Readdressing Recalcitrant Rashes: Alternate Approaches to Atopic Dermatitis

ABSTRACT

Atopic dermatitis is a common pediatric disease with a chronic relapsing-remitting course, causing distress to patients and family. In patients who remain recalcitrant following treatment with topical steroids, adjunctive therapies including bleach baths, wet wraps and phototherapy as well as systemic immunosuppressants may be considered. Many novel therapies are in development and act on various aspects of the immunologic cascades involved in atopic dermatitis. The following review briefly summarizes up-to-date evidence for the use of these therapies in the pediatric population.

KEYWORDS: atopic dermatitis, pediatric disease, therapies

Introduction

Atopic dermatitis (AD) is one of the most common dermatologic ailments in the pediatric population, affecting 10-20% children worldwide.[1] The associated pruritus contributes to significant physical, social and emotional distress for the patient and family. Although quality of life outcomes for these children and families have improved in recent decades with the advent of corticosteroids, AD remains a chronic condition with a relapsing-remitting course that can prove to be a management challenge for the patient and healthcare provider.[1]

Here we briefly outline the current evidence for optimization of AD management with the use of adjuncts, systemics and novel biologics.

Appropriate medication

Optimization of AD treatment involves appropriate use of the appropriate topical steroid. Steroid phobia can pose a challenge to this, as parents may have reservations

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about application of any quantity of corticosteroids on their children. Parents may also have barriers to adherence which include complex instructions, dislike of the vehicle and burden of cost and time.[2] Adherence can be as low as 32% 8 weeks following prescription.[2]

Historically, this has been exacerbated by well-meaning pharmacists who have instructed parents to use steroids sparingly to lessen the risk of steroid-associated side effects. Although what is meant by this is to minimize the duration of steroid use, it has sometimes been misunderstood to mean a reduction in amount of steroid use. This can, in turn, prolong duration of therapy as the steroids used are sub-therapeutic.[3]

In response to this phenomenon, Canadian pharmacists have recently released an AD treatment guideline describing the use of the fingertip unit in AD treatment, specifically that one fingertip-worth of topicals is needed to treat two palm sizes of disease.[3] This has provided a resource to help allay fears surrounding corticosteroid use.[3]

Other techniques to improve compliance to topicals and to maximize therapeutic effect include:

- Arrange to check-in with parents within the first 3 days of treatment. Adherence within smaller time frames presents as a less daunting task and early communication with the physician fosters accountability.[2]
- Simplify the regimen by limiting to monotherapy, whenever possible.[2]
- Create a blame-free environment when discussing adherence.[2]
- Legitimize parental concerns and involve parents in treatment planning.[2]

Adjuncts: Bleach baths, wet wraps

In patients who remain refractory despite appropriate use of topicals, adjuncts such as wet wraps may be considered. Wet wraps were first described in 1991 and have numerous variants including the open wet dressing consisting of a topical-saturated gauze only, the occlusive wet dressing consisting of an impermeable covering over saturated gauze and the closed wet dressing consisting of breathable covering over saturated gauze.[4] In a retrospective review at the Mayo Clinic, 218 pediatric patients with AD refractory to topicals, immunomodulators and/or phototherapy showed improvement with inpatient treatment with a wet wrap therapy following a mean treatment period of 3.61 days.[4] The regimen consisted of closed wet dressings with triamcinolone 0.1% or hydrocortisone 2.5% cream BID in addition to closed wet dressings with emollients 5-8 times per day.[4]

A randomized, double-blind, placebo-controlled study of 40 children with AD found a more rapid

and marked decline in patients' SCORing Atopic Dermatitis (SCORAD) score with wet wraps containing diluted corticosteroids, compared to controls with plain petrolatum.[5] There is no evidence of superiority between various subtypes of wet dressings.[4]

Wet wraps are thought to mediate AD improvement by decreasing skin temperature thus producing vasoconstriction and reducing inflammation.

Wet wraps are thought to mediate AD improvement by decreasing skin temperature thus producing vasoconstriction and reducing inflammation.[4] In addition, the increased moisture with occlusion facilitates penetration of topicals.[4] The physical barrier provided deters scratching and facilitates removal of scales during dressing changes.[4]

As hospitalization for treatment of AD is not currently common practice in Canada and may not be feasible in other locales due to access to resources, the inpatient treatment program can be simulated at home, with sufficient parent education. Challenges with wet wrap administration include the significant time commitment, discomfort for children and potential side effects of folliculitis[5] and more rarely, adrenal suppression.[4]

Another commonly used adjunct is the bleach bath. Bleach baths target the increased *Staphylococcus aureus* skin colonization in AD patients. While nonatopic individuals have a diverse microbiome on their skin with 3% *S. aureus* colonization, AD patients can be colonized by as much as 70% *S. aureus* on lesional skin and 39% on non-lesional skin.[6] Increased *S. aureus* colonization can decrease innate antibacterial activity, deteriorate epidermal barrier function and aggravate inflammation.[6]

Bleach baths act via the following mechanisms:

- Antibacterial: Studies have demonstrated an antimicrobial effect on atopic skin, decreasing *S. aureus* colonization, which appears to be dose-dependent *in vitro*.[6]
- Anti-inflammatory: In mice models, bleach mediates a decrease in inflammatory response through the inhibition of MAPK and NF-KB signalling, which clinically results in fewer skin lesions, less scratching, less xerosis, fewer excoriations and decreased serum IgE, compared to vehicle.[6]
- Anti-pruritus: Exposure to HOCl decreases intracellular calcium concentrations and

subsequently dampens stimulation of mice dorsal route ganglions, suggesting that bleach baths may decrease peripheral neuronal sensitization and thus act as an anti-pruritogen.[6]

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Clinical evidence for the efficacy of bleach baths remain mixed with regards to impact on Eczema Area and Severity Index (EASI), SCORAD and children's Dermatology Quality of Life Index (DLQI). In one meta-analysis, two of four studies found significant decreases in AD severity with bleach bath use.[7] On pooled analysis, no effect on EASI was seen.[7] It is thought that poor adherence, small studies and insufficient time to follow-up are contributory to the lack of clinically significant efficacy.[7]

Nevertheless, the American Academy of Dermatology recommends the use of ½ cup of 6% common household bleach (equivalent to 0.005% NaOCl) in a standard 150L bathtub full of water, with a five to ten-minute exposure 2-3 times weekly.[6] This regimen is thought to maximize the therapeutic effect of bleach while minimizing contact urticaria.[6]

Phototherapy

Phototherapy with narrowband UVB (NB-UVB) is another adjunct to topicals for those with access to facilities. In the 1920s, it was observed that AD tended to clear during summer months.[8] This precipitated the discovery of UVB therapy, in 1948, for treatment of AD.[9] It is thought that exposure to UV causes photo-immunosuppression and immunomodulation resulting in remission of skin lesions.[8] Specifically, this is believed to occur through suppression of the T helper cell 2 (Th2) and T helper cell 22 (Th22) axes in addition to a reduction of inflammatory leukocytes and cytokines and normalization of epidermal hyperplasia.[8,10]

In a retrospective review of 48 pediatric patients, 76% experienced clearance of AD lesions following an average of 29 NB-UVB treatments, which was provided on a three times weekly basis.[11] 52% of patients remained lesion-free at the 12-month follow-up.[11] In a comparative cohort study, 29 patients treated with NB-UVB were observed along with 26 patients who elected not to pursue NB-UVB. There was a significant difference in the Six Area, Six Sign Atopic Dermatitis (SASSAD) Severity Score (61% vs. 6% reduction) and

in quality of life scores at the end of 12 weeks with bi-weekly treatment.[12] These differences remained significant at 3- and 6-month follow ups.[12]

Many parents worry about the risks of regular UV exposure, particularly of the possibility of precipitating skin cancers later in life. Currently, there are no studies that report the long-term consequences associated with phototherapy in children.[13] In adult studies, no relationship has been established between phototherapy and non-melanoma or melanoma skin cancer.[9] Historically, there has been one report of what was believed to be melanoma in situ in an 11-year-old treated with NB-UVB, however this was ultimately established to be a Spitz nevus, which is benign in nature.[9] Case reports of skin cancer in children following phototherapy have exclusively been in the context of children receiving psoralen and UVA treatment (PUVA) for psoriasis, which provides a different spectrum of UV than the NB-UVB used in atopic dermatitis.[9] In NB-UVB, targeted waves of 311-313nm are provided,[8] whereas increased erythema, burning and carcinogenesis are associated with wavelengths of 300nm or less.[14]

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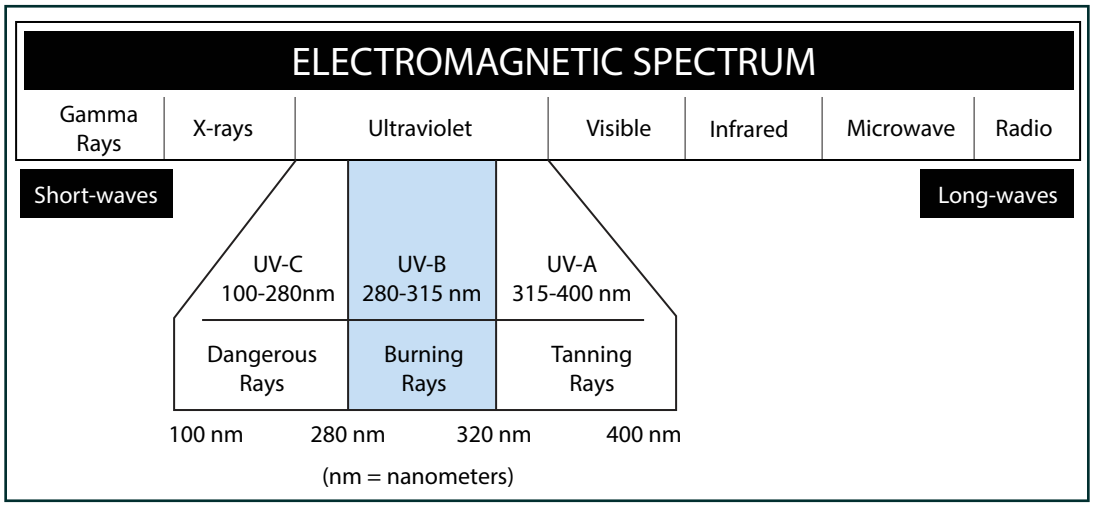
Established side effects of phototherapy include actinic damage, erythema, tenderness, pruritus, burning, stinging, claustrophobia and anxiety, which are all typically time-limited.[8,10,13] Less commonly, there have been reports of photosensitive eruptions, folliculitis, photo-onycholysis, HSV reactivation and facial hypertrichosis.[8,13] Access remains the main challenge with phototherapy as it requires trained staff and equipment, which may not be available at all sites.[8] Though home phototherapy may circumvent access-related difficulties, studies to support its efficacy is limited, with level IIIC evidence.[8]

Overall, phototherapy is safe and effective in the pediatric population and is second-line, after topical corticosteroids, for treatment of AD.[12,13]

Diagram showing light spectrum highlighting where NB-UVB occurs and where side effects peak



Immunosuppressants: Methotrexate, Cyclosporine, Azathioprine

Patients who fail the above treatments may benefit from a brief course of systemic immunosuppressants, allowing for control of their recalcitrant disease. Azathioprine, methotrexate and cyclosporine have been examined in the pediatric population, each targeting a different aspect of immune cell synthesis and activation.

Azathioprine prevents de novo purine synthesis and is thus cytotoxic.10 In a retrospective study of 48 children, 85% showed a good to excellent response to treatment with a mean duration to clinical improvement of 4 weeks.[15] Side effects include lymphopenia, neutropenia, elevated transaminases and cutaneous viral infections.[10,16] As such, it is advisable to assess for baseline blood panel and liver function tests with follow-ups at weeks 1, 3, 7 and 12.[10] In patients with inflammatory bowel disease and rheumatoid arthritis, azathioprine holds a black box warning of hepatosplenic T-cell lymphoma.[17] As azathioprine is metabolized by TPMPT, which has variable expression in different patients, TPMT must also be assessed on initial bloodwork and azathioprine should be titrated accordingly.[10,16]

Cyclosporine inhibits T-lymphocyte activation through down-regulation of cytokines and is also thought to reduce S. aureus colonization.[10] A meta-analysis of a total sample of 602 children and adults supported a dose-dependent reduction of AD with cyclosporine with a mean duration to improvement of 6 to 8 weeks.[16] However, patients tend to relapse within weeks of discontinuation.[18] Side effects include nephrotoxicity, hepatotoxicity, hypertension, headaches, abdominal pain, leukopenia and anemia, which limits its use in the pediatric population.[10,17,18] Monitoring requires a baseline blood pressure, CBC, LFT, fasting lipids and CRP which are repeated every 2 to 3 weeks while on treatment.[10]

Methotrexate is a dihydrofolate reductase inhibitor which prevents purine and pyrimidine synthesis and subsequently decreases proliferation of inflammatory cells.[10] A retrospective review of 30 children showed good to excellent responses with a mean duration to improvement of 3 to 5 weeks.[19] Side effects include dose-related nausea, mouth ulcers, elevated liver enzymes with no reported long-term effects.[10,17] This is arguably the most acceptable side effect profile of the systemics used in pediatric treatment of AD. Monitoring includes CBC, LFT, CRP and hepatitis serology at baseline followed by weekly CBC, LFT for 2-4 weeks.[10] In addition, methotrexate has been found to have a longer duration of relapse-free disease following treatment, compared to other immunosuppressants such as cyclosporine.[17] In a retrospective review of 47 children,

ongoing improvement in Investigator Global Assessment (IGA) was observed up to 3 to 5 months following cessation of treatment.[17]

Mycophenolate mofetil is an inosine monophosphate dehydrogenase which prevents de novo purine synthesis thus preventing B and T-lymphocyte proliferation.[10] As it has a delayed onset of action, it is better used as a maintenance therapy once patients have been stabilized on other immunosuppressants.[10] Side effects include nausea and vomiting, with no long-term safety profile.[13] Baseline CBC, CRP and LFT with follow up bloodwork every 2 weeks is suggested.[10]

Biologics and Novel Immunomodulators

The newest and rapidly-expanding area of development in AD treatment comprise of biologics and other immunomodulators. These medications target the immunologic basis of atopic dermatitis, specifically the increased activation of Th2 and Th22 cells, resulting in increased production of interleukin 4 (IL-4), IL-13, IL-5 and IL-22.[20,21] IL-4, 13 and 31 are pro-inflammatory and activate B-cells and other immune cells as well as increase pruritus signalling.[20] IL-22 induces epidermal hyperplasia and impairs differentiation of keratinocytes.[20]

While much advancement has been made with adult populations, many studies do not specifically address pediatric patients. This is a particularly important distinction as it is postulated that pediatric and adult AD may represent two distinct immunologic processes with adult AD predominantly impacting the Th2/22 pathways while pediatric AD implicates Th17/9.[20] Evidence for these medications in pediatric populations is mounting with many pediatric-focussed trials recently completed and several more on the horizon.

Dupilumab is an injectable monoclonal antibody which binds to the alpha-subunit of the IL-4 receptor found on IL-4 and IL-13.[21] This subsequently prevents Th2 deviation and the downregulation of filaggrin induced by Th2 cytokines.[21] In adult placebo-controlled studies, it has also been shown to reduce serum IgE and thymus-regulated chemokine CCL17, which may imply its role in reducing intrinsic AD, in addition to extrinsic.[21] Phase III trials are still ongoing for the pediatric population, however multicentre, open-label trials in 6- to 17-year-olds have demonstrated a significant improvement in EASI scores (up to 69.7% with doses of 4mg/kg) and in pruritus.[20] Another retrospective case series conducted in patients under the age of 18 who had previously failed systemic therapy demonstrated a decrease in IGA of 2 or more with dupilumab.[22] This was associated with a body surface area reduction of over 50%.[22] Potential side effects include injection site reaction, conjunctivitis and corneal inflammation.[21,22]

SUMMARY OF KEY POINTS

Topical corticosteroids, the first-line treatment for atopic dermatitis, can be optimized with usage of an appropriate amount and within a supportive, therapeutic alliance.

Those who fail to improve with topical corticosteroids may benefit from adjunctive treatment with wet wraps, bleach baths and phototherapy with narrowband UV therapy. These have been shown to be efficacious with a minimal side effect profile.

In those who remain recalcitrant, a brief course of immunosuppressants may be indicated. Methotrexate, azathioprine and cyclosporine have evidence in the pediatric population. Of these, methotrexate has been shown to have the most sustained duration of remission.

A recent explosion of novel immunomodulators and biologics may redefine atopic dermatitis treatment. Crisaborole is a topical PDE4 inhibitor, which has been approved for used in children. Dupilumab is an injectable monoclonal antibody, which has recently been approved for the adult population and remains off-label in pediatrics.

Other agents that impact the Th pathways are PDE4 inhibitors which reduce PDE4-mediated generation of pro-inflammatory cytokines and chemokines.[20] Crisaborole, a topical PDE4 inhibitor, has been FDA-approved for treatment of mild to moderate AD in children aged 2 or over.[20] A phase II randomized and double-blind study with 12 to 17-year-olds demonstrated a dose-dependent reduction in Atopic Dermatitis Severity Index (ADSI) scores following a 29-day treatment with 2% crisaborole ointment BID.[20] In phase II vehicle-controlled studies, crisaborole demonstrated reductions in Investigator's Static Global Assessment (ISGA). Side effects include possible stinging at the application site.[20] At present, no trials comparing crisaborole to topical corticosteroids exist. Two other topical PDE4 inhibitors are currently in phase II studies, with OP-15406/MM36 showing some promise in improvements in EASI, DLQI and pruritus ratings while studies TVT-501/E6005 did not

CLINICAL PEARLS

Monotherapy when possible and regular check-ins with parents can improve adherence to topical steroid regimens, particularly within the first 3 days of treatment.

The American Academy of Dermatology recommends the use of bleach baths (1/2 cup of 6% household bleach in a 150L bathtub full of water) for 5 to 10-minute intervals 2-3 times weekly as an adjunct to topicals.

Class	Mechanism of Action	Drugs & Route of Administration	Trials
JAK inhibitor	Prevents JAK-mediated Th2 cell differentiation	Ruxolitinib: topical, JAK1/2 Upadacitinib: oral, JAK1 PF-04965842: oral, selective JAK1	Phase I ongoing Phase III ongoing Phase III ongoing
Aryl hydrocarbon modulator	Binds to aryl hydrocarbon receptor to reduce proinflammatory cytokine expression	Tapinarof: topical	Phase II dose-finding studies showed improved IGA in 53% of patients
Phospholipase A2 inhibitors	Prevents formation of inflammatory mediators catalyzed by phospholipase A2	MRX-6: topical	Phase II studies showed no significant improvement in IGA
5-lipoxygenase inhibitor	Suppresses prostaglandin synthesis to reduce inflammation	Zileuton: topical	Phase II ongoing
Liver X receptor modulator	Involved in liver X receptor signalling which regulates keratinocyte differentiation to improve skin barrier function	ALX-101: topical	Phase IIb ongoing
Anti-IL-13	Neutralizes monoclonal IgG4 antibody implicated in interactions with IL-13 receptors	Tralokinumab: injectable	Phase III ongoing (in ages 12-17)
IgE neutralizer	Reduces IgE mediated mast cell, basophil, inflammatory dendritic epidermal cell and monocyte activation	Omalizumab: injectable	2 randomized, placebo-controlled trials with adults and children failed to show effect. New ADAPT trial with severe AD patients aged 4-19 ongoing.
IL-1R antagonist	Prevents inflammatory signalling mediated by IL-1 to reduce Th2 responses	Anakinra: injectable	Open-label, Phase I pilot study ongoing

demonstrate any statistically significant findings.[20]

A brief summary of recent and ongoing FDA trials for novel compounds in the treatment of pediatric AD is outlined below.[20]

In summary, though AD remains a chronic remitting disease posing challenges to the clinician and patient, the toolbox with which we can address AD is continually expanding. With consideration of appropriate use of corticosteroids, the addition of adjuncts such as bleach baths and wet wraps, phototherapy with NB-UVB and short courses of immunosuppressants, patient outcomes may be optimized, thus reducing the disease burden of AD.

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