Panel Backs New Biologic for Treating Psoriasis

BY ELIZABETH MECHCATIE
Senior Writer

SILVER SPRING, MD. — An expert panel has unanimously recommended that ustekinumab, a novel human monoclonal antibody, be approved for treating adults with moderate to severe plaque psoriasis, but said more safety data were necessary about potential long-term risks associated with treatment, particularly malignancies.

At a meeting of the Food and Drug Administration's dermatologic and ophthalmic drugs advisory panel in June, the panel voted 11 to 0 to support approval of ustekinumab, which is made by Centocor Inc.

It also unanimously agreed that more safety data in more patients treated for a longer period of time was critical, and that the potential for malignancy linked to ustekinumab was based on the theoretical risk as well as some animal data indicating an increased carcinogenic risk within the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), which ustekinumab targets.

Ustekinumab is a first in class new entity that has not been approved for any other indication. The company has proposed that the first two doses of ustekinumab be administered 4 weeks apart, then every 12 weeks during maintenance treatment; it is administered by subcutaneous injection.

Two phase III studies compared two doses of ustekinumab with placebo in almost 2,000 adult patients who had had plaque psoriasis for at least 6 months, with baseline Psoriasis Area Severity Index (PASI) scores of 12 or higher. At 12 weeks, the proportion of patients with a PASI 75 response (at least a 75% improvement in PASI score), the primary efficacy end point, and the proportion who had a physician's global assessment (PGA) of cleared or minimal plaques, a secondary end point, were significantly greater in those on ustemnimab than in those on placebo, according to the FDA.

In one study, 67% of those on the 45-mg dose and 66% of those on the 90-mg dose achieved a PASI 75 at 12 weeks, compared with 3% of those on placebo. In the second study, 67% of those on the 45-mg dose and 76% of those on the 90-mg dose achieved a PASI 75 at 12 weeks, compared with 4% of those on placebo. In the studies, the proportion of patients who achieved a PGA of cleared or minimal plaques at 12 weeks ranged from 60% to 73% of those on ustekinumab, compared with 4%-5% in those on placebo.

Because of its mechanism of action, treatment may increase the risk for malignancies, and other adverse events, such as serious infections. In the studies, rates of serious infections and malignancies were low "and consistent with the expected background rates," said Centocor.

The FDA usually follows its advisory panels' recomendations, which are not binding. Other biologic therapies approved for psoriasis are alefacept (Amevive), efalizumab (Raptiva), infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). ■

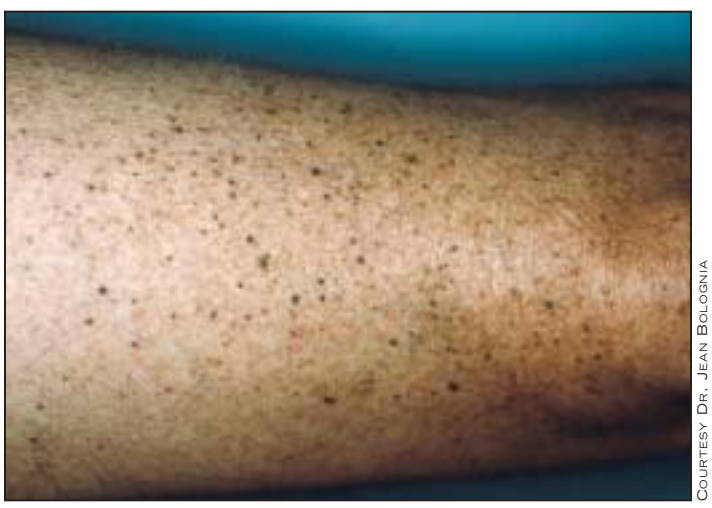
Find the Signature Nevus to Establish Phenotype, Reduce Number of Biopsies

BY CAROLINE HELWICK
Contributing Writer

NEW ORLEANS — Although the focus of checking for melanoma is usually on finding "the ugly duckling," the real challenge is to identify the signature nevus to determine the patient's particular phenotype, said Dr. Jean Bolognia.

"Identifying the signature nevus will reduce the number of biopsies you perform," said Dr. Bolognia, who discussed several varieties of signature melanocytic nevi at a dermatology update sponsored by Tulane University. She highlighted the two most challenging phenotypes—numerous lentiginous nevi, the"cheetah" phenotype, and multiple solid pink nevi—and some of the more common types, such as solid brown, eclipse, and multiple halo nevi.

The cheetah phenotype, represented by numerous small, dark nevi, can be difficult to manage, said Dr. Bolognia, professor of dermatology at Yale University, New Haven, Conn. The signature nevus is a brown-black compound or junctional lentiginous nevus that may or may not have a thin medium brown rim. The center of the lesion is extremely dark and solid, without a visible pigment pattern by dermoscopy.



COURTESY DR. JEAN BOLOGNIA

In the cheetah phenotype, seen here as a cluster of small, dark nevi, the signature nevus may have a thin, lighter brown rim.

"The patient can have 200 or more of these nevi. The anticipation is that this patient will undergo multiple biopsies, with a lower 'hit rate' for cutaneous melanoma than with other types of nevi. I share these patients with another dermatologist. Having two sets of eyes doing a skin examination is my solution to [this] phenotype."

Another difficult, though rare, phenotype is represented by multiple pink nevi. Patients with these tend to be skin type 1 or 2 and produce little, if any, melanin in their nevi.

Dr. Bolognia examines for texture and degree of erythema in these nevi. "I also look for the nevus with the darkest pink color or any red lesion [and] biopsy the latter, unless it is clearly acneiform." Again, she has another dermatologist also check the patient.

In contrast, solid brown nevi are easier to follow because they are symmetric and uniform in color, she noted. The large moles resembling fried eggs are often found on the back and are a source of concern to patients and nondermatologists. However, they are benign, and rather than labeling them as precursors of melanoma, they should be viewed as a phenotypic marker, alerting the physician the patient is at risk and should be closely examined.

A melanoma can arise in this type of nevus, so one should look for superimposed changes. Prophylactic excision is not recommended because scarring can be significant given their size and truncal location. In addition, these nevi age over time with gradual fading and formation of a skin-colored intradermal nevus centrally.

The eclipse nevi resemble a solar eclipse, with a solid tan center and a brown rim that may be stellate and discontinuous, leading to asymmetry. They are often seen on the scalp of children. "These nevi are benign but get attention because of their irregular outline and variation in color. Unless there is a superimposed change, they should not elicit concern. When the signature nevus is an eclipse nevus, you should focus on the 10 to 15 other nevi that are not in this 'family' and look for the one with the most atypical features," said Dr. Bolognia. She does not recommend surgically removing eclipse nevi because others will probably develop, but if she does biopsy, she makes sure to send the tissue to a dermatopathologist.

Multiple halo nevi are seen most often in younger patients. There are four stages of halo nevi: stages I and II, characterized by a depigmented halo surrounding either a pigmented nevus (I) or a pink nevus (II); stage III, an oval or circular area of depigmentation (with no central nevus), thus resembling a patch of vitiligo; and stage IV, which represents complete repigmentation. Getting from stage I to IV usually takes years and occurs in almost all patients. Everyone with multiple halo nevi deserves a total body skin examination. In older adults presenting with these nevi, one should also consider the possibility of an immune reaction to an ocular or cutaneous melanoma, Dr. Bolognia said. ■

Alefacept Still Useful in Psoriasis; 1 in 9 Remit

BY BRUCE JANCIN
Denver Bureau

WAIKOLOA, HAWAII — Alefacept, the first biologic agent to gain approval for treatment of psoriasis, still has a limited role to play.

"About one in nine patients will have a home run with this drug. They have … sustained remission for a long period after the last of their 12 weekly shots," said Dr. Boni E. Elewski, professor of dermatology at the University of Alabama at Birmingham. But there is no way to predict which patients will be the big responders, she told the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

Even those who don't hit a home run with alefacept (Amevive) can gain substantial benefit. The drug, a fully human fusion protein that inhibits T-cell activation and selectively reduces activated memory T cells, works slowly in clearing psoriasis but can bring further improvement for weeks after the last dose. Subsequent courses of alefacept may result in longer remission periods.

On the downside, the response rate is lower than with the anti–tumor necrosis factor–α drugs. In a phase III trial, 21% of 166 patients had at least a 75% reduction in Psoriasis Area and Severity Index (PASI) scores 2 weeks after their 12th dose of alefacept (15 mg IM). And 42% had at least a 50% reduction in PASI.

The safety profile of alefacept is quite favorable. Unlike other biologics approved for psoriasis, it isn't associated with opportunistic infections, heart failure, demyelinating diseases, psoriasis rebound, or reactivation of tuberculosis after the completion of treatment.

Dr. Elewski reserves the drug for psoriasis patients with relative contraindications or sensitivity to anti-TNF agents: those with a personal history of melanoma, an internal malignancy, heart failure, or systemic lupus erythematosus, or a personal or family history of multiple sclerosis or another demyelinating disease. "I don't give anti-TNF drugs in any patient who has had melanoma. Before I start a patient on a biologic, I look at their skin from head to toe for any atypical moles and I check for nonmelanoma skin cancer before and during biologic therapy."

The out-of-pocket expense for alefacept under Medicare Part D is at least $5,000. Patients who can't afford it are often ineligible for foundation assistance because they have Medicare. Astellas Pharma U.S. Inc., the manufacturer of alefacept, has formed the Amevive Start Assistance Program (866-263-8483) to help patients.

Dr. Elewski is a consultant to and/or investigator for Astellas, Amgen Inc., and Centocor Inc.

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