CHALLENGES IN THE MANAGEMENT OF MODERATE-TO-SEVERE Adult Atopic Dermatitis

SUPPORTED BY:

REGENERON

SANOFI GENZYME
PANELISTS

Norman Levine, MD, is a practicing dermatologist in Tucson, AZ. He graduated from the University of Michigan Medical School before completing his residency in dermatology at Albert Einstein College of Medicine in New York. He has been in private practice for 12 years after a 28-year career in academic dermatology at the University of Arizona.

Elaine Siegfried, MD, has been a practicing pediatric dermatologist since completing her residency training in pediatrics and dermatology in 1991. She is currently professor of pediatrics and dermatology at Saint Louis University School of Medicine and director of pediatric dermatology at SSM Health Cardinal Glennon Children’s Hospital in St. Louis, MO. The focus of her clinical practice is children with congenital and acquired skin and skin-related conditions. She has published more than 100 peer-reviewed articles and is an editor of The Textbook of Pediatric Dermatology. She has also served as principal investigator for multiple clinical trials in atopic dermatitis, psoriasis, acne, and other dermatology-specific disorders.

Matt Zirwas, MD, is a nationally recognized expert in eczema, psoriasis, and contact dermatitis who practices at Bexley Dermatology in Bexley, OH. He has published more than 150 peer-reviewed articles and is an author of the 7th Edition of Fisher’s Contact Dermatitis. His specific interests include adult atopic dermatitis, pruritus and urticaria, allergic and irritant contact dermatitis, rosacea, nonscarring alopecia, and psychodermatology.

Peter Lio, MD, is a clinical assistant professor of dermatology and pediatrics at Northwestern University Feinberg School of Medicine in Chicago, IL. He received his medical degree from Harvard Medical School and completed his internship in pediatrics at Boston Children’s Hospital and his dermatology training at Harvard where he served as chief resident in dermatology. Dr. Lio is the founding director of the Chicago Integrative Eczema Center and currently serves as a board member and scientific advisory committee member for the National Eczema Association. He has authored more than 100 publications and contributed to the publication of two textbooks.

Melissa Knuckles, MD, is a dermatologist in Corbin, KY. She completed her internship at Vanderbilt Medical Center and dermatology residency at the University of Louisville and St. John’s Institute of Dermatology through Guys, King’s College, and St. Thomas hospitals in London, United Kingdom. Her practice focuses on the treatment of adult and pediatric psoriasis, atopic dermatitis, carcinomas of the skin, acne, and urticaria. She has actively participated in clinical trials focused on psoriasis, atopic dermatitis, and acne rosacea, as well as several psoriasis studies registries.

COMMERCIAL SUPPORT

This educational supplement was developed by Dermatology Times with support from Sanofi Genzyme and Regeneron.
**EVALUATING THE PATIENT WITH NEWLY DIAGNOSED AD**

**DERMATOLOGY TIMES:** When you are seeing an adult patient with potential AD for the first time, what are the most important components of that initial evaluation?

**Norman Levine, MD:** AD is a clinical diagnosis, so the physical exam matters tremendously. Once I have been able to establish that the patient has eczema, there is really nothing more that needs to be done to make the diagnosis.

From there, it’s a matter of establishing a care plan based on several factors. One is the degree of disease severity. A second is the degree to which a patient is interested in addressing their symptoms. A third involves financial issues because insurance coverage often dictates what we can offer patients.

**Elaine Siegfried, MD:** My practice is exclusively pediatric. In that population, age of onset is an important diagnostic consideration. The great majority of cases of AD begin before age 5 years and most before age 2 years. It’s also important during an initial visit to find out what, if any, prior treatments the patient has tried and understand which have and have not had any impact.

**Peter Lio, MD:** In my new adult patients, if they tell me they have had eczema since childhood, that’s a pretty clear sign that true AD is the appropriate diagnosis. But if they tell me it’s a new-onset rash, this gets me worried about a couple of other possibilities, in particular allergic contact dermatitis. In those patients, I will perform a comprehensive patch test. If something looks unusual or test results are inconclusive, I may also consider a skin biopsy. In the majority of these patients, the diagnosis will indeed turn out to be AD, but a little blip in test results does make me concerned that something else may be going on.

**Matt Zirwas, MD:** Up until 2 years ago, I classified patients who primarily had spongiotic dermatitis on biopsy, negative patch testing, and onset of eczema later in life as having dermatitis unspecific (ie, dermatitis NOS [not otherwise specified]). The spongiotic biopsy confirmed it was dermatitis, but because they did not have childhood onset of eczema, it wasn’t classic AD, and the negative patch testing ruled out contact dermatitis, leaving no definitive cause of the dermatitis.

So even though a patient might in fact have met the Hanifin and Rajka criteria for the diagnosis of AD (Table 1), because the systemic treatments for dermatitis NOS and AD in adults were the same (ie, systemic steroids, cyclosporine, methotrexate, azathioprine, mycophenolate, phototherapy), formally diagnosing them with AD would not have affected how I treated them. Since the FDA’s approval of dupilumab, however, a formal diagnosis of AD absolutely matters because it determines if they are a candidate for that drug. As a result, I started applying the Hanifin and Rajka criteria to determine if a patient was a candidate for dupilumab, and it turns out that approximately 90% of my adult patients with dermatitis NOS do meet the Hanifin and Rajka criteria for AD, even though they didn’t have childhood-onset eczema.

**DERMATOLOGY TIMES:** What are some of the more common and challenging side effects of AD for a dermatologist to manage?

**Melissa Knuckles, MD:** The most common side effects include anxiety, depression, pruritis, ocular changes, and really just dealing with the burden of the disease. Because of the psychological and emotional impact of AD, the most important thing for dermatologists is to give our patients hope when they come into our office. Hope is a big thing for these people—so many of them have been everywhere trying to get relief before we see them.
Dr. Lie: I’m fortunate to work in a center that has an integrative, multidisciplinary approach to the care of AD. One of the things I have found to be unusually helpful is the presence of a hypnotherapist. It’s amazing. At our monthly group meetings, the hypnotherapist is such a beloved presence because she gives a great lecture about how stress, anxiety, and depression all play a part in the vicious cycle of AD.

I will definitely say that particularly for patients who feel there is a big stress or an anxiety component to their condition, cognitive behavioral therapy and similar approaches that include modalities such as hypnotherapy and relaxation can really be effective in helping them overcome some of those barriers.

Getting patients to buy into these types of sessions is not always easy. It’s important they understand that our recommendation for additional professional help is not because we think they are crazy or psychologically damaged, but because of the significant disease burden of AD and the stress it can put on patients. One of my favorite strategies is to zero in on sleep issues. We know that sleep problems alone are bad for mental health. So, I don’t care if patients turn to sessions of tai chi, meditation, acupuncture, or something else. What our patients need is that push to help them find peace in their lives.

Dr. Zirwas: In other words, make sure they understand we are saying that the eczema is causing psychological problems, not that psychological problems are causing the eczema.

Dr. Siegfried: It certainly can be difficult teasing out which of our patients with AD have psychiatric comorbidities and then helping them access professional mental care. A link between AD and attention deficit disorder, as well as anxiety and depression, has been well-established. It is not uncommon for AD to negatively impact school performance and attendance. A small handful of my patients have suffered from severe depression and even suicidal ideation requiring hospitalization. In a few, these psychiatric morbidities profoundly improved with the use of dupilumab. It’s been amazing to see that.

Dr. Zirwas: I have a story along those lines about a patient of mine with severe eczema who was part of a same-sex couple. They always came in for visits together. My patient always came across as sort of an odd person while his partner was a really interesting, cool person. I could never understand what the two of them were doing together. I couldn’t figure out what the partner saw in my patient that made him want to be with him.

Well, we got my patient’s eczema better and their personalities totally switched. Everything about my patient was different once his eczema cleared up and he started sleeping without sedatives. Now, he was the

### TABLE 1 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 dermographism, delayed blanch

Source: Hanifin JM, Rajka G.2
An Educational Supplement to *Dermatology Times*

more interesting person and I wondered what he saw in his partner. That just shows the dramatic effect that eczema can have on our patients and the impact we can make on them well beyond their visible skin issues.

**SETTING APPROPRIATE TREATMENT GOALS IN PATIENTS WITH AD**

**DERMATOLOGY TIMES:** Let’s talk about setting goals for your patients with moderate-to-severe AD (Table 2) and what level of improvement you tell your patients they can attain. What does that initial conversation sound like?

**Dr. Levine:** Well, I want them to get “all better.” Now what exactly does that mean? The biggest issue for me is that they are not itchy anymore. The itch is what ruins most of our patients’ lives, so whatever we can offer from a pharmacologic perspective to make their itch go away, I’m all for it. That’s the first step. And the second step is that if their itch is better, the eczema is going to get better. That’s my goal.

The first question I ask patients with AD when they come in for a return visit is: “Are you still itchy?” And the second question is: “Are you sleeping better?” If I get the answer I want to those two questions, then everyone is generally happy. If you get your patient better by whatever means, they will feel better, they will sleep better, and they will often be less depressed.

**Dr. Zirwas:** I’m struck by how much the introduction of dupilumab has changed the way I set goals for patients with AD. Before its approval, I would prescribe a lot of cyclosporine, methotrexate, and mycophenolate mofetil—and certainly I still do—but my goal when we were limited to those drugs was to get my patients 90% better. I would tell my patients: “If you are 90% better, we know we’ve got you on about the right dose of medication. I don’t want you 100% better because that means you are on too high a dose and we’ll need to lower it to reduce your risk of side effects.” These traditional systemic drugs are entirely dose dependent in regard to side effects.

Now that we have dupilumab in our arsenal, I am comfortable telling patients that our goal is to get them 100% better. That means no itch and no rash. It also means no systemic steroids. There was a study in 2017 showing that patients treated with a short course of systemic steroids have a 7-fold increased risk of developing sepsis.\(^3\) I always set the goal of getting patients well enough so that they will not need systemic steroids at all.

**Dr. Levine:** Let me offer a slightly different perspective. If you look at the trial data results for dupilumab—which are backed up with my personal experience, shooting for 100% improvement in patients with AD is perhaps overly optimistic. Yes, you can get patients a

---

**TABLE 2: DEFINITION OF MODERATE-TO-SEVERE AD**

1. Moderate-to-severe AD may be considered when 1 or more of the following features are present:
   - A minimum involvement of 10% BSA
   - Regardless of BSA
     - Individual lesions with moderate-to-severe features
     - Involvement of highly visible areas or those important for function (eg, neck, face, genitals, palms, and/or soles)
   - Significantly impaired QOL

2. Current disease severity scales and QOL scales, although validated for use in clinical trials, are not practical for routine utilization in clinical practice.

3. Although global assessment scores have not been validated in office settings, it is simple to classify disease as clear, almost clear, mild, moderate, or severe.

4. Clinicians should actively assess the impact of disease on QOL during clinic visits (i.e., sleep, pruritus, impact on activities of daily living and work).

5. No biomarkers, including serum IgE, are currently recommended for assessment of disease severity.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; QOL, quality of life.
lot better, but the data show that an improvement of approximately 80% is more realistic for the majority of patients.\(^4\) I tell this to my patients, and the majority of them are OK with that. If they end up getting completely better, that’s great, but that is not my expectation with dupilumab.

**Dr. Zirwas:** I agree, and I should have phrased my answer differently. I tell my patients that, on average, people get 80% better on dupilumab but that my experience is approximately 20% of patients will get 100% better, 5% won’t get better at all, and the rest improve between 60% and 80%. But I do tell everyone up front that there is a chance they will get 100% better, even if that is not what I am expecting for most of them. I find that setting the bar high makes patients more motivated.

**Dr. Siegfried:** Treatment goals for children with AD are somewhat different than for adults, in part because of the lag in available data supporting pediatric safety and efficacy for new treatments, along with barriers to medication access. I emphasize the importance of recognizing and addressing likely triggers rather than unlikely contributing factors. Many parents focus on environmental exposures like pets or dietary exposures. More important contributing factors not obvious to most are skin care products, skin germs, changes in ambient humidity, psychic stress, and illness.

I spend a lot of time educating patients to overcome myths and stop counterproductive use of OTC products that contain potential contact allergens. When they start topical treatment, I always provide guidance about therapy and monitor the amount of topical medications they use.

Topical treatment can be complicated. Patients need to understand the importance of using an adequate, but not excessive, amount of topical medication. I’m also a big believer in bleach baths. For children who do not fare well on conservative treatment, I don’t hesitate to start systemic therapy.

**DERMATOLOGY TIMES:** What are some of the other common myths you need to debunk among your patients with AD?

**Dr. Knuckles:** I tell all my patients who have eczema that “You don’t paint the house when the sewers are leaking.” They think AD is solely a skin disease and that they can just slap a cream on and it will all get better. I have to explain to them that there is an internal causation to their inflammation that makes it more complicated.

I also get a lot of patients who think the only places they have to worry about on their skin are where it is red. They need to be educated that it’s not just their lesional skin that has eczema, but that their unaffected skin is also inflamed.

**Dr. Zirwas:** The biggest myth I deal with is steroid phobia. Studies have shown that approximately 70% of patients have steroid phobia, meaning that in 70%, the fear of side effects is clearly out of proportion to the actual risk.\(^5\) I’m just talking about adults. In children, it might be a totally different balance. There are some conditions for which the treatment is potentially worse than the disease, but in AD the disease is far worse than the potentially worst things that can happen with topical treatment. I often ask patients what they are afraid of with the use of topical steroids, and most of them say “thinning of my skin.” I then ask if they would rather have thin skin or skin that is scratched and bleeding from eczema. It still usually doesn’t get through to them, though. There is just this specter of “badness” looming when topical steroids come up.

**Dr. Siegfried:** Food allergies are a big one for me. The great majority of people who believe they have food allergies do not react to placebo-controlled food challenges. However, many who have modified their diet for years develop an intrinsic fear of liberalizing their food intake. That is an unintended, potentially crippling consequence.

**Dr. Lio:** When I have a patient who won’t stop focusing on potential food allergies and continues to ask about more tests and questions like “Should I switch to a gluten-free diet?” long past the point of potential utility, I try to turn the story around. I try to provide a more modern take.

For a long time, the narrative was that food allergies are driving the disease. But now with new data we know that we’ve had it backwards and it’s really the leaky skin, the impaired barrier, that is causing transcutaneous sensitizations to certain foods.\(^6\) So instead of worrying about what the patient is eating, our priority needs to be getting their skin under control, with the idea that a better skin barrier could potentially decrease the development of future allergies, at least theoretically.
Relaying the story in that fashion can be very impactful. I often see the lightbulb go on in my patients’ heads and they tell me: “You know, that makes a lot of sense.”

**Dr. Siegfried:** A favorite sound bite of mine for patients who are convinced that food allergy is the cause of their eczema is: “Food allergies are more common in people who have eczema, but food allergy doesn’t cause eczema, just like asthma or allergic rhinitis doesn’t cause eczema.” While these may occur concurrently in any given patient, one does not drive the other.

**Dr. Zirwas:** I love how you both turn things around in such an impactful way. Just as with the psychological aspects of AD, you’re getting patients to realize that the eczema is causing the food allergies rather than the food allergies causing the eczema. That’s a great sound bite I’m definitely going to use in the future.

**CONVENTIONAL TREATMENT OPTIONS IN ADULT PATIENTS WITH MODERATE-TO-SEVERE AD**

**DERMATOLOGY TIMES:** What does your mental treatment algorithm look like for adult patients diagnosed with moderate-to-severe AD? Where do you typically start with them?

**Dr. Lio:** I typically begin by making sure the patient is following basic skin care procedures and avoiding obvious triggers such as the use of fragranced soaps, rubbing/scratching their skin, or wearing wool. I’ll then move on to talking about moisturizers, typically by bringing over a palette of different options that I like and letting the patient try them to find one that feels good on their skin.

Once we establish a moisturization protocol, my first line in most patients is a topical steroid for up to 2 weeks. Once there is significant improvement, if it’s a patient with only mild eczema, I’ll typically simply continue with moisturizer, but if it’s someone with a more persistent condition, I’ll typically switch them to a nonsteroidal agent such as a calcineurin inhibitor to “finish the job” and get the skin totally clear, hopefully keeping it that way.

For those patients who present with moderate-to-severe AD, I’ll try to see them about 2 weeks after they have started on the topical steroid, when I will look for three things:

1. Are they better?
2. Can I keep them clear safely without overusing potent corticosteroids?
3. Can I keep them clear sanely without the patient losing their mind by constantly needing to apply tons of ointments and being endlessly greasy and ruining their clothing?

If the answer to any of those questions is no, that’s when I consider the jump to systemic therapies. I think we are all becoming much more aggressive with our treatments these days because our patients do not need to suffer anymore. We have the tools available to get and keep them better.

I will typically turn to dupilumab or phototherapy at this stage. Phototherapy can be a good option, but it involves so many issues related to time, money, and logistics that it’s not a viable option for a lot of my patients. I used to use cyclosporine in many of my AD patients, but now I try to reserve it and only use it in those patients for whom I cannot get dupilumab or for the smaller group that does not achieve enough improvement on dupilumab alone.

**Dr. Levine:** My general approach is similar. For adults, I will typically start them on a topical steroid, usually triamcinolone. And of course, I have my AD patients use moisturizers. If these patients’ lives are being impacted in a significant fashion—which is often the case in adults with moderate-to-severe AD—I’m quick to move to systemic therapy if the topical steroid is not working.

I will often try to get dupilumab for these patients, but there are some significant regulatory and insurance barriers to getting that drug. If I can get it approved, that is where I’ll typically go, but if not, cyclosporine, methotrexate, and azathioprine are all options. I deal with a lot of insurance companies that require a patient fail a systemic therapy before they will approve dupilumab, and oddly enough, many also require that they fail a topical calcineurin inhibitor.

The problem with our current systemic therapies is that patients need lifelong treatment. While these
therapies can help induce remission of an AD patient’s symptoms, they do not produce a cure. Patients need to understand that once they start on something, they are going to be on it for the long haul. I try to get a sense early on from my patients whether they will have the motivation to adhere to our plan. For instance, I will not start a patient on methotrexate if I’m reasonably sure they won’t come in for the necessary blood tests.

**DERMATOLOGY TIMES**: For a patient you are considering starting on an immunosuppressant, how long will you wait for that patient to respond to topical therapy before you move to something else?

**Dr. Knuckles**: I’ll usually wait about 2 weeks. If I don’t see a response by then, I’ll switch to systemic therapy. I tend to move pretty fast.

**Dr. Levine**: I’ll usually wait a little longer, perhaps 1 month, because the next step into systemic therapies is fairly significant. I want to make sure that patients have given the simpler, less expensive, and safer medications a try before I move forward with something else.

**Dr. Siegfried**: My practice is not restricted by insurance type or ability to pay, so the demand limits my ability to follow up as soon as I would like. Although frequent follow-up definitely supports better adherence, 1 month is the best I can do and it’s usually 2 to 3 months. For children, it takes longer to recognize that they may have failed what I call “maximum conservative treatment,” a failure which is often related to adherence.

**Dr. Zirwas**: How does everyone feel about melatonin? A couple of studies have come out in favor of melatonin as improving objective measures of disease severity as well as quality of life and sleep quality in patients with AD. Combined with other recent studies that have shown anticholinergics such as hydroxyzine and doxepin effectively double an individual’s risk of developing Alzheimer’s disease late in life if taken for more than 3 years, I find myself recommending melatonin much more frequently, but I honestly can’t tell if it’s working in my patients with AD or not.

**Dr. Siegfried**: I have recommended melatonin as a presumably safe and readily available, inexpensive option, but I have not seen any patients who have reported that it was helpful. I have moved away from using sedating antihistamines in patients with AD. Not only is there growing literature about under-recognized neuropsychiatric risks but these are also not that effective. I recommend daily, nonsedating antihistamines for patients with dermatographism and a history suggestive of concomitant hives. I also caution patients about the lack of efficacy and risks of montelukast for treating eczema. This drug continues to be prescribed for patients with AD but can cause behavioral side effects in a subset of children. In addition, the chewables contain aspartame, which cross-reacts with formaldehyde and can cause systemic allergic contact dermatitis in patients with formaldehyde allergy.

**DUPILUMAB FOR THE TREATMENT OF AD**

**DERMATOLOGY TIMES**: Throughout this discussion, we have touched on how you all use dupilumab in your adult patients with moderate-to-severe AD, but let’s talk about some specific issues. First, when you prescribe dupilumab, are you usually prescribing a corticosteroid along with it?

**Dr. Zirwas**: Occasionally, I will. Whenever I am starting a patient on dupilumab, I ask the patient to truthfully tell me how miserable they are. I explain that on dupilumab alone, if we’re lucky, it will be a couple of days before their itch starts getting better. If we’re not lucky, it might be 6 weeks before their itch starts getting better. Do they want relief badly enough that it’s worth taking the small risk of getting a severe infection with a short course of systemic corticosteroid? I leave the decision up to them. I’m willing to prescribe it if they really are desperate for the relief, but most patients end up opting not to go on the steroid short term whenever they start dupilumab.

**Dr. Lio**: I try as best I can to avoid using oral steroids in patients taking dupilumab. When we all first began using dupilumab, most patients were transferred over
INDICATION

DUPIXENT is indicated for the treatment of adult patients 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.

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.

ADVERSE REACTIONS: The most common adverse reactions (incidence >1%) in atopic dermatitis patients are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

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

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.
see the evidence of continuous
CONTROL

Itch relief

Clear or almost-clear skin

Improvement in lesion extent and severity

No requirement for initial lab testing or ongoing lab monitoring, according to the full Prescribing Information

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS (cont’d)

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 page.

Visit DupixentHCP.com/AtopicDermatitis to learn more

References:
1. DUPIXENT Prescribing Information. October 2018.
4. Data on file, Regeneron Pharmaceuticals, Inc.
1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPLEXENT® is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPLEXENT can be used with or without topical corticosteroids.

1.2 Asthma

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

Limitations of Use

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

4 CONTRAINDICATIONS

DUPLEXENT® is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients. See Warnings and Precautions (5.1). See Contraindications (4).

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 DUPLEXENT in clinical trials. Two subjects with 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 (6.1). If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPLEXENT® (see Adverse Reactions (6.1, 6.2)). See Hypersensitivity Reactions.

5.2 Conjunctivitis and Keratitis

 Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPLEXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovered during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPLEXENT and placebo. In placebo subjects keratitis was reported in 4% of the DUPLEXENT group (12 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 corticosteroid asthma trial, keratitis was reported in 4% of the DUPLEXENT + 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. Among asthma subjects the frequency of keratitis was similar between DUPLEXENT and placebo [see Adverse Reactions (6.1)]. Advise patients to report new or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious eosinophilic conditions 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 a reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neutropenia presenting in these patients with evidence of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPLEXENT®. A causal association between eosinophilia and DUPLEXENT® has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPLEXENT® should be used to treat acute asthma exacerbations or acute exacerbations.

Do not use DUPLEXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPLEXENT®.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPLEXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neutropenia presenting in these patients with evidence of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPLEXENT®. A causal association between eosinophilia and DUPLEXENT® has not been established.

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consulting with their physician.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPLEXENT® will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPLEXENT®. If a helminth infection is diagnosed during treatment with DUPLEXENT® and do not respond to antihelminth treatment, discontinue treatment with DUPLEXENT® 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))
- Injection site reactions (see Section 5.3 Eosinophilic Conditions)

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.

6.2 Adverse Reactions in Clinical Trials

6.2.1 Dermatitis

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPLEXENT Monotherapy</th>
<th>DUPLEXENT + TCS</th>
<th>Placebo N=597</th>
<th>Placebo N=315</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>51 (10) 28 (5) 11 (10)</td>
<td>18 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>51 (10) 12 (2) 10 (9)</td>
<td>15 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>0 0 0</td>
<td>4 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 0 0</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>0 0 0</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 0 0</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>0 0 0</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2.2 Asthma Trials 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N=779</th>
<th>Placebo N=788</th>
<th>Placebo N=792</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (8%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

6.2.3 Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation

Eosinophilia = blood eosinophil ≥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 Eosinophilic Conditions].

6.2.4 Conjunctivitis

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 76% of the DUPLEXENT + TCS group (20 per 100 subject-years) and in 3% of the placebo group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPLEXENT and placebo [see Warnings and Precautions (5.2)].

6.2.5 Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPLEXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPLEXENT 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 DUPLEXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPLEXENT + 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 DUPLEXENT and placebo.

6.2.6 Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPLEXENT-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)].

6.2.7 Eosinophilia

DUPLEXENT-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 were 100 and 0 cells/mcL, respectively.
increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUXPEN'T and placebo groups. Treatment-emergent eosinophilia (≥500 cells/mcL) was reported in <2% of DUXPEN'T-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatement [see Warnings and Precautions (5.3)].

Cardiovascular (CV)

In the 1-year placebo controlled trial in subjects with asthma (ASTRA Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUXPEN'T 200 mg Q2W group (0.8%) of the DUXPEN'T 300 mg Q2W group, and 2 (0.3%) of the placebo group. In the 1-year placebo controlled trial in subjects with atopic dermatitis (Tria1), CV thromboembolic events (CV deaths, non-fatal MI, non-fatal strokes) were reported in 1 (0.9%) of the DUXPEN'T + TCS 300 mg Q2W group, 0 (0.0%) of the DUXPEN'T + TCS 300 mg Q2W group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immune Reactions

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 occurrence of antibodies (both neutralizing and non-neutralizing) 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 6% of subjects with atopic dermatitis or asthma who received DUXPEN'T 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 DUXPEN'T 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ≥4% exhibited persistent ADA responses, and ≥4% had neutralizing antibodies. Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for ADA antibodies to DUXPEN'T; ≥2% exhibited persistent ADA responses, and ≤1% had neutralizing antibodies. The antibody titers detected in both DUXPEN'T and placebo subjects were mostly low. In subjects who received DUXPEN'T, development of vaccine antibodies to the vaccine was associated with lower serum dupilumab concentrations [see Clinical Pharmacology (12.3)].

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUXPEN'T therapy [see Warnings and Precautions (5.1)].

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUXPEN'T.

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 dosage frequency). After 12 weeks of DUXPEN'T 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 measured 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

Risk Summary

Available data from case reports and case series with DUXPEN'T 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, DUXPEN'T may be transmitted to the mother from 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 postnatal 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-4Ra) during organogenesis through parturition after exposure 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 pre-eclampsia 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 postnatal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Ra up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/wk) from the beginning of organogenesis to parturition. No treatment-related adverse events 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’s growth, development, and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUXPEN'T and any potential adverse effects on the breastfed child from DUXPEN'T or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

Safety and efficacy in pediatric patients [≥12 years of age] with atopic dermatitis have not been established.

Hypersensitivity

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in a V3 trial and received either 200 mg (N=21) or 300 mg (N=18) DUXPEN'T (or placebo, including placebo [N=16]) and the proportion of asthma exacerbations and lung function were assessed in both adolescents and adults. For the 200 mg and 300 mg Q2W doses, improvements in FEV1 (1.3 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 in adults at the respective dose level which was mainly accounted for by difference in body weight [see Clinical Pharmacology (12.3)].

The adverse event profile in adolescents was generally similar to the adults [see Adverse Reactions (6.1)].

9.8 Pregnancy

The safety and efficacy of DUXPEN'T have not been established in pregnant women. 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.

9.9 Lactation

The safety and efficacy of DUXPEN'T have not been established in breastfeeding women. 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.

10 OVERDOSAGE

There is no specific treatment for DUXPEN'T overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUXPEN’T and each time the prescription is renewed as there may be new information they need to know.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUXPEN’T prior to use. Advise patients to follow sharp disposal recommendations.

Manufacturer of: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License # 1760; Marketed by sanofi-aventis U.S. LLC, (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc., (Tarrytown, NY 10591). DUXPEN’T is a U.S. registered trademark of Sanofi Biotechnology® 2018 Regeneron Pharmaceuticals, Inc®, sanofi-aventis U.S. LLC. All rights reserved. Issue Date: October 2018. US-DUP-1104
from cyclosporine, azathioprine, or methotrexate, so that was a bridge for those people. In today’s environment, as we noted earlier, there will be a percentage of patients who won’t be helped at all by dupilumab, so those are the patients in whom I will use full-dose cyclosporine for a few weeks to cool things down.

I’ve also had a few patients who have done well on weekend-dosing cyclosporine, which has typically been used as a psoriasis treatment. A study done a few years ago showed that this sort of regimen can be effective in AD, and my experience has been largely positive as well. I have patients take a full dose of cyclosporine on Saturday and Sunday only along with their twice-monthly dupilumab. The cyclosporine has helped to extend the impact of the medication. There will be some patients who flare 7 to 10 days after every dose of dupilumab, so this is an option for those patients who can’t quite make it to a full 2 weeks.

I do have a few female patients in my practice for whom I have been able to successfully argue for weekly dupilumab. You can imagine, though, how difficult it was convincing their insurance companies. In a handful of others who might have seen benefit from weekly dosing, I have not been able to achieve coverage.

Dr. Zirwas: I tried the weekend regimen of cyclosporine in a few of my patients in the pre-dupilumab era, and it didn’t do much. I can see the logic, however, of using a regimen like that for those patients who are mostly better but are getting the breakthrough rash a few days before their next injection of dupilumab.

DERMATOLOGY TIMES: How do the rest of you use dupilumab in your patients with AD?

Dr. Knuckles: In Kentucky, it’s unfortunately mandated by all our insurance providers that AD patients need to fail at least one nonsteroidal topical medication—typically either pimecrolimus or tacrolimus—or an immunosuppressant for at least 30 days before they will approve something else. I call it the “one and done” rule. The nice part about it is that it allows me to bypass other systemic agents and go right to dupilumab.

My practice is in a semirural area and I have a lot of patients who drive several hours to see me, so it’s not often realistic to have them see me 2 weeks after their initial injection. Instead, I’ll have them call my office to tell me how they are doing.

Dr. Levine: I don’t typically use a bridge drug when I start a patient on dupilumab, but for those who are using a systemic agent such as cyclosporine or methotrexate already, I’ll usually keep them on it for at least a month. It can take several weeks for dupilumab to begin having an effect, but if there is improvement when the patient comes back for that initial 1-month visit, I’ll discontinue their systemic drug and continue with dupilumab into the sunset. The one thing I do tell my patients is that if they are not better after 3 months of dupilumab, we’re going to stop.

DERMATOLOGY TIMES: What are some of the more common and significant adverse events you have seen in patients starting dupilumab?

Dr. Lio: Conjunctivitis has been probably the biggest issue. It occurs in approximately 10% of patients who start dupilumab, and I’ve had to take a handful of patients off of therapy. I wrote a paper recently that focused on a case series of 12 patients with AD who developed conjunctivitis secondary to their use of dupilumab. We found that severe conjunctivitis was more likely to develop in patients with more severe baseline AD who had a good response to dupilumab and an increased atopic phenotype, so from that perspective, it is unfortunate. But there has been a silver lining. In each of the 4 patients in whom we had to discontinue dupilumab, their AD remained relatively improved and stable up to 18 weeks after cessation. No one regressed to baseline or had a rebound flare. This shows me that perhaps dupilumab does not have to be a lifelong therapy in all of our patients and that there may be hope of remission in at least some patients.

There is vicious cycling in AD. The skin barrier is broken, the immune system has gone crazy, allergens and irritants are getting in, bacterial imbalance is rampant, and behavioral aspects are practically uncontrolable. The whole thing is a mess. But perhaps if you can get it all back into a virtuous cycle, now the skin barrier heals, now the immune system calms down, now the little nerve endings to the skin regress back down, and that can become the patient’s “new normal.” Maybe it just requires maintenance dosing of cyclosporine or dupilumab every 3 months. It’s a hypothesis at this point, but something worth thinking about.

Dr. Zirwas: A recent patient of mine who developed conjunctivitis had a close friend who is an optometrist.
They kept trying different drops to see if anything would work while this patient stayed on dupilumab. He ended up using lifitegrast, a drop commonly used to treat chronic dry eye. It’s a competitor to cyclosporine ophthalmic, with which we are likely more familiar. This patient had significant conjunctivitis for several months and had tried and failed several previous drops, including cyclosporine and steroid drops, but his response to lifitegrast was remarkable. His conjunctivitis basically resolved immediately.

Lifitegrast is an interesting agent. It blocks the interaction between lymphocyte function-associated antigen-1 (LFA-1) and its ligand intercellular adhesion molecule-1 (ICAM-1). It is considered safe for long-term use.15 My experience with it was only in this patient, so we will have to see if it is repeatable, but it’s the one example I know of a patient with dupilumab-related conjunctivitis who got better.

Dr. Siegfried: I’ve had the same experience with lifitegrast. It definitely needs further evaluation.

DERMATOLOGY TIMES: Are there any other potential side effects that you point out to your patients before they start dupilumab?

Dr. Levine: Injection site reactions are a possibility. You’ve got to tell patients in advance that they may have soreness for about 24 hours after an injection.4

Dr. Lio: I will typically mention two other concerns. Although extremely rare, it is possible to have a systemic reaction to the injection itself.4 I am also always sure to ask patients if they will be traveling to a place where they may be exposed to parasites before starting them on dupilumab. I had one patient who was in the midst of filling out the paperwork to start on dupilumab, and he started telling me about some upcoming work he would be doing in remote villages in Africa. I told him we would wait until he came back to start the drug. I was a little worried that if he was exposed to a parasite while abroad, his immune response to the parasite could be impaired.

DERMATOLOGY TIMES: What is the impact of dupilumab on patients with contact dermatitis?

Dr. Zirwas: My experience is that dupilumab often makes it worse. I’ve had a number of patients who were diagnosed with AD by outside dermatologists who then put them on dupilumab. When I saw these patients, their rash was worse and we patch tested them. Typically, results showed they had contact dermatitis, so we modified their treatment and they got better.

Dr. Siegfried: While I agree that dupilumab does not have proven efficacy in contact dermatitis, there are a growing number of reports on the subject.16 Improvement has been reported more often than worsening. Although we have yet to determine which allergens may be more or less responsive to Th2 blockade, a trial of dupilumab can benefit some patients, especially adults with secondary contact dermatitis.

Dr. Zirwas: In the literature, the data are certainly mixed. There are some case reports showing that dupilumab is effective in patients with contact dermatitis and some showing it is ineffective.17

The problem is that in many studies showing dupilumab works in patients with contact dermatitis, the benchmark criterion defining the condition was a positive skin patch test. In these reports, if a patient had a positive patch test and was treated with dupilumab and got better, that patient was characterized by the authors as having contact dermatitis responding to dupilumab.

But it’s not that simple. I patch test dozens and dozens of bad atopics every year. The vast majority of the time, when patients have a positive patch test and I have them avoid the allergen, they don’t get better. I then treat them for AD, and they do get better. In these patients, what is really going on is that they have AD and a positive patch test that is not relevant to their dermatitis. When they get better on dupilumab, it is not because the dupilumab worked for contact dermatitis, it is because the dupilumab worked for AD.

Dr. Siegfried: By the same token, if they have a negative patch test, it doesn’t mean they don’t have contact dermatitis.

Dr. Zirwas: Exactly. A positive patch test doesn’t mean someone has contact dermatitis, and a negative patch test doesn’t mean they don’t. The only way to definitively diagnose contact dermatitis is to have someone avoid an allergen and get better, then re-expose them to the allergen and see their dermatitis return. A positive patch test is not even required in many cases.
Let’s take an example. You have a 50-year-old man who has had a rash for 3 years on his upper back, flank, and anterior thighs. He has a positive patch test to fragrance, biopsy shows spongiosis, he has no history of childhood rashes, no other allergies, no hay fever, and no asthma, but he does have a second cousin who is allergic to cats. According to the Hanifin and Rajka criteria, that person has AD, and according to the patch test, they may also have contact dermatitis. Now, which is it? Do they have one or the other, or both? They certainly don’t have classic AD. The only way to find out if it is contact dermatitis or AD is to do allergen avoidance and see if they get better. If they do, we have confirmed contact dermatitis and don’t have to do anything else. If they don’t, then we have essentially ruled out contact dermatitis and initiate a trial of dupilumab. If they get better, we still don’t know if they truly have AD that improved thanks to dupilumab or if they have dermatitis NOS that was helped by dupilumab.

What I’m getting at is because dupilumab has worked for me in essentially every case of “noncontact dermatitis” that I’ve treated—whether classic atopic dermatitis or not—I don’t know if I should be thinking, “Gee, there are a lot of people with adult-onset dermatitis that gets better with dupilumab, and as it gets better on dupilumab, it must be adult onset AD” or if I should be thinking, “Well, because it isn’t classic atopic dermatitis, it must be dermatitis NOS, and this must mean that dupilumab works for dermatitis NOS and not just for AD.” I don’t know which one of those is the right answer. I also don’t know how you would answer that question right now.

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 management of moderate-to-severe AD.