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REVIEW ARTICLE

Management of Itch in Atopic Dermatitis

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Abstract Atopic dermatitis (AD) is the most common itchy dermatosis that affects millions of children and adults worldwide. Chronic itch in this condition has significant impact on measures of quality of life, such as sleep. Treating itch in AD has been challenging for decades, but new drugs have emerged in the last year with significant anti-pruritic effect. The optimal treatment regimen for atopic itch addresses barrier dysfunction, inflammation, neural hypersensitivity, and the itch–scratch cycle. Topical moisturizers remain the foundation of treatment and should be used by all patients with AD-associated pruritus. Step-wise therapy, from topical anti-inflammatory creams to systemic monoclonal antibodies and immunosuppressants, is recommended. There are multiple adjuvant therapies that can be used, especially to target itch in the setting of minimal skin inflammation. Finally, patient education, sleep management, and stress relief are important components to optimize outcomes. This review assesses the latest advances and treatment recommendations for pruritus in AD. Finally, suggested therapeutic ladders and emerging treatments are discussed.

Key Points

Itch in atopic dermatitis is triggered by a complex cascade of immune dysregulation and is mediated through non-histaminergic C-fibers.

Management of pruritus is difficult and often requires a step-wise approach, starting with emollients and topical corticosteroids and advancing to systemic agents.

Newer therapies have been developed, such as the IL-4 and IL-13 blocking monoclonal antibody dupilumab, which offers a promising option and is especially effective for pruritus.

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with clinical features of pruritus, xerosis, and lichenification. Pruritus is considered a defining features of AD and is so common that many describe AD as the itch that rashes [1]. In patients with AD, severe pruritus is the most important, yet most difficult symptom to control. Chronic pruritus occurs in the majority of patients with AD, with published point prevalence between 87 and 100% [2]. Itch leads to scratching, triggering inflammation and infection, worsening the underlying disease (‘itch–scratch cycle’). Furthermore, a patient’s quality of life (QoL) and psychosocial wellbeing are directly impacted by the degree of pruritus that they experience [3]. Pruritus is known to cause

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sleep disruption, depression, anxiety, anger, helplessness, reduced self-esteem, and difficulty concentrating [3–5].

The cause of AD is multifactorial, including genetic predisposition, impaired skin barrier, environmental triggers, and immune dysregulation [6, 7]. The sensation of itch in AD is similarly complex. Chronic itch in AD is mediated by a complex interplay between keratinocytes, cutaneous nerve fibers, pruritogenic molecules, and the peripheral and central nervous system. In order to adequately treat pruritus in AD, it is important to first understand the complex mechanism of itch in these patients. This review is meant to be a broad, yet comprehensive, overview of the etiology and best treatments for itch in patients with AD. Information included in this review is based on a literature search using the PubMed and Cochrane databases and supplemented with the authors' clinical expertise. Database search terms included AD, eczema, pruritus, and itch with the following modifiers based on applicable section: management, treatment and mechanism. All available articles in English were reviewed. Emerging therapy information was supplemented with recent presentations at national and international conferences.

2 Pathogenesis of Itch

2.1 Barrier Dysfunction

It is now understood that an intact epidermal barrier functions not only to prevent entry of exogenous factors such as irritants and allergens, but also in regulating cutaneous inflammation [4]. The epidermal barrier is disrupted in AD in lesional and non-lesional skin [8, 9]. A dysfunctional barrier allows entry of irritants and itch-causing agents such as bacterial proteases, allergens, mechanical irritation from fabrics and alkaline soaps. *Filaggrin* is a well characterized gene with an important role in skin barrier function [7, 10]. *Filaggrin* mutations cause ichthyosis vulgaris, a congenital ichthyosis highly associated with AD [10]. Recently, several mutations in the *filaggrin* gene were discovered in patients with AD, explaining in part the genetic predisposition seen in families [7]. The epidermal barrier can also be damaged by enzymes such as proteases, which promote stratum corneum turnover and desquamation. Finally, the skin–nerve interface is altered in atopic skin with increased expression of various pro-inflammatory neuropeptides (substance P, calcitonin, gene-related peptide, and vasoactive intestinal peptide) [11].

2.2 Neural Pathways

We now know that itch is a distinct sensation, with two independent pathways activated by histamine-sensitive and non-histaminergic C nerve fibers [12, 13]. Pruritus in AD is mediated by non-histaminergic C fibers [14]. The classic histamine-sensitive C fibers respond to antihistamines; however, oral type 1 antihistamines are ineffective in most types of chronic pruritus and have limited utility in AD.

The distinct and parallel pathway of non-histaminergic C fibers is a relatively recent discovery [15, 16]. Non-histaminergic C fibers are activated by spicules of cowhage [15, 17]. In the spinal cord, nociceptor C neurons synapse with secondary neurons in the gray matter of the dorsal horn [18, 19]. Cowhage-induced itch stimulates a distinct population of spinothalamic neurons that cross over and ascend in the lateral spinothalamic tract to the thalamus and then to the cerebral cortex [15, 20]. Pruritus causes activation of multiple brain areas, suggesting that there is no solitary itch processor in the brain [18, 20]. The sensation of itch is perceived after activation of the somatosensory cortex and a scratching response is generated in the pre-motor cortex and striatum. In acute itch, scratching dampens the perception of itch; however, in chronic itch the relationship is more complicated and not completely understood [18, 21].

The perceived sensation and intensity of pruritus can be modified at various points along the peripheral, spinal, and cortical pathways. Itch intensity can be dampened by other incoming pain or tactile sensations. Similarly, mood and attention influence the perceived intensity of itch. In one study, AD patients exhibited more intense activation of several brain areas when exposed to itch compared with healthy controls [22]. Psychophysical studies have confirmed patients with AD also have reduced threshold for induction of itch [14].

2.3 Pruritogenic Mediators

Numerous exogenous irritants and endogenous signals such as cytokines, proteases, histamine, leukotrienes, and neuropeptides activate cutaneous itch-sensing nerves [16, 19]. Better understanding of these various substances may allow for expanded therapeutic targets.

Interleukins (IL) are an important current and future therapeutic target for itch in AD. IL-2, a product of T-lymphocyte activation, can directly stimulate pruritus in AD by stimulating nerves [23]. Inhibition of IL-2 production is the basis for treating AD with topical and systemic immunosuppressants. Next, IL-4 and IL-13 are necessary for the initiation and maintenance of a specific T_h2 subset of cells, type 2, which are known to be involved in AD [24]. Transgenic mice overexpressing IL-4 and IL-13 in the epidermis show an AD phenotype [25]. Furthermore, human lesional AD skin shows elevated levels of IL-4 and IL-13 compared with controls [26]. These findings led to the development of a novel monoclonal antibody targeting

IL-4 and IL-13, dupilumab, which is showing great efficacy in treating AD and rapidly improving AD-associated pruritus [27].

IL-31 and IL-33 have both been implicated in AD [28, 29]. IL-31 and oncostatin M receptor (OSMR) and the IL-31 receptor act as inducers of itch and dermatitis in mice [30]. Furthermore, promising studies have demonstrated that blockade of IL-31 signals by a specific antibody alleviates pruritus in patients with AD, and in children serum levels of IL-31 correlate with disease severity [28, 31]. IL-33 expression is increased in lesional skin in patients with AD, and serum levels of IL-33 correlate with disease severity and decline with disease improvement [32, 33].

2.4 Neural Hypersensitization in Atopic Dermatitis

There is a growing degree of evidence implicating neural hypersensitivity as a leading cause of chronic pruritus. The origins of this theory were predicated on the observation that the perception of itch in response to a previously non-itchy stimulus (alloknesis) is seen in chronic itch patients [14]. A common example of this phenomena in atopic eczema is that mild mechanical stimuli such as exposure to wool clothing can cause intense itch in patients with AD [14]. The phenomenon of neural hypersensitivity is also reflected in the central nervous system. Brain imaging studies in AD patients demonstrate increased activity in the anterior cingulate cortex and dorsolateral prefrontal cortex, areas that are also known to be involved in the hypersensitization phenomena of chronic pain [14]. Neuromediators such as substance P and its receptor, NK-1, glutamate, and *N*-methyl-D-aspartate (NMDA) have a role in inducing this neural hypersensitization and serve as potential therapeutic targets for reducing neural hypersensitization [14].

2.5 Hypothalamic-Pituitary-Adrenal Axis

Skin is especially sensitive to psychological stress and evidence shows that the skin's innate and adaptive immune systems are altered by stress [34, 35]. Stressful conditions have been shown to reduce recovery time of barrier dysfunction in animal skin [34]. Furthermore, in animal models, psychological stress can trigger AD [36]. Stress relief is thus important to include in treatment of atopic itch.

3 Management of Pruritus

Given the complexity of itch in AD, the optimal approach to manage atopic itch should target multiple points along the itch pathway. Targeting barrier dysfunction, inflammation, neural hypersensitivity, and the itch–scratch cycle is paramount to relief of pruritus. Most patients respond best to a combination of therapies. Topical moisturizers remain the foundation of treatment and should be used in all patients with AD pruritus. Step-wise therapy, from topical agents to systemic monoclonal antibodies and immunomodulators, is recommended. There are also multiple adjuvant therapies that can be used, especially to target pruritus in the setting of minimal skin inflammation. Finally, patient education, sleep management, and stress relief are important components to optimize outcomes.

In this section, we will discuss various treatment strategies and therapeutic options in managing itch in patients with AD. We will focus on evidence-based strategies and will discuss our clinical pearls. Finally, examples of treatment regimens for patients based on disease severity and possible future therapies will be mentioned.

3.1 Topical Agents

There are many topical therapies available to address pruritus with a range of potency. Emollients or moisturizers with anti-pruritic agents, along with avoidance of alkaline bar soaps, should be used in all patients with AD. Some patients with mild pruritus can be optimally managed with only over-the-counter therapy. For others, options include moderate potency corticosteroids, compounded topical analgesic agents, or topical immunosuppressants. In more severe cases, wet-wrap therapy and UV treatment may be utilized.

3.1.1 Emollients/Skin-Barrier Protection

Barrier creams and emollients are considered first line in the treatment of AD and AD pruritus. The function of topical emollients and moisturizers is to repair the dysfunctional skin barrier and prevent penetration of irritants, which are known to drive atopic itch and inflammation. Emollients act as an occlusive dressing, preventing transepidermal water loss [37]. Topical moisturizers also contain humectant ingredients, which attract water and rehydrate the epidermis. Emollients have been shown to reduce atopic itch and are known to be steroid-sparing agents [38–42]. The combination of emollients with topical corticosteroids is more efficacious than either alone, leading to greater improvement in pruritus [43, 44].

Occlusive agents contain petrolatum, dimethicone, or mineral oils. Examples of humectants include glycerin, hyaluronic acid, lactic acid, urea, glycyrrhetinic acid, propylene glycol, butylene glycol, and allantoin. In choosing an emollient, dermatologists often recommend agents based on consumer preference and cost. A recent Cochrane review supports this practice and does not support the use of one product over another. In the Cochrane

review of emollients and moisturizers in patients with AD/eczema, there is no evidence that one moisturizer or emollient works better than another [44]. The review concluded that most moisturizers demonstrate at least some beneficial effects, leading to a reduction in the number of flares and the need for topical corticosteroids [44].

3.1.2 Ceramides

Ceramide-containing skin products are found in multiple over-the-counter moisturizers, soaps, shampoos, and sunscreens. Ceramides are a family of waxy lipid molecules found in the stratum corneum and represent approximately half of the lipid-rich matrix surrounding mature keratinocytes [45]. There is some evidence to suggest that ceramides are beneficial. For example, in a cohort study of 150 patients, a ceramide-containing cleanser and moisturizer regimen improved SCORAD (Scoring Atopic Dermatitis) scores, QoL measures, itch severity, and overall disease activity in patients with AD; however, there was no non-ceramide comparator [46].

3.1.3 Colloidal Oatmeal

Colloidal oatmeal is widely available over the counter in various formulations including moisturizers, cleansers, and bath soaks. Oatmeal has been used for hundreds of years in the treatment of dermatitis and pruritus due to its soothing properties [47]. A review of colloidal oatmeal as a treatment of AD showed that adjunctive daily use of moisturizers and/or cleansers containing colloidal oatmeal significantly improved itch in patients with AD [48]. Another recent, non-comparator clinical study showed that use of 1% colloidal oatmeal as monotherapy is effective in reducing pruritus in mild to moderate AD [49]. Colloidal oatmeal has anti-inflammatory and moisturizing properties and has been shown to aid in barrier repair [48, 50]. Avenanthramides are one component in the colloidal suspension, which are implicated as the agent driving the antipruritic effects [51]. Oatmeal extract has furthermore been shown to decrease arachidonic acid, cytosolic phospholipase A2, and tumor necrosis factor alpha (TNFα) and inhibits the activity of nuclear factor kappa B, all of which are known inflammatory mediators [47].

3.1.4 Optimizing Skin pH

Preserving skin pH is an often overlooked component in the management of AD-induced pruritus. In a healthy state, human skin is naturally coated with a thin, slightly acidic film known as the acid mantle [52, 53]. This film is formed by sebaceous gland secretions and contributes to the barrier against environmental irritants [53]. The natural pH of healthy skin is acidic, ranging from 4.5 to 6.2 [52]. In contrast, patients with AD have a more basic pH [53]. Several studies have shown a significantly higher pH, in both eczematous skin and uninvolved skin in AD patients compared with healthy controls [9, 54]. Non-soap–based cleansers maintain a healthy pH and are available over the counter. These gentle cleansers have been shown to improve skin condition and hydration in patients with AD [55]. In contrast, alkaline cleansers, such as many common bar soaps, should be avoided. Alkaline cleansers can increase secretion of serine proteases, which result in activation of PAR2, an itch-mediating receptor [56].

3.1.5 Topical Corticosteroids

The benefit of topical corticosteroids for AD has been clearly accepted and these agents are considered first-line treatment for acute flares [57–60]. Relatively few trials have specifically focused on the efficacy of topical steroids for pruritus in AD [61, 62]. Topical corticosteroids have an indirect anti-pruritic effect by reducing inflammation in the skin. Available products differ in terms of corticosteroid class, potency, concentration of the active molecule, and formulation. The US classification considers both drug concentration and formulation and ranges from ultra-high potency (group I) to low potency (group VII) [63]. Evidence suggest that low potency topical steroids are less effective at reducing pruritus than moderate or high potency options [62, 64]. Interestingly, there is no evidence that high potency steroids are more efficacious than moderate potency formulations [61]. Therefore, we recommend that clinicians start treatment with moderate potency topical corticosteroids when treating acute flares.

3.1.6 Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus were introduced as steroid-sparing topical agents and have been available for more than 15 years. They are considered second-line agents after topical steroids, but are recommended for use in delicate areas such as face and eyelids and as prophylactic treatment to prevent flares [59]. TCIs are immunomodulators that are thought to regulate T-cell activation and inhibit the release of inflammatory cytokines [65–67]. The antipruritic effect of these agents may also be due to overstimulation of TRPV1 ion channels on cutaneous nerve fibers, resulting in desensitization of itch-transmitting nerve fibers [68]. TCIs have been shown to reduce erythema and pruritus in patients with AD and are particularly effective in treatment of children or as an alternative to topical steroids on the face, eyelids, and skin folds [65, 66, 69, 70]. In double-blind placebo-controlled trials, TCIs improved pruritus

within 48 h and maintained their antipruritic effects with continued use [71, 72]. In our experience, patients who have initial skin burning from the use of TCIs often respond better, likely due to effective overstimulation of TRPV1 ion channels [73]. Clinicians and patients are often concerned about the black box warning concerning the theoretical risk of increased malignancy with use of TCIs. The FDA's decision was primarily based on a 39-week toxicity study using high oral doses in monkeys [74]. To date, no causal relationship between malignancy and TCI use has been proven. Furthermore, long-term safety studies and post-marketing surveillance demonstrate that the number of malignancies in TCI-exposed patients is much lower than you would expect in a general population [75].

3.1.7 Crisaborole

Crisaborole 2% topical ointment is a recently approved selective PDE4 inhibitor, indicated for mild to moderate AD [76]. Crisaborole suppresses the release of various inflammatory cytokines such as TNFα, IL-12, and IL-23 [77, 78]. There are several large clinical trials evaluating crisaborole versus a vehicle control [79, 80]. Crisaborole was more effective than the vehicle in reducing symptoms of AD and AD pruritus in patients as young as 2 years, with a favorable safety profile [79]. In another trial, pruritus scores were improved by approximately 60% as early as 5 days after initiation of treatment [81]. A post-hoc analysis of two phase III trials in mild to moderate AD has shown that crisaborole has a rapid itch relief response in 2 days [79]. The most common adverse event is mild application site discomfort. This novel therapy offers an alternative to topical steroids and TCIs.

3.1.8 Capsaicin

Capsaicin, an alkaloid compound, is one of the active components of chili peppers. Topical application of capsaicin can be used for treatment of pruritus due to multiple skin disorders [82–84]. Clinically, capsaicin is best used in the setting of localized atopic itch. The mechanism to relieve pruritus involves desensitization of TRPV1-expressing cutaneous nerve fibers [82, 85]. Application of capsaicin causes an initial period of burning and erythema. Instructing patients to apply a topical anesthetic (such as lidocaine or EMLA®) before capsaicin during the first 2 weeks of treatment may reduce patient discomfort and increase compliance [86, 87].

3.1.9 Topical Analgesics

There are several topical analgesics which show benefit in AD pruritus. These agents work on peripheral neural pathways and are often used as adjunctive therapy. In the authors' opinion, the best option is a compounded agent: topical 10% ketamine, 5% amitriptyline, 5% lidocaine (TKAL) in a liposomal base. A retrospective analysis done by our group showed TKAL to be effective in reducing chronic itch in patients with AD [88]. Side effects often include a local burning sensation and application-site redness. These agents are generally safe; however, patients should be instructed to apply sparingly to areas with the most severe pruritus, limiting to < 30% of body surface area up to three times daily. Polidocanol, another option, has both anesthetic properties and moisturizing effects. An open-label study of 5% urea and 3% polidocanol showed a significant reduction in pruritus in patients with AD [89]. Other topical anesthetics such as pramoxine 1% and lidocaine 5% have also demonstrated antipruritic effects [90, 91].

3.1.10 Topical Cannabinoids

Targeting the cannabinoid receptor represents an interesting area of development for pruritus. An example is palmitoylethanolamide (PEA), an endogenous fatty acid with endocannabinoid-like properties. PEA does not directly interact with cannabinoid receptors, rather it inhibits the breakdown of anandamide, a potent endocannabinoid, increasing its activity [92]. Anandamide is known to reduce mast cell degranulation [93]. Incorporation of PEA into topical creams has been shown to decrease the severity of atopic itch [93, 94]. PEA creams are well tolerated with minimal side effects such as mild burning or erythema.

3.1.11 Topical Cooling Agents

There is a subset of AD patients who report that cooling their skin alleviates symptoms. In these patients, topical cooling agents may be helpful. Available cooling agents—common in anti-itch lotions—include menthol, camphor, and phenol. Menthol and camphor exert their effects via activation of thermosensitive TRP channels expressed by keratinocytes and peripheral nociceptors [95]. Menthol is an agonist of TRP melastatin-8 (TRPM8), which evokes the sensation of cold and can modulate the perception of itch [95–97].

3.1.12 Wet Wrap Treatment

Wet wrap treatment (WWT) is a useful method for controlling AD and can be used with either emollients or corticosteroids alone or in combination. This method involves soaking the skin for 10–15 min in lukewarm bath water, patting dry, and then a thick layer of the emollient, or corticosteroid followed by emollient, is applied and covered with damp cotton pajamas or cotton wraps, then a dry layer.

WWT more rapidly controls AD flares than corticosteroids alone in randomized controlled trials (RCTs) and multiple observational case series [59, 98–100]. WWT produces a cooling sensation to the skin, allows for better penetration of topical steroids, and serves as a mechanical barrier to prevent scratching. The predominant mechanism driving improvement of atopic itch with WWT seems to be the mechanical barrier that prevents exogenous neural stimulation and reduces scratching, which can break the itch–scratch cycle in patients.

3.1.13 Sodium Hypochlorite

Atopic skin is predisposed to develop secondary bacterial, viral, and fungal skin infections. Staphylococcus aureus is the most common and is known to colonize many AD patients [101]. Staphylococcus-derived exotoxins and super-antigens aggravate AD symptoms and may contribute to AD pruritus [101]. Sodium hypochlorite, the active ingredient in household bleach, has been used for more than 70 years for its bactericidal, antiviral, and sporicidal properties without development of antimicrobial resistance [102]. RCTs have demonstrated the benefit of bleach baths in controlling AD severity [102, 103]. With regard to itch, there was a significant reduction in itch severity after 2 months of treatment [103]. Bleach baths are safe when patients are given detailed instructions. Patients should add a half cup of household bleach to a full bathtub of lukewarm bath and soak for 5–10 min. Sodium hypochlorite is also available as an over-the-counter wash or a topical solution [102].

3.2 Phototherapy

Phototherapy is a safe and effective treatment for AD and atopic itch. There are numerous wavelengths that may be used, but the most effective appears to be narrow band UBV [104]. In a study of atopic itch, 90% of patients reported decreased itch severity when treated with NB-UVB, compared with a reduction in 63% of patients receiving UVA treatment [104]. The mechanism of action is not fully understood, but the use of phototherapy results in reduction of cutaneous sensory nerve fibers, which may explain its anti-pruritic effect [105]. Phototherapy also decreases inflammation by reducing T cells, indirectly targeting itch [106]. When initiating therapy, it is important to educate patients that in the first 2 weeks, itch can be aggravated.

3.3 Systemic Agents

In patients with severe AD and atopic itch, initial management may require systemic agents. The idea is to use these agents for a limited period of time, transitioning to preventative strategies once the disease is well controlled. In some cases, however, monoclonal antibodies may be used for longer periods of time to suppress disease activity. Monoclonal antibodies, immunosuppressants, immunomodulators, and antidepressants are beneficial in the treatment of AD and atopic itch.

3.3.1 Monoclonal Antibodies

Future publications on optimal treatment for AD and atopic itch will likely be dramatically different given the emergence of targeted monoclonal antibodies. It is unclear at this point if these agents will replace immunosuppressive treatments or be used as monotherapy; however, medications in the pipeline show great promise.

3.3.1.1 Dupilumab Dupilumab is a fully humanized monoclonal antibody that blocks IL-4 receptor A and IL-4 and IL-13 signaling, key mediators in type 2 helper T-cell inflammation. Dupilumab has shown significant benefit in AD with a dramatic anti-pruritic effect as soon as the first 2 weeks [27]. In the two identical, randomized, double-blinded, placebo-controlled studies of 1379 adults with moderate to severe AD, doses of 300 mg administered subcutaneously either weekly or every other week were associated with a 44.3–51% reduction in pruritus as measured by a numerical rating scale (NRS) after 16 weeks, compared with a 15.4–26.1% reduction with placebo [27]. The major adverse effects included conjunctivitis and injection site reactions [27]. In patients with severe AD and AD pruritus, dupilumab is now our first-choice agent.

3.3.2 Oral Immunosuppressants

3.3.2.1 Cyclosporine A Cyclosporine A (CsA) is a potent immunosuppressant which targets T cells. CsA binds to the intracellular receptor cyclophilin, leading to decreased IL-2 production and T-cell activation [107]. CsA was originally used for prevention of transplant rejection, but is now used for multiple inflammatory skin conditions. A systematic review of systemic treatment for AD recommended CsA as the first-line treatment for short-term use in moderate to severe AD [108]. In the context of atopic itch, CsA remains an excellent option. In multiple RCTs, continuous treatment with CsA resulted in a decline in itch severity by 71–78% [108–110]. The side effects of CsA often limit its use and include hypertension, elevated creatinine, elevated blood urea nitrogen, opportunistic infection, immunosuppression, and renal toxicity. Given the side effects, CsA is best used as a short-term solution to achieve rapid control of an acute flare of AD. Another limitation in using CsA is that after its cessation a rebound flare of atopic eczema may occur. For

this reason, we often use CsA in combination with other systemic agents, then titrate off after several months.

3.3.2.2 Mycophenolate Mofetil Mycophenolate mofetil (MMF) is an immunosuppressive medication that works by selectivity inhibiting lymphocyte proliferation and antibody production. MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, leading to inhibition of both T- and B-cell growth and proliferation [111]. MMF has been shown to be safe and effective for the treatment of severe AD and atopic itch [112, 113]. A 2011 randomized but un-blinded trial comparing MMF with CsA found that MMF is just as effective as CsA for maintenance therapy in patients with severe AD [114]. Despite these findings, MMF often requires a longer period of time to achieve a therapeutic response, thus we recommend that MMF be started in conjunction with CsA. After 3 months of combination therapy, CsA can be tapered.

3.3.2.3 Azathioprine Azathioprine is a purine analog that inhibits normal purine synthesis, which limits T-cell and B-cell proliferation [115]. A 2014 systemic review of immunomodulators in the treatment of severe AD recommended azathioprine as a second-line treatment option [108]. Trials have found that azathioprine is as efficacious as methotrexate in improving disease severity, itch severity, and quality of life [116]. In trials, the adverse events were low for short-term use up to 1 year, with the most common AE being abnormal lymphocyte counts [108, 117]. The only important consideration is testing for thiopurine methyltransferase (TPMT), as 11% of the population, especially in the African American population, have reduced enzyme activity [118]. Patients with lower TPMT activity carry the risk of toxic drug levels and bone marrow myelosuppression so dosage adjustments are necessary [118].

3.3.2.4 Methotrexate Methotrexate, an inhibitor of dihydrofolate reductase, indirectly inhibits purine synthesis and limits T-cell proliferation [108, 116]. Methotrexate is commonly used in the treatment of many inflammatory skin diseases and is recommended as a third-line agent for moderate to severe AD [108]. When compared with azathioprine, methotrexate has similar efficacy regarding AD severity, quality of life, and pruritus assessments [116]. We recommend methotrexate, especially when treating papular eczema, in doses up to 15 mg weekly. When using methotrexate, lab monitoring is recommended; however, side effects are generally low, including nausea and gastrointestinal complaints.

3.3.3 Systemic Corticosteroids

While systemic corticosteroids are excellent immunosuppressants, they are contraindicated for prolonged use in the treatment of AD due to side effects and the risk of rebound flaring [119]. We use them rarely for flares of disease for 2–3 weeks.

3.3.4 Non-immunomodulating Systemic Therapies

3.3.4.1 Antihistamines Although H_1 antihistamines have been found of limited benefit for most types of chronic itch, they are still commonly used for treatment of itch in AD. The mild improvement sometimes seen with antihistamines in atopic itch may be due to the sedating effects of traditional antihistamine therapy [120]. Concomitant use of H_1 antihistamines with topical steroids may be beneficial in a subgroup of children with more severe AD, leading to shorter duration of topical steroid use [121].

3.3.4.2 Mirtazapine Mirtazapine, an atypical antidepressant, antagonizes noradrenergic (α_1, α_2), serotonergic (5-HT_2, 5-HT_3), and histaminergic (H_1) receptors and has demonstrated efficacy in relieving pruritus in AD. It is especially helpful in alleviating nocturnal itch due to various pruritic conditions, including AD [122, 123]. The anxiolytic effect of 5-HT_{2A} antagonism and the sedative effect of H_1 antagonism likely aid in the efficacy seen for atopic itch [123]. The optimal dose is 7.5–15 mg nightly, below the threshold for antidepressant activity. Mirtazapine may be a useful first-line therapy for nocturnal itch in AD, as it is generally well tolerated. In addition, mirtazapine can be used in combination with GABAergic agents with a synergistic effect. The safety profile of mirtazapine is favorable compared with most other antidepressants [123]. Increased appetite and weight gain are among the most frequently reported side effects [66]. It is not recommended for use in children under 10 years old.

3.3.4.3 GABAergic Antiepileptics Antiepileptics such as gabapentin and pregabalin are structural analogs of γ-aminobutyric acid. GABAergic drugs are another option for treatment of pruritus in AD. Their exact actions are unknown but they may work by modulating itch perception and reduce neural hypersensitization to itch, a phenomenon that plays a significant role in atopic itch. The most frequently reported side effects include increased appetite, weight gain, and somnolence [124].

3.3.4.4 Opioid Modulators Butorphanol, a κ-opioid agonist and partial μ-antagonist has demonstrated efficacy in relieving intractable nocturnal pruritus. An imbalance between the mu and kappa opioid systems is implicated in generalized pruritus [125]. Butorphanol is administered intranasally at doses ranging from 1 to 4 mg daily and has been shown to reduce itch and improve sleep in patients with severe pruritus [125]. Data demonstrating

improvement in atopic pruritus is limited, but has shown benefit [126]. Butorphanol is well tolerated, has a rapid onset of action, and does not cause reversal of analgesia or dependency.

3.4 Complementary and Alternative Therapies

3.4.1 Patient Education

We have discussed many beneficial treatments for atopic itch; however, poor adherence to treatment plans can make the most efficacious treatment ineffective. Numerous studies have documented steroid phobia, lack of understanding, and poor adherence to long term oral medications, with detrimental effects for disease control [127–130]. Patient and caregiver education about AD and disease management is a necessary component of treatment. Therapeutic patient education (TPE) is one example of a patient-centered process that can be used [131]. TPE aims to transfer information and strives for shared decision making between the healthcare provider and patient. TPE programs are generally provided by multidisciplinary teams that utilize different methods such as group-based sessions and individual care plans. TPE has been shown to improve outcomes in AD such as disease severity, treatment adherence, QoL, and improve coping with itch [131]. Another educational program, first developed in Germany and adopted by many European dermatology centers, are so-called 'eczema schools'. These age-based educational programs led to improved eczema scores and measures of QoL [132]. The focus was on age-appropriate patient education and shared decision making. Topics may include triggering factors in eczema, scratching alternatives, coping mechanisms, diet tips, and education on therapy.

In our clinics, we utilize our electronic medical records to populate after-visit summaries with a verbatim copy of everything written in the assessment and plan portion of visit notes. Furthermore, we provide all patients complaining of itch with instruction regarding 'best practices' to reduce itching: avoidance of bar soaps and irritants, proper clothing, and specific recommendations regarding common over-the-counter moisturizers and emollients. The use of short patient-oriented web-based videos, educational groups, and a book on coping with itch is also something we support and use [133].

3.4.2 Stress Reduction

Many patients with AD can benefit from stress management as stress is known to aggravate itch in atopic eczema [134, 135]. One of the techniques we often use for itch reduction is a progressive muscle relaxation (PMR) technique [136]. This relaxation technique is usually conducted in a quiet room while sitting comfortably on a chair or on a mattress. PMR involves the tension of certain muscle groups followed by the subsequent relaxation of these muscles [136]. Other techniques of stress reduction that have been successfully used for atopic eczema itch include habit reversal methods and cognitive restructuring techniques, included in some stress management training [137].

3.4.3 Sleep

It is necessary to address adequate sleep in patients with atopic itch. In our patients, we ask about sleep and prescribe target therapies to address both pruritus in general and pruritus that impacts sleep. There are several resources that can also be shared with patients including educational resources and coping strategies [133].

3.4.4 Acupuncture

Acupuncture is a practice of traditional Chinese medicine, wherein practitioners stimulate specific points of the body, often via insertion of thin needles through the skin. Acupuncture has been shown to reduce histaminergic itch in healthy volunteers [138, 139]. It also has been shown to reduce allergen-induced itch in patients with AD. Acupuncture, particularly at the L11 meridian, appears to be an effective adjunct in the setting of atopic itch [140]. However, the specific neurochemical processes underlying the activity remains unknown.

3.5 Treatment Recommendations and Therapeutic Ladder

Based on the authors' treatment algorithms, we have included a therapeutic ladder (see Fig. 1). We will discuss patient treatment based on severity of pruritus and extent of eczematous rash. Our patient interview includes patient-subjective assessment of pruritus on a scale of 0–10, with 0 being no itch and 10 being the worse itch possible. We also discuss sleep and if the patient's pruritus impacts their sleep. This information allows us to place most patients in the following categories: mild to moderate pruritus (1–4 out of 10) with or without eczematous rash, moderate pruritus (5–7 out of 10) with sleep interruption and with eczematous rash, moderate pruritus (rated 5–7 out of 10) with sleep interruption but with no significant eczematous rash, and finally severe pruritus (8–10) with sleep interruption and extensive eczematous rash). In general, we start at the bottom of our therapeutic ladder and move to the next level as clinically needed. Patients that present with more extensive or severe rash with high pruritus ratings may be started at the second tier based on clinical impression, especially in patients that have failed conventional therapies.

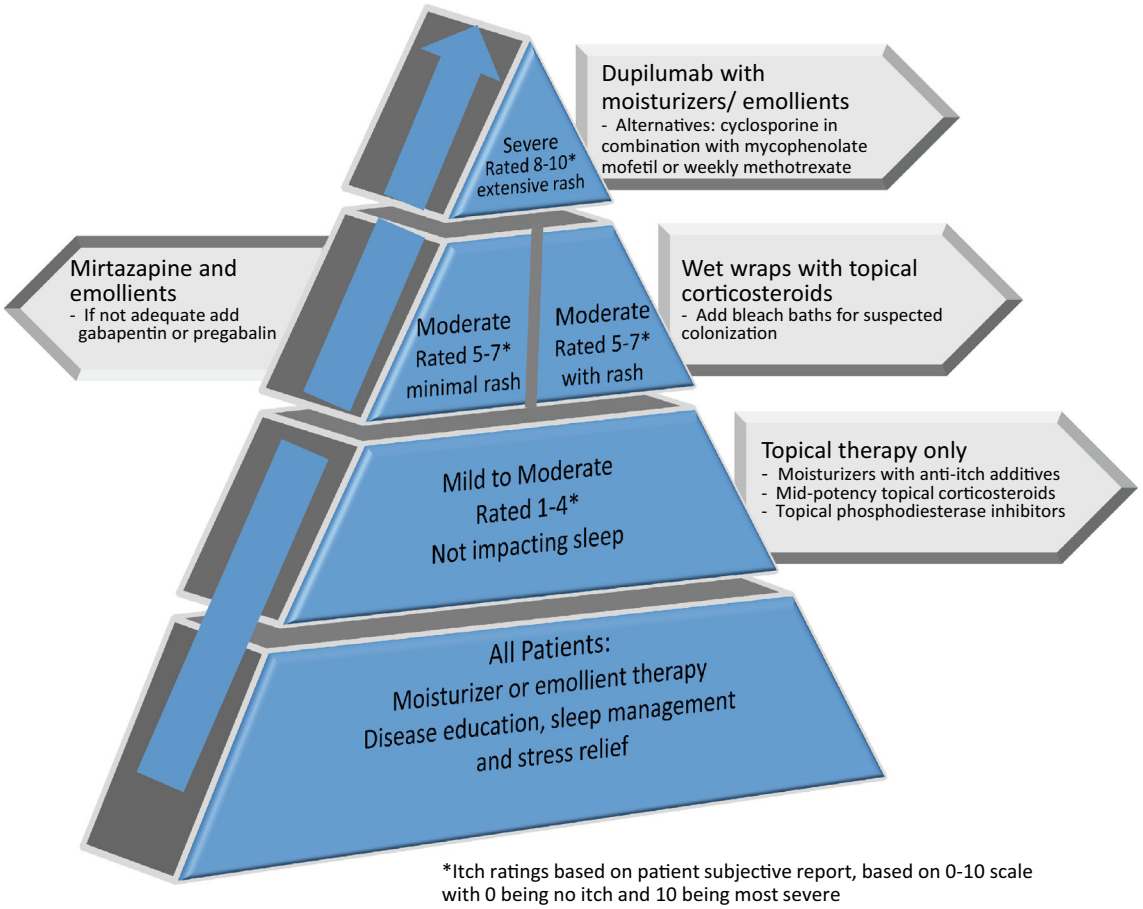

Fig. 1 Recommended therapeutic ladder for patients with AD-associated pruritus. Patients categorized based on severity of itch, impact on sleep and presence or relative absence of eczematous rash. All patients receive patient education and moisturizers. Based on patient severity, treatment should progress up the ladder. Patients with pruritus with minimal eczematous rash may require a district treatment strategy

3.5.1 Mild to Moderate Itch

For mild to moderate atopic itch with a numeric rating scale of 1–4, which does not affect sleep, we usually provide topical treatments with moisturizers containing anti-itch additives, such as oatmeal and topical ceramides with pramoxine. Depending on the patient, we may also use mid-potency topical corticosteroids or topical phosphodiesterase inhibitors (crisaborole). Another option is a compounded topical steroid in a silicone base. In our experience, our compounded agent is very effective in itch reduction [139].

3.5.2 Moderate Atopic Itch with Limited Skin Inflammation

Patients with AD may have chronic pruritus, even without significant eczematous rash. These patients tend to have significant sleep disruptions due to itch. If a patient rates their itch intensity 5–7, and/or has significant sleep disturbance, but has no significant eczematous rash, we usually start with low-dose oral mirtazapine in addition to emollients. As mentioned above, mirtazapine works particularly well for night-time pruritus. If itch is not well controlled, gabapentin or pregabalin may be added with synergistic effects.

3.5.3 Moderate Itch with Significant Skin Inflammation

The primary goal for patients with moderate eczema is reducing inflammation in the skin. These patients often have itch intensity ≥ 5 and have difficulty sleeping. We recommend wet wraps with topical steroids and bleach baths if skin colonization is suspected. If not well controlled with this regimen, we would move up the therapeutic ladder to dupilumab.

3.5.4 Severe Itch with Skin Inflammation

For severe atopic itch with a significant eczematous rash, dupilumab is our go-to agent. If not available due to

insurance issues, we use cyclosporine in combination with mycophenolate mofetil and taper the cyclosporine after 3 months. Another alternative is a weekly dose of methotrexate, up to 15 mg. In addition to systemic agents, we recommend emollients or moisturizers with anti-itch ingredients.

3.6 Emerging Drugs on the Horizon

Interleukin 31 has been coined an itchy cytokine due to its role in itch of AD, prurigo nodularis, and cutaneous lichen amyloidosis [28, 30, 141]. An emerging drug that has not been approved targets IL-31. Nemolizumab, an IL-31 receptor A antagonist, was recently studied in a randomized, double-blinded, placebo-controlled phase II trial of 264 adults with moderate to severe AD [142]. Nemolizumab in doses of 0.1, 0.5, or 2.0 mg/kg administered subcutaneously every 4 weeks was shown to decrease pruritus by 43–63% in a dose-dependent fashion over a 12-week period as measured using a visual analog scale (VAS), compared with a 21% decrease with placebo [142]. Treatment was also associated with an improvement in sleep disturbance [142]. Other biologics in development, tralokinumab and lebrikizumab, both monoclonal antibodies against IL-13, are undergoing clinical trials for AD. Similarly tezepelumab, a human monoclonal antibody specific for the epithelial-cell–derived cytokine thymic stromal lymphopoietin (TSLP) may be beneficial for AD.

Asimadoline is an oral κ-opioid receptor agonist that is currently being evaluated at a dose of 2.5 mg twice daily for efficacy in pruritus associated with AD in phase II clinical trials [143]. Nalbuphine hydrochloride is another agent targeting the κ-opioid receptor. Nalbuphine is a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist. It is currently marketed for the treatment of chronic pain [144]. Currently, phase II and III clinical trials of nalbuphine hydrochloride extended release in doses from 90 to 180 mg twice daily are underway to examine its efficacy in prurigo nodularis [145].

Serlopitant, oral neurokinin-1 (NK-1) receptor antagonist has been investigated in treatment of chronic itch [146, 147]. In a recent randomized, placebo-controlled, phase II clinical trial of 127 patients, Serlopitant was evaluated in patients with prurigo nodularis, several of whom had underlying AD. Serlopitant was shown to cause a 46% reduction in pruritus in an 8-week period at a dose of 5 mg daily, compared with a 26% reduction with placebo [146]. In another phase II RCT of 257 patients with chronic pruritus of different types, including a significant number of patients with AD, patients were randomized to serlopitant 0.25 mg ($n = 64$), 1 mg ($n = 65$), and 5 mg ($n = 64$), and placebo ($n = 64$) (146). Serlopitant 1 and 5 mg provided statistically significant improvement in chronic pruritus compared with placebo, and was safe and well tolerated. All treatment-related adverse effects were of mild or moderate intensity. Another NK-1 antagonist, tradipitant, was evaluated in a phase II drug trial for the treatment of atopic eczema and had mixed results with improvement in baseline itch, but no statistical difference from placebo [147].

Newer H_4 antihistamines show promise in treatment of atopic itch. JNJ-39758979 is an H_4 histamine receptor antagonist. In a randomized, double-blinded, placebo-controlled study of 88 patients with moderate AD, a significant decrease in pruritus severity and duration was seen with JNJ-39758979 compared with placebo [148]. There was also a trend towards improved sleep hygiene and decreased impact of pruritus on daily living; however, the study was terminated early due to the development of severe agranulocytosis by two study participants [148]. Another compound, ZPL-389, a selective histamine H_4 receptor antagonist, is being studied as a potential oral treatment for moderate to severe AD [149]. The proof of concept study for ZPL-389 showed a clinically and statistically significant reduction of eczema by 50%, measured by EASI score (Eczema Area and Severity Index), after 8 weeks; however, no data was provided on itch scores [149].

4 Conclusion

Pruritus is the predominant symptom in many patients with AD and is often difficult to control. The mechanism of chronic pruritus in AD is complex; however, multiple treatment strategies are available. Barrier repair, sleep assessment and patient education should be addressed in all patients. In severe AD flares, systemic control of inflammation with targeted monoclonal antibodies or immunosuppressants may be necessary. Adjuvant therapies can be used to control nighttime pruritus or in cases of atopic itch without significant eczematous rash. Patient treatment should be tailored based on disease presentation and patient preference. Alternative therapies can and should be incorporated into management strategies. The future treatment of AD and AD-associated chronic pruritus will likely shift toward more targeted therapies. Dupilumab has already become a go-to agent in patients with severe AD.

Compliance with Ethical Standards

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Conflict of interest Dr. Yosipovitch has been a consultant and investigator and advisory board member of Sanofi and Regeneron, Galderma, TREVI Menlo, TIOGA. He received royalties as the author of *Living with Itch*. Dr. Pavlis has no conflicts of interest to declare.

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