Pimecrolimus Tops Betamethasone in New Study

BY BRUCE JANCIN

BUDAPEST, HUNGARY — The calcineurin inhibitor pimecrolimus exerted more beneficial effects than betamethasone on the disrupted epidermal barrier of atopic dermatitis both structurally and immunologically, according to the results of a small randomized, double-blind study.

The take-away message from this study is that pimecrolimus (Elidel) may be the better option for long-term management of atopic dermatitis, Dr. Jens-Michael Jensen said at the annual congress of the European Society for Dermatological Research.

He reported on 15 atopic dermatitis patients with symmetrical lesions on their upper arms.

The patients were randomized to 3 weeks of twice-daily topical therapy with pimecrolimus 1% on one arm and betamethasone valerate cream 0.1% on the other.

Changes in epidermal barrier function were probed via electron microscopy, immunohistochemical staining, and gene array analysis of protein expression.

Betamethasone resulted in significantly greater clinical improvement and a more pronounced reduction in the epidermal hyperproliferation that is a hallmark of atopic dermatitis.

That being said, the change in epidermal proliferation induced by betamethasone went too far, with suppression to below-normal levels and epidermal thinning, whereas epidermal proliferation in the pimecrolimus-treated lesions was akin to that seen in healthy skin, according to Dr. Jensen.

After pimecrolimus therapy, the lipid bilayer architecture became regular and continuous, as in normal skin, while after betamethasone therapy, the lipid bilayer remained disrupted.

The treatment-related ultrastructural changes seen through the electron microscope were more favorable with pimecrolimus, as were the changes in expression of genes playing key roles in skin immunologic function, according to Dr. Jensen of the University of Kiel (Germany).

Electron microscopy showed extensive baseline disruption of the lipid bilayers at the stratum granulosum and stratum corneum interface in lesional skin.

The integrity of this lipid bilayer is critical to a well-functioning skin barrier, he explained.

After pimecrolimus therapy, the lipid bilayer architecture became regular and continuous, as in normal skin, while after betamethasone therapy, the lipid bilayer remained irregular and disrupted.

At baseline, lesional skin contained just 9% physiological lamellar bodies, while healthy skin contained 91%.

After treatment with pimecrolimus, 82% of lamellar bodies identified on electron microscopy were categorized as physiological.

In contrast, following betamethasone therapy only 9% of lamellar bodies were categorized as physiological—the same as in untreated atopic dermatitis.

Current thinking is that barrier repair prevents penetration of allergens into the skin, with subsequent immune sensitization and inflammation.

The emerging concept of atopic dermatitis is that barrier disruption is not a secondary event occurring in response to immunologic reaction, but rather is a primary event, he explained.

The expression of psoriasin, a chemotactic protein that plays an important role in fighting off penetration of the skin by *Escherichia coli*, essentially disappeared after 3 weeks of betamethasone therapy. So did expression of other antimicrobial peptides involved in innate immunity, including human beta-defensin-2 and -3 and RNase 7. The expression of genes controlling for stratum corneum keratin production was suppressed as well.

"This decrease is related to broad downregulation of general protein synthesis by the corticosteroid, which is not what we see with pimecrolimus," Dr. Jensen noted.

The expression of antimicrobial peptides was only mildly to moderately suppressed following pimecrolimus therapy. And the gene expression pattern for keratins became normalized, he said.

Dr. Jensen disclosed that the study was supported by Novartis (manufacturer of Elidel), which provided him with a travel grant. ■

Filaggrin Mutations Linked to Greater Skin Barrier Dysfunction in Atopy

BY BRUCE JANCIN

BUDAPEST, HUNGARY — Mild atopic dermatitis in patients with filaggrin mutations was associated with significantly greater skin barrier dysfunction than in patients with comparable wild-type atopic dermatitis in a comparative laboratory study.

This more pronounced epidermal barrier defect and skin permeability should allow greater penetration of antigens—which then draw an immune response resulting in contact sensitization and irritancy reactions—as well as predisposition to other atopic diseases such as hay fever and asthma, Dr. Sharizan Abdul-Ghaffar said at the annual meeting of the European Society for Dermatological Research.

'This certainly suggests that filaggrin-related eczema patients are less able to cope with irritancy.'

DR. ABDUL-GHAFFAR

This hypothesized chain of events was supported by the findings in the lab study of 13 patients with filaggrin-related atopic dermatitis (AD) and 45 controls with similarly mild AD without filaggrin mutations, according to Dr. Abdul-Ghaffar of the University of Edinburgh (Scotland). The subjects with filaggrin-related AD displayed significantly greater baseline transepidermal water loss on uninvolved flexor forearm skin than did controls. Moreover, the number of tape strips required to mechanically break the skin barrier, as signalled by achieving transepidermal water loss in excess of 20 g/m^2 per hour, was significantly less in the filaggrin-related AD group.

A 24-hour application of the irritant sodium lauryl sulfate in various concentrations resulted in dose-dependent increased transepidermal water loss in both patient groups. The increases, however, were consistently greater in the patients with filaggrin mutations.

"This certainly suggests that filaggrin-related eczema patients are less able to cope with irritancy and would explain the increased likelihood of developing problems such as irritant hand dermatitis," she said.

Eleven of the 13 (85%) AD patients with filaggrin mutations had hay fever, compared with 22 of 45 (49%) controls, but the prevalence of asthma in the two groups was similar.

In patch testing using the European Standard Series, 3 of 7 (43%) subjects with filaggrin-related AD developed more than five positive reactions, compared with just 1 of 25 (4%) controls with wild-type AD.

"All of these results certainly support an underlying barrier defect in the pathogenesis of filaggrin-related eczema," concluded Dr. Abdul-Ghaffar.

Several audience members said that they would have expected to see even bigger differences in the test results between AD patients with and without filaggrin mutations.

Dr. Abdul-Ghaffar said the explanation may reside in the selection bias deliberately introduced in the study. Filaggrin-related AD is often at the more severe end of the disease spectrum, but to be eligible for this study patients had to have mild AD. ■

Consider Ladder Approach To Treating Atopy in Kids

BY DAMIAN McNAMARA

SAN FRANCISCO — Start simple and use a step-wise approach to treat children with atopic dermatitis, Dr. Sheila Fallon Friedlander recommended.

"Atopic dermatitis matters so much because it can become infected, can impair physical and psychologic function, and has a tremendous effect on family quality of life," Dr. Friedlander said at a seminar on women's and pediatric dermatology sponsored by Skin Disease Education Foundation.

Using a ladder analogy, start at the bottom with repair of the skin barrier. The next rung is an intervention to short circuit inflammation. Then take care of itching, treat infections, address triggers, and educate patients and their family.

Is the family compliant? "This is extremely important. You need to get family to buy in to a treatment plan that is often complicated," said Dr. Friedlander of the University of California, San Diego.

Consider the age of the child, severity and duration of disease, and how much body surface area is affected.

Bathing can be beneficial to atopic skin if it hydrates the stratum corneum and removes dirt, scales, and bugs, but breaks in the skin can occur during evaporation, so bathing and moisturizers together are better than either alone, Dr. Friedlander said.

She is a fan of ceramide-based creams for atopic dermatitis. "Ceramides can decrease the amount of steroid you use or perhaps you can use [them] instead of steroids and do as well," she said.

If barrier repair does not work, the next step of the ladder is short circuiting inflammation. With corticosteroids for atopic dermatitis, use the weakest strength to do the job, blast and taper off, or consider weekend pulses of high potency steroids.

Topical calcineurin inhibitors are another therapeutic option. "There are a lot of data out there, so we know a lot about them," she said.

Dr. Friedlander's relevant disclosures include being a consultant for Astellas, Graceway Pharmaceuticals, and Novartis. She also receives research support from Astellas, Novartis, Promius Pharma, and SkinMedica. SDEF and this news organization are owned by Elsevier. ■