

AJMC[®] PERSPECTIVES

THE AMERICAN JOURNAL OF MANAGED CARE[®]

JULY 2024

Managing Atopic Dermatitis: Clinical Considerations, Payer Perspective, and 2024 Guidelines

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Monoclonal Antibodies and JAK Inhibitors in Atopic Dermatitis Management: 2024 Guidelines and Managed Care Considerations

Introduction

ATOPIC DERMATITIS (AD), also known as *atopic eczema*, is a pruritic inflammatory skin disorder characterized by recurrent eczematous lesions with reddened, blistered, crusty, or oozing skin; lichenification; and xerosis.¹⁻³ Its clinical presentation varies greatly, and signs and symptoms can manifest on any area of the body.¹ The disease has a complex pathogenesis and heterogeneous presentation that is often associated with allergic, immune-mediated, and psychological comorbidities.^{1,4-6} Contrary to the common perception of it being primarily a childhood disease, AD affects approximately twice as many adults in the United States as it does children.^{7,8}

The significant burden imposed by AD on patients and the health care system includes increases in hospitalizations, health care costs, loss of work productivity, and disability.⁹⁻¹⁴ This impact is particularly pronounced among patients with moderate or severe AD, because inadequate control of the disease can dramatically decrease quality of life (QOL).^{10,15}

The 2024 American Academy of Dermatology (AAD) guidelines of care for the management of AD using phototherapy and systemic therapies in adults provide an important update to the AAD's 2014 guidelines and offer recommendations on the use of monoclonal antibodies and JAK inhibitors.¹⁶ This article offers an overview of the clinical and economic impacts of AD, reviews the 2024 guidelines with a focus on strong recommendations, and discusses managed care considerations related to guideline implementation.

Clinical Impact

Pruritus, or itching, stands out as a central feature of AD and significantly contributes to the heavy burden experienced by patients.^{2,17} Outcomes of a study involving 380 adults with moderate to severe AD revealed that the majority reported experiencing daily itching, with nearly 60% describing it as *unbearable* or *severe*.¹⁰ In the United States, AD demonstrates a notable association with immune-mediated comorbidities such as ulcerative colitis and pernicious anemia.⁵ Moreover, adults with AD in the US exhibit a higher prevalence of cardiovascular conditions (eg, heart disease, high blood pressure) and psychological issues (eg, depression, anxiety) compared with those who are unaffected by the disease.⁶

The clinical impact of AD can be quantified through disability-adjusted life years (DALYs), a measure indicating the years of full health lost due to premature death or disability caused by a disease.^{18,19} Data from the Institute for Health Metrics and Evaluation's Global Burden of Disease study indicated that in terms of all skin diseases in 2017, AD had the highest age-standardized DALY rate (123 per 100,000 individuals; 95% uncertainty interval [UI], 66.8-205 individuals)

followed by psoriasis (70.0 per 100,000 individuals; 95% UI, 49.7-92.5 individuals).¹⁸

Further underscoring the burden of AD, an analysis of data from the 2013 US National Health and Wellness Survey (NHWS) revealed that adults with AD were more than twice as likely as matched controls without AD to report sleep disorders, depression, and anxiety ($P < .001$ for all).²⁰ These statistics highlight the significant impact of AD on patients' daily lives, mental well-being, and overall health.

Economic Impact

The economic impact of AD in the United States amounts to approximately \$7 billion annually (2024 US\$) for both direct and indirect costs.²¹⁻²³ Direct costs include expenses related to visits to the hospital, emergency department (ED), and medical office and to prescription and over-the-counter medications.²¹ Indirect costs encompass expenditures associated with the time invested by patients, families, or caregivers in medical care; loss of work productivity; inability to engage in leisure activities; and costs of lost future earnings.²¹ In 2018, unadjusted annual health care costs for 31,164 adults with AD were \$4979 higher than were costs for 93,492 matched controls (\$14,603 vs \$9624, respectively); this was primarily driven by increased outpatient services and pharmacy expenditures.²⁴ Further analysis from health care claims data across various populations consistently shows that adults with AD have greater use of health care resources; further, higher disease severity correlates with increased ED visits, outpatient visits, and pharmacy prescriptions compared with not having a diagnosis of AD.^{25,26}

2024 AAD Guidelines

The AAD's 2024 guidelines for treating adults with AD using phototherapy and systemic therapies provide an update to the 2014 guidance. The treatment landscape has changed substantially since 2014. The 2024 update involves new evidence for established treatments and provides guidance for newer treatment options (eg, biologics, JAK inhibitors).¹⁶

The update was developed by an expert multidisciplinary work group using a systematic evidence review process. Members of the work group gathered safety and effectiveness data through systematic reviews and meta-analyses of randomized clinical trials (RCTs), where available, or consultations with experts in review groups. To ensure that patient values and preferences were considered, a patient representative was included, and a literature search for patient-reported outcomes, resource use, and feasibility was conducted. Assessment of evidence and formulation of recommendation strength used the Grading of Recommendations, Assessment, Development, and Evaluations framework.¹⁶

TABLE 1. Strong AAD Recommendations on Phototherapy and Systemic Therapies to Manage Atopic Dermatitis^{16,a}

Intervention	US regulatory status
Monoclonal antibodies (biologics)	
Dupilumab	On-label
Tralokinumab	On-label
Upadacitinib	On-label
JAK inhibitors	
Abrocitinib	On-label
Baricitinib	Off-label

AAD, American Academy of Dermatology.

^aAll recommendations are for patients with moderate to severe disease and are associated with a moderate certainty of evidence.

Recommendations discussed in the guidelines are for adults with moderate to severe disease. Concurrent use of topical agents with phototherapy or systemic agents is permitted for rescue, treatment of flares, or maintenance of response.¹⁶

The work group provided updated recommendations on therapies included in the 2014 guidelines. Conditional recommendations were made for the on-label use of phototherapy using UV radiation based on reports of the efficacy and safety of narrow-band UV-B. Conditional recommendations were also made for the off-label usage of methotrexate, mycophenolate, azathioprine, and cyclosporine with proper monitoring for adverse events (AEs). In response to immunosuppressants, members of the work group conditionally recommended against the use of systemic corticosteroids due to low-certainty evidence of efficacy and a substantial risk of serious AEs. Use of systemic corticosteroids should be limited to short courses in acute exacerbations for which no other options are available or as a bridge to other systemic therapy.¹⁶

Strong Recommendations

Strong recommendations were made for the use of monoclonal antibodies (biologics) and oral JAK inhibitors in adults with moderate to severe disease (**Table 1**).¹⁶

Monoclonal Antibodies

The updated AAD guidelines provided strong recommendations for the on-label use of dupilumab and tralokinumab.¹⁶ These biologics are FDA-approved for AD in adults; overall, their use has resulted in strong efficacy and safety data.^{16,27,28} However, due to statistical inconsistency in AE analyses, members of the work group downgraded the overall certainty of evidence for these

agents to *moderate*.¹⁶ Unlike other systemic options for the treatment of AD, no laboratory monitoring is required with use of dupilumab and tralokinumab. Conjunctivitis remains a common AE with both monoclonal antibodies (incidence, $\geq 1\%$); however, it is generally self-limiting, and it can be managed with artificial tears.^{16,27,28}

DUPILUMAB The first FDA-approved targeted systemic treatment for AD was dupilumab, a human monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling.^{27,29} Dupilumab is indicated for the treatment of adult and pediatric patients 6 months and older with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when use of those therapies is not advisable.²⁷ The efficacy and safety of dupilumab in adults with moderate to severe AD was evaluated in 3 large RCTs (SOLO 1 [NCT02277743], SOLO 2 [NCT02277769], and LIBERTY AD CHRONOS [NCT02260986]) including a 52-week trial assessing the long-term outcomes and AEs.^{30,31} In 2024, an update of the dupilumab label included data that further supported use of the drug in patients with moderate to severe hand and foot AD involvement; this population is especially difficult to treat.³²

More recent real-world evidence supports long-term use of dupilumab in AD. The PROSE trial (NCT03428646) is a prospective, observational, multicenter study conducted in the United States and Canada that is gathering real-world data from patients with AD who have received dupilumab therapy for at least 2 years.³³ Patients 12 years or older with moderate to severe AD are given dupilumab per country-specific prescribing information. The collected data include objective clinician-assessed measures of AD disease severity (eg, body surface area [BSA] affected by AD, Eczema Area and Severity Index [EASI] scores) and patient-reported measures of symptoms and QOL (eg, Pruritus Numerical Rating Scale [P-NRS] and Dermatology Life Quality Index [DLQI]). Patients were assessed at baseline, at month 3, at month 6, and then every 6 months thereafter through year 5. Data are still being collected for this ongoing registry. At the time of data cut-off for this report, 632 of 764 enrolled patients remained in the study (mean duration of treatment, 18.9 months). In the interim analysis, consistent improvements in clinician-assessed measures and patient-reported outcomes were seen during the first clinic visit after 3 months of therapy; these effects were sustained throughout the 24-month observation period, supporting the long-term efficacy of dupilumab in AD. The drug was well tolerated in the cohort; AEs were consistent with experiences in previous clinical trials, with the most common being conjunctivitis (2.4%). Findings of this real-world evidence and claims-based analysis are limited by the lack of a comparator group, of control over concomitant adjunct

treatments received by patients, and of the selection of sites and patients who chose to enroll in this study.³³

Another real-world, retrospective cohort study was conducted in patients with AD to evaluate satisfaction with and tolerability of dupilumab therapy as shown by patient persistence with treatment at 12 months.³⁴ Data from 2016-2018 were collected from IBM MarketScan commercial and Medicare claims databases, and patients 18 years or older were identified by 1 or more *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* diagnosis codes for AD. The index date was recorded as the first dupilumab dispensing event. Patients were assumed to have discontinued the medication if they did not have dupilumab dispensed again within the 30-day grace period between doses. Patients were considered reinitiators if they received dupilumab again after discontinuation. In all, 1963 patients were followed for an average of 314.5 days, and high rates of treatment persistence were observed. Persistence rates were 91.9% at 6 months and 77.3% at 12 months. Interestingly, 78.8% of individuals who discontinued therapy subsequently reinitiated treatment, usually within 4 months of discontinuation. These persistence rates were substantially higher than were real-world 12-month persistence rates found in other studies of patients with psoriasis who were given the biologics adalimumab (50%-62%) or infliximab (19%-50%).³⁴

Patient-reported outcomes can provide valuable real-world insights into the impact of the disease on a patient's QOL and daily functioning and may help improve management of AD.³⁵ Patients can report on their mood, self-esteem, sleep disturbances, and ways that the condition affects their relationships and daily activities. In the prospective, longitudinal, real-world RELIEVE-AD study, patient-reported disease control and QOL were evaluated after the first year of dupilumab use for AD.³⁵ Patients 18 years or older who had been prescribed dupilumab in routine clinical practice were enrolled in the trial and in the dupilumab patient support program. Patient outcomes were reported using the Atopic Dermatitis Control Tool (ADCT), a 6-point questionnaire evaluating symptom severity, number of days experiencing intense itch, and the degree to which AD was bothersome to affect sleep, daily activities, and mood over the past week. Additionally, patients reported the number of flares experienced over the past 4 weeks, documented their DLQI scores, and responded to the Work Productivity and Activity Impairment Questionnaire for AD (WPAI:AD) to elucidate a multifaceted evaluation of disease management. The survey was completed by 632 patients at month 1 and 483 patients at month 12. The results demonstrated rapid and sustained improvements in the patient-reported assessments throughout the study duration. The majority (>60%) of patients achieved adequate disease control

(ADCT score, < 7) at month 1 with further improvement noted at each subsequent monthly follow-up; the mean (SD) ADCT score at month 12 was 4.4 (4.9). No flares were reported in 21 of 699 patients (3%) at baseline and 210 of 483 patients (43.5%) at month 12; no days of intense itch was reported in 22 of 699 patients (3.1%) at baseline and 257 of 483 patients (53.2%) at month 12. Substantial improvements in sleep behaviors were observed with the proportion of patients experiencing sleep problems decreasing from 77.5% (542 of 699 patients) to 14.1% (68 of 483 patients). Improvements in DLQI and WPAI:AD scores on all scales were also observed, and patient satisfaction was high (85.1%). The overall medication discontinuation rate was 10.9%, with AEs and lack of efficacy being the most common reasons for discontinuation.³⁵

TRALOKINUMAB In December 2021, tralokinumab became the second biologic indicated for the treatment of AD and the first treatment to specifically target IL-13.^{28,36} Tralokinumab is indicated for the treatment of moderate to severe AD in patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when use of those therapies is not advisable.²⁸ The safety and efficacy of tralokinumab in treating adults with AD was evaluated in the ECZTRA series [ECZTRA 1 (NCT03131648), ECZTRA 2 (NCT03160885), and ECZTRA 3 (NCT03363854)] of 3 large, randomized, double-blind, placebo-controlled trials in subjects 18 years and older with a diagnosis of moderate to severe AD for at least 1 year that was not adequately controlled with topical therapies.^{37,38}

Tralokinumab has not been evaluated in any head-to-head studies against other systemic therapies. In a systematic review and meta-analysis, tralokinumab showed slightly lower effectiveness compared with dupilumab after 16 weeks of treatment; use of tralokinumab resulted in a slightly reduced EASI score versus dupilumab (mean difference, -3.5; 95% CI, -5.8 to -1.3).³⁹

Results from a 6-month interim analysis of an ongoing, 52-week, real world-evidence study evaluating patient-reported outcomes of AD treatment with tralokinumab were presented at the 2023 Fall Clinical Dermatology Conference.⁴⁰ Data were collected from adult patients enrolled in the Adbry Advocate Program who completed surveys at baseline, at 1 month, and at 6 months; outcomes were stratified by previous dupilumab use. Of the 102 patients included in the interim analysis, half or more reported meaningful improvements in mean sleep, average weekly itch, and worst weekly itch NRS (57.1%, 57.1%, and 50.0%, respectively). Among all patients, 68.7% had an improvement in DLQI scores, with a 4.81-point improvement noted from baseline (range, 0-30 points). The study authors also identified a downward trend in the use of

concomitant medications to treat AD. Treatment response varied within the cohort of patients who previously used dupilumab. Some individuals reported improvements in patient-reported outcomes, whereas others did not experience a response to treatment.⁴⁰

Oral JAK Inhibitors

The updated AAD guidelines also provide strong recommendations for the use of systemic JAK inhibitors for the treatment of moderate to severe AD in adults including the on-label usage of upadacitinib and abrocitinib and the off-label usage of baricitinib.¹⁶ Upadacitinib and abrocitinib are FDA-approved for patients with moderate to severe AD for whom use of other systemic therapies, such as biologics, has failed to adequately manage disease or when use of other therapies are inadvisable.^{41,42} Upadacitinib and abrocitinib exhibit preferential targeting of JAK-1.^{41,42} Baricitinib, a dual JAK-1 and JAK-2 inhibitor, is approved for use in Europe in patients with moderate to severe AD.^{16,43} Its availability in the US for other immune-mediated conditions underscores its potential as an effective, off-label therapy for AD.¹⁶

The safety and efficacy of abrocitinib as monotherapy and in combination with topical corticosteroids (TCS) were established by the results of the 3 randomized, double-blind, placebo-controlled trials: JADE MONO-1 (NCT03349060), JADE MONO-2 (NCT03575871), and JADE COMPARE (NCT03720470).⁴⁴⁻⁴⁶ The safety and efficacy of upadacitinib were evaluated in 3 randomized, double-blind, multicenter trials—Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318)—involving patients with moderate to severe AD who were not adequately controlled by topical medication and who were candidates for systemic therapy.⁴⁷⁻⁴⁹ Baricitinib is the first JAK inhibitor approved in the European Union and Japan to treat patients with moderate to severe AD who have an inadequate response to topical treatments.⁵⁰ Despite not being approved by the FDA for this indication, baricitinib is widely used in clinical practice, and it has been given a strong recommendation by the updated AAD guidelines for use in adults with moderate to severe AD.¹⁶

All JAK inhibitors carry a black box warning regardless of treatment indication based on safety concerns from clinical trials investigating the JAK inhibitor tofacitinib in patients with rheumatoid arthritis.^{41,42,51,52} Serious AEs such as increased risk of serious heart-related events, cancer, blood clots, and death were seen in the tofacitinib studies.⁵¹

A systematic review and meta-analysis was conducted to determine the association of AD with incident venous thromboembolism (VTE) and to evaluate the risk of VTE among patients who were receiving treatment with JAK inhibitors for AD. The meta-analysis showed that compared with findings in cohorts receiving placebo or

dupilumab, there was not an increased risk of VTE among patients with AD or a significant difference in the risk of incident VTE in patients with AD who were receiving JAK inhibitors. However, the relatively short durations of the included trials may limit these findings, and further data from long-term real-world evidence are needed.⁵³

In clinical trials of patients with AD, AEs including death and thromboembolic events were also observed. Due to potential safety concerns with this class of medications, the JAK inhibitors are not regarded as first-line systemic therapy. To mitigate potential safety concerns, treatment should be initiated at lower doses, especially in older adults at greater risk.¹⁶

In addition to the cardiovascular risks, a potential for serious and opportunistic infections, including herpes zoster infection, is related to use of JAK inhibitors. Vaccination against shingles with special attention in older patient populations is recommended before JAK inhibitor therapy is begun. Furthermore, patients should receive necessary live vaccines before commencing treatment. The FDA advocates for comprehensive monitoring of patients on JAK inhibitors; this involves baseline assessments and subsequent evaluations. Recommendations include complete blood count with differential and liver enzyme checks at baseline along with additional monitoring after therapy initiation or dose escalation. Lipid assessments are advised after initiation; testing intervals vary for abrocitinib and upadacitinib. Baseline testing for viral hepatitis, tuberculosis, and pregnancy status is also recommended.¹⁶

The AAD's strong recommendations for JAK inhibitors is supported by the high efficacy of these agents that has been demonstrated in clinical trials.^{16,44,46,49,54} As with the biologics dupilumab and tralokinumab, the overall certainty of evidence for JAK inhibitors was downgraded

from high to moderate due to statistical inconsistency in AE analyses.¹⁶

Managed Care Considerations

The implementation of the updated AAD guidelines on systemic treatments for AD should involve a comprehensive approach that considers the limitations of long-term topical agents and Institute for Clinical and Economic Review (ICER) recommendations on the use of JAK inhibitors and monoclonal antibodies in AD treatment (**Table 2**).⁵⁵

Shortcomings of Long-Term Use of Topical Agents

The 2024 AAD guidelines strongly recommend against the use of systemic corticosteroids.¹⁶ Moreover, medium- to high-potency TCS are not intended for daily, long-term use given the risk of systemic absorption and AEs.² The guidelines permit the use of TCS and topical calcineurin inhibitors (TCIs) for maintenance of response, rescue, or treatment of flares as an adjunct to phototherapy or systemic therapy in patients with moderate to severe disease.¹⁶ However, findings from a study using 2015 data sourced from the Truven Health Analytics MarketScan Commercial and Medicare Supplemental databases showed that the use of TCS or TCIs for AD impacts pharmacy expenditures regardless of the treatment choice.⁵⁶ Annual prescriptions per individual for TCS and/or TCIs ranged from 1 to 6. Similarly, the annual prescription cost per patient varied based on the type of medication (TCI vs TCS) and the strength of the TCS. While patients using medium-potency TCS alone had an annual prescription cost as low as \$53.11, most patients had annual costs exceeding \$250, with some reaching as high as \$1465.03 each year.⁵⁶

TABLE 2. ICER Final Evidence Report: Key Policy Recommendations⁵⁵

Stakeholders	Recommendation
All	Introduction of effective new treatment options for patients with atopic dermatitis should promote health equity.
Payers	Patient eligibility: Clinicians need mechanisms for seeking coverage exceptions for patients who are near the age cutoff for coverage and who have serious unmet needs.
	Clinical eligibility: Given the lack of clear consensus on how <i>moderate to severe</i> atopic dermatitis is defined, the definition of <i>disease severity</i> should be kept broad to include multiple measures of disease intensity.
	Duration of coverage and renewal criteria: The initial coverage period should be 6-12 months to allow for dose titration, assessment of adverse events, or disease progression.
	Step therapy: Step therapy should be used only when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.
Manufacturers	Coverage: If multiple agents for severe atopic dermatitis are approved, at least 1 biologic (dupilumab and/or tralokinumab) and at least 1 JAK inhibitor should be included given how different these classes are in their onset of action and their risk profile.
	Long-term registries should be established for assessment of the benefits and harms of chronic oral JAK inhibitor use for patients with atopic dermatitis, as there are potentially serious risks and adverse events associated with their use.

Recommendations From the 2021 ICER Report on JAK Inhibitors and Monoclonal Antibodies for the Treatment of AD

ICER is an independent nonprofit research institute dedicated to furthering evidence regarding the effectiveness and value of medications and various medical services.⁵⁷ The institute’s reports feature evidence-based calculations of prices for new drugs that align with anticipated long-term improvements in patient outcomes.⁵⁸ In 2021, ICER assessed the comparative clinical effectiveness and value of AD agents.⁵⁷ The final evidence report (“JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value”) compared tralokinumab, abrocitinib, baricitinib, and upadacitinib with topical emollients and dupilumab and offered policy recommendations for stakeholders.⁵⁷

Using a Bayesian network meta-analysis based on available data from monotherapy RCTs, the authors conducted a quantitative, indirect comparison of the systemic treatments for AD. The authors concluded that the net health benefit of baricitinib and tralokinumab were comparable or inferior when compared with dupilumab and that the evidence

for net health benefit for abrocitinib and upadacitinib compared with dupilumab was insufficient. The authors also favored dupilumab with respect to safety, citing both the agent’s long-term safety profile and concerns surrounding the safety of oral JAK inhibitors. Finally, the authors cited dupilumab’s proven efficacy in patients with comorbid conditions such as asthma or chronic rhinosinusitis.⁵⁷

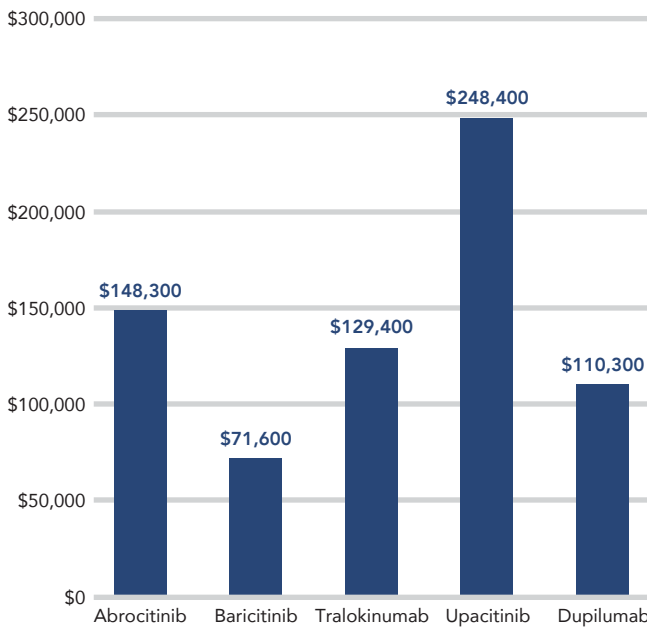
The authors also conducted a cost-effectiveness analysis comparing the oral JAK inhibitors with dupilumab and using placeholder prices for abrocitinib and tralokinumab. This demonstrated that baricitinib and tralokinumab would be less costly and less effective than dupilumab (Figure A).⁵⁷ As compared with dupilumab, the cost per QALY or equal-value life year gained with use of abrocitinib and upadacitinib would be \$303,400 and \$1,912,200, respectively (2021 US\$) (Figure B).⁵⁷

Ensuring Access to at Least 1 Monoclonal Antibody and 1 JAK Inhibitor

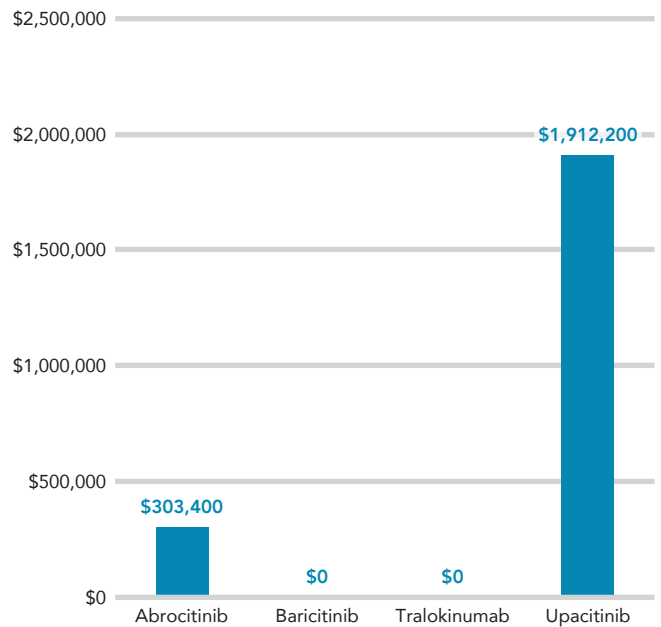
When considering formulary coverage for severe AD, the ICER report recommends that if multiple agents for severe AD are approved, payers include at least 1 biologic and at

FIGURE. Incremental Cost-Effectiveness Ratios for Systemic AD^{57,a}

A. Cost per QALY/evLY Gained Compared With Standard of Care



B. Cost per QALY/evLY Gained Compared With Dupilumab^b



AD, atopic dermatitis; evLY, equal-value life-year; QALY, quality-adjusted life-year.

^aTreatments have not been shown to lengthen life. Consequently, the ratios of cost per QALY and cost per evLY gained were the same. In the study, placeholder prices were used for abrocitinib and tralokinumab.

^bBaricitinib and tralokinumab were found to be less costly and less effective than dupilumab.

least 1 JAK inhibitor. This approach recognizes the distinct characteristics of these medication classes including differences in onset of action and risk profiles. The offer of both classes of medications gives patients and health care providers access to diverse treatment options that cater to individual preferences, responses, and safety profiles.⁵⁷

Accounting for Multiple Measures of Disease Severity

The ICER report advises payers to develop a broad, clinically relevant definition of AD that includes multiple specific measures of disease intensity. This recommendation accounts for the lack of a universally accepted definition of *moderate to severe* disease. It also reflects clinicians' lack of familiarity with AD scoring systems used in clinical trials. Finally, the recommendation acknowledges that severity of AD can fluctuate significantly over time and that it encompasses a multitude of factors from the patient's perspective (eg, itch intensity, affected body areas, skin impairment, and overall QOL impact).⁵⁷

The report authors noted that a definition of moderate to severe AD might include, for instance, "any of the following: Body Surface Area (BSA) \geq 10%, Investigator's Global Assessment (IGA) \geq 3, Eczema Area and Severity Index (EASI) \geq 16," or "affected BSA \geq 10% OR involvement of challenging-to-treat body sites (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) or severe itch unresponsive to topical therapies."⁵⁷

Whereas some payers may accept clinician attestation, others may base criteria on clinical trial eligibility.⁵⁷ Clinical eligibility criteria are crucial in determining access to newer-generation treatments for AD, especially considering the diverse range of patients with varying levels of severity and the potential for AEs associated with these medications. However, it is equally important that limitations imposed by payers do not unduly restrict patient access to necessary therapies.

Limitations to Step Therapy

ICER report authors also advise that formulary decision makers approach step therapy for AD with flexibility, transparency, and efficiency to meet the diverse needs of patients.⁵⁷

Clinical experts and patient representatives note common challenges such as delayed access to treatment, documentation burdens, and inadequate procedures for exceptions that lead to frustration and poor outcomes for some patients. Payers should consider offering at least 1 biologic and 1 oral JAK inhibitor as first-step therapy options, recognizing the differences in onset of action and risk profiles between these classes of drugs. The heterogeneity of AD supports the need for access to a range of different therapies rather than limiting step therapy to only 1 treatment option across biologics and oral JAK inhibitors.

Step therapy policies should consider patient-specific characteristics and offer options that align with their particular needs (eg, periodic use of a JAK inhibitor for patients with seasonal disease, biologic treatment for patients with more year-round severity or asthma). Overall, the guidance underscores the importance of considering individual patient needs, clinical appropriateness, and treatment efficacy when implementing step therapy for AD.⁵⁷

Conclusions

Commonly known as *eczema*, AD is a prevalent, chronic skin condition characterized by itchy, inflamed, and dry lesions that can persist or recur. It affects both children and adults, impacting various aspects of their lives including sleep, psychological well-being, and productivity. Further, this disease is associated with substantial clinical and economic impact. There are several treatment options that have shaped the landscape of systemic therapy for AD management; these include the biologics dupilumab and tralokinumab and the oral JAK inhibitors abrocitinib, baricitinib, and upadacitinib.

The AAD published updated clinical guidelines in 2024 for the use of phototherapy and systemic therapies to treat adults with AD; these guidelines strongly recommend that monoclonal antibodies and JAK inhibitors be given as systemic treatments for moderate to severe disease. These guidelines build upon the previous 2014 recommendations for AD management in patients who do not respond to topical therapies and underscore the importance of incorporating multiple measures of disease severity. Implementation of these guidelines is crucial to ensure equitable access to effective AD treatments. To promote effective new treatment options that reduce health inequalities, health care providers should incorporate findings from the 2021 ICER review on the clinical and cost-effectiveness of treatments for AD as they manage this chronic disease. ♦

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Clinical Considerations in Treatment Selection for Atopic Dermatitis

A Q&A With Jonathan Silverberg, MD, PhD, MPH



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AJMC®: What has your experience been in treating atopic dermatitis and participating in clinical trials?

SILVERBERG: As a board-certified dermatologist in an academic referral center, I encounter a substantial caseload of patients with atopic dermatitis and other chronic inflammatory skin conditions. Often, these cases are complex, having been referred after assessment by other dermatologists in private practice. Through my academic setting, I've had the privilege of witnessing the evolution of innovative therapies in this field. Regarding clinical trials, my involvement spans over a decade, beginning with the original phase 1 trials of dupilumab for atopic dermatitis. Since then, I've participated in numerous clinical trials for emerging therapies including those currently in late-stage development. This period has been marked by significant advancements in our understanding and treatment of atopic dermatitis, making it an incredibly exciting time for clinical research in the field.

AJMC: Which other diseases have a similar pathophysiology as atopic dermatitis, and what are the roles of the key mediators of type 2 inflammation?

SILVERBERG: Atopic dermatitis is a complex and heterogeneous disease involving the activation of various immune pathways. Key mediators such as interleukin (IL)-13 and -4 along with the broader Th2 pathway play pivotal roles. Additionally, cytokines like IL-31 and possibly IL-22 may contribute, although further research is needed for the latter. In terms of overlapping pathophysiology, several diseases share similarities with atopic dermatitis, particularly those mediated by type 2 inflammation. These include asthma, hay fever, food allergies, and eosinophilic esophagitis. Recent discussions also highlight the potential involvement of IL-31 in conditions like prurigo nodularis with emerging considerations for disorders such as scleroderma and urticaria. Thymic stromal lymphopoietin, implicated in atopic dermatitis, also plays a significant role in asthma. While some overlaps are practical, like the manifestation of prurigo nodules in some patients with atopic dermatitis, others remain theoretical. Understanding these overlaps is crucial for improved management and targeted treatment approaches.

AJMC: How has the treatment landscape for atopic dermatitis changed over the past 20 years?

SILVERBERG: The treatment landscape for atopic dermatitis has undergone remarkable evolution over the past 2 decades. Initially overshadowed by psoriasis in terms of drug development, atopic dermatitis has seen a surge in therapeutic innovation. In the topical space, significant strides have been made with the approval of various agents. Crisaborole, a phosphodiesterase inhibitor, was a pivotal addition for mild to moderate atopic dermatitis in 2016. Subsequently, topical ruxolitinib (a JAK inhibitor) and topical roflumilast (a PDE4 inhibitor) have further expanded our options with ongoing developments in early-stage modalities. However, the most revolutionary advancements have

occurred in the biologic realm. Pre-2017, atopic dermatitis lacked clean biologics until the approval of dupilumab (a monoclonal antibody targeting IL-4 and -13 signals) for moderate to severe disease. Following this, tralokinumab and lebrikizumab (both targeting IL-13) gained approval, with nemolizumab (which targets the IL-31 α subunit) soon to follow. These biologics offer targeted relief particularly in managing itch and related conditions like prurigo nodularis. Moreover, the oral realm, previously limited to off-label use of medications like methotrexate or cyclosporine, now boasts 2 approved oral JAK inhibitors—upadacitinib and abrocitinib—for moderate to severe atopic dermatitis. While highly effective, these medications can present with challenges regarding safety. This broadening toolbox encompasses oral agents, injectables, and innovative topical agents catering to diverse patient needs and preferences. With options for long-term management and effective itch relief, the current landscape signifies an exciting era in atopic dermatitis treatment.

AJMC: When do you consider switching therapies from topical steroids or adding another therapy in your patients with atopic dermatitis?

SILVERBERG: Determining when to switch therapies or add additional treatments for patients with atopic dermatitis is not a one-size-fits-all decision. Several important considerations come into play. Shared decision-making is a key approach I advocate for. This involves discussing treatment options with patients, understanding their goals and perspectives, and aligning the right medication with their individual needs and preferences. This process is essential after recognizing that the current therapy may not be effective for the patient. To effectively identify patients with inadequate responses, structured approaches in clinical practice are beneficial. Routinely tracking parameters such as body surface area and severity of lesions along with assessing symptoms like itch, sleep disturbances, and skin pain provides valuable insight. Utilizing tools like numeric rating scales for itch helps to capture the full spectrum of the disease's symptomatology. If patients exhibit moderate or severe symptoms despite current therapy, it's time to consider stepping up treatment. This prompts the initiation of shared decision-making discussions to explore alternative options tailored to the patient's specific needs and treatment goals.

AJMC: Why was it necessary to update the American Association of Dermatology (AAD) guidelines for patients who don't respond to topical therapies for atopic dermatitis?

SILVERBERG: The last update to the AAD guidelines occurred before significant advancements occurred in the field about a decade ago. This outdated version did

not reflect the emergence of therapies like dupilumab and crisaborole, the first of many innovations in atopic dermatitis treatment. With the introduction of multiple biologics, topical agents, and oral medications, the guidelines needed urgent revision to align with current practices. The necessity for updating the guidelines stemmed from their inability to address these new treatment modalities. For instance, reliance on older guidelines would suggest using cyclosporine—which was backed by weak evidence—as a primary treatment approach. Therefore, updating the guidelines was imperative to provide clinicians with accurate and up-to-date recommendations. The revised guidelines encompass 4 key areas: comorbidities, topical therapies, systemic treatments, and biologics. Each component reflects the evolving landscape of atopic dermatitis management. Furthermore, a forthcoming update will specifically address pediatric atopic dermatitis, recognizing the unique considerations in this patient population.

AJMC: What were the key recommendations for patients who do not respond to topical therapy?

SILVERBERG: The updated guidelines offer flexible recommendations for patients who don't respond to topical therapies and allow clinicians to make informed clinical decisions based on individual patient needs. When topical treatments prove ineffective, the guidelines suggest considering biologics such as dupilumab or tralokinumab for moderate to severe atopic dermatitis as supported by high-grade evidence. Additionally, oral medications like abrocitinib and upadacitinib are recommended for similar cases. While these recommendations align with FDA labeling, the guidelines do not favor 1 treatment over another, leaving the choice to clinical discretion based on patient-specific factors.

AJMC: Why is it important to have real-world data in addition to what was studied in the clinical trials?

SILVERBERG: Real-world data play a vital role complementing findings from clinical trials for several reasons. First, clinical trials maintain strict inclusion and exclusion criteria to minimize confounding factors, but this can limit the representation of patients encountered in everyday clinical practice. Real-world data provide insights into how treatments perform in broader patient populations, ensuring the generalizability of trial results and confirming efficacy. Moreover, real-world studies are crucial for long-term pharmacovigilance, particularly in identifying rare safety signals that may not surface in smaller clinical trials. While regulatory requirements mandate large safety pools, real-world data offer a more extensive and prolonged observation period and enhance postmarketing surveillance. Additionally, real-world data shed light on treatment outcomes in specific patient subsets or off-label scenarios

not typically addressed in clinical trials. For instance, assessing the effectiveness of a medication in patients with overlapping conditions like atopic dermatitis and urticaria provides valuable insights that may not be captured in trial settings. In summary, real-world data serve to validate and enhance the understanding of treatment efficacy and safety beyond what clinical trials alone can provide, making them indispensable for informed decision-making in clinical practice.

AJMC: What are the important real-world studies with dupilumab in terms of treatment adherence and other outcomes such as disease severity and quality of life?

SILVERBERG: Real-world studies provide robust evidence supporting the effectiveness and safety of dupilumab in treating atopic dermatitis and other conditions. These studies consistently reproduce the positive clinical outcomes observed in clinical trials, demonstrating the real-world efficacy and safety of dupilumab. Beyond clinical efficacy, real-world studies explore various end points not extensively studied in trials. For instance, significant improvements in sleep quality and reduction in sleep disturbances were noted with dupilumab treatment. Additionally, dupilumab use was associated with decreased hospitalization rates, comorbidities, and secondary infection rates. Studies on treatment persistence indicate favorable long-term effectiveness and tolerability with patients adhering to the medication over time. Moreover, dupilumab treatment has demonstrated significant enhancements in quality of life across multiple domains, including school and work performance, and was cost-effective. These findings underscore the holistic benefits of dupilumab in improving outcomes for patients with atopic dermatitis.

AJMC: What has real-world evidence demonstrated with tralokinumab in patients with atopic dermatitis?

SILVERBERG: Tralokinumab, a newer therapy when compared with dupilumab, has garnered increasing real-world evidence over the years since its approval that reaffirmed its effectiveness and safety in treating atopic dermatitis. Studies including case reports, case series, and larger investigations have demonstrated real-world effectiveness and safety profiles consistent with clinical trial outcomes without observations of any new safety signals. In addition to replicating clinical trial results, investigators involved in real-world studies have explored various end points such as sleep quality and quality of life outcomes, further supporting the holistic benefits of tralokinumab in atopic dermatitis management. An interesting aspect is the comparison between tralokinumab and dupilumab,

with tralokinumab emerging as a potential alternative for patients who may not have responded optimally to dupilumab. Real-world evidence suggests that tralokinumab can be effective even in patients who previously had an inadequate response to dupilumab, providing clinicians with valuable insights into treatment options for a diverse patient population.

Determining when to switch therapies or add additional treatments for patients with atopic dermatitis is not a one-size-fits-all decision. Several important considerations come into play. Shared decision-making is a key approach.

—Jonathan Silverberg, MD, PhD, MPH

AJMC: How do you balance safety and efficacy of JAK inhibitors when considering their use in patients with atopic dermatitis?

SILVERBERG: When considering the safety and efficacy of JAK inhibitors for atopic dermatitis, it's crucial to prioritize patient safety in clinical decision-making. There are class-wide safety considerations mandated by the FDA, but not all JAK inhibitors share the same safety profile. Therefore, it's essential to assess how each specific JAK inhibitor performs in atopic dermatitis and how it may affect an individual patient. Overall, data from clinical trials offer reassuring insights into the safety profile of JAK inhibitors in atopic dermatitis. Cases of adverse events were reported in longer-term studies, yet the event rates remain relatively low and comparable to those of placebo arms. Additionally, real-world evidence does not suggest an elevated risk compared to previous observations in other health conditions. However, it's important to acknowledge that no medication is entirely risk free. Patients should be informed about the potential rare but serious risks associated with JAK inhibitors, although these occurrences are exceedingly rare. This discussion forms an integral part of shared decision-making, in which patients can weigh the benefits of oral medications like JAK inhibitors against their potential risks. Ultimately, the decision to use JAK inhibitors in atopic dermatitis should involve collaboration between clinicians and patients and consider individual

clinical characteristics and treatment preferences. Shared decision-making ensures that patients are actively involved in their treatment journey, which leads to the best possible outcome for their needs and circumstances.

AJMC: What are you most excited about for the future of atopic dermatitis management?

SILVERBERG: I'm particularly excited about the imminent advancements in atopic dermatitis management. The upcoming approvals of therapies like lebrikizumab, nemolizumab, and topical tapinarof are on the horizon,

promising new options for patients in the near future. These developments are actionable, and their use requires thorough preparation as they approach approval. Additionally, ongoing phase 3 trials, especially those exploring IL-40 and IL-40 ligand inhibitors, showcase the continuous progress in understanding and targeting the underlying biology of atopic dermatitis. Overall, while I'm intrigued by the innovative exploration of novel pathways and technologies in early-stage trials, my current excitement lies in the tangible advancements that we anticipate in the management of atopic dermatitis. ♦

Payer Considerations in Treatment Selection for Atopic Dermatitis

A Q&A With Maria Lopes, MD, MS



MARIA LOPES, MD, MS

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AJMC®: What is your experience with determining coverage criteria for patients with atopic dermatitis?

LOPES: As a physician with extensive experience in managed care, I've been deeply involved in determining coverage criteria for patients with atopic dermatitis. Serving on P and T (pharmacy and therapeutics) committees, my role is to assess the value of new treatments and their appropriateness for patients. This involves evaluating clinical data, comparing efficacy and safety, and considering factors such as the severity of the condition and unmet patient needs. Budget impact, particularly with biologics, is also a crucial consideration in formulary decisions. Ultimately, we craft authorization criteria that balance clinical effectiveness with fiscal responsibility, ensuring we can justify our decisions to employers and relevant stakeholders.

AJMC: Please describe some of the direct and indirect costs of atopic dermatitis.

LOPES: When it comes to managing atopic dermatitis, the direct costs mainly revolve around the expenses associated with treatments. Moisturizers are usually inexpensive. Moving on to topical corticosteroids and calcineurin inhibitors, however, there are some costs involved, although these agents are often generic and relatively low-priced. However, biologics are frequently used for more severe cases, and they represent a significant expense; thus, we typically manage their usage closely due to their high cost. On the other hand, indirect costs tend to be overlooked. These include lost work time for parents or caregivers due to a child's itching and scratching as well as lost sleep and out-of-pocket expenses for prescriptions, which can range from moderate to high, particularly for certain agents like crisaborole. Despite these indirect costs being substantial, direct costs tend to be the primary focus. Biologics account for a significant portion despite the relatively low incidence of hospitalizations or antibiotic use related to biologic therapy.

AJMC: Why is it important for payers to keep apprised of updates in treatment guidelines?

LOPES: As a payer, it's crucial for me to stay informed about updates in treatment guidelines. These guidelines define the standard of care and ensure evidence-based practices. Clear guidelines help in determining appropriate treatments, which, in turn, aids in decision-making regarding coverage and appeals. Updated guidelines grounded in evidence-based care assist in the understanding of the most effective and safe treatments for different populations, thus impacting budgeting and reducing the cost of potential treatment failures. Keeping abreast of these updates ensures that we prioritize the right treatment in the right manner and at the right time and ultimately optimize patient care and resource allocation.

AJMC: How will you incorporate the key recommendations from the 2024 American Association of Dermatology (AAD) guidelines for patients who do not respond to topical therapies for atopic dermatitis?

LOPES: Often, we conduct annual therapeutic class reviews, but if there are updated guidelines referenced in appeals, they prompt us to revisit our criteria and utilization management tools. Discrepancies between our approach and that of the recommended guidelines highlight opportunities for adjustment in our policies. We aim to align our criteria with those of the guidelines while still maintaining effective utilization management controls. Awareness of new guidelines allows us to adapt our processes accordingly and ensure that patients receive appropriate treatments.

[C]onsideration of the cost of treatment failure is crucial; inadequate management may lead to costly consequences like hospitalizations or emergency department visits.

—*Maria Lopes, MD, MS*

AJMC: How are prior authorizations (PAs) and step therapy edits used to help manage the newer medications for atopic dermatitis?

LOPES: The PA typically applies to higher-cost medications with an emphasis on starting with safe and effective lower-cost alternatives first, aligning with evidence-based guidelines. If there's a need for deviation due to contraindications or intolerance, we facilitate peer-to-peer discussions or appeals. The aim is to minimize overturns while ensuring appropriate utilization. Step therapy protocols guide the progression from lower-cost options like topical corticosteroids and calcineurin inhibitors to higher-cost agents like biologics with considerations for intermediate options such as crisaborole. These steps ensure that cost-effective treatments are explored before resorting to more expensive options, thus balancing efficacy, safety, and cost-effectiveness in managing atopic dermatitis.

AJMC: What other payer considerations go into coverage criteria for branded medications like dupilumab, tralokinumab, and JAK inhibitors?

LOPES: Several factors influence coverage criteria for branded medications like dupilumab, tralokinumab, and JAK inhibitors. First, we consider comparative efficacy,

often relying on indirect comparisons across trials to assess clinical significance. Safety is paramount, especially when using products associated with risk evaluation and mitigation strategies. Despite lower prices, safety concerns may influence step therapy decisions. Typically, PAs align across high-cost products, progressing through corticosteroid and calcineurin inhibitor steps before potentially leaving options open, especially for preferred products like JAK inhibitors or TNF inhibitors. Contracting also plays a role, with market share and product indications impacting decisions. Use of multiple biologics is typically restricted for safety and cost considerations. PAs for preferred products require meeting with step criteria; such products include topical corticosteroids, calcineurin inhibitors, and, possibly, crisaborole. Beyond these steps, prescribers may have more flexibility in choosing subsequent treatments provided that safety and efficacy standards are met and contractual obligations are considered.

AJMC: How can barriers to access of medications for atopic dermatitis be overcome?

LOPES: Overcoming barriers to accessing medications for atopic dermatitis involves understanding and addressing several key factors. First, navigating PA and step therapy requirements can be challenging. Patients may face different cost-sharing structures from nominal co-pays for common treatments to substantial co-insurance for high-cost medications, potentially hindering access. Education and updates to treatment guidelines can help refine step therapy protocols and reduce barriers. Additionally, consideration of the cost of treatment failure is crucial; inadequate management may lead to costly consequences like hospitalizations or emergency department visits. While bypassing steps may be challenging, safety concerns or medical justifications can prompt peer-to-peer discussions or appeals. Payers prioritize evidence-based approaches and lower total costs of care, and they respond to appeals when evidence suggests a deviation from established guidelines. Effective communication, education, and data-driven decision-making are essential in overcoming access barriers for atopic dermatitis medications.

AJMC: How do you incorporate safety and efficacy of JAK inhibitors as you develop coverage criteria?

LOPES: JAK inhibitors are significant in our treatment options; they span autoimmune, inflammatory bowel disease, and atopic dermatitis realms. Safety concerns exist but are being addressed. As a payer, I may have preferred JAK inhibitors, although they're costly, due to contractual agreements. We typically implement PA to ensure appropriate usage in moderate to severe cases, and we step through lower-cost alternatives. However, if costs are comparable, we often leave the choice to the

provider. Safety and efficacy are paramount in developing coverage criteria, as they ensure patient well-being and effective treatment.

AJMC: How do you use Institute for Clinical and Economic Review (ICER) reports as you develop coverage criteria for agents used in atopic dermatitis?

LOPES: Payers like me find ICER reports valuable as a reference point as we develop coverage criteria for agents used in atopic dermatitis. We appreciate ICER's increasing transparency in methodology and stakeholder perspectives. However, while ICER reports can influence our decision-making, they are just 1 aspect that we consider in our overall assessment. We primarily focus on evidence-based care, total costs, and contractual negotiations. If an ICER report provides clear guidance on cost versus value, it can significantly impact our approach to PA criteria and contracting strategies. Yet if the report is less conclusive, we may rely more on our internal analysis and comparisons across treatment options. Ultimately, our decisions

prioritize efficacy, safety, and net cost with contracting playing a significant role in formulary placement and utilization rather than solely relying on ICER reports.

AJMC: What are other payer considerations when determining a therapy for patients with atopic dermatitis?

LOPES: When determining therapy for patients with atopic dermatitis as a payer, I find it crucial to consider potential overlaps in indications, especially in pediatric cases. Atopic dermatitis often intersects with conditions like asthma, respiratory issues, and skin infections. Assessing whether a drug addresses multiple conditions can offer additional benefits and potential cost offsets, particularly if use of the agent reduces the need for multiple treatments. This holistic view becomes significant, especially in pediatric patients in whom comorbidities like food allergies and asthma are prevalent. Real-world data play a crucial role in evaluating these considerations to ensure comprehensive care and optimal cost management for patients with atopic dermatitis. ♦

