

**Pediatric Advisory Subcommittee to the Anti-Infective Drugs Advisory Committee
Open Meeting
October 29-30, 2003**

Overview

Atopic dermatitis (AD) is a chronic inflammatory disease of the skin that most commonly presents in early childhood. Lifetime prevalence of AD is approximately ten to twenty percent in children, and one to three percent in adults; recent evidence suggests that the occurrence of AD is on the increase. At the October 29th and 30th meeting of the Pediatric Advisory Subcommittee to the Anti-Infective Drugs Advisory Committee, the Subcommittee will be asked to consider the risks associated with two classes of drugs that are approved for the treatment of AD and similar conditions, and the management of these risks in pediatric patients. Each day will focus on issues for a specific drug class. We will then ask you to discuss and advise the FDA on the risk assessment and possible risk management strategies for hypothalamic pituitary adrenal (HPA) axis suppression from treatment with topical corticosteroid preparations on Wednesday, October 29, and long term monitoring for cancer occurrence among pediatric patients treated for AD with topical immunosuppressants (the calcineurin inhibitors) on Thursday, October 30.

To prepare you for these deliberations, you will hear a series of presentations from FDA staff and outside experts. Topics to be covered on the 29th include: an overview of AD (including a review of therapeutic options); a review of the diagnosis and management of acquired HPA axis suppression secondary to corticosteroid use; a summary of available evidence on the occurrence of this complication; and general approaches to risk assessment and risk management of these drug products. On October 30th, speakers will discuss the calcineurin inhibitor drug class (including a review of the toxicology evidence that suggests a cancer risk), and research issues inherent in the evaluation of this complex epidemiological issue.

This briefing book provides additional background material on these issues, including several recent review articles, relevant drug labels, post-marketing safety reviews, and other relevant information. FDA encourages meeting participants to review the drug labels and the FDA review documents first, and then turn to the literature provided. Additional background on the issues to be discussed is provided below.

On the afternoon of October 29, you will also hear from Dr. Solomon Iyasu, Medical Team Leader with the Division of Pediatric Drug Development. Per section 17 of the Best Pharmaceuticals for Children Act, Dr. Iyasu will report on adverse events for the following drugs that were granted market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act: Zyrtec (cetirizine), Busulfex (busulfan), Cozaar (losartan), Nolvadex (tamoxifen), Accupril (quinapril), and Serzone (nefazodone). We have included the labels for each of these drugs in your background package so you can review them prior to the meeting.

Introduction

Topical corticosteroids have long been available over-the-counter and by prescription in varying concentrations and in a variety of vehicles. Some topical corticosteroids are approved

for use in pediatric patients down to three months, while others may not be approved for pediatric use at all. In addition to their labeled use, topical corticosteroids are frequently used in a manner that is off-label for the treatment of AD and other steroid-responsive dermatoses in pediatric patients.

Among the adverse events associated with topical corticosteroid use, the most serious is HPA axis suppression, which in some circumstances, can be life threatening. The occurrence of HPA axis suppression with topical corticosteroid use has come to light following recent efforts to strengthen pediatric labeling of these products, when clinical trials in pediatric patients demonstrated significant levels of HPA axis suppression among those enrolled.

Within the last three years, topical immunosuppressants (the calcineurin inhibitors tacrolimus and pimecrolimus) were approved for second line treatment of AD in patients two years of age and older when these patients fail to respond to, or are unable to tolerate, other approved therapies. Prior to the approval of topical preparations of these drugs, calcineurin inhibitors have been approved for use as systemic immunosuppressants in organ transplant recipients. In these patients, systemic treatment has long been known to increase the risk of skin cancers and lymphomas.

The preclinical and clinical studies of the topical calcineurin inhibitor formulations suggested that these drugs may increase cancer risk in the pediatric population. The latency period between exposure to a cancer-causing agent and occurrence of a tumor is long, usually ten years or more, and the tumors of concern are rare in children and young adults. Both of these factors make timely post-marketing safety monitoring to identify increased cancer risk extremely difficult. None-the-less, the approval of the topical immunosuppressants for treatment of AD in children included a post-marketing commitment to conduct a registry study to assess risk for developing cutaneous or systemic malignancies among pediatric patients who undergo long-term intermittent treatment with these drugs.

Topical Corticosteroids

Exogenous corticosteroids can suppress the HPA axis, resulting in decreased circulating adrenocorticotropin (ACTH) levels, atrophy of glucocorticoid-secreting cells in the adrenal cortex, and secondary adrenal insufficiency. Pediatric patients with dermatitis being treated with steroid creams, lotions, and ointments may be at risk for this potentially life-threatening adrenal suppression.

Even relatively short-term therapy with topical corticosteroids can suppress the HPA axis such that a normal stress-related increase in serum cortisol fails to occur. The FDA has reviewed studies of adrenal suppression using an adrenal stimulation test in pediatric patients treated with topical corticosteroids for corticosteroid responsive dermatitis. A subnormal rise and/or peak in serum cortisol concentrations following adrenal stimulation with synthetic ACTH (cosyntropin, 1-24 ACTH, or CortrosynTM) was used to establish the diagnosis of secondary adrenal insufficiency. Adrenal suppression among some of the study participants occurred in the clinical studies reviewed for drug approval. These data will be reviewed at the meeting.

The potential for topical steroid preparations to have systemic effects such as HPA axis suppression depends on absorption and systemic exposure. Absorption of topical medications is dependant on several factors, including molecular size, charge and partition coefficient of the active drug ingredient, concentration of ingredients, solvents used in the marketed substances, duration of application, amount of body surface area treated, degree of inflammation of skin (i.e. integrity of barrier to percutaneous penetration), and occlusion of site treated. In addition, pediatric patients may be at higher risk than adults for systemic exposure because of their higher surface area to body volume ratio.

HPA axis suppression from the topical steroid use may generally go unnoticed and may resolve without consequence as the skin heals or when topical corticosteroid use ceases. However, pediatric patients who are suppressed from topical steroid use and experience a significant physiologic stress (such as trauma, surgery, or serious infection) may have life-threatening complications from their suppression (including death) which are preventable if the suppression is recognized and treated appropriately with stress doses of glucocorticoids.

The diagnosis of HPA axis suppression secondary to topical steroid use in pediatric patients may easily be missed. The FDA is concerned that the public does not understand the potential systemic risks from topical steroid use, and may fail to inform their health care providers of use of a steroid cream, lotion, or ointment. Such failure to report could result in a missed diagnosis of HPA axis suppression, suboptimal treatment, and potentially serious adverse consequences for the patient.

While topical corticosteroids are an essential part of the armamentarium used in treating corticosteroid responsive dermatoses in pediatric patients, use of some topical corticosteroid products, even as labeled, could pose a potential risk of HPA axis suppression. While the life-threatening consequence of this risk may be rare because a physiologic stress must occur concurrent with adrenal suppression, clinical recognition of HPA axis suppression is critically important because, once recognized, this complication is easily managed with stress doses of systemic corticosteroids. Though the current labeling for these products includes precautions about this risk and highlights the likelihood of this adverse event in pediatric patients, the FDA would like public discussion as to whether additional approaches to risk management of HPA axis suppression secondary to use of topical corticosteroids are needed.

Topical Immunosuppressants

The mechanism of action of topical immunosuppressants in AD are not known, though these drugs are known to inhibit T cell activation and prevent the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE. The clinical significance of these findings is not known. Patients with AD are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption). Treatment with topical immunosuppressants may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

Children developed lymphadenopathy in clinical studies of the approved immunosuppressants. These events were usually related to infections and resolved following appropriate antibiotic therapy. Concern does remain however, because the oral administration of

immunosuppressants, where systemic exposure is much greater than that which results from topical application, is associated with lymphoproliferative disorders.

Topical immunosuppressant use shortened the time to skin tumor formation in an animal photo-carcinogenicity study, however clinical studies did not demonstrate similar photo-carcinogenicity in humans. The significance of this finding in pediatric patients is unknown, and the FDA would like to consider how to best monitor pediatric patients for potential skin cancer risk from these products over the long term.

Topical immunomodulators are not recommended for use in pediatric patients below the age of 2 years. Infants enrolled in studies of the immunosuppressants had an increased incidence of some adverse events compared to vehicle. These adverse events included pyrexia, URI, nasopharyngitis, gastroenteritis, otitis media, and diarrhea. In addition to these differences in infection observed in the Phase 3 trials, the effects of topical immunosuppressants on the developing immune system in infants are unknown.

Summary

Topical corticosteroids and topical immunosuppressants are now widely used by pediatric patients. Both of these drug classes are important components of the armamentarium for atopic dermatitis. While each of these drug classes provide benefit to pediatric patients, they each also have a different set of risks.

At the Pediatric Advisory Subcommittee meeting, you will be asked to consider the risks associated with two classes of drugs that are approved for the treatment of these conditions, and the management of these risks in pediatric patients. Issues to be discussed include:

- How to best develop and conduct a risk management program for prevention of life threatening HPA axis suppression secondary to the use of topical corticosteroid preparations;
- How to communicate this risk to pediatric patients and their families, as well as child health care providers and others; and
- How to best design a long term follow up registry program to evaluate the potential cancer risk from exposure to topical immunosuppressants.

The FDA relies on the knowledge, judgement, experience, and wisdom of scientists and practitioners such as yourself to help it determine how to move forward and address newly emerging issues related to drug safety. Thank you for your time and effort, and we look forward to seeing and hearing from you on October 29 and 30.

Susan K. Cummins, MD, MPH
Medical Team Leader
Division of Pediatric Drug Development