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Title: Interim update: Guidelines of Care for the Management of Atopic Dermatitis in Adults with systemic Janus kinase inhibitors and biologics

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Disclaimer

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the appropriateness of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Abstract

Background: In 2023 and 2025, the AAD published recommendations on the use of systemic Janus kinase inhibitors (JAKis) and biologics for the management of atopic dermatitis (AD) in adults. Since the publication of these guidelines, additional trials on the systemic therapies have been published prompting an interim update to the existing recommendations.

Objective: To update the current guidance on the use of systemic JAKis and biologics for the management of AD in adults.

Methods: An expert workgroup conducted a systematic review and applied the GRADE approach for assessing the certainty of evidence and formulating and grading recommendations.

Results: The updated review identified four new trials not included in prior 2023 or 2025 guidelines. Certainty of evidence was revised for 3 interventions. The workgroup maintained strong recommendations for the use of abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab with concomitant topical therapy, tralokinumab, and upadacitinib.

Limitations: This analysis is based on the best available evidence at the time it was conducted. Most randomized controlled trials of the considered therapies for AD are of short duration, limiting comparative long-term efficacy and safety conclusions.

Conclusions: This guideline makes strong recommendations for the use of seven targeted therapies for adults with AD.

Abbreviations Used

AAD: American Academy of Dermatology

AD: Atopic dermatitis

DLQI: Dermatology Life Quality Index

EASI: Eczema Area Severity Index

FDA: US Food and Drug Administration

JAKis: Janus kinase inhibitors

POEM: Patient Oriented Eczema Measure

PP-NRS: Peak Pruritus Numerical Rating Scale

RCT: Randomized controlled trial

TCI: Topical calcineurin inhibitor

TCS: Topical corticosteroids

Scope & Objective

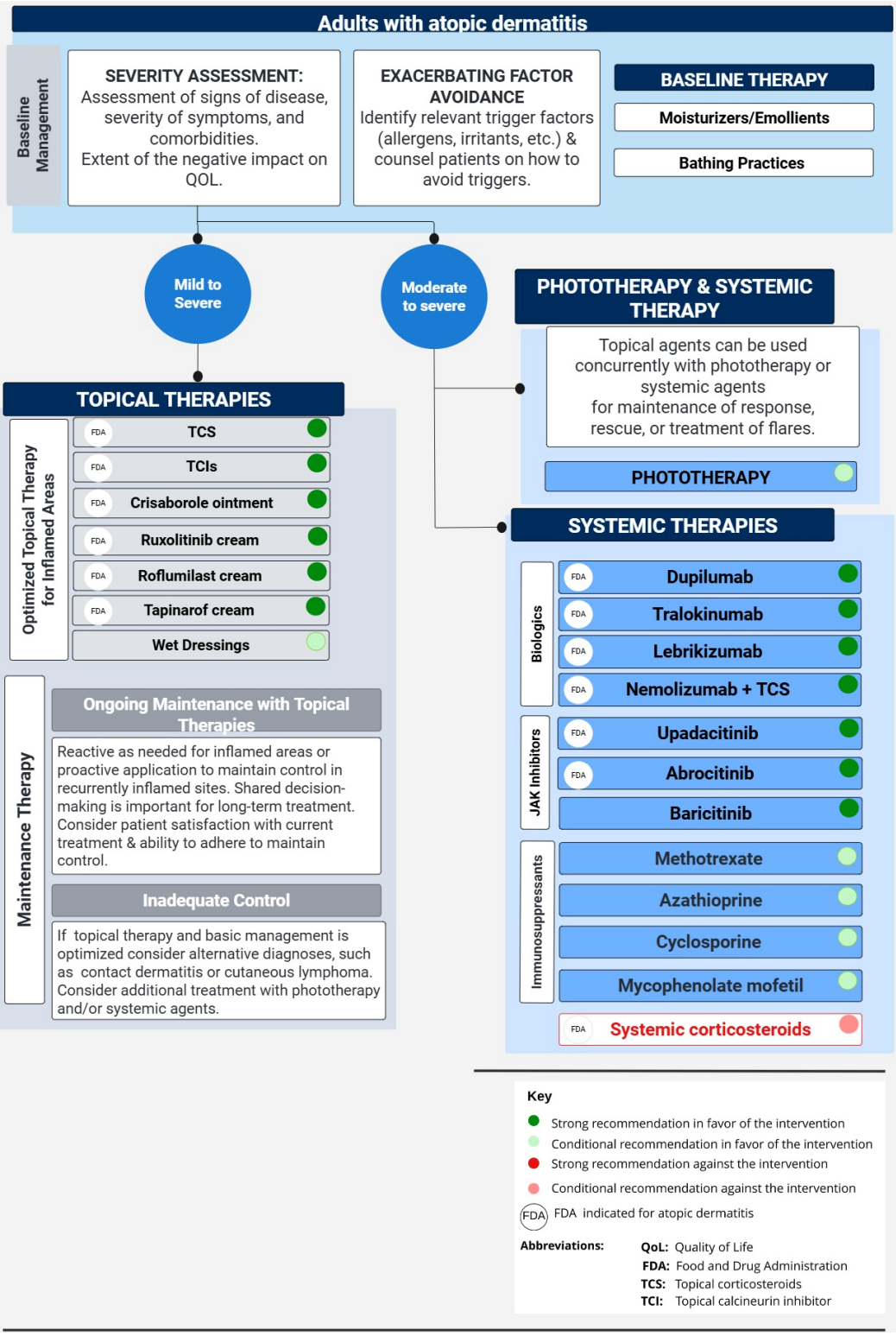
The rapid expansion of evidence for the use of targeted systemic therapies for atopic dermatitis (AD) necessitates updating the American Academy of Dermatology's (AAD) evidence-based guidance on the use of these therapies to manage AD in adults. In 2023 and 2025, the AAD published recommendations on the use of systemic Janus kinase inhibitors (JAKis) and biologics for the management of AD in adults.[1, 2] Since the publication of these guidelines, additional trials on these medications have been published prompting an interim update to the existing recommendations. The scope of the present update is to incorporate novel evidence specific to abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab, tralokinumab, and upadacitinib into the AAD's existing recommendations for the management of AD in adults, and to standardize the evidence synthesis approach across all recommendations considered.

The seven reevaluated evidence-based recommendations for the management of AD in adults are available in **Table I**. A complete list of the current recommendations for the management of AD with topical and systemic therapies is available in **Supplemental Appendix 1** and presented in **Figure 1**.

Table I. Reevaluated Recommendations for the Management of Atopic Dermatitis in Adults. *AD*, Atopic dermatitis

Recommendation	Strength	Certainty of evidence	Evidence
Biologics			
For adults with moderate to severe AD, we recommend dupilumab.	Strong	High	8-11
For adults with moderate to severe AD, we recommend tralokinumab.	Strong	Moderate	17, 18
For adults with moderate to severe AD, we recommend lebrikizumab.	Strong	High	12-14
For adults with moderate to severe AD, we recommend nemolizumab with concomitant topical therapy	Strong	Moderate	15, 16
JAK inhibitors			
For adults with moderate to severe AD, we recommend upadacitinib. Remarks: Upadacitinib is approved by the FDA in patients with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable.	Strong	High	19, 20
For adults with moderate to severe AD, we recommend abrocitinib. Remarks: Abrocitinib is approved by the FDA in patients with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable. The evidence supporting abrocitinib 200 mg is of high certainty.	Strong	Moderate	3-5
For adults with moderate to severe AD, we recommend baricitinib. Remark: Baricitinib is not approved by the FDA for use in AD.	Strong	Moderate	6, 7

Figure 1. Treatment algorithm for adults with atopic dermatitis. *FDA*, U.S. Food and Drug Administration, *TCI*, Topical calcineurin inhibitor, *TCS*, Topical corticosteroids, *QoL*, Quality of life.



Methods

Cognizant of the need for a process for timely updates to clinical guidance within the scope of existing, recently published (< 5 years) AAD guidelines, the AAD's Clinical Guidelines Committee developed an interim update process. For details of the interim update process, see **Supplemental Appendix 2**. Per this process, new evidence on the use of systemic JAKis and biologic therapies was identified as potentially impacting the current AD guidance resulting in the initiation of this update.

This update is based on a systematic review by an expert workgroup supported by AAD guidelines staff with health research methodology expertise and applied the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach for assessing the certainty of the evidence and formulating and grading clinical recommendations.

In accordance with GRADE methodology, strength of recommendation and certainty of evidence are distinct and independently assigned components of each recommendation (**Table II**).[21-23] Certainty of evidence reflects the degree of confidence the available evidence accurately estimates the true effect of an intervention, rated as high, moderate, low, or very low. Strength of recommendation, by contrast, reflects the workgroup's judgment about whether the desirable consequences of an intervention outweigh the potential undesirable effects. Strength is informed by, but not determined solely by, certainty of evidence. A strong recommendation indicates the panel is confident the benefits outweigh the harms (or vice versa) for the vast majority of patients, and should be interpreted consistently regardless of the attached certainty of evidence rating: a strong recommendation based on moderate-certainty evidence conveys the same directive intent as one based on high-certainty evidence, even though the underlying evidentiary confidence differs. Certainty of evidence should be understood as characterizing the body of evidence, not as qualifying or attenuating the strength of the recommendation or creating a hierarchy within the strength of recommendations categories.

In addition to identifying and analyzing new evidence, this interim update standardized the evidence synthesis approach across all considered recommendations. The 2023 guideline derived effect estimates from network meta-analysis, reporting dichotomous outcomes as odds ratios and continuous outcomes as mean differences or standardized mean differences.[24, 25] To ensure methodological consistency with the 2025 focused update and across JAKi and biologic recommendations, the present update employed pairwise meta-analysis, with effect estimates expressed as risk ratios and mean differences. Furthermore, whereas the 2023 guideline analyses pooled monotherapy trials with trials of systemic therapy combined with concomitant topical therapy, this interim update analyzed these trial types separately for all interventions, with the exception of those with FDA indications for use in combination with topical therapy. For detailed methodology, see **Supplemental Appendix 3.**

Table II. Strength of Recommendation and Certainty of Evidence

Strength of Recommendation	**Wording**	**Implication**[21-23]
Strong recommendation	"We recommend…"	Benefits clearly outweigh risk and burdens, or vice versa; When fully informed, almost all patients would choose this course of action
Conditional recommendation	"We conditionally recommend"	Benefits are closely balanced with risks and burdens; Most informed patients would opt for this course of action, though a substantial minority would not
Certainty of Evidence	**Wording**	**Implication**[21, 22]
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low certainty evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

Considered Recommendations

Clinical Questions

This interim update focuses on two clinical questions addressed in previously published guidelines: 1) What is the efficacy and safety of biologic therapies for AD? and 2) What is the efficacy and safety of systemic JAKis for AD?[1, 2] This update introduces new evidence and standardizes analyses for these targeted interventions only. Evidence for other topical and systemic therapies addressed in the prior guidelines was not updated or re-evaluated. Recommendations from the prior guidelines not addressed in this update remain current for five years from their original publication date, or until superseded by a subsequent update or full revision of the guidelines.

Biologics (Monoclonal Antibodies)

Dupilumab

Background

Dupilumab is a monoclonal antibody that inhibits signaling of both interleukin-4 and interleukin-13. It was the first US Food and Drug Administration (FDA)-approved targeted systemic treatment for AD.

Summary of Evidence and Analysis

The updated literature search identified one additional monotherapy trial and two trials on the use of dupilumab in combination with topical therapy not included in the previous guidelines' analyses.[9, 26, 27] The standardized analysis approach revised the original evidence base to consider monotherapy and concomitant topical therapy trials separately, with the monotherapy evidence analyzed to support the recommendation.

Five randomized controlled trials (RCTs) (n=1,340) compared dupilumab, 600 mg loading dose followed by 300 mg every 2 weeks, monotherapy to placebo over 16 weeks in adolescents and adults with moderate-to-severe AD.[8-11] Dupilumab demonstrated large improvements across all critical efficacy outcomes, with high certainty evidence across the full range of skin clearance, itch, flare, quality-of-life, and key safety outcomes (**Supplemental Table 1**).

For skin clearance, dupilumab increased Investigator Global Assessment (IGA) success (defined as achieving an IGA of 0 or 1), Eczema Area Severity Index (EASI)-75, and EASI-90 response rates by 25% (95% Confidence Interval [CI] 15 to 38%), 36% (95% CI 27 to 48%), and 26% (95% CI 17 to 38%), respectively compared to placebo. Itch responder rates (≥4-point Peak Pruritus-Numerical Rating Scores [PP-NRS] improvement) increased by 30% (95% CI 20 to 40%). Disease flares were markedly reduced, with the rate of participants experiencing an AD exacerbation decreasing by 19% (95% CI 22 to 15%) with dupilumab. Patient-reported outcomes improved meaningfully, with mean Patient Oriented Eczema Measure (POEM) and Dermatology Life Quality Index (DLQI) scores decreasing by 7.52 and 5.04 points, respectively, both exceeding prespecified minimally important differences of 3.4 and 3.3 points, respectively.[28-30]

Dupilumab did not meaningfully increase overall adverse events or treatment discontinuation. Notably, the rate of serious adverse events was significantly decreased with dupilumab (2.6% [95% CI 4 to 0.3%]). However, the rate of conjunctivitis increased with dupilumab use compared to placebo (3% [95% CI 0.6 to 8%).

The overall certainty of evidence is high due to precise treatment effects across all critical efficacy and safety outcomes derived from multiple large RCTs.

Supplemental Combination Therapy & Long-Term Data

Five RCTs (n=1,472) evaluated dupilumab in combination with topical corticosteroids (TCS) versus placebo plus TCS over 12 to 16 weeks in adolescents and adults with moderate-to-severe AD.[26, 27, 31-33] Findings were consistent with and supportive of the monotherapy evidence, demonstrating large improvements in skin clearance, itch, and patient-reported outcomes with high certainty across all critical efficacy outcomes (**Supplemental Tables 2**). Itch responder rates and patient-reported POEM and DLQI improvements similarly exceeded minimally important differences with high certainty. The safety profile was consistent with the monotherapy evidence, with no significant increases in serious adverse events, infections, upper respiratory tract infections, nasopharyngitis, or herpes infections were observed. Conjunctivitis occurred more frequently with dupilumab plus TCS than placebo plus TCS, consistent with the known class effect. Overall, the combination therapy evidence reinforces the favorable benefit-harm profile of dupilumab and suggests concomitant topical therapy does not meaningfully impact its safety.

One RCT (n=425) compared dupilumab plus TCS to placebo plus TCS over 52 weeks. While all outcomes were rated moderate certainty due to the single-study evidence base and associated imprecision, findings were directionally consistent with the short-term monotherapy and combination therapy evidence and supported sustained efficacy over one year of treatment (**Supplemental Table X**[32] At 52 weeks, IGA success, EASI-75, EASI-90, and itch responder rates remained higher with dupilumab than placebo plus TCS, and mean POEM and DLQI improvements continued to exceed minimally important differences. Notably, treatment discontinuation due to adverse events was significantly less frequent with dupilumab than placebo at 52 weeks, consistent with the short-term finding of reduced serious adverse events with active treatment. No statistically significant differences in serious adverse events, overall infections, herpes infections, upper respiratory tract infections, or conjunctivitis were observed at 52 weeks, though all estimates were imprecise due to the single-trial evidence base. Collectively, the available long-term data provides reassuring preliminary evidence of sustained efficacy and an acceptable safety profile with dupilumab over one year, while underscoring the need for additional long-term comparative data.

Rationale for Recommendation

The workgroup maintained the strong recommendation for dupilumab in adults with moderate-to-severe AD based on large, consistent desirable effects across all critical outcomes and a favorable safety profile. The overall certainty of evidence was revised from moderate to high as the evidence is characterized by uniformly high certainty across both key benefit and harm outcomes.

Based on input from a patient partner during the original guideline development process and a systematic review of patient values and preference literature, reducing symptoms, specifically dermatitis and pruritus, and minimizing therapeutic risks are key goals of AD therapy.[2] Given this, the workgroup considered the magnitude and consistency of benefit across multiple outcome domains with the use of dupilumab to be large. The favorable safety profile suggests dupilumab is well tolerated with treatment-emergent adverse effects consisting primarily of mild or moderate events that did not lead to discontinuation. The large improvement in desirable effects in the absence of substantial risk of undesirable effects favors the use of dupilumab.

Other Considerations

Dupilumab has a well-established evidence base and long-term real-world safety record across multiple indications, providing additional experience beyond the trial data reviewed.[34-37] Dupilumab is a viable treatment option across a broad range of patients with moderate-to-severe AD, including those who may not be candidates for JAKis due to age, comorbidities, or other risk factors. Patients should be counseled regarding the risk of conjunctivitis and the importance of reporting ocular symptoms promptly. Dupilumab

should be avoided if cutaneous lymphoma (mycosis fungoides or Sézary syndrome) is suspected or confirmed; lack of response to therapy or worsening should prompt additional diagnostic workup.

Lebrikizumab

Background

Lebrikizumab, a monoclonal antibody targeting interleukin-13, was FDA-approved for the management of moderate-to-severe AD in individuals aged 12 years and older in 2024.[38]

Summary of Evidence and Analysis

The updated literature search identified one additional trial on the use of lebrikizumab in combination with topical therapy not included in the previous guidelines' analysis.[39] The standardized analysis approach aligned with the original analysis considering the monotherapy evidence to support the recommendation.

Four RCTs (n=1,225) evaluated lebrikizumab, 500 mg loading dose followed by 250 mg every 2 weeks, monotherapy versus placebo over 16 weeks in adolescents and adults with moderate-to-severe AD.[12-14] Lebrikizumab demonstrated large, consistent improvements across all critical efficacy outcomes, with high certainty evidence across key skin clearance, itch, patient-reported, and safety outcomes (**Supplemental Table 3**).

For skin clearance, lebrikizumab increased IGA success, EASI-75 and EASI-90 response rates by 25% (95% CI 16 to 36%), 36% (95% CI 18 to 63%), and 24% (95% CI 11 to 43%), respectively compared to placebo. Itch responder rates (≥4-point PP-NRS improvement) increased by 29% (95% CI 11 to 60%). Patient-reported disease burden improved meaningfully, with mean POEM and DLQI scores decreasing by 5.68 (95% CI 7.66 to 3.7 lower) and 4.79 (95% CI 6.62 to 2.97 lower) points, respectively.

Lebrikizumab was not associated with a meaningful increase in overall adverse events, serious adverse events, or treatment discontinuation. However, the rate of conjunctivitis increased with lebrikizumab use compared to placebo (4% [95% CI 1 to 9%]).

The overall certainty of evidence was rated high, reflecting precise treatment effects across all critical efficacy and safety outcomes derived from multiple large RCTs.

Supplemental Combination Therapy & Long-Term Data

Three RCTs (n=747) evaluated lebrikizumab, 500 mg loading dose followed by 250 mg every 2 weeks, plus TCS versus placebo plus TCS over 16 weeks in adolescents and adults with moderate-to-severe AD.[39-42] Lebrikizumab plus TCS demonstrated consistent improvements in skin clearance, itch, and patient-reported outcomes over placebo plus

TCS, with effect sizes similar to those observed in monotherapy trials (**Supplemental Table 4**). Higher background response rates in the placebo plus TCS arms, relative to placebo monotherapy, likely attenuated observed absolute effect sizes for several outcomes.

The safety profile was generally consistent with that observed in monotherapy trials. No significant increases in serious adverse events, treatment discontinuation, upper respiratory tract infections, opportunistic infections, or herpes infections were observed. Treatment-related adverse events were modestly more frequent with lebrikizumab plus TCS than placebo plus TCS. Conjunctivitis occurred at a higher rate with lebrikizumab plus TCS than placebo plus TCS, with a numerically higher absolute rate than observed in monotherapy trials, though the findings were imprecise.

Two RCTs (n=173) used a randomized-withdrawal design in which initial lebrikizumab responders at week 16 were re-randomized to lebrikizumab 250 mg every 2 weeks or placebo through week 52.[43] These trials were characterized by small sample sizes and predominantly moderate certainty evidence across all outcomes due to imprecision, and findings should be interpreted accordingly (**Supplemental Table 5**).

In the re-randomized period after 16-weeks, lebrikizumab maintained clinically meaningful improvements in skin clearance vs placebo. Patient-reported outcomes showed modest continued improvement, with mean POEM scores 2.26 points lower with lebrikizumab than placebo, though DLQI improvement was not meaningful at 52 weeks. The high response rates in both arms at 52 weeks may reflect enrichment for responders in the trial designs, limiting direct comparability with short-term placebo-controlled data.

The long-term safety profile was reassuring within the constraints of the available evidence. No meaningful differences in serious adverse events, conjunctivitis, herpes infections, nasopharyngitis, opportunistic infections, or parasitic infections were observed at 52 weeks, though all safety outcomes were rated moderate certainty due to small sample sizes leading to imprecision. Treatment discontinuation due to adverse events was rare in both arms. The limited sample sizes and study durations preclude definitive conclusions regarding long-term safety, and continued real-world surveillance and longer-term extension data are needed to fully characterize the durability of benefit and safety profile of lebrikizumab beyond 52 weeks.

Rationale for Recommendation

The workgroup maintained the strong recommendation for lebrikizumab in adults with moderate-to-severe AD based on large, consistent desirable effects across all clinically important outcomes.

Lebrikizumab produced clinically meaningful improvements in skin clearance, itch, and patient-reported outcomes compared to placebo. The workgroup considered the

magnitude of benefit to be large. The favorable safety profile suggests lebrikizumab is well tolerated with treatment-emergent adverse effects consisting primarily of mild or moderate events that did not lead to discontinuation. The large improvement in desirable effects in the absence of substantial risk of undesirable effects favors the use of lebrikizumab.

Other Considerations

Lebrikizumab is a viable treatment option across a broad range of patients with moderate-to-severe AD, including those who may not be candidates for JAKis due to age, comorbidities, or other risk factors. Patients should be counseled regarding the risk of conjunctivitis and the importance of reporting ocular symptoms promptly.

Nemolizumab

Background

Nemolizumab, a monoclonal antibody targeting the interleukin-31 receptor, was FDA-approved in December 2024 for the management of moderate-to-severe AD that is inadequately controlled with topical therapies in individuals aged 12 years and older in combination with topical corticosteroids and/or topical calcineurin inhibitors.[44]

Summary of Evidence and Analysis

No additional trials were identified by the updated literature search. As nemolizumab is FDA-indicated for use in combination with topical therapy, the combination therapy evidence was analyzed to support the recommendation.

Three RCTs (n=1,842) evaluated nemolizumab 30 mg every 4 weeks plus topical corticosteroids and/or topical calcineurin inhibitors (TCS/TCI) versus placebo plus TCS/TCI over 16 to 24 weeks in adolescents and adults with moderate-to-severe AD.[15, 16] Nemolizumab with concomitant topical therapy demonstrated improvements across skin clearance, itch, flares, and quality-of-life outcomes compared with topical therapy alone (**Supplemental Table 6**).

For skin clearance, nemolizumab increased IGA success, EASI-75 and EASI-90 response rates by 12% (95% CI 7 to 18%), 14% (95% CI 8 to 20%), and 9% (95% CI 3 to 16%), respectively, compared to placebo. Itch responder rate (≥4-point PP-NRS improvement) was 23% (95% CI 16 to 31%) higher than placebo. Disease flares were statistically significantly reduced (3% lower [95% CI 4 to 0.5% lower]) compared to placebo. Patient-reported outcomes numerically improved at both assessed timepoints, with a mean DLQI reduction of 2.5 (95% CI 3.39 to 1.61 lower) points and POEM reduction of 3.95 (95% CI 4.84 to 3.06 lower) points; however, the point estimate reduction for DLQI did not meet the prespecified minimally important difference and the CIs for both outcomes include the possibility of no meaningful difference.

Nemolizumab use did not result in clinically meaningful increases in serious adverse events, serious infections, or overall infections compared with placebo plus TCS/TCI. Treatment-related adverse events were more frequent with nemolizumab (5% more [95% CI 1 to 10% more), though this did not translate to increased discontinuation rates.

The overall certainty of evidence is moderate, driven by imprecision across several key skin clearance, patient-reported, and safety outcomes where confidence intervals for absolute effects crossed prespecified minimally important difference thresholds.

Supplemental Combination Therapy & Long-Term Data

Unlike the other agents reviewed in this guideline, nemolizumab's FDA approval specifies use in combination with topical therapies. Accordingly, the combination therapy trials formed the primary evidence base supporting the recommendation and are reported in the evidence summary above rather than presented here as supplementary evidence. No placebo-controlled, long-term data were identified by the updated systematic review for nemolizumab. Long-term placebo-controlled trials evaluating the durability of efficacy and the extended safety profile of nemolizumab in combination with topical therapy are needed.

Rationale for Recommendation

The workgroup maintained the strong recommendation for nemolizumab with concomitant topical therapy for adults with moderate-to-severe AD based on consistent desirable effects across clinically important outcomes and a favorable safety profile. The overall certainty of evidence was revised from high to moderate, reflecting imprecision across several key efficacy outcomes including EASI-75, IGA success, EASI-90, DLQI, and POEM.

Use of nemolizumab with concomitant TCS/TCI resulted in improvements in skin clearance, itch, and disease flares compared with topical therapy alone. The largest magnitude of benefit was observed for itch, where the proportion of patients achieving a clinically meaningful reduction in pruritus more than doubled relative to placebo plus TCS/TCI. These benefits were observed on top of ongoing topical therapy, representing incremental gains beyond what topical treatment alone achieves.

The safety profile of nemolizumab was favorable. Treatment-related adverse events were modestly more frequent with nemolizumab, though this did not translate into higher discontinuation rates.

Given the moderate magnitude of benefits in terms of improvements in disease severity and patient-reported outcomes, the large magnitude of benefit for itch reduction, and the favorable safety profile, the workgroup determined that the overall balance of benefits and potential harms as reported at 16 to 24 weeks favors using nemolizumab in addition to topical TCS/TCI for the management of AD.

Other Considerations

Nemolizumab represents a mechanistically distinct treatment option within the AD therapeutic landscape, targeting the IL-31 receptor pathway rather than the IL-4/IL-13 or JAK-STAT pathways addressed by other approved systemic therapies. Nemolizumab is approved for use in combination with topical therapy, and this is advisable in clinical practice.

Tralokinumab

Background

Tralokinumab, a monoclonal antibody targeting interleukin-13, was the second biologic FDA-approved for the treatment of AD.

Summary of Evidence and Analysis

The updated literature search identified one new trial on the use of tralokinumab in combination with TCS compared to placebo plus TCS.[45] The standardized analysis approach considered monotherapy evidence to support the recommendation.

Three RCTs (n=1,805) evaluated tralokinumab, 600 mg loading dose followed by 300 mg every 2 weeks, monotherapy versus placebo over 16 weeks in adolescents and adults with moderate-to-severe AD.[17, 18] Tralokinumab demonstrated improvements across skin clearance, itch, disease flares, and patient-reported outcomes compared with placebo (**Supplemental Table 7**).

For skin clearance, tralokinumab increased IGA success, EASI-75 and EASI-90 response rates by 10% (95% CI 5 to 17%), 17% (95% CI 4 to 36%), and 12% (95% CI 6 to 21%), respectively compared to placebo. Itch responder rates (≥4-point PP-NRS improvement) increased by 13% (95% CI 6 to 21%). Disease flares were reduced, with the rate of participants experiencing an AD exacerbation decreasing by 17% (95% CI 26 to 3%) with tralokinumab compared to placebo. POEM scores decreased by a mean of 4.85 (95% CI 5.88 to 3.82) points, exceeding the prespecified minimally important difference, and DLQI scores decreased by a mean of 3.0 (95% CI 4.76 to 1.23) points, but the point estimate did not meet the minimally important difference threshold.

Tralokinumab did not result in clinically meaningful increases in serious adverse events or treatment discontinuation. However, the rate of conjunctivitis increased with tralokinumab use compared to placebo (5% [95% CI 1 to 11%).

The overall certainty of evidence is moderate, driven by imprecision across the primary skin clearance, itch, and quality of life outcomes, where confidence intervals were consistent with both no clinically meaningful difference and benefit**.**

Supplemental Combination Therapy & Long-Term Data

Two RCTs (n=653) evaluated tralokinumab, 600 mg loading dose followed by 300 mg every 2 weeks, plus TCS versus placebo plus TCS over 16 weeks in adolescents and adults with moderate-to-severe AD.[45, 46] Tralokinumab plus TCS demonstrated consistent improvements in skin clearance, itch, flare prevention, and patient-reported outcomes over placebo plus TCS, with effect sizes similar to those observed in monotherapy trials, though absolute gains were attenuated by higher background response rates in the placebo plus TCS arms (**Supplemental Table 8**).

The safety profile was generally consistent with that observed in monotherapy trials. Serious adverse events were numerically lower with tralokinumab plus TCS than placebo plus TCS, and no significant increases in treatment discontinuation were observed. Conjunctivitis occurred more frequently with tralokinumab plus TCS than placebo plus TCS, consistent with the known class effect of IL-13 inhibitors. Several safety outcomes were derived from a single, small RCT so should be interpreted with caution.

Two RCTs (n=196) used a randomized-withdrawal design in which initial tralokinumab responders at week 16 were re-randomized to tralokinumab 300 mg every 2 weeks or placebo through week 52. [18] Evidence was substantially limited by small sample sizes, with certainty rated low for most outcomes (**Supplemental Table 9**). In the re-randomized period after 16 weeks, skin clearance outcomes were directionally favorable, suggesting maintained efficacy over the longer term. However, the small sample and the enriched trial populations in the long-term extension studies preclude definitive conclusions regarding the durability of benefit and long-term safety profile of tralokinumab. Larger studies are needed to fully characterize the benefit-harm balance over extended treatment durations.

Rationale for Recommendation

The workgroup maintained the strong recommendation for tralokinumab for adults with moderate-to-severe AD based on consistent desirable effects across clinically important outcomes and a favorable safety profile.

The workgroup considered the magnitude of benefit across multiple outcome domains with the use of tralokinumab to be moderate. The favorable safety profile suggests tralokinumab is well tolerated with treatment-emergent adverse effects consisting primarily of mild or moderate events that did not lead to discontinuation.

Other Considerations

Tralokinumab is a viable treatment option across a broad range of patients with moderate-to-severe AD, including those who may not be candidates for JAKis due to age, comorbidities, or other risk factors. Patients should be counseled regarding the risk of conjunctivitis and the importance of reporting ocular symptoms promptly.

Janus Kinase Inhibitors

Abrocitinib

Background

Abrocitinib is a selective JAKi that preferentially targets JAK-1. It is FDA-approved for use in patients with moderate-to-severe AD who have failed other systemic therapies, including immunosuppressants, corticosteroids, antimetabolites, and biologics, or when they are inadvisable.

Summary of Evidence and Analysis

No additional trials were identified by the updated literature search. However, the standardized analysis approach revised the original evidence base to consider monotherapy and concomitant topical therapy trials separately, with the monotherapy evidence analyzed to support the recommendation.

Three RCTs evaluated abrocitinib 100 mg (n=570) or 200 mg (n=575) daily monotherapy versus placebo over 12 weeks in adolescents and adults with moderate-to-severe AD.[3-5] Both doses demonstrated clinically meaningful improvements in skin clearance, itch, and quality of life, with consistently larger absolute effects at the 200 mg dose (**Supplemental Tables 9 & 10**).

For skin clearance, abrocitinib 200 mg increased IGA success, EASI-75 and EASI-90 response rates by 33% (95% CI 17 to 58%), 50% (95% CI 30 to 78%), and 32% (95% CI 16 to 61%), respectively. With 100 mg, the magnitude of effect was smaller yet still meaningful, with IGA success, EASI-75 and EASI-90 response rates increased by 19% (95% CI 8 to 36%), 29% (95% CI 16 to 49%), and 16% (95% CI 6 to 33%), respectively. Itch responder rates (≥4-point PP-NRS improvement) increased by 39% (95% CI 20 to 69%) with 200 mg and 25% (95% CI 11 to 47%) with 100 mg compared to placebo. Patient-reported outcomes likewise improved at both doses, with POEM and DLQI score reductions exceeding or approaching established minimally important differences, though certainty was moderate at 100 mg due to imprecision.

Neither dose was associated with a clinically meaningful increase in serious adverse events or treatment discontinuation, though both doses were associated with higher rates of any infection versus placebo.

The overall certainty of evidence is moderate, driven by imprecision across several key efficacy and safety outcomes at the 100 mg dose, while the certainty of evidence for critical outcomes is high at 200 mg.

Supplemental Combination Therapy & Long-Term Data

One RCT (n=369) evaluated abrocitinib 100 mg or 200 mg daily plus TCS versus placebo plus TCS over 16 weeks.[31] Consistent with monotherapy findings, both abrocitinib 100 and 200 mg plus TCS demonstrated large, clinically meaningful improvements across all efficacy outcomes with high certainty **(Supplemental Tables 11 & 12)**. The effect sizes at both doses in combination with TCS were broadly consistent with those observed in monotherapy trials, while/and higher background response rates in the placebo plus TCS arms likely attenuated the absolute effect estimates. The safety profile was favorable, with no significant increases in serious adverse events, treatment-emergent adverse events, treatment discontinuation, conjunctivitis, nasopharyngitis, upper respiratory tract infections, or herpes viral infections relative to placebo plus TCS. Overall infection rates were higher with abrocitinib 100 mg plus TCS than placebo plus TCS, though this finding was based on a small subsample and should be interpreted with caution.

One RCT (n=533)evaluated using an induction and randomized-withdrawal design: participants received open-label abrocitinib 200 mg daily for 12 weeks, after which responders were re-randomized to abrocitinib 200 mg, abrocitinib 100 mg, or placebo through week 52.[47] In the re-randomized period after 12 weeks, both abrocitinib 100 mg and 200 mg maintained efficacy vs placebo with high certainty across all outcomes (**Supplemental Tables 13 & 14**). Notably, flare prevention was substantial at both doses through week 40.

No significant increases in serious adverse events, serious infections, herpes viral infections, treatment discontinuation, nasopharyngitis, or upper respiratory tract infections were observed at 40 weeks with abrocitinib 100 mg relative to placebo. Overall infection rates were higher with abrocitinib 100 mg than placebo at 40 weeks and treatment-emergent adverse events were modestly increased, while severe adverse events were numerically lower with abrocitinib 100 mg. At 200 mg, serious adverse events, infections, and treatment-emergent adverse events rates were statistically significantly higher but the estimates were generally imprecise with CIs consistent with no meaningful difference and potential harm. Treatment discontinuation due to adverse events was also statistically significantly higher with abrocitinib 200 mg than placebo, and as with the other adverse events, the estimate of effect is imprecise. These generally imprecise findings, derived from a single trial, should be interpreted with appropriate caution but represent clinically meaningful signals that warrant consideration in the context of long-term prescribing at the 200 mg dose.

Rationale for Recommendation

The workgroup maintained the strong recommendation for abrocitinib in adults with moderate-to-severe AD based on large, consistent desirable effects across clinically important outcomes and acceptable safety profile. The overall certainty was rated moderate, reflecting high certainty across nearly all outcomes at the 200 mg dose and moderate certainty at the 100 mg dose due to imprecision in several key outcomes. A

remark was added to the recommendation to reflect the varying overall certainty of the evidence by dose.

The workgroup considered the magnitude and consistency of benefit across multiple outcome domains with the use of abrocitinib to be large. The favorable safety profile suggests abrocitinib is well tolerated. The large improvement in desirable effects in the absence of substantial risk of undesirable effects favors the use of abrocitinib.

Other Considerations

As abrocitinib is FDA-indicated for patients with moderate-to-severe AD who have had an inadequate response to other systemic therapies or for whom such therapies are inadvisable it is generally not considered a first-line systemic option.

Baricitinib

Background

Baricitinib preferentially inhibits both JAK-1 and -2. It is approved in Europe for the treatment of moderate-to-severe AD, and is approved and available in the US for other immune-mediated conditions, but is not approved by the FDA to treat AD.

Summary of Evidence and Analysis

No additional trials were identified by the updated literature search. However, the standardized analysis approach revised the original evidence base to consider monotherapy and concomitant topical therapy trials separately, with the monotherapy evidence analyzed to support the recommendation.

Three RCTs compared baricitinib 2 mg (n=1,032) or 4 mg (n=741) daily monotherapy to placebo over 16 weeks in adolescents and adults with moderate-to-severe AD.[6, 7] Both doses demonstrated consistent improvements in skin clearance, itch, and patient-reported outcomes compared with placebo, with larger absolute effects with the 4 mg dose (**Supplemental Tables 15 & 16**).

For skin clearance, baricitinib 4 mg increased IGA success, EASI-75 and EASI-90 response rates by 11% (95%CI 5 to 21%), 16% (95%CI 8 to 26%), and 11% (95%CI 5 to 21%), respectively compared to placebo. With 2 mg, responses were similar in direction and magnitude, with increases of 10% (95%CI 5 to 18%), 14% (95%CI 8 to 23%), and 10% (95%CI 4 to 18%), respectively compared to placebo. Itch responder rates (≥4-point PP-NRS improvement) increased by 14% (95%CI 7 to 26%) with 4 mg and 12% (95%CI 6 to 21%) with 2 mg compared to placebo. Both doses meaningfully reduced the need for rescue therapy, with an 18% (95%CI 24 to13%) reduction with 2mg and a 22% (95%CI 29 to 15%) reduction with 4mg. Patient-reported outcomes improved at both doses, with mean POEM reductions of 5.58 (95%CI 7.18 to 3.97) points and 4.57 (95%CI 6.04 to 3.11) points,

and DLQI reductions of 4.26 (95%CI 5.46 to 3.06) and 3.03 (95%CI 3.14 to 1.92) points at 4mg and 2mg doses, respectively.

Neither dose meaningfully increased serious adverse events, treatment-emergent adverse events, or treatment discontinuation compared to placebo.

The overall certainty of the evidence is moderate, driven by imprecision across efficacy outcomes at both doses, where confidence intervals for absolute effects were consistent with benefit and no meaningful difference.

Supplemental Combination Therapy & Long-Term Data

Three RCTs (n=582 per dose) evaluated baricitinib 2 mg or 4 mg daily plus TCS versus placebo plus TCS over 16 weeks in adolescents and adults with moderate-to-severe AD.[48-50] Similar to the monotherapy trials, both doses demonstrated consistent improvements in skin clearance, itch, and patient-reported outcomes over placebo plus TCS, with generally larger absolute effects at the 4 mg dose, though certainty was moderate across most efficacy outcomes due to imprecision (**Supplemental Tables 17 & 18**). Higher placebo arm response rates in these trials likely attenuated observed absolute effect sizes relative to monotherapy trials.

Neither dose was associated with statistically significant increases in serious adverse events, serious infections, herpes simplex, or treatment discontinuation relative to placebo plus TCS, confidence intervals for several of these outcomes were wide and certainty was moderate or low. Treatment-emergent adverse events were more frequent with both doses, reaching statistical significance at 4 mg and approaching significance at 2 mg.

One RCT (2 mg: n=278; 4 mg: n=185) evaluated baricitinib 2 mg or 4 mg daily plus TCS versus placebo plus TCS over 52 weeks.[48] Evidence across all outcomes was rated moderate certainty at both doses, driven by small sample sizes leading to imprecision, and efficacy findings were notably attenuated compared with short-term data (**Supplemental Tables 19 & 20**). At 52 weeks, neither dose demonstrated statistically significant improvements in IGA success, EASI-75, or itch responder rates relative to placebo plus TCS, with confidence intervals for all three outcomes consistent with no meaningful difference at both doses. Directional trends favoring baricitinib were observed across these outcomes, particularly at 4 mg, but effect sizes were smaller than those observed at 16 weeks. The attenuation of efficacy signals at 52 weeks relative to 16 weeks, in the context of small sample sizes and an active comparator background of TCS, limits the interpretability of these findings for assessing long-term durability of benefit compared to the monotherapy trials.

Regarding long-term safety, treatment-emergent adverse events, serious adverse events, serious infections were numerically more frequent with baricitinib plus TCS than placebo

plus TCS at 52 weeks at both doses, though the findings were imprecise with wide CIs consistent with both no meaningful difference and clinically important harm. Larger studies are needed to adequately characterize the durability of benefit and extended safety profile of both doses.

Rationale for Recommendation

The workgroup maintained the strong recommendation for baricitinib in adults with moderate-to-severe AD based on consistent desirable effects across clinically important outcomes and an acceptable safety profile.

The workgroup considered the magnitude of benefit with the use of baricitinib to be moderate. The favorable safety profile suggests baricitinib is well tolerated. The moderate improvement in desirable effects in the absence of substantial risk of undesirable effects favors the use of baricitinib.

Other Considerations

Baricitinib is not currently approved by the FDA for AD.

Upadacitinib

Background

Like abrocitinib, upadacitinib is a selective JAKi that preferentially targets JAK-1. It is approved for use in patients with moderate-to-severe AD who have failed other systemic therapies or when they are inadvisable.

Summary of Evidence and Analysis

No additional trials were identified by the updated literature search. However, the standardized analysis approach revised the original evidence base to consider monotherapy and concomitant topical therapy trials separately, with the monotherapy evidence analyzed to support the recommendation.

Three RCTs evaluated upadacitinib 15 mg (n=1,199) or 30 mg (n=1,209) daily monotherapy versus placebo over 16 weeks in adolescents and adults with moderate-to-severe AD.[19, 20] Both doses demonstrated large, consistent improvements across all efficacy outcomes, with substantially larger absolute effects with the 30 mg dose (**Supplemental Tables 21 & 22**).

For skin clearance, upadacitinib 30mg increased IGA success, and EASI-75, EASI-90 and EASI-100 response rates by 50% (95%CI 32 to 75%), 61% (95%CI 47 to 77%), 53% (5%CI 37 to 75%) and 20% (95%CI 9 to 42%), respectively compared to placebo. At 15 mg, corresponding increases were also substantial but smaller in magnitude: 35% (95%CI 24 to 51%), 49% (95%CI 38 to 64%), 39% (95%CI 27 to 56%), and 12% (95%CI 5 to 27%), respectively. Both doses produced marked reductions in disease flares, with the rate of

participants experiencing an AD exacerbation decreasing by 39% (95%CI 41 to37%) at 30 mg and 35% (95%CI 38 to 32%) at 15 mg compared to placebo. Itch responder rates (≥4-point PP-NRS improvement) increased by 59% (95%CI 44 to 78%) with 30 mg and 37% (95%CI 26 to 51%) with 15 mg compared to placebo. Meaningful improvements in patient-reported outcomes were also observed at both doses, with POEM and DLQI ≥4-point responder rates exceeding 80% at 30 mg and 70% at 15mg compared with 26 to 29% with placebo.

Neither dose resulted in meaningful increases in serious adverse events, serious infections, or treatment discontinuation due to adverse events.

The overall certainty of evidence is high, reflecting precise treatment effects across all critical efficacy and safety outcomes derived from multiple large RCTs.

Supplemental Combination Therapy & Long-Term Data

Two RCTs (n=785, per dose) evaluated upadacitinib 15 mg or 30 mg daily plus TCS versus placebo plus TCS over 16 weeks in adolescents and adults with moderate-to-severe AD.[51, 52] Both doses demonstrated large, consistent improvements across all efficacy outcomes with high certainty, producing effect sizes broadly consistent with, and in some cases comparable to, those observed in monotherapy trials, despite higher background response rates in the placebo plus TCS arms (**Supplemental Tables 23 & 24**). Neither dose was associated with meaningful increases in serious adverse events, treatment discontinuation, or upper respiratory tract infections compared to placebo plus TCS. Treatment-emergent adverse events did not differ significantly from placebo plus TCS at the 15 mg dose. While at the 30 mg dose, treatment-emergent adverse events were numerically higher, but the CI was wide and consistent with both meaningful benefit and harm. Serious infection data at 30 mg were similarly imprecise, with a wide confidence interval. The favorable short-term combination therapy safety profile was consistent with monotherapy findings.

No placebo-controlled long-term data were identified by the updated systematic review for either dose of upadacitinib. Long-term placebo-controlled trials evaluating the durability of efficacy and extended safety of upadacitinib at both approved doses are needed. This evidence gap should be considered in the context of shared decision-making regarding long-term treatment planning.

Rationale for Recommendation

The workgroup maintained the strong recommendation for upadacitinib based on large, consistent desirable effects across all clinically important efficacy and patient-reported outcomes, and a favorable safety profile. The certainty of evidence was revised from moderate to high based on the consistent, precise high-certainty findings across the critical efficacy and safety outcomes at both doses.

The workgroup considered the magnitude of benefit across both doses of upadacitinib to be large. The favorable safety profile suggests upadacitinib is well tolerated. The large improvement in desirable effects in the absence of substantial risk of undesirable effects favors the use of upadacitinib.

Other Considerations

As upadacitinib is FDA-indicated for patients with moderate-to-severe AD who have had an inadequate response to other systemic therapies or for whom such therapies are inadvisable, it is generally not considered a first-line systemic option.

Janus Kinase Inhibitor Considerations

Pertinent to all JAKis considered and based on safety data from other JAKis used in non-AD populations, the FDA applied a warning of increased risk of serious heart-related events, cancer, blood clots, and death for the JAKi class.[53] In light of the warning, it is recommended by the FDA and other regulatory bodies that JAKi medications be started at lower doses, particularly in older adults, a population considered to be at higher risk for adverse events. Other potential safety concerns with JAKis include an increased risk of serious and opportunistic infections, including herpes zoster.[5, 19] When feasible, it is recommended to vaccinate for shingles and receive any other needed live vaccines before initiating a JAKi. The FDA recommends checking complete blood count with differential and liver enzymes at baseline and following initiation or dose escalation at 4 weeks for abrocitinib and per routine management for upadacitinib. Lipid panels should be obtained after initiation at 4 weeks for abrocitinib and 12 weeks for upadacitinib. Testing for viral hepatitis, tuberculosis, and pregnancy is also recommended at baseline. Shared decision-making regarding individual patient risk factors, monitoring requirements, and the FDA warning is essential prior to initiation. Rigorous long-term, placebo-controlled trials evaluating the durability of efficacy and extended safety of JAKis are needed. This evidence gap should be considered in the context of shared decision-making regarding long-term treatment planning, particularly given the class-level safety considerations applicable to JAKis.

Cost

The workgroup recognizes the therapies considered may be cost prohibitive without adequate insurance coverage and other recommended treatments for AD may be available for a lower cost. Given the available evidence of efficacy and safety, the Workgroup concluded the use of the recommended therapies is likely acceptable to patients and clinicians, and cost should be considered during the shared decision-making process.

Research Needs

These recommendations were formulated and based on data for patients with a diagnosis of AD; patients with an atypical history, presentation, or response to AD therapy should be further evaluated for comorbid or alternative skin conditions.

Despite the substantial evidence base informing these recommendations, important gaps remain that should guide future research priorities. Long-term efficacy and safety data and data on patient-reported outcomes in real-world settings are needed to provide additional insights into the efficacy, effectiveness, and safety of these therapies for the management of AD. While head-to-head studies comparing dupilumab vs each of upadacitinib and abrocitinib have been completed, comparative studies among other agents (biologics to biologics, JAKi to JAKi, biologics to standard therapies, JAKi to standard therapies) would provide a better understanding of the role of these therapies in the armamentarium of AD treatments.

Conclusions

The workgroup recommends the use of abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab with concomitant topical therapy, tralokinumab, and upadacitinib for the management of moderate-to-severe AD in adults. Across all interventions, the benefit-harm balance was considered favorable, and the workgroup concluded most patients with moderate-to-severe AD who are candidates for systemic therapy would place high value on the magnitude of benefit observed. Treatment selection should be guided by disease severity, patient comorbidities, prior treatment history, FDA approval status and labeling, patient preferences regarding route and frequency of administration, and formulary considerations.

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