Editorial

The New Therapeutic Dilemma in Pediatrics

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Topical calcineurin inhibitors (ie, tacrolimus ointments 0.03% and 0.1%, pimecrolimus cream 1%) have revolutionized the way in which pediatric and adult patients are treated for atopic dermatitis (AD). Patients have been pleased to have an alternative to topical corticosteroids, which are not always effective. Furthermore, parents have requested that physicians prescribe topical calcineurin inhibitors for their children to avoid the feared side effects of corticosteroids (eg, growth suppression, cutaneous atrophy). Critics refer to parents harboring these fears as *steroid phobic*, especially because the Pediatric Advisory Committee (PADAC) of the US Food and Drug Administration (FDA) reviewed adrenal suppression studies in October 2003 that demonstrated no growth suppression with certain class 4 or weaker nonfluorinated topical corticosteroids approved by the FDA for use in children.[1] Physicians also may be steroid phobic, promoting parental fears of relatively safe short-term use of topical corticosteroids.

From June 2003 to May 2004, 4.9 million prescriptions for calcineurin inhibitors were dispensed, half a million for children aged 1 to 2 years.[2] The number of prescriptions for calcineurin inhibitors for pediatric patients has increased by 47% for pimecrolimus cream and 16% for tacrolimus ointment in this time span, in part because of the fear of topical corticosteroids.[2]

Because of a societal milieu of consumer fear and rising class action litigation regarding cyclooxygenase-2 inhibitors, the FDA has continued to revise the postmarketing evaluation committee process. These committees are responsible for relabeling or removing approved medications from the market when new adverse events are reported. Two such advisory committees are coming to the forefront of media attention: the new Drug Safety Oversight Board[3] and the existing PADAC.

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On February 15, 2005, the PADAC met and voted to add a box warning to topical calcineurin inhibitors that labeled the drugs as having a potential risk for lymphomas and skin cancers,[4] which was followed by the posting of a public health advisory for physicians and consumers.[5] The committee's decision was based on cutaneous animal studies available when these medications were approved for pediatric use and on a recent unpublished oral pimecrolimus study in monkeys.[6] The initial cutaneous studies submitted to the FDA served as the basis for carcinoma risk noted with the original FDA labeling. In a recent Novartis-conducted study, monkeys who ingested oral pimecrolimus developed lymphoma; however, blood levels of pimecrolimus in the monkeys were 30 times the maximum seen with human topical application, and the monkeys' high blood levels were maintained for 39 weeks.[6] In addition to these data, a few reports of eczema herpeticum and malnutrition in patients taking calcineurin-inhibitors were acknowledged by the PADAC, though these problems also are seen in untreated patients with AD.[7] Furthermore, the PADAC failed to adequately acknowledge that there are good data showing that delayed-type hypersensitivity and immunoglobulin production with vaccination are preserved in children with AD treated with calcineurin inhibitors,[8] even with oral tacrolimus.[9,10]

Since topical tacrolimus was approved for moderate to severe AD in December 2000,[2] more than 9.5 million prescriptions for calcineurin inhibitors have been dispensed in the United States.[2] Only 7 cases of lymphoma caused by these agents have been reported worldwide, with one case involving a 2½ year old.[2] Does a single case of pediatric lymphoma constitute a true biological potential? On the flip side, topical corticosteroids will rightfully regain their status as first-line agents for AD; however, topical corticosteroids do not have cancer registry data supporting a status of less risky biological potential.

The FDA will soon decide how to act on the recommendations of the PADAC and the Division of

Pediatric Drug Development.[11] The intentions of the PADAC are good (eg, keeping the public informed, limiting off-label use in children younger than 2 years, establishing pediatric cancer registries for the labeled medications). However, the incidence of AD has tripled in the past 3 decades.[12] With rising incidence has come an increase in moderate to severe disease and an increase in the absolute number of corticosteroid-resistant patients. These corticosteroid-resistant patients can achieve a better quality of life and less sleep disturbance with topical calcineurin inhibitors. Will these patients now develop phobias to topical calcineurin inhibitors and miss out on a better life because of animal studies that have not been corroborated in human clinical trials?

In upcoming months, physicians prescribing calcineurin inhibitors will have to balance unsubstantiated fears and the realities of patients in need. Although patients deserve to be told about animal studies such as the study reported by Novartis and other pharmaceutical companies,[6] how can they wade through the "deep" science of these studies when no scientist can fully extrapolate extremely high-dose sustained oral challenges in animals to human topical therapy? This is further exacerbated by the absence of significant blood levels of calcineurin inhibitors in most patients after a few days of application, when the skin barrier is repaired. A lack of drug levels in the blood suggests no appreciable risk of systemic side effects.

In my own practice, I received an onslaught of telephone calls from patients by mid-day February 16, 2005. I established a "script" for myself on calcineurin inhibitors. I share my knowledge of the available human and animal data on calcineurin inhibitors, the indication for the medication prescription, the concepts of biological potential versus scientific proof and follow-up with alternative therapeutics available, and the risk-benefit profile of the alternatives. The patient and I make a decision regarding continuation or discontinuation of the calcineurin inhibitor based on all these factors. Practitioners should prepare themselves for the next few months; they will surely be marked by consumer fear and an increase in the number of calls they receive.

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