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THE MANAGEMENT OF
ATOPIC DERMATITIS
ACROSS GENERATIONS



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PANELISTS



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director of the Center for Excellence in Eczema, and director of the Laboratory of Inflammatory Skin Diseases at the Icahn School of Medicine at Mount Sinai Medical Center in New York. Dr. Guttman's major areas of clinical focus include atopic dermatitis and contact/occupational dermatitis. She has done groundbreaking research and published extensively on inflammatory skin diseases.

ATOPIC DERMATITIS (AD) is a chronic, relapsing skin disease commonly seen by pediatricians and dermatologists, although its prevalence in older populations is on the rise. The management of AD has traditionally involved corticosteroids, nonsteroidals, and other topical agents. In recent years, however, systemic biologic

therapy has been introduced. New-onset AD is relatively straightforward to diagnose in young children, but it can be more complicated in older patients.

In this supplement, three physician experts discuss the differences in presentation and treatment of new-onset AD across generations.

AGE-BASED DIFFERENCES IN AD

DERMATOLOGY TIMES: How common is new-onset AD after early childhood (ie, after age 5 years)?

Peter Lio, MD: Certainly, most cases of new-onset AD will appear before age 5 years, somewhere in the neighborhood of 90%.¹ The remaining group of individuals develop de novo AD later, even into adulthood, and we know a lot less about what drives the onset of their condition. There certainly are some adults who have had AD in a mild form since childhood but just never had it recognized as such until they became older and sought medical help for their symptoms.

DERMATOLOGY TIMES: How often do young children diagnosed with AD have a family history of the condition?

Robert Sidbury, MD, MPH: In approximately 80% of all cases, patients diagnosed with AD will have a family history of AD, asthma, hay fever, allergies, or immunoglobulin-E reactivity to certain foods.² That said, the manifestation of the condition doesn't really differ in young children with and without a relevant family history. The rash itches the same way, manifests and progresses in the same areas, and seems to react similarly to triggers such as temperature and humidity.

DERMATOLOGY TIMES: What is different about the diagnostic workup for new-onset AD when you are dealing with teens, adults, or the elderly population compared to young children?

Dr. Sidbury: When you are dealing with any case of suspected AD in an older patient, you first want to make sure that you have the right diagnosis, that you are not seeing something that may itch and have a rash but is not actually AD at all. In young children, we'll often just use our clinical judgment because AD is such a common diagnosis and is typically rather obvious on visual inspection, but that isn't recommended in older patients. Of course, the

Hanifin and Rajka diagnostic criteria can be used in cases in which there is diagnostic uncertainty (Table).³

Older teens, adults, and the elderly are exposed to more in the environment than young children. They have a greater risk of allergic contact dermatitis, which can mimic eczema. There is often a superimposed allergic contact dermatitis over a patient's baseline eczema that is causing the majority of the problem.

In teens and adults, we should also remember to evaluate any dermatitis on the head and neck, which, in patients with corresponding eczema, can be a reaction to pityrosporum.

Dr. Lio: It's also important to remember that AD can change its appearance and distribution in a given patient over time. That may, as Dr. Sidbury noted, be related to exposure to something like pityrosporum yeast on the skin. It may also have to do with occupational or environmental exposures, changes to the microbiome, or perhaps other factors that we do not yet fully understand.

DERMATOLOGY TIMES: Is the diagnosis of AD often delayed in older patients whose primary care physician or other provider simply doesn't have the condition on their diagnostic radar screen?

Dr. Lio: When I did my medical training, AD was considered almost exclusively a pediatric disease. New-onset adult AD was considered unique and interesting. As residents, those were the patients we would all want to look in on and discuss because they were such fascinating cases.

In today's environment, new-onset adult AD is beginning to be recognized as an important disease in its own right, with an incidence as high as 10% of all cases of new-onset AD.⁴

But there are still some unresolved questions. Is that increasing incidence a real trend, or is it an epiphenomenon? Is this something where now that we're talking

about it more, we're finding it more in the general population? It's hard to know whether the incidence of new-onset adult AD is actually on the rise or whether it's been there all along.

The reason why AD is more difficult to diagnose in adults compared to young children is because there are a variety of other entities that mimic the condition that are uncommon in young children but more common in

adults. In particular, cutaneous T-cell lymphoma can look a lot like severe AD. That is an extremely rare condition in children. Contact dermatitis may be a mimicking diagnosis, but it also can be a comorbidity of AD, exacerbating the condition and making the rash and itching worse than it would be otherwise. Again, although it can be seen in the pediatric office, it is much more common in adults exposed to a broader environment.

TABLE HANIFIN AND RAJKA CRITERIA FOR THE DIAGNOSIS OF AD

MAJOR CRITERIA (MUST HAVE AT LEAST 3)

- Pruritus
- Dermatitis affecting flexural surfaces in adults and the face and extensors in infants
- Chronic or relapsing dermatitis
- Personal or family history of cutaneous or respiratory atopy

MINOR CRITERIA (MUST HAVE AT LEAST 3)

- Xerosis
- Ichthyosis/palmar hyperlinearity, keratosis pilaris
- Immediate (type 1) skin test reaction
- Elevated serum IgE
- Early age of onset
- Tendency toward cutaneous infections (especially *Staphylococcus aureus* and herpes simplex), impaired cell-mediated immunity
- Tendency toward nonspecific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie–Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor, facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental and emotional factors
- White dermatographism, delayed blanch

IgE = immunoglobulin E.

Source: Hanifin JM, Rajka G.³

Dr. Sidbury: Pediatricians certainly are seeing babies with diaper dermatitis due to contact allergies with products in the baby's diaper. Additionally, there are children who are allergic to nickel, which is a common juvenile exposure. Perhaps the pediatric community should be thinking more about contact dermatitis as a possible diagnosis, but it is clearly still more of an issue for adult patients.

DERMATOLOGY TIMES: How long do older patients display some of the primary symptoms of new-onset AD before they will eventually end up in your practices?

Dr. Lio: There's no doubt that I see a range, although there is a personal bias because I tend to see more severe cases referred to my practice. That said, I see many individuals who have been suffering for a few months and are frustrated that they're not getting the proper diagnosis or proper treatment plan, but I also have many patients who have been suffering for years.

When I'm talking to pediatricians or primary care physicians, I'll tell them there is a broad misconception that everyone who has new-onset AD as a young child is going to grow out of the disease. I see a lot of these patients 25 or 30 years later who are now angry because they were told for years that the disease would simply go away with age and yet they have never "grown out of it." It is true that most young children with AD will eventually grow out of it, but that is not a justification to avoid treating the condition. It is not yet possible to predict how long an individual patient's symptoms are going to last.

Dr. Sidbury: Do you have adult patients who had given up on dermatology, perhaps because we had nothing substantial to offer them, who are coming back into the fold now that there are treatments that can make a difference?

Dr. Lio: Absolutely. A lot of times, it's the parents of children I am seeing who are the ones I will eventually treat. They have their children with them who are miserable, but when we start talking about the new options available to treat their child's AD, mom or dad will pull

up their sleeve to show me their eczema and ask if they could come in for a separate assessment on their own.

DERMATOLOGY TIMES: Because of the unpredictable nature of AD, what do you tell young children and their parents about the likely progression of the condition? Do you avoid telling them it is something they will likely grow out of naturally?

Dr. Sidbury: I do avoid that language. Now, I don't avoid the idea that there's hope, because parents are typically distraught and not sleeping and everyone's stressed out. To take away the idea that their child will likely grow out of the condition is just cruel. The language I use is that

their child's condition will likely evolve. Some parents may already see an evolution from a condition that was more extensor based and facial when their child was a baby but then becomes more flexural as their child gets a bit older. I will often tell parents that this evolution will likely continue with the hope that, by the time their child turns age 5 or 6 years, they may be able to simply use occasional moisturizer to manage any lingering rash.

Dr. Lio: There are families who come to us looking really despondent and discouraged, so we do need to give them hope. I don't think there is anything wrong with telling a family, "Don't worry. Time is on our side. It is probably going to get better."

DEVELOPMENT OF NEW-ONSET AD

DERMATOLOGY TIMES: In a general sense, how does AD develop in babies and toddlers?

Dr. Sidbury: The classic presentation of AD is when the infant will start to have facial redness on the cheeks that gets bumpy. Initially, parents will often link this to food, which is logical in babies when half of their food ends up on their face. Food allergies are therefore often the first thought. But then the infant will start getting the same sort of itchy, extensor-based rash on their arms and sometimes on the trunk. The rash typically spares the underarm and diaper region. The elbows and knees may be involved in a little bit older child.

DERMATOLOGY TIMES: How does the developmental process differ in adult patients?

Dr. Lio: In adults who have had the condition since childhood, their severity of disease tends to follow a J-shaped curve. Their symptoms were bad when they were young children, but then these go into a relatively quiet phase for a few years before picking up again. In my experience, it's typically patients in their late teens or early 20s who notice their symptoms getting worse. That's one group of patients.

A second group of patients, those with true new-onset or de novo disease, will often trace back the onset of their symptoms to some sort of specific trigger. I find that if I question these patients long enough, a lot of them will remember getting an itchy rash on their arms or legs that they figured was due to some sort of irritation, such as a

contactant. But then that rash either didn't go away or went away and flared up a few weeks later. For this group of patients, it does seem that there was a triggering event, either a contact dermatitis, allergic reaction, viral exanthem, or some other type of insult that triggered the onset of symptoms. Many patients will often tell you they had sensitive skin as a child, but it was only after this triggering event that they demonstrated signs of AD.

DERMATOLOGY TIMES: What about new-onset elderly AD? How does the condition develop in those patients?

Dr. Lio: New-onset elderly AD is a relatively recent phenomenon, but it's a real thing. These are generally patients older than age 60 or 65 years. In my experience, these are patients who tell me they never had any symptoms consistent with AD as adults.

Their symptoms typically start out with dry skin and itching. That often naturally occurs as we age because our lipid synthesis is down and our skin barrier decreases. Once the dry skin and itching start, that's when immune activity will begin in some of these individuals. Elderly patients have immunosenescence, which refers to the gradual deterioration of the immune system brought on by natural aging. It becomes a paradox. These are patients whose immune system is a bit weakened, yet they develop what is considered to be an inflammatory disease. It's an interesting phenomenon that we don't yet fully understand.

TREATING AD: AGE-BASED APPROACHES

DERMATOLOGY TIMES: What do you typically set as the primary goal of treatment when talking to the families of babies and young children with AD?

Dr. Sidbury: My primary goal is to decrease the itch. A lot of the secondary issues such as sleep deprivation stem from the itchiness of eczema, so if you solve that one problem, you've solved other downstream problems as well. You need to make the child more comfortable.

A secondary goal, when appropriate, is to focus the parents' attention on the value of proper skin care as a first priority and less on potential contributors such as food allergies absent a compelling history.

DERMATOLOGY TIMES: How do those goals potentially change in teenagers and adults?

Dr. Lio: My first goal in my older patients with AD is to relieve the discomfort, which almost always involves itch but can sometimes include pain as well, especially among patients with more severe disease. As Dr. Sidbury noted, relieving that itch and discomfort can impact many other issues such as sleep discomfort and the inability to concentrate.

I always talk about the three great hurdles of treating AD:

The first hurdle is, "Can I get you clear?" That is fairly easy for many patients today if we get them on the right treatment.

The second hurdle is, "Can I keep you clear safely?" That's where things get a bit trickier. Many less experienced clinicians and especially nondermatologists who don't see a lot of AD get stuck. They know to prescribe triamcinolone, which will often clear up a patient's symptoms, but then they will stop treatment and the patient will flare again. So the patient gets confused. Their physician tells them not to use this medication for an extended duration of time, but whenever they stop, their symptoms come back. It takes careful planning to keep a patient clear for an extended period.

And then the third hurdle is, "Can you keep up with your treatment regimen?" The proper skin care necessary to keep AD at bay can be complicated, and some patients simply get overwhelmed having to constantly apply moisturizers, nonsteroidals, and cortisones depending on the ups and downs of their symptoms. Some patients simply tell me they need to find a way to get out of the exhausting loop of constantly monitoring and adjusting medications for their AD symptoms.

DERMATOLOGY TIMES: What do you do for those patients?

Dr. Lio: Those are the patients for whom we need to think about systemic therapies and treating the whole person instead of just the skin. In many of them, their immune system is highly compromised and there is such a wide surface area of eczema or their disease is so severe that topicals are not enough.

Dr. Sidbury: I deal with a lot of parents and their children as they get older who absolutely hate putting all of these topical agents on their skin every day. Parents especially are fearful of the long-term impact of these topicals, no matter how much we reassure them of their safety.

So you have both the inconvenience of using these medications and this underlying fear of them that makes some of the treatment recommendations, even when successful, fraught with difficulties.

DERMATOLOGY TIMES: What are the primary safety concerns that you typically hear about from parents?

Dr. Sidbury: These are mostly related to the use of steroids. Just the term "steroid" has become such a loaded term in our culture because of its association with athletes, body builders, and the like. It can be a challenge to get parents to realize that not all steroids are the same, and topical steroids are significantly different than those they hear about on television.

The second big concern I hear about is the potential thinning of the skin that can be caused by topical steroids. This perhaps is more legitimate, but it's something we absolutely can manage. I always make an effort to talk with families about the signs of thinning skin, how it can be avoided, and how it can be reversed in its early stages.

The boxed warnings on some of the nonsteroidals that we often use to treat AD can be frightening. So, it's important to walk patients and parents through which risks are real and, for the ones that are, how we can avoid them.

Dr. Lio: It's a narrow tightrope in our patients with AD to maximize the benefits of topical steroids and avoid some of those more common side effects. One thing I am hearing about more and more from my older patients is the concept of topical steroid withdrawal. To me, the secret when using steroids is to use them intermittently. I will often use them for a short time until we see some

improvement and then switch to a nonsteroidal alternative. I'll then go back and forth with that regimen pretty much indefinitely, maybe 2 weeks on, 2 weeks off. I think that is a fairly safe approach for most patients, although there are some patients for whom even 1 week a month of a steroid makes them concerned about long-term effects.

SYSTEMIC TREATMENTS FOR AD

DERMATOLOGY TIMES: What are some of the more common safety concerns related to systemic therapies commonly used to treat AD?

Emma Guttman, MD, PhD: I find anything that needs to be ingested or injected is associated in patients' minds with greater safety concerns than something that they use topically. I often have to spend considerable time explaining to my patients that these systemic therapies actually have fewer safety issues than a strong topical steroid used for an extended period of time.

Total avoidance of, or inadequate, treatment in young children is another issue I often have to combat. Often due to parental safety concerns, I will see children referred to me who are being treated with hydrocortisone 1% or 2.5% despite having severe AD from head to toe, and they are failing to thrive. These are the families I talk to about studies showing that children can have systemic inflammation that can lead to downstream manifestations such as asthma, hay fever, eosinophilic esophagitis, and food allergies.⁵ Systemic therapies are clearly a viable option in these patients.

Dr. Lio: In general, there is a much greater fear about using systemic therapies among my pediatric patients compared to adolescents and adults. Parents are just nervous, and understandably so. Every side effect is magnified, because we have to look beyond the immediate effects and consider potential impact on growth and development. Of course, it should also be mentioned that these systemic therapies are currently off-label in pediatric patients younger than age 12 years, which is another concern for many parents. Those are among the reasons why I try to avoid or at least minimize immunosuppressants in my pediatric patients with AD whenever I can. Even in the best scenario, you will likely need an immunosuppressant for many months or even years, and there are too many unknowns at play. The FDA has taken a positive step by pushing for more pediatric

Historically, we have been really limited beyond corticosteroids in patients with AD, but now that there is a U.S. Food and Drug Administration (FDA)-approved systemic therapy and more in the pipeline, we can offer patients better options.

studies with these systemic therapies so that we can hopefully have formal data and potential extended approvals in the future.

Route of administration is another significant issue with pediatric patients. You can't use pills in the same manner in young children as you do in adults, and shots can be scary. When I suggest the use of dupilumab in young children, for instance, I often have to deal with needle phobia. Although that can still be an issue in older patients, it is particularly pronounced in pediatric patients.

Dr. Guttman: I will sometimes prescribe dupilumab for my adolescent patients after a thorough discussion about the drug and then receive a call from the pharmacy a few weeks later telling me that the drug was never picked up. It's almost always due to a fear of needles, even in this older population. I almost feel like an injectable is easier for younger patients whose parents can hold them still and give them the injection.

DERMATOLOGY TIMES: When you are contemplating a proposed treatment regimen for a 6 month old with AD, what are the primary factors you are considering and discussing with the child's parents?

Dr. Sidbury: I start by going through the same foundational things that I cover with any patient with AD: proper moisturization, proper bathing, and trigger avoidance. I'll also talk about the appropriate use of our first-line agents, the topical anti-inflammatories, where the skin is inflamed. There is always a discussion of food and its role in the development of AD, usually triggered by parents. We tend to focus on skin care first and allergy care second, unless there is a reason to do otherwise.

DERMATOLOGY TIMES: What is the youngest age at which you will consider offering dupilumab in a patient with AD?

Dr. Guttman: I consider dupilumab in any patient for whom I would have previously had to settle for cyclosporine. I would rather have a young child on dupilumab than cyclosporine any day.

Dr. Lio: I feel the same way. I have children all the way down to 6 to 8 months whom I have treated with cyclosporine just because I had no other option. I haven't treated anyone quite that young with dupilumab, although I have treated children ages 4 to 6 years with severe cases of AD who have failed everything else we currently have available.

What's important to discuss with parents of any young child initiating treatment for AD is the importance not only of making the skin clearer but also the impact that can have on preventing the development of future comorbidities.

Dr. Sidbury: There are many medications that are not FDA approved in our youngest patients, including crisaborole and topical calcineurin inhibitors. Those, of course, are used commonly in patients younger than age 2 years, but when you tell parents that these agents are not approved at that age, alarm bells start going off in their heads. And then if there is a boxed warning with the calcineurin inhibitors that you have to review, things become even more complicated.

When you are dealing with young children, it's always important to talk about any medication being prescribed, whether it is FDA approved or not, regarding our experience with the medication, dosing requirements, and other issues. For example, an infant at age 4 months is going to absorb a topical medication differently than a child at age 4 years due to differences in weight/surface area ratio, which needs to be taken into consideration.

DERMATOLOGY TIMES: When do you start seeing some of the common psychological problems that are typically attributed to AD?

Dr. Sidbury: One of the comorbidities that we are seeing more in patients with untreated or suboptimally treated AD is attention-deficit hyperactivity disorder (ADHD) among young children between the ages of about 5 and 7 years. Historically, we have usually looked at these children and said, "Oh gosh, you are losing sleep because of your eczema. That must be why you are having trouble concentrating at school and are so fidgety." Now we are recognizing that there may be a

separate diagnosis of ADHD that needs to be made in some of these patients.

As you get into early adolescence and the teenage years, that's where some of the more well-publicized psychological issues such as depression and suicidal ideation become a problem.⁶ I have certainly seen my share of children with intractable eczema who have been depressed and suicidal, so it is a very real problem many of us have to face. It's incumbent upon our profession not to ignore these issues.

DERMATOLOGY TIMES: What are some of the specific red flags that you look for?

Dr. Sidbury: I have started having all of my teenage patients with eczema complete the Public Health Questionnaire 2 (PHQ-2) form at every visit. It's a very simple 2-question form that asks, "Over the last 2 weeks, how often have you had little interest or pleasure in doing things?" and then, "Over the last 2 weeks, how often have you felt down, depressed, or hopeless?" They rate themselves on a 0 to 6 scale, with a score of 3 or greater indicating the need for further intervention. I have found that to be pretty good at flushing out those patients who need to be referred for appropriate management.

Dr. Guttman: What I find interesting is that I am getting calls from psychiatry and psychology colleagues who are involved in the care of some of my teenage patients with AD and they are telling me that patients whose disease is well controlled on dupilumab or on some newer agents in clinical trials are no longer displaying suicidal ideation. These colleagues feel that their improvement in symptoms directly corresponds to their demeanor, which makes sense.

Think about it. When you are a teenager and appearance is so important among your peers and you aren't sleeping, your entire social life is out of balance. Your academics suffer. Now you take away the impediment to sleep and appearance, and your grades improve and you start hanging out with your friends again. In turn, your depression and suicidal ideation subside. In a sense, among these teenage patients with AD, it's almost as if they have a reactive depression that may go away or at least dissipate with proper treatment of their AD.

Dr. Lio: Could depression be related directly to a patient's inflammation? For a long time, we tied a patient's depression to the fact that their skin was bad, but we are beginning to wonder if there is also a direct psycholog-

ical effect of inflammation in the body. It's an interesting theory that is gaining traction within some circles.

DERMATOLOGY TIMES: Are there any unique problems related to polypharmacy, especially in adult and elderly patients with new-onset AD?

Dr. Lio: There are two major issues. The first is that in adult patients who are taking multiple medicines, sometimes we have to rule out an eczematous drug eruption before we can make a diagnosis of AD, and that can be difficult. There are patients who often have a medication list that is 2 pages long, with frequent additions and dosage changes to follow. Pediatric patients, generally speaking, have a much cleaner medical history and are taking few, if any, other medications when they come to see us for help with their AD.

The second issue is that conventional immunosuppressants we use to treat AD have a number of drug–drug interactions. Cyclosporine, for example, can be particularly problematic. For instance, it raises a patient's blood pressure, which can be a problem for many adult patients who have hypertension. If cyclosporine is our best option, the patient will likely need to work with their prima-

ry care physician or cardiologist to modify the dosage of their hypertension medicine. A lot of our patients are obese and may have fatty liver disease. You may want to avoid methotrexate in those patients.

Those factors are among the reasons why dupilumab is often the best choice in adult and older patients with AD. Biologics in general don't often have any direct interactions with other medicines, and because dupilumab is not an immunosuppressant, you can use it in circumstances in which a traditional immunosuppressant would be otherwise contraindicated.

Dr. Guttman: I typically explain to patients that dupilumab is an immune corrector rather than an immune suppressant. Cyclosporine and oral prednisone affect T cells, B cells, and other cells. Dupilumab affects only one molecule, and that is why the only significant safety concerns are ocular.⁷ As Dr. Lio said, there aren't typically concerns about drug–drug reactions in our youngest patients being treated with AD, but there are still safety concerns with long-term use of cyclosporine such as impaired kidney function that can become permanent after a year of use.

LOOKING TO THE FUTURE OF TREATMENT FOR AD

DERMATOLOGY TIMES: How has your treatment paradigm changed in the last 5 years for children with AD who are age 5 years or younger?

Dr. Sidbury: The biggest difference in the last couple of years was the introduction of crisaborole, which is approved for use in children age 2 years and older. It's a nonsteroidal that does not have a boxed warning, both of which are positives. However, I have not used crisaborole as much as I might have initially expected in young children for a combination of reasons. It's almost expected these days that any new medication is going to be expensive, and crisaborole is no exception, so it's been inaccessible for some of my patients from a financial standpoint. In addition, I have witnessed a fair amount of application-site stinging, especially on the face, which has been a barrier. So while crisaborole has worked well for some of my patients and it's of course good to have another option to consider for patients with AD, it hasn't had a profound approach on how I treat my patients age 5 years or younger.

DERMATOLOGY TIMES: How about any changes in older children and adults with AD? What changes have you noted in your approach to their treatment?

Dr. Guttman: The introduction of crisaborole has had an impact, particularly in areas where we don't like administering topical steroids such as folds in the genital areas as well as in areas such as the back of the hands. I do, however, agree with Dr. Sidbury about the stinging, particularly on the face. I find that if you tell the patient about the expected stinging, it is tolerable and typically subsides in about 20 minutes. But if you don't warn the patient in advance, they will not use the drug after the first application.

Of course, the biggest change in the last 5 years has been the introduction of dupilumab to treat moderate-to-severe AD. That has revolutionized our ability to control these patients for whom we previously had little to offer.

Dr. Sidbury: My approach to treatment has completely changed in my 12- to 18-year-old patients in recent years.

When I can get it approved, dupilumab is my first and best option for those teenagers with moderate-to-severe AD who need systemic therapy. And even in children under age 5 years for whom I'm not yet using dupilumab, just the idea that we have these new medicines being approved and a robust clinical trial pipeline gives patients the promise of a better future.

DERMATOLOGY TIMES: What about elderly patients with new-onset AD? How has their treatment evolved in recent years?

Dr. Lio: My biggest change conceptually has been the target to which I'm treating. I feel like I have really raised the bar. My goal now is to try to get people clear or almost clear and hold them there for at least a few months. I find that if I can keep a patient clear for several months, they seem to enter a state of partial or full remission where their disease severity stays quiet even after I have de-escalated therapy. That's a concept I employ not only in my elderly patients but also for all of my patients with AD.

The other piece for elderly patients with AD is that I try to avoid immunosuppression whenever possible by excluding medications that may interact with other medicines they are taking. Now that we have dupilumab as an option, it has become my first-line systemic therapy in those elderly patients who do not respond to phototherapy. I still try to use phototherapy whenever I can, but because it can be cumbersome and difficult to get patients to stay with over the long term, it does not end up being utilized by as many patients.

DERMATOLOGY TIMES: What specific research currently under way in AD do you find particularly promising?

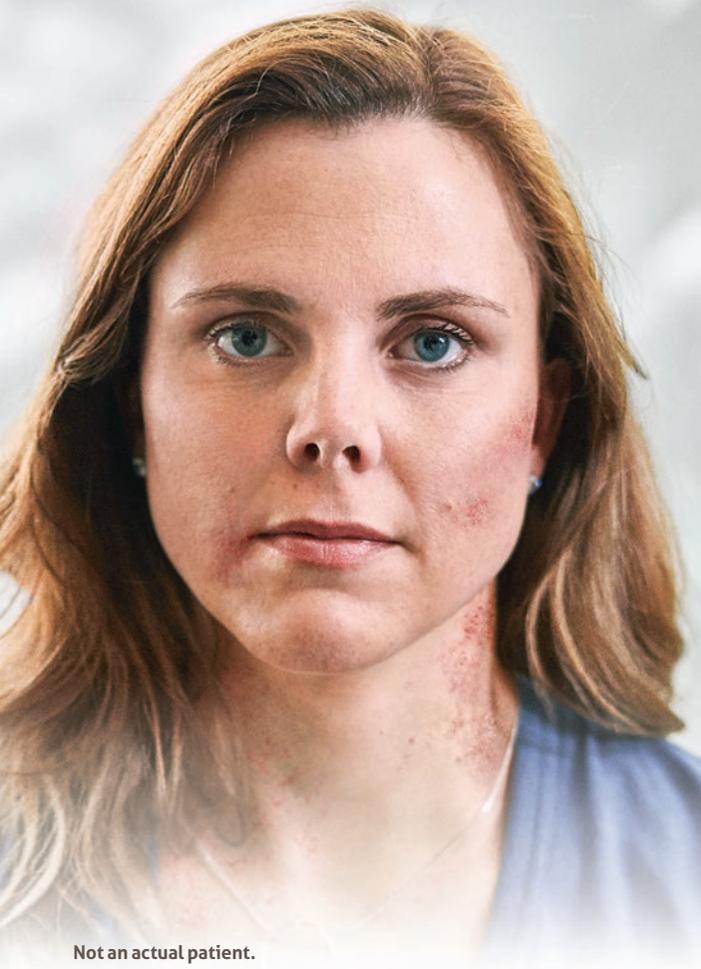
Dr. Guttman: I'm excited to see if early treatment with either dupilumab or other systemic agents can prevent the atopic march we see so often, especially in children. I think we also will learn more about whether these treatments, again given early in the disease process, can halt or reverse disease progression. If we can tell a child and/or a parent that, "Listen, we're going to use an injectable systemic therapy, but we'll only need to use it for X amount of time and then you are done," that is going to be a huge breakthrough. Today, we can't assure them that they won't need these injectables for a lifetime.

Dr. Lio: I have been thinking a lot about the microbiome. We know the microbiome is abnormal in the gut and on the skin of children and adults with AD, and many of our current treatments impact the microbiome in some manner. I'm fascinated with the idea that perhaps we can affect the disease by manipulating the microbiome. We have always been taught that microbiome changes are really secondary with these medications, but I wonder if *Staphylococcus aureus* is the primary driver of AD, at least in a subgroup of patients. Right now, we have not really stratified patients with AD into subgroups like we have, for instance, with asthma patients, but perhaps we'll begin to do that in the near future and develop unique treatment pathways.

DERMATOLOGY TIMES: This has been a terrific discussion. We want to thank you all for your insights. I hope that our audience is able to take away some helpful information from our discussion to inform their practice's approach to the treatment of AD across the various age groups affected by this condition.

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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.

DUPIXENT[®] 
(dupilumab) Injection
200mg • 300mg



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 ≥ 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 ≥ 3 (overall atopic dermatitis lesion severity scale of 0 to 4), an EASI score ≥ 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.¹

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 ≥ 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, $P < 0.0001$; 24% of adolescents treated with DUPIXENT vs 2% with placebo in Trial 6, $P < 0.0001$; 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 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, $P < 0.0001$; 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 ≥ 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, $P < 0.0001$; 59% of adults with DUPIXENT + TCS vs 20% with placebo + TCS in Trial 3, $P < 0.0001$).¹⁻⁴

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 reduction¹
- > A biologic—not a steroid treatment or an immunosuppressant¹
- > Clear or almost-clear skin¹
- > No requirement for initial lab testing or ongoing lab monitoring, according to the full Prescribing Information¹

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://www.dupilumab.com/atopicdermatitis) TO LEARN MORE

DUPIXENT[®]
(dupilumab) Injection
200mg · 300mg
CONTINUOUS CONTROL

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. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

1.3 Chronic Rhinosinusitis with Nasal Polyposis

DUPIXENT is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

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 DUPIXENT 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. One subject in the asthma development program experienced anaphylaxis [see *Adverse Reactions (6.2)*]. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see *Adverse Reactions (6.1, 6.2)*].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. 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 DUPIXENT 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 DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + 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)*].

Among asthma subjects, the frequencies of conjunctivitis and keratitis were similar between DUPIXENT and placebo [see *Adverse Reactions (6.1)*].

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [see *Adverse Reactions (6.1)*].

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

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy 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.

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 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 antihelminth treatment, discontinue treatment with DUPIXENT 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 DUPIXENT 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 DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4)

In DUPIXENT 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 DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + 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 DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

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

^aPooled analysis of Trials 1, 2, and 4.

^bAnalysis of Trial 3 where subjects were on background TCS therapy.

^cDUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

^dConjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

^eKeratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

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

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

Adolescents with Atopic Dermatitis

The safety of DUPIXENT 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 DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT 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 DUPIXENT 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 DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions ^a	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia ^b	17 (2%)	16 (2%)	2 (<1%)

^aInjection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

^bEosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions [see Section 5.3 Warnings and Precautions].

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety pool consisted of data from the first 24 weeks of treatment from both studies.

In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in CSNP Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

Adverse Reaction	CSNP Trial 1 and Trial 2	
	DUPIXENT 300 mg Q2W N=440 n (%)	Placebo N=282 n (%)
Injection site reactions ^a	28 (6%)	12 (4%)
Conjunctivitis ^b	7 (2%)	2 (1%)
Arthralgia	14 (3%)	5 (2%)
Gastritis	7 (2%)	2 (1%)
Insomnia	6 (1%)	0 (<1%)
Eosinophilia	5 (1%)	1 (<1%)
Toothache	5 (1%)	1 (<1%)

^aInjection site reactions cluster includes injection site reaction, pain, bruising and swelling.

^bConjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

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 DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. In the 52-week CRSwNP study (CSNP Trial 2), the frequency of conjunctivitis was 3% in the DUPIXENT subjects and 1% in the placebo

subjects; all of these subjects recovered [see Warnings and Precautions (5.2)].

Eczema Herpeticum and Herpes Zoster

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

Herpes zoster was reported in <0.1% of the DUPIXENT 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 DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo. Among CRSwNP subjects there were no reported cases of herpes zoster or eczema herpeticum.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-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/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-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 asthma (AS Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

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.

In the 24-week placebo controlled trial in subjects with CRSwNP (CSNP Trial 1), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the DUPIXENT group and 0 (0.0%) of the placebo group. In the 1-year placebo controlled trial in subjects with CRSwNP (CSNP Trial 2), there were no cases of CV thromboembolic events (CV deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

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 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% 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®) and a meningococcal polysaccharide vaccine (Menomune®). 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. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see *Clinical Considerations*). 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-4Rα) 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.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

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-4Rα 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.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were

assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV₁ (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight [see *Clinical Pharmacology* (12.3) in the full prescribing information]. The adverse event profile in adolescents was generally similar to the adults [see *Adverse Reactions* (6.1)].

CRSwNP

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<18 years of age) with CRSwNP 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].

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

Of the 440 subjects with CRSwNP exposed to DUPIXENT, a total of 79 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

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)].

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis [see *Warnings and Precautions* (5.3)].

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT [see *Warnings and Precautions* (5.4)].

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic 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)].

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.

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