Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies

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Background: For people with atopic dermatitis (AD) refractory to topical therapies, treatment with phototherapy and systemic therapies can be considered. Multiple biologic therapies and Janus kinase (JAK) inhibitors have been approved since 2014 to treat AD. These guidelines update the 2014 recommendations for management of AD with phototherapy and systemic therapies.

Objective: To provide evidence-based recommendations on the use of phototherapy and systemic therapies for AD in adults.

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

Results: The workgroup developed 11 recommendations on the management of AD in adults with phototherapy and systemic agents, including biologics, oral JAK inhibitors, and other immunomodulatory medications.

Limitations: Most randomized controlled trials of phototherapy and systemic therapies for AD are of short duration with subsequent extension studies, limiting comparative long-term efficacy and safety conclusions.

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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 propriety 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.

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Conclusions: We make strong recommendations for the use of dupilumab, tralokinumab, abrocitinib, baricitinib, and upadacitinib. We make conditional recommendations in favor of using phototherapy, azathioprine, cyclosporine, methotrexate, and mycophenolate, and against the use of systemic corticosteroids. (J Am Acad Dermatol 2024;90:e43-56.)

Key words: atopic dermatitis; azathioprine; biologic; cyclosporine; dupilumab; eczema; JAK inhibitor; methotrexate; phototherapy.

SCOPE AND OBJECTIVES

For most people with atopic dermatitis (AD), emollients and prescription topical therapies are sufficient to achieve AD control. In contrast, people with more severe or widespread AD, people with substantially impaired quality of life (QOL), and individuals whose AD is refractory to optimized topical therapy may consider the use of phototherapy or systemic therapies to improve disease control and QOL.[1] Systemic therapies considered in these guidelines include oral medications (immunosuppressants, corticosteroids, antimetabolites, Janus kinase [JAK] inhibitors) and injectable medications (biologics) (Fig 1). The decision to initiate these more advanced therapies should be made using shared decision-making between patients and clinicians, taking into account the severity of AD, its impact on the patient, and the efficacy, safety, and accessibility of the available interventions.[1] Some clinical trials for phototherapy and systemic therapies allow or encourage the concomitant use of topical anti-inflammatory medications, whereas other clinical trials do not; in clinical practice, most patients will use evidence-based topical therapies, including emollients and topical anti-inflammatory medications, concomitantly with phototherapy and systemic therapies. When AD is refractory to standard treatments, including topical therapy and systemic therapies, alternate diagnoses such as allergic contact dermatitis and cutaneous lymphoma should be considered.[2,3]

The objective of this guideline is to provide evidence-based recommendations for the management of AD in adults using phototherapy modalities and systemic (oral or injectable) therapies available for use in the United States (US). Specifically, this evidence review covers the use of ultraviolet (UV) B, UVA1, and psoralen plus UVA (PUVA) phototherapy, injectable monoclonal antibodies (biologics), oral JAK inhibitors, older oral or injectable immunomodulators and antimetabolites, oral antibiotics, antihistamines, and phosphodiesterase-4 inhibitors. Recommendations herein serve to update previously published systemic therapy and phototherapy recommendations.[4] Use of phototherapy and systemic therapies to manage AD in children will be covered in a forthcoming guideline.

CAPSULE SUMMARY

- These guidelines update the AAD's 2014 recommendations for the management of AD in adults with phototherapy and systemic therapies.
- Analysis of the evidence resulted in 11 evidence-based recommendations, including new recommendations on the use of biologics and Janus kinase inhibitors.

METHODS

A multidisciplinary workgroup developed these guidelines using a systematic evidence review process, which included (1) identifying and prioritizing clinical questions and outcomes (Table I), (2) systematic retrieval and assessment of evidence, and (3) assessment of the certainty of the evidence and formulation of recommendations using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) (Table II).

Evidence of the effectiveness and safety of phototherapy and systemic therapies was derived from systematic reviews and meta-analyses of randomized controlled trials (RCTs). Existing, current, high-quality, eligible systematic reviews were identified via a systematic search.[8-11] If relevant systematic reviews were not available, they were commissioned[12] from expert systematic review groups or conducted de novo by the workgroup and AAD staff.

Literature searches were conducted for evidence of patient values and preferences, resource use, and feasibility. The workgroup also included a patient representative to provide input on preferences and values. This evidence, along with the effectiveness and safety data, were compiled in GRADE

Abbreviations used:

AAD:	American Academy of Dermatology
AD:	atopic dermatitis
EASI:	Eczema Area and Severity Index
FDA:	Food and Drug Administration
JAK:	Janus kinase
PUVA:	Psoralen plus ultraviolet A
QOL:	quality of life
RCT:	randomized controlled trial
US:	United States
UV:	ultraviolet

evidence-to-decision frameworks for each clinical question to facilitate recommendation development.

For detailed methodology, see Supplementary Appendix 1, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1.

Definition

AD, also known as atopic eczema, is a chronic, pruritic inflammatory skin disease that occurs most frequently in children, but also affects many adults. It follows a relapsing course. AD is often associated with a personal or family history of allergic rhinitis and asthma.

Phototherapy

Phototherapy using UV radiation is effective for treatment of multiple skin conditions, including psoriasis, AD, and cutaneous lymphomas. Likely because it has been in use for decades, there are few modern, high-quality RCTs evaluating the efficacy and safety of phototherapy for AD.[12] A Cochrane review commissioned to support this guideline included 32 clinical trials with 1219 randomized participants, including children and adults.[12] Narrowband UVB (313 nm wavelength) was the most commonly studied treatment (13 clinical trials), followed by UVA1 (340-400 nm) (6 trials) and broadband UVB (290-320 nm) (5 clinical trials). The heterogeneity of outcome measures used across the different clinical trials, and deficiencies in reporting, precluded meta-analyses for most comparisons. Use of older, inadequately validated outcome measures also made the results for individual clinical trials difficult to interpret.

Based on low certainty evidence (downgraded due to imprecision from small sample sizes and risk of bias), we make a conditional recommendation for the use of phototherapy to treat AD (Table III). Narrowband UVB is the most widely used form of phototherapy; this may be because of its established efficacy for psoriasis and safer track record than UVA1 and broadband UVB. Notably, our conditional recommendation does not include the use of PUVA, for which we have insufficient evidence to make any recommendation.

Potential adverse effects from phototherapy include sunburn-like reactions, intolerance due to the heat from the light source, and the risk of skin cancer associated with exposure to UV radiation.[53] While an association with skin cancer is well-established for PUVA, it appears to be less of a concern with other modalities.[54,55] Perhaps the biggest shortcoming of UV phototherapy is accessibility. Most regimens require treatments 2 to 3 times per week for 10-14 weeks; since most phototherapy is delivered in medical clinics, this requires a substantial time commitment for patients and may not be feasible depending on the distance required to travel, as well as school, work or other responsibilities. Insurance coverage for phototherapy is variable; some plans require substantial co-pays per phototherapy session, making the cost prohibitive for many patients. Home UVB phototherapy units, with appropriate patient training and clinician supervision, can increase the accessibility of phototherapy; studies on the efficacy and safety of home phototherapy units for people with AD are not available.

Monoclonal antibodies (biologics)

Dupilumab and tralokinumab are food and drug administration (FDA)-approved biologics for AD in adults. Dupilumab is a monoclonal antibody targeting the interleukin-4 receptor α. It is the first FDA-approved targeted systemic treatment for AD. Its efficacy in improving the signs and symptoms of AD and QOL in adults compared with placebo was established in large RCTs, including a 52-week randomized trial (Supplementary Tables II and III, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).[18-20] Since then, it was also compared in short-term RCTs against abrocitinib and upadacitinib. Dupilumab at standard dosing (600 mg subcutaneously at initiation, then 300 mg every 2 weeks) is somewhat less efficacious than higher doses of those JAK inhibitors, with somewhat better efficacy than abrocitinib 100 mg daily and comparable efficacy to upadacitinib 15 mg daily.[9,17,56,57] It has an excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice. We surveyed guideline workgroup members as to their favored first-line systemic agent, and all participants favored dupilumab. It was also considered first-line by an international expert panel (conducted before the approval of tralokinumab and JAK inhibitors) for use in special populations of adults, including older adults and those with renal disease,

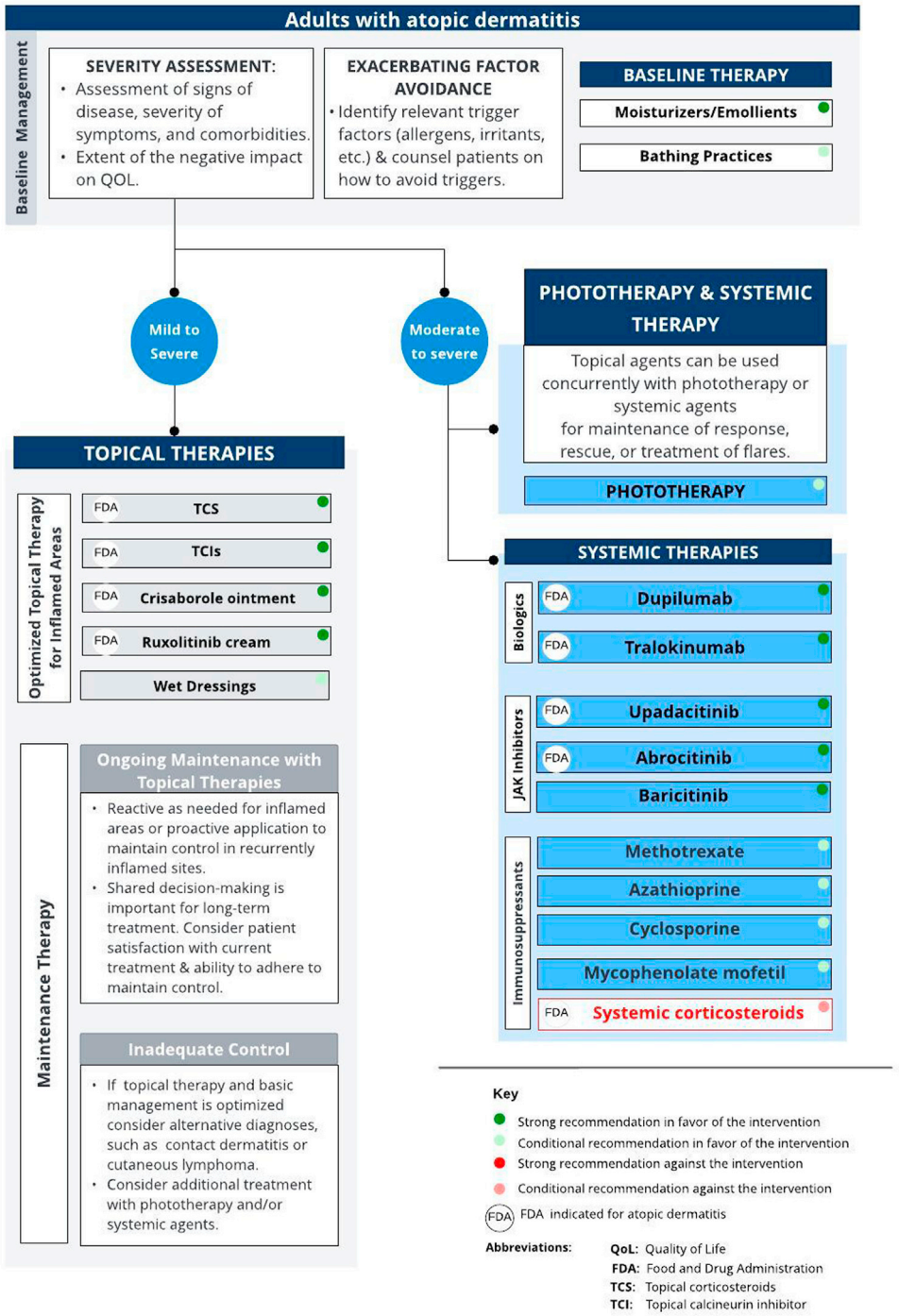

Fig 1. Treatment algorithm for adults with atopic dermatitis. *FDA*, U.S. Food and Drug Administration; *QoL*, quality of life; *TCI*, topical calcineurin inhibitor; *TCS*, topical corticosteroids.

liver disease, viral hepatitis, HIV, or a history of cancer.[58]

Tralokinumab, a monoclonal antibody targeting interleukin-13, is the second biologic approved for AD. In multiple clinical trials, tralokinumab at standard dosing (600 mg at initiation followed by 300 mg every 2 weeks) significantly improved the signs and symptoms of AD as well as QOL.[24,25] Like dupilumab, there were no major safety concerns identified in clinical trials. There are no head-to-head studies evaluating tralokinumab against any other systemic therapies; in network meta-analysis, it is somewhat less effective than dupilumab at 16 weeks of treatment, with differences in change in Eczema Area and

Table I. Clinical questions and scope

1. What are the efficacy and safety of systemic immunomodulatory, antimicrobial, and antihistamine agents for the treatment of AD?
2. What are the efficacy and safety of phototherapy or photochemotherapy for the treatment of AD?
3. What are the comparative efficacy and safety of individual systemic therapies for the treatment of AD?
4. What are the efficacy and safety of combination therapies including a systemic agent for the treatment of AD?

Outcomes of interest	
Efficacy outcomes	Change in clinical signs/symptoms of disease as assessed by a clinician
	Prevention of flares
Safety outcomes	Serious adverse events
	Withdrawal due to adverse events
	Infection
Patient-reported outcomes	Change in patient-reported signs/symptoms
	Change in quality of life
	Change in itch severity

Scope		
Characteristic	**Inclusion criteria**	**Exclusion criteria**
Population	Adults (≥18 y of age) with a clinical diagnosis of AD (including "eczema" or "atopic eczema")	Immunocompromised patients, contact dermatitis, seborrheic dermatitis, varicose eczema, discoid eczema; infected AD
Intervention	Systemic therapies or phototherapy/photo chemotherapy interventions available and approved for use (for any indication) in the US	Treatments not available or approved for use (for any indication) in the US
Study design	Published RCTs in which study participants are investigated (inter-individual, parallel-arm trials)	Unpublished research, observational studies, case series, case reports, modeling studies, narrative reviews

AD, Atopic dermatitis; *RCT*, randomized controlled trial; *US*, United States.

Table II. Strength of recommendation and certainty of evidence

Strength of recommendation	Wording	Implication[5-7]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risks and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; the recommendation applies to most patients in most circumstances.
Good practice statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[7]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burdens; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"We conditionally recommend against…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Certainty of evidence	**Wording**	**Implication[5,6]**
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

Table III. Recommendations for the management of atopic dermatitis in adults with phototherapy and systemic therapies

No.	Intervention	US regulatory status*	Recommendation†	Strength	Certainty of evidence	Evidence
Phototherapy						
1.1	Phototherapy (all types)	On-label	For adults with AD, we conditionally recommend phototherapy. Remarks: Most current literature reports on the efficacy and safety of narrow band UVB. Wherever possible, use a light source that minimizes the potential for harm under the supervision of a qualified clinician.	Conditional	Low	12-16
Monoclonal antibodies (biologics)						
2.1	Dupilumab	On-label	For adults with moderate to severe AD, we recommend dupilumab.	Strong	Moderate	9,17-22
2.2	Tralokinumab	On-label	For adults with moderate to severe AD, we recommend tralokinumab.	Strong	Moderate	9,23-25
JAK inhibitors						
3.1	Upadacitinib	On-label	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	Moderate	9,26-28
3.2	Abrocitinib	On-label	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.	Strong	Moderate	9,17,29-31
3.3	Baricitinib	Off-label	For adults with moderate to severe AD, we recommend baricitinib. Remark: Baricitinib is not approved by the FDA for use in AD.	Strong	Moderate	9,32-36
Antimetabolite						
4.1	Methotrexate	Off-label	For adults with moderate to severe AD, we conditionally recommend methotrexate with proper monitoring. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients. The FDA has not approved methotrexate for use in AD.	Conditional	Low	9,37,38

Continued

Table III. Cont'd

No.	Intervention	US regulatory status*	Recommendation†	Strength	Certainty of evidence	Evidence
Immuno-suppressants						
5.1	Systemic corticosteroids (eg, prednisone)	On-label	For adults with AD, we conditionally recommend against systemic corticosteroids. Remarks: Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy to other systemic, corticosteroid-sparing therapy.	Conditional	Low	11,39
5.2	Mycophenolate mofetil‡	Off-label	For adults with refractory moderate to severe AD, we conditionally recommend mycophenolate mofetil with proper monitoring. Remarks: Mycophenolate mofetil is not approved by the FDA for use in AD. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Very low	40,41
5.3	Azathioprine	Off-label	For adults with refractory moderate to severe AD, we conditionally recommend TPMT-dosed azathioprine with proper monitoring. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Low	9,42,43
5.4	Cyclosporine	Off-label	For adults with refractory moderate to severe AD, we conditionally recommend limited-term use of cyclosporine with proper monitoring. Remarks: Evidence suggests an initial dose of 3 mg/kg/d to 5 mg/kg/d is effective. The FDA has not approved cyclosporine for use in AD§. The FDA has approved limited-term use (up to 1 y) in psoriasis. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Low	9,37,44-52

AD, Atopic dermatitis; *FDA*, Food and Drug Administration; *PUVA*, psoralen plus ultraviolet A.

*For medications, whether they are used on- or off-label for atopic dermatitis based on US Food and Drug Administration approval.

†There are insufficient data at this time to make a recommendation regarding the use of PUVA phototherapy, systemic antibiotics, oral antihistamines, montelukast, apremilast, ustekinumab, intravenous immunoglobulin, interferon gamma, omalizumab, tumor necrosis-alpha inhibitors, systemic calcineurin inhibitors (other than cyclosporine), or mepolizumab in the management of AD (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).

‡Mycophenolic acid can be used interchangeably depending on availability. Note that dosing differs for mycophenolic acid and mycophenolate mofetil.

§While not approved by the US FDA for use in AD, cyclosporine is indicated for atopic dermatitis in other jurisdictions such as the European Union.

Table IV. Medication dosing table for use in adults

Medication	Dose	Notes
Dupilumab	600 mg then 300 mg SC every 2 wk	Pediatric and adolescent dosing will differ. Please see the product package insert for details.
Tralokinumab	600 mg then 300 mg SC every 2 wk	Dose reduction to 300 mg every 4 weeks may be considered after 16 weeks if an adequate response is achieved.
Upadacitinib	15 or 30 mg PO daily	It is recommended to start at 15 mg daily and increase if needed.
Abrocitinib	100 or 200 mg PO daily	It is recommended to start at 100 mg daily and increase if needed.
Baricitinib	2 or 4 mg PO daily	Off-label in the US; approved for use for AD in Europe.
Methotrexate	10-25 mg PO or SC weekly	Once control is achieved, the dose may be lowered to the lowest possible effective dose.
Azathioprine	2.5-5 mg/kg PO daily	Thiopurine methyltransferase genotype or enzyme activity should be checked before treatment initiation and the dose lowered, or the medication not started, depending on the results.
Cyclosporine	3 to 5 mg/kg PO daily	It is suggested to start at the higher end of the dosing range and decrease the dose once control is achieved. Use is generally limited to 1 year. Prescribers should be aware of whether the modified or nonmodified form of cyclosporine is being dispensed as this can alter bioavailability, efficacy, and safety.
Mycophenolate mofetil	Up to 3000 mg PO daily, divided BID	For mycophenolate sodium/acid, 360 mg is equivalent to 500 mg of mycophenolate mofetil.

BID, Twice a day; *PO*, oral; *SC*, subcutaneous.

Severity Index (EASI) score within the minimal clinically important difference threshold.[9]

We recommend both dupilumab and tralokinumab; while there is high-certainty evidence for their efficacy and they appear safe, the overall certainty of evidence was downgraded to moderate certainty due to statistical inconsistency in adverse events analyses. No laboratory monitoring is required before initiation or during treatment. Conjunctivitis is a common adverse event with both dupilumab and tralokinumab (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1). For most patients, conjunctivitis is self-limited and can be managed conservatively with the use of artificial tears. Referral to ophthalmology should be considered, particularly if conjunctivitis is more severe, persistent, or refractory to conservative measures.

Janus kinase (JAK) inhibitors

JAK inhibitors work by blocking the JAK-STAT intracellular signal transduction pathway. Those pathways are important in the response to multiple different cytokines, including type-2 cytokines important for AD (including interleukin-4 and -13), as well as unrelated cytokines important for other inflammatory disorders. JAK inhibitors are approved or under investigation for the treatment of multiple conditions including AD, rheumatoid arthritis, psoriatic arthritis, alopecia areata, and inflammatory bowel disease.

Upadacitinib and abrocitinib are 2 selective JAK inhibitors that preferentially target JAK-1. They are approved for use in moderate-to-severe AD patients who have failed other systemic therapies (immunosuppressants, corticosteroids, antimetabolites, and injectable biologics) or when they are inadvisable. As such, in most circumstances, these medications are not considered to be first-line systemic therapy. Both upadacitinib and abrocitinib demonstrated very high efficacy at reducing the signs and symptoms of AD and improving QOL, with rapid onset of action in their Phase III clinical trial programs among adolescents and adults with AD, leading to moderate certainty evidence (similar to dupilumab and tralokinumab, the overall certainty of evidence was downgraded from high due to statistical inconsistency for adverse event outcomes) (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).[17,26,28,31,56,57] The higher doses of upadacitinib (30 mg daily) and abrocitinib (200 mg daily) demonstrate the highest efficacy at reducing EASI scores up to 16 weeks of treatment among all currently available treatments in a network meta-analysis and were superior to

dupilumab in head-to-head clinical trials.[9,17,56,57] Lower doses (upadacitinib 15 mg daily, abrocitinib 100 mg daily) are somewhat less efficacious than higher doses but still show excellent improvement in the signs and symptoms of AD.[9] Because of potential safety concerns, it is recommended by the FDA and other regulatory bodies that these medications be started at their lower doses (Table IV), particularly in older adults, a population considered to be at higher risk for adverse events (Supplementary Table VI, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).

Baricitinib, which preferentially inhibits both JAK-1 and -2, is also effective for AD.[32-36,59] 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. While no head-to-head clinical trials were done, network meta-analysis suggests baricitinib is less efficacious than upadacitinib and abrocitinib.[9]

Based on safety data from other JAK inhibitors used in other populations, the FDA applied warnings of increased risk of serious heart-related events, cancer, blood clots, and death for the JAK inhibitor class.[60] In a noninferiority trial of people with active rheumatoid arthritis despite methotrexate treatment, aged 50 years and older, and with at least one cardiovascular risk factor, 1455 patients were randomized to either tofacitinib (a JAK-1 and -3 inhibitor) or a tumor necrosis alpha inhibitor and followed for a median of 4 years.[61] Major adverse cardiovascular events and malignancies were higher among people randomized to tofacitinib.[61] Importantly, that trial's population and therefore baseline risk for serious adverse events differs substantially from most people initiating systemic treatment for AD, and tofacitinib is a different JAK inhibitor with less selective inhibition compared to the approved JAK-1 inhibitors for AD. Still, those safety signals warrant some caution when prescribing JAK inhibitors for AD, as serious adverse effects, including death and thromboembolic events, have occurred in clinical trials of AD patients. Other potential safety concerns with JAK inhibitors include an increased risk of serious and opportunistic infections, including herpes zoster.[26,31] When feasible, it is recommended to vaccinate for shingles before initiating a JAK inhibitor, particularly for older patients. In the US and Canada, the recombinant zoster vaccine (nonlive) is approved for immunocompetent adults ages 50 years and older as well as adults ages 19 years and older who are immunocompromised or will be taking medications that increase the risk of herpes zoster; use of JAK inhibitors is included in the latter category. Patients should also receive any other needed live vaccines before initiating treatment. It is recommended by the FDA to check complete blood count with differential, liver enzymes at baseline, and after initiation or dose-escalation (4 weeks for abrocitinib, and per routine management after baseline for upadacitinib); lipids should be checked only after initiation (4 weeks for abrocitinib, 12 weeks for upadacitinib); testing for viral hepatitis, tuberculosis, and pregnancy should be performed at baseline. The optimal frequency of ongoing lab monitoring required for patients who are continuously using JAK inhibitors is unclear.

Antimetabolites and immunosuppressants

Cyclosporine, methotrexate, azathioprine, and mycophenolate are the most commonly recommended older systemic therapies for AD. We gave each of these medications conditional recommendations based on low or very low certainty evidence (Supplementary Tables VII-XII, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1). Evidence was downgraded for risk of bias and imprecision due to small sample sizes. In one head-to-head clinical trial, cyclosporine was more effective than methotrexate for up to 16 weeks, after which they were similarly effective.[37] In another clinical trial, azathioprine and methotrexate had essentially identical efficacy through 12 weeks of treatment.[38] In a network meta-analysis, cyclosporine dosed between 3 and 5 mg/kg per day is more effective than methotrexate and azathioprine, which, in turn, are more effective than placebo, but with substantial uncertainty due to small sample sizes in the underlying clinical trials.[8,9]

There is less randomized trial evidence supporting the use of mycophenolate. One trial randomized patients who were already treated with cyclosporine during a run-in period to maintenance with either mycophenolate sodium or cyclosporine, with little difference in efficacy between the arms at 10 weeks.[40]

Cyclosporine, methotrexate, azathioprine, and mycophenolate require baseline and ongoing laboratory monitoring for adverse effects. Specific guidance can be found in the 2014 AAD guidelines.[4] Each of these medications can also increase the risk of serious infections. Additionally, each has its own specific potential end-organ toxicities. Among other effects, cyclosporine is most prominently associated with renal impairment and hypertension, methotrexate with liver damage, and azathioprine and mycophenolate with cytopenias. Cyclosporine is not suitable for long-term use, as the potential for renal damage increases with cumulative dose. We

suggest limiting treatment to no more than 12 months (and preferably less) based on the FDA recommendations regarding use in psoriasis.[62]

Cyclosporine, methotrexate, azathioprine, and mycophenolate are substantially less expensive than biologics and oral JAK inhibitors; however, we are unaware of formal cost-effectiveness analyses comparing these treatments. Because of lower certainty evidence relative to newer medications, the potential for serious adverse events including infections and organ dysfunction, the need for stringent laboratory monitoring, and the absence of FDA approval for use in AD, we do not consider these medications to be first-line treatments.

Systemic corticosteroids are commonly prescribed for people with moderate-to-severe AD.[63] This may be because they are very effective in the short term and easy to prescribe, with general practitioners and specialists familiar with their use for many other diseases. However, we conditionally recommend against systemic corticosteroids for use in AD. The clinical trial evidence base is low-certainty, consisting only of a single trial of prednisolone vs cyclosporine that was discontinued prematurely due to rebound flares in the prednisolone arm (Supplementary Table XIII, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1).[39] Because of the substantial risk of serious adverse events with systemic corticosteroids, even with short-term use,[64]they are not recommended for AD. Clinicians might consider short courses of systemic corticosteroids in limited circumstances, such as when no other options are available, or as a bridge to other long-term therapies.[65]

Systemic therapies with insufficient evidence to make recommendations

There are insufficient data currently to make a recommendation regarding the use of PUVA phototherapy, systemic antibiotics, oral antihistamines, montelukast, apremilast, ustekinumab, intravenous immunoglobulin, interferon gamma, omalizumab, tumor necrosis-alpha inhibitors, systemic calcineurin inhibitors (other than cyclosporine), or mepolizumab in the management of AD (Supplementary Tables I, IV, VII and XIV, available via Mendeley at https://data.mendeley.com/datasets/s72kbfrfcv/1). The use of systemic antibiotics should be limited to instances of clinically evident infection.

Gaps in research

More RCT evidence is needed to better understand the role of phototherapy in the treatment of AD. Clinical trials comparing different phototherapy modalities and comparing phototherapy to other treatment strategies, including systemic therapies, would be helpful. Larger clinical trials would also be helpful for cyclosporine, methotrexate, azathioprine, and mycophenolate to improve the certainty of evidence for those medications. Furthermore, formal cost-effectiveness analyses comparing older to newer treatments are needed.

As new systemic therapies continue to be developed and tested, we encourage the inclusion of active comparator arms in RCTs, rather than relying solely on placebo-controlled trials. Active comparators enable a better understanding of how new treatments fit into the current treatment paradigm, improving shared decision-making for patients and clinicians. Robust evidence would also be helpful to understand how phototherapy and systemic medication regimens can be best used to achieve long-term control of AD. Future clinical trials should also strive to include a more diverse and generalizable patient population; clinical trials for systemic therapies to date have preferentially excluded older adults and people with comorbidities.[58,66]

All clinical trials for AD should include the core outcome measures from the Harmonizing Outcomes Measures for Eczema (HOME) group — EASI (assessing clinical signs of AD), Patient Oriented Eczema Measure (POEM, assessing symptoms), 24-hour Peak Pruritus Numeric Rating Scale (PP-NRS, assessing itch), Dermatology Life Quality Index (DLQI, assessing quality of life) and either the Recap of Atopic Eczema (RECAP) or Atopic Dermatitis Control Tool (ADCT) (assessing AD control) — and trial manuscripts should report results for these measures, including baseline and follow-up mean scores with standard deviations.[67,68] Standardized measurements and reporting of AD outcomes enable a more complete understanding of the results of clinical trials and allow for trial data to be synthesized in meta-analysis.

The long-term safety of systemic medications for AD should be continuously monitored with rigorous pharmacovigilance studies. Studies evaluating the risk of venous thromboembolism, cardiovascular events, and cancer associated with JAK inhibitors used for AD are necessary.

CONCLUSIONS

When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. In this clinical practice guideline, we make strong recommendations for the use of dupilumab, tralokinumab, abrocitinib, baricitinib, and upadacitinib. We make conditional recommendations in favor of phototherapy, cyclosporine, methotrexate, azathioprine,

and mycophenolate, and against systemic corticosteroids.

Conflicts of interest

Dr Drucker receives research grants paid to his institution from the National Eczema Association, Eczema Society of Canada, Canadian Dermatology Foundation, Canadian Institutes for Health Research, US National Institutes of Health, and Physician Services Incorporated Foundation. Dr Cohen serves on the board of directors for Timber and Evommune receiving stock options and/or fees; as a consultant for Asana Biosciences, Ferndale Laboratories, Inc, Novartis, Facilitation of International Dermatology Education, Dermavant Sciences, Leo Pharma, Inc, UCB, and Cosmetic Ingredient Review receiving honoraria and/or stock options. Dr Eichenfield serves on the board of directors for Forte Biosciences and Verrica Pharmaceuticals, Inc, receiving honoraria and/or stock options; as an investigator for AbbVie, Arcutis, Dermavant, Galderma Laboratories, Pfizer, and Bausch receiving research grants, fees, and/or honoraria; as a consultant for AbbVie, Almirall, Arcutis, Asana, Dermavant, Eli Lilly, Galderma, Ichnos/Glenmark, Incyte, Janssen, Leo Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme, honoraria; as an independent contractor for Elsevier, Inc receiving royalties. Dr Paller serves as a consultant for Abbvie, Abeona, Almirall, Amagma, Anaptysbio, Arena, Bausch, Bristol Myer Squibb, Dermavant, Dermira, Eli Lilly, Exicure, Forte, Leo, Lifemax, Novartis, Phoenix, Pierre Fabre, Pfizer, Rapt, Regeneron, Sanofi, Sol-Gel, UCB, and Venthera receiving honoraria; as an investigator for Anaptysbio, Eli Lilly, Incyte, Janssen, Krystal Bio, Lenus, Regeneron, and UCB receiving no compensation. Dr Schwarzenberger is the founder of Pretel, Inc and serves as a data safety monitoring board member for Pfizer, Inc receiving fees. Dr Sidbury serves as an advisory board member for Pfizer, Inc receiving honoraria; as a principal investigator for Regeneron receiving grants and research funding; as an investigator for Brickell Biotech, Inc, and Galderma USA receiving grants and research funding; as a consultant for Galderma Global and Microes receiving fees or no compensation. Dr Silverberg serves as an advisory board member for BioMX, Boehringer Ingelheim, RAPT Therapeutics, Celgene, Ortho Dermatologics, TARGET Pharma, AFYX Therapeutics, Corrona, Inc, Dermira, Pfizer, Inc, Leo Pharma, Inc, and Menlo Therapeutics receiving honoraria and/or fees; as an investigator for DS Pharma, TARGET Pharma, Kiniksa Pharmaceuticals, Ltd, Menlo Therapeutics, GlaxoSmithKline, AbbVie, Leo Pharma, Inc, and Regeneron receiving research funding, honoraria, or no compensation; as a consultant for AOBiome, Bluefin Biomedicine, Bodewell, BiomX, Inc, Galderma Research & Development, LLC, Arena Pharmaceuticals, Dermavant Sciences, Incyte Corporation, DS Biopharma, Sun Pharmaceutical Industries, Ltd, AnaptysBio, Asana Biosciences, LLC, Pfizer, Inc, Glenmark Generics, Inc, Sanofi, Kiniksa Pharmaceuticals, Ltd, GlaxoSmithKlein, Eli Lilly and Company, AbbVie, Regeneron, and Medimmune receiving honoraria or fees; as a speaker for the Fall Clinical Dermatology Conference, Maui Derm, and Regeneron receiving honoraria or fees. Dr Singh serves as an advisory board member for Incyte receiving honoraria. DR Wu is an author for UpToDate, Inc receiving honoraria. Dr Davis, Dr Alikhan, Dr Bercovitch, Athor Darr, and Dr Frazer-Green have no conflicts of interest to declare.

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