Address PML Symptoms

Efalizumab *from page 1*

individuals, the virus remains latent throughout life and is present in the kidneys, lymphoid tissue, and sometimes, the bone marrow.

The virus can be reactivated by immunosuppression. "HIV and organ transplant patients have a lot of issues with PML. So do immunocompromised cancer patients." Dr. Chapman noted.

A negative PCR test for polyomavirus JC DNA in the cerebrospinal fluid indicates a psoriasis patient should not be at increased risk for PML with efalizumab. But how many patients are going to get a lumbar puncture as a precondition for starting efalizumab, particularly when there are a range of effective alternative biologic therapies for psoriasis? Presumably not many of the estimated 45,000-50,000 patients who are now on efalizumab.

"We're going to have to reevaluate our niche for efalizumab, considering this PML issue," Dr. Chapman observed.

Rather than calling in his patients specifically to discuss PML, Dr. Chapman said that he is bringing it up when they come in for their routine quarterly visit. Of the seven patients thus far with whom he has had the discussion, all have opted to stay on the drug for now, although they made clear this is not a final decision.

For patients who elect to stay on efalizumab, dermatologists will need to periodically inquire as to the emergence of PML-like symptoms—such as ataxia, dementia, visual field changes, limb weakness—and make a prompt neurology referral for any suspicious findings.

Survival following a diagnosis of PML averages 6 months.

Dr. John Y.M. Koo said he's heard from many physicians in the San Francisco Bay area who've run into tremendous difficulty with severe psoriasis rebound in attempting to transition patients from efalizumab to various other therapies. It has been a problem even in trying to switch to adalimumab (Humira), a particularly fast-onset biologic.

"In my personal experience, by far the most effective treatment to minimize rebound with [efalizumab] is cyclosporine. It makes sense because cyclosporine really goes after the T cells, and the mechanism of rebound is thought to involve activated T cells moving into the skin," he said.

"A nonwimpy dose—5 mg/kg—is the best choice. But if someone has been on [efalizumab] for many years, even cyclosporine doesn't guarantee that the patient won't end up with a horrendous rebound," said Dr. Koo, professor and vice chairman of the department of dermatology at University of California, San Francisco.

All three panelists disclosed receiving research grants from and serving as consultants to and/or on the speakers bureaus for multiple manufacturers of biologic agents for psoriasis.

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Efalizumab Risk Advisory Issued

BY ELIZABETH MECHCATIE

Three confirmed cases and one possible case of progressive multifocal leukoencephalopathy in patients treated with efalizumab for psoriasis have triggered the Food and Drug Administration to issue a public health advisory.

In the advisory, the FDA warned that the cases of progressive multifocal leukoencephalopathy (PML)—a rare, usually fatal brain infection—occurred in patients aged 47-73 years treated with efalizumab (Raptiva) for moderate to severe plaque psoriasis for more than 3 years.

Two of the patients with confirmed PML and the patient with suspected PML died. None of the patients were on other immunosuppressive drugs. Efalizumab was approved for adults with moderate to severe plaque psoriasis in 2003.

The FDA advisory noted that the agency is reviewing information "and will take appropriate steps to ensure that the risks of Raptiva do not outweigh its benefits; that patients prescribed Raptiva are clearly informed of the signs and symptoms of PML; and that health care professionals carefully monitor patients for the possible development of PML."

According to the advisory, physicians should "carefully monitor patients on Raptiva, as well as those who have discontinued the drug, for any signs or symptoms of neurologic disease, and … periodically reassess the benefits of continued treatment." Patients should be familiar with the symptoms of PML, and should be told to contact their health care providers "immediately" if they experience any of the symptoms.

The association between PML and efalizumab was first reported by the FDA in October 2008 in a letter to health care practitioners. The letter noted that a 70-year-old man who had been treated with efalizumab for over 4 years was diagnosed with PML, and the drug was also suspected in a second case of PML in a 62-year-old man.

At that time, the agency announced that a boxed warning would be added to the label of efalizumab regarding the risk of PML and other potentially fatal infections associated with treatment. The agency also announced that the manufacturer, Genentech Inc., had been asked to develop a Risk Evaluation and Mitigation Strategy (REMS) for the drug, which would include a patient medication guide distributed with each prescription (including refills) that would explain treatment risks.

Genentech wrote in a statement "We take the risk of PML very seriously and are working diligently with the FDA to put the right plans in place that will help protect patient safety. We are evaluating all possible approaches to address the risk of PML with Raptiva use including a risk minimization plan. It is premature to disclose the scope of our plans until we've reached a formal agreement on these plans with FDA."

In an interview, Dr. Craig L. Leonardi, who has been involved with the research of efalizumab since 1999, said most dermatologists have been taking their patients off efalizumab, especially those who have been treated for more than 3 years.

"It appears that this is a drug you cannot use safely over time," said Dr. Leonardi, who believes that the drug is the cause of PML, which does not seem to be related to the age of the patient, but more with the length of treatment.

This is "a very rare and devastating infection that is almost uniformly fatal and as such, has to be taken very seriously," said Dr. Leonardi of the department of dermatology at Saint Louis University. He disclosed that he is an adviser and speaker and has been an investigator for Genentech but owns no stock.

Only a handful of his patients opted to continue treatment after being appraised of the risk. Efalizumab might be used in an "extraordinary" circumstance where a patient with severe psoriasis cannot take a TNF-antagonist because of a history of multiple sclerosis, and they have failed methotrexate, cyclosporine, and phototherapy and had no good options left, said Dr. Leonardi.

The FDA advisory is available at www.fda.gov/cder/drug/advisory/efalizumab.htm. Possible cases of PML and other adverse events associated with the drug can be reported to the FDA's MedWatch program at www.fda.gov/medwatch/index.html. A copy of Genentech's letter is available at www.gene.com/gene/products/information/immunological/raptiva/. ■

Biologics Have 'Therapeutic Niche' in Pediatric Psoriasis

BY DIANA MAHONEY

Most pediatric cases of psoriasis are mild and can be managed adequately with combinations of topical medicines, but some cannot, according to Dr. Kelly M. Cordoro.

"The true challenge exists in treating the subset of children who present with severe, rapidly evolving, and debilitating generalized plaque or pustular psoriasis and/or psoriatic arthropathy," said Dr. Cordoro of the department of dermatology at the University of California, San Francisco.

The management of this subset of patients "requires immediate response with the utilization of systemic medications that are neither well studied nor [Food and Drug Administration] approved for this indication in children," said Dr. Cordoro, who discussed such medications in a presentation at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation in Maui.

Targeted therapies that are aimed at specific components of the inflammatory cascade, such as anti–tumor necrosis factor agents, are widely used in adults with psoriasis and psoriatic arthritis.

Off-label use of the three TNF antagonists has demonstrated some promise in children with severe disease.

DR. CORDORO

Although none of the three TNF antagonists that have received FDA approval for adult psoriasis—etanercept, infliximab, and adalimumab—have been approved for pediatric psoriasis, off-label use of these agents has demonstrated some promise in children with severe disease, Dr. Cordoro said in an interview.

"Etanercept has the most significant published literature, and the fact that the drug has received FDA approval for use in children for other indications [ankylosing spondylitis and psoriatic arthropathy for children aged 2 years and older, and juvenile rheumatoid arthritis in children aged 4 years and older] substantiates recommendations for its use in the pediatric psoriasis population," she said.

A recent, randomized controlled trial showed that etanercept can safely and effectively reduce disease severity in children and adolescents aged 4-17 years who have moderate to severe plaque psoriasis (N. Engl. J. Med. 2008;358:241-51).

Biologic agents have also been used in the treatment of children with generalized pustular psoriasis, a serious and rare form of the disease that can be fatal.

With respect to drug safety, "critical evaluation of the potential risk of the anti-TNF agents in children with psoriasis is difficult because of the small number of children treated and the short follow-up period," Dr. Cordoro said.

Even so, "because the known side effect profiles of traditional systemic agents used for severe psoriasis in children [including methotrexate, cyclosporine, and acitretin] are unacceptable, the documented benefits of the TNF inhibitors in children affected by severe, debilitating psoriasis create a therapeutic niche for these agents," she said.

Dr. Cordoro reported having no conflicts of interest with respect to her presentation.

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