

Reactivation Risk of Latent Tuberculosis or Inactive Hepatitis B Virus Infection and Effectiveness of Ustekinumab in Chinese Plaque Psoriasis Patients: A 28-Week Retrospective, Observational Study

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Introduction: This study observed the effectiveness of ustekinumab and reactivation risk of concurrent latent tuberculosis infection (LTBI) and inactive hepatitis B virus (HBV) infection in Chinese mainland psoriasis patients on ustekinumab treatment.

Methods: This retrospective, multicenter, observational study was conducted in three centers in China. Adult patients with moderate to severe plaque psoriasis were treated with ustekinumab for 28 weeks. The effectiveness endpoint included 75% and 90% improvement in Psoriasis Area Severity Index (PASI75/90) response rate, percentage of PASI improvement, change of absolute PASI score and body surface area involvement (BSA) score, absolute PASI $\leq 1/3$ and Physicians' Global Assessment (PGA)=0/1, as well as Dermatology life quality index (DLQI)=0/1 response rate at week 4, 16 and 28. Screening of tuberculosis and hepatitis were performed at baseline and week 28.

Results: A total of 82 patients were enrolled between March 2021 and May 2023 and the number of patients combined with LTBI and inactive HBV infection was 20 and 21 respectively. The PASI75 and PASI90 response rate at week 28 was 95.1% and 81.7% respectively. The mean PASI score decreased from 14.93 ± 12.07 at baseline to 0.78 ± 1.86 at week 28, and the mean BSA score decreased from $21\% \pm 18\%$ at baseline to $1\% \pm 2\%$ at week 28 (both $P < 0.001$ compared with baseline). DLQI 0/1 response rate at week 28 was 73.2%. No reactivation of LTBI and inactive HBV infection and also no new-onset tuberculosis and hepatitis B occurred in patients without LTBI and inactive HBV infection at baseline.

Conclusion: Ustekinumab demonstrated great effectiveness in Chinese plaque psoriasis patients and good safety in psoriasis concurrent with LTBI and inactive HBV infection under the real-world setting.

Keywords: ustekinumab, plaque psoriasis, real-world effectiveness, LTBI, inactive HBV infection

Introduction

Psoriasis is a chronic, recurrent, inflammatory and systematic skin disease which affects around 0.47% of Chinese people and causes large impairments to the quality of life of patients; 89.1% of Chinese psoriasis patients suffer from mental health problems caused by psoriasis.^{1,2} The most common subtype of psoriasis is plaque psoriasis (PsO), which accounts for 84.5% of Chinese psoriasis patients and is characterized by well demarcated, red and raised plaques covered by silvery scales.³ In recent years, the improvements of anti-interleukin biologics included IL12/23i, IL-17Ai and IL-23i brought great improvement for the treatment of PsO.⁴ However, the infection risk of biologics still requires special attention in patients combined with HBV and tuberculosis infection, especially in countries with high HBV and tuberculosis burden such as China. Nearly half of Chinese population are infected with mycobacterium tuberculosis and the infection rate ranking top 2 globally.⁵ About 70 million people are chronic HBV infection patients in China.⁶ With the high skin lesion clearance rate of new anti-interleukin biologics, more and more physicians pay attention to the

quality of life of psoriasis patients. Several trials used patient-reported outcomes such as DLQI as an important endpoint to evaluate the impact of biologics on patients' quality of life.^{7–9}

Ustekinumab, a fully human anti-IL12/23 monoclonal antibody that binds to the P40 subunit shared by IL-12 and IL-23 therefore inhibits the downstream inflammatory signal pathway, is the first approved anti-interleukin biologic for the treatment of plaque psoriasis which was approved by FDA in 2009.¹⁰ In 2017, ustekinumab was approved for the treatment of Chinese adult moderate to severe plaque psoriasis patients and in 2023 it was approved for the treatment of Chinese 6–17 year old pediatric plaque psoriasis patients weighing 60–100 kg.^{7,11,12} Previous genome-wide association studies found that IL-12B and IL-23R are susceptibility genes of Chinese psoriasis patients.^{13,14} A randomized, double-blind, placebo-controlled study also indicated that ustekinumab demonstrated great efficacy and quality of life improvement in Chinese plaque patients with no new safety signal was found,⁷ in which the efficacy response rate was numerically higher than that of Phase 3 trials conducted in Western countries.^{8,9} Several real-world studies also proved that psoriasis patients combined with latent tuberculosis infection and inactive HBV infection treated with ustekinumab were safe.^{15–17} However, no real-world data of ustekinumab in Chinese plaque psoriasis has been published up to now, especially after Ustekinumab had been incorporated into medical insurance system from 2022 in China, vast growth of application in clinical practice brought great attention and interest of real-world effectiveness and safety, especially infection risk of Ustekinumab to Chinese Dermatologists. In addition, another widely-used anti-17A biologic secukinumab in China has been proved safe in Chinese patients combined with LTBI or inactive HBV infection in a real-world study,¹⁸ but there is a lack of evidence for Ustekinumab in terms of safety in patients combined with LTBI or inactive HBV infection, especially previous mechanism research display inconsistent outcome, two studies pointed out interferon inhibited by Ustekinumab play positive role in anti-tuberculosis and hepatitis,^{19,20} and another demonstrated that Ustekinumab improves skin lesion without affecting T cell immune response,²¹ which brought much confusion to Chinese dermatologists. Compared to randomized-controlled trial, real-world data can reflect the effectiveness and safety of a biologic in daily clinical practice taking account of different complications and concomitant medications,²² especially the heavy burden of HBV and tuberculosis infection in Chinese patients,^{5,6} so it is essential to identify the real-world effectiveness and safety of Ustekinumab in Chinese psoriasis patients.

This observational study aimed to assess the real-world effectiveness, quality of life improvement and safety of ustekinumab in Chinese plaque psoriasis patients, as well as the safety profile of ustekinumab in Chinese psoriasis combined with latent tuberculosis and inactive HBV infection.

Materials and Methods

Study Design and Patients

This retrospective, multicenter, observational real-world study was conducted in three centers (The No. 1 Affiliated Hospital of University of Science and Technology of China, The Lu'an Hospital Affiliated to Anhui Medical University, The No. 1 Affiliated Hospital of Anhui University of Traditional Chinese Medicine) in Anhui province, China between March 2021 and May 2023. Eligible patients were aged at least 18 years old, and were diagnosed as moderate to severe plaque psoriasis meeting one of the following criteria: i) Body surface area involvement (BSA) $\geq 3\%$; and ii) Psoriasis area and severity index (PASI) ≥ 3 according to “Guideline for the diagnosis and treatment of psoriasis in China (2023 edition)”.² All patients were screened for tuberculosis and Hepatitis B infection at baseline, active tuberculosis infection as well as active Hepatitis B infection were excluded. Patients combined with LTBI and inactive HBV infection were permitted to participate in this study and underwent preventive treatment in accordance with the “Guidelines for the treatment of psoriasis with biologic agents in China (2021)”, namely isoniazid alone or isoniazid combined with rifampicin programme for patients with LTBI, anti-hepatitis B viral drug entecavir for patients combined with inactive HBV infection.²³ Enrolled patients received a standard dose of ustekinumab treatments (45 mg at week 0 and week 4, followed by 45 mg every 12 weeks administrated subcutaneously for patients weighing 100 kg or less; 90 mg at week 0 and week 4, followed by 90 mg every 12 weeks administrated subcutaneously for patients weighing more than 100 kg) for 28 weeks. Hepatitis B were monitored every three months using serological examination and tuberculosis were

monitored at baseline and week 28 using T-spot and chest-imaging.²³ Baseline demographics and clinical characteristics of patients were recorded.

Diagnosis and Reactivation Criterion of LTBI and Inactive HBV Infection

Patients with positive outcome of T-spot, no symptoms of active tuberculosis and active tuberculosis focus showed on chest-X ray/CT were defined as LTBI. The manifestations of coughing for more than 2 weeks, fever, weight loss, night sweats were defined as reactivation of LTBI; abnormal chest-imaging manifestation indicating active tuberculosis and positive microbiological finding.^{24,25}

Inactive HBV infection was defined as HBsAg positive with HBV-DNA negative ($<10^4$ /mL) and normal liver function or isolated HBcAb positive with HBV-DNA negative and normal liver function.²³ Reactivation of HBV was defined as meeting with at least one of the following criteria: HBV DNA load increase more than 100-fold compared with baseline; detectable HBV DNA in patients previously with undetectable DNA; positive HBsAg in patients previously with negative HBsAg as well as liver dysfunction defined as threefold increase in ALT compared with baseline or absolute value of ALT level more than 100 U/L.²⁶

Study Outcomes

The effectiveness outcome included PASI75/90/100 and PASI improvement at week 4, 16 and 28; change of absolute PASI score and BSA score during the whole treatment period; percentage of patients achieved absolute PASI $\leq$ 1, absolute PASI $\leq$ 3 and PGA=0/1. DLQI 0/1 response rate was used to evaluate the quality of life improvement reported by patients. The safety outcome were the reactivation or new-onset of active tuberculosis and hepatitis B as well as any adverse event during the 28-week treatment.

Statistical Analysis

The data was analysed with the statistical software R (Version 4.2.2) and the quantitative data was presented as mean $\pm$ SD and median (interquartile range), the categorical data was presented as frequency and percentage. Statistical difference of absolute PASI and BSA between each visit (week 4, 12 and 28) and baseline was analysed with Bonferroni because of biased distribution. Two-tailed $P < 0.05$ was considered as significantly different.

Results

Baseline Demographics and Clinical Characteristics

A total of 82 patients was enrolled between March 2021 and May 2023, and the numbers of patients with LTBI and inactive HBV infection was 20 and 21 respectively. Six patients were combined with LTBI and inactive HBV infection simultaneously. The average age of all the patients was 43.33 ± 14.18 years old. The mean weight and BMI were 69.07 ± 11.90 kg and 24.02 ± 3.32 kg/m². 67.1% of patients were male and 43.9% of patients had family history. The mean disease duration was 14.68 ± 9.65 years and 7.1% of patients previously received biologic treatment. The average absolute PASI score and BSA score was 14.93 ± 12.0 and 20.65 ± 18.06 respectively. The percentage of patients with PGA marked or severe (PGA $\geq$ 4) was 23.2%. The mean DLQI score was 14.50 ± 7.23 (Tables 1 and 2).

Clinical Response of Ustekinumab in Chinese Psoriasis Patients in the Real-World Setting

Ustekinumab showed effectiveness as early as the first visit at week 4, the PASI75 response rate was 12.2% and mean PASI improvement was 49.89% at week 4. The percentage of patients achieved PASI75 and PASI90 at week 16 was 87.8% and 63.4%, and the response rate at week 28 was 95.1% and 81.7% respectively. The mean PASI improvement at week 28 was 94.27% (Figure 1). The mean PASI score decreased from 14.93 ± 12.07 at baseline to 0.78 ± 1.86 at week 28, the mean BSA score decreased from $21\% \pm 18\%$ at baseline to $1\% \pm 2\%$ at week 28 (both $P < 0.001$ compared with baseline, Figure 2). In consideration of disease severity at baseline, the absolute PASI and BSA score no more than 1 or 3 was also calculated, as well as PGA=0/1. At week 28, the percentage of patients achieved aPASI $\leq$ 3, aPASI $\leq$ 1 and

Table 1 Baseline Demographics and Clinical Characteristics of the Patients

Characteristic	Mean $\pm$ SD	Median (IQR)
Age (year)	43.33 $\pm$ 14.18	42 (32, 54.5)
Male sex, n/N (%)	55/82 (67.1%)	
Weight (kg)	69.07 $\pm$ 11.90	70 (60, 76)
BMI (kg/m ²)	24.02 $\pm$ 3.32	23.96 (21.77, 26.1)
Disease duration (year)	14.68 $\pm$ 9.65	12 (8, 20)
Family history, n/N (%)	36/82 (43.9%)	
Prior biologic treatment history, n/N (%)	5/82 (6.1%)	
PASI score, 0–72	14.93 $\pm$ 12.0	10.6 (5.85, 19.8)
BSA (%)	20.65 $\pm$ 18.06	15.5 (6.25, 30.5)
PGA marked or severe (≥ 4), n/N (%)	19/82 (23.2%)	
DLQI score	14.50 $\pm$ 7.23	14 (9, 20)
Combined with LTBI, n/N (%)	20/82 (24.4%)	
Combined with inactive HBV infection, n/N (%)	21/82 (25.6%)	

Abbreviations: BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; BSA, body surface area involvement; PGA, Physicians' Global Assessment; DLQI, Dermatology life quality index; LTBI, latent tuberculosis infection; HBV, hepatitis B virus; n/N, n, number of each group N, total number.

Table 2 Tuberculosis and Hepatitis B Screening Outcomes at Week 28 of Patients Combined with LTBI or Inactive HBV Infection at Baseline

NO.	Baseline Complication	Tuberculosis Screening Outcome at Week 28			HBV Screening Outcome at Week 28			
		Imaging Abnormality [#]	T-SPOT	Active TB Symptoms	HBV Serology Screening	HBV DNA	ALT	AST
5	LTBI, HBV carrier	-	+	-	HbsAg ⁺ , HBcAb ⁺ , HBeAb ⁺	1.44*10 ³	N	N
9	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
11	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
18	HBV carrier	/	/	/	HBcAb ⁺	<100	N	N
28	HBV carrier	/	/	/	HbsAg ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
19	LTBI	-	+	-	/	/	/	/
24	LTBI	-	+	-	/	/	/	/
27	LTBI	-	+	-	/	/	/	/
30	LTBI, HBV carrier	-	+	-	HBsAb ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
31	HBV carrier	/	/	/	HbsAb ⁺ , HBeAb ⁺	<100	N	N
32	LTBI, HBV carrier	-	+	-	HBsAb ⁺ , HBeAb ⁺	<100	N	N
35	LTBI, HBV carrier	-	+	-	HBsAb ⁺ , HBeAb ⁺	<100	N	N
37	LTBI, HBV carrier	-	+	-	HbsAg ⁺ , HBcAb ⁺	<100	N	N
38	LTBI	-	+	-	/	/	/	/
43	LTBI	-	+	-	/	/	/	/
44	LTBI	-	+	-	/	/	/	/

(Continued)

Table 2 (Continued).

NO.	Baseline Complication	Tuberculosis Screening Outcome at Week 28			HBV Screening Outcome at Week 28			
		Imaging Abnormality [#]	T-SPOT	Active TB Symptoms	HBV Serology Screening	HBV DNA	ALT	AST
47	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺	<100	N	N
50	LTBI	-	+	-	/	/	/	/
54	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺	<100	N	N
59	LTBI	-	+	-	/	/	/	/
60	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
61	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺ , HBeAb ⁺	<100	N	N
63	LTBI	-	+	-	/	/	/	/
64	LTBI	-	+	-	/	/	/	/
68	LTBI	-	+	-	/	/	/	/
69	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺	<100	N	N
72	HBV carrier	/	/	/	HBcAb ⁺	<100	N	N
74	LTBI, HBV carrier	-	+	-	HBcAb ⁺	<100	N	N
75	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺	<100	N	N
76	LTBI	-	+	-	/	/	/	/
77	LTBI	-	+	-	/	/	/	/
78	HBV carrier	/	/	/	HBcAb ⁺	<100	N	N
79	HBV carrier	/	/	/	HBsAb ⁺ , HBcAb ⁺	<100	N	N
81	LTBI	-	+	-	/	/	/	/
82	HBV carrier	/	/	/	HBcAb ⁺	<100	N	N

Notes: [#]Signs of active tuberculosis infection demonstrated by imaging included chest X-ray or CT; -: Negative; +: Positive; N: Normal. Normal range of ALT is defined as 9–50 U/L, and Normal range of AST is defined as 14–40 U/L; /: Not have been screened because no corresponding complication at baseline.

Abbreviations: LTBI, latent tuberculosis infection; HBV, hepatitis B virus; TB, Tuberculosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

PGA=0/1 was 93.9%, 84.1% and 96.3% respectively (Figure 3). The men DLQI score decreased from 14.50 ± 7.23 at baseline to 1.32 ± 2.35 at week 28, and the DLQI 0/1 response rate was 73.2% at week 28 (Figure 4).

Reactivation Risk of LTBI and Inactive HBV Infection in Chinese Patients Treated with Ustekinumab

During the whole 28 week treatment period, there was no reactivation of LTBI and inactive HBV infection under the preventive treatment against tuberculosis and hepatitis B according to the Chinese guideline in patients combined with LTBI and inactive HBV infection at baseline. There was also no new-onset tuberculosis and hepatitis in patients without tuberculosis and hepatitis B at baseline. Blood biochemical examination included alanine aminotransferase and aspartate aminotransferase did not transit to be abnormal at week 28 in all patients. The screening outcomes of patients at baseline and week 28 were respectively described in Table 2. Also, no other adverse event including fungal infection, malignancy, severe infection, inflammatory bowel disease or major cardiovascular events happened during the study.

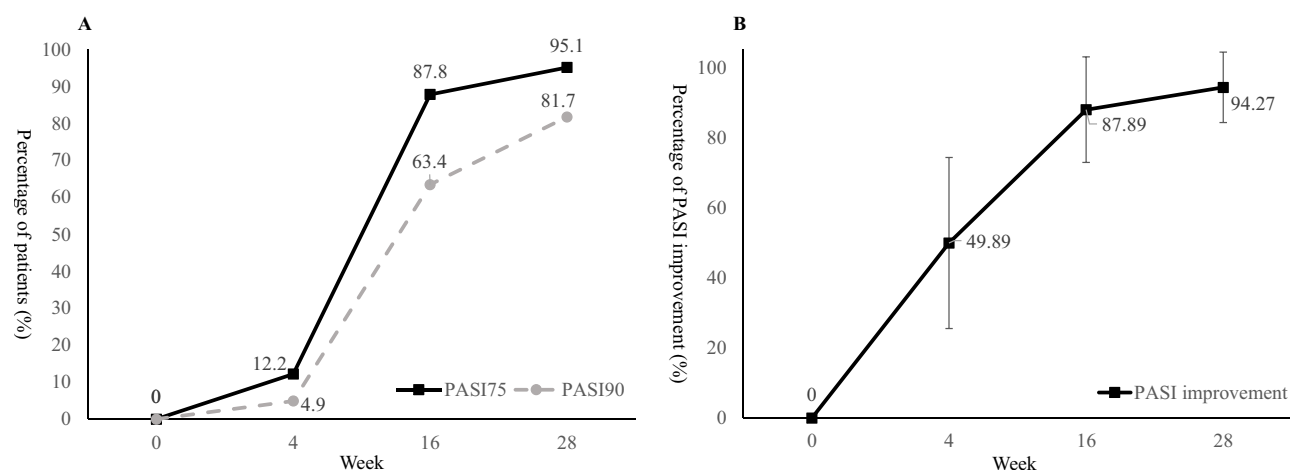


Figure 1 PASI 75 and PASI 90 response rate (A) and percentage of PASI improvement (B) during the 28-week treatment period.

Abbreviation: PASI, Psoriasis Area Severity Index.

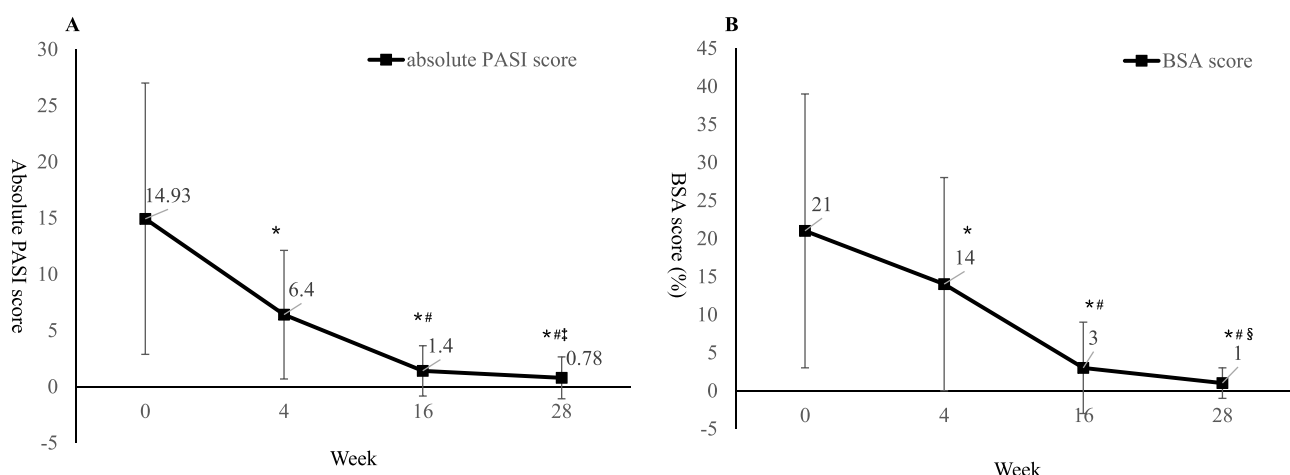


Figure 2 Change of absolute PASI score (A) and BSA score (B) during the 28-week treatment period. * $P < 0.001$ compared with baseline; # $P < 0.001$ compared with week 4; ‡ $P < 0.001$ compared with week 16; § $P < 0.001$ compared with week 16.

Abbreviations: PASI, Psoriasis Area Severity Index; BSA, body surface area involvement.

Discussion

As high disease burden of LTBI and HBV infection in China mainland,^{5,6} as well as lack of effectiveness and safety real world data of ustekinumab in moderate to severe plaque psoriasis patients in China mainland, in which situation more complicated condition such as complications and concomitant medications were taken into consideration,²² especially after been incorporating into national medical insurance of China, real-world effectiveness and infection risk of Ustekinumab aroused great interest and attention to Chinese dermatologists. This first retrospective, observational study verified the effectiveness of ustekinumab in Chinese psoriasis patients and safety of ustekinumab in Chinese psoriasis patients combined with LTBI and inactive HBV infection in the real-world setting. The PASI75 and PASI90 response rate at week 28 was up to 95.1% and 81.7%. The quality of life was also obviously improved with 73.2% of patients achieved DLQI 0/1 response at week 28. No reactivation was observed in 20 LTBI patients and 21 inactive HBV infection patients, as well as no adverse event was observed throughout the 28-week treatment of ustekinumab.

A multicenter, randomized, double-blind and placebo-controlled phase 3 study investigated the efficacy and safety of ustekinumab in Chinese moderate to severe psoriasis showed that 91.5% of patients achieved PASI75 and 80.4% of patients treated with ustekinumab achieved PASI90 at week 28.⁷ Our study showed similar response rate compared with

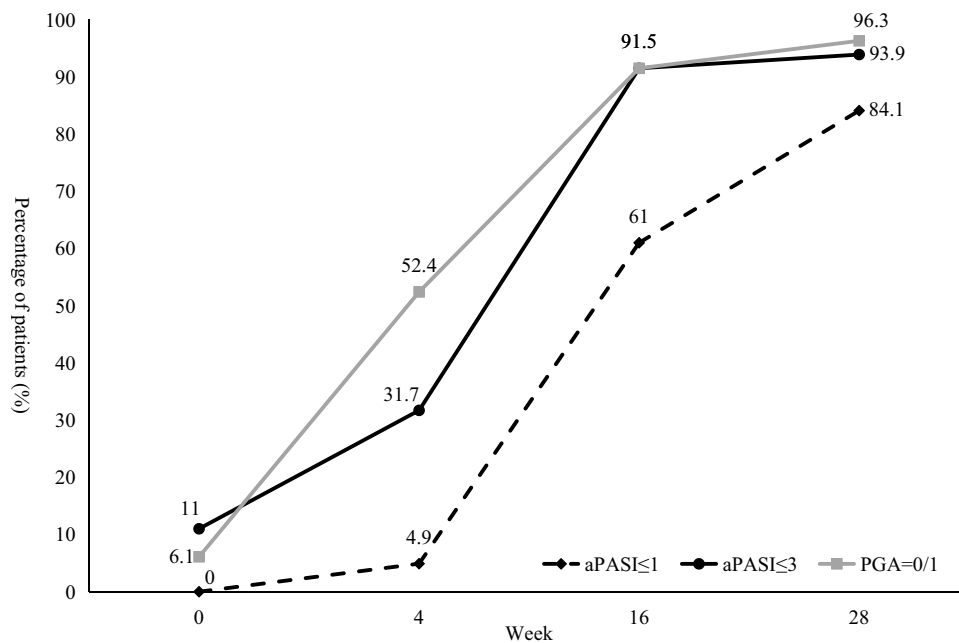


Figure 3 Percentage of patients achieved aPASI≤1, aPASI≤3 and PGA=0 during the 28-week treatment period.

Abbreviations: aPASI, absolute Psoriasis Area Severity Index; PGA, Physicians' Global Assessment.

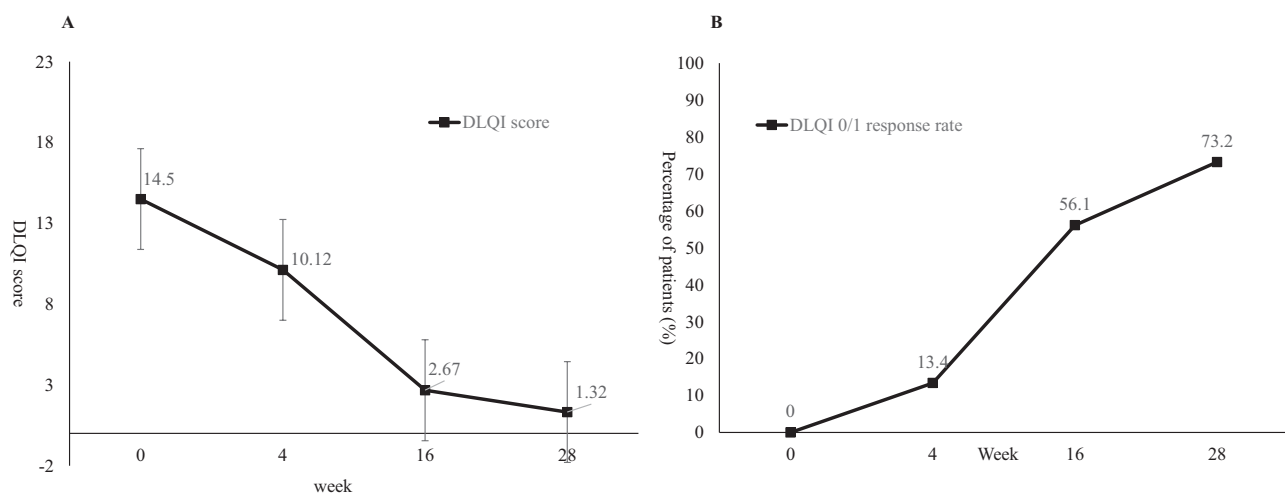


Figure 4 (A) Change of DLQI score and **(B)** percentage of patients achieved DLQI 0/1 during the 28-week treatment period.

Abbreviation: DLQI, Dermatology life quality index.

the study. Proportion of patients previously received biologic in both studies were comparable and relatively low, which is considered as a predictor of good response.⁸ Two randomized controlled phase 3 trials enrolled moderate to severe plaque psoriasis patients mainly from Europe and North America showed lower PASI 90 response rate at week 28, 49.2% of 45 mg group and 55.6% of 90 mg group in PHOENIX 1 and 44.8% of 45 mg group and 54.3% of 90 mg group in PHOENIX 2 respectively, effectiveness results of these two trials were lower than our study, which may be interpreted by higher weight (90.3 kg to 93.8 kg across different groups) and higher proportion of biologic-experienced patients (36.5% to 52.5% across different groups) in the two trials.^{8,9} Another explanation may be genetic difference, IL-12B and IL-23R are susceptibility genes in Chinese psoriasis patients and ustekinumab binds to IL-12 and IL-23 may display better effectiveness in these genetic susceptible patients.^{13,14} Patient-reported outcomes are becoming more and more important in evaluating the severity and efficacy of treatment. Several guidelines use DLQI as one of the major endpoints in

assessing the severity and treatment goal of psoriasis.^{2,27,28} Several randomized controlled trials demonstrated similar DLQI 0/1 response rate at week 28 compared with our study.⁷⁻⁹ And consistent with previous study, DLQI 0/1 response rate kept increasing with the continuously improvement of PASI or BSA, indicating the importance of high skin lesion clearance in improving the patients' quality of life.²⁹

In terms of safety of tuberculosis and HBV infection, IL-12 and Th1 cytokine interferon induced by it were considered to play a positive role in clearing virus, thus biologic bind to IL-12 arouse concern for immunosuppression and increased infection risk.^{19,20} Kenshiro Tsuda et al demonstrated that ustekinumab improves psoriasis without affecting the T cell immune response compared with controls,²¹ several Phase 2/3 trials also verified no significant risk for infection of ustekinumab in psoriasis patients,³⁰ several other trials confirmed the safety of ustekinumab in psoriasis combined with LTBI and inactive HBV infection,¹⁵⁻¹⁷ so as several retrospective studies demonstrated safety of other biologics including IL-17 inhibitors and IL-23 inhibitors in patients combined with LTBI or inactive HBV infection,³¹⁻³⁴ but none of them was conducted in China where the tuberculosis and hepatitis burden are high. An observational study confirmed the safety of another widely used biologic in China, IL-17A inhibitor secukinumab in 43 Chinese patients combined with HBV infection or LTBI,¹⁸ and we firstly confirmed the safety of IL-12/23 inhibitor ustekinumab in Chinese psoriasis patients combined with inactive HBV infection and LTBI. Apart from hepatitis B and tuberculosis, other concerned safety events of biologic such as fungal infection, malignancy, severe infection, inflammatory bowel disease and major cardiovascular events was also not observed in our study, confirmed the safety of ustekinumab in Chinese mainland psoriasis patients. A greater sample size and longer follow-up duration of the effectiveness and safety of ustekinumab in Chinese mainland moderate to severe plaque psoriasis patients is still under observed.

In conclusion, ustekinumab demonstrated great skin lesion clearance ability and brought great improvement of quality of life to Chinese plaque psoriasis patients under a real-world setting. The safety of ustekinumab in psoriasis concurrent with LTBI and inactive HBV infection were also confirmed with no reactivation or new-onset throughout the whole 28-week treatment. Also no new safety signal was observed during the study.

Data Sharing Statement

The data of this study can be available from Dr Wen-Sheng Lu (492051693@qq.com) for reasonable request.

Ethics Approval

This study was conducted in accordance of Helsinki and the protocol was approved by the ethics committee of all participating centers including The No.1 Affiliated Hospital of University of Science and Technology of China, The Lu'an Hospital Affiliated to Anhui Medical University and The No.1 Affiliated Hospital of Anhui University of traditional Chinese medicine.

Consent to Participate

All patients provided written informed consent.

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Disclosure

The authors have no potential conflicts of interest or financial disclosures that are pertinent to this article.

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