

## REVIEW ARTICLE

# Neuroimmune interactions in chronic itch of atopic dermatitis

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## Abstract

Itch is a defining symptom of atopic dermatitis. Crosstalk between keratinocytes, the immune system and non-histaminergic sensory nerves is responsible for the pathophysiology of chronic itch in atopic dermatitis. An expanding understanding of the contribution of the nervous system and its interaction with immune pathways in atopic itch are helping to identify new therapeutic strategies.

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## Conflicts of interest

Dr. Yosipovitch is a consultant and advisory board member for AbbVie, Bayer, Cervae, Eli Lilly, Galderma, Menlo Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Sienna and Trevi Therapeutics and is an investigator funded by Kiniksa Pharmaceuticals, LEO Pharma, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Inc., Sun Pharma. Dr. Berger is a consultant and advisory board member for Sanofi and Menlo Therapeutics. Dr. Fassett is a consultant for Regeneron Pharmaceuticals, Inc.

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## Introduction

Chronic itch that induces scratching is a defining symptom of atopic dermatitis (AD).<sup>1,2</sup> Inadequately controlled itch in AD significantly affects quality of life, with high levels of work impairment, loss of productivity and sleep interference.<sup>3</sup> Pro-inflammatory cytokines from T cells and keratinocytes play a key role in the pathogenesis of AD and atopic itch, as previously reviewed.<sup>4</sup> The central nature of inflammatory pathways in AD is evidenced by the potent therapeutic effects of the interleukin-4 receptor alpha (IL-4R $\alpha$ ) antagonist dupilumab and the interleukin-31 receptor alpha (IL-31RA) antagonist nemolizumab.<sup>5–11</sup> However, there is growing appreciation for the contribution of the nervous system in AD-associated itch.<sup>12</sup> Crosstalk between the nervous system, the cutaneous immune system and keratinocyte populations is central to the development and persistence of atopic itch.<sup>13</sup> While immunosuppressants and corticosteroids reduce inflammatory components of AD, as well as itch, most of these treatments fail to target the substantial neural component of itch pathophysiology and are associated with suboptimal risk–benefit profiles.<sup>14</sup> Alternative therapeutic

strategies may directly target the nervous system, or target points of intersection between nerves, immune cells and keratinocytes. Here, we review the pathways that link keratinocytes, the immune system and the nervous system in the pathophysiology of chronic itch in AD and outline possible therapeutic strategies to target these circuits.

## Neural pathways that mediate pruritus in AD

Itch occurs when sensory nerves are exposed to exogenous and endogenous stimuli (pruritogens) including allergens, amines, proteases, neuropeptides and cytokines.<sup>4,15,16</sup> In the peripheral nervous system, the first event is binding of pruritogens to a subset of primary afferent C-fibre somatosensory neurons (pruritoceptors) that innervate skin. Pruritoceptor cell bodies are located in the dorsal root ganglia (DRG); they synapse to interneurons in the dorsal horn of the spinal cord. After pruritogens activate pruritogen receptors on the cutaneous nerve endings of pruritoceptors, calcium influx and activation of intracellular signalling pathways result in the transmission of an electrical impulse from the skin to the DRG and the spinal cord. This impulse is

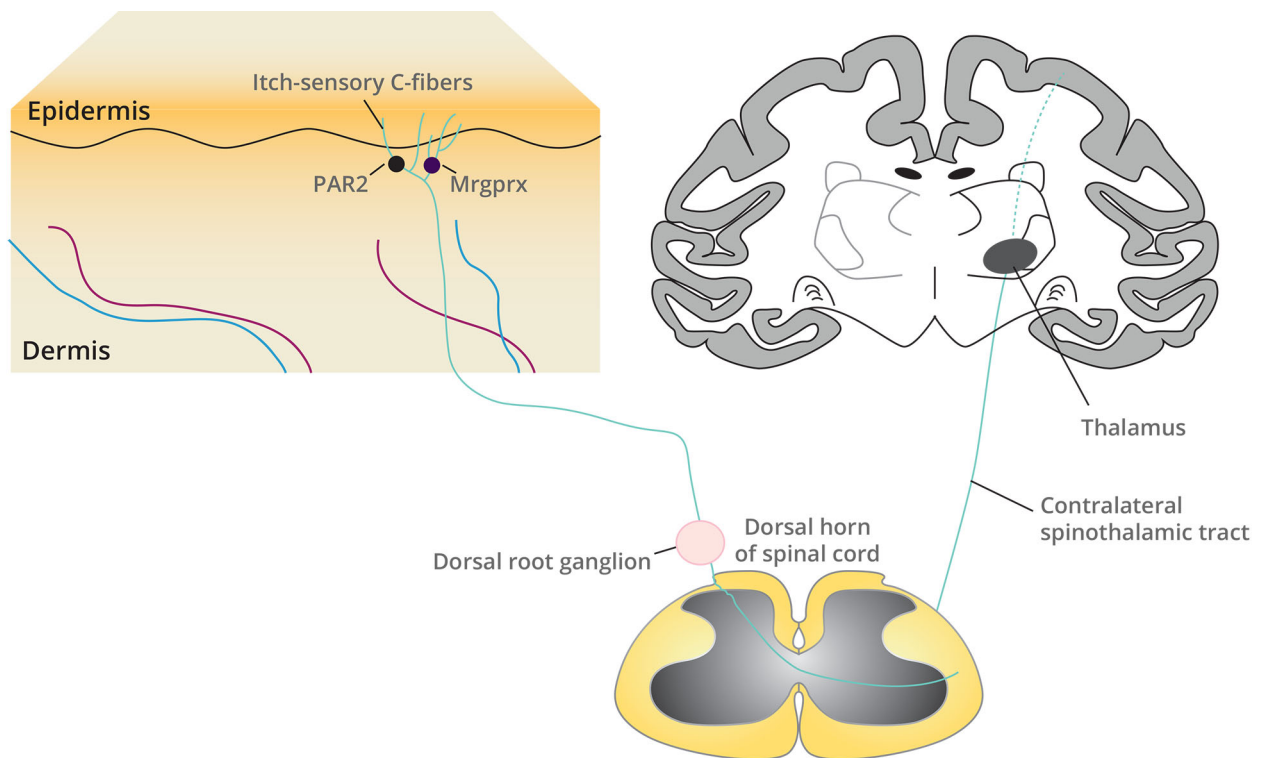
subsequently conveyed to the brain via the spinothalamic tract neurons.<sup>17–19</sup> The brain processes the itch signal, and motor activity (scratching) is induced.<sup>20</sup>

Individual pruritoceptors are defined by their signalling response to specific pruritogens. One system for functionally classifying groups of pruritoceptors is by sensitivity to histamine, a common pruritogen. Histamine-responsive (histaminergic) and non-histaminergic pruritoceptors use largely distinct receptors and distinct cutaneous nerve fibres that follow separate spinothalamic tracts to connect with different neural pathways in the central nervous system (CNS).<sup>4,21</sup> Figure 1 depicts the neuroanatomy of both pathways from the periphery to the CNS. This review focuses on non-histaminergic pathways, as histamine-dependent pathways do not contribute substantially to chronic itch in AD.<sup>18,22</sup>

Activation of many different pruritogen receptors can trigger non-histaminergic pathways relevant to AD. Pruritogens that activate these receptors include keratinocyte-derived proteins, mast cell factors, environmental chemicals, pathogen-derived molecules and cytokines (discussed below; also reviewed in

Voisin *et al.* 2017, Dong and Dong 2018<sup>23,24</sup>). A few notable examples of pruritogen receptor–pruritogen pairs relevant to AD are as follows: (i) proteinase-associated receptor 2 (PAR2), which binds a pro-peptide released by mast cell proteases or house dust mite extract proteases<sup>4,25</sup>; and (ii) several members of the Mas-related G protein-coupled receptor (Mrgprx) family, in particular Mrgprx2, which can be activated by the neuropeptide substance P.<sup>16,26–28</sup>

Many non-histaminergic pruritoceptors require the calcium ion channels TRPA1 and TRPV1 for itch signalling to the spinal cord.<sup>26,29</sup> Within the spinal cord, itch signals are transmitted through the spinothalamic tract via gastrin-releasing peptide receptors (GRPR)+ neurons.<sup>4,30</sup> Transmission of pruritoceptive signals via GPR+ spinal cord neurons is regulated by inhibitory gamma-aminobutyric acid (GABA)ergic interneurons. Several studies have demonstrated that loss of GABAergic interneurons or downregulation of a GABA receptor subunit is essential for chronic itch in mice, suggesting GABA agonists could effectively treat itch in AD patients as well.<sup>31–33</sup>



**Figure 1** The neuroanatomy of itch pathways from the skin to the CNS. Itch is mediated by pruritogen binding to pruritogen receptors, such as PAR2 and Mrgprx, located on a subset of itch-sensitive primary afferent somatosensory neurons whose nerve endings innervate the dermis and epidermis. Itch-sensory neurons are C fibres; their cell bodies reside in the dorsal root ganglia of the spinal cord. Itch is perceived after signals initiated in cutaneous C-fibre neurons are transmitted by relay through the dorsal root ganglia to interneurons in the dorsal horn of the spinal cord and then via contralateral spinothalamic tracts to the brain. CNS, central nervous system; Mrgprx, Mas-related G protein-coupled receptors, in particular the subfamily X; PAR2, proteinase-associated receptor 2.

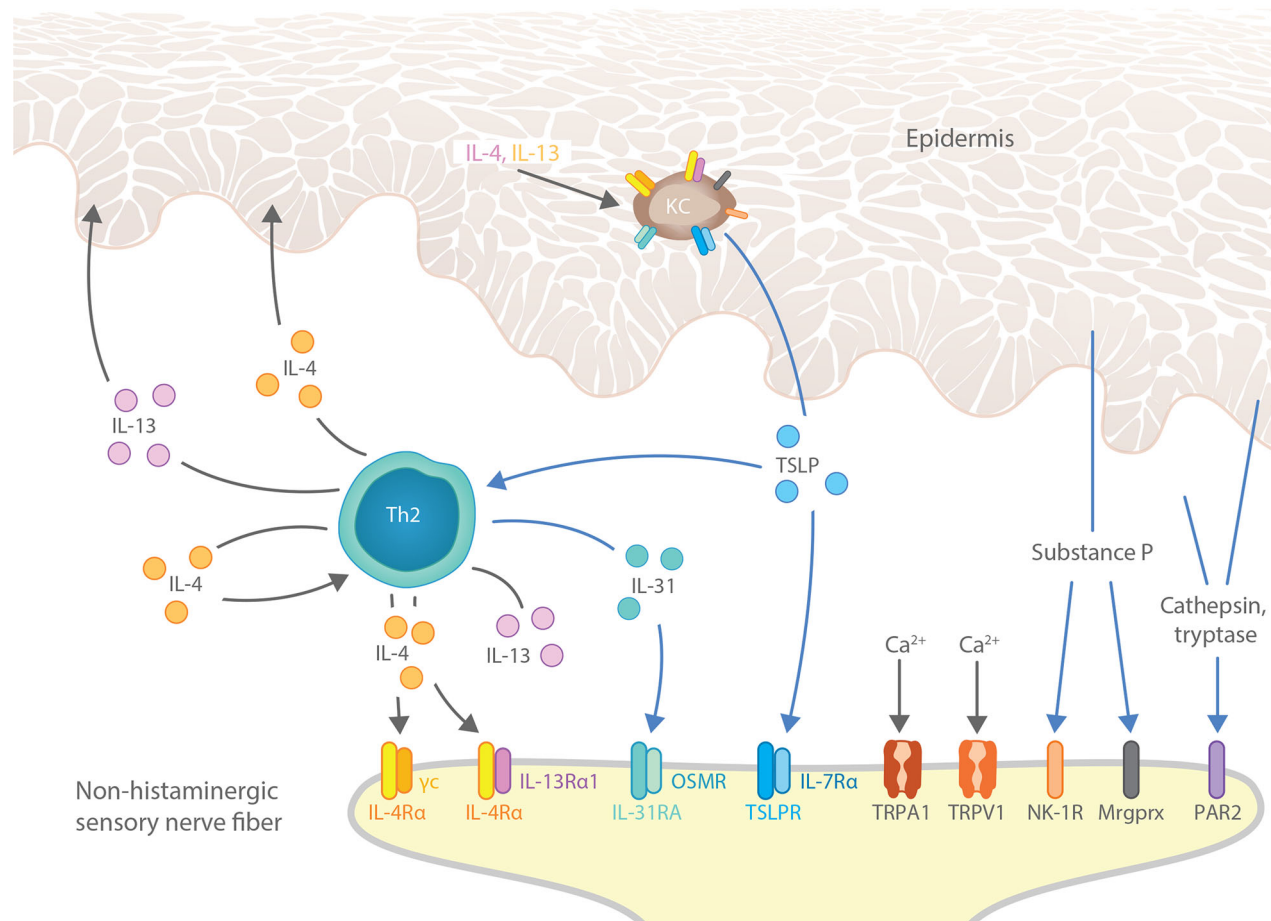
### Crosstalk between immune cells, keratinocytes and peripheral nerves mediates atopic itch

Pruritus in AD results from orchestrated interactions between histamine-independent C fibres in the skin, keratinocytes and immune cells. Figure 2 illustrates lines of communication between these key populations in chronic itch in AD.

#### Immune cell-derived factors

T helper cell 2 (Th2) lymphocytes, eosinophils, neutrophils and mast cells amplify inflammatory and pruritoceptive

pathways in AD by releasing cytokines and neurogenic peptides.<sup>4,34,35</sup> Some AD-associated cytokines, IL-31 and thymic stromal lymphopietin (TSLP), can directly promote itch via activation of pruritoceptive TRPV1+ TRPA1+ neurons that express their receptors.<sup>36,37</sup> In addition, IL-4 may potentiate itch by sensitizing itch-sensory neurons to direct pruritogens, such as histamine and IL-31.<sup>38</sup> Cytokine-to-neuron signalling by IL-31, TSLP and IL-4 – all present in skin during AD flares – may explain the rapid benefit of JAK1/2 and IL-4R $\alpha$  inhibition vs. chronic pruritus and pruritus in AD.<sup>36–41</sup>



**Figure 2** Crosstalk between nerves, immune cells and keratinocytes fuel pruritus in AD lesional skin. Immune cells and keratinocytes release pruritogens (IL-31, TSLP, substance P) and other factors that alter sensitivity to pruritus in AD, including the type 2 cytokine IL-4. These factors promote pruritus by interacting with their receptors (IL-31RA, TSLPR, NK-1R, IL-4R $\alpha$ , respectively) expressed on histamine-independent C fibres innervating skin. Blue arrows designate direct pruritogenic signalling pathways. Keratinocyte-derived factors (TSLP, substance P) can also promote itch indirectly by activating Th2 immune cells, leading to further production of IL-31, IL-4 and IL-13. Finally, feedback loops involving IL-4 and IL-13 contribute to pruritus by inducing more TSLP expression in keratinocytes. The widespread expression of pruritogen and cytokine receptors on both keratinocytes and cutaneous C fibres illustrates the potential for crosstalk between keratinocytes, immune cells and the peripheral nervous system to drive itch in AD. AD, atopic dermatitis; CNS, central nervous system; KC, keratinocyte; Mrgprx, Mas-related G protein-coupled receptors, in particular the subfamily X; OSMR, oncostatin M receptor; PAR2, proteinase-associated receptor 2; TRPA1, transient receptor potential cation channel subfamily A member 1; TRPV1, transient receptor potential cation channel subfamily V member 1; TSLP, thymic stromal lymphopietin.

Pruritoceptors bearing receptors for IL-31 and TSLP express high levels of JAK1.<sup>42</sup>

In addition to communicating with neurons, IL-31 binds to its receptor IL-31RA on keratinocytes. A role for the IL-31:IL-31RA pathway in atopic itch is supported by the genetic association between IL-31 and lichen amyloidosis, an itchy skin condition associated with mutations that result in increased epidermal expression of IL-31RA.<sup>43</sup>

### Contributions from keratinocytes

Keratinocytes promote itch by releasing additional pruritogens, including the alarmin TSLP, to directly activate pruritoceptive neurons.<sup>25,37,44</sup> Interestingly, keratinocytes express some of the same receptors that mediate pruritus sensation when expressed on neurons; this shared gene expression program may facilitate feed-forward loops in AD-associated itch. For example, mast cell proteases not only trigger pruritus via activation of PAR2<sup>+</sup> sensory afferent neurons,<sup>25</sup> but also stimulate release of TSLP from keratinocytes.<sup>37</sup> In addition to its direct role as a pruritogen, TSLP from keratinocytes promotes atopic skin inflammation and pruritus pathways indirectly by activating immune cells. TSLP binds to TSLPR on Th2 cells and type 2 innate lymphoid cells, leading to production of pruritogenic type 2 cytokines.<sup>45–47</sup> Additional keratinocyte alarmins (e.g. IL-33) function similarly.<sup>4</sup> IL-4 and IL-13 can also synergize to induce TSLP expression in keratinocytes,<sup>48</sup> suggesting that additional pathogenic signalling networks may sustain the inflammatory response and associated pruritus pathways in AD.<sup>46</sup>

### Neuronal inputs

Neuropeptides released by activated cutaneous neurons can also stimulate keratinocyte release of pro-inflammatory mediators, including substance P and calcitonin gene-related peptide (CGRP)<sup>49</sup>; this feed-forward mechanism could fuel further neurogenic inflammation, keratinocyte proliferation and epidermal thickening – processes implicated in AD lesion formation.<sup>25,50</sup> Both substance P and its receptor, neurokinin-1 (NK-1R), are overexpressed in pruritic AD lesional skin, as are TRPV2, TRPA1, Mrgprs, PAR2 and PAR4.<sup>27</sup> Substance P is a neuropeptide, i.e. factor secreted by peptidergic neurons, but it is also produced by keratinocytes.<sup>51</sup> In fact, as keratinocytes largely outnumber all other cell types in skin and therefore dominate whole-tissue transcriptional profiling, upregulation of TRP and PAR gene expression in AD lesional skin biopsy tissue probably also reflects gene expression in keratinocytes as well as neurons. These molecules represent potential new therapeutic targets to address the neuroimmune pathophysiology of itch in AD.

### Itch–scratch phenomenon in AD

Scratching itchy AD lesional skin injures epithelial keratinocytes, the consequences of which include release of inflammatory alarmins, direct and indirect activation of type 2 immune cells and

release of pruritogenic cytokines from both keratinocytes and immune cells.<sup>25</sup> Binding of these pruritogenic factors to pruritoceptive nerves triggers the desire to continue scratching. These feed-forward loops form the cellular and molecular basis of the ‘itch–scratch cycle’ in AD.<sup>52,53</sup>

### Neural sensitization of pruritus in AD

Sensitization describes the phenomenon that occurs with chronic itch (or pain) wherein a minimal stimulus leads to an enhanced neural response. In the setting of sensitization, the perception of itch (or pain) is enhanced, triggered by a lower threshold stimulus and may persist after the stimulus is removed. Many AD patients with chronic pruritus exhibit sensitization.

Neural sensitization of pruritus can occur peripherally and centrally.<sup>12</sup> Peripheral sensitization, defined by a decreased activation threshold of nociceptors on neurons, is induced by inflammatory mediators<sup>54</sup> and results in increased nerve fibre responsiveness and release of neurotransmitters such as glutamate and brain-derived neurotrophic factor.<sup>54,55</sup> In central sensitization, which can also be induced by decreased inhibitory synaptic transmission via GABA and glycine receptors,<sup>54</sup> CNS pathways couple non-pruritic stimuli to pruritic sensation (alloknesis) and overreact to pruritic stimuli (hyperknesis).<sup>56</sup> Within the spinal cord, both interneurons and astrocytes contribute to central sensitization.<sup>57,58</sup> In the skin of patients with AD, the threshold for electrically evoked itch is lower than in healthy controls,<sup>18,59,60</sup> and the sensitivity to pruritogens is increased.<sup>18</sup> Furthermore, a recent study found increased susceptibility to both cowhage and mechanically evoked itch, particularly intra-lesionally, in AD patients, a finding suggesting involvement of sensitization of the non-histaminergic pathway as well as mechanosensitive circuitry not normally associated with itch.<sup>61</sup> NK-1R- and GRPR-expressing dorsal spinal neurons were shown to play a key role in central sensitization, with involvement of NK-1R in both alloknesis and hyperknesis, and GRPR in hyperknesis alone.<sup>15</sup>

Inflammation plays a key role in neural sensitization, as peripheral sensitization induces activation of glial cells in the spinal cord via the release of adenosine triphosphate, chemokines and proteases.<sup>54,62</sup> Importantly, due to sensitization, alloknesis and hyperknesis persist after dermal inflammation has subsided, as illustrated by the intense itching experienced by patients with relatively mild eczema.<sup>63,64</sup>

Keratinocyte-derived nerve growth factor (NGF) has been linked to peripheral sensitization through induction of hyperinnervation.<sup>65,66</sup> It has also been associated with enhanced membrane current via upregulation of TRPV1 expression on cutaneous nerve endings.<sup>4</sup> In addition, NGF upregulates the release of substance P and CGRP by nerve fibres, which contribute to hyperknesis and neurogenic inflammation.<sup>18</sup> Direct communication between substance P and mast cells plays a role

**Table 1** Products approved or in development that have potential to manage itch in AD

Target	Compound	Status	Key clinical data	Magnitude of effect on itch	Reference		
Small molecule products	Upadacitinib	Phase 2b	Significantly reduced itch in moderate-to-severe AD by Week 1 throughout Week 16 and further to Week 32	Mean percent change from baseline in pruritus Numerical Rating Scale (NRS): <ul style="list-style-type: none"> <li>• Week 1: -19–36% (range for 7.5, 15 and 30 mg upadacitinib) vs. 1% with placebo; <math>P &lt; 0.001</math> vs. placebo</li> <li>• Week 16: -40–69% vs. -10%; <math>P &lt; 0.01</math> (7.5 mg) and <math>P &lt; 0.001</math> (15 and 30 mg) vs. placebo</li> <li>• Week 32: At all doses, treatment cohorts who continued to receive treatment rather than placebo after week 16 achieved further reduction in pruritus (NRS -44 to -53%), compared to treatment cohorts randomized to placebo (NRS +3 to +13%). Placebo cohorts randomized to treatment after Week 16 achieved -94% NRS</li> </ul>	AbbVie 2018 <sup>67</sup> ; AbbVie 2018 <sup>69</sup> ; ClinicalTrials.gov identifier: NCT02925117		
			JAK1, JAK3	Phase 2a	Significantly reduced itch in mild-to-moderate AD by Day 2 throughout Week 4	Least squares (LS) mean percent change from baseline in Itch Severity Item: <ul style="list-style-type: none"> <li>• Day 2 to Day 14 (diary-based LS mean) and Weeks 2 and 4 (clinical-based LS mean): <math>P &lt; 0.001</math> with 2% tofacitinib vs. placebo</li> </ul>	Bissonnette 2016 <sup>40</sup>
			PDE4	Phase 2	Significantly reduced itch in moderate-to-severe AD by Day 1 (night-time) and Week 1	Mean percent change from baseline in pruritus NRS: <ul style="list-style-type: none"> <li>• Day 1 (night-time score): <math>P &lt; 0.001</math> for the 0.5%, 1%, and 3% JTE-052 groups vs. placebo</li> <li>• Week 1 (night-time and daytime): <math>P &lt; 0.001</math> for the 0.5%, 1% and 3% groups vs. placebo</li> </ul>	Nakagawa 2018 <sup>70</sup>
PDE4	Crisaborole	Approved (mild-to-moderate AD)	Significantly improved itch in mild-to-moderate AD as early as Day 2 through Day 29	Proportions of patients achieving improvement in pruritus score 0 or 1 and $\geq 1$ -grade reduction (scale 0–4) from baseline: <ul style="list-style-type: none"> <li>• Day 2: 34.3% vs. 27.3%; <math>P = 0.013</math>; crisaborole vs. placebo-treated patients, respectively</li> <li>• Day 6: 56.6% vs. 39.5%; <math>P &lt; 0.001</math>; crisaborole vs. placebo-treated patients, respectively</li> </ul>	Yosipovitch 2018 <sup>68</sup>		
			Approved (COPD) Phase 2a	Significant improvement in patient assessment of itch in moderate AD by Day 15	Mean difference in pruritus score between the roflumilast- and placebo-treated groups: <ul style="list-style-type: none"> <li>• Day 15: 1.56, <math>P = 0.013</math></li> </ul>	ClinicalTrials.gov Identifier: NCT01856764	
			Approved (psoriasis and PsA); Phase 2 in AD	Significant improvement in itch in AD in an open-label trial by Week 2	Reduction in pruritus visual analog scale (VAS) by Week 2: <ul style="list-style-type: none"> <li>• <math>P = 0.045</math> (20 mg apremilast) and <math>P = 0.059</math> (30 mg apremilast)</li> </ul>	Samrao 2012 <sup>71</sup>	
PDE4	Apremilast	Approved (psoriasis and PsA); Phase 2 in AD	Non-significant improvement in itch in moderate-to-severe AD by Week 12	Mean percent change from baseline in pruritus VAS at Week 12: <ul style="list-style-type: none"> <li>• -3.9 and -16.2 vs. -9.8 (<math>P =</math> not significant) with 40 mg and 30 mg apremilast vs. placebo, respectively</li> </ul>	Simpson 2018 <sup>72</sup>		

Table 1 Continued

Target	Compound	Status	Key clinical data	Magnitude of effect on itch	Reference
	E6005/RVT-501	Phase 2	Non-significant reduction in itch in AD by Week 12	Mean percent difference (95% confidence interval [CI]) in Itch Behavioral Rating Scale score between the E6005 group and placebo: <ul style="list-style-type: none"> <li>Week 4: <math>-0.9</math> (<math>-19.9</math> to <math>18.2</math>); <math>P = NS</math></li> <li>Week 12: <math>P = 0.462</math></li> </ul>	Furue 2014 <sup>73</sup>
NGF (TrkA)	Pegcatriatinib (CT327) <sup>†</sup>	Phase 2b	Significantly reduced itch in adults with mild-to-moderate psoriasis	Significant reductions from baseline at Week 8 in pruritus VAS and Psoriasis Area Severity Index with 0.05% and 0.1% CT327 vs. placebo, respectively	Roblin 2015 <sup>74</sup>
$\alpha_2\delta$ -1 subunit of spinal N-type $Ca^{2+}$ channels	Gabapentin <sup>†</sup> , Pregabalin <sup>†</sup>	Approved (pain)	Significantly reduced itch of neuropathic origin	Commencement of pregabalin 75 mg twice daily and increased to 150 mg twice daily resulted in a more than 70% reduction in itch 5–8 weeks after treatment initiation	Ehrohen 2008 <sup>75</sup>
NK-1 receptor (antagonist)	Aprepitant <sup>†</sup> (oral)	Phase 1	Anti-pruritic effect observed as early as Day 2 in severe refractory chronic pruritus associated with several non-malignant conditions, including atopic diathesis and prurigo nodularis	16 out of 20 patients (80%) with chronic pruritus responded to short-term aprepitant monotherapy <ul style="list-style-type: none"> <li>Pruritus intensity on the VAS before treatment ranged from 5 to 10 (mean, 8.4; SD <math>\pm</math> 21.7; median VAS, 8)</li> <li>After treatment with aprepitant, pruritus intensity was reduced to a mean of 4.9 points (standard deviation [SD] <math>\pm</math> 3.2; <math>P &lt; 0.001</math>; CI, 1.913 to 5.187)</li> </ul>	Ständer 2010 <sup>76</sup>
	Serlopitant (oral) <sup>†</sup>	Phase 2	Significantly reduced itch in patients with severe refractory chronic pruritus of various aetiologies	Mean percent changes from baseline in pruritus NRS at Week 6: <ul style="list-style-type: none"> <li><math>-41.4</math> and <math>-42.5</math> vs. <math>-28.3</math> (<math>P = 0.022</math> and <math>P = 0.013</math>) with 1 mg and 5 mg serlopitant, respectively, vs. placebo (primary endpoint)</li> </ul>	Yosipovitch 2018 <sup>77</sup>
			Non-significant reduction of itch in a phase 2 trial in adolescents and adults with a history of AD	Mean absolute change from baseline in pruritus NRS at Week 6: <ul style="list-style-type: none"> <li>Treatment effect with 1 mg and 5 mg serlopitant, respectively vs. placebo: <math>-0.32</math> and <math>-0.23</math> (<math>P = 0.11</math> and <math>P = 0.17</math>)</li> </ul>	Menlo Therapeutics 2018 <sup>78</sup> , ClinicalTrials.gov Identifier: NCT02975206
			Significantly reduced several measures of itch in patients with prurigo nodularis	LS mean difference (95% CI) in average itch VAS scores between the serlopitant and placebo group: <ul style="list-style-type: none"> <li>Week 2: <math>-0.9</math> (<math>-1.5</math> to <math>-0.2</math>); <math>P = 0.0110</math></li> <li>Week 8: <math>-1.0</math> (<math>-1.8</math> to <math>-0.1</math>); <math>P &lt; 0.0001</math></li> </ul>	Ständer 2019 <sup>79</sup>
	Tradipitant (oral)	Phase 2	Significant and clinically meaningful improvements in several measures of itch in AD	Mean difference (95% CI) in average itch NRS scores between the serlopitant and placebo group: <ul style="list-style-type: none"> <li>Week 2: <math>-0.9</math> (<math>-1.6</math> to <math>-0.2</math>); <math>P = 0.009</math></li> <li>Week 8: <math>-1.4</math> (<math>-2.3</math> to <math>-0.4</math>); <math>P = 0.007</math></li> </ul>	Vanda Pharmaceuticals 2017 <sup>80</sup> , ClinicalTrials.gov Identifier: NCT02651714

Table 1 Continued

Target	Compound	Status	Key clinical data	Magnitude of effect on itch	Reference
Serotonin norepinephrine reuptake inhibitor	Mirtazapine†	Case series	Significant reduction in chronic nocturnal pruritus	Two of three cases had underlying AD, both reported itch symptom alleviation within 1 week on mirtazapine	Hundley 2004 <sup>81</sup>
µ-opioid receptor (antagonist)	Naltrexone	Placebo-controlled case series	Non-significant decrease in alokinesis and duration of acetylcholine-induced acute itch in AD patients		Heyer 2002 <sup>82</sup>
	Nalmefene (SRD174; topical)	Phase 2	Non-significant reduction in itch after two 7-day periods of treatment in adults with persistent moderate-to-severe pruritus associated with AD	The LS mean difference (95% CI) in sum of pruritus intensity difference from 0 to 4 h (SPID <sub>0-4</sub> ) between the SRD174 cream and placebo group was -1.3 (-25.9 to 23.3); <i>P</i> = 0.914 The LS mean difference (95% CI) in average daily pruritus score between the SRD174 cream and placebo group was -0.1 (-0.2 to 0.0); <i>P</i> = 0.095	Herzog 2011 <sup>83</sup>
κ-opioid receptor (agonist)	Nalfurafine (oral)†	Approved in Japan for uraemic pruritus	Significant reduction in pruritus in patients with liver disease in a phase 3 randomized, placebo-controlled trial	The changes in pruritus scores at Week 4 were: • 0.74 (95% CI, 0.59 to 0.90), 1.09 (0.94 to 1.24) and 1.01 (0.86 to 1.16) in the placebo, 2.5 µg and 5 µg nalfurafine groups, respectively The difference between the 2.5 µg group vs. placebo was 0.35 (0.13 to 0.56, <i>P</i> = 0.0007), and between 5 µg vs. placebo, 0.26 (0.05 to 0.47, <i>P</i> = 0.0071)	Kumada 2017 <sup>84</sup>
κ-opioid receptor (full agonist) and µ-opioid receptor (partial agonist)	Nalbuphine/Nubain† (extended-release tablet formulation)	Phase 2/3	Significant reduction in severe chronic uraemic pruritus in haemodialysis patients	The mean NRS (±SE) declined by 3.5 (2.4) and 2.8 (2.2) in the 120 mg nalbuphine and placebo groups, respectively ( <i>P</i> = 0.017 vs. placebo) from a baseline NRS of 6.9 (1.5)	Mathur 2017 <sup>85</sup> , ClinicalTrials.gov Identifier: NCT02373215
	Butorphanol†		Successfully completed a phase 2 trial for pruritus in patients with prurigo nodularis	Among the 12 of 18 enrolled patients who completed the 10-week study, the proportion who reported > 50% reduction in 7-day worst itch NRS vs. baseline achieved significance ( <i>P</i> = 0.028)	Trevi Therapeutics 2016 <sup>86</sup> , ClinicalTrials.gov Identifier: NCT02174419
κ-opioid receptor (agonist) and µ-opioid receptor (antagonist)			Significantly reduced itch in 5 patients with severe, chronic intractable pruritus	No specific data are reported (anecdotal only)	Dawn 2006 <sup>87</sup>
Spinal cannabinoid 1 receptor (agonist)	WIN 55,212-2†	Preclinical	Dose-dependently decreased serotonin-induced scratching in an animal study		Bilir 2018 <sup>88</sup>
Spinal cannabinoid 2 receptor (agonist)	N-palmitoyl ethanolanine (PEA)†	Open application observation	Reduced itch by 86.4% in 14/22 patients with prurigo, lichen simplex, and pruritus	The average reduction in itch was 86.4%	Ständer 2006 <sup>89</sup>
	S-777469†	Preclinical	Significantly reduced scratching behaviour induced by histamine or substance P in animal studies		Haruna 2015 <sup>90</sup>

Table 1 Continued

Target	Compound	Status	Key clinical data	Magnitude of effect on itch	Reference
Histamine 4 receptor (H4R)	ZPL-3893787	Phase 2	Non-significant decrease in pruritus in both treatment and control groups at Week 8; clinical implications unclear	Worst pruritus NRS mean change (SD) from baseline to Week 8 was -3.03 (2.186) with ZPL-3893787 and -2.66 (2.057) with placebo ( $P = 0.249$ ); TCS permitted as rescue (75.4% ZPL-3893787 and 84.8% placebo patients received rescue)	Werfel 2019 <sup>81</sup>
<b>Biologics</b>					
TSLP	Tezepelumab (monoclonal antibody)	Phase 2a	Marginal reduction in itch in moderate-to-severe AD	Adjusted mean percentage improvement ( $\pm$ SE) in pruritus NRS from baseline to Week 12 with tezepelumab + TCS vs. placebo + TCS was 35.53 (5.9) vs. 21.05 (5.9); $P = 0.050$ vs. placebo Adjusted mean percentage improvement ( $\pm$ SE) in peak pruritus NRS from baseline to Week 12 with tezepelumab + TCS vs. placebo + TCS was 33.54 (6.0) vs. 25.41 (6.1); $P = 0.258$ vs. placebo	Simpson 2019 <sup>92</sup>
IL-33 (ST2)	IL-33 mouse antibody†	Preclinical	Scratching behaviour was reduced in an animal model		Peng 2018 <sup>83</sup>
IL-4R $\alpha$ (IL-4 and IL-13)	Dupilumab (monoclonal antibody)	Approved (moderate-to-severe AD)	Significantly reduced itch in moderate-to-severe AD for up to 52 weeks in phase 3 studies; reduction in itch was reported as early as Day 2 in a post-hoc analysis	LS mean percent change from baseline ( $\pm$ SE) in peak pruritus NRS score: • At Day 2 (pooled LIBERTY AD SOLO 1 and 2 phase 3 studies): -4.0% (0.1) and -4.5% (1.0) vs. -0.6% (1.0); $P = 0.0110$ and $P = 0.0033$ ; qw and q2w vs. placebo, respectively LS mean percent change from baseline ( $\pm$ SE) in peak pruritus NRS score: • At Week 52 (LIBERTY AD CHRONOS): -54.4% (2.6) and -56.2% (4.4) vs. -27.1% (2.7); $P \leq 0.0001$ ; qw + TCS and q2w + TCS vs. placebo + TCS, respectively Proportions of patients achieving peak pruritus NRS $\geq 3$ -point improvement from baseline: • At Week 52 (LIBERTY AD CHRONOS phase 3 study): 43% and 56% vs. 16%; $P < 0.0001$ ; dupilumab 300 mg qw and 300 mg q2w vs. placebo, respectively	Silverberg 2017 (pooled SOLO 1 and 2) <sup>41</sup> ; Blauvelt 2017 (CHRONOS) <sup>8</sup> ; Simpson 2016 <sup>7</sup>
IL-22	Fezakinumab (monoclonal antibody)	Phase 2a	Non-significant difference in itch in moderate-to-severe AD by Week 12	No significant differences in SCORing Atopic Dermatitis VAS pruritus score, but a sustained treatment effect was observed among patients with baseline pruritus > 5 after Week 12 vs. placebo	Guttman-Yassky 2018 <sup>94</sup>
IL-13	Lebrikizumab (monoclonal antibody)	Phase 2; phase 2b	Numerical reduction in itch in moderate-to-severe AD by Week 12 (phase 2); no itch data available yet from phase 2b study	Adjusted mean percent reductions from baseline pruritus VAS at Week 12 were: • Placebo response group 27.5% • Lebrikizumab 125 mg single dose 34.9% ( $P = 0.40$ ), 250 mg single dose 32.8% ( $P = 0.54$ ), 125 mg q4w 40.7% ( $P = 0.13$ )	Simpson 2018 <sup>95</sup> , ClinicalTrials.gov Identifier: NCT03443024 (phase 2b)



Table 1 Continued

Target	Compound	Status	Key clinical data	Magnitude of effect on itch	Reference
IL-17A	Tralokinumab (monoclonal antibody)	Phase 2b	Significant reduction in itch in moderate-to-severe AD by Week 12	Improvements (95% CI) with tralokinumab-treated patients vs. placebo for pruritus NRS at Week 12: <ul style="list-style-type: none"> <li>• 45 mg tralokinumab adjusted mean difference, -0.77 (-1.52 to -0.02); nominal <math>P = 0.04</math>, and 300 mg tralokinumab -1.14 (-1.88 to -0.41); nominal <math>P = 0.002</math></li> </ul> No data available yet	Wollenberg 2019 <sup>96</sup>
IL-17A	Secukinumab (monoclonal antibody)	Phase 2; approved for psoriasis	A placebo-controlled trial assessing the efficacy and safety of secukinumab in moderate-to-severe AD is currently in recruitment	No data available yet	Clinicaltrials.gov Identifier: NCT02594098
IL-17A	Ixekizumab (monoclonal antibody)	Phase 3	Significant, rapid reduction in itch in moderate-to-severe psoriasis by Week 12	Greater differences in time to pruritus NRS $\geq 4$ -point improvement for patients treated with ixekizumab every 2 weeks or every 4 weeks vs. placebo ( $P < 0.001$ ) The median time for 50% of patients to achieve a $\geq 4$ -point reduction in pruritus NRS was shorter for ixekizumab-treated patients (2 weeks, with both 80 mg ixekizumab every 4 weeks and every 2 weeks) compared with placebo-treated patients ( $> 12$ weeks)	Leonardi 2017 <sup>97</sup>
IL-31RA	Nemolizumab (monoclonal antibody)	Phase 2; phase 2 long-term extension	Significantly decreased itch in moderate-to-severe AD by Week 12 (phase 2 randomized trial) and Week 64 (open-label extension)	Changes on the pruritus VAS were: <ul style="list-style-type: none"> <li>• At Week 12: -43.7% (0.1 mg q4w nemolizumab group), -59.8% (0.5 mg q4w group), and -63.1% (2.0 mg q4w group), vs. -20.9% with placebo (<math>P &lt; 0.01</math> for all comparisons)</li> <li>• At Week 64: -73.0% (0.1 mg q4w nemolizumab group), -89.6% (0.5 mg q4w group), -74.7% (2.0 mg q4w group), and -79.1% (2.0 mg q8w group)</li> </ul>	Ruzicka 2017 <sup>10</sup> , Kabashima 2018 <sup>11</sup>

†Agents effective in itch but not tested in AD.

AD, atopic dermatitis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GABA, gamma-aminobutyric acid; LS, least squares; NGF, nerve growth factor; NRS, numerical rating scale; PsA, psoriatic arthritis; q2w, every 2 weeks; q4w, every 4 weeks; qw, every week; SD, standard deviation; SE, standard error; VAS, visual analog scale.

in the sensitization of nociceptors on nerve terminals by enhancing their responsiveness.

### Current therapeutic targets and treatments for atopic itch

Studies of neuroimmune pathways have provided novel approaches for reducing itch in AD. New and emerging treatments for atopic itch are discussed here and summarized in the Table 1. We included agents that have been tested in AD, and also those which may be of benefit based upon current scientific understanding of the pathogenesis of itch in AD.

Several monoclonal antibodies targeting IL-4, IL-13, IL-22 or IL-31 have been investigated in AD clinical trials (Table 1). Nemolizumab (anti-IL-31RA), tralokinumab (anti-IL-13) and dupilumab (anti-IL-4R $\alpha$ ) all significantly reduced itch in AD, whereas lebrikizumab (anti-IL-13) only numerically reduced AD-related itch (Table 1). Dupilumab is a human monoclonal antibody that blocks the shared receptor subunit for IL-4 and IL-13 (IL-4R $\alpha$ ), thus inhibiting signalling of both IL-4 and IL-13. As IL-4R $\alpha$ -mediated type 2 cytokine signalling via Janus kinase-signal transducers and activators of transcriptions (JAK-STAT) in sensory neurons promotes itch,<sup>38</sup> dupilumab may also directly attenuate itch symptoms by inhibiting neuronal IL-4R $\alpha$  and JAK signalling in addition to reducing type 2 inflammation. A novel human monoclonal anti-TSLP antibody (MEDI9929), given concomitantly with topical corticosteroids, only marginally reduced itch (compared with placebo) in a recently completed study in adults with moderate-to-severe AD (Table 1), a finding suggesting that not all compounds targeting specific itch mediators have an anti-pruritic effect in AD. Antibody-mediated inhibition of IL-33, on the other hand, has been effective in an AD animal model and safe and tolerable in a phase 1 clinical trial (Table 1).

As a result of increasing appreciation for the neural contribution to AD-associated itch pathophysiology, neurally acting agents may serve as new therapeutic alternatives to immunomodulatory agents for AD. Treatments targeting GABA, TRPA1, NK-1R, opioid and cannabinoid receptors are yet to be investigated in AD but have been effective in chronic itch of other aetiologies. Based upon their mechanisms of action, they have potential to alleviate AD-associated itch. Selective JAK inhibitors and phosphodiesterase 4 (PDE4) inhibitors have shown efficacy in AD. Oral upadacitinib, a JAK1-selective inhibitor, was recently granted Breakthrough Therapy designation for AD by the US Food and Drug Administration,<sup>67</sup> and crisaborole, a topical treatment that inhibits PDE4 signalling, was approved in Europe and the US for the treatment of mild-to-moderate AD in patients aged  $\geq 2$  years.<sup>17,68</sup> Both agents were effective in reducing itch (Table 1).

### Conclusions

Recent studies provide strong support for crosstalk between the nervous and immune systems in chronic atopic itch. Further

elucidating the roles of peripheral and central sensitization and hypersensitization is key to understanding the chronicity and severity of itch in AD. Novel approaches, such as the use of agents that target neural or neuroimmune pathways, may provide additional treatment options for AD, thereby improving outcomes for AD patients and potentially other chronic pruritic diseases.

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