SCC) in patients with rheumatoid arthritis receiving etanercept, a tumor necrosis factor antagonist, for up to 5 years.

Design: An etanercept clinical trials' database and an etanercept postmarketing surveillance database were retrospectively analyzed for the incidence of SCC.

Setting: Patients enrolled in clinical trials of etanercept were from private and institutional practices. The postmarketing database comprised reports from postmarketing trials and solicited and spontaneous reports.

Patients: A total of 1442 patients with rheumatoid arthritis with 4257 patient-years of etanercept exposure (median exposure, 3.7 years) are included in the clinical trials' database. More than 125 000 patients with more than 250 000 patient-years of etanercept exposure are included in the etanercept postmarketing database.

Interventions: Most patients enrolled in clinical trials of etanercept received a dosage of 25 mg of etanercept subcutaneously twice weekly for most of the time they received etanercept therapy.

Results: Only 4 cases of SCC were observed in the etanercept clinical trials' database, an incidence that compares favorably with the expected incidences based on general population data from Arizona (13.1) and Minnesota (5.9). Similarly, few cases of SCC (1 per 10 000 patient-years) have been reported during postmarketing surveillance of etanercept therapy.

Conclusion: In patients with rheumatoid arthritis, etanercept use of up to 5 years does not seem to be associated with an increase in the incidence of cutaneous SCC.

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TUMOR NECROSIS FACTOR (TNF) plays a central proinflammatory role in many chronic inflammatory diseases. The TNF antagonist etanercept is a fully human soluble TNF receptor fusion protein that competitively binds and neutralizes TNF, preventing cell surface binding and the resultant proinflammatory cascade. Etanercept is indicated for use in patients with rheumatoid arthritis (RA), juvenile RA, ankylosing spondylitis, psoriatic arthritis, and psoriasis. Given the expanding indications of etanercept, dermatologists are likely to treat patients receiving etanercept therapy or to prescribe it themselves.

Because of the dual role that TNF plays in inflammation and cellular immunity, an initial concern with TNF antagonist therapies has been the potential for pathological immunosuppression, such as impaired tumor surveillance. Although no increase above the expected background rate of malignancies has been observed in the RA population receiving etanercept therapy,1 the expanding indications for etanercept together with the increasing incidence of squamous cell carcinoma (SCC) in the general population2 have heightened interest in a potential relationship between the two. As part of an ongoing pharmacovigilance program, a clinical trials' database of 1442 RA patients receiving etanercept (4257 patient-years) and a postmarketing database of more than 125 000 patients receiving commercial etanercept (>250 000 patient-years) were analyzed to determine the incidence of SCC in patients receiving etanercept.

METHODS

CLINICAL TRIALS' DATABASE POPULATION

A clinical trials' database of 1442 RA patients receiving etanercept therapy was analyzed to
determine the incidence of SCC. For the current analysis, the clinical trials’ database included the time frame in which all adverse events (serious or nonserious) were reported and represents 4257 patient-years of etanercept exposure. The time frame in which all adverse events were reported was followed by a period in which only serious adverse events were reported; data from the later period were not included in this analysis because it is more likely that skin cancers might be underreported during that time.

Patients included in the clinical trials’ database were from various studies; all studies were approved by the appropriate institutional review boards. All patients had active RA at enrollment and received 10 to 50 mg of subcutaneous etanercept once or twice weekly. Most patients received a dosage of 25 mg subcutaneously twice weekly for most of their time receiving etanercept therapy. Specific inclusion criteria for the studies varied. The largest subgroup consisted of adult (n = 714) and juvenile (n = 69) patients who previously had a suboptimal response to at least 1 disease-modifying antirheumatic drug and participated in 1 or more of 8 initial etanercept studies and/or a large open-label safety study of long-term etanercept therapy. Another subgroup consisted of 557 adult patients who had been diagnosed as having RA within the past 3 years and had not previously received methotrexate. The remaining patients were from either a pharmacokinetic study of etanercept in adult patients with RA (n = 25) or a phase 3 study investigating the safety and efficacy of 2 dosages (25 and 50 mg subcutaneously twice weekly) of etanercept (n = 77) in adult patients with RA.

**POSTMARKETING DATABASE POPULATION**

A database consisting of safety data generated by postmarketing surveillance was analyzed for the reporting rate of SCC. The data set includes 4 years of commercial experience with etanercept, capturing more than 125,000 patients with more than 250,000 patient-years of etanercept exposure. All reported cases of SCC from postmarketing experience were based on reports from postmarketing trials and solicited and spontaneous reports.

**DIAGNOSIS OF SCC**

Physical examinations were conducted at clinical trial monitoring visits. Patients with skin lesions suggestive of SCC (detected during physical examinations or during routine care outside of the trial) were referred for diagnosis and biopsy. Cutaneous SCC was diagnosed clinically and confirmed via histologic examination of biopsy specimens.

For the postmarketing database, patients and/or physicians reported the occurrence of SCC, with or without histologic confirmation.

**CALCULATION OF EXPECTED SCC RATES**

Expected SCC incidence rates from general population groups can offer an epidemiological perspective on the observed incidence of SCC in the clinical trials’ database. Although the National Cancer Institute’s Surveillance, Epidemiology, and End Results cancer registry does not include information on SCC, previous epidemiological studies have reported the incidence of SCC in Arizona1 (high sun exposure) and Minnesota4 (low sun exposure). The SCC incidence rates in Arizona and Minnesota were age- and sex-adjusted to the clinical trials’ population and the postmarketing population by indirect standardization to generate ranges of expected SCC incidences for the etanercept cohorts.

**RESULTS**

**PATIENT POPULATION CHARACTERISTICS**

The clinical trials’ database that was analyzed for the occurrence of SCC included data on 1442 patients with RA receiving etanercept therapy, representing a total exposure of 4257 patient-years. The patient population was 76.5% female and 87.4% white, and the mean age was 49.9 years. Patients had been diagnosed as having RA for a mean of 7.1 years, and the mean number of prior disease-modifying antirheumatic drugs was 2.1. The median duration of etanercept exposure in the clinical trials’ database population was 3.7 years, and the maximal exposure was 5.7 years.

**OBSERVED AND EXPECTED INCIDENCES OF SCC IN THE ETANERCEPT CLINICAL TRIALS’ DATABASE**

Of 1442 RA patients with 4257 patient-years of etanercept exposure, analysis of the clinical trials’ database revealed 4 cases of SCC, resulting in a crude rate of 2.8 cases per 1000 patients or 0.9 cases per 1000 patient-years. The patients diagnosed as having SCC ranged in age from 41 to 79 years, half were women, and all were white and receiving concomitant medications (2 were receiving corticosteroids, 1 was receiving corticosteroids and nonsteroidal anti-inflammatory drugs, and 1 was receiving methotrexate). The locations of all tumors were potentially sun-exposed areas (ear, cheek, shoulder, and back). At SCC diagnosis, 1 patient was in the third year of etanercept therapy, 1 was in the fourth year, and 2 were in the fifth year.

Whereas 4 cases of cutaneous SCC were observed in the clinical trials’ database, the expected incidences of SCC based on the Arizona and Minnesota incidence studies were 13.1 and 5.9 cases, respectively (Figure).

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**Figure.** Expected vs observed incidence of squamous cell carcinoma (SCC). Only 4 cases of SCC were observed in the clinical trials’ database of patients with rheumatoid arthritis receiving etanercept for up to 5 years. This incidence compares favorably with the expected age- and sex-matched incidences in Arizona (13.1)2 and Minnesota (5.9).1
REPORTED AND EXPECTED RATES OF SCC IN POSTMARKETING SURVEILLANCE OF ETANERCEPT USE

Of more than 125,000 RA patients with more than 250,000 patient-years of etanercept exposure, an analysis of the postmarketing database revealed 25 cases of SCC. Thus, the reporting rate of SCC was 1 case per 5,000 etanercept-treated patients or 1 case per 10,000 patient-years of etanercept exposure. The postmarketing reports of SCC occurred in patients whose age ranged from 50 to 78 years. Of the 25 cases, 16 were medically confirmed (15 of these with a biopsy) and 9 were from a consumer report (3 of these with a biopsy). For the 14 cases with data available, the mean duration of etanercept exposure before SCC diagnosis was 13.5 months (range, 2-30 months).

Acknowledging the underreporting of adverse events in postmarketing surveillance, the reported number of SCC cases in the etanercept postmarketing database (n=25) is less than 10% of the number of cases expected (n=367-836) based on the Arizona and Minnesota SCC incidence studies.3,4

COMMENT

The purpose of this analysis was to compare the incidence of SCC in RA patients receiving etanercept with the expected incidence of SCC in the general population. Results from this analysis of 1,442 patients with RA (4,257 patient-years of etanercept exposure) show no increase in cutaneous SCC in patients with RA receiving etanercept for up to 5 years. In fact, the observed incidence (4 cases) compares favorably with the expected age- and sex-matched incidences from the Arizona and Minnesota studies (13.1 and 5.9 cases, respectively).3,4 Moreover, postmarketing experience (>125,000 patients with >250,000 patient-years of exposure) supports the finding that etanercept does not seem to be associated with an increased risk of SCC, although skin cancer is likely to be underreported in this forum.

Immunocompromised patients are more prone to tumor development,6,7 and lesions in these patients may be more aggressive.6,7 The association between broadly immunosuppressive treatments and the development of SCC is well established.8 For example, rapid development of SCC in psoralen–UV-A–treated patients with psoriasis who started receiving cyclosporine has been reported,9 and is seen in clinical practice. More important, etanercept is not a general immune suppressant but rather a target-specific modulator of TNF. Etanercept, at dosages administered in humans, is believed to reduce TNF activity from excessive inflammatory levels to normal physiologic levels.

A recent report10 has described 7 RA patients with rapid onset of cutaneous SCC shortly after starting etanercept therapy (25 mg subcutaneously twice weekly). All patients had long-standing histories of RA and experienced unsuccessful treatment with multiple prior medications. All were white, with fair to moderately pigmented skin, had a history of heavy cumulative UV exposure with long-term actinic damage, and had a high prevalence of basal cell carcinoma. Although the researchers acknowledged that UV exposure was likely to have been key in the development of subclinical tumors, they suggested that etanercept therapy might have led to the presentation of clinical tumors. This was primarily based on the short duration between starting etanercept therapy and the onset of the tumors.

Notably, the time frame of SCC development in etanercept-treated patients in the large clinical trials’ database and in postmarketing surveillance is vastly different from that in the case series. Whereas the SCC cases from the case series were diagnosed 2 to 4 weeks after the start of etanercept therapy, the 4 cases of SCC from the current analysis of the clinical trials’ database were not diagnosed until 3 to 5 years after the start of etanercept treatment and the 25 cases of SCC reported through postmarketing surveillance occurred after 2 to 30 months. Therefore, the current findings do not support the idea that inhibiting TNF releases subclinical skin cancers from containment.

The follow-up of this analysis (≤5 years of etanercept exposure) is not long enough to exclude the possibility that long-term exposure to etanercept may affect the development of SCC, because a prolonged induction period is theoretically possible. However, with other immunosuppressive agents, an increase of SCC has been seen early after exposure to the medication. For example, patients previously treated with psoralen–UV-A and receiving cyclosporine for at least 3 months had nearly a 4-fold increase in SCC, even when adjusting for high exposure to psoralen–UV-A and methotrexate.9 Although we cannot rule out long-term etanercept use affecting the development of SCC, the current analysis suggests that exposure of up to 5 years in patients with RA is not associated with an increase in SCC.

The epidemiological studies used in the calculation of the expected range of incidences of SCC represent the general population of Arizona and Minnesota and, more important, do not adjust for potential confounding by underlying disease or concomitant medications. Moreover, these historical controls do not account for the continually increasing incidence rate of SCC. Thus, the expected SCC incidence rate used may be a conservative Comparator for RA population. Squamous cell carcinoma may occur more frequently in patients with RA than in those without RA. In fact, a Danish study11 found SCC to be 1.4 times more likely in RA patients than in the general population. However, even without adjusting the expected incidence rate of SCC for potential confounding by RA, prior and concomitant medications, and the increasing incidence of SCC, patients receiving etanercept had a lower incidence than would be expected.

To more thoroughly explore the association between SCC and etanercept use, the analysis of the clinical trials’ database was supplemented with an analysis of the reported rate of SCC from etanercept postmarketing surveillance. While postmarketing data are not definitive, they are useful for the detection of a signal of a potential relationship between exposure to a therapeutic agent and a specific adverse event. An inherent limitation of postmarketing surveillance is the underreporting of adverse events. However, if we assume that only 10% of actual
SCC cases were captured during postmarketing surveillance, the incidence of SCC in patients receiving commercial etanercept would be 250 cases, which compares favorably with the expected number of cases (n=367-836). Furthermore, using this 10% assumption, the rate of SCC would be 1 per 1000 patient-years, a rate that is similar to that demonstrated in the clinical trials’ database and is substantially lower than the background incidence rate of the general population. Overall, the postmarketing data support the results from the clinical trials’ database, indicating that up to 5 years of etanercept exposure in patients with RA does not seem to be associated with an increase in SCC.

Caution should be taken when extrapolating the results of this analysis to a psoriatic population. First, SCC may be underrecognized in rheumatologic studies, although continuous follow-up in a clinical trial is likely to be more sensitive in detecting adverse events associated with a therapeutic agent than would a typical rheumatology clinical setting. Second, patients with psoriasis may have an even higher risk of skin cancer, largely attributable to previous carcinogenic treatments. With the expanded indications of etanercept for the treatment of psoriatic arthritis and psoriasis, dermatologic use of this biologic is increasing. The long-term risk of SCC in patients with psoriasis receiving etanercept is unknown, but future analyses in the psoriatic population with extended exposure to etanercept will help to answer this question.

In conclusion, this analysis of 1442 RA patients with a total of 4257 patient-years of etanercept exposure shows no increase in the incidence of SCC with up to 5 years of etanercept use. The observed incidence of SCC from the clinical trials’ database (4 cases) compares favorably with age- and sex-matched incidences from regional general population groups (5.9-13.1). The low reported incidence of SCC from postmarketing surveillance of etanercept therapy (1 per 10 000 patient-years) further supports the lack of an association between SCC and etanercept therapy. Future studies may provide additional insight on the relationship between TNF antagonist therapies and SCC.

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REFERENCES


