Ustekinumab for Psoriasis and Psoriatic Arthritis

ALICE BENDIX GOTTLIEB and ARI MICHAEL GOLDMINZ

ABSTRACT. Ustekinumab, which is approved for the treatment of moderate to severe psoriasis, has been shown in phase II clinical trials to be efficacious in controlling the signs and symptoms of psoriatic arthritis. Ustekinumab appears to be well tolerated, but its longterm safety profile is not yet known. (J Rheumatol 2012;39 Suppl 89:86–9; doi:10.3899/jrheum.120253)

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TARGETING INTERLEUKIN 12 AND INTERLEUKIN 23 FOR PSORIASIS AND PSORIATIC ARTHRITIS

Th-17 and Th-1 T cells, which arise from naive CD4+ T cells under the influence of different cytokines, play a pathogenic role in psoriasis and psoriatic arthritis (PsA)[1,2]. Interleukin 12 (IL-12) and IL-23, both 2-protein chain structures that share a common p40 subunit, are produced by professional antigen-presenting cells, especially dendritic cells. Receptors for both cytokines are also 2-protein chain structures, with 1 common chain, ß1, as well as 1 unique receptor chain. In the presence of IL-12, naive CD4+ T cells differentiate into Th-1 T cells, which produce a variety of proinflammatory molecules, including tumor necrosis factor-α (TNF-α) and interferon-γ. IL-23 induces differentiation of naive CD4+ T cells into Th-17 T cells, which produce IL-17 and IL-22 as well as TNF-α. While the role of TNF-α in the formation of Th-17 and Th-1 T cell lineages is not well understood, the dramatic response of both psoriasis and PsA to TNF inhibition demonstrates the key role that this inflammatory mediator plays in the pathogenesis of both diseases[3,4]. Additionally, while some have attempted to classify PsA and other chronic inflammatory conditions as either Th-17 or Th-1 specific, there is a certain degree of overlap and interaction between the 2 pathways, making it difficult to separate them into distinct pathogenic entities. However, elevated levels of IL-23 messenger RNA (mRNA), but not IL-12 mRNA, have been demonstrated in psoriatic plaques. Genetic polymorphisms in both the p40 chain and the IL-23-specific receptor chain are also associated with increased susceptibility to psoriasis and PsA[5].

Ustekinumab, a fully human monoclonal antibody directed against the common p40 chain of both IL-12 and IL-23, is currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of moderate to severe psoriasis.

From the Department of Dermatology, Tufts Medical Center, Boston, Massachusetts, USA.

A.B. Gottlieb, MD, PhD, Harvey B. Ansell Professor of Dermatology, Chair and Dermatologist-in-Chief; A.M. Goldminz, BA, Medical Student, Department of Dermatology, Tufts Medical Center.

Address correspondence to Dr. A.B. Gottlieb, Tufts University School of Medicine, Tufts Medical Center, 800 Washington St. #114, Boston, MA 02111, USA. E-mail: agottlieb@tuftsmedicalcenter.org

USTEKINUMAB FOR PSORIASIS

Efficacy. The results of PHOENIX 1 and PHOENIX 2, a set of phase III, multicenter, double-blind, placebo-controlled trials, have been published. They tested the efficacy of monotherapy with ustekinumab in patients with moderate to severe psoriasis[6,7]. Three cohorts of patients were given either ustekinumab 45 mg, ustekinumab 90 mg, or placebo subcutaneously at weeks 0 and 4. The primary efficacy endpoint was the percentage of patients achieving a 75% decrease in the Psoriasis Area Severity Index (PASI75) at Week 12. For both trials, 3-4% of placebo-dosed patients achieved a PASI75 response. In PHOENIX 1, 67% and 66% of the ustekinumab 45 mg and 90 mg cohorts, respectively, achieved a PASI75 response at Week 12, while in PHOENIX 2, 67% and 76% achieved a PASI75 response. Most patients in both studies, maintained on the same doses of ustekinumab every 12 weeks, continued achieving a PASI75 response through the 3-year study period to date. In PHOENIX 1, quality of life was measured using the Dermatology Quality of Life Index (DLQI). At Week 28, 58.6% and 69.0% of the ustekinumab 45 mg and ustekinumab 90 mg cohorts, respectively, achieved a DLQI score of 0 or 1.

Safety. An update on the cumulative safety experience of ustekinumab in the psoriasis clinical development program, with up to 4 years followup, has been published[8]. The analysis included 3117 patients with 6791 patient-years of followup and 20% of patients treated for 4 years. This safety study was limited by its relatively small size and short duration. During the double-blind, placebo-controlled phases of clinical trials on ustekinumab, no statistically significant increase in rates of malignancies or serious infections was observed, with nasopharyngitis, upper respiratory tract infection, headache, and fatigue as the most commonly reported adverse events.

Cumulative rates of serious infections were stable over the 4 years of available safety data. Although the rate of serious infections in the ustekinumab 90 mg group was higher

than that in the ustekinumab 45 mg group, the calculated CI overlapped. Previous studies have also shown that patients with genetic deficiencies in IL-12/23 function are susceptible to disseminated infections with mycobacterium, salmonella, and bacillus Calmette-Guerin. Therefore, because of this association, screening for tuberculosis infection or exposure prior to starting ustekinumab as well as regular monitoring for reactivation during treatment is recommended.

The cumulative rates of malignancies and nonmelanoma skin cancers were stable and no statistically significant differences were seen between the 2 ustekinumab dosing groups. One case of reversible posterior leukoencephalopathy syndrome, a potentially fatal condition, was reported in a patient treated with ustekinumab. However, after discontinuation of ustekinumab and appropriate treatment, the associated signs and symptoms of headache, seizures, confusion, and visual disturbances were reversed. A full investigation also excluded demyelination and polyoma virus infection[9].

In addition, by blocking the actions of IL-12 and therefore the differentiation into Th-1 T cells, there is a theoretical risk of immune deviation toward Th-2 T cell lineages and more allergic reactions. Serious allergic reactions, including angioedema and possible anaphylaxis, have been reported with ustekinumab use[6,7].

Immunizations also may not be as effective in patients treated with ustekinumab. Live vaccination during ustekinumab treatment is contraindicated; caution is recommended for immunizing close household contacts with live vaccines.

Except for the reported phase II PsA trial with ustekinumab, combination of ustekinumab with other immunosuppressive agents or phototherapy has not been formally studied. In transgenic mice deficient in both IL-12 and IL-23 or IL-12 alone, ultraviolet-induced skin cancers developed earlier and more frequently than in healthy mouse controls.

Recently, a metaanalysis of randomized controlled trials of biologics for chronic plaque psoriasis studied the association between biologic therapies and cardiovascular events[10]. The data, collected from the literature and not the primary study databases themselves, yielded a small number of events and thus the study may be underpowered. Compared with placebo, there was no significant difference in the rate of major adverse coronary events (MACE; nonfatal myocardial infarction, nonfatal stroke, and fatal cardiovascular death). However, it was noted that 10/3179 patients receiving anti-IL-12/23 monoclonal antibodies (ustekinumab and briakinumab) experienced MACE compared with none of the 1474 patients receiving placebo (0.012 events/person-year, p = 0.12). In contrast, only 1/3858 patients receiving TNF inhibitors compared with 1/1812 patients receiving placebo experienced MACE (–0.0005 events/person-year, p = 0.94). In large practice databases, TNF blockade has been shown to decrease cardiovascular morbidity and mortality in patients with either rheumatoid arthritis (RA) or psoriasis. To further evaluate whether anti-IL-12/23 blockade increases MACE, it is essential to study large numbers of patients with psoriasis who were treated over many years and to further investigate the biological effect of IL-12 and IL-23 blockade on atherogenesis, thrombosis, and the pathogenesis of sudden death, stroke, and myocardial infarction.

PSORIATIC ARTHRITIS

TNF blockers have dramatic efficacy in controlling signs and symptoms, inhibiting disease progression, and improving quality of life in patients with PsA. However, there are many patients for whom the available TNF blockers no longer control their disease or who have contraindications to their use. Targeting the IL-12/23 pathway is an attractive alternative approach in the expanding therapeutic repertoire for PsA. There are 2 ongoing phase III studies of the effect of ustekinumab on controlling signs and symptoms, inhibiting radiographic progression, and improving quality of life in patients with PsA.

Phase III studies were based upon a successful phase II, double-blind, randomized, placebo-controlled, crossover study of ustekinumab[11]. Patients with active PsA were recruited from dermatology practices and randomized to receive either subcutaneous ustekinumab (most receiving 63 mg; a minority receiving 90 mg) at weeks 0, 1, 2, and 3, followed by placebo at weeks 12 and 16 (n = 76) or placebo at weeks 0, 1, 2, and 3, followed by ustekinumab (63 mg) at weeks 12 and 16 (n = 70). The primary endpoint was the percentage of patients achieving an ACR20 response at Week 12. The first 12 weeks were placebo-controlled and patients were followed up to Week 36. In particular, patients who had received ustekinumab at weeks 0, 1, 2, and 3 received no further treatment from Week 3 to Week 36. During the study, patients were allowed to receive nonsteroidal antiinflammatory drugs (NSAID), methotrexate (MTX) and/or oral corticosteroids under certain defined conditions. It should be noted that the patient population in this study was not comparable to those of the phase II and III studies of infliximab, adalimumab, and etanercept in PsA for the following reasons. In the ustekinumab study (1) the percentage of patients using concomitant MTX was only 20%, NSAID use was only 50%, and no oral corticosteroids were used; (2) up to 20% of patients had previously received TNF blockers; (3) baseline C-reactive protein (CRP) values and Health Assessment Questionnaire Disability Index scores were lower; and (4) polyarticular disease occurred in roughly only 30% of patients in the ustekinumab trial. These differences at baseline make comparison with the infliximab, adalimumab, and etanercept studies difficult. At Week 12, 42.1% of the ustekinumab-dosed cohort achieved an American College of Rheumatology (ACR)20 response as compared to only 14.3% of the placebo-dosed cohort. At

Week 36, that is, 33 weeks with no additional treatment, 34% or roughly three-quarters of these patients retained their ACR20 response. When the placebo-dosed cohort received ustekinumab (63 mg) at weeks 12 and 16, their ACR20 response 12 weeks later was 45%. Higher baseline CRP levels also predicted a higher percentage of ACR20 and PASI75 responders. The median percent improvement in morning stiffness at Week 12 was 0% in the placebo cohort and 50% in the ustekinumab-dosed group. No additional safety signals were observed in the PsA study compared with the psoriasis studies.

How does ustekinumab fit into the therapeutic repertoire? In choosing a treatment for psoriasis, the first question to consider is whether the patient has PsA. In patients with PsA who have failed NSAID treatment, the first choices are MTX, TNF blockers, or a combination of the two. However, while there are extensive, well-powered studies showing the additive efficacy of MTX plus TNF blockers in RA, these data do not exist for PsA. Ustekinumab can be offered as an alternative for patients who cannot take TNF blockers, whether because of contraindication or poor disease response. For patients with moderate to severe psoriasis who have failed topical treatments, the next step will be phototherapy, MTX, cyclosporine, acitretin, or biologics (TNF blockers, ustekinumab, or alefacept; Figure 1). How does one choose a biologic therapy for psoriasis? Again, the first question is whether the patient has PsA. TNF blockers remain the first-line biologics for PsA, with ustekinumab serving as a second-line therapy until more data are available. Alefacept is another FDA-approved psoriasis treatment, yet it has shown a low response rate. In patients with moderate to severe psoriasis who have failed topical treatments, TNF blockers, if not contraindicated, remain the first choice because of the longterm experience with their use and the large safety database that is available. Additionally, TNF blockers appear to be cardio-protective[12]. While ustekinumab has a high degree of efficacy, its longterm effects on patient safety are still unknown, and once determined will help shape how it is used in the treatment of psoriatic disease (Figure 2).

REFERENCES

1. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suárez-Fariñas M, Fuentes-Duclulan J, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 2007;204:3183-94.
2. Gottlieb AB, Chamian F, Masud S, Cardinale I, Abello MV, Lowes MA, et al. TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. J Immunol 2005;175:2721-9.
3. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001;357:1842-7.
4. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90.
5. Stuart PE, Nair RP, Ellinghaus E, Ding J, Tejasvi T, Gudhonsson JE, et al. Genome-wide association analysis indentifies three psoriasis susceptibility loci. Nat Genet 2010;42:1000-4.
6. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al; PHOENIX 2 study investigators. 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.
7. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al; PHOENIX 1 study investigators. 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.
8. Reich K, Papp KA, Griffiths CE, Szapary PO, Yeilding N, Wasfi Y, et al. An update on the long-term safety experience of ustekinumab: results from the psoriasis clinical development program with up to four years of follow-up. J Drugs Dermatol 2012;11;300-12.
9. Gratton D, Szapary P, Goyal K, Fakharzadeh S, Germain V, Saltiel P. Reversible posterior leukoencephalopathy syndrome in a patient treated with ustekinumab: case report and review of the literature. Arch Dermatol 2011;147:1197-202.
10. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE,

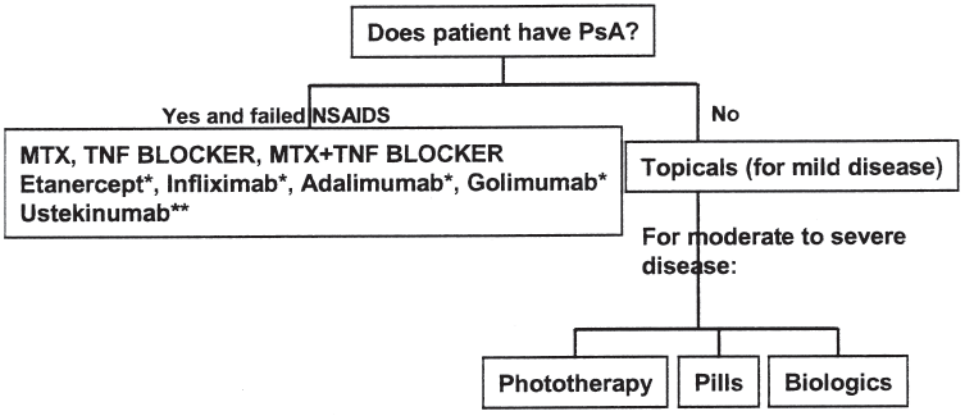

Figure 1. Algorithm for choosing a therapy for psoriasis. *Approved by the US Food and Drug Administration (FDA) for the treatment of PsA. **FDA/European Medicines Agency approved for psoriasis. PsA: psoriatic arthritis; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; TNF: tumor necrosis factor.

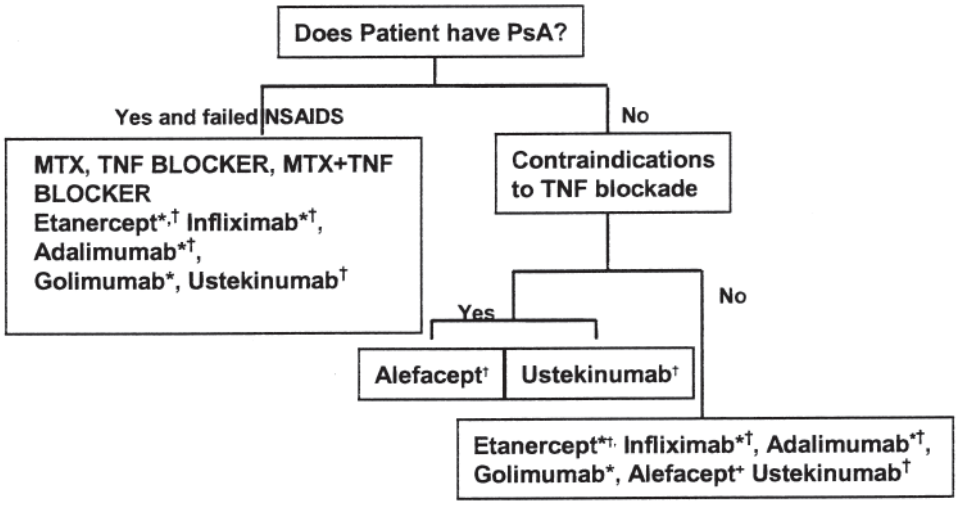

Figure 2. Algorithm for choosing a biologic therapy for psoriasis. *Approved by the US Food and Drug Administration (FDA) for the treatment of PsA. †FDA approved for the treatment of plaque psoriasis. PsA: psoriatic arthritis; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; TNF: tumor necrosis factor.

Gordon KB, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA 2011;306:864-71.

11. Gottlieb AB, Menter A, Mendelsohn A, Shen YK, Shu L, 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.
12. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al; CORRONA Investigators. Tumor necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576-82.