[mAbs 1:3, 216-221; May/June 2009]; ©2009 Landes Bioscience

Mini-Review

Ustekinumab

Oya Cingoz

Department of Molecular Biology and Microbiology; Tufts University School of Medicine; Boston, MA USA

Key words: ustekinumab, CNTO-1275, Stelara, psoriasis, psoriatic arthritis, Crohn disease, multiple sclerosis

Ustekinumab is an anti-IL12/23 IgG1 kappa human monoclonal antibody currently undergoing US Food and Drug Administration review for use as a psoriasis treatment. The candidate has also been evaluated in Phase 2 studies as a treatment for psoriatic arthritis, Crohn disease and multiple sclerosis. In large clinical trials, ustekinumab has proven effective for treating moderate to severe plaque psoriasis. Although long-term follow-up studies are needed to address safety concerns, the hopes are high for psoriasis treatment. Ustekinumab has recently been approved for marketing in Canada and Europe.

Introduction

Psoriasis is a chronic inflammatory disease of the skin, affecting an estimated 125 million people worldwide. The most prevalent form, plaque psoriasis, is marked by the appearance of skin lesions in the form of scaly, red plaques. Psoriasis is caused by the overproduction and immature migration of keratinocytes to the surface of the skin, due to abnormal immune-mediated signaling. Primarily considered as a skin disease, psoriasis can be physically and psychologically debilitating since it is associated with a variety of symptoms ranging from arthritis to depression, thus immensely affecting the quality of life.

Ustekinumab (CNTO-1275, Stelara) is a human monoclonal antibody (mAb) developed by Centocor, a subsidiary of Johnson & Johnson, for treatment of autoimmune diseases. The mAb was generated from transgenic mice using genetic engineering techniques. Ustekinumab targets the p40 subunit shared by two cytokines, interleukin (IL)-12 and 23, prevents their interaction with the receptor, thereby blocking subsequent signaling, differentiation and cytokine production central to inflammatory diseases. The candidate has been studied as a treatment for four indications: psoriasis, psoriatic arthritis, Crohn disease (CD) and multiple sclerosis (MS), although it has been discontinued for the latter indication for lack of efficacy.

Marketing applications for ustekinumab as a treatment for chronic plaque psoriasis were submitted to both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) in late 2007. In June 2008, an advisory committee for FDA unanimously recommended ustekinumab for this indication. However, a response letter issued by the FDA in December 2008 requested additional information, including a Risk Evaluation and Mitigation Strategy (REMS). FDA will issue another decision regarding whether ustekinumab can enter the US market in 2009. The product was approved for marketing in the 27 countries of the European Union in January 2009. In December 2008, ustekinumab was also approved in Canada, where it is being marketed by Janssen-Ortho Inc.

Correspondence to: Oya Cingoz; Department of Molecular Biology and Microbiology; Tufts University School of Medicine; Boston, MA 02111 USA

Submitted: 3/26/09; Accepted: 3/26/09

Previously published online as a *mAbs* E-publication:
www.landesbioscience.com/journals/mabs/article/8593

Preclinical Analysis

Early therapies for treatment of psoriasis included topical steroids, which are useful in treating mild cases, but have limited efficacy since one-third of clinical cases are considered moderate to severe. Systemic agents, such as methotrexate, and radiotherapy have been widely used and were more effective. However, high toxicity and side effects have raised concerns over long-term usage. Current treatment options include various immune modulating biologics that inhibit T cell trafficking, e.g., alefacept, and TNF-α signaling, e.g., etanercept, infliximab and adalimumab.[1] A substantial proportion of patients with psoriasis fail to respond to these therapies, and tachyphylaxis is not uncommon among responders, underscoring the importance of alternative treatment options.

With the finding that IL-12 and IL-23 play an important role in the pathogenesis of psoriasis[2,3] the development of IL-12/23 inhibitors has been on the rise. IL-12 stimulates IFN-γ and TNF-α production through T-helper 1 (Th1) cell differentiation, while IL-23 causes activation of IL-17 producing T cells (Th17).[3] IL-12 contains subunits p40 and p35, whereas IL-23 contains subunits p40 and p19. Ustekinumab binds with high affinity and specificity to the p40 subunit shared by both cytokines and blocks signaling through the IL-12β1 receptor found on natural killer (NK) cells or T cells.

Anti-IL-12/23 p40 antibodies have been shown to antagonize key pathways in inflammatory autoimmune diseases. In mouse models, IL-12 and IL-23 blockers prevented arthritis and colitis.[4,5] When peripheral blood mononuclear cells were cultured in the presence of IL-12, ustekinumab inhibited the up-regulation of cutaneous lymphocyte antigen (CLA), IL-2Rα and IL-12R expression, as well as the secretion of IFN-γ, TNF-α and IL-17A.[3]

Two in vivo studies assessing the effects of ustekinumab were performed in marmosets with experimental autoimmune encephalomyelitis (EAE), which models chronic MS.[6,7] In the first of these studies, EAE was induced by myelin, followed by injection of ustekinumab or vehicle. While all animals in the control group developed EAE symptoms, only one animal in the ustekinumab group did so, and the disease progression was delayed compared to the control animals.[6] In a second study, the efficacy of ustekinumab in treating ongoing EAE was assessed. Weekly ustekinumab injections significantly delayed the progression of disease; the mean volume of EAE-associated brain lesions increased four-fold in the treated group, compared with 14-fold in the control group.[7] Taken together, preclinical data indicated potential benefits for ustekinumab to be tested in clinical trials for various autoimmune disorders.

Clinical Studies in Psoriasis

Ustekinumab has been investigated as a treatment for psoriasis in one Phase 2 study and a total of five Phase 3 studies, two of which were recently initiated. The double-blind, randomized, placebo-controlled Phase 2 trial was carried out in 320 patients with moderate-to-severe plaque psoriasis.[8] In this multicenter study, patients received subcutaneous injections of either a single dose of 45 mg or 90 mg ustekinumab or four weekly injections of the same doses or placebo. Patients in the placebo group crossed over to receive one 90 mg dose of ustekinumab at week 20. The primary endpoint was the percentage of patients with at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12. The percentage of patients reaching PASI 75 at week 12 ranged from 52–81% in the ustekinumab groups, compared with 2% in the placebo group. The DLQI scores at week 12 also proved significant improvement in quality of life in the treated groups. Although the number of patients experiencing an adverse event was slightly higher in the ustekinumab groups than the placebo, the study was not large enough to address the significance of uncommon adverse events. The results demonstrated therapeutic efficacy of ustekinumab and implied the need for larger-scale trials for complete assessment of effectiveness and safety.

Two randomized, double-blind, placebo-controlled phase 3 studies were carried out in Europe and North America (PHOENIX 1 and 2), to test the safety and efficacy of ustekinumab in patients with moderate-to-severe plaque psoriasis.[9,10] A third study, ACCEPT, compared ustekinumab with etanercept as treatments for moderate-to-severe psoriasis. Two additional Phase 3 trials are currently on-going. The studies will assess efficacy and safety of ustekinumab in Japanese, Korean and Taiwanese subjects with moderate-to-severe plaque-type psoriasis. The clinical studies in plaque-type psoriasis are outlined in Table 1.

PHOENIX-1

Patients were randomly assigned to one of three groups receiving subcutaneous injections of either 45 or 90 mg ustekinumab or placebo at weeks zero and four. Patients receiving ustekinumab continued taking the same dose every 12 weeks, while those in the placebo group were randomly crossed over to receive 45 mg or 90 mg ustekinumab at weeks 12 and 16, and then every 12 weeks onwards. The primary endpoint was the percentage of patients achieving PASI 75 at week 12. Among the patients who initially received ustekinumab at the start of the study, those achieving the desired PASI score at week 40 were re-randomized to either continue following the same regimen, or were withdrawn from treatment by receiving placebo. The percentage of patients treated with 45 and 90 mg ustekinumab, who achieved PASI 75 at 12 weeks was 66 and 67% respectively, compared with only 3% in the placebo group. Forty-two percent and 37% of patients reached PASI 90 or neared total clearance of psoriasis in the treated groups, compared with 2% in the placebo group. Moreover, patients who continued treatment at week 40 showed 87 and 90% maintenance of PASI 75, whereas the response rates in the placebo-switched groups ranged between 62–64%.[9]

PHOENIX-2

The initial placebo-controlled phase of the study was designed identically to that of the PHOENIX 1 trial until week 28. By week 12, 67 and 76% of patients in the test groups (receiving 45 mg and 90 mg ustekinumab, respectively) had reached a PASI 75 score, compared with 4% in the placebo group. At the same time point, patients achieving a PASI 90 score were 42 and 51%, while it was 1% in placebo-treated patients. At week 28, partial responders (achieving at least PASI 50, but less than 75) were re-randomized to receive the initial dose they had been assigned, either every 8 weeks or every 12 weeks until the end of the study at week 52. In the 90 mg arm, the proportion of patients achieving PASI 75 by week 52 was significantly higher in the 8-week group compared with the 12-week group (69 vs 34%), while the 45 mg group did not show any response to dose intensification.[10]

Both studies assessed the efficacy and safety of ustekinumab in patients with moderate-to-severe psoriasis. While Phoenix 1 study included a withdrawal phase following active treatment, Phoenix 2 assessed the effects of dose intensification in patients who responded only partially to ustekinumab. The results from the trials involving over 2,000 patients revealed that ustekinumab is efficacious in treating moderate-to-severe psoriasis, and seems to be generally well tolerated for at least 52 to 76 weeks.[9,10] The incidence of adverse events was similar in all groups, with serious adverse events occurring in 0.2–1.2% of the ustekinumab groups and 2% of the placebo groups. Although most patients seem to respond well to treatment with ustekinumab every 12 weeks, dose intensification might be necessary for partial responders.

ACCEPT

A Phase 3, multicenter, randomized study that compared ustekinumab with etanercept, a TNF-α antagonist, revealed that ustekinumab was more effective in treating moderate-to-severe psoriasis. Over 900 patients enrolled in the 12 week study were given subcutaneous injections of either 45 or 90 mg ustekinumab at weeks zero and four, or 50 mg etanercept twice a week for 12 weeks. At week 12, the proportion of patients achieving PASI 75 in the ustekinumab-treated groups were 68 and 74% respectively, compared with 57% of etanercept-treated patients. The results

Table 1 **Clinical studies of ustekinumab in plaque psoriasis**

Study Design	Doses	Results	Reference	Clinical Trial
Phase 2	Patients with severe plaque psoriasis were administered a single dose of 45 mg or 90 mg ustekinumab (sc) or four weekly injections of the same doses, or placebo.	At week 12, the proportion of patients reaching the primary endpoint (PASI 75) in groups treated with ustekinumab ranged from 52% to 81%, compared with 2% in the placebo group. The DLQI scores at week 12 also proved significant improvement in quality of life in the treated groups.	8	NCT00320216
Phase 3 (PHOENIX 1)	Patients with moderate to severe plaque psoriasis were given 45 or 90 mg ustekinumab (sc) or placebo at weeks 0 and 4. The ustekinumab-receiving group continued the same regimen every 12 weeks, the placebo group randomly crossed over to receive 45 mg or 90 mg ustekinumab at weeks 12 and 16, and then every 12 weeks onwards. Patients achieving PASI 75 at week 40 were re-randomized to either continue following the same regimen, or were withdrawn from treatment.	At week 12, 67% of ustekinumab receiving patients reached PASI 75, compared with 3% in the placebo group. 42% and 37% of patients (for 45 and 90 mg groups, respectively) reached PASI 90 or neared total clearance of psoriasis, compared with 2% in the placebo group. 87% and 90% of patients who continued treatment at week 40 maintained PASI 75, compared with 63% in the placebo-switched group.	9	NCT00267969
Phase 3 (PHOENIX 2)	Patients with moderate to severe plaque psoriasis were given 45 or 90 mg ustekinumab (sc) or placebo at weeks 0 and 4. The ustekinumab-receiving group continued with the same regimen every 12 weeks, the placebo group randomly crossed over to receive 45 mg or 90 mg ustekinumab at weeks 12 and 16, and then every 12 weeks onwards. At week 28, partial responders (50≤PASI<75) were re-randomized to receive the initial dose they had been assigned, either every 8 weeks or every 12 weeks until week 52.	At week 12, 67% and 76% of patients, receiving 45 mg and 90 mg ustekinumab respectively, had reached a PASI 75 score, compared with 4% in the placebo group. At the same time point, the proportion of patients achieving PASI 90 were 42% and 51%, while it was 1% in placebo-treated patients. At week 52, while the 45 mg group did not show any response to dose intensification, in the 90 mg arm 69% of the 8-week group achieved PASI 75 compared with 34% of patients in the 12-week group.	10	NCT00307437
Phase 3 (ACCEPT)	Patients with moderate to severe plaque psoriasis were given 45 or 90 mg ustekinumab (sc) at weeks 0 and 4, or 50 mg etanercept twice a week for 12 weeks.	At week 12, 68% and 74% of ustekinumab-treated patients (45 or 90 mg) reached PASI 75, compared with 57% of etanercept-treated patients.	EADV* (abstract FP1336)	NCT00454584
Phase 3	Taiwanese and Korean patients with moderate to severe plaque psoriasis will be assigned to one of two groups: Group 1 will receive 45 mg ustekinumab (sc) at weeks 0, 4 and 16; and placebo at week 12. Group 2 will receive placebo at weeks 0 and 4; followed by ustekinumab at weeks 12 and 16. Patients will be followed up until week 36.	On-going (Currently recruiting participants)	N/A	NCT00747344
Phase 3	Japanese patients with moderate to severe plaque psoriasis will be administered 45 or 90 mg ustekinumab (sc) or placebo at weeks 0 and 4. The ustekinumab-receiving group will continue the same regimen every 12 weeks, the placebo group will be re-randomized to receive 45 mg or 90 mg ustekinumab at weeks 12 and 16, and then every 12 weeks onwards.	On-going (Active, but not recruiting)	N/A	NCT00723528

SC, subcutaneous; IV, intravenous.*17th European Academy of Dermatology and Venereology (EADV) Congress

Table 2 **Clinical studies of ustekinumab in additional indications: psoriatic arthritis (PsA), Crohn disease (CD) and multiple sclerosis (MS)**

Indication	Study Design	Doses	Results	Reference	Clinical Trial
Psoriatic arthritis	Phase 2	Patients with PsA, who also had active plaque psoriasis were assigned to one of 2 groups: 1) 90 mg or 63 mg ustekinumab for the first 4 weeks, followed by placebo at weeks 12 and 16; 2) placebo for the first 4 weeks, followed by 63 mg ustekinumab at weeks 12 and 16. Patients were followed up until week 36.	At week 12, 42% of the patients in Group 1 achieved an ACR20 score, compared with 14% in Group 2. 25% and 11% of Group 1 patients achieved ACR50 and ACR70, respectively, compared with 5% and 0% in Group 2. 52% of ustekinumab treated group achieved PASI 75, compared with 5% in the placebo group.	12	NCT00267 956
Crohn's Disease	Phase 2a	Two populations of patients with a CDAI between 220-450 were enrolled. Population 1 had previously received conventional treatments. Patients were divided into 4 groups: 1) Weekly placebo between weeks 0-3, plus 90 mg ustekinumab (sc) between weeks 8-11; 2) Weekly ustekinumab (sc) between weeks 0-3, plus 90 mg placebo between weeks 8-11; 3) Placebo at week 0, then 4.5 mg/kg ustekinumab (iv) at week 8; 4) 4.5 mg/kg ustekinumab (iv) at week 0, then placebo at week 8. Population 2 consisted of non-responders to infliximab, who were given either 90 mg ustekinumab (sc) weekly between weeks 0-3 or 4.5 mg/kg ustekinumab (iv) at week 0.	Population 1: At weeks 4 and 6, 53% of combined ustekinumab treated patients (Groups 2 and 4) were in clinical response, compared with 30% in the placebo treated patients (Groups 1 and 3). At week 8, the proportion of patients with a complete clinical response in the combined ustekinumab group was 49% compared with 40% in the placebo group. Population 2: At weeks 2 and 4, 22% and 41% of patients in the combined ustekinumab group were in clinical response, the proportion reached 48% by week 6. At week 8, the clinical response rates were 43% for Group 1 and 54% for Group 2.	14	NCT00265 122
	Phase 2/3	Patients with a history of anti-TNF therapy will be assigned to one of 4 groups receiving intravenous injections of 1mg/kg, 3mg/kg or 6mg/kg ustekinumab (iv) or placebo at the start of the study. Ustekinumab-treated groups will be re-randomized to receive placebo or 90 mg ustekinumab (sc) at weeks 8 and 16. The placebo group will be re-randomized to receive placebo at weeks 8 and 16, or 270 mg ustekinumab (sc) at week 8 followed by 90 mg at week 16. Patients will be followed up until week 36.	On-going (Currently recruiting participants)	N/A	NCT00771 667
Multiple Sclerosis	Phase 2 (Discontinued)	Patients with relapsing-remitting MS were given 27, 90, 90q8w or 180 mg ustekinumab (sc) or placebo at weeks 0, 1, 2, 3, 7, 11, 15 and 19; 90q8w group received placebo at weeks 7 and 15.	Ustekinumab was well tolerated, but was not effective in decreasing the cumulative number of newly formed Gd-enhancing T1-weighted lesions in MS.	15	NCT00207 727

were presented at the European Academy of Dermatology and Venereology (EADV) Meeting in September 2008.

Clinical Studies in Additional Indications

Ustekinumab has been investigated in three Phase 2 trials as a treatment for psoriatic arthritis, Crohn disease and multiple sclerosis. An additional Phase 2/3 study in CD is currently on-going. Clinical studies of ustekinumab in these indications are outlined in Table 2.

Psoriatic Arthritis

A substantial proportion of patients with psoriasis also show joint manifestations. The estimates vary considerably among different studies, however, between 6–42 % of psoriasis patients are thought to be affected with psoriatic arthritis (PsA).[11] The potential role of IL-12/23 in the pathogenesis of PsA is underscored by the finding that patients display increased serum levels of p40 subunit, suggesting potential therapeutic benefits for ustekinumab in treating PsA.[11]

A double-blind, randomized, placebo-controlled, crossover study was conducted in multiple sites in North America and Europe, assessing the safety and efficacy of ustekinumab in patients with psoriatic arthritis.[12] In this multicenter Phase 2 trial, 146 patients with active plaque psoriasis and inadequate responses to conventional drug treatments were enrolled. Patients were randomly assigned to one of two groups: Group 1 received weekly subcutaneous injections of 90 or 63 mg ustekinumab for the first four weeks, followed by placebo at weeks 12 and 16, while Group 2 received weekly placebo injections the first four weeks, followed by 63 mg ustekinumab at weeks 12 and 16. Patients were followed until week 36. The primary endpoint of the study was the proportion of patients at week 12 with minimum 20% improvement in the American College of Rheumatology criteria (ACR20). At week 12, 42% of the patients in Group 1 achieved an ACR20 score, while only 14% of Group 2 patients did so. Comparing ACR50 and ACR70 values achieved by the participants at the same time point also revealed a significant difference between the groups: 25 and 11% (for ACR50 and ACR70, respectively) in Group 1, compared with 7 and 0% in Group 2. Furthermore, among the patients with psoriasis covering at least 3% of their body surface area, a higher proportion in the ustekinumab treated group reached PASI 75 score compared with the placebo group (52 vs 5%), lending further support to the findings of the Phoenix trials. Crossover at week 12 from placebo to ustekinumab resulted in similar proportions of patients achieving ACR20 by week 24. The ACR20 response was well maintained in around one third of the patients at least as far as week 36, several months after the last dose.

Crohn Disease

Crohn disease is an autoimmune disease, marked by the inflammation of the gastrointestinal tract. Symptoms include abdominal pain, weight loss, diarrhea and bowel obstruction.[13] CD results from abnormal signaling in the gastrointestinal mucosa, where the innate and adaptive immune systems respond excessively to the intestinal microbiota. Both IL-12 and IL-23 have been implicated in the pathogenesis of CD.

A Phase 2a trial assessing the effects of ustekinumab in inducing a clinical response was carried out in patients with moderate-to-severe CD.[14] In this randomized, double-blind, placebo-controlled, parallel-group trial, 104 patients with a Crohn Disease Activity Index (CDAI) score of 220–450 were enrolled. CDAI scores can range from zero to 600, higher scores indicating the severity of disease. Two populations of patients were examined and followed until week 28.

Population 1 consisted of participants who had previously received conventional treatments for CD. Subjects were randomly assigned to one of four groups receiving: (1) weekly subcutaneous injections of placebo between weeks 0–3, plus 90 mg ustekinumab between weeks 8-11; (2) weekly subcutaneous injections of ustekinumab between weeks 0–3, plus 90 mg placebo between weeks 8–11; (3) intravenous placebo injection at week 0, then 4.5 mg/kg ustekinumab at week 8; (4) intravenous injection of 4.5 mg/kg ustekinumab at week 0, followed by placebo at week 8. The primary endpoint was the proportion of patients achieving a reduction in CDAI score by at least 70 points and 25% at week 8. At weeks 4 and 6, 53% of combined ustekinumab treated patients (Groups 2 and 4) were in clinical response, compared with 30% in the placebo treated patients (Groups 1 and 3). At week 8, the proportions of patients with a complete clinical response in the combined groups were 49 and 40%, respectively. Eight weeks after the cross-over (week 16), the results became more complicated to interpret due to the long half-life of ustekinumab (possibly inducing a carryover effect) and the high response rates in the placebo groups in the first eight weeks. The occurrence of adverse events was slightly higher in the placebo group than the ustekinumab group, and included worsening of CD symptoms, nausea and fatigue.

Population 2 consisted of primary or secondary non-responders to infliximab, a chimeric mAb that neutralizes TNF-α. This population was examined in an open-label study; half of the patients were randomly assigned to receive weekly subcutaneous injections of 90 mg of ustekinumab between weeks 0–3 (Group 1), while the other half received 4.5 mg/kg ustekinumab intravenously at week zero (Group 2). At weeks two and four, 22 and 41% of patients in the combined ustekinumab group were in clinical response, respectively, the proportion reaching 48% by week six. At week eight, the clinical response rates were 43% for Group 1 and 54% for Group 2. Findings from the trial were published in October 2008.[14] Ustekinumab displayed efficacy in patients with moderate-to-severe CD, but the highest clinical response was induced in patients who were previously administered infliximab. A Phase 2/3 study is currently underway, in patients with active CD who have been previously treated with anti-TNF therapy.

Multiple Sclerosis

A Phase 2 study of ustekinumab for treatment of patients with relapsing-remitting MS was conducted in North America, Europe and Australia. In this randomized, double-blind, placebo-controlled study, 249 patients were assigned randomly to one of five groups receiving placebo or four different doses of ustekinumab. Drug-treated groups were subcutaneously administered 27, 90 or 180 mg of ustekinumab (groups 1-3) every week between weeks 0–3, then every four weeks, while the last group received 90 mg every week between weeks 0–3, then every eight weeks until week 19. The primary endpoint was the cumulative number of contrast-enhancing cranial MRI lesions at week 23. Patients were followed up through week 37. Results from the trial showed that while ustekinumab was generally well tolerated, improvement was not evident in any of the treated groups.[15]

Segal et. al. provide potential explanations as to why ustekinumab was not effective in MS.[15] First, the agent may not have crossed the blood-brain barrier as easily as the gut or the skin. Although increased levels of cerebrovascular permeability is often observed in MS patients, permeability may still be limiting sufficient concentrations of neutralizing antibodies from entering the CNS. Alternatively, critical immune mediated events such as differentiation and cytokine secretion might have already occurred during disease progression and may not have been dependent on the

presence or activity of IL-12/23 at the time of drug administration. In a recent evaluation of the MS clinical trial findings, Longbrake and Racke argue that analyzing the effects of ustekinumab in a fraction of MS patients with very early disease might actually reveal a treatment effect.[16] A final possibility is that an alternative pathway exists in the MS pathophysiology that remains unaffected, or that the IL-12/23 axis of signaling is irrelevant overall to MS phenotype, despite evidence from animal models underscoring the importance of this pathway in disease progression.[6,7] Further clinical and non-clinical studies will be important in assessing the potential therapeutic benefits of ustekinumab in MS.

Future Prospects

Large-scale, Phase 3 clinical studies have demonstrated the efficacy and safety of ustekinumab for plaque psoriasis, making it an attractive candidate for the psoriasis market. Ustekinumab is not the only molecule in development targeting the IL-12/23 pathways. ABT-874 (Abbott Laboratories) is a human mAb targeting the same p40 subunit of both interleukins. The candidate is currently in Phase 2 development for CD, MS and psoriasis. Abbott's IL-12/23 inhibitor seems to be well tolerated and highly effective in treating chronic plaque psoriasis, with up to 90% of patients achieving PASI 75 at the primary endpoint and no serious infectious adverse events.[17] Although results for ABT-874 cannot be directly compared to those for ustekinumab due to dosing differences and the lack of Phase 3 clinical data, the two mAbs are likely to be close rivals if both eventually enter the psoriasis market.

Another IL-12/23 inhibitor, apilimod mesylate (STA-5326, Synta Pharmaceuticals), is currently under development for treatment of rheumatoid arthritis (RA), common variable immunodeficiency (CVID) and CD. It differs from ustekinumab and ABT-874 in that it is an orally-administered small molecule which inhibits IL-12/23 production at the transcriptional level by blocking the nuclear translocation of a transcription factor, c-Rel. A Phase 2 trial in psoriasis has been discontinued for lack of apparent efficacy. Three Phase 2 studies have been recently completed in North America in patients with moderate-to-severe CD.[18] It is currently in Phase 2 development for treating active, moderate-to-severe RA. Results from the CD trials seem promising, although large-scale Phase 3 studies will be necessary for proper assessment of its safety and efficacy.

Although the PHOENIX trials suggest that ustekinumab is well tolerated over the course of 52 to 76 weeks, it is still a relatively short time frame to assess the safety of an immunosuppressive biologic. The concerns over long-term usage, particularly the potential risk of malignancy and infection have been addressed by the FDA, requesting an eight-year comparative follow-up study of patients receiving ustekinumab. Nevertheless, the strong clinical effectiveness of ustekinumab in treating chronic plaque psoriasis apparently justified its marketing authorization in Europe and Canada, and marketing in the US may soon follow.

References

1. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008; 58:826-50.
2. Shaker OG, Moustafa W, Essmat S, Abdel-Halim M, El-Komy M. The role of interleukin-12 in the pathogenesis of psoriasis. Clin Biochem. 2006; 39:119-25.
3. Reddy M, Davis C, Wong J, Marsters P, Pendley C, Prabhakar U. Modulation of CLA, IL-12R, CD40L, and IL-2Ralpha expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. Cell Immunol 2007; 247:1-11.
4. Butler DM, Malfait AM, Maini RN, Brennan FM, Feldmann M. Anti-IL-12 and anti-TNF antibodies synergistically suppress the progression of murine collagen-induced arthritis. Eur J Immunol 1999; 29:2205-12.
5. Liu Z, Geboes K, Heremans H, Overbergh L, Mathieu C, Rutgeerts P, et al. Role of interleukin-12 in the induction of mucosal inflammation and abrogation of regulatory T cell function in chronic experimental colitis. Eur J Immunol 2001; 31:1550-60.
6. Brok HP, van Meurs M, Blezer E, Schantz A, Peritt D, Treacy G, et al. Prevention of experimental autoimmune encephalomyelitis in common marmosets using an anti-IL-12p40 monoclonal antibody. J Immunol 2002; 169:6554-63.
7. 't Hart BA, Brok HP, Remarque E, Benson J, Treacy G, Amor S, et al. Suppression of ongoing disease in a nonhuman primate model of multiple sclerosis by a human-anti-human IL-12p40 antibody. J Immunol 2005; 175:4761-8.
8. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med. 2007; 356:580-92.
9. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371:1665-74.
10. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008; 371:1675-84.
11. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol 2008; 58:851-64.
12. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 2009; 373:633-40
13. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007; 369:1641-57.
14. Sandborn WJ, Feagan B, Fedorak RN, Scherl E, Fleisher MR, Katz S, et al. A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology 2008; 135:1130-41.
15. Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH, et al. Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study. Lancet Neurol 2008; 7:796-804.
16. Longbrake EE, Racke MK. Why did IL-12/IL-23 antibody therapy fail in multiple sclerosis? Expert Rev Neurother 2009; 9:319-21.
17. Kimball AB, Gordon KB, Langley RG, Menter A, Chartash EK, Valdes J. 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 2008; 144:200-7.
18. Burakoff R, Barish CF, Riff D, Pruitt R, Chey WY, Farraye FA, et al. A phase 1/2A trial of STA 5326, an oral interleukin-12/23 inhibitor, in patients with active moderate to severe Crohn's disease. Inflamm Bowel Dis 2006; 12:558-65.