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RESEARCH perspectives

Expert Analysis of Emerging Atopic Dermatitis Therapy Studies

A CE/CME Activity

Overview

Lawrence F. Eichenfield, MD, and Jonathan I. Silverberg, MD, PhD, MPH, provide their perspectives on the clinical impact of 6 recently published studies involving the management of patients with atopic dermatitis.

Content Areas:

- Crisaborole
- Dupilumab
- Omalizumab
- Sodium hypochlorite (bleach)
- Tofacitinib
- Ustekinumab

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CE/CME Information

Target Audience
This activity was developed for dermatologists, pediatricians, primary care physicians, allergists, nurse practitioners, nurses, physician assistants and other health care professionals who have an interest in atopic dermatitis.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Describe the pathogenesis of atopic dermatitis (AD) and the relevance to development of new treatments for the disease
- Describe the mechanisms of action, efficacy and safety data for emerging nonsteroidal topical therapies and biologic therapies for AD
- Discuss how new data and recommendations can impact clinical practices to improve patient care

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1. Pathogenesis: Lawrence Eichenfield, MD, provides a brief overview of the pathogenesis of atopic dermatitis.
Eichenfield, L.

Lawrence F. Eichenfield, MD

I'm Dr. Lawrence Eichenfield, and before we go into a discussion on new articles about atopic dermatitis, I thought we should discuss a little bit about an overview of the pathogenesis of atopic dermatitis. We should remember the clinical manifestations of eczema are really mediated through a mixture of genetic, immunologic and environmental factors. Been a lot of research on barrier dysfunction. We know subsets of individuals have deficiency in filaggrin, with these mutations in the skin which give a higher rate of the development of atopic dermatitis. It's also responsible for the xerosis (dry skin) of atopic dermatitis. It's also an association with decreased ceramides, overactive epidural proteases, and this setup of the skin probably creates a scenario where the skin is more easily penetrated by antigens, which can set up some of the inflammatory responses in atopic dermatitis.

Much research on the immunology of atopic dermatitis. We know it's a Th2 predominate disease or T helper cells, and T regulatory cells are important in the inflammation of atopic dermatitis. Also, antigen presenting dendritic cells, innate lymphoid cells, mast cells, and eosinophils, all contribute to the inflammation of atopic dermatitis. And of course we know a variety of environmental factors can influence atopic dermatitis, both microbes on the skin, and there's higher *Staphylococcus aureus* colonization. There are environmental climatic factors that can influence flairs of the disease. Skin pH also regulates epidermal function and there is a loss of some of the acidic pH in atopic dermatitis skin. So, a variety of factors that mediate the clinical aspects of atopic dermatitis, but also reflect the underlining pathogenesis, which is a mixture of barrier dysfunction and inflammation.

2. *Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults*

Paller A, et al.

Lawrence F. Eichenfield, MD

Hello, I'm Larry Eichenfield, chief of pediatric and adolescent dermatology at Rady Children's Hospital in San Diego and professor of dermatology and pediatrics at the University of California, San Diego. I'll be discussing Efficacy and Safety of Crisaborole Ointment, a Novel, Nonsteroidal Phosphodiesterase 4 Inhibitor (or PDE4 inhibitor) for the Topical Treatment of Atopic Dermatitis in Children and Adults. This is a paper by Dr. Amy Paller and colleagues. I was an investigator on this study and the study appeared in the September 2016 issue of the *Journal of the American Academy of Dermatology.*

To start off with a summary of the paper, these were the results from 2 identically designed phase 3 studies that show that crisaborole, a phosphodiesterase 4 inhibitor, improved disease severity, pruritus and other signs of atopic dermatitis with a favorable safety profile, compared with vehicle, in patients with mild-to-moderate atopic dermatitis. The importance of this paper: these results support the role of crisaborole, a nonsteroidal topical treatment, and the seminal paper was associated with the file that has led to recent approval in the US by the Food and Drug Administration—actually in December 2016—of crisaborole for the management of patients with mild-to-moderate atopic dermatitis.

Let's view the details of the study. Let's start with the methodology. There were 2 identically designed, randomized, double-blind, vehicle-controlled studies. These were core phase 3 studies that involved 1527 patients, age 2 and older, who had mild-to-moderate atopic dermatitis with a minimum of 5% body surface area that could be treated with the medication. Patients were randomized 2:1 to crisaborole 2% ointment or vehicle ointment, applied twice a day for a 28-day period to all areas affected by atopic dermatitis except for the scalp.

The primary efficacy endpoint for success was the Investigator's Static Global Assessment, the ISGA score, on day 29. And in order to be treatment success, patients had to make it to a designation of clear or almost clear and at least a 2 grade or more improvement from baseline. If a patient had mild atopic dermatitis, they couldn't make it to almost clear because that would only be a 1 grade improvement. It had to be 2-grade improvement and being clear or almost clear. The secondary endpoints were measurable—discuss some of those—as well as safety being assessed.

The key findings of the study: It was a big study! One thousand five hundred twenty seven patients randomized; 1398 patients completed the study. Twelve patients in the crisaborole and 6 in the vehicle withdrew due to adverse events, about the same rate of withdrawal. Remember it was 2:1 assignment to crisaborole. There were 2 parallel studies. One of them was named Study 301, and 32.8% of the patients made it to clear and almost clear and that minimum 2-grade improvement. They made it to success vs 25.4% with the vehicle ointment. In Study 302, in which 31.4% had treatment success as compared to 18%. Significantly more patients in the crisaborole- than the vehicle-treated patients were clear or almost clear at the end of the study. If you take clear and almost clear, it was about 51.7% in the first study vs 40.6% with the vehicle ointment and 48.5% vs 29.7% in the vehicle in the second study.

Significantly more patients with crisaborole achieved improvement of the study endpoint in objective signs of eczema. This included erythema, exudation, excoriation, induration/papulation, and lichenification. Patients treated with crisaborole achieved success in the Investigator's Static Global Assessment, as well as improvement in pruritus, earlier than those in the vehicle. There was a quicker response obviously in the group that received the crisaborole ointment.

From an adverse event standpoint, treatment adverse events were infrequent and only mild-to-moderate severity in both groups. There was application site burning or stinging. This was the most common adverse event. This was at a low rate and the majority of this effect was seen in the first day, with resolution within the first day of use.

My thoughts and analysis of this study. First of all, this paper relates to the core studies that led to the recent approval of topical crisaborole for mild-to-moderate atopic dermatitis, and really the first new topical product approved for atopic dermatitis since 2001. This was a large study. It actually had a large number of children. Eighty-six percent of the patients in the study were children and teenagers with a range of 2 years up to 17 years of age.

In terms of looking at the population that was studied, two thirds of the patients had moderate atopic dermatitis at entry. This was using the Investigator's Global Scale, and about a third had mild disease. The average body surface area involvement that was treatable was around 18%. It was a high vehicle response rate in the study. Clearly, the drug is designed to have a decent vehicle with a hydrating effect, but that's something that we had to look at, but of course, clearly, the drug did well enough to show statistical superiority to the vehicle.

This is also the first topical PDE-4 inhibitor, a new pathway for treatment of atopic dermatitis management. Also, the safety component of the study looked quite good, without evidence of some of the systemic side effects seen with an oral PDE-4 drug, apremilast, which is presently approved for plaque psoriasis, not for atopic dermatitis. It's a different molecule, but it is an oral PDE-4 inhibitor.

I think that the study impacts our current patient management because this is a new, nonsteroidal topical agent. It's in a different class of medicines than topical corticosteroids. It does not have atrophy associated with it. There's no vasoconstriction and therefore no telangiectasia. This is a big difference than topical corticosteroids, where we have these local effects. Also, obviously there's not cortisone absorption concern because it's not a cortisone-based product. It's marvelous to have a new nonsteroidal for topical care. Something in addition to topical corticosteroids and in addition to our topical calcineurin inhibitors, pimecrolimus and tacrolimus, which have box safety warning associated with them, though we certainly use them in care.

I think the study will impact the future state of patient management. We're going to have to work to incorporate this new medication in our regimens of care. I hope that having another agent will help to drive the message home to patients, as well as to health care practitioners, that patients with eczema shouldn't be walking around with a lot of eczema. They should have adequate disease control. I think we can treat our patients to the level where they have minimal rashes, minimal itch, minimal sleep disturbance, and this will minimize the secondary effects of chronic eczema.

Now, finally, there are a few unanswered questions. How do we mix and match topical crisaborole with our present agents, and then also access is going be a big issue. Are the barriers of cost of the product going to be an impediment in our use of these with our patients? A few questions out there, but exciting to have a new topical therapy.

2. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults

3. *Two phase 3 trials of dupilumab versus placebo in atopic dermatitis Simpson E, et al.*

Lawrence F. Eichenfield, MD

Hello, I'm Dr. Larry Eichenfield, chief of pediatric and adolescent dermatology at Rady Children's Hospital in San Diego and professor of dermatology and pediatrics at the University of California, San Diego. I'll be discussing the paper, Two Phase 3 Trials of Dupilumab Versus Placebo in Atopic Dermatitis, by Dr. Eric Simpson and colleagues. This study appeared in the December 15, 2016, issue of *The New England Journal of Medicine.*

A summary of this paper: this paper presents the results of 2 identically designed phase 3 studies showing that dupilumab improved the signs and symptoms of moderate-to-severe atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life as compared to placebo. This is a very important study. These results confirm and extend findings on dupilumab from earlier studies involving patients with moderate-to-severe atopic dermatitis who had inadequate response to topical therapy.

Let's drill down into the methodology of the studies and look at the key findings. This study reported 2 independent, randomized, double-blind, placebo-controlled, parallel-group studies of identical design, involving 1379 adults with moderate-to-severe atopic dermatitis. Patients were randomized by disease severity and geographic region and they were randomized on a 1:1:1 ratio to receive either dupilumab 300 mg weekly, dupilumab 300 mg every other week, or placebo weekly. Patients treated with dupilumab received a 600 mg loading dose on day 1.

The primary efficacy measure in the study was the percentage of patients who made it to clear or almost clear on the Investigator's Global Assessment score or IGA score and they had to have at least a 2-grade improvement from baseline, and this was on week 16 of therapy. There were several secondary endpoints we'll discuss, as well as assessment of safety.

Key findings of this really landmark study. Of the 1379 randomized patients, 73 dupilumab patients and 86 placebo patients did not complete the study. Eighteen patients in the dupilumab group and 24 patients in the placebo group withdrew due to an adverse event. From an outcome standpoint—the primary endpoint—significantly more dupilumab- than placebo-treated patients met the primary endpoint of clear or almost clear and at least a 2-grade improvement in their score.

In the SOLO-1 study, it was 38% of the patients who received dupilumab every other week and 37% of those who received dupilumab every week that made it to clear or almost clear and the 2-grade improvement, as compared to only 10% in the vehicle. In SOLO-2, 36% that received dupilumab every week made the treatment success. The same 36% actually who made treatment success with the dupilumab each week, and there was 8% of those who received the placebo. Significantly more patients with dupilumab than placebo achieved improvement from baseline in the objective EASI score. At week 16, there was a much higher rate who made it to EASI-75, at least a 75% improvement on the EASI score with dupilumab as compared to the vehicle. Interestingly, the proportion of patients who made it to EASI-75 was the same whether they received dupilumab injection on a weekly basis or on an every-other-week basis.

Now, looking at pruritus was quite interesting. Improvement with pruritus was much greater with dupilumab and this was seen by week 2, a very early response in itch. Another interesting point of the study is that they looked at patient-reported measures, patient-reported outcomes, including symptoms of

atopic dermatitis, and there was not only the decrease in pruritus, which is obviously patient reported, but dupilumab had an effect on sleep, minimizing sleep disturbance. It decreased the symptoms of anxiety and depression and it improved quality of life.

Fewer patients on dupilumab received rescue treatment. There were injection site reactions that were more common with dupilumab, most were scored as mild-to-moderate in severity. There were exacerbations of atopic dermatitis in both groups, as well as skin infections, but more common in the placebo group. One of the interesting things is—in using this medicine that blocks inflammation in the skin—a question of whether you see more infections because it has some impact on the immune system, but actually, there were less infections with dupilumab than in the placebo group.

My thoughts and analysis of this paper. First of all, this is really a landmark paper, heralding a world of change in eczema therapy. Never before have we had a prospectively developed, selective immunologic agent to target atopic dermatitis. The study really brings home the importance of Th2 cytokines, particularly the cytokines IL-4 and IL-13, both of which are blocked by the IL-4A receptor blocker, which is what dupilumab is working on. This actually blocks the IL-4A receptor and blocks IL-4 and IL-13, and this study really shows the potency of this pathway in manifestations of atopic dermatitis.

I think it's remarkable to see the objective scores, the percentage of patients who made it to EASI-75, meaning they were 75% percent improved. As well as the change in EASI, the clear and almost clear percentage of patients, as well as the drop in pruritus and other patient outcome measures. There was a drop in depression and anxiety scores in the dupilumab group, which really shows that it's impacting the clinical manifestations of the disease externally, but also some of the tremendous secondary consequences of the disease. It really shows the reversibility of some of the wide impact of atopic dermatitis. The patients in this study had really severe disease. For example, these patients on average had over 50% body surface area. As I already pointed out, the infection rates look lower with the drug than with the placebo.

I think the study really impacts state-of-the-art management as dupilumab is just approved. It'll be a change in our therapy. We've had no approved systemic therapy in the United States other than prednisone, which is not advised because it has tremendous side effects, toxicities. There are other immunosuppressives, but they're hardly used, both because they're not approved and because there are side effects and toxicity concerns. Cyclosporine, azathioprine, mycophenolate, and methotrexate have been utilized, but not at a high rate. Dupilumab potentially can be a revolution in care.

I think that this study, which is the core phase 3 study to back up the approval of dupilumab, really is going to impact the future state of patient management as well. To start with, this becomes the systemic drug of choice for our more severe patients with atopic dermatitis. I think the big issue now is figuring out who are the appropriate patients for this therapy.

We do have some unanswered questions. For instance, for how long do we treat? What will happen if we treat for an extended period of time and then stop? Will there be relapse? We don't think there will be big relapse, but are there going to be subsets of patients who have sustained remissions or not?

Conjunctivitis was seen as a side effect in this study. That's an interesting side effect. It didn't force anyone to come off the study. I don't think it's certain what the cause is and what we should do from a management standpoint if we see conjunctivitis in patients on dupilumab.

The pediatric studies, a big question mark. We'll be very excited to consider pediatrics down the line, not ready for prime time now, but one of the questions is can we mediate the disease over time? Can it be disease-modifying, potentially, to use this agent in early treatment?

A big question is will insurance companies require the use of other systemic agents before approving dupilumab? Even though they're unapproved and don't seem to have the efficacy-safety ratio of dupilumab. These are important questions. Basically, this paper sort of harkens this transition to a new age of eczema care and one that I think is really quite exciting and can really change the lives of our more severe eczema patients.

4. *Efficacy of sodium hypochlorite (bleach) baths to reduce Staphylococcus aureus colonization in childhood onset moderate-to-severe eczema: A randomized, placebo-controlled cross-over trial*

Hon KL, et al.

Jonathan I. Silverberg, MD

Hello. This is Dr. Jonathan Silverberg. I'm an assistant professor of dermatology, medical social sciences, and preventive medicine at Northwestern University Feinberg School of Medicine. Today I will be discussing the Efficacy of Sodium Hypochlorite (Bleach) Baths to Reduce *Staphylococcus Aureus* Colonization in Childhood Onset Moderate-to-Severe Eczema: A Randomized, Placebo-Controlled Cross-Over Trial, by Dr. Hon and colleagues. The study results appear in the second issue of 2016 of the *Journal of Dermatological Treatment.*

The summary of study results as presented by the authors. This is a 4-week, twice-weekly regimen of diluted bleach baths in children with moderate-to-severe atopic dermatitis, and they found that bleach was not more effective than water in reducing *Staphylococcus aureus* colonization and improving the symptoms of moderate-to-severe atopic dermatitis.

The importance of this study, as stated by the authors, was that *Staphylococcus aureus* colonization, and/or infections, are important factors in the pathophysiology of atopic dermatitis. The results of previous studies have provided conflicting results regarding the efficacy of diluted bleach baths in treating moderate-to-severe atopic dermatitis. This study shows that short-term use of diluted bleach baths is no more beneficial in reducing *Staphylococcus aureus* colonization or infections or improving the symptoms of moderate-to-severe atopic dermatitis than baths in water alone.

When approaching the methods of this study: this was a randomized, double-blind, placebo-controlled, crossover, single-center study in 40 children and adolescents between the ages of 4 and 18 years with moderate-to-severe atopic dermatitis. Patients were randomized 1:1 to bleach at the 0.005% concentration or placebo. Patients and their families were instructed how to prepare the bath using a bottle provided to them, taking into account the bathtub's size and height. Patients were instructed to bathe 2 to 3 times weekly for 4 weeks, followed by a 4-week washout period and then crossover treatment for another 4 weeks. Usage of emollients was kept stable and patients were asked not to use their prior medications. The primary outcome was to compare the presence of *Staphylococcus aureus* at the right antecubital fossae and most severely infected or eczematous lesions before, vs following, each treatment period.

The key finding, as presented by the authors, was that 40 patients were randomized and completed the trial, although nonadherence was noted in 14 patients. Now, nonadherence was defined as either bathing less than twice weekly; or delayed follow-up after each treatment period; or the use of an oral antibiotic that might confound things. *Staphylococcus aureus* colonization was found in 80% and 85% of patients in the bleach and placebo groups, respectively, at baseline. Reduced *Staphylococcus aureus* growth was observed in 25% and 28% of bleach and placebo patients, respectively. No significant effect on *Staphylococcus aureus* resistance was observed. There was a significantly greater reduction in the Scoring Atopic Dermatitis or SCORAD index observed with

the water baths alone, or placebo group, compared with the bleach group. Bleach baths conferred no significant efficacy benefit in measures of quality of life, skin hydration, and transepidermal water loss. Bleach baths caused significantly greater reduction in topical corticosteroid use, however, and topical antibiotic use. Adverse events included primarily stinging and itch, but did not really differ between the different groups.

Here are my thoughts and analysis of this study. Bleach baths are a compound intervention. They're ones that have really been adopted widely within the pediatric dermatology, and the dermatology community at large, for the management of atopic dermatitis, but they're really a compound intervention and it's important to understand what's included within them. What I mean by compound intervention is that they include really several interventions bundled together. One, is that a water soak that may, in and of itself, be beneficial by washing away cerumen crust from the skin. Two, you have the use of emollients or topical corticosteroids immediately after coming out of the bath, which can act as a sealant and seal in the moisture obtained from prolonged immersion, and also potentially augment the absorption and efficacy of topical treatments. Three, the actual addition of the bleach itself that may have its either disinfecting or anti-inflammatory properties.

Now, the present study standardized the first component of the intervention by everyone doing that water bath part of it, and specifically examined the third component with direct comparison of bleach vs just placebo or water alone. It's not clear from the manuscript, however, about that second part of the intervention, whether patients applied emollients immediately after the bath or at other times. I think that's one part that we could use a little bit more insight into.

The results show that twice-weekly water baths are a clinically effective strategy, but that the addition of bleach may not actually be needed and may confer no additional benefit. These results may have considerable impact on the current state of patient management because clinicians may simply be able to recommend the use of water baths followed by the application of emollients and/or topical medicaments like topical corticosteroids without the need for bleach per se. This may be preferable from a safety and tolerability standpoint since bleach can cause stinging and burning on open erosions or fissures in the skin, and certainly bleach around the eyes would also be not a great idea because of stinging and burning. Further, many patients report that bleach baths will release fumes that can be irritating to the upper airways, and bleach has been shown previously to be a trigger of asthma. The use of just a straight water bath may actually be as effective and perhaps safer.

In terms of the impact on future state of management, more well done studies, such as the one performed by Dr. Hon, are needed to provide further evidence about the benefits of adding bleach to water baths in patients with atopic dermatitis. This is one well done study. We need more of them to really put together a better body of evidence and understand how this treatment actually works.

There are still some questions that remain unanswered. If bleach does have some efficacy as a treatment for atopic dermatitis, what's the mechanism? Previous studies have called into question whether or not it really is killing off the *Staphylococcus aureus* or if that is the true mechanism of action. Is the mechanism pH dependent? You may get a very different pH in a bath setting than you would with a topic preparation, for example. Does bleach work by killing *Staphylococcus aureus* or might it have direct anti-inflammatory effects? Further studies are definitely needed to better elucidate these points.

5. *Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis*

Khattri S, et al.

Jonathan I. Silverberg, MD

Hello. This is Dr. Jonathan Silverberg. I'm an assistant professor of dermatology, medical social sciences, and preventive medicine at Northwestern University Feinberg School of Medicine. I will be discussing today the Efficacy and Safety of Ustekinumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis, by Dr. Khattri and colleagues. The study results appeared in the January 2017 issue of *Experimental Dermatology.*

The summary of the study is that treatment with ustekinumab resulted in improved clinical response, compared to placebo, in patients with moderate-to-severe atopic dermatitis with early and sustained modulation of markers of inflammation. The importance of this study, as stated by the authors, is that the results establish the likely contribution of the p40 cytokines, interleukin 12 and interleukin 23, to inflammatory pathways in atopic dermatitis.

When reviewing the methods, this was a randomized, double-blind, placebo-controlled, phase 2 study in 33 adults with moderate-to-severe atopic dermatitis. Patients were randomized 1:1 to ustekinumab or placebo at weeks 0, 4, and 16, with a crossover at week 16. The dose of ustekinumab was analogous to that of psoriasis, so 45 mg for patients weighing <100 kilos and 90 mg for patients weighing >100 kilos. Background therapy consisted of triamcinolone 0.025% twice daily, which is a low-potency, topical corticosteroid.

The primary and secondary efficacy endpoints were a 50% or greater decrease from baseline in the Scoring of Atopic Dermatitis, or SCORAD-50 score, at weeks 16 or 32, respectively.

These are the key findings reported in the study. Thirty-three patients were randomized, with 21 completing the study through week 40. Nine withdrew due to a lack of efficacy, 5 of which were in the ustekinumab group and 4 in the placebo group, but none discontinued due to an adverse event. There was a similar decrease in SCORAD from baseline through 40 weeks in both groups. At week 16, about 31% of ustekinumab and 19% of the placebo patients achieved a SCORAD-50.

Responses were relatively flat in the placebo group between weeks 2 and 16. The number of SCORAD-50 responders increased through week 20 in the ustekinumab group; decreased during weeks 16 through 28; and then remained stable from weeks 32 to 40. The SCORAD-50 results suggest an optimal response 8 weeks after administration of ustekinumab, in this study. Gene profiling showed a strong treatment with ustekinumab—but not placebo—by 4 weeks, that increased through 32 weeks, which was 16 weeks after that last ustekinumab injection. The same treatment effect was observed with Th1, Th2, Th17, and Th22 inflammation.

Fourteen patients experienced a total of 24 adverse events, all of which were mild or moderate. There were no significant differences between groups with respect to the frequency of adverse events.

Here are my thoughts of this particular study. Ustekinumab is a relatively well-tolerated treatment, really, across the board, when it's used in psoriasis, and is something that from this study we can see is well tolerated even in adults with moderate-to-severe atopic dermatitis, but based on the results, may not be a reliably effective treatment or consistently effective treatment for moderate-to-severe atopic dermatitis. Combination therapy with ustekinumab and topical

corticosteroids, as used in this study, was not significantly more effective than placebo plus topical corticosteroids. While the study demonstrated numerical differences between the groups, they were not statistically significant.

With respect to how do these results impact the current state of patient management, there may be a small subset of patients who might have some clinical benefit from ustekinumab. However, we don't really have a way, at this point, of predicting who those patients are. From my own personal experience, I've used ustekinumab off-label in a number of patients with moderate-to-severe atopic dermatitis and seen no improvement, not just that it wasn't effective enough, but as if it wasn't even touching the patient, as if it was almost touching the wrong disorder. Again, in some patients it may be that this is a more effective treatment for psoriasis than for atopic dermatitis. Currently, ustekinumab is not recommended as a treatment for moderate-to-severe atopic dermatitis.

This study was associated with a high clinical response rate in the placebo group. This was likely because this is not really just a placebo group, but this is a group that's using a fairly aggressive daily, or twice daily, concomitant use of topical corticosteroids. It sheds light into the design and analysis of future studies that use combination therapy, that whenever you're testing a systemic agent together with a topical corticosteroid, one can expect much higher response rates in the placebo group because the topical corticosteroids are providing some benefit there. Future studies really need to take that into account with respect to the design of the study, the powering of the study, and the analysis approach.

There are still some questions that remain unanswered. Might there be a subset of moderate-to-severe atopic dermatitis patients that have clinical benefit from ustekinumab? Perhaps, but if so, which subset? Because it doesn't seem like it's all patients that are benefiting universally from it. I think future studies are certainly warranted to answer some of these questions.

6. *Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial*

Bissonnette R, et al.

Lawrence F. Eichenfield, MD

Hello, this is Lawrence Eichenfield, chief of pediatric and adolescent dermatology at Rady Children's Hospital and professor of dermatology and pediatrics at the University of California, San Diego. I'll be discussing Topical Tofacitinib for Atopic Dermatitis: a Phase IIa Randomized Trial, by Dr. Robert Bissonnette and colleagues. The study results appear in the November 2016 issue of the *British Journal of Dermatology.*

In summary, the result of this phase 2a study showed that treatment with the Janus kinase (JAK) inhibitor tofacitinib resulted in significantly greater efficacy vs the vehicle, with early onset of effect and comparable safety and local tolerability vs the vehicle. The importance of this study is that despite our present armamentarium of therapy, it's been basically almost 15 years, until recently, in terms of approval of a new topical therapy, and we would be excited to have another therapy with a new mechanism of action for atopic dermatitis. This study indicates that topical administration of a Janus kinase inhibitor is potentially a promising therapeutic option for patients with atopic dermatitis.

The methods of the study: this was a 4-week phase 2a, randomized, double-blind, vehicle-control, parallel-group study involving 69 adults with mild-to-moderate atopic dermatitis. Patients were randomized 1:1 to 2% tofacitinib or vehicle ointment, twice daily, and the application was a daily target rate of about 3 mg per square centimeter.

Patients were instructed to continue the treatment of all treatment-eligible areas that were delineated on day 1, regardless of whether they cleared or improved. The primary endpoint for the study was the percent change from baseline in the Eczema Area and Severity Index, the so-called EASI score at week 4 of treatment. There were secondary endpoints that were included, including safety and local tolerability being assessed.

The key findings of the study: so 69 patients were randomized with 65 completing the study. There were 2 withdrawals due to an adverse event. The mean percentage change from baseline to week 4 in the EASI score was 81.7% for tofacitinib, compared to 29.9% for vehicle. An impressive decrease in the objective Eczema Area and Severity Index.

The patients treated with tofacitinib experienced a more rapid response, based upon the EASI, the Physician Global Assessment, and change from baseline in the total body surface area, with significantly greater improvement in the tofacitinib group improving at week 1. The pruritus was improved, as well, by day 2 in the tofacitinib group. At week 4, the proportion of patients with the Physician Global Assessment of clear or almost clear, for tofacitinib was 73% as compared to 22% with the vehicle. Safety and tolerability were generally similar for both treatments. More adverse events were observed with the vehicle than for tofacitinib, although mild-to-moderate infection occurred in 6 tofacitinib and 3 vehicle patients.

Here are my thoughts and analysis of this study. First, highlighting the main points of the study. Number one, this is an intriguing study for many reasons. First of all, it's the first paper on a JAK inhibitor, which is a pathway of inflammation that may be quite important in inflammation of atopic dermatitis. Second, tofacitinib is a novel topical agent and showed very positive results using standard objective methods, in a

blinded fashion, from a well-respected research center. Third, an important aspect was the display that pruritus was decreased and this occurred rapidly. I think this study may impact current management—but in the future. Because what it shows now is the potential promise of JAK inhibitors for atopic dermatitis therapy.

Now, an insight into this paper. Unfortunately, the company that produces tofacitinib decided to drop the topical tofacitinib program. At the time this study was being done, the drug was being approved orally or it was under evaluation for systemic use. A systemic tofacitinib—which has been approved for rheumatoid arthritis—was being developed for cutaneous plaque psoriasis. But the approval got held up during development, perhaps due to the need to monitor for lymphopenia, anemia, neutropenia, changes in lipids or liver function when patients are using it systemically. However, the promise of oral and topical JAK inhibitors is still tremendous, even though it appears that tofacitinib won't be developed in topical formulation for atopic dermatitis.

I think this paper whets our appetite for further studies on JAK inhibitors for atopic dermatitis. You should be aware that some of the JAK inhibitors are already being used off label for other inflammatory diseases and may be developed for this as well in the future. That includes alopecia areata as well as vitiligo.

There are some unanswered questions. Number one, can we get more topical studies with JAK inhibitors. We hope to—in the promise of topicals with low systemic absorption—bypass some of the issues with systemic JAK administration. Also, there are different pathways of JAKs that are present in the biology of humans, and so one of the questions we have is, which of the JAK pathways will work out to have the best efficacy and safety ratios for atopic dermatitis. Much to figure out in the next few years but, a very, very intriguing paper.

7. *Efficacy of omalizumab in patients with atopic dermatitis: A systematic review and meta-analysis*

Wang HH, et al.

Jonathan I. Silverberg, MD

Hello. This is Dr. Jonathan Silverberg. I'm an assistant professor of dermatology, medical social sciences, and preventive medicine at Northwestern University Feinberg School of Medicine. Today I will be discussing the Efficacy of Omalizumab in Patients With Atopic Dermatitis: A Systematic Review and Meta-Analysis, by Dr. Wang and colleagues. The study results appear in the December 2016 issue of the *Journal of Allergy and Clinical Immunology.*

The overall summary of study result, as presented by the authors, is that there's no concrete evidence found to support the effectiveness of omalizumab for atopic dermatitis, although 43% of patients achieved an excellent clinical response. Clinical response was best in patients with lower serum Immunoglobulin E or IgE levels.

The importance of the study, as discussed by authors, is that this systematic review and meta-analysis has clarified the existing data regarding the efficacy of omalizumab for the treatment of patients with atopic dermatitis. It has also demonstrated the need for more rigorous phase 3 clinical trials with adequate sample sizes.

Let's review the methods. This was a systematic review that searched a number of different databases, MEDLINE or PubMed, Embase, and the Cochrane Library, from inception through November 30, 2015, to include any randomized controlled trials, comparative studies, or case series for review. Omalizumab dosing regimens were somewhat heterogeneous, and, therefore, divided into 2 different groups for comparison, either >600 mg per month, or <600 mg per month. For the >600 mg per month, that included either 300 mg every 2 weeks or 150 mg every week. For the <600 mg per month, that included either 150 mg every 2 weeks or 300 mg every 3 weeks.

Clinical responses were defined as either excellent, which was defined in this study as SCORAD reductions of >50%, or an EASI, an Eczema Area and Severity Index score reduction of 75% from baseline, or an Investigator's Global Assessment of clear or any improvement of >2 degrees in this Investigator's Global Assessment. What was referred to as a satisfying improvement was a SCORAD or Scoring Atopic Dermatitis of 25% to 50%, an Eczema Area and Severity Index reduction of about 25% to 50%, or only 1 degree improvement in this Investigator's Global Assessment severity score. No improvement—or at least not satisfying improvement—was referred to as a Scoring Atopic Dermatitis or SCORAD reduction of <5%, an Eczema Area and Severity Index or EASI score reduction of <50%, or no improvement of this Investigator's Global Assessment score. Disease severity was defined as being either mild, moderate, or severe, at baseline and then at follow-up.

Now the key findings of this study were that they identified 13 studies involving a total of 103 patients that were able to be included into this meta-analysis. Two were clinical trials and 11 were case series. At baseline, 60.5% had severe atopic dermatitis, 76% also had a history of allergic asthma, and 25% also had total serum Immunoglobulin E or IgE levels of <700 IU per mL, 43.4% had serum IgE levels of >5,000 IU per mL. About two-thirds were treated with >600 mg per month of omalizumab. With respect to clinical response, about 42.7% had an excellent clinical response, 25.2% had a satisfying

response, and 33.1% had no improvement or deterioration in their disease state.

The mean Scoring Atopic Dermatitis or SCORAD index score decreased from 65.1 at baseline to 36.8 at the end of the treatment, which ranged from about 3 to 29 months. Serum IgE levels <700 IU per mL were significantly associated with an excellent clinical response compared with those with IgE levels of 700 to 5,000 IU per mL, with a substantial odds ratio of about 12:3. That's a strong effect size.

No significant association between clinical response and patient's age, sex, baseline clinical disease severity, or history of concomitant asthma, or, for that matter, the omalizumab dose, whether or not it was >600 mg per month or <600 mg per month. A major adverse event occurred in only 1% of patients.

Here are my thoughts and analysis of this study. There's really very limited evidence, at this point, to support the use of omalizumab in the management of patients with any atopic dermatitis, but certainly with moderate-to-severe atopic dermatitis. Most of the case series and studies of omalizumab and atopic dermatitis have suffered from major methodologic flaws and selection bias. The few controlled studies performed, show no significant benefit from omalizumab in atopic dermatitis.

These results really impact the current state of patient management because they show us that omalizumab is not a consistently effective treatment for moderate-to-severe atopic dermatitis. There may be a subset of atopic dermatitis patients that have more benefit from omalizumab than others. I personally have seen profound benefit from omalizumab in some patients with overlapping atopic dermatitis and urticaria or dermatographism, aka hives. In those patients, the urticaria or dermatographism are histamine-mediated, which is likely to be an IgE- or immunoglobulin E-mediated disorder, and can be intensely itchy, thereby triggering the itch-scratch cycle in atopic dermatitis patients. The omalizumab can be quite effective at treating the underlying urticaria or hives, thereby reducing one of the triggers of itch in such patients who have the overlap of atopic dermatitis with urticaria. However, the omalizumab is technically treating the hives and not the atopic dermatitis, but only getting secondary improvement in the atopic dermatitis.

In terms of the future state of patient management, at this point, omalizumab is not recommended as systemic treatment for moderate-to-severe atopic dermatitis, but there are still questions that remain unanswered. Future studies may shed light on those specific subsets of atopic dermatitis patients that might have a more consistent benefit from omalizumab. For now, omalizumab is not a preferred treatment for the management of moderate-to-severe atopic dermatitis.

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