Ustekinumab Approved With Safety Requirement

BY ELIZABETH MECHCATIE

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 3-year follow-up of patients in the clinical trials for malignant neoplasms, serious infection, 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 patients 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 department 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 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 dermatological 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.

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 psoriaticlike disease for which they were genetically programmed (J. Invest. Dermatol. 2009;129:1294).

The satellite symposium was sponsored by Calderma SA.

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