Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study

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Background: Safe and effective therapies are needed for pediatric patients with psoriasis.

Objective: The purpose of this study was to evaluate ustekinumab in patients age 12 to 17 years who had moderate-to-severe psoriasis.

Methods: Patients (n = 110) were randomly assigned to ustekinumab standard dosing (SD; 0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg]) or half-standard dosing (HSD; 0.375 mg/kg [≤60 kg], 22.5 mg [>60-≤100 kg], and 45 mg [>100 kg]) at weeks 0 and 4 and every 12 weeks or placebo at weeks 0 and 4 with crossover to ustekinumab SD or HSD at week 12. Clinical assessments included the proportion of patients achieving a Physician's Global Assessment of cleared/minimal (PGA 0/1), at least 75% improvement in Psoriasis Area and Severity Index (PASI 75), and at least 90% in PASI (PASI 90). Adverse events (AEs) were monitored through week 60.

Results: At week 12, 67.6% and 69.4% of patients receiving ustekinumab HSD and SD, respectively, achieved PGA 0/1 versus 5.4% for placebo ($P < .001$). Significantly greater proportions receiving

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Conflicts of interest: Dr Landells has served as a consultant to AbbVie, Allergan, Amgen, Astellas, Basilea, Celgene, Dermik, Galderma, GlaxoSmithKline, Graceway, Janssen, L'Oreal, Leo, Merck/Schering-Plough, Roche, Stiefel, Valeant, and Wyeth; has received research grants from AbbVie, Amgen, and Janssen; has served as a trial investigator for AbbVie, Allergan, Amgen, Astellas, Basilea, Galderma, GlaxoSmithKline, Janssen, Leo, Merck/Schering-Plough, Pfizer, Roche, Stiefel, and Wyeth; has received honoraria from AbbVie, Amgen, Astellas, Graceway, Janssen, Merck/Schering-Plough, Steifel, and Wyeth; and has served as a speaker for AbbVie, Allergan, Amgen, Merck/Schering-Plough, Janssen, Roche, Valeant, and Wyeth. Dr Eichenfield has served as a consultant for Janssen and Leo; has served as a trial investigator for Galderma and Leo; and has served on a safety monitoring board for Amgen. Dr Hoeger has served as a consultant for Janssen and as a speaker for Allmirall, Galderma, and Pierre Fabre. Dr Menter has served as a consultant for AbbVie, Allergan, Amgen, Convoy Therapeutics, Eli Lilly, Janssen, Leo, Maruho, Novartis, Pfizer, Syntrix, Wyeth, and XenoPort; has served as a trial investigator for AbbVie, Allergan, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Convoy Therapeutics, Eli Lilly, Genentech, Janssen, Leo, Maruho, Merck, Novartis, Pfizer, Syntrix, and Wyeth; and has served as a speaker for AbbVie, Amgen, Janssen, Leo, and Wyeth. Dr Paller has served as a consultant for AbbVie, Anacor, and Janssen and as an investigator for Abbvie, Amgen, and Anacor. Dr Taieb has served as a consultant for Janssen. Dr Philipp has served as a consultant Biogen Idec, Eli Lilly, and Pfizer; has received research support from Biogen Idec and Pfizer; has served as an investigator for AbbVie, Almirall, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, Dermipsor Biomed LTD, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Leo, Maruho, MSD, Novartis, Pfizer, UCB Pharma, and VBL Therapeutics; has served as a speaker for Almirall, Amgen, Biogen Idec, Leo, Novartis, and Pfizer; and has served on an advisory board for AbbVie and Novartis. Drs Marano, Hsu, Li, Zhu, Szapary, and Randazzo are employees of the study sponsor and own stock in Johnson & Johnson, of which Janssen Research & Development, LLC is a subsidiary.

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ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%) at week 12 ($P < .001$). Through week 12, 56.8% of placebo patients, 51.4% of HSD patients, and 44.4% of SD patients reported at least one AE; through week 60, 81.8% reported AEs.

Limitations: The study was small relative to adult trials.

Conclusions: In this patient population (12−17 years), the standard ustekinumab dose provided response comparable to that in adults with no unexpected AEs through 1 year. (J Am Acad Dermatol 2015;73:594-603.)

Key words: adolescent; biologic; children; pediatric; psoriasis; systemic therapy; ustekinumab.

INTRODUCTION

Psoriasis can present at any age, with approximately one-third of patients having symptoms before age 20 years.[1] Treatment of pediatric patients is complicated by limited approved treatments and the relative paucity of data from randomized, controlled trials available for this population.[2,3] Safe, effective, and convenient therapies are needed for pediatric patients with moderate-to-severe psoriasis.

CAPSULE SUMMARY

- Few clinical studies of psoriasis therapies in children are available in the medical literature.
- Every-12-week dosing with ustekinumab was beneficial, with no unexpected adverse events, in treating patients age 12 to 17 years with moderate-to-severe psoriasis.
- Ustekinumab appears to be a viable treatment option for moderate-to-severe plaque psoriasis in the pediatric adolescent population.

Ustekinumab, a human monoclonal antibody targeting the p40 subunit of interleukin-12/23, has proven to be a safe and effective treatment for moderate-to-severe psoriasis in adult patients.[4] In the PHOENIX trials, ustekinumab effectively reduced psoriasis signs and symptoms in adult patients.[5,6] Results of the CADMUS trial of ustekinumab in adolescent patients age 12 to 17 years with active psoriasis are reported here.

METHODS

Eligible patients were age 12 to 17 years, (inclusive), had a diagnosis of moderate-to-severe plaque psoriasis (ie, baseline Psoriasis Area and Severity Index [PASI] ≥12, a Physician's Global Assessment [PGA] ≥3; and ≥10% body surface area involved with psoriasis) for ≥6 months, were candidates for phototherapy or systemic treatment, or had psoriasis that was poorly controlled with topical therapy.

The pharmacokinetics of ustekinumab is affected by body weight. Hence, dosing for adult patients with psoriasis is weight based (45 mg for patients weighing ≤100 kg and 90 mg for patients weighing >100 kg) and administered as subcutaneous injections at weeks 0 and 4 and every 12 weeks subsequently.[4] No clinically meaningful effects of age on the catabolism of immunoglobulins, including ustekinumab,[7] have been reported to date. After accounting for body weight differences, the pharmacokinetics of ustekinumab in pediatric patients in this trial was expected to be similar to that in adults. A standard dose (SD) of 0.75 mg/kg was chosen by adjusting the 45-mg adult dose by a body weight of 60 kg (45/60 = 0.75 mg/kg) leading to the following study dosages: (1) weight-based dose of 0.75 mg/kg (patients weighing ≤60 kg), (2) fixed 45-mg dose (patients weighing >60 to ≤100 kg), and (3) fixed 90-mg dose (patients weighing >100 kg). Additionally, a half-standard dose (HSD) (ie, 0.375 mg/kg for patients weighing ≤60 kg, 22.5 mg for patients weighing >60 to ≤100 kg, and 45 mg for patients weighing >100 kg) was included to identify an optimal dose regimen for pediatric patients.

In this phase 3, multicenter, double-blind, placebo-controlled study, randomization was stratified by investigational site and baseline weight (≤ or >60 kg). Treatment was allocated using a minimization algorithm with a biased-coin assignment[8] via an interactive voice/web response system. Patients were randomly assigned (2:2:1:1) to receive ustekinumab HSD or SD at weeks 0, 4, and 16 and thereafter every 12 weeks through week 40 or placebo at weeks 0 and 4, with crossover to either ustekinumab HSD or SD at weeks 12 and 16 and every 12 weeks through week 40 (Fig 1). At week 8, patients with a PASI increase ≥50% from baseline were eligible to commence treatment with moderate-to-high potency topical steroid preparations through week 12 (early escape).

The protocol was approved by an institutional review board or ethics committee, and all patients or