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CONTROVERSIES IN DERMATOLOGY

Topical Pimecrolimus and Tacrolimus and the Risk of Cancer

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Abstract. In this review the controversy regarding the association between topical pimecrolimus and tacrolimus and the development of tumors is unfolded. After reviewing the literature we conclude that, currently, there is no scientific evidence of an increased incidence of skin cancer, lymphomas or systemic immunosuppression in those patients that use or have used topical calcineurin inhibitors. Published studies lack adequate number of patients and/or the follow-up time is short enough to conclude that topical use of calcineurin inhibitors might be associated with the reported cases of skin cancer and lymphoma. Nevertheless the possibility of long term cutaneous and/or systemic side effects cannot be excluded.

Key words: pimecrolimus, tacrolimus, nonmelanoma skin cancer, melanoma, lymphoma, posttransplant lymphoproliferative disease, experimental studies.

PIMECROLIMUS/TACROLIMUS TÓPICOS Y RIESGO DE CÁNCER

Resumen. En esta revisión se expone la controversia que existe acerca de la relación que hay entre el pimecrolimus y tacrolimus tópicos y la aparición de tumores. Después de revisar la literatura médica se concluye que actualmente no existe evidencia científica de un incremento de cáncer de piel ni de linfomas ni del desarrollo de una inmunosupresión sistémica en aquellos pacientes que han utilizado o están utilizando los inhibidores tópicos de la calcineurina. Los estudios publicados carecen de suficiente número de pacientes y/o el periodo de seguimiento es corto como para concluir que el uso tópico de los inhibidores de la calcineurina puede asociarse a los casos notificados de cáncer de piel y linfoma. Sin embargo, no se puede excluir la posibilidad de que aparezcan efectos secundarios cutáneos y/o sistémicos a largo plazo.

Palabras clave: pimecrolimus, tacrolimus, cáncer de piel no melanoma, melanoma, linfoma, enfermedad linfoproliferativa postrasplante, estudios experimentales.

Introduction

Tacrolimus ointment (Protopic, Astellas Pharma GMBH, Tokyo, Japan) and pimecrolimus cream (Elidel, Novartis Pharma AG, Basel, Switzerland; Rizan, Dr Esteve SA, Barcelona, Spain) are nonsteroidal drugs approved for the treatment of atopic dermatitis in Japan, the European Union, and the United States of America (USA).[1] Topical tacrolimus and pimecrolimus were approved in the USA in 2000 and 2001, respectively. Since January 2006, these drugs have carried a black box warning,[2] the most serious health warning in the USA, in which it is indicated that their long-term safety has not been demonstrated. The US Food and Drug Administration (FDA) bases this warning on the following considerations: *a)* the appearance of sporadic cases of lymphoma and skin tumors in patients treated with those 2 drugs; *b)* the appearance of cancer in studies of animals that have received high doses of calcineurin inhibitors; *c)* the possibility of greater systemic absorption in subsets of treated patients; and *d)* the promotion of topical calcineurin inhibitors as first-line treatments for atopic dermatitis. In March 2006, the European Medicines Evaluation Agency (EMEA) could not conclude to what extent the use of topical calcineurin inhibitors could be associated with reported cases of skin cancer and lymphoma, and recommended the introduction of changes in the prescribing information sheet and product information.[3]

The appearance of cancer in animal studies and the systemic absorption of calcineurin inhibitors in patients generate a biologically feasible situation for the development of adverse effects in patients. However, it is necessary to evaluate data obtained in human subjects to adequately assess adverse effects. This review briefly describes the indications and hypothetical carcinogenic mechanisms for

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calcineurin inhibitors along with the controversy regarding the association between the use of these drugs and the appearance of tumors.

Indications

Although the FDA and EMEA have modified the prescribing information sheet for topical tacrolimus and pimecrolimus, the indications for their use in clinical practice remain the same.[4] Both drugs are indicated for the second-line treatment of atopic dermatitis in nonimmunosuppressed patients who do not respond adequately to topical corticosteroids or in whom they are contraindicated. Treatment is applied to the skin lesion and should be intermittent and used in short courses. Tacrolimus ointment at 0.1% and 0.03% is approved for adults with moderate or severe atopic dermatitis, while 0.03% tacrolimus ointment is indicated for children older than 2 years. Pimecrolimus (1%) cream is indicated in mild or moderate atopic dermatitis in adults and children older than 2 years.[5]

Hypothetical Mechanisms of Carcinogenesis

We should consider at least 3 hypothetical mechanisms through which topical calcineurin inhibitors could increase the risk of cancer in patients with atopic dermatitis. The first mechanism would act via a direct effect of calcineurin inhibitors on keratinocytes. A number of studies have shown that tacrolimus inhibits apoptosis in various cell types.[6] Topical calcineurin inhibitors inhibit DNA repair and reduce apoptosis in healthy human epidermal keratinocytes following UV-B irradiation[7]; thus, they may behave as tumor promoters in precancerous cells. However, in preclinical studies, topical calcineurin inhibitors display no mutagenic, genotoxic, or photocarcinogenic effects.[8-10] In human skin treated with pimecrolimus, no increase in pyrimidine dimers have been demonstrated in the first 24 hours following UV irradiation when compared with control subjects, nor was any interference with DNA repair mechanisms observed.[11]

The other 2 mechanisms that could lead to carcinogenesis of calcineurin inhibitors would involve the development of local immunosuppression at the application site and/or systemic immunosuppression due to systemic absorption, which is stronger in the case of tacrolimus than pimecrolimus. Calcineurin inhibitors inhibit the activation and proliferation of T lymphocytes, favoring apoptosis of those cells.[12] The immunomodulatory specificity of these drugs is influenced by the low level of expression of calcineurin in lymphocytes compared with other cells from other tissues, and the requirement for calcineurin in immunologic activation. Tacrolimus also reduces the expression of the FcεRI receptor by Langerhans cells, unlike pimecrolimus.[13]

Calcineurin Inhibitors

Immunosuppression

Administration of systemic tacrolimus at sustained high concentrations over a period of many years in transplant patients alongside other immunosuppressant drugs has been associated with an increased rate of lymphomas, nonmelanoma skin cancer, and melanomas in sun-exposed areas.[14-16] The rate of appearance of cancer is related to the level of immunosuppression, among other factors. However, it has not been demonstrated that topical application of calcineurin inhibitors in human subjects leads to a reduced systemic immune response. It has been demonstrated that patients who have received topical calcineurin inhibitors display a normal immune response to vaccination,[17,18] an adequate delayed hypersensitivity reaction,[19,20] and a rate of cutaneous and systemic infections similar to that of a control group.[21-24]

Substantial systemic absorption of topical calcineurin inhibitors could lead to adverse effects on the immune system. Absorption of pimecrolimus[25-27] and tacrolimus[28,29] creams has been assessed in children and adults with moderate or severe atopic dermatitis, and in most cases was found to be very low. Use of pimecrolimus cream twice daily has led to blood concentrations less than 0.5 to 1 ng/mL in numerous studies,[25-27] without any observable differences according to the age of the child or the severity or extent of the atopic dermatitis lesions.[23] The blood concentration reached with topical tacrolimus is less than 1 to 5 ng/mL, but that concentration tends to be higher in those patients in whom the disease is more extensive,[28,29] in patients with Netherton syndrome,[30] when the cream is applied to cutaneous ulcers, and when it is applied with an occlusive dressing.[31] The plasma levels reached following topical application of calcineurin inhibitors are much lower than those during systemic treatment of transplant patients.[32]

Lymphomas

There is no evidence of increased prevalence of lymphomas associated with short-term, intermittent, topical application of calcineurin inhibitors, despite their widespread use.[10] Clinical trials have not observed lymphoma in close to 10 000 patients treated with tacrolimus, and only 2 cases of solid tumors were observed in adults from 25 000 patients treated with pimecrolimus, a rate which was lower than that

observed in the control group.[32] Pharmacovigilance data compared with the general population following marketing of the drugs reveal no increased risk of lymphoma in close to 7 million prescriptions of topical pimecrolimus and in 2 million prescriptions of topical tacrolimus in the USA. Since its approval, at least 28 cases of lymphoma have been verified in the pimecrolimus group and 25 in the tacrolimus group, rates that are lower than those observed in the general population.[32,33] In a study undertaken in a cohort of 293 253 patients with atopic dermatitis, no increased risk of lymphoma was observed, although the follow-up period from the marketing of topical calcineurin inhibitors was short.[34]

The clinical characteristics of lymphomas that appear in transplant patients treated with cyclosporine and oral tacrolimus differs from those observed in lymphomas with topical calcineurin inhibitors. The frequency of posttransplant lymphoproliferative disease ranges between 2% and 60% in patients receiving solid-organ transplants, and is most common in transplants of the small intestine. The disease involves B-cell lymphomas, characteristically associated with Epstein–Barr virus, that appear weeks, months, or occasionally years after immunomodulatory treatment in unusual sites such as soft tissues, joints, and lungs. The lymphomas regress spontaneously upon suspension of immunomodulatory therapy in 30% to 50% of cases.[12,28]

Skin Cancer

Currently, there is no evidence of increased prevalence of skin cancer associated with the topical use of calcineurin inhibitors,[10,35] although isolated cases have been reported.[6,36] The system of spontaneous reporting used by the FDA to observe early signs of drug toxicity has various limitations that hinder comparison with other databases.[37] The isolated clinical cases that have been published correspond to epidermoid carcinomas in mucosal tissue following the use of tacrolimus to treat inflammatory processes, which occasionally become malignant.[6,36]

In clinical trials of tacrolimus, 13 cases of nonmelanoma skin cancer, 10 basal cell epitheliomas, and 3 squamous cell carcinomas were observed in a total of 10 000 patients treated. Also, in pharmacovigilance studies following marketing of the drugs the frequency of nonmelanoma skin cancer is lower in patients treated with topical calcineurin inhibitors than in the general population.[32,33] Up to December 2004, the FDA had reported 10 cases of skin tumors in patients treated with tacrolimus following commercial release, including squamous cell carcinomas and melanomas,[38] and in a subsequent publication the number of cases in the USA had increased to 21.[32] In a prospective study of 9813 patients with atopic dermatitis treated with 0.1% and 0.03% tacrolimus no increase was observed in the incidence of nonmelanoma skin cancer during a mean follow-up period of 208 days.[39]

The frequency of nonmelanoma skin cancer in clinical trials involving patients treated with topical pimecrolimus is low.[33] In December 2004 the FDA had collected 6 cases of skin cancer, including squamous cell and basal cell carcinomas, during the monitoring period following marketing of the drug.[40]

Cancer and Experimental Animals

Although animal models are useful for analysis of the cellular and molecular mechanisms of cancer, the results obtained from such experiments cannot be directly extrapolated to human beings.[35,41]

In preclinical studies undertaken in vivo and in vitro, the topical use of calcineurin inhibitors was not associated with any carcinogenic or mutagenic effects.[8,9,41] Nevertheless, carcinogenic effects have been observed in various animal models (mouse, rat, monkey) in which calcineurin inhibitors have been administered at high oral doses and using experimental formulations that lead to high systemic exposure. The appearance of skin tumors and lymphomas depends on the dose and length of exposure to calcineurin inhibitors. In mice, lymphomas appear following application of tacrolimus and pimecrolimus dissolved in ethanol to achieve plasma concentrations 26 and 47 times the maximum observed level in humans.[8,9] Systemic exposure at high levels in monkeys over a period of at least 3 months with oral pimecrolimus and tacrolimus leads to the appearance of lymphoproliferative diseases associated with immunosuppression.[8,9]

Conflicting results have been obtained in the 2-stage chemical carcinogenesis model in the mouse, using an initiator agent or chemical mutagen (7,12-dimethylbenzanthracene) and another substance acting as a promotor or activator and stimulator of cell proliferation (12-O-tetradecanoylphorbol-13-acetate). According to Jiang et al,[42] it reduces the rate of formation of skin tumors by 80%, while Niwa et al[43] observed an increase in benign papillomas and an increase in the incidence of squamous cell carcinomas at 20 weeks, although these findings were not confirmed when the study was extended to 2 years. It is possible that methodological differences between the studies can explain the results, since the effects are a balance between the local antiinflammatory effects and systemic immunosuppressive effects of the calcineurin inhibitors.[44]

No photocarcinogenic effects of calcineurin inhibitors have been observed in animal studies. A reduction in thymidine dimers has been observed in the epidermis of mice an hour after UV-B irradiation, suggesting that tacrolimus and pimecrolimus have a protective effect on

DNA following irradiation.[45] Studies of photocarcinogenesis in mouse skin with topical application of tacrolimus and pimecrolimus over a period of 10 consecutive days of UV-B irradiation have shown that neither of the topical calcineurin inhibitors lead to an increase in DNA damage, the increase observed being greatest with the vehicle. In longer term studies it has been observed that the appearance of papillomas caused by the human papilloma virus and of squamous cell carcinomas occurs more rapidly in those animals that received vehicle.[41]

Opinions of the Different Professional Associations Regarding Tacrolimus and Pimecrolimus

Following the FDA report in 2005 in which it was proposed that a black box warning be included in the prescribing information sheet and product information of tacrolimus and pimecrolimus indicating that their long-term safety had not been demonstrated, numerous professional organizations communicated their opinion regarding the safety of topical calcineurin inhibitors.

The Spanish Academy of Dermatology and Venereology (Academia Española de Dermatología y Venereología), watching over the health and safety of Spanish patients with skin conditions, considers that the rare cases of cancer published have not demonstrated an association with the use of the medication and that there is no scientific evidence available demonstrating that the appropriate use of these drugs is harmful to health.

The Spanish Society of Pediatrics (Asociación Española de Pediatría) observed that the number of cases of lymphoma reported in patients treated with pimecrolimus and tacrolimus is lower than the incidence expected in the general population and that reliable data are unavailable demonstrating that the use of pimecrolimus and tacrolimus according to the recommendations of the prescribing information sheet is hazardous to health.[46]

The European Academy of Dermatology points out that it is difficult to know how the FDA can justify its conclusions when the data obtained show no causal relationship between the use of topical calcineurin inhibitors and cancer in human subjects.[47]

The American Academy of Dermatology published a declaration in response to the FDA proposal of a black box warning in which it set forth its disagreement with the proposal and indicated that data are not available demonstrating that the topical use of pimecrolimus and tacrolimus is dangerous and that this information could lead to unnecessary confusion and concern among patients and their carers.[48]

In 2005, the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed the relationship between topical calcineurin inhibitors and cancer and found no current data establishing a causal relationship between them.[28]

Conclusions

Currently, no scientific evidence exists supporting an increase in skin cancer or lymphoma, nor of systemic immunosuppression in patients who have used or are currently using topical calcineurin inhibitors. The studies that have been published lack a sufficient number of patients and/or the follow-up period is too short to conclude that the topical use of calcineurin inhibitors can be associated with the reported cases of skin cancer and lymphoma.[10,28,35] However, the possibility cannot be excluded that cutaneous and/or systemic side effects could become apparent in the long-term. The FDA and EMEA have requested that the pharmaceutical companies holding the licenses for these drugs design epidemiology studies addressing the long-term safety of the drugs and involving a sufficient number of patients to determine the true risk associated with exposure to pimecrolimus and tacrolimus; those studies should also include a group of patients aged less than 2 years.

Some studies of this type are already underway following the marketing of tacrolimus and pimecrolimus. One prospective long-term observational study in children who received pimecrolimus cream for at least 6 weeks in the previous 6 months, known as the Pediatric Eczema Elective Registry (PEER), has been initiated to undertake follow-up in a large number of patients. A long-term prospective observational study has also begun in individuals treated with tacrolimus for at least 6 weeks known as the Atopic Prospective Pediatric Longitudinal Evaluation Study (APPLES) and includes a cohort of 8000 patients in whom follow-up will be undertaken for 10 years.[37]

Conflicts of Interest
The author declares no conflicts of interest.

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