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Topical Calcineurin Inhibitors and Malignancy Risk

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Abstract

Context: The approval of topical calcineurin inhibitors (TCIs) has been a significant breakthrough for the treatment of atopic dermatitis due to much lower systemic absorption and not causing skin atrophy even after long-term use that have made them become popular replacements for topical corticosteroids being almost equally effective. In January 2006, the US food and drug administration (FDA), followed later also by the European medicine agency (EMEA), issued the "black box" warning causing controversy regarding a potential increased risk of lymphoma in patients with atopic dermatitis and treated with TCIs.

Evidence Acquisition: PubMed and MEDLINE® databases were systematically searched utilizing a variety of terms relating to the subject matter. Articles written only in English over the past 15 years were analyzed and selected for review.

Results: So far, no scientific evidence of the association has been found between use of TCIs, and increased incidence of skin cancers and lymphomas in patients with AD. The systematic review and meta-analysis by Legendre et al. found the role of TCIs unlikely to be a significant risk factor of lymphoma in those patients.

Conclusions: Despite an extensive body of evidence regarding the TCIs safety, the box warning still remains leaving the physicians and patients unduly uncertain and confused about the safety of TCI use.

Keywords: Topical Calcineurin Inhibitors, Skin Cancer, Lymphoma

1. Context

Topical calcineurin inhibitors (TCIs) are nonsteroidal, immunosuppressive agents approved for the treatment of atopic dermatitis (AD) in patients in whom topical corticosteroids (TCSs) have failed or are contraindicated. Two TCIs are tacrolimus ointment (trademark Protopic) and pimecrolimus cream (trademark Elidel). Tacrolimus ointment was approved by the FDA in December 2000 as second-line for short-term and intermittent long-term therapy in patients with moderate to severe atopic dermatitis (AD); 0.03% for patients $\geq$ 2 years of age and 0.1% for patients > 15 years of age (1). One year later, in December 2001, pimecrolimus cream 1% was approved by the FDA for the similar indication in patients $\geq$ 2 years of age for the treatment of mild to moderate AD (2). Off-label use includes treatments for lichen planus, psoriasis, pyoderma gangrenosum, vitiligo, seborrheic dermatitis, cutaneous lupus erythematosus, lichen sclerosus and allergic contact dermatitis (1, 2). Both TCIs are macrolactams; tacrolimus, naturally produced by the fungus-like bacterium *Streptomyces tsukubaensis*, originally developed as a systemic immunosuppressant, and pimecrolimus, chemically modified derivate of asomycin produced by *Streptomyces hygroscopicus*, developed specifically to treat inflammatory skin conditions (3, 4). Their main immunosuppressive effect involves inhibition of T-cell activation and proliferation as well as pro-inflammatory cytokines and mediators production by blocking the activity of the enzyme calcineurin. In comparison with TCSs, TCIs show higher immunomodulatory selectivity and 70- to 100-fold lower transepidermal penetration without compromising skin barrier even after long-term use since they do not affect fibroblast function and collagen production (5-7). According to available data, they appear to be equally or more effective than mild TCSs and equally or slightly less effective than potent TCSs in controlling AD. Tacrolimus ointment, especially 0.1% preparation, appears to be more effective than pimecrolimus cream although it may also cause greater local adverse effects of which are the most frequently reported transient skin burning, erythema and pruritus (1, 2, 7). Considering lower potential for systemic absorption than that of topical corticosteroids and high efficiency in aim to avoid potential TCSs side effects, TCIs soon became the first significant alternative to topical corticosteroids in the treatment of AD. Despite numerous side effects associated with chronic use of potent TCSs including skin atrophy, striae, rebound dermatitis, teleangiectasie as well as adrenal suppression, and Cushing's syndrome topical corticosteroids still remain a mainstay of AD treatment (8).

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1.1. The US FDA "Black Box" Warning for TCIs and FDA Comprehensive Review of TCIs Safety

Due to the increasingly off-label use in children as first-line treatments for atopic dermatitis, and in children younger than two years, in February 2005, the FDA's pediatric advisory committee (PAC) recommended "black box" warnings for tacrolimus ointment and pimecrolimus cream indicating potential malignancy risk including skin cancers and particularly lymphomas (9, 10). Safety concerns were based on possible risk of systemic absorption, potential carcinogenic mechanism of action, data from animal studies, malignancy reports in the FDA's adverse reporting system, and high association between systemically administered tacrolimus and increased cancer risk in organ transplant patients (6, 7, 11). In January 2006, despite very low incidence of lymphoma in clinical trials and post-marketing surveillance (no higher than in general population), the FDA accepted the PAC's recommendation and placed a boxed warning on the prescribing information for these medications. FDA concluded, without establishing definitive causal link, that the risk is possible and compelling (7, 11). Although the indication for the use of TCIs in clinical practice remained the same, the labeling was updated with a black box warning of a potential cancer risk, strictly clarifying that this drug should be used only as "second-line" therapy for the short-term and non-continuous treatment of AD in non-immunocompromised patients who are unresponsive to topical corticosteroid treatment or in whom topical corticosteroids are contraindicated (12). In addition, creating unjustified uncertainty and fear among healthcare providers and patients without considering evidence demonstrating high efficacy, the FDA recommendation was followed by dramatic decrease of TCI sales and off-label use among children within a year (13). This also implies increase of TCS use, along with all its adverse effects, especially when used in young infants or in areas such as the face, eyelids, neck, genitals or intertriginous areas due to higher systemic exsposure (4, 14). Many opinion leaders and medical associations, including the American academy of allergy, asthma and immunology (AAAAI), American college of allergy, asthma and immunology (ACAAI), American academy of dermatology, canadian dermatology association (CDA), and Canadian society of allergy and clinical immunology (CSACI) released position statements, expressing disagreement about box warning, promoting the safety of the TCIs and demanding reconsideration of the alert (15-18). In September 2010, the FDA released a comprehensive review of TCI safety summarizing data from six studies including more than 6 million patients (19-26). Later on, in May, 2011 according to a total of 72 cases of malignancy that had been reported in children treated with TCI, the FDA issued an addendum (27, 28). Despite extensive epidemiological and clinical studies with no evidence found for increased risk, FDA reviewers concluded that there still may be a possible association between tacrolimus use and lymphoma and that reported cases support the previously observed potential malignancy risk associated with TCI use. However, they also declared that causality was difficult to determine considering potential study biases and insufficiency of the available information (27).

2. Evidence Acquisition

In order to collect data about TCIs and malignancy risk, we performed a computerized search of the PubMed and MEDLINE databases with the key words: topical calcineurin inhibitors, skin cancer and lymphoma. We also performed a search of the same databases to retrieve articles related to the possible link between atopic dermatitis and increased risk for lymphoma. Articles written in English from the past 15 years were selected and reviewed by each of the authors gathering in the current study only those ones providing valuable information to the topic.

2.1. TCIs and Theoretical Malignancy Risk Factors

One of the potential mechanisms of carcinogenesis includes direct effect of TCIs on keratinocytes inhibiting spontaneous DNA repair and reducing apoptosis in healthy human epidermal keratinocytes following UV-B irradiation (29). However, in preclinical studies the topical use of TCI was not associated with any mutagenic, genotoxic and photocarcinogenic effects (30, 31). Another potential mechanism that could lead to carcinogenesis is systemic immunosuppression as a result of systemic absorption. Considering that systemically administered calcineurin inhibitors for graft rejection in organ transplant patients are highly associated with an increased rate of lymphomas, melanomas and non-melanoma skin cancers, theoretically substantial systemic absorption of TCIs could also increase the risk (11). However, there is no evidence that topical use of calcineurin inhibitors leads to systemic immunosuppression considering normal immune response to vaccination, appropriate delayed-type hypersensitivity reaction and no increased incidence of cutaneous and systemic infections in patients treated with TCIs (32-35). According to pharmacokinetic studies, the systemic absorption rate for both TCIs was very low in more than 99% of the patients presenting with moderate or severe AD including infants and adults making the risk of systemic immunosuppression not biologically plausible. Topical use of pimecrolimus cream twice a day led to blood

concentrations of less then 1 ng/mL with no measurable increase when used under occlusion. The blood concentrations reached after topical application of tacrolimus were less than 5 ng/mL but showing significant systemic absorption in patients with extensive skin disorders such as Netherton syndrome, pyoderma gangrenosum or when applied with an occlusive dressing (6, 11, 36). In summary, the plasma levels following topical administration of calcineurine inhibitors are at least 10-fold lower than those during systemic treatment such as in organ transplant patients (37, 38). Also, the lymphomas that had been reported as spontaneous adverse advent associated with TCI use did not have clinical presentation and histology of those one occurring in transplant patients (6). The results of animal toxicology studies in mice, rats and monkeys, in which calcineurin inhibitors had been administered at high oral doses and using topical experimental formulations, showed increased risk for lymphoma and skin cancers due to high systemic exposure. The lymphomas described in animal studies appeared after topical application of tacrolimus and pimecrolimus dissolved in ethanol reaching blood levels 26 and 47 times higher than those ever measured in patients treated with TCI. Taking into consideration the administration of toxic doses of TCI, enormous differences in systemic exposure, differences in administration and irreconcilable differences between animal and human beings make this risk completely theoretical (30, 31, 36). The "black box" warning was based on 25 case reports of malignancies worldwide in more than 6.7 million patients treated with TCIs during post-marketing surveillance, of which 13 were lymphomas (7). In clinical trials no lymphoma was reported in almost 10,000 patients treated with tacrolimus, and only two cases of solid tumors were described in 25,000 patients treated with pimecrolimus. Since TCIs were approved until 2010, there were more than 50 sporadic cases of lymphoma reported in the FDA's adverse event reporting system, but considering more than 7 million TCIs users at that time, the incidence was still lower compared with the general population (11).

2.2. Atopic Dermatitis Per se and Increased Risk for Lymphoma

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by relapsing and remitting course that affects up to 25% of children and 2% - 3% of adults. Dry skin and severe pruritus are the hallmarks of atopic dermatitis. Personal or family history of atopy and gene mutations for epidermal structural protein fillagrin that lead to epidermal barrier dysfunction are the major risk factors for developing AD. Clinical presentation includes skin dryness, typically eczematous lesions on flexural folds, excoriations, and lichenification (39, 40). The main goals of treatment are to reduce pruritus and skin inflammation, and to prevent exacerbations avoiding potential therapeutic side effects. The optimal management of atopic dermatitis involves moisturization and hydration of the skin aiming to restore the skin barrier function, elimination of exacerbating triggers and use of topical anti-inflammatory drugs (41, 42). Topically administered corticosteroids and emollients are currently the mainstay of treatment for atopic dermatitis (40). Legendre et al. (2015) performed a meta-analysis of 4 cohort studies and 18 case-control studies, and found a modest increase in risk of lymphoma in patients with AD compared with the general population (43). The increased risk was statistically significant in the meta-analysis of the cohort studies (RR 1.43, 95% CI, 1.12 - 1.81) (24, 44-46). In the meta-analysis of the case-control studies the increased risk for lymphomas was insignificant (OR 1.18, 95% CI 0.94 - 1.47) (43). Three of the studies involved in this meta-analysis indicated a significant association between severity of atopic dermatitis and lymphoma (21, 22, 45). In the cohort study by Margolis et al. the RR of lymphoma in patients with severe AD was 1.95 (95% CI, 1.15 - 3.12) (45) while in the two case control studies the adjusted OR varied from 2.4 (95% CI, 1.5 - 3.8) to 3.72 (95% CI, 1.40 - 9.87) (21, 22). However, considering the potential misclassification bias and possibility of independent association between atopic dermatitis and risk of developing lymphoma, this result should be interpreted with caution (47). Because of the overlapping clinical presentations, early forms of cutaneous T-cell lymphoma (CTCL) might have been initially misdiagnosed for severe AD. Such misdiagnosis probably occurred in the study reported by Hui et al. with an overrepresentation of CTLC among tacrolimus users (23). In the meta-analysis by Legendre et al. which included two case control studies by Arellano et al. (21, 22), statistically significant association between highly potent topical corticosteroids and increased risk of lymphoma with an overall OR for lymphoma of 1.73 (95% CI, 1.52 - 1.97) might have also been confounded by severity of AD due to low exposure to TCSs before lymphoma occurrence (< 6 months to 12 months). According to the fact that in one case control study by Legendre et al. the increased risk disappeared after adjusting for AD severity, this makes the potential link even more questionable (43). It should also be considered that early pruritus of non-cutaneous lymphomas might have been undiagnosed and treated as symptom of AD (48).

3. Results

A meta-analysis by Arellano et al. published in 2015 was conducted to determine the role of AD treatment with TCIs on lymphoma risk. The meta-analysis included two case control studies (21, 22) and two cohort studies (23, 24).

The analysis conducted with pimecrolimus revealed the overall OR from case control studies of 0.85 (95% CI, 0.47 - 1.55) and the overall RR from cohort studies of 1.58 (95% CI, 0.83 - 3.00). For tacrolimus the overall OR from case control studies was 1.04 (95% CI, 0.54 - 2.02) and the overall RR from cohort studies was 3.13 (95% CI, 0.67 - 14.57). The Legendre et al. concluded that there was no statistically significant association between TCIs use and risk of lymphoma in patients with atopic dermatitis (43). Although, in one included the cohort study by Hui et al. a fivefold increased risk of T-cell lymphoma (TCL) was reported among tacrolimus ointment users (RR 5.44, 95% CI, 2.51 - 11.79) of which 81% were CTCLs. According to the Surveillance, Epidemiology and End Result data, the CTCLs represent about 29% of TCL cases in general population. An overrepresentation of patients with CTLC in study by Hui et al. refers to possible initial misdiagnosis of CTLC as atopic dermatitis and needs to be further substantiated. The risk of TCL associated with use of pimecrolimus cream was insignificantly increased (RR 2.32, 95% CI, 0.89 - 6.07) (23, 43). A cohort study by Schneeweiss et al. reported no significant association between lymphoma and both TCIs (tacrolimus; RR 1.36, 95% CI, 0.47 - 3.98, pimecrolimus: RR 1.63, 95% CI, 0.75 - 3.54) (24). In case control studies, the risk for developing lymphoma was even more insignificant (21, 22). The low level exposure to TCIs before appearance of lymphoma in the study by Hui et al. and in the study by Schneeweiss et al. amounting to only 2 to 3 tubes does not support a causal association between TCIs and lymphoma preventing us from drawing a definitive conclusion of potential malignancy risk (43).

The pediatric eczema elective registry (PEER) is a long-term cohort study initiated in 2004 to evaluate the risk of malignancy in children with atopic dermatitis that were treated with pimecrolimus. PEER study included children $\geq$ 2 and $<$ 18 years of age that had been treated with pimecrolimus for at least six weeks in the previous six months with a follow-up for ten years. In this post-marketing study, five malignancies were reported (two leukemias, one osteosarcoma and two lymphomas) among 7457 children enrolled between 2004 and 2014 (49). The standardized incidence ratio (SIR) based on age standardized surveillance, epidemiology and end results program (SEER) population was for all malignancies 1.2 (95% CI 0.5 - 2.8), for lymphoma 2.9 (95% CI 0.7 - 11.7) and for leukemia 2.0 (95% CI 0.5 - 8.2). The PEER study concluded that none of the findings were statistically significant (49).

A prospective pediatric longitudinal evaluation to assess the long-term-safety (APPLES) is still ongoing, prospective long-term observational study established in 2005 to assess the long-term safety of tacrolimus for the treatment of atopic dermatitis. This post-marketing study includes a cohort of 8000 patients who were no older then 16 years at the time of first tacrolimus ointment exposure and were treated for at least six weeks for the treatment of AD (36).

As yet, there is no evidence of the association between the use of TCIs and increased risk of skin cancers. In numerous clinical trials and post-marketing surveillance for both TCIs incidence of skin cancers was even lower than seen in general population (11, 50). In the case control study by Margolis et al. a negative association was found between nonmelanoma skin cancer and the TCIs use (OR 0.5, 95% CI, 0.4 - 0.7) due to possible selective prescription of these drugs to patients with decreased risk for developing skin cancer (20, 48). In the study by Hui et al, no evidence was found that appearance of melanoma was associated with tacrolimus (RR 0.3, CI 95%, 0.1 - 0.8) or pimecrolimus use (RR 0.7, CI 95%, 0.4 - 1.3) (23, 48).

4. Conclusions

The development of topical immunomodulatory treatment with TCIs was a major breakthrough in management of atopic dermatitis, especially in children. However, the FDA's labeling restrictions, based on theoretical possibilities of malignancy have led to "calcineurin-phobia" putting patients at risk for adverse effects associated with prolonged use of potent topical corticosteroids. Comprehensive scientific evidence from clinical trials, post-marketing surveillance and epidemiological studies found potential safety concerns regarding increased incidence of skin cancers and lymphoma in patients treated with TCIs unjustified, bringing into question the validity of "black box" warning. A systematic review and meta-analysis, published in 2015 indicate modest increased risk of lymphoma in patients with AD compared to the general population noting AD severity as a significant risk factor for lymphoma while the use of TCIs does not appear to significantly contribute to the overall risk. However, no definitive conclusions can be made due to large heterogeneity in study designs including diagnostic criteria for AD, lymphoma diagnostic validation, various population groups and different types of analysis, especially in case-control studies. Further long-term safety studies are required before a definitive evidence-based conclusion of a potential malignancy risk can be reached. Despite scientific evidence that demonstrates efficacy and safety of TCIs use "black box" warning still remains having a significant influence on physician prescribing habits that leads to unsuccessful AD control and reduced quality of life in these patients.

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Footnotes

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