

Supplement to



December 2017

From Symptom Control to Targeted Treatment: The Shifting Paradigm of Atopic Dermatitis, Part II

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Distributed by *Practical Dermatology*®.

Supported by an unrestricted educational grant from
Sanofi Genzyme and Regeneron Pharmaceuticals



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Release Date: December 2017

Expiration Date: December 2018

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lesions present as erythematous patches, excoriations, and oozing papules and vesicles. Subacute lesions are erythematous, dry, and scaly, while chronic lesions present as scaly, thickened, lichenified plaques. AD cannot be cured, but it can be managed. The fundamental management principle is lifestyle modification, including maintaining a hydrated stratum corneum with the liberal application of moisturizers, avoiding irritants, and using mild cleansers. Mild disease usually responds to topical therapy, including corticosteroids and calcineurin inhibitors. Short-term phototherapy can be used. Novel therapies are being developed.

TARGET AUDIENCE

This certified CME activity is designed for dermatologists, physician assistants, and residents in this field.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Identify the mechanisms of action, efficacy, and safety of emerging targeted therapies for AD
- Recognize the lifestyle measures and daily skincare practices that are the foundation of an AD treatment plan
- Discuss the prevalence, presentation, and quality-of-life effects of AD in adults
- Interpret and explain the recognized and emerging comorbidities associated with AD in children, adolescents, and adults

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion held in September 2017.

ACTIVITY DESCRIPTION

Atopic dermatitis (AD) is an inflammatory cutaneous disease that is one of the most common chronic skin conditions. It is characterized by intense pruritus and eczematous lesions. Acute

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From Symptom Control to Targeted Treatment: The Shifting Paradigm of Atopic Dermatitis, Part II

A panel of leading experts convened to discuss the current treatment of atopic dermatitis (AD), with an emphasis on new and emerging therapies. The objective is to review the new treatment landscape for AD within a practical clinical framework that translates new drugs and research into meaningful patient care.

PATHOGENESIS AND TREATMENT: NEW CONCEPTS, NOVEL TREATMENTS

Peter Lio, MD: We are on the precipice of the most exciting time ever for atopic dermatitis (AD). Dr. Guttman, you've been at the helm of the ship navigating the revolution in our understanding of the pathogenesis of AD. Could you summarize where we've come from and where we're going?

Emma Guttman, MD, PhD: Yes, I'll give the short version. For some time, we didn't know what we needed to target to treat AD. There were basically two camps: the immune pathogenesis camp and the barrier function camp.¹⁻³ Now we understand it's actually a combination of the two. It's clear that in order to improve AD you need to improve the immune abnormalities and you also need to improve the barrier.

Historically, the treatments that worked in AD targeted the immune system. But these treatments were not specific to any one of the cytokines that are increased in AD. These treatments include phototherapy, which basically penetrates the outer layers of the skin and reduces inflammatory cells, and cyclosporine and other immunosuppressants that reduce multiple inflammatory cells such as T cells, B cells, and dendritic cells. The efficacy of these treatments hinted that we should be targeting the immune system.

Then came dupilumab, the first monoclonal antibody developed for AD that targets the interleukin-4 (IL-4) receptor alpha. Due to the fact that it targets the receptor it affects two important cytokines from the Th2 pathway: IL-4 and IL-13. We demonstrated—and it was very important to have biopsies to achieve these findings—that dupilumab improved inflammation in tissues by reducing Th2 axis-driven inflammation and also other inflammatory molecules that are important in AD.⁴⁻⁶ It also reverses the barrier abnormalities present in AD. These include increased epidermal hyperplasia—so there is skin thickening—and increases in proteins

called S100s that are increased in the initiation of the disease.⁷ There is also inhibition of terminal differentiation proteins. I'm sure that people have heard mainly about filaggrin, but it's not just filaggrin.^{2,8,9} There are many differentiation proteins that are very, very low in people with AD. Dupilumab was able to reverse these abnormalities in tissues, showing that by reversing the immune abnormalities underlying the disease, the barrier is also improved. This finding opened the door to the development of many other treatments for the disease.

Dr. Lio: I agree. And I think one of the things that's been so interesting is that until we had the option of dupilumab—and of course crisaborole, the novel, nonsteroidal, topical phosphodiesterase 4 (PDE4) inhibitor—we simply weren't talking about this. The therapeutic armamentarium empowers us, but it is also giving us insight into how the disease works.

My eureka moment was a paper that demonstrated that in the presence of inflammation, particularly IL-4 and IL-13, there is decreased expression of filaggrin.¹⁰ I thought, "Oh my gosh! It's all connected." Like so many great scientific debates over the centuries, there were two groups that seemed to be taking polar opposite positions, and the truth turns out to be somewhere in between or some combination of the two. And it's been off to the races with so many new innovations.

Bruce Strober, MD, PhD: Dr. Guttman and I were just in Geneva at the European Academy of Dermatology and Venereology Congress, and an interesting topical Janus kinase (JAK) inhibitor was presented as very effective for AD.^{11,12} The next generation of oral JAK inhibitors, including baricitinib and upadacitinib, is being developed by more than one company and is showing a lot of promise.^{13,14}

Other potential therapies on the horizon include ustekinumab, an injectable IL-12/23p40 antagonist approved for the treatment of moderate to severe psoriasis and psoriatic arthritis that is also being

studied in moderate to severe AD.¹⁵ Nemolizumab, which targets IL-31, and tralokinumab, which targets IL-13, are also being studied in AD.^{16,17}

Dr. Lio: I'm interested in the skin microbiota and *Staphylococcus aureus* imbalance in terms of pathogenesis and potential treatments. The original story was that *S aureus* is taking advantage of skin barrier damage, so we have to be careful of infection and treat it when it occurs. Now we're changing that narrative, at least in part.

Heidi Kong, MD, MHSc, at the National Institutes of Health, is positing that perhaps *S aureus* colonization is actively driving disease.¹⁸ So if we could potentially decrease *S aureus* colonization and rebalance bacteria, we could prevent flares. It will be interesting to see if we can modulate bacterial imbalance in creative ways. Will there be topical antimicrobials that we can use more broadly? Will there be probiotics? Perhaps we can change the skin environment to foster helpful bacteria by using prebiotics. I'm excited to see, as we learn more about the microbiome, where we will take this next phase.

Dr. Guttman: The question of the chicken and the egg is still there. We do not know what's first—the bacteria or the immune abnormalities. It may be that the immune abnormalities are first: They cause barrier dysfunction and the bacteria penetrate and contribute to the cycle of inflammation. There is evidence that dupilumab may reduce staph-related IgEs, so I think we need more studies to understand the relationship between bacteria and inflammation.¹⁹

Dr. Lio: Now we're looking at the next frontier: prevention. The work of Eric Simpson, MD, MCR, demonstrating that we could potentially prevent AD with just moisturization in neonates has been very exciting.^{20,21} Just imagine—as we learn more we can actually start thinking about prevention or perhaps even cure for those who already have the disease.

CASES IN ATOPIC DERMATITIS

Dr. Lio: Let's take a look at some cases.

I would like to start with the case of an 11-year-old girl with a lifelong history of AD. She had been prescribed numerous topical treatments, suffered a lot, and had recurrent infections. She had been hospitalized for several skin infections, would improve with antibiotics, but then would flare again. It was at that point that she came to see me.

I decided to initiate cyclosporine, because her condition was so severe. In addition to a solid topical regimen consisting of good moisturization, triamcinolone twice daily for flares, and tacrolimus twice weekly for "hot spots" as proactive topical therapy, she improved greatly on cyclosporine dosed at 5mg/kg/day. After three months, she was almost totally clear. Her monthly laboratory work and blood pressure were reassuring, but I don't like to continue



"Like so many great scientific debates over the centuries, there were two groups that seemed to be taking polar opposite positions, and the truth turns out to be somewhere in between or some combination of the two. And it's been off to the races with so many new innovations.."

—Dr. Lio

cyclosporine any longer than needed, so I tapered her off cyclosporine over one month and she continued to do very well on topical therapy alone.

With the onset of winter, she began to have flares again, so we instituted narrowband ultraviolet B (NB-UVB) phototherapy three times weekly, and she improved significantly after about six weeks. She has now been maintained for more than one year on intermittent phototherapy.

Phototherapy is used for several months at a time when she feels her skin is worsening, and then she is treated for several months with topical therapy alone. Her skin has remained clear or almost clear, her sleep quality has been excellent, and she feels that she finally has control over her skin disease, which is especially important now that she is a teenager.

Jacob Levitt, MD: I treated a 19-year-old African American woman with a history of Crohn's disease and longstanding AD. She had methicillin-resistant *Staphylococcus aureus* (MRSA) infection associated with her AD. In fact, her AD was so severe that she had to be home schooled. She had been treated unsuccessfully for her Crohn's disease with infliximab but was doing well on vedolizumab.

When she presented to me in 2015, at age 17, she had generalized lichenification and excoriations affecting the trunk, arms, hands, wrists, and face. Initially I recommended bleach baths to decrease the burden of *S aureus*, and the application of mupirocin to the nares to stop some of the colonization, while providing immediate relief of her AD with prednisone. I also elected, at the same time, to initiate NB-UVB phototherapy.

Ultimately, she got a home unit, and she did well for some time. However, once the prednisone wore off she flared again. I then decided to use injectable methotrexate; a 15mg dose was not sufficient so the dose was increased to 20mg weekly. I find that both children and adults respond quite well to methotrexate.

We tried apremilast off label in an effort to get her off methotrexate, but she experienced headaches. Ultimately, we found that in order to control the disease we had to increase the methotrexate dose yet again to 25mg weekly. She was holding steady—not perfect but not terrible—when dupilumab was approved by the US Food and Drug Administration. Treatment with dupilumab was initiated in April 2017 and was relatively life-changing for her. We were able to wean her off methotrexate, she is going to college, and she has experienced a dramatic decrease in itch. So she's prednisone-free, methotrexate-free, and itch-free.

Dr. Strober: I can discuss a similar case but with a twist. The patient is a 32-year-old woman with a lifelong history of AD. Consistently present were very pruritic, erythematous, variably lichenified plaques, primarily on the face periorbitally and periorally but also affecting the neck, trunk, and the antecubital and popliteal fossae. Approximately 15 percent of her body surface area was affected.

She had previously received and failed to respond to a variety of immunosuppressive agents, such as subcutaneous methotrexate up to 17.5mg weekly, which I think works in 40 to 50 percent of patients with this presentation. She received azathioprine; usually I go up to a dose of 200mg daily, as I did with this patient. She received mycophenolate mofetil up to 3g daily, as well NB-UVB, which often works but is not always convenient. She improved with cyclosporine, 4.25mg/kg/day, but over time she developed renal insufficiency on this medication.

I initiated dupilumab, concomitantly weaning her off cyclosporine. After eight weeks she had nearly full resolution of AD and was satisfied with the response.

However, she developed, over the first eight weeks, bilateral ocular irritation and erythema with conjunctival injection. Essentially, she had conjunctivitis in the setting of a good response to dupilumab. So the question I have is, how do we deal with conjunctivitis in the setting of a good cutaneous response to dupilumab?

Dr. Lio: That's a great question, and we'll talk about it after we finish the case presentations.

Dr. Guttman: I treated two patients who were in the dupilumab trials. One patient was in a Phase 2B trial and one was in a Phase 3 trial. Both of them are continuing on the drug to this day.

The first patient is a 35-year-old woman who came to see me from Mexico. She had received cyclosporine for more than one year, which is against the guidelines. She also received oral prednisone



A 35-year-old woman with eczema, before dupilumab.



A 35-year-old woman with eczema, after dupilumab

and phototherapy. She was covered with very lichenified lesions and open wounds from head to toe. The pictures above, which were sent by the patient, actually don't do justice to the severity of her lesions.

The next set of images (above) shows how she looked after less than 16 weeks of dupilumab treatment. I think she cleared in eight weeks, so this photograph was taken between eight and 16 weeks after initiating treatment. You still see some scarring caused by excessive scratching, but basically she is clear, and she's clear to this day. She is a very high-functioning woman and will go back to her very demanding work.

The next patient was in a Phase 3 dupilumab study. This patient was a high-functioning scientist with an important position, but he had to take early retirement because of the severity of his AD. This is how he looked (on the next page) when he came to see me; he could barely get to the office.

He had received cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, and prednisone. Eventually prednisone was the only drug that offered relief, so when he came to see me he was on multiple rounds of prednisone.

We put him in the dupilumab trial. The next set of images show



Phase 3 study patient with severe eczema at baseline.



Phase 3 study patient after 16 weeks of dupilumab therapy.

how he looked after 16 weeks in the trial.

He did develop conjunctivitis, and in consultation with an ophthalmologist, we successfully treated him with topical steroid drops. The conjunctivitis did recur, and we treated him again, and he has not had another recurrence.

Dr. Lio: Thank you for those great cases. We all seem to have chosen really tough ones.

Let's begin our discussion of the cases with the issue of conjunctivitis. In the clinical trials of dupilumab, conjunctivitis occurred on the order of 10 percent. I have a lot of patients on dupilumab, and a number of them have had at least some conjunctivitis.

We want patients to be aware of the potential for conjunctivitis before we even start dupilumab therapy, and then we want to ensure that they're working closely with an ophthalmologist so we know they are getting the proper care and the proper diagnosis.

It seems as if first-line therapy is topical steroid drops. Where do we go from there? What else have you had experience with?

Dr. Guttman: I work very closely with an ophthalmologist at

Mount Sinai who specializes in atopy. I send every patient I put on dupilumab to her to get a baseline. But I learned from her what steroid drops she prescribes, so now I've started to give them as a first-line treatment before they see her. Also, I noticed that the patients who develop conjunctivitis tell me they have dry eyes. So I tell patients to use lubricating drops when they start using dupilumab, and from my experience that seems to be helpful.

Dr. Strober: Which strength ocular drops are you prescribing, Dr. Guttman?

Dr. Guttman: Loteprednol etabonate, 0.5%.

Dr. Lio: I think patient education, early involvement of an ophthalmologist, and preemptive use of lubricating drops is key. First-line, short-term therapy, with the involvement of an ophthalmologist, would be to try one of the steroid drops.

Dr. Levitt: I think there is going to be a bit of trial and error among dermatologists and ophthalmologists to see what works. But this is definitely an area of unmet need in terms of management guidance.

Dr. Guttman: It may be important to mention that we've done cultures both in the trial and also in my clinic of patients using dupilumab who developed conjunctivitis, and we have never had a positive culture. So we believe it's not infectious.

Dr. Lio: The most common adverse effect with crisaborole is application site pain, or stinging and burning.²² How do people deal with this adverse effect with their patients?

Dr. Guttman: I think it's important to set patient expectations. I always tell my patients that they should expect crisaborole to sting—otherwise they will be put off the drug and may not use it again. Patients tell me that the stinging lasts 20 to 30 minutes and then goes away. In my clinic, I recommend that patients also apply a topical corticosteroid during their first few days of applying crisaborole. I recommend that they slowly reduce the corticosteroid as they get used to the crisaborole.

Dr. Lio: That's a great pearl, which is similar to proactive therapy in the maintenance phase. You use a topical steroid for induction, and once patients have improved and are used to the topical crisaborole, they could potentially stay on crisaborole only.

CLINICAL PRESENTATION AND DIAGNOSIS

Dr. Lio: Let's talk a bit generally about clinical presentation and diagnosis of atopic dermatitis. In babies, we see AD as early as the first week of life. Babies often have facial and scalp involvement. In toddlers, we see involvement of the flexural areas and folds. In young adults, we often see head and neck dermatitis. In adults,

we see the hands affected and the appearance may be more lichenified.

There are also subtypes. In pediatric disease, we have a group of patients with an AD/psoriasis overlap. That's something we almost never see in adults. As Dr. Guttman's laboratory works on phenotyping, we may eventually be able to say that the clinical findings in a particular case correlate with a particular T-cell subset or a filaggrin mutation or an involucrin mutation.

The other piece, of course, is nerves. What role is the nerve ending playing? Drugs like neurokinin-1 receptor antagonists that may reduce scratching are in development, and we all know that scratching and rubbing behaviors can play a huge role in the morphology of the disease as well. Any other thoughts about the presentation of AD?

Dr. Guttman: We need to remember that some people with AD also have contact dermatitis. I actually see that more and more now. I sometimes see people clear with dupilumab who still have some facial involvement. We do patch testing and find that they are allergic to propylene glycol or another agent. So coexisting contact dermatitis is something to think about.

There are people who have eczema affecting only the hands and feet, or people with just a bit of nummular eczema. So it's important to note that there are clearly clinical phenotypes that we need to think about.

Dr. Levitt: The differential diagnosis tends to be age-based. With adults you have to think about allergic contact dermatitis. With children, you have to think about Netherton syndrome and Job syndrome and various other more rare genetic entities that shouldn't be forgotten when initial therapies are not working.

Dr. Lio: That's important. So if your initial treatments are not working as you would expect, your clinical suspicion needs to increase.

THE POWER OF PATIENT EDUCATION

Dr. Lio: Let's talk about the power of patient education. I think that patients with severe disease need quite a bit more education than standard patients do, especially about potential adverse effects. But most patients need some education and help establishing and maintaining a regimen. Atopic dermatitis is a chronic disease; we don't have a cure. You can't give patients one prescription and say "good luck."

Teaching patients about the safe use of corticosteroids is important to me because we have to use them in almost every patient. Using them safely has a lot to do with treatment duration. Can we use corticosteroids for a limited time and then take a break and use a nonsteroidal topical medication? Or is moisturization sufficient in milder cases?

How do you teach patients about treatment regimens and drug safety? What are the tricks?



"It's important to emphasize the waxing and waning natural history of the condition, especially to younger people. It's important to establish that regular skincare, including the use of emollients, is required, even when a good medication or modality is being employed."

—Dr. Strober

Dr. Strober: It's important to emphasize the waxing and waning natural history of the condition, especially to younger people. It's important to establish that regular skincare, including the use of emollients, is required, even when a good medication or modality is being employed.

Individuals with AD have a labile skin condition that is very responsive to a number of external factors, including unknown allergens and seasonal effects related to temperature and humidity. Therefore, expectations should be set so you don't promise cure or 100 percent disease control. I think you might want to assign a percentage that's in a range lower than 100 percent with the idea that we'll always try to continually optimize good disease control over many visits.

Dr. Levitt: As far as steroids are concerned, I take the same approach with all dermatoses, whether it's psoriasis or AD: twice daily application for two weeks, avoiding the face and groin. The issue is determining appropriate patients for the use of topical corticosteroids. If the patient has mild disease, you can hope to achieve a cure, or at least very good control, with topical steroids. If the patient has moderate to severe disease, corticosteroids become adjunctive rather than primary therapy. But I always emphasize short-term use. I very much welcome the calcineurin inhibitors and now crisaborole as maintenance options.

Dr. Lio: That's a great point. I think short-term, intermittent use of topical corticosteroids is key. As cases become more severe with greater body surface area involvement, they become less and less of an option.

TABLE 1. BLEACH BATH INSTRUCTIONS. ²⁴⁻²⁶

1. Fill the bathtub with lukewarm water (approximately 40 gallons for a standard bathtub)
2. Add ½ cup unconcentrated household bleach (5.25% sodium hypochlorite)
3. Mix bleach in the water thoroughly (or add bleach while the tub is filling)
4. Soak for 10 minutes
5. Rinse completely with lukewarm or warm tap water
6. Pat dry
7. Apply topical medications or moisturizers

Bleach baths are generally recommended two to three times per week.

Now that we finally have a biologic that's pretty powerful, dupilumab, we can start to think about AD in the same terms that people have been thinking about psoriasis for quite some time. We can tell our patients, or at least a group of patients, that there is a chance we can get them clear or almost clear.

The availability of a biologic also allows us to use other medications in different ways. A lot of my patients clear significantly with dupilumab, but they'll have some stubborn areas. So for those patients I'll still use topical corticosteroids on more localized areas. I can use crisaborole or a topical calcineurin inhibitor to help maintain clearance. I'm also excited about the pipeline, because patients who can't tolerate or haven't improved with dupilumab may do better with the upcoming agents, such as the oral JAK inhibitors or the anti-IL-31 agents, or some of the other biologics in development.

Do you use AD action plans or written treatment plans for your patients? Do you find these helpful in terms of patient education and designing treatment regimens?

Dr. Strober: I never hand out documents—not that it's a bad idea. I try to keep topical treatment plans simple, because we can overwhelm and ultimately "paralyze" patients if we give them too many topical agents for too many different areas of the body. I also keep it simple regarding emollients and systemic therapy. I emphasize the need for follow-up at regular intervals. I also make it possible for patients to come in more frequently during flares that seem to be out of control.

Dr. Levitt: I'm not a big fan of handouts, either. I think you have to give the appropriate medication for the appropriate severity of disease. If you match the intensity of the therapy with the intensity

TABLE 2. QUALITY OF LIFE IN ADULT PATIENTS WITH ATOPIC DERMATITIS. ²⁷⁻²⁸

- 53% reported that their disease negatively affected their daily lives
- 82% made lifestyle changes, such as avoiding social engagements, being in pictures, and participating in sports and exercise
- 55% reported that their confidence was negatively affected by their disease
- 16% had made career choices that limit face-to-face interactions
- 55% reported sleep disturbances
- 85.8% reported experiencing pruritus every day of the week
- 43% experienced anxiety or depressive symptoms

of the disease, you can achieve efficacious, efficient outcomes with a single modality—plus or minus an adjunctive topical steroid, calcineurin inhibitor, or crisaborole.

Dr. Lio: I'm perhaps guilty of being a little overwhelming. I develop a two-phase action plan for all patients, which addresses treatment when they experience flares and when they've achieved improvement. I like this approach because it can empower patients. A lot of patients tell me that before receiving their action plan, they didn't know what to do if the disease flared. Many of my patients are looking for a longitudinal approach.

I try to keep the action plan simple but flexible so I can build on the framework. When patients are clear, I recommend a proactive regimen of applying a calcineurin inhibitor, or crisaborole, or a low-potency topical corticosteroid to trouble spots to prevent flares. Using this regimen, I think we can keep some moderate and severe patients under good control without needing systemic treatment. I love phototherapy, but it's cumbersome for many people. Of course cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil are options, but they are time-limited because of the side effects and sometimes difficult because of their off-label status.

What about eczema schools? Dr. Guttman, I know you host a support group and an educational session. I do one every other month in Chicago. We have an educational session and then we conduct a support group that offers psychological support. Do other people do that?

Dr. Guttman: I think it's important to develop education. I edu-

TABLE 3. EMERGING COMORBIDITIES OF AD IN ADULTS³²⁻³⁴

- Cardiovascular disease
- Hypertension
- Inflammatory bowel disease
- Lymphoma
- Obesity
- Osteoporosis
- Rheumatoid arthritis

TABLE 4. EMERGING COMORBIDITIES OF AD IN CHILDREN³⁵⁻³⁸

- Central adiposity
- Hypertension
- Anemia
- Headache
- Speech disorders

cate every patient who comes to me, no matter the severity of their disease, about bleach baths (Table 1). I would say that two-thirds of patients have never heard of bleach baths, even though they are now part of the guidelines.²³ I recommend moisturization and discuss its importance but I don't recommend a specific moisturizer; I give them some options and let them pick their own. I'm a great believer in achieving 100 percent clearance for patients, but I also think it's important to set expectations so patients aren't disappointed. Even with dupilumab we don't obtain clearance for all patients, so we use a topical to reach clearance. Many patients will be happy if they have a few remaining lesions, but I'm not happy. I want them to be completely clear.

Dr. Lio: When you have a support group, patients can teach each other about realistic expectations of treatment—especially patients with more severe disease.

Early in my career it was hard for me to see patient after patient with AD who felt alone and isolated in their suffering. Yet in the next examination room there would be a patient going through the same thing. That's when I came up with the idea of a monthly meeting so patients could talk and connect. At almost every meeting, people sob with happiness with the relief of connecting with others who are going through what they are going through.

I hear comments like, "I never knew there were this many people like me." That's education at its best. We can show people they're not alone and that if we get them the right treatment plan, the right medication, and the right doctor, we can make a huge impact.

Dr. Levitt: If you've never had AD, you can't understand the degree of social isolation in relationships, in school, in work (Table 2). I remember as a kid, there was a boy in my class with severe AD, and he was a pariah. No one wanted to touch him, no one wanted to be his friend. And it was because of complete ignorance about the condition. The doctor's office is a safe haven where we can offer understanding and the tools to get better. Thankfully, those tools are evolving over time.

COMORBIDITIES AND TREATMENT

Dr. Lio: One issue that comes up a lot is comorbidities. I see families who are afraid to treat at all. Perhaps a young patient with mild to moderate disease has been prescribed hydrocortisone by the pediatrician, and now the family comes in saying, "We want you to cure this. We want to get to the root cause of this disease, but we don't want to use any steroids. Actually, we don't really want to use any medicines. Can we just wait this out?"

During my training it was thought that most patients would outgrow their AD, but new research is showing that as many as 50 percent of patients may continue to have symptoms into adulthood.²⁹ The first population-based prevalence estimate of adult eczema in the United States found the one-year prevalence of AD to be 10.2 percent.³⁰

And, of course, we have the comorbidities that come with atopic dermatitis. These include, for example, established comorbidities, such as attention deficit hyperactivity disorder (ADHD) and sleep problems—those two may be intimately related. And then we have other potential comorbidities that may develop later. Current and ongoing research is also identifying emerging comorbidities (Tables 3 and 4).

I feel strongly that if we're a bit more aggressive with patients, even those who are treatment-phobic or steroid-phobic, we are doing more good than harm. Do you agree with that?

Dr. Strober: I totally agree. I believe that withholding manageable therapies that can be monitored in systemic disease states, such as psoriasis and AD, does more harm than good. I believe even the older therapies, such as methotrexate, can be used indefinitely with proper monitoring. Lack of treatment, as you said Dr. Lio, can be every bit as harmful as any of the treatments I employ. Probably 100 times more harmful in fact.

Dr. Guttmann: I couldn't agree more. Dr. Strober actually published the first paper on increases in C-reactive protein in psoriasis, and that was followed with all the information about systemic abnormalities in psoriasis.³¹ Now there is a parallel development



"To me, biologics are not necessarily immunosuppressants. I actually see them as immune-correcting medications because they correct either a deficiency or an upregulation that the patient has. So it's very different from decreasing the entire immune system."

—Dr. Guttman

in AD, with similar comorbidities. Basically, if these patients don't get treated, it may lead to systemic manifestations that we should try to prevent.

Dr. Strober: A lot of patients' fear is simply lack of information. Practitioners need to be willing to put in the time to describe how the benefit-to-risk ratio is very high with most of our therapeutics. The right approach with correct monitoring and visit frequency should allow patients and parents or caregivers the confidence that the clinician is willing to do the right thing and do it safely, and ultimately, is not going to give up.

Dr. Guttman: And if practitioners don't feel comfortable with the newer therapies, they need to refer to people like us, because it's not fair if patients aren't offered available therapies.

CLOSING COMMENTS

Dr. Lio: I'd like to ask the panel if you have any other questions or comments.

Dr. Strober: I would like to make a point about something that Dr. Guttman has often made a point of—the use of systemic steroids to control flares. In the long run, is this a negative thing to do in terms of destabilization of AD? Should we reserve systemic steroids as a last resort?

Dr. Guttman: I see patients who initially had moderate disease but were prescribed oral prednisone, triggering exacerbations and leading to severe disease. It essentially creates a loop from which there is no return. I'm not saying that steroids always trig-

ger severe disease, but why would we give steroids when they can have such a detrimental effect and we now have many, many other options?

Dr. Levitt: I think there are a couple of considerations. One is cost. Prednisone is inexpensive, so I think considering a single taper as first-line systemic therapy is not unreasonable. The second point is that phototherapy shouldn't be ignored. It's safe and effective, even though it can be a bit of a hassle.

Dr. Lio: I think there is still a place for conventional agents. There has to be, in part because of the experience we have had with these drugs. I agree with Dr. Guttman about prednisone. I get so worried that we're going to eventually trigger even more severe disease. But there's no doubt that I have to use it sometimes. A patient is going to Europe on an extended vacation or has a wedding coming up, and I'll do a taper. I've inherited patients who have been receiving prednisone intermittently for years. I think we have to look towards the future and try to make sure we're preventing some of those terrible train wrecks.

The other piece, of course, is the pediatric piece. I think kids run the risk of being undertreated. Dupilumab is not approved now for the pediatric population, so phototherapy and conventional immunosuppressants are still important for those kids. Otherwise, you have a group nobody wants to treat. They're not improving with topical steroids, but they're still really suffering.

Dr. Levitt: Going back to the cases, one of the reasons I chose my case was because there was another biologic on board for a different disease working by a completely different mechanism. I'd be interested in Dr. Guttman's take on this.

Dr. Guttman: I think of the original treatments that basically treat the entire immune system, such as cyclosporine and others, as very immunosuppressant. These are real immunosuppressants. To me, biologics are not necessarily immunosuppressants. I actually see them as immune-correcting medications because they correct either a deficiency or an upregulation that the patient has. So it's very different from decreasing the entire immune system.

Dr. Levitt: One thing to remember is that the first-generation biologics, specifically the TNF inhibitors like infliximab, have some immunosuppressant properties. I think every subsequent biologic gets saddled with the side effects that were associated with the initial approved biologic. But the newer drugs are much more focused.

Dr. Guttman: I agree that anti-TNFs are an older generation, and also TNF is a molecule that may be more widespread. I do like to think of the newer biologics as immune-correcting molecules.

Dr. Lio: As I said earlier, it's an exciting time in AD, and I'm so glad that we are practicing and deeply involved during this time. I want to thank you all for your time and energy and thoughts on this topic. ■

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FROM SYMPTOM CONTROL TO TARGETED TREATMENT: THE SHIFTING PARADIGM OF ATOPIC DERMATITIS, PART II

Release Date: December 2017

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Name _____ MD participant non-MD participant

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DEMOGRAPHIC INFORMATION

Profession	Patients Seen Per Week (with the disease targeted in this educational activity)	Setting
<input type="checkbox"/> MD/DO	<input type="checkbox"/> 0	<input type="checkbox"/> Solo Practice
<input type="checkbox"/> NP	<input type="checkbox"/> 1-5	<input type="checkbox"/> Community Hospital
<input type="checkbox"/> Nurse/APN	<input type="checkbox"/> 6-10	<input type="checkbox"/> Government or VA
<input type="checkbox"/> PA	<input type="checkbox"/> 11-15	<input type="checkbox"/> Group Practice
<input type="checkbox"/> Other		<input type="checkbox"/> Other
		<input type="checkbox"/> I do not actively practice
Years in Practice	Region	Models of Care
<input type="checkbox"/> >20	<input type="checkbox"/> Northeast	<input type="checkbox"/> Fee for Service
<input type="checkbox"/> 11-20	<input type="checkbox"/> Northwest	<input type="checkbox"/> ACO
<input type="checkbox"/> 6-10	<input type="checkbox"/> Mid-West	<input type="checkbox"/> Patient-Centered Medical Home
<input type="checkbox"/> 1-5	<input type="checkbox"/> Southeast	<input type="checkbox"/> Capitation
<input type="checkbox"/> <1	<input type="checkbox"/> Southwest	<input type="checkbox"/> Bundled Payments
		<input type="checkbox"/> Other

Training of Fellows Yes No

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Identify the mechanisms of action, efficacy, and safety of emerging targeted therapies for AD	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Recognize the lifestyle measures and daily skincare practices that are the foundation of an AD treatment plan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Discuss the prevalence, presentation, and quality-of-life effects of AD in adults	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Interpret & explain recognized and emerging comorbidities associated with AD in children, adolescents, adults	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

POST TEST QUESTIONS

1. Which of the following statements best describes the mechanism of action of dupilumab?

- A. Janus kinase (JAK) inhibitor that blocks the JAK 1 and 2 pathways
- B. Phosphodiesterase 4 inhibitor
- C. Fully human monoclonal antibody that blocks IL-4 and IL-13 signaling
- D. Humanized monoclonal antibody that inhibits IL-31 signaling

2. Which of the following statements best describes the mechanism of action of crisaborole?

- A. Janus kinase (JAK) inhibitor that blocks the JAK 1 and 2 pathways
- B. Phosphodiesterase 4 inhibitor
- C. Fully human monoclonal antibody that blocks IL-4 and IL-13 signaling
- D. Humanized monoclonal antibody that inhibits IL-31 signaling

3. Which of the following potential atopic dermatitis comorbidities is supported by the strongest evidence?

- A. Osteoporosis
- B. Cardiovascular disease
- C. Obesity
- D. Attention deficit hyperactivity disorder

4. What was the most frequent treatment-related adverse effect, other than injection site reactions, in pivotal clinical trials investigating dupilumab?

- A. Oral herpes
- B. Induction of Crohn's disease
- C. Conjunctivitis
- D. Headache

5. What was the most frequent treatment-related adverse effect in pivotal clinical trials investigating crisaborole?

- A. Cutaneous atrophy
- B. Application site pain (burning or stinging)
- C. Pruritus
- D. Folliculitis

6. You are treating a 32-year-old woman who has been diagnosed with atopic dermatitis. She had mild atopic dermatitis as a child, but has not experienced symptoms since the age of 11. She now has pruritic, erythematous, variably lichenified plaques on the neck, trunk, and antecubital and popliteal fossae, and has experienced several bacterial infections. Approximately 20% of her body surface area is affected. She tells you that she read about bleach baths and wants to know if they would help her. What would be the best response?

- A. Bleach baths are an "old school" remedy for eczema that are no longer used in modern dermatologic practice. They have been replaced by the use of topical antimicrobials.
- B. Bleach baths may be useful. The concentration is $\frac{1}{2}$ cup of unconcentrated bleach in a 40-gallon tub of lukewarm water.
- C. Bleach baths offer a powerful antimicrobial treatment that can be used as monotherapy against staphylococcal infections of the skin, even active infections.
- D. Bleach baths should be strictly avoided because they are almost universally irritating, drying, and aggravating to eczematous skin.

7. Based on a 5-point Likert scale, where 1 = not at all confident and 5 = completely confident, how confident will you be treating atopic dermatitis patients with the recently approved medications dupilumab and crisaborole now that you have completed this activity?

- 1
- 2
- 3
- 4
- 5

8. Based on a 5-point Likert scale, where 1 = not at all confident and 5 = completely competent, now that you have completed this activity, how confident are you diagnosing atopic dermatitis in adults?

- 1
- 2
- 3
- 4
- 5

9. Based on a 5-point Likert scale, where 1 = never and 5 = always, now that you have completed this activity, how often do you intend to discuss quality-of-life issues with your patients with atopic dermatitis?

- 1
- 2
- 3
- 4
- 5

10. In order to help us assess your knowledge of select topics that were covered in this activity, please review the brief patient scenario and rate each of the statements as consistent with or inconsistent with your clinical approach. You are treating a 26-year-old man with atopic dermatitis. He was originally diagnosed as an infant, and has experienced worsening of his condition over the past two years. He has been unresponsive to topical therapies as well as oral glucocorticoids, phototherapy, and cyclosporine. His disease has had a significant impact on his social and professional life. He does not date, and he is self-employed as an accountant because he is too embarrassed about his skin to work in an office environment. For the past 11 months he has been treated with mycophenolate mofetil. He originally had a good response, although he is currently experiencing partial relapse. His body mass index is 31 kg/m².

	Consistent	Non Consistent
Prescribe dupilumab	—	—
Refer to a mental health professional	—	—
Discuss the use of bleach baths	—	—
Increase the dose of mycophenolate mofetil	—	—
Provide education on the association between atopic dermatitis and obesity	—	—
Prescribe crisaborole	—	—

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Name and email: _____

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom Yes No

I plan to make changes to my practice based on this activity? Yes No

Please identify the barriers to change.

____ Cost	____ Lack of consensus or professional guidelines
____ Lack of administrative support	____ Lack of experience
____ Lack of time to assess/counsel patients	____ Lack of opportunity (patients)
____ Reimbursement/insurance issues	____ Lack of resources (equipment)
____ Patient compliance issues	____ No barriers
____ Other Please specify: _____	

Satisfaction Measures

The design of the program was effective for the content conveyed Yes No

The content supported the identified learning objectives Yes No

The content was free of commercial bias Yes No

The content was relative to your practice Yes No

The faculty was effective Yes No

You were satisfied overall with the activity Yes No

Would you recommend this program to your colleagues Yes No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care
____ Practice-Based Learning and Improvement
____ Professionalism
____ Medical Knowledge
____ Interpersonal and Communication Skills
____ System-Based Practice

Additional comments: _____

____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

