

Safety and Tolerability of Ixekizumab: Integrated Analysis of Injection-Site Reactions from 11 Clinical Trials

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ABSTRACT

Background: Injection-site reactions (ISRs) are reported with biologic therapies. The objective of this study was to comprehensively characterize ISRs among moderate-to-severe psoriasis patients treated with ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A.

Methods: ISRs are presented from UNCOVER-1, UNCOVER-2, and UNCOVER-3 (12 weeks) and all ixekizumab-exposed patients in 11 controlled and uncontrolled trials (156 weeks).

Results: At week 12, reported ISR frequency with 80 mg ixekizumab every 2 weeks (IXE Q2W, 16.8%) was comparable with etanercept twice weekly (16.4%); both were significantly higher than placebo (3.3%). With IXE Q2W, ISRs were mild (12.3%), moderate (3.9%), or severe (0.7%), typically reported in the first 2 weeks (median onset, 6.6 days), and most commonly characterized as nonspecified, erythema, and pain. Generally, erythema onset was delayed, whereas pain occurred around drug administration. Discontinuation from ixekizumab due to ISRs (0.4%) occurred in the first 12 weeks. After 2 weeks, ISR frequency decreased and remained stable (≤4.2%) through week 156. No ISR-related serious adverse events were reported in ixekizumab-treated patients. ISR data were solicited if patients reported injection-associated events. Since nonspecified ISR was the most commonly reported term, specific types might be underreported.

Conclusions: ISRs have been reported with ixekizumab during clinical trials. These reactions are typically tolerable, manageable, and decrease over time.

Clinicaltrials.gov: NCT01474512 (UNCOVER-1); NCT01597245 (UNCOVER-2); NCT01646177 (UNCOVER-3); NCT01777191 (UNCOVER-A); NCT01624233 (UNCOVER-J); NCT01107457 (I1F-MC-RHAJ); NCT02561806 (I1F-MC-RHBS); NCT02387801 (I1F-US-RHBO);NCT02513550 (I1F-MC-RHBP); NCT02634801 (I1F-EW-RHBZ)

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INTRODUCTION

During the last decade, biologic therapies have contributed to the revolution of treatment for moderate-to-severe plaque psoriasis. Common adverse events that have been noted with biologics are injection-site reactions, which are typically defined as local skin reactions occurring after an injection and are often characterized by erythema, edema, and/or pain.[1-3] Some injection-site reactions may represent a type of hypersensitivity reaction to the active agent or to one of the components of the formulation.[4] The etiology of injection-site reactions can be multifactorial, nonspecific, and may include immunologic and non-immunologic factors such as volume, temperature, pH, speed of injection, and needle size, among others.[3]

Ixekizumab, a high-affintiy monoclonal antibody that selectively targets interleukin (IL)-17A, was recently approved for treatment of moderate-to-severe psoriasis. The efficacy of ixekizumab has been established to be superior to placebo,

etanercept, and ustekinumab in clinical trials; the safety and tolerability of ixekizumab has been established with both short-term and long-term use.[5-10]

Regarding tolerability, ixekizumab is similar to etanercept in that one of the common adverse events is injection-site reaction.[5,9,11] Both ixekizumab and etanercept have been reported to have higher frequencies of injection-site reactions than patients receiving placebo in controlled trials.[5,9,11] Recommended ixekizumab dosing is a 160 mg initial dose followed by 80 mg every 2 weeks (IXE Q2W) for 12 weeks (weeks 2, 4, 6, 8, 10, 12) and 80 mg every 4 weeks (IXE Q4W) thereafter.[12] Here, a comprehensive characterization of injection-site reactions among patients who have received ixekizumab in clinical trials at the recommended dosing regimen is presented.

MATERIALS AND METHODS

Data were derived from an integrated database of 11 controlled and uncontrolled psoriasis clinical trials investigating the efficacy and safety of ixekizumab. The designs of 7 of these studies have been previously published[5,6,8,13-16] and the designs of the 4 other studies are available at clinicaltrials.gov (NCT02561806, NCT02387801, NCT02513550, NCT02634801). The main focus of data was 3 randomized, double-blinded, placebo-controlled phase 3 psoriasis trials: UNCOVER-1, UNCOVER-2, and UNCOVER-3.[5,6] The UNCOVER-1, -2, and -3 studies had a 12-week placebo-controlled induction dosing period where patients were randomized to receive subcutaneous injections of placebo, IXE Q2W, IXE Q4W or, in UNCOVER-2 and -3 only, an active comparator: etanercept (50 mg twice weekly). UNCOVER-1 and -2 had a randomized withdrawal period from week 12 to week 60 where patients received subcutaneous injections of IXE Q4W, 80 mg ixekizumab every 12 weeks (IXE Q12W), or placebo. Patients were allowed to use topical or systemic antihistamines prior to receiving any injections. The UNCOVER trials had a long-term extension period to week 264. Study drug was administered by pre-filled syringe with a few exceptions: in UNCOVER-A (a phase 3 study), either a prefilled syringe or an autoinjector device was used[15]; in Part A of RHAJ (a phase 2 study), the study drug was administered by syringe, but it was not prefilled[14]; and in RHAG (a phase 1 study), study drug was administered intravenously in a small group of patients (n=6).[13] All patients are included in the results, regardless of route of administration. Each injection contained ixekizumab (80 mg) in a buffer consisting of anhydrous citric acid, polysorbate, sodium chloride, sodium citrate dihydrate, and sterile water with a pH of 5.3–6.1.[12] Each placebo injection to match ixekizumab contained the excipients of ixekizumab and to match etanercept contained the excipients of etanercept.

Eligibility criteria were similar across studies. Patients (≥18 years) with moderate-to-severe psoriasis (≥10% body surface area involvement, static Physician's Global Assessment ≥3, Psoriasis Area and Severity Index ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy met prespecified inclusion and exclusion criteria for enrollment in all 11 studies. Patients with a known allergy or hypersensitivity to any biologic therapy that would pose an unacceptable risk were excluded. In the UNCOVER-2 and -3 studies, patients who had previously received etanercept were excluded. The clinical trials were conducted according to the principles expressed in the Declaration of Helsinki. The study protocols received ethical review board approval, and patients gave written informed consent.

Evaluations of Injection-Site Reactions

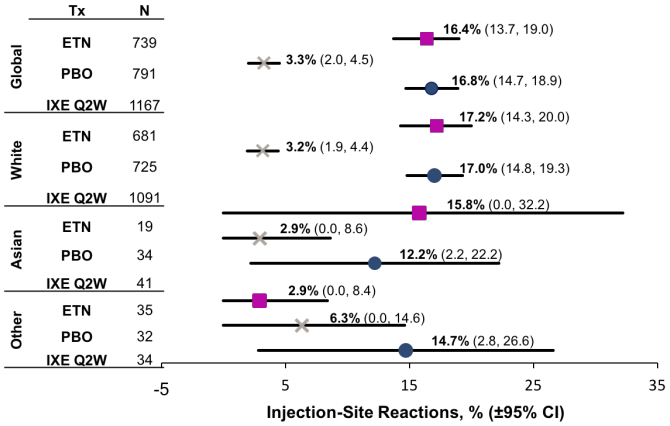
Two cohorts from the integrated data of 11 psoriasis studies were analyzed: 1) patients from the 12-week induction period (through September 2014) of placebo-controlled UNCOVER-1, -2, and -3 (primary placebo-controlled population [PPC]) and etanercept-controlled UNCOVER-2 and -3 (placebo and active-controlled population [PAC]), and 2) all patients from the 11 clinical trials who received any dose of ixekizumab during any period of any study up to 319 weeks (median duration of exposure: 883 days; through September 2016; all ixekizumab population [AP]).

At each study visit, patients spontaneously reported any adverse events that had been experienced since the previous visit. For injection-site related events, additional data were obtained from the study site and patient, to better characterize the event. Because the visit schedule varied across treatment periods, the recollection period varied for any adverse event or follow-up form. However, in the UNCOVER trials, the visit schedule during induction was 1, 2, and 4 weeks after the initial start of therapy. In the follow-up form, patients were asked to rate pain (including burning) on a scale from 0 (none) to 4 (severe), redness on a scale from 0 (no redness) to 5 (dark with scar), and swelling on a scale from 0 (no bump) to 5 (clear bump 2 mm thick or more). For the purposes of this report, the term "bump" is hereafter referred to as "papule." The patients were also asked about the timing of the event after drug administration (during administration, within 60 minutes, 1 to 6 hours after, >6 hours to 14 days after, or >14 days after).

Verbatim terms related to the injection or injection site were coded into different preferred terms based on the Medical Dictionary for Regulatory Activities (https://www.meddra.org). The term "injection-site reactions" (plural) refers to the high-level grouping of the different preferred terms used to describe various injection-site reactions, such as "erythema," "swelling," and "pain." In some cases, the study sites did not provide additional descriptors so the verbatim term "injection-site reaction" (singular) was used and is referred to herein as "nonspecified."

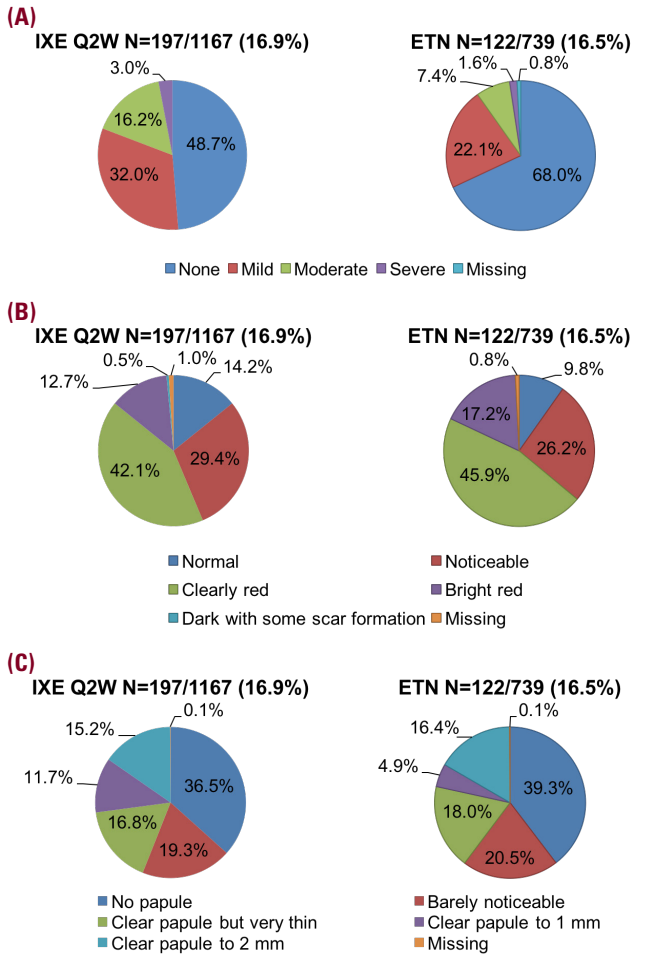
A treatment-emergent injection-site reaction was defined as any type of event associated with any injection, including the first injection, which first occurred or worsened in severity after

FIGURE 1. Incidence (± 95% CIs) of injection-site reactions per 100 patient-years globally (N=3858 patients) and by race in the first 12 weeks of treatment of three phase 3 UNCOVER psoriasis studies.



CI, confidence interval;
ETN, etanercept;
IXE Q2W, 80 mg ixekizumab every 2 weeks;
PBO, placebo;
Tx, treatment group.

FIGURE 2. Patient characterization of injection-site reactions in the first 12 weeks of treatment of three phase 3 UNCOVER psoriasis studies. (A) Maximal pain of injection-site reactions. (B) Maximal redness of injection-site reactions. (C) Maximal swelling of injection-site reactions.



ETN, etanercept;
IXE Q2W, 80 mg ixekizumab every 2 weeks.

baseline. Frequencies and 95% confidence intervals (CIs) of treatment-emergent injection-site reactions are presented for the treatment groups for the PPC, PAC, and AP analysis sets. The 95% CIs of the frequencies were calculated based on binomial distributions. Treatment comparisons for frequencies were analyzed for PPC and PAC analysis sets using the Cochran-Mantel-Haenszel test stratified by study. Frequencies of treatment-emergent injection-site reactions are also presented by race, for those with or without previous biologic experience, and for those with or without treatment-emergent antidrug antibody (TE-ADA) positive status. A TE-ADA positive patient was defined as having a post-baseline antibody titer with a ≥4-fold increase over a positive baseline antibody titer (Tier 3) or an increase from a negative baseline titer to a level of ≥1:10. Frequencies included any injection-site reaction reported within (±)14 days of a positive TE-ADA result.

RESULTS

Injection-Site Reactions During the Induction Dosing Period of the UNCOVER Studies

During the 12-week induction period of the phase 3 UNCOVER studies (N=3858 patients), the overall frequency of reported injection-site reactions with IXE Q2W (16.8%) was similar to those reported with etanercept administered twice weekly (16.4%; Figure 1); the frequencies with IXE Q2W and etanercept were both higher than with placebo (3.3%). Five ixekizumab-treated patients (nonspecified, n=4; erythema, n=1) and 3 etanercept-treated patients (nonspecified, n=2; hypersensitivity, n=1) discontinued due to injection-site reactions that occurred during the 12-week induction period. No patients in the placebo group discontinued due to injection-site reaction. Among injection-site reactions reported, the severities were mild (IXE Q2W: 12.3%; etanercept: 11.2%), moderate (IXE Q2W: 3.9%; etanercept: 3.7%), or severe (IXE Q2W: 0.7%; etanercept: 1.4%). The most common injection-site reactions following IXE Q2W treatment were nonspecified (10.0%), erythema (4.5%), and pain (2.4%).

The median time to first onset of injection-site reactions after week 0 injections was 6.6 days with IXE Q2W. At subsequent injection weeks (weeks 2 and 4), the median time to onset of injection-site reactions decreased to 1.5 days. In general, a delay in the onset of injection-site erythema was reported. The median time to first onset of erythema was 8.3 days with IXE Q2W. The median duration of erythema was 4.0 days, although in a few outlier cases, patients reported erythema for up to 7 weeks. Typically,

TABLE 1.

Patients With Single or Multiple Injection-Site Reactions: First 12 Weeks of UNCOVER-1, -2, and -3

	IXE Q2W N=1167	ETN N=739	PBO N=791
≥1 injection-site reactions	196 (16.8%)	121 (16.4%)[a,b]	26 (3.3%)
Patients with 1 event	93 (8.0%)	46 (6.2%)	12 (1.5%)
Patients with 2 or 3 events	70 (6.0%)	38 (5.1%)	9 (1.1%)
Patients with ≥4 events	33 (2.8%)	37 (5.0%)	5 (0.6%)
≥1 injection-site reaction	117 (10.0%)[c]	80 (10.8%)[a,b]	9 (1.1%)[c]
Patients with 1 event	56 (4.8%)	29 (3.9%)	7 (0.9%)
Patients with 2 or 3 events	46 (3.9%)	28 (3.8%)	0
Patients with ≥4 events	15 (1.3%)	23 (3.1%)	2 (0.3%)
≥1 injection-site erythema	52 (4.5%)[c]	29 (3.9%)[a,b]	2 (0.3%)[c]
Patients with 1 event	37 (3.2%)	11 (1.5%)	2 (0.3%)
Patients with 2 or 3 events	12 (1.0%)	9 (1.2%)	0
Patients with ≥4 events	3 (0.3%)	9 (1.2%)	0
≥1 injection-site pain	28 (2.4%)[c]	9 (1.2%)[a,b]	14 (1.8%)[c]
Patients with 1 event	19 (1.6%)	5 (0.7%)	5 (0.6%)
Patients with 2 or 3 events	4 (0.3%)	3 (0.4%)	6 (0.8%)
Patients with ≥4 events	5 (0.4%)	1 (0.1%)	3 (0.4%)

ETN, etanercept;
IXE Q2W, 80 mg ixekizumab every 2 weeks;
PBO, placebo.
[a]Data from Strober et al. J Am Acad Dermatol. 2017;76(3):432-440.[9]
[b]Data from Griffiths et al. Lancet. 2015;386(9993):541-551.[5]
[c]Data from Gordon et al. N Engl J Med. 2016;375(4):345-356.[6]

injection-site pain occurred during and resolved shortly after the injection of ixekizumab (median time to onset: 1.0 day; median duration: 1.0 day); however, in a few cases, the resolution of pain took longer.

While the frequency of injection-site pain was comparable among ixekizumab- and etanercept-treated patients, more patients treated with IXE Q2W (19.2%) than those treated with etanercept (9.0%) characterized the maximal pain experienced with the injection as "moderate" to "severe" (Figure 2A). Ixekizumab- and etanercept-treated patients characterized the redness and swelling associated with injections similarly (Figure 2B and 2C). Overall, the most common characteristics of pain were "none" and "mild," of redness were "clearly red" and "noticeable," and of swelling were "no papule" and "barely noticeable."

A single injection-site reaction event was reported in 93/196 patients (47.4%) in IXE Q2W group and 46/121 (38.0%) in the etanercept group. A total of 103/196 (52.6%) patients in the IXE Q2W and 75/121 (62.0%) in the etanercept group reported multiple events (Table 1).

The use of concomitant medications to treat injection-site reactions was uncommon (1.5% of IXE Q2W-treated patients and 1.6% of etanercept-treated patients). Among those who received treatment, the majority received antihistamines (Table 2).

Injection-Site Reactions at Any Time During All 11 Ixekizumab Psoriasis Studies

Across all 11 ixekizumab psoriasis studies, 5689 individuals received at least 1 dose of ixekizumab and 840 (14.8%)

TABLE 2.

Concomitant Medications Used to Treat Injection-Site Reactions: First 12 Weeks of UNCOVER-1, -2, and -3

	IXE Q2W N=1167	ETN N=739
Patients who received ≥1 concomitant medication[a]	17 (1.5%)	12 (1.6%)
Aminoalkyl ethers	3 (0.3%)	3 (0.4%)
Piperazine derivatives	4 (0.3%)	3 (0.4%)
Anilides	2 (0.2%)	0
Antihistamines for topical use	2 (0.2%)	0
Antihistamines for systemic use	2 (0.2%)	3 (0.4%)

ETN, etanercept;
IXE Q2W, 80 mg ixekizumab every 2 weeks.
[a]Concomitant medications used to treat ≥2 patients are reported in the table.

reported injection-site reactions. Consistent with the 12-week induction period of the UNCOVER studies, the most common injection-site reactions across all 11 studies were classified as nonspecified (9.5%), erythema (3.1%), and pain (1.7%). After the first 2 weeks of treatment, the frequency of injection-site reactions decreased and then remained stable (≤4.2%) out to week 156 (Figure 3). A similar pattern was reported for pain and erythema. The incidence of injection-site pain was stable at 0.1% and injection-site erythema remained below 0.3% from week 36 to week 156.

There were no serious adverse events related to injection-site reactions.

Relationship Between Injection-Site Reaction, Previous Exposure to Biologic Agents, Race, and Development of ADA

Of the 1167 patients treated with IXE Q2W in the 12-week induction period of the UNCOVER studies, 13.7% of those who had previously used biologic therapy reported injection-site reactions relative to 18.0% of patients who had never used biologic therapy. In a subgroup analysis of injection-site reactions by race, the frequency of injection-site reactions among White, Asian, and Other races was comparable with the global population during the 12-week induction period (Figure 1). No association of injection-site reactions and TE-ADA against ixekizumab was established (Table 3).

DISCUSSION

In clinical trials demonstrating the efficacy and safety of ixekizumab as a treatment for moderate-to-severe psoriasis, injection-site reactions were among the most commonly reported adverse events. This report details the injection-site reactions reported in ixekizumab psoriasis trials to provide more comprehensive information for patients and clinicians. While injection-site reactions were not reported by all patients who received ixekizumab, it is important that patients be informed of the possibility and reported pattern of injection-site reactions.

Typically, injection-site reactions were reported within the first 2 weeks of treatment. In addition, longer-term safety data, summarized by 2 week intervals through 156 weeks of treatment, demonstrate a decrease in the rate with longer durations of ixekizumab exposure. The frequencies of the injection-site reactions tapered off rapidly and over time. The reactions were generally mild-to-moderate in severity, nonserious, resolved spontaneously without concomitant treatment, and did not usually lead to treatment discontinuation. The most typically described injection-site reaction was characterized as a clearly red papule, but there were cases (13% to 15%) in which the reaction was of greater magnitude (ie, bright red [1 patient had a dark scar] or ≥2 mm papule). In subgroup analyses, no relationship between injection-site reactions and previous exposure to biologic agents, race, or development of TE-ADA were identified. Consistent with the findings that a few injection-site reactions were characterized as more remarkable, a case study reported a 47-year-old female whose injection-site reaction resulted in significant coverage and discontinuation of treatment.[17] Apart from this case report, recall injection-site reactions have been reported postmarketing, although such a phenomenon was not reported during clinical trials.

In general, the etiology of injection-site reactions is multifactorial and may be associated with both immunologic and non-immunologic

FIGURE 3. Incidence (± 95% CIs) of injection-site reactions over 156 weeks of treatment across 11 ixekizumab clinical trials of psoriasis (N= 5689 patients). (A) Injection-site reactions in the first 12 weeks of treatment. (B) Injection-site reactions from week 12 to 156. CI, confidence interval; n=number of patients who entered each time interval.

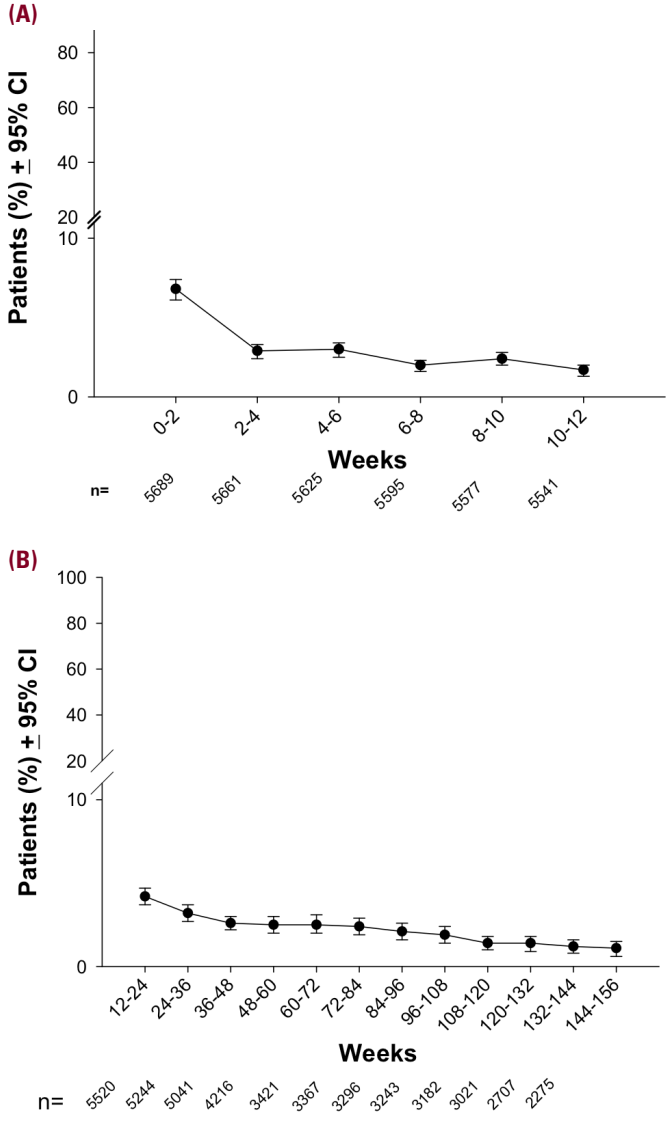


TABLE 3.

TE-ADA Status: First 12 Weeks of UNCOVER-1, -2, and -3		
	IXE Q2W Nx=1150	PBO Nx=781
TE-ADA positive status, n (%)	103 (9.0%)	4 (0.5%)
TE-ADA positive and ≥1 injection-site TEAE, n/n (%)	12/103 (11.7%)	0
TE-ADA negative status, n (%)	1047 (91.0%)	777 (99.5%)
TE-ADA negative and ≥1 injection-site TEAE, n/n (%)	163/1047 (15.6%)	26/777 (3.3%)

IXE Q2W, 80 mg ixekizumab every 2 weeks;
Nx, number of patients with an evaluable baseline sample and at least 1 evaluable postbaseline sample;
PBO, placebo
TE-ADA, treatment-emergent antidrug antibody.

factors.[3] Potential patient risk factors for adverse reactions can include race, gender, age, concomitant illness, concomitant medications, psychologic factors, and comorbidities. Similarly, numerous factors may be associated with the molecule or injection, such as molecular weight, volume, speed of injection, and excipients. For ixekizumab, the pH is 5.3–6.1,[12] and its excipients were balanced to support chemical and structural stability while minimizing irritation (data on file). Overall, given the multitude of variables, the exact pathogenesis of injection-site reactions, including injection pain, is not known for ixekizumab.

One difference between the ixekizumab clinical trials and the experience of patients postmarketing is that the clinical trials, and hence the data in this report, were primarily conducted with self-administration using a prefilled syringe in contrast to increased use of the autoinjector device postmarketing. Ixekizumab should be kept at room temperature for 30 minutes before administration and the cap should not be removed. The autoinjector "instructions for use" should be reviewed by all patients, even those with prior experience with biologic injections, due to the difference in the technique for proper administration of the ixekizumab autoinjector. Some patients may find that they prefer the control of using the prefilled syringe and may benefit from this option if they are uncomfortable with the autoinjector.

This report includes one of the largest cohorts of patients being treated with an IL-17A antagonist for the treatment of moderate-to-severe psoriasis. When interpreting the results, it should be considered that the placebo-controlled periods of the UNCOVER studies are limited to 12 weeks. Additionally, solicited injection-site reactions were collected using a standardized questionnaire only if patients reported an event associated with the injection; therefore, minor events might be underreported. In the analyses described within, the most common term reported was "nonspecified" injection-site reaction. As a result, specific forms of injection-site reactions might be underreported. Other factors that may impact the reporting of injection-site reactions may be documentation errors, potentially related to investigator fatigue as well as a patient's recall bias or reservation to report to the investigator. This report is limited to data collected in clinical trials. Based on limited preliminary postmarketing data, the presented profile of injection-site reactions is consistent with real-world use, although the magnitude of postmarketing reporting could be different.

In conclusion, previously reported safety data supports an overall favorable safety profile of ixekizumab,[5,7-10] including injection-site reactions as among the commonly reported adverse events. The injection-site reactions reported with ixekizumab treatment have been tolerable and clinically manageable, and the incidence decreases over time. These data may help clinicians counseling patients experiencing such reactions. Clinicians and patients should balance the risk of potential injection-site reactions with the efficacy benefits of the drug.

DISCLOSURES

NH Shear has acted as a paid consultant for AbbVie, Amgen, Celgene, Janssen, Leo Pharma, Eli Lilly and Company, Novartis, and Valeant.

C Paul has been investigator or consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermira, Inc., Eli Lilly and Company, GlaxoSmithKline, Janssen, Leo Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi Genzyme, and UCB Pharma.

A Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Inc., Eli Lilly and Company, Genentech/Roche, GlaxoSmithKline, Janssen, Leo Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, Valeant, and Vidac, and as a paid speaker for Eli Lilly and Company, Janssen, Regeneron, and Sanofi Genzyme.

M Gooderham has been an investigator, speaker, advisory board member, or consultant for Amgen, AbbVie, Boehringer Ingelheim, Celgene, Dermira, Inc., Eli Lilly and Company, Galderma, GlaxoSmithKline, Janssen, Kyowa Kirin, Leo Pharma, Medimmune, Merck, Novartis, Pfizer, Roche, Regeneron, Sanofi Genzyme, Takeda, UCB, and Valeant.

C Leonardi has been a consultant/advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Dermira Inc., Eli Lilly and Company, Janssen, Leo Pharma, Pfizer, Sandoz, UCB, and Vitae, has been an investigator for Actavis, AbbVie, Amgen,

Boehringer Ingelheim, Celgene, Coherus, Cellceutix, Corrona, Dermira, Inc., Eli Lilly and Company, Galderma, Glenmark, Janssen, Leo Pharma, Merck, Novartis, Novella, Pfizer, Sandoz, Stiefel, Wyeth, and has been a speakers bureau participant for AbbVie, Celgene, Novartis, and Eli Lilly and Company.

K Reich has served as adviser and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo Pharma, Eli Lilly and Company, Medac, Merck Sharp & Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Sanofi, Takeda, UCB, and Xenoport.

M Ohtsuki has received honoraria as consultant and/or advisory board member and acted as paid speaker and/or participated in clinical trials sponsored by AbbVie, Boehringer Ingelheim, Celgene, Eisai, Janssen, Kyowa-Kirin, Leo Pharma, Eli Lilly and Company, Maruho, Novartis, Pfizer, and Mitsubishi-Tanabe.

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