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DERMATOLOGY NURSE PRACTICE

New Treatment Pathways in the Management of Atopic Dermatitis

INSIDE THIS ISSUE:

What are some of the molecular pathways being investigated in the treatment of atopic dermatitis (AD)?

What are the primary limitations of traditional systemic therapies that are used in the treatment of AD?

How are newer biologic and small molecule therapeutics being incorporated into the treatment of AD?

What are some of the new topical treatment options for patients with AD with which providers need to become familiar?

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LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

- Identify the primary molecular pathways under investigation for the treatment of atopic dermatitis (AD)
- Assess the limitations of traditional systemic therapies used to treat AD
- Determine the primary factors to be considered when selecting a biologic or small molecule therapeutic for patients with moderate-to-severe AD
- Discuss the rationale behind the development of black box warnings for specific therapeutics

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This activity has been designed to meet the educational needs of nurses, nurse practitioners, and physician assistants. Other healthcare providers may also participate.

ACTIVITY DESCRIPTION

To help clinicians become knowledgeable about the new atopic dermatitis (AD) treatment landscape, this issue of *Dermatology Nurse Practice* will focus on the unique targets and characteristics of new and emerging therapeutic options.

ACCREDITATION AND CREDIT DESIGNATION

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NEW TREATMENT PATHWAYS IN THE MANAGEMENT OF ATOPIC DERMATITIS

Roughly 13% of children and 7% of adults in the United States have atopic dermatitis (AD), a disease whose prevalence has been on the rise for decades.[1-3] Despite the large number of individuals affected by AD, therapeutic progress remained elusive for many years. Topical corticosteroids, a therapeutic mainstay since the 1950s, remain the most common treatment prescribed for AD.[4,5]

The lack of convenient, safe, and effective AD treatment options, especially for patients with moderate-to-severe disease, has traditionally been a major problem. Many patients with AD require lifelong therapy, and most will need to try a number of different regimens over time as their symptoms change, they stop responding to treatments that previously worked, or their lifestyles and preferences evolve.[4] In addition, AD is a very heterogenous disease, with many different subtypes and endotypes.[6] Given this heterogeneity, it is not surprising that a specific therapeutic regimen may work well for one patient but not for another. To serve a patient population with diverse needs, many therapeutic options are needed. For all these reasons, patients with AD and their healthcare providers have long awaited novel therapies that are both effective and safe for long-term use.

Fortunately, several novel AD treatments have recently launched, and more than 70 new therapies for AD are in the research pipeline, with several agents potentially receiving FDA approval in the coming months.[7] This influx of novel agents should allow providers to better tailor treatment plans for individual patients.[8] In order to optimize AD treatment, however, specialists treating AD will need to become familiar with these agents, including their clinical utility and common adverse effects, to help determine which patients are candidates for their use.

DRUG NAMES INCLUDED WITHIN THIS ISSUE

Generic	Brand
Dupilumab	Dupixent
Lebrikizumab	NA
Nemolizumab	NA
Baricitinib	Olumiant
Orismilast	NA
Tralokinumab	Adbry
Abrocitinib	Cibinqo
Ruxolitinib	Opzelura
Delgocitinib	Corectim
Tapinarof	Vtama
Upadacitinib	Rinvoq
Cyclosporine	Sandimmune, Neoral, Gengraf
Methotrexate	Otrexup, Rasuvo, RediTrex
Pimecrolimus	Elidel
Tacrolimus	Astagraf XL, Envarsus XR, Prograf, Protopic

THE MOLECULAR BASIS OF AD

Recent research has revealed that a complex network of molecular alterations underly the symptoms of AD. Investigators are now using this knowledge to develop novel therapies that target a variety of molecules and pathways implicated in the disease.

Most new and emerging therapies target the Th2 immune axis, which has long been known to be central to AD pathogenesis, particularly in the initial acute phase of the disease (see Figure 1).[8-10] The inflammatory cytokine **interleukin 4** (IL-4) plays an important role in initiating the Th2 pathway, while **IL-13** is key to maintaining the pathway's activity. Both cytokines downregulate production of key proteins that maintain the skin barrier, such as filaggrin and loricrin. They also decrease production of antimicrobial peptides, which in turn increase patients' susceptibility to skin infections. Another molecular player in the Th2 pathway is the cytokine **IL-31**, which drives itch symptoms.

Many of the cytokines involved in the Th2 pathway underlying AD—such as IL-4, IL-13, and IL-31—activate the JAK-STAT signaling pathway (see Figure 2).[11,12] This pathway, in turn, modulates multiple immune axes involved in AD, including the Th1, Th2, Th17, and Th22 pathways.[9]

ROLE OF SYSTEMIC THERAPIES IN AD TREATMENT

In general, AD therapy progresses in a stepwise fashion, starting with topical treatments such as corticosteroids and calcineurin inhibitors before progressing to systemic therapies in patients who do not respond (see Figure 3).[13] Systemic therapy is generally appropriate when topical therapies are not sufficient to control AD symptoms or when a patient's symptoms are only controlled by applying large amounts of topical corticosteroids over prolonged periods, which is neither feasible nor safe. Before resorting to systemic therapy, providers should ensure that patients have received comprehensive education on how to apply topical therapy and that a period of intensive topical therapy has been attempted and closely monitored. Phototherapy should also be considered for some patients whose symptoms are not adequately controlled by topical therapies before systemic therapy is initiated.[14]

Until recently, systemic therapy options for patients with AD primarily consisted of corticosteroids and cyclosporine (used for treating flares or providing temporary symptom relief), or slower-acting therapies such as azathioprine and methotrexate (for longer-term management).[15] However, due in part to the age of these drugs, none have been approved

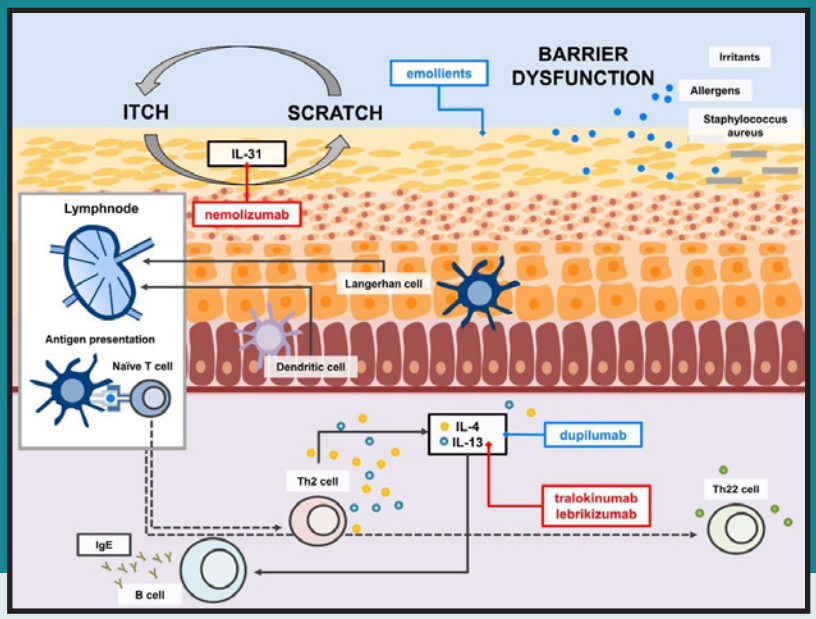


FIGURE 1
Various molecules altered in the Th2 immune pathway in AD, along with the therapies that target them.
Adapted from Salvati et al, 2021[10]

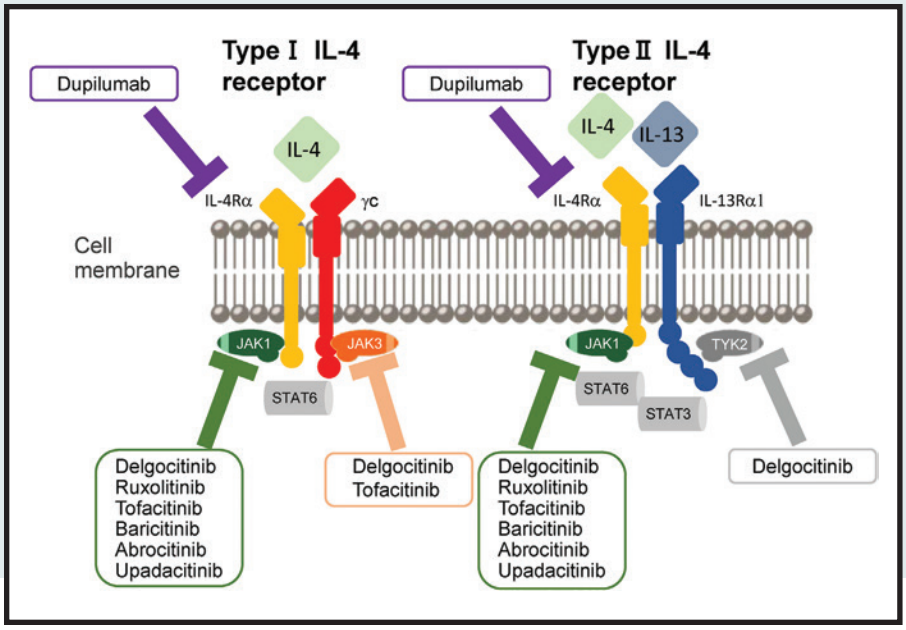


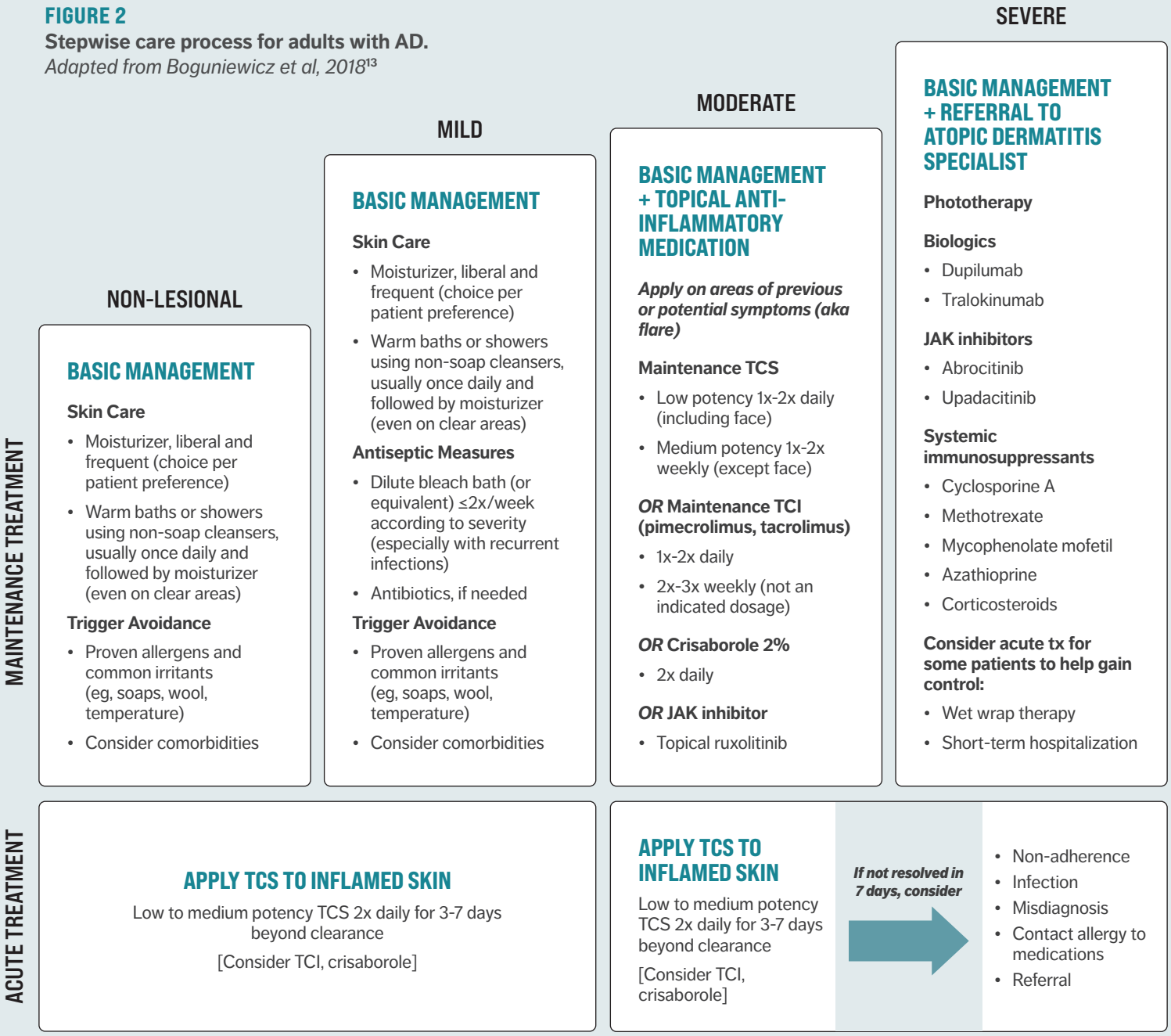
FIGURE 2
Molecules involved in altered JAK/STAT signaling through the IL-4 receptor in AD, and the JAK inhibitors that target them.
Adapted from Nakashima et al, 2022[12]

by the FDA to treat AD. Because of this, clinicians and patients have traditionally been wary of using systemic therapies to treat AD.

In recent years, however, as novel treatments have been approved by the FDA to treat AD, the use of systemic therapy has rapidly become more prevalent. For example, analysis of a national claims dataset showed that the number of adult patients with AD in the United States initiating systemic treatment more than quadrupled after dupilumab became the first systemic biologic therapy approved to treat AD in 2017, increasing from 358 patients in 2015-2016 to 1,358 in 2019-2020, with likely many thousands more today.[16] By 2019-2020, 78% of patients with AD receiving systemic treatment were receiving dupilumab monotherapy while another 6% were taking dupilumab in combination with systemic glucocorticoids. Among patients with AD who initiated dupilumab in 2020-2021, 92% had never received a systemic treatment before. Now that additional approved agents are available, and with more potentially on the way, it is likely that the use of systemic treatments for AD will continue to expand.

Because safe and effective systemic therapies for AD are relatively new, it is important to educate patients about these treatments' benefits, their route of administration, and their adverse effect profiles (see Table 1).[15,17] Surveys of patients with moderate-to-severe AD reveal that, when considering the attributes of AD therapies, they prioritize risk of malignancy, mode of administration (daily, oral medications are often preferred over

FIGURE 2
Stepwise care process for adults with AD.
Adapted from Boguniewicz et al, 2018[13]



biweekly injectables), the probability of clear skin at 16 weeks, and time to itch relief, in order of descending importance.[18] Patients also prioritize avoiding serious infections and venous thromboembolism, and are willing to accept some increase in the risk of adverse effects in exchange for improved efficacy and a preferred mode of administration.

When discussing systemic therapies with patients, it may be helpful to keep in mind that they value being informed about potential next steps in the treatment pathway.[19] Knowing that multiple options are available if the first medication they try does not work can feel reassuring. In addition, some patients voice frustration with the step-up approach to therapy if it prevents them from accessing novel, effective therapies in a timely fashion. Thus, conversations about systemic treatment options should cover all of these topics.

SYSTEMIC AGENTS APPROVED TO TREAT AD

Currently, two biologics and two JAK inhibitors are approved to treat AD. The first of these agents, dupilumab,

TABLE 1
Currently Approved Non-traditional Systemic Therapies for AD[15,17]

Class	Agent	Time to Response	Monitoring Requirements	Notable Adverse Effects
IL-4Ra inhibitor	Dupilumab	4-6 weeks	None	Conjunctivitis, upper respiratory infections, arthralgia, injection site reactions
IL-13 inhibitor	Tralokinumab	4-6 weeks	None	Upper respiratory tract infections, conjunctivitis, injection site reactions
JAK inhibitor	Abrocitinib	1-2 weeks	Complete blood count, lipid profile	Nasopharyngitis, nausea, headache, infections including herpes simplex and urinary tract infections, creatine kinase elevation, dizziness, fatigue, acne, mortality, thrombosis, malignancy, major adverse cardiovascular events
	Upadacitinib	1-2 weeks	Complete blood count, lipid profile, liver profile	Infections including upper respiratory tract and herpes virus infections, acne, headache, anemia and neutropenia, creatine kinase elevation, increase in LDL cholesterol, nausea and abdominal pain, mortality, thrombosis, malignancy, major adverse cardiovascular events

was approved in 2017. Tralokinumab, another biologic, was approved in 2021, while two JAK inhibitors—abrocitinib and upadacitinib—were approved in 2022. With this recent spate of approvals, clinicians and patients are still learning about how these therapies best fit into the overall AD treatment landscape. It is important for all dermatology specialists to become familiar with these newer agents so they can use them to optimize patients' treatment plans. Despite the 2014 American Academy of Dermatology guidelines recommending against the sustained use of systemic steroids, one study found that in 2018, nearly one-quarter of patients with severe AD continued to receive these medications, emphasizing the need to better integrate newer, safer therapies into the treatment armamentarium.[20]

Dupilumab

Dupilumab binds to the subunit of the IL-4 receptor, or IL-4Ra.[8,10] This inhibits the activity of both IL-4 and IL-13, preventing downstream signaling in the Th2 pathway. Numerous phase 3 clinical trials have shown that dupilumab monotherapy is safe and efficacious for treating moderate-to-severe AD. Dupilumab is currently approved to treat adult and pediatric patients as young as 6 months of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when use of those therapies are not advisable.[8] One of the most common adverse effects associated with dupilumab is conjunctivitis. In a real-world study of a national German registry of patients with AD, 23% of those who took dupilumab for 6 months developed conjunctivitis.[21] Upper respiratory infections and arthralgia are also common among patients taking dupilumab.[15]

While effective for many patients with AD, dupilumab unfortunately does not adequately control symptoms for everyone. In the German registry study, for example, only 52% of patients who were treated with dupilumab achieved a 75% improvement in their Eczema Area and Severity Index (EASI-75) at 6 months, and only 32% achieved EASI-90.[21] Twelve percent of patients did not show any clinically meaningful response to dupilumab. These findings are consistent with another real-world study conducted at the University of California, Irvine, in which only 30% of patients taking dupilumab experienced complete clearance of skin lesions.[22] In addition, in an analysis of U.S. prescription claims for patients with AD, 23% of patients taking dupilumab discontinued the medication within a year.[23] In real-world studies, the most common reasons that patients discontinue dupilumab are lack of effectiveness, followed by ophthalmologic side effects such as conjunctivitis.[22]

Tralokinumab

Like dupilumab, tralokinumab is a biologic that targets the Th2 pathway, but whereas dupilumab blocks the activity of IL-4Ra, tralokinumab blocks the activity of IL-13.[8,10]

Tralokinumab is currently approved to treat patients ≥18 years of age with moderate-to-severe AD that is not well controlled with topical therapies or who cannot use topical therapies.[24] Multiple randomized controlled trials have demonstrated that tralokinumab improves AD symptoms and quality of life, especially by ameliorating itchiness and the sleep problems caused by itchiness.[25] In the two pivotal phase 3 trials for tralokinumab, 16-22% of patients with moderate-to-severe AD achieved clear or nearly clear skin at week 16 (vs. 7-11% for placebo), and 25-33% achieved EASI-75 (vs. 11-13% for placebo). These trials also showed that tralokinumab reduced the need for systemic treatment of skin infections by decreasing colonization by *Staphylococcus aureus.* In addition, treatment with tralokinumab reduced the frequency of eczema herpeticum. Like dupilumab, tralokinumab is associated with conjunctivitis and upper respiratory infections.

JAK/STAT INHIBITORS

JAK/STAT signaling is a master regulator of immune function. Thus, treatment with JAK inhibitors blocks multiple proinflammatory cytokines involved in the development of AD.[6] As a result, in clinical trials of JAK inhibitors, some patients with AD have achieved EASI-100, a level of response not previously observed for AD therapies. In January 2022, the FDA approved two JAK inhibitors—abrocitinib and upadacitinib—for the treatment of moderate-to-severe AD that is refractory to treatment with biologics or other systemic therapies, or to treat patients with moderate-to-severe AD who cannot take other systemic therapies.

Abrocitinib

Abrocitinib is currently approved for use in patients with AD ≥18 years of age.[6] In multiple phase 3 trials, up to 50% of patients who received abrocitinib achieved clear/nearly clear skin at week 12, and 50-72% achieved EASI-75. Itching improved by 2 weeks and, in some cases, as soon as a day or two after treatment was initiated. A 48-week extension trial indicated that these improvements in skin clearance and itch persisted over time.

Upadacitinib

Upadacitinib is currently approved for use in patients with AD ≥12 years of age.[6] In phase 3 trials, as many as 60% of patients who received upadacitinib achieved clear/almost clear skin by 16 weeks, and 80% of patients achieved EASI-75. As with abrocitinib, improvement with upadacitinib was rapid, with significant reduction in itch being evident as early as 1 week after initiation, and improvement in skin clearance observed as early as week 2.

For both JAK inhibitors, common adverse effects include nausea, headache, acne, creatine kinase elevation, and herpes infections.15 Treatment with abrocitinib requires a clinician to monitor a patient's complete blood count and lipid profile. Treatment with upadacitinib requires a clinician to monitor these factors, along with a patient's liver profile.

In addition, both abrocitinib and upadacitinib have black box warnings for increased risk of serious infections, death, cancer, major cardiovascular events, and blood clots (see Figure 4). This warning is primarily based on postmarketing safety data collected for the JAK inhibitor tofacitinib, which is associated with a possible elevation in the incidence of these rare adverse events among patients with rheumatoid arthritis.[26] When evaluating the risk that JAK inhibitors pose for patients with AD, it is important to keep in mind several considerations. First, tofacitinib is a pan-JAK inhibitor: Instead of just inhibiting one JAK family protein, it has multiple targets. Tofacitinib shows the greatest selectivity for JAK1 and JAK3, but it also exhibits some activity against the JAK2 and TYK2 proteins.[27] It is unclear to what extent tofacitinib's safety profile might differ from that of abrocitinib and upadacitinib, which are both selective JAK1 inhibitors. Second, patients with AD tend to be younger than patients with rheumatoid arthritis, to take different concomitant medications, and to have different comorbidities. All of these factors may affect the safety profile of JAK inhibitors in a given patient population. In short, to better understand the safety profile of abrocitinib and upadacitinib for patients with AD, additional long-term safety data must be collected for these specific agents for this specific indication.

SELECTING A SYSTEMIC AD THERAPY

When selecting a systemic therapy for a patient with AD, it is important to remember that JAK inhibitors are indicated for patients with moderate-to-severe AD who do not respond to available biologics or who cannot take them. In clinical trials, ≤40% of patients taking dupilumab or tralokinumab were able to achieve clear or almost clear skin, even if they used topical corticosteroids concurrently.[6] For patients who fail to adequately respond to the biologics, JAK inhibitors may bring relief. In a phase 3 trial, up to 80% of patients who did not respond to dupilumab were able to achieve EASI-75 after 12 weeks of abrocitinib therapy.[28] JAK inhibitors, which have an oral

route of administration, may also be a good option for the 25% of adults who are afraid of needles.[29]

In addition, JAK inhibitors rapidly improve AD symptoms, so they may be appropriate for patients who are in desperate need of relief.[11,30] For example, in a 26-week phase 3 trial comparing abrocitinib to dupilumab, by week 2, 48% of patients taking abrocitinib had achieved a ≥4 point improvement in itch vs. only 26% of patients taking dupilumab; by week 4, 29% of patients on abrocitinib had achieved EASI-90 vs. only 15% of patients on dupilumab.[30] These differences in efficacy narrowed over time. By week 26, 68% of patients taking abrocitinib and 63% of patients taking dupilumab had achieved a ≥4 point improvement in itch, and 55% of patients taking abrocitinib and 48% of patients taking dupilumab had achieved EASI-90. However, some patients—especially those who are unable to sleep or otherwise function because of their symptoms—may benefit from the more rapid action of the JAK inhibitors.

A patient's insurance coverage may also be a significant factor when selecting a systemic therapy. Some insurance carriers may require a patient to try an older, less-expensive therapy before initiating a newer, more expensive option.[31] For instance, in a recent survey of prescriber requirements for dupilumab, many insurance plans required patients with AD to first fail treatment with a topical steroid and a calcineurin inhibitor.[32] One plan required patients to fail five prior treatments: two topical steroids, one calcineurin inhibitor, phototherapy, and one traditional systemic agent. Many insurance carriers also require certain clinical criteria to be met. For example, in order to cover dupilumab therapy, an insurance carrier may require that a patient has particular symptoms (eg, erythema, edema, lichenification), that ≥10% of their body surface area is affected, that symptoms have been present for ≥3 years, or that a patient has an Investigator's Global Assessment score of 3 or 4 (ie, severe disease).[32] In some cases, an insurance carrier may cover one of the newer therapies, but the copay and out-of-pocket costs associated with the treatment may still be prohibitive for a patient.

Selecting a systemic therapy for AD is a prime opportunity to engage patients in shared decision making. Although the rapid onset and oral mode of administration of JAK inhibitors may be attractive to some patients, others may find their safety profile—including the possible risk of serious infections, venous thromboembolism, and malignancy—to be

FIGURE 4

Black Box Warnings: A Primer

What is a black box warning?

A black box warning, or boxed warning, is the highest safety-related warning that the FDA can issue for medications. Currently, more than 400 different medications have black box warnings, including nonsteroidal anti-inflammatory drugs, opioids, oral contraceptives, antipsychotics, antidepressants, antiplatelet agents, some antibiotics, and a diverse array of other agents.[48,49] In dermatology, common medications with black box warnings include cyclosporine, methotrexate, mycophenolate mofetil, pimecrolimus, tacrolimus, ruxolitinib cream, abrocitinib, and upadacitinib.[26]

Why are black box warnings necessary?

These warnings, prominent at the top of a medication's package insert, are also listed in the Physician's Desk Reference, on the FDA's website, and on the websites of drug manufacturers. They are intended to draw prescribers and consumers' attention to a drug's major risks.[50]

What do they mean?

Typically, black box warnings are issued in response to postmarket safety concerns identified through the FDA's Adverse Event Reporting System by its Office of Surveillance and Epidemiology.[50] The most common type of black box warning is about potentially serious adverse events. Black box warnings can also be issued regarding dosing, monitoring requirements, patients who should not take a medication, potential drug-drug interactions, or mandatory prescribing restrictions.

What do patients need to know about them?

Sharing the information in black box warnings with patients is an important component of the shared decision-making process.[26] It can be helpful to follow the STEPS approach when discussing whether a medication with a black box warning is an appropriate treatment option. In this approach, patients and providers evaluate whether an agent's **s**afety (including the black box warning), **t**olerability, **e**ffectiveness, **p**rice (including for monitoring), and **s**implicity (in terms of the overall treatment plan) is acceptable, especially in relation to other potential therapies.[50] When discussing black box warnings with patients, it is important to put the safety information into context. For example, patients will want to know how common a potential serious adverse effect is.

unacceptable. In addition, traditional systemic agents such as corticosteroids are likely to continue to play an important role in the treatment of AD.[33] For example, corticosteroids may be combined with biologics to improve response or they may be used if a patient does not adequately respond to one or more of the newer agents.

EMERGING SYSTEMIC AGENTS

The novel agents just described herald the beginning of a new era in AD treatment. Many additional AD therapies in late-stage development may further accelerate progress and provide additional options for patients. The novel mechanisms of action of some of these agents might make them attractive for patients whose symptoms are not adequately controlled by existing therapies. Here we discuss the most up-to-date clinical findings for some of the most promising emerging systemic agents.

Lebrikizumab

Lebrikizumab is an antibody that binds to IL-13 via a different non-receptor-binding domain than that used by tralokinumab.[8] Lebrikizumab works by preventing the downstream Th2 signaling that drives AD symptoms. In two phase 3 trials conducted in patients with moderate-to-severe AD, 33-43% of patients who received lebrikizumab achieved clear or almost clear skin at 16 weeks (vs. only 11-13% for placebo) and 52-59% achieved an EASI-75 response (vs. only 16-18% for placebo).[34] Measures of itch and sleep disturbance also improved in patients taking lebrikizumab. In an extension trial, patients who had responded to lebrikizumab injections every 2 weeks were randomized to continue this regimen, receive lebrikizumab injections every 4 weeks, or receive placebo injections every 2 weeks.[35] Among patients who continued to receive lebrikizumab, 71-77% maintained clear or almost clear skin at 52 weeks, whereas only 48% of those who received placebo did so. Most adverse events associated with lebrikizumab, including conjunctivitis, were mild or moderate and did not lead to trial discontinuation. A phase 3 trial is now underway to test lebrikizumab in combination with topical corticosteroids.[8]

Nemolizumab

Nemolizumab is an antibody that binds the receptor of IL-31, the Th2 cytokine that drives itch—and thus some of the consequences of AD that most trouble patients, including sleep deprivation.[8,36] In a 16-week phase 3 trial conducted among patients with AD, the median visual analog score for pruritis decreased 43% for patients who received nemolizumab and topical agents vs. only 21% for those who received placebo and topical agents.[37] The mean decrease in EASI scores was 46% for the nemolizumab group and 33% for the placebo group, a difference that was not statistically significant. However, in a 68-week extension trial, patients who continued to receive nemolizumab displayed continuous improvement, eventually achieving a 66% decrease in pruritus and a 78% decrease in EASI scores (in this extension study, there was no comparator group for patients taking placebo).[38] These clinical improvements were accompanied by quality-of-life improvements, including those associated with sleep, interpersonal relationships, and the ability to conduct social or work activities.[39] Adverse events were mostly mild or moderate in severity, although roughly one-quarter of patients taking nemolizumab developed rashes with mild pruritus within 3 months. In the initial 16-week trial, treatment-related adverse events that were bothersome enough to result in discontinuation included new or worsening AD, Meniere's disease, alopecia, and peripheral edema.[37] In addition, the incidence of injection-related reactions was 8% for nemolizumab vs. only 3% for placebo.

Baricitinib

Baricitinib is a first-generation oral selective JAK1/2 inhibitor currently being reviewed by the FDA for the treatment of AD.[6] It has been tested in seven phase 3 trials that have shown that 14-31% of patients taking baricitinib achieve clear/nearly clear skin, a significantly higher rate than for placebo. However, a recent systematic review and meta-analysis found that 4 mg baricitinib **daily** was slightly less effective than 600/300 mg dupilumab **every 2 weeks**.[40] As with other JAK inhibitors, improvements in itch can occur as quickly as 1-2 days after a patient initiates treatment with baricitinib. The most common adverse events noted in clinical trials have been nasopharyngitis and headache.[41] Currently, a 68-week extension study is investigating the long-term efficacy of baricitinib therapy in patients with AD. The FDA's review of this agent has been delayed due to an ongoing assessment of JAK inhibitors for all indications (see the previous discussion of the black box warning for JAK inhibitors).[42]

Recently, results from a real-life study of baricitinib were reported for 12 patients with moderate-to-severe AD in Europe, where baricitinib was approved for this indication in 2020.[43] By the end of the 3-month study, 10 of the 12 patients had drastically reduced their use of topical steroids, 100% had achieved EASI-50, and 90% had achieved EASI-75. Mean reduction in itch was 66%, and mean reduction in insomnia was 86%. The gains were found to be greater for patients without previous use of dupilumab, but even patients with use of this prior therapy showed improvement. Time will tell what the future role of baricitinib is in the U.S. treatment landscape for AD.

"Given the limitations of available topical agents, a critical need exists for topical agents with a more favorable safety profile. Fortunately, several novel topical therapies for AD have recently been approved or are in late-stage development."

Orismilast

Orismilast is a second-generation oral phosphodiesterase-4 inhibitor (PDE4) that has received a Fast Track designation from the FDA for the treatment of moderate-to-severe AD. Inhibition of PDE4 modulates a broad range of pro-inflammatory cytokines involved in AD and other chronic inflammatory skin diseases. Some of these cytokines (eg, IL-4, IL-5, IL-13) are involved in the Th2 immune response, whereas others are involved in the Th1 and Th17 immune responses, which have also been implicated in the development of AD.[44] Currently, a phase 2b study is underway to identify the appropriate dose regimen for future phase 3 trials investigating the use of orismilast to treat AD.

NEW AND EMERGING TOPICAL THERAPIES FOR AD

Thanks to their ability to reduce skin inflammation and itch, topical corticosteroids have been a mainstay of AD treatment since the 1950s.[4] However, inappropriate long-term use of these agents can cause skin atrophy, telangiectasis, striae, perioral dermatitis, and acne. In rare cases, systemic absorption can suppress the hypothalamic-pituitary-adrenal axis, suppressing growth in children and reducing bone density in children and adults. It should be noted that the majority of these side effects only occur with long-term use of moderate to high potency topical corticosteroids. Unfortunately, because of these potential adverse effects, many patients are reluctant to use topical corticosteroids as prescribed. Topical calcineurin inhibitors are considered a second-line option for patients who cannot tolerate topical corticosteroids or who do not wish to use them. However, calcineurin inhibitors can cause skin burning and irritation, and in 2006, the FDA added a black box warning indicating that they may increase long-term cancer risk (though multiple studies have not shown such a risk). Given the limitations of available topical agents, a critical need exists for topical agents with a more favorable safety profile. Fortunately, several novel topical therapies for AD have recently been approved or are in late-stage development.

Ruxolitinib

Ruxolitinib cream is a topical JAK inhibitor approved for short-term and non-continuous treatment of mild-to-moderate AD.[7] In phase 3 clinical trials for this agent, 39-54% of patients with mild-to-moderate AD who used ruxolitinib achieved clear or nearly clear skin at 8 weeks compared to only 8-15% for placebo.[4] Ruxolitinib also improved itch as soon as day 2 of treatment. It was well tolerated, and the most common adverse effect was nasopharyngitis.

Delgocitinib

Delgocitinib is another topical JAK inhibitor. Though not yet approved in the United States, delgocitinib ointment is approved to treat AD in Japan. In the pivotal phase 3 trial for delgocitinib that was conducted in patients ≥12 years of age, 27% of those using delgocitinib achieved EASI-75 at 4 weeks vs. only 6% of those using placebo.[4]

The most common adverse events included nasopharyngitis, contact dermatitis, application site folliculitis, and acne. A 52-week extension trial did not reveal any significant long-term adverse effects associated with extended use of delgocitinib. A phase 3 trial has also been conducted in children with AD, with similar results: 37% of those using delgocitinib achieved EASI-75 (vs. 4% of those taking placebo), and systemic exposure was low, indicating that delgocitinib is unlikely to pose a risk of systemic adverse effects such as infections. A cream formulation of delgocitinib is also currently under investigation; it has received Fast Track designation from the FDA for the treatment of chronic hand eczema.[45]

Tapinarof

Tapinarof is the first topical aryl hydrocarbon receptor (AHR)-modulating agent used as therapy for the treatment of AD. The FDA approved its use to treat psoriasis, and tapinarof is now being investigated for the treatment of AD. By activating AHR, tapinarof inhibits the IL-4/IL-13-mediated signaling key to AD pathogenesis.[4] Preliminary results from a phase 3 trial of tapinarof cream conducted among adult and pediatric patients with AD showed that roughly half of patients achieved clear or almost clear skin, a significantly higher rate than placebo.[46] Tapinarof cream was found to be well tolerated, with only mild-to-moderate adverse events and a low rate of discontinuation due to adverse events. Results from a parallel phase 3 trial are expected in the near future.

Currently, American Academy of Dermatology guidelines strongly recommend the following topical treatments for managing AD in adults: topical corticosteroids (for AD of any severity level), ruxolitinib cream (for mild-to-moderate AD), and crisaborole (a PDE-4 inhibitor; for mild-to-moderate AD).[47] The role that other emerging topical agents discussed in this section might play in AD therapy remains unclear, though they will most likely be used to manage mild-to-moderate AD or as adjuncts to systemic therapies for patients with moderate-to-severe AD. To date, these new and emerging topical therapies have only been tested in short-term trials. In addition, no head-to-head comparisons of these agents against topical corticosteroids or calcineurin inhibitors have been performed, either as short-term or maintenance therapy.[7] Additional data from these types of studies should clarify how these topical medications can best be deployed to manage AD. Real-world studies will also be important in determining how cost-effective, well-tolerated, and safe these agents are.

CONCLUSION

The recent approval of multiple novel agents for the treatment of AD, with more therapies on the way, makes this an exciting time for patients with AD and their healthcare providers. As more real-world studies, long-term trial data, and findings from head-to-head trials comparing treatment options emerge for these new therapies, we will be able to better understand how these agents can be used alongside conventional systemic agents and topical therapies to optimize patients' treatment plans. In the meantime, providers can ensure that they are up to date on available clinical information so they are able to quickly adopt new therapies, explain their benefits and limitations to patients, and work with patients to create effective, individualized treatment plans. It is critical for clinicians to become comfortable with key data for these agents, as research shows that patients are more motivated to adhere to their treatment plans when they understand the underlying principles.[19] By staying abreast of the most recent information about novel and emerging agents for AD, dermatology specialists can help usher in a new era of treatment for their patients.

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My Most Memorable Patient

by Keischa Cash, DNP, APRN, DCNP, FNP-BC

I vividly remember the day that Paul walked into my exam room. He was wearing a hoodie and long pants, his face covered almost completely by his oversized outfit. He sat down in the exam room and, as with all of my new patients, I started by asking him, "Why are you here?"

That's when Paul slipped off his hood so we could see his face, and I got the answer to my question without Paul needing to say a word. I found myself staring at an excoriated face with weeping and crusted lesions surrounding the patient's eyes and overtaking his cheeks. Paul was clearly in extreme discomfort, and you could see the despair in his red, watery eyes.

As we started talking with Paul about his medical history and recent symptoms, he slowly peeled back more layers of clothing, and the story of his suffering started to become clearer. He was covered with eczematous patches, plaques, excoriations, and crusted lesions nearly from head to toe. His clothing stuck to him uncomfortably as he peeled it loose for us layer by layer so that we could perform a full skin examination.

Not surprisingly, Paul told us that he couldn't sleep at night because he was so itchy. He had to change his bed linens most mornings after waking up with blood on his sheets and pillows due to all of his overnight scratching. Paul also told us about his concomitant allergies, which had contributed to his runny nose, watery eyes, and sinus symptoms that were visibly apparent. He said there was nothing that seemed to relieve his symptoms.

Approximately 2 years before we met, Paul had been enrolled in a clinical trial for dupilumab but was unfortunately one of the participants in the placebo arm. He said he saw how other patients in the trial were dramatically improving, which quickly told him he was not receiving the active drug. While he was in the placebo arm of the trial, Paul was only allowed to use adjunctive moisturizers and topical steroids, which did little to improve his condition.

Paul's first question for us once our physical exam was done and we concurred with his previous diagnosis of severe atopic dermatitis (AD) was whether he would be able to initiate use of dupilumab now that it had been approved by the U.S. Food and Drug Administration. Because he had seen how dramatically it had helped others with severe AD, Paul was

AUTHOR:

Keischa Cash, DNP, APRN, DCNP, FNP-BC, is a Dermatology Nurse Practitioner at DNP Derm LLC in Tampa, FL

desperate to try it himself. At the time, I had no personal experience with dupilumab, although I had heard and read plenty about it. Being a new medication, I was wary, but because Paul was such an informed patient and had such a severe baseline level of disease, we determined that he was an appropriate candidate for my first foray into dupilumab. Not surprisingly, there was one potential problem – because the drug had only been approved for 2 months at this time, we knew it would not be easy to get the medication approved by Paul's insurance company without documented proof that he had tried and failed more conservative measures.

Fortunately, Paul had commercial insurance, so we thought there might be a chance he would be able to get dupilumab approved without jumping through too many hoops. Consequently, we had him enroll in the manufacturer's patient assistance program to lessen the potential financial burden. It took time—nearly 2 months—before Paul's insurer signed off on dupilumab. In the meantime, Paul's disease had finally showed minor signs of improvement thanks to adjustments to his skincare regimen (we introduced very high potency topical steroids, topical and oral antibiotics, and calcineurin inhibitors).

When we received official notification of insurance approval for dupilumab, it was as if a giant balloon of hope had tethered itself to Paul's spirit. He finally saw light at the end of the tunnel. When we first brought him into the office to demonstrate how to inject dupilumab and answer any other questions he might have. Paul still had patches and plaques all over his body, along with severe itching. His sleep was also still significantly impaired.

We scheduled an initial follow-up for 2 weeks after his first injection. I was both nervous and excited to see how dupilumab would impact my first patient trying this new biologic therapy. Paul walked into our office looking like a different person. He had lost the hoodie, he was in shorts, and his face was uncovered. He said was feeling much better overall, his itching had dissipated significantly, and the skin lesions on his trunk and face were not nearly as prominent as before. Paul even mentioned that his allergies seemed to be improving, which was an unexpected benefit.

While this issue of *Dermatology Nurse Practice* details how dupilumab doesn't work wonders for every patient with AD and how we have other options now at our disposal, I have seen many patients like Paul for whom it has been a life changer. As healthcare professionals, we have all come across new medications that are supposedly going to change the lives of our patients, only to fall well short of accomplishing that feat in real life. Accordingly, many times I look at these new "game changers" with skepticism until I see how they truly work in my patients. Paul isn't my only patient with severe AD whose life has been profoundly improved by dupilumab, but it's his story I think about every time I prescribe the medication to a new patient with AD. I haven't seen Paul in several years—I left the practice where we met and moved several hours away—so I often wonder how he's doing and if dupilumab is still working for him 5 years after we started down this road together.

It is crucial as healthcare providers, and especially nurses and nurse practitioners, that we should not be afraid of the difficult path that requires us to advocate for our patients, especially those whose quality of life is so profoundly impacted by their disease. Especially in dermatology, there are going to be patients like Paul who are "the worst I've ever seen." Sometimes, we can help them. Sometimes, despite our best efforts, we can't. But it's the try that makes all the difference.

My Most Memorable Patient

by Patricia Delgado, DNP, AGPCNP, DCNP

About 18 months ago, I was working in my usual dermatology clinic outside Tampa, FL, at one of our regional branches located in a part of town made up predominantly of individuals from lower socioeconomic status households with a large number of uninsured/underinsured patients.

I distinctly remember the moment I met Steve when he was called into the exam room by my medical assistant. A tall Black man, Steve's tattered shorts and t-shirt seemed to sag on him as if they were dangling from a clothes hanger. It was fairly evident that he had lost considerable weight at some point recently since these clothes didn't come close to fitting him. In addition, every nook of Steve's visible skin was excoriated and oozing. I vividly remember that we had to wrap Steve's legs in dressings to prevent him from dripping onto the floor.

AUTHOR:

Patricia Delgado, DNP, AGPCNP, DCNP, is the Founder and CEO of Sunrise Skin and Wellness LLC, in St. Petersburg, FL, as well as an Adjunct Professor at the University of Central Florida in Orlando, FL

Steve's initial appearance in my office concerned me so much that my first step was to perform an urgent, comprehensive physical exam. His left lower leg was extremely swollen, almost twice as big as his right leg. My first inclination was to order an ultrasound to rule out deep vein thrombosis, but upon further discussion and examination, it was clear that Steve's scratching had introduced bacteria into the open skin on his leg, resulting in cellulitis. In case there were any other contributory underlying medical conditions, I also ordered a full panel of labs, and even included an HIV test to rule out another possibility that might be causing Steve's significant weight loss and widespread skin lesions. Steve was polite but quiet when I asked him about his symptoms, not able to provide much information to me except that he had a lengthy history of AD and that his skin would not stop itching.

While we waited for his lab results to come in, I started Steve on a round of antibiotics, a first- and second-generation antihistamine, and a highly potent topical corticosteroid. I explained to him the dangers of constant scratching and emphasized the importance of moisturizing to combat his persistent itch. Before he left, I gave Steve a trade size sprayable ointment and instructed him to use it every time he felt the urge to scratch. I also recommended that he avoid hot showers and utilize fragrance-free soaps.

Our initial follow-up was set for 2 weeks later to review Steve's lab results and gauge any improvement in his symptoms. Because his skin issues were so severe at our initial meeting, I instructed Steve to go immediately to the emergency room if the swelling in his leg got worse or if he developed a fever (fortunately, this did not happen). It was obvious that he had atopic dermatitis (AD), and a pretty severe case at that, but I suspected that there might be something more going on.

Two weeks later, Steve was back in our office looking and feeling much better. His lab results were normal with the exception of a mild elevation in his white blood cell count. The swelling in his left leg had all but disappeared. His skin was no longer oozing, and while there were still some excoriations present, there were no new lesions. Indeed, it did seem like it was AD and AD alone that was the cause of Steve's problems. At this visit, Steve quietly told me that while he looked and felt better, there were still times every day where his itch was almost unbearable.

Now that we had ruled out other underlying factors that might have been affecting Steve's immune system, it was time to start trying to get his disease under long-term control. Knowing that we would not be able to keep him on a high-potency topical corticosteroid long term, we talked about transitioning to dupilumab as a next step. Unfortunately, Steve had about the most limiting insurance coverage I had ever seen (and yes, like all of you, I have seen some really frightening insurance plans over the years) so I told him it was likely that the process would take weeks, if not months, for dupilumab to be approved. Nonetheless, I assured him that we would fight tooth and nail for him so that his AD would never get as bad as it did in the period before he first came to our practice. In the meantime, I fortunately had several drug samples to provide him with on a temporary basis.

At his next follow-up 2 weeks later, there was still no word from Steve's insurance company, so we provided him with another sample of dupilumab. The improvement in just the 1 month since I met Steve was remarkable. The old excoriations all over his skin were now beginning to heal, and the widespread lichenification was beginning to disappear. Steve told me—quietly as usual—that he was happier than he had been in years. For this visit, he even dressed up in clothes that fit him and brought a friend along to show off our team as "the people who changed my life."

There are a few things that make Steve one of those patients who will always make an imprint on my life:

1. Steve was among the most downtrodden patients I have ever seen due to AD. When we first met, his disease had completely overwhelmed him. His baggy clothes were merely a visible indication of how much he had given up on life. He had lost his appetite and consequently shed 20 pounds in the 9 months before he came to our office simply because of his AD.
2. I was so sure *something* more must be going on in an individual with skin issues as bad as Steve's were, but instead it was merely a stark reminder of the devastating impact that AD can have for some individuals.
3. Steve's turnaround—both physically and psychologically—in such a short amount of time was a great reminder of the powerful impact we can have on our patients. The arrival of new and more powerful systemic therapies has truly been a game changer for our patients.

As promised, our practice continued to fight for Steve to get insurance approval for dupilumab, which finally happened about 8 weeks after we filed the initial paperwork. This allowed us to extend the interval between Steve's visits. After about 6 months since the insurance approval came through, Steve's skin was completely clear, and his clothes fit perfectly.

Autoimmune diseases like AD typically have effects that are more than skin deep. They involve so many aspects of a person's well-being and can totally destroy someone's life. As dermatology healthcare providers, we have the responsibility and honor of being able to meet people like Steve who so desperately need our assistance to help turn their lives completely around.

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My Most Memorable Patient

by Noreen Heer Nicol, PhD, RN, FNP, NEA-BC

We grow up hearing in the news about "cures" in healthcare. That unfortunately isn't the case for many of our patients with skin disease, especially those with chronic conditions. For these individuals, it's not about "cure" but rather "control." And achieving that control means empowering our patients through shared decision making to make choices that allow for comprehensive management of their disease(s).

Callie is one of those patients of mine who helped reinforce for me the need to build a strong partnership. She is now a 19-year-old female who has been managed within our practice for control of her atopic dermatitis (AD) and asthma for more than 7 years.

We first met Callie when she was 12 years old. She came to our practice along with her mother and had a visibly aggressive, erythematous, eczematous rash covering much of her face, flexural areas of the neck, chest, palms, and flexural areas of the knees (estimated 40% body surface area [BSA]). She also had severe itchiness that kept her awake at night, resulting in poor sleep that significantly impacted her schoolwork, social life, and extracurricular activities.

Callie was one of those unfortunate adolescents who had been through the healthcare wringer most of her life. She was diagnosed with AD as an infant, with the condition waxing and waning throughout her childhood. When we met, Callie's disease was flaring worse than it had in years (every 4-6 weeks), which was contributing to some natural social anxiety in school. Callie was one of those children to experience the "atopic march," having infantile AD, then seasonal allergies beginning at age 5, followed by asthma beginning at age 7 (treated with an albuterol inhaler, as needed). She lived at home with her parents in a pet-free environment.

Over the years, Callie had seen multiple pediatricians, dermatologists, and allergists. She had been to the emergency room at least 4 times during the worst of her disease flares. Not surprisingly, everywhere she went, there were a different series of suggestions from healthcare providers, typically delivered in short, 15-minute appointments where Callie and her mother were hustled in and out without any real education about why specific strategies were being

AUTHOR:

Noreen H. Nicol, PhD, RN, FNP, NEA-BC, is Associate Professor Emerita at the University of Colorado School of Nursing in Aurora, CO

suggested. It was "healthcare by decree"—we tell you what we think you should do, and you either follow our suggestions or you don't. End of discussion.

Unfortunately, this is a story I hear too often in clinical practice. Given the familiar tale and Callie's current level of disease, we talked to her and her mom about enrolling for 1 week in the special AD Day Program that we host at National Jewish Health in Denver, CO.[1] This unique program allows patients and caregivers to interact with members of our multidisciplinary team from 8 am-5 pm (and sometimes overnight, if necessary) in a controlled environment. During this outpatient program, there are nurse-supervised skin care sessions each day, along with opportunities for families to interact with others who are being impacted by AD to exchange ideas and provide support. Each day a patient is enrolled in the program, there are also clinical review meetings between one or more providers and the patient/caregiver. Some patients come for 1-2 days, while some, like Callie, come for a full week or more. On rare occasions, we will even admit a patient to the hospital for round-the-clock evaluation or overnight studies such as pH probes or a sleep evaluation. A Plan of Care conference at the end of the patient's time with us incorporates input from all involved parties and leads to a written AD Care Plan.[2]

The goal of the program is to formulate personalized management strategies for patients with moderate-to-severe AD based on individual and disease-related factors. The stepwise treatment algorithm we develop with each patient allows them to move up and down this ladder and choose when to modify treatment following their outlined AD care plan.

Spending extended 1-on-1 time with Callie and her family allowed me to get additional insight into Callie's history. I learned that the recommendations we were discussing in our AD Care Plan were quite different than those suggested by some of her previous providers, and she had rarely had a chance to ask any questions about why certain recommendations had been made in the past.

Here are a few of the questions Callie and her family asked me, along with my responses, that perhaps will give you some insight into some of the things on the minds of patients and families like this:

We've heard a lot of mixed messages around recommendations regarding bathing or water avoidance for patients with severe AD. What are your recommendations around bathing?

NN: *Bathing is now suggested for all patients with AD as part of routine maintenance. While there is no clear standard relative to the frequency or duration of appropriate bathing, many experts recommend a daily, warm soaking bath for 10-15 minutes.[3,4] As a patient's skin improves, showers may be used instead of baths. Limited use of skin cleansers that are neutral to low pH, hypoallergenic, and fragrance free is recommended. These cleansers are thought to remove bacteria, viruses, irritants, and allergens. The addition of oils and emollients to bath water is not recommended at this time. After bathing, the patient should pat their skin dry and avoid rubbing with towels. Moisturizers or medications, when used, should be applied within 3 minutes of patting the skin dry to improve hydration.*

> *Callie had been taking infrequent baths and showers, and was not using any specific cleanser. Her medications and moisturizer were rarely applied within 3 minutes of patting herself dry.*

How important is it to choose the correct moisturizer/emollient? Do I need to use moisturizers if my skin appears normal?

NN: *We know that skin in patients with AD is never normal despite how it may look on the surface. Regardless of any additional therapies that are used, a quality moisturizer or emollient should be applied in all patients with AD at least daily. There is strong evidence that the use of a daily moisturizer can reduce disease severity and the need for pharmacologic intervention.[5] While the ingredients and vehicle are important considerations when choosing a moisturizer, it is most critical to choose a moisturizer that the patient likes and will actually use.*

> *Callie had a poor history of using moisturizers, despite having several recommended to her. She instead was only applying topical water-based lotions that were drying instead of moisturizing her skin. After discussion with our team about these issues, Callie was given a short list of our team's recommended moisturizers. Callie chose Vanicream®, a fragrance-free, dye-free, paraben-free moisturizer geared to patients with sensitive skin.*

Since you feel that we have neither been prescribed nor use enough topical treatment, how much do you think we should be using?

NN: *When we met Callie, her current medication regimen included hydrocortisone 1%-2.5% cream (low potency topical corticosteroid [TCS], group 7) for her face twice a day and sometimes triamcinolone 0.1% cream (medium potency TCS, group 4) for her body twice a day. Most clinical guidelines suggest applying 30 g or 1 oz of topical therapy for each total-body application in a standard-sized adult.*[4,6] *Therefore, when applied twice daily (as in Callie's case), the total amount should be 60 g/2 oz per day. The general consensus among providers is that most patients with AD fall far short of this benchmark.*[7]

I find that patients often benefit from a visual demonstration to appreciate the quantity of 1 ounce. Common everyday items that approximate this amount include a travel-sized tube of toothpaste, 4 ketchup packets, 3 coffee creamers, or 2 liquid tablespoons.[7]

> *Callie and her mother admitted that the 8 oz bottle of lotion she used at home had lasted her 1-2 months instead of the 3-4 days that it should have. In addition, the topical steroid was being severely underapplied – it was prescribed in 15-30 g tubes in the past, which Callie and her mother thought were also supposed to last 1-2 months. After our education, Callie was armed with the largest possible jars/tubes of moisturizer and other topicals to ensure she wouldn't quickly run out.*

We've heard some other people talk about wet wrap therapy, but we don't know a lot about it or how it works in patients with AD. What can you tell us about it?

NN: *Wet wrap therapy is used by people with moderate-to-severe AD to relieve inflammation, itching, and burning. These wraps are typically comprised of two layers—an initial layer of warm, damp fabric/clothing or gauze, and a second layer of dry cloth, such as cotton pajamas—and used following a soaking bath and application of appropriate topicals such as corticosteroids or moisturizers. Wet wraps facilitate the removal of scale and increase penetration of topical medications in the stratum corneum. It is important to recognize that wet wrap therapy should only be initiated under the supervision of a healthcare provider and should not be used as part of routine AD maintenance.*[3,8]

> *During her 5-day stay within our AD Day Program, Callie used wet wraps twice a day following baths. She also applied desonide ointment to her face, triamcinolone ointment to affected areas on her body, and moisturizer to unaffected areas of her body. In subsequent years, Callie would continue to use wet wraps during the worst of her disease flares for 2-3 hours as she found them cooling and protective of her skin. Her topical steroids were tapered back slightly at discharge from the 5-day program.*

WHAT CAME NEXT: AGES 13-16

When Callie left our AD Day Program, her skin was almost clear, and her sleep was greatly improved. She felt in much better control of her condition, and while she suffered periodic disease flares for the next several years, these were generally short lived and easily reversed. Callie's psychological health also improved as she worked periodically with our psychosocial team, and she thrived as both a student and a competitive gymnast.

But not everything was perfect. Callie's skin had itched for so long that scratching had become an involuntary habit. We worked with Callie to develop replacement behaviors and relaxation techniques to help overcome this potentially dangerous habit. In addition, while Callie's asthma was generally improved, her asthma was not, and she required increasing dosages/dose frequencies of controller medications.

WHAT CAME NEXT: AGE 17

As she neared high school graduation and enrollment at an out-of-state university, Callie's old anxieties re-emerged. She showed up to our clinic in tears, and we spent a long time talking about her fears related to college life and being away from home. In a nutshell, Callie felt that her daily skin care regimen would not be feasible in the college dorm setting, and she wanted to know if there were any other options for her. Callie was tired of being embarrassed of how she looked (the past 12 months had seen more regular flares of her AD, along with worsening asthma) and was exhausted with her busy schedule.

"I'm not sure that I will have access to a bathtub when I'll need one, and I am so tired of putting on these creams and medications every day," she told me. "My skin can feel so greasy and uncomfortable at times. I just don't know that I can do it for much longer."

Callie is fortunate that the timing of her departure for college coincided with the introduction of multiple systemic biologic therapies. We knew that she was adherent to her topical regimen, and with her more recent regular disease flares along with the upcoming changes in her life, Callie was an appropriate candidate to move to systemic therapy.

I sat down with Callie (she was now old enough to come to our appointments on her own) and talked about some of the options in our current treatment arsenal, including agents that targeted interleukin (IL)-4, IL-13, phosphodiesterase-4, IL-31, and Janus kinase (JAK). Because of Callie's concurrent diagnoses of AD and asthma, I recommended dupilumab, an IL-4/13 inhibitor that is approved for the treatment of both AD and asthma. I was a bit worried about Callie's ability to self-inject herself while she was away at college, but Callie assured me she could handle the responsibilities with support from myself and others in her close circle of support. We also spoke about other systemic options, including daily oral treatments such as JAK inhibitors, if adherence to dupilumab became an issue.

Fortunately, Callie was true to her word, and after two initial injections at our practice before leaving for college, she maintained her biweekly injection regimen at college. Eventually, she was able to move to every 4 week injections. I check in with Callie from time to time, and she seems happy and healthy, with none of the anxiety or social issues that plagued her in adolescence. Of course, it helps that her disease remains well controlled. I'm looking forward to getting a graduation announcement from her in a few years.

While I have been practicing as a nurse practitioner for more than three decades, my education never stops. Patients like Callie remind me to stop, ask questions, and really listen to what I'm being told. While treatments continue to evolve, the importance of basic skin care is as important as ever, the bedrock of care despite other therapies. As we move into more personalization of care, it's only going to get more challenging for all of us to stay on top of what's happening with our patients and intervene quickly when things start going awry. Working with Callie reinforced the critical need for in-depth patient education and ongoing support in the management of chronic diseases such as AD and asthma. Our goal, as always, is to do our best to do what's best for those who seek our care.

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My Most Memorable Patient

by Megan Lewis, MSN, RN, CPNP

Compassion and empathy for individuals struggling with a chronic disease is a unique skill that many nurses possess. In the world of pediatrics, though, that compassion and that empathy typically extends beyond the patient and touches mom, dad, brother, sister, and perhaps others as well. With chronic conditions such as atopic dermatitis (AD), asthma, and food allergy, the whole family can be impacted in various ways, and it's up to us to help figure out how to help as many people as possible.

I met the Maxey family (not their real name) more than 10 years ago as a newly-minted nurse practitioner (NP) starting in my first professional role. At the time, I felt confident in my ability to assess new patients with AD and provide them with appropriate guidance that would put them on the right path to help manage their disease. I knew the current practice guidelines backward and forward, and was well aware of the specifics of "step-up therapy." But as I soon found out—and what my experienced colleagues already knew—is that managing a child with severe AD goes far, far beyond what anyone can learn from a textbook.

I first met the Maxey family's oldest son, Christopher, when the 7-year-old first grader showed up with his parents for help with multiple food allergies. By the time I met him, Christopher's family had learned how to navigate through their day-to-day lives despite Christopher's peanut and tree nut allergies that had emerged in infancy. His newest symptom was mild AD, which resolved after a few weeks of applying hydrocortisone 2.5% to the flexural areas and regular moisturizer use. While I saw Christopher from time to time over the years for minor issues, his condition was generally well controlled and unremarkable.

But then at one of Christopher's regular checkups, his mother told me that she was expecting their second child. Knowing her family history (both parents had a history of asthma and AD), I provided some anticipatory guidance about introducing early food allergens for their soon-to-be newborn.

I first met baby No. 2, William, at approximately 3 months of age after he developed a systemic erythematous rash. William was primarily being breastfed, with supplementation of milk-based formula. As a young infant, he was growing appropriately and gaining weight on a normal schedule. We initially treated William's rash with topical emollients

AUTHOR:

Megan Lewis, MSN, RN, CPNP-PC, is a pediatric nurse practitioner at Children's Hospital of Philadelphia in Philadelphia, PA

> "The frustrations that our families experience at different phases, as well as the unpredictability of their childrens' disease, can be an incredible burden that requires clarity and honesty."

and mild corticosteroids, expecting that he would respond quickly as his older brother did. But that didn't happen. Even after some changes to his physical environment at home, William's AD flared every time he visited his grandparents' house with their two dogs. And despite frequent changes of clothing, anticipatory antihistamine use, and limited exposure to his grandparents' dogs, William's AD continued to flare.

It turns out that was just the beginning. During a family event when he was 10 months old, William grabbed a piece of birthday cake and immediately started vomiting. His AD flared significantly as well. After skin testing, William was ultimately diagnosed with an IgE-mediated food allergy. Based on his history and risk factors for further issues, we suggested peanut testing before introducing that food at home. Unfortunately, those test results also came back positive.

In the meantime, as he neared his first birthday, the severity of William's AD continued to worsen, and we stepped up treatment to incorporate daily topical corticosteroids, a calcineurin inhibitor applied to his face, along with regular wet wraps and bleach baths. If dupilumab (or another biologic therapy) had been approved for young children at that time, we certainly would have considered its use, but William's issues predated our current era.

Not surprisingly, all of these issues were taking their toll on William's parents, which I could sense every time they came to our office. They were getting increasingly frustrated with the cyclical nature of their youngest son's AD and his growing number of food allergies. William was sent home from daycare a week after he started after some parents complained that his condition was contagious, despite the fact that William's parents held a conference call with school officials before his enrollment to discuss his condition. William's skin became so sensitive that even touching foods with any level of acidity would trigger a flare of his AD.

I had several discussions with William's parents to find the best times to perform skin tests to assess specific food allergies. We tried to wait until his skin was calm, but these periods became less and less frequent over time. William struggled with chronic itch and woke frequently throughout the night, crying so loudly that he would wake not only his parents but his older brother as well. Fortunately, a trial of melatonin helped improve William's sleeping habits and allowed his whole family to get some restorative sleep.

Fortunately, William physical development didn't seem to be stunted as he was one of the tallest boys for his age as a young child. He developed periodic skin infections as he grew that typically required a short course of antibiotics, eventually requiring an assessment by our immunology department due to his unremitting disease. Frustrated by the lack of improvement despite traditional pharmacologic therapies, William's family began looking for alternative solutions, asking me about articles they saw online or social media posts that purported to offer "amazing results." They were worried about William's chronic steroid use and amplified their frustrations to me. I tried my hardest to assure them that there was no magic bullet that was going to make William's issues magically go away, but I could tell that there was skepticism in the room.

And so began this family's journey into alternative medicine: essential oils, yoga, visits to the chiropractor, and aromatherapy. They had hibiscus tea sent from foreign countries to be added to a restorative bath. I did my best to listen with an open mind, especially because some of the things they were trying weren't necessarily harmful. This is important for clinicians to remember – if we dismiss our patients' efforts as "silly" or "stupid," they are much more likely to keep quiet and stop trusting us. I worked together with William and his parents, corresponding honestly about the potential risks and benefits of some of the alternative medicine options they wanted to try.

Fortunately, William's parents kept bringing him to our regularly-scheduled appointments, where they would sometimes grudgingly admit to me their latest efforts that never did much to improve William's symptoms. By the time William was ready to enter elementary school, behavior issues likely related to his moderate-to-severe AD were becoming apparent. He was having trouble sitting for extended periods of time and was frequently disruptive in class. I talked to his parents about the link between AD and inattentiveness, ultimately suggesting evaluation from a child development specialist. William was eventually diagnosed with attention deficit hyperactivity disorder (ADHD) and received additional support from his teachers and the school nurse which, in addition to new ADHD medication, helped his performance at school.

I ended up caring for the Maxey family for more than a decade, gaining valuable hands-on experience as I learned and grew as a healthcare professional. Our interactions taught me the importance of creating a care team for a child with a chronic disease. In pediatric practices, we have the unique privilege to partner with a family and provide regular care over prolonged periods of childhood developmental stages. The frustrations that our families experience at different phases, as well as the unpredictability of their childrens' disease, can be an incredible burden that requires clarity and honesty. Without our open communication, I have little doubt that William's family would have become desperate enough to try treatment regimens that touted a "cure" but were unsafe. The stress faced from lack of sleep, chronic discomfort, parental guilt, and public perception can exhaust even the most resilient mom and dad.

Throughout my more than 15-year career in nursing, I have had the opportunity to witness many of my colleagues go above and beyond for the neediest of our families. Yes, it takes time and patience, but the kindness we can show, the extra effort we can make, and the support that we can provide can have immeasurable benefits.

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