Symposium 2: State of art: New treatment for moderate to severe atopic dermatitis

Treatment targeting itch in atopic dermatitis

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Like any eczematous skin disorders, itch is a crucial component of atopic dermatitis (AD). During the clinical course of recurrence and aggravation, itching itself plays a central role in 'vicious cycle' where scratching and inflammatory reactions are followed or preceded. Until now, the treatment of itch in AD is difficult as it is originated from multifactorial causes where antihistamine only works in a restricted manner. The quality of life in AD patients is significantly affected by itching (and scratching behavior) which induces psychosocial disturbances, thus we have to understand the many faces of itch in the pathophysiology of AD, and establish the strategy to manage this malady for long-term improvement of AD.

1. Characteristics of itch in AD

It is known that itch (pruritus) can be triggered by either endogenous or exogenous stimuli, which is perceived by afferent sensory nerve system of specific peripheral unmyelinated C-fiber. This small nerve fiber relays the signal into spinal level where sensory ganglion (dorsal root ganglion) directed to brain cortex area via opposite direction of spinothalamic tract. Precentral cortex, for example, or nearby areas of the cortex are associated with motor-cortex, thus the scratching reflex is initialized by interaction between sensory and motor cortex. It is also suggested that some cortical and subcortical regions can even modulate the itch response and itch-associated mood changes. Thus, the perception of itch and desire to scratch can be modulated under complex interactions of central nervous system, which is currently under investigations.

Itch signal is mediated with the so-called pruritoception pathway at different perception levels. For example, the gastrin-releasing peptide receptor in dorsal lamina plays a specific role in mediating itch sensation at the spinal cord level. The receptor for substance P (SP), the neurokinin-1 receptor, is also highly expressed in the same spinal neurons, which appears to be crucial for the transmission of itch signal

to the brain. Histamine is well-known cutaneous stimulators of itch, but proteases, neuropeptides, acetylcholine, cytokines, neurotrophins, platelet-activating factor, endothelin, and certain leukotrienes are also triggers in certain conditions. Moreover, enhanced nerve fiber plasticity and increased receptor density along with neuronal sensitization are also be involved in itch characteristics of AD.

Alloknesis, a touch evoked itch sensation which was seen in histamine injected in vivo model, is frequently observed at the peri-lesional or non-lesional skin of AD. Itch caused by non-pruritogenic light touch stimuli or minimal noxious stimuli suggesting the complex nature of sensory perception which is still poorly understood.

2. Systemic treatment of itch; Antihistamines, opioid modulators and others

Although histamine has been long known as a mediator of itch, it is not a major player in AD. Therefore, oral non-sedating antihistamines are believed not very effective against itch in AD. Evidence-based review of multiple randomized, placebo-controlled trials reported, anecdotally, sedating antihistamines can be more useful to reduce scratching at bedtime, thereby generating less eczema. Recently, histamine 4 receptor antagonist showed positive efficacy in pruritus of AD and asthma, yet further clinical data needs to be explored.

Opioids activate spinal μ-, κ-, and δ-opioid receptors, leading to analgesia, but they often induce or intensify itching sensations. The antagonists of μ-opioid receptor (MOR), which are also expressed in the skin, naltrexone and nalfamene have been tested in the treatment of itch in AD with variable results. Because of the lack of clear efficacy in controlled studies and many side effects such as dizziness, fatigue, nausea, vomiting, diarrhea, headache, cramps and etc, MOR antagonists should be recommended as second- or third-line treatment.

Certain medications like gabapentin, pregabalin (GABA analogue binds voltage gated calcium channels), amitriptyline (tricyclic antidepressant), mirtazapine (noradrenergic and specific serotonergic antidepressant), and paroxetine (selective serotonin reuptake inhibitor) may target itch through indirect or direct interaction with nerves and neurotransmitters. Immunomodulator (Cyclosporin A, etc.), antiemetic (Aprepitant), and biologics (Dupilumab, etc.) also shown to relieve itch symptom. However above described many therapeutic strategy is rather based on non-specific mode of action, so its action mechanism over itch pathogenesis in AD needs further investigation.

Ultraviolet light therapy (phototherapy) is a useful therapeutic option for AD for long time. Dermatologists have found effective wavelengths and types of phototherapy include ultraviolet B (UVB, narrow band UVB), ultraviolet a (UVA), ultraviolet A1 (UVA1), combined UVA/B, and psoralen plus UVA (PUVA). Various mechanisms of action have been proposed such as the reduction of epidermal nerve fibers, decreased IgE-binding and dermal mast cell numbers, inhibit Langerhans cell migration and less of

HLA-DR+ T cells in the skin of AD patients. Though phototherapy is believed as a relatively safe treatment, associated side effects are reported including erythema burning, pain, itching, tanning, hyperpigmentation, headache, nausea and increased risk of nonmelanoma skin cancers.

3. Treatment of itch with topical agents

The proper treatment of itch in AD can be performed by recognizing the complexity of itch where dermatologists must identify its triggering factors, and how to protect the skin barrier and control inflammations through topical and/or systemic therapeutic options. Known topical management of itch are as follows.

Doxepin, a tricyclic antidepressant with antihistaminic effects, is available as a 5% cream and is approved for the management of moderate pruritus in adult patients with AD. Clinical studies showed symptom relief of pruritus compared to placebo, and faster relief of itch when combined with topical steroids. But its effective potency in clinical practice seems not much strong to control itch, so it could be regarded as second- or third-line topical treatment for pruritus in AD.

Capsaicin, derived from natural alkaloids of hot chili peppers, induces neurogenic inflammation. Repeated capsaicin application leads the deletion of certain neuropeptide (SP, CGRP) in peripheral neurosensory junction and/or desensitization of TRPV1+ C fibers which eventually relieves the nociceptive perception such as itch. It also binds to the TRPV1 ion channel, which is a crucial receptor in the pain pathway. Topical capsaicin (0.025~0.075%) has been known to be effective in prurigo nodularis and severe itch in chronic kidney diseases.

Menthol, a natural compound of cyclic terpene alcohol, induces a prompt cooling sensation when applied to the skin. It is used as a gel, cream or patch for antipruritic efficacy, and acts on the TRPM8 channel which is a thermally sensitive receptor to innoxious cold. The antipruritic mechanism of menthol is short acting and overlapped with irritation (erythema and burning) where the activation of TRPM8 on C-fibers and/or direct stimulation of A-delta fibers or activation of κ-opioid receptors are inter-related. Although menthol appears to be a fairly safe product, it has been shown to lead to more transepidermal water loss than alcohol, so menthol formulation should not be used as a substitute for an emollient.

Interestingly, cooling skin in a water bath has been shown to reduce itch in AD patients, therefore, the cooling sensory evoke under well-regulated TRPM8 activation can be a promising candidate of antipruritic in AD. A novel TRPM8 agonist, cryosims have been developed with an improved bioavailability, duration of action and minimal irritation, thus its clinical efficacy is highly expected.

Other topical such as topical N-palmitoylethanolamine (PEA) and naltrexone have been tried to control itch in AD, and clinical trials showed some efficacy though the potency is not enough. Future double-blind, vehicle-controlled trials are needed to determine the true efficacy and safety of PEA creams.

4. Further consideration to control itch in AD

No matter what the details of complex pathogenesis stay behind in AD, itch and its abnormal perception should be managed adequately. The interaction between peripheral and central nerve system is not fully understood and somewhat beyond our understanding.

AD patients are suffered from both acute and chronic psycho-emotional stress, for example, depression, anxiety, fear and anger are highly associated with the vicious itch-scratch cycle which can eventually progress to psychosocial morbidity. In addition autonomic dysfunction or imbalance in AD needs to be further controlled, thus it is necessary to find the effective way of psychological intervention such as mental relaxation to control urges to scratch.

Besides neuropsychiatric drug therapy, some studies where the stress management group program based on the ABC model (awareness, balance, and control) and cognitive-behavioral treatment, autogenic training (biofeedback of self-relaxation) or combined education did show an improvement in itching intensity regardless of no significant difference in eczema severity. Overall, a meta-analysis of these various psychological techniques suggested that there is a strong evidence for such interventions in the future management of AD and associated itch symptom.

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