Research letter

Prevalence and outcome of latent tuberculosis in patients receiving ixekizumab: integrated safety analysis from 11 clinical trials of patients with plaque psoriasis

DOI: 10.1111/bjd.17604

Dear Editor, Tuberculosis (TB) is one of the top 10 causes of death worldwide, with approximately 10·0 million (range 9·0–11·1) active TB cases in 2017, occurring in all countries and age groups, and estimates of 1·7 billion people having latent TB infection (LTBI).[1,2] The lifetime risk for reactivation of LTBI is 5–10%,[1] and some immunosuppressant therapies increase this risk.[3] Data on TB risk after anti-interleukin (IL)-17A treatment in people are limited,[4–7] with no cases of LTBI reactivation reported so far.[3]

We performed a post hoc analysis of the integrated safety data from 11 phase I–III clinical trials of patients with moderate-to-severe plaque psoriasis treated with any dose of the anti-IL-17A antibody ixekizumab.[5] We report the baseline rates and long-term outcomes of 5730 patients, including patients with a history of treated active TB or newly diagnosed LTBI. At screening, patients diagnosed with active TB were excluded from participation, whereas patients with a documented history of successfully treated TB without subsequent re-exposure could enter the study. Presumed LTBI was based on a positive tuberculin skin test (TST), defined as ≥ 5 mm induration 2–3 days after intradermal injection, or interferon-γ release assay [IGRA; QuantiFERON®-TB Gold or Gold-In-Tube (Cellestis, CA, U.S.A.), or T-SPOT.TB® (Oxford Diagnostic Laboratories, Memphis, TN, U.S.A.)]. Patients with LTBI were included after they underwent ≥ 4 weeks of LTBI-specific therapy (isoniazid and/or rifampicin) without hepatotoxicity and completed an appropriate course of treatment during the trial. Patients were retested annually. The integrated analysis included 5730 patients with a total of 13 479 patient-years' exposure to ixekizumab (median 1006 days, range 1–2236). The majority were white (n = 5028; 87·8%) and male (n = 3874; 67·6%) with a mean ± SD age of 45·9 ± 13·1 years and duration of psoriasis of 18·8 ± 12·2 years. Multiple data collection methods were used to maximize the identification of historical TB cases and/or presumed LTBI at baseline. We identified 188 patients (3·3%) meeting one or more of the following, based on medical history data-entry terms: (i) positive IGRA results (n = 111; 1·9%); (ii) positive TST results (n = 31; 0·5%); (iii) documented history of TB in the medical history data-collection form [n = 104 (1·8%): one pulmonary TB; three TB (unspecified); one erythema induration; 95 LTBI or positive TB test; four unspecified]; and (iv) documented history of completing TB treatments in the previous or concomitant medication data-collection form [n = 123 (2·1%): one TB, 101 LTBI or positive TB test; 21 unspecified]. These 188 patients were enrolled in the studies: upon retesting, four had positive IGRA/TST results after 286–819 days on ixekizumab treatment, with three discontinuing and one continuing ixekizumab.

The risk of active TB in the general population varies significantly worldwide and is associated with LTBI prevalence.[1,2] The majority of the study population (n = 4676; 81·6%) came from countries with a low incidence rate of active TB.[1] Region-specific analysis of the presumed LTBI cases in ixekizumab-treated populations confirmed a smaller proportion of positive IGRA/TST results/LTBI cases at baseline in lower-burden regions than in regions with a higher burden of active TB (Table 1). During ixekizumab treatment, 72 patients (1·3%) developed treatment-emergent LTBI or positive IGRA/TST results. Patients identified at < 52 weeks discontinued from the study owing to protocol requirements; after protocol amendment, patients identified at ≥ 52 weeks with no signs of active TB could remain in the study with concurrent LTBI therapy.[7] During the observation period (including a protocol-

Table 1 Baseline latent tuberculosis cases by region ranked according to World Health Organization (WHO) tuberculosis incidence rate

WHO region	TB incidence[a]	Safety population (n = 5730)[b]	LTBI baseline[c]
The Americas	28	3238 (56·5)	82 (2·5)
Europe	30	2114 (36·9)	83 (3·9)
Western Pacific	94	378 (6·6)	23 (6·1)
Eastern Mediterranean	113	0 (0)	0
South-East Asia	226	0 (0)	0
Africa	237	0 (0)	0
All Regions	133	5730 (100)	188 (3·3)

Data cut-off date was February 2017. TB, tuberculosis; LTBI, latent tuberculosis infection. [a]Active TB infection cases/100,000 population (data from WHO).[1] [b]Patients receiving ≥ 1 dose of ixekizumab in published studies (see Langley *et al.*).[5] [c]Includes cases positive for any of the following: tuberculin skin test, interferon-γ release assay, history of TB, completed TB treatments.

specified minimum 12-week follow-up after the last scheduled or early termination visit), no cases of active TB were reported in the ixekizumab clinical development programme.

Group size and study length are important factors when investigating infrequent safety events, including LTBI reactivation or *Mycobacterium tuberculosis* infection. This report includes one of the largest cohorts of patients treated with an IL-17A inhibitor and represents one of the longest exposures to ixekizumab reported to date. Nevertheless, this study is limited by the lack of a suitable longer-term control group.

Available data do not indicate that anti-IL-17A treatments increase the risk of active TB in patients with a history of active TB or with LTBI.[5–8] The findings are encouraging and of particular value to physicians who treat patients with an elevated risk of TB. Nevertheless, ixekizumab should not be administered to patients with active TB, and prophylactic treatment should be initiated in patients with LTBI before starting ixekizumab treatment and completed in line with country-specific guidelines. Regular evaluation of patients for risk factors, and signs and symptoms of active TB is indicated while on any immunomodulatory treatment.

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Funding sources: Eli Lilly and Company (Indianapolis, IN, U.S.A.) sponsored this study, and medical writing (Kaye L. Stenvers, Syneos Health) and editing support (Antonia Baldo, Syneos Health).

Conflicts of interest: Research support and consulting fees have been received from Eli Lilly and Company, Novartis, Pfizer (R.R., F.V., E.N.C.), AbbVie, LeoPharma, Janssen (R.R., F.V.), Galderma (R.R., E.N.C.) and Merck (F.V.). W.X., B.P., S.G., E.R. and S.R.M. are employees of and may own stock in Eli Lilly and Company.