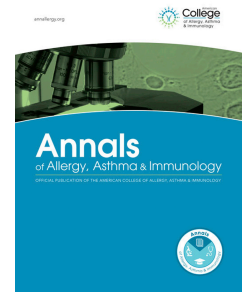


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New and Emerging Treatments for Inflammatory Itch

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Objective:

Chronic pruritus, or itch lasting >6 weeks, is a common symptom and has a profoundly negative impact on quality of life. While many primary dermatologic disorders such as atopic dermatitis and chronic urticaria are characterized by pruritus, numerous other allergic, hepatobiliary, lymphoproliferative, neurologic, and renal disorders are associated with chronic pruritus. Itch involves complex interactions orchestrated by a variety of factors released from and acting on the skin, immune system, and the sensory nervous system. This review summarizes recent therapeutic developments for chronic pruritus with a focus on allergic and type 2 inflammatory pathways.

Data Sources:

Literature search via PubMed, industry websites, and review of the ClinicalTrials.gov database.

Study Selections:

Peer-reviewed publications and public disclosures by industry relating to chronic pruritus pathophysiology and therapeutics.

Results:

Histamine and immunoglobulin E (IgE) remain primary targets for the treatment of itch in the setting of chronic urticaria. More recently, blockade of type 2 immune cell-associated cytokines including IL-4, IL-13, IL-31, and the epithelial cell-derived cytokines, specifically IL-33 and TSLP, has, and is, revolutionizing the treatment of chronic pruritic dermatoses such as atopic dermatitis and prurigo nodularis. Other novel targets also include histamine receptor 4 (H4R), Janus kinases (JAKs), kappa opioid receptor (KOR), neurokinin 1 receptor (NK-1R), and phosphodiesterase 4 (PDE4).

Conclusion:

Advances in our understanding of the neuroimmunology of chronic pruritus has led to the identification of new therapeutic targets and the rapid development of cutting-edge clinical trials. Although incredible advances have already been made, chronic itch continues to be an area of great unmet need.

1 Introduction

2 In the late 17th century, German physician Samuel Hafenreffer defined pruritus,
3 or itch, as an, “unpleasant sensation that elicits the desire or reflex to scratch”.¹ In the
4 acute setting, scratching in response to itch may provide protection against noxious
5 environmental stimuli and insects. However, chronic itch, or itch lasting greater than 6
6 weeks, is highly pathologic, affects approximately 15% of the population, and has a
7 profoundly negative impact on sleep, mental health, and overall quality of life.²⁻⁷
8 Although often considered a single symptom, chronic itch underlies many different
9 medical disorders including primary dermatologic disorders like atopic dermatitis (AD) or
10 eczema, allergic contact dermatitis (ACD), chronic urticaria, and prurigo nodularis (PN).
11 Moreover, chronic itch is also associated with a number of other allergic, hepatobiliary,
12 neurologic, renal, and lymphoproliferative disorders.^{8,9} Emerging evidence indicates that
13 the mechanisms that drive itch are diverse and that there likely many different kinds of
14 itch. Despite its widespread nature and high prevalence, effective therapies for chronic
15 itch remain limited. Indeed, a number of different medications including antihistamines,
16 neuromodulators like gabapentin, topical and intralesional steroids, and systemic
17 immunosuppressants are often employed with limited efficacy.¹⁰ Herein, we review a
18 variety of itch mechanisms and disorders that pertain to the broader fields of type 2
19 immunology and allergy.

20 The sensation of itch involves complex interactions orchestrated by a variety of
21 factors released from and acting on the skin, immune system, and the sensory nervous
22 system (**Figure 1**). Briefly, pruritus begins when itch inducing-factors, or pruritogens,
23 interact with sensory nerve fibers innervating itch-sensing tissues including the skin,

some mucous membranes, and the cornea. These itch-specific nerve fibers or pruriceptors originate from cell bodies in the dorsal root ganglia (DRG) and carry signals into the spinal cord and ultimately the brain for itch to be perceived.¹¹

Recent discoveries of itch-specific receptors including the gastrin-releasing peptide receptor (GRPR), the Mas-related G protein-coupled receptor (Mrgpr) family, and natriuretic peptide receptor 1 (NPR1) highlight how heterogeneous pathways underlie itch sensation.¹²⁻¹⁴ Indeed, such complexity in itch-sensory pathways may account for the diverse clinical presentations of chronic itch. Furthermore, recent studies have also demonstrated that the proinflammatory cytokines IL-4, IL-13, IL33, and thymic stromal lymphopoietin (TSLP) can function as pruritogens, particularly in the context of AD.¹⁵⁻¹⁸ Encouragingly, recent and emerging therapeutic advances, coupled with our understanding of novel neuroimmune pathways, are driving the rapid development of new treatments for various chronic itch disorders. Herein, we review new mechanistic studies and relate them to emerging clinical trials to discuss how various neurotransmitters and cytokines may be targeted for the treatment of chronic itch disorders.

The Immune Response in Cutaneous Inflammation

The skin immune response can be organized into three general modules. Type 1 immunity is mainly designed to combat intracellular bacteria and viruses and characterized by the production of IFN- γ and TNF- α and underlies ACD and psoriasis. Type 2 immunity promotes the expulsion of toxins, environmental pollutants, and macro-parasites, and is driven by the production of IL-4, IL-5, and IL-13 and drives the atopic

march and AD pathology. The third broad type of immunity involves group 3 innate lymphoid cells (ILC3), T helper type 17 (Th17) and Th22 cells and is specialized for defense against extracellular bacteria and fungi. It is associated with the production of IL-17A, IL-22 and/or IL-23, and is strongly implicated in the pathogenesis of psoriasis.^{19,20} In terms of new therapies, understanding the specific pathways that underlie various inflammatory skin disorders have proved critically important for the success of new treatments, especially for AD and psoriasis.^{11,21}

Recent advances in our understanding of the type 2 immune axis have provided deeper insight into different inflammatory disorders including AD and, in particular, its associated itch. Indeed, while pruritus is a symptom associated with activation of all three immune modules, type 2 inflammation appears particularly well-equipped to drive chronic itch. The epithelial cell-derived cytokines IL-33 and TSLP are induced in stressed keratinocytes in the context of barrier dysfunction and potently promote the activation of type 2 immune cells including basophils, ILC2s and Th2 cells. Collectively, these cells produce the effector cytokines IL-4, IL-5, IL-13, and IL-31, which all contribute to the pathogenesis of AD and potentially to other inflammatory skin disorders. Additionally, elevated levels of type 2 cytokines promote production of immunoglobulin E (IgE), activation of mast cells, and release of histamine, which underlie conditions like urticaria (**Figure 1**).²⁰ Thus, increasing knowledge of the complex interplay between various effector cells and cytokines represents an opportunity to better understand the relationship of skin inflammation with itch.

Antihistamines: H1R and H4R

There are four known histamine receptors: H1R, H2R, H3R, and H4R. Each exhibit distinct tissue distributions and pharmacologic characteristics. Of these, H1R and H4R appear to be relevant therapeutic targets for itch (**Figure 2**). H1R antagonists are widely used in acute urticaria and are also first-line therapy for chronic spontaneous urticaria (CSU), although their efficacy is often limited.²² Notably, H1R antagonists are ineffective in the treatment of itch secondary to AD and a variety of other chronic inflammatory skin disorders.¹¹ While most H1-antihistamines have little to no affinity for H4R, H1R and H4R are both expressed on sensory neurons in the DRG and directly mediate itch.^{23,24} In experimental models of histamine-induced itch, dual blockade of H1R and H4R was more effective than either treatment alone, although the effect from H4R appears greater.²⁵ Furthermore, H4R antagonism has been shown to have both anti-pruritic and anti-inflammatory effects.²⁶ The anti-inflammatory effects of H4R modulation are likely due to the fact that this receptor is expressed in various immune cells including lymphocytes, eosinophils, and mast cells, where it plays a role in multiple processes such as chemotaxis and cytokine production.²⁷ For example, H4R activation on Th2 cells leads to induction of the pruritogenic cytokine IL-31.²⁸ H4R is also expressed on keratinocytes, where it drives proliferation.²⁹ Thus, inhibition of H4R on keratinocytes might break a vicious cycle whereby increased epithelial-derived cytokines from histamine-stimulated keratinocytes drives further inflammation in AD. These findings suggest H4R is an attractive target for anti-itch therapeutics. However, its precise role in itch remains to be clearly defined.

H4-antihistamines are currently in development for potential use in a variety of chronic itch disorders (**Table 1**). In two recent phase 2 clinical trials in patients with

moderate-to-severe AD, the oral H4R antagonists JNJ-39758979 and ZPL-3893787 demonstrated significant reductions in pruritus, although the former study was discontinued prematurely due to two patients developing neutropenia.^{30,31} Notably, ZPL-3893787 also demonstrated anti-inflammatory effects, inducing a 50% reduction in eczema area and severity index (EASI) score compared to 27% with placebo.³¹ It is important to note that although EASI scores measure excoriations as a part of overall disease severity in AD, it is not considered a tool to measure itch severity. Indeed, EASI and numerical rating scale (NRS) itch scores demonstrate poor correlation.³² Notwithstanding these observations, whether antihistamines derive their anti-itch properties by disrupting histamine-neuron interactions or by their activity on other intermediary immune or stromal cells remains to be more formally defined.

IgE Antagonists

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody (mAb) that blocks IgE binding to its receptor FcεRI, thereby preventing activation of basophils and mast cells (**Figure 1**). Further, omalizumab also reduces circulating IgE levels and FcεRI expression and function on target cells.³³ In two phase 3 clinical trials, omalizumab significantly reduced itch in H1-antihistamine refractory CSU.^{34,35} While these findings raise the possibility that omalizumab blocks the release of pruritogens other than histamine, the mechanisms by which omalizumab improves symptoms in CSU are not well understood. In a recent clinical trial of omalizumab in children with severe AD, there was a statistically significant mean treatment group difference in EASI score of 6.7 between the omalizumab and placebo groups. Notably, higher doses of

omalizumab were used in this trial, and it was the first clinical trial of omalizumab in AD with a positive clinical outcome. It may be that IgE plays a more significant role in AD in children or that higher doses of omalizumab are required for efficacy in AD.^{36,37} Notwithstanding this, the role of omalizumab in AD remains unclear and controversial.

Ligelizumab, another humanized mAb with higher affinity for IgE than omalizumab, has recently been developed (**Table 1**).³³ In a phase 2 clinical trial in patients with CSU inadequately controlled by H1-antihistamine therapy, ligelizumab showed significantly higher efficacy with complete control of urticaria in 51% versus 26% of the patients in the omalizumab group at week 12. There were similar reductions in pruritus with responses observed as early as week 4.³⁸ A phase 3 trial comparing ligelizumab and omalizumab is underway (NCT03580369). Again, although studies are limited, IgE blockade has shown little efficacy in AD, suggesting additional and/or distinct itch pathways and mediators may be operative in the pathogenesis of AD in comparison to CSU.³⁷

IL-4 and IL-13 Antagonists

IL-4 and IL-13 act as key promoters of type 2 inflammation by acting on a variety of immune cells and have been implicated in the pathogenesis of AD for years based on multiple preclinical and translational studies.³⁹ More recently, they have been shown to act directly on itch-sensory neurons to promote itch (**Figure 2**).^{15,20} Notably, the shared receptor for IL-4 and IL-13 (IL-4R α) is expressed and functionally active on both murine and human sensory neurons, and IL-4 promotes neural hypersensitivity to a multitude of other pruritogens including histamine, chloroquine, IL-31 and TSLP.¹⁵ Dupilumab, a fully

human mAb targeting IL-4R α (**Figure 2, Table 1**), demonstrated unprecedented efficacy in phase 2 and 3 clinical trials with regard to AD disease severity, quality of life, and itch severity.⁴⁰⁻⁴² Notably, the marked reduction in pruritus severity was significant after only two weeks of treatment in comparison to the placebo control group.⁴¹ In case studies, dupilumab has also shown success in patients with other chronic itch conditions like PN, a multifactorial condition characterized by pruritic lichenified nodules, and also in other pruritic disorders such as chronic pruritus of unknown origin (CPUO), uremic pruritus, lichen planus and malignancy-associated pruritus.⁴³⁻⁴⁵ Collectively, these clinical findings support the role of IL-4 and IL-13 in a broad array of pruritic disorders.

Similar to dupilumab, the anti-IL-13 mAbs tralokinumab and lebrikizumab (**Figure 1, Table 1**) disrupt type 2 immune signaling and have shown promising results in patients with AD. While not yet published, in three recently completed phase 3 clinical trials for the treatment of moderate-to-severe AD in adults as monotherapy and in combination with topical corticosteroids, tralokinumab met all primary and secondary endpoints including reduction in pruritus on the NRS itch score (NCT03131648; NCT03160885; NCT03363854).⁴⁶ In a recent phase 2 clinical trial, lebrikizumab significantly reduced skin lesions and pruritus with reductions in itch observed by day 2 of treatment for adults with moderate-to-severe AD.⁴⁷ Future studies will likely better characterize the efficacy of IL-13 blockade versus dual IL-4/IL-13 blockade, particularly with regard to itch symptoms.

IL-31 Antagonists

IL-31 was the first pruritogenic cytokine shown to directly stimulate sensory nerves and mediate itch (**Figure 1**).¹⁶ Its heterodimeric receptor is composed of IL-31 receptor alpha (IL-31RA) and oncostatin M receptor (OSMR) subunits (**Figure 2**).⁴⁸ Increased IL-31 expression was found in lesional and non-lesional skin from patients with AD, and serum levels correlated with disease severity.^{49,50} Strikingly, lesional skin from patients with PN has shown 50-fold and 4.5-fold higher expression of IL-31 compared to healthy skin and even AD lesions, respectively.⁴⁹ There is also evidence that IL-31 plays a significant role in other pruritic disorders such as CSU and bullous pemphigoid.⁵¹ However, the broad role of IL-31 in a variety of pruritic disorders remains to be investigated and is an exciting area of clinical investigation.

The humanized anti-IL-31RA mAb nemolizumab (**Figure 2, Table 1**) recently demonstrated unique anti-itch properties in phase 2 clinical trials in patients with moderate-to-severe AD.^{52,53} Notably, significant reduction in pruritus was observed as early as day 2 of treatment. One study utilized mean percent improvement from baseline score on the pruritus visual analogue scale (VAS) as the primary outcome measure with a 63.1% reduction observed with nemolizumab versus 20.9% with placebo.⁵² A phase 3 clinical trial of nemolizumab in AD is underway (NCT03985943). Nemolizumab has also shown efficacy in PN. In a recently published phase 2 clinical trial of nemolizumab in patients with moderate-to-severe PN, the primary outcome measure of percent change from baseline in the mean peak score for pruritus on the NRS scale at week 4 was met with a 53.0% improvement in the treatment group versus 20.2% with placebo and similar improvement in skin lesions.⁵⁴ Taken together, these

clinical studies are demonstrating that anti-IL-31 mAb may represent not just an anti-inflammatory approach but a direct anti-pruritic therapeutic strategy.

IL-33 and TSLP Blockade

The epithelial cell-derived cytokines IL-33 and TSLP promote type 2 immunity in the setting of skin barrier disruption through multiple cell types including Th2 cells, basophils, and ILC2s and have been implicated in the pathogenesis of pruritic disorders such as AD (**Figure 2**).²⁰ Further, IL-33 and TSLP also act as pruritogens, directly stimulating sensory neurons to mediate itch.^{17,18} Because the epithelial cell-derived cytokines act upstream of effector cytokines such as IL-4, IL-13, and IL-31, they are potentially excellent targets in AD and other pruritic disorders (**Figure 1**).

Tezepelumab, an anti-TSLP mAb (**Table 1**), was evaluated in a phase 2 clinical trial in patients with moderate-to-severe AD in combination with class 3 topical corticosteroids. At 12 weeks, 64.7% of patients treated with tezepelumab achieved the primary endpoint of a $\geq 50\%$ reduction in EASI scores versus 48.2% with placebo, although the difference was not statistically significant. Similar, but not statistically significant, improvements in pruritus were also seen at 12 weeks with a 35.5% versus 21.1% mean percent improvement in NRS itch score in the treatment versus placebo groups, respectively.⁵⁵ Another phase 2 clinical trial of Tezepelumab in AD is currently underway (NCT03809663). Thus, whether TSLP represents a potent clinical target remains an exciting question.

The anti-IL-33 mAb etokimab (ANB020) showed improvement in a phase 2 proof-of-concept clinical trial in adults with moderate-to-severe AD (**Table 1**). Twelve

patients received a single dose of etokimab and at 29 days there were significant improvements in EASI scores with 83.3% and 33% of patients achieving EASI-50 and EASI-75, respectively, along with significant reductions in pruritus. Notably, there was not a placebo group.⁵⁶ A randomized phase 2 clinical trial of etokimab in AD is currently underway (NCT03533751). While data are currently limited with regard to the efficacy of these agents in AD-associated itch, they remain exciting therapeutic prospects.

Janus Kinase Inhibitors

Small molecule Janus kinase (JAK) inhibitors are promising new options for the treatment of pruritus, particularly in AD. JAK inhibitors provide anti-inflammatory effects through disruption of the JAK-STAT signaling pathways utilized by multiple cytokine receptors, including those for IL-4, IL-13 and IL-31 (**Figure 2**). Selective targeting of one or more of the four JAKs (JAK1, JAK2, JAK3, and TYK2) allows for inhibition of multiple cytokine pathways at once.⁵⁷ JAK inhibitors also likely have itch-specific effects. Notably, JAK1 is selectively expressed in itch-sensory neurons compared to JAK2 and JAK3, and in mouse models of AD-like disease, neuron-specific genetic deletion of JAK1 results in markedly reduced pruritus independent of the level of skin inflammation.¹⁵ Taken together, these findings indicate that JAK inhibitors likely have anti-itch neuromodulatory properties.

The oral JAK inhibitor oclacitinib, FDA-approved for canine AD, potently targets JAK1 and treatment demonstrates reduction of pruritus beginning on day 1 of administration.⁵⁸ No clinical trials have been conducted in humans, but in a case report, oral oclacitinib led to significant improvement in a patient with AD.⁵⁹ A case series of six

patients demonstrated efficacy of oral tofacitinib (JAK1/3 selective) in human AD as well.^{57,60} A recent phase 2 clinical trial in AD with upadacitinib, another oral JAK1-selective inhibitor, demonstrated improvement of itch as early as week 1 of treatment. The primary endpoint of percentage improvement in EASI score from baseline at week 16 was 74% for the upadacitinib group versus 23% with placebo.⁶¹ A phase 3 clinical trial of upadacitinib in AD is currently underway (NCT03569293). Abrocitinib (JAK1-selective) recently completed a phase 2 clinical trial in moderate-to-severe AD. The primary outcome measure of the proportion of patients achieving an Investigator Global Assessment (IGA) of clear or almost clear with an improvement from baseline of 2 grades or more at week 12 was achieved by 43.8% versus 5.8% of patients with placebo. Further, in patients with a baseline pruritus NRS itch score of ≥ 4 , 63.6% versus 25.5% with placebo improved by 4 points or more at week 12 with significant reductions in pruritus observed by day 2 of treatment.⁶² A phase 3 clinical trial of abrocitinib in AD is currently underway (NCT03575871). In recent phase 3 clinical trials with oral baricitinib (JAK1/2 selective) in patients with moderate-to-severe AD, the primary endpoint of a validated IGA of clear or almost clear was achieved by 16.8% vs 4.8% with placebo at 16 weeks at the highest dose. Significant reductions in pruritus were seen by week 1 and at all key timepoints in terms of NRS itch score compared with placebo as well.^{57,63} Collectively, although the only oral JAK inhibitor approved for AD is available in canines, these studies indicate that there will likely be multiple oral JAK inhibitors approved for moderate-to-severe AD in the near future.

There are also a number of topical JAK inhibitors in development (**Table 2**). Topical tofacitinib showed promising results in a phase 2 clinical trial in patients with

mild-to-moderate AD with significant reductions in itch achieved starting on day 2 of treatment. Notably, 68% versus 13% of the control subjects achieved an IGA score of clear or almost clear and an improvement of 2 or more points from baseline at 4 weeks.⁶⁴ Similarly JTE-052, a pan-JAK inhibitor now known as delgocitinib and recently approved for AD in Japan, also demonstrated rapid improvement of itch and favorable efficacy in AD in phase 2 clinical trials in both adults and children. In both trials, delgocitinib achieved significant reductions in EASI scores with a mean percentage reduction from baseline of 61.8% in children with 0.5% ointment and 72.9% with 3% ointment versus 4.8% and 12.2% in the vehicle groups, respectively, at 4 weeks. Pruritus on the NRS scale was also significantly reduced after 1 week of treatment, with improvement noted within 1 day of treatment.^{65,66} Another recent phase 2 clinical trial for hand eczema also demonstrated favorable tolerability and efficacy with delgocitinib with 46% versus 15% in the vehicle only group achieving clear or almost clear with an improvement from baseline of 2 grades or more on the Physician's Global Assessment of disease severity at week 8.⁶⁷ In a recent dose-ranging phase 2 clinical trial, topical ruxolitinib (JAK1/2 selective) showed significant reductions in EASI scores of 71.6% vs 15.5% with placebo at 4 weeks. Significant improvements in pruritus occurred within 36 hours on the NRS itch score and topical ruxolitinib appeared to do remarkably well against its mid-potency corticosteroid active comparator.⁶⁸ Phase 3 clinical trials for topical ruxolitinib in AD are currently underway (NCT03745638; NCT03745651). Whether in oral or topical form, collectively, these studies demonstrate that JAK inhibitors will represent a major new class of therapeutics for AD.

Phosphodiesterase 4 Inhibitors

Topical and oral phosphodiesterase 4 (PDE4) inhibitors are potential therapies that have also been recently evaluated for pruritus as well (**Table 1-2**). PDE4 regulates multiple proinflammatory signals by catalyzing the degradation of cyclic AMP in both immune and non-immune cells including keratinocytes (**Figure 2**).⁶⁹ In patients with mild-to-moderate AD, phase 3 clinical trials of the topical PDE4 inhibitor crisaborole showed significant reductions in pruritus with 63% of patients, versus 53% with vehicle alone, achieving a score of 0 or 1 and improvement by 1 or more points on a 4 point itch scale after 29 days of treatment. Notably, reduction in pruritus was significant at the earliest evaluation after 8 days of treatment.⁷⁰

Apremilast, an oral PDE4 inhibitor, received FDA approval for psoriasis and psoriatic arthritis in 2014. In the ESTEEM 1 trial for psoriasis, it led to significant improvements in the secondary endpoint measure of pruritus VAS score.⁷¹ Apremilast is currently undergoing clinical trials in AD. A phase 2 clinical trial in patients with moderate-to-severe AD showed a significant improvement in EASI scores of 31.6% (40 mg twice daily) versus 11.0% with placebo at 12 weeks. However, improvements in EASI scores were not statistically significant in 30 mg twice daily dosing group, and adverse events including cellulitis were more frequent with 40 mg twice daily dosing leading to discontinuation. Improvements in pruritus were not statistically significant.⁷² A small open label clinical trial in patients with PN showed limited improvement in pruritus after 12 weeks of treatment.⁷³ More recently, a phase 2 proof-of-concept trial in chronic pruritus of unknown origin (CPUO) demonstrated poor tolerability of apremilast 30 mg

twice daily in this population.⁷⁴ Further studies will likely provide additional information on the efficacy of PDE4 blockade in the treatment of pruritus.

Neurokinin Receptor Antagonists

Substance P (SP) is a neuropeptide released from activated cutaneous sensory neurons following scratching and other triggers (**Figure 1**). In addition to multiple other functions, SP indirectly induces pruritus by stimulating the release of pruritogens from keratinocytes, endothelial cells, mast cells, and other immune cells by signaling via the neurokinin 1 receptor (NK1R) (**Figure 2**). Notably, an increased density of cutaneous nerve fibers staining for SP has been reported in both AD and PN lesions.¹¹ The small molecule NK1R antagonists aprepitant, serlopitant, and tradipitant hold potential to treat pruritus of multiple etiologies. Aprepitant is currently approved for use as an anti-emetic and has shown potential in many chronic pruritic disorders such as lymphoma-associated pruritus in case studies.⁷⁵ In phase 2 clinical trials for PN and chronic pruritus, serlopitant led to significant reductions in pruritus; however, phase 2 clinical trials for CPUO and phase 3 clinical trials for PN did not meet primary endpoints and thus serlopitant was recently discontinued for these indications.⁷⁶⁻⁷⁹ In a phase 3 clinical trial in AD, tradipitant did not achieve the primary endpoint; however, subgroup analysis in the mild AD group showed significant improvement in the worst itch NRS and another phase 3 clinical trial is underway (NCT04140695).⁸⁰ Additional clinical trials will likely further delineate the role of targeting neuroinflammatory processes in the treatment of chronic pruritus.

Kappa Opioid Agonists

It is thought that imbalance in mu- and kappa-opioid receptor (MOR, KOR) activity in the peripheral and central nervous systems may contribute to chronic itch.⁸¹ Opioid-induced pruritus is a known side effect of morphine and other MOR agonists, and MOR antagonists like naloxone and naltrexone are reported to suppress cholestatic and uremic pruritus in certain cases.⁸² Opioid receptors also play a role in inflammation, and in vitro studies show that KOR activation down-regulates cytokines and chemokines in human inflammatory cells (**Figure 2**).⁸³ Further, KOR expression is decreased in lesional skin from AD patients.⁸² The KOR agonists nalfurafine and difelikefalin (CR845) have shown promise in the treatment of chronic pruritus. Nalfurafine was efficacious in treating uremic and cholestatic pruritus, as demonstrated in phase 3 clinical trials and is approved for use in uremic pruritus in Japan.^{81,84} Nalfurafine also reduced itch in an AD mouse model and is a potential treatment for patients with AD.⁸⁵ In a recent phase 3 clinical trial in uremic pruritus in the US, difelikefalin (CR845), a peripherally restricted KOR agonist, showed significant reductions in pruritus with 51.9% versus 30.9% in the placebo group achieving a decrease of at least 3 points from baseline in the weekly mean score on the worst intensity itch NRS at 12 weeks.⁸⁶ Phase 2 clinical trials of difelikefalin (CR845) in AD and cholestatic pruritus are currently underway (NCT04018027; NCT03995212). Additionally, clinical trials evaluating use of the KOR agonist and MOR antagonist/partial agonist nalbuphine in PN are currently underway (NCT03497975). Overall, modulation of opioid receptor activity shows promise in the treatment of a variety of chronic pruritic conditions.

Conclusion

Chronic pruritus, or itch lasting >6 weeks, is common and highly pathologic with a profoundly negative impact on quality of life. While many primary dermatologic disorders such as AD and chronic urticaria are characterized by itch, numerous other allergic, hepatobiliary, neurologic, renal, and lymphoproliferative disorders are also associated with intractable pruritus. The sensation of itch involves complex interactions orchestrated by a variety of factors released from and acting on the skin, immune system, and the sensory nervous system. Novel topicals, oral medications, and biologics are revolutionizing the treatment of itch. Specifically, in AD, mAbs targeting type 2 associated cytokines have shown striking results. Further, topical and oral JAK inhibitors exhibit unique anti-itch effects and target multiple cytokine pathways. Novel targets also include H4R, PDE4, NK1R, and KOR. Advancements in our understanding of the pathophysiology of chronic pruritus had led to the development of new therapeutic targets and completion of clinical trials at a rapid pace. Although remarkable advances have been made, chronic itch continues to be an area of great unmet need.

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Table 1: Summary of selected systemic therapeutics for various inflammatory itch disorders.

Target	Therapeutics	Mechanism	Condition and Selected Studies
H4R	JNJ-39758979	H4R Antagonist	AD: phase 2 ³⁰
	ZPL-3893787	H4R Antagonist	AD phase 2 ³¹
IgE	Omalizumab	Anti-IgE mAb	CSU: phase 3 ^{34,35} AD: phase 3 ³⁶
	Ligelizumab	Anti-IgE mAb	CSU: phase 2, ³⁸ phase 3 underway (NCT03580369*)
IL-4 and IL-13	Dupilumab	Anti-IL-4R α mAb (shared receptor for IL-4 and IL-13)	AD: phase 2, 3 ⁴⁰⁻⁴²
IL-13	Tralokinumab	Anti-IL-13 mAb	AD: phase 3 (NCT03131648; NCT03160885; NCT03363854*)
	Lebrikizumab	Anti-IL-13 mAb	AD: phase 2 ⁴⁷
IL-31	Nemolizumab	Anti-IL-31RA mAb	AD: phase 2, ^{52,53} phase 3 underway (NCT03985943*) PN: phase 2 ⁵⁴
IL-33	Etokimab	Anti-IL33 mAb	AD: phase 2, ⁵⁶ phase 2 underway (NCT03533751*)
TSLP	Tezepelumab	Anti-TSLP mAb	AD: phase 2, ⁵⁵ phase 2 underway (NCT03809663)
JAK	Abrocitinib	JAK 1 selective	AD: phase 2, ⁶² phase 3 (NCT03575871*)
	Oclacitinib	JAK 1 selective	AD: case report ⁵⁹
	Upadacitinib	JAK1 selective	AD: phase 2, ⁶¹ phase 3 underway (NCT03569293*)
	Baricitinib	JAK1/2 selective	AD: phase 3 ⁶³
	Tofacitinib	JAK1/3 selective	AD: case series ⁶⁰
PDE4	Apremilast	PDE4 antagonist	AD: phase 2 ⁷² CPUO: phase 2 ⁷⁴
NK1R	Aprepitant	NK1R antagonist	Malignancy-associated pruritus: case study ⁷⁰
	Serlopitant	NK1R antagonist	PN: phase 2, ^{76,77} phase 3 discontinued ⁷⁸ CPUO: phase 2 discontinued ⁷⁹
	Tradipitant	NK1R antagonist	AD: phase 3 ⁸⁰
KOR	Nalfurafine	KOR agonist	Uremic pruritus: phase 3 ⁸¹ Cholestatic pruritus: phase 3 ⁸⁴
	Difelikefalin (CR845)	KOR agonist	Uremic pruritus: phase 3 ⁸⁶

Abbreviations: Atopic dermatitis (AD); Chronic spontaneous urticaria (CSU); Prurigo nodularis (PN); Chronic pruritus of unknown origin (CPUO); Histamine H4 receptor (H4R); Immunoglobulin E (IgE); Interleukin (IL); Monoclonal antibody (mAb); Janis kinase (JAK); Phosphodiesterase 4 (PDE4); Neurokinin 1 receptor (NK1R); Kappa opioid receptor (KOR)

*ClinicalTrials.gov Identifier

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Table 2: Summary of selected topical therapeutics for chronic inflammatory itch disorders.

Target	Therapeutics	Mechanism	Selected Studies
JAK	Tofacitinib	JAK1/3 selective	AD: phase 2 ⁶⁴
	Ruxolitinib	JAK1/2 selective	AD: phase 2, ⁶⁸ phase 3 (NCT03745638; NCT03745651*)
	Delgocitinib (JTE-052)	All JAK types	AD: phase 2 ^{65,66} Hand eczema: phase 2 ⁶⁷
PDE4	Crisaborole	PDE4 inhibitor	AD: phase 3 ⁷⁰

Abbreviations: Atopic dermatitis (AD); Janus kinase (JAK); Phosphodiesterase 4 (PDE4)

*ClinicalTrials.gov Identifier

Figure Legends:

Figure 1: Type 2 immunity and chronic pruritus. Overview of interactions between the skin, immune, and nervous system including key cells and molecules mediating the sensation of itch. Molecules currently in use or in development to modulate mediators of itch are shown in red with lines indicating their molecular targets. H1R = type 1 histamine receptor. H4R = type 4 histamine receptor. IL = interleukin. ILC2 = type 2 innate lymphoid cell. Th2 cell = type 2 T helper cell. KOR = kappa opioid receptor. NK1R = neurokinin 1 receptor (substance P receptor). TSLP = thymic stromal lymphopoietin. Created with BioRender.com.

Figure 2: Key immune and pruriceptive signaling pathways in chronic itch. Overview of key intracellular pathways mediating inflammatory itch in immune cells and sensory neurons. Molecules currently in use or in development to modulate receptors or downstream signaling in itch are shown in red (antagonist) or green (agonist) with lines indicating their molecular targets. Abbreviations: AC = adenylyl cyclase. cAMP = cyclic adenosine monophosphate. H1R = type 1 histamine receptor. H4R = type 4 histamine receptor. IL = interleukin. JAK = Janus kinase. PDE4 = phosphodiesterase-4. NK1R = neurokinin 1 receptor (substance P receptor). OSMR = oncostatin M receptor. PLC = phospholipase C. STAT = signal transducer and activator of transcription. Created with BioRender.com.

Key Messages

- Chronic pruritus, or itch lasting >6 weeks, is a major unmet need with no universally effective therapeutics.
- Chronic itch underlies many primary dermatologic disorders such as atopic dermatitis and chronic urticaria but is also associated with a number of other allergic, hepatobiliary, neurologic, renal, and lymphoproliferative disorders; it can also present commonly in idiopathic forms.
- Itch involves complex interactions between the skin, immune system, and the sensory nervous system; emerging therapeutics selectively target these interactions.
- Beyond histamine and IgE, type 2 cell-associated cytokines including IL-4, IL-13, IL-31, and the epithelial cell-derived cytokines have become prime targets for itch therapeutics.
- New potential anti-itch therapeutic targets include histamine receptor 4 (H4R), Janus kinases (JAKs), kappa opioid receptor (KOR), neurokinin 1 receptor (NK-1R), and phosphodiesterase 4 (PDE4).

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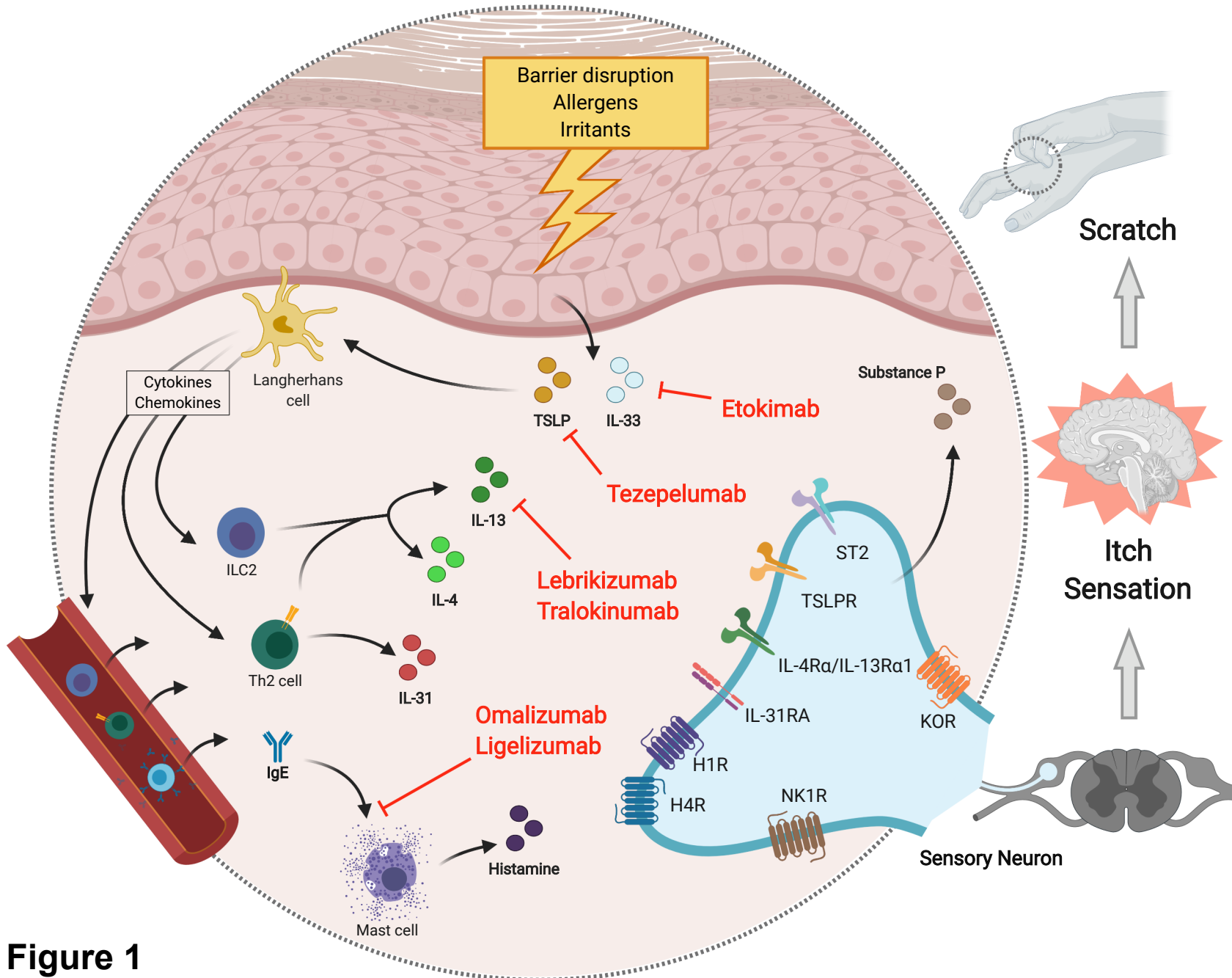


Figure 1

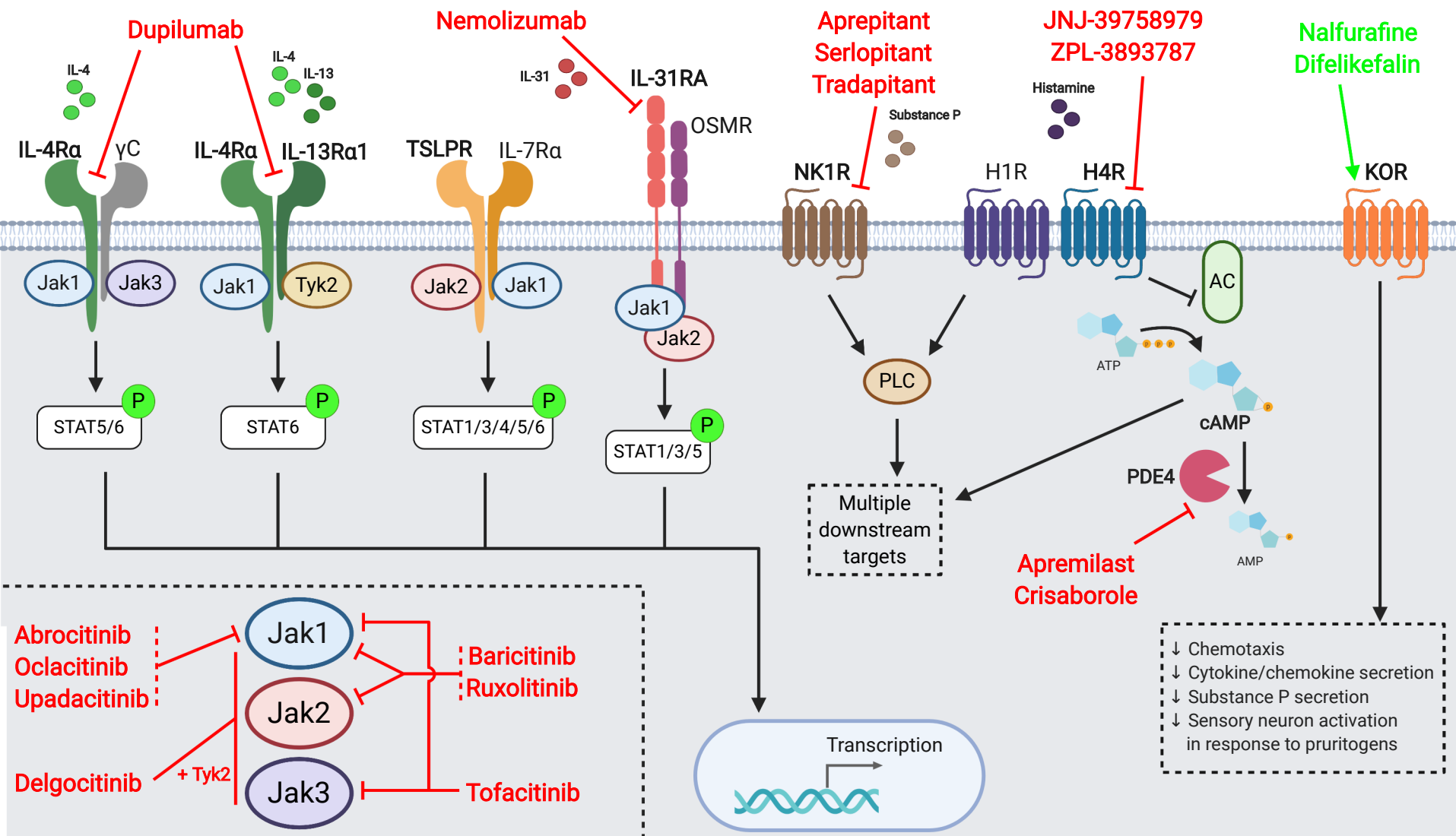


Figure 2

Figure Legends:

Figure 1: Type 2 immunity and chronic pruritus. Overview of interactions between the skin, immune, and nervous system including key cells and molecules mediating the sensation of itch. Molecules currently in use or in development to modulate mediators of itch are shown in red with lines indicating their molecular targets.

Figure 2: Key immune and pruriceptive signaling pathways in chronic itch. Overview of key intracellular pathways mediating inflammatory itch in immune cells and sensory neurons. Molecules currently in use or in development to modulate receptors or downstream signaling in itch are shown in red (antagonist) or green (agonist) with lines indicating their molecular targets. Abbreviations: AC: adenylate cyclase; PLC: phospholipase C.

Table 1: Summary of selected systemic therapeutics for various inflammatory itch disorders.

Target	Therapeutics	Mechanism	Condition and Selected Studies
H4R	JNJ-39758979	H4R Antagonist	AD: phase 2 (Murata et al, 2015)
	ZPL-3893787	H4R Antagonist	AD phase 2 (Werfel et al, 2018)
IgE	Omalizumab	Anti-IgE mAb	CSU: phase 3 (Maurer et al, 2013; Saini et al, 2015) AD: phase 3 (Chan et al, 2020)
	Ligelizumab	Anti-IgE mAb	CSU: phase 2 (Maurer et al, 2019); phase 3 underway (NCT03580369*)
IL-4 and IL-13	Dupilumab	Anti-IL-4R α mAb (shared receptor for IL-4 and IL-13)	AD: phase 2, 3 (Beck et al, 2014; Simpson et al, 2016; Thaci et al, 2016)
IL-13	Tralokinumab	Anti-IL-13 mAb	AD: phase 2, 3 (Wollenberg et al, 2018; NCT03131648; NCT03160885; NCT03363854*)
	Lebrikizumab	Anti-IL-13 mAb	AD: phase 2 (Guttman-Yassky et al, 2020)
IL-31	Nemolizumab	Anti-IL-31RA mAb	AD: phase 2 (Ruzicka et al, 2017; Silverberg et al, 2020), phase 3 underway (NCT03985943*); PN: phase 2 (Ständer et al, 2020)
IL-33	Etokimab	Anti-IL33 mAB	AD: phase 2 (Chen et al, 2019); phase 2 underway (NCT03533751*)
TSLP	Tezepelumab	Anti-TSLP mAb	AD: phase 2 (Simpson et al, 2019); phase 2 underway (NCT03809663)
JAK	Abrocitinib	JAK 1 selective	AD: phase 2 (Gooderham et al, 2019) phase 3 (NCT03575871*)
	Oclacitinib	JAK 1 selective	AD: case report (Haugh et al, 2018)
	Upadacitinib	JAK1 selective	AD: phase 2 (Guttman-Yassky et al, 2020); phase 3 underway (NCT03569293*)
	Baricitinib	JAK1/2 selective	AD: phase 2 (Guttman-Yassky et al, 2018); phase 3 (Simpson et al, 2020)
	Tofacitinib	JAK1/3 selective	AD: case series (Levy et al, 2015)
PDE4	Apremilast	PDE4 antagonist	AD: phase 2 (Simpson et al, 2018)

NK1R	Aprepitant	NK1R antagonist	Lymphoma: Pojawa-Golab et al, 2019
	Serlopitant	NK1R antagonist	PN: phase 2 (Stander et al, 2019); phase 3 discontinued CPUO: Phase 2 discontinued
	Tradipitant	NK1R antagonist	AD: phase 3 (prnewswire, 2020; NCT04140695*).
KOR	Nalfurafine	KOR agonist	Uremic pruritus: phase 3 (Phan et al, 2012); cholestatic pruritus: phase 3 (Kumada et al, 2017)
	Difelikefalin (CR845)	KOR agonist	Uremic pruritus: phase 3 (Fishbane et al, 2020)

Abbreviations: Atopic dermatitis (AD); Chronic spontaneous urticaria (CSU); Prurigo nodularis (PN); Histamine H4 receptor (H4R); Immunoglobulin E (IgE); Interleukin (IL); Monoclonal antibody (mAb); Janis kinase (JAK); Phosphodiesterase 4 (PDE4); Neurokinin 1 receptor (NK1R); Kappa opioid receptor (KOR)

*ClinicalTrials.gov Identifier

Table 2: Summary of selected topical therapeutics for chronic inflammatory itch disorders.

Target	Therapeutics	Mechanism	Selected Studies
JAK	Tofacitinib	JAK1/3 selective	AD: phase 2 (Bissonnette et al, 2016)
	Ruxolitinib	JAK1/2 selective	AD: phase 2 (Kim et al, 2020); phase 3 (NCT03745638; NCT03745651*)
	Delgocitinib (JTE-052)	All JAK types	AD: phase 2 (Nakagawa et al, 2017; Nakagawa et al, 2019); Hand eczema: phase 2 (Worm et al, 2019)
PDE4	Crisaborole	PDE4 inhibitor	AD: phase 3 (Paller et al, 2016)

Abbreviations: Atopic dermatitis (AD); Janus kinase (JAK); Phosphodiesterase 4 (PDE4)

*ClinicalTrials.gov Identifier