Upcoming topical TRPV1 anti-pruritic compounds

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Abstract

Transient receptor potential vanilloid type 1 (TRPV1) is found on sensory neurons, keratinocytes, sebocytes, and dendritic cells. Activated TRPV1 channels are believed to help propagate the itch sensation. Therefore, there has been great interest in targeting TRPV1 to treat pruritus. Since oral formulations aimed at TRPV1 have led to adverse effects such as hyperthermia, there has been emphasis on developing novel topical agents. Several companies are investigating topical TRPV1 anti-pruritic compounds and the initial data has been very promising. These drugs have the potential to be important treatment options for the management of itch. This paper reviews topical products in current development for pruritus that target TRPV1 channels.

Keywords: TRPV1, transient receptor potential vanilloid, pruritus, itch, topical

Introduction

Itch is defined as the sensation leading to the urge to scratch. Similar to pain, itch is the body's normal protective response to noxious stimuli. However, chronic itch, defined as pruritus lasting longer than 6 weeks, can develop due to underlying neuropathic, psychogenic, or dermatologic diseases. Common cutaneous conditions that result in chronic itch include atopic dermatitis (AD) and psoriasis [1].

The itch pathway (**Figure 1**) is intricate and has not been completely elucidated. Part of the pathway may include histamine and non-histaminergic pruritogens such as proteases, cytokines, or chemokines, which are believed to be involved in the activation of receptors on non-myelinated C fibers. These receptors, in turn, activate ion channels such as those of the super-family transient receptor potential (TRP). It is likely that activated TRP channels stimulate voltage-gated sodium channels to create an action potential that transmits the itch signal to the spinal cord and continues to the brain via the spinothalamic tract [2].

Transient receptor potential is a super-family composed of sub-families, each of which, in turn, is made up of ion channel proteins. Transient receptor potential vanilloid type 1 is the first member of the sub-family vanilloid. TRPV1 is expressed in cutaneous sensory nerve fibers, specifically type C and Aδ, and is a non-selective, cation-permeable channel stimulated by a variety of agents such as heat, capsaicin, and acid [1,3,4]. TRPV1 can be found on sensory neurons, keratinocytes, sebocytes, and dendritic cells [5].

Interleukin (IL) 31 is a cytokine produced by T helper type two cells and a key inflammatory marker in AD. The activation of IL31 receptor by IL31 is believed to cause pruritus via TRPV1, which has led to TRPV1 becoming a target of interest for developing novel drugs to treat pruritus, especially in AD [6,7]. The development of the first oral TRPV1 antagonist was discontinued in phase I clinical trials owing to significant hyperthermia [8]. To avoid adverse systemic effects, there has been an emphasis on developing topical formulations that target TRPV1 channels. This paper reviews topical investigational products in current development for pruritus that target TRPV1 channels (**Table 1**).

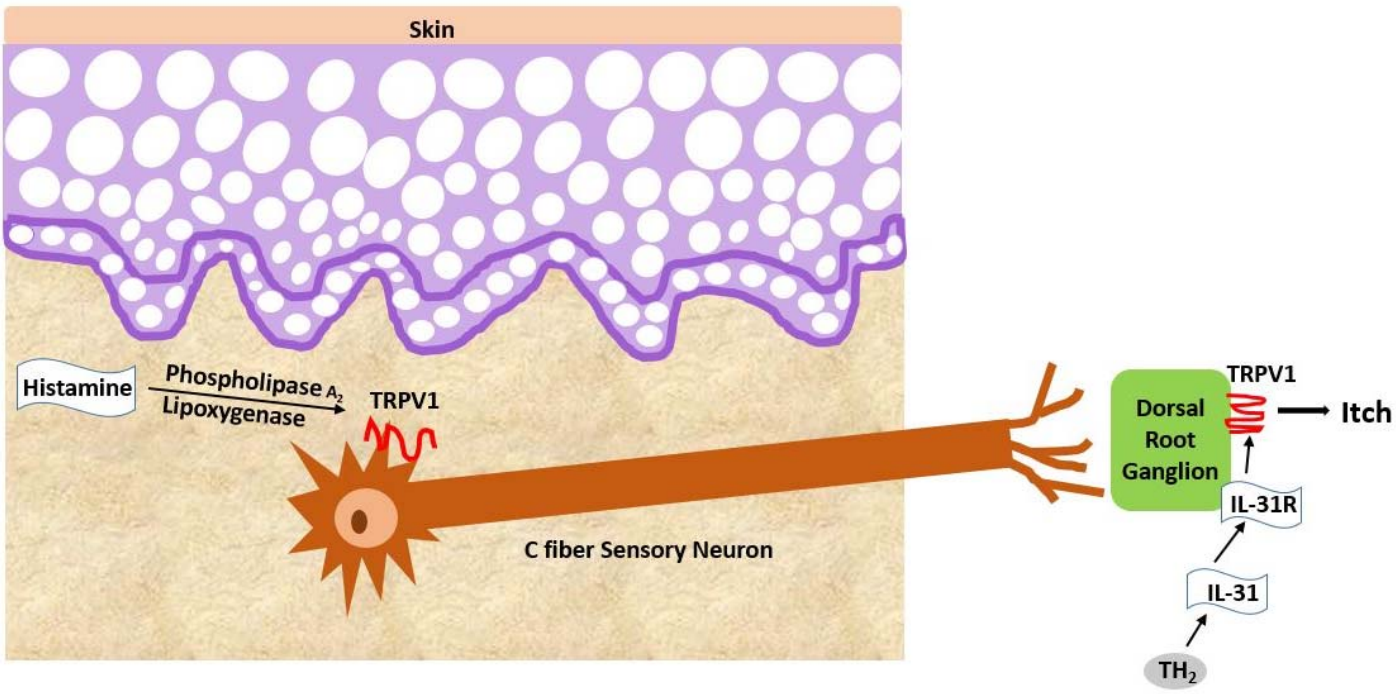

Figure 1. *Itch transmission by histamine is believed to occur on cutaneous C fiber sensory neurons by phospholipase A_2 and lipoxygenase activating transient receptor potential vanilloid type 1 (TRPV1). T helper type two (TH_2) cells produce IL31 which is believed to transmit itch by activating IL31 receptors and TRPV1 at the dorsal root ganglion.*

Asivatrep (PAC-14028)

Asivatrep is a topical TRPV1 antagonist that has shown the most promising results. In a phase IIa trial of asivatrep in AD, it was shown that asivatrep cream was superior to its vehicle and had similar efficacy to pimecrolimus cream. No safety concerns were observed. Recently, phase IIb results have been published. The phase IIb study was a double-blind, eight-week study that enrolled patients with mild to moderate AD who were randomized to receive asivatrep cream in concentrations of 0.1%, 0.3%, 1.0%, or vehicle cream. The primary endpoint was an improvement in the Investigator's Global Assessment (IGA) score defined as the percentage of patients reaching "clear" (IGA score 0) or "almost clear" (IGA score 1) at week 8. The secondary endpoints included a 75% or 90% improvement from baseline of the severity Scoring of Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI), [5].

Pruritus was measured using the pruritus-related Visual Analog Score (VAS). The results showed a statistically significant reduction in pruritus-related VAS for the 1.0% cream compared to placebo by week 8. Also, IGA success rates of 14.58% for vehicle, 42.55% for asivatrep 0.1% (P=0.0025), 38.30% for asivatrep 0.3% (P=0.0087), and 57.45% for asivatrep 1.0% (P<0.001) were seen. Therefore, there was a

Table 1. *Characteristics of topical TRPV1 anti-pruritic compounds,*

Compound	Mechanism of action	Findings
Asivatrep (PAC-14028)	Direct TRPV1 antagonist	In a phase 2 trial, there was a statistically significant reduction in pruritus-related VAS. Avisatrep has the ability to restore the skin barrier in a murine model [5].
Pegcantratinib (CT327/SNA-120)	TRPV1 inhibition via TrkA antagonism	A phase 2 study showed statistically significant reduction in pruritus VAS. The results of a second phase 2 trial are pending [10].
ASN008	Enters TRPV1 channels and blocks voltage-dependent sodium channels	A phase 1b study showed clinically meaningful reduction in NRS pruritus scores two to three hours after application. The reduction in scores lasted greater than eight hours [12].

statistically significant improvement for IGA scores across all concentrations with 1.0% showing the most improvement. The SCORAD index and EASI 75/90 showed a trend toward improvement but were not statistically significant. There were no safety concerns [5]. Another interesting aspect of asivatrep cream is its ability to restore the skin barrier in a murine model [9].

Pegcantratinib (CT327/SNA-120)

Pegcantratinib is a topical potent tropomyosin-receptor kinase A (TrkA) inhibitor. Tropomyosin-receptor kinase A receptor is located adjacent to TRPV1 on sensory nerves. Tropomyosin-receptor kinase A upregulates the expression and sensitivity of TRPV1. Nerve growth factor is the normal ligand that stimulates TrkA. A phase IIb study was performed in patients that had pruritus associated with psoriasis. There was a statistically significant reduction in pruritus with all concentrations of pegcantratinib tested using VAS. However, there was no improvement seen in the IGA or modified Psoriasis Area and Severity Index (PASI). Another phase II trial has also been completed but the results have not been published (clinicaltrials.gov identifier: NCT03448081), [10].

ASN008

ASN008 is a compound analogous to QX-314, a quaternary lidocaine derivative that has been researched extensively for pain [11]. ASN008 is a permanently positively charged molecule with a unique mechanism of action. This molecule blocks voltage-dependent sodium channels intracellularly. While ASN008 is not a TRPV1 channel blocker, ASN008 enters the neuron via activated TRPV1 channels and subsequently blocks voltage-dependent sodium channels. Since TRPV1 channels are activated during itch, it is postulated that ASN008 cream would selectively affect neurons that are actively stimulated by itch.

Asana BioSciences, LLC recently announced the results of its phase Ib study with topical ASN008 for pruritus. The trial was a double-blind, two-week dose escalation study in 25 adult subjects with atopic dermatitis who also had a Numerical Rating Scale (NRS) pruritus itch score $\geq$7. The subjects were randomized in a ratio of 3:1 to receive the ASN008 gel or vehicle. The subjects applied the gel either once or twice daily. The results showed a clinically meaningful reduction in NRS pruritus itch score to <4 in two-to-three hours which was maintained for greater than eight hours after application of ASN008 gel. Overall, ASN008 gel was well tolerated [12].

Conclusion

Although itch is part of the body's normal defense mechanism, chronic itch diminishes many aspects of a patient's quality of life including mood, sleep, and personal relationships. However, effectively managing itch can be a daunting task. Drug development for pruritus is targeting TRPV1 as a means to manage itch. Owing to the unacceptable adverse effect of hyperthermia in some oral formulations, there has been great interest in developing novel topical agents. The current activities in clinical research have been promising and may offer the potential for important options to patients and physicians in the management of itch.

Potential conflicts of interest

The authors declare no conflicts of interest.

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