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Ustekinumab

USAN

Anti-IL-12/23p40 Monoclonal Antibody
Treatment of Psoriasis

Anti-IL-12/23p40
12B75
C340
CNTO-1275
MAb C340

Immunoglobulin G_1, anti-(human interleukin 12 p40 subunit) (human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer

Immunoglobulin G_1, anti-(human interleukin-12 subunit beta (IL-12B, CLMF p40, NKSF2)) (human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer

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Abstract

The inflammatory symptoms of psoriasis are caused in part by the infiltration of T-cells into the affected areas of the skin and their differentiation to Th1- and Th17-type effector cells. The interleukins IL-12 and IL-23 lie behind the T-cell response in psoriasis and other Th1/Th17-associated autoimmune disorders such as multiple sclerosis and Crohn's disease. Ustekinumab (CNTO-1275) is a monoclonal antibody against the p40 subunit that is common to both IL-12 and IL-23. In phase II clinical trials, the agent reduced symptoms in patients with plaque psoriasis and was associated with few adverse events. The antibody is in phase III development for the treatment of patients with psoriasis and a BLA and an MAA were submitted in December 2007 seeking approval for this indication in the U.S. and Europe.

Background

Psoriasis is a common skin disorder affecting approximately 2% of the general population. The skin lesions of patients with psoriasis are marked by thickening of the epidermis, infiltration of inflammatory cells such as neutrophils, T-cells and dendritic cells, vasodilatation and angiogenesis (1, 2). Psoriasis is considered to be a T-cell-dependent autoimmune disease and the proinflammatory cytokines IL-12 and IL-23 have been implicated in its pathogenesis based on their ability to drive the differentiation of T-cells into T helper type 1 (Th1) and type 17 (Th17) cells, respectively. These cytokines share a common subunit (p40), although they appear to have different roles in regulating the immune response. The involvement of IL-12 and IL-23 in the pathogenesis of psoriasis is indicated by the fact that: 1) both have been detected at higher levels in the skin lesions of psoriasis patients than in normal skin; 2) psoriasis therapy reduces the levels of IL-12 and IL-23; and 3) genetic polymorphism in the shared IL-12p40 subunit increases the susceptibility to psoriasis. Recently, the IL-12p40 and IL-23p19 subunits, but not the IL-12p35 subunit, were shown to be elevated in the lesions of psoriasis patients, suggesting a dominant role for IL-23 rather than IL-12 in the pathogenesis of psoriasis. Both cytokines are also associated with inflammation and a Th1/Th17 response in other autoimmune diseases such as rheumatoid arthritis, asthma, lupus, Crohn's disease and multiple sclerosis, and thus IL-12 and IL-23 are potential targets for the treatment of these diseases (3-5).

Ustekinumab (CNTO-1275) is a human monoclonal antibody directed against the shared IL-12p40 subunit of IL-12 and IL-23. Therapy based on the neutralization of the IL-12p40 subunit is expected to alter the downstream cytokine induction pathways of both IL-12 and IL-23 and may result in clinical efficacy in the treatment of certain autoimmune diseases (3, 5). Phase III trials of ustekinumab for the treatment of psoriasis are in progress and the antibody was recently submitted for regulatory review in the U.S. and the E.U. for this indication (6). Ustekinumab has also been evaluated for its potential in the treatment of multiple sclerosis and Crohn's disease, but no development has been reported of late for these indications.

P. Revill, N. Mealy. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Preclinical Pharmacology

The effect of ustekinumab on cytokine production was explored *in vitro* using activated peripheral blood mononuclear cells (PBMCs) from healthy donors in the presence or absence of exogenous IL-12 and IL-23. Addition of ustekinumab to IL-12-treated cell cultures depleted exogenous IL-12 and prevented the induction of the cell-surface markers cutaneous lymphocyte antigen (CLA), IL-12Rβ2, CD25, CD40L and the secretion of the proinflammatory cytokines interferon gamma (IFN-γ), IL-2 and tumor necrosis factor α (TNF-α), as well as the anti-inflammatory cytokine IL-10. Exogenous IL-12 decreased secretion of the Th2 cytokine IL-5 and ustekinumab reversed this effect. Exogenous IL-23 boosted the secretion of IL-17A but not IFN-γ or that of several other cytokines or cell-surface markers, and ustekinumab reversed the effect on IL-17A secretion. This study showed that IL-12 and IL-23 have distinct cytokine induction profiles, and suggested that targeting both cytokines may be an effective strategy to treat psoriasis (5, 7, 8).

Safety

Preclinical toxicology studies in cynomolgus monkeys showed that ustekinumab administered i.v. once weekly for a month or s.c. twice weekly for 6 months was well tolerated at the maximum dose tested of 50 mg/kg, irrespective of the dosing schedule. Administration of 50 mg/kg ustekinumab to pregnant monkeys during the period of fetal organogenesis caused no fetal or maternal abnormalities. In a monkey model of induced asthma, two doses of 50 mg/kg of ustekinumab given 4 weeks apart had no effect on pulmonary function, indicating that asthma is not exacerbated by treatment (see Ref. 9).

To assess its potential impact on the humoral immune system, 32 cynomolgus monkeys that had been treated with ustekinumab (22.5 or 45 mg/kg s.c. twice weekly for 26 weeks) and 54 patients participating in the three phase I studies (46 received 0.09-4.5 mg/kg ustekinumab i.v. or s.c. and 8 received placebo) were tested for antibody responsiveness. The monkeys were challenged with keyhole limpet hemocyanin (KLH) and antibody titers to KLH in the ustekinumab-treated animals were comparable to those treated with placebo. The humans were challenged with pneumococcal and tetanus antigens, and again there was little difference between the active and placebo treatment groups, suggesting that a single dose of ustekinumab does not impair the innate and recall humoral immune system functions. In addition, there was no impact of ustekinumab on the numbers of circulating T-, B- and natural killer (NK) cells (10-12).

The development of antibodies to ustekinumab was assessed in 17 patients who received a single dose of ustekinumab (0.27-2.7 mg/kg s.c.) as part of a phase I study and in 301 patients who received either a single dose or four weekly doses of ustekinumab (45 or 90 mg s.c.) as part of a phase II study. Eighty-five patients received an additional injection at week 16. One patient in the phase I study developed antibodies against ustekinumab. Of those in the phase II study, 4% were positive for anti-ustekinumab antibodies, 85% were negative and 11% were inconclusive. There were no cases of anaphylaxis, severe allergic reactions or delayed hypersensitivity, and injection-site reactions were uncommon (13).

Clinical Studies

An open-label, dose-escalating phase I study (C0379T01) in 18 psoriasis patients with at least 3% body surface area involvement treated with single doses of ustekinumab of 0.1, 0.3, 1.0 or 5.0 mg/kg i.v. found no dose-limiting toxicities and the majority of adverse events were mild, with no relationship to dose. Laboratory investigations showed that $CD4^+$ T-cell counts dropped below 400/mm^3 for 5 days in 2 patients, and $CD16^+/CD56^+$ counts (markers of NK cells) also decreased transiently in some patients. No adverse events were associated with these changes in the levels of lymphocyte subsets. The pharmacokinetic parameters were linear and the terminal half-life was 24 days. Improvements in the Psoriasis Area and Severity Index (PASI) and the Physician's Global Assessment (PGA) were secondary endpoints in this study; 67% of the patients had at least 75% improvement in PASI (PASI-75) and 61% had an improved PGA score, with maximal responses observed between weeks 12 and 16 (9). A pharmacodynamic analysis of the skin lesions of patients in this study at week 2 showed a ustekinumab-dependent drop in the mRNA levels of IFN-γ, IL-8, interferon-inducible protein 10 (IP-10), monocyte chemotactic protein 1 (MCP-1) and IL-10, as well as the levels of IL-12p40 and IL-23p19. Additionally, the baseline levels of TNF-α correlated with clinical improvement at week 16, suggesting that this may serve as a marker to predict therapeutic response (14).

In another phase I study, 21 psoriasis patients with at least 3% body surface area involvement were randomized to ustekinumab (single s.c. injections of 0.75, 1.5 or 3.0 mg/kg) or placebo. There were no serious adverse events or injection-site reactions. The t_{max} was 12 days and the half-life was 20 days. Of those receiving active treatment, 77% achieved 75% improvement in the PASI score compared to none in the placebo group. Those on the highest dose showed a sustained response throughout the 24-week assessment period (15). A pharmacokinetic/pharmacodynamic model was developed using data from these patients in order to design dosing regimens for phase II trials. Serum antibody levels were measured using an ELISA and PASI was used to evaluate lesion severity. Single or weekly doses of 45 or 90 mg were predicted to achieve at least a 75% improvement in PASI at week 12 and maintenance doses every 2 or 3 months were predicted to maintain clinical response in most patients (16).

A double-blind, multicenter phase II study (CR005416) randomized 320 patients with moderate to severe plaque psoriasis to 1 of 4 regimens of s.c. ustekinumab (45 mg as a single dose, 90 mg as a single dose,

45 mg once weekly for 4 weeks or 90 mg once weekly for 4 weeks) or placebo. At week 16, those receiving ustekinumab and with a PGA score of less than excellent received an additional injection at the same dose. At week 20, all patients originally receiving placebo were crossed over to receive a single dose of ustekinumab 90 mg. The frequency of adverse events through to week 20 was similar between the placebo group (72% mild, 1% serious) and the active treatment groups (79% mild, 4% serious). Injection-site reactions were seen in 2% of patients in both the placebo and active treatment groups. There was no difference among the treatment groups in changes in lymphocyte counts or lymphocyte subsets, and the infection rate was similar among the groups, although this study was not powered to detect small differences in infection rates. The primary endpoint, a 75% improvement in PASI score at week 12, was achieved by 2%, 52%, 59%, 67% and 81%, respectively, of the patients receiving placebo, 45 mg (single dose), 90 mg (single dose), 45 mg (4 doses) and 90 mg (4 doses). The Dermatology Life Quality Index (DLQI) also showed significant improvements in those receiving active treatment at week 12. Responses were maintained through week 24 and began to decline thereafter (17-24).

Pharmacodynamic and histological evaluation of a subset of the patients in this study at weeks 0 and 12 showed that epidermal thickness, cell proliferation and $CD3^+$ T-cell infiltration into the skin lesions were all reduced in association with active treatment. In the serum, active treatment had no impact on the levels of Th1 cytokine and chemokine markers, T-cell subsets or the ability of PBMCs to differentiate *ex vivo* to Th1 and Th2 subtypes. Only the levels of circulating CLA-expressing cells were reduced in comparison to placebo-treated patients. This study indicates a minimal impact of ustekinumab treatment on circulating immune cell populations (25, 26).

The PHOENIX 1 study was a double-blind, randomized, placebo-controlled phase III trial in 766 patients with plaque psoriasis. The patients received ustekinumab as two doses of 45 or 90 mg s.c. 4 weeks apart followed by the same doses every 12 weeks or placebo; patients in the placebo group were crossed over to active treatment at weeks 12 and 16 followed by dosing every 12 weeks. Furthermore, patients responding to ustekinumab at week 40 were then randomized to continue active treatment or switch to placebo. At week 12, the primary endpoint (PASI-75) was achieved by 67% and 66% of patients, respectively, on 45 and 90 mg ustekinumab compared to 3% of those on placebo. A PGA of cleared or minimal was achieved by 60% and 62% of patients, respectively, on 45 and 90 mg ustekinumab *versus* only 4% of those on placebo. At 12 weeks, 42% and 37% of patients, respectively, on ustekinumab 45 and 90 mg had a PASI-90 compared to 2% of those on placebo (27). Long-term continuous therapy with ustekinumab was associated with maintenance of efficacy. At week 52, 87% and 91% of patients, respectively, continuing on ustekinumab 45 and 90 mg maintained PASI-75 compared to 64% and 62% of patients, respectively, who were switched to placebo; 97% and 98% of patients, respectively, who continued on 45 and 90 mg ustekinumab maintained at least PASI-50 at this time point. Although most patients with a PASI-90 response at week 40 (66% and 73% of patients, respectively, on 45 and 90 mg ustekinumab) continued to show response at week 52 on treatment with ustekinumab, the percentage significantly decreased in those switched to placebo (37% and 38%, respectively) (28). Ustekinumab was generally well tolerated in this study.

An international, double-blind phase III trial is evaluating ustekinumab in 1,230 patients with moderate to severe plaque-type psoriasis (PHOENIX 2, CR006325). Patients are randomized to ustekinumab (45 or 90 mg s.c.) or placebo administered at weeks 0, 4 and every 12 weeks thereafter until week 52, with a dosing interval adjustment to 8 weeks in those showing partial response. Patients who had initially been randomized to placebo treatment were crossed over to ustekinumab treatment at week 12. The primary endpoint, the proportion of patients achieving PASI-75 at week 12, was achieved by 67-76% of patients receiving ustekinumab *versus* 4% of those receiving placebo. Following the third dose (week 16), a substantial proportion of patients had maintained a PASI-75 response through week 28, consistent with the planned maintenance regimen of every 12 weeks. Quality of life measures also showed significant improvements with active treatment from as early as week 4. Adverse events were mostly mild and the frequencies were similar between the active and the placebo treatment groups (49% and 48-53%, respectively). In a long-term extension to this study, patients will continue to receive ustekinumab for up to 264 weeks (29-31).

Ustekinumab is also being assessed in two other phase III studies in patients with moderate to severe plaque-type psoriasis. One (CR006328) is a placebo-controlled study that started in December of 2005 and was expected to recruit 750 patients (32). Another study (CR013015), which started to enroll in March 2007 and was expected to enroll 650 patients, will compare ustekinumab with etanercept (33). The agent is also being investigated in a phase II study in 140 patients with active psoriatic arthritis (CR006322) (34).

Sources

Centocor, Inc. (US); Janssen-Cilag holds exclusive marketing rights outside the U.S. The antibody was generated using Medarex's UltiMAb® technology.

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