Safety Issues with the use of Calcineurin Inhibitors

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• The data provided hereafter is not intended to create uncertainty for patients, their families, or for medical caregivers.
Pimecrolimus (Elidel) & Tacrolimus (Protopic)

- Elidel cream (1%) and Protopic ointment (0.1% & 0.03%) are topical immunosuppressant calcineurin inhibitors that are applied to the skin for the treatment of Atopic Dermatitis.
- Both Elidel and Protopic are sometimes absorbed through the skin, though usually at a very low amounts.
- Occasionally, children who have been treated with Elidel or Protopic have had high blood levels of these drugs.
- Some children given topical tacrolimus have blood levels of the drug similar to those given its systemic form.

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Pimecrolimus(Elidel) & Tacrolimus(Protopic)

- The precise mechanism of action of topical PIM & tTAC in patients with Atopic Dermatitis is unknown.

- However, both drugs inhibit calcineurin and subsequently inhibit T-cell activation by blocking the transcription of early cytokines.

- Both drugs are immunosuppressant and have been associated with malignancies in animal models.
Tacrolimus (Prograf):

- In addition to an ointment, the oral and parenteral forms of tacrolimus are available on the market as (Prograf).
- Prograf is approved to prevent liver or kidney transplant rejection in transplant patients.
- Prograf have been associated with both skin cancers and lymphoma in humans (by suppressing the body’s normal immune defenses against cancer).

The cancer risk increases with higher doses and longer treatment courses with Prograf.
Tacrolimus (Prograf): continued

- Studies showed that tacrolimus significantly increases the growth of experimental tumors.¹

- Studying the immunosuppressant effect on Fas antigen expression and p53 of an experimental tumor, confirmed that the effect of tacrolimus on the increased tumour growth can be based on its effect on Fas antigen expression and suppression of p53.²

*p53 tumor suppressor protein is required for the induction of apoptosis, particularly those with Fas-associated apoptosis.

*The FAS (CD95, APO-1)/FAS LIGAND (FasL) system constitutes an important cellular pathway regulating the induction of apoptosis in a wide variety of tissues. Fas is expressed on a wide variety of cell types such as T and B cells, monocytes, neutrophils, eosinophils, macrophages, keratinocytes, and endothelial cells


Tacrolimus (Prograf): continued

- The risk of using tacrolimus topically with respect to carcinogenesis became of concern due to the fact that systemic long term treatment with tacrolimus in organ transplant recipients increases the incidence of malignant tumors, particularly squamous cell carcinoma.¹
- The suspected causal relationship between topical use of tacrolimus and the development of a squamous cell carcinoma prompted researchers to test the notion that the carcinogenicity of tacrolimus may go beyond mere immune suppression. To this end, tacrolimus has been shown to have an impact on cancer signaling pathways such as the MAPK and the p53 pathway.
- The carcinogenic potential of tacrolimus might be also mediated via direct effect thereby promoting oncogenic transformation of initiated cells.²

MAPK: Is a signal transduction pathway that couples intracellular responses to the binding of growth factors to cell surface receptors.

**Pimecrolimus (Elidel)**

- Repeat dose toxicity studies conducted with topical application of pimecrolimus demonstrated in *mice* dose dependant development of lymphoma.
- Carcinogenicity studies conducted with oral administration in *mice* demonstrated dose dependant development of lymphoma, and benign thymoma.
- Topical administration studies in *rats* demonstrated development of follicular cell adenoma of the thyroid.
- Oral administration study in *monkey* showed a dose related increase in Virus-associated lymphoma.
- These studies were conducted at doses higher than that generally used by patients and the risk of cancer increased with increasing drug dose and duration.

US FDA alert, Pimecrolimus (Elidel):
Pimecrolimus (Elidel): continued

- Human studies over the past few years identified several potential health risks associated with the use of topical PIM:
  - Lymphoma (attributed to systemic immunosuppression).
  - Skin Malignancies.
  - Herpes Zoster.
  - Pneumonia.
  - Asthma/bronchospasm.
  - Skin infections (Local immunosuppression)
Update on Malignancies in children
US FDA Adverse Event Reporting System
(January 2004 - January 2009)

• The FDA identified 46 new cases of malignancies in children 0-16 years old who used PIM and/or tTAC.

- Lymphoma: 17 cases.
  3 Cases of Hodgkin’s lymphoma.
  14 cases of non-Hodgkin’s lymphoma.

- Leukaemia: 13 cases.
  9 cases of ALL (acute lymphocytic leukaemia).
  2 cases of AML (acute myeloid leukaemia).
  2 cases of other leukaemia.

• Skin Malignancies: 8 cases.
  5 cases of Melanoma
  3 cases of other skin malignancies.
• CNS tumors: 3 cases.
• Hepatoblastoma: 1 case.
• Rhabdomyosarcoma: 1 case.
• Wilm’s tumor: 1 case.
• Lung cancer: 1 case.
• Neuroplastoma: 1 case.
• 4 cases (4/46) were fatal:
  - AML: 2 cases.
  - T-cell ALL: 1 case.
  - Wilm’s tumor: 1 case.
Update on Malignancies in children
FDA Adverse Event Reporting System
(January 1, 2010 – February 25, 2010)

- The FDA identified additional 10 new cases of malignancies in children 0-16 years old who used PIM and/or tTAC:
  - Acute Lymphocytic Leukemia (ALL): 5 cases.
  - Chronic myeloid Leukemia (CML): 1 case.
  - Anaplastic Large Cell Lymphoma (ALCL): 1 case.
  - Cutaneous T-cell and B-cell Lymphoma: 1 case.
  - Mycosis Fungoides: 1 case.
  - Wilm’s tumor: 1 case.

• 2 cases were fatal.
• 4 cases were life threatening.
• 3 cases required hospitalization.
• 1 case was reported as other serious event.
- The time to onset from start of therapy ranged from 9.7 months to 5.5 years. (median= 2.3 years).
- The duration of therapy ranged 40 days to 5.5 years (median ~ 1.5 years).

► 50% of all reported malignancy cases were in children less than 2 years of age.
**CUIs’ product label Warning**

- **Long-term safety of Topical Calcineurin Inhibitors has not been established.**

- Although a casual relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical CUIs.

- Topical CUIs are not indicated for use in children less than 2 years of age.
Utilization patterns for PIM (Elidel) cream, and tTAC (Protopic) in the US.

- In 2004 approximately 4.82 million prescriptions for both drugs were dispensed.
- In 2008 only 1.27 million prescriptions were dispensed.
- The pediatric subgroup age 0-1 experienced the largest decline in total number of projected patients.

The 74% decline was a direct result of the boxed warning introduced in 2005 by the FDA.
Conclusion and recommendations:

Although the role of topical CUIs in the development of malignancy related events is unknown, the benefits CUIs are still considered to outweigh the risks and there is still a place for these effective agents in the treatment/control of atopic dermatitis when treatment is indicated because there are safety issues with alternative therapy (corticosteroids) as well.

The use of CUI should be:
1- A second line treatment.
2- Intermittent Course and for a short period of time.
3- Application should be limited to areas of involvement with AD.
4- Topical Calcineurin Inhibitors should not be prescribed for use in children below 2 years of age.

Finally, there is a need for long term safety studies in children (0-5 years old). Additionally, long term monitoring of children treated with CUIs is highly recommended (at least for 5 years post treatment).
Thank You

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