Review of the safety and efficacy of ustekinumab

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Abstract: Ustekinumab is a subcutaneously and intravenously administered fully human monoclonal immunoglobulin (IgG1) antibody targeting the interleukin (IL)-12/23 shared P40 subunit. The pivotal role of IL-12/23 inflammatory-mediated pathways is increasingly recognized in a plethora of immune-mediated inflammatory disorders including Crohn's disease, psoriasis, and multiple sclerosis. In a randomized controlled trial of ustekinumab in moderate-to-severe Crohn's disease, clinical response was achieved most notably in infliximab-experienced primary and secondary nonresponders and suboptimal responders.

Keywords: anti-interleukin 12/23, antitumor necrosis factor, Crohn's disease, infliximab, primary nonresponder, secondary nonresponder, suboptimal infliximab response, ustekinumab

Introduction

Ustekinumab is a subcutaneously and intravenously administered fully human monoclonal immunoglobulin (IgG1) antibody targeting the interleukin (IL)-12/23 shared P40 subunit [Iwakura and Ishigame, 2006; Trinchieri *et al.* 2003]. IL-12 and IL-23 inflammatory pathways are inhibited by neutralizing antibodies targeting the common P40 subunit. The central role of IL-12 and IL-23 inflammatory-mediated pathways reflects a unique mechanism of action for a plethora of immune-mediated disorders including Crohn's disease, psoriasis, and multiple sclerosis. Crohn's disease has been associated with increased IL-12 production by intestinal antigen-presenting cells [Monteleone *et al.* 1997; Parronchi *et al.* 1997]. IL-12 and IL-23 along with inflammatory cytokines tumor necrosis factor (TNF)-alpha and interferon gamma are associated with granulomatous inflammation and bowel wall thickening, which are characteristics of Crohn's disease [Mannon *et al.* 2004]. The gene encoding IL-23 receptors is associated with acquired immune response mediating T helper 17 regulatory cells in psoriasis [Cargill *et al.* 2007] and Crohn's disease [Abraham and Cho, 2009; Barrett *et al.* 2008; Cho, 2008; Duerr *et al.* 2006]. The subcutaneous and intravenous (IV) routes of administration of ustekinumab offer patients the potential for convenience of self administration, administration with nursing supervision, and infusion center or hospitalization-related administration. Furthermore,

these modes of administration allow for the transition between and IV infusions and subcutaneous injections in individual patients. Oral administration of IL-12/IL-23 inhibitor STA-5326 (apilimod mesylate) has been investigated in experimental autoimmune uveoretinitis and evaluated for the treatment of active Crohn's disease [Sands *et al.* 2009; Keino *et al.* 2008].

Ustekinumab offers a significant treatment option to Crohn's disease patients who have never responded to infliximab, primary nonresponders, as well as patients who have attenuated anti-TNF response or become intolerant to anti-TNF therapy. One third of anti-TNF naïve patients are primary nonresponders [Colombel *et al.* 2007; Sandborn *et al.* 2007a; Schreiber *et al.* 2007; Hanauer *et al.* 2006, 2002; Targan *et al.* 1997]. Approximately one third of initial anti-TNF responders lose response or become intolerant over time, secondary nonresponders [Colombel *et al.* 2007; Schreiber *et al.* 2007; Hanauer *et al.* 2002], requiring dose escalation or switching to another anti-TNF agent [Sandborn *et al.* 2007b; Rutgeerts *et al.* 2004]. Typically, response rates among anti-TNF naïve patients are higher than response rates among secondary nonresponders who switch within the anti-TNF class [Colombel *et al.* 2007; Schreiber *et al.* 2007; Sandborn *et al.* 2007a, 2007b]. Anti-IL-12 and anti-IL-23 offer a welcomed and much needed therapeutic option for both anti-TNF primary and secondary

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nonresponders. In this review we underscore ustekinumab's efficacy and safety in Crohn's disease while briefly summarizing its use in other immune-mediated inflammatory disorders such as psoriasis and multiple sclerosis. Specific attention is paid to the role of ustekinumab in the context of anti-TNF primary and secondary nonresponders.

Pharmacokinetics

Ustekinumab, previously known as CNTO-1275, inhibits T-cell-mediated immune response and is absorbed and eliminated slowly. The long median half life is 20–39 days and the drug demonstrates a dose-dependent increase in serum drug concentration with linear pharmacokinetics [Kasper *et al.* 2006]. Anti-IL-12 has been associated with decreased secretion of IL-12, interferon gamma, and TNF-alpha by colonic lamina propria mononuclear cells with a corresponding histologic improvement associated with decreased numbers of neutrophils, lymphocytes, and plasma cells as well as reduced epithelial damage with repopulation of globulin cells [Mannon *et al.* 2004]. Ustekinumab has been associated with serum C-reactive protein reductions [Toedter *et al.* 2009].

Efficacy

To date, there have been two phase 3 trials investigating the safety of ustekinumab in the treatment of moderate-to-severe psoriasis. PHOENIX 1 [Leonardi *et al.* 2008] was a double-blind, placebo-controlled study of 766 patients who were assessed over three phases: a placebo-controlled phase (weeks 0–12), a placebo-crossover and active treatment phase (weeks 12–40), and a randomized withdrawal phase (weeks 40–76). Subjects were randomized to receive either ustekinumab 45 or 90 mg subcutaneously at weeks 0 and 4, then at every 12 weeks or placebo in the placebo-controlled phase. During the placebo-crossover phase, half of the placebo population was started on ustekinumab 45 mg every 12 weeks and the other half was started on ustekinumab 90 mg every 12 weeks. When subjects who were withdrawn from active treatment lost 50% of psoriasis area and severity index (PASI) improvement, they were retreated.

A statistically significant proportion of subjects receiving ustekinumab 45 or 90 mg achieved the primary endpoint by week 12 compared with subjects receiving placebo (67.1% and 66.4%

versus 3.1%; $p < 0.0001$ *versus* placebo). Onset of efficacy was seen by week 2, with maximum efficacy seen by week 24. During the randomized withdrawal phase, the median time to loss of response in patients who were withdrawn from treatment was approximately 15 weeks. Ustekinumab 45 or 90 mg every 12 weeks is efficacious for the treatment of moderate-to-severe psoriasis.

PHOENIX 2 was a phase 3, double-blind, placebo-controlled trial of 1230 patients with moderate-to-severe psoriasis who were assessed in three phases: placebo-controlled (weeks 0–12), placebo-crossover and active treatment (weeks 12–28), and randomized dose intensification (weeks 28–52) [Papp *et al.* 2008]. The placebo-controlled and placebo-crossover phases were the same as for PHOENIX 1. During the randomized dose intensification phase, partial responders (defined as achieving >50% but <75% improvement) were randomized to either continue to receive their current dose every 12 weeks or to intensify dosing by receiving their current dose of ustekinumab every 8 weeks.

Similarly to PHOENIX 1, a statistically significant proportion of subjects receiving subcutaneous ustekinumab 45 or 90 mg achieved the primary endpoint, when compared with subjects in the placebo group. Onset of efficacy was again seen by week 2 (as measured by PASI 50) and week 4 (as measured by PASI 75). At week 28, 22.7% of subjects receiving ustekinumab 45 mg and 15.8% of subjects receiving ustekinumab 90 mg were considered to be partial responders. Partial responders who were then randomized to receive dose intensification (by receiving doses every 8 weeks) did not have a statistically significant increase in the number of visits with PASI 75 response compared with the every 12-week group, and thus did not achieve the secondary efficacy endpoint. However, specific subgroup analysis performed on patients who had initially received ustekinumab 90 mg every 12 weeks and were randomized to receive ustekinumab 90 mg every 8 weeks did reveal a statistically significant increase in both the number of visits with PASI 75 response. Subgroup analysis showed that partial responders were more likely to have higher bodyweight, more severe disease, and a higher incidence of psoriatic arthritis. Antibodies against ustekinumab were found in 12.7% of partial responders compared with 2.0% of responders

at week 52 (statistical analysis not performed). Partial responders were noted to have lower trough serum drug levels at week 28 than PASI 75 responders, although statistical analysis was not performed. There does not, however, appear to be a correlation between trough serum drug levels and clinical response. Although partial responders who were initially randomized to receive ustekinumab 45 mg and then began dose intensification did achieve comparable trough levels compared with responders, there was no corresponding increase in clinical response. Partial responders most likely had more resistant disease.

Fully human monoclonal antibody ABT-874 was highly effective and well tolerated in the treatment of plaque psoriasis in a phase 2 multicenter, 12-week, double-blind, randomized, placebo-controlled trial [Kimball *et al.* 2008]. The majority of patients (90%) in the ABT-874 dose ranging group achieved a 75% reduction in PASI or greater by week 12 compared with only 3% in the placebo group. One hundred and eighty patients were randomized to ABT-874 200 mg single dose, 100 mg every other week, 200 mg weekly for 4 weeks, 200 mg every other week, 200 mg weekly, or placebo. Notably, 63% of patients who received a single 200 mg dose achieved at least a PASI 75 response by week 12. The demonstrated efficacy of ABT-874 and ustekinumab has been consistent in psoriasis.

A phase 2, double-blind, placebo-controlled study investigated the efficacy of ustekinumab in multiple sclerosis [Segal *et al.* 2008]. This study of 249 patients with relapsing–remitting multiple sclerosis randomized subjects into five groups, each receiving either placebo or a different dose of ustekinumab at weeks 0, 1, 2, 3, 7, 11, 15, and 19. The ustekinumab doses were 27 mg, 90 mg, 90 mg every 8 weeks (this group received placebo at weeks 7 and 15), or 180 mg. The primary endpoint was the cumulative number of new enhancing lesions on cranial MRI from baseline to week 23. Secondary endpoints included the total number of multiple sclerosis relapses, and changes in a disability status scale. There was no statistically significant difference in the cumulative number of new enhancing lesions on MRI between subjects receiving placebo and subjects receiving each of the different ustekinumab dosages; thus, the primary endpoint was not achieved. The authors also noted that there was no clinically significant difference as

well. There was no median change in disability status scale scores from baseline, and the authors noted that similar percentages of subjects in all of the groups had objective relapses. The authors concluded that ustekinumab did not show efficacy in reducing the number of enhancing lesions or clinical events in patients with relapsing–remitting multiple sclerosis.

A phase 2a trial conducted in 2008 investigated the efficacy of ustekinumab in patients with moderate-to-severe Crohn's disease [Sandborn *et al.* 2008]. This study included a double-blind, placebo-controlled, parallel-group, crossover design that randomized 104 patients (population 1) into four subsets of ustekinumab and placebo combinations and an open-label study that randomized 27 patients to subcutaneous or IV ustekinumab (population 2). Population 1 involved 104 patients who were initially randomized to one of four treatments: subcutaneous placebo at weeks 0, 1, 2, and 3, then 90 mg ustekinumab at weeks 8, 9, 10, and 11; subcutaneous 90 mg ustekinumab at weeks 0, 1, 2, and 3, then placebo at weeks 8, 9, 10, and 11; IV placebo at week 0, then 4.5 mg/kg ustekinumab at week 8; or IV 4.5 mg/kg ustekinumab at week 0, then placebo at week 8. Patients in population 2 were randomized to either subcutaneous 90 mg ustekinumab at weeks 0, 1, 2, and 3, or IV 4.5 mg/kg ustekinumab at week 0. Although the primary endpoint of a reduction of $\geq 25\%$ and > 70 points from baseline Crohn's disease activity index (CDAI) score was not achieved in this study, ustekinumab did achieve clinical response in population 1 patients with moderate-to-severe Crohn's disease and, furthermore, clinical response to ustekinumab was greater than to placebo in the subgroup of patients who had received suboptimal infliximab exposure (patients who received less than three-dose induction followed by every 8- to 12-week maintenance without shortening the interval, without receiving at least one 10-mg/kg dose escalation, without receiving an alternative anti-TNF therapy, or who were intolerant to infliximab). In contrast, population 2 consisted of nonresponders of infliximab. This group was further divided into primary nonresponders (i.e. patient who failed to respond to a three-dose induction of infliximab 5 mg/kg) and secondary nonresponders (i.e. patients with an initial response to a three-dose induction followed by an attenuated response during every 8-week maintenance therapy and failure to respond to at least one dose escalation to 10 mg/kg).

Focusing on infliximab-experienced patients in this study, 47% of patients in population 1 (49 of 104) and all patients in population 2 (27 of 27) received and discontinued infliximab prior to entering the study. In population 1, a greater proportion of patients were receiving baseline aminosalicylates (46 of 104 patients [44%]) compared with the subgroup of patients receiving suboptimal infliximab (14 of 49 patients [29%]). This aminosalicylate discrepancy may explain the higher placebo response in population 1, compared with the greater response of ustekinumab in the subgroup of 49 patients who were suboptimally infliximab experienced. Other than the divergence in aminosalicylate use in the infliximab exposed and naïve patients, concomitant use of other Crohn's disease medications were comparable in population 1.

At the primary endpoint of week 8 in population 1, 49% of patients in the combined ustekinumab group (i.e. those on IV or subcutaneous ustekinumab) were in clinical response compared with 40% of patients in the combined placebo group (Figure 1). However, at the earlier time points of week 4 and 6, 53% of patients in the combined ustekinumab group were in clinical response compared with only 30% in the placebo group. This finding suggests that week 8 may be too late to evaluate the optimal response for ustekinumab. In the subgroup of 49 patients treated previously with suboptimal infliximab, the rate of clinical response to ustekinumab was greater than that for placebo at every visit through week

8 (Figure 2). This finding suggests that the response rate for ustekinumab is greater in patients with more severe disease given that patients previously treated with infliximab are more likely to have severe disease warranting infliximab prescription. Patients in population 1 who were not previously treated with infliximab may have had less severe disease and, thus, be more likely to respond to placebo. In the infliximab subgroup in population 1, the treatment effect, the difference between ustekinumab and placebo, tended to be greater for IV compared with the subcutaneous administration and the reason for this is unclear.

In population 1, lower baseline bodyweight and a higher CDAI score were associated with greater clinical response to ustekinumab at week 8, again suggesting that there may be subgroups that are more likely to respond to ustekinumab. Furthermore, C-reactive protein levels were decreased at week 8 in patients who initially received either IV and subcutaneous ustekinumab, again suggesting that there is a subgroup that may be more likely to respond to ustekinumab.

In population 2, an open-label trial examining the effects of 4-weekly subcutaneous injections or IV infusion of ustekinumab in 27 patients who were primary or secondary nonresponders showed clinical responses at week 8 of 43% and 54%, respectively. In addition, 48% of patients in the combined IV and subcutaneous ustekinumab

Figure 1. Efficacy of ustekinumab. Clinical response over time in the combined ustekinumab and placebo groups in population 1. Reproduced with permission from Sandborn *et al.* [2008].

group had a clinical response at week 6 and 8. There were generally numerically higher rates of clinical response (100-point response) and clinical remission in the IV ustekinumab group compared with the subcutaneous ustekinumab group. In addition, there was a decrease in C-reactive protein at week 8 in both subcutaneous (0.75 versus 0.6 mg/dL) and IV (1.1 versus 0.6 mg/dL) ustekinumab groups.

In terms of efficacy at week 16, there was generally a decrease over time, which may reflect the attenuation of ustekinumab beyond 6–8 weeks. In population 1, a decrease in both clinical response and clinical remission rates was found between week 12 and week 16. In population 2, a robust response rate of 62% was found at week 12 in the subgroup that received IV ustekinumab 4.5 mg/kg (8 out of 13 patients). By week 16, the response rate decreased to 46% (6 out of 13 patients). Similarly, in the subgroup that received 90 mg ustekinumab subcutaneously, the 100-point response rate decreased from 36% at week 12 to 21% at week 16. Remission rates in population 2 also showed a decrease from 31% at week 12 to 0% at week 16 in the IV ustekinumab subgroup and from 21% at week 12 to 14% at week 16 in the subcutaneous subgroup. The findings suggest that ustekinumab given for a short duration becomes less effective over time. The findings also suggest that every 8-week dosing may not be the ideal dosing strategy and illustrate the need to define an optimal

maintenance strategy for the administration of ustekinumab.

A phase 2 induction and maintenance randomized, double-blind, placebo-controlled trial evaluated the efficacy apilimod mesylate (STA-5326) 220 adult patients with moderate-to-severe Crohn's disease [Sands *et al.* 2009]. Patients were randomized to receive placebo or apilimod mesylate 50 mg daily or 100 mg daily. Patients were stratified according to C-reactive protein levels and corticosteroid use. The induction phase was 6 weeks and the maintenance phase was 4 months. Apilimod did not demonstrate improved efficacy although it was well tolerated.

Safety

We have reviewed efficacy and now review safety data on ustekinumab. In general, adverse events with ustekinumab have been reported as mild and nonserious.

In PHOENIX 1, the most common adverse events were reported as upper respiratory tract infections, nasopharyngitis, headache, and arthralgia [Leonardi *et al.* 2008]. The rate of these events was about 50% among all subject populations. Serious adverse events occurred in 0.8% of the subjects receiving ustekinumab 45 mg, 1.6% of the subjects receiving ustekinumab 90 mg, and 0.8% of the subjects receiving placebo. No malignancies were reported during

Figure 2. Efficacy of ustekinumab. Clinical response over time in the combined ustekinumab and placebo groups in Population 1 who previously had been treated with infliximab. Reproduced with permission from Sandborn *et al.* [2008].

the placebo-controlled phase, although they were reported during the crossover phase (one case each of prostate cancer and thyroid cancer) and the withdrawal phase (one case of colon cancer).

In PHOENIX 2, adverse events were reported in similar numbers in the different populations. One percent of subjects receiving ustekinumab injections and 0.4% of subjects receiving placebo injections reported injection site reactions [Papp *et al.* 2008]. No episodes of anaphylactic or serum-like sickness reactions, lymphoma, tuberculosis, or demyelinating diseases were reported. Serious adverse events were similar in type in all populations, with the most common events reported as infections and cardiac disorders.

Ustekinumab was well tolerated by patients with relapsing–remitting multiple sclerosis [Segal *et al.* 2008]. The most frequently reported adverse event was infection, including upper respiratory tract infection and nasopharyngitis. Other common events included injection-site reactions, headache, and fatigue. At least one adverse event was reported by 78% of patients in the placebo group and 79–94% of patients in all groups receiving ustekinumab.

In population 1, the incidence of nausea, fatigue, and worsening Crohn's disease through 8 weeks was higher in the placebo group than in the ustekinumab group. The incidence of anxiety and pruritus was marginally higher in the ustekinumab group. Serious adverse events were found in three patients (6%) in the placebo group including small intestinal stenosis and nonsteroidal anti-inflammatory drug-induced gastrointestinal ulceration in one patient, worsening Crohn's disease and erythema nodosum in one patient, and worsening Crohn's disease and small intestinal obstruction in one patient. In the ustekinumab group, two patients (4%) had one or more serious adverse events including small bowel obstruction and coronary artery disease.

If we follow these patients over time, administration site reactions (which were generally mild) were found more often in patients who were treated with subcutaneous placebo (4%) than subcutaneous ustekinumab (0%). Mild adverse events involving pyrexia, flushing, and pruritus occurring within 1 hour of IV administration occurred more frequently for patients treated with IV ustekinumab (19%) than IV placebo (0%).

Adverse events recorded through week 28 in both populations showed that six patients (6%) in population 1 experienced serious adverse events (worsening Crohn's disease in two patients, colonic stenosis and pneumothorax in one patient, small intestinal obstruction in two patients, and prostate cancer in one patient). In population 2, four patients (15%) experienced one or more serious adverse events including one case of disseminated histoplasmosis in a patient who had 10 mg/kg 3 months prior to study entry, was febrile at baseline and had received both azathioprine and 80 mg prednisone in addition to IV ustekinumab. In population 2, there was also a case of viral gastroenteritis in one patient and malignancies in two patients: one 54-year-old male had increased prostate-specific antigen levels before entering the study and was diagnosed with prostate carcinoma 2 months after receiving IV ustekinumab and one woman was diagnosed with squamous and basal cell skin carcinomas after week 28 (approximately 6 months after the last ustekinumab dose) following treatment with subcutaneous ustekinumab starting at week 8.

In population 1, 25% of patients (19 of 77) had undetectable anti-ustekinumab antibodies owing to detectable serum ustekinumab levels, and 75% of patients (58 of 77) were negative for anti-ustekinumab antibodies. Similarly, in population 2, 23% of patients (5 of 22) had undetectable anti-ustekinumab antibodies and 77% of patients (17 of 22) were negative for anti-ustekinumab antibodies.

Conclusion

Medically refractory Crohn's disease including nonresponse to anti-TNF therapy is a continuing clinical challenge. While one-third of anti-TNF-treated patients are primary nonresponders, secondary nonresponse is increasingly being recognized as a primary problem in managing Crohn's disease. Inhibition of IL-12/23 inflammatory pathways via ustekinumab, an IgG1 monoclonal antibody, which neutralizes the shared P40 subunit of IL-12/23 represents a unique mechanism of action in treating moderate-to-severe medically refractory Crohn's disease as well as psoriasis and multiple sclerosis and offers a welcomed alternative to anti-TNF therapy in primary and secondary nonresponders.

In Crohn's disease, the definition of infliximab primary nonresponse is a patient who has failed

a proper three-dose induction 5 mg/kg regimen; secondary nonresponse is defined as a patient who has attenuated response after a completed three-dose induction with every 8-week maintenance and failed at least one 10 mg/kg dose; suboptimal response is defined as a patient who received less than three-dose induction followed by every 8- to 12-week maintenance without shortening the interval, without receiving at least one 10-mg/kg dose escalation, without receiving an alternative anti-TNF therapy, or who were intolerant to infliximab. A phase 2a trial of ustekinumab defines and stratifies suboptimal infliximab responders into population 1 (a randomized, controlled, double-blind, parallel group crossover study) and defines and stratifies infliximab primary and secondary nonresponders into population 2 (an open-label study) [Sandborn *et al.* 2008]. At the primary endpoint of week 8 in population 1, 49% of patients in the combined ustekinumab group (i.e. those on IV or subcutaneous ustekinumab) were in clinical response compared with 40% of patients in the combined placebo group. However, at the earlier time points of week 4 and 6, 53% of patients in the combined ustekinumab group were in clinical response compared with only 30% in the placebo group. In population 2, an open-label trial examining the effects of 4-weekly subcutaneous injections or one IV infusion of ustekinumab in 27 patients who were primary or secondary nonresponders showed clinical responses at week 8 of 43% and 54%, respectively. In addition, 48% of patients in the combined IV and subcutaneous ustekinumab group had a clinical response at weeks 6 and 8. Ustekinumab induced a clinical response in moderate-to-severe Crohn's disease especially in infliximab experienced patients. The optimal induction and maintenance dose for ustekinumab in Crohn's disease remains to be determined; currently, a phase 2b study is ongoing. Further studies evaluating IV, subcutaneous and oral anti-IL-12/23 in Crohn's disease and other immune-mediated inflammatory diseases such as psoriasis, multiple sclerosis, and uveoretinitis are warranted.

Conflict of interest statement

Ellen Scherl, MD, has served as a consultant or advisory board member for Abbott, AstraZeneca, Axcan, Berlex, Centocor, Cerimon, Crohn's & Colitis Foundation of America (CCFA), PDL BioPharma, Proctor & Gamble, Prometheus Laboratories, Questcor, Salix, Shire, Sigma Tau, Solvay, TAP, and UCB. She has received grants or

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