



Systemic therapy of childhood atopic dermatitis

Nathaniel A. Slater, BA, Dean S. Morrell, MD*



*Department of Dermatology, School of Medicine, University of North Carolina-Chapel Hill,
410 Market Street, Suite 400 Chapel Hill, NC, 27516*

Abstract Atopic dermatitis (AD) is a common childhood inflammatory disease that, in a small percentage of cases, can become severe enough to require potent systemic treatment. Many trials have been conducted with systemic agents for the treatment of severe pediatric AD; we review the evidence here. Although corticosteroids are widely used in practice, they are not generally recommended as a systemic treatment option for AD in children. Most patients experience a relatively rapid and robust response to cyclosporine. Treating children with cyclosporine long term is troubling; however, azathioprine, mycophenolate mofetil, and methotrexate are all reasonable alternatives for maintenance therapy in recalcitrant cases. Several additional options are available for the most refractory cases, including interferon- γ , intravenous immunoglobulin, and various biologics. Phototherapy is another modality that can be effective in treating severe AD. Ultimately the choice of agent is individualized. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. Nonsystemic approaches toward prevention of flares and long-term control of atopic dermatitis in pediatric patients should be continued in conjunction with systemic therapy. In the future, more targeted systemic treatments hold the potential for effective control of disease with fewer side effects than broadly immunosuppressive agents.

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Introduction

Atopic dermatitis (AD), which affects more than 20% of children in some developed countries, is among the most prevalent diseases of childhood and has been increasing in incidence.¹ AD encompasses a wide range of severity, with a small percentage of cases requiring potent systemic therapy for either short- or long-term control. Clinical predictors of a severe course of AD, as well as a higher likelihood of persistence into adulthood, include an early age of onset, severe manifestation in infancy, other concurrent atopic diseases, and a family history of atopy.² Several objective clinical scoring systems for AD have been developed to

quantify disease severity and response to treatment for study purposes, such as the Severity Scoring of Atopic Dermatitis (SCORAD). Defining severe AD in terms of its resistance to topical treatments and its effect on a child's daily activities holds more clinical relevance.³ Severe AD has considerable morbidity and can affect growth and development in affected children, as well as quality of life for patients and families.^{4,5}

Pathogenesis

The pathogenesis of AD provides rationale to the various targets for treatment that have been investigated. AD is characterized by the complex interplay between multifactorial abnormalities of the skin barrier, dysregulated immune response to cutaneous microbes and common allergens, and

* Corresponding author. Tel.: 919 843 5539; fax: 919 966 6460.
E-mail address: morrell@med.unc.edu (D.S. Morrell).

development of autoinflammation. Filaggrin gene mutations underlie familial AD and can portend severe and chronic disease.⁶ Mutations in multiple other barrier-related genes have been implicated as well. Aberrant host immune response to cutaneous microbes, environmental irritants, and allergens also plays a role,⁷ leading to pruritus and excoriation. The resulting inflammatory response is thought to be of a Th2 polarity, especially early in the disease course, although Th1 markers are present in chronic disease.⁸ In severe, chronic AD, a self-perpetuating inflammatory response further impairs the skin barrier.⁹ Regulatory T cell (TH17 axis) abnormalities contribute to the development of autoinflammation.⁹ At this stage of severe AD, treatment is directed at immune targets. There is evidence to suggest that reducing immune activation leads to improvement of the skin barrier.¹⁰

Topical treatment strategies

The American Academy of Pediatrics (AAP) and the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines detail an overall treatment strategy for AD, which is aimed at restoration of the skin barrier, avoidance of triggers, and reduction of inflammation.^{11,12} Regular emollient use, identification and avoidance of exacerbating factors, and topical immunosuppressive therapy with topical corticosteroids or other immunosuppressants provide the foundation of therapy for AD. Increasing potency of topical immunosuppressant therapy and application with wet wraps are employed according to disease severity. Current evidence supports proactive treatment with topical corticosteroids or topical calcineurin inhibitors for prevention of flares.¹³ In addition to these guideline-supported mainstays of topical treatment, alternative approaches, such as allergen desensitization, dietary and environmental control, or bleach baths may be implemented for severe AD before or in conjunction with systemic therapy. In all cases, patient and family education is an important part of a treatment plan.¹⁴

Common causes of treatment failure

When severe AD remains uncontrolled despite maximal topical treatment, the diagnosis is confirmed by ruling out potential alternative diagnoses such as allergic or irritant contact dermatitis, psoriasis, and genodermatoses, among others.¹¹ Common causes of failure of topical therapy are also considered. Nonadherence to treatment is foremost among these; a stealth monitoring study was able to quantifiably demonstrate poor adherence to topical therapy in a cohort of children.¹⁵ Superimposed infection, including antibiotic-resistant infection with *Staphylococcus aureus* or

streptococcal species, can contribute to failure of topical treatment.¹⁶ Contact allergy, including allergy to topical glucocorticoids, is another source of treatment failure,¹⁷ and can be ruled out by spot testing for delayed-type hypersensitivity to corticosteroids on unaffected skin.

Oral antimicrobial and antipruritic agents

Severe AD in children may be complicated by secondary infection, and systemic antibiotics are commonly used in treatment. Impetiginized AD is treated with an oral antistaphylococcal antibiotic, chosen according to local resistance patterns.¹⁸ Some practitioners also prescribe topical mupirocin for nasal carriage. Evidence supporting the efficacy of antibiotic treatment on AD outcomes is weak, and guidelines recommend limiting antibiotic use to a short course of treatment for cases with signs of overt infection.¹⁴ In children with superinfected AD who were treated with oral cephalosporins and topical corticosteroids, improvement of AD led to resolution of infections even when MRSA was cultured, suggesting that resolution of infection did not depend on antibiotic treatment.¹⁹ In light of the continuing emergence of multidrug resistant organisms, avoiding the use of systemic antibiotics in children and targeting the underlying inflammation is the generally preferred approach to the treatment of AD, in the absence of overt infection. Suspicion of superimposed eczema herpeticum, however, merits a low threshold for initiating antiviral therapy.¹⁴

Due to their sedative properties, first generation antihistamines, such as hydroxyzine, are widely used to counteract eczema-induced sleep loss in children older than 2 years. Doxepin has also been used for its antipruritic, sedative, and psychotherapeutic effects.² Available antipruritic measures are suboptimal at best, and daytime drowsiness is a potential drawback, especially in school-aged children. Although nonsedating antihistamines are a popular daytime alternative, they appear to have minimal effect on pruritus. Pruritus generally improves with control of inflammation.¹⁸

Immunomodulating systemic therapies

In cases of severe AD involving widespread lesions, a long disease course, and recalcitrance to topical treatments, systemic immunosuppressive therapy may be required. In addition to disease severity, individual patient factors such as age, localization, and especially effect on quality of life, which may be subjective, determine the decision to proceed with systemic therapy. Other indications for systemic treatment include involvement of the eyes or eyelid.²⁰ Available systemic therapies for severe AD are immunomodulatory, targeting various elements of the immune response. Strategies include depletion or inactivation of

immune cells involved in pathogenesis, modulation of the cytokine milieu, or broadly immunosuppressive therapy. Most systemic therapy options require laboratory monitoring of blood count, renal profile, and liver function. In children, balancing safety with efficacy is especially important. Particular concern is exercised to avoid effects on growth or development, weighing potential adverse effects of therapy against the morbidity of the disease. The choice of therapy is tailored to individual patients, with consideration of convenience, cost, and the prescribing physician's experience in addition to risk/benefit analysis. Overall, however, AD is a heterogeneous disease,²⁰ and not all systemic treatments are effective in all patients.

Approach to this review

Many studies of systemic treatments for AD have been published since the most recent AAP (2008) and NICE guidelines (2007). Most reviews include only adults or children and adults. Limited evidence is available for efficacy and safety of systemic treatments of AD in children. Conducting drug trials in children is generally difficult, although inferences on dosing and long-term safety can be drawn from rheumatologic or transplant studies.¹⁶ Our approach is to collate and synthesize the available evidence for systemic treatment of atopic dermatitis specific to children, from birth to 18 years of age. A systematic search was performed to identify all contributions associated with systemic treatment of atopic dermatitis in children (Appendix 1). Experimental modalities in the treatment of AD, including allergen-specific immunotherapy, peroxisome proliferator-activated receptor ligands, mast cell stabilizers, and phosphodiesterase inhibitors, as well as herbal medicines, synbiotics, and oral ceramides, are not covered here. This review begins with consideration of the most commonly used systemic treatment options. Dosing and monitoring information is given in Table 1.

Systemic corticosteroids

Corticosteroids exert immunosuppressive effects by altering multiple pathways at the transcriptional level. Although systemic corticosteroids are commonly used in practice and are FDA-approved for the treatment of AD, evidence supporting the use of systemic corticosteroids for the treatment of severe AD in children is poor. Two early, small, randomized controlled trials (RCTs) in children showed moderate short-term clinical improvement in AD scores with beclomethasone and flunisolide, respectively, versus placebo.^{21,22} One case series also showed clinical improvement in 5 of 7 children with AD treated with intravenous methylprednisolone bolus.²³ Studies of the

commonly used agent prednisolone in the pediatric population are not available.²⁴ Contrary to the evidence for short-term efficacy of corticosteroids in children, a small RCT in adults comparing oral prednisolone to cyclosporine showed a failure of prednisolone to achieve stable remission of severe AD, compared to modest efficacy in the cyclosporine arm.²⁵

Adverse effects of corticosteroids are well known; of particular concern in children are endocrine effects which may interfere with normal growth. "Steroid rebound" is also a familiar phenomenon. High relapse rates were seen in adult AD patients treated with prednisolone,²⁵ and severe relapse of AD has been described in children treated with systemic corticosteroids.²⁶

In summary, although several early reports demonstrated that systemic corticosteroids may be helpful for short-term reduction of severe AD scores in children, these findings have not always been corroborated by later reports, and outcomes beyond a few months are lacking. Evidence in adults support the superiority of cyclosporine for reduction of AD scores and stability of remission.²⁵ Long-term treatment of children with systemic corticosteroids is problematic, with predictable and significant side effects.²⁴ Short-term treatment may have some benefit, but treatment with short courses of systemic corticosteroids can lead to a cycle of dependency on steroids for repeated flares.³ The questionable efficacy, likelihood of relapse, and inevitable long-term side-effect profile support the conclusion that systemic corticosteroids are not the treatment of choice for most children with severe AD.

Cyclosporine

No other systemic therapies are FDA-approved for the treatment of atopic dermatitis in children, but cyclosporine A (CsA) is approved in Europe as a first-line systemic treatment for severe AD in children and adults. CsA binds to cyclophilin and forms a complex that inhibits calcineurin, which ultimately down regulates transcription of cytokines that play a role in T-cell activation, particularly IL-2. In children with AD, CsA has been shown to reduce the percentage of circulating CLA+ (cutaneous lymphocyte antigen) T cells, which likely corresponds with reduced T-cell activation.²⁷ In addition to directly reducing T-cell activity, CsA affects the balance of regulatory T-cell populations, even at low doses.²⁸ The use of CsA in severe AD is supported by more abundant evidence than any other systemic immunosuppressant. An early case series of 27 children with severe, refractory AD treated with CsA demonstrated good short-term improvements in disease scores and quality of life for most patients, with good overall tolerability, despite some children reporting headaches or abdominal pain.²⁹ A follow-up study involving 43 children treated over the course of 1 year indicated that

Table 1. Dosing and monitoring guidelines *

Systemic Agent	Starting Dose	Dose Adjustment	Recommended Baseline Testing	Monitoring	Adverse Effects
Cyclosporine	2.5-5 mg/kg, divided twice daily; 5 mg/kg usually considered max. 1. Start with initial high dose (5mg) and taper, OR 2. Start with lower dose (2.5-3.5 mg) and gradually increase.	1. After response, decrease by 1 mg/kg every 2 weeks until minimum effective dosage for patient is reached. Treatment can be continued up to a year. 2. Increase in Increments of 0.5-1 mg/kg every 2 weeks until good response (5 mg/kg max).	Measure blood pressure; CMP with creatinine, CBC; consider LFTs and fasting lipids.	Repeat CBC, CMP every 2 weeks for first 1–2 months, then every 4–6 weeks. Check blood pressure at each visit. Discontinue or reduce dose when Creatinine > 30% above baseline.	<i>Most Common:</i> GI disturbances, neurologic effects (headaches, paresthesias). <i>Also watch for:</i> mucocutaneous lesions, arthralgias renal dysfunction/increased creatinine, other laboratory abnormalities, hypertension.
Azathioprine	1. If TPMT 15.1-26.4 U/ml → start with 2.5 (range 2–3.5) mg/kg daily. 2. If TPMT 6.3-15 U/ml, start with 1 (range 0.5-1.25) mg/kg daily. 3. If TPMT <6.3 U/ml → consider alternative treatment.	Consider dose adjustment or repeat TPMT measurement if response changes. Treatment often continued for more than 1 year, then gradually tapered after stable remission.	TPMT assay, CBC, CMP; consider pregnancy test.	CBC with differential, CMP, and LFTs every other week for 2 months, then every 2–3 months.	<i>Most Common:</i> GI disturbances, increased LFTs. <i>Also watch for:</i> severe myelosuppression (rare), malignancy (rare), cutaneous infections, hypersensitivity, teratogenicity.
Mycophenolate Mofetil	2-3 g divided BID (adults); 20–50 mg/kg/day (younger patients).	Increase daily total dose in 500 mg increments every 2–4 weeks. Can be used for more than 1 year.	CBC, CMP, LFTs; consider tuberculosis test, pregnancy test.	CBC with differential, CMP, LFTs every 2–4 weeks following dose increase, and every 2–3 months on stable dose.	<i>Most common:</i> GI disturbances. <i>Also watch for:</i> increased predisposition to infections, malignancy (rare), myelosuppression, neurologic effects (headache, fatigue), teratogenicity.
Methotrexate	Initiate with test dose of 5–10 mg (or 10–15 mg/m ² in children [†]). Typically given once weekly; alternative schedule (4 consecutive days) may be preferred in AD.	Escalate by 2.5-5 mg each week to effective dose. Taper by 2.5mg each week to lowest effective dose	CBC with platelets, LFTs, Hepatitis B, C; CMP with creatinine; consider pregnancy test. Folic acid typically given on nontreatment days.	CBC, LFTs every 1–2 weeks for 2–4 weeks and after dose escalations; decrease to every 3–4 months.	<i>Most common:</i> GI disturbances, hepatotoxicity. <i>Also watch for:</i> neurologic effects (headache, fatigue), stomatitis, pneumonitis (rare), pancytopenia, abortifacient.

Abbreviations: CMP=complete metabolic panel, CBC=complete blood count, LFT=liver function test, TPMT=thiopurine methyltransferase.

Official monitoring guidelines for systemic treatment in AD do not exist; recommendations vary, and depend in part on studies of other inflammatory diseases. When starting pediatric patients on systemic immunosuppressive therapy, additional considerations are as follows: varicella exposure/vaccination status should be ascertained; live vaccines are contraindicated when taking CsA, AZA, or MTX; influenza and pneumococcus vaccines are recommended; sun protection is especially important in this population, and Vitamin D supplementation may be indicated. CsA is a FDA pregnancy category C; AZA and MMF are category D; MTX is category X. (Flohr & Irvine, 2013).

* Dosing and monitoring recommendations are drawn primarily from Wolverton, Comprehensive Dermatologic Drug Therapy, 2013, with reference to additional review articles (for ranges).

[†] Per GKJR guidelines for treatment of juvenile idiopathic arthritis (Dueckers et al., 2012).

durable remissions could be achieved in a few patients after one or more 12-week courses of therapy, while more steady remission was seen in children kept on a maintenance dose.³⁰ Patients experienced a mean improvement in AD scores of at least 50% regardless of dosing schedule, though some patients relapsed shortly after discontinuation of CsA.^{29,30} One small, randomized trial in children showed that daily CsA had greater efficacy than a single infusion of IVIg.³¹ Other RCTs investigating CsA have included primarily adults, with a few including adults and children. A 2007 meta-analysis of CsA trials (controlled and uncontrolled) showed greater than 50% improvement in symptom scores after 2 months for all treated, with similar effectiveness in children and adults.³² One retrospective study in pediatric population suggested that CsA was most effective in cases where flares were precipitated by secondary infection,³³ though this association has not been confirmed.

Gastrointestinal (GI) symptoms and headache were the most commonly reported adverse events in children treated with CsA for severe AD.³² Renal dysfunction and increased blood pressure are the most concerning long-term adverse effects associated with CsA. No evidence of these serious effects was seen in a 1-year follow-up of 40 pediatric AD patients treated with CsA.³⁰ Studies addressing the long-term safety profile in children are lacking.³² Although changes in blood pressure and serum creatinine are rarely seen in children, these parameters should be monitored in patients receiving CsA therapy along with complete blood counts and complete metabolic panels. CsA use is also known to increase the risk of non-melanoma skin cancers with long-term use in transplant patients; this risk is theoretically increased by phototherapy.⁶ Finally, inhibitors of CYP3 A4 can increase adverse potential of CsA.³⁴

In summary, although long-term studies of safety and efficacy are lacking, CsA has been repeatedly shown to be effective for the induction of remission in patients with severe AD. Multiple RCTs support the use of CsA for recalcitrant AD, and a dose–response relationship further strengthens the evidence.³⁵ The short-term tolerability is good for most patients. A rapid onset of action also makes CsA an attractive choice for physicians, patients, and families. Its effect on kidney function in particular raises concerns about long-term administration in children. Despite durable disease control in some patients, eventual relapse is the norm even after slow tapering, highlighting the need for safer maintenance treatments.²

Azathioprine

Azathioprine (AZA) is precursor to a purine analog that interferes with purine synthesis and selectively inhibits lymphocytes, especially T lymphocytes.³⁶ Two retrospective case series and a prospective case series, involving 28 children and adolescents, 17 adolescents, and 12 children,

respectively, indicated that AZA may be an effective and well-tolerated medium-term treatment for pediatric recalcitrant atopic dermatitis.^{36–38} Two RCTs in adults, enrolling 100 patients in total for 3 months, showed mean reduction in severe AD scores ranging from 17% to 23% over placebo, although some patients withdrew from the AZA arms.^{39,40}

AZA has been associated with potentially severe myelosuppression. As with CsA, treatment of high dose and long duration has also been associated with malignancy, including a rare but dangerous lymphoma (hepatosplenic T-cell lymphoma), for which AZA has received a black box warning.⁷ In a case series involving pediatric patients, laboratory abnormalities (most commonly abnormal liver function tests) and increased incidence of cutaneous infection were seen at a relatively low monthly rate, and GI disturbance was the most common patient complaint.³⁷ In RCTs involving adults, GI disturbances and abnormal liver enzymes were the most common adverse events seen in the AZA arms. Complete blood counts and liver enzymes should be monitored during treatment with AZA. As with CsA, photoprotection should be advised.⁶

AZA has special dosing considerations. One major pathway for metabolism of AZA is via the thiopurine methyl-transferase (TPMT) enzyme, and patients with reduced or absent TPMT activity (about 10% and 0.3% of the population, respectively) are at higher risk of profound immunosuppression.⁴¹ TPMT activity should be checked before initiating treatment with AZA, because serious side effects are dose dependent. Reports exist of TPMT activity varying during a course of treatment, but measuring activity once is typically sufficient, barring significant change in response.⁴² AZA can be a relatively safe and effective treatment if dose-adjusted when necessary.⁴⁰ Case reports of excellent response to AZA when dose-adjusted for reduced TPMT activity have been reported in children,⁴¹ and a case series corroborates the effectiveness of treatment with dose-adjusted AZA in pediatric patients heterozygous for TPMT.³⁷

In summary, AZA can be an effective treatment for severe atopic dermatitis in the pediatric population. Overall, there is less evidence, and an apparently less robust effect, compared to CsA (at least in adults, where more direct comparison is possible). AZA requires a baseline assay of TPMT activity to determine appropriate dosage, as well as laboratory monitoring of complete blood counts, complete metabolic panels, and liver enzymes. AZA has a slow onset of action, requiring several weeks to 2 months of treatment before response is observed.¹⁶ For these reasons, it can be considered a second-line treatment for the induction of remission in severe pediatric AD. AZA may be favorable for longer term therapy without the risk of kidney dysfunction posed by CsA. Case series show safety in many children treated for more than 1 year.^{36,37}

Mycophenolate mofetil

Mycophenolate mofetil (MMF) blocks inosine monophosphate dehydrogenase, which is required for de novo purine

synthesis, exerting immunomodulatory effects similarly to AZA.²⁴ One pediatric case series of 14 patients treated with MMF for varying duration showed a very positive response to this agent with minimal adverse effects.⁴³ Another case series showed significant improvement in two thirds of children on MMF who had previously failed to show a response to AZA treatment, as well as better tolerability.³⁷ Two case series in adults (30 patients total) further support the effectiveness of MMF for the treatment of refractory AD.^{44,45} One RCT has compared maintenance therapy with MMF against CsA, after initial induction of remission with CsA; the two maintenance regimens showed broadly similar efficacy.⁴⁶ MMF tended toward delayed initial efficacy but more durable response after withdrawal of medication compared with CsA, consistent with the different mechanisms of action between the two drugs.⁴⁶ Interestingly, this result suggests that the using MMF for maintenance therapy after induction of remission with the more rapidly acting CsA may be an effective sequence.

Mild headaches and GI disturbance are the most commonly reported adverse effects in AD studies. Treatment with MMF also poses an increased risk of infection, and blood counts should be followed along with complete metabolic panels and liver enzymes.

In summary, MMF appears to be a promising agent for the treatment of recalcitrant AD. Early studies show equal or greater effectiveness compared with AZA, and potentially better tolerability; it remains to be seen if these putative advantages will be borne out in larger trials with quantitative response measurements. To date, the use of MMF in severe AD is backed by considerably less evidence than AZA.

Methotrexate

More recently, methotrexate (MTX) has been studied as an additional systemic immunosuppressive option in patients with refractory AD. MTX inhibits dihydrofolate reductase, and at low doses, MTX is thought to interfere with T-cell activation without exerting broad cytotoxicity.⁴⁷ An RCT including 40 patients from ages 8 to 14 has shown very similar efficacy between MTX and CsA, with a mean SCORAD reduction of 45% in both arms.⁴⁸ In this study, time to response was marginally longer for patients in the MTX arm, but the response proved more durable after discontinuation of the drug. A high-quality RCT involving a head-to-head comparison of MTX with AZA in the treatment of adult atopic patients showed similar efficacy between the two treatments (42% versus 39% SCORAD reduction, respectively).⁴⁹ Greater incidence of decreased blood count was seen in the AZA group, with otherwise equivalent rates of adverse effects.⁴⁹

Potential adverse effects of MTX include bone marrow suppression, hepatotoxicity, and GI side effects, and adverse effects were seen to some degree in one third to two thirds of patients in adults with AD.⁴⁹ In the pediatric RCT, adverse

effects were reported in the MTX and CsA arms, with GI effects and abnormal liver function tests seen more often in the MTX arm.⁴⁸ Folic acid supplementation reduces the risk of side effects.⁶ In children, divided daily doses result in fewer GI side effects than a single larger dose.⁴⁸ Compared with the commonly used weekly dosing regimen for psoriasis, MTX may show better results in AD when administered for 4 consecutive days out of the week.²

In summary, good evidence supports MTX as a potentially effective treatment for severe AD. MTX is not without side effects, but overall good tolerability was reported in the pediatric atopic dermatitis population, with no patients being withdrawn from the study or requiring dose adjustment.⁴⁸ Complete blood counts and liver function tests should be monitored during treatment. Similar to MMF, there is overall less evidence to support treatment with MTX than exists for AZA, although the available evidence suggests similar efficacy and tolerability, making MTX a valid alternative.

Interferon- γ

In addition to the use of general immunosuppressive agents, other strategies have been aimed at modulating the Th2 predominant response characteristic of atopic dermatitis. Hypothetically, interferon- γ (IFN- γ) promotes re-normalization of Th1/Th2 balance in patients with known atopic phenotype, as evidenced by high IgE levels.⁵⁰ Two RCTs in adults support the effectiveness of IFN- γ in the treatment of patients with moderate or severe recalcitrant AD.^{51,52} Curiously, in a study of children and young adults with known allergy to house dust mites, the combination of IFN- γ and a hyposensitization protocol with house dust mite allergens appeared to have a pronounced effect on AD severity scores.⁵³ In a follow-up study in children and adults with moderate AD and multiple allergies, treatment with IFN- γ appeared to reduce cutaneous sensitization to certain allergens; however, clinically relevant reduction in AD scores was very limited.⁵⁰ Adverse effects were not reported in trials including children; in adults, 60% reported headache, and another one third experienced myalgias, fatigue, and/or chills.⁵¹ Interferon can be difficult to tolerate, is expensive, and requires frequent injections, making this option less attractive in the pediatric population. IFN- γ remains a potential treatment in refractory patients to multiple other systemic therapies, given evidence of efficacy in some patients. IFN- γ may be of special benefit in patients predisposed towards cutaneous viral infections.⁷

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) is thought to reduce T-cell activation, dampen the Th2 response, and opsonize

pathogenic antigens in AD.⁵⁴ Case reports of severe AD treated with IVIg monotherapy show a robust response in several children who had high levels of IgE.⁵⁵ A retrospective observational study of children with severe, recalcitrant AD on various systemic therapies showed a temporal association between initiation of IVIg therapy, marked improvement of symptoms after several months, and reduced levels of IgE.⁵⁴ An RCT in children with severe AD showed only modest and temporary reduction in SCORAD after 3 monthly infusions of IVIg, with no subjective symptom improvement,⁵⁶ and another small trial has shown superiority of CsA compared with IVIg in children.³¹ The use of IVIg in the treatment of AD may be limited to a subgroup of children, as IVIg has not shown efficacy in adults.⁵⁴ The evidence for IVIg is weak, but there is the potential for benefit with prolonged treatment, either adjunctive or as monotherapy, in some children refractory to other systemic therapies.

Leukotriene inhibitors

Several pilot studies suggested that montelukast exhibits a positive effect in children with atopic dermatitis.^{57–59} These pilot studies enrolled small numbers of patients, who tended to have more moderate disease, and only very modest clinical benefits were seen. Later, two RCTs in adults failed to show improvement with montelukast over placebo.^{60,61} It may be that, despite the putative Th2-mediated nature of AD, a strong Th1 component underlies severe and refractory AD.⁵⁸ Although it is possible that a subgroup of pediatric patients with AD may receive modest benefit from leukotriene inhibitors, overall evidence does not support their routine use.

Omalizumab

Biologics comprise another treatment modality that has been investigated for severe AD. Very high levels of IgE and a Th2 predominant cellular response in many patients with AD suggested omalizumab (anti-IgE) as a targeted treatment, though the extent to which IgE plays a role in pathogenesis is unclear.⁶² Multiple case series and pilot studies in children and adults suggested modest benefit of omalizumab in at least some patients, particularly those with high IgE levels.^{63–66} A case series of combination treatment with omalizumab and IVIg showed relatively robust clinical responses in a few patients.⁶⁷ At least one case series in adults showed no benefit of omalizumab over placebo.⁶⁸ A single RCT involving 20 adults demonstrated laboratory and immunohistochemistry changes consistent with dramatic reduction of IgE, but did not find a clinical benefit over placebo.⁶² Good data on adverse events are lacking, though small studies suggest that omalizumab is well tolerated by children. Data are also conflicting on whether proper dosage

of anti-IgE therapy requires adjustment for patients' IgE titers, and there is evidence that even low-dose omalizumab in patients with high IgE titers can be effective.⁶⁵ In summary, IgE seemed to be a promising target, but the evidence has been underwhelming. It has been suggested that anti-IgE therapy may be of benefit earlier in the course of disease, before chronic inflammation with Th1 bias has developed.⁶² A role for anti-IgE cannot be ruled out, but IgE does not appear to be a primary target.

Other biologics

Multiple other biologic agents have been investigated, mostly in small pilot studies. The Th2 cytokine IL-5 was considered as a target, but a small RCT comparing mepolizumab (anti-IL5) with placebo failed to demonstrate efficacy of this agent.⁶⁹ Treatment of 3 patients with tocilizumab (anti-IL6) showed modest efficacy, but was complicated by superimposed infections.⁷⁰ Anti-IL4 has been considered but not yet tested in AD.⁹ The TNF- α inhibitor infliximab showed beneficial results early, especially in adults with more severe AD, but responses did not endure through the maintenance phase.⁸ Treatment with etanercept was unsuccessful in 2 children with recalcitrant AD.⁷¹

T cells and B cells have also been targeted. There is one case report of a child with severely refractory AD who achieved an excellent response with efalizumab (anti-CD11), which blocks T-cell adhesion⁷²; however, case series of patients with severe AD treated with efalizumab have yielded conflicting results,^{73,74} and further development of this agent in psoriasis patients was stopped due to JC virus reactivation.⁹ Alfacept (anti-CD58), which inhibits T-cell co-stimulatory signals, has shown limited success in 2 pilot studies in adults.⁹ Rituximab, which depletes B cell populations and potentially reduces allergen presentation, was actually found to be very effective in a single pilot with 6 adult patients,⁷⁵ although this finding was not corroborated in 2 other extremely refractory patients.⁷⁶ Sequential therapy with omalizumab and rituximab was successful in 4 out of 6 patients.⁷⁷

Potential adverse events from different biologics are known from their use in other diseases. Broadly, risks include increased risk of infection (include reactivation of latent tuberculosis) and certain malignancies, in addition to the risk of infusion reactions. Biologics that target Th2 pathways may be relatively safer. Close follow up is required with this class of medications.

In summary, consideration of certain biologics in children should be reserved for the most treatment-refractory cases. The lack of robust clinical improvement in patients treated with omalizumab and mepolizumab confirm that AD pathogenesis is not simply IgE-driven.⁶ Targeting IgE is possibly more effective earlier in the disease course, whereas targeting TNF- α or T-cell surface markers may be more effective in chronic, severe disease. Follow-up studies are

needed to determine the effectiveness of rituximab in severe, refractory AD.

Retinoids and vitamin D

In addition to direct immunomodulation, vitamin D has recently been explored as a potential therapeutic approach, with potential for promoting restoration of the skin barrier, immunomodulation, and increasing antimicrobial defense.⁷⁸ Conflicting results have been reported regarding a putative association of low vitamin D levels with AD.^{79,80} Vitamin D supplementation may have adjunctive beneficial effects in patients with AD, but more data are needed.^{78,81,82} Curiously, alitretinoin has also been proposed for the treatment of atopic dermatitis. Two RCTs in chronic hand eczema provide strong support for the use of alitretinoin for this condition.⁸³ In six adult patients who had moderate widespread AD as well as chronic hand eczema, treatment with alitretinoin resulted in robust improvement of AD symptoms.⁸⁴

Phototherapy

Phototherapy has emerged as an alternative option to systemic therapy for severe AD. Narrowband UVB is the preferred form of phototherapy for treatment of AD, and suppresses multiple inflammatory pathways including those related to Th2.¹⁰ One trial of 12 adult patients showed a reduction in SCORAD of 50%, and, notably, correlated clinical improvement with reduction of inflammatory biomarkers and improvement of skin barrier.¹⁰ Trials of phototherapy in children are limited to retrospective studies. These trials show good responses on average in a majority of patients, but the limited data on duration suggests a median in the 3- to 5-month range.^{85,86}

The AAP considers phototherapy an effective choice for some children, and the NICE guidelines (2007) even recommend phototherapy before systemic therapy. Although phototherapy is generally well tolerated, difficulties of this modality for children can include the inconvenience of frequent in-office treatment regimens, and the potential for provoking anxiety in younger children, in addition to common side effect of transient erythema. In pediatric patients, additional weight should be given to the concern for skin cancer, especially in patients who are likely to receive subsequent immunosuppressive therapy.⁶ Long-term treatment effects are unknown, especially in children who may require aggressive treatment for AD over many years. Some authors recommend against the use phototherapy in children, despite the lack of clear data. In summary, phototherapy may best be employed as a potential adjunctive treatment in older children, especially those with chronic, lichenified AD.¹⁷ It

also offers the potential for prevention of relapse after treatment with CsA. The possibility of serious adverse events from cumulative ultraviolet exposure limits long-term use.

Summary of the evidence

Evidence-based practice for the treatment of severe AD in the pediatric population is often limited to results from case series, and most available RCTs enroll small numbers over short periods. In general, the preponderance of evidence is against systemic steroid use, and supports the use of systemic antibiotics only for confirmed superinfections. CsA has the strongest evidence of effectiveness, and induces the most rapid remission, but may be less suitable for long-term maintenance.¹⁶ The available evidence supports AZA, MTX, and MMF as the next line of treatment, and suggests similar efficacy among these three options. GI disturbances are the most common adverse events for each of these treatments. AZA has the most placebo-controlled evidence, while MMF is backed by less evidence but may have fewer side effects. CsA, AZA, and MTX are all supported by RCT evidence for use in adults with severe atopic dermatitis.⁶ More aggressive, novel approaches may be merited in some patients, even in the absence of definitive studies showing efficacy, given the serious morbidity for the developing child caused by the disease. Among these options, IFN- γ and IVIg have the most support, while available evidence for biologics is very limited. There remains a need for safer and more efficacious therapeutic options, especially for long-term maintenance.

Conclusions

Currently, CsA is a consensus first line treatment especially for patients in whom rapid improvement is desirable, with most patients experiencing a rapid, relatively robust response. Treating children with CsA long-term is troubling, however. AZA, MMF, and MTX are all reasonable alternatives for maintenance therapy, with MMF possibly showing better tolerability. The rapid onset of action of CsA, versus the potentially more durable remissions for AZA, MMF, and MTX, are consistent with the mechanisms of action of these drugs. Phototherapy also shows efficacy, but can be a difficult treatment modality for children. Ultimately the choice of agent is individualized. Systemic therapy options are associated with potentially severe adverse effects, and should be administered by an experienced dermatologist, with careful monitoring for response and for adverse events. In conjunction with systemic therapy, other approaches towards long-term control of atopic dermatitis in pediatric patients should be considered, including psychological counseling, education for patients and families, and environmental control.

As we learn more about the pathogenesis of atopic dermatitis, we may be better able to prevent progression before the point where potent systemic immunomodulatory therapies become necessary.⁶ One arm of prevention is systems-based patient education, and proactive treatment addressing the skin barrier, allergic, and inflammatory components of the disease. Future treatments targeting early pruritogenic factors and disrupting the amplification loop early in the disease course hold the potential for altering the long-term course of AD.⁹ Further characterization of the underlying pathogenesis may elucidate different AD phenotypes and allow for more informed individualization of therapy.⁸⁷

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