

# PEDIATRIC DERMATOLOGY

A supplement to **Pediatric News & Dermatology News**

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**Early onset of atopic dermatitis linked to poorer control, could signify more persistent disease**

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Lawrence F. Eichenfield, MD**

# Dermatologic treatments can be complementary

BY ROBERT SIDBURY, MD, AND  
LAWRENCE F. EICHENFIELD, MD

The articles described herein contain a variety of diagnostic and therapeutic updates, sometimes with complementary themes. The discussion of patch testing is a good example. Jonathan I. Silverberg, MD, PhD, reminds us that patients with atopic dermatitis (AD) are at greater risk for allergic contact dermatitis (ACD), and the culprit often is a product being used to treat the disease itself. Traditional IgE-based allergy tests assessing immediate Type 1 hypersensitivity such as a prick test or radioallergen sorbent test (RAST) will not help; patch testing for Type IV delayed-type hypersensitivity is indicated. Because ACD can be challenging to uncouple from concomitant AD, most experts advise patch testing prior to consideration of systemic therapy, including newer biologic medications.

One such agent, omalizumab, typically is indicated for chronic urticaria or asthma, but Chan et al. demonstrate benefit in AD. Dupilumab, the only Food and Drug Administration–approved nonsteroidal systemic medication for AD, has revolutionized the care of moderate to severe disease, but providers should be alert to potential ocular adverse effects.

Topical calcineurin inhibitors such as tacrolimus and pimecrolimus have been FDA-approved AD therapies for 2 decades, but Ollech et al. point to a potential role treating periorificial dermatitis.

high-risk infants will help better target prevention efforts as they continue to evolve.

In a separate article, Wan et al. demonstrate that earlier onset of AD correlates with persistence, increasing the importance of early identification and intervention for high-risk infants. Armed with risk stratification data, pediatricians can intervene earlier in infancy as rash and itch that might otherwise be attributed to irritants may sooner be labeled AD.

New treatments for acne and molluscum as well as tips for reducing procedural stress in pediatric patients compose other ground covered in this wide-ranging sample of the literature from the past year.



Dr. Robert Sidbury



Dr. Lawrence F. Eichenfield

We continue to learn more about the genetic basis, natural history, and best care practices for AD. While a genetic basis for AD has long been known, studies such as that by Ayelet Ravn, MD, put a finer point on related questions. Does a maternal history of AD and atopy confer greater risk upon the child than a paternal history as long suspected? This does not appear to be the case. Does a parental history of AD as opposed to asthma or allergic rhinitis confer greater risk of AD to the child? Yes, it does. These are important questions not only because they are of great interest to parents, but because improved identification of

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*Dr. Eichenfield is chief of pediatric and adolescent dermatology at Rady Children's Hospital-San Diego. He is vice chair of the department of dermatology and professor of dermatology and pediatrics at the University of California, San Diego. He disclosed that he has served as an investigator and/or consultant to Abbvie, Lilly, Pfizer, Regeneron, Sanofi-Genzyme, and Verrica.*

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**MDedge** **FRONTLINE**  
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# Which children are at greatest risk for AD?

BY BRUCE JANCIN

REPORTING FROM THE EADV CONGRESS

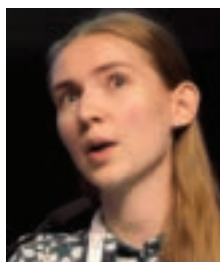
**MADRID** – A parental history of asthma or allergic rhinitis significantly increases the risk that a child will develop atopic dermatitis, and that risk doubles if a parent has a history of atopic dermatitis rather than another atopic disease, Nina H. Ravn reported at a meeting of the European Task Force on Atopic Dermatitis held in conjunction with the annual congress of the European Academy of Dermatology and Venereology.

She presented a comprehensive meta-analysis of 149 published studies addressing the risk of developing atopic dermatitis according to parental history of atopic disease.

The studies included more than 656,000 participants. The picture that emerged from the meta-analysis was one of a stepwise increase in the risk of pediatric atopic dermatitis according to the type and number of parental atopic diseases present.

“This is something that hopefully can be useful when you talk with parents or parents-to-be with atopic diseases and they want to know how their disease might affect their child,” explained Ms. Ravn of the University of Copenhagen.

It’s also information that clinicians will find helpful in appropriately targeting primary prevention interventions if and when methods of proven efficacy become available. That’s a likely prospect, as this is now an extremely active field of research, she noted.



Dr. Ravn



Dr. Wollenberg

The meta-analysis showed that a parental history of atopic dermatitis was associated with a 3.3-fold greater risk of atopic dermatitis in the offspring than in families without a parental history of atopy. A parental history of asthma was associated with a 1.56-fold increased risk, while allergic rhinitis in a parent was linked to a 1.68-fold increased risk.

“It does matter what type of atopic disease the parents have,” she observed. “Those with a parental history of asthma or allergic rhinitis can be considered as being at more of an intermediate-risk level, while those with

a parental history of atopic dermatitis are a particularly high-risk group.”

Of note, the risk of pediatric atopic dermatitis was the same regardless of whether the father or mother was the one with a history of atopic disease. If one parent had a history of an atopic disease, the pediatric risk was increased 1.3-fold compared to when the parental history was negative. If both parents had a history of atopic illness, the risk jumped to 2.08-fold. And if one parent had a history of more than one form of atopic disease, the pediatric risk of atopic dermatitis was increased 2.32-fold.

“An interesting result that was new to me what that fathers’ and mothers’ contribution to risk is equal,” said session cochair Andreas Wollenberg, MD, professor of dermatology at Ludwig Maximilian University of Munich. “For the past 2 decades we were always taught that the mother would have a greater impact on that risk.”

“I was also surprised by our findings,” Ms. Ravn replied. “But when we pooled all the data there really was no difference, nor in any of our subanalyses.”

She reported having no financial conflicts regarding her study.

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**SOURCE:** Ravn NH. THE EADV CONGRESS.

## Commentary by Dr. Eichenfield

**ATOPIC DERMATITIS (AD)** continues to be the focus of much research, including epidemiologic work and the development of new therapies.

The large meta-analysis by Nina H. Ravn from the University of Copenhagen presented several months ago included over 650,000 individuals in 149 published studies looking at the influence of parental eczema and other atopic conditions. It showed, as have other studies, that having parents with a history of AD markedly increases a child’s risk of developing AD (3.3-fold increase), and that other atopic diseases (asthma, allergic rhinitis) increased the odds of a child developing AD, but by less of an amount. Interestingly, this study found the effects were similar for both parents, not favoring maternal influences as other studies have shown. These findings are consistent with other studies,

including studies of twins, showing strong hereditary factors in AD development, as well as incredibly strong genetic influences on the association of AD and asthma.

Others have postulated that different pathways could mediate some of the parental effects, including epigenetic modifications, as well as common “clustering” of environmental hazards.

Is this kind of research important? Absolutely! The individual and global burden of AD is significant, with its high prevalence and association with the development of other atopic conditions. Can we prevent its development in high-risk children? Research to prevent its development includes emollient application studies in early life, pre- and probiotic supplementation, environmental modification studies, and others. While the answers are elusive currently, we look forward to the time when we can decrease AD onset rates in infants and young children, and studies to identify risk factors may help us to do this.

# Early onset of AD linked to poorer control

BY BIANCA NOGRADY

FROM THE JOURNAL OF THE AMERICAN  
ACADEMY OF DERMATOLOGY

**E**arlier onset of atopic dermatitis (AD) in children could signify more difficult to control and persistent disease, results of a study suggest.

Atopic dermatitis most commonly arises in infancy but also can emerge in later childhood and even adolescence, leading to a distinction between early- and late-onset disease, wrote Joy Wan, MD, of the University of Pennsylvania, Philadelphia, and coauthors. “Early-onset, mid-onset, and late-onset AD appear to differ in the presence of ac-

tive disease over time; however, whether these groups also differ in terms of the severity of AD is unknown.”

In this observational cohort study, 8,015 individuals with childhood-onset AD – 53% of whom were female – were assessed twice yearly for up to 10 years. Nearly three-quarters (72%) of the group had early-onset AD – defined as onset before 2 years of age – while 19% had mid-onset disease (3-7 years) and 9% had late-onset disease (8-17 years).

The study found that older age of onset was associated with better control, such that, for each additional year of age at the onset of disease, there was a 7% reduction in the odds of poorer control of disease. Those who had mid-onset disease had a 29% lower odds of poorer control compared with those with early-onset disease, while those with late-onset disease had a 49% lower odds of poorer control.

The likelihood of AD persisting beyond childhood also appeared to be linked to the age of onset. Those with mid-onset disease had a 55% lower odds of persistent AD, compared with those with early-onset disease, while those with late-onset disease had an 81% lower odds.

“In all 3 groups, the proportion of subjects reporting persistent AD gener-

ally declined with older age, and the differences among the 3 onset age groups were most pronounced from early adolescence onward,” the authors wrote.

They noted that there was considerable research currently focused on identifying distinct AD phenotypes and endotypes, and their evidence on the different disease course for early-, mid-, and late-onset disease supported this idea of disease subtypes.

“However, additional research is needed to understand whether and how early-, mid-, and late-onset AD differ molecularly or immunologically, and whether they respond differentially to treatment,” they wrote. They also suggested that the timing of onset could help identify patients who were at greater risk of persistent or poorly controlled disease, and who benefits from more intensive monitoring or treatment.

The study was partly supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Dermatology Foundation. Three authors declared links with the pharmaceutical sector. No other conflicts of interest were declared.

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**SOURCE:** Wan J et al. *J Am Acad Dermatol.* 2019 Dec;81(6):1292-9.



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## Commentary by Dr. Eichenfield

**THE STUDY BY WAN ET AL.** represents important work trying to “tease out” different aspects of atopic dermatitis (AD) onset and course. The classic teaching that AD is a childhood disease that starts very early and “goes away” in a few years is an oversimplification, and several studies have shown that there are varying times of disease onset, subsets of the pediatric AD that remit or seem to be “cured,” and other subsets that persist into adolescence or adulthood. In addition, later-childhood, adolescent, and adult-onset AD are increasingly appreciated as part of our AD patient pool. The University of Pennsylvania researchers have explored the different time courses of AD, using a long-term registry cohort study that was designed to assess long-term safety of pimecrolimus in pediatric patients.

Major findings of the group? That later-onset AD has less associated risks of asthma and seasonal allergies than younger-onset

children, and that patients with earlier onset may have more long-standing disease, as well as more chance of having poorly controlled disease. This is a bit tricky to consider – that is, that younger-onset patients experience disease resolution commonly, while others have persistent and poorly controlled disease.

Of course, all studies have their limitations, as did this one, as it was a long-term registry study of patients using a second-line, non-steroid medication, and early-onset, early-resolving children may be underrepresented in the cohort study.

My takeaway from a practice standpoint? Assess each child independently. Query not just their age of onset, but their course and severity: continuous versus intermittent, frequent versus infrequent flares, easily responsive to therapy versus hardly responsive. And develop a therapeutic regimen that doesn’t treat just flares, but allows long-term disease control with minimal rash, itch, and sleep disturbance.

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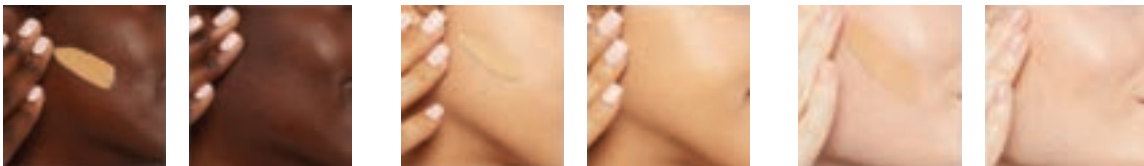
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# Patients with AD should routinely be asked about conjunctivitis

BY JEFF CRAVEN

FROM THE JOURNAL OF THE EUROPEAN  
ACADEMY OF DERMATOLOGY  
AND VENEREOLOGY

Patients with atopic dermatitis (AD) should regularly be asked about conjunctivitis and referred to an ophthalmologist for diagnosis and therapy, if they develop conjunctivitis, according to a recent position statement from the International Eczema Council.

Patients with AD who develop conjunctivitis during dupilumab treatment may experience “bilateral inflammation of the anterior conjunctiva and hyperaemia of the limbus, which may cause nodular swelling,” according to the statement, which pertains to conjunctivitis in AD patients, “with and without dupilumab therapy” (*J Eur Acad Dermatol Venereol.* 2019 May 6. doi: 10.1111/jdv.15608). Currently, there are no predictive factors of conjunctivitis and no guidance in the literature on how to manage conjunctivitis associated with dupilumab, which in some cases can make it necessary to stop treatment, the authors wrote.

The International Eczema Council polled 86 dermatologists in 22 countries who are experts in AD; 46 members responded from 19 countries, including dermatologists from Australia, Canada, Denmark, France, Germany, Japan, Korea, the Netherlands, the United Kingdom, and the United States. The questions centered on the diagnosis and management of conjunctivitis in AD patients, and whether to refer cases to an ophthalmologist. Consensus was achieved if less than 30% of participants disagreed with a statement. IEC members then met in person at a European Academy of Dermatology and Venereology meeting in Paris to discuss the results of the survey. Survey respondents

noted they had seen dupilumab-associated conjunctivitis in both pediatric and adult patients.

The IEC members recommended:

- Patients should be informed about the risks of conjunctivitis before being prescribed dupilumab.
- AD patients should be asked “routinely” about ocular complaints or symptoms.
- AD patients with conjunctivitis should be referred to an ophthalmologist for diagnosis and treatment.
- AD patients with new-onset conjunctivitis during dupilumab treatment always should be referred to an ophthalmologist, especially in more severe cases such as when they do not respond to treatment with antihistamine or artificial tears.



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noted they had seen dupilumab-associated conjunctivitis in both pediatric and adult patients.

- Dermatologists also should rule out keratoconjunctivitis before treating with dupilumab, as it may cause keratitis and blindness.
- Patients who have had keratoconjunctivitis in the past should not be precluded from treatment with dupilumab, and those who develop conjunctivitis during treatment should be referred to an ophthalmologist – but should stay on treatment while waiting for the consult.

“It was stressed that at this moment there are also no reliable data on the course of atopic keratoconjunctivitis and vernal keratoconjunctivitis during dupilumab treatment,” according to Jacob P. Thyssen, MD, PhD, Herlev and Gentofte Hospital, Hellerup, Denmark, and coauthors. These patients “should be carefully monitored by an ophthalmologist before and during treatment with dupilumab.”

The recommendations also centered around which treatments should be initiated by dermatologists, and which should be referred to ophthalmologists. Those patients with conjunctivitis should receive eye drops,

eye ointment, or oral antihistamines from their dermatologists before an ophthalmology referral, the IEC members said. Dermatologists also should perform, or refer patients for, skin prick testing or specific IgE testing for aeroallergens in patients with AD who have conjunctivitis, and patch testing

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## Commentary by Dr. Sidbury

**EIGHT PERCENT OF PATIENTS** with atopic dermatitis have ocular pathology including atopic keratoconjunctivitis, cataracts, and keratoconus; however, clinicians do not always take a thorough ocular review of systems and exam. It has taken the new biologic medication dupilumab to remind us that this should not be optional. The most notable dupilumab-related adverse effect is conjunctivitis, occurring in up to 10% of treated patients in clinical trials and in an even greater number in some postmarketing cohorts. This has rightfully renewed emphasis on eye disease in AD patients. An international consortium of AD experts (International Eczema Council) recommended an ophthalmology consultation for new-onset conjunctivitis in dupilumab-treated patients. Artificial tears and oral antihistamines should be considered, and if access to specialty care is delayed, prescription topical corticosteroids or other immunosuppressants like cyclosporine may be necessary. Although the patho-mechanism of dupilumab-induced conjunctivitis remains obscure, it is intriguing to note that such a signal has not been seen in asthma patients treated with the same medication. This suggests that atopic dermatitis patients may be uniquely susceptible to dupilumab-induced conjunctivitis, which further highlights the need for ocular scrutiny for all AD patients on the front end.

# New cantharidin formulation alleviates molluscum contagiosum in pivotal trials

BY ERIK GREB

REPORTING FROM AAD 2019

**WASHINGTON** – A novel, standardized preparation of topical cantharidin effectively cleared lesions in patients with molluscum contagiosum, compared with placebo, according to the results of two trials presented at the annual meeting of the American Academy of Dermatology.

VP-102, a drug-device combination, was well tolerated and was not associated with serious adverse events.

No Food and Drug Administration–approved treatment is available for treating molluscum contagiosum, which is routinely treated with cantharidin, a naturally occurring vesicant.

VP-102 is a novel formulation of 0.7% cantharidin solution, provided in a single-use applicator, to provide consistent delivery and long-term drug stability.

To test the efficacy and safety of VP-102, Lawrence F. Eichenfield, MD, chief of pediatric and adolescent dermatology at Rady Children’s Hospital–San Diego, and his associates conducted the CAMP-1 (Cantharidin Application in Molluscum Patients) and CAMP-2 phase 3 studies, which had similar designs. The studies enrolled patients with molluscum contagiosum aged 2 years and older who had not received any treatment in the 2 weeks before enrollment. Patients were randomized to VP-102 or

vehicle for 12 weeks. Treatment was administered topically to each lesion every 3 weeks for a maximum of four applications, and washed off with soap and warm water 24 hours after application.

The trials’ primary endpoint was the percentage of patients with complete clearance of their lesions. Secondary endpoints were the percentage of patients with complete clearance and decrease in lesions over time.

In the two studies, 528 patients aged 2-60 years (mean age, approximately 7 years) were randomized to treatment or vehicle. About 30% of participants had prior treatment. The baseline lesion count ranged from 1 to 184.

At day 84, the proportion of patients in the VP-102 arm who achieved complete clearance of lesions was 46% in CAMP-1 and 54% in CAMP-2, compared with 18% and 13%, respectively, among

controls (*P* less than .0001). By day 84, among treated patients, the lesion count had decreased by a mean of 69% in CAMP-1 and 83% in CAMP-2, compared with 20% and 19%, respectively, among controls. Results among controls were “probably consistent with natural history,” Dr. Eichenfield observed.

The researchers observed a high incidence of treatment-emergent adverse events among patients receiving VP-102. “Any crust or vesiculation was considered to be a treatment-emergent adverse event,” he said. Pruritus and application-site pain were reported as well. Most adverse events were mild.

Verrica Pharmaceuticals developed VP-102 and funded the study. Dr. Eichenfield’s institution received funding from the company; several other investigators are employees of Verrica.

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## Commentary by Dr. Sidbury

**CANTHARIDIN HAS A STAR-CROSSED HISTORY** as a therapeutic intervention for molluscum contagiosum. It has been used for this purpose for decades without official FDA sanction. For reasons that are not entirely clear, accessing cantharidin has become difficult even though many pediatric dermatologists, myself included, prefer it to most, if not all, other treatments. VP-102 is a single-use form of cantharidin that is working its way toward FDA approval. Dr. Eichenfield describes results that show unsurprising benefit relative to placebo, and equally unsurprising adverse effects. Cantharidin is a chemovesicant, so some crusting and vesiculation should be expected. These studies – and my own experience – demonstrate that when used appropriately cantharidin can be a safe, effective intervention for molluscum contagiosum.

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with an “ophthalmologic series, and native eye drops/ointments to diagnose possible delayed type hypersensitivity reactions to topical ingredients.”

Among the treatments for conjunctivitis best left to ophthalmologists are cyclosporine, tacrolimus, or corticosteroid eye drops.

“Despite the more limited experience with eye drops by dermatologists, rapid access to ophthalmological service may be difficult, sometimes warranting

a short course of corticosteroid eye drops without ophthalmological consultations,” Dr. Thyssen and associates said. “However, persistent or recurrent conjunctivitis requiring repeated or prolonged use of corticosteroid, tacrolimus, and ciclosporin-containing eye drops, must be managed by an ophthalmologist, given the risk of glaucoma, cataract, and infections.”

“The AD severity, conjunctivitis severity, possible contraindications, possible effect of dupilumab therapy on con-

comitant asthma or other comorbidities, as well as other treatment options, should be considered on an individual patient basis,” the authors concluded.

The IEC survey was limited by the small survey response and reliance on expert opinion.

The authors reported personal and institutional relationships with a variety of pharmaceutical companies, agencies, societies, and other organizations. No funding was obtained for the study.

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# Patch testing in atopic dermatitis: When and how

BY BRUCE JANCIN

EXPERT ANALYSIS FROM SDEF  
HAWAII DERMATOLOGY SEMINAR

**WAIKOLOA, HAWAII** – The prevalence of allergic contact dermatitis is elevated among patients with atopic dermatitis (AD) – and it pays to know their major sources of risk, according to Jonathan I. Silverberg, MD, PhD.

“What are atopic dermatitis patients allergic to? It’s all coming from their personal care products and the things being used to treat their atopic dermatitis,” Dr. Silverberg said at the Hawaii Dermatology Seminar provided by the Global Academy for Medical Education/Skin Disease Education Foundation.

Dr. Silverberg, of the department of dermatology at Northwestern University, Chicago, coauthored a systematic review and meta-analysis that examined the association between AD and contact sensitization. In their examination of 74 published studies, the investigators found that the likelihood of allergic contact dermatitis was 1.5-fold greater in adults and children with AD than in healthy individuals from the general population (*J Am Acad Dermatol.* 2017 Jul;77[1]:70-8).

This finding is at odds with an earlier widespread belief that AD patients should not be at increased risk because the immune profile of their primarily Th2-mediated disease would have a suppressant effect on Th1-mediated hypersensitivity.

“Recent data are calling into question old dogmas and reshaping the way we think about this. And this is not just an academic exercise, this is highly clinically relevant,” the dermatologist asserted.

The results of the meta-analysis prompted Dr. Silverberg and colleagues to conduct a retrospective study of more than 500 adults patch tested to an expanded allergen series at

Northwestern’s patch test clinic with the purpose of identifying the common offending allergens in patients with AD. The key finding: The patients with AD were significantly more likely to have positive patch test reactions to ingredients in their repetitively used personal care products, topical corticosteroids, and topical antibiotics than the individuals without AD. The probable explanation for this results is that the skin barrier disruption inherent in AD allows for easier passage of weak allergens through the skin (*J Am Acad Dermatol.* 2018 Dec;79[6]:1028-33.e6).



Dr. Silverberg

Lanolin was identified as a particularly common allergen in the AD group. “Lanolin is found in one of the most commonly used moisturizers we recommend to patients: Aquaphor. It’s also found in tons of lip balms and emollients. Pretty much every soft soap out there contains lanolin, and it’s in a variety of other personal care products,” Dr. Silverberg noted.

Other common offenders in the AD population included fragrance mix II, cinnamal, quaternium-15, budesonide, tixocortol, carba mix, neomycin, bacitracin, rubber mix, and chlorhexidine. Relevance was established in more

than 90% of the positive reactions.

“You can patch test them directly to their personal care products and make that connection beautifully and see how they’re reacting to them,” he said.

## When to patch test atopic dermatitis patients

Dr. Silverberg was a coauthor of multidisciplinary expert consensus guidelines on when to consider patch testing in AD (*Dermatitis.* 2016 Jul-Aug;27[4]:186-92). “We had to go consensus because we don’t have nearly enough studies to provide true evidence-based recommendations,” he explained.

Because allergic contact dermatitis is a potentially curable comorbid condition in AD patients, it’s important to recognize the scenarios in which patch testing should be considered. These include AD refractory to topical therapy; adolescent- or adult-onset atopic dermatitis; and in AD patients with an atypical or evolving lesional distribution, such as localized dermatitis on the eyelids, head and neck, or hands and feet. Patch testing is also warranted before initiating systemic therapy for AD.

“If you’re about to put a patient on a biologic or phototherapy and step them up to a whole new class of risk

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## Commentary by Dr. Sidbury

**FOR PATIENTS WITH ATOPIC DERMATITIS**, it is important to remember that sometimes friend can be foe. Dr. Silverberg and colleagues remind us that allergic contact dermatitis is more common in AD patients, and is often caused by personal care products including the emollients and topical steroids that are foundations of their care. Important points highlighted include the fact that many such relevant allergens in this population are not represented on the T.R.U.E. test; the more complete NAACD (North American Allergic Contact Dermatitis) tray is indicated if accessible. Indications for patch testing can include atypical presentations or distribution, refractory disease, or a suggestive history. Dr. Silverberg notes anecdotally that extensive nummular eczema also should raise suspicion for allergic contact dermatitis. He echoes the American Academy of Dermatology management guidelines when he advises strong consideration be given to patch testing prior to initiation of systemic therapy. For primary care providers, it is also worth noting that a skin biopsy is not helpful in the discrimination of allergic contact dermatitis from atopic dermatitis: Both share an identical spongiotic histopathology.



# Fast, aggressive eczema treatment linked to fewer food allergies by age 2 years

BY JENNIE SMITH

FROM THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY: IN PRACTICE

Researchers in Japan report that infants with atopic dermatitis who are treated early and aggressively with corticosteroids develop fewer food allergies by age 2 years.

Yumiko Miyaji, MD, PhD, of Japan's National Center for Child Health and Development in Tokyo and colleagues looked at 3 years' worth of records for 177 infants younger than 1 year of age seen at a hospital allergy center for eczema. Of these infants, 89 were treated with betamethasone valerate within 4 months of disease onset, and 88 were treated after 4 months of onset. Most (142) were followed up at 22-24 months, when all were in complete remission or near remission from eczema.

At follow-up, clinicians collected information about anaphylactic reactions to food, administered specific food challenges, and tested serum immunoglobulin E levels for food allergens. Dr. Miyaji and colleagues found a significant difference in the prevalence of allergies between the early-treated and late-treated groups to chicken egg, cow's milk, wheat, peanuts, soy, or fish (25% vs. 46%, respectively;  $P$  equal to .013). For

individual food allergies, only chicken egg was associated with a statistically significant difference in prevalence (15% vs 36%,  $P$  equal to .006).

"Our present study may be the first to demonstrate that early aggressive topical corticosteroid treatment to shorten the duration of eczema in infants was significantly associated with a decrease in later development of [food allergies]," Dr. Miyaji and colleagues wrote in their analysis.

The investigators acknowledged as limitations of their study some be-

tween-group differences at baseline, with characteristics such as *Staphylococcus aureus* infections and some inflammatory biomarkers higher in the early-treatment group.

The Japan Agency for Medical Research and Development supported the study, and the investigators disclosed no relevant conflicts of interest.

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**SOURCE:** Miyaji Y et al. *J Allergy Clin Immunol Pract.* 2019. doi: 10.1016/j.jaip.2019.11.036.

## Commentary by Dr. Sidbury

**THE CONCEPT OF THE ATOPIC MARCH** – the idea that some affected individuals will develop food allergies and eczema as babies, asthma as children, and hay fever as adults in an orderly sequence – is well described. Recent work has raised the question whether early aggressive intervention in susceptible infants may prevent eczema and possibly other comorbidities along this "march." Miyaji and colleagues have compared infants treated with a topical steroid within 4 months of onset with those treated later and found that indeed the early-treatment group developed fewer food allergies. This idea aligns with lessons learned from the LEAP studies of peanut allergy prevention, in which it seemed that the abnormal atopic skin barrier was a point of allergic vulnerability. These are early data, and comparative groups were not identical, but it is exciting to contemplate that successful atopic dermatitis treatment might not only confer great physical relief, decrease the risk of skin infection, and improve quality of life, but also possibly prevent the development of food allergies. Risks and benefits of therapy always must be considered, but the benign neglect often demonstrated because a child's itchy rash is "just eczema" is increasingly obsolete.

◀ Continued from previous page

of adverse events, that's an ideal time to think about reversible options," Dr. Silverberg advised.

Another situation in which he considers patch testing advisable, although this one isn't covered in the consensus guidelines, is in AD patients with prominent nummular eczema lesions. "Widespread nummular eczema lesions may be a sign of allergic contact dermatitis in atopic dermatitis patients. I'm not saying everyone with nummular lesions is going to have a positive patch test, but it's definitely a situation you want to think about," he said.

## How to patch test atopic dermatitis patients

Most of the common topical allergens in AD patients are not included in the T.R.U.E. Test. An expanded allergen series, such as the American Contact Dermatitis Society core 80 series, is the better way to go.

Once the dermatologist determines that a patient's positive patch test reaction is relevant, it's important to recommend the use of personal care products that are "pretty clean," he said.

"Clean in my opinion is not a matter of 'It should be all organic and all natural,'" he emphasized. "I'm not anti- any

of that, but clean means having the fewest ingredients possible and trying to steer clear of those really common allergens that patients are highly likely to have been exposed to and potentially sensitized to over the many years of their tenure of atopic dermatitis."

Dr. Silverberg reported receiving research grants from Galderma and GlaxoSmithKline and serving as a consultant to more than a dozen pharmaceutical companies.

SDEF/Global Academy for Medical Education and this news organization are owned by the same parent company.

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# Topical calcineurin inhibitors are effective treatment option for periorificial dermatitis

BY DOUG BRUNK

REPORTING FROM SPD 2019

**AUSTIN, TEX.** – Topical calcineurin inhibitors (TCIs) are an effective therapeutic option for pediatric patients with periorificial dermatitis (POD), as monotherapy or as part of a combination regimen, results from a retrospective cohort study showed.

The mainstays of treatment for POD include topical and oral antibiotics. In an interview prior to the annual meeting of the Society for Pediatric Dermatology, Ayelet Ollech, MD, said that the most

common systemic agents used include erythromycin, azithromycin, and, in patients older than 8-10 years of age, minocycline or doxycycline. Topical agents, which are often used as monotherapy in mild disease, include metronidazole, clindamycin, erythromycin, sodium sulfacetamide, and, less often, azelaic acid, topical retinoids, and ivermectin. “TCIs (pimecrolimus 1% cream and tacrolimus 0.03% or 0.1% ointment) are a good steroid-sparing option for POD,” said Dr. Ollech, a pediatric dermatology fellow at Ann & Robert H. Lurie Children’s Hospital of Chicago. “In the adult population, two randomized controlled studies of pimecrolimus 1% cream showed good results. In the pediatric population, there are only a few case series and case reports of TCIs for the treatment of POD.”

In what is believed to be the largest study of its kind, Dr. Ollech, Anthony J. Mancini, MD, and colleagues assessed the clinical utility of TCI in 132 pediatric patients with POD who were treated in the division of dermatology at Children’s Hospital of Chicago between 2008 and 2018. The researchers made note of epidemiologic variables, personal and family medical histories, possible triggers, duration of illness, previous treatments, distribution (periocular, perinasal, perioral, extra facial regions), severity of

POD, treatment(s) prescribed, duration of therapy, clinical response, recurrences, and side effects. In an effort to capture missing data, the researchers performed follow-up via telephone for all patients who lacked appropriate follow-up documentation in the medical record.



Dr. Ollech

Of the 132 patients, the female:male ratio was 1.2:1 and the median age at diagnosis was 4.2 years. About one-third of patients (33%) had involvement of one region, 38% had involvement of two regions, 26% had involvement of three regions, and 3% patients had involvement of all regions. The most common

disorders on medical history were atopic dermatitis (AD) and asthma (in 29% and 17% of patients, respectively).

Dr. Ollech reported that 72 of the 132 patients (55%) had evaluable follow-up data via either medical record documentation or the phone questionnaire. Of these, 67% were treated with TCI alone, 19% were treated with a combination of TCI and topical metronidazole, and 10% were treated with a combination of TCI and a systemic antibiotic. The median duration of treatment was 60 days. The researchers observed complete response in 65% of patients treated with TCI alone, in

64% of those treated with TCI and metronidazole, and in 70% of those treated with TCI and a systemic antibiotic. Adverse events attributed to TCI were rare and mild in severity.

“We were surprised that there were almost no reported side effects from the usage of TCIs as it is known that these agents can cause a burning or stinging sensation,” Dr. Ollech said. “Only one case described this side effect. We found 30% of the patients to have associated atopic dermatitis as well as a few patients with irritant dermatitis. We were also surprised how convenient the TCI treatment was for a patient who had POD and concomitant facial AD or even irritant dermatitis as an agent that can treat both. This can be very helpful for the parents that apply the medication to have a single solution to more than one rash.”

The researchers noted recurrence of POD in 14% of patients overall, including 6% of patients treated with TCI alone, 29% of patients treated with TCI and metronidazole, and 30% of patients treated with TCI and a systemic antibiotic.

Dr. Ollech and her colleagues reported having no financial disclosures.

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**SOURCE:** Ollech A et al. SPD 2019, Poster 23.

## Commentary by Dr. Sidbury

**PERIORAL DERMATITIS IS NOTORIOUSLY STUBBORN**, necessitating a well-stocked therapeutic toolkit. Topical calcineurin inhibitors (TCIs) have been used off label to treat perioral dermatitis for nearly the entire 20 years they have been on the market; Dr. Ollech and colleagues characterize their experience over the past decade. In their cohort of young children (mean age = 4 years), they demonstrated just why this drug class has been an enduring weapon against perioral dermatitis: It can work! As monotherapy, roughly 65% of patients cleared. This means of course that over a third of patients will not clear with this medication alone, a figure that jibes with my own experience; practitioners utilizing this option should have a plan B in mind at the outset. Insurance coverage can be another barrier for this off-label indication; however, Dr. Ollech’s secondary finding that one in three patients in her cohort had comorbid atopic dermatitis, for which TCIs are indicated, suggests coverage may be easier for some.



Not an actual patient.

# APPROVED FOR PATIENTS AGED 12 YEARS AND OLDER WITH UNCONTROLLED MODERATE-TO-SEVERE ATOPIC DERMATITIS

## INDICATION

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

## IMPORTANT SAFETY INFORMATION

**CONTRAINDICATION:** DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

### WARNINGS AND PRECAUTIONS

**Hypersensitivity:** Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

**Conjunctivitis and Keratitis:** Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder in these patients. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

**Reduction of Corticosteroid Dosage:** Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

**Atopic Dermatitis Patients with Comorbid Asthma:** Advise patients not to adjust or stop their asthma treatments without consultation with their physicians.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

AD, atopic dermatitis.

**DUPIXENT**<sup>®</sup>  
(dupilumab) Injection  
200mg · 300mg  
REVOLUTIONIZING AD



# SHARED RESULTS

**TRIAL DESIGNS:** A total of 917 adult patients in Trials 1 and 2 (16-week trials), 251 adolescent patients in Trial 6 (16-week trial), and 421 adult patients in Trial 3 (52-week trial) with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription treatments were randomized to DUPIXENT or placebo. For all patients in Trial 3, lesions were treated with concomitant TCS. All adults received 300 mg Q2W following a 600 mg loading dose. Adolescents  $\geq 60$  kg also received this dose, while adolescents  $< 60$  kg received 200 mg Q2W following a 400 mg loading dose. Eligible patients had an IGA score  $\geq 3$  (overall atopic dermatitis lesion severity scale of 0 to 4), an EASI score  $\geq 16$  on a scale of 0 to 72, and body surface area involvement of  $\geq 10\%$ . At baseline, 52% of adults and 46% of adolescents had an IGA score of 3 (moderate atopic dermatitis), 48% of adults and 54% of adolescents had an IGA of 4 (severe atopic dermatitis), mean EASI score was 33 for adults and 36 for adolescents, and weekly averaged peak pruritus NRS was 7 on a scale of 0 to 10 for adults and 8 for adolescents.<sup>1</sup>

**TRIAL RESULTS:** The primary endpoint was the change from baseline in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and  $\geq 2$ -point improvement at Week 16 (38% and 36% of adults treated with DUPIXENT vs 10% and 9% with placebo in Trials 1 and 2, respectively,  $P < 0.001$ ; 24% of adolescents treated with DUPIXENT vs 2% with placebo in Trial 6,  $P < 0.001$ ; 39% of adults treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 3,  $P < 0.0001$ ). Other endpoints included change from baseline in the proportion of subjects with EASI-75 at Week 16 (improvement of  $\geq 75\%$ ; 51% and 44% of adults treated with DUPIXENT vs 15% and 12% with placebo in Trials 1 and 2, respectively,  $P < 0.001$ ; 42% of adolescents treated with DUPIXENT vs 8% with placebo in Trial 6,  $P < 0.001$ ; 69% of adults treated with DUPIXENT + TCS vs 23% with placebo + TCS in Trial 3,  $P < 0.0001$ ) and reduction in itch as defined by  $\geq 4$ -point improvement in the Peak Pruritus NRS at Week 16 (41% and 36% of adults treated with DUPIXENT vs 12% and 10% with placebo in Trials 1 and 2, respectively,  $P < 0.001$ ; 37% of adolescents treated with DUPIXENT vs 5% with placebo in Trial 6,  $P < 0.001$ ; 59% of adults with DUPIXENT + TCS vs 20% with placebo + TCS in Trial 3,  $P < 0.0001$ ).<sup>1,5</sup>

EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, numerical rating scale; Q2W, once every 2 weeks; TCS, topical corticosteroids.

## IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (cont'd)

**Parasitic (Helminth) Infections:** It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.



Not an actual patient.

# SHARED RELIEF

- > Itch reduction<sup>1</sup>
- > A biologic—not a steroid treatment or an immunosuppressant<sup>1</sup>
- > Clear or almost-clear skin<sup>1</sup>
- > No requirement for initial lab testing or ongoing lab monitoring, according to the full Prescribing Information<sup>1</sup>

## IMPORTANT SAFETY INFORMATION

**ADVERSE REACTIONS:** The most common adverse reactions (incidence  $\geq 1\%$  at Week 16) in adult patients with atopic dermatitis are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. The safety profile in adolescents through Week 16 was similar to that of adults with atopic dermatitis. In an open-label extension study, the long-term safety profile observed in adolescents through Week 52 was consistent with that seen in adults with atopic dermatitis.

**DRUG INTERACTIONS:** Avoid use of live vaccines in patients treated with DUPIXENT.

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Please see brief summary of full Prescribing Information on the following pages.

Visit [DUPIXENTHCP.COM/ATOPICDERMATITIS](https://DUPIXENTHCP.COM/ATOPICDERMATITIS) TO LEARN MORE

**DUPIXENT**<sup>®</sup>  
(dupilumab) Injection  
200mg · 300mg  
REVOLUTIONIZING AD

**Brief Summary of Prescribing Information**

**1 INDICATIONS AND USAGE**

**1.1 Atopic Dermatitis**

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUXIPENT can be used with or without topical corticosteroids.

**4 CONTRAINDICATIONS**

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients [see *Warnings and Precautions (5.1)*].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Hypersensitivity**

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUXIPENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUXIPENT [see *Adverse Reactions (6.1, 6.2)*].

**5.2 Conjunctivitis and Keratitis**

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUXIPENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in <1% of the DUXIPENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUXIPENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUXIPENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period [see *Adverse Reactions (6.1)*].

Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

**5.5 Reduction of Corticosteroid Dosage**

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUXIPENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

**5.6 Patients with Comorbid Asthma**

Advise patients with atopic dermatitis or CRSwNP who have co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

**5.7 Parasitic (Helminth) Infections**

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUXIPENT will influence the immune response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with DUXIPENT. If patients become infected while receiving treatment with DUXIPENT and do not respond to antihelminth treatment, discontinue treatment with DUXIPENT until the infection resolves.

**6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity [see *Warnings and Precautions (5.1)*]
- Conjunctivitis and Keratitis [see *Warnings and Precautions (5.2)*]

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adults with Atopic Dermatitis**

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUXIPENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUXIPENT, with or without concomitant topical corticosteroids (TCS). A total of 739 subjects were treated with DUXIPENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis. Trials 1, 2, and 4 compared the safety of DUXIPENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUXIPENT + TCS to placebo + TCS through Week 52.

**Weeks 0 to 16 (Trials 1 to 4)**

In DUXIPENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUXIPENT 300 mg Q2W and placebo groups. Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUXIPENT 300 mg Q2W monotherapy groups, and in the DUXIPENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

**Table 1: Adverse Reactions Occurring in ≥1% of the DUXIPENT Monotherapy Group or the DUXIPENT + TCS Group in the Atopic Dermatitis Trials through Week 16**

Adverse Reaction	DUPIXENT Monotherapy <sup>a</sup>		DUPIXENT + TCS <sup>b</sup>	
	DUPIXENT 300 mg Q2W <sup>c</sup> N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W <sup>c</sup> + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis <sup>d</sup>	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis <sup>e</sup>	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection <sup>f</sup>	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

<sup>a</sup>Pooled analysis of Trials 1, 2, and 4.

<sup>b</sup>Analysis of Trial 3 where subjects were on background TCS therapy.

<sup>c</sup>DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

<sup>d</sup>Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

<sup>e</sup>Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

<sup>f</sup>Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

**Safety through Week 52 (Trial 3)**

In the DUXIPENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUXIPENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUXIPENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

The safety profile of DUXIPENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

**Adolescents with Atopic Dermatitis**

The safety of DUXIPENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUXIPENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUXIPENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUXIPENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUXIPENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

**Specific Adverse Reactions**

**Conjunctivitis**

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUXIPENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). [see *Warnings and Precautions (5.2)*].

**Eczema Herpeticum and Herpes Zoster**

The rate of eczema herpeticum was similar in the placebo and DUXIPENT groups in the atopic dermatitis trials.

Herpes zoster was reported in <0.1% of the DUXIPENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUXIPENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUXIPENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).

**Hypersensitivity Reactions**

Hypersensitivity reactions were reported in <1% of DUXIPENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis [see *Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)*].

**Eosinophils**

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mL respectively. Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mL) was similar in DUXIPENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mL) was reported in <2% of DUXIPENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment [see *Warnings and Precautions (5.3)*].

## Cardiovascular (CV)

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal MIs, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

## 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; ~3% exhibited persistent ADA responses, and ~5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; ~1% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations [see *Clinical Pharmacology* (12.3) in the full prescribing information].

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy [see *Warnings and Precautions* (5.1)].

## 7 DRUG INTERACTIONS

### 7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

### 7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel<sup>®</sup>) and a meningococcal polysaccharide vaccine (Menomune<sup>®</sup>). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please contact 1-877-311-8972 or go to <https://mothertobaby.org/ongoing-study/dupixent/> to enroll in or to obtain information about the registry.

#### Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4R $\alpha$ ) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (see *Data*). The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**References:** 1. DUPIXENT Prescribing Information. 2. Simpson EL, Bieber T, Guttman-Yassky E, et al; SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. 3. Data on file, Regeneron Pharmaceuticals, Inc. 4. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303. 5. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial [published online November 6, 2019]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2019.3336

## Data

### Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4R $\alpha$  up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

### 8.4 Pediatric Use

#### Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults [see *Adverse Reactions* (6.1) and *Clinical Studies* (14.2) in the full prescribing information]. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

### 8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects [see *Clinical Pharmacology* (12.3) in the full prescribing information].

## 10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

## 17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

#### Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry [see *Use in Specific Populations* (8.1)].

#### Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations [see *Instructions for Use*].

#### Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

#### Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see *Warnings and Precautions* (5.2)].

#### Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic, topical, or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see *Warnings and Precautions* (5.5)].

#### Patients with Comorbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians [see *Warnings and Precautions* (5.6)].

# New mechanisms, therapies for acne considered

BY JIM KLING

EXPERT ANALYSIS FROM COASTAL DERM

**SEATTLE** – It used to be thought that acne begins with microcomedones, which go on to develop either inflammatory lesions or noninflammatory lesions, but more recent evidence has changed that perception, according to Linda Stein Gold, MD, director of dermatology research at Henry Ford Hospital, Detroit.

Biopsies of acne-prone areas have found that, before the development of microcomedones, “it appears that there is inflammation around the hair follicles,” Dr.

Stein Gold said at the annual Coastal Dermatology Symposium. “All acne is inflammation acne,” and inflammation also persists, she added. Biopsies of scarred lesions, once considered post-inflammatory, also have revealed persistent inflammation, she noted.

One study found that persistent scars can evolve from closed comedones, papules, and pustules, but the most common was a papule that turned into a postinflammatory lesion (*J Drugs Dermatol.* 2017 Jun 1;16[6]:566-72).

“So when patients come in and they have these red spots on their face, it’s not over. There’s still time to be aggressive because those inflammatory lesions are more likely to lead to scars than anything else,” Dr. Stein Gold

said. “And we also know that papules that develop into scars do so because they’re there for a longer period of time. Those that develop scars are present about 10.5 days, compared with 6.6 days for those that don’t develop into scars.”

She went on to review some of the new treatments for acne that can be brought to bear in such cases. These include developments with topical retinoids that are aimed at improving delivery and reducing skin irritation.

A new topical retinoid, trifarotene cream, 0.005%, showed efficacy and tolerability for both the face and

trunk in a recent phase 3 trial of patients with moderate facial and truncal acne and was recently approved for patients aged 9 years and older. In the study, about 30%-40% of people aged 9 years and older treated with once-daily trifarotene cream (Aklief) achieved clear or almost-clear status of the face at 12 weeks, vs. about 20% and 26%, of those on the vehicle cream (*J Am Acad Dermatol.* 2019 Jun;80[6]:1691-9).

The drug can also treat papules and pustules, nearly as well as it treats blackheads and whiteheads, according to the dermatologist.

Like other retinoids, it produces some redness and scaling, and rather than letting these adverse events dis-

courage patients, she leans in. “I tell patients they’re going to have some sloughing of the skin the first 2 weeks. I tell them that people pay money for that. It’s called a chemical peel,” said Dr. Stein Gold, noting that patients respond well to this information.

If patients find the treatments too irritating, she advises them to avoid applying it to wet skin. They can also apply it every other night, or even less frequently, and then work up to more frequent use, she said at the meeting, jointly presented by the University of Louisville and Global Academy for Medical Education.

Tazarotene is another topical retinoid that can be very irritating. A new lotion formulation of tazarotene 0.045% contains a lower dose than the 0.1% typically used in creams, and has similar efficacy but reduced irritation, Dr. Stein Gold said. In August, the manufacturer submitted an application for approval with the Food and Drug Administration for treatment of acne.

Dr. Stein Gold also talked about using retinoids to minimize scarring, referring to a study of patients with moderate and severe facial acne, and atrophic acne scars, comparing adapalene 0.3% plus benzoyl peroxide 2.5% gel on one side of the face and vehicle on the other side of the face for 24 weeks, followed by application of the active treatment to both sides of the face for 24 weeks. Treatment was

Continued on following page ▶



Dr. Stein Gold

## Commentary by Dr. Sidbury

**DR. STEIN GOLD ADVISES NOT BEING COMPLACENT** on either end of the acne spectrum. In early microcomedonal acne, historically dubbed “noninflammatory,” inflammation is present and can be deleterious; similarly, “old” red macules thought to represent resolved acne also can have a residual inflammatory component that can affect outcome. Her principal message is this: All acne is inflammatory, and topical retinoids can benefit all phenotypes. Trifarotene 0.005% cream is a new topical retinoid approved down to 9 years of age. This agent continues a trend of acne drug approval at younger ages, mirroring the decreasing average age of acne presentation. Dr.

Stein Gold also described a weaker strength tazarotene preparation (0.045% lotion) that also has shown promise, with similar efficacy but decreased irritation, compared with available 0.05% and 0.1% tazarotene products.

Dr. Stein Gold wisely prepares patients for expected retinoid-induced dryness and expertly repurposes this expected adverse effect as a benefit (e.g., like a chemical peel patients pay lots of money for!). Finally, Dr. Stein Gold describes clascoterone, a pipeline topical androgen receptor antagonist that among other things inhibits sebum production. This is the principal mechanism underpinning the efficacy of isotretinoin, so having a novel topical agent achieve this same effect is exciting.



# Destress dermatologic procedures with honesty, distraction, and relaxation

BY HEIDI SPLETE

FROM PEDIATRIC DERMATOLOGY

**R**educing fear and anxiety in children undergoing dermatologic procedures is possible with techniques based on cognitive-behavioral therapy, according to a report published in *Pediatric Dermatology*.

For many children, the anticipation of pain and the anxiety about a procedure results in a more painful experience, wrote Andrew M. Armenta, MD, of the University of Texas, Galveston, and colleagues.

Preparing children in advance and using cognitive-behavioral therapy (CBT) strategies in the moment can help reduce their anxiety.

“CBT is a skill-based approach that focuses on the present and aims to teach efficient ways of identifying distorted thinking, modifying beliefs, and changing behaviors for a more favorable outcome of real-life situations,” they wrote.

First, Dr. Armenta and his associates advised, be honest with children about what to expect from a procedure. Evidence does not support phrases such as, “It won’t hurt,” or “It will be over soon,” to reduce anxiety.

Timing the disclosure of a procedure and creating the appropriate setting also can help reduce anxiety. For very young children, short notice of a procedure is often best, with the promise of a small reward or outing afterward. Older children may want some advance notice so they can feel prepared, but their specific

concerns should be addressed.

CBT-based techniques include deep breathing and positive coping statements such as “I can do this” for older children, or encouraging them to talk about a family pet or listen to music. Younger children may be distracted with pinwheels, rattles, or songs. “Additionally, in recent years, virtual reality headsets have even proved to be effective distractors, resulting in an overall reduction in both pain and fear,” Dr. Armenta and his associates noted.

Other useful strategies include allowing children to choose their position and location for an injection or procedure when possible. Small children may be able to sit on the lap of an adult, and older children may prefer sitting up to lying down. Avoid physical restraint unless it is absolutely necessary for safety, they emphasized.

Incorporating CBT-based strategies of breathing and distraction with honesty and respectful disclosure of what



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is being done and why “not only makes practicing pediatric dermatology easier, but also can improve patient adherence to painful procedures,” they said.

No disclosure information was given.

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**SOURCE:** Armenta AM et al. *Pediatr Dermatol*. 2019. doi: 10.1111/pde.13739.

## Commentary by Dr. Sidbury

**PROCEDURES – INCLUDING NEEDLE STICKS** – are stressful for children. Dr. Armenta reminds us that tepid reassurance like “it will be over soon” or white lies like “it won’t hurt” are not the best way to decompress anxious children. He uses cognitive-behavioral therapy to help children modify their beliefs and behaviors to decrease procedure-related anxiety. One size will not fit all, as younger children may do best with short notice to minimize anticipation, whereas an older child may do better with time to mentally prepare. When possible, allowing children a modicum of control (e.g., sit up or lie down) can be helpful. Physical restraint, the ultimate loss of control, should be avoided unless absolutely necessary. And sometimes it is.

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associated with a reduction of atrophic acne scars at 24 weeks, which was maintained for up to 48 weeks (*Am J Clin Dermatol*. 2019 Oct[5];20:725-32).

“We can now say to patients, ‘Not only can I help you with your acne, but I can potentially even improve your atrophic scarring,’” she said.

Finally, she discussed clascoterone,

a novel androgen receptor antagonist, which inhibits sebum production and prevents colonization by *Cutibacterium acnes* (formerly called *Propionibacterium acnes*) and subsequent inflammation. “It does a lot of good things in terms of the pathogenesis of acne, but more importantly, it is one of the first drugs that topically has been shown to decrease the production of sebum,” Dr.

Stein Gold said. A 1% cream formulation is being studied for acne.

Dr. Stein Gold is a consultant, investigator, and/or speaker for Galderma, Ortho Derm, Sol Gel, Foamix, Cassiopea, and Almirall. This publication and Global Academy for Medical Education are owned by the same parent company.

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# Omalizumab proves effective for treating patients with severe pediatric atopic dermatitis

BY STEVE CIMINO

FROM JAMA PEDIATRICS

**A** new study has found that omalizumab (Xolair) reduced severity and improved quality of life in pediatric patients with severe atopic dermatitis.

“Future work with an even larger sample size, a longer duration, and higher-affinity versions of omalizumab would clarify the precise role of anti-IgE therapy and its ideal target population,” wrote Susan Chan, MD, of Guy’s and St. Thomas’ NHS Foundation Trust in London and her co-authors. The study was published in *JAMA Pediatrics*.

To determine the benefits of omalizumab in reducing immunoglobulin E levels and thereby treating severe childhood eczema, the researchers launched the Atopic Dermatitis Anti-IgE Pediatric Trial (ADAPT).

This randomized clinical trial recruited 62 patients between the ages of 4 and 19 years with severe eczema, which was defined as a score over 40 on the objective Scoring Atopic Dermatitis (SCORAD) index.

They received 24 weeks of treatment with either omalizumab (n = 30) or placebo (n = 32) followed by 24 weeks of follow-up. Participants had a mean age of 10.3 years.

After 24 weeks, the adjusted mean difference in objective SCORAD

index between the two groups was  $-6.9$  (95% confidence interval,  $-12.2$  to  $-1.5$ ;  $P = .01$ ) and significantly favored omalizumab therapy.

The adjusted mean difference for the Eczema Area and Severity Index ( $-6.7$ ; 95% CI,  $-13.2$  to  $-0.1$ ) also favored omalizumab. In regard to

**“Future work with an even larger sample size, a longer duration, and higher-affinity versions of omalizumab would clarify the precise role of anti-IgE therapy and its ideal target population.”**

quality of life, after 24 weeks the Children’s Dermatology Life Quality Index/Dermatology Life Quality Index favored the omalizumab group with an adjusted mean difference of  $-3.5$  (95% CI,  $-6.4$  to  $-0.5$ ).

In an accompanying editorial, Ann Chen Wu, MD, of Harvard Medical School in Boston noted that the results of the study from Chan et al. were promising but “more questions need to be answered before the drug can be used to treat atopic dermatitis in clinical practice” (*JAMA Pediatr*. 2019 Nov 25. doi: 10.1001/jamapediatrics.2019.4509).

Her initial concern was price; she

acknowledged that “omalizumab is a costly intervention” but said atopic dermatitis is also costly, raising the question as to whether the high costs of both justify treatment.

In addition, omalizumab as treatment can come with both benefits and harms. Severe atopic dermatitis can decrease quality of life, and though omalizumab appears to be safe, there are adverse effects and logistical burdens to overcome, she said.

More than anything, she recognized the need to prioritize, wondering what level of atopic dermatitis patients would truly benefit from this level of treatment. “Is using a \$100,000-per-year medication for an itchy condition an overtreatment,” she asked, “or a lifesaver?”

The study was funded by the National Institute for Health Research Efficacy and Mechanism Evaluation Programme and Guy’s and St. Thomas’ Charity. The authors had numerous financial disclosures, including receiving grants from the NIHR EME Programme and Guy’s and St. Thomas’ Charity along with active and placebo drugs from Novartis for use in the study. Dr. Wu reported receiving a grant from GlaxoSmithKline.

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**SOURCE:** Chan S et al. *JAMA Pediatr*. 2019 Nov 25. doi: 10.1001/jamapediatrics.2019.4476.

## Commentary by Dr. Sidbury

**THE CAUSAL ROLE OF** IgE in atopic dermatitis (AD) is not clear. Most AD patients have elevated interleukin-4 and IL-5 which would lead to elevated IgE and eosinophil levels, but which is the chicken and which the egg is less clear. An available therapy targeting IL-4 signaling, dupilumab, has proven very effective. However, prior to the work by Chan et al., treatments directed at IgE have been largely ineffective. My own experience with omalizumab for AD has not been encouraging. In Dr. Chan’s cohort, however, children with severe eczema show

marked benefit across several metrics including severity indices and quality of life reports.

As Dr. Wu pointed out in her editorial, we will need to learn more before this expensive biologic (redundant?) medication can assume its place in the AD armamentarium. Do IgE levels matter? Are specific dosing schedules necessary? Are certain AD subtypes more amenable? Until these questions are answered, or trials with more than 62 patients at a single center yield similar results, I will reserve omalizumab for other conditions such as chronic urticaria.

# Review looks at alopecia areata's natural course

BY JAKE REMALY

FROM PEDIATRIC DERMATOLOGY

**M**ost children who develop alopecia areata before age 4 years have mild disease with less than 50% hair loss, and present between ages 2 and 4, according to a retrospective chart review of 125 children.

Almost 90% of the children presented between ages 2 and 4 years, compared with 11.9% between ages 1 and 2 years, and 1.6% aged under 1 year, "in keeping with the existing literature," the study authors reported in *Pediatric Dermatology*. "A high percentage of patients continued to have mild, patchy alopecia at their follow-up visits," they added.

Epidemiologic studies of children with alopecia areata are few and have not focused on the youngest patients, said Sneha Rangu, of the section of dermatology at Children's Hospital of Philadelphia, and coauthors. They performed a retrospective chart review of 125 patients, who initially presented at the hospital with alopecia areata between Jan. 1, 2016, and June 1, 2018, when they were younger than 4 years. Patients who received systemic therapy or topical Janus kinase (JAK) inhibitors for alopecia were excluded. Severity was measured with the Severity of Alopecia Tool (SALT) score, to monitor progression of hair loss, analyzing scores at the initial presentation, at 3-6 months, at 1 year, and at 2 or more years.

Almost 70% were female, and 86.6% were between ages 2 and 4 years when they first presented. The initial diagnosis was alopecia areata in 72.0%, alopecia totalis in 8.8%, and alopecia universalis in 19.2%. Of the 41 boys, 39% had alopecia totalis or alopecia universalis, as did 22% of the girls, which suggested that boys presenting under aged 4 years were more likely to have more severe disease, or that "guardians of boys are more likely to present for therapy when disease is more severe."

About 40% of the children presented

with a history of atopic dermatitis, and 4% had an autoimmune disease (vitiligo, celiac disease, or type 1 diabetes). Twenty-eight percent of patients had a family history of alopecia areata, 27.2% had a family history of other autoimmune diseases, and 32% had a family history of hypothyroidism.

At the first visit, 57.6% had patch-stage alopecia and SALT scores in the mild range (0%-24% hair loss), which was present in a high proportion of these patients at follow-up: 49.4% at 3-6 months, 39.5% at 1 year, and 42.9% at 2 or more years.

At the first visit, 28% had high SALT scores (50%-100% hair loss), increasing to 36% at 3-6 months, 41.8% at 1 year, and 46.4% at 2 or more years. They

calculated that, for those with more than 50% hair loss at the initial presentation, the likelihood of being in a high category of hair loss, as measured by increasing SALT scores, was significantly higher at 1 year (odds ratio, 1.85;  $P = .033$ ) and at 2 or more years (OR, 2.29;  $P = .038$ ). "While there is a likelihood of increasing disease severity, those with higher severity at initial presentation are likely to stay severe after one or 2 years," the authors noted.

They had no conflicts of interest to disclose.

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**SOURCE:** Rangu S et al. *Pediatr Dermatol*. 2019 Aug 29. doi: 10.1111/pde.13990.

## Commentary by Dr. Eichenfield

**ALOPECIA AREATA** (AA) is a not uncommon inflammatory autoimmune skin disorder manifesting as focal nonscarring hair loss. It is highly variable in the extent of hair loss and course of the disease over time and can be very distressing for involved children and adolescents as well as their families. Rangu and colleagues at Children's Hospital of Philadelphia have made a great contribution to our knowledge base by investigating 125 children presenting with AA at age 4 years or younger. How did this relatively young group present and were there associated autoimmune or other diseases? Did they have mild or more severe disease? Was their course worse than older children diagnosed with AA?

The study showed that AA was quite rare under 2 years, with almost 90% of the children being aged 2-4 years when presenting. Female predominance, seen in other studies, was significant (about 70%), but it is impossible to assess how this is affected by referral bias or differential parental concern for boys versus girls. Only 4% of patients had an autoimmune disease history (vitiligo, celiac disease, type 1 diabetes), while more than 40% had a history of atopic dermatitis. Family history of AA was seen in 28%, with about 27% and 32% having family history of other autoimmune conditions or hypothyroidism. Alopecia totalis (all of the scalp involved) or universalis (all hair bearing surfaces involved) was seen in just less than 30% of patients, a higher number than I would expect, but probably affected by referral patterns into a specialty pediatric hair center. Most importantly to me, the study showed in a 2-year observation period that those patients who did not have high percentage loss (50%+) generally did well, while those who had more severe disease initially had more of a chance of remaining more severe over time. This is consistent with other studies in older children and consistent with our experience at Rady Children's Hospital, in San Diego. I often counsel families that, when a young child has focal hair loss, if they don't reach the 50%-plus hair loss threshold, the prognosis is generally quite good, with it being uncommon for them to progress to very severe losses.

Finally, there are many studies ongoing for alopecia areata, including new therapeutic studies evaluating Janus kinase inhibitors and other systemic and possible topical agents. There are no approved drugs for treating AA, and there is great interest in these studies both for adults and pediatric patients.

# Psychology consult for children's skin issues can boost adherence, wellness

BY DOUG BRUNK

EXPERT ANALYSIS FROM SPD 2019

**AUSTIN, TEX.** – One day each week, Sasha D. Jaquez, PhD, visits with patients in the dermatology clinic at Dell Children's Medical Center of Central Texas who wrestle with some aspect of their skin condition, from noncompliance to a recommended treatment regimen to fear of needles when an injection of medicine is required to keep them well.

“Our goal is to help promote the health and development of children, adolescents, and families through the use of evidence-based methods like cognitive-behavioral therapy,” said Dr. Jaquez, who is a pediatric psychologist at the University of Texas, Austin. “We do assessment and treatment of behavioral and emotional difficulties related to their skin condition or medical condition. So if they're depressed but it's not related to their skin condition, we will likely refer the patient to a community mental health system.”

During 1-hour visits at the dermatology clinic, Dr. Jaquez uses a mixed approach that includes cognitive-behavioral therapy and motivational interviewing to help patients and family members cope with their problematic behavior or negative thought patterns related to their skin conditions. “We do not have magic wands; we focus on the here and now,” she explained. “We



COURTESY DR. SASHA D. JAQUEZ

**Pediatric psychologist Sasha D. Jaquez (center) consults with two pediatric dermatologists at Dell Children's Medical Center, Austin: Dr. Lucia Diaz (left) and chief of pediatric dermatology, Dr. Moise Levy (right).**

focus on how to move forward in the most efficient way possible by teaching skills, practicing those skills with them in the office, and sending them home to use those skills. I don't have 100% compliance on this, so if I notice that they're not doing what I asked of them, we'll have a conversation about what the barrier is. 'What is getting in the way?' I'll ask. 'Is this something you're really wanting, or do you want a magic pill? If you want a magic pill, then our office isn't where that's going

to come from.' Sometimes patients aren't ready to work on feeling better, and that is good for us to know.”

During consultations, she often talks with children and adolescents about how thoughts, feelings, and behaviors are related. She'll use phrasing like, “The way that you think about something changes the way that you feel, and it changes the way that you act. We have control over our thoughts and behaviors, so if we think

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## Commentary by Dr. Sidbury

**THE PSYCHOSOCIAL IMPACT OF CHRONIC SKIN DISEASE** is apparent to anyone who cares for children with dermatologic issues. For those who do not, a raft of recent literature rams this point home: Adolescents with severe atopic dermatitis are more likely to consider suicide; psoriasis patients more often suffer anxiety; depression is overrepresented among hidradenitis suppurativa sufferers. Dr. Jaquez, a pediatric psychologist working at Dell Children's Hospital in Austin, highlighted her approach to helping such individuals. First, she has 1-hour appointments. These problems

are complex, and solutions come gradually. Second, she focuses on positive, collaborative, realistic suggestions to help not just the affected child but the entire family to better cope.

Her approach is grounded in empathy and seeks to destigmatize the psychological comorbidities that can accompany chronic skin disease.

She acknowledges that a staff psychologist is a luxury most dermatology practices do not have, and certainly none have hour-long visits, but all providers can be alert to red flags; proactively probe for concerns; and offer appropriate support where it may best be found.

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it's going to be a bad day, it's going to be a bad day. If we think it's going to be a good day, then we're going to find the positive aspects in the day and we might let those bad aspects go away. If I do something different [for my skin condition], then I'm going to feel different."

She recalled the case of a 3-year-old boy with atopic dermatitis who was referred for excessive scratching. His mom stays at home, while dad works and travels frequently. "The parents had differing views on how to treat his medical condition. Mom wanted to do wet wraps while dad wanted to do bleach baths. Their son was getting no treatment because the parents couldn't agree on anything. Mom noticed that her son scratches when he wants attention and when he's angry."

When Dr. Jaquez met with his parents, she encouraged them to agree on a plan to implement at home so that their son would gain some relief. She also advised them to ignore when their son scratches or when he gets angry. "Give him something else to do besides scratch, because if those hands are busy, he won't be scratching. Let's change the way this behavior happens. Let's give him attention all the time instead of just when he's scratching. That will work very quickly. And it did."

She makes it a point to talk with patients and their families about living

with the stress of a chronic illness like psoriasis or atopic dermatitis. "Let's figure out, 'How do we accept that this is how it is, and that they're going to have to find their own 'normal?'" she said. "I don't know how many

**"Give him something to do besides scratch, because if those hands are busy, he won't be scratching. Let's change the way this behavior happens. Let's give him attention all the time instead of just when he's scratching. That will work very quickly."**

times someone comes into my office and says, 'I just want to be normal.' I like to ask patients, 'what is your normal?' These kids might have a lower quality of life than a child without a chronic illness, but we want to make sure that they're living their lives to the fullest. You want to monitor not only adherence [to medication] but also quality of life. Sleep concerns are big. A lot of our kids might not be going to school, or they're afraid to go to school because they get picked on because people don't understand their skin condition."

Dr. Jaquez acknowledged that not all dermatologists have a psychologist on staff or in their referral network, but all are capable of destigmatizing psy-

chological and mental health issues for their patients. "Psychological comorbidities such as depression and anxiety can be associated with certain skin conditions," she said. "Let them know that this is stressful stuff. Have discussions early, so if the time comes for a referral they won't think you're giving up on them. Don't be afraid to say you have a psychologist that you want to refer to. Say, 'I have an added team member I would love for you to meet. She's our psychologist. She works with patients who are having difficulties.'"

Giving patients perceived control of their care could also help improve the behavior of concern. For example, when patients with needle phobia require an injection, ask if they would like to lay down, or sit down for the injection. "Giving them this tiny bit of control is going to help them feel more empowered," she said.

Dr. Jaquez also recommends that clinicians pay attention to nonverbal cues and steer clear of using scare tactics to change their behavior. "Use positive behavioral strategies and try to avoid punishment. Children don't want to hear 'stop' all the time. Parents are tired of saying it, and kids are tired of hearing it. We focus on praising the things that are going well. I advise parents all the time: 'Catch them being good.'"

Dr. Jaquez reported having no financial disclosures.

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## Frequent soaks ease pediatric atopic dermatitis

BY HEIDI SPLETE

FROM THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY: IN PRACTICE

**A** regimen of twice-daily baths followed by occlusive moisturizer improved atopic dermatitis in children with moderate to severe disease more effectively than did a twice-weekly protocol, based on data from 42 children.

Guidelines for bathing frequency for children with atopic dermatitis are inconsistent and often confusing for

parents, according to Ivan D. Cardona, MD, of Maine Medical Research Institute, Portland, and colleagues.

In a study published in the *Journal of Allergy and Clinical Immunology: In Practice*, the researchers randomized 42 children aged 6 months to 11 years with moderate to severe atopic dermatitis to a routine of twice-weekly "soak and seal" (SS) procedures consisting of soaking baths for 10 minutes or less, followed by an oc-

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# Acne before puberty: When to treat, when to worry

BY RANDY DOTINGA

REPORTING FROM SDEF WOMEN'S & PEDIATRIC DERMATOLOGY SEMINAR

**NEWPORT BEACH, CALIF.** – Acne – which can appear anytime from the neonatal period to puberty – is most worrisome when it appears during the midchildhood years, from ages 1 to 7 years, according to Sheila Fallon Friedlander, MD.

“This is something you are going to see in your practice,” said Dr. Friedlander, a pediatric dermatologist at Rady Children’s Hospital–San Diego. It’s important to know when it’s time to be concerned and when another condition may be masquerading as acne, she said at the at Skin Disease Education Foundation’s Women’s & Pediatric Dermatology Seminar.



Dr. Friedlander

Dr. Friedlander, who is professor of dermatology and pediatrics at the University of California, San Diego, talked about treating acne in the following prepubertal age groups:

## Neonatal acne (ages birth to 4 weeks)

Acne appears in this population up to 20% of the time, according to research, and it is much more common in males than in females, at a ratio of five to one.

The cause is “most likely the relationship between placental androgens and the baby’s adrenal glands,” Dr. Friedlander said. However, something

more serious could be going on. “Look at the child and see if he’s sick. If he looks sick, then we need to worry.”

Hormonal abnormalities also could be a cause, she said. Refer a baby to a spe-

cialist if there are other signs of hyperandrogenism. However, “the likelihood is very low,” and she’s never needed to refer a neonate with acne for evaluation.

As for treatment, she said, “Mainly, I’m using tincture of time.” However, “many of my mothers have told me that topical yogurt application will work.” Why yogurt? It’s possible that its bacteria could play a role in combating acne, she said.

*Masquerader alert!* Beware of neonatal cephalic pustulosis, Dr. Friedlander cautioned, which may be an inflammatory response to yeast. Ketoconazole cream may be helpful.

## Infantile acne (ages 0-12 months)

This form of acne is more common in males and may hint at the future development of severe adolescent acne. It does resolve but it may take months or

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clusive emollient, or to twice-daily SS with baths of 15-20 minutes followed by emollient. The groups were treated for 2 weeks, then switched protocols. The study included a total of four clinic visits over 5 weeks. All patients also received standard of care low-potency topical corticosteroids and moisturizer.

Overall, the frequent bathing (“wet method”) led to a decrease of 21.2 on the SCORing Atopic Dermatitis Index

(SCORAD) compared with the less frequent bathing (“dry method”). Improvements in SCORAD (the primary outcome) correlated with a secondary outcome of improved scores on the parent-rated Atopic Dermatitis Quickscore.

The findings were limited by factors including small sample size, lack of data on environmental factors such as water temperature and quality, and the lack of a washout period between the treatment protocols. They acknowledged that “twice-daily SS bathing in the real world

can be time consuming, making adherence difficult for families.” However, the results suggest that the frequent bathing protocol was safe and effective at improving symptoms of atopic dermatitis, and may reduce steroid use.

The researchers had no financial conflicts to disclose.

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**SOURCE:** Cardona ID et al. *J Allergy Clin Immunol Pract.* 2019 Nov 13. doi: 10.1016/j.jaip.2019.10.042.

## Commentary by Dr. Eichenfield

**THERE HAVE BEEN VARIABLE APPROACHES** to recommendations on bathing practices for individuals with atopic dermatitis (AD), with one older methodology stressing avoidance of bathing to “minimize drying of the skin.” Studies have clearly shown that moisturizing after bathing obviates any drying effect of bathing and evaporation, which can occur without moisturizers. However, there is still inconsistency in advice about how frequent someone with AD should bathe. Dr. Cardona and colleagues from the Maine Research Institute carried out a well-designed, prospective study of 42 children randomized to 2 weeks of infrequent (twice-weekly) 10-minute or less baths, or to twice-daily

soaking baths for 15-20 minutes, followed by emollient. After 2 weeks, patients were changed to the other regimen, and throughout the 4 weeks, all received standard low-potency topical corticosteroids and moisturizer. The “wet method” won! Frequent bathing improved the objective eczema scores much more than the “dry method.”

It’s uncertain if the bathing is helping by impacting on skin moisture content, debriding the skin of antigens and impacting bacteria, or by changing the utility of the topical medications and moisturizers. My takeaway from this study? While twice-a-day bathing might be hard to do in “real-life” eczema care, bathing can be a helpful intervention, and avoidance of bathing has no justification from an eczema standpoint.



DR. P. MARAZZI/SCIENCE SOURCE

**Infantile acne does resolve but it may take months to years.**

◀ Continued from previous page

years, Dr. Friedlander said.

In general, this acne isn't a sign of something more serious. "You do not need to go crazy with the work-up," she said. "With mild to moderate disease, with nothing else suspicious, I don't do a big work-up."

However, do consider whether the child is undergoing precocious puberty, Dr. Friedlander said. Signs include axillary hair, pubic hair, and body odor.

As for treatment of infantile acne, "start out topically" and consider options such as Bactrim (sulfamethoxazole/trimethoprim) and erythromycin.

*Masquerader alert!* Idiopathic facial aseptic granuloma can be mistaken for acne and abscess, and ultrasound is helpful to confirm it. "It's not so easy to treat," she said. "Ivermectin may be helpful. Sometimes you do cultures and make sure something else isn't going on."

### Midchildhood (ages 1-7 years)

"It's not as common to have acne develop in this age group, but when it develops you need to be concerned," Dr. Friedlander said. "This is the age period when there is more often something really wrong."

Be on the lookout for a family history of hormonal abnormalities, and check

if the child is on medication. "You need to look carefully," she said, adding that it's important to check for signs of premature puberty such as giant spikes in growth, abnormally large hands and feet, genital changes, and body odor. Check blood pressure if you're worried about an adrenal tumor.

It's possible for children to develop precocious puberty – with acne – because of exposure to testosterone gel used by a father. Dehydroepiandrosterone (DHEA) creams also may cause the condition. "The more creams out there with androgenic effects, the more we may see it," Dr. Friedlander said. "This is something to ask about because families may not be forthcoming."

*Masquerader alert!* Perioral dermatitis may look like acne, and it may be linked to inhaled or topical steroids, she said.

Other masqueraders include demodex folliculitis, angiofibromas (think tuberous sclerosis), and keratosis pilaris (the most common type of bump on a children aged 1-7 years). The latter condition "is not the end of the world," said Dr. Friedlander, who added that "I've never cured anyone of it."

### Prepubertal acne (ages 7 years to puberty)

Acne in this group is generally not worrisome, Dr. Friedlander said, but

## Commentary by Dr. Sidbury

**DR. FRIEDLANDER NOTES THAT** acne can span the pediatric age spectrum from 0 to 18 years of age, and different concerns may be appropriate depending on the age of presentation. Neonatal acne does not generally cause alarm if the infant is otherwise well. Parents often suffer dissonance as they stridently wish for resolution yet eschew any potentially harmful interventions at this age. Yogurt to the rescue! There is anecdotal evidence (oxymoron?) that topically applied yogurt may treat neonatal acne, and parents feel very comfortable with its use; at the very least it may safely bide time for this spontaneously resolving affliction. Dr. Friedlander also calls out midchildhood acne (affecting children aged 1-7 years) as a context in which underlying pathology must more carefully be considered. Such children always should have their growth plotted, and examination should screen for signs of androgenization such as pubic hair or body odor. Distinctive clinical mimics such as facial angiofibromas in tuberous sclerosis always should be considered when the pieces do not fit.

investigate further if there's significant inflammation and signs of early sexual development or virilization.

Benzoyl peroxide wash may be enough to help the condition initially, and consider topical clindamycin or a combination product. "Start out slow," she said. Twice a week to start might be appropriate. Moisturizers can be helpful, as can topical adapalene.

Also, keep in mind that even mild acne can be emotionally devastating to a child in this age group and worthy of treatment. "Your assessment may be very different than hers," she said. It's possible that "she has a few lesions, but she feels like an outcast."

Dr. Friedlander reported no relevant financial disclosures. SDEF and this news organization are owned by the same parent company.

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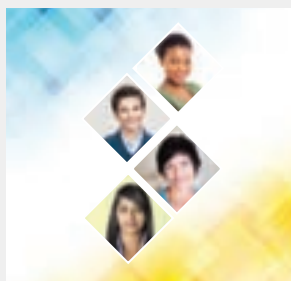
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