Primary Care Cuts Use of Calcineurin Inhibitors

BY BRUCE JANCIN
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KOLOA, HAWAII — The Food and Drug Administration's black box warnings issued earlier this year for the topical calcineurin inhibitors have had a major impact on prescribing by primary care physicians but very little effect on how pediatric dermatologists use the drugs, panelists agreed at the annual Hawaii dermatology seminar, sponsored by the Skin Disease Education Foundation.

"My impression is that those of us who work at the pediatrics/dermatology interface haven't changed our practice patterns as much as the pediatricians have since this whole controversy developed. We didn't use these drugs first line very much in the first place, whereas the pediatricians were using pimecrolimus as first-line therapy for many skin conditions, including cases of diaper dermatitis, for example. They've rushed away from that—and I think appropriately so," said Dr. Ilona Frieden of the dermatology and pediatrics departments at the University of California, San Francisco.

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DR. COHEN

Some primary care physicians have gone to the opposite extreme in response to the black boxes for pimecrolimus (Elidel) and tacrolimus (Protopic). Dr. Elaine C. Siegfried recalled a recent telephone call from a nurse inquiring about the fine points of using tar in severe atopic dermatitis. The nurse was resorting to this time-honored but messy and unpleasant therapy because the pediatric group where she works has forbidden the use of topical calcineurin inhibitors (TCIs) altogether.

It's ironic that these physicians feel more comfortable in prescribing tar—a well-known carcinogen and a therapy that defines the low extreme of the elegance scale—than the TCIs, for which there is no proof of serious toxicity, observed Dr. Siegfried, a pediatric dermatologist at St. Louis University.

Dr. Lawrence F. Eichenfield said he's doing a couple of things differently since the FDA action. One is spending more time counseling patients and reassuring those who have developed what he considers unwarranted fear and panic as a result of the FDA black box warnings, which he characterized as placing "unusual emphasis on systemic risks despite low systemic effects" of these topical agents.

The other change is that he now pushes harder to see how little maintenance therapy a patient can tolerate after the atopic dermatitis is under control. Patients vary enormously in this regard. He tries decreasing the frequency of therapy with the topical calcineurin inhibitors and introducing prescription-free periods.

But although the black box warning states that TCIs are to be used for short periods of time and not continuously, "I may go months and months and months before I try a break in the action" in severely affected patients, explained Dr. Eichenfield, professor of pediatrics and dermatology at the University of California, San Diego.

Dr. David E. Cohen shares a copy of the black box warning with his patients, pointing out to them that despite the dire reports they may have read in the newspaper or on the Internet, the FDA concedes there is no persuasive evidence of serious harm due to the drugs. But he urged physicians not to resort to signed informed consent forms in an effort to reduce medicolegal liability.

"I don't do signed letters for the innumerable patients I put on cyclosporine, a drug which has real risks, or for methotrexate, or for the biologics. I always document our discussion of the genuine risks, but I'm not getting signed letters for those things, so I don't know why we'd need to do it for TCIs, where the first line on the warning is, 'Although a causal relationship has not been established . . . " said Dr. Cohen, director of allergic, occupational and environmental dermatology at New York University.

The panelists indicated they continue to use TCIs in selected patients less than 2 years old despite the black box warnings not to do so.

"Children under age 2 often have the worst disease. I don't think we should be afraid to use the drugs there. We have to do what's in our patients' best interest. I certainly don't use TCIs as first-line [therapy]. If a patient will respond to topical corticosteroids, I'm there.

"But there are lots of patients whose lives are miserable, and I do believe that the TCIs are safer than putting kids on systemic cyclosporine, methotrexate, or systemic steroids. So you need to use a risk/benefit model," said Dr. Sheila Fallon Friedlander, of the pediatrics and dermatology departments at the University of California, San Diego.

The product labeling indicates tacrolimus 0.03% is second-line therapy in children older than 2, and tacrolimus 0.1% carries an indication as second-line treatment in adults. Dr. Eichenfield shared a dramatic albeit anecdotal demonstration suggesting that the 0.1% formulation is the more effective one in children.

"We were involved in some of the early tacrolimus studies in children. In between the time the studies were completed and the drug was approved, the company allowed children who'd been enrolled in the trials to continue to use the 0.1% ointment in open-label fashion," he recalled.

"When approval came with the differential recommendations based on age, we switched the kids to 0.03% to try to be on label. Probably 30% of the kids who'd been in excellent control flared within 2 months. So, yeah, I think there's a dose-dependent effect. We try to stay on-label, but the more severe the patient's disease is, the more I'll go right to the 0.1%," Dr. Eichenfield said.

Dr. Eichenfield, Dr. Siegfried, and Dr. Friedlander serve as consultants to numerous pharmaceutical companies, including Novartis, which markets pimecrolimus. Dr. Frieden is on the speakers' bureau for Novartis.

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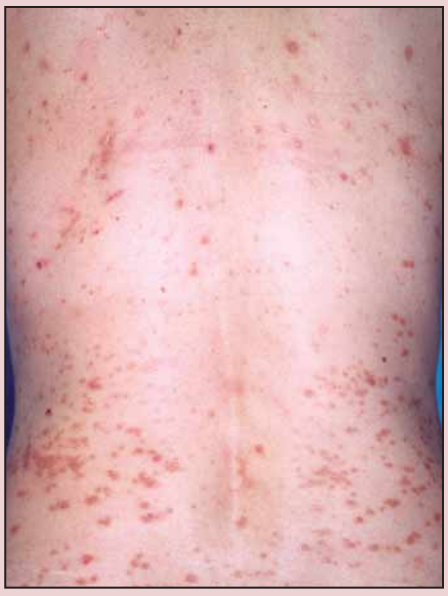
DERM DX

A 42-year-old woman presented with a 2-month history of disseminated, intensely pruritic erythematous papules that had initially appeared on her trunk. The lesions were round and up to 0.5 cm in diameter. She had been treated with topical and systemic corticosteroids, with little effect. What's your diagnosis?



COURTESY DR. MIRA KADURINA

Laboratory evaluation revealed leukocytosis, with 10%-28% eosinophils, anemia, and an elevated erythrocyte sedimentation rate. Histology findings included hyperkeratosis, irregular acanthosis, and a mixed inflammatory infiltrate of lymphocytes, plasmocytes, and numerous eosinophils. Thrombosis of small vessels in the dermis and edema of the vessel walls was also noted.

Immunohistochemical staining of tissue specimens from this patient revealed the presence of CD43-positive and CD4-positive cells, as well as CD8-negative and CD20-negative lymphocytes.

No cause for her eosinophilia could be identified, despite a meticulous search. Reactive eosinophilia, which can occur with parasitic infections, and clonal disorders of the bone marrow associated with eosinophilia, (e.g., various types of leukemia), were ruled out. The diagnosis therefore was idiopathic hypereosinophilia syndrome.

Some investigators have proposed that idiopathic hypereosinophilia syndrome is a Th2-mediated disease characterized by clonal expansion of a T-cell population able to produce interleukin (IL)-5 and IL-4. Pathogenic T cells—usually CD3 negative, CD4 positive—display an aberrant surface phenotype.

The clinical presentation is heterogeneous and includes myeloproliferative and lymphocytic variants. In the more aggressive myeloid variant, patients can have chromosomal abnormalities, hepatosplenomegaly, cardiac complications, and myeloid malignancies. The prognosis is poor, said Dr. Mira Kadurina of the Military Medical Academy in Sofia, Bulgaria.

The lymphocytic variant may be a primitive lymphoid disorder characterized by nonmalignant expansion of an IL-5–producing T cell population. Cutaneous manifestations can include pruritus, eczema, erythroderma, and urticaria.

She was treated with prednisone, 60 mg/day, which was gradually tapered to 15 mg/day over a month's time. After treatment was withdrawn, she again developed disseminated, erythematous, pruritic lesions, this time involving the hands and feet. The fingers became painful, cyanotic, and swollen, initially after exposure to cold. A painful ulcer appeared on the third finger of the right hand.

Raynaud's phenomenon, identified by capillaroscopy, was an unusual cutaneous complication of the idiopathic hypereosinophilia syndrome in this patient, Dr. Kadurina wrote.

The administration of methylprednisolone, 60 mg/day, and pentoxifylline, 800 mg/day, led to a remission; the corticosteroid dosage was tapered to 5 mg/day over 45 days.

During 3 months of follow-up, no new lesions appeared, the vasoconstriction of the patient's hands disappeared, and the finger ulcer healed.

One explanation for the development of Raynaud's phenomenon and digital gangrene, in association with hypereosinophilia, is that major basic protein and eosinophil cationic proteins located within the eosinophil granule matrix contributed to the formation of microthrombi.

Efforts continue to further explicate the pathogenesis. "Future progress in unveiling variants of the syndrome is likely to consign to history the term idiopathic, replacing it with an array of well-defined hematologic disorders," Dr. Kadurina wrote.

—Nancy Walsh

DR. KADURINA *reported this case as a poster at the 14th Congress of the European Academy of Dermatology and Venereology.*