centres. Randomized controlled studies are required to confirm that our patients should be offered more individualized treatment regimens.

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Integrated safety analysis of treatment-emergent eczematous reactions in patients with moderate-to-severe psoriasis treated with ixekizumab, etanercept and ustekinumab

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Dear Editor, Eczema and eczematous reactions induced by interleukin (IL)-17 inhibitors in patients with psoriasis are established adverse events.[1] They may be reported as adverse events (AEs) in up to 12·1% of patients on anti-IL-17 treatment in controlled clinical trials.[2–5] We performed an integrated safety analysis of 13 clinical studies to evaluate the frequency and management of the treatment-emergent AEs (TEAEs) of eczema and clinical variants in patients with moderate-to-severe psoriasis treated with ixekizumab (IXE), a selective inhibitor of IL-17A, to understand better the nature of these events.

Integrated analysis of 5930 patients with psoriasis (17 367 patient-years) treated with IXE for up to 5 years in a clinical trial setting showed that 361 patients (6·1%) had TEAEs. These events were defined by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of eczema, dermatitis, dyshidrotic eczema, allergic dermatitis, atopic dermatitis, asteatotic eczema, neurodermatitis, hand dermatitis, nummular eczema and vesicular eczema. Of these 361 patients, 335 (92·8%) were < 65 years old, 245 (67·9%) were male, and 289 (80·1%) were of white ethnicity. The baseline characteristics are reflective of the entire study population. At the time of IXE treatment initiation, 78 patients (21·6%) had undergone previous treatment with biologics, and 74 (20·5%) had a history of atopy and/or allergic disease.

Of the 361 patients with eczematous reactions, 268 (74·2%) experienced one event; the mean number of events per patient experiencing at least one eczematous reaction was 1·4. Events were mostly mild, and three patients (0·8%) discontinued IXE due to eczematous reactions. Significant differences were observed between patients who experienced eczematous reactions and those who did not for baseline alcohol use (34·9% vs. 23·3%, respectively, $P < 0·001$), tobacco use (21·1% vs. 14·3%, $P < 0·001$) and history of eczema (3·0% vs. 0·8%, $P < 0·001$). Patients with eczema [n = 169, incidence rate per 100 patient-years (IR) 1·0, 95% confidence interval (CI) 0·8–1.1] and dermatitis (n = 92, IR 0·5, 95% CI 0·4–0·6) accounted for the majority of the 361 patients with eczematous reactions (Table 1). The median times to onset for eczema and dermatitis were 292 and 466 days, respectively. The median duration of AEs was 12·1 weeks (range 0·1–274). Of the 361 patients with eczematous reactions, 64·5% received some treatment, with topical corticosteroids (TCS) as the predominant therapy (46·8%). The median duration of TCS use was 4·6 weeks (range 0·3–267).

Table 1 Incidence rates of cutaneous adverse events (AEs) in patients with psoriasis in clinical trials who received either placebo (PBO), etanercept (ETN), ixekizumab (IXE) or ustekinumab (UST)

	Double-blind 0–12 weeks UNCOVER-2 (NCT01597245) UNCOVER-3 (NCT01646177)			Double-blind 0–52 weeks IXORA-S (NCT02561806)		All IXE exposure up to 5 years
Parameter	PBO	ETN[a]	IXE	UST[b]	IXE	IXE[c]
Total patients	360	739	1463	166	135	5930
Total patient-years[d]	83·2	169·2	336·5	159·5	131·4	17 367
AEs[e,f]	0	5 (3·0)	13 (3·9)	2 (1·3)	5 (3·8)	361 (2·1)
Eczema	0	3 (1·8)	5 (1·5)	0	2 (1·5)	169 (1·0)
Dermatitis[g]	0	2 (1·2)	6 (1·8)	0	1 (0·8)	92 (0·5)
Dyshidrotic eczema	0	0	1 (0·3)	0	1 (0·8)	33 (0·2)
Allergic dermatitis	0	0	0	0	0	26 (0·1)
Atopic dermatitis	0	0	0	0	0	20 (0·1)
Asteatotic eczema	0	0	0	1 (0·6)	0	19 (0·1)
Neurodermatitis	0	0	0	1 (0·6)	1 (0·8)	19 (0·1)
Hand dermatitis	0	0	1 (0·3)	0	0	17 (0·1)
Nummular eczema	0	0	0	0	0	7 (0·0)
Vesicular eczema	0	0	0	0	0	1 (0)
Relative risks for all AEs	IXE vs. ETN: 1.3 IXE vs. PBO: not applicable			IXE vs. UST: 3·0		

The results are descriptive and presented as *n* (incidence rate per 100 patient-years) unless noted otherwise. The psoriasis studies are I1F-EW-RHBZ, I1F-JE-RHAT, I1F-MC-RHAG, I1F-MC-RHAJ, I1F-MC-RHAZ, I1F-MC-RHBA, I1F-MC-RHBC, I1F-MC-RHBL, I1F-MC-RHBP, I1F-MC-RHBQ, I1F-MC-RHBS, I1F-MC-RHBU and I1F-US-RHBO. [a]Etanercept 50 mg twice weekly. [b]Ustekinumab 45 mg or 90 mg at weeks 0, 4, 16, 28 and 40. [c]Ixekizumab 80 mg every 2 weeks or every 4 weeks after a 160-mg starting dose. [d]Total time patients were in each treatment period. [e]Adverse events are coded using Medical Dictionary for Regulatory Activities version 22·1. [f]Contact dermatitis was not included. [g]Dermatitis did not include psoriasis.

Analyses comparing rates for IXE, placebo (PBO), etanercept (ETN) and ustekinumab (UST) showed no clinically meaningful differences in overall IRs for eczematous reactions between IXE and other treatments (Table 1).

With increased use of biologic therapies for psoriasis, reports of eczematous reactions potentially associated with their use have been observed, in some cases in up to 12·1% of patients. Here we report an integrated safety analysis from 13 psoriasis studies regarding the frequency, clinical subtypes, predisposing factors, time of onset and treatment discontinuations in patients developing eczematous reactions while receiving IXE and, for comparison, PBO, ETN and UST. Numerical values for history of allergic events and history of eczema were higher for those patients who developed eczematous reactions. Numerical differences in alcohol and tobacco consumption were also noted, although the significance of these associations is not clear. Our findings differ from previously published data;[5] however, those results were limited by a small sample size and no information about predisposing factors.

Real-world evidence depicts data from more diversified settings than clinical trials. While the two types of data supplement each other, data from clinical trials allow for more stringent analysis due to the controlled environment. Although patients in clinical trials may not entirely reflect real-world patient populations, our integrated safety analysis included 5930 patients, minimizing selection and information bias. Limitations of this analysis include potential misdiagnosis or reporting error of eczematous reactions. For instance, paradoxical psoriasis, an adverse event more specific for tumour necrosis factor-α inhibitors, can sometimes resemble eczema, and differentiation in the clinical setting could be ambiguous.[6] Also, the patient-years method used in reporting AEs may potentially miss early-onset or late-onset AEs.[7] While the difference was not statistically significant, numerically more events were reported for patients receiving IXE than those receiving ETN or UST.

In summary, trial data comprising 17 367 patient-years demonstrated that the overall frequency of eczematous reactions was low across the treatments, and no statistically significant differences were noted between IXE, ETN and UST. The events were generally mild in nature, appeared more often in patients with a history of eczema, and rarely led to treatment discontinuation.

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