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# Recent Advances in the Management of Atopic Dermatitis

## Proceedings of a Clinical Roundtable

### Topic Areas

The Clinical Landscape of  
Atopic Dermatitis

Recent Developments in the  
Management of Atopic Dermatitis

Quality-of-Life Issues

Infection in Atopic Dermatitis

Conventional Treatment Options:  
Corticosteroids, Calcineurin Inhibitors

Safety Issues

New Nonsteroidal Option

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## Recent Advances in the Management of Atopic Dermatitis

- 3 **Introduction:  
The Clinical Landscape of Atopic Dermatitis**
- 4 **Recent Developments in the Management of Atopic Dermatitis**
- 4 **Quality-of-Life Issues**
- 5 **Infection in Atopic Dermatitis**
- 6 **Conventional Treatment Options:  
Corticosteroids, Calcineurin Inhibitors**
- 7 **Safety Issues**
- 7 **New Nonsteroidal Option**

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# Introduction:

## The Clinical Landscape of Atopic Dermatitis

As pediatricians, dermatologists, and allergists know, atopic dermatitis is a chronic relapsing skin disorder that manifests as itchy, dry skin and a characteristic rash that cycles through periods of exacerbation and remission. Epidemiologic studies have documented a steady increase in the prevalence of atopic dermatitis since the 1960s.

Current prevalence estimates indicate that atopic dermatitis affects between 7% and 21% of the population in the United States. Approximately 60% of cases arise during the first year of life, and an additional 25% of cases develop between 1 and 5 years of age.<sup>1-3</sup>

Atopic dermatitis has a strong genetic component. The likelihood that a child will develop atopic dermatitis, asthma, or allergic rhinitis is about 60% if one parent has an atopic diathesis and 80% if both parents are affected.<sup>4</sup>

In many cases, the appearance of skin symptoms early in life marks the beginning of what is commonly called the “atopic march.” At least half of all children with atopic dermatitis develop asthma or allergic rhinitis later in life, suggesting an ongoing atopic process. Atopic dermatitis seen in infancy or early childhood is often followed by food allergies and then asthma within 7 years of age. The prevalence tends to peak at 5 to 6 years of age. Allergic rhinitis is often a later manifestation of the atopic cascade.<sup>5</sup>

In many cases, atopic dermatitis improves by late adolescence. However, in a substantial proportion of cases, the condition will continue to affect patients into adulthood.

Currently, no cure exists for atopic dermatitis, although the condition can be controlled with various maintenance and therapeutic strategies. A comprehensive disease management strategy comprises patient/parent education, skin hydration, symptom relief, and prevention of secondary complications.

Corticosteroids have long represented the basis for effective treatment of atopic dermatitis. Other therapies, including antibiotics and antihistamines, are also used frequently, but generally as adjuvant therapies, with modest benefits. More recently, calcineurin inhibitors have been evaluated and used as therapy for atopic dermatitis. Use of these agents has been accompanied by concerns about cancer risks and potential hazards related to immunosuppressive effects, although data documenting these effects with topical use are scant. New nonsteroidal topical agents may be useful to improve barrier dysfunction and minimize symptoms of atopic dermatitis.

A nonsteroidal cream called Atopiclair™ (MAS063DP) has provided clinicians with a new tool to manage atopic dermatitis. It received US Food and Drug Administration clearance as a prescription medical device for relief of symptoms of atopic dermatitis. The product has been shown to provide rapid improvement of pruritus and erythema and reduce the skin area affected by atopic dermatitis. Atopiclair improves the skin environment which may reduce the occurrence of future flares.

Emollients, topical corticosteroids, and topical calcineurin inhibitors remain essential components of the overall clinical management of atopic dermatitis. Regular use of an emollient prevents drying and helps maintain skin condition and integrity. Topical corticosteroids are available in a variety of formulations and potencies that make them applicable to the entire spectrum of atopic dermatitis severity. Several years of clinical experience with topical calcineurin inhibitors have established the agents as a component of standard pharmacologic therapy for atopic dermatitis. Calcineurin inhibitors offer an effective alternative when topical corticosteroids are undesirable to use or prove to be ineffective.

This supplement to SKIN AND ALLERGY NEWS summarizes the data, information, and expert opinions presented during a recent roundtable discussion of current issues related to the management of atopic dermatitis. The expert roundtable was chaired by Lawrence F. Eichenfield, MD, of the University of California, San Diego. He was joined by Sarah L. Chamlin, MD, of Northwestern University in Chicago; Sheila Fallon Friedlander, MD, of the University of California, San Diego; and Wm. Philip Werschler, MD, of the University of Washington in Seattle.

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## Recent Developments in the Management of Atopic Dermatitis

**DR EICHENFIELD:** Why don't we begin the discussion with the landscape of therapy in atopic dermatitis? When you see a patient for the first time, what is your general approach to treatment?

**DR CHAMLIN:** I want to know what treatments patients are already using, which treatments they think have worked, and which have not worked. I often advise them to try the same therapies again, emphasizing the importance of using therapies in combination. I address the issues of skin inflammation, dry skin, itch, and infection, if they are present.

I encourage them to use a bland, fragrance-free emollient that is a thick, not a light, lotion. I discuss the importance of bathing daily or every other day in lukewarm water. Patients should apply emollients after bathing and several other times during the day.

**DR WERSCHLER:** If patients are using what I consider to be a reasonable emollient and they do not seem to have any problems, then I discuss the frequency of use. If patients are using a scented product, I might suggest that they switch to an unscented product.

**DR FRIEDLANDER:** With pediatric patients, I try to determine the parents' expectations right away. Many parents are fearful of topical corticosteroids. Some have unfounded fears that virtually any type of product will cause an allergic reaction or some other problem. Some parents have concerns about elegance. They are unwilling to use a product because they consider it too greasy or they don't like the way it feels. I also want to know what treatments my patients have been using.

**DR CHAMLIN:** Many parents begin a visit by saying that certain treatments didn't work. I have to determine what they mean by that. A product might have been ineffective because the patient had an infection

that was not treated. A treatment might have seemed ineffective because the patient was not having all aspects of disease managed, such as sleep disruption.

**DR WERSCHLER:** Education of the family is critical in the management of atopic dermatitis. I use printed informational materials, but I also spend some time educating patients about the disease process, about how skin grows, and about the principles and approaches to managing the problem.

I discuss seasonal flares, and I ask the parents about their child's activities. I want to know about potential irritants or allergens in the patient's environment. Are pets in the house? Do the pets sleep with the child? Psychosocial stressors, such as parental discord, divorce, or problems in school, are often overlooked as a source of flares. I think there is a psychosomatic component to the disease, and it is very important to discuss these issues.

**DR FRIEDLANDER:** Many parents need to be educated about the difference between prevention of flares and intervention during a flare. Parents often view atopic dermatitis as an acute condition that will resolve with treatment and never recur. Parents need to understand that atopic dermatitis is a chronic condition and that regular use of emollients and other medications may be necessary to prevent flares.

**DR WERSCHLER:** When discussing non-pharmacologic intervention, clinicians should identify lifestyle issues that can be managed. Many parents have false beliefs about the causes of atopic dermatitis. Clin-



"Education of the family is critical in the management of atopic dermatitis."

—Dr Werschler

icians should take time to explore those beliefs. Otherwise, the patient may continue to live in a household with aggravating factors. Parents may think their child needs to be bathed three times a day. Identifying and discussing false beliefs or misinformation, whether from the Internet or another source, is a good starting point for discussions with parents, but the process takes time.

**DR CHAMLIN:** Many parents unnecessarily restrict their child's diets because of unfounded fears and false beliefs. If parents are anxious about the home environment, they might want to replace carpeting with hardwood floors, purchase dust mite covers and special air filters, and get rid of the family pet. In most cases, those types of changes do not make a big difference with respect to prevention of flares or managing the disease. I encourage parents to minimize drastic environmental measures because management of the household environment is a small part of the overall approach to clinical management.

**DR FRIEDLANDER:** Sometimes parents carry dietary restrictions too far, which can lead to drastic results. At Children's Hospital, periodically we see children who are protein deficient and malnourished because well-intentioned family members have eliminated everything from their diet that they think their child is allergic to. They have removed milk protein, they have removed soy, and children are admitted in life-threatening conditions because they are protein wasted.

### Quality-of-Life Issues

**DR EICHENFIELD:** Do you think it is helpful to discuss quality-of-life issues with families?

**DR CHAMLIN:** I do. I always ask parents how they feel about their child's condition. Physicians must be prepared for parents' responses and reactions, because quality of life comprises a separate list of issues and problems.



"Many parents are fearful of topical corticosteroids."

—Dr Friedlander

**DR EICHENFIELD:** What is the role of pruritus management?

**DR CHAMLIN:** I think pruritus is at the center of quality-of-life issues in atopic dermatitis. Itch increases the likelihood of sleep disruption in the child, which will disrupt the parents' sleep. A comparison of scores on an itch scale and a quality-of-life scale will show a high correlation.

Co-sleeping and sleep disruption due to atopic dermatitis affect the entire family. Children with atopic dermatitis are much more likely to sleep with their parents and to be patted all night to keep them from scratching.<sup>1</sup> Parents might lie with the child between them, and each parent holds a hand to keep the child from scratching. Parents might sleep in separate bedrooms and alternate sleeping with the itchy child. Pruritus affects a child's overall function, activities, social interactions, and friends they can visit.

In my own qualitative and quantitative studies, I have found that emotional issues have a key role in atopic dermatitis, and that role has not been emphasized in previous quality-of-life research.<sup>2</sup> The parents feel guilty about their child's condition. The parents are embarrassed by the child's appearance, but they have great difficulty acknowledging that embarrassment. As children with atopic dermatitis grow older, they have problems with self-esteem and other forms of social and personal dysfunction. Quality-of-life issues have been summarized in *Pediatrics*.<sup>3</sup>

**DR FRIEDLANDER:** Clinicians believe pruritus is extremely important. I think the best hope for effective pruritus management is to restore the skin barrier and reduce local irritation.

**DR EICHENFIELD:** Some relatively new data have emphasized the importance of addressing skin-barrier dysfunction. Immunologic studies have shown that immunoglobulin E responsiveness to specific antigens that penetrate the barrier strongly influences the clinical course. In partic-



"I think pruritus is at the center of quality-of-life issues in atopic dermatitis."

— Dr Chamlin

ular, atopic patients develop a significant, ongoing inflammatory response, with some patients having something akin to "autoallergic" eczema. Antigens that penetrate the skin barrier may cause reactions that evolve into ongoing autoreactive processes. Also, recognition of a subset of atopic dermatitis patients with genetic barrier dysfunction, as well as information on the atopic march, might provide the impetus over the next few years to become more

aggressive about identifying an abnormal skin-barrier function in early life and taking steps to improve barrier health. I would be interested to see whether increased diligence in treating barrier dysfunction influences the overall course of atopic dermatitis.

**DR WERSCHLER:** I think it would be fair to say that as part of the paradigm shift in the management of atopic dermatitis, we have gone from a more reactive approach to therapy—such as managing flares—to a more proactive approach. We have a better understanding of the disease process, and we consider not only barrier repair, but also prevention of barrier breakdown.

**DR FRIEDLANDER:** If a patient has an intact skin barrier, exogenous agents are less likely to penetrate the skin and trigger a reaction. That emphasizes the importance of emollients and other treatments to protect the skin barrier.

### Infection in Atopic Dermatitis

**DR EICHENFIELD:** How important is infection in atopic dermatitis?

**DR FRIEDLANDER:** Infection can be an important issue in patient management. If physicians treat infected children with topical therapies and antihistamines—without treating the infection—the treatments may do little or no good. Bacterial infections are the principal concern, but viral and fungal infections can also be a problem, particularly in childhood atopic dermatitis. A new concern is community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). The prevalence is very high in many cities. MRSA is even more of a concern for those of us who treat children with atopic dermatitis because we cannot casually give infected children a cephalosporin or some other antibiotic and expect that to solve the problem.

When children itch, they scratch, and the act of scratching can inoculate and give rise to an infection. Physicians also have to worry about skin-surface bacteria that may be elaborating toxins that can initiate a tremendous inflammatory cascade (the superantigen effect). Inflammation is an important issue in atopic dermatitis, so anything that stimulates the inflammatory cascade may lead to difficulty in eliminating pruritus and eradicating skin lesions.

**DR EICHENFIELD:** There is marked regional variation in the prevalence of MRSA. Some areas have such a high prevalence of MRSA in their patients with atopic dermatitis that the standard recommendations for bathing have been changed. In Houston, for instance, many patients are treated with bleach baths. Historically, bleach baths have been avoided because of concern that the bleach would dry the skin and complicate the management of atopic dermatitis. In Houston, a dilute bleach has become part of the standard regimen because bleach has very broad anti-infective properties.

San Diego has a very high prevalence of community-acquired MRSA, but the prevalence of MRSA in the very large patient population with atopic dermatitis is



"Some relatively new data have emphasized the importance of addressing skin barrier dysfunction."

— Dr Eichenfield

not very high. I have wondered whether the low prevalence of MRSA in patients with atopic dermatitis is a reflection of an aggressive approach to antiinflammatory and maintenance therapy. We know that inflammation promotes bacterial colonization. I wonder whether good skin-care regimens minimize bacterial colonization, decreasing the need for frequent intermittent antibiotics, which may promote resistance.

**DR FRIEDLANDER:** Bleach baths probably are a good idea for all children who have recurrent infection, regardless of whether it is MRSA, as long as they are not unduly irritated by the baths. Dr Moise Levy, Professor of Dermatology, Baylor College of Medicine, Houston, and others have investigated the effect of such bleach-bath treatments on the prevalence of infection in patients with atopic dermatitis, and we are all awaiting the results of that study. We know that such treatments have been used with success by the surgical and dental communities. I think physicians are becoming more comfortable with dilute-concentration bleach baths for children who are at risk for recurrent infections, but it will be helpful to have data from studies to confirm the efficacy of such treatments.

### Conventional Treatment Options: Corticosteroids, Calcineurin Inhibitors

**DR EICHENFIELD:** Traditional antiinflammatory therapy now includes topical corticosteroids and topical calcineurin inhibitors (TCIs). Dermatologists and pediatricians are experienced in the use of topical corticosteroids and TCIs such as pimecrolimus (Elidel<sup>®</sup>) and tacrolimus

## New Clinical Strategies Aim to Restore Barrier Function

Investigation of new therapeutic strategies for atopic dermatitis increasingly focuses on the concept of barrier repair. Atopic dermatitis compromises skin-barrier function, resulting in transepidermal water loss and xerosis.

In part, barrier disruption appears to arise from depletion of physiologic lipids, including triglycerides and polyunsaturated fatty acids. Recent studies have demonstrated that physiologic lipid replacement accelerates dermal restoration of the stratum corneum, which plays a key role in healthy skin-barrier function.<sup>1,2</sup> Restoration of the normal epidermal barrier may facilitate moisture retention and afford protection from irritants. As a result, therapies aimed at barrier restoration might help reduce flares in atopic dermatitis and other inflammatory skin disorders.

Current management strategies for atopic dermatitis focus on symptom relief, including pruritus, erythema, and inflammation. Moisturizers help relieve symptoms by providing a temporary skin barrier. Prescription therapies for symptom relief often do not support skin-barrier function, and in some instances, might even damage the stratum corneum.<sup>3,4</sup>

A desirable therapy for atopic dermatitis would contribute toward four key therapeutic goals:

- Provide symptom relief and reduce the risk of recurrence by nonsteroidal mechanisms
- Restore skin lipid barrier function
- Be safe for use in patients of all ages
- Enhance long-term clinical management

Topical agents containing lipophilic and hydrophilic compounds offer one promising strategy to address those goals.

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(Protopic<sup>®</sup>) as antiinflammatory therapy for atopic dermatitis. What are the trends with these therapies? How do they figure into families' or physicians' concerns?

**DR CHAMLIN:** For a flare, I think most physicians are using a mid-potency or

mid- to high-potency corticosteroid. As soon as the patient improves, we step down to a calcineurin inhibitor or a lower-potency corticosteroid. At the same time, we recommend the use of emollients and address itch and infection.

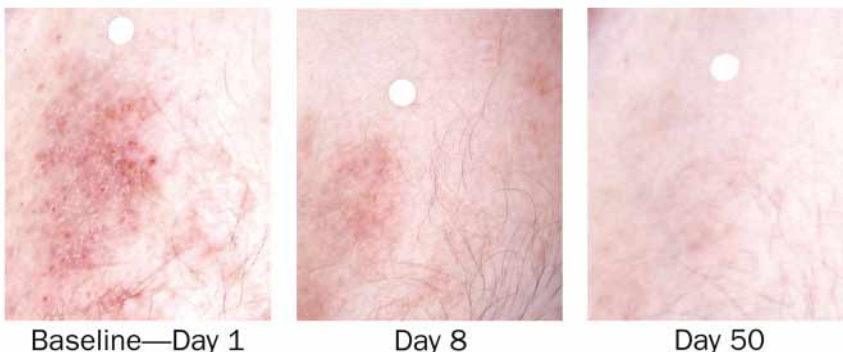
**DR EICHENFIELD:** How long do you continue the therapy?

**DR CHAMLIN:** If the patient is using a mid- to high-potency corticosteroid, the treatment is administered twice a day for 5 to 7 days. Usually within a week, a patient will be under better control and can be stepped down to a calcineurin inhibitor.

**DR EICHENFIELD:** How long does that continue?

**DR CHAMLIN:** Patients periodically might use corticosteroids locally on "hot spots" for a month. Often, patients have persistent areas of disease requiring treatment, typically

Images: Improvement vs baseline with MAS063DP (Atopiclair)



This series of clinical photographs of a target atopic dermatitis lesion show that treatment with MAS063DP (Atopiclair) resulted in rapid improvement by day 8 and near-total resolution by day 50.

on thicker-skinned areas, such as the hands, the elbows, and the knees.

**DR FRIEDLANDER:** With some difficult cases, patients cannot stop using corticosteroids or TCIs. Sometimes, these children have to use TCIs during the week and moderate-potency corticosteroids on the weekend. That regimen helps patients avoid problems. The goal always is to get patients off treatment as soon as possible, but some children with really severe disease go through periods of their lives when they cannot stop treatment right away. Often, the only recourse to such chronic therapy would be systemic agents, such as cyclosporine or systemic corticosteroids, which have a significantly higher risk profile.

### Safety Issues

**DR EICHENFIELD:** For acute flares, we still rely on topical corticosteroids. Depending on the age of the patient and the severity of the flare, we will use a higher-strength topical corticosteroid. There is remarkably good concordance between potency and side effect profile. As a result, there is more concern about longer-term use of more potent agents than of a milder topical corticosteroid.

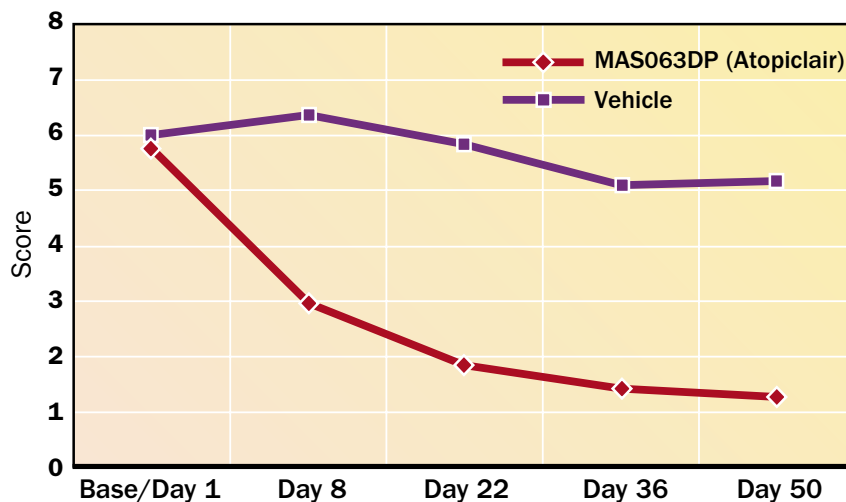
With respect to the TCIs, several years of experience have helped make us comfortable in terms of their safety, but there certainly have been concerns expressed, as noted in the US Food and Drug Administration (FDA) black-box warning about continuous use of these products. I think there has been a marked change in perspective in the landscape of therapy when it comes to what to do beyond the acute flare of the disease. Treatment algorithms are evolving to incorporate a variety of different products designed to improve and maintain the skin barrier.

The FDA has recently approved some new products that are topical nonsteroidal agents, which may offer some advantages in terms of their use as maintenance therapies.

**DR FRIEDLANDER:** Safety issues are important to address with families. The FDA has expressed concern about both the TCIs and topical corticosteroids. There have been published reports of severe adverse effects from topical corticosteroids. There is no completely safe harbor for a child who has severe disease.

In the last decade, new information has

Figure 1: EASI score ( $P<0.0001$ )



The Eczema Area and Severity Index (EASI) was the primary outcome parameter in a recent study of MAS063DP (Atopiclair) in adults with mild to moderate atopic dermatitis. Between day 1 and day 50, the mean EASI score decreased from 6 to slightly greater than 1 in patients treated with Atopiclair, compared to a decrease from 6 to 5 in the placebo group ( $P<0.0001$ ).<sup>4</sup> Used with permission.

become available about the safety profiles of topical corticosteroids, particularly their safety when used for children. Some products on the market, including moderate-potency agents, have been tested in children and clearly can be used for 3 or 4 weeks at a time without any significant adverse events. However, there also are data

on products that are much less safe and that have significant risks in children that should be avoided. Those data do not always appear in the literature.

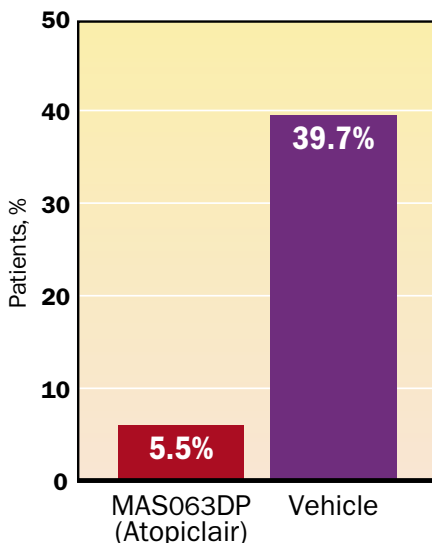
### New Nonsteroidal Option

**DR EICHENFIELD:** Atopiclair is a new prescription nonsteroidal cream that was introduced in 2005 for relief of itching, burning, and pain associated with various types of dermatoses, including atopic dermatitis. The formulation of Atopiclair includes glycyrrhetic acid, which has proven antiinflammatory properties, and sodium hyaluronate. In addition, its hydrolipidic base contains key skin lipids, such as triglycerides and polyunsaturated fatty acids, that help restore skin barrier function.

Results of a large clinical trial were published earlier this year.<sup>4</sup> The study was well designed and conducted in major investigative centers in the United States. It was randomized, double blind, and vehicle controlled and measured the safety and efficacy of Atopiclair. It involved 218 adult patients with mild or moderate atopic dermatitis.

Patients were randomized in a 2:1 ratio to Atopiclair or vehicle. The primary end point was the Eczema Area Severity Index (EASI) value at day 22. Secondary end points were EASI values at other time points, itch, percentage of affected body surface area, investigator global assessment of clinical response from baseline, and need for rescue medication in the event of a flare.

Figure 2: Percentage of patients requiring rescue medication ( $P<0.0001$ )



In a vehicle-controlled evaluation of MAS063DP (Atopiclair) in patients with mild or moderate atopic dermatitis, 5.5% of MAS063DP (Atopiclair) patients had a need for rescue medication to control symptomatic flares, compared to 39.7% of patients treated with vehicle ( $P<0.0001$ ).<sup>4</sup>

Assessment of the primary end point demonstrated a change in mean EASI value of -3.82 in the patients treated with Atopiclair, a highly significant difference ( $P < 0.0001$ ), compared to essentially no change in the vehicle group (-0.15) [See **Figure 1** on page 7]. For all of the secondary end points, Atopiclair demonstrated a significant advantage over vehicle ( $P < 0.0001$  for all comparisons) [See **Figures 2 and 3**].

At the end of the study, there was a 76% improvement in the EASI score in the Atopiclair group, compared to a 13% improvement in the vehicle group. Pruritus was also effectively decreased with Atopiclair, which was associated with an 82% improvement in mean itch score at day 50, compared to a 30% decrease in the vehicle group at day 50. The investigator global score differed substantially between groups after 1 week of therapy, as 60% of patients treated with Atopiclair had good improvement or total resolution compared to 13% of the vehicle group.

Relatively few adverse events were reported, and 80% were considered non-treatment related and resolved during the study. Treatment-related adverse events were minor in both groups, with the most common being rash, reported by 2.1% of the Atopiclair group versus 5.5% of the vehicle group.

**DR FRIEDLANDER:** The day 50 results showed no evidence of tachyphylaxis, and Atopiclair continued to work.

**DR EICHENFIELD:** Remember that this study evaluated this treatment as monotherapy, looking at core efficacy and safety. A very important point of the study design was the option to use a corticosteroid as rescue medication in the event of a flare. In the vehicle arm, 40% of patients required rescue medication, whereas only 6% of the patients treated with Atopiclair did.

In another clinical trial conducted in Europe, Atopiclair was evaluated in a randomized, double-blind, vehicle-controlled study involving 30 adults with mild to moderate atopic dermatitis.<sup>5</sup> The results showed consistent, statistically significant differences in favor of Atopiclair in body surface area involvement, pruritus score, EASI, and overall gradient severity of atopic dermatitis. The differences reflected changes from baseline to day 22. No adverse events were reported in either patient group.

**DR EICHENFIELD:** How do you evaluate these studies? How might you use Atopiclair in clinical practice?

**DR FRIEDLANDER:** In looking at the data, my first thought is that Atopiclair might increase the number of patients who can be on maintenance therapy all the time. This is very attractive because it may simplify treatment for many patients. It would increase both compliance and ease of care. It is also exciting to think that this might be a treatment that will decrease the need for topical corticosteroids or TCIs.

**DR CHAMLIN:** I would consider it a good choice for maintenance therapy or for mild flares.

**DR EICHENFIELD:** I think that is important as we translate the clinical trial data into clinical practice. At the beginning of our discussion, we agreed that multimodal management of atopic dermatitis is standard. It relies on education, good skin care, good control of itch, and minimizing problems with the barrier, followed by anti-inflammatory medication as needed.

**DR WERSCHLER:** I see this as an exciting new product that slots in as an intermediate step between basic skin maintenance with a moisturizer and introduction of a TCI, like pimecrolimus or tacrolimus, or a topical corticosteroid. It gives patients the opportunity to self-manage some of the mild to moderate flares and probably also

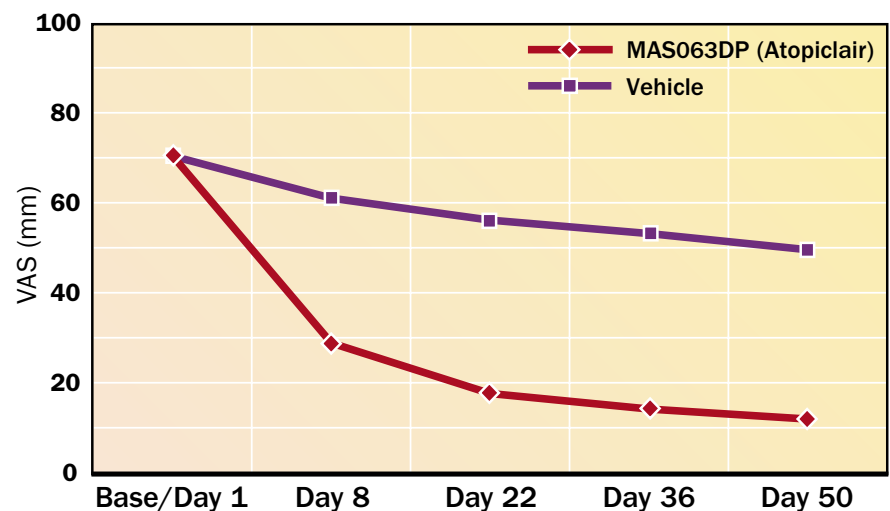
provides some additional assistance in the management of more severe flares.

**DR CHAMLIN:** Atopic dermatitis is not a “one size fits all” condition, as far as treatment is concerned. I am always happy to see something new developed for my patients. I am hopeful this will fit into the treatment algorithm as a corticosteroid-sparing agent with fewer adverse effects and that possibly decreases flares of the disease.

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**Figure 3: Itch for target lesion—Visual Analog Scale (VAS) 0-100 ( $P < 0.0001$ )**



Using a visual analog scale, patients with atopic dermatitis rated the degree of itch in a target lesion after treatment with MAS063DP (Atopiclair) or vehicle. The mean itch score decreased from about 70 (on a scale of 100) on day 1 to about 10 on day 50 in the Atopiclair group, compared to 50 in the vehicle group ( $P < 0.0001$ ).<sup>4</sup> Used with permission.