

Anti-p40 Antibodies Ustekinumab and Briakinumab: Blockade of Interleukin-12 and Interleukin-23 in the Treatment of Psoriasis

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The choice of therapeutic agents for patients with moderate-to-severe psoriasis has expanded significantly in the past decade. With new understanding of the immunologic basis of psoriasis, multiple new potential targets for therapy have been identified. It is likely that a series of new medications to focus on the newly identified pathways is on the horizon. The first pathway targeted by new medications focuses on the p40 subunit that is shared by interleukin (IL)-12 and IL-23. Two human anti-p40 antibodies have been used therapeutically in psoriasis to date, ustekinumab (CNTO-1275, Stelara, Centocor, Horsham, PA) and briakinumab (ABT-874, Abbott, Abbott Park, IL). Ustekinumab was recently approved by the United States Food and Drug Administration, making it the first medication approved in the United States to work by this pathway while briakinumab is currently in phase III clinical trials.

Semin Cutan Med Surg 29:48-52 © 2010 Elsevier Inc. All rights reserved.

The Immunology of IL-12 and IL-23 in Psoriasis

Our understanding of the immunopathogenesis of psoriasis has changed significantly in the past 2-3 years. Psoriasis was previously considered primarily a result of aberrant CD4⁺ T helper 1 (T_H1)-mediated immune responses that altered keratinocyte behavior.^{1,2} Since IL-12 is the primary cytokine responsible for the activation and differentiation of naive T cells into CD4⁺ T_H1 cells, anti-p40 medications were originally designed to alter the activity of this pathway. However, recent research has pointed to other possible mechanisms for the anti-p40 antibodies. Starting with the observation that there is significantly more IL-23 in the psoriatic plaques than IL-12, it has been hypothesized that the role of blocking IL-23 is the predominant effect of these medications.^{3,4}

The present understanding of the immunology of psoriasis is based on a complex interaction of multiple immune cells in the skin. Among the most important cells within this process are dendritic cells in the skin that express the cell surface marker CD11c and a newly described T-cell population

called Th17 cells.⁵ The CD11c⁺ dendritic cells secrete various cytokines that are critical for the development and maintenance of the psoriatic plaque. These cytokines include tumor necrosis factor- α and IL-23. In particular, the IL-23 produced activates the Th17 cells in the skin. The Th17 cells, in turn produce 2 critical cytokines, IL-17 and IL-22 that may directly associate the immune reaction with the aberrant behavior of keratinocytes that results in the clinical presentation of psoriasis.⁴⁻⁶ IL-17 may be primarily implicated in the continuation of the immune process in psoriasis, while IL-22 may directly induce keratinocytes to proliferate and mature abnormally. Importantly, the T_H1 arm of the immune system may play a significant role in regulating the initial activation of this process. Thus, medications that target p40 may affect psoriasis by blocking both the T_H1 and the Th17 branches of the inflammatory cascade.

Ustekinumab

Ustekinumab is a novel human immunoglobulin IgG1 κ monoclonal antibody that binds strongly with the p40 subunit of both IL-12 and IL-23, thus disrupting their respective signaling pathways.^{3,7,8} Pharmacokinetic evaluations in psoriatic patients resulted in a maximum serum concentration occurring 12 days after 90 mg subcutaneous dose; bioavailability was found to be 57.2%.^{3,9} Multiple studies confirm that serum trough concentrations are significantly lower in pa-

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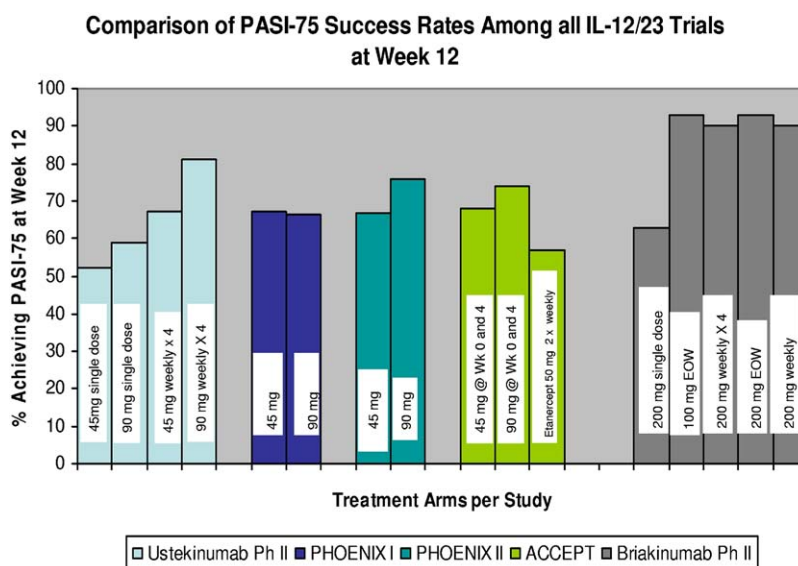


Figure 1

tients with a higher body mass (>100 kg) and drug clearance ranges from 2.7 to 5.3 mL/kg/d.³ The median half-life of ustekinumab is 3 weeks, with a range of 15-32 days.³

There have been 4 randomized clinical trials with ustekinumab that have analyzed the safety and efficacy of this medication for the treatment of moderate-to-severe plaque psoriasis.

Phase II

The initial phase II trial, conducted by Krueger et al, studied 320 patients with moderate-to-severe plaque psoriasis who were randomized into 1 of 4 subcutaneous dosing regimens or placebo.² Subjects were given a single dose of 45 or 90 mg or were treated with 4 weekly doses of 45 or 90 mg. The primary outcome measured of this trial was a 75% improvement in the Psoriasis Area and Severity Index (PASI-75) 12 weeks after initiating therapy. In general, the response to ustekinumab in this trial was quite significant. Fifty-two percent of the patients treated with 1 45 mg dose, 59% treated with 1 90 mg dose, 67% who received 4 weekly 45 mg doses, and 81% who received 4 weekly 90 mg doses, achieved a PASI 75 at week 12 (see Figure 1). This study was extremely well controlled, with the placebo group only 2% of these subjects achieving a PASI 75. Other measures of clinical outcome, including the Dermatology Life Quality Index assessment showed significant improvements in quality of life in the active group compared with the placebo group at both weeks 12 and 24. Physician's global assessment (PGA) scores were consistently better in all active groups versus placebo.

In general, subjects treated with ustekinumab tolerated the medication well. Specifically, rates of infection, serious infection, and malignancy were similar between the treatment groups and placebo. One area of concern in this phase II trial, however, was an imbalance in the number of major adverse cardiac events (MACE) in the first 12 weeks of this study. In the subjects treated with ustekinumab, there were 3 MACE events while there were no such events in the placebo group.

This finding led to close examination of potential cardiac events in the phase III program of ustekinumab.¹⁰

Phase III: PHOENIX I and II

There were 2 placebo-controlled pivotal phase III trials of ustekinumab termed the PHOENIX 1 and PHOENIX 2 studies. Both these trials assessed short- as well as longer-term efficacy and safety large parallel cohorts.^{11,12} Both studies shared a similar study design and had a combined sample size of approximately 2000 subjects. The PHOENIX 1 study was divided into the placebo-controlled phase (weeks 0-12), the placebo crossover and active treatment phase (weeks 12-40), and the randomized withdrawal phase (weeks 40-76). Subjects were randomized to receive subcutaneous administration of 45 or 90 mg of ustekinumab or placebo at weeks 0 and 4, and then subsequent injections every 12 weeks. At week 12, approximately 67% of both active groups achieved PASI-75 compared with 3% of the placebo group (see Figure 1). In addition, the ustekinumab groups had greater PGA assessment improvement measured at the end of the placebo-controlled phase. Maximum efficacy was achieved at week 24 in both dosing groups. Patients who were initially randomized to receive ustekinumab at week 0 who achieved PASI-75 at weeks 28 and 40 were rerandomized to either maintain active drug or withdraw from treatment until loss of response. The median time to loss of efficacy in the withdrawal group was 15 weeks and the active treatment groups maintained PASI-75 response through week 76.

The PHOENIX 2 trial was designed similarly; however, subjects who were identified as partial responders (ie, PASI-50 < X < PASI-75) at week 28 were rerandomized to continue dosing every 12 weeks or escalated to every 8 weeks. The primary endpoint, PASI-75, was achieved in 75.7% of the 90 mg dosing group and 66.7% of the 45 mg ustekinumab group. At week 52, more partial responders who escalated to q8 week dosing achieved PASI-75 compared with those who continued the same dose every 12

weeks. Dermatology Life Quality Index and PGA assessments mirrored data from the PHOENIX 1 study; active groups had overall better scores. It should be noted that partial responders tended to have higher body mass, more severe disease based on PGA, and increased incidence of psoriatic arthritis.

Adverse Events

In general, ustekinumab was well tolerated and adverse events experienced in clinical trials were mild. The most common adverse events were equally distributed across all treatment groups and included upper respiratory infection, nasopharyngitis, arthralgia, headache, cough, and injection site reaction.^{11,12} This medication should not be used in patients with severe infections such as tuberculosis, opportunistic infections, or those who are septic.⁹

In the PHEONIX trials, infection occurred in approximately 20% of patients in both placebo and active groups.^{11,12} The combined rate of infection was 1.39 per patient-year of follow-up in ustekinumab-treated patients and 1.21 per patient year of follow-up in the placebo-treated patients.⁷ Twenty-four serious infections were reported and included pneumonia, urinary tract infection, viral infection, osteomyelitis, diverticulitis, and cellulitis. The risk of malignancy, based on data from placebo-controlled trials, did not seem significant. The incidence of nonmelanoma skin cancer was 0.74 per 100 patient-years of follow-up for ustekinumab compared with 1.13 per 100 patient-years of follow-up for placebo-treated patients.⁹ The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate in the general population.

Of great importance, an imbalance of MACE events was not seen in the PHOENIX I and II trials. There were 2 events in the treatment groups in these large trials. Close monitoring of electrocardiograms and D-dimer values looking for cardiac events and thrombotic tendencies were performed in these studies and no areas of concern were identified with this testing.

Laboratory abnormalities including liver and renal function tests were equivalent between active and placebo groups in both PHEONIX trials.¹¹⁻¹³ Approximately 5% of patients treated with ustekinumab developed antibodies to the drug. Those with positive antibodies had consistently lower serum levels of the active drug and tended to have a lower response overall.

Phase III: ACCEPT

One randomized clinical trial has compared ustekinumab to etanercept, the ACCEPT study.¹⁴ This 12-week phase III trial evaluated 903 subjects randomized into 1 of 3 groups: ustekinumab 45 mg dosed at weeks 0 and 4, ustekinumab 90 mg at weeks 0 and 4, or etanercept 50 mg twice weekly. The primary endpoint, PASI-75 at week 12, was achieved by 74% of the ustekinumab 90 mg group, 68% of the ustekinumab 45 mg group, and 57% of the etanercept group (see Figure 1). The 90-mg ustekinumab group was significantly more efficacious compared with etanercept ($P < 0.001$). In general, ustekinumab subjects had better PGA assessments compared

with etanercept subjects ($P < 0.001$). Both ustekinumab groups demonstrated greater responses measured by PASI and PGA score.

There were no significant safety differences between ustekinumab and etanercept in the ACCEPT trial. Both drugs were generally well tolerated. The most common adverse events experienced across all 3 groups included headache, nasopharyngitis, upper respiratory tract infection, back pain, and pruritus. Notably, injection site reactions were seen with greater frequency in subjects treated with etanercept. Serious events such as infection and malignancy were equally distributed among study groups. Importantly, this trial only evaluated 12 weeks of therapy. Thus, the period of comparison is likely too short to adequately compare the safety of ustekinumab and etanercept.

Psoriatic Arthritis

Gottlieb et al¹⁵ have evaluated ustekinumab for the treatment of psoriatic arthritis in a phase II, multicenter, randomized, placebo-controlled trial. Patients with active psoriatic arthritis were admitted into this trial on stable doses of methotrexate. Subjects were randomized to either ustekinumab at a dose of 63 mg (or a small number at 90 mg, these groups were analyzed together) or placebo. The use of methotrexate was well balanced between the groups.

At 12 weeks, the primary endpoint of the study, 42% of patients had a greater than 20% improvement in the American College of Rheumatology core set measures (ACR20) when compared with a placebo rate of 14%. Upon crossover to active treatment, the placebo group attained a high level response to treatment, as well. The study was not powered to identify differences in response related to methotrexate use. Additionally, the rate of adverse events, infections, and serious infections was similar between the treatment and placebo groups. Thus, ustekinumab shows some promise in the treatment of psoriatic arthritis though further study is clearly needed.

Briakinumab

Briakinumab (ABT-874) is a recombinant, fully human, IgG1 monoclonal antibody that binds with high affinity to the p40 subunit shared by both IL-12 and IL-23 cytokines.¹⁶ By binding to the p40 subunit of the soluble forms of IL-12 and IL-23, briakinumab prevents binding of these IL's with T cells and natural killer cells, thereby limiting the effects of downstream signaling.^{17,18} As determined by phase I studies with healthy volunteers evaluating doses of briakinumab between 0.1 and 5.0 mg/kg by intravenous and subcutaneous doses, pharmacokinetic properties are consistent with what would be expected with IgG1 antibodies. The half-life of briakinumab is 8-9 days.¹⁹

Phase II

Unlike ustekinumab, briakinumab has, to date, only been evaluated at the level of a phase II, dose-finding study. This study evaluated the efficacy and safety of briakinumab in a multicenter, randomized, double-blinded, placebo-con-

trolled dose finding trial conducted in North America.¹⁶ The trial consisted of an initial 12-week phase, followed by a 36-week blinded observation/re-treatment phase. During the initial 12 weeks, 180 subjects were randomized into 1 of 6 groups ($n = 30$ per group) to receive one of the following treatment regimens: one 200 mg dose at week 0, 100 mg every other week (EOW) for 12 weeks, 200 mg weekly for 4 weeks, 200 mg EOW for 12 weeks, 200 mg weekly for 12 weeks, or placebo. Subjects were selected based on established eligibility criteria used in previous clinical trials using IL-12/IL-23 and other biological investigational agents.

The primary endpoint in this trial was the proportion of subjects achieving PASI-75 by week 12. The phase II trial demonstrated statistically significant improvement among the 5 treatment groups. By week 12, PASI-75 was observed in 90% of the patients receiving ABT-874 (63%, 93%, 90%, 93%, and 90% of these 5 groups, respectively [$P < 0.001$]), and 3% in the placebo group (see Figure 1).¹⁶ Importantly, these efficacy results are among the highest, if not the highest, seen in any placebo-controlled clinical trial for psoriasis.

Upon completion of the initial 12-week phase, subjects who achieved at least a PASI-75 were entered into the 36-week observation/re-treatment phase, at which point treatment with study drug was discontinued until the subject experienced a loss of response of at least 50% (\leq PASI-50) between weeks 12 and 24. For subjects who experienced a loss of response during the observation phase, an additional 12-week treatment period was resumed with the same dosing regimen assigned during the initial 12-week period.²⁰

Of the 180 patients initially enrolled, 130, including 1 subject from the placebo group, entered the re-treatment phase and of those 58 were re-treated. While more efficacious in the initial 12 weeks, a majority of patients were still able to achieve PASI-75 response after re-treatment. The percentages of patients who achieved \geq PASI-75 at week 12 and then again 12 weeks after re-treatment were as follows for each group consecutively: one 200 mg dose: 63% versus 55%; 100 mg EOW: 93% versus 94%; 200 mg weekly for 4 weeks: 90% versus 69%; 200 mg EOW: 93% versus 75%, and 200 mg weekly: 90% versus 83%.²⁰

Adverse Events

In the phase II trial, safety of briakinumab was evaluated through 48 weeks, regardless of efficacy, unless subject participation was discontinued before termination. Analysis of the phase II data demonstrated that subjects who received at least 1 dose of briakinumab were significantly more likely to experience an adverse event compared with the placebo group (36.1% vs 10%, $P = 0.03$).¹⁶

The most common adverse event in subjects receiving briakinumab was injection site reaction occurring in 16.7% (25/150) compared with 0 of 30 patients reported in the placebo group. These events highlight a major difference in the rate of injection site reactions between ustekinumab (CNTO-1275) and briakinumab; these events occurred in greater frequency with briakinumab (16.7%) versus ustekinumab in trials (1.2%-2%).^{2,11,12}

Infections were also common in subjects participating in the phase II trial, with 34.7% (52/150) of briakinumab-treated subjects and 23.3% (7/30) of the placebo group experiencing an infectious adverse event. Nasopharyngitis and upper respiratory tract infections were experienced with greatest frequency, followed by bronchitis and viral infection. Two subjects were diagnosed with malignant neoplasms. One placebo-treated subject was diagnosed with ovarian cancer, and 1 briakinumab-treated subject was diagnosed with nonmelanoma skin cancer. During the first 12 weeks, there were no serious infections, myocardial and/or cerebral infarctions, or deaths reported.

During the 36-week observation/re-treatment phase, injection site reactions were continued to be the most frequently occurring side effect (19.3%). Furthermore, patients receiving briakinumab experienced an increased incidence of infections (41.3%) compared with the placebo group (23.3%). No malignancies were reported after week 12.²⁰ A phase III trial has been enrolled and the initial results are expected soon.

Conclusions

The therapeutic armamentarium for treating psoriasis has been expanding over the past decade. Advances in understanding the immunology of psoriasis have led to new investigational pathways. The first new pathway to result in an approved medication is the blockade of the p40 subunit of both IL-12 and IL-23. Ustekinumab, recently approved by the United States Food and Drug Administration and briakinumab, which is still under investigation, have shown results in clinical trials in improving the severity of psoriasis.

One caution should be added to any discussion of new medications. Unlike the tumor necrosis factor- α inhibitors (etanercept, adalimumab, and infliximab), which were initially approved for other indications, ustekinumab and briakinumab represent new molecular entities with a unique mechanism of action but with limited use in the commercial arena. So, while it can be confidently said that these medications have impressive efficacy in treating psoriasis, it is only through continued use of these medications that we will appreciate their mature safety profiles.

References

1. O'Neill JL, Kalb RE: Ustekinumab in the therapy of chronic plaque psoriasis. *Biologics* 3:159-168, 2009
2. Krueger GG, Langley RG, Leonardi C, et al: A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 356:580-592, 2007
3. Scanlon JV, Exter BP, Steinberg M, et al: Treatment of adult moderate-to-severe chronic plaque psoriasis. *Ann Pharmacother* 43:1456-1465, 2009
4. Shear NH, Prinz J, Papp K, et al: Targeting the interleukin-12/23 cytokine family in the treatment of psoriatic disease. *J Cutan Med Surg* 12:S1-S10, 2008
5. Piskin G, Sylva-Steenland RM, Bos JD, et al: In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol* 176:1908-1915, 2006

6. Chien AL, Elder JT, Ellis CN, et al: A new option in psoriasis therapy. *Drugs* 69:1141-1152, 2009
7. Alwawi EA, Krulig E, Gordon KB: Long term efficacy of biologics in the treatment of psoriasis: what do we really know? *Dermatol Ther* 22:431-440, 2009
8. Ma HL, Liang S, Li J, et al: IL-22 is required for Th17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. *J Clin Invest* 118:597-607, 2008
9. Product Monograph. Stelara (ustekinumab). Toronto, Ontario: Janssen-Ortho Inc December 2008
10. Ustekinumab: New drug. Suspicion of carcinogenicity: too great a risk for psoriasis patients. *Prescrire Int* 18:202-204, 2009
11. Leonardi CL, Kimball AB, Papp KA, et al: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (Phoenix 1) [Erratum in: *Lancet* 371:1838]. *Lancet* 371:1665-1674, 2008
12. Papp KA, Langley RG, Lebwohl M, et al: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (Phoenix 2). *Lancet* 371:1675-1684, 2008
13. Lebwohl M, Papp K, Han C, et al: Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the phoenix 1 trial. *Br J Dermatol* (in press)
14. Griffiths CE, Strober BE, Van De Kerkhof P, et al: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 362:118-128, 2010
15. Gottlieb A, Menter A, Mendelsohn A, et al: Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 373:633-640, 2009
16. Kimball AB, Gordon KB, Langley RG, et al: Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. *Arch Dermatol* 144:200-207, 2008
17. Torti DC, Feldman SR: Interleukin-12, interleukin-23, and psoriasis: current prospects. *J Am Acad Dermatol* 57:1059-1068, 2007
18. Ding C, Xu J, Li J: ABT-874, a fully human monoclonal anti-IL-12/IL-23 antibody for the potential treatment of autoimmune diseases. *Curr Opin Investig Drugs* 9:515-522, 2008
19. Paulson S, Valdes J, Hruska M, et al: The pharmacokinetics of the fully human, interleukin-12/-23 monoclonal antibody (ABT-874) in normal healthy volunteers. *J Am Acad Dermatol* 60:AB168, 2009
20. Kimball AB, Zhong J, Valdes JM, et al: Retreatment efficacy and long-term safety of the fully human, interleukin-12/-23 monoclonal antibody ABT-874 in the treatment of moderate to severe psoriasis: 48 week results from a phase II trial. to severe psoriasis: 48 week results from a phase II trial. *J Am Acad Dermatol* 60:AB168, 2009