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Ustekinumab: A New Treatment Approach for Psoriasis

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Psoriasis is a systemic, dermatological disorder with a T-lymphocyte mediated pathogenesis. This condition presents with lesions characterized by sharply demarcated, erythematous plaques covered with silvery scales. Psoriasis affects 1.4 to 4.6% of the U.S. population, or approximately 7.5 million Americans.[1-4] Annual incremental direct and indirect costs amount to $900 and $600 per patient, respectively. Additionally, the annual cost to society due to absenteeism and lost productivity sum to $9.9 billion, or $2961 per worker.[5]

The treatment of psoriasis depends on its level of severity. Mild psoriasis is treated with topical therapy including retinoids, corticosteroids and coal tar. Moderate to severe disease is treated with phototherapy or systemic therapy including methotrexate, cyclosporine, acitretin or biologics.[3,4]

Ustekinumab (Stelara™) is a new biologic treatment indicated for adults 18 and older, with moderate to severe psoriasis, who are otherwise eligible to receive phototherapy or systemic treatment. Ustekinumab is marketed by Centocor Ortho Biotech Inc. and received FDA approval in September of 2009.[6,7]

The objective of this article is to review the pharmacology, pharmacokinetics, clinical trial data, safety, dosing and cost of ustekinumab.

Pharmacology

Ustekinumab is a human IgG1κ monoclonal antibody with high affinity and specificity for the p40 protein subunit shared by IL-12 and IL-23 cytokines. Ustekinumab inhibits these cytokines from binding to the shared receptor, IL-12Rβ1, on the surface of immune cells. IL-12 and IL-23 mediate inflammatory processes in psoriasis through the development of a novel T-cell subset, T-helper 1 cells, differentiation of CD4+ T-cells and activation of natural killer and CD4+ T-cells.[1,2,6]

Pharmacokinetics

The pharmacokinetics of ustekinumab are listed in **Table 1**. Although its metabolism has not been elucidated, ustekinumab is likely catabolized into its respective amino acids and peptides. Lower median serum concentrations occur in subjects ≤100 kg compared to subjects weighing >100 kg.[6]

Ustekinumab is a pregnancy category B drug; animal studies have not resulted in significant adverse outcomes. Although there is unknown risk to infants of nursing mothers receiving ustekinumab, it has been detected in the milk of lactating monkeys. Additionally, since IgG is excreted in human milk, the assumption is that this IgG1κ monoclonal antibody will be excreted as well. When compared to young adults, differ-

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Table 1. Pharmacokinetics of ustekinumab.[6]

	UST 45 mg	UST 90 mg
Absorption	T_{max}: 13.5 days Trough [SS]: 0.31 mcg/mL	T_{max}: 7 days Trough [SS]: 0.64 mcg/mL
Distribution	V_d: 161 mL/kg	V_d: 179 mL/kg
Metabolism	NC	NC
Elimination	Cl: 1.90 to 2.22 mL/day/kg $t_{1/2}$: 14.9 to 45.6 days	Cl: 1.90 to 2.22 mL/day/kg $t_{1/2}$: 14.9 to 45.6 days

ences in pharmacokinetics, safety and efficacy are not evident in the elderly population receiving ustekinumab. Data are not available in special populations including those with hepatic or renal impairment, as well as in pediatrics.[6]

Drug interaction studies have not been performed for ustekinumab. Although its metabolic pathway is unclear, it is not expected to interact with other dugs. However, the potential effect of cytokines on CYP450 enzymes requires cautious use and potential monitoring with concomitant therapy of CYP450 substrates with narrow therapeutic indices. Additionally, live vaccines should not be administered with ustekinumab; tuberculosis BCG vaccines should be avoided during treatment as well as one year prior to and one year after therapy. Although immunosuppressants and phototherapy are indicated for moderate to severe psoriasis, there are no data to support concurrent use with ustekinumab.[6]

Clinical Trials

Five clinical trials were conducted in the development of ustekinumab: two phase 1 trials, one phase 2 trial and two phase 3 trials.[8-12] Additionally, a third phase 3 trial was conducted to compare ustekinumab and etanercept, another biologic used for the treatment of moderate to severe psoriasis (**Table 2**).[13] All trials used the Psoriasis Area and Severity Index (PASI) score which is a measure of the percent of body surface area affected, as well as gradation of erythema, induration and scaling. Response to treatment is identified as PASI-75, a 75% reduction in the PASI score.[14]

Ustekinumab received approval following completion of the two phase 3 multicenter, randomized, double-blind, placebo-controlled trials: PHOENIX 1 and PHOENIX 2.

PHOENIX 1, a 76-week study, evaluated the safety and efficacy of ustekinumab in adult subjects eligible for phototherapy or systemic therapy, diagnosed with plaque psorasis for at least 6 months, and having a PASI score of 12 or higher. The primary endpoint was the proportion of subjects achieving a PASI-75 at 12 weeks. The study was performed in different phases: a placebo-controlled phase from weeks 0 to 12, a placebo-crossover and active treatment phase from weeks 12 to 40 and a randomized withdrawal phase from weeks 40 to 76. Upon random allocation to treatment groups, subjects received ustekinumab 45 mg or 90 mg at 0 and 4 weeks and then every 12 weeks. Subjects randomly assigned to the placebo group received placebo at 0 and 4 weeks with subsequent crossover randomization at 12 weeks, with half the subjects to 45 mg and the other half to 90 mg, followed by placebo retreatment during weeks 40 to 76. At 40 weeks, subjects initially randomly assigned to receive active treatment who achieved PASI-75 at 28 and 40 weeks were re-randomized to continue active maintenance therapy or received placebo until no response was present. Subjects with little or no response at these specified times either discontinued treatment or received treatment more frequently in 8 week intervals.[11]

The primary endpoint at 12 weeks was significantly higher in both active treatments groups compared to placebo. The response rates for the 45 mg versus placebo group were 67.1% and 3.1% ($p<0.0001$), respectively. The response rates for the 90 mg versus placebo group were 66.4% and 3.1% ($p<0.0001$), respectively. Maximum efficacy was achieved at week 24 in both active treatment groups. Upon re-randomization at 40 weeks, PASI-75 maintenance was significantly better in maintenance therapy groups compared to those withdrawn from therapy ($p<0.0001$). In the maintenance therapy groups, median percentage improvement in PASI scores remained stable until 76 weeks. Rebound psoriasis events and rates were not reported, however subjects withdrawn from therapy had a median time to loss of PASI-75 of about 15 weeks. Additionally, subjects who re-initiated active treatment achieved PASI-75 scores within 12 weeks.[11]

Similar to PHOENX 1, PHOENIX 2, a 52-week study, evaluated the safety and efficacy of ustekinumab in subjects with the same inclusion criteria and primary

Table 2. Summary of ustekinumab clinical trials.[8-13,15,16]

Trial	Design	Dose	Results
Kauffman, et al.[8] (2004)	• 16-week, first in human, NR, OL, SA, DE, phase 1 trial • Subjects with mean duration of disease 13.6 to 19.7 years (n=18) • Primary objective: clinical response of single, ascending, IV administration	• UST 0.1 mg/kg (n=4) • UST 0.3 mg/kg (n=4) • UST 1.0 mg/kg (n=5) • UST 5.0 mg/kg (n=5)	PASI-75 at week 16: • 1 (25%) • 2 (50%) • 4 (80%) • 5 (100%)
Gottlieb, et al.[9] (2005)	• 24-week, MC, R, DB, PC, phase 1 trial • Subjects with moderate-severe psoriasis (n=21) • Primary objective: clinical response of single, ascending, SC doses	• UST 0.3 mg/kg (n=5) • UST 0.75 mg/kg (n=4) • UST 1.5 mg/kg (n=4) • UST 3.0 mg/kg (n=4) • PCB (n=4)	PASI-75 at week 24: • --- • --- • --- • 4 (100%) • 0 (0%)
Krueger, et al.[10] (2007)	• 32-week, MC, R, DB, PC, phase 2 trial • ≥18 YO with moderate-severe psoriasis (n=320) • Primary endpoint: proportion of subjects achieving PASI-75 at week 12	• UST 45 mg, 1 dose (n=64) • UST 90 mg, 1 dose (n=64) • UST 45 mg, multidose (n=64) • UST 90 mg, multidose (n=64) • PCB (n=64)	PASI-75 at week 12: • 33 (52%)[a] • 38 (59%)[a] • 43 (67%)[a] • 52 (81%)[a] • 1 (2%)
Leonardi, et al.[11] (2008)	• 76-week, MC, R, DB, PC, phase 3 trial • ≥18 YO with moderate-severe psoriasis (n=766) • Primary endpoint: proportion of subjects achieving PASI-75 at week 12	• UST 45 mg (n=255) • UST 90 mg (n=256) • PCB (n=255)	PASI-75 at week 12: • 171 (67.1%)[b] • 170 (66.4%)[b] • 8 (3.1%)
Papp, et al.[12] (2008)	• 52-week, MC, R, DB, PC, phase 3 trial • ≥18 YO with moderate-severe psoriasis (n=1230) • Primary endpoint: proportion of subjects achieving PASI-75 at week 12	• UST 45 mg (n=409) • UST 90 mg (n=411) • PCB (n=410)	PASI-75 at week 12: • 273 (66.7%)[b] • 311 (75.7%)[b] • 15 (3.7%)
Griffiths, et al.[13] (2008)	• 64-week, MC, R, SB, AC, phase 3 trial • ≥18 YO with moderate-severe psoriasis (n=903) • Primary endpoint: proportion of subjects achieving PASI-75 at week 12	• UST 45 mg (n=209) • UST 90 mg (n=347) • ETA 50 mg (n=347)	PASI-75 at week 12: • 141 (67.5%)[c] • 256 (73.8%)[d] • 197 (56.8%)
Gottlieb, et al.[15] (2009)	• 36-week, MC, R, DB, PC, phase 2 trial • ≥18 YO with active psoriatic arthritis (n=146) • Primary endpoint: ACR20 response at week 12	• UST 63 or 90 mg (n=76) • PCB (n=70)	ACR20 response at week 12: • 32 (42%)[e] • 10 (14%)
Sandborn, et al.[16] (2008)	• 28-week, MC, R, CO, DB, PC, phase 2a trial • Adults with moderate-severe Crohn's disease (n=104) • Primary endpoint: clinical response of 25% reduction and 70 points from baseline CDAI at week 8	• UST 4.5 mg/kg and 90 mg(n=51) • PCB (n=53)	25% reduction/70 points from baseline CDAI at week 8: • 49%[f] • 40%

AC = active comparator; **ACR20** = 20% improvement from baseline in the American College of Rheumatology measures; **CDAI** = Crohn's disease activity index; **CO** = crossover; **DB** = double-blind; **DE** = dose-escalating; **ETA** = etanercept; **IV** = intravenous; **MC** = multicenter; **NR** = non-randomized; **OL** = open-label; **PC** = placebo-controlled; **PCB** = placebo; **R** = randomized; **SA** = single administration; **SB** = single-blind; **SC** = subcutaneous; **UST** = ustekinumab; **YO** = years old.

a. p<0.001 vs. PCB
b. p<0.0001 vs. PCB
c. p=0.01 vs. ETA
d. p<0.001 vs. ETA
e. p=0.0002 vs. PCB
f. p=0.34 vs. PCB

Table 3. Adverse Events at 12 Weeks in the PHOENIX 1 and PHOENIX 2 Trials.[11,12]

	PHOENIX 1			PHOENIX 2		
	Placebo (n=255)	UST 45 mg (n=255)	UST 90 mg (n=255)	Placebo (n=410)	UST 45 mg (n=409)	UST 90 mg (n=411)
URTI	16 (6.3%)	18 (7.1%)	16 (6.3%)	14 (3.4%)	18 (4.4%)	12 (2.9%)
Nasopharyngitis	22 (8.6%)	26 (10.2%)	21 (8.2%)	29 (7.1%)	30 (7.3%)	28 (6.8%)
Arthralgia	7 (2.7%)	7 (2.7%)	6 (2.4%)	12 (2.9%)	14 (3.4%)	10 (2.4%)
Headache	6 (2.4%)	14 (5.5%)	13 (5.1%)	17 (4.1%)	19 (4.6%)	19 (4.6%)
Injection site erythema	NR	NR	NR	1 (0.2%)	6 (1.5%)	6 (1.5%)
Cough	NR	NR	NR	7 (1.7%)	3 (0.7%)	4 (1.0%)

NR = not reported; **URTI** = Upper Respiratory Tract Infection.

endpoint. The study was performed in different phases: a placebo-controlled phase from weeks 0 to 12, a placebo-crossover and active treatment phase from weeks 12 to 28 and a randomized dose intensification phase from weeks 28 to 52. After allocation to treatment groups, subjects received ustekinumab 45 mg or 90 mg at 0 and 4 weeks and then every 12 weeks. Subjects randomly assigned to the placebo group received placebo at 0 and 4 weeks with crossover randomization to the 2 active treatments at weeks 12, 16 and every 12 weeks thereafter. At week 28, partial responders to active treatment, defined as those who achieved a PASI-50 but less than PASI-75, were re-randomized to either continue receiving the active treatment every 12 weeks or to receive intensified dosing, defined as 45 or 90 mg doses given every 8 weeks. Non-responders discontinued treatment at week 28 and those with PASI-75 continued receiving the 12 week maintenance dose.[12]

The primary endpoint at 12 weeks was significantly higher in both active treatments groups. The response rates for the 45 mg versus placebo group were 66.7% and 3.7% (p<0.0001), respectively. The response rates for the 90 mg versus place group were 75.7% and 3.7% (p<0.0001), respectively. Maximum response was achieved at 20 weeks in both groups. Upon random allocation from placebo to active treatments, at week 12, response rates were similar to initial active treatment groups. PASI-75 responders at week 28 who continued to receive maintenance therapy continued to respond until week 52.[12]

Partial responders typically had higher bodyweight and longer duration of psoriasis. Compared to 12 week dosing, dosing intensification among all the re-randomized partial responders did not improve efficacy. Subjects in the ustekinumab 90 mg treatment arm had a significantly greater number of visits with PASI-75 response (p<0.014), despite lack of response to dose intensification in those receiving ustekinumab 45 mg. Subjects in the 90 mg arm also had significantly higher response rates with 8 week versus 12 week dosing (p=0.004). At week 52, this intensified treatment arm converted two-thirds of the partial responders to PASI-75 responders.[12]

Although it has not received additional indications, ustekinumab may have additional uses based on other clinical trials. A phase 2 trial conducted for ustekinumab use in psoriatic arthritis achieved significant results.[15] Another phase 2 trial has assessed efficacy and safety in Crohn's disease (**Table 2**). Although significance was not achieved for the primary endpoint at 8 weeks (p=0.34) in this trial, significance was evident at 4 weeks (p=0.02) and 6 weeks (p=0.019), as well as in a subgroup of previous infliximab users (p<0.05).[16]

Safety

Ustekinumab is well tolerated for 52 to 76 weeks. Common adverse events reported in ≥1% of individuals, at week 12 of therapy, are shown in **Table 3**. Less common adverse reactions included cellulitis and injection site reactions.[6,11,12]

Serious adverse reactions reported include serious infections, malignancies, immunogenicity, and reversible posterior leukoencephalopathy syndrome (RPLS). Ustekinumab should not be administered if a patient is at risk for or currently has an active infection, such as tuberculosis. Additionally, individuals with genetic deficiencies of IL-12 and IL-23 are more susceptible to systemic infections, so diagnostic testing should be considered. Since ustekinumab is an immunosuppressant, inhibition of IL-12 and IL-23 may increase malignancy risk. Safety in patients with a history of malignancies has not been evaluated. Anti-ustekinumab antibodies have rarely been reported in clinical trials; however, immunogenicity may develop resulting in a

trend toward lower serum ustekinumab concentrations and reduced response rate. Although RPLS was only reported in one patient during clinical trials, ustekinumab should be discontinued if a patient experiences symptoms consistent with this neurological disorder.[6]

At present, ustekinumab's safety and efficacy have not been evaluated past a 2 year interval.[6]

Dosing & Administration

Stelara™ is supplied in single-use vials as well as single-use prefilled syringes with needle safety guards. Although injections must be performed by a health care provider, its ease of administration and safety features may one day permit self-administration.

Administration occurs subcutaneously through the upper arms, gluteal regions, thighs or abdomen; sites should be rotated for subsequent injections.

Phase 3 studies indicate that the optimal, initial subcutaneous dose appears to be 45 mg for patients weighing less than 100 kg and 90 mg for patients weighing more than 100 kg. The same dose is given throughout therapy with second doses given at 4 weeks and maintenance doses every 12 weeks thereafter.[6]

Cost

According to CVS Caremark's Specialty TrendsRx® Alert, the average wholesale price of Stelara™ is $5595.60 per 45 mg/0.5mL vial. The annual cost for initial and maintenance therapy with this dose totals $33,573.60.[17]

Stelara™ Support is available for qualifying patients. Individuals with private insurance are eligible for the instant savings program which reduces co-pay, deductible and co-insurance costs. These patients can receive a savings card which entitles them to their first 3 doses at no cost; doses 4 through 6 require patients to pay $50 for every $1,050 out-of-pocket expenses, with a $3,000 maximum benefit. The program expires after 12 months or 6 doses; however extended access programs and instant rebates are available. Medicare and Medicaid patients can be directed to independent foundations through Stelara™ care coordinators. Additionally, uninsured patients who meet financial and medical criteria can receive assistance from the Johnson & Johnson Patient Assistance Foundation, Inc.[7]

Summary

Ustekinumab is a safe and efficacious treatment option for the management of moderate to severe psoriasis. The dosage regimen and route of injection may improve compliance and convenience in patients suffering from psoriasis. Continued follow-up past a two year interval is necessary to further define its safety and efficacy profile. Current data reveal a promising future for ustekinumab with potential secondary indications for treating psoriatic arthritis and Crohn's disease.

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Drug Updates

Table 1. Top Generic Drugs in 2009 by Total Rx.

Rank	Drug	Total Rx's	% Change from 2008
1	Hydrocodone/APAP	120,478,000	-0.6%
2	Lisinopril	74,544,000	6.8%
3	Simvastatin	72,966,000	21.3%
4	Levothyroxine	63,710,000	8.7%
5	Amoxicillin	51,430,000	-1.2%
6	Azithromycin	49,902,000	1.3%
7	Hydrochlorothiazide	46,403,000	-1.4%
8	Amlodipine	45,107,000	15.6%
9	Alprazolam	44,467,000	2.0%
10	Metformin	42,161,000	5.3%
11	Omeprazole	38,791,000	33.0%
12	Atenolol	37,973,000	-7.2%
13	Furosemide	36,774,000	-1.8%
14	Metoprolol	36,016,000	21.4%
15	Sertraline	30,508,000	3.5%

http://drugtopics.modernmedicine.com/drug-topics/data/articlestandard/drugtopics/252010/674982/article.pdf

Table 2. Top Brand Drugs in 2009 by Retail Dollars.

Rank	Drug	Total Retail Dollars	% Change from 2008
1	Lipitor	$5,363,193,000	-8.8%
2	Nexium	$5,014,827,000	4.6%
3	Plavix	$4,223,124,000	11.2%
4	Advair DIskus	$3,653,410,000	2.3%
5	Seroquel	$3,117,591,000	7.2%
6	Abilify	$3,083,351,000	30.0%
7	Singulair	$3,027,378,000	4.5%
8	Oxycontin	$3,020,239,000	20.7%
9	Actos	$2,531,621,000	3.4%
10	Prevacid	$2,508,555,000	-23.9%
11	Cymbalta	$2,404,353,000	10.8%
12	Effexor XR	$2,385,507,000	-10.2%
13	Lexapro	$2,334,422,000	-3.2%
14	Crestor	$2,308,138,000	37.7%
15	Zyprexa	$1,855,436,000	6.1%

http://drugtopics.modernmedicine.com/drug-topics/data/articlestandard/drugtopics/252010/264961/article.pdf

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