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Efficacy and safety of ustekinumab in the treatment of moderate to severe plaque psoriasis in Singapore

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ABSTRACT

Introduction: Ustekinumab is a human monoclonal antibody that binds to the p40 subunit of both interleukin (IL)-12 and IL-23, and it is approved for the treatment of moderate to severe plaque psoriasis. In this study, we assessed the efficacy and safety of patients receiving ustekinumab for psoriasis.

Methods: This retrospective study included all adults with chronic plaque psoriasis who were prescribed ustekinumab in a tertiary dermatologic centre between December 2009 and December 2015. Efficacy end points included a proportion of patients achieving at least 50% and 75% improvement from baseline psoriasis area and severity index (PASI) and body surface area (BSA) at Weeks 4 and 16.

Results: A total of 99 patients were prescribed ustekinumab; 69% of these were Chinese, followed by 15% Indians and 9% Malays. 31 patients had documented PASI scores and 55 patients had documented BSA improvements. In patients with recorded PASI scores, 29 (93.5%) of 31 patients achieved PASI 50, and 21 (67.7%) of 31 achieved PASI 75 at week 16. In patients with recorded BSA, 43 (78.2%) of 55 had at least 50% BSA improvement, and 31 (56.4%) of 55 achieved 75% BSA improvement at 16 weeks. Regarding safety, no patient experienced tuberculosis reactivation. A total of 11 (11%) of 99 patients had latent tuberculosis infection and were treated with prophylactic isoniazid. No patient experienced serious adverse events. No cardiovascular events, cutaneous malignancies or deaths were reported over six years.

Conclusion: Ustekinumab is safe and efficacious in the treatment of patients with moderate to severe plaque psoriasis in a multiethnic Asian population.

Keywords: biologic, psoriasis, ustekinumab

INTRODUCTION

Psoriasis is a chronic inflammatory skin condition that affects 1%–3% of the world's population.⁽¹⁾ Patients with psoriasis can experience a burden on their quality of life and are at higher risk of comorbidities such as obesity, hypertension, insulin resistance and coronary heart disease.^(2,3)

The pathogenesis of psoriasis is not completely understood; however, abnormal immune response leading to keratinocyte hyperproliferation plays a key role.⁽⁴⁾ Overexpression of proinflammatory cytokines interleukin (IL)-12 and IL-23 has been demonstrated in psoriatic plaques.⁽⁵⁾ Both IL-12 and IL-23 have a p40 subunit, and genetic polymorphism of the genes that encode p40 has been linked to psoriasis in multiracial populations, including the Western and the Eastern countries.^(6,7) Hence, targeted therapy involving p40 subunit of IL-12 and IL-23 is useful in the treatment of patients with psoriasis.

Ustekinumab is a human monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23 cytokines. Binding of the antibody to the p40 subunit blocks the downstream signalling cascade with efficacy, aiding in the treatment of psoriasis. Ustekinumab is administered as a 45-mg subcutaneous injection in patients weighing less than 100 kg and as a 90-mg injection in patients weighing more than 100 kg at Week 0 and Week 4, and 12-weekly thereafter.⁽⁸⁾

Ustekinumab has shown to be efficacious in several phase II and III trials, including PHOENIX I and PHOENIX II, which were conducted in North America and Europe.^(9,10) Further studies LOTUS and PEARL have shown ustekinumab to be efficacious in large placebo-controlled trials in China and Taiwan/Korea, respectively.^(11,12) In this study, we sought to assess the efficacy of ustekinumab in a multiethnic population composed of Chinese, Indians and Malays.

METHODS

This retrospective study included all patients with plaque psoriasis who were prescribed ustekinumab between December 2009 and December 2015 at the National Skin Centre in Singapore. Patients weighing less than 100 kg received ustekinumab 45-mg injections and those weighing more than 100 kg received 90-mg injections. Efficacy end points included psoriasis area and severity index (PASI) 50, PASI 75 and documented body surface area (BSA) changes at Weeks 4 and 16.

Data on patients' age, gender, ethnicity, previous treatments for psoriasis, previous biologic therapy, PASI score and BSA was collected. Any adverse effects including headache, upper respiratory tract infection, allergic reaction, infection, malignancy and abnormal blood tests throughout treatment were also documented. Our centre's pre-biologic screening included baseline full blood count (FBC), conducting liver function tests (LFTs), determining creatinine levels, screening of infection with hepatitis B and hepatitis C, undergoing interferon- γ release assay (IGRA) with T-SPOT.TB test and taking a chest radiograph. All patients had their FBC, LFT and creatinine level tests repeated per visit at Weeks 0 and 4 and subsequently every 12 weeks on follow-up, and their IGRA test repeated annually.

To evaluate the efficacy of treatment, Wilcoxon signed-rank tests were used to compare the PASI scores before treatment and after subsequent visits. Similar tests were done for BSA. Statistical significance was set at $p < 0.05$, and data was analysed using STATA Statistical Software version 14.1 (StataCorp LLC., College Station, TX, USA). The study was approved by the local ethics review committee.

RESULTS

A total of 99 patients with plaque psoriasis were prescribed ustekinumab. Most of our patients were Chinese (69%), followed by Indians (15%) and Malays (9%). All patients were treated with topical corticosteroids in the past. Most (89%) patients had failed previous oral systemic therapy including methotrexate, acitretin or cyclosporine. About 64% of patients failed previous phototherapy. A total of 31 patients had documented PASI scores and 55 had documented BSA. 13 patients had unrecorded data or missing data; hence, the efficacy could not be ascertained. The baseline characteristics of the patients are summarised in Table I.

Table I. Baseline characteristics of patients on ustekinumab.

Characteristic	No. (%)
Gender	
Female	23 (23.2)
Male	76 (76.8)
Age* (yr)	44.0 ± 12.7
Ethnicity	
Chinese	68 (68.7)
Malay	9 (9.1)
Indian	15 (15.2)
Other	7 (7.1)
Dosage of ustekinumab	
45 mg	87 (87.9)
90 mg	12 (12.1)
Psoriatic arthropathy	13 (13.1)
Prior medications and exposure	
Topical agents (corticosteroid/vitamin D analogue)	99 (100.0)
Systemic agents	88 (88.9)
Phototherapy (narrow band UV-B, systemic or topical/bath psoralen UV-A)	63 (63.6)
Biologics	21 (21.2)
Concurrent systemic treatment (acitretin/cyclosporine/methotrexate)	26 (26.3)
Latent tuberculosis infection	11 (11.1)
Common adverse events	
Upper respiratory tract infection	1 (1.0)
Nasopharyngitis	0 (0)
Headache	0 (0)
Arthralgia	0 (0)

Injection-site reaction	0 (0)
Serious adverse events	
Serious allergic reaction	0 (0)
Tuberculosis reactivation	0 (0)
Infection	1 (1.0)
Adverse events of special interest	
Cutaneous malignancy	0 (0)
Noncutaneous malignancy	1 (1.0)
Cardiovascular events	0 (0)
Demyelinating disorder	0 (0)

**Data presented as mean \pm standard deviation. UV: ultraviolet*

For patients with recorded PASI scores, 17 (54.8%) of 31 patients achieved PASI 50 and 5 (16.1%) of 31 patients achieved PASI 75 at four weeks. For patients with recorded BSA, 24 (43.6%) of 55 patients reported at least 50% BSA improvement, and 4 (7.3%) of 55 achieved at least 75% BSA improvement at four weeks.

At Week 16, 29 (93.5%) of 31 patients achieved PASI 50, and 21 of 31 (67.7%) achieved PASI 75. In the patients with recorded BSA, 43 (78.2%) of 55 patients had at least 50% BSA improvement, and 31 (56.4%) of 55 patients achieved at least 75% BSA improvement at 16 weeks ().

The mean PASI score at baseline was 16.6, with a significant reduction to 8.2 after four weeks and to 3.1 after 16-week treatment with ustekinumab, with a mean reduction in PASI score of 13.5 ($p < 0.05$). The mean baseline BSA score was 24%, and it was significantly reduced to 15.1% after four weeks and to 9.3% after 16-week treatment, with a mean BSA reduction of 14.7% ($p < 0.05$) (Figs. 2a & b).

With regard to safety, no patient had tuberculosis (TB) reactivation. 11 (11%) of 99 patients had positive T-SPOT.TB at baseline screening and were treated with prophylactic isoniazid (INH) for 6–9 months. No patient suffered from serious adverse events or stopped treatment because of an adverse event within 16 weeks. No cardiovascular events, malignancies, demyelinating disease or death were reported. One patient developed

Haemophilus influenzae pneumonia requiring admission after two years of treatment, and ustekinumab was stopped.

DISCUSSION

This study assesses the efficacy and safety of ustekinumab in the treatment of a multiethnic Asian population. Ustekinumab is safe and efficacious in the treatment of patients with moderate to severe plaque psoriasis.

Efficacy data at 16 weeks in our study is comparable to that of PHOENIX I, with 67.1% of patients achieving PASI 75 at Week 12 on ustekinumab 45 mg.⁽⁹⁾ Similar efficacy was reported in the Taiwanese/Korean PEARL group, with a PASI 50 of 91.3% and PASI 75 of 67.2% at 12 weeks.⁽¹²⁾ The Chinese LOTUS group reported a higher efficacy, with 82.5% patients achieving PASI 75 at 12 weeks. A possible explanation is that 21% of our patients and 18% of patients in the PEARL group had been on previous biologic therapy, compared with only 9% of patients in the LOTUS group. The efficacy of ustekinumab in biologic-naive patients has been shown to be higher than in non-naive patients.⁽¹³⁾ Previous biologic therapy in our patients included etanercept, adalimumab and infliximab.

Compared with other biologics, studies have reported that 48% of patients on etanercept achieved PASI 75 at Week 12 of treatment,⁽¹⁴⁾ 53% on adalimumab achieved PASI 75 at Week 12,⁽¹⁵⁾ 72% of patients on infliximab achieved PASI 75 at Week 10,⁽¹⁶⁾ and 81.6% on secukinumab achieved PASI 75 at Week 12.⁽¹⁷⁾

Ustekinumab was well tolerated by our multiracial population with moderate to severe plaque psoriasis. There were no reports of injection-site side effects or serious allergic reactions, or common adverse events including nasopharyngitis, arthralgia and headache. There was only one case of upper respiratory tract infection (URTI) after injection. Information and recall bias is a possibility, as nasopharyngitis and URTI were the most

common side effects reported by 7.3%–11.5% and 4.4%–8.5% of patients in ustekinumab-treated groups, respectively.^(10,12)

TB is much more prevalent in Asia than in our Western counterparts. Singapore has an incidence rate of 36.9 per 100,000 population, with 84.5% of cases being pulmonary TB.⁽¹⁸⁾ Across five phase III trials of ustekinumab-treated patients with psoriasis, the prevalence of LTBI was 3.5% in non-Asians and 23.7% in Asian patients.⁽¹⁹⁾ Our study found a relatively lower incidence of LTBI of 11%, which is comparable to that in the Chinese LOTUS study, with 12.7% of 322 patients diagnosed at screening.

The lifetime risk of reactivation of LTBI is estimated to be 5%–15%, with most patients developing TB within the first five years after initial infection.⁽²⁰⁾ All our patients with LTBI had normal chest radiographs and were referred to the TB control unit for treatment. Prophylactic prevention of LTBI is reported to be 60%–90% effective in LTBI reactivation.⁽²¹⁾ Patients in our study received concurrent prophylactic treatment with INH upon starting ustekinumab. All patients tolerated the treatment well and completed a 6–9-month regimen. There were no cases of LTBI reactivation. Larger reviews have shown INH to be effective, with no cases of LTBI reactivation during the treatment of 167 of 3,177 patients with LTBI.⁽¹⁹⁾

Review of data of all patients prescribed ustekinumab within the six years showed that only one patient developed serious infection with *H. influenzae* pneumonia requiring admission; however, this occurred after two years of treatment. No cardiovascular events, cutaneous malignancies, demyelinating disease or death were reported. A 64-year-old woman was found to have breast cancer after two and a half years of treatment. She stopped treatment upon starting chemotherapy. This isolated case of malignancy was likely incidental and not related to biologic therapy. To date, ustekinumab has been reported to be safe, based on a five-year follow-up of patients on PHOENIX 2.⁽²²⁾ Further, in a recent meta-analysis

comparing the short-term safety and efficacy of biologic therapy in moderate to severe plaque psoriasis, ustekinumab demonstrated a better safety profile than infliximab and secukinumab did.⁽²³⁾

The main limitation of this study is its retrospective nature. Only 31 of 99 patients had a recorded PASI score. The low incidence of common adverse events, particularly nasopharyngitis and URTI, could be attributed to recall or information bias.

In conclusion, the safety and efficacy of ustekinumab in the treatment of multiethnic Asian patients are comparable to those reported in global studies. With an increased prevalence of LTBI in Asia, it is pertinent to screen and treat prophylactically when starting on any biologic therapy.

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FIGURES

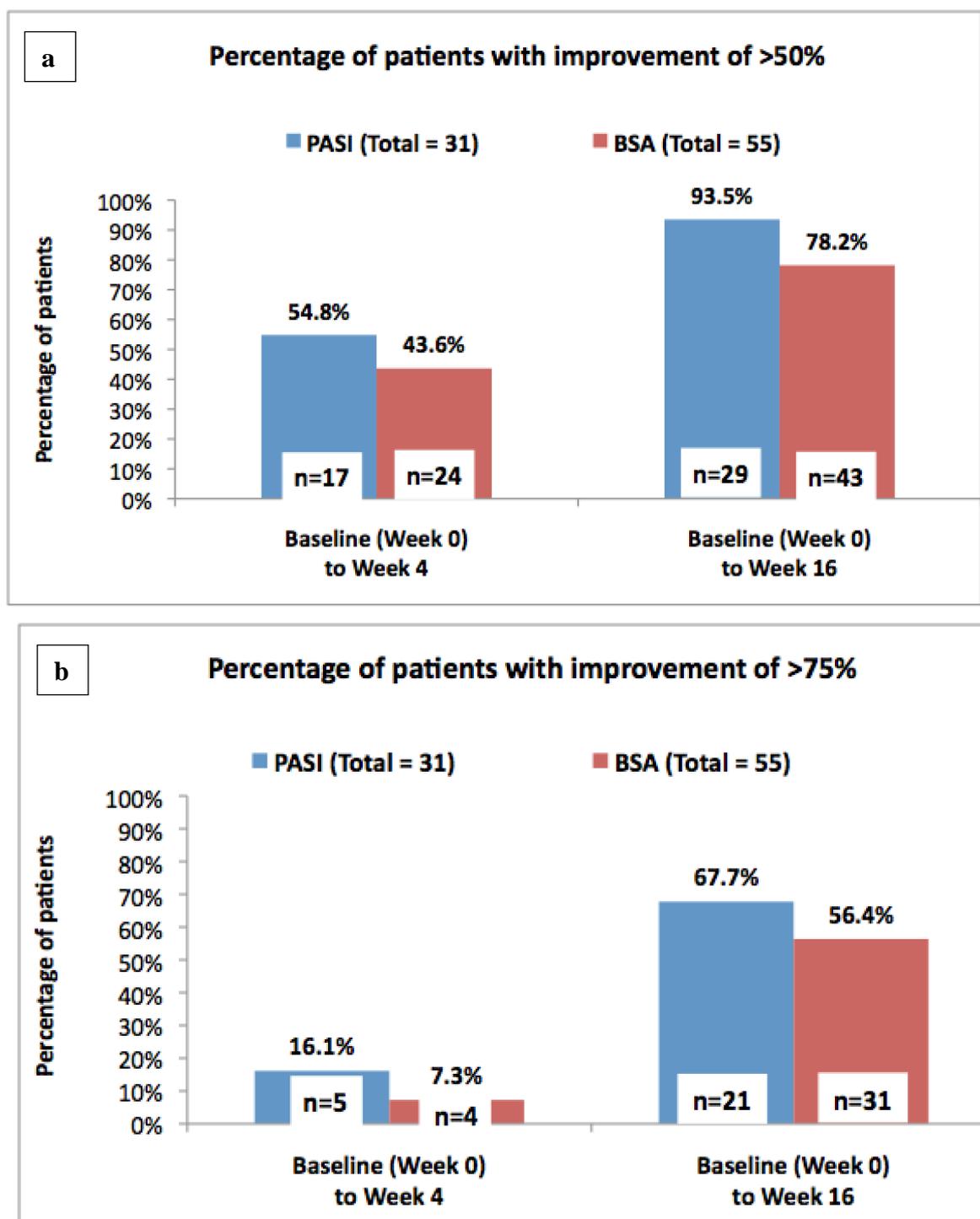


Fig. 1 Bar graphs show percentage of patients at Weeks 4 and 16 who achieved (a) PASI 50 or at least 50% BSA improvement and (b) PASI 75 or at least 75% BSA improvement. BSA: body surface area; PASI: psoriasis area and severity index

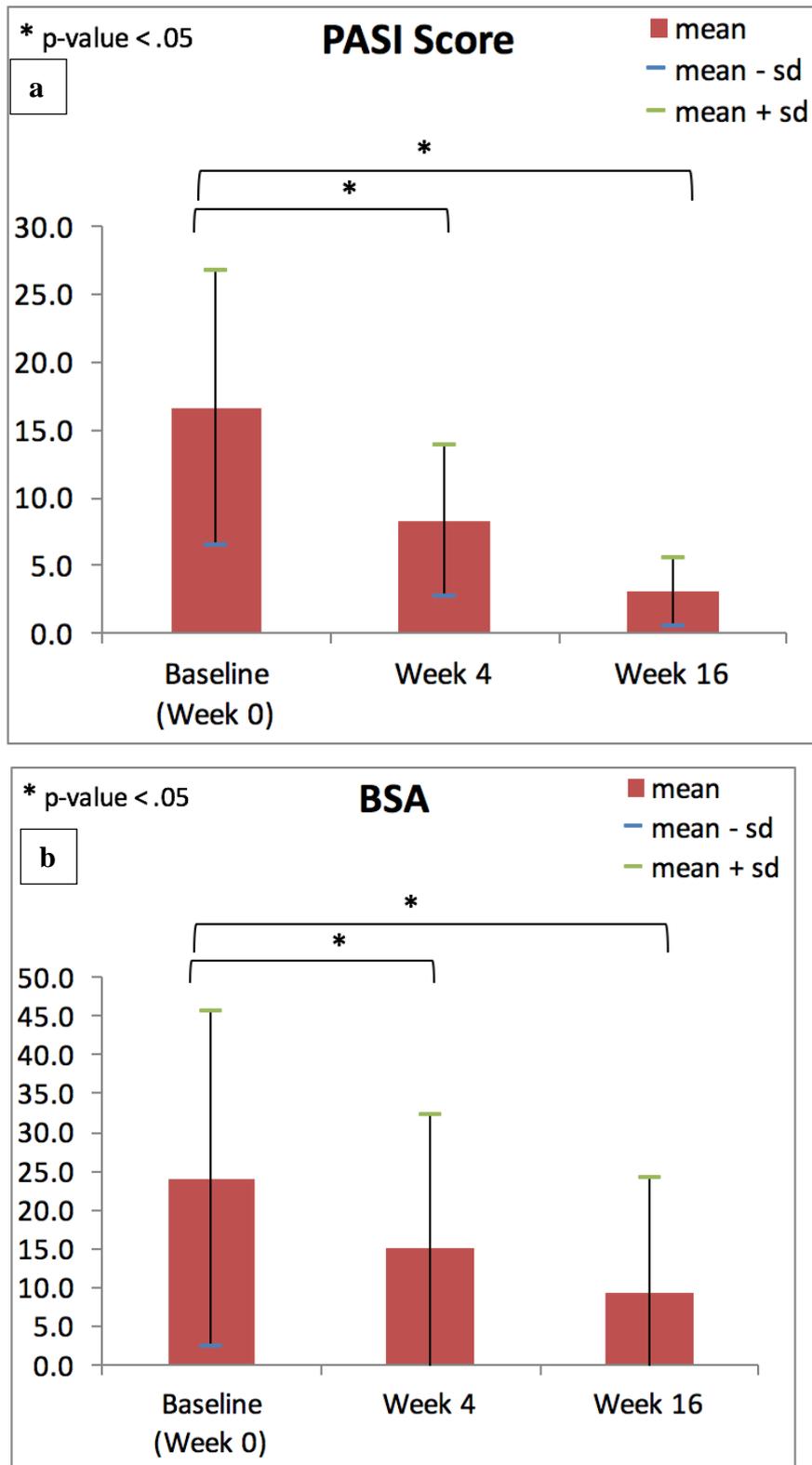


Fig. 2 Bar graphs show improvements in (a) psoriasis area and severity index (PASI) scores and (b) body surface area (BSA) between Weeks 0, 4 and 16.

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