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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.

Table 2 Proportion of patients regarding Psoriasis Area and Severity Index (PASI) reduction during previous biological therapy and ustekinumab.

	First biologic		Second biologic		Third biologic		Ustekinumab	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 16	Week 28
At least PASI 25	70	78	40	64	50	50	68	79
At least PASI 50	45	61	30	36	0	0	37	50
At least PASI 75	20	28	20	9	0	0	26	21

Data are presented as %.

least PASI 75 response; two patients lacked PASI scores at Week 24. During the second biological therapy, four patients (4/10, 40%) had at least PASI 25, three patients (3/10, 30%) had at least PASI 50, and two patients (2/10, 20%) had at least PASI 75 at Week 12. At Week 24, seven patients (7/11, 64%) had at least PASI 25, four patients (4/11, 36%) had at least PASI 50, and one patient had at least PASI 75 (1/11, 9%); two patients lacked PASI scores at Week 12, and one patient lacked PASI score at Week 24. During the third biological therapy, one patient (1/2, 50%) had at least PASI 25 in both Week 12 and Week 24 (Table 2 and Figure S5).

Clinical response to ustekinumab

Because several participants had not reached the respective follow-up time point at the study closure, only 19 patients could be followed to Week 16, and 14 patients to Week 28. At Week 16, three patients (3/19, 16%) had at least PASI 90, four patients (4/19, 26%) had at least PASI 75, seven patients (7/19, 37%) had at least PASI 50, and 13 patients (13/19, 68%) had at least PASI 25 response. In those patients who had at least PASI 50, three patients (3/7, 43%) weighed >70 kg, and six patients (6/7, 86%) were overweight or obese. At Week 28, two patients (2/14, 14%) had at least PASI 90, three patients (3/14, 21%) had at least PASI 75, seven patients (7/14, 50%) had at least PASI 50 and eleven patients (11/14, 79%) had at least PASI 25 response. In those patients who had at least PASI 50, four patients (4/7, 57%) weighed >70 kg, and five patients (5/7, 71%) were overweight or obese. In addition to body weight and BMI, number of switcher, history of psoriatic arthritis and erythrodermic psoriasis, sex, and disease onset and duration did not significantly affect PASI response at Week 16 (data not shown). The change of PASI scores is shown in Figure 1; PASI scores are shown in Table S1.

Comparing the numbers of at least PASI 25 and at least PASI 50, the clinical response to ustekinumab was worse than the first biologic agent but better than the first switcher at the comparative time points (Week 12 and Week 24 in etanercept and adalimumab; Week 16 and Week 28 in ustekinumab) in our series. The proportion of patients who had at least PASI 75 response was even higher than those of all previous biologics (Table 2 and Figure S5). Mean PASI reduction was −35.2% at Week 4, −42.6% at Week 16, and −55.8% at Week 28 (Table 3).

When we used PASI improvement at Week 4 to predict if PASI 50 response could be obtained at Week 16, the AUC-ROC was 75%, which showed acceptable predictability (Figure S4A) The YI reached the maximum between PASI 30 and PASI 40. Achieving ≥PASI 30 was associated with high NPV (90%) but lower PPV (57%). When we used PASI improvement at Week 4 to predict if there was PASI 50 at Week 28, the AUC-ROC was 67%, which showed less favorable predictability (Figure S4B) The YI reached the maximum between PASI 50 and PASI 60. Achieving ≥ PASI 50 was associated with moderate NPV (66%) but acceptable PPV (83%).

Eleven (46%) patients received systemic combination therapy, which was subclassified into three entities. We defined transitional therapy as therapy given at a crossover period to prevent psoriasis flare, rescue therapy as therapy used alongside ustekinumab for <3 months or <50% of the total duration of the ustekinumab treatment, and concomitant therapy as therapy used alongside ustekinumab for >3 months or >50% of the total duration of the ustekinumab treatment. Four patients received transitional therapy, including methotrexate, acitretin, and narrow band UV-B radiation. Three patients took methotrexate as rescue therapy, and two patients took methotrexate as concomitant therapy. Another two patients received both transitional and rescue therapy,

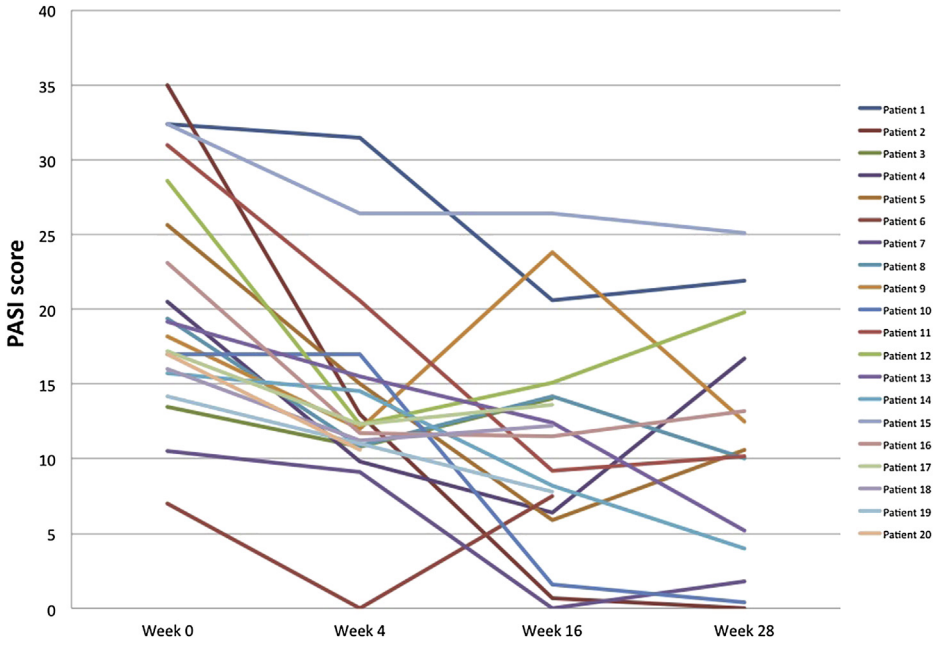

Figure 1 Changes in Psoriasis Area and Severity Index (PASI) score during ustekinumab therapy.

Table 3 Mean Psoriasis Area and Severity Index (PASI) reduction during ustekinumab therapy.

No.	Concomitant systemic therapy	Compare Week 4 to Week 0 mean PASI score change (%)	PASI response at Week 4 (<25, 25, 50, 75, 90, 100)	Compare Week 16 to Week 0 mean PASI score change (%)	PASI response at Week 16 (<25, 25, 50, 75, 90, 100)	Compare Week 28 to Week 0 mean PASI score change (%)	PASI response at Week 28 (<25, 25, 50, 75, 90,100)
1	(1) T: NBUVB (Week 0–8) (2) Adalimumab 40 mg once (Week 8)	−2.8	<25	−36.4	25	−32.4	<25
2	No	−62.9	50	−98	90	−100	100
3	No	−20	<25	+3.7	<25	NA	NA
4	No	−52.2	50	−68.8	50	−18.5	<25
5	No	−41.4	25	−77	75	−58.6	50
6	(1) T + R: CyS (Week 0–4, Week 9–13) (2) R: NBUVB (Week 24, twice)	−100	100	+7.1	<25	NA	NA
7	No	−13.3	<25	−100	100	−82.9	75
8	No	−43.8	25	−26.8	25	−48.5	25
9	C: MTX (Week 0–28)	−34.1	25	+30.8	<25	−31.3	25
10	No	NA	NA	−90.6	90	−97.6	90
11	T: acitretin (Week 0–4)	3–3.5	25	−70.3	50	−67.1	50
12	No	−57.0	50	−47.2	25	−30.8	25
13	R: MTX (Week 16–28)	−19.3	<25	−35.4	25	−72.9	50
14	R: MTX (Week 16–28)	−7.6	<25	−47.8	25	−74.5	50
15	(1) T + R: MTX (Week 0-4, Week 9–13) (2) R: CyS (Week16–28)	−12.2	<25	−12.2	<25	−22.5	<25
16	(1) R: MTX (Week 16–24) (2) Etanercept 25 mg BIW (Week 23–27)	−49.4	25	−50	50	−42.9	25
17	No	−28.5	25	−20.9	<25	NA	NA
18	T: NBUVB (Week 0, for twice)	−30.0	25	−23.8	<25	NA	NA
19	T: MTX (Week 0–4)	−22.5	<25	−45.1	25	NA	NA
20	C: MTX (Week 0–28)	−37.6	25	NA	NA	NA	NA
Mean		−35.2		−42.6		−55.8	

BIW = twice per week; C = concomitant therapy (therapy used alongside ustekinumab for >3 months or >half of the total duration of the ustekinumab treatment); CyS = cyclosporine; MTX = methotrexate; NA = not applicable; NBUVB = narrow band UV-B radiation; R = rescue therapy (therapy used alongside ustekinumab for <3 months or <half of the total duration of the ustekinumab treatment); T = transitional therapy (therapy given at a crossover period to prevent psoriasis flare).

including methotrexate, cyclosporine, and narrow band UV-B radiation. Patient 1 also received subcutaneous adalimumab 40 mg at Week 8, and Patient 16 received subcutaneous etanercept 25 mg twice/week at Weeks 23–27 due to poor disease control (Table 3).

Safety profiles of ustekinumab

No severe adverse events were recorded in our series. One patient had upper respiratory infection (moderate, Patient 4), one patient (Patient 9) with a history of chronic urticaria had one episode of attack, and one patient (Patient 2) had recent onset of seborrheic keratosis or verruca vulgaris on his dorsal hands.

Discussion

Biologics are increasingly used in the treatment of psoriasis. Results from the pivotal trials show a comparable PASI 75 response of adalimumab and ustekinumab[5,12,13] and a head-to-head study showed a more favorable PASI response of ustekinumab compared to etanercept.[11] However, failure in adalimumab or ustekinumab does not preclude the treatment response of etanercept, and vice versa.

Despite initial satisfactory results, biologic switch is often encountered in daily clinical practice, but studies on the efficacy between biologic switchers were mostly conducted in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and mainly among TNF blockers.[14–25] In time sequence, etanercept followed by adalimumab and ustekinumab is approved and reimbursed for the treatment of psoriasis in Taiwan and most countries. Thus, the switch first from etanercept to adalimumab, and then to ustekinumab is most often encountered. Most switches are due to either primary or secondary drug failure, with fewer switches due to adverse events.

In most countries, biologics are only reimbursed in patients with psoriasis who have failed conventional treatment. However, the exact criteria for reimbursement is different in regards to the need of baseline PASI and previous treatment.[26] The interpretation of failure and contraindication to prior treatment may also be different. Thus, it is important to understand the actual effectiveness in these highly selected patients, both for biologics-naïve and previous biologics users. We previously reported our experience of switch from etanercept to adalimumab.[27] The result is less favorable compared to the other reports of similar switches.[28–32] In this current study, a similar lower PASI response was found in patients who switched from etanercept to adalimumab (i.e., second biologic in Table 2 and Figure S5): 30% of patients had at least PASI 50 and 20% of patients had at least PASI 75 at Week 12; 36% of patients had at least PASI 50 and only 9% of patients had at least PASI 75 at Week 24.

There are fewer studies on switching from TNF blockers to ustekinumab.[12,33,34] In one Spanish study, 63% and 50% patients who had previous exposure to TNF blockers had at least PASI 75 response at Week 12 and Week 24, respectively, which were lower compared with TNF blocker-naïve patients, 85% of whom achieved at least PASI 75 at each comparable time point.[33] In another Danish study, no statistically significant differences were noticed between TNF blocker-naïve and TNF blocker-exposed patients.[34] In the Active Comparator (CNTO1275/Enbrel) Psoriasis Trial (ACCEPT) clinical trial, among patients who did not have a response to etanercept, 49% had at least 75% improvement in the PASI score after crossing over to 90 mg of ustekinumab for 12 weeks.[12] Our study showed less favorable results: only 26% of patients and 21% of patients had at least PASI 75 at Week 16 and Week 28, respectively.

Regarding the efficacy of ustekinumab based on body weight, in the Spanish study,[33] patients weighing <100 kg and treated with the 45 mg dose had significantly higher PASI 50 and response rates at Week 24 than heavier patients treated with 90 mg, which was inconsistent with previous pivotal studies which showed similar response rates between the two groups.[5,13,35] Most pivotal trials in Western countries showed that higher dosages were needed for heavier patients, and the prescribing information of ustekinumab also used 100 kg as the cut-off value. However, in one Asian pivotal study,[35] 70 kg (approximating the median Taiwanese population weight) was used as the cut-off value based on the subgroup analysis, and no apparent effect was found on the efficacy of ustekinumab under the dosage of 45 mg. The present study also used 70 kg as the cut-off value and yielded similar results: neither body weight nor BMI had a substantial influence on the effectiveness of ustekinumab, which may have been biased by the small sample size.

Several possibilities may explain the differences of the lower PASI 75 response in the present study. Firstly, the stringent reimbursement criteria of biologics may select a subgroup of high-need patients. Secondly, human leukocyte antigen (HLA) polymorphism in Taiwan compared to Western countries may also play a role.[36–38] HLA-Cw6 was reported to be associated with a more favorable response to ustekinumab,[39] but HLA-Cw6 is underrepresented in Taiwanese patients with psoriasis, especially in the moderate-to-severe group. Thirdly, 40% of patients in our study had a history of erythrodermic psoriasis. Biological drug survival rate and efficacy in patients with erythrodermic psoriasis appears to be lower than in patients with plaque type psoriasis treated with either TNF-α[40] or IL-12/23 blockers.[41–44] Fourthly, 70% of patients had psoriatic arthritis which was shown to adversely affect the ustekinumab efficacy.[13] Fifthly, patients who failed biological agents were more likely to have poor response, as shown in a phase III study of ustekinumab, where 36% PASI 75 responders at Week 28 were previously treated with biological agents.[13] However, our subgroup analysis did not show statistically significant differences of PASI response regarding the number of switchers, and history of erythrodermic psoriasis and psoriatic arthritis, which could be due to low patient number. With regards to the safety of ustekinumab, no serious adverse events were apparent in our study.

One recent study reported that early clinical response of ixekizumab, an IL17A monoclonal antibody, could be served as a predictor of subsequent response to treatment.[7] Our analysis by a similar method showed that patients not achieving PASI 30 at Week 4 were less likely to achieve PASI 50 at Week 16 based on YI analyses. However, our result is limited by the small sample sizes.

In our daily clinical practice, washout periods of systemic therapies are required to maintain optimal disease control in high-need psoriasis patients.[44] Previous studies reported that about 30–40% of psoriasis patients received concurrent biologics and traditional systemic agents in clinical practice.[4,45,46] In the current study, 46% of patients received systemic combination therapy, which may complicate the interpretation of the results. However, 55% of them did not reach PASI 50 response during the study period, revealing their demand for concomitant therapies to control the intractable disease.

Conclusion

This is a preliminary report of our experience of reimbursed ustekinumab users who had been treated previously with etanercept or adalimumab for psoriasis in Taiwan. This study was limited by the small sample size. However, it provides an important message when a biologic switch is needed due to loss of efficacy. Despite a less favorable response compared to our previous pivotal study, ustekinumab may still be suggested as the preferred biologic for psoriasis patients who had failed a previous TNF blocker, possibly due to a different mode of action.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dsi.2014.09.005.