Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Ustekinumab: differential use in psoriasis

This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dermatology
30 June 2011
Number of times this article has been viewed

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Abstract: Chronic plaque psoriasis is a systemic disease affecting over 3% of the population, and many patients are unsatisfied with their current treatment regimen. With advances in understanding of the pathophysiology of psoriasis, new therapeutic options are being developed. The newest of these agents, ustekinumab, offers patients rapid results and the convenience of four annual subcutaneous doses, with efficacy and safety profiles comparable with those of other biologics. However, ustekinumab has been on the market in the US for less than 2 years and will require years of extensive use before the full adverse event profile is fully understood. The purpose of this paper is to summarize the treatment options currently available for psoriasis, with an emphasis on ustekinumab in order to give prescribers an overview of the available data and allow them to make educated and informed prescribing decisions.

Keywords: psoriasis, treatment, ustekinumab, safety, biologics

Introduction

Psoriasis is a dermatologic condition characterized by plaques of scales and erythema that can involve virtually any area of the body. It is now recognized also as a systemic inflammatory disorder mediated by environmental and genetic factors, affecting 2%–3% of the population, with 80% having mild-to-moderate disease.[1,2]

New breakthroughs in our understanding of the immunologic mechanisms underlying the pathogenesis of psoriasis are rapidly emerging. Research suggests that dysregulation occurs in the Th1 and Th17 T cells, resulting in persistent T cell activation and high-level expression of certain proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin (IL)-12, IL-17, and IL-23, as well as their receptors.[3–7] As the etiological pathways of psoriasis are elucidated through basic science research, new clinical therapies are being developed to counteract these pathogenic targets. Biologic therapies have transformed the treatment of psoriasis and psoriatic arthritis in the last 10 years. While not for everyone, the biologics, especially the TNF-α blockers, have certainly been shown to improve the lives of many patients with psoriasis, both physically and mentally.[8–10] However, their novel clinical efficacy comes at the price of unknown potential side effects that need to be studied and monitored closely.

Most recently, levels of both IL-12 and IL-23 have been found in higher concentrations in psoriatic plaques compared with normal skin, and genetic polymorphisms in the gene encoding the shared p40 subunit of these cytokines have been linked to psoriasis.[11–13] The newest such biologic agent released for treatment of psoriasis is ustekinumab

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(Stelara®, Centocor Ortho Biotech Services, Horsham, PA) which targets these cytokines specifically and has shown promising results in recalcitrant psoriasis.[14–17] This paper gives a brief overview of therapeutic options for psoriasis, with a specific focus on ustekinumab, including its pharmacology, pharmacokinetics, efficacy, safety, and tolerability, as well as its specific role in the treatment of psoriasis.

Conventional and biologic therapeutics

There are various treatments available for psoriasis, each with their own unique benefits and risks. Likewise, there is great variety in the patient population with psoriasis, some having very little body surface area affected, some with extensive cutaneous as well as arthritis manifestations, and others with accompanying systemic comorbidities to consider, such as heart disease, hepatitis, history of cancer, or a neurological disorder. All of these factors must be taken into account in creating an appropriate therapeutic regimen.

Topical treatments, such as corticosteroids, vitamin D analogs, retinoids, and calcineurin inhibitors, are appropriate as monotherapy for localized disease and as adjunctive therapy for resistant lesions concurrently being treated with phototherapy or systemic medications.[18] Moderate-to-severe psoriasis with more extensive or disabling symptoms, such as deforming psoriatic arthritis, requires phototherapy or a systemic agent.

Phototherapy is generally the first-line treatment, but if not feasible or effective, systemic treatments using either conventional oral agents or biologics are used. Phototherapy, specifically psoralen and ultraviolet A, narrow band ultraviolet B, and more recently excimer laser, is efficacious and cost-effective, and lacks the systemic immunosuppression that occurs with traditional systemic agents and biologics, but requires more time commitment and disrupts the patient's life.[19] Photoaging and photocarcinogenesis are long-term side effects that must also be discussed when considering light therapy.[20–22]

Traditional oral agents like methotrexate, acitretin, and cyclosporine may be considered as the next line of therapy based on their low cost, ease of oral administration, and the more long-term side effect information available. These agents require close patient monitoring, inclusive of liver and kidney function, blood pressure, cholesterol, and/or blood counts.[23–25] Biologics are another option after failure of and/or intolerance to conventional systemic drugs or when a contraindication to the use of such drugs exists.[26] The first agents developed were the TNF-α inhibitors, ie, etanercept and infliximab, that have the most clinical data available regarding safety and efficacy. Despite the success of these biologics, there remains a population of patients with recalcitrant disease, which has led to the development of ustekinumab. This will be the focus of the remainder of this review.

Pharmacology and pharmacokinetics

Unlike other biologics, such as alefacept that target memory-effector T lymphocytes, or TNF-α inhibitors, such as adalimumab, etanercept, and infliximab, ustekinumab is a human monoclonal antibody that binds to the shared p40 protein subunit of IL-12 and IL-23, preventing binding to their receptors and subsequent inhibition of downstream signaling (Table 1). Ustekinumab is absorbed and eliminated slowly, with an average half-life of 15–45 days.[27] This long half-life enables convenient subcutaneous maintenance dosing once every 12 weeks, which is more appealing to patients than twice-weekly etanercept (half-life 102 hours) or every other week adalimumab (half-life 12–14 days).[28,29] The simple subcutaneous injection is preferable to intramuscular injection of weekly alefacept (half-life 270 hours) and intravenous infliximab (half-life 8–9.5 days) infusions given as maintenance every 6–8 weeks.[30,31] Ustekinumab has fixed dosing based on body weight, with current dosage recommendations of 45 mg (for patients weighing < 100 kg) or 90 mg (for patients weighing > 100 kg) given by subcutaneous injection once at week 0 and again at week 4. This loading dose is followed by maintenance injection once every 12 weeks thereafter.[32] This regimen has been shown to maintain efficacy for at least 1 year (Table 2).[33]

Efficacy, safety, and tolerability

Ustekinumab has been approved by the US Food and Drug Administration since September 2009 for adults with moderate-to-severe plaque psoriasis. There have been a small number of randomized controlled studies of the efficacy and safety and fewer comparative studies comparing ustekinumab against other standard psoriasis therapies.

The first Phase I trial of ustekinumab involved 18 patients with moderate-to-severe psoriasis who underwent intravenous administration of the drug and showed a sustained and dose-dependent improvement in Psoriasis Area and Severity Index (PASI), with 67% of subjects obtaining a 75% reduction in PASI (PASI 75) by week 16. Clearing of psoriatic plaques was noted as early as 2 weeks

Table 1 General characteristics of biologic agents

Biologic agent	Mechanism of action	Dosage	Route	Efficacy based on Phase III trials (PASI 75)[60]	Black box warning	Cost (US$)[58]
Alefacept	Human LFA-3 fusion protein preventing CD2 binding and reducing T helper cell function	15 mg every week given as intramuscular injection for 12 weeks, with 12-week nontreatment period	Intramuscular injection	21% at week 14	None	$1190 per 15 mg injection or $4760 monthly for 3 months
Adalimumab	Human monoclonal anti-TNF antibody	80 mg the first week, 40 mg the second week, followed by 40 mg every other week given subcutaneously	Subcutaneous injection	71% at week 16	Serious infections, malignancy	$959.19 per 40 mg injection or $1918 monthly
Infliximab	Chimeric monoclonal anti-TNF antibody	5 mg/kg dose infusion schedule at weeks 0, 2, and 6, then every 6–8 weeks	Intravenous infusion	80% at week 10	Serious infections, malignancy, T cell lymphoma	Cost for 70 kg person is $3156 every 8 weeks or $1578 monthly
Etanercept	Human p75 TNF-receptor fusion protein	50 mg twice/week given subcutaneously for 3 months, then 50 mg once a week	Subcutaneous injection	3%–56.8% at week 12	Serious infections, malignancy	$498.71 per 50 mg injection or $1995 monthly
Ustekinumab	Human monoclonal anti-p40 antibody	45 mg (patients $<$100 kg) or 90 mg (patients $>$100 kg) given by subcutaneous injection once at week 0 then week 4, followed by injection every 12 weeks for maintenance	Subcutaneous injection	67.1%–75.7% at week 12	None	$5595.60 per 45 mg or 90 mg injection or $1865 monthly after first year

Abbreviation: TNF, tumor necrosis factor.

after infusion, and maximal benefit appeared at 12 weeks for the majority of subjects.[34] The second Phase I trial was a randomized, double-blind, placebo-controlled study evaluating a single subcutaneous administration of ustekinumab at doses of 0.27, 0.675, 1.35, or 2.7 mg/kg.[35] In the 24-week study, 77% of all subjects on active treatment achieved PASI 75 between weeks 4 and 24 compared with 0% in the placebo group. As a part of the study, the participants agreed to skin lesion biopsies at baseline and 1 week after administration to assess the drug's effect on the expression of proinflammatory cytokines. In subjects who had PASI 75 through week 16, the expression of IFN-γ, IL-8, TNF-α, and IL-12p40 and IL-23p19 subunits was decreased compared with baseline.[35]

A 32-week, double-blind, placebo-controlled Phase II trial was performed in 320 patients randomized to receive one of four subcutaneous dosing regimens of ustekinumab (one 45 mg dose, one 90 mg dose, 4-weekly 45 mg doses, or 4-weekly 90 mg doses) or placebo. PASI 75 at week 12 was achieved in 52%, 59%, 67%, 81%, and 2% of the aforementioned groups, respectively.[36]

Two subsequent randomized, double-blind, placebo-controlled Phase III trials, known as Psoriasis Followed by Long Term Extension (PHOENIX) 1 and PHOENIX 2, assessed the long-term safety and efficacy of ustekinumab in large patient cohorts.[37,38] The studies have a combined population of nearly 2000 patients and are set to last a total of 5 years. The PHOENIX 1 and PHOENIX 2 study designs had subjects randomly assigned to receive standard dosing of ustekinumab (45 mg or 90 mg subcutaneously at weeks 0 and 4, and every 12 weeks thereafter) or placebo at weeks 0 and 4, and subsequent crossover to ustekinumab at week 12, with half receiving 45 mg injections and the other half receiving 90 mg injections every 12 weeks. Both trials found PASI 75 improvement in more than 50% of both ustekinumab groups at week 12 (67.1% and 66.7% in the 45 mg group, and 66.4% and 75.7% in the 90 mg group vs 3.1% and 3.7% for placebo, respectively). Similar response rates after crossover at week 12 from placebo to ustekinumab treatment were also found. Maximal efficacy was observed between weeks 20 and 24.

In the PHOENIX 1 trial, patients who achieved PASI 75 were re-randomized to maintenance ustekinumab or

Table 2 Summary of ustekinumab characteristics

Indication
• Moderate-to-severe psoriasis in patients 18 years and over
Mechanism of action
• Fully human monoclonal antibody targeting shared p40 subunit of IL-12 and IL-23, downregulating inflammatory cytokine cascade
Dosage
• 45 mg (<100 kg) or 90 mg (>100 kg) injection at weeks 0 and 4, then maintenance therapy every 12 weeks
Administration route
• Subcutaneous injection
Mean time to peak serum concentration
• Approximately 12 days
Half-life
• 20–24 days
Most frequent adverse events
• Upper respiratory tract infections, nasopharyngitis, headache, and arthralgia
Cost
• US$5595.60 per injection, first annual cost US$27,980 successive annual cost US$22,384
Efficacy
• PASI 75 at week 12 based on Phase III data 67.1%–75.7%
Contraindications
• Previous hypersensitivity reaction, active tuberculosis

Abbreviations: IL, interleukin; PASI 75, 75% reduction in the Psoriasis Area and Severity Index.

withdrawal from treatment at week 40. PASI 75 response was better maintained up to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment, suggesting that long-term therapy is necessary.[37] PHOENIX 2 examined dose intensification for those subjects who did not respond fully (50%–75% improvement in PASI). At week 28, partial responders were re-randomized to continue with their current dosing regimen every 12 weeks or to increase the dose frequency to every 8 weeks. Approximately 67% of partial responders in the 90 mg group achieved PASI 75 after increasing their dosing frequency, but no clinical improvement was found in the 45 mg group with dose intensification. Partial responders tended to have higher body weight, more severe disease by physician's global assessment (PGA), longer duration of skin disease, previous failure of biologic agent(s), and a higher incidence of psoriatic arthritis.[38]

Given the relatively short time for which ustekinumab has been clinically available, safety is a major concern for patients and physicians. However, there were no significant differences in adverse events observed between the treatment and placebo groups in the major Phase II and III trials.[36–38] Patients receiving maintenance ustekinumab therapy also did not experience increased rates of adverse events compared with patients in the randomized withdrawal group.[38] Upper respiratory tract infections, nasopharyngitis, headache, and arthralgia were the most commonly reported adverse events. As with other immunosuppressants, there is concern about increased risk of infection with ustekinumab. No cases of tuberculosis, latent reactivation of tuberculosis, other mycobacterial infections, or Salmonella infections were observed. However, cellulitis and herpes zoster reactivation have both been reported with patients receiving ustekinumab.[35–38] Patients were screened for active tuberculosis before participating in all studies, and although not mandatory, most clinicians also follow this practice before starting any biologic agent.

A theoretical increase in susceptibility to malignancy was suggested in a mouse model where IL-12 was demonstrated to have antitumor activity.[39–41] Thirty malignancies were reported in 26 patients treated with ustekinumab over 100 weeks in the PHOENIX 2 trial, two of which were solid tumors and the remaining 28 were cutaneous, with no malignancies reported in PHOENIX 1.[37,38] One cutaneous malignancy was reported in the Phase II trial in the placebo group and two in the treatment groups, as well as a case of prostate cancer.[36] No differences were observed in laboratory tests between active treatment and placebo groups, including liver function tests, fasting glucose, D dimer, or hemoglobin A1c levels.[37,38]

Cardiovascular risk has also been evaluated. In the placebo-controlled portions of the Phase II and III studies, five major adverse cardiac events including myocardial infarction or stroke were reported in 1582 ustekinumab-treated patients compared with no events in 732 placebo-treated patients. All cardiac events occurred in patients with at least three established cardiovascular risk factors.[36–38] Subsequent analysis of data from the Phase II and III trials show no increased risk of myocardial infarction or stroke compared with the general US and psoriasis populations.[42] This possible increased risk of cardiac events is complicated by the fact that psoriasis patients themselves have increased cardiovascular events even without treatment.[43,44]

A single-blind, head-to-head trial of etanercept and ustekinumab in 903 patients with moderate-to-severe psoriasis was recently performed by the manufacturers of ustekinumab.[45] Patients were assigned to receive ustekinumab either 45 mg or 90 mg at weeks 0 and 4 or high-dose etanercept (50 mg twice weekly) for 12 weeks. Approximately 67.5% patients receiving 45 mg ustekinumab, 73.8% receiving 90 mg ustekinumab, and 56.8% receiving etanercept

achieved PASI 75 at week 12. Those patients who did not respond to etanercept at week 12, defined as having PGA scores ≥3, received 90 mg ustekinumab at weeks 16 and 20, and those patients who did not respond to ustekinumab received one additional dose at their original dosage at week 16.

A major flaw in this study was the use of two different outcome measures, ie, PASI 75 as the primary outcome and PGA to determine which patients did not respond to therapies. Of the 347 patients that received etanercept, 295 (85.0%) were crossed over to receive ustekinumab based on a PGA score ≥3 (vs only 43.2% achieving less than PASI 75), which is comparable with the 174 of the 209 (83.3%) patients receiving ustekinumab 45 mg and 270 of the 347 (77.8%) receiving ustekinumab 90 mg for an additional time because of PGA scores ≥3.[46] Once crossed over to ustekinumab, 40.4% achieved a PGA score ≤1, but no such data were presented for the group of nonresponders that received additional ustekinumab. The proportions of patients who had at least one adverse event were similar in all groups. The only statistically significant difference was in the number of injection site reactions, ie, 24.8% in the etanercept group and 4.3% and 3.7% in the ustekinumab 45 mg and 90 mg groups, respectively.[45] Further studies are required to evaluate the more long-term tolerability and safety of ustekinumab in these patients.

Role in therapy

Many factors must be taken into account when developing a management plan for a patient with psoriasis, including the extent of cutaneous involvement and/or presence of systemic symptoms, convenience of therapy, expected results, likely duration of remission, cost, logistics of accessing therapy (ie, transportation to light therapy or administering biologics), insurance coverage, short-term and long-term safety concerns, and any comorbidities. Risks and benefits of treatment must be weighed because minor cutaneous involvement of plaque psoriasis with little impact on patient's lifestyle is not appropriate for a treatment with side effects of possible infection, sepsis, malignancy, and heart failure, as are associated with any biologic agent. Those patients with moderate-to-severe psoriasis are suited more for these products.

Given that there has been only one head-to-head trial comparing ustekinumab with other biologics, it is difficult to comment on the order in which medications should be attempted. The target population will be further defined when additional data become available. Most importantly, side effect profiles must be reviewed in each patient's case, as well as comorbidities that may preclude use of certain agents. Cost is another issue that must be factored in because the newer agents tend not to be covered by insurance companies, and most require evidence of prior failure of a cheaper alternative. In most clinical cases, insurance companies dictate which treatments clinicians can prescribe and in which order. In this regard, many physicians will keep ustekinumab as a last resort for patients with recalcitrant psoriasis not responsive to other agents, including anti-TNF drugs. With this in mind, a study in Denmark compared response rates in TNF-α inhibitor-naïve patients and TNF-α inhibitor-experienced patients after ustekinumab, and found that a lack of response to previous anti-TNF treatment did not impair the clinical response to ustekinumab, supporting other anecdotal reports of ustekinumab used for erythrodermic patients.[47,48]

Regarding psoriatic arthritis, a multicenter, randomized, double-blind, placebo-controlled Phase II trial of 146 patients was performed by Gottlieb et al to evaluate the efficacy and safety of ustekinumab. Subjects assigned to the ustekinumab group received 63 mg or 90 mg subcutaneously weekly for 4 weeks (weeks 0–3) followed by placebo injections on weeks 12 and 16; patients assigned to the control group received placebo injections at weeks 0–3, followed by ustekinumab 63 mg at weeks 12–16. The primary endpoint was American College of Rheumatology (ACR) 20 response at week 12, that corresponds to a 20% improvement of disease criteria as determined by a rheumatologist. The ACR 20 score for the active treatment group was higher (42%) than for placebo (14%) making ustekinumab a possible option for psoriatic arthritis.[49]

The effect and safety of ustekinumab has not yet been evaluated in patients under age 18 years or in pregnancy, although administration to cynomolgus monkeys demonstrated that ustekinumab does not have adverse effects on pre- or postnatal development.[50,51] Rotational or combination therapies are often utilized in the management of psoriasis to exploit synergistic effects and minimize side effects with toxic doses. To date, there have been no trials examining the outcomes of combining traditional systemic agents or light therapy with ustekinumab, and there is only one small case series showing efficacy when combining ustekinumab with other systemics.[52] This is yet another area in need of further investigation.

Conclusion

Ustekinumab is the first agent of its class to be developed for clinical use, and it is difficult to predict its exact role in the treatment of psoriasis and psoriatic arthritis. Additional data from 5 years of the pivotal PHOENIX trials, as well as

from registries, databases, and pharmacovigilance activity, will further define the safety profile and target population for ustekinumab.[53] However, ustekinumab has a convenient and rapid onset of action, making it an attractive option for patients. Increased compliance can be inferred, which also contributes to the appeal of this agent.[54] Ustekinumab has also been shown to improve symptoms of anxiety, depression, and skin-related quality of life significantly, and can help to offset the US$4.5 billion lost annually from loss of work productivity due to psoriasis.[55–57]

Cost of medication must be considered because ustekinumab is comparatively expensive at initiation of therapy. Two doses are administered in the first 30 days at weeks 0 and 4, with an average wholesale price of US$11,192, and US$5596 every 12 weeks thereafter, yielding an annual drug cost of approximately US$27,980 in the first year for five doses and US$22,384 annually thereafter for four doses per year. This can be compared with the US$1995 monthly cost of etanercept, giving an annual cost of US$23,940.[58] Additionally, a recent cost analysis was performed, showing that the cost per responder was around US$17,842 for ustekinumab vs US$20,007 for etanercept.[59] These data suggest that ustekinumab may actually save money in the long-term compared with other biologics. Given all the data thus far on ustekinumab, careful judgment by the clinician and patient, with consideration of risks and benefits, is required to optimize efficacy and safety.

Disclosure

The authors report no conflicts of interest in this work.

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