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Antihistamines in Psoriasis

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ABSTRACT

Psoriasis is polygenic, interleukin (IL)-17 and IL-23 driven chronic relapsing inflammatory multisystem disease caused by a complex interplay of endogenous and environmental factors. The most common and distressing symptom in psoriasis is itch, adding significantly to the burden of disease. Although histamine has historically not been considered a key itch mediator in psoriasis, there is some evidence from the literature that antihistamines may be effective to reduce itch in psoriasis. This review focuses on the role of antihistamines in the management of itch in psoriasis. The literature search included peer-reviewed articles published in English language (clinical trials or scientific reviews). Studies were identified by searching electronic databases (MEDLINE and PubMed) until January 2021 and by reference lists of respective articles.

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INTRODUCTION

Psoriasis is a polygenic, interleukin (IL)-17 and IL-23 driven chronic relapsing inflammatory multisystem disease caused by a complex interplay of endogeneous and environmental factors resulting in accelerated epidermal proliferation.[1] According to the World Health Organization (WHO), psoriasis is considered a serious global problem with at least 100 million individuals affected worldwide.[2] Itch is not only the most common cutaneous symptom in psoriasis affecting approximately 80% of patients[3,4] but also the most bothersome, adding significantly to the burden of disease. In most psoriasis patients, itch is associated with lesional skin, however, at times, it may be generalized.[3,5] Itch in non-lesional skin might indicate a subclinical inflammation, wherein normally innocuous stimuli elicit itch.[6,7] Hence, itching is important to address, not only to provide symptomatic relief, but also to prevent development of new lesions due to scratching-induced koebnerization.[8] Factors aggravating psoriatic itch are emotional stress, dry skin, sweating, and change of ambient temperatures. Itch frequently affects sleep quality, daytime performance, and quality of life, thus contributing to stress and aggravation of psoriasis.[9]

Pathogenesis of Itch in Psoriasis

The pathogenesis of itch in psoriasis is abundantly complex, multifaceted, and not yet fully elucidated. Various neuropeptides are released from keratinocytes, dermal cells, and dermal nerve endings resulting in neurogenic inflammation.[10] These include substance P (SP), calcitonin gene-related peptide (CGRP), β-endorphin, vasoactive intestinal peptide (VIP), somatostatin, and neuropeptide Y.[11] Downstream effects are hyperproliferation of keratinocytes, degranulation of dermal mast cells, and stimulation of angiogenesis. Downstream effects are hyperproliferation of keratinocytes, degranulation of dermal mast cells, and stimulation of angiogenesis.[8,11,12] It has also been hypothesized that itch in psoriasis arises due to abnormal skin innervation ("nerve sprouting"). Earlier studies have demonstrated elevated expression of nerve growth factor (NGF) and reduced expression of semaphorin-3A in lesional skin. This may act as a trigger for increased innervation of lesional skin by pruriceptive C fibers, resulting in itch.[13] The endogenous opioid system has also been postulated to be involved in the itch pathway in psoriasis.[14] Lesional skin was found to have more μ-opioid and less κ-opioid receptors, a

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dysbalance resulting in itch.[14] Other mediators which have been postulated to be involved in the pathogenesis of psoriatic itch are: E-selectin, γ-aminobutyric acid (GABA), vascular adhesion protein 1 interleukin (IL)-2, IL-31.[4,8,15,16] Although histamine is not a key mediator in psoriatic itch as compared to diseases like urticaria, mastocytoses,[4,17,18] there is evidence to support the assumption that antihistamines could play a role in treating itch in psoriasis patients.

1. Levels of histamine are elevated in lesional skin of patients with psoriasis,[19] and there is evidence of a direct mast-cell nerve interaction in psoriasis lesions.[20–22] Mast cells aggravate itch in chronic lesions of psoriasis by secreting proinflammatory mediators.[23]

2. In a double blind, placebo-controlled study, the H1-antihistamine cetirizine was found to significantly reduce expression of tryptase-positive mast cells and adhesion molecules in psoriasis.[24] A possible anti-inflammatory effect of anti-histamines was hypothesized by the authors.[24]

3. Studies have detected histamine receptor H (HRH)1, HRH2 and HRH4 mRNA expression in CD4+ T cells that were polarized to Th17 cells in the presence of IL-1β and IL-23.[25] It has been postulated that elevated histamine levels in psoriatic skin targets the HRH4 on T cells, which further leads to an increase of IL-17, thereby exacerbating the inflammatory process.[26]

4. H1-receptors are also widely distributed throughout the central nervous system, 1st generation H1-antihistamines shown to inhibit itch processing in regions such as the thalamus and cingulate gyrus, a finding that might be irrespective of the cutaneous condition present.[27–29]

5. During periods of stress, mast cells are activated to release histamine, potentially leading to direct activation of histaminergic itch pathways.[30,31] Even physical stressors like heat, UV radiation, physical exertion has been linked to upregulation of mast cells and release of histamine. However, whether this contributes to aggravation of itch in psoriasis needs further evaluation.[32]

Management of Pruritus

Therapy of itch in psoriasis is challenging as there is no single drug that has been found to be specifically effective. General measures to control itching include application of (polidocanol or menthol-containing) emollients, advice to wear light and loose cotton clothes, and avoid very hot baths.[34] Topical therapy includes capsaicin, calcineurin inhibitors such as tacrolimus, pimecrolimus, topical corticosteroids, salicylic acid, and topical anesthetic pramoxine. Systemic drugs include– methotrexate, cyclosporine, biologicals like adalimumab, etanercept, ustekinumab, secukinumab, JAK inhibitors– tofacitinib, phosphodiesterase-4 (PDE-4) inhibitor apremilast. Neuromodulators such as gabapentin, pregabalin, the μ-opioid atagonist naltrexone or antidepressants such as mirtazapine or sertralin might help to treat psoriatic itch in treatment refractory cases.[35,36] Currently, neurokinin-1 receptor antagonists are being evaluated for the management of pruritis in psoriasis.[37] Phototherapy (NBUVB, PUVA) therapy usually reduces itching effectively in many patients while in some patients might experience worsening due to phototherapy-induced skin dryness.[38] The various topical, systemic, and UV-based treatment options mentioned above usually do relieve itch, but only after a delay of weeks to months. As a result, treatment of itch, especially during acute exacerbations, is often dissatisfying.[39] Although histamine is not found to have a major role in the pathogenesis of itch, antihistamines, especially first-generation, are the most commonly prescribed drugs to patients to alleviate itch. They are thought to be effective mainly due to their sedative potential rather than histamine receptor blockade.[2,40,41] Previous studies[2] evaluating the role of histamine in psoriatic itch have shown variable results: A double-blinded placebo-controlled study by Domagala et al reported a higher itch reduction in patients receiving clemastin twice daily (first-generation anti-histamine) as compared to levocetrizine 5mg once daily (second-generation antihistamine), and no significant improvement was found in the placebo group.[42] An open label pilot study by Mueller et al showed a significant improvement of itch intensity, itch-related quality of life, anxiety and stress within only five days of treatment with levocetirizine 5–10 mg daily.[32,33] This may reemphasize how closely itch, quality of life, and psychosocial aspects are linked in psoriasis patients.[32] In a study by Stinco et al, 240 patients were enrolled to study aggravating and relieving factors in psoriasis. 184 patients (80%) were found to suffer from pruritus, 45 patients of whom (24.5%) used anti-histamines, but only approximately a third experienced some short symptomatic relief.[43] The authors stated that this very limited antipruritic effect of antihistamines in psoriasis may be explained by the fact that many pruritogens play a role in psoriatic itch with histamine being just one of many. In other studies, itch intensity and histamine plasma levels in psoriasis patients have not been associated, and no difference was found in histamine plasma levels between psoriasis patients with and without psoriasis.[4,22,44] (Table 1)

CONCLUSION

Although antihistamines were reported to be the most commonly used medications to relieve itch in psoriasis, data on their antipruritic efficacy are still conflicting. Additional basic research on the pathogenesis of psoriatic itch as well as prospective placebo-controlled clinical trials are warranted to better define the role of histamine and the use of antihistamines in psoriasis patients.

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TABLE 1.

Most Relevant Studies Published on Antihistamines on Psoriasis		
Studies	**Antihistamine Used**	**Result**
Domagala et al[42]	Clemastine 1mg BD in 1st group Levocetrizine 5mg OD in 2nd group	Anti-pruritic efficacy of Clemastine > Levocetrizine> placebo
Mueller et al[33]	Levocetrizine 5 mg	Effective
Mueller et al[32]	Levocetrizine 5–10 mg	Effective
Stinco et al[43]	Class of antihistamine unspecified	34.5% of patients experienced short term symptomatic relief.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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