Journal of Dermatological Science 63 (2011) 154–163

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.elsevier.com/jds

Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: A phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL)

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ARTICLE INFO

Article history:
Received 3 March 2011
Received in revised form 20 April 2011
Accepted 10 May 2011

Keywords:
Ustekinumab
Psoriasis
Taiwan
Korea
Interleukin-12/23 monoclonal antibody

ABSTRACT

Background: Ustekinumab has been evaluated in Caucasian patients with psoriasis, but no studies have been conducted in Asian patients.
Objective: To assess the efficacy and safety of ustekinumab in Taiwanese and Korean patients with moderate-to-severe psoriasis.
Methods: In this 36-week, multicenter, double-blind, placebo-controlled study, 121 patients with moderate-to-severe psoriasis were randomized (1:1) to receive subcutaneous injections of ustekinumab 45 mg at weeks 0, 4, 16 *or* placebo at weeks 0, 4 and ustekinumab 45 mg at weeks 12, 16. Efficacy endpoints at week 12 included the proportion of patients achieving at least 75% improvement from baseline in Psoriasis Area and Severity Index (PASI 75; primary endpoint), proportion of patients with Physician's Global Assessment (PGA) of cleared or minimal, and change from baseline in Dermatology Life Quality Index (DLQI).
Results: At week 12, the proportion of patients achieving PASI 75 was 67.2% and 5.0% in the ustekinumab 45 mg and placebo groups, respectively ($p < 0.001$). PGA of cleared or minimal was achieved by 70.5% (ustekinumab) and 8.3% (placebo; $p < 0.001$), and median DLQI changes were −11.0 and 0.0, respectively ($p < 0.001$). Efficacy was maintained through week 28 in ustekinumab-treated patients. Adverse event (AE) profiles at week 12 were similar between the ustekinumab and placebo groups: 65.6% and 70.0%, respectively, had at least one reported AE. Through week 36, no disproportionate increase in AEs was observed, with the exception of abnormal hepatic function, which was related to concomitant isoniazid treatment for latent tuberculosis. Injection-site reactions were rare and mild. No deaths, malignancies, or cardiovascular events were reported.
Conclusions: Treatment with subcutaneous ustekinumab 45 mg offers a favorable benefit/risk profile for Taiwanese and Korean patients with moderate-to-severe psoriasis. The efficacy and safety profile is consistent with the global phase III studies of ustekinumab in psoriasis.

1. Introduction

Psoriasis is a chronic, immunologically-mediated, inflammatory skin disease, which manifests clinically as well-demarcated, scaly, erythematous, indurated skin plaques that are typically distributed in a symmetrical pattern on the scalp, trunk, and limbs [1,2]. The physical manifestations of the disease are associated

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doi:10.1016/j.jdermsci.2011.05.005

with a substantial psychosocial burden [3,4], which has been shown to negatively affect patient quality of life. Psoriasis affects approximately 2–3% of the world's population [2,5]. When compared with Caucasian populations, Asian patients have a lower incidence of psoriasis; according to the National Insurance Bureau in Taiwan, the incidence of psoriasis is estimated to be 0.4% [6]. However, the results of an analysis comparing Western and Asian patients suggest a similar pathophysiology for psoriasis across these populations [7].

Conventional systemic treatments are commonly used to treat moderate-to-severe psoriasis in the Asia Pacific region. To mitigate the potential for long-term toxicity associated with such conventional systemic agents, several biological agents, such as anti-TNF agents, have been introduced and approved for the treatment of moderate-to-severe psoriasis in both Taiwan and Korea [8–15]. Additionally, based on limited and small-scale clinical trials of biological agents conducted in the Asia Pacific region, it appears that the clinical responses to alefacept and efalizumab were markedly lower in Taiwanese patients, while adalimumab responses were slightly lower in Japanese patients, compared with those observed in Caucasian patients [10,11,14,15]. Furthermore, evaluation of these biological agents in Asian patients has lagged compared with global patient populations, and implementation of reimbursement criteria for biologic agents in these Asian countries has further limited their use. Therefore, a significant unmet need remains for tolerable, highly effective, and convenient treatments in the Asian psoriasis patient population.

Ustekinumab is a human immunoglobulin monoclonal antibody that binds to the shared p40 subunit of human interleukin-12 (IL-12) and IL-23 [16]. Interleukin-12 and -23 are overexpressed in psoriasis plaques [17–19], and preclinical studies have indicated a role for these cytokines in psoriasis pathogenesis [20–23]. Furthermore, in both Caucasian and Asian patients, psoriasis pathogenesis has been linked to genetic polymorphisms that encode elements of the IL-12/23 mediated inflammatory pathway, supporting the concept that targeting IL-12/23 is clinically useful for treating psoriasis patients, regardless of ethnicity [24,25].

Ustekinumab has been studied extensively in several phase II and III trials, in which it was shown to be effective and generally well tolerated in predominantly Caucasian patients with psoriasis [26–29] and, thus, has been approved for the treatment of moderate-to-severe plaque psoriasis in more than 50 countries, including the United States and Europe. The two pivotal phase III studies of the ustekinumab clinical program for psoriasis (PHOENIX 1 and PHOENIX 2) were conducted in North America and Europe and enrolled a small number of patients identifying themselves as Asian. In these trials, ustekinumab provided a consistent benefit and comparable safety profile in Asian patients compared with Caucasian and Black subgroups [30]. The purpose of the PEARL study is to evaluate the therapeutic responses and safety profile of short-term use of ustekinumab in Taiwanese and Korean patients with moderate-to-severe psoriasis, which will provide a basis for the appropriate extrapolation for long-term use of ustekinumab observed in the placebo-controlled, phase III, global trials.

2. Materials and methods

2.1. Patients

Adults (age 20 years or older) were eligible to participate in this trial if they were of Korean or Taiwanese ancestry and had a diagnosis of moderate-to-severe plaque psoriasis. At baseline, patients were required to have a Psoriasis Area and Severity Index (PASI) of at least 12, to have at least 10% of their body surface area (BSA) affected by their psoriasis, and be candidates for systemic or phototherapy. Patients who received biologic psoriasis therapy within 3 months, systemic psoriasis medications or phototherapy within 4 weeks, or topical psoriasis medications within 2 weeks of randomization were excluded. Patients with newly identified latent tuberculosis (TB), based on a positive purified protein derivative (PPD) skin test or positive Quantiferon (QFT) at screening, were eligible for study participation if active TB was ruled out and appropriate treatment (i.e., isoniazid; INH) for latent TB was initiated either prior to, or simultaneously with, the first administration of study agent. Patients with a previous history of chronic or recurrent infectious disease or a history of malignancy were excluded. Institutional review board or ethics committee approval of the protocol and written informed consent from each patient were obtained before study procedures were undertaken.

2.2. Study design

Patients were enrolled in this multicenter (i.e., 13 sites in Korea and Taiwan), double-blind, placebo-controlled study, beginning on December 17, 2008, and were followed through March 11, 2010. Randomization was performed via an interactive voice response system based on minimization with bias-coin assignment; patients were stratified by investigational site and baseline body weight ($\leq$65 kg, $>$65 kg). Patients were randomized (1:1) to subcutaneous injections in one of two treatment regimens: (1) ustekinumab 45 mg at weeks 0, 4 and 16 and an injection of placebo at week 12 to maintain the study blind or (2) placebo at weeks 0 and 4, followed by crossover to ustekinumab 45 mg at weeks 12 and 16. Ustekinumab (Stelara®) was provided by Centocor Ortho Biotech, Inc. (Horsham, PA).

2.2.1. Study procedures and evaluations

Psoriasis was assessed based on PASI, which evaluated the extent and severity of skin disease on a scale of 0 (no psoriasis) to 72 (severe psoriasis) [31]. The degree of improvement was measured based on the percentage improvement from baseline, including PASI 50, PASI 75, PASI 90, and PASI 100, which represented at least 50%, 75%, 90% and 100% improvement from baseline, respectively. The Physician's Global Assessment (PGA) was also used to evaluate disease activity on a 6-item scale (0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe). To determine the effect of psoriasis on health-related quality of life, a 10-item questionnaire (i.e., the Dermatology Life Quality Index [DLQI]) was administered to patients, yielding a score of 0 (not at all affected) to 30 (very much affected) [32]. Investigators performed all skin assessments, while the DLQI was a patient-reported outcome. Efficacy was evaluated through week 28. Adverse events (AEs), including TB, were routinely monitored, and standard laboratory parameters were assessed at each study visit through week 36. Serum samples were collected at selected time points to evaluate antibodies to ustekinumab.

The primary efficacy endpoint was the proportion of patients with a PASI 75 response at week 12. Major secondary analyses included comparisons between the ustekinumab 45 mg and placebo groups for the proportion of patients with a PGA of cleared (0) or minimal (1) at week 12 and for the change from baseline at week 12 in the DLQI. The primary efficacy endpoint was also evaluated in subgroups of patients defined by baseline characteristics. Baseline demographic characteristics included country, sex, age, weight, body mass index, and smoking status. Baseline disease characteristics included age at diagnosis, duration of psoriasis, PASI, PGA, BSA, DLQI, and presence of psoriatic arthritis. Categories of psoriasis medication history included use of, and/or response to, phototherapy and conventional systemic therapies with or without biologic agents.