

Ustekinumab Approved With Safety Requirement

BY ELIZABETH MEHCATIE

The Food and Drug Administration's approval of ustekinumab for moderate to severe plaque psoriasis—the first interleukin-12 and -23 antagonist to be approved in the United States—is accompanied by requirements for a risk management plan and post-marketing studies that address uncertainties about the long-term safety of the biologic drug.

Ustekinumab was approved for the treatment of moderate to severe plaque psoriasis in adult patients (aged 18 and older) who are candidates for phototherapy or systemic therapy. Ustekinumab will be marketed by Centocor Inc. as Stelara.

Because of concerns over potential long-term risks of ustekinumab, which delayed approval, the FDA is requiring a risk evaluation and mitigation strategy (REMS) and postmarketing requirements that include a 5-year follow-up of patients in the clinical trials for malignancies, serious infections, and other serious adverse events; the enrollment of treated patients in a registry that will follow them for 8 years; and the establishment of a U.S.-based pregnancy registry.

Elements of the REMS include a communication plan targeted to health care providers, as well as a patient medication guide that explains the risks of treatment and will be distributed to patients with each prescription, including refills. The company is also required to provide the FDA with assessments of how well the REMS is working; such assessment will include evaluations of prescriber and patient understanding of the risks of treatment. Prescribers will also be evaluated in how well they select appropriate pa-

tients for treatment, according to the FDA's approval letter.

Ustekinumab "is the first drug that's based truly on a genetic defect recognized in psoriasis," Dr. Alan Menter, chairman of the division of dermatology at Baylor University Medical Center in Dallas, said in an interview.

Although precisely how IL-12 and -23 contribute to the pathophysiology of psoriasis is not entirely understood, "the fact is that the shared protein between them has a key role in the inflammatory aspect of psoriasis ... and we now have a drug that specifically targets that," he noted.

The most attractive features of this drug are rapid efficacy; "maintenance, if not improvement" of efficacy in most patients with continued treatment, especially through week 24 and beyond; and the convenient dosing schedule, which is every 12 weeks after the first two doses given 4 weeks apart, Dr. Menter said. Long-term safety is the "big unknown," so 5-year follow-up data are needed, he said.

Risk is a particular concern because of what happened to the biologic efalizumab (Raptiva), which was taken off the market after three cases of progressive multifocal leukoencephalopathy (PML), a progressive and often fatal brain infection, were reported in patients who were treated with the drug for psoriasis, including two fatal cases.

Another concern is that a significant proportion of psoriasis patients weigh more than 220 pounds and thus need the higher dose, which could be financially difficult for some patients, he added.

Dr. Menter was an investigator in clinical trials of ustekinumab, and is an investigator in phase III clinical trials of

ABT-874, another IL-12 and -23 antagonist for psoriasis that is being manufactured by Abbott. He said he has no financial ties to Centocor or Abbott.

The first two doses of ustekinumab are administered subcutaneously, 4 weeks apart, after which it is administered every 12 weeks; a 45-mg dose is recommended for those weighing 220 pounds or less, and 90 mg for those heavier than 220 pounds. Ustekinumab



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must be administered under the supervision of a physician.

At a June 2008 meeting of the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee, which backed the approval of ustekinumab, most of the panel favored office-based administration because it would provide an opportunity for clinicians to evaluate patients for responses and side effects every 3 months, and would help collect post-marketing data.

The wholesaler's acquisition cost or list price for a 45-mg vial of ustekinumab is \$4,663, according to Brian Kenney, a spokesperson for Centocor.

FDA approval was based primarily on two pivotal studies (PHOENIX I and PHOENIX II) of almost 2,000 patients, aged 18 years and older, who had plaque psoriasis and a PASI (Psoriasis Area and Severity Index) score of 12 or greater,

with at least 10% surface body involvement. At 12 weeks, 67% of those on the 45-mg dose and 66%-76% of those on the 90-mg dose had achieved a least a 75% reduction in psoriasis as measured by their PASI 75 response, compared with 4% of those on placebo. Response rates among those who weighed less than 220 pounds showed similar response to both doses, but those who were heavier than 220 pounds had better response rates with the higher dose.

Dr. Menter described the efficacy data as "very compelling," noting that at week 24 (8 weeks after the third injection), almost 50% of patients achieved a PASI 90.

As with the tumor necrosis factor blockers, the ustekinumab label includes warnings and precautions about the risk of serious infections and the possible increased risk of malignancies. Serious infections—including some that required hospitalization—have been reported in patients on ustekinumab. There has been one report of reversible posterior leukoencephalopathy syndrome (RPLS), a rare, potentially fatal neurologic disorder that is not caused by demyelination or a known infectious agent, according to the ustekinumab label. If RPLS is suspected, ustekinumab should be discontinued immediately and the patient should be treated.

Among the manufacturer's other post-marketing requirements is to enroll 4,000 ustekinumab-treated patients in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), and follow them for 8 years for serious infections, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune diseases, and neurologic or demyelinating diseases.

Dr. Menter is cochair of PSOLAR. ■

Antiangiogenesis Offers New Tactic for Inflammatory Disease

BY BRUCE JANCIN

BUDAPEST, HUNGARY — Topical or oral antiangiogenic therapy may offer a novel avenue of treatment in inflammatory skin diseases such as psoriasis and rosacea.

In what he described as the first proof-of-concept study to show that blocking the vascular endothelial growth factor (VEGF) receptor may provide an entirely new approach to treating chronic inflammatory skin conditions, Dr. Michael Detmar presented highlights of his research during a satellite symposium held in conjunction with the annual meeting of the European Society for Dermatological Research.

Antiangiogenesis therapy is a hot research area in oncology, as exemplified by the clinical and commercial success of bevacizumab (Avastin), a monoclonal antibody directed against VEGF-A signaling, but this approach has received surprisingly little attention for the treatment of chronic inflammatory skin diseases, noted Dr. Detmar, professor of pharmacogenomics and chair of the Institute of Pharmaceutical Sciences

at the Swiss Federal Institute of Technology Zurich.

In studying potential dermatologic applications of VEGF inhibition, Dr. Detmar and his colleagues at the Swiss institute and Novartis opted to eschew the monoclonal antibodies favored in oncology, selecting instead a Novartis small-molecule VEGF receptor tyrosine-kinase inhibitor, NVP-BAW2881.

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DR. DETMAR

The production costs for a small molecule are vastly less than for biologic monoclonal antibodies, and the small molecule can be formulated as an oral or topical agent, noted Dr. Detmar. Using a realistic transgenic mouse model of psoriasis, the investigators showed that topical application of NVP-BAW2881 addressed all three major inflammatory components of psoriasis pathogenesis: It inhibited leukocyte infiltration into the skin, reduced the abnormally large number of cutaneous blood and lymphatic vessels, and normalized epithelial architecture, curbing the keratinocyte hyperproliferation and abnormal differentiation. In effect, the VEGF receptor tyrosine kinase inhibitor essentially resolved the psoriatic phenotype, said Dr. Detmar.

In other studies using domestic pig skin, the topical

agent reduced VEGF-A-induced vascular permeability, and it inhibited contact hypersensitivity reactions and UVB-induced inflammation.

"We know the lymphatic vessels are activated in inflammation," Dr. Detmar said. "They are greatly enlarged in psoriasis and in mouse models of various chronic inflammatory conditions. The question is, what is the role of the lymphatic vessels in skin inflammation: Do they promote it, or do they try to inhibit it?"

His initial hypothesis was that lymphatic vessels promote inflammation. He and his coinvestigators put this notion to the test in laboratory mice by inhibiting lymphatic vessel function via blockade of VEGF receptor-3. This resulted in enhanced inflammation. Their hypothesis was wrong.

More recently, the investigators demonstrated that stimulation of the lymphatic vessels by chronic activation of the pathway involving VEGF receptor-3 resulted in greatly reduced skin inflammation. The mice did not develop the chronic severe psoriasislike disease for which they were genetically programmed (J. Invest. Dermatol. 2009;129:1292-8).

The satellite symposium was sponsored by Galderma SA.

Dr. Detmar reported no financial conflicts of interest in connection with his work. ■

