DRAFT

Title: Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic agents

Dawn M.R. Davis, MD (Co-Chair)[a], Aaron M. Drucker, MD, ScM[b,c]; Ali Alikhan, MD[d], Lionel Bercovitch, MD[e], David E. Cohen, MD, MPH[f], Jennifer M. Darr, LCSW[g], , Lawrence F. Eichenfield, MD[h], Lindsy Frazer-Green, PhD[i], Amy S. Paller, MD[j], Kathryn Schwarzenberger, MD[k], Jonathan I. Silverberg, MD, PhD, MPH[l], Anne Marie Singh, MD[m], Peggy A. Wu, MD, MPH[n], Robert Sidbury, MD, MPH (Co-Chair)[o]

Departments of Dermatology and Pediatrics, Mayo Clinic, Rochester, Minnesota[a]; Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada[b]; Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada[c]; Department of Dermatology, Sutter Medical Foundation, Sacramento, California[d]; Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, Rhode Island[e]; The Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, New York[f]; Department of Pediatrics, Department of Pediatrics/Pediatric Behavioral Health, National Jewish Health, Denver, Colorado[g]; Departments of Dermatology and Pediatrics, University of California San Diego and Rady Children's Hospital San Diego, San Diego, California[h]; American Academy of Dermatology, Rosemont, Illinois[i]; Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois[j]; Department of Dermatology, Oregon Health and Science University, Portland, Oregon[k]; Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC[l]; Departments of Pediatrics, Dermatology and Medical Microbiology/Immunology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin[m]; Department of Dermatology, University of California, Davis, Sacramento, California[n]; Division of Dermatology, Department of Pediatrics, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, Washington[o]

Corresponding author:
Lindsy Frazer-Green, PhD
American Academy of Dermatology
9500 Bryn Mawr Avenue, Suite 500
Rosemont, IL 60018
Email: lfrazer-green@aad.org

Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

Conflicts of Interest: Listed in text.

Keywords: atopic dermatitis, eczema, phototherapy, methotrexate, cyclosporine, azathioprine, JAK inhibitor, biologic, dupilumab

Publishable Conflict of Interest Statement

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

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.

Abstract

Background: For people with atopic dermatitis (AD) refractory to topical therapies, treatment with phototherapy and systemic agents 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 agents.

Objective: To provide evidence-based recommendations on the use of phototherapy and systemic agents 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 trials of phototherapy and systemic agents for AD are of short duration with subsequent extension studies, limiting comparative long-term efficacy and safety conclusions.

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 use of systemic corticosteroids.

Abbreviations Used

AAD: American Academy of Dermatology

AD: Atopic dermatitis

EASI: Eczema area severity index

FDA: Food and Drug Administration

JAK: Janus kinase

PUVA: Psoralen plus ultraviolet A

US: United States

UV: Ultraviolet

Scope & 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 and individuals whose AD is refractory to optimized topical therapy may consider use of phototherapy, systemic or biologic agents to improve disease control and quality of life.[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 agents allow or encourage the concomitant use of topical anti-inflammatory medications, whereas other 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 agents. When AD is refractory to standard treatments, including topical therapy and systemic agents, 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) agents 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 Janus kinase (JAK) inhibitors, older 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 agents to manage AD in children will be covered in a forthcoming guideline.

Methods

A multidisciplinary workgroup developed these guidelines using a systematic evidence review process, which included (i) identifying and prioritizing clinical questions and outcomes (**Table I**), (ii) systematic retrieval and assessment of evidence, and (iii) 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 agents was derived from systematic reviews and meta-analyses of randomized controlled trials. Existing, current, high-quality, eligible systematic reviews were identified via a systematic search.[5-8] If relevant systematic reviews were not available, they were commissioned[9] 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, was compiled in GRADE evidence-to-decision frameworks for each clinical question to facilitate recommendation development.

For detailed methodology, see **e-Appendix 1**.

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 agents 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 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 years of age) with a clinical diagnosis of AD (including "eczema" or "atopic eczema")	Immunocompromised patients, contact dermatitis, seborrheic dermatitis, varicose eczema, discoid eczema; infected atopic dermatitis
Intervention	Systemic agents or phototherapy/photochemotherapy 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

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

205

206

207

208

209

210

211

212

213

214

215

Table II. Strength of Recommendation and Certainty of Evidence

Strength of Recommendation	**Wording**	**Implication**[10-12]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risk 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; 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.[12]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burden; 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**[10, 11]
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

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.

222 **Table III**. Recommendation for the management of atopic dermatitis in adults with phototherapy

223 and systemic agents.

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 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	9, 13-16
Monoclonal antibodies (biologics)						
2.1	Dupilumab	On-label	For adults with moderate to severe AD, we recommend dupilumab.	Strong	Moderate	6, 17-22
2.2	Tralokinumab	On-label	For adults with moderate to severe AD, we recommend tralokinumab.	Strong	Moderate	6, 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.	Strong	Moderate	6, 26-28
3.2	Abrocitinib	On-label	For adults with moderate to severe AD, we recommend abrocitinib.	Strong	Moderate	6, 17, 29-31

			Remarks: Abrocitinib is approved by the FDA in patients with AD who have failed other systemic therapies.			
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	[6, 32-36]
Antimetabolite						
4.1	Methotrexate	Off-label	For adults with AD, we conditionally recommend methotrexate. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients. In the US, the FDA has not approved methotrexate for use in AD.	Conditional	Low	[6, 37, 38]
Immunosuppressants						
5.1	Systemic corticosteroids (e.g., 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, steroid-sparing therapy.	Conditional	Low	[8, 39]
5.2	Mycophenolate mofetil^	Off-label	For adults with refractory AD, we conditionally	Conditional	Very low	[40, 41]

			recommend mycophenolate mofetil. 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.			
5.3	Azathioprine	Off-label	For adults with refractory moderate-to-severe AD, we conditionally recommend TMPT-dosed azathioprine with proper monitoring. Remarks: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Low	6, 42, 43
5.4	Cyclosporine	Off-label	For adults with refractory moderate to severe AD, we conditionally recommend limited term use of cyclosporine. Remarks: Evidence suggests an initial dose of 3mg/kg/d to 5mg/kg/d is effective. The FDA has not approved cyclosporine for use in AD. The FDA has approved limited term use (up to one year) in psoriasis. Comorbidities or drug interactions that may	Conditional	Low	6, 37, 44-52

			exacerbate toxicity make this intervention inappropriate for select patients.			

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

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

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 (**e-Table 1**).

Phototherapy

Phototherapy using UV radiation is effective for treatment of multiple skin conditions, including psoriasis, atopic dermatitis, and cutaneous lymphomas. Likely because it has been in use for decades, there are few modern, high-quality randomized clinical trials evaluating the efficacy and safety of phototherapy for atopic dermatitis.[9] A Cochrane review commissioned to support this guideline included 32 trials with 1,219 randomized participants, including children and adults.[9] Narrowband UVB (313 nm wavelength) was the most commonly studied treatment (13 trials), followed by UVA1 (340-400 nm) (6 trials) and broadband UVB (290-320 nm) (5 trials). The heterogeneity of outcome measures used across the different trials, and deficiencies in reporting, precluded meta-analyses for most comparisons. Use of older, inadequately validated outcome measures also made the results for individual 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 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 two to three 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 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 quality of life in adults compared with placebo was established in large randomized trials, including a 52-week randomized trial (**e-Tables 2-3**).[18-20] Since then, it was also compared in short-term randomized trials against abrocitinib and upadacitinib. As discussed above, 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.[6, 17, 56, 57] Its excellent safety track record in clinical trials and few major emergent safety concerns after more than 5 years in clinical practice make it the favored first-line systemic agent for all participants on our guideline workgroup. It was also considered first-line by an international expert panel for use in special populations of adults, including older adults and those with renal disease, liver disease, viral hepatitis, HIV, and a history of cancer.[58]

Tralokinumab, a monoclonal antibody targeting interleukin-13, is the second biologic approved for AD. In multiple clinical trials, tralokinumab 600 mg at initiation followed by 300 mg every 2 weeks significantly improved the signs and symptoms of AD as well as quality of life.[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 agents; in network meta-analysis, it is somewhat less effective than dupilumab, upadacitinib, and abrocitinib at 16 weeks of treatment.[58]

We recommend both dupilumab and tralokinumab; the evidence is of moderate certainty due to inconsistency in adverse events analyses. Still, these medications appear safe. No laboratory monitoring is required before initiation or during treatment. Conjunctivitis is a common adverse event with both dupilumab and tralokinumab (**e-Table 4**). For most patients, conjunctivitis is self-limited and can be managed conservatively with 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 two selective JAK inhibitors that preferentially target JAK-1. They are approved for use in moderate-to-severe atopic dermatitis patients who have failed other systemic therapies. As such, in most circumstances, these medications are not considered to be first-line systemic therapy. Both upadacitinib and abrocitinib demonstrated very high efficacy with rapid onset of action in their Phase III clinical trial programs among adolescents and adults with AD, leading to moderate certainty evidence (downgraded from high due to inconsistency in adverse event outcome data) (**e-Table 5**).[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 eczema area and severity index (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 trials.[6, 17, 56, 57] Lower doses (upadacitinib 15 mg daily, abrocitinib 100 mg daily) are somewhat less efficacious, but still, show excellent improvement in the signs and symptoms of AD.[6] Because of potential safety concerns, it is recommended by the US Food and Drug Administration (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 (**e-Table 6**).

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 AD, and is approved and available in the US for other immune-mediated conditions, but is not approved by the US FDA to treat AD. While no head-to-head trials were done, network meta-analysis suggests baricitinib is less efficacious than upadacitinib and abrocitinib.[6]

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 non-inferiority trial of people with active rheumatoid arthritis despite methotrexate treatment, aged 50 and older, and with at least one cardiovascular risk factor, 1,455 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 atopic dermatitis, and tofacitinib is a different JAK inhibitor with less selective inhibition compared to the approved JAK1 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 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 (non-live) is approved for immunocompetent adults ages 55 years and older as well as adults ages 19 years and older who are immunocompromised or will be taking medications that increase 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 US FDA to check complete blood count with differential, liver enzymes at baseline and after initiation or dose-escalation (4 weeks for abrocitinib, 12 weeks 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 agents for AD. We gave each of these medications conditional recommendations based on low or very low certainty evidence (**e-Tables 7-12**). Evidence was downgraded for risk of bias and imprecision due to small sample sizes. In one head-to-head trial, cyclosporine was more effective than methotrexate for up to 16 weeks, after which they were similarly effective.[37] In another, trial, azathioprine and methotrexate had essentially identical efficacy through 12 weeks of treatment.[38] In 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 trials.[5, 6]

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 US 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-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 **(e-Table 13**).[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 treatments 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 (**e-Tables 1, 4, 7 & 14**). The use of systemic antibiotics should be limited to instances of clinically evident infection.

Gaps in Research

More randomized controlled trial evidence is needed to better understand the role of phototherapy in the treatment of AD. Trials comparing different phototherapy modalities and comparing phototherapy to other treatment strategies, including systemic treatments, would be helpful. Larger 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 agents continue to be developed and tested, we encourage the inclusion of active comparator arms in randomized trials, 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 trials should also strive to include a more diverse and generalizable patient population; trials for systemic agents to date have preferentially excluded older adults and people with comorbidities.[58, 66]

All 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 measurement and reporting of AD outcomes enable a more complete understanding of the results of 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.

Table IV. Medication dosing table for use in adults

Medication	Dose	Notes
Dupilumab	600 mg then 300 mg SC every 2 weeks	Pediatric and adolescent dosing will differ. Please see the product package insert for details.
Tralokinumab	600 mg then 300 mg SC every 2 weeks	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 non-modified 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

426

Work Group Members' Disclosures

The information below represents the authors' disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with AAD policy, a minimum 51% of Work Group members did not have any relevant conflicts of interest.

Participation in one or more of the listed activities below constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved.
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved

If a potential conflict was noted, the work group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

Drs. Alikhan, Bercovitch, Davis, Frazer-Green, and Jennifer M. Darr, LCSW, have no relationships to disclose. David E. Cohen*, MD, MPH, 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. Aaron M. Drucker, MD, ScM 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. Lawrence F. Eichenfield*, MD, 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. Amy S. Paller*, MD, 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. Kathryn Schwarzenberger, MD is the founder of Pretel, Inc. and serves as a data safety monitoring board member for Pfizer, Inc. receiving fees. Robert Sidbury*, MD, MPH 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. Jonathan I. Silverberg*, MD, PhD, MPH, 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. Anne Marie Singh, MD, as an advisory board member for Incyte receiving honoraria. Peggy Wu, MD, MPH is an author for UpToDate, Inc receiving honoraria.

References

1. Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. J Am Acad Dermatol 2017;77:623-33.
2. Park A, Wong L, Lang A, Kraus C, Anderson N , Elsensohn A. Cutaneous T-cell lymphoma following dupilumab use: a systematic review. Int J Dermatol 2022.
3. Chen JK, Jacob SE, Nedorost ST, Hanifin JM, Simpson EL, Boguniewicz M et al. A Pragmatic Approach to Patch Testing Atopic Dermatitis Patients: Clinical Recommendations Based on Expert Consensus Opinion. Dermatitis 2016;27:186-92.
4. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014;71:327-49.
5. Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis. JAMA Dermatol 2020;156:659-67.
6. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol 2022;158:523-32.
7. Ferguson L, Futamura M, Vakirlis E, Kojima R, Sasaki H, Roberts A et al. Leukotriene receptor antagonists for eczema. Cochrane Database of Systematic Reviews 2018.
8. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy 2021;76:1053-76.
9. Musters AH, Mashayekhi S, Harvey J, Axon E, Lax SJ, Flohr C et al. Phototherapy for atopic eczema. Cochrane Database Syst Rev 2021;10:CD013870.

10. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
11. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
12. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 2016;80:3-7.
13. Kwon S, Choi JY, Shin JW, Huh CH, Park KC, Du MH et al. Changes in Lesional and Non-lesional Skin Microbiome During Treatment of Atopic Dermatitis. Acta Derm Venereol 2019;99:284-90.
14. Reynolds NJ, Franklin V, Gray JC, Diffey BL , Farr PM. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. Lancet 2001;357:2012-6.
15. Tzung TY, Lin CB, Chen YH , Yang CY. Pimecrolimus and narrowband UVB as monotherapy or combination therapy in children and adolescents with atopic dermatitis. Acta Derm Venereol 2006;86:34-8.
16. Youssef R, Hafez V, Elkholy Y , Mourad A. Glycerol 85% efficacy on atopic skin and its microbiome: a randomized controlled trial with clinical and bacteriological evaluation. J Dermatolog Treat 2020:1-7.
17. Bieber T, Simpson EL, Silverberg JI, Thaci D, Paul C, Pink AE et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med 2021;384:1101-12.
18. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389:2287-303.
19. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). Br J Dermatol 2018;178:1083-101.
20. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med 2016;375:2335-48.
21. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016;387:40-52.
22. Zhao Y, Wu L, Lu Q, Gao X, Zhu X, Yao X et al. The efficacy and safety of dupilumab in Chinese patients with moderate-to-severe atopic dermatitis: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2021.
23. Merola JF, Bagel J, Almgren P, Røpke MA, Lophaven KW, Vest NS et al. Tralokinumab does not impact vaccine-induced immune responses: Results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2021;85:71-8.
24. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol 2021;184:450-63.
25. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184:437-49.

26. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021;397:2151-68.
27. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145:877-84.
28. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2169-81.
29. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol 2019;155:1371-9.
30. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:863-73.
31. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.
32. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP et al. Efficacy and Safety of Baricitinib in Combination With Topical Corticosteroids in Patients With Moderate-to-Severe Atopic Dermatitis With Inadequate Response, Intolerance, or Contraindication to Cyclosporine: Results From a Randomized, Placebo-Controlled, Phase III Clinical Trial (BREEZE-AD4). Br J Dermatol 2022.
33. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2019;80:913-21.e9.
34. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatology 2020;156:1333-43.
35. Simpson EL, Forman S, Silverberg JI, Zirwas M, Maverakis E, Han G et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). J Am Acad Dermatol 2021;85:62-70.
36. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-55.
37. Goujon C, Viguier M, Staumont-Salle D, Bernier C, Guillet G, Lahfa M et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. J Allergy Clin Immunol Pract 2018;6:562-9 e3.
38. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J , Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol 2011;128:353-9.
39. Schmitt J, Schakel K, Folster-Holst R, Bauer A, Oertel R, Augustin M et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol 2010;162:661-8.
40. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS , Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol 2011;64:1074-84.

41. Phan K , Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. J Dermatolog Treat 2020;31:810-4.
42. Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. Br J Dermatol 2002;147:324-30.
43. Meggitt SJ, Gray JC , Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. Lancet 2006;367:839-46.
44. Czech W, Brautigam M, Weidinger G , Schopf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. J Am Acad Dermatol 2000;42:653-9.
45. Granlund H, Erkko P, Remitz A, Langeland T, Helsing P, Nuutinen M et al. Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. Acta Derm Venereol 2001;81:22-7.
46. Koppelhus U, Poulsen J, Grunnet N, Deleuran MS , Obitz E. Cyclosporine and Extracorporeal Photopheresis are Equipotent in Treating Severe Atopic Dermatitis: A Randomized Cross-Over Study Comparing Two Efficient Treatment Modalities. Front Med (Lausanne) 2014;1:33.
47. Munro CS, Levell NJ, Shuster S , Friedmann PS. Maintenance treatment with cyclosporin in atopic eczema. Br J Dermatol 1994;130:376-80.
48. Pacor ML, Di Lorenzo G, Martinelli N, Mansueto P, Rini GB , Corrocher R. Comparing tacrolimus ointment and oral cyclosporine in adult patients affected by atopic dermatitis: a randomized study. Clin Exp Allergy 2004;34:639-45.
49. Salek MS, Finlay AY, Luscombe DK, Allen BR, Berth-Jones J, Camp RD et al. Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. Br J Dermatol 1993;129:422-30.
50. Sowden JM, Berth-Jones J, Ross JS, Motley RJ, Marks R, Finlay AY et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. Lancet 1991;338:137-40.
51. van Joost T, Heule F, Korstanje M, van den Broek MJ, Stenveld HJ , van Vloten WA. Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. Br J Dermatol 1994;130:634-40.
52. Wahlgren CF, Scheynius A , Hägermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. Acta Derm Venereol 1990;70:323-9.
53. Rodenbeck DL, Silverberg JI , Silverberg NB. Phototherapy for atopic dermatitis. Clin Dermatol 2016;34:607-13.
54. Stern RS, Thibodeau LA, Parrish JA , Fitzpatrick TB. Skin cancer after PUVA treatment for psoriasis. N Engl J Med 1979;301:555.
55. Ahad T, Wang EY, Liu YA, Lee TK, Lui H, Crawford RI et al. Incidence of skin cancers in patients with eczema treated with ultraviolet phototherapy. J Am Acad Dermatol 2022;87:387-9.
56. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2021;157:1047-55.
57. Reich K, Thyssen JP, Blauvelt A, Eyerich K, Soong W, Rice ZP et al. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. Lancet 2022;400:273-82.
58. Drucker AM, Lam M, Flohr C, Thyssen JP, Kabashima K, Bissonnette R et al. Systemic Therapy for Atopic Dermatitis in Older Adults and Adults With Comorbidities: A Scoping Review and International Eczema Council Survey. Dermatitis 2022;33:200-6.
59. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, DeLozier AM et al. Long-term Efficacy of Baricitinib in Adults With Moderate to Severe Atopic Dermatitis Who Were Treatment

Responders or Partial Responders: An Extension Study of 2 Randomized Clinical Trials. JAMA Dermatology 2021;157:691-9.
60. FDA. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions2021.
61. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med 2022;386:316-26.
62. Novartis. Neoral (cyclosporine) [package insert]. U.S. Food and Drug Adminiatration website. www.accessdata.fda.gov/drugsatfda_docs/label/2009/050715s027 slpRS.
63. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol 2016;74:491-8.
64. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 2017;357:j1415.
65. Drucker AM, Eyerich K, de Bruin-Weller MS, Thyssen JP, Spuls PI, Irvine AD et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. Br J Dermatol 2018;178:768-75.
66. Lam M, Zhu JW, Maqbool T, Adam G, Tadrous M, Rochon P et al. Inclusion of Older Adults in Randomized Clinical Trials for Systemic Medications for Atopic Dermatitis: A Systematic Review. JAMA Dermatol 2020;156:1240-5.
67. Williams HC, Schmitt J, Thomas KS, Spuls PI, Simpson EL, Apfelbacher CJ et al. The HOME Core outcome set for clinical trials of atopic dermatitis. J Allergy Clin Immunol 2022;149:1899-911.
68. Grinich EE, Schmitt J, Kuster D, Spuls PI, Williams HC, Chalmers JR et al. Standardized reporting of the Eczema Area and Severity Index (EASI) and the Patient-Oriented Eczema Measure (POEM): a recommendation by the Harmonising Outcome Measures for Eczema (HOME) Initiative. Br J Dermatol 2018;179:540-1.