Guselkumab (an IL-23–specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis☆

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Background: IL-23 expression is increased in psoriatic lesions and might regulate T_H17 T-cell counts in patients with psoriasis.
Objectives: We sought to test a novel IL-23–specific therapeutic agent for the treatment of psoriasis.
Methods: In this randomized, double-blind, placebo-controlled study the safety, tolerability, and clinical response of guselkumab, an anti–IL-23–specific mAb, were evaluated in patients with moderate-to-severe plaque psoriasis. A total of 24 patients were randomized to receive a single dose of placebo or 10, 30, 100, or 300 mg of guselkumab. Clinical response was assessed by using the Psoriasis Area and Severity Index (PASI). Additionally, histologic analysis and gene expression in skin biopsy specimens from guselkumab-treated patients were compared with those from placebo-treated patients.
Results: At week 12, 50% (10 mg), 60% (30 and 100 mg), and 100% (300 mg) of guselkumab-treated patients, respectively, achieved a 75% improvement in PASI scores from baseline compared with 0% of placebo-treated patients. Improvements in PASI scores were generally maintained through week 24 in all guselkumab-treated patients. The proportion of patients experiencing an adverse event was comparable between the combined guselkumab (13/20 [65.0%]) and placebo (2/4 [50.0%]) groups through week 24. Analysis of lesional and nonlesional skin biopsy specimens demonstrated decreases in epidermal thickness and T-cell and dendritic cell expression in guselkumab-treated patients compared with values seen in placebo-treated patients. At week 12, significant reductions in psoriasis gene expression and serum IL-17A levels were observed in guselkumab-treated patients.
Conclusion: IL-23 inhibition with a single dose of guselkumab results in clinical responses in patients with moderate-to-severe psoriasis, suggesting that neutralization of IL-23 alone is a promising therapy for psoriasis. (J Allergy Clin Immunol 2014;133:1032-40.)

Key words: *Histology, IL-23, gene expression, guselkumab, psoriasis, Psoriasis Area and Severity Index, serum, skin, T cell, T_H17*

Psoriasis is the most common immune-mediated skin disorder.[1,2] Psoriatic skin lesions contain increased infiltrates of T cells (T_H1, T_H17, and T_H22). Inflammatory $CD11c^+$ dendritic cells (DCs) and macrophages in the skin become activated and release IL-12 and IL-23, which stimulate cytokine production from T cells. Epidermal T cells are responsible for secreting cytokines, including IFN-γ (T_H1), IL-17A and IL-17F (T_H17), IL-22 (T_H22), and TNF-α.[3] The molecular disease profile of psoriasis, as defined by mRNA transcripts, contains hundreds of activated genes that can be linked to effects on individual or multiple cytokines.[4] IFN-γ, IL-17A or IL-17F, and IL-22 have distinct effects on epidermal keratinocytes, which have been implicated as key regulators of psoriatic skin inflammation.[3]

IL-12 and IL-23 levels are increased in psoriatic lesions. It is believed that IL-12 modulates the excess T_H1 population, whereas IL-23 is the major regulator of T_H17 T cells. The role of IL-12/T_H1 T cells to sustain the psoriasis phenotype is debated because other inflammatory diseases thought to be T_H1-dependent proved to be IL-23/T_H17-mediated[5] and because IL-17 antagonists can suppress the clinical, cellular, and molecular disease features of psoriasis.[6] Conversely, the IL-23/T_H17 axis is hypothesized to be important in patients with psoriasis; however, IL-17 can also be produced in skin lesions independently of IL-23 by neutrophils and mast cells.[7] Therefore,

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Abbreviations used
AE: Adverse event
DC: Dendritic cell
IL-12Rβ1: IL-12 receptor β1
IL-23R: IL-23 receptor
KRT16: Keratin 16
LCN2: Lipocalin 2
PASI: Psoriasis Area and Severity Index
PASI 75: 75% improvement in PASI score from baseline
PASI 90: 90% improvement in PASI score from baseline

the role of IL-23 in the pathogenesis of psoriasis can only be ascertained by means of selective antagonism of this cytokine.

IL-23 is a type 1 heterodimer comprised of p19 and p40 subunits that bind to the IL-23 receptor complex comprised of IL-23 receptor (IL-23R) and IL-12 receptor β1 (IL-12Rβ1). Binding of p19 (IL-23R) and p40 (IL-12Rβ1) to their respective receptors activates the IL-23 signaling pathway in which IL-23R associates with Janus kinase 2 and IL-12Rβ1 binds to tyrosine kinase 2 (Janus kinase protein).[8] IL-23p19 and IL-12/23p40 mRNAs are strongly upregulated in human psoriatic lesions.[9-11] The main cellular source of IL-23 in psoriatic lesions appears to be myeloid DCs, which can be immature inflammatory cells or mature populations (DC-lysosomal-associated membrane proteins [LAMP]$^{+}$[12,13] or CD83^{+}[1]).

Guselkumab (CNTO 1959; Janssen Research & Development, LLC, Spring House, Pa) is an investigational human mAb specifically directed against IL-23. Here the proof-of-concept study of an anti–IL-23 mAb in patients with moderate-to-severe plaque psoriasis is reported. The objectives of this double-blind, placebo-controlled study were to assess the safety, tolerability, and clinical response to guselkumab in patients with moderate-to-severe plaque psoriasis. Histologic and gene expression studies of skin biopsy specimens were included in this study to evaluate which cellular and molecular disease features might be selectively regulated by IL-23 in patients with psoriasis.

METHODS

This phase 1, first-in-human, randomized, double-blind, placebo-controlled trial included 24 patients with moderate-to-severe plaque psoriasis and was conducted at 5 sites in the United States. Patient eligibility criteria are reported in the Methods section in this article's Online Repository at www.jacionline.org. All patients provided written informed consent, and institutional review boards/ethics committees approved the protocol.

Study design

At baseline, 24 patients were randomly assigned to receive subcutaneous injections of 10 mg (n = 5), 30 mg (n = 5), 100 mg (n = 5), or 300 mg (n = 5) of guselkumab or placebo (n = 4).

Study assessments

Safety and efficacy parameters were analyzed through week 24. Safety evaluations included adverse event (AE) assessments, vital sign measurements, electrocardiographic measurements, clinical laboratory tests, and physical examinations. Psoriasis Area and Severity Index (PASI) response measures the severity of psoriasis, ranging from a score of 0 (no psoriasis) to 72 (very severe).[14] The proportion of patients achieving PASI responses was assessed through week 24.

Skin biopsy specimens

Two adjacent 4-mm punch biopsy specimens of lesional and nonlesional skin were obtained at baseline and at weeks 1 and 12 after treatment with guselkumab or placebo. One biopsy specimen from each site was embedded in OCT for cryosections, and the other was immediately snap-frozen in the dry ice/methanol slurry for RNA extraction. Both were stored at −80°C until analysis was performed.

Histology

Frozen skin tissue sections were prepared and analyzed by using methodology described previously.[6]

Gene expression

Skin biopsy specimens were processed and RT-PCR data were generated, as previously described.[4] For microarray, RNA was hybridized to the GeneChip HT HG-U133+ PM Array (Affymetrix, Santa Clara, Calif). Expression measures were obtained by using the Robust Multi-array Average (RMA) algorithm.[15] High-dose guselkumab was defined by combining samples from the 100- and 300-mg groups to increase analytic power. Comparison between baseline and posttreatment gene expression was also analyzed for each treatment group, excluding the 30-mg group because of smaller sample size (n < 5), to evaluate dose-associated trend. Raw data have been deposited in the National Center for Biotechnology Information's Gene Expression Omnibus (accession no. GSE51440).

Serum cytokine analysis

Serum was collected from patients receiving guselkumab or placebo at baseline and weeks 1 and 12 after treatment. IL-17A levels were measured with Singulex (Alameda, Calif) immunoassay kits. IFN-γ, IL-1β, IL-6, TNF-α, IL-12p40, and IL-12p70 levels were measured with Meso Scale Discovery (Rockville, Md) kits. IL-8, IL-23p19, and CCL22 levels were measured with R&D Systems (Minneapolis, Minn) kits, and C-reactive protein levels were measured with a Life Diagnostics (West Chester, Pa) kit.

Statistical analysis

The number of patients was chosen to provide a preliminary safety and efficacy assessment of guselkumab. No formal sample size determination was undertaken. Only descriptive statistical methods were used to summarize the data (no formal hypothesis testing); however, a *post hoc* trend analysis using asymptotic and exact Cochran-Armitage trend tests were performed. Demographics, baseline disease characteristics, and the proportion of patients achieving 75% improvement in PASI scores from baseline (PASI 75) and 90% improvement in PASI scores from baseline (PASI 90) responses at each visit were summarized by treatment group.

RESULTS

Study population

Overall, the demographics and disease characteristics of guselkumab-treated patients were generally comparable among treatment groups and with those of placebo-treated patients (see Table E1 in this article's Online Repository at www.jacionline.org); they were typical of patients with moderate-to-severe psoriasis and consistent with other studies of this patient population.

Neutralization of IL-23 improves clinical manifestations of psoriasis

Patients with psoriasis (n = 24) received a single subcutaneous injection of placebo or 10, 30, 100, or 300 mg of guselkumab.