Case Report

Observational Cases Report of A group of Severe Plaque Type Psoriasis Patients Treated with Ustekinumab

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Background: *Psoriasis is a common chronic immunologic disease which shares common inflammatory pathways to other disease like diabetes, cardiovascular disease, and irritable bowel disease. Ustekinumab is a human monoclonal antibody that reduces the expression of interleukin-12 and interleukin-23, the key inflammatory cells of the pathology of psoriasis.*
Main observation: *Four patients with severe chronic plaque type psoriasis who were not responding well to conventional systemic therapy were included in the ustekinumab treatment. The study revealed good clinical response with at least PASI 75 response at week 12, and long-term clearing of psoriatic lesions was observed.*
Conclusion: *Ustekinumab represents an effective alternative for the management of psoriasis; despite being used as a short-term treatment, it still shows efficacy on recalcitrant psoriasis.*

Keywords: *Psoriasis, Ustekinumab, Biologic agents*

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Psoriasis is a chronic immunologically-based, inflammatory skin disease suffered by approximately 2% of the world's population with men and women equally affected[1]. The course of the disease is unpredictable with multiple remissions and relapses. In addition, there also extensive coverage in the literature about its coexistence with other inflammatory conditions such as arthritis, diabetes, cardiovascular disease and irritable bowel disease[2]. As its incidence among patients has increased, psoriasis has had a more significant impact on the affected persons.

The cytokines released such as TNF-α, interleukin-12, and interleukin-23[3] have been shown to play a key part in the pathogenesis of psoriasis. Ustekinumab is a monoclonal antibody which targets the P40 subunit of both Interleukin-12 and -23 and hence reduces the expression of cytokines by selectively blocking steps in the cytokines cascade, a process which may result in the effective treatment of psoriasis[4]. Hence, it may be an alternative therapeutic option for patients who might not respond well and/or are intolerant to standard therapy.

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Case Report

Patients

Patients included for the treatment were adults (>20 years old) with a diagnosis of severe plaque psoriasis who: had a score on the psoriasis area- and-severity index (PASI) of more than 20 (on a scale of 0 to 72, higher scores indicating more severe disease); or had involvement of more than 10% of body surface area; who did not respond well to conventional therapy; and who were able to attend for 12 weeks of therapy. Routine blood tests were done to exclude hepatitis B, HIV and other blood, kidney or liver diseases, and chest radiographs were done to exclude pulmonary tuberculosis. Demographic characteristics of patients are shown in Table 1.

Study design

Four patients were treated with ustekinumab at a dose of 45 mg administered subcutaneously the first week. Patients who had a PASI 75 response received another injection at week 4, while those who had a response of less than 75.0% improvement in the PASI score from the baseline received only one 45 mg subcutaneous injection.

Patients were evaluated at weeks 2, 4, 6 and 12 for overall status of psoriasis lesions (erythema, induration and scaling) and all other medical events (Table 2).

Table 1. Baseline characteristics

No.	Age (years)	Sex	PASI*	% BSA**	Previous treatments
1	36	M	47.1	80	Topical agents
2	29	M	30	70	Topical agents, conventional systemic agents[+]
3	34	F	54	85	Topical agents, conventional systemic agents
4	24	F	38.6	70	Topical agents, conventional systemic agents, biologic agents[++]

* psoriasis area severity index score 0-72; ** body surface area 0-100%; [+] Conventional systemic agents including methotrexate, and cyclosporine; [++] Biologic agents including etanercept

Table 2. Clinical responses PASI*

	Week 2	Week 4	Week 6	Week 12
1	22.4	13.6	6	4.8
2[+]	27.5	27	25.4	20.6
3[+]	NA	31.5	35.4	36.4
4	31.7	33.6	6.8	4.5

* psoriasis area severity index score 0-72
[+] the patients received one injection of ustekinumab
NA = not assessed

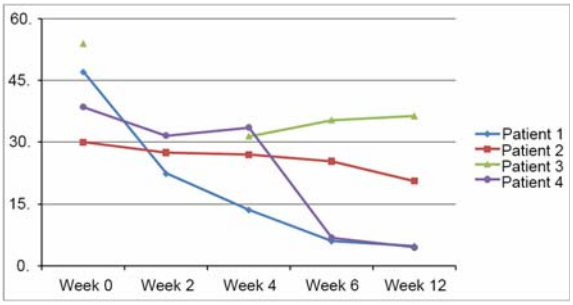

Fig. 1 PASI score of 4 patients during 12-weeks follow-up.

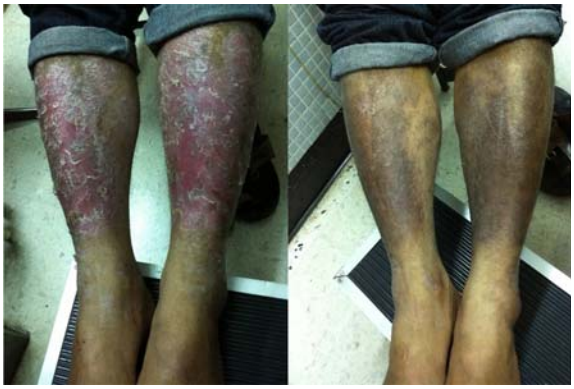

Fig. 2 PASI response of 45 mg ustekinumab subcutaneous injection (case 1) at baseline and week 12.

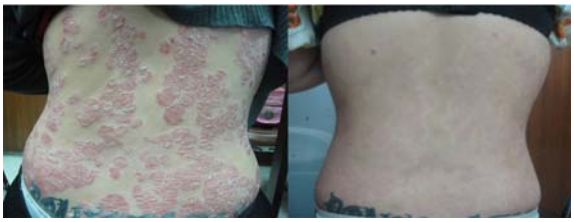

Fig. 3 PASI improvement of patient 4 at baseline and week 12.

Results

All patients achieved a good response to the drug with a PASI 75 improvement from their baseline PASI at week 4. The two patients (patients 1 and 4) who received two doses of 45 mg subcutaneous injections at week 0 and week 4 had more than 90% PASI improvement during treatment, and most of their psoriatic lesions had cleared at week 12 as shown in figures 2 and 3. For patients 2 and 3 who received only one treatment, there was also some improvement in their psoriasis with a PASI 75 and PASI 50 at weeks 4 and 12 respectively. One patient (patient 2) developed a superficial fungal infection on his left wrist, but no other serious side effects were detected in any patients.

At the end of their courses of treatment, the two patients (patients 1 and 4) who had received a complete course of 2 injections had their clinical condition maintained using only topical steroids and emollients. After 15 months and 18 months respectively, patient 1 with PASI 30.3 and patient 4 with PASI 30.9 were given systemic immunosuppressive drugs. For patient 4, ustekinumab was reinjected at 45mg intramuscular at weeks 0 and 4 with quite a good response with PASI 5.2 after the second injection (PASI 90 response).

Discussion

Biologic agents are proteins that produce pharmacologic activity and which are extracted from

animal tissue or synthesized in large quantities through recombinant DNA techniques. Based on the immunological pathogenesis of psoriasis, this treatment has proved to be significantly effective.

Ustekinumab, a newly developed biologic drug, was approved by the US FDA and the European Medicines Agency in late 2009. It is a fully human monoclonal antibody that binds to the p40 subunit that is shared by proinflammatory cytokines interleukin-12 and interleukin-23.

These cytokines are produced by activated antigen-presenting cells including dermal dendritic cells which will turn activated natural killer cells CD8+ T-cells into type 1 helper T-cells like Th1 and Th17 cells. The Th17 cells will then supply more broad inflammatory cells like TNF-alpha, interleukin-17 and interleukin-12. These cytokines affect many cell types, including keratinocytes and epithelial tissue resulting in hyperplasia of the epidermis as observed in psoriasis. The results of this study revealed the effectiveness of treatment with biologic agents: all patients achieved at least PASI 75 improvement from baseline at week 12, even the two patients who were given only one injection. Its pharmacodynamic effects were sustained for many weeks both after only a single dose or four weekly doses. This is similar to the findings of the multicenter double-blinded trials PHOENIX 1 and 2[8,9]; at week 12 significantly more patients achieved a PASI 75 response on ustekinumab 45 mg (67.1% and 66.7% respectively) compared to those on a placebo (3.1%, $p<0.0001$). One patient (case 4) who had previous experience of other biologic agents (etanercept 25 mg subcutaneous injection twice per week), had never achieved a PASI improvement of more than PASI 75 and his lesions had never cleared when on etanercept, but this agent seemed to have a more rapid effect than ustekinumab. The ACCEPT trial[10], following 12 weeks' treatment with ustekinumab 45 or 90 mg, found this agent more effective than etanercept 50 mg twice weekly, demonstrating superior efficacy with PASI 75 improvement of 67.5% and 73.8% respectively compared with etanercept 50 mg twice weekly at 56.8% ($p = 0.01$ and $p<0.001$ respectively). Furthermore, ustekinumab treatment provided effective symptomatic relief for the patients who showed no response to 12 weeks' treatment with etanercept.

There was only one minor adverse event: a cutaneous fungal infection occurred in one patient (case 2) who had had similar frequent fungal infections prior to biologic treatment. The common adverse reactions of biologics are injection-site reaction, nasopharyngitis, upper respiratory tract infection, headache, and back pain[11]. More serious reactions like infections such as cellulitis, diverticulosis, pneumonia, osteomyelitis, sepsis, and disseminated herpes zoster infection were also observed, but there were no reported cases of tuberculosis, atypical mycobacterial disease, or systemic fungal infection[12] even though it is unclear whether malignancies such as skin cancer and lymphoma are related to treatment or psoriasis. Prostate, breast, colorectal, renal, head and neck, and bladder cancers were detected[12].

Cost-efficacy was also considered as a factor among psoriasis treatments including systemic agents, phototherapy and all available biologics. One study revealed that even though a PASI 75 response from infliximab was the highest at 83.0% followed by ustekinumab 45 mg (74.0%) and adalimumab (59.0%), ustekinumab was nevertheless considered to be a more cost-effective treatment than adalimumab or infliximab[13], while phototherapy and methotrexate offer higher efficacy for their cost than biologics[14].

In conclusion, ustekinumab proved to be an effective treatment for plaque type psoriasis but managed care plans should also be considered along with cost effectiveness and long-term safety data.

Potential conflicts of interest

None.

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รายงานการรักษาผู้ป่วยโรคสะเก็ดเงินชนิดรุนแรงด้วยสารชีวภาพ Ustekinumab

อรศิริ เสรีรัตน์

ภูมิหลัง: *สะเก็ดเงินเป็นโรคผิวหนังเรื้อรังที่พบว่ามีความเสี่ยงกับการเกิดโรคหัวใจและหลอดเลือด เบาหวาน, metabolic syndrome, irritable bowel syndrome เนื่องจากอาจมีการหลั่งของสารที่ก่อให้เกิดอาการอักเสบที่จะนำไปสู่การก่อโรคเช่นเดียวกัน Ustekinumab เป็นอีกสารชีวภาพที่ออกฤทธิ์ต้านการอักเสบโดยออกฤทธิยับยั้งการหลั่งของสาร interleukin-12 และ interleukin-23 ที่กระตุ้นการเกิดโรคสะเก็ดเงิน*

รายงานผู้ป่วย: *การศึกษาครั้งนี้เป็นการติดตามอาการผู้ป่วยสะเก็ดเงินชนิดรุนแรงที่ไม่ตอบสนองต่อการรักษามาตรฐานจำนวน 4 รายโดยการให้ Ustekinumab 45 mg ฉีดเข้าใต้ผิวหนังพบว่ามีการตอบสนองดีอย่างน้อย PASI 75 improvement ที่อาทิตย์ที่ 12 ของการรักษาและหลังเสร็จสิ้นการรักษาผู้ป่วยยังคงอาการที่ดีได้เป็นระยะเวลานาน*

สรุป: *Ustekinumab สามารถควบคุมอาการของโรคสะเก็ดเงินที่ดื้อต่อการรักษาได้ดีแม้ว่าระยะเวลาการรักษาที่สั้นเพียง 12 อาทิตย์*