New Developments in the Treatment of Atopic Dermatitis: Clinical Highlights From Vienna

Course Director

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Expert commentary is based on data presented at the 25th European Academy of Dermatology and Venereology Congress*

Activity Description and Educational Objectives
In this activity, a renowned dermatologist discusses new data for current and emerging atopic dermatitis treatments recently presented at the 25th European Academy of Dermatology and Venereology (EADV) Congress in Vienna, Austria. Upon completion of this activity, participants will be able to:
• Discuss emerging data for the efficacy and safety of approved and investigational atopic dermatitis treatments, as well as the potential clinical impact of these findings.
• Apply approaches to treat patients with atopic dermatitis in the context of late-breaking data and patient-, disease-, and therapy-related factors.

Target Audience
This activity has been designed to meet the educational needs of dermatologists, allergist/immunologists, and other clinicians involved in the management of patients with atopic dermatitis.

Requirements for Successful Completion
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Updates in Current Treatment Options for Atopic Dermatitis

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Dr. Guttman-Yassky: Hello, this is Dr. Emma Guttman. I’m Professor and Vice Chair of the Department of Dermatology at the Icahn School of Medicine at Mount Sinai Medical Center in New York. I would like to welcome you to this educational activity that is focused on updates in atopic dermatitis treatments that were presented at the 25th European Academy of Dermatology and Venereology Congress in Vienna, Austria.

After completing the activity, please access the post-test and evaluation forms by clicking the red “Get Certificate” button. I would like to encourage you to download the slides, Practice Aids, and any other activity features that may interest you.

Atopic dermatitis (AD) has a significant impact on patients. In particular, patients with moderate to severe AD report a significant burden of itch, pain, sleep disturbances, anxiety, depression, and impact on health-related quality of life.

Additionally, data are emerging that atopic dermatitis has systemic abnormalities—perhaps even more so than psoriasis, another inflammatory skin disease associated with systemic abnormalities. Therefore, we must be able to effectively treat this disease.

Developments in the treatment of atopic dermatitis are continuously being made and many of these advances were recently presented at the 25th European Academy of Dermatology and Venereology, or EADV, Congress in Vienna. Let us begin with a discussion of updates on the current treatments that were presented at EADV.

Patient education is an important component of atopic dermatitis management. A randomized, multicenter study in Germany on the effects of structured patient education on adults with atopic dermatitis was presented. The education was a comprehensive 12-hour training session with a multiprofessional team consisting of a dermatologist, a psychologist, and a dietitian. Significant improvements in the signs of atopic dermatitis were observed with the training group compared with the control group. Therefore, a multidisciplinary approach could be an effective tool to improve outcomes of adult patients with atopic dermatitis.
A presentation of difficult-to-treat atopic dermatitis included a few recently published studies on the use of topical corticosteroids. For example, one study showed that after topical corticosteroid administration with or without bleach baths, bacterial compositions on lesional skin normalized, resembling that of nonlesional skin. Another study demonstrated that adding topical steroids to presoaked skin was not more effective compared with application to dry skin alone.

Patients frequently seek complementary and alternative medicines for atopic dermatitis. To gain insight on their efficacy and safety, a systematic review of use of topical herbal medicines in atopic dermatitis was conducted and presented at this EADV. Many of the studies included in the analysis had methodological flaws and those showing evidence of efficacy were single trials with only a few patients.

A meta-analysis was not conducted due to heterogeneity seen in the studies. The authors concluded that there was insufficient evidence of efficacy for the use of herbal extracts in atopic dermatitis and more studies are needed to clarify the role of these therapies.
There were also a few studies which explored factors that may predict response to treatment. For example, one study examined associations between filaggrin, or filaggrin null mutations, and atopic dermatitis in a Finnish population. The combined filaggrin null phenotype was associated with early-onset atopic dermatitis, palmar hyperlinearity, and asthma in the context of atopic dermatitis.

However, the filaggrin status did not have an effect on disease severity or on treatment responses. Furthermore, a recently published study that I was involved in found that filaggrin expression was not downregulated in early-onset atopic dermatitis in early childhood, challenging the notion of filaggrin as central for disease elicitation and as an instigator of the entire atopic march.

### Predicting Response to Mycophenolic Acid in Patients With AD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total (N = 65)</th>
<th>Responders (n = 33)</th>
<th>Nonresponders (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>40 (62.5)</td>
<td>23 (69.7)</td>
<td>17 (53.3)</td>
<td>.226</td>
</tr>
<tr>
<td>Age, y (mean ±)</td>
<td>42.5 (14)</td>
<td>39.9 (14.4)</td>
<td>45.2 (13.1)</td>
<td>.132</td>
</tr>
<tr>
<td>Duration of MPA tx, d (mean ±)</td>
<td>535 (616.7)</td>
<td>763.1 (753.6)</td>
<td>292 (277.5)</td>
<td>.063</td>
</tr>
<tr>
<td>UGT1A9-275T&gt;A and -2152C&gt;T heterozygote pts, n (%)</td>
<td>7 (10.7)</td>
<td>1 (3)</td>
<td>6 (18.8)</td>
<td>.033</td>
</tr>
</tbody>
</table>

### Factors Predicting Remission

<table>
<thead>
<tr>
<th>Factor</th>
<th>aOR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-flexural location of AD</td>
<td>2.50</td>
<td>1.30-4.79</td>
<td>.006</td>
</tr>
<tr>
<td>More severe AD</td>
<td>0.62</td>
<td>0.49-0.79</td>
<td>.000</td>
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<tr>
<td>AD of the father</td>
<td>0.55</td>
<td>0.35-0.88</td>
<td>.012</td>
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<tr>
<td>Rural living</td>
<td>1.52</td>
<td>1.05-2.20</td>
<td>.026</td>
</tr>
<tr>
<td>Condensation in the child’s room</td>
<td>0.60</td>
<td>0.43-0.85</td>
<td>.004</td>
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<tr>
<td>Parental smoking</td>
<td>0.65</td>
<td>0.42-0.99</td>
<td>.044</td>
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<td>Breastfeeding &lt;6 mo</td>
<td>1.45</td>
<td>0.99-2.10</td>
<td>.055</td>
</tr>
<tr>
<td>Paternal education higher than elementary school</td>
<td>0.64</td>
<td>0.38-1.07</td>
<td>.089</td>
</tr>
<tr>
<td>Older age</td>
<td>1.12</td>
<td>0.99-1.26</td>
<td>.064</td>
</tr>
</tbody>
</table>

1. Thijs JL. EADV 2016.

An additional study presented at EADV explored factors that predict remission of infant atopic dermatitis until adolescence. The analysis included more than 1,000 patients. The most important predictors were eczema location, the severity of eczema, paternal atopic dermatitis, and a few other parental factors.

So far, we have reviewed updates in currently available atopic dermatitis treatments that were presented at EADV. Stay tuned now for the next segment, where I will discuss new data on emerging therapeutics for atopic dermatitis.
Emerging Treatments for Atopic Dermatitis: Phase 3 Data Presented at EADV

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Emerging Treatment at EADV: Introduction

Many patients with moderate to severe AD are not adequately controlled with currently available treatments.

A variety of novel therapies are being investigated for use in AD and studies were presented at the 25th EADV Congress.

Emerging Therapies at EADV: Dupilumab

- Significant improvement in EASI score from baseline in both dupilumab arms versus placebo observed in both studies.
- Significant improvements in itch, DLQI, and POEM scores—as well as anxiety and depression—also observed.

*P < .0001 for both dupilumab groups vs PBO.
*Coprimaray endpoint in EU and Japan; key secondary endpoint in other regions.

1. Simpson EL. 25th EADV 2016. D3T01.1C.

Dupilumab is a human monoclonal antibody that targets the alpha subunit of the IL-4 receptor, thereby inhibiting the actions of the Th2 cytokines, IL-4 and IL-13. This agent is currently under FDA review for the treatment of adult patients with inadequately controlled moderate to severe atopic dermatitis.

Late-breaking data from the phase 3 SOLO 1 and SOLO 2 trials were presented at this EADV. These were two identical studies in which moderate to severe patients inadequately controlled with topical corticosteroids were randomized to receive placebo, 300 mg dupilumab every 2 weeks, or 300 mg dupilumab weekly for 16 weeks. Both dupilumab doses resulted in a significantly greater proportion of patients achieving an IGA of 0 or 1—that means clear or almost clear—and at least a two-point reduction from baseline compared with placebo. More patients in both dupilumab arms also achieved at least 75% reduction in their Eczema Area and Severity Index, or the EASI score, as compared with placebo. The improvement in EASI score from baseline in both dupilumab arms was significantly greater than that of placebo in both studies. Significant improvements in pruritus or itch were also observed as early as week 2, which is important as itch is a hallmark of atopic dermatitis and a very significant symptom for these patients.

In both studies, both doses of dupilumab were also associated with significant improvement in the Dermatology Life Quality Index and Patient-Oriented Eczema Measures, or POEM, as well as significant improvements in anxiety and depression. So not only does dupilumab improve symptoms, but it also restores the quality of life for patients with atopic dermatitis. Notably, patients in the study had a median affected body surface area of 50%, representing a population with severe atopic dermatitis or severe eczema for which there is a significant unmet need for novel treatments.
An example of a patient who achieved the primary endpoint with dupilumab weekly was presented. This was a patient with a duration of atopic dermatitis of 48 years. At week 16, the patient’s IGA score decreased from 4 to 1, the affected body surface area went from about 86.5% to 2.5%, and the EASI score went from 51.5 to only 3.1. And the pruritus NRS decreased from 7 to 1.6.

In general, dupilumab was well tolerated. Most adverse events were mild or moderate. Injection site reactions and conjunctivitis were more frequent with dupilumab. Therefore, dupilumab represents a promising option for adult patients with moderate to severe atopic dermatitis.

We are very excited that there is a new treatment that provides better safety and efficacy than the existing treatment options, and can be used long term as we currently do not have effective treatments that can also be used long term for our patients with severe atopic dermatitis.

1. Simpson E. EADV 2016. D3T01.1C.

Another atopic dermatitis treatment that is under FDA review is crisaborole, a topical phosphodiesterase inhibitor. This agent is being investigated for the treatment of mild to moderate atopic dermatitis in both children and adults. Recently published phase 3 studies showed improvement with crisaborole versus placebo in all measures of efficacy, including overall disease severity, pruritus, and other signs of atopic dermatitis. Results from these studies, demonstrating the effects of crisaborole on quality of life, were presented in Vienna. Crisaborole was associated with significant improvements in quality of life in both age groups—2-15 years old and also 16 and above—for patients as well as their families.

1. Paller AS. EADV 2016. FC02.08.
The long-term safety of crisaborole was investigated in patients 2 years of age and older with mild to moderate atopic dermatitis who were included in an open-label extension of the phase 3 studies.

Safety data were pooled from the two 28-day phase 3 studies, as well as the open-label, 48-week safety study. Pooled treatment-emergent adverse events occurred at a low frequency across all age groups and over time. The most frequently reported treatment-emergent adverse events were atopic dermatitis (3.1%), application site pain (2.3%), and application site infection (1.2%). The majority of treatment-emergent adverse events were considered mild or moderate and not related to treatment. There were no reports of long-term cutaneous adverse reactions.

In the extension study, none of the reported serious adverse events were considered treatment related. Less than 2% of patients discontinued the extension study due to treatment-emergent adverse events. Therefore, the safety profile of crisaborole topical ointment 2% was favorable for long-term treatment of patients age 2 years and older with mild to moderate atopic dermatitis.

We are excited to have new and safe topical treatments for our patients with atopic dermatitis.
Emerging Treatments for Atopic Dermatitis: Phase 2 Data Presented at EADV

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Emerging Therapies at EADV: Lebrikizumab

Lebrikizumab 125 mg q4w resulted in:
• Significantly higher proportions of patients achieving EASI-50, EASI-75, and SCORAD-50
• Trends for improvement in IGA 0/1 and pruritus VAS

Emerging Therapies at EADV: DS107

DS107 is another emerging treatment being studied in atopic dermatitis. This drug contains the active pharmaceutical ingredient DGLA, a 20-carbon polyunsaturated bioactive lipid. A phase 2a proof-of-concept study was presented in patients with moderate to severe atopic dermatitis.

Analysis of the primary endpoint, which was at least a two-point decrease in the IGA and a score of 0 to 1 showed a trend in favor of DS107 over placebo at 8 weeks. There was an increase in the number of responders when only patients who completed 8 weeks of treatment, the observed population, were included in the analysis.

A post hoc analysis showed statistically significant decreases in IGA score with DS107 compared with placebo when patients were stratified by site and severity of the atopic dermatitis at baseline. Statistically significant improvements in pruritus and POEM scores were also observed after 4 weeks.

DS107 capsules were well tolerated up to 2,000 mg on single dose. The majority of adverse events were GI-related, transient, and resolved without any intervention.

[A] late-breaking presentation of phase 2 data was for treatment of moderate to severe atopic dermatitis patients with lebrikizumab. Lebrikizumab is a humanized monoclonal antibody that binds IL-13, a key Th2 cytokine, with an important role in the pathogenesis of atopic dermatitis.

The patients included in the study were 18-75 years old with moderate to severe atopic dermatitis for at least a year with an inadequate response to topical corticosteroids. The patients were randomized to receive either placebo or lebrikizumab 125 mg single dose, 250 mg single dose, or 125 mg every 4 weeks. All patients also received topical corticosteroids twice daily.

Dosing every 4 weeks resulted in significantly higher proportions of patients achieving 50% and 75% improvements in the EASI scores, as well as 50% improvement in the SCORAD scores, another scoring index for atopic dermatitis, with trends for improvement in pruritus and the proportions of patients achieving clear or almost clear skin.

Significant improvements were also seen in the placebo group, and it would be good to have a monotherapy study in the future to really evaluate for drug effect without the effect of topical steroids. Adverse events were similar between treatment groups, and most were mild or moderate in severity.

1. Simpson E. 25th European Academy of Dermatology and Venereology Congress (EADV 2016). D3T01.1F.
Nemolizumab is a monoclonal antibody that targets IL-31—the itch cytokine—for which phase 2 data were presented at EADV. There was a rapid dose response reduction of the pruritus. Sleep and quality of life were also improved. Improvements in dermatitis, as determined by EASI, and achievement of an sIgA [secretory Immunoglobulin A] of 0 to 1 were also observed. Frequent adverse events occurring in at least 5% of patients included worsening of atopic dermatitis, nasopharyngitis, upper respiratory tract infections, and peripheral edema. No increases in infection or death were observed with nemolizumab.

A phase 2 study of adults with moderate to severe AD demonstrated that ustekinumab resulted in higher SCORAD-50 responses at week 12, 16 (primary endpoint), and 20 compared with placebo, but the difference between groups was not significant. Lack of effect could be due to small sample size, background TCS use, and/or insufficient dosing for AD.

The next study I would like to talk about is a phase 2a trial investigating the use of topical JAK inhibitor tofacitinib in atopic dermatitis. At week 4, 73% of patients receiving tofacitinib achieved a Physician Global Assessment, or PGA, score of 0 to 1, compared with only 22% of those receiving the control vehicle. A significant reduction in itch was also observed with tofacitinib. The most frequent treatment-emergent adverse event was respiratory tract infection, but in general adverse events with tofacitinib were similar to vehicle.
High-Affinity IgE Antibody: Clinical Efficacy

1. Bangert C. EADV 2016. FC03.03.

In this meeting, we obtained this time the final proof we needed for the lack of a pathogenic role of IgE in atopic dermatitis since a high-affinity anti-IgE molecule achieved no clinical benefit in patients with moderate to severe atopic dermatitis.

So to conclude, atopic dermatitis has a significant impact on patients and their lives. New insights are emerging on current treatments, including factors that can predict response to treatment. Studies have challenged the previously conceived notions of filaggrin and IgE playing important roles in the development of atopic dermatitis. Two new treatments, dupilumab and crisaborole, are under FDA review and may be available soon, and a variety of other treatments are in phase 2 of development. Therefore, the treatment of atopic dermatitis is likely to evolve in the near future and it is a very exciting time in this field for patients and their physicians. It will be important to have monotherapy studies conducted, as the background use of topical corticosteroids may affect and interfere with the interpretation of the clinical effects of these agents, as we saw in this meeting.

Well, that ends our discussion for today. I hope you found it informative and useful. Once again, I encourage you to download the slides and Practice Aids for this activity. Don’t forget to access the post-test and evaluation form by clicking the red “Get Certificate” button. Thank you very much for participating in this educational activity focused on updates in atopic dermatitis presented at the 25th EADV Congress.

Conclusions

- Atopic dermatitis has a significant effect on the lives of patients
- New insights are emerging for current treatments, including factors that predict response to therapy
- With a variety of therapies under development, the treatment paradigm for AD is likely to evolve in the near future
New Developments in the Treatment of Atopic Dermatitis: Clinical Highlights From Vienna

Expert commentary is based on data presented at the 25th European Academy of Dermatology and Venereology Congress*

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