



EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY
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Presidential Statement March 2006

New recommendations of FDA and EMEA regarding labels of topical calcineurin inhibitors

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently recommended changes regarding labelling of topical calcineurin inhibitors (TCIs) as used for the treatment of eczema.

EADV President Johannes Ring responds to the question: **Do physicians and patients have to be concerned about the changes in USA and Europe especially with regard to the safety of topical calcineurin inhibitors in eczema treatment?**

In USA the FDA has added boxed warnings to pimecrolimus cream and tacrolimus ointment stating that the long-term safety of topical calcineurin inhibitors has not been established. Until more long-term data become available, they have advised against continuous long-term use of these medications. The label makes it clear that no causal relationship has been established between use of these medications and rare reports of malignancy.

Quite recently the EMA has come to similar conclusions. They also do not see TCI as first line treatment and express concern about uncritical long-term use of these agents. EMA also sees a necessity that the initiation of topical treatment with tacrolimus or pimecrolimus should only be performed by a physician with experience in diagnosis and treatment of eczema.

While the FDA label makes it clear that no causal relationship has been established between use of these medications and rare reports of malignancy, this is not so clearly evident from the EMA statement.

Professor Ring's statement

28 March 2006:

The president of the European Academy of Dermatology and Venereology (EADV) has today commented to these developments. Prof. Ring said the revised warnings were relatively mild in tone and should not return physicians from prescribing these medications, which have proved therapeutic value as an alternative to other anti-inflammatory treatments especially topical glucocorticosteroids. The TCIs have been extensively researched and widely used in clinical practice; dermatologists have a good understanding of their safety profile. Prof. Ring would like to reassure physicians and patients that the additional warnings in USA and Europe labels should not cause concerns regarding the use of these therapies within their labelled indication.

The statements issued by FDA and EMEA are largely based on the results of experience using the drugs in oral form at high doses resulting in far higher exposure to the active ingredients than occurs in human patients using a topical form applied to the skin as a cream or an ointment.

Although both agencies have received post marketing reports of skin malignancies in patients using TCIs, the incidence of these events is not higher than that seen in the normal population. Today there is no evidence of an increased incidence of lymphoma or other malignancy with TCIs use in thousands of patients involved in clinical trials or several millions people treated with the two preparations. Furthermore, there is no evidence of systemic immunosuppression after short term or intermittent long-term topical application of pimecrolimus or tacrolimus in eczema patients. The actual rate of lymphoma reported in people treated with TCIs is considerably lower than predicted for the general population.

Professor Ring referred to a recent position statement of the European Dermatology Forum concerning the potential risk of TCIs which appeared in the Journal of the European Academy of Dermatology and Venereology (JEADV).

Professor Ring stated that these medications have proved of enormous benefit to millions of patients worldwide suffering from a disease which can be painful and distressing. "We would regard it as extremely unfortunate if these patients were deterred from using these substances because of warnings which are based on mainly theoretical assessment of risk. Dermatologists always are in the first line when allocating patient's safety. Following extensive reviews of all available information, I believe that the benefit of using TCIs largely outweighs the risks."

Professor Ring said he was concerned that the FDA's and EMEA's actions could mean an increasing reliance on systemic immunosuppressives or strong topical corticosteroids in the treatment of eczema. He said: "It is important that physicians and patients are able to recognize the benefits and risks of all the available therapies before forming a balanced judgement on the most suitable form of treatment."

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