Itch, or pruritus, is the predominant symptom associated with acute and chronic cutaneous disease, and in some cases may be debilitating. To date, there is no single universally effective anti-itch treatment. Because the pathophysiology of itch in most cutaneous or systemic disorders remains unclear, antipruritic therapy is often directed against a variety of targets, including the epidermal barrier, immune system, or the nervous system. Topical therapy is the mainstay of dermatologic management of acute or localized itch or in patients with contraindications to systemic therapies. This review will summarize current topical therapies to treat pruritus and discuss potential future therapies.

Semin Cutan Med Surg 30:118-126 © 2011 Elsevier Inc. All rights reserved.

Itch, also known as pruritus, is defined as an unpleasant sensation evoking the desire to scratch. Despite being the major symptom associated with skin disease, our understanding of the pathogenesis of most types of itch is limited, and current therapies are often inadequate. Moreover, although the treatment of acute itch is usually straightforward, management of chronic itch frequently poses a therapeutic dilemma for many clinicians. Topical therapy remains the cornerstone in managing acute or localized itch, or more widespread dermatoses in patients in whom systemic therapy is less desirable because of polypharmacy, disease comorbidities, or other contraindications. Depending on the clinical scenario, patients may benefit from judicious use of different topical formulations that are directed at different cutaneous, immune, or neural targets. This review will summarize current topical therapies to treat itch and discuss emerging antipruritic therapies based on our growing understanding of itch pathophysiology.

**Moisturizers, Emollients, and Barrier Protection**

Moisturizers have long been used to maintain the integrity of the epidermal barrier and promote its protective function against dehydration, irritants, allergens, and infectious pathogens, all of which may precipitate itch and/or pain. Increases in transepidermal water loss, which suggest decreased barrier function, are associated with increased intensity of pruritus in atopic dermatitis (AD) and other itchy dermatoses (Table 1). Disturbances in the cornified layer in particular may be attributable to the loss of specific structural proteins, poor hydration, or may be multifactorial and lend to altered barrier protection.

Moisturizing is aimed at replenishing the cornified layer to restore normal barrier function, in part by rehydrating or “plumping” the corneocytes and by restoring the structure of the lipid bilayer of corneocytes within the lower stratum corneum. All commercially available moisturizer formulations contain a combination of humectants (which attract and hold water in the skin, e.g., glycerol, lactate, urea), occlusives (which prevent evaporation, e.g., petrolatum, mineral oil), and emollients (oils or lipids that provide partial hydration and occlusion, e.g., sterols, lanolin, glycol and glyceryl stearates). In general, moisturizers should be applied one to three times daily to xerotic skin and especially within minutes of bathing for optimal occlusion of a hydrated stratum corneum.

No particular moisturizer formulation has consistently proven superior to others for improving skin barrier function. In general, ointments or thick creams containing high lipid content are preferred over lotions or gels. Glycerol-based moisturizers have been shown to increase stratum corneum hydration and thickness and can alleviate inflammation and itch in atopic skin. Several nonsteroidal barrier creams, recently introduced on the market as “medical devices” for the treatment of AD, are thought to incorporate directly into the structural framework of the skin and are safe and effective in treating atopic pediatric and adult patients.
These formulations contain various combinations of lipids, such as triglycerides and free fatty acids, cholesterol, phospholipids, ceramides, squalene, and phytosterol, all of which are thought to reinforce the cornified layer scaffold. Barrier cream preparations may also contain hyaluronic acid or various humectants to hydrate corneocytes, as well as antiinflammatory agents, such as glycyrrhetinic acid, N-palmitoylthanolamine, and antioxidants. Although more comparative clinical trials are needed, several investigators suggest that pure petrolatum and lipid-containing creams are equally effective in repairing the skin barrier after experimental perturbation and in the setting of chronic dermatitis.8,9 Emollients rich in ceramides have also been shown to be effective in blocking transepidermal water loss and improving clinical disease scores.10

In addition to hydration and structurally barrier reinforcement, emerging agents may accelerate recovery from barrier damage via yet-unknown mechanisms. Application of capsaicin, a transient receptor potential vanilloid type 1 (TRPV1) antagonist, accelerates recovery from barrier damage in humans and can attenuate dermatitis-associated barrier damage in mouse models.11,12 Similarly, a newly developed prostanooid (ie, DP1) receptor agonist known as TS-022 can significantly accelerate the repair of the cutaneous barrier disruption caused by mechanical scratching.13 The exact mechanism by which these agents act to improve barrier repair is unknown, but such agents may soon be incorporated into moisturizers and may prove helpful in preventing exacerbations in various pruritic skin disorders.

**Topical Corticosteroids**

Topical corticosteroids (Table 2) are first-line therapy for acute pruritus associated with moderate-to-severe inflammatory skin diseases, such as AD, allergic contact dermatitis,
psoriasis, and lichen planus. Although the exact mechanism of action is not known, topical corticosteroids are thought to activate glucocorticoid receptors that inhibit cytokine activation, thereby decreasing local inflammation and indirectly controlling pruritus. Thus, although frequently used by health practitioners to treat patients with pruritus of unknown etiology, it must be emphasized that topical corticosteroids are of limited to no benefit in patients with non-inflammatory itch.

There are more than 30 different topical steroid formulations available in the United States, and these are prepared in different bases (eg, solution, lotion, cream or ointment). Topical corticosteroids range in potency from low (class VII) to high or ultrapotent (class I). It is generally accepted that the clinical efficacy to treat inflammation, and indirectly pruritus, correlates with steroid potency.

Optimal use of topical corticosteroids usually involves the use of medium to ultrapotent formulations on a daily to twice-daily basis for short courses lasting one to three weeks to pruritic areas or dermatitis on the trunk or extremities and lower-potency agents on the face or intertriginous areas. One study demonstrated that twice-daily application of fluocinonide 0.1% cream for three days was well tolerated by atopic patients and resulted in a 79% decrease in pruritus from baseline using the pruritus visual analog scale. A small pilot study in patients with pruritus from undefined etiologies demonstrated that topical application of hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% in a hydro lipid lotion reduced pruritus by 30% from baseline as rated by patients using the visual analog scale within 24 hours of initiation of therapy.

In various clinical scenarios, prolonged use of medium to ultrapotent topical steroids with close clinical monitoring may be indicated. A randomized, double-blind study demonstrated that twice-weekly application of fluticasone propionate, a medium potency steroid, in both cream and ointment forms, was sufficient to control relapses of rash and pruritus in atopic patients during a 16-week duration. Ultrapotent topical steroids, such as betamethasone dipropionate, are often used as first-line agents in prurigo nodularis, and when combined with occlusive bandages, are thought to be particularly useful to interrupt the itch–scratch cycle. Similarly, prolonged but localized application of potent topical steroids has been helpful at controlling pruritus associated with dermatoses affecting mucosal sites. For example, a double-blind, randomized trial comparing the effects of clobetasol 0.05% cream with pimecrolimus 1% cream in patients with vulvar lichen sclerosus showed a significant decrease in inflammation, pruritus, and burning with use of clobetasol once daily during a 12-week treatment period, and this was shown to be superior overall to pimecrolimus.

### Table 2: Topical Corticosteroid Formulations

<table>
<thead>
<tr>
<th>Potency Class</th>
<th>Corticosteroid Available Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (ultra high)</td>
<td>Clobetasol propionate 0.05% Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Halobetasol propionate 0.05% Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Augmented betamethasone dipropionate 0.05% Gel, ointment</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.1% Cream Ointment</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate 0.05%</td>
</tr>
<tr>
<td>II (high)</td>
<td>Betamethasone dipropionate 0.05% Ointment</td>
</tr>
<tr>
<td></td>
<td>Augmented betamethasone dipropionate 0.05% Lotion, cream</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone 0.25% Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Amcinonide 0.1% Ointment</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone 0.05-0.25% Gel, cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate 0.05% Cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide 0.05% Solution, gel, cream, ointment</td>
</tr>
<tr>
<td>III (medium)</td>
<td>Betamethasone dipropionate 0.05% Cream</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate 0.1% Ointment</td>
</tr>
<tr>
<td></td>
<td>Amcinonide 0.1% Cream</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.005% Ointment</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone diacetate 0.5% Ointment</td>
</tr>
<tr>
<td>IV (medium)</td>
<td>Hydrocortisone valerate 0.2% Ointment</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate 0.1% Lotion, cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide 0.1% Ointment</td>
</tr>
<tr>
<td>V (medium)</td>
<td>Betamethasone valerate 0.1% Cream</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate 0.05 Solution, cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone butyrat 0.1% Cream</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone valerate 0.2% Cream</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide 0.025-0.1% Cream</td>
</tr>
<tr>
<td>VI (low)</td>
<td>Alclometasone dipropionate 0.05% Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Desonide 0.05% Cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide 0.01% Solution, cream</td>
</tr>
<tr>
<td>VII (very low)</td>
<td>Hydrocortisone 0.5-2.5% Lotion, cream, ointment</td>
</tr>
</tbody>
</table>
The use of topical steroids should be limited and potentially avoided in cases of generalized cutaneous disease or prolonged daily treatment duration because of the risk of local side effects, including atrophy, striae, pigment alteration, acne, petechiae, telangiectasia, and the potential risk from systemic absorption, including hypothalamus-pituitary axis suppression. Although tachyphylaxis, defined as a decreasing response after administration of a few doses, has been demonstrated with use of topical steroids in several experimental settings, the clinical significance of this in pruritic disorders, such as AD and psoriasis, is unclear.19,20

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, are immunomodulators that have been shown to be effective in reducing pruritus in patients with AD, chronic irritant hand dermatitis, rosacea, lichen sclerosis, anogenital pruritus, and prurigo nodularis.21,22 The underlying mechanisms of the ability of TCIs to reduce pruritus are unclear and may be multifactorial. TCIs regulate T-cell activation and inhibit release of various inflammatory cytokines.23,24 Although initially thought to act solely via their antiinflammatory properties, TCIs may also mediate their antipruritic effects by activating and then desensitizing TRPV1 on peripheral nerves.30 Unlike topical corticosteroids, TCIs do not cause skin atrophy with prolonged use and are considered safe for use on facial, genital, and intertriginous skin. Moreover, studies on chronic use of TCIs in AD patients have revealed no significant risk of systemic immunosuppression or increase in rate of serious infections.33 In addition, although TCIs are only approved for use in adults and children >2 years old, retrospective studies of patients younger than two years with moderate-to-severe AD have demonstrated that use of tacrolimus ointment (0.1% or 0.03%) improved symptoms of AD with minimal systemic absorption and no significant adverse effects.37

Despite the Blackbox warning issued by the Food and Drug Administration in 2006 based on studies in animals and transplant patients, no prospective clinical studies demonstrate an overall increase in the risk of cancer in pediatric or adult atopic populations following use of TCIs.33,38 One retrospective cohort study found that the hazard ratio for T-cell lymphoma was 5.44 for users of topical tacrolimus, and slightly, but not significantly, elevated for users of pimecrolimus.39 There was no statistically significant increase in the risk for nonmelanoma or melanoma skin cancers.39 Ongoing longitudinal observational studies are being conducted to address the risk of lymphoma and long-term safety concerns with use of TCIs.

Topical Vitamin D Modulators

Topical vitamin D3 or its analogues, such as calcipotriol that has been used widely for the treatment of pruritus in some clinical scenarios. Vitamin D3 down-regulates cellular adhesion molecule expression by inhibiting tumor necrosis factor-α mRNA expression and influences keratinocyte proliferation and differentiation. In two randomized, double-blind clinical trials, twice-daily application of calcitriol ointment for eight weeks resulted in significant improvements in pruritus compared with vehicle ointment, in addition to reducing other symptoms of psoriasis.40 Topical vitamin D3 has also been reported to be effective in treating the intensely pruritic lesions of prurigo nodularis.41 A double-blind, right/left comparison of calcipotriol 50 mg g⁻¹ ointment and betamethasone valerate 0.1% ointment in the treatment of prurigo nodularis demonstrated that calcipotriol was more effective in reducing the size and number of prurigo nodules.42 Vitamin D3 has been shown to reduce the number of epidermal FcR1+ dendritic cells in prurigo lesions; however, the significance of this finding to understanding its antipruritic effects remains unclear. Finally, a randomized, double-blind right/left comparison study of calcipotriol and placebo creams in patients with polymorphous light eruption showed that twice daily application of calcipotriol for seven days before ultraviolet irradiation significantly decreased pruritus compared with placebo.43

Topical vitamin D3 analogues have been shown to be safe and well-tolerated in several short-term and long-term clinical trials. Pharmacokinetic studies in both healthy and psoriasis patients have demonstrated that topical calcitriol ointment produces little systemic absorption and does not alter systemic calcium or phosphorous metabolism significantly even when applied to approximately one-third of the body surface area.49
Topical Antihistamines

Topical antihistamines, although widely used to treat itch and available without a prescription, offer limited benefit in the treatment of pruritic conditions. In general, studies on topical antihistamines, including topical diphenhydramine, have been inconsistent, inconclusive or limited in design (small patient number, no placebo group, nonrandomized). Only topical doxepin, a tricyclic antidepressant and potent H1 and H2 antagonist, has been shown to significantly reduce pruritus in patients with AD, lichen simplex chronicus, contact dermatitis and nummular dermatitis. However, topical doxepin may cause localized burning, allergic contact dermatitis, and has been reported to cause drowsiness because of systemic absorption in up to 25% of patients. Thus, despite its potential benefit, use of topical doxepin is limited by its side effect profile and it is best avoided in children and used with caution in elderly patients.

Topical Neuromodulators

Topical anesthetics (Table 3), such as lidocaine 5% or the eutectic mixture of lidocaine 2.5%—prilocaine 2.5%. pramoxine 1%, and polidocanol 3%, have all been shown to have antipruritic effects and have been used successfully in several pruritic conditions. Lidocaine and prilocaine are both aminoamide anesthetics which inhibit sodium flux through voltage-gated sodium channels and thereby stabilize sensory fibers and block itch and pain sensation. Topical lidocaine alone or as a eutectic mixture with prilocaine has been used to effectively treat pruritus in patients with natalga paresthetica, pruritus ani, and postburn pruritus. Potential side effects of “Caine” anesthetics include paresthesias, allergic contact dermatitis (usually because of metabolites of aminoester formulations), and methemoglobinemia necessitating avoidance in infant and pregnant patients.

Pramoxine, which is thought to exert antipruritic effects by stabilizing membranes of sensory nerves, effectively decreases itch in patients with xerosis, uremic pruritis, and psoriasis and has been used as a single agent or in combina-
Topical antipruritic therapy

Future Therapies

As our understanding of the immune and neural pathophysiology of itch evolves, novel antipruritic therapies are emerging that may prove helpful in the treatment of both acute and chronic itch. Several topical and systemic agents that target receptors on the unmyelinated, polymodal C-fibers that initiate the sensation of itch in the periphery or on the spinal and supraspinal neuronal circuits that further relay this sensation have already shown promise in the treatment of different pruritic conditions.

Cannabinoid receptors, CB1 and CB2, are expressed on cutaneous sensory nerve fibers, mast cells and keratinocytes. When administered topically to patients via patch delivery, a cannabinoid receptor agonist reduced the severity of histamine-induced itch in humans. This effect was thought to be due to decreased neurogenic stimulation as opposed to decreased histaminergic activity because histamine-induced protein extravasation was still elevated in the skin as measured by microdialysis. N-palmitylolethanolamine, a cannabinoid receptor CB2 agonist, has been compounded into creams and shown to reduce pruritus within days in patients with AD, lichen simplex chronicus, prurigo nodularis, and urtic pruritus. Thus far, compounds with N-palmitylolethanolamine have been tolerated well with few to no side effects.

With the growing observation that members of the opioid receptor family modulate both pain and itch, opioid signaling has become a recent target for antipruritic therapy. In a pilot study of 18 patients with different chronic pruritic disorders, more than 70% of the patients using the µ-opioid receptor antagonist naltrexone in a topical 1% cream experienced a significant reduction of pruritus. A subsequent, randomized, placebo-controlled, crossover trial was performed with the same formulation in 40 patients with AD and demonstrated that naltrexone had an overall 29.4% better effect compared with placebo, with the ability to reduce itch to 50% within 46 minutes. Butorphanol, a combined µ-receptor antagonist and κ-receptor agonist that has shown considerable promise in the management of intractable pruritus, is currently administered as a nasal spray and is not available in a topical formulation.

Future antipruritic strategies may target other receptor families expressed in the skin and peripheral nervous system, including TRP family members as previously discussed, protease-activated receptor 2 (PAR2), neurokinin-1 receptors (NK1R), or interleukin-31 receptors. PAR2 is expressed by sensory nerve fibers in the skin and can be activated by mast cell mediators, such as tryptase or other endogenous or exogenous proteases. Activation of PAR2 elicits pruritus and scratching in animal models, and PAR2 expression appears up-regulated in afferent nerve fibers in lesional skin from patients with AD. Thus, PAR-2 antagonists may be a reasonable target to suppress peripherally induced pruritus.

Neurokinin-1 receptors are expressed by neurons in the dorsal horn, as well as by multiple cell populations within the skin, including keratinocytes, endothelial cells and mast cells. In response to binding substance P, NK1R stimu-
lates elaboration of proinflammatory cytokines in the skin and stimulates neural transmission of itch. A small pilot study recently demonstrated that treatment with the NKR1 antagonist apreptinant decreased pruritus in patients with prurigo nodularis, nephrogenic pruritus, Sézary syndrome, paraneoplastic and drug-induced pruritus.82 Finally, interest in targeting interleukin-31 signaling has grown in recent years because of observations that elevations in interleukin-31 are associated with severe pruritus and AD lesions in mice and humans.84,85 Because interleukin-31 receptors are expressed by primary sensory afferent neurons and keratinocytes in the skin, these may pose a reasonable target for novel topical antipruritic therapies.86,87

Conclusions

Chronic itch arising in the setting of primary cutaneous or systemic disease may be severe and incapacitating. Choosing the appropriate therapy must reflect an understanding of the pathogenesis of a given disease and must be individualized and optimized for a given patient. Although many of the topical antipruritic preparations have been shown to be effective within the highly regimented and monitored framework of the aforementioned clinical studies or trials, the practical use of these agents by individual patients may vary dramatically. To optimize patient compliance and therefore improvement in their symptoms, it is critical that patients have a realistic expectation of the timeline of therapy and potential side effects. This expectation is crucial with respect to topical agents with direct neuromodulatory effects, such as capsaicin, tacrolimus, greater concentrations of menthol, and others, because these can initially induce a burning sensation that frequently precipitates discontinuation. Although topical therapies are the cornerstone of antipruritic treatment, combining such therapies with systemic anti-itch agents may prove beneficial for more challenging cases involving generalized pruritus or pruritus because of systemic disease. Our armamentarium of antipruritic agents is growing, however more thorough investigation of older, established and newer emerging therapies must be performed, with an emphasis on double-blind, randomized, placebo-controlled or active comparator trials.

References

effective new possibility for treating chronic pruritus [in German]. Hautarzt 57:801-807, 2006


