

TIMs for AD: What are the Risks?



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Atopic dermatitis (AD) is a chronic, relapsing inflammatory disease affecting approximately 15% of the pediatric population. The spectrum of disease is variable from mild-to-severe forms with a significant medical, psychological and financial impact on the affected children and families. Multiple concomitant interventions are required to control the disease, such as:

- allergen avoidance,
- moisturization,
- control of inflammation (using anti-inflammatories such as topical corticosteroids and/or topical immunomodulators) and
- control of pruritus.

Historically, topical corticosteroids have been the mainstay of anti-inflammatory treatment. In December 2000, the FDA approved topical tacrolimus ointment 0.03% for use in children over two-years-of-age and 0.1% for patients over 16-years-of-age with moderate-to-severe AD. In 2001, the FDA approved pimecrolimus 1% cream for patients over two-years-of-age with mild to moderate AD. In February 2005, the FDA issued a public health advisory regarding the potential increased risk of carcinogenicity with topical immunomodulators (TIMs) and recommended a black box warning. The warning was based on circumstantial evidence, such as high rates of off-label prescriptions (13% of pimecrolimus and 8% of tacrolimus prescriptions in the US were for children under two-years-of-age), dose-dependent carcinogenicity in animals and post-marketing reports of malignancies.

Despite advice from professional associations (American Academy of Dermatology, American Association of Asthma Allergy and Immunology and the Canadian Dermatology Association), the warning was followed by a change in labeling on January 19th, 2006. Currently, the label contains a black box warning about a possible risk for lymphomas and cutaneous malignancies. The FDA recommended using TIMs as a second line therapy for unresponsive patients, limiting their use to short and intermittent therapy, avoiding them in patients with an impaired skin barrier who may have increased absorption, in immunocompromised patients and patients under two-years-of-age.

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Scientific data

Increased malignancies, including skin cancer, have been well documented in post-transplant patients who require long-term systemic tacrolimus.¹ The implicated mechanism of cancer development is primarily a viral-related neoplasia (i.e., Epstein-Barr virus and papilloma virus) as a result of systemic immunosuppression.

A similar mechanism is to be expected in the case of topical application of immunomodulators. Therefore, to understand the risk of neoplasia after topical application of immunomodulators, we need to:

1. Establish the possible mechanisms of neoplasm formation in patients with AD
2. Evaluate the magnitude of the problem
3. Ascertain if the reported neoplasms in patients using TIMs were compatible with the proposed mechanisms

Pro-tumour mechanisms

Several mechanisms leading to neoplasm formation have been postulated:²

- a. Increased predisposition as a result of the AD
- b. Increased mutagenesis or genotoxicity as a result of TIMs
- c. Absorption of TIMs leading to systemic immunosuppression
- d. Local inhibition of immunosurveillance
- e. Any combination of the above

To date, it is unclear if patients with AD have an increased risk of tumour formation, particularly lymphoma. Depending on age, the risk of lymphoma development in the general population ranges from 0.1% to 1%.³ No studies separated AD patients from non-AD patients. In a few studies specifically looking at AD, the odd ratios of developing lymphoma were approximately 1%.⁴ The second possible mechanism, direct carcinogenicity of TIMs, was not demonstrated in any of the lab studies. However, animal data suggests that rodents treated with high doses of oral tacrolimus and pimecrolimus developed lymphomas. This risk cannot be transposed to humans because the doses used were 26 times to 47 times higher than the recommended human doses, the vehicle was ethanol and rodents have thinner skin

which increases their chances of systemic absorption.⁵ Moreover, the type of tumours that developed in animals suggested a systemic effect of TIMs similar to the tumours that developed in post-transplant patients. In humans, systemic absorption after topical application of tacrolimus and/or pimecrolimus is minimal and indirect evidence of prolonged immunosuppression, such as altered responses to vaccination, delayed hypersensitivity or increased rates of infections, have not been documented in any studies to date.⁶⁻⁸ The fourth mechanism has not been elucidated.²

As of June 2006, 29 cases of TIMs related neoplasias have been reported with seven of those reported in children.

Post-marketing tumour data

As of June 2006, 29 cases of TIM-related neoplasias have been reported (19 related to tacrolimus, 10 to pimecrolimus) with seven of those reported in children (four with pimecrolimus and three with tacrolimus).⁹ Thirteen of the tumours were lymphomas and the remainder were cutaneous tumours (squamous cell



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Take-home message

1. Currently, there is no evidence of an increased risk of cancer with the use of topical pimecrolimus and tacrolimus
2. More long-term controlled studies are needed to assess the real risk of neoplasia
3. Patient education about the pros and cons of TIMs will alleviate unnecessary fears and prevent under-treatment

carcinoma, melanoma, *etc*).⁹ An independent panel of experts analyzed the reported data in the lymphoma cases and concluded that causality (based on site of development, B-cell morphology, presence of EBV, timing of tumour development) could not be demonstrated in any of the spontaneous reported cases.¹⁰ The true magnitude of the problem is hard to evaluate at present, because all of the cases are spontaneous reports that lack scientific rigor and large population-based comparison rates are lacking.

Summary

Although theoretically possible, the association between neoplasia formation and chronic use of TIMs is not currently supported by the available data. Since black box labels are based on direct evidence rather than on a potential risk, the current labeling is not warranted. However, more controlled, long-term studies are needed, particularly in the pediatric population, given the potentially higher systemic exposure and increased susceptibility. Until this data become available, it is advisable to use TIMs for the approved indications, in the appropriate concentrations (0.03% tacrolimus in those two-years-of-age

to 16 years-of-age and 0.1% in > 16-years-of-age and 1% pimecrolimus in those older than two-years-of-age).

The black box labeling shifted the swing towards non-treatment, leading to poor quality of life of the affected children. It is a physician's duty to:

- alleviate unnecessary fears and explain scientific data to their patients/families,
- be vigilant about potential complications,
- accurately report should any side effects occur and
- stay informed about safety data.

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