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ORIGINAL ARTICLE

# Practical experience of ustekinumab in patients with moderate-to-severe psoriasis who had inadequate therapeutic response to previous tumor necrosis factor blockers

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ABSTRACT

*Background/Objective(s):* Few studies have evaluated the therapeutic response among switchers of biologics in patients with psoriasis. We report our experience of ustekinumab in patients with psoriasis who did not respond adequately to tumor necrosis factor (TNF) blockers treatment previously.
*Methods:* We retrospectively reviewed the therapeutic response of 20 patients with moderate-to-severe psoriasis who had failed conventional treatment and had inadequate therapeutic response to previous etanercept and/or adalimumab between 2012 and 2013. Inadequate therapeutic response is defined by <50% improvement in Psoriasis Area and Severity Index (PASI) compared to baseline. Ustekinumab 45 mg was given at Week 0, Week 4, and Week 16, and patients were evaluated for safety and effectiveness at Week 0, Week 4, Week 16, and Week 28.
*Results:* Nineteen patients were followed to Week 16, and 14 patients to Week 28. At Week 16, at least PASI 90, PASI 75, PASI 50, and PASI 25 responses were seen in three patients (3/19, 16%), four patients (4/19, 26%), seven patients (7/19, 37%), and 13 patients (13/19, 68%), respectively. At Week 28, at least PASI 90, PASI 75, PASI 50, and PASI 25 responses were seen in two patients (2/14, 14%), three patients (3/14, 21%), seven patients (7/14, 50%), and 11 patients (11/14, 79%), respectively. No severe adverse events were recorded in our series.
*Conclusion:* Despite a less favorable response compared to the pivotal studies, at least PASI 50 response was achieved in 50% of patients at Week 28 after three injections of ustekinumab without serious adverse events.



## Introduction

Psoriasis is a chronic inflammatory skin disease which significantly impairs quality of life.[1] With the clarification of psoriasis pathogenesis,[2] biologic agents targeting either tumor necrosis factor (TNF) blockers (such as etanercept[3] and adalimumab[4]) or anti-interleukin (IL)-12/23 (e.g., ustekinumab[5]) are increasingly used. Switches between biologics are common, due to either safety or efficacy reasons, but few studies have evaluated the therapeutic response among the switchers. This is a single-center, open-labeled, retrospective study on the effects of ustekinumab in patients with moderate-to-severe psoriasis who had inadequate response to previous etanercept and/or adalimumab.

## Methods

This was a retrospective study in which we included 20 ustekinumab users for chronic plaque type psoriasis (with ethics approval from National Taiwan University Hospital, Taipei, Taiwan; approval number 200712123R) during the period from May 2012 to July 2013. All of the patients had received subcutaneous etanercept 25 mg or 50 mg twice/week and/or adalimumab 40 mg every other week previously in a tertiary medical center in Taiwan. All participants fulfilled the reimbursement criteria for biologics use for psoriasis patients which had: (1) baseline Psoriasis Area and

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Severity Index (PASI) >10 prior to etanercept, adalimumab, and ustekinumab injection; and (2) inadequate response, contraindication or intolerance to at least two of the three conventional systemic agents including methotrexate (at least 15 mg/week), acitretin (0.3–1 mg/kg/day) and cyclosporine (up to 5 mg/kg/day) in addition to narrow-band UV-B or psoralen UV-A phototherapy at least twice/week for 3 months.[6]

Reasons for adalimumab or etanercept discontinuation were: (1) inadequate therapeutic response, defined by <50% improvement in PASI compared to baseline: (2) loss of efficacy defined by failure to maintain the original PASI 50 response; or (3) other reasons such as significantly impaired quality of life or short remission duration after the previous TNF blockers. We collected data on age, sex, disease duration of psoriasis, body height and weight, body mass index (BMI), previous systemic treatments, history of erythrodermic psoriasis, and psoriatic arthritis. Subcutaneous ustekinumab 45 mg was given at Week 0, Week 4, and Week 16, and patients were evaluated for safety and PASI response at Week 0, Week 4, Week 16, and Week 28.

We also evaluated the feasibility of predicting a PASI 50 response at Week 16 and Week 28 by PASI improvement at Week 4. Receiver operating characteristic (ROC) curves were used to determine the level of PASI improvement that had optimal negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity. The area under the ROC curve (AUC-ROC) at Week 4 was used to assess overall predictability at each time point. The Youden Index (YI = sensitivity + specificity −1) was used to determine the range of PASI responses that had the greatest predictive value.[7]

Before treatment, patients were checked for the presence of hepatitis B virus (HBV) surface antigen (HBsAg), hepatitis C virus(HCV) antibody, and latent tuberculosis (TB) by chest X-ray and Quantiferon TB Gold, QFT-G, Cellestis Limited, Carnegie, Victoria, Australia.[8] HBV and HCV viral loads were checked on a regular basis and antiviral treatment was provided as indicated.[9,10] Patients with latent TB were treated concomitantly with 9-month isoniazid prophylaxis.[8]

## Results

### *Demographics*

Among 20 patients enrolled in the study, the male-to-female ratio was 13:7, median age was 44.0 years (range: 26–60 years), and median disease duration was 14.5 years (range: 2–31 years). Eight patients (40%) weighed <70 kg, and the average BMI was 27.4. Sixteen patients (16/20, 80%) were overweight or obese (defined by BMI ≥24 according to the classification of the Ministry of Health and Welfare of Taiwan[11]). Eight patients (40%) had a history of erythrodermic psoriasis, and 70% (14/20) of patients had psoriatic arthritis. With regards to the status of hepatitis and TB, one patient was an HCV carrier, four patients were HBV carriers, and two patients had a positive Quantiferon TB Gold test result (Table 1).

### *Clinical response to previous biologics and causes of drug discontinuation*

Two patients (Patients 12 and 16) had three switches of biologics, 10 patients had two switches of biologics, and eight patients had one switch of biologics. The causes of drug discontinuation are depicted in Table 1. With regards to the cause of the first biologic discontinuation, 35% of patients were nonresponders, 40% of patients lost the efficacy, and 20% of patients had an unsatisfactory response that might still impair their quality of life. For the second, 50% were nonresponders, 33% of patients lost the efficacy, and 17% of patients had an unsatisfactory response. For the third, 50% of patients were nonresponders, and 50% of patients lost the efficacy. The change of PASI scores are shown in Figures S1–S3. Based on information of Table 2 and Figure S5, the response to biologics was less satisfactory if there were more switches.

During the first biological therapy, 14 patients (14/20, 70%) had at least PASI 25, nine patients (9/20, 45%) had at least PASI 50, and four patients (4/20, 20%) had at least PASI 75 response at Week 12. At Week 24, 14 patients (14/18, 78%) had at least PASI 25, 11 patients (11/18, 61%) had at least PASI 50 and five patients (5/18, 28%) had at

**Table 1** Basic demographics of the patients.

| No. | Sex/age | History of psoriasis (y) | BH (cm)/ BW (kg)/ BMI | Previous conventional systemic therapy for psoriasis | Previous biological therapy (cause of drug switch) | Erythrodermic psoriasis | Psoriatic arthritis | Quantiferon TB Gold test | HBV | HCV |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M/53 | 2 | 177/62/19.8 | NBUVB, MTX, acitretin | E (N) → A (N) | + | − | + | − | + |
| 2 | M/42 | 13 | 173/73/24.5 | NBUVB, PUVA, MTX, CyS, acitretin, hydroxyurea | E (N) → A (N) | + | + | − | + | − |
| 3 | M/32 | 17 | 183/110/32.8 | NBUVB, MTX, acitretin | E (L) | − | − | − | − | − |
| 4 | F/34 | 28 | 160/65/25.2 | NBUVB, MTX, no acitretin due to future pregnancy plan; no CyS due to hypertension) | E (N) → A (N) | − | + | − | − | − |
| 5 | F/48 | 8 | 152/67/29.1 | PUVA, MTX, CyS, acitretin | E (L) → A (N) | + | + | − | − | − |
| 6 | M/44 | 3 | 165/71/25.9 | NBUVB, CyS, acitretin | E (L) | + | − | + | + | − |
| 7 | F/55 | 11 | 149/51/22.9 | NBUVB, MTX, CyS, acitretin | A (N) | − | + | − | + | − |
| 8 | M/26 | 9 | 175/79/25.9 | NBUVB, MTX, CyS, acitretin | A (L) | + | + | − | − | − |
| 9 | M/42 | 26 | 163/82/30.9 | NBUVB, MTX, acitretin | E (O) → A (L) | + | + | − | − | − |
| 10 | M/37 | 18 | 180/115/35.7 | NBUVB, MTX, CyS, acitretin | E (O) | − | + | − | − | − |
| 11 | M/49 | 16 | 176/101/32.6 | NBUVB, PUVA, MTX, acitretin | E (L) → A (N) | − | + | − | − | − |
| 12 | M/35 | 23 | 170/81/28.0 | NBUVB, MTX, CyS, acitretin | E (N) → A (N) → E (N) | + | + | − | − | − |
| 13 | F/60 | 12 | 158/70/28.0 | NBUVB, MTX, acitretin | E (L) → A (L) | − | + | − | − | − |
| 14 | F/32 | 12 | 172/68/22.9 | NBUVB, MTX, CyS | E (O) | + | − | − | − | − |
| 15 | M/26 | 4 | 168/77/27.3 | NBUVB, MTX, CyS, acitretin | E (N) → A (L) | − | + | − | − | − |
| 16 | F/49 | 25 | 160/67/26.2 | NBUVB, MTX, CyS, acitretin | E (O) A (O) → E (L) | − | + | − | − | − |
| 17 | M/52 | 31 | 170/80/27.7 | NBUVB, MTX, acitretin | E (O) | − | + | − | − | − |
| 18 | M/53 | 22 | 163/90/33.9 | NBUVB, MTX, acitretin | E (L) → A (O) | − | + | − | + | − |
| 19 | M/48 | 16 | 172/67/22.6 | NBUVB, MTX, acitretin | E (L) → A (L) | − | − | − | − | − |
| 20 | F/44 | 12 | 156/63/27.2 | NBUVB, MTX, CyS, acitretin | A (N) | − | − | − | − | − |

A = adalimumab; BH = body height; BMI = body mass index; BW = body weight; CyS = cyclosporine; E = etanercept; HBV = hepatitis B virus; HCV = hepatitis C virus; L = loss of efficacy at the end of the treatment course; MTX = methotrexate; N = nonresponder; NBUVB = narrow band UV-B radiation; O = other reasons such as impaired quality of life or short remission duration; PUVA = psoralen and UV-A radiation.