A randomized, double-blind, placebo-controlled, phase I study of MEDI-545, an anti–interferon-alfa monoclonal antibody, in subjects with chronic psoriasis

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Background: Interferon-alfa (IFN-α) has been implicated in the pathogenesis of psoriasis.

Objective: To evaluate the safety profile of MEDI-545, a fully human anti–IFN-α monoclonal antibody and to explore its effect on the involvement of type I IFN-α activity in the maintenance of established plaque psoriasis.

Methods: We conducted an 18-week, randomized, double-blind, placebo-controlled, dose-escalating study in 36 subjects with chronic plaque psoriasis. Subjects received one intravenous dose of MEDI-545 (0.3-30.0 mg/kg) or placebo. Study outcomes were safety profile, pharmacokinetics, immunogenicity, and clinical effects.

Results: There was no difference in adverse events between MEDI-545 and placebo. Two serious adverse events were reported; one drug-related hypotensive infusion reaction occurred in one subject in the 30.0 mg/kg MEDI-545 dose group, causing discontinuation of study drug in that subject and study dismissal of the other subjects in the same cohort; and a myocardial infarction occurred in one subject in the 10 mg/kg MEDI-545 dose group, which was considered to be unrelated to treatment. MEDI-545 was nonimmunogenic, had a half-life of 21 days, showed no significant inhibition of the type I IFN gene signature, and had no clinical activity.

Limitations: The study addressed only IFN-α and chronic psoriatic lesions.

Conclusion: The safety profile of MEDI-545 supports further clinical development. IFN-α does not appear to be significantly involved in the maintenance of established plaque psoriasis. (J Am Acad Dermatol 2010;62:427-36.)

Psoriasis is a chronic inflammatory skin disorder with a complex pathophysiology that can have a significant impact on subjects' physical and mental health.[1,2] The pathology of psoriasis is characterized by abnormal keratinocyte differentiation and proliferation, with activated T cells.[3,4] Psoriatic lesions also show elevated levels of tumor necrosis factor-alfa (TNF-α), a cytokine that is produced (not exclusively) by T-helper 1 cells. Inhibition of TNF-α results in clinical improvement of

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psoriasis.[5,6] Interferons (IFNs) are cytokines that play a central and complex role in defending the mammalian host against pathogens. Type I IFNs such as IFN-α and -β are believed to play an important role in host defense against viral and bacterial infections and are involved in many immunoregulatory processes.[7]

There are several observations that suggest a role for IFN-α in chronic plaque psoriasis. First, treatment with recombinant IFN-α, for unrelated conditions such as viral infection, can induce the formation of new psoriatic lesions[8-11] and exacerbate established lesions.[8] Likewise, treatment with imiquimod, a toll-like receptor 7 agonist that induces type I IFN production from plasmacytoid dendritic cells, exacerbates chronic psoriatic plaques and induces the formation of new psoriatic lesions in the surrounding and distant skin.[11] Second, type I IFN signaling pathway is activated in psoriatic keratinocytes.[12-16] Additionally, Eriksen et al[17] demonstrated that T cells within psoriatic lesions have an increased and prolonged response to IFN-α. Third, increased expression of genes induced by type I IFN—inducible genes is found in psoriatic plaque lesions, but not in uninvolved or normal skin.[16,18] Finally, data from animal models demonstrated that mice lacking IFN regulatory factor-2, a transcriptional attenuator of IFN-α/β signaling, have increased expression of type I IFN—inducible genes and spontaneously develop new psoriasis-like inflammatory skin lesions that are characterized by CD8+ infiltrating T cells.[19] Moreover, in a xenograft murine model of psoriasis, an increase in IFN-α level preceded the development of typical psoriatic changes in the transplanted skin. In this model, the development of psoriatic changes in the skin, including T-cell infiltration, was blocked with anti—IFN-α/β receptor antibody. In the same model, production of IFN-α by plasmacytoid dendritic cells was suppressed by anti-BCDA-2 antibody, inhibiting the development of psoriatic lesions.[18]

A gene signature is a characteristic gene activity pattern elicited by a given stimulus or condition such as type I IFN-α. Type I IFNs stimulate the expression of multiple genes in a recognizable and distinct pattern that is characteristic for a specific disease, such as in systemic lupus erythematosus (SLE),[20] psoriasis,[16] dermatomyositis,[21,22] rheumatoid arthritis,[23] and scleroderma.[24] These molecular signatures can serve as pharmacodynamic biomarkers to measure the biological activity of a drug regardless of therapeutic effect. MEDI-545 is a fully human monoclonal immunoglobulin (Ig) G1κ antibody that binds to and neutralizes IFN-α. Wallace et al[25] demonstrated the success of MEDI-545 in neutralizing the most highly expressed type I IFN—inducible genes compared with placebo in whole blood and skin lesions in subjects with SLE, who were dosed with a single intravenous (IV) dose ranging from 0.3 to 30 mg/kg. Exposure to MEDI-545 was not associated with an increased frequency of clinical viral reactivation events nor was there any laboratory evidence suggesting increased viral reactivation during the course of the study, compared with placebo.[25]

CAPSULE SUMMARY

- MEDI-545 is a fully human anti—interferon-alfa (IFN-α) monoclonal antibody.
- MEDI-545 blocks IFN-α, yet it did not inhibit the type I IFN gene signature in involved skin, although MEDI-545 has inhibited this gene signature in lupus.
- MEDI-545 showed no clinical activity in psoriasis, consistent with no inhibition of type I IFN gene signature.
- IFN-α is unlikely to be significantly involved in the maintenance of chronic plaque psoriasis.

The present study was conducted to evaluate the safety profile of MEDI-545 and to explore the effect of MEDI-545 on the biological activity of type I IFN-α in skin biopsies and on measures of disease activity. The study also examined the immunogenicity and pharmacokinetics of a single IV dose of MEDI-545 compared with placebo in adult subjects with active chronic plaque psoriasis. The hypothesis of the study was that administration of MEDI-545 would block the type I IFN gene signature in the skin, leading to improvement of the signs and symptoms of chronic plaque psoriasis while maintaining an acceptable safety profile.

SUBJECTS AND METHODS

This was a phase I, randomized, double-blind, placebo-controlled, single-dose, dose-escalation, multicenter (N = 3) clinical study. Adult subjects 18 years of age or older, with a documented clinical history of chronic stable plaque psoriasis involving greater than or equal to 3% body surface area (BSA) in affected skin other than the face and scalp were enrolled in the study. Subjects were required to have at least two target plaques that were suitable for serial photographic assessments. No systemic corticosteroids or systemic psoriasis therapy, phototherapy, or photochemotherapy were allowed within 28 days of baseline screening or throughout the study. Subjects were allowed to apply mild and moderate topical corticosteroids on psoriatic lesions other than the