

# Black Box Recommended for Elidel and Protopic

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ROCKVILLE, MD. — The Food and Drug Administration's Pediatric Advisory Committee has recommended the addition of a black box warning to the prescription labels of topical formulations of pimecrolimus and tacrolimus because higher systemic exposure in children and infants may lead to malignancies. The topical agents are indicated for the treatment of mild to severe atopic dermatitis.

Pimecrolimus cream 1% (Elidel), manufactured by Novartis Pharmaceuticals, is indicated for short-term and long-term intermittent therapy for mild to moderate atopic dermatitis (AD) in nonimmunocompromised patients aged 2 years and older. Tacrolimus ointment (Protopic) is made by Fujisawa Healthcare Inc., and is indicated for moderate to severe AD. Only the 0.3% strength is approved for use in children aged 2 years and older. (Protopic is also available in a 1% strength.)

Both drugs are nonsteroidal, calcineurin inhibitors and immunosuppressants, with an unknown mechanism of action.

While neither drug is approved for children under age 2 years, according to FDA data collected between June 2003 and May 2004, almost 2 million prescriptions were dispensed to pediatric patients in the United States and patients aged 1-2 years accounted for 8% and 13% of all tacrolimus and pimecrolimus prescriptions, respectively. Prescriptions by nondermatologists now account for the majority of the use of pimecrolimus.

## Inappropriate Prescribing

Panel members were adamant that these treatments should be used strictly as indicated, but recognized off-label prescribing as a problem. "As recently as a couple of weeks ago I had an 8-week old who had been treated with one of these. Whether it's indicated or not, it's happening," said

Roselyn Epps, M.D., chief of the division of dermatology at Children's National Medical Center, Washington.

"The increasing use may be related to aggressive and inappropriate advertising with portrayal of these products as safer than steroids and the implication that they can be used as first-line therapy and for unlimited periods of time," Jean Temeck, M.D., acting medical team leader with the FDA, said in a written statement.

High blood levels of the agents are more frequently seen in children, says the FDA, and higher systemic exposure may be related to a greater surface area to mass ratio.

Since topical tacrolimus was approved in 2000 and topical pimecrolimus in 2001, there have been seven reported cases of lymphoma in patients. One was in a patient of unreported age, and one in a 2-year old.

Topical immunosuppressants may trigger malignancies by "breaking local immune surveillance resulting in skin cancers. [Tacrolimus and pimecrolimus] draining from atopic skin into regional lymph nodes may result in immunosuppression," Bindi Nikhar, M.D., of the FDA's division of dermatologic and dental drugs, said at the meeting. She was critical of the "steroid-free" statements contained in aggressive direct-to-consumer advertising by the drug makers.

## Black Box Alternatives

The panel debated several prescriber-targeted tactics, before voting for a black box warning. Suggestions of beefed up surveillance via a registry, professional organization letters with electronic alerts, and CME courses appeared problematic and insufficient. A "Dear Health Care Provider" letter was also deemed inadequate, as the committee wanted to be sure that the message of the increased cancer risk would be continuous and widespread.

A patient medication guide (MedGuide) dispensed by the pharmacy was preferred for patient-targeted information.

## Manufacturers' Opposition

Drug company representatives strenuously objected and claimed the black box warning would be based primarily on animal studies. Novartis is conducting two large, long-term safety studies of pimecrolimus use in infants, with regular reviews by an independent body. The company is also in the midst of a 10-year registry study of children, with "yearly evaluation of the data." For tacrolimus, there is a long-term "pharmaco-vigilance" study being conducted outside of the United States, and another long-term safety study going on in Europe. A 10-year, multinational registry study is being initiated this year focusing on tacrolimus and children, with regular evaluations for cutaneous and systemic malignancy risk.

In a prepared statement, Novartis agreed that "patients suffering from mild to moderate eczema need to be informed about the safe and effective use of Elidel Cream 1%, but we believe a recommendation to add a black box warning to the label is unsubstantiated by clinical evidence and experience in more than 5 million patients worldwide."

## The Panel's Concerns

"There is no evidence of systemic immune suppression or increased risk of malignancies," said M. Joyce Rico, M.D., senior medical director with Fujisawa. "There is minimal blood absorption after topical application, and most patients have blood levels less than 0.5 ng/mL, with no systemic accumulation."

However, the FDA gave several examples from adverse event reports of children with high blood levels of tacrolimus or pimecrolimus after the therapies were greatly reduced or halted. "The most significant case was that of an 8-month-old male who developed eczema herpeticum with Pseudomonas sepsis and subsequent cardiac arrest. Protopic ointment was applied over his entire body for 6 months. The serum

tacrolimus level was 3.5 ng/mL 2 weeks after Protopic had been discontinued. The patient survived," Dr. Temeck said.

The manufacturers maintain that no causal relationship has been proved between the ointments and malignancies; a position echoed in FDA documents.

Latency was another concern among the panel members, and they debated the possibility of serious adverse events developing several years after discontinued use. "If we are going to be observing lymphomas in this patient population, it's not going to be a spurt of B-cell lymphomas . . . there's going to be a longer period of observation that we need in order to conclusively say that we are going to see an increased incidence trait," said Victor Santana, M.D., of the department of hematology/oncology at St. Jude Children's Research Hospital, Memphis. He also claimed the preclinical data were more convincing of causality.

Dr. Epps expressed further concern that health care providers without dermatologic experience may not provide adequate follow-up care for patients who have used the topical treatments, and that "many don't necessarily know what they're treating." Specifically, there are skin syndromes for which pimecrolimus and tacrolimus should not be used. They include molluscum, ataxia-telangiectasia, syndromes with eczema, or those that already carry an increased risk of infection or malignancies.

One dissenting panel member said that a black box warning would exert an unnecessary burden on patients and consumers. "The human data presented don't convince me there's a clear risk . . . The data have not been collected for a sufficient length of time, but I'm weighing that against the argument that it could cause a lot of grief in the parents of the people who have to take these medications. That potential level of grief is unwarranted given the data," said Dennis Bier, M.D., professor of pediatrics, Baylor College of Medicine, Houston. ■

# Check for Infection With Frequent Atopic Dermatitis Flares

BY SHERRY BOSCHERT  
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KOHALA COAST, HAWAII — A secondary infection may be at the root of atopic dermatitis flares, Timothy G. Berger, M.D., said at a conference on clinical dermatology sponsored by the Center for Bio-Medical Communications Inc.

In many patients, the flares are due simply to severe disease. But Dr. Berger looks for secondary infection as well as four other factors to find opportunities to intervene. He listed the five factors in descending order: noncompliance (for example, the patient is tired of taking medications, leading to a flare); secondary infection; photosensitivity; allergic or contact dermatitis; or conversion to cutaneous T-cell lymphoma.

Of the five factors, infection is where most of the action is when sleuthing the cause of atopic dermatitis flares, said Dr. Berger, professor of clinical dermatology at the University of California, San Francisco. Infection is "an axis of atopic dermatitis that we tend to undertreat," he said.

He described a typical case: a 47-year-old man with moderate to severe chronic atopic dermatitis who had a 3-week-long severe flare of disease at presentation. He had extensive excoriations, redness, focal erosions, and crusts. He had been on and off systemic steroids to treat atopic dermatitis flares several times in the past.

When you see crusts or erosions, get cultures. This patient's culture grew methicillin-resistant *Staphylococcus aureus* (MRSA) even though he had no association with

traditional avenues for exposure to MRSA such as intravenous drug use or stays in a hospital, nursing home, or prison, he said.

Doxycycline is recommended by infectious disease specialists as the first choice for treating MRSA because 95% of MRSA strains will be sensitive to the drug. Minocycline is an alternative, but is a bit more expensive, he said.

Second choice for treatment would be trimethoprim-sulfamethoxazole (TMP/SMZ), except in patients with AIDS, who are almost guaranteed to have a strain of MRSA resistant to TMP/SMZ, Dr. Berger said.

He adds rifampin to one of these drug choices for a better shot at success with combination therapy. He usually prescribes doxycycline 100 mg b.i.d. for 10 days plus rifampin 600 mg/day

for 5 days to treat atopic dermatitis flares related to MRSA.

Clindamycin also can be a good therapeutic option, but if the culture produced bacteria resistant to erythromycin, the MRSA will have a gene for inducing resistance to clindamycin. These patients will start to improve on clindamycin only to relapse.

Linezolid also is an option "if your patient is Bill Gates," because it's extremely expensive, Dr. Berger said. Don't use macrolides or cephalosporins, because of high rates of resistance in MRSA. Avoid quinolones, because the infection tends to recur, leading to overuse of these drugs, he added.

Dr. Berger's MRSA patient improved dramatically on doxycycline-rifampin combination therapy but returned 1 month later with another flare and cultures

again showing MRSA. Dr. Berger sent him home with a repeat prescription and a swab to get samples from his girlfriend's nose and groin. Cultures showed that the girlfriend carried MRSA and infected the patient.

"When the axis is along infection and patients flare, I look into family members and close contacts," and treat them, he said. "That stabilizes their disease."

In similar situations, be sure to ask if the female partner uses oral contraceptives, because rifampin will interfere with the pills' effectiveness, he cautioned. Dr. Berger treated the patient's girlfriend with doxycycline and mupirocin (instead of rifampin). The patient's atopic dermatitis now is stable, and he has stopped intermittent systemic steroids because his flares have ended. ■