INSIDE THIS ISSUE:

Why are systemic therapies so important to help control disease activity in patients with moderate to severe atopic dermatitis (AD)?

How has the introduction of dupilumab changed the short- and long-term prognosis of patients with moderate to severe AD?

What impact might the recent introduction of additional FDA-approved systemic therapies have on the care of patients with moderate to severe AD?

What are some of the class-specific safety concerns with systemic agents either recently approved or under late-stage investigation for the treatment of AD?
LEARNING OBJECTIVES

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

• Discuss the unmet need among patients with moderate to severe atopic dermatitis (AD) who have not been treated with systemic therapies
• Identify the pros and cons of conventional systemic therapies commonly used off-label to treat patients with moderate to severe AD
• Assess the potential clinical impact of new and emerging systemic therapies for the treatment of patients with moderate to severe AD
• Recognize the role and limitations of fundamental building blocks of skin care, topical agent administration, and trigger avoidance among patients with AD

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PE: Promotional event talks
H: Honoraria
O: Other

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Keischa Cash, DNP, APRN, DCNP, FNP-BC, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

Megan Lewis, MSN, RN, CPNP-PC, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

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Amy Karon, DVM, MPH, MA. Medical Writer, has disclosed that she does not have any relevant financial relationships specific to the subject matter of the content of the activity.

OFF-LABEL PRODUCT DISCLOSURE

This activity includes discussion of investigational and/or off-label use of the following products or devices: cyclosporine A, methotrexate, prednisone/prednisolone, lebrikizumab, baricitinib, nemolizumab, and orismilast.
Systemic therapies play an important role in the management of moderate-to-severe atopic dermatitis (AD) that is refractory to guideline-recommended practices (topical treatments, appropriate skin care, and reductions in environmental triggers). Until recently, systemic therapies for AD all were used off label and had suboptimal safety profiles. Hence, there has been a substantial unmet need for effective and safer treatments. A major breakthrough came with the development and U.S. Food and Drug Administration (FDA) approval of dupilumab, a biologic therapy that inhibits two pro-inflammatory cytokines involved in the pathophysiology of AD. In December 2021, a second biologic therapy – the interleukin (IL)-13 inhibitor tralokinumab—was approved for use by the FDA. This was followed in January 2022 by the approval of two Janus kinase (JAK) inhibitors—abrocinib and upadacinib. There also have been pivotal studies of other novel systemic therapies, including another IL-13 inhibitor (lebrikizumab), a third JAK inhibitors (baricitinib), a IL-31 agonist (nemolizumab), and a phosphodiesterase 4 (PDE4) inhibitor (orismilast).

**RATIONALE/UNMET NEED**

Accurate, timely diagnosis is the foundation of effective AD management. However, even when a patient has been correctly diagnosed, a variety of factors can lead to
inadequate disease control. These include undiagnosed or inadequately managed comorbidities, an inability or unwillingness to consistently adhere to first-line interventions (environmental changes, skin care, and topical therapies), psychosocial factors that exacerbate stress and inflammation, and even hypersensitivity reactions to vehicles found in some topical treatments.1

Even when these factors are all adequately addressed, some patients with AD may simply not respond adequately to non-systemic interventions. Importantly, AD is both complex and heterogeneous, with a wide range of clinical and molecular phenotypes that can vary based on age, ethnicity/race, family history of atopy, and individual risk factors and triggers.2-4 Single-nucleotide polymorphism analyses and genome-wide association studies have implicated more than 60 genes that play a role in the development of AD, many of which relate either to innate and adaptive immunity or skin barrier function.5 Such complexity helps explain why different patients respond differently to the same AD treatment and points to a need for a diverse pharmacopeia with varied mechanisms of action.

Systemic therapy is used most commonly in patients with moderate-to-severe AD. In the United States, 40-50% of patients with eczema have moderate-to-severe disease, which is equivalent to approximately 6.6-8.25 million individuals according to findings of recent population-based studies.6,7 Moderate-to-severe AD is associated with increased risk of cutaneous infection, sleep disturbances, depression, anxiety, and impaired quality of life.6 Hence, there is a significant need for safe and effective systemic AD therapies.

CONVENTIONAL/NON-BIOLOGIC SYSTEMIC THERAPIES

Conventional (non-biologic) systemic therapies have been used to manage AD that is refractory to skin care and environmental interventions and topical therapies for many years. In the United States, these therapies primarily include cyclosporine A, methotrexate, and systemic glucocorticoids (prednisone/prednisolone), all of which are used off-label in patients with AD.

Cyclosporine A is an oral calcineurin inhibitor that acts by suppressing the T-cell transcription factor (NF-AT), thereby inhibiting the transcription of cytokines such as IL-2 to reduce inflammation.6 In one systematic review and meta-analysis, administration of cyclosporine A therapy for a duration between 10 days and 8 weeks improved AD signs and symptoms by approximately 50-85%.6 However, it is generally thought that cyclosporine A is best used as a short-term or stopgap measure while transitioning patients with AD to a safer treatment regimen. This is because cyclosporine A is nephrotoxic and exposure for as little as 1-2 total years has been found to lead to irreversible kidney disease.5,10 Cyclosporine A also can cause hypertension, gingival hyperplasia, low serum magnesium levels, nausea, diarrhea, headaches, and hypertrichosis (excessive hair growth on the face or body).6 In a recent study at an outpatient university dermatology clinic, more than 40% of patients receiving cyclosporine A for AD stopped treatment because of side effects, lack of efficacy, or both.11

Methotrexate inhibits dihydrofolate reductase, which impairs purine metabolism and thereby reduces RNA and DNA synthesis to suppress lymphocyte activity.6 Data from small randomized trials suggest that the efficacy of methotrexate in patients with AD is comparable to that of cyclosporine A, although methotrexate has a somewhat slower time to response—typically 3-5 weeks.12 Methotrexate can cause bone marrow suppression, pulmonary fibrosis, and hepatotoxicity, as well as more common but less serious side effects such as stomatitis and gastrointestinal symptoms.6 Experts recommend that methotrexate be used as a later-line AD therapy for patients with moderate-to-severe symptoms who are not responding to or are not candidates for topical therapies or oral cyclosporine A.8

As is the case for cyclosporine A and methotrexate, there are no large, high-quality, controlled, randomized studies of systemic glucocorticoids (e.g., prednisone, prednisolone) in patients with AD. While these drugs can be highly effective for curtailing severe AD flares, their long-term use, even at low doses (e.g., the daily equivalent of <15 mg prednisone) can lead to gastrointestinal hemorrhage, fractures, obesity, cataracts, infections, and, in pediatric patients, delayed or diminished bone growth.8,10 Thus, experts and consensus guidelines recommend that systemic glucocorticoids be limited to use in patients with severe, treatment-refractory AD, for the immediate relief of acute flares, or as a transition to steroid-sparing therapy.8,10 When glucocorticoids are discontinued, they should be gradually tapered to reduce the risk of rebound, with the tapering overlapping with the initiation of steroid-sparing therapy.8

DUPILUMAB

The cytokines IL-13 and IL-4 were some of the earliest to be definitively implicated in the development of AD.13,14 These cytokines, which mediate type 2 (Th2) inflammation, have overlapping biologic functions due to a subunit that is shared between IL-4 receptor alpha and IL-13 receptor alpha-1. Dupilumab is a first-in-class, subcutaneously
injected, fully human monoclonal antibody that decreases type 2 (Th2) inflammation by blocking this shared subunit, thereby inhibiting cytokine signaling.\textsuperscript{15} Dupilumab was initially approved by the FDA in March 2017, and is now indicated for the treatment of patients ages 6 years and older with moderate-to-severe AD that has been inadequately controlled by topical prescription therapies, or for whom such therapies are inadvisable.\textsuperscript{16} The development and approval of dupilumab was a breakthrough that ended a longstanding therapeutic drought in the systemic treatment of AD and confirmed that targeting key drivers of Th2 inflammation can reverse the disease process.

\textbf{Efficacy}

In phase 3 clinical trials, the administration of dupilumab either as monotherapy or in combination with topical corticosteroids led to statistically significant, clinically meaningful improvements in validated measures of AD severity, as well as significant improvements in secondary outcome measures such as pruritus, anxiety, and depression (see Tables 1 and 2).\textsuperscript{17-25} These secondary measures are all well documented as negatively impacting quality of life in patients with treatment-refractory AD. In pivotal studies, dupilumab usually improved both the extent

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Summary of Key Studies of Dupilumab in Adults</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment period</th>
<th>Patients</th>
<th>No. patients</th>
<th>Primary outcome measure(s)</th>
<th>Was (were) primary endpoint(s) met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO 1\textsuperscript{17}</td>
<td>16 weeks</td>
<td>AD not adequately controlled by topical medications</td>
<td>671</td>
<td>IGA 0 or 1, with at least a 2-point reduction from baseline</td>
<td>Yes</td>
</tr>
<tr>
<td>SOLO 2\textsuperscript{17}</td>
<td></td>
<td></td>
<td>708</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>SOLO-CONTINUE\textsuperscript{28}</td>
<td>36 weeks after completion of SOLO 1 or 2</td>
<td>Patients whose responses met predefined endpoints in SOLO 1 or 2\textsuperscript{*}</td>
<td>422</td>
<td>Safety, maintenance of treatment effect</td>
<td>Patients who stayed on their original treatment regimen (either weekly or every 2 weeks) showed the most consistent responses. Longer treatment intervals (every 4 or 8 weeks) and placebo treatment both showed a dose-dependent decrease in response with no safety advantage.</td>
</tr>
<tr>
<td>LIBERTY AD CHRONOS\textsuperscript{20}</td>
<td>Up to 52 weeks</td>
<td>Moderate-to-severe AD inadequately controlled by TCS</td>
<td>740</td>
<td>IGA 0-1, with at least a 2-point improvement from baseline; EASI-75 at week 16</td>
<td>Yes, and results were maintained through week 52 in most patients.</td>
</tr>
<tr>
<td>LIBERTY AD CAFE\textsuperscript{24}</td>
<td>16 weeks</td>
<td>Severe AD only; uncontrolled by/intolerant of/ineligible for oral CSA</td>
<td>325</td>
<td>EASI-75</td>
<td>Yes</td>
</tr>
<tr>
<td>LIBERTY AD OLE\textsuperscript{22}</td>
<td>Open-label extension for up to 3 years, topical therapy permitted as needed</td>
<td>Adults who participated in prior studies (moderate to severe AD)</td>
<td>2.677</td>
<td>Efficacy, TEAEs</td>
<td>Improvements in EASI and PNRS were sustained through week 148. Common TEAEs (≥ 5% of patients): nasopharyngitis, upper respiratory tract infection, conjunctivitis, headache, oral herpes, injection-site reactions</td>
</tr>
</tbody>
</table>

\textsuperscript{IGA, Investigator’s Global Assessment; TCS, topical corticosteroids; EASI, Eczema Area and Severity Index; EASI-75, 75% improvement in EASI score compared with baseline; CSA, cyclosporine A; TEAEs, treatment-emergent adverse events; PNRS, Pruritus Numerical Rating Scale}
(that is, the percent of affected body surface area) and severity of AD signs and symptoms in all affected anatomic regions. Responses were observed in patients with severe, chronic, treatment-refractory AD that had failed to respond to other systemic therapies, including cyclosporine A and oral prednisone (see Figure 1). Long-term follow-up has shown that responses often are durable.

Dupilumab can be used either alone or with topical corticosteroids. In adults, the recommended treatment regimen consists of a loading dose of 600 mg (two 300-mg injections), followed by 300 mg every other week. For children and adolescents (6-17 years old), the recommended dosage is based on body weight (see Table 3).

**Safety**

In general, dupilumab has demonstrated a good safety profile. The most common side effects associated with the drug include injection site reactions (which affected

**TABLE 2**

Summary of Major Placebo-controlled Studies of Dupilumab in Children and Adolescents

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment period</th>
<th>Patients</th>
<th>No. patients</th>
<th>Primary endpoint(s)</th>
<th>Was (were) primary endpoint(s) met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab without TCS (or other topical medications)</td>
<td>LIBERTY AD ADOL&lt;sup&gt;19&lt;/sup&gt;</td>
<td>16 weeks</td>
<td>12-18 years old, moderate to severe AD not adequately controlled by topical medications</td>
<td>251</td>
<td>IGA 0 or 1, with at least a 2-point reduction from baseline</td>
</tr>
<tr>
<td></td>
<td>LIBERTY AD PEDS&lt;sup&gt;23&lt;/sup&gt;</td>
<td>16 weeks</td>
<td>Age 6-11 years, severe AD not adequately controlled by TCS</td>
<td>367</td>
<td>IGA 0-1, with at least a 2-point reduction from baseline; EASI-75</td>
</tr>
<tr>
<td></td>
<td>LIBERTY AD PRESCHOOL&lt;sup&gt;25&lt;/sup&gt;</td>
<td>16 weeks</td>
<td>6 months to 5 years with uncontrolled, moderate-to-severe AD</td>
<td>40</td>
<td>Drug concentration and PK parameters; TEAEs</td>
</tr>
<tr>
<td></td>
<td>LIBERTY AD PED-OLE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Up to 52 weeks</td>
<td>Patients aged 6 months to 17 years who participated in previous dupilumab studies</td>
<td>800 (estimate)</td>
<td>Safety, maintenance of treatment effect</td>
</tr>
</tbody>
</table>

IGA, Investigator’s Global Assessment; TCS, topical corticosteroids; EASI, Eczema Area and Severity Index; EASI-75, at least a 75% improvement in EASI score compared with baseline; PK, pharmacokinetic; TEAEs, treatment-emergent adverse events

**TABLE 3**

Recommended Dosing of Dupilumab in Children and Adolescents<sup>16</sup>

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading Dose</th>
<th>Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-&lt;30 kg</td>
<td>600 mg (two 300-mg injections)</td>
<td>300 mg every 4 weeks</td>
</tr>
<tr>
<td>30-&lt;60 kg</td>
<td>400 mg (two 200-mg injections)</td>
<td>200 mg every other week</td>
</tr>
<tr>
<td>≥60 kg</td>
<td>600 mg (two 300-mg injections)</td>
<td>300 mg every other week</td>
</tr>
</tbody>
</table>
approximately 10% of patients in registrational trials), conjunctivitis, blepharitis, keratitis, eye pruritus, dry eye, oral herpes, and other herpes simplex virus infections. Among the eye reactions, conjunctivitis is most common, followed by blepharitis and keratitis (these two reactions appear to be more likely when patients are also receiving topical corticosteroids). In a real-world observational study of 156 adults who received dupilumab at a tertiary care center, 2% stopped treatment because of severe conjunctivitis and 1% stopped treatment because of either a vasovagal reaction or an inability to tolerate the subcutaneous mode of administration. The overall rate of treatment discontinuation was similar to or slightly higher than that shown in the pivotal trials of dupilumab. No patient stopped therapy because of laboratory abnormalities.

Uncommonly, dupilumab has induced hypersensitivity reactions such as urticaria (hives), rash, erythema nodosum, erythema multiforme, anaphylaxis, and serum sickness. These affected <1% of patients in clinical trials, but they are important to know about because if they occur, dupilumab should be stopped immediately. If patients are also receiving topical or oral corticosteroids, it is important not to abruptly stop them at the same time. If steroids need to be discontinued, they should be tapered gradually.

OTHER NOVEL AGENTS

Although the development and approval of dupilumab represented a breakthrough in AD treatment, not all patients respond, and side effects such as conjunctivitis uncommonly require patients to stop or pause treatment. Thus, there is a need for a wider armamentarium of targeted systemic therapies. There have been three recently approved systemic agents added to the treatment armamentarium, with several more in late-stage development.

IL-13 INHIBITORS

Although both IL-4 and IL-13 contribute to AD pathogenesis, IL-13 plays a more central role. In a study that utilized semiquantitative reverse transcription polymerase chain reaction (PCR), IL-13 expression was detected in 27 of 28 AD lesions (acute, subacute, and lichenified), and was detected at significantly higher levels than in healthy controls, while IL-4 expression was modest to absent. In patients with AD, IL-13 has been found to recruit immune cells in the skin, alter the skin microbiome, and degrade epidermal barrier function.

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Such findings have spurred interest in developing monoclonal antibodies that impede the Th2 inflammatory response by targeting IL-13. Thus far, two IL-13 inhibitors, lebrikizumab and tralokinumab, have been evaluated in late-stage AD trials. Both are administered subcutaneously, usually at intervals of 2-4 weeks. Tralokinumab met its primary and secondary endpoints in randomized, placebo-controlled, phase 2 and phase 3 trials of patients with moderate-to-severe AD, including in patients who had responded inadequately to or been unable to tolerate cyclosporine A. In these studies, significantly more patients achieved IGA 0-1 and EASI-75 after 16 weeks of tralokinumab therapy compared with placebo (patients also received topical corticosteroids). The most common adverse events were nasopharyngitis and conjunctivitis, which were more frequent with tralokinumab than placebo but were usually mild and rarely led to treatment discontinuation. Serious adverse events were infrequent and similar between study groups. Based on these results, tralokinumab was approved in December 2021 for the treatment of moderate-to-severe AD in adults 18 years or older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

In a phase 2b trial of lebrikizumab that included 280 adults with moderate to severe AD, 16 weeks of treatment led to statistically significant, dose-dependent improvements in EASI compared with baseline and placebo. Although 2.6% of lebrikizumab recipients developed conjunctivitis, most adverse events were mild or moderate and did not cause patients to stop treatment. Herpes infections (simplex and zoster) also were infrequent and generally mild. More recently, the manufacturer of lebrikizumab announced positive results from the phase III, randomized, double-blind, 52-week ADvocate 1 and ADvocate 2 trials, which compared lebrikizumab monotherapy with placebo in patients ages 12 years and older whose chronic, moderate-to-severe AD was inadequately controlled by topical treatment. The coprimary endpoints (EASI-75 and IGA 0-1) were met; lebrikizumab also significantly improved secondary endpoints such as the effect of itch on sleep and quality of life. Full results from these trials are expected to be released in 2022.

**FIGURE 2**

**JAK Inhibitor Mechanism of Action**

JAK inhibitors target Janus kinase (JAK) proteins, blocking their ability to activate the JAK/STAT pathway and thereby reducing STAT-facilitated transcription of cytokines inside the cell nucleus.
Lebrikizumab has received FDA Fast Track designation to expedite its development for the treatment of moderate-to-severe AD in adolescents and adults. Thus far, the efficacy and safety profiles of lebrikizumab and tralokinumab suggest that targeted IL-13 inhibition may offer an effective and safe option for the systemic treatment of moderate-to-severe disease.

**JAK INHIBITORS**

Pro-inflammatory cytokines are central to the pathology of many immune-mediated diseases, including AD. Janus kinases (JAK) are a family of proteins that upregulate the expression of multiple cytokines by interacting with their receptors as part of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors block this process, which reduces cytokine expression (see Figure 2). Abrocitinib, upadacitinib, and baricitinib are oral, once-daily JAK inhibitors that have been studied extensively in late-stage trials in patients with AD. In January 2022, abrocitinib and upadacitinib were approved by the FDA for the treatment of AD while baricitinib remains under FDA review.

Abrocitinib, a JAK1 inhibitor, has been evaluated as monotherapy and in combination with background topical therapies in randomized, double-blind, placebo-controlled clinical trials of adults and adolescents with moderate-to-severe AD that is refractory to topical treatment alone. After 12 weeks of treatment, abrocitinib achieved statistically significant improvements in key objective endpoints such as IGA, EASI-75, and the Peak Pruritus Numerical Rating Scale when compared with placebo. When abrocitinib responders were switched to a lower maintenance dose, flares were infrequent, and they usually responded to higher-dose rescue abrocitinib therapy plus topical treatment. It was approved by the FDA for the treatment of adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Abrocitinib is approved for use at both 100 mg and 200 mg doses, with the 200 mg dose being recommended for patients who are not responding to the 100 mg dose. Additionally, a 50 mg dose was approved to treat moderate-to-severe AD specifically in patients with moderate renal impairment, certain patients receiving treatment with inhibitors of cytochrome P450 (CYP) 2C19, or patients who are known or suspected to be poor metabolizers of CYP2C19. For patients with moderate renal impairment who are not responding to 50 mg once daily, 100 mg once daily may also be prescribed.

The JAK1 inhibitor upadacitinib also has been studied as monotherapy and in combination with topical corticosteroids in randomized, double-blind, placebo-controlled trials of adolescents and adults with moderate-to-severe AD. Upadacitinib significantly improved the co-primary endpoints of EASI-75 and IGA. The greatest efficacy occurred at the highest doses. Upadacitinib was recently approved by the FDA for the treatment of adults and children 12 years of age and older with moderate to severe AD whose disease did not respond to previous treatment and is not well controlled with other pills or injections, including biologic medicines, or when use of other pills or injections is not recommended. Upadacitinib 15 mg once daily can be initiated in adults and children 12 years of age and older weighing at least 40 kg. In these children and adults <65 years of age who do not achieve an adequate response, the dose may be increased to 30 mg once daily.

A third JAK inhibitor, baricitinib, inhibits both JAK1 and JAK2. In clinical trials, the use of baricitinib significantly improved IGA when given alone or in combination with topical corticosteroids in randomized, double-blind, placebo-controlled studies of adults with moderate-to-severe AD. At 16 weeks, response rates were as high as 36%, which is somewhat lower than other JAK inhibitors; however, this response was usually maintained over time.

A few studies of adults with moderate-to-severe AD have included both dupilumab and a JAK inhibitor. In the multicenter, randomized, double-blind JADE COMPARE trial, abrocitinib (200 mg or 100 mg once daily) significantly outperformed placebo for the co-primary endpoints of IGA (clear or almost clear) and EASI-75. In this study, proportionally more patients who received abrocitinib 200 mg met the primary endpoints both compared with those who received abrocitinib 100 mg and those who received dupilumab. However, study investigators did not assess the statistical significance of these results (see Table 4). Compared with dupilumab, the higher (200 mg) dose of abrocitinib did lead to a significantly greater improvement in itch at week two, which was a key secondary endpoint. It is important to note that patients in this study were permitted to stay on background AD medications, including low or medium potency topical corticosteroids, topical calcineurin inhibitors, and topical phosphodiesterase-4 inhibitors.

In the randomized, double-blind, Heads Up trial, EASI-75 was achieved by 71% of upadacitinib recipients, compared with 61% of dupilumab recipients (P=0.006). Upadacitinib also met secondary outcome measures, such as itch, speed of response, and achievement of EASI-100.
The JAK-STAT pathway is used by many different molecules, which explains the efficacy of JAK inhibitors in immune-mediated diseases but also their potential for side effects.\(^5\) In clinical trials of patients with AD, the most common side effects of JAK inhibitors were upper respiratory tract infections, herpes zoster, herpes simplex, acne, nausea, diarrhea, headache, increased blood creatine phosphokinase levels, and decreased platelet counts.\(^5\) The likelihood of these events increased when treatment exceeded 12 weeks.

Serious and opportunistic infections are a known risk of JAK inhibitor treatment and have occurred in AD trials of abrocitinib, upadacitinib, and baricitinib.\(^5\) Baricitinib and upadacitinib carry FDA black box warnings concerning an increased risk for serious infections, as well as cancer, blood clots, serious heart-related events, and death.\(^5\) Other than serious infections, these events have not been reported in the AD trials, but they need further study, especially in children and adolescents.\(^5\)

### IL-31 INHIBITION

Interleukin-31 plays an important role in several aspects of AD. Receptors for this cytokine are expressed on the surface of keratinocytes, eosinophils, and small-diameter neurons.\(^5\) In the skin, increased expression of IL-31 can markedly reduce the production of filaggrin protein, leading to decreased differentiation and proliferation of epidermal keratinocytes as well as abnormal skin development, skin defects, and skin barrier dysfunction.\(^5\) Interleukin-31 also stimulates sensory neurons in the skin related to pruritus, which can cause persistent itch even with relatively minimal stimuli.

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### Table 2: Summary of Key Efficacy Data from Phase III JADE COMPARE Trial\(^48\)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Abrocitinib 200 mg, once daily (N=226)</th>
<th>Abrocitinib 100 mg, once daily (N=238)</th>
<th>Dupilumab 300 mg, every other week (N=242)</th>
<th>Placebo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coprimary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGA response (0-1) at week 12</td>
<td>48.4%(*)</td>
<td>36.6%(*)</td>
<td>36.5%</td>
<td>14.0%</td>
</tr>
<tr>
<td>EASI-75 response at week 12</td>
<td>70.3%(*)</td>
<td>58.7%(*)</td>
<td>58.1%</td>
<td>27.1%</td>
</tr>
<tr>
<td><strong>Key Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itch response at week 2</td>
<td>49.1%(†)</td>
<td>31.8%(#)</td>
<td>26.4%</td>
<td>13.8%</td>
</tr>
<tr>
<td>IGA response at week 16</td>
<td>47.5%(*)</td>
<td>34.8%(*)</td>
<td>38.8%</td>
<td>12.9%</td>
</tr>
<tr>
<td>EASI-75 response at week 16</td>
<td>71.0%(*)</td>
<td>60.3%(*)</td>
<td>65.5%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>

\(*\) P-value for difference between abrocitinib and placebo: <0.001.

\(†\) P-value for difference between abrocitinib and dupilumab: <0.001.

\(\#\) P-value for difference between abrocitinib and dupilumab: Not significant.

IGA, Investigator’s Global Assessment; EASI-75, ≥75% improvement in Eczema Area and Severity Index from baseline; CI, confidence interval; N, number in subgroup.

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\(\)
Patients with AD have increased serum levels of IL-31 compared with healthy individuals, which correlates to greater itch and disease severity.\textsuperscript{57,58} However, IL-31 overexpression is found even in patients with relatively non-severe AD, highlighting its importance in disease pathophysiology. In a study in which researchers performed quantitative real-time PCR of 149 skin biopsy specimens, individuals with AD had significantly more IL-31 messenger RNA even when they had relatively mild symptoms and unremarkable serum IgE levels.\textsuperscript{13}

\textit{Nemolizumab} is a first-in-class, subcutaneous, humanized monoclonal antibody that targets IL-31 receptor A, thereby blocking cytokine IL-31 signaling.\textsuperscript{59} In two long-term, phase 3 studies of adolescents and adults with AD who had inadequately controlled moderate or severe pruritus, subcutaneous nemolizumab (60 mg every 4 weeks) combined with topical therapy led to a 66\% decrease in the pruritus visual analogue scale and a 78\% decrease in EASI from the beginning of treatment. Nemolizumab also led to improvements in quality of life that were sustained throughout follow-up. Injection site reactions were more common with nemolizumab than placebo but were usually mild. Serious adverse events, including Meniere's disease, acute pancreatitis acute, and worsening of AD, were uncommon.

\section*{PDE4 INHIBITION}

Phosphodiesterase-4 (PDE4) is a class of enzymes that hydrolyze cyclic adenosine monophosphate (cAMP), an intracellular messenger that helps regulate immune and inflammatory responses.\textsuperscript{60} PDE4 is found in many types of immune cells, including basophils, mast cells, eosinophils, B and T lymphocytes, monocytes, macrophages, and neutrophils. In addition, greater PDE4 expression is associated with increases in various proinflammatory cytokines. While the precise role of PDE4 in the development and progression of AD is somewhat unclear, PDE4 levels are increased in both lesional and non-lesional skin, even when AD has been in remission for years.\textsuperscript{61} Furthermore, PDE4 inhibition reduces levels of certain cytokines in a manner that is similar to topical calcineurin inhibitors and corticosteroids. In studies of mice with AD, PDE4 inhibition reduced skin lesion severity, fibroblast proliferation, and T-cell activity—in some cases, more rapidly and to a greater extent than cyclosporine A.\textsuperscript{62,63}

However, because PDE4 is expressed in the central nervous system, its inhibition can cause a range of side effects, particularly gastrointestinal issues such as nausea, dyspepsia, emesis, and diarrhea.\textsuperscript{59} Because these have been shown to be dose-limiting, investigators are working to develop more selective PDE4 inhibitors that exhibit fewer off-target effects.\textsuperscript{64} \textit{Orismilast} is an oral, next-generation PDE4 inhibitor that has been developed with these goals in mind. In November 2021, orismilast received FDA Fast Track designation to facilitate its development for the treatment of moderate-to-severe AD. Orismilast is currently being studied in early to mid-phase AD clinical trials, while other selective PDE4 inhibitors are in preclinical trials.\textsuperscript{65}

\section*{SUMMARY}

For decades, the AD treatment landscape was relatively stagnant, and patients who needed systemic treatment had few options besides conventional, off-label treatment with methotrexate, systemic corticosteroids, and/or cyclosporine A. However, recent advances in characterizing the complex immunology and inflammatory pathogenesis of AD have spurred the development of new systemic agents for the treatment of moderate-to-severe disease. Dupilumab, a subcutaneously injected, monoclonal anti-IL-13/IL-4 antibody that can markedly decrease clinical severity and has a good safety profile, was the first biologic to receive FDA approval. It was joined in December 2021 by the IL-13 inhibitor tralokizumab and in January 2022 by the JAK inhibitors upadacitinib and abrocitinib, with several other systemic agents currently under FDA review. While the development and approval of dupilumab was a major breakthrough in the treatment of AD, not all patients respond to this medication and some experience treatment-limiting adverse effects (particularly conjunctivitis). Other systemic biologic agents utilizing distinct mechanisms of action in late-stage development include an additional subcutaneously injected IL-13 inhibitor (lebrikizumab), a oral JAK inhibitor (baricitinib), the subcutaneous IL-31 inhibitor nemolizumab, and the oral PDE4 inhibitor orismilast. Thus far, these agents have shown considerable promise for the systemic treatment of moderate-to-severe AD, although certain safety concerns, particularly with JAK inhibitors, merit careful consideration.
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To bathe or not to bathe with atopic dermatitis (AD)? Is that really the question?

Few topics are quite as hotly debated throughout journals as the appropriate frequency and duration of baths for patients with AD. Providers, patients, and family members have very strong, and often divergent, opinions on the topic.

We all know that adherence to fundamental skin care recommendations is essential for the successful treatment of AD. It’s the foundation of care and the base of the “AD Yardstick” that is so frequently cited when discussing the management of AD. While it’s often magnetizing to focus our attention on the use of anti-inflammatories and prescription medications, without appropriate basic skin care, our patients with AD don’t have a chance of controlling their disease.

Let’s start by breaking down what we know about bathing. Submerging in a tub of water allows the skin to rehydrate. In general, a bath of 15-20 minutes in lukewarm, not hot, water is recommended. If the patient has comorbid environmental allergies and triggers such as pet dander, more frequent bathing may be recommended. A mild, fragrance-free soap with a neutral-to-low pH should be used, although it does not need to be applied to areas that aren’t dirty. Washcloths should be avoided as they can harbor bacteria that may further irritate the skin.

As soon as the patient has completed their bath, it is important to dry themselves by patting with a towel. Both air drying and vigorous scrubbing should be avoided as they increase transepidermal water loss. Remember that the goal of bathing is to rehydrate the skin, so any actions that counteract that must be discouraged.

Emphasizing the Building Blocks of Skin Care

by Megan Lewis, MSN, RN, CPNP-PC

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After patting off any excess water, patients should immediately apply a hydrating moisturizer. This is commonly referred to as the “soak and seal” approach that helps lock in as much moisturization as possible. It’s important to emphasize to patients that moisturizer needs to be applied both to lesional and non-lesional skin. We’ll often hear that moisturizer is only being used on affected areas, even though AD impacts the entire skin and not just visible plaques. That’s an educational pearl I always try to emphasize to my patients and their families.

Choosing an appropriate soap and moisturizer is another area where our patients often need our guidance. Take a brief stroll down the soap and moisturizer aisle the next time you are at your local pharmacy—there are dozens and dozens of options for patients with “sensitive skin.” It’s important to familiarize yourself with the specific details your patients should look for on product labels to save them both time and money. There are many different types of moisturizers: some with emollients that lubricate and soften skin, some with occlusive agents that form a layer to prevent water evaporation, and some with humectants that attract and hold onto water. There is no one “right” type of moisturizer for our patients, so it sometimes requires an evaluation of the patient’s specific needs and an economic assessment. Using moisturizer over the entire body once or twice a day is not cheap. I spend a lot of time during my initial visits with patients asking them what qualities are important to them regarding a moisturizer. Some are averse to “stickiness” or moisturizers that sting, while others want a moisturizer without an odor. In general, I tell families to try to avoid using lotions or anything that is dispensed through a pump, as these are often too thin in consistency to properly seal the skin. Many lotions contain water and alcohol that can irritate and dry out the skin. If patients are amenable, I will often suggest ointments since they typically lack preservatives and do not have that “stinging” quality. Ointments, however, can be a problem for some patients due to their greasiness, especially among patients who require moisturization twice a day.

The ultimate goal is to find a moisturizer that is inexpensive, additive-free, and fulfills your patient “wish list” of qualities. If you have samples of moisturizers in your office, I recommend offering families several different types so they can see which one is best for their needs. This eliminates the requirement to purchase a whole costly tube or jar of a brand they find they do not like. If samples are not an option, you may want to send patients to the Travel section found in most larger convenience stores that sell moisturizers in smaller quantities. I often give patients a list of different products I think will be good options for them to help guide their choices.

Petroleum jelly is an example of an occlusive agent that helps seal moisture within the skin. It is frequently the least expensive moisturizer on the market, which also makes it popular for families. Because of its stickiness, I have many patients who will use petroleum jelly at night and a more costly cream in the morning.

Here are some other fundamentals of skin care that I emphasize for all of my patients with AD:

1. Keep your fingernails short and smooth to decrease the likelihood of excoriations that may introduce bacteria into the skin. This is especially important in toddlers with extreme pruritis.

2. Use laundry detergent that is free of perfumes and dyes. Only use the recommended amount of detergent and make sure enough water is being used to fully rinse clothes. If the patient is a young child, parents’ clothes should be treated in the same manner as their child’s to reduce irritation.

3. Avoid use of fabric softeners, wash all new clothes before being worn, and remove all possible tags.

While many families tell me that their child’s disease resolves during the “summer” or “winter” (interesting how these can both be true in different patients!), it remains important to follow these building blocks of skin care year-round. As much as possible, the indoor environment should be kept at a moderate temperature, and patients should be urged to avoid spending significant time outdoors on days with extreme heat and low humidity.

The basic management of AD highlights the importance of shared decision making between providers and families. Flexibility with our management plan is essential as we can often meet our goals by pivoting slightly to improve adherence.

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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by intense pruritus and impaired skin barrier function. This impaired skin barrier function allows enhanced allergen penetrance and sensitization to irritants. Causes of barrier function impairment are likely complex, involving genetic, environmental, and immunologic factors.¹

The basic treatment of AD typically includes a combination of barrier hydration, topical therapies, and avoidance of provocation factors.² Common factors that influence the development and progression of AD include dust mites, pollen, and pet dander. Other potential irritants such as sweating, changes in temperature, stress, hormones, detergents (i.e., bleach), and some food may also play a role in disease development. Even certain contact allergens such as nickel, latex, and rubber can be irritants. Because of the impact these factors can have on skin disease, it is imperative to educate patients on ways to limit disease flares by deploying a simple strategy of avoidance to commonly-known irritants.³

While it’s not always easy to pinpoint potential disease-related irritants in all of our patients with AD, there are some patients whose evolving disease history continually offers us clues. Brianna is a current patient of mine who fits into this category.

When we first met, Brianna was an 11-year-old who came to our practice after a referral from her primary care provider (PCP). Her father, Gary, accompanied Brianna to this initial visit. Her main complaint involved a persistent, itchy rash that was significantly affecting her sleep despite a combination of triamcinolone 0.025% cream and over-the-counter moisturizer that had been prescribed by her PCP.

While taking a history of her condition, Brianna told me that she was both a soccer player in the spring and fall, and a volleyball player in the winter. She noted
that she often gets a runny nose, sore throat, and nasal congestion during her sports seasons; her symptoms are additionally exacerbated during those periods when she has to help out most often at home with yard work. For the last few years, Brianna said she'd taken cetirizine 10 mg daily for symptom relief during the worst periods.

I probed a little deeper, asking if there is anything else that accompanies the congestion and other symptoms. Brianna thought for a moment before telling me that her legs often itch after soccer practice, especially when she doesn't take a shower immediately after getting home. Brianna's father added that he often forgets to wash Brianna's shin guards and knee pads after practice, and that he notices her scratching the insides of her legs more after several days without washing.

There was more.

Brianna said that some of her worst days come after she stays overnight with her friend and volleyball teammate, Makenzie. Makenzie's family has a cat, a dog, carpeting in every room, and lots of dust mites behind the furniture. Brianna said she almost immediately becomes congested, starts sneezing, and feels sinus pressure when she walks into her friend's house, and she develops an itchy rash around her eyes that only resolves once she returns home. She added that her symptoms are similar when she helps her dad with yardwork on the weekends.

During our skin examination, I noticed apparent excoriations and erythematous patches on the flexural creases of the antecubital and popliteal fossa as well as broad erythema and lichenification in those areas. There were also erythematous, dry patches on both eyelids, Dennie-Morgan lines, as well as infraorbital discoloration and maxillary sinus tenderness upon palpation on Brianna's face.

Due to her history and physical symptoms, we diagnosed Brianna with both AD and allergic rhinitis. As I explained to Brianna and her father, her condition continued to recur despite treatment with triamcinolone 0.025% cream and moisturization due to multiple external factors, especially environmental triggers.

Trigger avoidance, or even trigger maintenance, is crucial for many of our patients with AD. Many of the recommendations I made for Brianna, and

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**Common AD Triggers**

**Dust Mites**

Aeroallergens such as dust mites can lead to skin exacerbation of AD. House dust mites are the main allergen blamed for household dust allergies; the two most common are *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*.

I educated Brianna and her father on the importance of adequately ventilating the house, vacuuming weekly, cleaning upholstered furniture regularly, eliminating stuffed animals, and, if possible, replacing carpeting with hardwood or solid surface flooring. I also noted that frequently-touched surfaces should be wiped down regularly with a wet sponge or mop.

**Animal Dander**

Cat dander is the second most common indoor environmental allergen, and sensitization to pet dander and house dust mites can increase an individual’s risk of developing allergic rhinitis and asthma.

Because of the frequent issues associated with visits to Makenzie’s house, I suggested to Brianna that she invite Makenzie to stay over at her house more frequently on weekends of volleyball tournaments. If she does decide to visit Makenzie’s house, I urged her to be careful not to stay for very long.

**Pollen**

Pollen is one of the most influential external environmental allergens. Multiple studies have shown that airborne pollen can exacerbate AD skin lesions; these lesions typically become more pronounced on areas of exposed vs. protected skin.

This includes areas such as the face, eyelids, neck, upper chest, and hands. In other words, several of the areas where Brianna said she noticed exacerbations.

I advised Brianna that she should wipe off her clothing to remove pollen that may vectorize aeroallergens. I also recommended that she wear glasses or masks when helping her dad outside with yardwork, or avoid outdoor lawn work altogether (she liked that suggestion). Air filters in the home and car that filter pollen particles might also be helpful.

**Sweating**

Sweating can induce pruritus in some AD patients and may lead to exacerbated itching and irritation. Studies have shown...
that patients with AD exhibited positive reactions to sweat antigens in a histamine release test.⁰²

Since it is next to impossible to avoid sweating (especially here in Florida) and isn’t recommended as it maintains homeostasis and thermoregulation, I advised Brianna to avoid tight clothing or clothing that is too warm. I also suggested that she change out of her sweaty workout clothes as soon as possible after practice and shower immediately after arriving home. Lingering excess sweat on the surface of the skin can induce itching in patients with AD, and several studies have shown that showering can effectively reduce and relieve symptoms.⁰²

I also suggested to Brianna that she carry hypoallergenic wipes to remove excess sweat if she is unable to shower or would be away from home for some time after practice. Regularly washing her shin guards and knee pads to prevent skin irritation was also at the top of the to-do list.

Other irritants

Because skin barrier function is compromised in patients with AD, it is imperative that known or potential irritants be avoided to reduce exacerbation of skin lesions. Patients should bathe with low pH-based soaps ranging between 5 and 6 (or lower).³ Soaps and shampoos should be carefully selected to ensure that they don’t use irritants, harsh detergents, or alkaline ingredients.

I advised Brianna to replace the Ivory bar soap she was using (it has a pH of 9.5) with a less abrasive option and urged her to shower as soon as possible after practice. I also suggested that she buy shin pads and knee guards made of hypoallergenic materials such as cotton and avoid synthetic materials and fibers such as polyester and wool.

Contact allergens

Allergic contact dermatitis is a delayed type II hypersensitivity reaction to haptenants or prehaptenants that meet the skin. Contact allergens can cause refractory skin lesions as well as atypical skin lesion distribution. These findings may be indicative of contact allergies. Metals such as nickel, some fragrances, rubber accelerators, and over-the-counter topical drugs are among the most common causes of contact allergens.⁰²

Although there was no evidence that Brianna had any specific contact allergies, I did educate her on some of the most common issues we see in young girls (nickel-based jewelry, scented cleaners, specific cosmetics, etc.).

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For our newly diagnosed patients with atopic dermatitis (AD), discussions about the appropriate use of topical medications are among our educational cornerstones. There is often a lot to review and a lot for patients and families to digest. My personal experience has taught me that the primary conversation surrounds the issues of when and where to use topical agents. Here is a short list of some of the key issues that come up over and over again:

1. How will I know what medication to use?
2. How will I know where to use the medication?
3. When do I switch from topical steroid to topical anti-inflammatory?
4. How long do I use each medication for?
5. How do I know when to stop the medication?
6. What medication do I put on first?

As dermatology providers, we have a lot of information to share with our patients, and it’s extremely important that we find appropriate and effective ways for this information to sink in. Education about a chronic condition such as AD needs to be ongoing and fluid—we cannot address every key issue at the initial visit. This can be hard in some of our more complex patients who are so desperate for our help, but it’s all about prioritizing our messaging so that they can take small steps toward improving their condition.

Janie is a 7-year-old girl with moderate-to-severe AD who we first saw in our clinic about a year ago. There was nothing particularly notable or unique about her presentation—frequent itching during the day, trouble sleeping, occasional flares that caused her to miss...
school—but there was a lot I knew we needed to do, and quickly, to put her on the right path to halting the advance of her disease. At our initial visit, we agreed on a skin care plan that included the daily application of a topical corticosteroid to areas impacted by eczema for 2 weeks followed by 2 weeks of a topical anti-inflammatory. I provided Janie and her mother with what I thought was a sensible, comprehensive written skin care plan, offered extensive education on why we were suggesting this topical medication regimen, and sent them on their way. We scheduled our initial follow-up appointment in 1 month to gauge our progress.

When they arrived for their follow-up appointment, Janie’s skin looked better—not completely clear, but better. I thought to myself, “Well, I guess our treatment plan worked.”

Not so fast.

“I followed the plan you gave us exactly,” Janie’s mom told me. “For the first two weeks, it seemed like nothing was happening. It was only when we switched medications that Janie’s skin started to improve.”

This was a bit of a surprise. The expectation is that our patients’ skin will improve quickly with topical corticosteroids and then that improvement will hopefully be maintained with the topical anti-inflammatory. It is unusual for things to work in reverse, as Janie’s mom seemed to suggest had happened here.

My next step was to ask Janie’s mom to show me the medications they had been using for her daughter’s skin. That is one recommendation I have for all dermatology providers—since many of our patients use a combination of over-the-counter as well as prescription agents at some point in their care, it is extremely helpful to have them bring in everything that they are using so that they don’t have to remember all of the various product names. In Janie’s case, the prescriptions I had initially written were for two of our standbys—triamcinolone (our corticosteroid) and tacrolimus (our anti-inflammatory). Put the two product names side-by-side and you can see how there are some similarities that might confuse people.

When Janie’s mother took out the two medications to show me that they had been used in the last month, I asked her when and where they had been applied. She told me that they had initially used the tacrolimus because they were dispensed a smaller tube at their pharmacy (60 g, which was all her insurance would approve). To her, this was a sign that tacrolimus was going to be applied for a short duration, so she thought it was the corticosteroid. The triamcinolone, meanwhile, came in a 1-pound jar that I typically prescribe because it is cheaper when bought in larger quantities and patients are less likely to run out of it in times of crisis. But to Janie’s mom, this larger-sized jar seemed like an indication that the triamcinolone was the anti-inflammatory that her daughter would likely need for a more prolonged period of time.

Lesson learned!

After my experience with Janie, I have added a few tidbits to the education I deliver at our critical initial follow-up visit when we go over the first few weeks of treatment. These include the following:

1. Pointing out any chronic areas where there seems to be improvement—“This is a spot where you can apply tacrolimus (or other anti-inflammatory). You can apply tacrolimus daily for many weeks/months as long as the area doesn’t flare again. It is intended to maintain your child’s skin health.”

2. Pointing out any areas where the patient’s eczema has flared—“This is a spot where you can apply triamcinolone (or other corticosteroid). You can apply triamcinolone twice daily as often as 2 weeks per month for flares, or a few times a week as directed by our team. It is intended to improve your child’s skin when their disease is flaring.”

3. Pointing out any areas that seem infected/fissured/oozy—“This is a spot where you can apply mupirocin (or other antibiotic) to help fight infection. You can apply mupirocin 3 times a day until the affected area heals.”

4. Pointing to the whole body—“This is where you should apply moisturizer twice a day. In specific problem areas, you can apply it more frequently if you’d like.”

With Janie, once we cleared up the triamcinolone vs. tacrolimus issue, I inquired further with her mother about their topical application regimen. She told me that she was first applying moisturizer and then the topical prescription medication. Again, she had it backwards, so I gently reinforced to her that the topical medications needed to be applied first so that they could start working before the moisturizer is
applied. I also reviewed “the 3-minute rule”—pat the patient’s skin dry after a bath/shower and apply the topical agents while the skin is still damp.

Because there is unfortunately no “magic bullet” that works for every patient with AD, especially those with more significant baseline disease, I also emphasized to Janie and her mother that it was likely going to take some time to find a treatment regimen that would work and they would be able to stick with over the long term. We talked about the need for regular check-ins and appointments, even when Janie’s disease was well controlled, so that we could review what was working—and what wasn’t—and tweak our approach as needed.

At our next follow-up appointment a month later, it seemed like the bumps in the road had been smoothed out. Janie’s eczema was much improved, and her mother seemed confident following the details of the topical application regimen. Clearly, the plan was now working.

As any nurse will tell you, patient education is the pillar of managing any disease, and especially a chronic condition like AD that requires diligence and patience to maintain. It is important to not just throw everything at our patients and their families all at once. Instead, we must continually check-in to ensure that there is no confusion or misinterpretation so that any issues are corrected quickly.

REFERENCE

As dermatology providers, we all see many patients with atopic dermatitis (AD). The vast majority of these patients obtain adequate control of their disease through the use of topical treatments and avoidance of known triggers. However, in patients with more severe, recalcitrant disease, a more aggressive approach is warranted, which often involves the use of systemic therapy in order to provide relief for relentless pruritus and cutaneous inflammation. There are several systemic therapies proven to be beneficial in patients with AD, although providers must carefully weigh the benefits and risks of specific options before a recommendation can be made.

Let’s start by discussing **systemic corticosteroids**, which have been available for decades and are easily accessible and affordable. The potentially dramatic effect of systemic steroids makes them an option that patients readily embrace, and many are reluctant to stop taking them. This puts pressure on the healthcare provider, making it crucial that we proactively educate patients about the potential downstream side effects of long-term use of systemic corticosteroids so that patients understand the importance of limiting their use. Some of the more notable side effects of corticosteroids include Cushing’s syndrome, cataracts, increased intraocular pressure (which can lead to glaucoma), and osteoporosis. While long-term use of systemic corticosteroids should be avoided, short bursts of a tapering dose over a 1-2–week period may help to calm an acute AD flare as patients transition to safer, long-term therapy.

**Cyclosporine** is commonly used in transplant patients to prevent rejection as well as graft vs. host disease. As an immune modulator, cyclosporine has the ability to selectively suppress T cells, which makes it an effective treatment for inflammatory skin diseases. Cyclosporine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe psoriasis but not for the treatment of AD, so it is used off-label in these patients, typically in children and adults with severe, recalcitrant disease. Cyclosporine has been shown to substantially reduce pruritus, allowing patients to sleep better and improving their quality of life. Due to the potential of serious side effects such as hirsutism, hypertension, and nephrotoxicity, cyclosporine is best used as short-term therapy (<6 months) or as a bridge while waiting for insurance coverage of another medication. For patients who are prescribed cyclosporine, it is recommended that they have their blood pressure, blood urea nitrogen, and creatinine levels checked on a monthly basis.

**Methotrexate** is a chemotherapy agent and immunosuppressant that has been shown to be helpful in treating several autoimmune conditions. Methotrexate is FDA approved for the treatment of psoriasis and rheumatoid arthritis but is prescribed off-label for patients with AD. Methotrexate can be administered either orally or by injection. As with other systemic therapies, methotrexate is often utilized on an interim basis while patients transition to another treatment. Common side effects associated with methotrexate include hepatotoxicity, ulcerative stomatitis, leukopenia, nausea, abdominal pain, fatigue, fever, dizziness, acute pneumonitis and kidney failure. One important note for providers: as a teratogenic drug, use of methotrexate is contraindicated in women attempting to get pregnant. All patients of childbearing age should be on birth control prior to initiating methotrexate.

Other traditional systemic agents used off-label in the treatment of AD include **mycophenolate mofetil (MMF)** and **azathioprine (AZA)**. Both are immunosuppressive drugs that are FDA approved for multiple indications but not for the treatment of AD; however, some providers who have prescribed these treatments in patients with severe AD have reported reduction of pruritus and improvement of skin inflammation. The most common side effects of MMF are nausea and upset stomach. Headaches, dizziness, sleep disturbances, tremor, and skin rashes are also known side effects. If MMF is used for a prolonged period of time (which is not recommended), more serious side effects such as lymphoma or other cancers may emerge. Consequently, providers considering the short-term use of MMF in patients with AD should have an alternate therapeutic plan in place. Additionally, regular blood tests to monitor blood chemistries, liver function, and complete blood count are required in patients taking MMF. AZA, meanwhile,
is sometimes considered as a second-line treatment option for patients with AD. Its use is recommended only as short-term induction therapy or for longer-term use up to 24 weeks. As with other traditional systemic medications, MMF and AZA are most commonly used as bridge therapies for patients transitioning to other treatment regimens or for those waiting on insurance approval for another medication.

Lastly among our more traditional systemic options for patients with AD, ultraviolet light therapy, and specifically narrowband ultraviolet B (NB-UVB), is often recommended based on its confirmed efficacy in randomized controlled trials. Studies have shown that NB-UVB can lead to skin clearance/near-clearance in some patients with moderate-to-severe AD and reduce the need for topical corticosteroids. NB-UVB is used most frequently in combination with other therapies or when patients are transitioning off of other systemic agents.

For many years, this list of off-label agents was all we had from a systemic standpoint to help patients with AD. That all changed, as we know, with the approval of dupilumab in 2017. Dupilumab is a fully human interleukin (IL)-4 and IL-13 inhibiting monoclonal antibody currently approved for the treatment of moderate-to-severe AD in patients aged 6 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab blocks dual pathways that are responsible for the development of inflammation and pruritis. In clinical trials, side effects related to dupilumab have been mild and show no significant differences from those treated with placebo medications.

I have had many individuals with long-standing disease for whom the introduction of dupilumab into their therapeutic plan has put their skin “at peace” for the first time in their lives. These are patients like Paul, a 40-year-old with lifelong AD who is married with two children. Paul recently told me that he can remove his shoes and socks at the end of the day for the first time in his life without his feet itching. And patients like Sally, a 66-year-old who has suffered with severe AD for decades and typically needed to take multiple courses of prednisone simply to be able to function at work. Sally had run out of traditional medical options and turned to alternative therapy for several years only to find that her disease continued to wax and wane with frequent severe flares regardless of her treatment. It was only when Sally was prescribed dupilumab that her symptoms calmed and her quality of life dramatically improved.

It is extremely gratifying to have more, and better, systemic tools in our arsenal to treat patients with moderate-to-severe AD. These are patients who often suffered for decades without much hope that their disease would get substantially better. As new agents become available, it will challenge the abilities of providers both to educate their patients on the key differences of each option and determine which option is most likely to lead to optimal outcomes.

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The opinions expressed in this publication are those of the participating faculty and not those of the Dermatology Nurses’ Association, Incyte, Pfizer, or any manufacturers of products mentioned herein.

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