New Treatments for Atopic Dermatitis – Facts, Comparisons and Uncertainties*

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Atopic dermatitis is associated with asthma and allergic rhinitis, and presents with a typical morphology and distribution. Eighty-four per cent of cases of atopic dermatitis are mild, 14% moderate, and 2% severe.[1] There are 10 randomised controlled trials, and 1 systematic review addressing the appropriate frequency of application of topical corticosteroids for atopic eczema.[2] In none of the studies was more frequent application superior to once-daily application. However, the point estimates suggest that a small difference in favour of more frequent application cannot be excluded. As there is insufficient evidence for twice daily versus daily application, topical corticosteroids should be prescribed once or twice daily, using the lowest appropriate potency and acquisition cost.

In the prevention of relapse, a randomised controlled trial of 154 adults found that using fluticasone propionate 0.05% cream twice weekly for 16 weeks was superior to placebo.[3] With regard to pulsed versus continuous treatment, a randomised controlled trial of 207 children found no clinically significant difference between betamethasone valerate 0.1% ointment 3 days per week and daily hydrocortisone 1% ointment for 18 weeks.[4]

In 2005, several American pharmaceutical companies requested conversion of some topical corticosteroids to become over-the-counter (OTC) drugs rather than by prescription. In response, the Food and Drug Administration (FDA) requested that an advisory panel consider the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression with topical corticosteroid use. Several small studies documented the development of HPA axis suppression with weak topical corticosteroid use in atopic dermatitis patients. Under the FDA's adverse event reporting system, there have been 46 cases of adrenal insufficiency, 32 cases of Cushing's syndrome, 34 hospitalisations, and 2 deaths with the use of topical corticosteroids in adults. In children, there have been 11 cases of adrenal insufficiency, 17 cases of Cushing's syndrome, 13 cases of growth retardation, 14 hospitalisations and 2 deaths.[5]

The bottom-line for the use of topical corticosteroids would therefore be to prescribe them once daily unless there are compelling reasons to do otherwise, and to choose the lowest appropriate potency. Biweekly use may prevent flares. Physicians should be mindful of potential HPA axis suppression.

In studies assessing the efficacy of the calcineurin inhibitor, tacrolimus, for moderate to severe atopic dermatitis, 1 study showed a 90% improvement in 44% of patients using topical tacrolimus versus 20% using placebo; another showed a 75% improvement in 62% of patients versus 29% using placebo. In another study utilising another calcineurin inhibitor, topical pimecrolimus, for mild to moderate atopic dermatitis, 33% of treated subjects were clear or almost clear of eczema at 3 weeks, compared with 10% of subjects on placebo. Topical tacrolimus may be recommended as alternative short-term or long-term intermittent treatment for moderate to severe atopic dermatitis, whilst topical pimecolimus may be recommended for alternative short-term or long-term intermittent treatment for mild to moderate atopic dermatitis.[1]

The risk of malignancy is of concern with the use of calcineurin inhibitors.[6,7] However, the complexities and uncertainties about registry studies remain unresolved. First, there is difficulty with measuring and quantifying exposure to a topical drug, as well as confounding variables. Secondly, non-melanoma skin cancer ascertainment in population registries is lacking. Thirdly, there is a long latency between exposure and cancer, and studies of at least 10 to 15 years are required. The cost involved in tracking and ensuring high retention rates is substantial. Finally, the rarity of cancer in children and youth implies that a very large cohort is required.

What evidence is there for a risk of malignancy with the use of calcineurin inhibitors? Lymphomas and accelerated murine UV-induced skin cancers have been documented in mouse dermal studies, whilst lymphomas have been

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documented in monkeys after systemic exposure. There have been 21 cases of malignancies reported with tacrolimus (18 adults, 3 children) and 9 cases with pimecrolimus (6 adults, 3 children). Of 19,000 patients treated with pimecrolimus over 2 years, there were 2 malignancies reported. Over the same period, 5 malignancies were reported in 4000 controls. Of 19,000 patients with tacrolimus for 2 years, there was no increase in skin tumours, warts or lymphoma. The nearly unanimous opinion of a FDA advisory panel that examined the evidence was, however, that this additional information about the potential carcinogenicity of these products in humans should be communicated to the patient. What we are dealing with is an unknown degree of risk. It will take too many years before we will have a definitive answer, if we are able to define the problem and have a definitive answer. Many people, but particularly children, will have been exposed and we are concerned that it will be too little information, too late. [6,7]

We can therefore conclude that tacrolimus is effective for moderate to severe atopic dermatitis, but pimecrolimus has limited utility in atopic dermatitis, and should be used only if you have a compelling reason. The risk of malignancy, though unestablished, is of concern. Thus, use in children under 2 years is discouraged.

Available treatment options for severe atopic dermatitis include systemic corticosteroids, phototherapy or photochemotherapy, oral cyclosporine, and azathioprine. A randomised controlled trial of 46 patients treated with cyclosporine showed moderate improvement at 6 weeks. Whilst there is sufficient evidence to support the use of cyclosporine and ultraviolet light, there are no randomised controlled trials for the use of systemic corticosteroids or azathioprine.[1]

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