

## Original Article

# Ustekinumab for severe treatment-resistant psoriasis: a 24-week pilot study in Hong Kong Chinese

## 生物製劑Ustekinumab對香港華裔銀屑病重症病人之二十四週先導性試驗

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**Introduction:** Ustekinumab, an interleukins 12 and 23 antagonist, is shown to be an effective treatment in patients with moderate to severe psoriasis. However, little is known about its efficacy or safety of in Chinese patients with recalcitrant psoriatic disease. **Method:** Five patients with treatment-resistant psoriasis (mean baseline PASI 22.8) receiving ustekinumab (week 0, 4 and 16) were followed up for 24 weeks. **Results:** All patients (100%, 5/5) attained PASI 50 and two (40%, 2/5) patients attained PASI 75 at week 12 after initiated the two doses at week 0 and week 4. Minor relapse in PASI score before the third dose at week 16 was noted in 4 patients (80%, 4/5). The clinical response could be maintained at week 24 after the third dose at week 16. No major adverse event was noted. **Conclusion:** Ustekinumab may be a useful treatment alternative for patients with severe recalcitrant psoriasis. Long term study with larger patient cohort is needed to establish its long term efficacy and side effects.

**簡介:** Ustekinumab 為白介素 -12 及白介素 -23 的阻斷劑，對治療一般中度至嚴重的銀屑病病人有顯著功效，但其對華裔銀屑病重症病者的功效及安全性則所知甚少。**方法:** 五名對傳統治療無效的銀屑病病人（銀屑病面積嚴重程度指數基線平均值達 22.8）接受 ustekinumab 生物製劑治療，包括起始、第四週及第十六週共三劑的療程，並予跟進共二十四週。**結果:** 所有病患（100%，5/5）都達致銀屑病面積嚴重程度的五成改善，其中兩人（40%，2/5）更在接受兩劑治療後的第十二週，達到銀屑病面積嚴重程度的七成半改善。另在第十六週的第三劑治療前，其中四名病人的銀屑病面積嚴重程度評分有輕微反彈，但其後的臨床功效則可維持到第二十四週。此外，在研究期間並無嚴重不良反應發生。**總結:** Ustekinumab 可以是治療頑固銀屑病的另類選擇，更大型的長期病人追蹤研究，可有助確立其長期療效及副作用。

**Keywords:** Chinese, biologics, psoriasis, ustekinumab

**關鍵詞:** 華人，生物製劑，銀屑病，ustekinumab

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## Introduction

Psoriasis is a chronic immune-mediated inflammatory disease of the skin that significantly impairs patients' physical and mental functioning and wellbeing. The condition affects about 2-3% of the population worldwide.<sup>1</sup> There is considerable racial variations and psoriasis is estimated to affect 0.3% of the Chinese population.<sup>2</sup>

Patients with severe psoriasis constitute approximately 20-30% of all patients with psoriasis, and represent a major economic burden to the health service.<sup>3</sup> Standard systemic therapies are associated with a risk of toxicity with long-term use, many are relatively expensive, and a proportion of patients is resistant to such treatments. Widespread dissatisfaction among patients with commonly used therapies also contributes to the already substantial morbidity and impaired quality of life associated with severe disease.<sup>4</sup>

Characterization of the immunopathophysiological basis of psoriasis has led to the development of novel therapeutic agents that selectively target aberrant immune responses putatively involved in psoriasis, including agents that target leucocyte function-associated antigen-3, CD11a, and tumour necrosis factor  $\alpha$ .<sup>5</sup> However, currently available therapeutic options have left substantial unmet need for treatments that are convenient, effective, and well tolerated, especially for long-term treatment. More recently, interleukin-12 and interleukin-23, cytokines that induce naive CD4+ lymphocytes to differentiate into type 1 helper T cells (Th1 cells) and type 17 helper T cells (Th17 cells), respectively, have been identified as key mediators of the pathogenesis of psoriasis. Ustekinumab is a human monoclonal antibody that binds to the shared p40 protein subunit of human interleukins 12 and 23 with high affinity and specificity, thereby preventing interaction with their cell surface IL12R $\beta$ 1 receptor.<sup>6</sup> The phase III PHOENIX 1 study, together with

PHOENIX 2, examined the safety and efficacy of ustekinumab compared with placebo for 12 weeks in patients with moderate-to-severe plaque psoriasis and also used a randomised withdrawal design to assess the safety and efficacy of long-term ustekinumab treatment for up to 76 weeks.<sup>7,8</sup> In these two phase III, double-blind, placebo-controlled studies, which involved over 2000 patients with moderate to severe psoriasis, the proportions of patients achieving the primary endpoint were significantly greater in the ustekinumab groups (66-76%) than in the placebo groups (3-4%). Not only was the response well maintained for 3 months at a time between the injections, but the adverse events (52% and 49%, respectively) and the serious adverse events were also similar (1.4% and 1.5%, respectively) between the ustekinumab and placebo groups. Ustekinumab was efficacious and well tolerated for 52-76 weeks. In another head-to-head randomised controlled trial (ACCEPT), the efficacy of ustekinumab at a dose of 45 or 90 mg was superior to that of high dose etanercept over a 12-week period in patients with psoriasis.<sup>9</sup>

However, relatively little is known about the efficacy or safety of ustekinumab in Chinese patients with recalcitrant psoriatic disease. We reported our experience with the use of ustekinumab in the treatment of patients with psoriasis attending a government specialist dermatologic clinic with severe recalcitrant disease.

This paper aims to summarize the results of a small case series of its use in Chinese people with recalcitrant psoriasis at a public dermatology clinic in Hong Kong.

## Method

### *i) Patient selection*

Patients attending the Yaumatei Dermatologic Outpatient Clinic, Social Hygiene Service, Department of Health, from November 2009 to

March 2010 were considered for treatment with ustekinumab if they satisfied the following clinical criteria for inclusion: (i) those who were intolerant to or unable to achieve satisfactory response to our available systemic treatments (including phototherapy, acitretin, methotrexate, cyclosporine and hydroxyurea); (ii) those who had developed, or were, at significant risk of developing clinically important drug-related toxicity to our available systemic treatments or (iii) those who were currently or had history of receiving anti-tumor necrosis factor treatment however with suboptimal clinical response.

#### **ii) Pretreatment assessment**

All patients underwent a full history taking with particular reference to infection (including risk factors for tuberculosis), demyelinating disease, cardiac disease or malignancy. Clinical examination included verification of Bacillus Calmette-Guérin (BCG) scar in those vaccinated, and assessments of disease severity by Psoriasis Area and Severity Index (PASI) and clinical photography. Clinical assessments were conducted by two dermatologists with experience in conducting clinical research in psoriasis including performing PASI scoring. Baseline investigations were performed as follows: complete blood count (CBC), renal and liver function, antinuclear antibodies (ANA), and specific screening for hepatitis B in those identified to be at risk; clinical photography; tuberculin skin test and chest X-ray (CXR).

#### **iii) Intervention**

Following informed, written consent, 3 doses of subcutaneous injections of ustekinumab (45 mg for <90 kg, 90 mg for >90 kg) at weeks 0 and 4 and 16 were given. In view of the severity of disease in this patient cohort, any concomitant systemic therapies were continued until adequate disease control was achieved and then reduced or stopped over subsequent months as clinically indicated.

#### **iv) Outcome measure and assessments**

Disease severity assessments comprised Psoriasis

Area and Severity Index (PASI) Clinical photography was performed at baseline and at 4-weekly intervals. Fifty and 75% improvement in Psoriasis Area and Severity Index (PASI 50 and PASI 75 respectively) at 12 weeks were adopted as the primary outcome measurements. Prior to each injection, patients were reviewed by the investigators. All patients were followed up for 24 weeks. Adverse events were asked in each visit as the other outcome measure.

#### **v) Laboratory investigations**

Monitoring investigations (CBC, renal and liver profiles) at baseline and were repeated at approximately monthly intervals, prior to ustekinumab injection, together with additional investigations as clinically indicated.

#### **vi) Statistical analysis**

Data was analyzed and presented with descriptive statistics.

## **Results**

### **Baseline demographics**

Five patients have been treated with ustekinumab during the study period: four men, one woman; age  $48.0 \pm 10.2$  (mean  $\pm$  SD) years. All had recalcitrant disease and had received therapy with at least two systemic therapies prior to treatment with ustekinumab (Table 1). The mean duration of disease was  $16.8 \pm 0.5$  (mean  $\pm$  SD) years. Baseline PASI was 22.8 (range 17.4 to 27.6). The disease course was complicated by history of erythroderma requiring admission in 3 patients. None of them are active smoker nor drinker and their past medical history were unremarkable. Significant psoriatic arthritis requiring specific rheumatological treatment was absent in our study patients.

## **Efficacy**

All patients completed 3 doses of ustekinumab

**Table 1.** Past history of systemic treatment

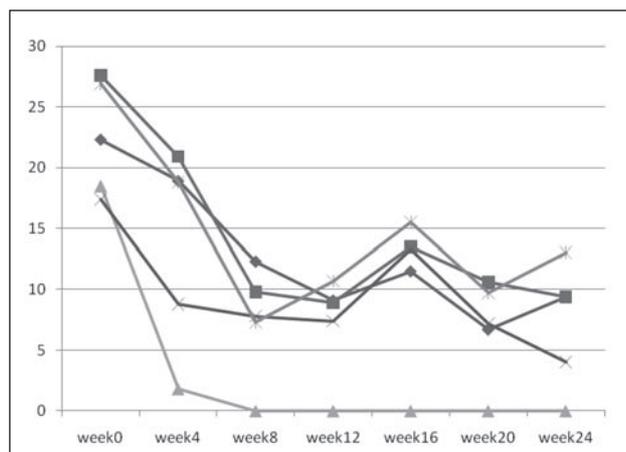
Patient no.	Age years/sex	Phototherapy	Cyclosporine	Methotrexate	Acitretin	AntiTNF
1	49/F	•	–	–	•	•
2	42/M	•	–	–	•	–
3	64/M	•	–	•	•	•
4	48/M	–	•	•	•	•
5	37/M	–	–	–	•	•

(week 0, 4, 16) and followed up for 24 weeks. The PASI score changes were shown in Figure 1.

All patient (100%, 5/5) attained PASI 50 and two (40%, 2/5) patients attained PASI 75 at week 12 after initial the two doses at week 0 and week 4. Minor relapse in PASI score at week 16 i.e. before the third dose was noted in 4 patients (mean PASI 7.2 at week 12 vs mean PASI 10.8 at week 16). The clinical response could be maintained at week 24 after the third dose at week 16.

### Concomitant treatment

Patients previously receiving acitretin was continued in 3 patients and it was tailed off in week 6. One patient receiving etanercept and one



**Figure 1.** Psoriasis Area and Severity Index (PASI) over 24 weeks.

receiving methotrexate were discontinued their treatment after administration of ustekinumab.

### Progress

One patient remained on ustekinumab (self financed) to date with satisfactory disease control. Of the remaining 4, all of them had significantly relapse of disease (>50% of baseline PASI) after week 28 and traditional systemic treatments were resumed for disease control.

### Adverse effects

All patients received 3 doses of ustekinumab with no major adverse events. Serial monitoring of complete blood count, liver and renal function test and Chest X-ray were unremarkable. Two patients had an episode of upper respiratory tract infection and course of systemic antibiotics was given by general practitioner with no major consequences.

### Discussion

Patients with severe psoriasis can present major therapeutic challenges and dilemmas. While standard traditional systemic therapies are, for the most part, effective in the short term, predictable toxicity and gradual decline in efficacy may complicate long-term use. Rotating or combining

different treatment modalities mitigates against these problems. But for a significant group of patients with severe disease, adequate disease control is impossible or achieved only with actual, or high risk of, drug toxicity and consequent morbidity. Our experience with ustekinumab suggests that this agent represents an alternative treatment option for this group of patients.

In this report, we have shown ustekinumab to be rapidly effective with the onset of improvement being evident after the first or second dose and all of them achieving a PASI 50 and 40% of patients achieving a PASI 75 at week 12. This level of efficacy is slightly lower than that reported in the three randomized, placebo-controlled trials examining efficacy of ustekinumab in moderate to severe, stable chronic plaque psoriasis published to date.<sup>7-9</sup> Our patient cohort probably represents a more severely affected, treatment-resistant group as evidenced by higher mean baseline scores on measures of disease severity (PASI 22.8), multiplicity of previous therapies and the fact that most patients were on concomitant therapy at the initiation of ustekinumab.

The benefit of ustekinumab in combination with other agents in psoriasis is not established, and all the trials to date have used ustekinumab alone. However, in clinical practice, as evidenced in our case series, concomitant therapy may need to be continued to avoid unacceptable deterioration in quality of life and/or a potentially dangerous flare in disease activity while waiting for the therapeutic effects of ustekinumab. Wherever possible, concomitant therapy was rationalized prior to ustekinumab treatment, and agents of questionable or minimal benefit should be stopped. Once disease control was achieved, doses of concomitant therapy were reduced or stopped over relatively short periods of time and with no consequent destabilizing of disease. Data concerning drug-related toxicity developing with the co-administration traditional systemic treatments and ustekinumab was limited, the additional burden of immunosuppression from

concomitant therapy should be carefully monitored.

In this 24 week study period, severe adverse effects were not noticed and no patient discontinued therapy due to serious side-effects. From the analysis of the 3-year safety data of ustekinumab in 2009, there were over 3000 patients exposed to ustekinumab in which 157 patients had been using the medication for over 3 years. Infection of all causes was observed in 48% of the patient receiving ustekinumab, in which majority of them are upper respiratory tract infection. Serious adverse events were observed in up to 5% of the treatment patients. However, these adverse events may or not be directly related to the administration of ustekinumab. The combined incidence of serious infection was 1.19 per 100 patient-year (95% CI 0.90-1.54) while 1.70 per 100 patient-year (95% CI 0.35-4.96) for the control patients.<sup>10</sup>

There was one reported case of pulmonary tuberculosis (TB) in Taiwan in the 3 year safety data. No other reported case of tuberculosis in the 97 subjects with latent TB who were treated with isoniazid before commencing ustekinumab. No environmental mycobacterial infection, salmonella or systemic fungal infection were reported.<sup>10</sup>

However, we have a high disease prevalence of tuberculosis in our locality. Careful patient selection, pretreatment assessment and monitoring during and after completion of therapy remain essential. Newer screening test for latent tuberculosis by  $\gamma$ -interferon assay may possibly further lower the risk of treatment-related adverse events from TB.

Considering that interleukins 12 and 23 have an important role in immune surveillance, long-term toxicity of ustekinumab is largely unknown at this moment and legitimate concern exists particularly about long term risks of malignancy. Risks of skin cancer and lymphoma are already elevated in

patients with psoriasis, particularly in severe disease although the relative contribution of antipsoriatic immunosuppressive therapy to this risk is not known.<sup>11</sup> Actual and relative risks associated with ustekinumab and biological therapies as a whole, especially in the context of this already very difficult to treat population, will become evident only with careful, long-term follow-up and continued pharmacovigilance. Central registration of all patients receiving ustekinumab and other biological therapies should facilitate this process. From the 3-year safety data of ustekinumab, there were no excessive increase risk in melanoma skin cancer (MSC), non-MSC, solid organ tumors and cardiovascular events when compared to the controls or expected rates in the general population.<sup>10</sup>

Our study is limited by small sample size and no controlled comparison for treatment response. Establishment of local registry with large cohort of psoriasis patients using biological agents may provide useful insights to our local dermatologists.

Although ustekinumab seems to be a good alternative option for the therapy of moderate to severe psoriasis, many questions remain. What is the long-term safety of ustekinumab in terms of infections and malignancies? Will tachyphylaxis eventually develop after long-term use? Will ustekinumab benefit psoriatic arthritis and cardiovascular risk? Hopefully, longer-term studies with ustekinumab and other monoclonal antibodies to interleukins 12 and 23 will answer these questions.

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