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No reactivation of tuberculosis in patients with latent tuberculosis infection receiving ixekizumab: A report from 16 clinical studies of patients with psoriasis or psoriatic arthritis

To the Editor: Reactivation of latent tuberculosis infection (LTBI) and/or active tuberculosis (TB) has been associated with certain immunomodulatory therapies for psoriasis (Pso) or psoriatic arthritis (PsA).[1] Ixekizumab (IXE), a high-affinity anti–interleukin (IL)-17A monoclonal antibody, has shown safety and efficacy in patients with these conditions,[2,3] but more data on the risk of TB infection are needed.

This post hoc analysis of integrated safety data (derived via naive pooling) from 13 clinical trials in Pso[4,5] and 3 studies of PsA[3] evaluated treatment-emergent (TE) LTBI in IXE-treated patients (Fig 1). The purified protein derivative skin test or QuantiFERON-TB Gold assay (Cellestis Inc, Valencia, CA, USA) was used for LTBI assessment. Patients testing negative for LTBI at screening or less than 3 months before baseline were included in this analysis. Patients with a positive LTBI test result at screening could enroll in the studies after initiating LTBI-specific therapy if they met all other study inclusion criteria, but they were otherwise excluded from this analysis. Annual LTBI testing and discontinuation of patients with TE-LTBI after randomization were required per protocol. Amended protocols allowed patients with TE-LTBI to continue IXE treatment if they received LTBI therapy.

In this analysis, 7016 IXE-treated patients, 5898 with Pso (16,313 patient-years of IXE exposure; 1010 mean days of exposure) and 1118 with PsA (1822 patient-years of IXE exposure; 596 mean days of exposure) were evaluated for TE-LTBI during the study program (Fig 2). A total of 101 (1.7%) patients with Pso developed TE-LTBI; of these, 65 discontinued according to study protocol. Of the 36 patients who remained in the studies, LTBI-specific therapy was initiated in 30 patients, while 6 patients did not receive LTBI-specific treatment (Fig 2). In total, 5 patients with TE-LTBI subsequently discontinued IXE in the Pso studies, 3 patients in the LTBI-treatment group, and 2 in the group without LTBI treatment. Of the 32 (2.9%) patients who developed TE-LTBI in the PsA studies, 20 were discontinued per protocol. Seven of the 12 patients continuing IXE treatment received LTBI therapy (1 patient discontinued IXE); 5 patients were not treated for LTBI (of these, 3 also discontinued IXE). No reactivation of TB was reported in the 6 patients with TE-LTBI in the absence of LTBI-specific therapy during IXE treatment.

This integrated safety analysis, reporting data from one of the largest IXE databases, identified a small number of patients with TE-LTBI, most of whom received LTBI-specific therapy. No cases of reactivation of TB were identified.

Limitations of this analysis are the small number of events, a missing control group, and the limited observation period, preventing long-term risk assessment for active TB. Data interpretation needs to take into consideration that these studies were designed to assess the overall safety and the efficacy of IXE and not to investigate the risk of TB reactivation.

Nevertheless, these data contribute to the growing evidence for the use of therapeutic antibodies targeting IL-17A, such as IXE, in patients with LTBI. Real-world data are needed to address the clinical question of the potential long-term risk for reactivation of TB under anti–IL-17 therapy.

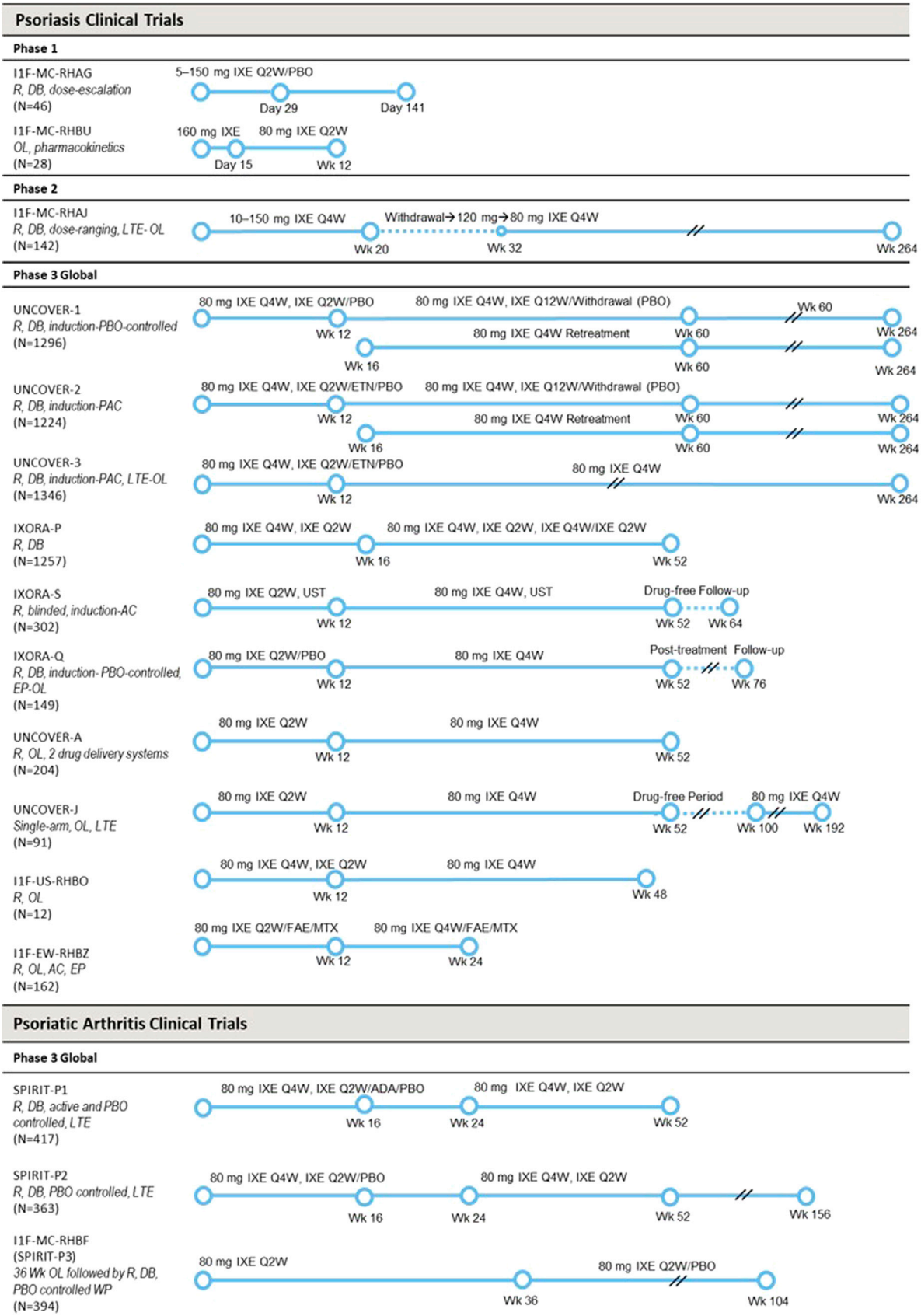

Fig 1. Study design. *AC*, Active comparator; *ADA*, adalimumab; *DB*, double-blind; *EP*, extension period; *ETN*, etanercept; *FAE*, fumaric acid esters; *IXE*, ixekizumab; *LTE*, long-term extension; *MTX*, methotrexate; *OL*, open label; *PAC*, placebo-controlled and active comparator; *PBO*, placebo; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q12W*, every 12 weeks; *R*, randomized; *UST*, ustekinumab; *Wk*, week; *WP*, withdrawal period.

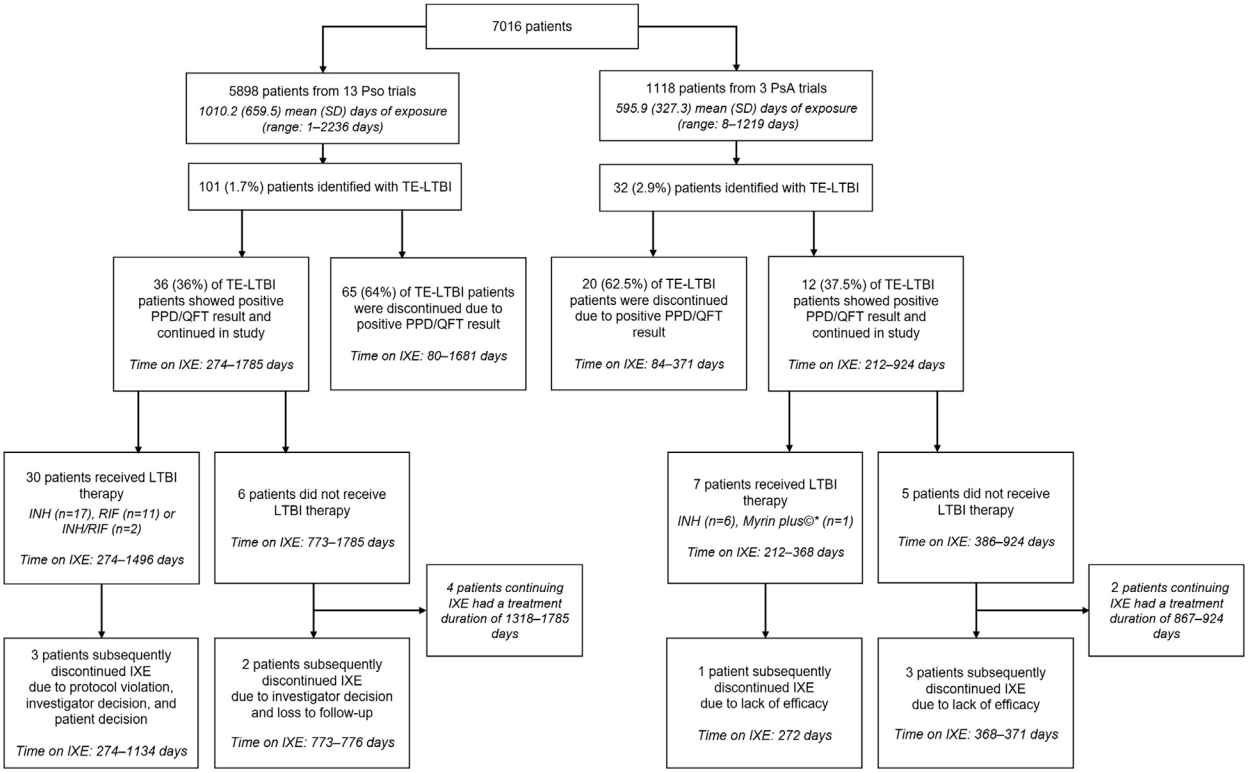

Fig 2. Patients receiving at least 1 dose of ixekizumab with TE-LTBI pooled from 16 clinical trials. *Myrin Plus (Wyeth Pakistan Ltd, Karachi, Pakistan) is ethambutol hydrochloride, isoniazid, pyrazinamide, and rifampicin. *INH*, Isoniazid; *IXE*, ixekizumab; *LTBI*, latent tuberculosis infection; *PPD*, purified protein derivative test for tuberculosis; *PsA*, psoriatic arthritis; *Pso*, psoriasis; *QFT*, QuantiFERON-TB Gold (Cellestis Inc, Valencia, CA, USA); *RIF*, rifampicin; *SD*, standard deviation; *TE*, treatment-emergent.

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Table I. Demographics and surgery information

Characteristics of study population	n	%
Sex		
Male	37	74
Female	13	26
Age, y		
Mean	70.6	
Standard deviation	10.0	
Median	70.0	
Race		
White	49	98
American Indian/Alaska Native	1	2
Surgery location		
Cheeks	14	28
Forehead	12	24
Neck	9	18
Preauricular	5	10
Temple	3	6
Eyelid	3	6
Posterior auricular	2	4
Chin	1	2
Nose	1	2
Surgeon code		
Surgeon	24	48
Fellow	19	38
Resident	7	14
Indication for surgery		
Mohs	45	90
Excision	5	10
Mean wound closure length, cm	5.7	

Wound eversion versus planar closure for wounds on the face or neck: A randomized split-wound comparative effectiveness trial

To the Editor: Minimization of postsurgical skin defects remains a challenging aspect of reconstruction after Mohs micrographic surgery.[1] Although some experts advocate for the necessity of wound eversion for ideal scar formation,[2-4] a 2015 study conducted at our institution showed that wound eversion was not associated with better cosmetic outcomes when compared to planar closure.[5] It has been suggested that certain body regions are disproportionally responsive to the effects of eversion.[3] In this follow-up investigation of our original study, we sought to establish whether wound edge eversion improves the cosmetic outcome of operative wounds closed exclusively on the head or the neck.

In this prospective, randomized, split-scar and evaluator-blinded comparison trial, we evaluated the effects of wound eversion on scar formation of postoperative closures on the head and neck. Enrollment and follow-up were completed between October 2015 and July 2017 at the University of California, Davis dermatology clinic. Study design and statistical methods and analysis were largely held consistent with our previous article.[5] Fifty patients were enrolled; per our a priori analysis, 43 patients were required to achieve a power of 90% in detecting a 3-point difference in the 60-point Patient Observer Scar Assessment Scale (POSAS, version 2.0) scale.

Before study commencement, a training session was held for all surgeons to standardize planar and everting closure techniques. Each patient simultaneously received both everted and planar interventions in a split-scar format, achieving wound eversion through buried vertical mattress sutures and simple running cuticular sutures. Comparisons of POSAS scores, scar width, scar elevations, and mean total complications were performed at the 3-month follow-up visit. Data were analyzed using a paired *t* test for parametric data. Categorical data were examined using the Wilcoxon signed rank test for nonparametric data.

A total of 46 patients completed a 3-month postinterventional follow-up visit (Table I). At 3 months, clinician- and patient-determined POSAS and overall