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Systemic Therapy for Atopic Dermatitis in Children and Adolescents: A US Expert Consensus

Lawrence F. Eichenfield[a, b] Mark Boguniewicz[c, d] Christine T. Lauren[e] Donald Y.M. Leung[c, d] Moise L. Levy[f, g] Lynda C. Schneider[h] Elaine C. Siegfried[i, j] Wynnis L. Tom[a, b] Amy S. Paller[k]

[a]Departments of Dermatology and Pediatrics, University of California San Diego, La Jolla, CA, USA; [b]Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, CA, USA; [c]Division of Allergy-Immunology, Department of Pediatrics, National Jewish Health, Denver, CO, USA; [d]University of Colorado School of Medicine, Denver, CO, USA; [e]Departments of Dermatology and Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA; [f]Departments of Pediatrics and Internal Medicine (Dermatology), Dell Medical School at The University of Texas at Austin, Austin, TX, USA; [g]Dell Children's Medical Center, Austin, TX, USA; [h]Division of Immunology, Boston Children's Hospital, Boston, MA, USA; [i]Department of Pediatrics, Saint Louis University, St. Louis, MO, USA; [j]Department of Pediatric Dermatology, Cardinal Glennon Children's Hospital, St. Louis, MO, USA; [k]Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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Abstract
Atopic dermatitis (AD) is a chronic, type-2 mediated, inflammatory skin disease characterized by intense pruritus, disruption of skin barrier function, and immune dysregulation. Management strategies for AD are routinely determined based on disease severity. First-line treatment begins with basic skin care and topical anti-inflammatory medication, which is typically sufficient for the management of mild-to-moderate disease. For those patients with moderate-to-severe disease, systemic therapy is often required. This can involve off-label treatment with conventional immunosuppressant medications. However, this approach is limited by a lack of robust clinical trial data and safety concerns that necessitate close monitoring. The emergence of novel targeted biologics and small molecules to treat AD presents an opportunity to optimize AD management and patient outcomes by offering greater efficacy than traditional immunosuppressants and a favorable safety profile. As the treatment landscape shifts, clinicians can benefit from a standardized process of patient assessment and treatment, along with resources to help maintain contemporary knowledge of available therapeutic options. This US-based, expert-led consensus used a modified Delphi process to develop core recommendations for the use of systemic medications for the management of pediatric patients <18 years of age with moderate-to-severe AD.

karger@karger.com
www.karger.com/drm

Correspondence to:
Lawrence F. Eichenfield, leichenfield@rchsd.org

Introduction

Atopic dermatitis (AD) is a chronic, type 2-mediated, inflammatory skin disease that is characterized by intense pruritus and disruption of skin barrier function [1, 2], with a global prevalence of approximately 12–15% in children and adolescents [3]. Many pediatric patients with AD can achieve disease control with basic skin care (i.e., use of low-allergenicity emollients and nondrying bathing practices, and avoiding disease-exacerbating irritants), and adequate use of topical anti-inflammatory medication [4–6]. However, up to one-third of children with AD have moderate-to-severe skin disease that is insufficiently controlled with topical therapy and requires systemic treatment [7]. Previously, only oral immunosuppressant drugs, which are limited by variable efficacy and challenging side effects, along with systemic corticosteroids (SCSs) were available in these cases [8, 9]. Since 2017, the development and subsequent implementation of targeted biologic and small-molecule agents in routine clinical practice has generated robust data to support the use of these systemic therapeutics in the management of moderate-to-severe AD in patients of all ages, including children [8]. Dupilumab, an anti-interleukin (IL)-4 receptor-α monoclonal antibody that blocks IL-4 and IL-13 signaling, was the first biologic approved for moderate-to-severe AD in children 6 months of age and older [10]. Recently, the IL-13 blocker tralokinumab was approved for children aged 12 years and older [11]. Oral Janus kinase (JAK) inhibitors have subsequently been approved for adolescents and adults, with approval for pediatric patients (≥2 years of age) recently granted to the JAK inhibitor, baricitinib, in Europe [8, 12]. Several other novel therapeutic agents are currently under development [8]. With the continued evolution of the AD systemic therapy landscape, healthcare professionals can benefit from a consistent approach to patient assessment and management and should be knowledgeable of when and how to incorporate these therapeutics into treatment pathways. For these reasons, an expert-led consensus was convened to develop recommendations on the use of systemic therapies for pediatric AD.

Methods

In January 2022, a US-based group of six dermatologists and three allergists convened online to identify key questions concerning the management of moderate-to-severe AD in children and adolescents using systemic therapies. These experts were selected based on their experience, expertise, clinical research activity, publication volume (post 2017), and social media outreach in the context of pediatric AD. For expediency, nurse practitioners, physician assistants, and expert adult patients with AD were not included in the consensus process. These stakeholders would be considered for future consensus papers.

A systematic literature review was conducted using Medline and EMBASE to identify publications relevant to four key themes relating to AD management: defining control, current and emerging treatments, referral care pathways, and patient-caregiver experience. Search strings incorporated terms aligned to each of these themes. Initial search results were then filtered for relevance by title and abstract. Full details of the literature search can be found in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540920). The expert panel then reviewed the literature results and developed 29 management recommendation statements based on the initial questions in facilitated virtual/email discussions (shown in the online suppl. material). Draft statements were reviewed and refined independently by the panel in November 2022, and submitted for two rounds of voting using an online platform in January and February 2023.

Consensus was achieved via modified Delphi methodology. During each round of voting, individual members voted anonymously on each statement using a 9-point scale (1 = strong disagreement; 9 = strong agreement). For each statement, consensus for inclusion was considered achieved if ≥75% of the experts voted within the 7–9 range on the 9-point scale, or for exclusion if ≥75% of the experts voted within the 1–3 range. A second round of voting and refinement was needed for statements that did not achieve the threshold for consensus or exclusion. Details of the final statements are shown in Table 1.

Results

After two rounds of voting, consensus for inclusion was reached on 24 out of 29 statements on the use of systemic therapy for the management of pediatric AD (shown in Table 1 and online suppl. Fig. 1 and 2). Nine statements reached a score of 7–9 by 100% of the experts (Table 1). These statements addressed key topics, including the criteria required for

Table 1. Statements for systemic therapy recommendations reaching consensus

Statement	Level of consensus (scores 7–9), %	Strength of recommendations (median)	Strength of recommendations (mean)
Poor adherence to systemic therapy may lead to an inadequate response	100	9	8.89
Systemic therapy should be considered for those patients with moderate-to-severe AD for whom optimized topical therapy does not adequately improve disease severity and/or quality of life	100	9	8.78
There is a need for more evidence on specific escalation of therapy across the <2 years, 2–<6 years, and 6–12 years of age groups	100	9	8.78
PCPs play an important role in the management of AD, treating patients with mild-to-moderate disease, referring those with moderate-to-severe disease for specialist care, and providing ongoing maintenance care	100	9	8.78
Ongoing consultation and dialogue between the PCP, families, and specialists may be helpful in determining effective treatment approaches	100	9	8.78
It is important that PCPs understand AD pathophysiology and diagnosis, management of mild-to-moderate disease, potential adverse events, and when to refer to specialty care	88.89	9	8.78
AD is a disease that may spontaneously improve with age in some patients, so the disease-modifying effects of systemic therapy on AD over the longer term may be difficult to establish[1]	77.77	9	8.78
The impact of early successful management of AD on the natural history of the disorder and development of other atopic and nonatopic morbidities (e.g., neuropsychiatric conditions) during a patient's lifetime is not currently known[1]	77.78	9	8.78
Reasons for inadequate adherence to treatment are varied but include concerns about adverse effects, inadequate patient or parent/caregiver education, child resistance to treatment, a lack of trust in/rapport with clinician, and high out-of-pocket costs/limitations in access to treatment	100	9	8.00
Systemic therapy may be considered in some patients requiring higher than recommended use of TCSs to control AD	100	8	8.00
Clinicians should refer to specific prescribing information, data from clinical trials, and relevant guidelines to guide treatment escalation	100	8	8.33
Comparative evidence for the use of systemic therapies in AD is limited, especially in children	100	9	8.33
Treatment may be switched because of inadequate response, but there is a need to first consider contributory factors through discussion with the patient/caregivers	88.89	9	8.44
Treatment taper may be considered when there is a long period of clear or almost clear skin, or in response to tolerability or safety issues	88.89	9	8.33

Table 1 (continued)

Statement	Level of consensus (scores 7–9), %	Strength of recommendations (median)	Strength of recommendations (mean)
Factors to take into consideration in choosing systemic therapy include AD phenotype, the presence of comorbidities, risk-benefit profile of treatments, patient preferences (e.g., oral vs. injectable therapy), the need for laboratory monitoring, drug interactions, and access to therapy	88.88	8	7.89
The use of SCSs is associated with frequent disease recurrence and safety risks and is not generally recommended	88.88	8	8.00
Discontinuation of treatment may result in disease recurrence	88.88	8	8.11
Possible effects of systemic treatment on immune response to immunization need to be considered; however, there is limited evidence on coadministration of systemic treatments and vaccines in children with AD	88.88	8	8.00
The ability to use systemic therapy such as biologics in patients as young as 6 months of age offers the potential for a disease-modifying effect	88.88	8	8.00
Biologics should be considered first-line systemic therapy in most patients unless contraindicated	77.78	9	7.33
Biologic therapy does not need to be interrupted for administration of inactivated vaccines, but safety of coadministration with live-attenuated vaccines is not known	77.78	9	8.11
Total steroid burden, including the use of oral and intranasal corticosteroids, should be taken into consideration when assessing patients	77.77	8	7.67
Conventional systemic therapies may be used off-label	77.77	8	7.56
Ongoing education and support will help ensure patient comfort with systemic therapy	77.77	8	7.78

[1]Statements required a second round to achieve consensus.

consideration of systemic therapy; the relationship between poor adherence and response to treatment; the importance of coordinated management between primary care providers (PCPs) and secondary care specialists; the potential for disease modification via systemic therapy; along with the existence of knowledge gaps regarding dose escalation in the pediatric population and the lack of comparative data between systemic treatment options. One statement was excluded as the experts agreed that the optimal approach for tapering systemic therapy was unclear. The overall approach was discussed, but in-depth recommendations for specific therapies were beyond the scope of this consensus. Further work may explore specific tapering recommendations for given systemic therapies.

When to Consider Systemic Therapy

Management decisions, including when to initiate systemic therapy, should be made collaboratively between clinicians and the patients or caregivers [4]. Multidisciplinary approaches to AD care are common in view of the complex interplay between the multiple factors affecting AD control, and the broad range of expertise and support that patients and families need to manage AD effectively. Such an approach often includes medical evaluation and

management by an AD specialist, education and nursing care, psychological and behavioral support, and nutritional assessment and guidance [13]. The AD specialist may be an allergist or dermatologist, and often a collaboration between these specialties [13]. If the patient has poorly controlled AD despite optimized skin care and medical management with topical therapies, engagement of an allergist to consider comorbidities and allergic triggers (e.g., allergy testing and possible food elimination/challenges) is advisable [13, 14].

Factors to consider before initiating systemic therapy include disease severity, effect to quality of life, associated comorbidities, degree of response to topical therapy, disease-exacerbating factors (such as allergies, allergic contact dermatitis, and irritants), and the risk-benefit ratio of both systemic agents and topical agents [9]. Phototherapy may also be considered as a treatment option in these cases, but requires frequent office visits 2–3 times weekly and can be limited in its capability to manage acute flares due to the time delay between treatment onset and disease control [15, 16].

Systemic therapy may also be considered if excessive amounts of topical corticosteroids (TCSs) are needed to control persistent or frequently recurring AD. Ongoing daily or increasingly frequent use of high potency TCSs, or using more than the recommended quantity, can result in adverse effects including skin thinning, hypopigmentation, striae formation, and percutaneous absorption with potential systemic toxicity [17]. It is therefore advised that clinicians monitor TCS use closely. For children who use potent TCSs chronically but show no evidence of local or systemic side effects, it is unclear how "excessive use" should be defined. In these cases, the clinician must decide whether switching to a systemic therapy would provide greater benefit and/or safety to the patient than continuing with the current TCS application regime.

Total corticosteroid burden, including the use of oral/systemic, intranasal, inhaled, and TCSs, should be factored into the decision to initiate non-corticosteroid systemic therapy. This is particularly important when evaluating patients receiving corticosteroids for comorbid conditions, e.g., asthma and chronic rhinitis, as these patients may be candidates for earlier initiation of non-corticosteroid-based systemic therapy to minimize cumulative corticosteroid exposure [18, 19].

Choice of Systemic Therapy

SCS use is generally not recommended for pediatric patients with AD and should be restricted to short-term use. Although short-term SCS use is commonly prescribed for managing AD flares, the most recent AD guidelines recommend against this approach as discontinuation can result in rebound disease worsening [7, 20, 21]. Long-term SCS use is contraindicated due to significant safety risks, which include adrenal suppression, changes in linear growth, hyperglycemia, and inappropriate weight gain [20, 21]. In certain clinical settings, SCSs may be used selectively as a bridging therapy during initiation of more sustainable systemic therapies [20].

Factors to take into consideration when choosing a systemic therapy include AD phenotype, the presence of comorbidities, the risk-benefit profile of treatments, patient preferences (e.g., oral vs. injectable therapy), the need for laboratory monitoring, drug interactions, cost, adverse events, and access to therapy. Some novel systemic therapeutics used to treat AD may also be effective in reducing the severity of atopic comorbidities (e.g., asthma, allergies, eosinophilic esophagitis) [10, 22, 23]. Associated extracutaneous atopic diseases should, therefore, be considered when making medical decisions about the most appropriate treatment. As AD is a heterogeneous disease with a variety of clinical presentations, it is important to identify any unique features that may inform appropriate treatment selection [24–26]. Patient age should also be considered in the context of age-restricted medication indication, difficulty with injections and/or venipuncture, and childbearing potential [27, 28].

Conventional systemic therapies such as cyclosporine and methotrexate have been used off-label for decades to treat moderate-to-severe AD, with well-recognized risks and mitigation strategies [29, 30]. Azathioprine and mycophenolate mofetil have also been used off-label but less frequently [29, 31]. Although these immunosuppressants can provide therapeutic benefit for refractory AD, they have been associated with safety concerns that require close laboratory monitoring [31, 32]. As an increasing number of alternative therapies for AD have been approved, the use of conventional immunosuppressant medications has decreased. Nonetheless, careful consideration should be given to when these agents should be used, such as when there are concomitant conditions (e.g., juvenile arthritis, inflammatory bowel disease) that could be managed by these drugs [33].

Biologic drugs or JAK inhibitors should be considered as a first-line systemic treatment for moderate-to-severe AD, unless contraindicated, in instances where standard topical therapies have proven insufficient/inadequate for disease control. Dupilumab, an IL-4 receptor-α

antagonist, has shown sustained symptom reduction in children ≥6 months of age and is currently the only approved biologic for pediatric AD ≥6 months of age in major world regions including the USA, Europe, UK, Japan, China, and Australia [10, 34–38]. Recently, the IL-13 blocker tralokinumab was approved for children aged ≥12 years with AD [11]. In addition, a number of other promising biologic therapies targeting IL-13 and IL-31 are undergoing clinical and regulatory evaluation in the USA for pediatric indications [6]. Biologic drugs have a more favorable safety profile than conventional therapies, with fewer immunosuppressive adverse events [39]. They are, however, associated with increased rates of conjunctivitis, although most cases are managed with ophthalmic agents and do not require stopping the biologic drug [10].

Currently, JAK inhibitors (abrocitinib and upadacitinib) approved in the USA are indicated for patients ≥12 years of age with moderate-to-severe AD whose disease is not adequately controlled with other systemic drugs, including biologics, or when the use of those therapies is inadvisable [23, 39, 40]. Several more JAK inhibitors are in development [41]. These agents have been associated with a rapid reduction in pruritus and high response rates [42–44]. Adverse effects include nausea, acne, headaches, and impaired immune function requiring laboratory monitoring [42, 45]. Uncommon but serious adverse effects include cardiac events, cancer, blood clots, and increased all-cause mortality, prompting a drug-class-associated black box warning by the US Food and Drug Administration (FDA) [46, 47]. Clinicians must discuss the risk-benefit profile with all potential JAK inhibitor candidates before initiating patient treatment with a therapeutic agent from this class. Furthermore, patients treated with oral JAK inhibitors should undergo appropriate screening and lab monitoring [39].

Comparative evidence for the use of conventional and novel systemic therapies in AD is limited, especially in children [48]. As systemic therapy options continue to expand, comparative data will be essential to inform further comprehensive guidance for clinicians.

When to Escalate Systemic Therapy

Evidence on specific escalation of therapy across all pediatric age groups (often divided into <2 years, 2–<6 years, and 6–12 years in clinical practice) needs to be generated. This includes clinical trial data, pharmacokinetic studies, and real-world studies from clinical practice settings. Generating this evidence in the pediatric population will help inform clinicians on how to optimize and tailor systemic therapy in difficult to treat patients.

Clinicians should refer to specific prescribing information, data from clinical trials, and relevant guidelines where available to guide treatment escalation. Clinicians should be aware that options to escalate treatment will vary depending on factors such as the patient's age and therapeutic needs, as well as medical insurance coverage, which may limit treatment access [31, 49]. The clinician should also consider whether there is evidence to support dose escalation for a given systemic therapy in pediatric patients, as well as the likelihood and magnitude of increased efficacy if the dose of treatment is increased [50–53]. For pediatric patients with an inadequate response to initial systemic treatment, a dose increase or an increase in administration frequency may be considered [52]. For instance, in young children receiving treatment with dupilumab every 4 weeks, dosing could be escalated to every 2 weeks; however, this regimen would be off-label [10]. In patients ≥12 years of age, both abrocitinib and upadacitinib are administered with an initial standard dose (100 mg daily for abrocitinib and 15 mg daily for upadacitinib) in adult and adolescent patients, with subsequent dose escalation (200 mg and 30 mg, respectively) recommended in patients unresponsive to the initial dosing regimen [23, 40].

When to Consider an Alternative Systemic Therapy

Alternative treatment may be considered for patients whose AD is not adequately controlled on the initially recommended systemic therapy; however, potential contributory factors to poor response should be reviewed beforehand. Inadequate response to systemic treatment suggests the need for an alternate medication or combination therapy [54–56]. However, data on the safety and efficacy of combination treatments are limited at present. Prior to changing treatment, factors contributing to an inadequate therapeutic response should be considered (e.g., poor adherence, concomitant infection, contact allergy, coexisting psoriasis, and suboptimal treatment duration) [6, 9, 55]. When switching to a new systemic treatment, it is recommended to continue topical therapy until the new systemic medication is fully effective, or as an adjunctive therapy during ongoing systemic therapy [6, 15, 57]. For patients who are switching from another systemic therapy, consideration should be given to a brief (1–2 months) overlap period where the original systemic medication is tapered and the new systemic medication is allowed time to take effect.

Tapering and Discontinuation of Systemic Therapy

Treatment taper may be considered after the skin has remained clear or almost clear for several months, or in response to safety and tolerability concerns, but the optimal approach has not been defined. The timing of medication taper depends on the reason: prolonged skin clearance or concerns about safety or tolerability [11, 31, 39, 58–61]. The taper regimen depends on the systemic drug being used, and may involve increasing the time interval between doses or reducing the dose quantity. There is no specific prescribing information for the tapering of biologics in AD, but off-label extension of dosing intervals can be used in clinical practice where appropriate [62]. Additionally, the frequency at which dose tapering should occur has not been defined. Theoretical concerns include the potential for developing antidrug antibodies when using long dosing intervals, or with frequent stopping/starting of biologics [63].

Discontinuing systemic therapy may result in disease recurrence, from as early as 2 weeks with cyclosporine, to 3 months or more with methotrexate or novel therapies such as dupilumab and abrocitinib [64–68]. It is important that clinicians are proactive and cautious when formulating treatment strategies, to ensure that the most suitable systemic therapy is selected and the likelihood for discontinuation due to adverse effects and restricted accessibility is minimized. Patients should be monitored closely if treatment is stopped and a post-discontinuation management plan should be in place.

Adherence to Systemic Therapy

Inadequate response to systemic therapy may be associated with poor adherence. Although poor adherence is less frequently encountered with systemic therapy than with topical therapy, adherence may be difficult to monitor and can be overlooked [69, 70]. Adherence can vary between different systemic agents, with patients on immunosuppressants demonstrating significantly lower compliance at 12 months compared to patients receiving dupilumab [71, 72]. Reasons for inadequate adherence to treatment are varied, including concerns regarding adverse effects, inadequate patient/caregiver education, child resistance to treatment, a lack of trust in/rapport with the clinician, and high out-of-pocket costs and/or limitations to treatment access [55, 69–72].

Ongoing education and support are important to help to ensure patients and caregivers are comfortable with, and adherent to, systemic treatment. Education is critical for successful treatment of AD, and should cover information surrounding the disease itself, the treatments being used, and how to apply (topical treatments) or administer (injectable biologics) these treatments [73, 74]. This should include tips on managing the itch-scratch cycle, improving sleep, engaging children in their treatment plan, and managing AD at school and daycare [75]. As injections can be distressing for children, coaching on what to expect, the potential benefits, and giving the child some control around treatment administration (where to give the injection, where to sit, etc.) can be helpful [76]. In addition to anticipatory guidance and education, creating a routine, using distraction techniques, and positive rewards can lead to successful administration [75].

Immunizations

When prescribing systemic therapy to pediatric patients, the potential for an attenuated vaccine response needs to be considered. There is currently limited evidence to guide coadministration of systemic therapies and vaccines. Bridging this evidence gap is critical as many routine vaccinations are scheduled within the first few years of life [77]. In the interim, evidence may be extrapolated from data on the use of these systemic therapies in other diseases (adult or pediatric), or from observations of adults with AD.

Based on studies of other diseases, systemic therapies, including methotrexate, SCSs, and JAK inhibitors, may reduce protective antibody titers in adults following vaccination [77–84]. In addition, JAK inhibitors significantly increase the risk of herpes zoster reactivation [85–87]. For these reasons, international expert groups recommend that vaccines are administered before starting treatment wherever possible, with a longer delay to initiation of treatment if administering a live-attenuated vaccine as opposed to an inactivated vaccine [88, 89]. Furthermore, a European panel recommends that inactivated vaccines can be safely administered in immunosuppressed pediatric patients with autoimmune inflammatory rheumatic disease, except when patients are receiving high doses of glucocorticoids or B-cell-depleting therapies [90]. The safety of coadministration with live-attenuated vaccines is not currently known and is usually avoided due to the theoretical risk of infection with the attenuated pathogen [88, 89, 91]. However, with delaying/avoiding particular vaccines, there is also a risk associated with not being immunized [91, 92]. Overall, data suggest that inactivated vaccines may be

safely administered while receiving systemic treatment for AD, but further consideration and a thorough risk-benefit analysis need to be undertaken for live-attenuated vaccines [88, 89].

Biologic therapy does not need to be interrupted for administration of inactivated vaccines, but the safety of coadministration with live-attenuated vaccines is not known. General recommendations for patients who are treated with conventional systemic immunosuppressants are to complete age-appropriate vaccinations according to immunization guidelines prior to starting therapy, where possible, and to avoid live-attenuated vaccines during immunosuppressive treatment [93–95]. Prior to initiating an approved JAK inhibitor, or biologic, current regulatory labeling states that patients should be brought up to date with all immunizations, with the avoidance of live vaccines during or immediately prior to treatment [10, 23, 40]. Hesitancy around live-attenuated vaccination during biologic therapy may stem from a lack of data on the true risk of pathogen reactivation during coadministration of live vaccines. However, data from adults with moderate-to-severe AD suggest that treatment with dupilumab may not weaken the immune response, nor reduce protective antibody titers, following inactivated vaccine administration [96]. Furthermore, as dupilumab exerts an inhibitory effect on type 2 cytokines, it is suggested that treatment may improve the patient's functional response to vaccination by shifting the cytokine milieu toward a T helper type 1-mediated antiviral response [96]. A recent prospective case series of nine children with severe AD treated with dupilumab who received the live-attenuated measles, mumps, and rubella vaccine, with or without the live-attenuated varicella vaccine, found no vaccine-related viral infections or serious adverse events within the 4-week postvaccination period [97]. In five of the nine cases, vaccination occurred less than 12 weeks after cessation of dupilumab (deviation from study protocol) and dupilumab was resumed 2–43 days thereafter [97]. Based on available data regarding the timing of live vaccines around dupilumab therapy, coadministering live-attenuated vaccines and dupilumab may be considered on a case-by-case basis after a thorough risk-benefit analysis [97, 98]. Many of the expert panel have reported live vaccine administration 1 month after stopping dupilumab and then reinitiating dupilumab 1 month postimmunization. As primary prescribers of biologics, specialists should remain knowledgeable and up to date on evolving vaccination recommendations for biologics currently approved for AD, along with those that may emerge in the future.

Involvement of Primary Care

PCPs play an important role in the management of AD. As the first point of care for most patients with AD, PCPs most often treat patients with mild-to-moderate disease [53, 99], refer those requiring specialist care, provide ongoing maintenance care, and manage acute infections [53, 99]. For this reason, it is important for PCPs to understand AD pathophysiology and diagnosis, as well as treatment strategies and potential treatment-related adverse effects. As PCPs are primarily community-based, their participation within the shared care system can also help foster a proactive, collaborative, and patient-centered approach to AD management [53, 99]. Specialists should effectively coordinate and collaborate with PCPs to achieve optimal patient outcomes.

Ongoing consultation and dialogue between the PCP, families, and specialists may be helpful in determining effective treatment approaches. For example, while PCPs do not typically prescribe systemic treatments for AD, they should be informed when these therapies are being considered or initiated, as this may affect other treatments or conditions. They may also be called upon to help monitor or address side effects or complications.

Disease-Modifying Effect

The ability to use systemic therapy such as biologics in patients as young as 6 months of age offers the potential for a disease-modifying effect. However, as AD is a disease that can spontaneously improve with age in some patients, it may prove difficult to establish the disease-modifying effects of systemic therapy [8].

The impact of early intervention on the natural history of disease and the development of AD-associated morbidities is not currently known. In other chronic diseases, such as rheumatoid arthritis, selected systemic treatments are known to improve the lifetime risk of developing commonly associated comorbidities [100, 101]. Atopy typically manifests in early childhood with AD and food allergy and often progresses to include other atopic morbidities, such as rhinitis, asthma, and eosinophilic esophagitis [102, 103]. Researchers have proposed that by preventing or treating AD in early infancy or childhood, it may be possible to prevent the development of food allergy and atopic respiratory diseases. Some studies suggest that the development of atopic disease later in life can be predicted by the presence of early onset and severe AD, along with immunoglobulin E sensitization (potentially facilitated by AD-associated skin barrier

dysfunction) [104, 105]. As type 2 inflammatory cytokines, especially IL-4, are known to mediate both immunoglobulin E sensitization and AD pathogenesis, modulation of IL-4 signaling via dupilumab may present a therapeutic approach to halt the atopic march [104–106]. A recent meta-analysis of clinical trial data found that dupilumab reduced the incidence of new allergies and the worsening of preexisting allergic conditions in patients with AD [104]. This benefit was most prominent in younger patients (<18 years), especially those with early onset of AD (<2 years) [104]. This protective effect persisted, in an attenuated form, after discontinuation, suggesting a potential disease-modifying effect [104]. Although a longer follow-up period will be required, these results provide positive data following previous unsuccessful attempts to halt the atopic march with other systemic agents [104]. It is also important to note that AD is commonly associated with nonatopic morbidities (e.g., neuropsychiatric conditions), but there are currently little data on how early successful AD management influences their development.

Conclusions

The physical signs and symptoms of AD, its associated comorbidities, and its psychosocial consequences constitute a substantial burden on affected children and their parents/caregivers. As the systemic treatment landscape for moderate-to-severe AD continues to evolve, it is hoped that therapies that offer greater efficacy and more favorable risk-benefit profiles will help individuals with AD achieve disease control where topical and adjunctive therapies alone have not been sufficient. The recommendations provided here are aimed at guiding clinicians in optimizing outcomes for their patients.

Key Message

Clinical guidance on the use of systemic medications for management of atopic dermatitis in patients <18 years.

Conflict of Interest Statement

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Author Contributions

Prof. Lawrence Eichenfield, Prof. Mark Boguniewicz, Dr. Christine Lauren, Prof. Donald Leung, Prof. Moise Levy, Prof. Lynda Schneider, Prof. Elaine Siegfried, Dr. Wynnis Tom, and Prof. Amy Paller all joined steering committee meetings to develop the consensus statements, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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