Published in final edited form as:

Dermatol Ther. 2013 ; 26(2): 110–119. doi:10.1111/dth.12032.

The effects of treatment on itch in atopic dermatitis

Kevin B. Yarbrough, Kristin J. Neuhaus, and Eric L. Simpson

Department of Dermatology, Oregon Health & Science University, Portland, Oregon, USA

Abstract

Pruritus causes significant impairment in the quality of life of patients suffering from atopic dermatitis. Treatments for itch in atopic dermatitis range from simple avoidance of pruritus triggers to more complicated systemic therapy. Several treatments aim to target specific mediators of itch in atopic dermatitis, while others improve pruritus by reducing inflammation. Currently, the most effective treatments for atopic dermatitis-associated itch are primarily topical or systemic anti-inflammatory agents. Better management of pruritus in atopic dermatitis is an important goal, and necessitates the development of novel targeted treatments as well as efficient use of current therapies.

Introduction

Patients with atopic dermatitis (AD) suffer from many symptoms of inflamed skin, but none more prevalent and potentially debilitating than pruritus (1,2). Pruritus has been defined as an “unpleasant sensation, eliciting the urge to scratch” (3) and is one of the few symptoms defined by the action it often evokes. Both the symptom and the action contribute significantly to the morbidity of AD, leading to psychosocial sequelae including depression, anxiety, difficulty concentrating, as well as physical damage to the epidermal barrier leading to increased water loss, susceptibility to infection, lichenification and increased inflammation. Ideally, treatment of AD would be aimed at not only alleviating the skin inflammation but also at providing patients relief from the intense pruritus.

Pathophysiology of itch in AD

The pathophysiology of AD is complex and not fully understood, but the so-called itch/scratch cycle perpetuates the disease. Nocturnal itch leads to intense scratching, leading to skin damage and poor sleep quality. Early research attempting to understand the pruritus of AD focused on the role of histamine. Unfortunately, clinical studies revealed that histamine receptor (H1, H2) blockade does not lead to significant improvement in itch or inflammation in AD (4). More modern concepts of itch pathophysiology in AD involve understanding the close relationship between the nervous system and the skin; two organ systems derived from the same embryological origin (ectoderm). Recent human studies in AD identify roles for neuropeptides such as calcitonin, gene-related peptide, substance P, as well as neurotrophins such as nerve growth factor. Newly identified itch mediators include the

histamine 4 receptor and interleukin-31. The roles of opioid receptors, other cytokines and proteinase-activated receptors have also been explored, but no one molecule or pathway has emerged as the predominant mediator of itch in AD. These neurophysiological and neuroimmune itch pathways have been recently reviewed in detail elsewhere (5,6). Histamine-independent cholinergic mechanisms of itch have also been postulated to play a role in AD itch. While significant progress has been made in understanding the itch of AD, these advances have not yet led to effective targeted therapies.

Measuring itch

One barrier to studying itch and the effect of therapy on itch is our inability to accurately measure it. The measurement of a patient's itch level has traditionally been assessed using a 10 cm visual analogue scale (VAS), similar to pain scales. More recently, measurement tools have been developed to measure the impact of pruritic skin conditions on a patient's quality of life, such as the Dermatology Quality of Life Index (7). Work from Rees and colleagues, however, has shown these subjective measures of itch do not correlate with objective measures of itch such as nocturnal scratching (8). Using scratch monitors placed on a patient's wrist (actigraphy) overnight, this group brought to light the inherent error in using subjective measurements of pruritus. They demonstrated discrepancies between subjective measures of itch and objectively recorded actigraphy activity (9,10). Increased actigraphy scores, independent of subjective pruritus scores, correlated with poor sleep quality. Their results support the importance of developing and using objective measurements of itch, and suggest that the relation between subjective and objective measures of disease severity may not be straightforward (8).

Overview of the treatment of itch in AD

Few studies have solely focused on itch as a primary outcome in AD therapy. Fortunately, many studies include itch as a secondary outcome or include itch as only a part of a composite score. The aim of this review is to summarize the literature regarding topical and systemic therapies routinely used in the management of AD with a focus on their effects on itch.

Search Methods

We performed a search of the English literature using PubMed for the highest quality and most recent systematic review for each subsection, turning to individual randomized control trials (RCTs) if no systematic reviews or summarized itch data were available.

Avoidance of Itch Triggers

The first and most simple intervention that should be recommended when attempting to treat the itch associated with AD is avoidance of provocative agents and environments. Itch triggers lead to immediate itching, not necessarily to flares of the disease (11). Lists of potential triggers of itch vary by source but several seem to have reached consensus (Table 1).

In general, the most commonly described provocative agents are heat, sweating, hot water, dust, irritants, xerosis, wool fibers, harsh soaps and emotional stress. In a survey of 100 Chinese patients with AD, daily life activities that increased the severity of itch were sweat in 96% of the patients' dryness in 71%, stress in 71%, physical effort in 73%, specific fabrics in 64% and hot water in 48% (12).

Pruritus induced by sweating is the most common trigger of itching in patients with AD (12–16). Measures often recommended to reduce sweating include wearing light breathable clothing to bed, as well as avoidance of hot environments. Pruritus induced by direct contact with wool fibers has been well described (17,18). How wool induces pruritus in AD is not entirely clear but seems to be related to the thickness of the fibers (19).

In our experience, patients often are aware of, and avoid, the factors leading to exacerbation of their pruritus. For those not aware of triggers, as is often the case with children, encouraging avoidance of the most common culprits may be helpful.

Topical Treatments

Corticosteroids

Topical steroids have been the cornerstone of treatment for AD since their introduction nearly 50 years ago (20–23). Use of these agents is recommended as a first line treatment for acute management of AD (24). Over 30 different topical steroids are available commercially giving the prescriber a wide range of vehicles and potencies from which to choose.

While the usefulness of corticosteroids in treating AD is well-established, relatively few studies have looked specifically at their usefulness in relieving the pruritus of AD. A systematic review published in 2000 by Hoare and colleagues identified 83 RCTs that evaluated the use of topical steroids in AD (25). Of the 83 RCTs identified in the systematic review, 39 evaluated pruritus; however, most of these studies combined pruritus scores into composite severity scores. We identified only seven studies from this systematic review that reported individual data for pruritus. Two RCTs compared topical steroids to a vehicle control and the remaining five compared two different topical steroids.

The two vehicle-controlled RCTs that reported data on pruritus found a significant improvement in itch in patients treated with topical steroids compared to the vehicle control (26,27). A study by Maloney and colleagues compared clobetasol propionate cream 0.05% (class 1) to vehicle in 81 patients with moderate to severe AD. By Day 4 a statistically significant improvement in pruritus was reported in the clobetasol-treated group when compared to the placebo-treated group, although the specific pruritus data were not presented. Physician-reported gross assessment at Day 43 showed 78% of clobetasol-treated patients were good, excellent, or cleared compared with 33% of placebo-treated patients (27). A second study by Wahlgren and colleagues evaluated betamethasone dipropionate cream 0.05% (class 3) versus vehicle in 30 adult patients with atopic dermatitis using a novel approach to measure itch (26). Each patient tracked itch using a device that prompted them every 60 minutes to log the presence and intensity of pruritus on a scale from 0–6. Patients reporting “no pruritus” on Days 3–4 was 35.8% during betamethasone and 21.5%

during placebo therapy. The onset of the antipruritic effect of betamethasone was rapid, with a statistically significant difference in pruritus noted between the two groups in the first 24 hours. They also noted that the intensity of itch seemed to be greatest in the mornings and evenings. (26).

When evaluating the five trials comparing two or more topical steroids, it appears that very mild steroids (i.e., class 7) are less effective at reducing pruritus than moderate (class 4–6) or high potency (class 1–3) topical steroids, while moderate and high potency topical steroids are similar in efficacy. Roth and Brown studied hydrocortisone valerate cream 0.2% (class 5) versus hydrocortisone cream 1.0% (class 7) in a prospective randomized, left/right parallel study. They reported improvement in both groups but noticed a statistically significant improvement in pruritus in the hydrocortisone valerate group when compared to the hydrocortisone group after 5–9 days, a difference that was maintained to the end of the study at 26–35 days. They did not notice, however, a statistically significant difference in reduction of pruritus between hydrocortisone valerate cream and betamethasone valerate cream 0.1% (class 5) (28). Similarly, Kaplan and colleagues found that betamethasone valerate 0.1% cream (class 5) was superior to hydrocortisone hydrophilic ointment 0.5% (formulation unclear) in reducing pruritus after three weeks. Mean pruritus was significantly reduced from 3.6 to 1.7 (scale of 0–5) in the hydrocortisone-treated group and from 3.7 to 0.7 in the betamethasone valerate group (29).

Other groups, however, found little difference in improvement in pruritus between different topical steroids. Stefon and Kyriakopolulos compared hydrocortisone valerate ointment 0.2% (class 4) with betamethasone valerate ointment 0.1% (class 3), triamcinolone acetonide ointment 0.1% (class 3) and fluocinolone acetonide ointment 0.025% (class 4) in a prospective randomized, left/right parallel study of 145 patients with mild to moderate AD. They reported that all four topical steroids reduced pruritus to similar degrees within three days (data not presented). In their study, hydrocortisone valerate ointment demonstrated similar efficacy when compared to more potent preparations in improvement over baseline in investigator-assessed pruritus, erythema, scaling, papulation, lichenification, and vesiculation (30). In two separate studies, Lassus compared aclometasone dipropionate cream 0.05% (class 6) versus hydrocortisone butyrate cream 0.1% (class 5) and clobetasone butyrate cream 0.05% (class 5). After two weeks of treatment, mean pruritus score was reduced from a maximum of 3.00 (scale of 0–3) from the start of the study, to a range of 0.05–0.25, with no significant between-group difference (31,32).

A recent systematic review by Sher published in 2012 meta-analyzed 6 RCTs examining topical steroid use in AD and found an estimated 34% overall reduction in itch (33). The data are difficult to interpret, as varying potencies of topical steroids were included. In addition, per their protocol, only partial data was included from one study examining twice-a-week application of topical steroid that showed an *increase* in pruritus with topical steroid use. The uncontrolled clearance phase of the study, not included in the analysis, showed a dramatic reduction in itch with topical steroids (34).

Topical calcineurin inhibitors

At the time of their introduction nearly 10 years ago, topical calcineurin inhibitors (TCIs) were the first new class of medication for the treatment of AD since the introduction of topical corticosteroids in the 1950s. The topical calcineurin inhibitors offered an alternative, targeted anti-inflammatory treatment without the side effects associated with corticosteroid use. The systematic review published in 2012 by Sher and colleagues identified 22 RCTs that assessed change in pruritus with TCI treatment using a VAS or 4-point ordinal scale. When compared to vehicle, TCIs had an estimated reduction of itch compared to placebo of approximately 36% (33). Therefore, TCIs do appear to significantly reduce pruritus in AD compared to placebo. The authors conclude that TCIs are the most effective topical therapy for improving pruritus, although no formal comparative analyses were reported. Therefore, it appears both topical steroids and TCIs improve itch in AD; however, there are not sufficient data in this meta-analysis to adequately compare treatments.

Relatively few studies compare treatment with topical corticosteroids to TCI therapy, and of those that do, an even smaller number include pruritus as an end point. In the few studies we identified that did compare these two topical treatments, the results varied based on the potency and frequency of application of both agents. Luger and colleagues compared different concentrations of pimecrolimus from 0.05% to 0.1% against vehicle alone and betamethasone valerate cream 0.1% (class 5) (35). While pimecrolimus improved pruritus more than vehicle, betamethasone valerate was more effective than pimecrolimus at any concentration in reducing pruritus (35). In a large RCT of 623 children, Reitamo and colleagues compared hydrocortisone acetate ointment 1% (class 7) applied twice daily with tacrolimus 0.03% applied either once or twice daily. They found that patient-reported itch and assessment of sleep quality improved during the treatment period for all three treatment groups, with no statistically significant between-group difference. However, the greatest improvement was reported by the patients applying 0.03% tacrolimus ointment twice daily, with patients experiencing a mean decrease in itch of almost 60% and a mean increase of 45% in sleep quality over the 3-week period (36).

Doxepin

Doxepin is a tricyclic compound and a potent, H1 and H2 receptor antagonist. Its antagonism of the H1 receptor is estimated to be 775 times that of diphenhydramine and 56 times that of hydroxyzine (37). It is used orally in the treatment of AD largely for its soporific effects (see oral antihistamine section). Given past studies that pointed to a possible role of histamine in AD pruritus, topical preparations of doxepin have been studied in AD. These topical preparations were shown to reduce pruritus in patients with AD (38). However, topical doxepin is not an appropriate therapy for the pruritus of AD, given the concerns for topical sensitization as well as systemic absorption and drowsiness (39,40).

Menthol

Studies have shown menthol-containing compounds to have some efficacy in relieving pruritus (41). Recently, menthol was found to activate a skin cold-sensing neuron receptor, TRPM8, explaining why menthol provides a cold sensation without actually cooling the skin (42). Other effects of menthol that may explain its antipruritic effects include activation of

k-opioid receptors and of A-delta fibers. Its efficacy in reducing the pruritus of AD has not been studied, but cooling of the skin from any source has been reported to help relieve the pruritus of AD. Menthol is usually used at a 1% concentration (43). Additional evaluation of the effectiveness of menthol at relieving AD induced pruritus is needed.

Cannabinoids

The cannabinoid system is an attractive target for therapy as interruption of this pathway could interfere directly with several itch pathways. Topical application of a synthetic cannabinoid, HU210, led to suppressed histamine-induced pruritus and reduced axon reflex erythema (44). Eberlein and colleagues showed improvement in pruritus in patients with AD who used a *N*-palmitoylethanolamine-containing cream (MimyX). This compound belongs to the *N*-acylethanolamine family, which is thought to down-regulate the inflammatory response via cannabinoid receptors. After six days of using the study cream, patient-reported pruritus was 45.6% lower compared with baseline and at study end, pruritus had diminished by 60%. They also reported a 57.6% reduction in physician-reported pruritus at study end when compared to baseline (45).

Systemic Treatments

Oral antihistamines

Antihistamines are commonly prescribed for the treatment of the pruritus associated with skin conditions with little data to support their use (46).

Traditional wisdom supports the use of antihistamines due to the presumed role of mast cell histamine release in pruritus, along with their sedative effect to lessen the scratching and subsequent skin barrier damage during sleep (47,48).

In 2000, a systematic review of 21 studies found that there are no RCTs demonstrating that sedating antihistamines have any clinical benefit in treating AD. They found limited and conflicting RCT evidence of less-sedating antihistamines (26). The Guidelines of Care for Atopic Dermatitis from the American Academy of Dermatology published in 2004 by Hanifin and colleagues stated there was little evidence that sedating or non-sedating antihistamines are effective in relieving itch in AD (49). Additionally, the safety of sedating antihistamine use in children has been called into question. A recent review on the safety of antihistamines in the treatment of allergic diseases points out that, despite diphenhydramine being available over-the-counter and widely used in children, practically all of the current treatment guidelines for allergic rhinitis and skin allergies do not recommend the use of first generation sedating antihistamines in children due to the sedative effects and danger of cognitive and developmental impairment (50).

Cyclosporine

Cyclosporine (CsA) was introduced as an immunosuppressant drug in the 1980s to prevent transplant organ rejection. It has subsequently been used in the treatment of inflammatory diseases, and was FDA-approved for the treatment of psoriasis and rheumatoid arthritis in 1997 (51). It has become a recommended first-line agent in the treatment of severe,

refractory AD. While not FDA-approved for the treatment of AD in the United States, it is the only immunosuppressant approved for the treatment of AD in the United Kingdom and Europe.

The ability for CsA to induce dramatic and rapid clinical improvement in AD has been clearly established, and available data supports the efficacy of CsA in the treatment of itch. In a systematic review and meta-analysis of the effectiveness of CsA in patients with severe AD by Schmitt and colleagues in 2007, all 15 studies included found a decrease in mean severity of AD after CsA treatment. After six to eight weeks of continuous CsA treatment, most studies found a reduction in mean severity of AD by about 50% (52).

Of the 15 studies included in this review by Schmitt's group, seven were RCTs. Of the seven RCTs, three included data on itch as an endpoint. All three demonstrated improvement of pruritus with CsA therapy. Extracting data from papers by Harper and colleagues and Pacor and colleagues on CsA dosed 3–5 mg/kg for six to eight weeks, pruritus improved in a range of 71–78%. This reflected a mean reduction of itch scores of 5 mm on a 10 mm VAS and a 0.8 step on a 1 to 3 itch scale (53,54). A paper by Czech and colleagues examining CsA dosed independent of body weight at either 150 or 300 mg daily for eight weeks demonstrated a reduction in pruritus of 50% and 54%, respectively (55).

Azathioprine

Azathioprine is an immunosuppressant FDA-approved for the prevention of rejection in renal transplantations and for refractory, severe rheumatoid arthritis. Its immunosuppressant effects have been utilized as a relatively inexpensive off-label treatment of a myriad of diseases since the 1960s, including Crohn's disease, ulcerative colitis, myasthenia gravis, malignancies, and autoimmune diseases.

We identified two RCTs from a systematic review by Schmitt and colleagues in 2007 and one RTC by Schram and colleagues in 2011 that measured itch as an endpoint in the treatment of AD with azathioprine (52,56,57). A 2006 double-blind RCT with 63 patients by Meggitt and colleagues examined azathioprine in AD dosed by thiopurine methyltransferase activity and found a mean reduction of itch score of 2.4 mm on a VAS scale in the azathioprine group (compared to 1 mm in the placebo group) at 12 weeks (58). The 2002 study by Berth and colleagues found a trend toward improvement of itch at 12 weeks, but the data was not significant (59). Schram and colleagues recently published the first head-to-head study comparing azathioprine to methotrexate (57). This RCT demonstrated similar statistically significant improvement of AD in both groups. The mean VAS itch scores decreased by 2.6 mm (SD 2.2 mm) in the azathioprine group at 12 weeks compared to 2.5 mm (SD 2.2 mm) in the methotrexate group.

Methotrexate

With more than 50 years of safety data, methotrexate has become an inexpensive alternative immunosuppressant used off-label by dermatologists for the treatment of many inflammatory skin conditions including atopic dermatitis, pemphigus, and pemphigoid (60).

We identified only one RCT evaluating methotrexate use in AD. As described above, Schram and colleagues published the first head-to-head study comparing methotrexate with azathioprine in patients with AD, demonstrating equal clinical efficacy and improvement of itch (57). Mean VAS itch scores decreased similarly in both groups at 12 weeks.

Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) is an immunosuppressant widely used to prevent transplant organ rejection. It is a reversible inhibitor of inosine monophosphate dehydrogenase resulting in inhibition of T- and B-cell growth. Only one RCT was identified examining MMF for AD. In 2011, Haeck and colleagues compared CsA to enteric-coated mycophenolate sodium (EC-MPS) in a randomized unblinded trial of 55 adult patients with severe AD (61). They noted a positive effect on VAS score itch, but did not publish the data. The authors concluded EC-MPS is as effective as CsA for maintenance therapy; however, seven patients in the EC-MPS group required prednisone rescue during the maintenance phase. Three of these seven patients required two courses. None of the patients in the low-dose CsA required prednisone during the maintenance phase.

Systemic corticosteroids

Systemic corticosteroids are excellent immunosuppressant and anti-inflammatory agents. They have wide reaching inhibitory effects on various white blood cells subsets and other immunologic cells including B cells, T cells, macrophages, fibroblasts, mast cells, and Langerhans cells. Despite an extensive well-known list of potential adverse effects, systemic corticosteroids are prescribed frequently in routine practice for patients with severe AD, despite lack of data demonstrating its safety and efficacy. To this end, Schmitt and colleagues recently conducted a double-blind placebo-controlled multicenter trial comparing 0.5 – 0.8 mg/kg/day prednisolone, tapered to 0 within 2 weeks, to CsA for severe adult eczema (52). They did not report the effect on itch as an endpoint in this study. This study was terminated early by recommendation from an independent data monitoring and safety board due to unexpectedly high numbers of withdrawals related to significant exacerbations of eczema in the prednisolone group. Almost all patients treated with prednisolone experienced a significant rebound after the end of the active treatment phase (62).

Interferon-gamma

Interferons have effects on multiple components of the immune system including antiviral, antiproliferative, and immunomodulatory activities. Interferon-gamma is a cytokine that plays a role in T cell-mediated viral pathogen destruction and *in vitro* has been shown to suppress IL-4-mediated IgE production and shift T cells to differentiate towards a type 1 subset. Atopic dermatitis was initially viewed as a purely type 2 helper T cell disease, which led people to hypothesize that interferon-gamma could correct the immunological imbalance by decreasing serum IgE and IL-4 levels (63).

A systematic review on the treatment of severe AD by Schmitt and colleagues in 2007 identified two RCTs demonstrating interferon-gamma was superior to placebo in the treatment of AD (52). Both of these RCTs included itch as an endpoint. Using an interferon-gamma dose of 1.5×10^6 IU/m²/day three times per week, Jang and colleagues found a

significant reduction in pruritus and Hanifin and colleagues found a mean percent improvement in itch scores of 35.1% (latter data not statistically significant) (64,65).

Other Treatments

Phototherapy

Prompted by the clinical observation that many patients with AD improve in the summer months, investigators began to use ultraviolet (UV) phototherapy in the management of AD (66). Following a study demonstrating successful treatment of AD with use of PUVA by Morison and colleagues in 1978 (67), many reports of improvement in AD with various UV modalities have been published. One systematic review identified nine RCTs evaluating the use of UV light in AD (68). Overall these studies demonstrated that UV phototherapy (UVB, UVAB, narrow band UVB, and high intensity UVA) can be useful for management of AD in certain circumstances (25,68). Most of these RCTs do evaluate itch but only as a part of a composite AD severity score.

One RTC by Reynolds and colleagues comparing nbUVB, UVA and placebo (visible light) evaluated itch separately from overall disease improvement. They found that the proportion of patients reporting reduction in itch over 24 treatments was 90% for narrowband UVB, 63% for UVA and 53% for placebo (69). Interestingly, one RCT comparing nbUVB and 8-MOP bath PUVA for 12 patients with severe AD noted that resolution of the skin lesions was preceded by relief of pruritus, which generally occurred within the first two weeks of treatment (70).

While improvement in AD severity with UV phototherapy has been shown, its utility in treating the pruritus of AD is less clear. Some studies, especially those using UVA1, report an increase in pruritus with treatment, at times leading to cessation of treatment (71). This could represent a response to the heat, a well-known trigger of pruritus in AD, generated during UV treatments. Likely, UV treatment leads to a temporary short-term exacerbation of pruritus in some while decreasing itching overall in the long-term. More studies are needed to investigate the role of UV phototherapy in the treatment of AD pruritus (68).

Alternative Therapy

Other non-traditional modalities such as acupuncture, acupressure, massage and field stimulation may be of some benefit (72), although there are few RCTs to support their use. Acupuncture has been shown to reduce histamine and allergen-induced itch in healthy volunteers (72–75) and in patients with AD (76). A recent RCT compared acupuncture with cetirizine in the ability to reduce type I hypersensitivity induced itch in patients with AD. Both interventions lead to significant reductions in type I hypersensitivity itch (77). Most promising, a recent RCT by Lio and colleagues randomized 15 patients with AD to receive either acupressure plus standard care or standard care alone. After four weeks they report a significant decrease in pruritus, measured by VAS, in the acupressure group when compared to the group receiving standard care alone (78). Massage is another potentially beneficial addition to traditional therapy. In a month-long RCT of 20 patients with AD, the group that

received a 20-minute daily massage plus standard therapy had a slight but significant reduction in pruritus when compared to patients that received standard therapy alone (79).

Future Directions

Therapeutic modalities that target specific mediators of itch in AD will undoubtedly be developed as the complex pathophysiology of pruritus is better elucidated. Several targeted treatments are currently being evaluated. These include agents such as transient receptor potential ion channel (TRPV1) antagonists/or agonists (80), mu-opiate receptor antagonists (81), kappa-opioid receptor agonists, PAR2 receptor antagonists, histamine-4 receptor antagonists, cannabinoid agonists, nerve-growth factor or nerve-growth factor receptor antagonists, and neurokinin-1 receptor antagonists. We eagerly await the development of novel therapeutics that target these newly recognized mediators of itch in AD.

Conclusions and Therapeutic Recommendations

While pruritus is the most distressing and interruptive symptom of AD, our review revealed that pruritus outcomes are infrequently reported. The data we reviewed support the use of anti-inflammatory therapy as the primary approach to pruritus in AD. Topical glucocorticoids appear to have the best anti-pruritic properties of all topical agents, with higher potency topical steroids having more potent antipruritic effects. Topical calcineurin inhibitors were also found to significantly improve pruritus. Although there are only limited data available, more potent topical steroids appear to better control pruritus than TCIs. These findings support a sequential approach to therapy based on controlling the inflammation of AD using a topical steroid of adequate potency for disease clearance followed by maintenance of the disease with TCIs and/or intermittent topical steroids (twice weekly) when appropriate (82). This treatment approach should allow for aggressive control of skin inflammation while delivering significant relief from pruritus.

Patients with disease refractory to aggressive topical therapy should be considered for systemic immunosuppressant therapy. Of the systemic therapies, our review identified cyclosporine as having the most potent antipruritic effect supporting the idea that inflammation is the key driver of pruritus in AD. The studies we reviewed also found significant antipruritic effects with the use of azathioprine, methotrexate, and interferon-gamma in AD, although the magnitude of the effect was modest with these agents. These data also support a sequential therapeutic regimen based on systemic immunosuppressant therapy. Cyclosporine should be used to gain acute control of the inflammation and pruritus followed by maintenance therapy with a safer systemic therapy such as methotrexate. Phototherapy, especially with NBUVB, may also be incorporated for the long-term management of itch. Acupressure and massage therapy may also be considered. These “alternative” treatments could address the often neglected role the central nervous system plays in itch perception, and may serve as a useful, safe adjunct in the management of pruritus. The use of systemic antihistamines cannot be recommended for controlling the itch associated with AD, although their use may be beneficial for managing allergic comorbidities. Consider more aggressive anti-inflammatory therapy if antihistamines are used primarily for their sedative effects.

In conclusion, the most effective therapies for the pruritus of AD primarily target inflammation. The data from topical steroid trials reveal that there is a direct relationship between the potency of the anti-inflammatory effect and the antipruritic effect. Thus, adequate control of the inflammation with topical or systemic immunosuppressant therapies will lead to the best improvement of itch in AD (Figure 1). We eagerly await new therapies and approaches that specifically target the itch of AD. Improved instruments to measure itch should be developed that take can evaluate both subjective and objective aspects of itch such as nocturnal scratching. Measuring and reporting pruritus should be a high priority for all clinical trials in AD moving forward.

References

1. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh). 1980; 92:44–47.
2. Williams HC, Burney PG, Pembroke AC, Hay RJ. The UK Working Party's Diagnostic Criteria for Atopic Dermatitis III Independent hospital validation. *Br J Dermatol*. 1994; 131(3):406–416.
3. Hafenreffer S, De pruritu. *Nosodochium, in Quo Cutis, Eique Adhaerentium Partium, Affectus Omnes, Singulari Methodo, Et Cognoscendi Et Curandi Fidelissime Traduntur*. Ulm. Typis & Expensis Balthasar. Kuhnlen. 1660:98–102.
4. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. *Br J Dermatol*. 2000; 142(6):1114–1120. [PubMed: 10848733]
5. Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? *Curr Allergy Asthma Rep*. 2008; 8(4):306–311. [PubMed: 18606082]
6. Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. *Allergy*. 2010; 65(7):805–821. [PubMed: 20384615]
7. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994; 19(3):210–216. [PubMed: 8033378]
8. Rees JL. Measurement of itch using actigraphy in pediatric and adult populations. *J Am Acad Dermatol*. 2004; 51:893–898. [PubMed: 15583579]
9. Murray CS, Rees JL. Are subjective accounts of itch to be relied on? The lack of relation between visual analogue itch scores and actigraphic measures of scratch. *Acta Derm Venereol*. 2011; 91(1): 18–23. [PubMed: 21103852]
10. Bringhurst C, Waterston K, Schofield O, Benjamin K, Rees JL. Measurement of itch using actigraphy in pediatric and adult populations. *J am Acad Dermatol*. 2004; 51(6):893–898. [PubMed: 15583579]
11. Langan S, Williams H. What causes worsening of eczema? A systematic review. *Br J Dermatol*. 2006; 155(3):504–514. [PubMed: 16911274]
12. Yosipovitch G, Goon AT, Wee J, Chan YH, Zucker I, Goh CL. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. *Int J Dermatol*. 2002; 41(4):212–216. [PubMed: 12031029]
13. Hanifin JM. Pharmacophysiology of atopic dermatitis. *Clin Rev Allergy*. 1986; 4:43–65. [PubMed: 3008974]
14. Beltrani VS. The clinical spectrum of atopic dermatitis. *J Allergy Clin Immunol*. 1999; 104(3 Pt 2): 87–98.
15. Hanifin JM. Basic and clinical aspects of atopic dermatitis. *Ann Allergy*. 1984; 52(6):386–393. [PubMed: 6145376]
16. Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: An overview. *Exp Dermatol*. 2002; 11(1):12–24. [PubMed: 11952824]
17. Bendsøe N, Björnberg A, Asnes H. Itching from wool fibres in atopic dermatitis. *Contact Dermatitis*. 1987; 17(1):21–22. [PubMed: 3652686]

18. Wahlgren CF. Itch and atopic dermatitis: clinical and experimental studies. *Acta Derm Venereol Suppl* (Stockh). 1991; 165:1–53. [PubMed: 1686130]
19. Fisher AA. Nonallergic “itch” and “prickly” sensation to wool fibers in atopic and nonatopic persons. *Cutis*. 1996; 58(5):323–324. [PubMed: 8934071]
20. Saeki H, Furue M, Furukawa F, Hide M, Ohtsuki M, Katayama I, Sasaki R, Suto H, Takehara K. Committee for Guidelines for the Management of Atopic Dermatitis of Japanese Dermatological Association Guidelines for management fo atopic dermatitis. *J Dermatol*. 2009; 36(10):563–577. [PubMed: 19785716]
21. Ellis C, Luger T, abeck d, allen R, Graham-Brown RA, de Prost Y, Eichenfield LF, Ferrandiz C, Giannetti a, Hanifin J, Koo JY, Leung D, Lynde C, Ring J, Ruiz-Maldonado R, Saurat JH. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICAAD II): clinical update and current treatment strategies. *Br J Dermatol*. 2003; 148(Suppl 63):3–10. [PubMed: 12694268]
22. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus Conference on Pediatric Atopic Dermatitis. *J Am Acad Dermatol*. 2003; 49(6):1088–1095. [PubMed: 14639390]
23. Tadicherla S, Ross K, Shenefelt P, Fenske N. Topical corticosteroids in dermatology. *J Drugs in Dermatol*. 2009; 8(12):1093–1105. [PubMed: 20027937]
24. Hanifin JM. Atopic dermatitisBroadening the perspective. *J Am Acad Dermatol*. 2004; 51(1):S23–S24. [PubMed: 15243497]
25. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess*. 2000; 4(37):1–191. [PubMed: 11134919]
26. Wahlgren CF, Hägermark O, Bergström R, Hedin B. Evaluation of a new method of assessing pruritus and antipruritic drugs. *Skin Pharmacol*. 1988; 1(1):3–13. [PubMed: 3272748]
27. Maloney JM, Morman MR, Stewart DM, Tharp MD, Brown JJ, Rajagopalan R. Clobetasol propionate emollient 0.05% in the treatment of atopic dermatitis. *Int J Dermatol*. 1998; 37(20):142–144. [PubMed: 9542676]
28. Roth HL, Brown EP. Hydrocortisone valerate Double-blind comparison with two other topical steroids. *Cutis*. 1978; 21(50):695–698. [PubMed: 348406]
29. Kaplan RJ, Daman L, Rosenberg EW, Feigenbaum S. Topical use of caffeine with hydrocortisone in the treatment of atopic dermatitis. *Arch Dermatol*. 1978; 114(1):60–62. [PubMed: 339846]
30. Sefton J, Kyriakopoulos AA. Comparative efficacy of hydrocortisone valerate 0.2 percent ointment in the treatment of atopic dermatitis. *Cutis*. 1983; 32(1):89–91. 94. [PubMed: 6349943]
31. Lassus A. Clinical comparison of alclometasone dipropionate cream 0.05% with hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis in children. *J Int Med Res*. 1983; 11(5):315–319. [PubMed: 6357892]
32. Lassus A. Alclometasone dipropionate cream 0.05% versus clobetasone butyrate cream 0.05% A controlled clinical comparison in the treatment of atopic dermatitis in children. *Int J Dermatol*. 1984; 23(8):565–566. [PubMed: 6389385]
33. Sher LG, Chang J, Patel IB, Balkrishnan R. Relieving the pruritus of atopic dermatitis: A meta-analysis. *Acta Dermato-Venereologica*. 2012; 92(5):455–461. [PubMed: 22773026]
34. Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol*. 2008; 158(4):801–807. [PubMed: 18284403]
35. Luger T, Van Leent EJ, Graeber M, Hedgecock S, Thurston M, Kandra a, Berth-Jones J, Bjerke J, Christophers E, Knop J, Knulst AC, Morren M, Morris A, Reitamo s, Roed-Petersen J, Schoepf E, Thestrup-Pedersen K, Van Der Valk PG, Bos JD. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. *Br J Dermatol*. 2001; 144(4):788–794. [PubMed: 11298538]
36. Reitamo S, Harper J, Bos JD, Cambazard F, Bruijnzeel-Koomen C, Valk P, Smith C, Moss C, Dobozy A, Palatsi R. European Tacrolimus Ointment group 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized, double-blind controlled trial. *Br J Dermatol*. 2004; 150(3):554–562. [PubMed: 15030341]

37. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. *Mayo Clin Proc.* 1983; 58(1):40–46. [PubMed: 6130192]
38. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream The Doxepin Study Group. *J Am Acad Dermatol.* 1994; 31(4):613–616. [PubMed: 8089287]
39. Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitisDoxepin Study Group. *Arch Dermatol.* 1995; 133(12):1403–1408. [PubMed: 7492129]
40. Shelley WB, Shelley ED, Talanin NY. Self-potentiating allergic contact dermatitis caused by doxepin hydrochloride cream. *J Am Acad Dermatol.* 1996; 34(1):143–144. [PubMed: 8543684]
41. Bromm B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neurosci Lett.* 1995; 187(3):157–160. [PubMed: 7624016]
42. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, Patapoutian A. A TRP channel that senses cold stimuli and menthol. *Cell.* 2002; 108(5):705–15. [PubMed: 11893340]
43. Patel T, Ishiuiji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol.* 2007; 57(5):873–878. [PubMed: 17498839]
44. Dvorak M, Watkinson A, McGlone F, Rukwied R. Histamin induced responses are attenuated by a cannabinoid receptor agonist in human skin. *Inflamm Res.* 2003; 52(6):238–245. [PubMed: 12835895]
45. Eberlein B, Eicke C, Reinhardt HW, Ring J. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). *J Eur Acad Dermatol Venereol.* 2008; 22(1):73–82. [PubMed: 18181976]
46. Weisshaar E, Szepletowski JC, Darsow U, Misery L, Wallengren J, Mettang T, Gieler U, Lotti T, Lambert J, Maisel P, Streit M, Greaves MW, Carmichael AJ, Tschachler e, Ring J, Ständer S. European guideline on chronic pruritus. *Acta Derm Venereol.* 2012; 92(5):563–581. [PubMed: 22790094]
47. Hanifin JM. The role of antihistamines in atopic dermatitis. *J Allergy Clin Immunol.* 1990; 86(4 Pt 2):666–669. [PubMed: 1699988]
48. Behrendt H, Ring J. Histamine, antihistamines and atopic eczema. *Clin Exp Allergy.* 1990; 20(Suppl 4):25–30. [PubMed: 1980856]
49. Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, Schachner LA, Sidbury R, Whitmore SE, Sieck CK, Van Voorhees AS. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD/American Academy of Dermatology Association “Administrative Regulations for Evidence-Based Clinical Practice guidelines.” *J Am Acad Dermatol.* 2004; 50(3):391–404. W1. [PubMed: 14988682]
50. Yanai K, Rogala B, Chugh K, Paraskakis E, Pampura AN, Boev R. Safety considerations in the management of allergic diseases: focus on antihistamines. *Curr Med Res Opin.* 2012; 28(4):623–642. [PubMed: 22455874]
51. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: Part 1. *J Am Acad Dermatol.* 2010; 63(6):925–946. [PubMed: 21093659]
52. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* 2007; 21(5):606–619. [PubMed: 17447974]
53. Harper JJ, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, Finlay AY, Wilson NJ, Graham-Brown RA, Sowden JM, Beard AL, Sumner MJ, Berth-Jones J. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol.* 2000; 142(1):52–58. [PubMed: 10651694]
54. Pacor ML, Di Lorenzo G, Martinelli N, Mansueto P, Rini GB, Corrocher R. Comparing tacrolimus ointment and oral cyclosporine in adult patients affected by atopic dermatitis: a randomized study. *Clin Exp Allergy.* 2004; 34(4):639–645. [PubMed: 15080819]
55. Czech W, Bräutigam M, Weidinger G, Schöpf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. *J Am Acad Dermatol.* 2000; 42(4):653–659. [PubMed: 10727313]

56. Schmitt J, Schäkel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. *Acta Derm Venereol.* 2007; 87(2):100–111. [PubMed: 17340015]
57. Schram ME, Roekevisch E, Leeftang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol.* 2011; 128(2):353–359. [PubMed: 21514637]
58. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomized controlled trial. *Lancet.* 2006; 367(9513):839–846. [PubMed: 16530578]
59. Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I, Hotchkiss K, Graham-Brown RA. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol.* 2002; 147(2):324–330. [PubMed: 12174106]
60. Denby KS, Beck LA. Update on systemic therapies for atopic dermatitis. *Curr Opin Allergy Clin Immunol.* 2012; 12(4):421–426. [PubMed: 22622476]
61. Haecck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol.* 2011; 64(6):1074–1084. [PubMed: 21458107]
62. Schmitt J, Schäkel K, Fölster-Holst R, Bauer A, Oertel R, Augustin M, Aberer W, Luger T, Meurer M. Prednisolone versus ciclosporin for severe adult eczema An investigator-initiated double-blind placebo controlled multicentre trial. *Br J Dermatol.* 2010; 162(3):661–668. [PubMed: 19863501]
63. Chang TT, Stevens SR. Atopic dermatitis: the role of recombinant interferon-gamma therapy. *Am J clin dermatol.* 2002; 3(3):175–183. [PubMed: 11978138]
64. Jang IG, Yang JK, Lee HJ, Yi JY, Kim HO, Kim CW, Kim TY. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *J Am Acad Dermatol.* 2000; 42(6):1033–1040. [PubMed: 10827410]
65. Hanifin JM, Schneider LC, Leung DYM, Ellis CN, Jaffe HS, Isu AE, Bucalo LR, Hirabayashi Se, Tofte SJ, Cantu-Gonzales G, Milgrom H, Boguniewicz M, Cooper K. Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol.* 1993; 28(2 Pt 1):189–197. [PubMed: 8432915]
66. Brehler R, Hildebrand A, Luger TA. Recent developments in the treatment of atopic eczema. *J Am Acad Dermatol.* 1997; 36(6 Pt 1):983–994. [PubMed: 9204066]
67. Morison WL, Parrish J, Fitzpatrick TB. Oral psoralen photochemotherapy of atopic eczema. *Br J Dermatol.* 1978; 98(1):25–30. [PubMed: 626712]
68. Meduri NB, Vandergriff T, Rasmussen H, Jacob H. Phototherapy in the management of atopic dermatitis: A systematic review. *Photodermatology, Photoimmunology & Photomedicine.* 2007; 23(4):106–112.
69. Reynolds NJ, Franklin V, Gray JC, Diffey BL, Farr PM. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomized controlled trial. *Lancet.* 2001; 357(9273):2012–2016. [PubMed: 11438134]
70. Der-Petrossian M, Seeber A, Hönigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J dermatol.* 2000; 142(1):39–43. [PubMed: 10651692]
71. von Kobyletski G, Pieck C, Hoffmann K, Freitag M, Altmeyer P. Medium-dose UVA1 cold-light phototherapy in the treatment of severe atopic dermatitis. *J Am Acad Dermatol.* 1999; 41(6):931–937. [PubMed: 10570376]
72. Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain.* 1997; 71(1):49–55. [PubMed: 9200173]
73. Pfab F, Hammes M, Bäcker M, Huss-Marp J, Athanasiadis GI, Tölle TR, Behrendt H, Ring J, Darsow U. Preventive effect of acupuncture on histamine-induced itch: a blinded, randomized, placebo-controlled, crossover trial. *J Allergy Clin Immunol.* 2005; 116(6):1386–1388. [PubMed: 16337477]
74. Belgrade MJ, Solomon LM, Lichter EA. Effect of acupuncture on experimentally induced itch. *Acta Derm Venereol.* 1984; 64(20):129–133. [PubMed: 6203300]

75. Lundeberg T, Bondesson L, Thomas M. Effect of acupuncture on experimentally induced itch. *Br J dermatol*. 1987; 117(6):771–777. [PubMed: 3426954]
76. Pfab F, Huss-Marp J, Gatti A, Fuqin J, Athanasiadis G, Irnich D, Ring J. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema - a blinded, randomized, placebo-controlled, crossover trial. *Allergy*. 2010; 65(7):903–910. [PubMed: 20002660]
77. Pfab F, Kirchner MT, Huss-Marp J, Schuster T, Schalock PC, Fugin J, Athanasiadis GI, Behrendt H, Ring J, Darsow U. Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis: a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. *Allergy*. 2012; 67(4):566–573. [PubMed: 22313287]
78. Lee KC, Keyes A, Hensley JR, Kwasny MJ, West DP, Lio PA. Effectiveness of acupressure on pruritus and lichenification associated with atopic dermatitis: a pilot trial. *Acupunct Med*. 2012; 30(1):8–11. [PubMed: 22207450]
79. Schachner L, Field T, Hernandez-Reif M, Duarte AM, Kraasnegor J. Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatr Dermatol*. 1998; 15(5):390–395. [PubMed: 9796594]
80. Ständer S, Weisshaar E. Medical treatment of pruritus. *Exp Opin Emerg Drugs*. 2012; 17(3):335–345.
81. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological disease. *J Am Acad Dermatol*. 1999; 41(4):533–539. [PubMed: 10495371]
82. Simpson EL. Atopic dermatitis: a review of topical treatment options. *Curr Med Res Opin*. 2010; 26(3):633–640. [PubMed: 20070141]

Figure 1.

Table 1

Triggering factors leading to pruritus in atopic dermatitis (AD)

ITCH TRIGGERS	EXAMPLES
Endogenous triggers	Perspiration
	Xerosis
	Physical exertion
	Emotional stress
Exogenous triggers	Warm environments
	Wool fibers
	Soaps, detergents
	Hot water
	Contact with allergens
	Flare of atopic dermatitis

Modified from Ständer S: Experimental Dermatology 2002; (11):12–24.