Topical tacrolimus and malignancy risk: Should the theory be put to rest?

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For 2 decades, topical calcineurin inhibitors (TCIs) have been United States Food and Drug Administration-approved mainstays of therapy for atopic dermatitis (AD). Every seasoned dermatologist can discuss their off-label experience using TCIs with good evidence for their efficacy—vitiligo, psoriasis of the face, genitals, and intertriginous regions; seborrheic dermatitis, contact dermatitis, oral lichen planus, lichen sclerosus, morphea, and cutaneous lupus.[1]

This commentary focuses on topical tacrolimus (although likely applicable to pimecrolimus).

The mechanism of action of TCIs is by suppressing production of inflammatory cytokines, by initially binding to macrophilin-12 (aka FK506 binding protein [FKBP]) in the cytoplasm of target cells. Additionally, TCIs inhibit mast cell and neutrophil activation, with pimecrolimus exerting its action on T cells and mast cells, whereas tacrolimus also reduces the function of basophils and eosinophils, and inducing Langerhans cell apoptosis. This explains the broad anti-inflammatory effect of tacrolimus.[2]

Hanna et al state, "Despite the demonstrated benefits of TCIs in treating atopic dermatitis (AD) in adult and pediatric populations, and notwithstanding the considerable evidence that had been collected on their safety and tolerability, use of TCIs decreased sharply in 2005, when national and international regulatory authorities, notably the US FDA, took public action to inform patients and physicians of a potential risk for malignancy with TCIs as a result of postmarketing case reports of cancer (skin and lymphoma)."[3] According to Fiorillo et al, "Despite the large body of evidence and extensive clinical experience with these agents, there remain concerns among parents and clinicians regarding the long-term safety of this class of therapy, particularly with respect to the boxed warning about the potential risk of lymphoma and malignancy associated with TCIs."[4]

Abbreviations used:

AD:	atopic dermatitis
FKBP:	FK506 binding protein
TCI:	topical calcineurin inhibitors
US FDA:	United States Food and Drug Administration

In this issue of the *Journal of the American Academy of Dermatology*, Paller et al[5] report the results of an observational prospective cohort study quantifying incident malignancies during 10 years in children with AD who used topical tacrolimus for ≥6 weeks. Standardized incidence ratios for cancer events were analyzed relative to sex-, age-, and race-matched control data from national cancer registries. A total of 7954 eligible patients enrolled, and 2125 patients completed the study. During 44,629 person-years, 6 confirmed incident cancers occurred (standardized incidence ratio, 1.01). Six events in 6 individuals were deemed incident cancers—a cutaneous tumor (Spitzoid melanoma), and 5 other cancers: chronic myeloid leukemia, alveolar rhabdomyosarcoma, carcinoid tumor of the appendix, spinal cord neoplasm, and malignant paraganglioma. No keratinocyte carcinomas or incident lymphomas were observed. Despite the ongoing controversy whether AD itself is a risk factor for malignancy, the authors concluded that the cancer incidence was as expected, providing

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no support for the hypothesis that topical tacrolimus increases long-term cancer risk in children with AD.[5]

The black box warning for tacrolimus ointment states: "Although a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors." For years I have advised ignoring this warning to diminish parental fear and increase drug adherence. Perhaps this study will serve as the impetus to eliminate the black-box warning—a maneuver that will benefit both providers and patients.

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