CANADIAN DERMATOLOGY ASSOCIATION POSITION STATEMENT

TOPICAL CALCINEURIN INHIBITORS

The Canadian Dermatology Association (CDA) produced a position statement on the use of topical calcineurin inhibitors in 2005. The statement was in response to a US Food and Drug Administration (FDA) Pediatric Advisory Committee expression of concern about a theoretical risk of malignancies in pediatric patients treated for atopic dermatitis with topical calcineurin inhibitors.

The Pediatric Advisory Committee statement followed a meeting to discuss the risk evaluation, labeling, risk communication and dissemination on potential risks among pediatric patients treated for atopic dermatitis with topical calcineurin inhibitors. During this meeting all available data collected from clinical programs and post marketing surveillance were examined for evidence of increased risks of cancer development, particularly lymphoproliferative conditions. Representations were made by the manufacturers of these products at the time, and independent testimony from experts in lymphoma and immunology were heard. The Committee recommendation to the FDA was that topical calcineurin inhibitor labels should include a "black box" warning. The Therapeutic Product Directorate (TPD) of Health Canada recommended that a "Dear Doctor" letter be sent to all physicians in Canada outlining these concerns. Both of these steps were taken.

By 2005, topical calcineurin inhibitors had been studied collectively in over 38,000 subjects, including 14,000 children under the age of 17 years. Furthermore, over 6.7 million patients have used either tacrolimus or pimecrolimus since approval for market. At that time there had been two cases (squamous cell carcinoma and colonic carcinoma) reported with pimecrolimus; and no cases reported with tacrolimus in the clinical trial programs. In the spontaneous reporting programs, there are six cases (four lymphomas, two nonmelanoma skin cancers) reported with pimecrolimus; and nine cases of lymphoma with tacrolimus and 10 other types of tumors. The expected incidence of lymphoma within the clinical trial programs is 3; and the expected incidence of lymphoma in the spontaneous programs is 61. None of the cases of malignancy were reported in children less than two years old.

In the ensuing 12 years significant amounts of data have been added to the medical literature that has failed to show any increase in lymphoma, leukemia or other malignancy rates in patients treated with the topical calcineurin inhibitors (tacrolimus and pimecrolimus). In fact, one published study noted that the lymphoma incidence in the topical pimecrolimus-exposed population is up to approximately 54-fold less than that seen in the general population.[1]

An update of the evidence for topical calcineurin inhibitor use and lymphoma use published in 2013 showed the number of malignancies and lymphomas observed both in post-marketing surveillance and reported to the FDA using its adverse events reporting system “is much lower among topical calcineurin inhibitor-exposed patients than the expected number for the general population. Furthermore, among children enrolled in post-marketing pediatric registry studies for both tacrolimus and pimecrolimus followed for up to 5.5 years or 6.5 years respectively, the observed number of malignancies and lymphomas is very low and similar to the number expected for a sample of similar size in the general population.”[2] The same year, the Canadian Society of Allergy and Clinical Immunology published a position paper stating “there is no current published evidence showing that topical calcineurin inhibitors clearly predispose to malignancy.”[3]

In 2015, the Cochrane network published a review of topical tacrolimus use for atopic dermatitis in 20 studies involving 5885 subjects and did not find any evidence associating the risk of malignancy with use of the drug.

After a review of most current data[4,5,6,7], the CDA Pharmacy & Therapeutics Advisory Board concludes that there continues to be no evidence of increased malignancy rates in adult and pediatric patients treated with topical calcineurin inhibitors. We note that this mirrors the conclusions of our international colleagues from the American Academy of Dermatology, the European Academy of Dermatology & Venereology Eczema Task Force and the Asia-Pacific Consensus Group for Atopic Dermatitis.

The CDA believes that topical calcineurin inhibitors are an important therapeutic class for the treatment of atopic dermatitis in children and adults. The CDA believes that the FDA and TPD recommendation for a warning of this nature remains unsupported by medical evidence and ever broadening clinical experience.

For topical calcineurin inhibitors:

- There is no evidence of an increased rate of lymphoma when compared to the general population.
- The clinical and histological patterns of the observed lymphomas are not consistent with typical immunosuppression- related lymphomas.
- There is minimal absorption of topical calcineurin inhibitors, with non-detectable or negligible blood levels, making long-term intense immunosuppression unlikely.
- There is no evidence of interference with effectiveness of immunization, delayed hypersensitivity skin responses, or rates of systemic infections.

The CDA will continue to monitor the situation closely in the future, in order to best safeguard the skin care needs of Canadians.

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