The Role of topical Immunomodulators in the Management of Atopic Dermatitis

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Atopic dermatitis is a common chronic inflammatory, pruritic, relapsing skin condition which occurs most frequently in children, but can also occur in adults. Currently estimates suggest that 15%-23% of children suffer from atopic dermatitis in industrialized countries and it may persist in 40% to 60% of patients into adulthood.

Topical corticosteroids are presently the mainstay in treating atopic dermatitis, owing to their broad immunosuppressant and anti-inflammatory effects. Prolonged steroid therapy has the potential for adverse effects such as skin atrophy, striae distensae and vascular fragility and systemic effects that include hypothalamic-pituitary-adrenal axis suppression and growth inhibition. There is a need for nonsteroid alternatives that can safely suppress the aberrant immune activity associated with atopic dermatitis and avoid steroid side effects.

Tacrolimus ointment (Protopic®) was FDA approved in December 2000 and pimecrolimus 1% cream (Elidel®) was FDA approved in December 2001. Both are non-steroid closely related macrolide compounds that hold promise in the management of atopic dermatitis. Both share the same cellular binding targets, macrophilins and the complex of tacrolimus/pimecrolimus and macrophilin-12 blocks calcineurin, a phosphatase required for the translocation of the nuclear factor of activated T cells (NF-AT) to the nucleus. This in turn prevents the formation and release of inflammatory cytokines (e.g. IL-2, IL-4, IFN-ϒ and other cytokines) and the proliferation of T cells, which is an essential part of atopic dermatitis. While both drugs act as inhibitors of calcineurin, their pharmacological profile is different. Tacrolimus, when used systemically, is a potent immunosuppressive drug enhancing graft survival after organ transplantation. Pimecrolimus is a selective pro-inflammatory cytokine inhibitor specifically developed for treatment of inflammatory skin diseases and is virtually inactive in transplant models. Pimecrolimus permeates through the skin less than tacrolimus and this may be explained by its higher lipophilicity. This means a lower degree of percutaneous absorption by pimecrolimus and a lower risk of systemic side effects.

Both tacrolimus ointment and pimecrolimus cream are applied twice daily and both have a rapid onset of action within 8 days of start of treatment. Tacrolimus ointment is indicated for the management of moderate to severe atopic dermatitis in patients 2 years of age and older. Two strengths are available: 0.03% ointment (age 2 years and up) and 0.1% ointment (age 16 years and up). Both concentrations are more effective than 1% hydrocortisone. 0.1% tacrolimus ointment has been shown to be equivalent

to a mid potency steroid (0.1% hydrocortisone-17-butyrate oint). Pimecrolimus cream is indicated in the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. There has been no trials comparing pimecrolimus cream to mild topical steroids. Comparison studies have shown that pimecrolimus cream is of similar efficacy to tacrolimus ointment 0.03%, but is less efficacious compared to tacrolimus ointment 0.1% or a mid potency steroid (0.1% betamethasone valerate). Both pimecrolimus cream and tacrolimus ointment can be applied safely to all skin areas and is useful for sensitive areas such as the face, eyelids, neck and skin folds. When applied at the first signs or symptoms of atopic dermatitis, both pimecrolimus cream and tacrolimus ointment have been shown to prevent flares and improve long-term disease control. The main side effect of both topical immunomodulators is irritation e.g. burning or pruritus and this is most common during the first few days and improves as lesions heal. The incidence of application site pruritus and burning ranges from 7% to 11% and is similar for both tacrolimus ointment and pimecrolimus cream. There does not appear to be a significant increase in systemic or cutaneous infections (with the possible exception of cutaneous HSV infections) and the response to immunization appears to be normal. Because of concerns regarding the potential for the development of cutaneous malignancy, patients should be counseled about sun protection, including the use of sunscreen when using the topical immunomodulators. Other long term safety issues pertaining to suppression of the immune system leading to an increased risk of lymphomas is still unsettled and the risk/benefit ratio of topical calcineurin inhibitor use must be explained and weighed for each patient, and the patient/parent and physician must decide what the best treatment regimen is at that time.

In conclusion, both pimecrolimus cream and tacrolimus ointment are welcome additions to the treatment of atopic dermatitis.