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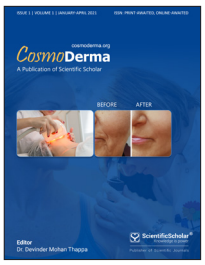

Perspective

Scratching the surface: Unveiling the complex interplay of itch and psoriasis through contemporary research

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ABSTRACT

The long-lasting presence of itch is an unbearable symptom for people with psoriatic disease, having a profound effect on their quality of life. The itch experience in psoriasis is complex and multifaceted. It is underpinned by neuroimmune interactions, skin barrier dysfunction, and central sensitization pathways. While it has recently been realized that there are neuroimmune interactions in the pathophysiology of itch, tackling chronic itch still proves to be a challenge. The aim of this Perspective Article is two-fold: to assess the novel optimal management strategies for psoriasis-associated itch, while considering the mechanisms of itch in psoriasis and future directions for research.

Keywords: Psoriasis, Chronic itch, Patient-reported outcomes, Quality of life, Biologics, Janus kinase inhibitors, Dermatology, Patient-centered care, Digital health, Treatment adherence

INTRODUCTION

Psoriasis is a life-long, chronic inflammatory skin disorder characterized by erythematous plaques and scales. Although patients with psoriasis are known for its visible symptoms, pruritus or chronic itch is often considered as one of the most troublesome symptoms experienced.[1] What frequently aggravates itch in psoriasis is that it can be bothersome as it contributes significantly to the burden of illness and impacts the overall quality of people's lives.[2] Previously, management strategies for psoriasis have focused on lesion reduction and the control of inflammation, with less consideration for treating itch specifically.[3] However, with the recognition that chronic itch has biological mechanisms underpinning it, the coherent need for management strategies has begun to take shape.[4] In this article, we explore the most recent understanding of itch mechanisms in psoriasis, while also reviewing current management strategies and interventions in the contemporary management of itch.[5]

MECHANISMS OF CHRONIC ITCH IN PSORIASIS

Neuroimmune interactions

The neuroimmune axis plays a key role in the pathophysiology of chronic itch in psoriasis.[6] In recent years, numerous studies have begun to unravel the putative interactions between innate and adaptive immune cells' needs, cytokines, and sensory neurons, thereby suggesting a complex interplay of immune cells and other factors in the perception of itch which eventually leads to

chronic itch.[7] Cytokines and sensory neurons: Cytokines namely interleukin (IL)-31, IL-33, and thymic stromal lymphopoietin (TSLP) have in recent times emerged to be pivotal mediators of itch in psoriasis.[8,9] IL-31 is produced by activated T-cells and mast cells. It exerts its effects directly on IL-31 receptors located in sensory neurons. This interaction activates Janus kinase (JAK) signaling pathways within the neuron, ultimately producing the itch sensation.[10] IL-33 and TSLP are also involved in more optimal immune activation to further enhance pruritus through the release of additional pruritic cytokines.[11]

JAK-STAT pathway

The JAK-STAT signaling pathway is essential in mediating the pruritogenic cytokine effects on sensory neurons.[12] Inhibition of this very pathway is currently considered as an optimal therapeutic approach. This is because JAK inhibitors were shown to be beneficial in reducing chronic itch.[13] These inhibitors block the phosphorylation of STAT proteins, thereby blocking the transcription of itch-associated genes.[14]

Peripheral sensitization

Finally, the chronic inflammatory context of psoriatic skin results in the sensitization of peripheral sensory neurons, known as peripheral sensitization, causing an exaggerated itch response to increased stimuli.[15] The main mediators of sensory neuron activation involved in this peripheral sensitization are nerve growth factor which activates the sprouting of nerve fibers into inflamed skin,[16] and transient receptor potential (TRP) channels – primarily TRPV1 and TRPA1 that are stimulated by pruritogens – contribute to itch signal transduction.[17]

Skin barrier dysfunction

The barrier function of the skin is crucial in limiting the penetration of irritants and allergens that can trigger itch.[18] The skin barrier is more often than not inactive in psoriasis, leading to transepidermal water loss and sensory nerve endings exposed to the environment.[19]

Altered lipid composition

The lipid composition in psoriatic skin is altered, relating to lower values of ceramides and the free fatty acids that are necessary to support barrier function.[20] This deficiency of lipids compromises the barrier and allows for deeper penetration by pruritogens such as histamine and proteases to accelerate the activation of sensory neurons.[21]

Protease-activated receptors (PAR-2)

PAR-2 is present in keratinocytes and sensory neurons and is involved in responses to itch.[22] In psoriatic skin, proteases, for example, tryptase and kallikreins, protectively activate PAR-2 resulting in the release of inflammatory mediators and direct activation of sensory neurons, driving augmenting itch, particularly with a disrupted skin barrier.[23]

Filaggrin deficiency

Filaggrin is a key protein for skin barrier repair. Filaggrin gene mutations have been linked to barrier dysfunction and chronic itch susceptibility in psoriasis.[24] Filaggrin deficiency leads to impaired keratinocyte differentiation and accumulation of pruritogens in the stratum corneum which drives itch [Appendix A].

Central sensitization

Chronic itch related to psoriasis is not solely peripheral, as central sensitization can impact the persistence and amplification of pruritus.[25] Central sensitization here refers to a heightened responsiveness of neurons in the central nervous system (CNS) to unexpected stimuli from the peripheral physiology leading to a greater itch.[26]

Neurotransmitter imbalance

In psoriasis, there are inflammatory cytokines such as IL-31 and tumor necrosis factor-alpha (TNF-α) which amplify neurotransmitter substances such as substance P and histamine that mediate itching. It presents a disparity that boosts the itch sensation by increasing the sensitivity of sensory neurons as well as the itch pathways. Chronic itching disorders display altered concentrations of neurotransmitters, including substance P, glutamate, and gamma-aminobutyric acid, within the CNS. The neuropeptide substance P specifically is critical for transmitting scratch signals from the external surface to the spinal cord and brain.[27] Many patients are found to have heightened levels of substance P and its receptor, neurokinin-1 receptor (NK1R), in chronic itch disorders, which stipulates the participation of central sensitization in psoriasis-related pruritus.[28]

Spinal cord plasticity

Chronic itch associated with psoriasis leads to central sensitization in the spinal cord. This involves an enhancement in neuronal excitability and a drop in the threshold for itch stimuli. The spinal cord's plastic transformations make neurons more reactive and modify neural circuits, leading to persistent and exaggerated itch sensations. The chronic activation of itch pathways is associated with tissue and functional adjustments in the spinal cord, collectively termed spinal cord plasticity.[29] This phenomenon is illustrated by the alleviation of receptors and ion channels that enforce/resist itch transmission, in addition to the recruitment of non-itch pathways, such as pain, into the itch circuit. As a

result, itch networks undergo hyperexcitability, where minor stimuli propel itch, for instance.[30]

Cortical reorganization

The non-cognitive dimension and brain correlates of itch are also aspects of chronic itch.[31] Chronic itch is also linked with the reorganization of cortical areas that are authoritative for sensory processing. Neuroimaging has examined the activation of the somatosensory cortex, anterior cingulate cortex, and insula involved with processing itch and chronic itch displays significant aberration in the broad formulation of itch.[32] Cortical reorganization represents evidence for the persistence of itch and how the emotional fundamental accords to chronic itch in psoriasis.[33]

CURRENT AND INTERVENTIONAL MANAGEMENT

Topical therapy

Topical therapies exist at the forefront of treatment for governing chronic itch in psoriasis as they address itching directly to the skin and have demonstrated a significant rebate in local inflammation.[34]

Topical corticosteroids

Topical corticosteroids persist to be effective therapies for itch associated with psoriasis.[35] These agents act through a multitude of mechanisms, primarily through the inhibition of proinflammatory cytokines, preventing immune cell infiltration within the skin, and interfering with pathogenic Immunoglobulin E responses.[36] However, long-term use of high-potency corticosteroids may result in adverse outcomes, including skin atrophy, tachyphylaxis, and rebound flares requiring emergent steroid-sparing agents.[37]

Calcineurin inhibitors

Topical calcineurin inhibitors (TCI: Tacrolimus, pimecrolimus) are effective alternatives to corticosteroids to treat itch in sensitive areas including facial and intertriginous regions.[38] TCIs act by inhibiting T-cell activation and the proliferation of pruritogenic cytokines responsible for inflammation and itch. The addition of a TCI with a high-potency topical corticosteroid is noted to enhance efficacy while also dampening the risk of adverse effects when compared to topical corticosteroid application alone.[39]

Vitamin D analogs

Calcipotriol and calcitriol are frequently used in the administration of psoriasis due to their competence to target keratinocyte differentiation and inflammation and these agents also apply to the treatment of chronic itch by normalizing epidermal proliferation while reducing imbalance,[40] or dysfunction of the skin barrier. Recent formulations containing a topical corticosteroid and Vitamin D analog could contribute to both an anti-inflammatory agent and assisted skin restoration.[41]

Barrier Repair therapies

Given the role of barrier dysfunction in the pathobiology of chronic itch, overhaul strategies to restore barrier integrity are an important differential therapeutic approach to consider therapy in patients with chronic itch.[42] Emollients and moisturizers containing lipids such as ceramides and free fatty acids aid in the repair of the integrity of the skin barrier and reducing transepidermal water loss, and topical agents that enhance epidermal barrier, such as urea and lactic acid are acclaimed to reduce chronic itch as observed by improvised skin hydration and barrier function against irritating agents.[43]

Systemic therapies

Deeply rooted in immune-mediated methods for moderating lesion activity to control itch, moderate-to-severe psoriasis systemic therapies are often required to achieve adequate control of symptoms including itch.[44]

Biologics

Recent research highlighting biologic agents directly targeting specific cytokines embroiled in the pathophysiology of psoriasis such as TNF-α, IL-17, and IL-23 has changed the treatment of this disease.[45] These agents not only hamper skin disease severity but also treat the related pruritus (itching) that occurs with psoriasis by modulating the underlying immune physiology.[46] More recent studies, particularly some of the newer biologics, have hinted that IL-31 plays an important role in inducing itch and led to new biologic drugs that selectively inhibit IL-31 mediators. Biologics, targeting the IL-31 pathway, like nemolizumab, have shown efficacy in reducing chronic itch in psoriasis patients.[47]

JAK inhibitors

JAK inhibitors are a new class of systemic therapies for chronic itch in psoriasis. These agents act by blocking the JAK-STAT signaling pathway, preventing the transcription of itch genes after JAK-STAT receptor phosphorylation and reducing the activation of sensory neurons.[48] Tofacitinib and upadacitinib are both effective in curing chronic itch and reducing skin lesions associated with psoriasis. Although longer-term safety studies are needed to understand the role of JAK inhibitors in chronic itch, they persist as a novel option for managing chronic itch in psoriasis patients.[49]

Neuromodulators

Due to central sensitization associated with chronic itch, neuromodulators such as gabapentin and pregabalin have been researched as potential treatment modalities. Neuromodulators act by inhibiting the release of excitatory neurotransmitters (e.g., glutamate) and reducing CNS neuron hyperexcitability. Neuromodulators are particularly useful for patients who have refractory itch that has not responded to traditional therapies but they are often limited due to associated side effects (e.g., sedation and dizziness).[50]

Oral antihistamines

While we frequently use antihistamines for itch relief, we often see finite efficacy in patients with psoriasis due to the non-histaminergic nature of their itch. Sedating antihistamines like hydroxyzine can be effective for managing itch associated with improved sleep, especially at night. Recently, antihistamine therapy has evolved to utilize non-histaminergic pathways.[51]

Photobiomodulation

Photobiomodulation is still a key component in the treatment of chronic itch in psoriasis. Ultraviolet (UV) light treatment, both narrowband UVB (NB-UVB), and psoralen plus UVA (PUVA), utilizes an anti-inflammatory response by inducing T-cell apoptosis and regulating cytokine production.[52]

NB-UVB treatment

The NB-UVB treatment is the most prevalent photobiomodulation treatment in psoriasis, and there is evidence that it can reduce skin lesions and the associated itch. The exact mechanism of NB-UVB and its effects on the itch response is poorly understood but is adhered to associate inhibition of inflammatory mediators, including IL-17 and IL-23, and a reduction in sensory nerve density within the skin.[53] NB-UVB is also very well tolerated, although the peril associated with long-term use may lead to skin aging and skin carcinogenesis, requiring diligent management.

PUVA treatment

PUVA treatment includes either the adhesion of a photosensitizing agent (psoralen) or the generation of UVA light after ingestion. PUVA treatment is more effective in patients with moderate and severe psoriasis who were otherwise unresponsive or intolerant to other treatments with chronic itch.[54] The mechanism of action for PUVA is associated with inducing DNA damage, leading to T-cell apoptosis and mediated inflammation. PUVA also links an uncertainty of the formation of skin neoplasia and requires management and strict follow-up based on the risk involved.[55]

Nouveau treatment options

With further investigation into the structure of chronic itch due to psoriasis, treatment options targeting specific pathways for generating pruritus have been developed.

IL-31 blockage

IL-31 blockage appears to be an enticing option for managing chronic itch with itch-controlling IL-31 blockers emerging, such as nemolizumab. These treatments inhibit the receptor to block interactions with IL-31 in sensory neurons assisting in itch relief without impacting the immune system. Clinical trials with nemolizumab showed a significant reduction in the severity of itch for patients with atopic dermatitis, and studies for the effect of psoriatic itch are ongoing.[56]

TRP channel modulators

TRP channels are a family of ion channel proteins that are present in the cellular membranes in a wide range of tissues. This group is generally engaged in the realization of perception from heat-cold, painful sensations, and chemical factors that may be present. TRP channels, specifically TRPV1 and TRPA1, play a key role in mediating the transmission of itch signals. TRP channel modification is a new paradigm for treating the sensation of itch. TRP channel antagonists, such as capsaicin and camphor, have been used topically to reduce itch by desensitizing sensory neurons.[57] New therapeutics targeted at TRP channels are being researched for systematic pruritus due to their potential to eliminate chronic itch more effectively, and their duration of effect may be longer than any existing therapies.[58]

NK1R antagonists

Anti-NK1R antagonists, such as aprepitant, have been studied to treat chronic itch due to the blocking action of substance P and subsequent anti-nociceptive effects of the NK1R antagonists. Aprepitant has been trialed for itch in an array of chronic pruritic situations, including psoriasis; however, the utility of this therapy and others in this class of NK1R antagonists does have limitations of adverse effects including nausea and vomiting [Appendix B]. Future efforts are aimed at creating a selectively acting NK1R antagonist to improve the adverse side effect profile.[59]

NOVEL FINDING

The neuroimmune itch loop: A novel conceptual model

Chronic itching due to psoriasis is a complex issue involving diverse pathways in its often unidentifiable or neglected etiological components. We now propose a novel concept: The "Neuroimmune Itch Loop." This model is proposed as an

index of chronic pruritus intensity and perpetuation of itch in psoriatic patients by maintaining a sustained bidirectional relationship between immune mechanisms and sensory sensitization.

Immunogenic activation-nerve sensitization

The neuroimmune itch loop is predominantly organized within the concept of cross-talk between immune cells and sensory nervous system neurons. In the case of psoriasis, T-cells and mast cells dispense cytokines, such as IL-31, IL-33, and TSLP, that bind to the respective receptors on sensory neurons, which then activate a chain of cellular processes that lead to the sensation of itch. The activated sensory neurons, which with activation also release genes promoting the production of peptides such as substance P, can reciprocate stimulation of immune cells. The effects of cross-talk in immunogenic activating and nerve sensitization represent a circular pathway whereby immune mechanisms lead to nerve sensitization, and nerve sensitization leads to further immune-mediated itch.[60,61]

Maintenance of chronic itching

Overall, the neuroimmune itch loop is a concept for understanding why pruritus from psoriasis is chronic and challenging to manage. Concurrently during the neuroimmune itch loop, there is a continuous cycle of repopulation of immune cells, the inductive release of additional immune-derived pruritic cytokines, and sensory nerve depolarization and ultimately nerve "hyperactivity" whereby the threshold for itch signaling can occur after small, minimal stimuli are considered. Essentially, the loop will continuously rotate circularly, spawning persistent pruritus associated week to week and month to month in the case of psoriasis, and therefore disposition of basic treatments on targeting itch as the singular outcome.[62,63]

Therapeutic implications

Targeting the neuroimmune itch loop represents a new treatment paradigm in chronic itch management in psoriasis. JAK inhibitors that interrupt the cytokine signaling cascade and neuromodulators that mitigate neural sensitization are examples of effective interventions that can disrupt this cycle and meet the therapeutic goals of psoriasis patients.[64,65]

Future study directions

To the fullest, researchers will need to investigate these two aspects to clear up the neuroimmune itch loop, and at minimum, to find ways of treating it. Revealing the different roles of the cytokines, neuropeptides, and receptors that run the neuroimmune itch loop will greatly contribute to revealing the heroes in our story. It will also be a key element in discovering specific inhibitors of these loops.[66-68]

CONCLUSION

Finally, the complexity of the mechanism of chronic itch in psoriasis is reflected in the multifactorial management of the symptom where neuroimmune interaction and skin barrier defects, as well as central sensitization, play a considerable role. We found that nuclear immune response gene products IL-31 and IL-33, and epithelial cell-derived protein TSLP orchestrating the JAK-STAT signaling pathway are implicated in a complex multi-stage interaction with cytokines and itch sensory neurons. This is made worse by skin barrier dysfunction; changes in the lipid profile and impaired barrier lead to deeper penetration of pruritogens, hence increasing itch. Transmitter-mediated changes in the spinal cord increase the itch perception, thus proving that chronic itch is a central as well as peripheral problem. The current treatment methods involve topical therapies, systemic treatments, and photobiomodulation where most offer varying degrees of relief while emphasizing the need for new ideas. Localized corticosteroids and calcineurin inhibitors are regular topical treatments that present certain drawbacks. The expansion of target biologic agents and recent JAK inhibitors has targeted more amorphous inflammatory cascades but needs longer-term safety studies. That is why photobiomodulation continues to be useful to many while its constant utilization presents dangers. New therapeutic targets such as IL-31 blockers and/or TRP channel modulators offer a major area of focus toward understanding and managing the pruritus associated with psoriasis. These novel antipruritic agents are under development to modulate selective itch signals to provide longer and perhaps more effective alleviation of pruritus. In addition to describing a new concept known as the neuroimmune itch loop, this article also focuses on the cyclic nature of activation and sensitization of the immune system and nerves which leads to the augmentation of chronic itch. This model supports the appeal that excess efficient mesothelial clearance or immune responses should find therapeutic approaches to break this itch cycle and reduce both the immune and neural responses to itching.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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