BJD
British Journal of Dermatology

The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection

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Accepted for publication
30 June 2012

Funding sources
This study was funded by Janssen Research & Development, LLC, Spring House, PA, U.S.A.

Conflicts of interest
Listed in the Appendix.

DOI 10.1111/j.1365-2133.2012.11142.x

Summary

Background Ustekinumab is a monoclonal antibody that targets interleukin (IL)-12/23 p40 to treat psoriasis. The IL-12 pathway is also important in regulating immunity to *Mycobacterium tuberculosis*.

Objectives To evaluate the safety of isoniazid (INH) prophylaxis for newly identified latent tuberculosis infection (LTBI) in ustekinumab-treated patients with psoriasis.

Methods Safety data from 3177 psoriasis patients evaluated across five phase III trials of ustekinumab (45 or 90 mg) conducted in North America, Europe and Asia were analysed. LTBI was diagnosed based on positive tuberculin skin test or QuantiFERON®-TB test (Cellestis, Carnegie, Vic., Australia) without evidence of active tuberculosis.

Results At baseline, 101/2898 (3·5%) non-Asian and 66/279 (23·7%) Asian patients were newly identified with LTBI, and all were treated with INH. Through week 12, among patients who received INH, rates of adverse events (AEs) representative of INH toxicity were generally comparable between control and ustekinumab-treated patients, as well as between ustekinumab dose groups. Markedly abnormal alanine transaminase values occurred with comparable incidences between control and ustekinumab-treated patients. The rate of study agent discontinuation due to INH toxicity was low (5/167, 3·0%) and comparable between control and ustekinumab groups through week 12. The rate of INH-related AEs did not increase disproportionately through week 28. No cases of active tuberculosis were reported in patients who received concomitant INH starting at baseline.

Conclusions Across five trials of ustekinumab-treated patients with psoriasis, no cases of LTBI reactivation were observed in patients receiving concomitant INH prophylaxis for LTBI. INH prophylaxis was generally well tolerated by these patients with psoriasis.

The incidence of tuberculosis varies worldwide, with the highest global burden in South-East Asia (35%), Africa (30%) and Western Pacific regions (21%).[1] Of those infected with *Mycobacterium tuberculosis*, only about 5–10% develop active tuberculosis during their lifetime.[2] Most other patients carry latent tuberculosis infection (LTBI), remaining asymptomatic and noninfectious while their host immune response contains the infection. The immune system may then eradicate the LTBI, or the infection may remain and become activated at a later point in time, sometimes several years later.[3] However, patients with LTBI and an impaired immune system, such as those co-infected with human immunodeficiency virus or those receiving immunosuppressive treatment, have a much higher likelihood of developing active tuberculosis.[4,5]

The immune response produced by the interleukin (IL)-12 and IL-23 pathways is important for host protection against bacterial and parasitic infections and intracellular pathogens.[6–9] Studies show that individuals with inborn errors in the IL-12/23–interferon (IFN)-γ circuit are particularly vulnerable to infections caused by mycobacteria, especially atypical mycobacterial infections as well as *M. tuberculosis*.[10] Therefore, it is important to identify asymptomatic LTBI and mitigate the risk of potential LTBI reactivation with appropriate chemoprophylaxis in patients who are treated with an anti-IL-12/23 agent.

Ustekinumab, a human monoclonal antibody against the shared p40 subunit of IL-12 and IL-23 cytokines, is approved for the treatment of moderate-to-severe plaque psoriasis. Five phase III clinical trials conducted in North America and Europe (PHOENIX 1, PHOENIX 2 and ACCEPT),[11–13] Korea and Taiwan (PEARL)[14] and Japan (Japanese trial)[15] have confirmed the efficacy of ustekinumab in the treatment of psoriasis across different ethnic populations and geographical regions. In this report, we further analyse the data collected across these trials to evaluate the safety of isoniazid (INH) prophylaxis for newly identified LTBI in patients with psoriasis treated with ustekinumab.

Materials and methods

Study designs

The PHOENIX 1, PHOENIX 2, ACCEPT, PEARL and Japanese trials included in this analysis were all randomized, blinded, controlled, parallel-group studies that evaluated the efficacy and safety of ustekinumab in patients with moderate-to-severe psoriasis. PHOENIX 1, PHOENIX 2, PEARL and the Japanese trial were placebo-controlled trials, while ACCEPT was an active-comparator trial (ustekinumab vs. etanercept).

Details of the trial designs have been reported previously.[11–15] Briefly, in PHOENIX 1, PHOENIX 2 and the Japanese trial, patients were randomized to treatment with ustekinumab 45 or 90 mg by subcutaneous injection at weeks 0, 4, and every 12 weeks thereafter or placebo at weeks 0 and 4 with crossover to ustekinumab 45 or 90 mg at weeks 12, 16, and every 12 weeks thereafter. The PEARL study design was similar, but only the 45 mg dose of ustekinumab was evaluated. All five studies had a controlled period from weeks 0 through 12. After week 12, all studies (with the exception of ACCEPT) had a similar design through week 28. In ACCEPT, patients were randomized to ustekinumab 45 or 90 mg at weeks 0 and 4 or etanercept 50 mg twice weekly during the controlled period (weeks 0 through 12). Per the study protocol, treatment was interrupted at week 12 and restarted if psoriasis recurred; patients randomized to ustekinumab 45 or 90 mg resumed ustekinumab treatment at their respective dose and patients randomized to etanercept 50 mg received ustekinumab 90 mg.

All patients were required to provide written informed consent prior to the initiation of any study-related procedures, and either institutional review boards or ethics committees approved the study protocols at each site.

Eligibility criteria, including those related to tuberculosis

The patient selection criteria were similar across the five trials, and details of the enrolment criteria have been reported previously.[11–15] Briefly, eligible patients were adults who had a diagnosis of moderate-to-severe plaque psoriasis for at least 6 months prior to study entry and no history of active or latent tuberculosis. In all five studies, LTBI was defined as a positive tuberculin skin test (TST), according to local country guidelines for immunocompromised patients, or a positive QuantiFERON®-TB test (QFT) (Cellestis, Carnegie, Vic., Australia), and no evidence of active tuberculosis based on symptoms or chest X-ray. Patients with indeterminate QFT results received a second QFT. Patients with newly identified LTBI could be enrolled if concomitant antituberculosis prophylaxis was initiated before, or at the time, the patient received the first dose of study agent. Of note, the Japanese trial required patients with LTBI to have started antituberculosis therapy at least 3 weeks prior to receiving their first dose of study agent. In summary, patients with LTBI were treated according to local country or U.S. guidelines for immunocompromised patients and were required to receive prophylactic antituberculosis treatment, such as INH for at least 6 months. Per protocol, patients who were unable to complete the required course of antituberculosis treatment were discontinued from the study. Consistent across all trials and geographical regions, INH was considered first-line prophylactic LTBI treatment.[16]

Patients with signs and symptoms suggestive of active tuberculosis were ineligible, as were patients with a recent serious infection or a history of chronic or recurrent infection (including hepatitis B or C). The use of the Bacille Calmette–Guérin (BCG) vaccine was not allowed during the study or for 12 months following study agent administration.

Safety evaluations

Because INH-induced toxicity, including transient increases in serum transaminase levels, is typically exhibited by patients within the first 9–12 weeks of INH treatment,[17] safety data from the five trials were evaluated through week 28 using several approaches to capture the majority of INH treatment-related adverse events (AEs). These assessments included: (i) specific AEs consistent with INH toxicity,[18] including hepatobiliary, neurological and gastrointestinal disorders as well as hepatic laboratory AEs [i.e. abnormal laboratory values of alanine transaminase (ALT), aspartate transaminase (AST) or bilirubin] that were identified by study investigators; (ii) laboratory ALT data that were assessed based on predetermined criteria, as detailed in the next section; and (iii) treatment discontinuation due to INH toxicity. In addition, the rates of overall AEs and serious AEs were evaluated.

Data analyses

Safety data for the five studies were summarized and presented by geographical location (non-Asian vs. Asian), latent tuberculosis status (non-INH-treated vs. INH-treated), and study agent

(control vs. ustekinumab). Based on similar study designs through week 28 and common patient selection criteria, data for the non-Asian trials (PHOENIX 1, PHOENIX 2 and ACCEPT) were combined, as were those for the Asian trials (PEARL and Japanese trial). All randomized patients who received at least one injection of study agent were included, and patients were analysed according to the actual treatment received. All patients randomized at baseline to receive placebo or etanercept (ACCEPT) were included in the safety summaries through week 12 only, while data from patients randomized to treatment with ustekinumab at baseline were summarized through week 12 and through week 28; this approach facilitated the comparison of results over two distinct time periods of follow-up for ustekinumab-treated patients.

Through weeks 12 and 28, the following data were summarized: (i) proportions of patients who reported specific AEs consistent with INH toxicity, (ii) proportions of patients with markedly abnormal ALT values (defined as ≥ 100% increase from baseline and a value > 150 IU L^{-1} with normal ranges between 6·0 and 48·0 IU L^{-1} based on the selected central laboratories), (iii) proportions of patients who discontinued the study agent due to INH toxicity, and (iv) proportions of patients who reported overall AEs and serious AEs. In addition, through week 12, the proportions of patients with varying ALT levels were summarized and reported relative to the upper limit of normal (ULN) for patients with normal baseline values: ≤ 1 × ULN; > 1 × ULN and ≤ 2 × ULN; > 2 × ULN and ≤ 3 × ULN; and > 3 × ULN. To consider other clinically relevant measures of liver injury, we also evaluated patients with ALT or AST values ≥ 3 × ULN and serum bilirubin ≥ 2 × ULN per U.S. Food and Drug Administration Guidance.[19]

Results

Baseline demographics

The study cohort consisted of 3177 treated patients: 2898 patients from non-Asian trials and 279 from Asian trials (Table 1). The majority of patients were men, and the mean age ranged from approximately 43 to 49 years across the trials. The mean body weight of patients in the non-Asian trials was higher than that in the Asian trials (Table 1). At baseline, 101 (3·5%) patients in the non-Asian trials and 66 (23·7%) in the Asian trials were treated with INH for LTBI. Of the 167 patients treated with INH across the five studies, 63 (37·7%) received concurrent treatment with pyridoxine (vitamin B_6).

Through week 12 (controlled period)

The mean duration of follow-up for the controlled period was similar across trials (range 11·4–12·2 weeks). AEs observed through week 12 are summarized in Tables 2 and 3. The results of our analyses focused on the INH-treated group, whereas the non-INH-treated group primarily served as a comparative reference.

Through week 12, among INH-treated patients in the non-Asian trials, rates of specific AEs consistent with INH toxicity (gastrointestinal, hepatobiliary or neurological disorders or hepatic laboratory AEs) were reported for 25·7% of patients in the control group, 20·0% in the ustekinumab 45 mg group and 22·2% in the ustekinumab 90 mg group. In the Asian trials, 17·6%, 14·8% and 40·0% of INH-treated patients in the control, ustekinumab 45 mg and ustekinumab 90 mg groups, respectively, experienced these INH-related AEs through week 12 (Table 2). It is important to note that only five INH-treated patients in the Asian trials received ustekinumab 90 mg through week 12, as the 90-mg dose was not studied in the PEARL trial of Korean/Taiwanese patients. As compared with patients who were not treated with INH, significantly higher proportions of patients with hepatic laboratory AEs, markedly abnormal ALT values and various levels of ALT elevations > 1 × ULN were observed among INH-treated patients through week 12 (Table 2 and Fig. 1). However, the proportions of patients who experienced ALT elevations > 3 × ULN among INH-treated patients were similar between the ustekinumab-treated (12·9%) and control (17·9%) patients in the non-Asian trials (Fig. 1). There was no clear association between either the 45- or 90-mg dose of ustekinumab and the rates of overall AEs and serious AEs in INH-treated patients

Table 1 Patient demographics in all treated patients in the non-Asian and Asian trials

	Non-Asian trials[a]		Asian trials[b]	
	Non-INH-treated	INH-treated	Non-INH-treated	INH-treated
Patients treated[c]	2797	101	213	66
Male, n (%)	1904 (68·1)	79 (78·2)	175 (82·2)	55 (83·3)
Race, n (%)				
White	2592 (92·7)	71 (70·3)	0	0
Black	55 (2·0)	7 (6·9)	0	0
Asian	82 (2·9)	13 (12·9)	213 (100·0)	66 (100·0)
Other	68 (2·4)	10 (9·9)	0	0
Mean age, years	45·6	48·7	44·7	42·8
Mean weight, kg	91·8	87·6	72·3	74·7

INH, isoniazid. [a]Non-Asian trials include PHOENIX 1, PHOENIX 2 and ACCEPT. [b]Asian trials include PEARL and the Japanese trial. [c]Includes all patients treated at baseline.

Table 2 Summary of adverse events (AEs) consistent with isoniazid (INH) therapy and overall AEs through week 12 in all treated patients in non-Asian and Asian trials

	Non-Asian trials[a]						Asian trials[b]					
	Non-INH-treated			INH-treated			Non-INH-treated			INH-treated		
	Control[c]	UST 45 mg	UST 90 mg	Control[c]	UST 45 mg	UST 90 mg	Control[d]	UST 45 mg	UST 90 mg[e]	Control[d]	UST 45 mg	UST 90 mg[e]
Patients treated, n	977	843	977	35	30	36	58	98	57	34	27	5
Mean duration of follow-up, weeks	12·1	12·2	12·2	11·9	12·2	12·1	11·7	11·8	11·7	11·4	12·0	11·7
Patients with ≥ 1 AE of interest[f], n (%)	30 (3·1)	35 (4·2)	42 (4·3)	9 (25·7)	6 (20·0)	8 (22·2)	2 (3·4)	3 (3·1)	2 (3·5)	6 (17·6)	4 (14·8)	2 (40·0)
GI disorder	21 (2·1)	22 (2·6)	20 (2·0)	2 (5·7)	0	1 (2·8)	0	0	0	0	0	0
Hepatobiliary disorder	1 (0·1)	1 (0·1)	0	1 (2·9)	0	2 (5·6)	0	2 (2·0)	0	3 (8·8)	2 (7·4)	0
Neurological disorder	3 (0·3)	7 (0·8)	8 (0·8)	1 (2·9)	1 (3·3)	0	1 (1·7)	0	0	1 (2·9)	1 (3·7)	0
Hepatic laboratory AEs[g]	6 (0·6)	8 (0·9)	14 (1·4)	7 (20·0)	5 (16·7)	5 (13·9)	2 (3·4)	1 (1·0)	2 (3·5)	3 (8·8)	1 (3·7)	2 (40·0)
Patients with any markedly abnormal ALT value[h], n (%)	2 (0·2)	3 (0·4)	3 (0·3)	8 (22·9)	2 (6·7)	6 (16·7)	0	0	0	0	2 (7·4)	0
Patients with > 1 markedly abnormal ALT value[h]	0	0	1 (0·1)	6 (17·1)	2 (6·7)	4 (11·1)	0	0	0	0	1 (3·7)	0
Patients who discontinued study agent due to INH toxicity, n (%)	NA	NA	NA	3 (8·6%)	0	1 (2·8)	NA	NA	NA	0	1 (3·7)	0
Patients with ≥ 1 AE, n (%)	540 (55·3)	480 (56·9)	546 (55·9)	27 (77·1)	19 (63·3)	22 (61·1)	41 (70·7)	64 (65·3)	34 (59·6)	22 (64·7)	18 (66·7)	3 (60·0)
Patients with ≥ 1 SAE[i], n (%)	13 (1·3)	14 (1·7)	11 (1·1)	1 (2·9)	0	2 (5·6)	1 (1·7)	0	3 (5·3)	3 (8·8)	0	0

ALT, alanine transaminase; GI, gastrointestinal; NA, not applicable; SAE, serious AE; UST, ustekinumab. [a]Non-Asian trials include PHOENIX 1, PHOENIX 2 and ACCEPT. [b]Asian trials include PEARL and the Japanese trial. [c]Control includes patients who received placebo or etancercept (ACCEPT). [d]Control includes patients who received placebo. [e]Among the Asian trials, UST 90 mg was studied only in the Japanese trial. [f]AEs of interest include AEs representative of INH toxicity. [g]Included AEs reported by the investigators based on assessments of abnormal ALT, aspartate transaminase and bilirubin levels. [h]Based on patients with evaluable post-treatment ALT data and defined by ≥ 100% increase from baseline and a value > 150 IU L^{-1}. [i]Defined as an AE that resulted in any of the following outcomes: death, a life-threatening condition, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or a congenital anomaly or birth defect, regardless of its relationship to study agent.

Table 3 Summary of adverse events (AEs) consistent with isoniazid (INH) therapy and overall AEs through weeks 12 and 28 in patients treated with ustekinumab starting at baseline in non-Asian and Asian trials

	Non-Asian trials[a]				Asian trials[b]			
	Non-INH-treated		INH-treated		Non-INH-treated		INH-treated	
	Through week 12	Through week 28[c]	Through week 12	Through week 28[c]	Through week 12	Through week 28[c]	Through week 12	Through week 28[c]
Patients treated	1820	1819	66	67	155	155	32	32
Mean duration of follow-up, weeks	12·2	27·8	12·1	27·3	11·7	27·6	12·0	28·0
Patients with ≥ 1 AE of interest[d], n (%)	77 (4·2)	121 (6·7)	14 (21·2)	16 (23·9)	5 (3·2)	15 (9·7)	6 (18·8)	7 (21·9)
GI disorder	42 (2·3)	65 (3·6)	1 (1·5)	2 (3·0)	0	1 (0·6)	0	0
Hepatobiliary disorder	1 (0·1)	2 (0·1)	2 (3·0)	2 (3·0)	2 (1·3)	4 (2·6)	2 (6·3)	4 (12·5)
Neurological disorder	15 (0·8)	23 (1·3)	1 (1·5)	1 (1·5)	0	0	1 (3·1)	2 (6·3)
Hepatic laboratory AEs[e]	22 (1·2)	37 (2·0)	10 (15·2)	12 (17·9)	3 (1·9)	10 (6·5)	3 (9·4)	3 (9·4)
Patients with any markedly abnormal ALT value[f], n (%)	6 (0·3)	14 (0·8)	8 (12·1)	11 (16·4)	0	2 (1·3)	2 (6·3)	3 (9·4)
Patients with > 1 markedly abnormal ALT value[f]	1 (0·1)	4 (0·2)	6 (9·1)	7 (10·4)	0	0	1 (3·1)	2 (6·3)
Patients who discontinued study agent due to INH toxicity, n (%)	NA	NA	1 (1·5)	1 (1·5)	NA	NA	1 (3·1)	1 (3·1)
Patients with ≥ 1 AE, n (%)	1026 (56·4)	1361 (74·8)	41 (62·1)	53 (79·1)	98 (63·2)	136 (87·7)	21 (65·6)	28 (87·5)
Patients with ≥ 1 SAE[g], n (%)	25 (1·4)	58 (3·2)	2 (3·0)	2 (3·0)	3 (1·9)	5 (3·2)	0	1 (3·1)

ALT, alanine transaminase; GI, gastrointestinal; NA, not applicable; SAE, serious AE. [a]Non-Asian trials include PHOENIX 1, PHOENIX 2 and ACCEPT. [b]Asian trials include PEARL and the Japanese trial. [c]Values at week 28 are cumulative from baseline. [d]AEs of interest include AEs representative of INH toxicity. [e]Included AEs reported by the investigators based on assessments of abnormal ALT, aspartate transaminase and bilirubin levels. [f]Based on patients with evaluable post-treatment ALT data and defined by ≥ 100% increase from baseline and a value > 150 IU L^{-1}. [g]Defined as an AE that resulted in any of the following outcomes: death, a life-threatening condition, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or a congenital anomaly or birth defect, regardless of its relationship to study agent.

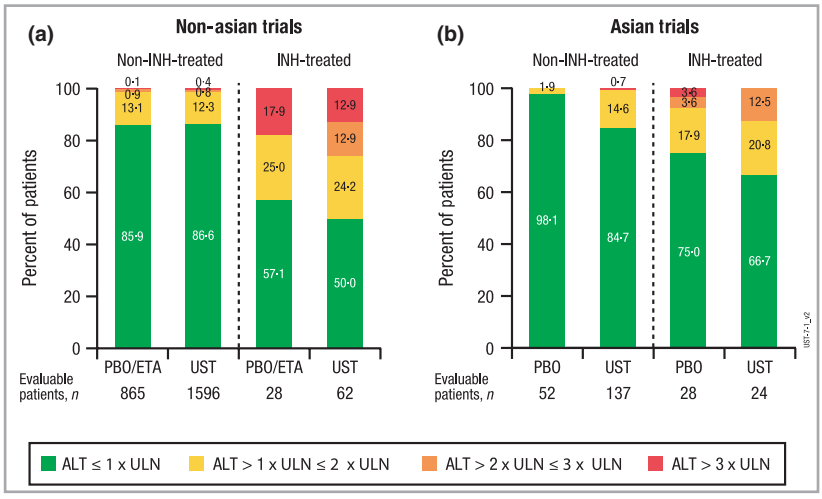

Fig 1. Alanine transaminase (ALT) elevations through week 12 in (a) non-Asian (PHOENIX 1, PHOENIX 2 and ACCEPT) and (b) Asian (PEARL and Japanese) trials by isoniazid (INH) treatment status. ETA/PBO, etanercept (ACCEPT) or placebo (PBO); ULN, upper limit of normal; UST, ustekinumab.

across trials (Table 2). Additionally, none of the six serious AEs reported among INH-treated patients were related to INH toxicity.

Among INH-treated patients, the rates of study agent discontinuation due to INH toxicity through week 12 were low in both the non-Asian (4/101, 4·0%) and Asian (1/66, 1·5%) trials. Among the five patients who discontinued, three were treated with etanercept (ACCEPT) and two were treated with ustekinumab (PHOENIX 2, PEARL). Two of the etanercept-treated patients from ACCEPT and one ustekinumab-treated patient from PHOENIX 2 discontinued INH therapy and received no further antituberculosis treatment; ALT levels returned to normal by week 32 in these patients. The remaining etanercept-treated patient from ACCEPT had markedly abnormal ALT levels beginning at the baseline assessment; these abnormal ALT levels did not resolve as of the last assessment at week 5. The ustekinumab-treated patient from the PEARL study completed an alternate antituberculosis treatment (rifampicin) after INH discontinuation, and follow-up safety assessments showed that the patient's ALT levels had returned to normal by week 20.

Through week 12, three ustekinumab-treated patients (one each from PHOENIX 1, PHOENIX 2 and PEARL) had clinically relevant levels of ALT or AST $\geq 3 \times$ ULN in combination with serum bilirubin $\geq 2 \times$ ULN. The PHOENIX 2 and PEARL patients were receiving concomitant INH treatment, and follow-up safety assessments in both patients showed that elevated hepatic enzyme and bilirubin levels returned to normal by week 20. Note that one of these patients was the PHOENIX 2 patient who discontinued from the study through week 12 due to INH toxicity, as discussed earlier. The PHOENIX 1 patient, who received ustekinumab 45 mg but did not receive INH, had elevated bilirubin/ALT/AST levels and was subsequently discontinued from the study. Although no definitive conclusion can be made regarding this patient, these elevations may have been related to a previous disease of biliary origin, as the patient had presented with a similar episode 2 years earlier.

Through week 12, rates of overall AEs and serious AEs were generally comparable between the ustekinumab and control groups among INH-treated patients in all studies (Table 2). These AE rates were comparable with those in patients who were not treated with INH.

Through week 28

With an additional 16 weeks of follow-up in INH-treated patients who were randomized to ustekinumab at baseline, the cumulative rates of AEs of interest at week 28 were similar to rates at week 12 [23·9% (week 28) and 21·2% (week 12) in the non-Asian trials and 21·9% (week 28) and 18·8% (week 12) in the Asian trials; Table 3]. Likewise, the proportions of patients with markedly abnormal ALT levels did not increase disproportionately between weeks 12 and 28 [12·1% and 16·4%, respectively, in the non-Asian trials and 6·3% and 9·4% in the Asian trials (Table 3)]. Only one additional patient, who was treated with ustekinumab 90 mg but did not receive INH in PHOENIX 1, displayed transient increases in transaminase levels (i.e. ALT/AST $\geq 3 \times$ ULN and serum bilirubin $\geq 2 \times$ ULN at weeks 20 and 24). This patient continued study participation, and ALT/AST levels returned to normal by week 36. After week 12, no additional patients discontinued study treatment due to INH toxicity.

No cases of active tuberculosis were reported in patients who initiated INH chemoprophylaxis with, or before, the first dose of study agent. One patient from the PEARL study, who did not receive INH prophylaxis and had an abnormal chest X-ray but normal TST/QFT at baseline, developed asymptomatic pulmonary tuberculosis. This patient was successfully treated with antituberculosis medications, and further details of this case are reported elsewhere.[20]

Finally, there were no disproportionate increases in the rates of overall AEs or serious AEs in either the INH-treated or the non-INH-treated patients across all five trials through week 28 (Table 3).

Discussion

The National Psoriasis Foundation recommends that patients with psoriasis who are candidates for biologic treatment should be screened for LTBI and, where appropriate, receive antituberculosis prophylaxis before initiating biologic treatment.[5] Patients treated with tumour necrosis factor-α blocking agents are at increased risk for reactivation of LTBI.[22–24] While most cases of LTBI reactivation have been documented in patients with rheumatic diseases,[25–27] there have been recent reports in patients with psoriasis as well.[28–30] Our analysis across five clinical studies indicates that ustekinumab, when given concurrently with INH prophylaxis, does not appear to increase the risk of tuberculosis reactivation or the rate or severity of INH-related toxicity in patients with psoriasis with LTBI.

In the clinical development programme for ustekinumab in psoriasis, we proactively evaluated patients for LTBI and required tuberculosis chemoprophylaxis in all studies, where appropropriate. This was particularly important in the PEARL and Japanese trials because the prevalence of tuberculosis infection is high in Asian countries.[1,2] In our analysis, the incidence of LTBI in the studies conducted in Japan, Taiwan, and Korea (23·7%) was more than sixfold higher than that observed in studies conducted in Western countries (3·5%), although our conservative screening approach may have overestimated the incidence of LTBI in our studies.

INH is commonly employed as first-line tuberculosis chemoprophylaxis in most countries.[16,30] Across the five studies included in our analyses, AEs related to INH toxicity were observed in approximately 20% of INH-treated patients, which is consistent with rates reported in the medical literature.[31,32] Contrary to a previous report among patients with active tuberculosis who were treated with various first-line antituberculosis medications (INH, rifampicin, pyrazinamide and ethambutol),[33] the rate of INH toxicity was similar between

Asian and non-Asian patients in our analysis. In our study, the impact of INH toxicity was most apparent for hepatic laboratory AEs. Larger proportions of patients treated than not treated with INH had hepatic laboratory AEs and markedly abnormal ALT values, which is consistent with observations of INH toxicity reported in the literature.[17] Among INH-treated patients, comparable rates of AEs were observed between control and ustekinumab groups, indicating that ustekinumab treatment did not worsen INH-induced toxicity. Additionally, AE rates did not differ between the 45- and 90-mg groups.

INH-induced toxicity is usually acute and transient, with elevations of ALT commonly observed within 12 weeks of initiating INH treatment.[17] Consistent with these observations, the proportions of patients with INH-related toxicity in our analyses were similar through both 12 and 28 weeks of follow-up, with no significant incremental increase over time. Furthermore, the overall rate of study discontinuation due to INH toxicity was low in these studies, suggesting that the majority of patients (162/167; 97·0%) tolerated INH and can continue ustekinumab treatment as long as they receive INH treatment.

While studies indicate that patients with inborn errors of IL-12/23–IFN-γ-mediated immunity are at high risk for developing *M. tuberculosis* infections,[10] the impact of ustekinumab blockade of IL-12 and IL-23 on pathogen immunity in genetically normal humans is unknown. In this analysis, no cases of active tuberculosis were reported among the 167 patients with psoriasis with newly identified LTBI who were treated concomitantly with INH at, or before, the start of ustekinumab treatment. Among the 3177 treated patients evaluated in these studies, only one asymptomatic patient – who did not receive antituberculosis treatment – experienced reactivation of LTBI. This case, however, further supports the critical need to identify and treat patients with LTBI before, or at the time of, initiation of treatment with ustekinumab to minimize the risk of developing active tuberculosis.

Several limitations warrant caution in the interpretation of our study findings. The relatively small number of patients with LTBI, especially Asian patients, may limit our ability to draw definitive conclusions regarding the impact of concurrent treatment with ustekinumab and INH on both the incidence of LTBI reactivation and INH-related toxicity. Additionally, differences in tuberculosis screening procedures across countries may limit the generalizability of our findings to the broader psoriasis population. Finally, because either positive TST or QFT tests were considered as LTBI in Asian trials, given low specificity of TST testing and BCG vaccination commonly used in these countries, our conservative approach to identify LTBI may have overestimated the true rate.

In conclusion, the findings of this report indicate that, with concomitant use of INH chemoprophylaxis, patients with moderate-to-severe psoriasis and LTBI can initiate ustekinumab treatment without increasing the risk of INH toxicity or tuberculosis reactivation. The incidence of INH toxicity and LTBI reactivation will continue to be monitored closely in patients treated with ustekinumab in clinical trials across indications, in postmarketing surveillance reports, and in global patient registries.

Acknowledgments

The authors thank Cynthia Arnold (Janssen Services, LLC) and Nichole Orlowsky (formerly Janssen Services, LLC) for their medical writing and editorial support; Mai Kato (Janssen Pharmaceutical K.K.) and Yin You (Janssen Research & Development, LLC) for their statistical analysis and programming support; and Daphne Chan, PhD (Janssen Research & Development, LLC) for her critical review of the manuscript.

What's already known about this topic?

- Antituberculosis prophylaxis for latent tuberculosis infection (LTBI) is recommended in patients with psoriasis treated with biologic agents.
- The safety of isoniazid (INH) prophylaxis with concomitant ustekinumab treatment has not been reported.

What does this study add?

- Across five phase III trials of 3177 patients treated with ustekinumab for psoriasis, 167 of whom were concomitantly treated with INH prophylaxis for LTBI, no reactivation of LTBI was observed and INH was generally well tolerated.

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Appendix

T.-F.T. has conducted clinical trials or received honoraria for serving as a consultant for Wyeth Pharmaceuticals (now Pfizer Pharmaceuticals), Serono International SA (now Merck Serono International), UniPharma/Biogen Idec and Janssen-Cilag Pharmaceuticals, and has received speaking fees from Abbott. C.L. has served as a consultant for Abbott, Amgen, Centocor, Eli Lilly and Pfizer, as an investigator for Abbott, Amgen, Celgene, Eli Lilly, Galderma, Genentech, Genzyme, GlaxoSmithKline, Incyte, Janssen, Maruho, Novartis, Novo Nordisk, Pfizer, Schering Plough, Sirtris, Stiefel, Vascular Biogenics and Wyeth, and as a speaker for Abbott and Amgen. V.H. has performed clinical trials for Amgen, Abbott, Merck/Centocor/Janssen and Novartis; received research grants from Amgen and Abbott; and received honoraria for lecturing or participating in advisory boards from Amgen, Abbott and Merck/Centocor/Janssen. M.S., P.S., Y.W., Y.K.S. and S.L. are employees of Janssen Research & Development, Spring House, PA, USA, and own stock in the parent company, Johnson & Johnson. T.K. is an employee of Janssen Pharmaceutical K.K., Tokyo, Japan.