INSIGHTS ON ATOPIc DERMAtITIS

An expert discussion of pharmacologic management and emollient skin care

Xerosis is a hallmark feature of atopic dermatitis (AD) and is the result of skin barrier dysfunction that is now considered a factor in the pathogenesis of the disease. Recently released guidelines of care for the management of AD strongly recommend the use of moisturizers to treat xerosis based on Level I evidence showing that they can reduce disease severity and the need for pharmacologic therapy.1

There are a host of moisturizer options for patients to choose from, and they encompass both over-the-counter products, which are formulated with different emollient, occlusive, and/or humectant ingredients, and prescription medical device creams.2

In January, 2014, Eau Thermale Avène introduced three new products intended for the hygiene and care of dry skin prone to AD or itching: XeraCalm A.D Lipid-Replenishing Cream, XeraCalm A.D Lipid-Replenishing Balm, and XeraCalm A.D Lipid-Replenishing Cleansing OIl. Appropriate for use by individuals of all ages, both on the face as well as on the body, the XeraCalm A.D products came to the over-the-counter market after more than a decade of research and development, offering unique ingredients and other formulation characteristics desirable in topical agents for patients with AD.3

Recently, a group of leading dermatologists convened to discuss these new products in the context of understanding AD pathophysiology, principles of AD management, the findings of in vitro and clinical studies pertaining to the XeraCalm A.D product line, and early patient experience. Following are highlights of their conversation.

FAcULTY

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Table 1. XeraCalm A.D Product Line

<table>
<thead>
<tr>
<th>Product</th>
<th>Key Ingredients</th>
<th>Main Characteristics</th>
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<tbody>
<tr>
<td>XeraCalm A.D</td>
<td>Avène Thermal Spring Water 66%</td>
<td>Formulated for sensitive dryness</td>
</tr>
<tr>
<td>Lipid-Replenishing Cream</td>
<td>Hydrocortisone 2.5%</td>
<td>Fragrance-free</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 0.4%</td>
<td>Prescription-free</td>
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</table>
|                           | Cer-omega 2.3%                                                                   | Ointment maintains skin integrity and prevents 
|                           | Lipid phase 20%                                                                  |    noninflammation during use                             |
| XeraCalm A.D              | Avène Thermal Spring Water 56%                                                  | Formulated for severe dryness                             |
| Lipid-Replenishing Balm   | Hydrocortisone 2.5%                                                             | Fragrance-free                                            |
|                           | Hydrocortisone 0.4%                                                             | Prescription-free                                         |
|                           | Lipid phase 30%                                                                 | Ointment maintains skin integrity and prevents 
|                           |                                                                             |    noninflammation during use                             |
| XeraCalm A.D              | Avène Thermal Spring Water 70.6%                                                | For use in the shower or bath                             |
| Lipid-Replenishing        | Hydrocortisone 2.5%                                                             | Physiological pH                                          |
| Cleansing OIl             | Hydrocortisone 0.4%                                                             | Soap-free                                                |
|                           | Lipid phase 7%                                                                  | Fragrance-free                                            |

DFI = Device for Exclusive Formula Integrity

ISSUES IN AD MANAGEMENT

Dr. Eichenfield: Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease that has increased in prevalence in much of the industrialized world.1 It usually begins in infancy and often resolves or goes into sustained remission by adulthood. Recent data from the United States and other industrialized countries indicate that AD affects between 15% and 30% of children and 2% to 10% of adults.2

AD is well known to have a profound negative impact on quality of life, both for patients and the families of affected children, related to the signs and symptoms of the disease, particularly the itching and rash, and its association with sleep disruption and secondary infections.

Dr. Goldenberg, do you want to emphasize other features of AD that are important issues for our patients?

Dr. Goldenberg: I think the cyclical nature of the disease is something that a lot of patients struggle with and that many physicians fail to clearly explain. Due to the nature of my university practice setting, many of the patients I see with AD are coming in for a second or third opinion, and in my conversations with them, it is clear that they don’t understand the relapsing and remitting nature of their disease. I think it is very important to bring that point home to patients so that they will expect to have periods of good control and periods of worsening.

Dr. Lio: totally agree with that. Something that I like to emphasize is the fruitlessness of trying to identify a single trigger for AD flares. Patients with AD may be sensitive to a variety of triggers, which might include emotional stressors, weather changes, and environmental irritants. That knowledge establishes a foundation for understanding the importance of a maintenance care regimen that will optimize the skin barrier and keep it fortified, so to speak, even between flares. That is where the use of moisturizers to improve skin hydration has an essential role in the care of AD.

Dr. Goldenberg: These are great points. I primarily treat adults in my practice, and I often see patients in my population with AD who have been trying to achieve disease control by focusing on a specific trigger. Some patients have been identified as allergic to various substances though patch testing and swear that they have been avoiding exposure to those agents. Therefore, they are puzzled and frustrated that they are still experiencing AD flares. So, it is extremely important that patients realize that there are numerous triggering factors for AD.

Dr. Eichenfield: The potential for AD to be a persistent disease is another feature that I think is not completely appreciated by some physicians, particularly primary care physicians. There is a subset of patients with AD who have active disease for months, and occasionally years, at a time. Although these disease may be fairly well controlled with a variety of topicals, these patients still have a burden of disease that mandates a level of care different than what would be used in patients who are able to achieve sustained clearing.

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—Peter A. Lio, MD

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AD PATHOPHYSIOLOGY

Dr. Eichenfield: Now, let’s discuss the pathophysiology of AD because understanding it guides our treatment.

Dr. Lio: The pathophysiology of AD is complex and multifactorial, and that is why it can be a therapeutic challenge. In my mind, I don’t think about AD as being a single disease, but rather as a heterogeneous disorder with multiple underlying causes that can result in a similar clinical manifestation. The concept that there are likely different subtypes of AD is something that I am increasingly coming to terms with because I think it may explain why patients with inflammatory disease are not responding to our standard therapies.

We know that impaired skin barrier function is a major factor in the pathophysiology of AD, and in that regard, it has been very exciting to learn more about the role of filaggrin gene mutations in skin barrier dysfunction. There is also a proinflammatory, immunologic component, but I think any discussion about whether the impaired skin barrier or an immunologic abnormality is the primary factor in AD pathophysiology is like talking about which came first, the chicken or the egg. We know that both are involved and need to be addressed from a therapeutic standpoint.

Dr. Eichenfield: I agree with those concepts. It is interesting that our insights on the pathogenesis of AD change based on emerging research and that there may be a focus on a particular area for perhaps years at a time, but then the emphasis may shift when new findings are reported. However, we can say there is evidence that a significant subset of patients with AD have a fundamental genetic defect in their skin barrier that explains the dry skin, and to some degree, their susceptibility to develop a proinflammatory response to exogenous agents. There is still a lot of debate on the general aspect of the pathogenic pathway. At the same time, with the advent of advanced laboratory techniques, including genomic profiling, researchers are taking a more extensive look at the immunologic characteristics of lesional and non-lesional skin in patients with AD and skin of normal controls.

Another area of active research is evaluating microbial colonization. Findings from some recent studies have suggested new ideas on how colonization with Staphylococcus aureus drives inflammation in AD, and I believe we are entering into a period that will, at least initially, be very confusing as researchers try to figure out if and how microbial colonization of the skin and the gut influence each other and impact the immune system. There is also interest in sorting out whether or not mediating exposure to microbes early in life, or in patients with established AD, affects the onset and course of disease.

The bottom line in terms of translating current scientific understanding about the pathophysiology of AD into clinical practice is that management must account for the fact that AD is a multifactorial disease. Meanwhile, we will stay tuned for new research advances that elucidate the contributions and interactions between genetics, immunology, and environmental factors.

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—Peter A. Lio, MD

AD MANAGEMENT PRINCIPLES

Dr. Eichenfield: Let us shift now to the management of AD. Dr. Lio, could you please talk about the standard goals?

Dr. Lio: Management of AD requires a multipronged approach involving four major areas that may all need to be addressed for optimal disease control. Skin hydration is the first aspect, and it is an integral part of the management regimen for all patients, whether or not they have active disease. Secondly, there is anti-inflammatory treatment. Topical corticosteroids are the mainstay, but there is a need to balance their benefit and potential risks, and so there is also a role for use of nonsteroidal medications, such as topical calcineurin inhibitors. The third area relates to antimicrobial management, and that is important not only with respect to treating secondary infections, but also because of evidence that bacterial colonization may be promoting disease activity through a variety of mechanisms. For example, a recent paper described delta-toxin released by Staphylococcus aureus that could stimulate the immune system to cause inflammation. Because abnormal microbial colonization appears to be fueling the disease more generally, the strategies have been forced to change from those used for simply treating an infection. While topical and oral antibiotics might still be helpful, decreasing colonization through the use of broad antiseptics, such as diluted bleach baths, may be more appropriate and carry less risks for some. Information on how to use for treating bacterial flora is controversial, and while exciting, their use is something that we currently have limited data on. Finally, we need to think about management of pruritus. Sometimes AD is referred to as “the itch that rashes.” It is not only a bothersome symptom affecting quality of life, but the scratching it induces promotes inflammation that exacerbates both the rash and the itch. Unfortunately, finding effective antipruritic agents to break the itch-scratch cycle remains the Holy Grail for effective management of AD. Part of the challenge has to do with the fact that the itch is mediated by multiple mechanisms involving neural pathways and immunologic factors.

Dr. Eichenfield: It is important that we also mention the potential need for more aggressive treatment with phototherapy or systemic immunomodulating agents. The nature of my practice in an academic setting is that I need to see mostly patients who have very severe or refractory disease, and that group of patients, there is an important role for more aggressive therapies. I think we need to highlight their role, recognizing that today in the United States, a lot of medical dermatology patients are being seen by physician assistants and nurse practitioners who, while working under the supervision of a dermatologist, may not be familiar with the role of systemic medications.

Dr. Eichenfield: It is important to realize that systemic therapy may sometimes be needed for the management of AD. I think that experts in AD management understand that patients will do much better in the long run if they receive treatment that is appropriately aggressive to control their inflammation. The analogy I like to use is that effective anti-inflammatory treatment rebalances the system. When there is significant persistent inflammation, even locally, the burden of the disease ends up being much higher.

Dr. Goldenberg: I totally agree with you. I think it is easier and better to use whatever treatment we need to achieve disease control and then maintain the improvement with topical agents than to be relying only on topical medications and having the disease was and were for years, never really getting the patient to a state of good control. I think we should also mention that there are several investigational agents for AD in the pipeline, including new biologics and small-molecule therapeutics. Dr. Eichenfield, I believe you have said that dermatology has seen a decade of drug development for psoriasis, and we now can anticipate a decade of new therapies for AD. I think it is important for physicians and patients to understand that there are new treatments coming around the corner.

Dr. Eichenfield: It is certainly helpful for patients to know that there is a lot happening, and a lot of promises, in the area of new treatments for AD. Dr. Lio and I have discussed the idea that the lack of advances in pharmacother- apy for AD is one of the reasons why patients are often seeking out alternative or complementary medicine options. The situation is changing, and we are now in a time of rapid development, with emerging systemic agents and other modalities that will give us new tools to help control the disease.

XeraCalm A.D.—RESEARCH & DEVELOPMENT

Dr. Eichenfield: While we have just emphasized the importance of anti-inflammatory agents in treating AD, Dr. Lio stated previously, management of xerosis is a mainstay of care for all patients with AD, regardless of their disease severity. Increasing skin hydration will help improve the skin barrier and help control pruritus and inflammation. To address this need, Pierre Fabre has introduced a new line of XeraCalm A.D. Lipid-Replenishing products consisting of a cream preparation, a balm, and a cleansing oil. These products have an interesting development history, and based on their ingredients and other features, they seem very well suited for patients with AD.

All three products contain a high concentration of Avène Thermal Spring Water, Xeracalm A.D., and Cer-omega. Xeracalm A.D. is a patented complex of lipopolysaccharides, amino acids, and sugars derived from natural microflora species found in the thermal spring water. Cer-omega is a proprietary complex of ceramide-like molecules and omega-6 fatty acids that has been shown to restore the skin barrier and reduce xerosis.6 For hundreds of years, and in this day, patients with dermatological diseases have gone to the Avène hydrotherapy center for treatments with thermal spring water, and there are clinical and in vivo study data showing its benefits.1,4

“Management of xerosis is a mainstay of care for all patients with AD, regardless of their disease severity. Increasing skin hydration will help improve the skin barrier and help control pruritus and inflammation.”

—Lawrence F. Eichenfield, MD

Pierre Fabre has been incorporating Avène thermal spring water into their skin care products for years, but about a decade ago, scientists of the company’s research center began undertaking studies to better understand what active ingredients in the water, in addition to its mineral content, might explain its benefits. Their work led to the identification of a bacteria, A. dolomiae, which is part of the water’s microflora, and the determination that compounds produced by A. dolomiae were biologically active.

Pierre Fabre was able to scale up production of the bacteria’s active substances to produce the complex they named Xeracalm®. Subsequently, results published as a promotional supplement to Dermatology Times®

Published: a promotional supplement to Dermatology Times®
**XeraCalm A.D Clinical Trials**

The effects of XeraCalm A.D products when used by patients with AD were investigated in a series of clinical studies. 6,12,13,18,19 Patients enrolled in all trials had to have documented atopic dermatitis and be at least 12 weeks old and used XeraCalm A.D products for 1-3 months. 6,12,13,18,19 A controlled study enrolled 54 children ages 1 to 4 years old with mild AD (SCORAD 5 to 25), who were randomized to use either XeraCalm A.D Balm or XeraCalm A.D Cream. 6,12,13,18,19 After 3 weeks, mean SCORAD scores were reduced by 80% from baseline in the pediatric subgroup and 85% in children over 12 years. After 4 weeks of treatment in the pediatric subgroup, mean SCORAD was reduced by 84% from baseline (P < .0001), and at study conclusion, xerosis severity was rated as 1 (scale 0 to 3) and SCORAD of 15 to 25. After 3 weeks, the pediatric subgroup showed a significant improvement in SCORAD and xerosis severity compared to baseline. 6,12,13,18,19

Changes in the SCORAD and pruritus severity scores can be depicted in Figures 1 and 2. In addition to the in vitro tests with Modulia, Pierre Fabre conducted clinical studies with the XeraCalm A.D products. The clinical research program included a series of studies using standard protocols to document tolerance in both healthy individuals and patients with AD. Additionally, there were clinical tolerance and efficacy studies in both adults and children with AD. 6,12,13 [SEE SIDEBAR]

**Dr. Eichenfield:** In first learning about the XeraCalm A.D products, I was very impressed by the work undertaken by Pierre Fabre to isolate, identify, and characterize the active bioactive component in the botanical thermal spring water and by the extent of the clinical research performed. The development program was much more comprehensive than we might expect to see for a non-prescription product, but I believe Pierre Fabre decided not to pursue medical device approval in order to make the products more affordable and more easily accessible for patients. The fact that the cream and balm products are sterile and contain no preservatives is something I think is particularly exciting, and Pierre Fabre should be congratulated for their innovative manufacturing and packaging methods that make it possible for these products to be preservative-free.

**Dr. Goldenberg:** Before I do, I also want to mention how impressed I was with the research commitment Pierre Fabre made to develop these skin care products and by the amount of data that is available. The in vitro data on the effects of Modulia on inflammation and itch is particularly interesting.

In terms of my personal experience, I have a handful of patients who have used the XeraCalm A.D products so far. A few of those patients had more severe AD and did not achieve much improvement after just a couple of weeks of use.

In contrast, patients whose disease was more moderately severe achieved greater benefit. One patient with a particularly good response had moderate disease that was being treated with a topical corticosteroid, and he achieved complete clearing of 2 weeks after starting use of XeraCalm A.D (Figure 5).

However, regardless of the extent of their improvement, most patients preferred XeraCalm A.D over the moisturizer they were using at baseline. And, the patient I discussed who had such a great response continues to call my office periodically to see if any samples are available.

Notably, some of my patients seemed to particularly like the balm, which is a thicker product and seems more protective than some other moisturizers that are available.

**Dr. Goldenberg:** I think the XeraCalm A.D products are good for addressing patients with severe AD (Figures 6 and 7), which is a critical clinical feature of AD. They are not a replacement for our standard anti-inflammatory medications, but I believe that they can be a valuable addition to our management plan.

**Dr. Eichenfield:** Based on my experience, I think these products are great for addressing patients with severe AD, and they are an important part of our standard treatment regimen for patients with AD.

**“Some of my patients seemed to particularly like the balm, which is a thicker product and seems more protective than some other moisturizers that are available.” — Gary Goldenberg, MD**

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**XeraCalm A.D — USER EXPERIENCE**

**Dr. Eichenfield:** We have all had the opportunity to use these products on our patients. Let’s talk about that experience. Dr. Goldenberg, please begin.

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**Dr. Eichenfield:** The clinical research program involved almost 1300 subjects, of whom more than 650 were patients with AD. The tolerance studies established gynecologic and eye tolerance in addition to skin tolerance, and benefits in patients with active AD were demonstrated using a number of standard assessments. The clinical studies showed patients using the XeraCalm A.D products had decreased transdermal water loss and improvements in the SCORAD of patients treated with XeraCalm A.D products (SCORAD) Index, in addition to changes in pruritus, severity, and quality of life. So, overall I think we can say there exists a broad set of data from a number of studies that establish tolerance and utility for the XeraCalm A.D products.

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**Dr. Goldenberg:** I also think the cream and balm products can be considered an excellent moisturizer option, and in patients with mild or moderate disease who need anti-inflammatory treatment, perhaps they may be combined with an intermittently used topical corticosteroid or calcineurin inhibitor.
The fact that the Xeracalm A.D Balm and Cream contain no preservatives really distinguishes them from other moisturizers. Some products may be paraben-free, but still contain other preservatives, such as BHT.

—Gary Goldenberg, MD

Dr. Goldenberg: I agree that it would be especially nice to see head-to-head comparisons between the Xeracalm A.D products and available OTC bland emollient products, which may be less expensive. Price is not a major sticking point for a sizeable segment of the patients I see in my Manhattan practice. However, it may become a bigger issue in the future as insurers are increasingly pushing the costs of AD care onto the patients. In that regard, the prescription emollient devices that can be used for AD management are almost never covered by insurance. Compared to agents in that category, the Xeracalm A.D products are more accessible to patients and perhaps more affordable.

Dr. Eichenfield: It is nice to have products that patients can directly purchase so that we can avoid issues with formulary restrictions. Cost is something that physicians should always be conscious about whether we are prescribing medications or recommending OTC products to our patients. We also need to consider whether or not a more expensive product has benefits that justify or outweigh a higher cost for a particular patient. Pricing of the Xeracalm A.D products compared to some other OTC moisturizers likely reflects the investment spent on research and development, and the costs of the sterile manufacturing process and novel packaging. While we don’t have any information from comparative studies with the Xeracalm A.D, these products do appear to stand out from some of the OTC competitors based on their being preservative-free, the wealth of tolerance data, and the science behind the natural ingredients. As we see how the products fit into the maintenance regimens that are so important for our patients, perhaps we will find that they enhance control of the disease and lessen the development of flares requiring treatment with prescription medications, which could be a cost-saving advantage. To conclude, I think our discussion highlights the features of the Xeracalm A.D line and puts that information into perspective in terms of our understanding of AD pathophysiology and our needs for management options to control inflammation by optimizing the skin barrier. This review should be helpful to dermatologists to familiarize them with these new products as they explore how the products may fit into their clinical practice.

REFERENCES