Emerging Therapeutic Options for Chronic Pruritus

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Abstract
Chronic pruritus, defined as an unpleasant sensation resulting in a need to scratch that lasts more than 6 weeks, is a prevalent and bothersome symptom associated with both cutaneous and systemic conditions. Due to complex pathogenesis and profuse contributing factors, chronic pruritus therapy remains challenging. Regardless of the well-established antipruritic properties of classic pharmacotherapy (topical therapy, phototherapy and systemic therapy), these methods often provide insufficient relief for affected individuals. Owing to the growing interest in the field of pruritic research, further experimental and clinical data have emerged, continuously supporting the possibility of instigating novel therapeutic measures. This review covers the most relevant current modalities remaining under investigation that possess promising perspectives of approval in the near future, especially opioidergic drugs (mu-opioid antagonists and kappa-opioid agonists), neurokinin-1 receptor antagonists, biologic drugs, Janus kinase inhibitors, ileal bile acid transporter inhibitors, aryl hydrocarbon receptor agonists and histamine H4 receptor antagonists.

1 Introduction
Chronic pruritus (CP), defined as an unpleasant sensation resulting in a need to scratch that lasts more than 6 weeks, is a prevalent and bothersome symptom associated with cutaneous conditions (such as psoriasis, atopic dermatitis [AD], lichen planus [LP], etc.); however, primarily extracutaneous ailments may also play a role in the occurrence of CP [1, 2]. Prominent examples of the latter include end-stage renal disease (ESRD), diabetes mellitus, hypothyroidism, chronic hepatobiliary conditions, or malignancies, to name just a few. The etiology of CP may be comprehensively classified as dermatologic, systemic, neurologic, psychogenic, mixed or unknown. Therefore, physicians other than dermatologists also frequently encounter this phenomenon in both outpatient and clinical settings. The burden of CP stems from a marked decrease in various domains of health-related quality of life (HRQoL) [3–5].

The pathogenesis of CP is particularly complex. Two major neuronal pathways are mentioned: histaminergic and non-histaminergic, with the latter mainly associated with CP [6]. CP in the course of AD (serving as an example of a ‘classic’ itchy disorder) may be regarded as a result of crosstalk between nervous system, cutaneous immune system and keratinocyte populations [7]. The crucial pathogenetic aspects of CP, such as the interactions between various pruritogens and their receptors, and the description of itch pathways with regard to peripheral nervous system (PNS)
and central nervous system (CNS) processing in different regions, including neural sensitization, have been reviewed in great detail by Yosipovitch et al. [6, 7].

Despite the abundance of therapeutic measures, the alleviation of CP remains challenging. According to expert consensus, the therapeutic measures may be divided into several groups: general recommendations (including frequent application of emollients), topical therapy (e.g. corticosteroids, calcineurin inhibitors, crisaborole), phototherapy and systemic therapy [2]. The latter is usually reserved for patients with the most severe symptoms. Currently, the majority of antipruritic modalities are still utilized off-label. The detailed characteristics of well-established antipruritic modalities lie beyond the scope of this review and are described in detail elsewhere. Owing to the growing interest in the field of pruritic research, further experimental and clinical data emerge, continuously supporting the possibility of instigating novel therapeutic measures. This review covers the most relevant current drugs, predominantly remaining under investigation, with promising perspectives of approval in the near future, especially opioidergic drugs (mu-opioid antagonists and kappa-opioid agonists), neurokinin-1 receptor (NK-1R) antagonists, biologic drugs, Janus kinase (JAK) inhibitors, ileal bile acid transporter (IBAT) inhibitors, aryl hydrocarbon receptor (AhR) agonists and histamine receptor type 4 antagonists, as well as other modalities (Table 1).

2 Opioid Receptor Agonists and Antagonists

An endogenous opioid system is associated with numerous functions in the organism, with its key elements constituting endogenous opioid peptides (β-endorphin, enkephalins and dynorphins) and opioid receptors (mu, kappa, delta and nociceptin/orphanin FQ receptor (NOP-R)), which are especially prevalent in the CNS, PNS and the skin [8–10]. Exogenous opioids implemented in clinical practice may stimulate pruritic responses in an individual, mostly as adverse effects (AEs) of epidural, intraspinal or intrathecal administration [11]. Relevant studies performed on primates revealed not only that mu-opioid agonists induced pruritus but also the sensation was relieved following the administration of mu-opioid antagonists or kappa-opioid agonists [12–14]. In fact, decreased expression of kappa-opioid receptors in human skin was associated with pruritus in the course of AD [15], psoriasis [16, 17] and ESRD [18]. Throughout the years, several drugs targeting opioid receptors have revealed certain antipruritic properties, especially as a preoperative prophylaxis, as well as in uremic pruritus (UP) or cholestatic pruritus (CP). ‘Classic’ antipruritics with predominant mu-opioid antagonist activity comprised naltrexone [19–21], naltrexone [22–25] and nalmefene [26, 27]. Drugs possessing mixed mu-opioid antagonism and kappa-opioid agonism (butorphanol, nalbuphine) also alleviated itch in a variety of conditions [28–32].

2.1 Nalbuphine

A recent phase II/III randomized, double-blind trial on nalbuphine was performed in patients with UP [33]. Nalbuphine in extended-release tablets was administered orally in 128 and 120 patients (starting with 60 and 120 mg/day, respectively, and later increasing to 120 and 240 mg/day, respectively), while 125 patients received placebo. The mean changes from baseline Worst Itch Numeric Rating Scale (WI-NRS) score (6.8–6.9 points) were −3.1, −3.5 and −2.8 points, respectively; p=0.017 compared with placebo. In patients with a baseline NRS score of at least 7.0 points (mean 8.0 points), nalbuphine 240 mg/day provided better WI-NRS score alleviation than placebo (−4.5 vs. −3.2; p<0.01). Nalbuphine was also successfully evaluated in patients with chronic prurigo (n=62) [34], and the results of a further phase IIb/III study on 240 participants (PRISM) are awaited in 2020 [35].

2.2 Nalfurafine

Nalfurafine possesses a selective kappa-opioid agonism and currently remains the only drug registered for the treatment of UP and CP (exclusively in Japan). Its properties have been initially confirmed in 144 hemodialysis patients with pruritus who experienced a higher number of days with non-disturbing itching and number of nights with good sleep after intravenous administration [36]. Subsequent studies on nalfurafine administered orally supported its effectiveness and safety in managing UP [37–39], including patients on peritoneal dialysis [40]. Notably, a postmarketing surveillance study was conducted in 3762 patients on hemodialysis, revealing good antipruritic response within 12 weeks in 82.5% of patients [41]. Recent studies have also evaluated nalfurafine as a drug potentially ameliorating pruritus due to chronic liver diseases [42, 43]. Unfortunately, a preliminary study suggested that within 4 weeks of nalfurafine discontinuation there is a 100% risk of pruritus recurrence [44]. Moreover, excluding the initial study by Wikström et al. [36], several subsequent studies have concordantly mentioned insomnia as the most common AE associated with nalfurafine intake [37, 38, 40, 41].

2.3 Difelikefalin

Another compound currently receiving growing interest, difelikefalin (CR845), is selective towards peripheral kappa-opioid receptors in the skin as it is not able to cross the blood–brain barrier [45]. In a phase II randomized trial among subjects with UP, difelikefalin was administered intravenously (after a
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#### Table 1  Emerging drugs with antipruritic properties

| Drug name          | Mechanism of action                                      | Route of administration | Indications                                                                 | References |
|--------------------|-----------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------|------------|
| **Mu-opioid antagonists/kappa-opioid agonists**          |                                                           |                         |                                                                             |            |
| Nalbuphine         | Mu-opioid antagonist, kappa-opioid agonist                | Intravenous, oral       | UP, chronic prurigo                                                        | [33–35]    |
| Nalfurafine        | Kappa-opioid agonist                                      | Intravenous, oral       | UP, cholestatic pruritus                                                   | [36–44]    |
| Difelikefalin       | Kappa-opioid agonist (peripheral)                         | Intravenous, oral       | UP, PBC<sup>a</sup>                                                        | [46–49]    |
| **NK-1R antagonists** |                                                           |                         |                                                                             |            |
| Aprepitant         | NK-1R antagonist                                          | Oral                    | Pruritus in Sezary syndrome, Pruritus in solid tumors, Pruritus due to antitumor therapies, Chronic prurigo | [54–59]    |
| Serlopitant        | NK-1R antagonist                                          | Oral                    | Chronic prurigo, psoriasis, epidermolysis bullosa<sup>a</sup>               | [60, 61, 65, 67] |
| Tradipitant        | NK-1R antagonist                                          | Oral                    | AD                                                                          | [68, 70]   |
| **Biologic drugs** |                                                           |                         |                                                                             |            |
| **IL-13 antagonists** |                                                           |                         |                                                                             |            |
| Dupilumab          | IL-4 and IL-13 antagonist                                 | Subcutaneous            | AD, urticaria, chronic prurigo, BP, chronic refractory pruritus             | [79–97]    |
| Lebrikizumab       | IL-13 antagonist                                          | Subcutaneous            | AD                                                                          | [100, 101] |
| Tralokinumab       | IL-13 antagonist                                          | Subcutaneous            | AD<sup>a</sup>                                                             | [103–106]  |
| **IL-17 antagonists** |                                                           |                         |                                                                             |            |
| Secukinumab        | IL-17A antagonist                                         | Subcutaneous            | Psoriasis, AD<sup>a</sup>                                                  | [111–114, 243, 244] |
| Ixekizumab         | IL-17A antagonist                                         | Subcutaneous            | Psoriasis                                                                  | [116–118, 123, 245–247] |
| Brodalumab         | IL-17A receptor antagonist                               | Subcutaneous            | Psoriasis                                                                  | [120]      |
| **IL-23 antagonists** |                                                           |                         |                                                                             |            |
| Ustekinumab        | IL-12 and IL-23 antagonist                                | Subcutaneous            | Psoriasis                                                                  | [123, 129] |
| Risankizumab       | IL-23 antagonist                                          | Subcutaneous            | Psoriasis, AD<sup>a</sup>                                                  | [124, 248] |
| Guselkumab         | IL-23 antagonist                                          | Subcutaneous            | Psoriasis                                                                  | [129, 247, 249] |
| Tildrakizumab      | IL-23 antagonist                                          | Subcutaneous            | Psoriasis<sup>a</sup>                                                      | [132–136]  |
| **Drugs targeting the IL-31 pathway**                   |                                                           |                         |                                                                             |            |
| Nemolizumab        | IL-31RA antagonist                                        | Subcutaneous            | AD, chronic prurigo                                                        | [139, 140, 250–254] |
| Vixarelimab (KPL-716) | OSMRβ antagonist                                      | Subcutaneous            | AD, chronic pruritic disorders (chronic idiopathic urticaria, chronic idiopathic pruritus, LP, lichen simplex chronicus, plaque psoriasis),<sup>a</sup> chronic prurigo | [141–143]  |
| **IgE antagonists** |                                                           |                         |                                                                             |            |
| Ligelizumab        | IgE antagonist (targets free IgE, FceRI and surface IgE) | Subcutaneous            | Chronic spontaneous urticaria                                              | [145]      |
| **JAK inhibitors** |                                                           |                         |                                                                             |            |
| Ruxolitinib        | JAK inhibitor                                             | Topical, oral           | AD, polycythemia vera, essential thrombocytosis, primary myelofibrosis, LP,<sup>a</sup> cGvHD<sup>a</sup> | [149–157]  |
| Baricitinib        | JAK inhibitor                                             | Oral                    | AD, psoriasis                                                              | [158–164]  |
| Tofacitinib        | JAK inhibitor                                             | Oral, topical           | Psoriasis, AD                                                              | [166–174]  |
| Abrocitinib        | JAK inhibitor                                             | Oral                    | AD                                                                         | [175–179]  |
| Upadacitinib       | JAK inhibitor                                             | Oral                    | AD                                                                         | [181–186]  |
| Delgocitinib       | JAK inhibitor                                             | Topical                 | Chronic hand eczema, AD                                                   | [188–191]  |

<sup>a</sup> AD: Atopic dermatitis, BP: Bullous pemphigoid, CGVHD: Chronic graft-versus-host disease, LP: Lichen planus, PBC: Primary biliary cirrhosis, UP: Urticarial prurigo.
hemodialysis session) thrice weekly for 8 weeks in doses of 0.5, 1.0 or 1.5 mg/kg to 44, 42 and 44 patients, respectively, while 45 patients received placebo [46]. At week 8, patients receiving difelikefalin were significantly more prone to experience alleviation of pruritus (at least -3 points in the WI-NRS) when compared with placebo (59% vs. 29%; p = 0.001), as well as significant improvement in itch-related QoL. The reduction from the baseline Skindex-10 total score at week 8 was −16.4 and −8.2, respectively (p < 0.001). Moreover, the active group reported less problems with sleep, as measured by the Medical Outcomes Study sleep disturbance questionnaire (p = 0.005).

A further double-blind, placebo-controlled, phase III trial (KALM-1) encompassed 189 patients receiving difelikefalin (0.5 mg/day intravenously after hemodialysis) and 188 patients receiving placebo [47]. Significantly more patients receiving difelikefalin experienced at least 3 points of improvement in pruritus (49.1% vs. 27.9%; p < 0.001). The most common AEs were diarrhea, dizziness and nausea/vomiting [46, 47]. Notably, the beneficial WI-NRS response of difelikefalin started to unveil after 1 week of treatment. The results of further studies on oral difelikefalin, especially in UP [48] and primary biliary cholangitis (PBC) [49], are highly anticipated.

### 3 Neurokinin-1 Receptor Antagonists

Substance P (SP) belongs to the group of tachykinins, which are small neuropeptides released by neurons and inflammatory cells [50]. SP binds to NK-1R, as well as the Mas-related G protein-coupled receptor (Mrgpr). NK-1R is more substantiated in eliciting pruritic response in humans as it induces vasodilatation, degranulation of mast cells, nerve growth factor (NGF) expression in keratinocytes and stimulates neurogenic inflammation [51]. In the study by Nattkemper et al. [52], the authors utilized RNA sequencing and observed increased levels of both SP and NK-1R in lesional skin of patients with psoriasis and AD who experienced severe pruritus.

#### 3.1 Aprepitant

Aprepitant is an oral NK-1R antagonist that is currently registered for the prevention of chemotherapy-induced and postoperative nausea and vomiting [53]. Aprepitant demonstrated antipruritic activities in patients with Sezary syndrome, solid tumors and those receiving antitumoral drugs such as epidermal growth factor receptor inhibitors (EGFRIs) and tyrosine kinase inhibitors [54–57]. In a German study, 20 patients with chronic refractory pruritus (due to systemic and mixed causes) received aprepitant 80 mg/day for 3–13 days (mean 6.6 days) [58]. Eighty percent of patients (16/20) responded to the regimen. Agelopoulos et al. [59] recently reported on the usefulness of aprepitant in chronic prurigo. Of 12 patients receiving aprepitant (80 mg/day), the mean visual analog scale (VAS) pruritus score decreased from 6.3 ± 1.3 points at baseline to 4.5 ± 2.9 points after 8 weeks (p < 0.05).
3.2 Serlopitant

Two phase II studies on a novel oral NK-1R antagonist, serlopitant, were also reported. Yosipovitch et al. [60] utilized serlopitant among patients with CP refractory to standard treatment in doses of 0.25 mg/day (n = 64), 1 mg/day (n = 65) and 5 mg/day (n = 64), whereas 64 patients received placebo. On the first day of treatment, patients in the active groups received loading doses of either 0.75 mg/day, 3 mg/day or 15 mg/day. At week 6, the mean percentage decreases from baseline in terms of VAS pruritus score were statistically significantly greater in the 1 mg/day (p = 0.02) and 5 mg/day (p = 0.01) groups when compared with the placebo group. Moreover, the beneficial effects remained 4 weeks after the completion of treatment. In the study by Ständer et al. [61], serlopitant (5 mg/day; on the first day patients received a loading dose of 15 mg/day) was administered to 65 patients with chronic prurigo, while placebo was administered to 63 subjects. The mean baseline average itch VAS score was approximately 7.9 in both arms. At weeks 2, 4 and 8, the mean average itch VAS scores decreased to 6.2, 5.5 and 4.4, respectively (serlopitant group), and 7.1, 6.5, 6.1, respectively (placebo group). At weeks 4 and 8, there was a statistically significantly greater decrease from baseline in pruritus intensity (measured by average VAS score) when comparing serlopitant with placebo (p = 0.025 at week 4 and p = 0.001 at week 8). Unfortunately, a phase II trial on serlopitant in CP of unknown origin, and two phase III trials on serlopitant in chronic prurigo, have all failed to meet their primary endpoints regarding pruritus alleviation [62, 63]. Moreover, the ATOMIK study revealed that serlopitant failed to provide additional benefit over placebo in managing pruritus in the course of AD [64]. In 2020, Pariser et al. [65] reported the results of a phase II, randomized, double-blind, placebo-controlled trial among patients with mild-to-moderate psoriasis. Serlopitant (5 mg/day, starting with a loading dose of 15 mg/day on the first day) or placebo were administered to 102 patients each. At week 8, 33.3% of patients treated with serlopitant achieved a 4-point improvement from baseline (assessed with WI-NRS), compared with 21.1% in patients treated with placebo (p = 0.028). Additionally, 20.8% of patients treated with serlopitant achieved a 4-point improvement from baseline on the WI-NRS at week 4 (compared with 11.5% of patients treated with placebo; p = 0.039). A preliminary study on serlopitant in epidermolysis bullosa (mainly recessive dystrophic type; n = 14) revealed no benefit over placebo in terms of itch reduction or wound size at week 8 [66]. A study involving a larger group of participants is ongoing [67].

3.3 Tradipitant

A phase II study on the effectiveness of tradipitant (VLY-686) in managing pruritus in the course of AD (n = 168) revealed promising results [68]. In the subsequent phase III study (EPIONE), the primary endpoint was not met in the overall study population (n = 341) [69], whereas the EPIONE2 study (n = 200) is ongoing [70].

3.4 Orvepitant

Finally, a randomised, placebo-controlled, phase II trial evaluated orvepitant in patients (n = 44) experiencing severe pruritus caused by EGFRIs, revealing no benefits over placebo [71].

4 Biologic Drugs

Biologics are large molecules targeting specific proteins implicated in immune-mediated diseases. In dermatology, the approved therapies alter T-cell activation and differentiation, block cytokines or eliminate pathogenic B cells. Depending on their mechanism of action, biologic medications have been used for a variety of dermatologic indications, mainly psoriasis and AD [72]. Cytokines are ‘messenger’ proteins, which mediate a series of cellular functions, including immune cell recruitment, activation and differentiation [73]. It has been long known that cytokines create part of the immune system and modulate both adaptive and innate immune responses. They have also been identified as modulators of pain and neurogenic inflammation [74]. Additionally, they can act on resident skin cells, including keratinocytes, Langerhans cells, endothelial cells, fibroblasts and mast cells [75]. In recent years, a considerable amount of proof regarding cytokines playing a role in pruritus has been presented, substantiating the use of targeted therapies with biologics for several chronic inflammatory dermatoses.

4.1 Interleukin (IL)-4 and IL-13

Both interleukin (IL)-4 and IL-13 are cytokines produced by T-helper 2 (Th2) cells and play an important role in the development of AD. Their expression correlated with IL-31 levels in the skin biopsies of patients with AD [76]. Additionally, the studies on murine model in atopic-like mice indicated that IL-4 could play a significant role in inflammation and pruritus of AD patients [77].

4.1.1 Dupilumab

Dupilumab is a commercialized monoclonal antibody (mAb) against the IL-4 receptor-α (IL-4Rα) subunit, blocking
IL-4 and IL-13 signaling [78]. Several randomized trials have been performed on the efficacy of dupilumab in patients with moderate to severe AD, enabling its registration for this indication [79–86]. All the studies confirmed the efficacy of dupilumab in terms of improvement of skin lesions and alleviation of pruritus. Dupilumab was generally well-tolerated and had a placebo-like safety profile. A representative phase III report recounted the SOLO 1 and SOLO 2 trials (n = 671 and n = 708, respectively) [81]. At week 16, an improvement of at least 3–4 points in the peak pruritus NRS score was significantly more common among patients receiving dupilumab than patients receiving placebo (p < 0.001). A meta-analysis of 1505 patients with moderate to severe AD revealed that dupilumab started to unveil its antipruritic properties by days 2 and 5 in adults and adolescents, respectively [87]. The response increased over time and was sustained until the end of the studies (up to 1 year). Recent papers have also reported on 31 patients receiving dupilumab due to chronic prurigo [88–93]. The majority of patients experienced significant pruritus reduction starting to unfold within 4 weeks, followed by more gradual flattening or disappearance of lesions within several months of the initiation of therapy. Furthermore, dupilumab established its efficacy in case reports regarding patients with bullous pemphigoid (BP) [94, 95], chronic refractory pruritus [96] and UP [97]. Clinical trials on the use of dupilumab in chronic spontaneous and cholinergic urticaria are in progress [98, 99].

4.1.2 Lebrikizumab

Lebrikizumab is an anti-IL-13 humanized mAb that binds specifically to soluble IL-13 with high affinity and blocks subsequent signaling [100]. In a recent phase IIb randomized, double-blind study, AD patients received subcutaneous injections of lebrikizumab in different dosages, i.e. 125 mg every 4 weeks (250 mg loading dose; n = 73), 250 mg every 4 weeks (500 mg loading dose; n = 80) or 250 mg every 2 weeks (500 mg loading dose at baseline and week 2; n = 75), while 52 patients received placebo. At week 16, the mean NRS pruritus score percentage changes were −35.9%, −49.6%, −60.6%, and 4.3% of patients, respectively (p = 0.05, p < 0.001 and p < 0.001 compared with placebo, respectively) [101].

4.1.3 Tralokinumab

Tralokinumab is a sole anti-IL-13 human mAb that prevents binding of IL-13 to its receptor [102]. The efficacy and safety of tralokinumab in patients with AD was evaluated in a phase IIb, double-blind, randomized study. The decrease in pruritus assessed with NRS at week 12 was statistically significantly greater than in the placebo group for all dosing regimens (p = 0.04 for the 45 mg dose; p = 0.002 for the 300 mg dose). Notably, the decrease began from the first week and was maintained until the end of the observation period [103]. Trials are currently being undertaken on the use of tralokinumab in AD, its interaction with other drugs and its combination with topical corticosteroids [104–106].

4.2 IL-17

The IL-17 family consists of six cytokines (17A–17F) and five receptors (17RA–17RE). IL-17A is an inflammatory cytokine produced by Th17 cells [107, 108]. It is commonly associated with autoimmune diseases, cancer progression and pathoimmunology [109]. There is wide evidence suggesting its role in the pathogenesis of psoriasis. IL-17 acts on a variety of cells, including keratinocytes, to stimulate the production of a number of molecules known to be elevated in psoriasis lesions (cytokines, chemokines, β-defensins) [110]. Additionally, the expression of IL-17 in skin biopsies is significantly elevated in lesional skin of patients with psoriasis [110].

4.2.1 Secukinumab

Secukinumab is a human mAb selectively neutralizing IL-17A and has been shown to be effective in the treatment of psoriasis. In two representative, phase III, double-blind, randomized studies (FIXTURE and ERASURE) [111] regarding the use of secukinumab in psoriatic patients (n = 1306 and n = 738, respectively), a significant antipruritic response was observed at week 12 according to the Psoriasis Symptom Diary (p < 0.001 compared with placebo and etanercept). Thaci et al. [112] evaluated the use of secukinumab and ustekinumab and exhibited a significantly greater decrease of itch (NRS) at week 16 in patients treated with secukinumab (−5.0 vs. −4.6; p = 0.0053). Two phase II clinical trials on the role of secukinumab in AD treatment are currently underway [113, 114].

4.2.2 Ixekizumab

IxEkizumab is a high-affinity, humanized mAb that targets IL-17A [115]. In their analysis of two phase III studies, Yosipovitch et al. [116] established that a large number of psoriatic patients, regardless of baseline itch severity, achieved a clinically meaningful reduction in itch severity preceding Psoriasis Area Severity Index (PASI 90) responses. IxEkizumab also significantly reduced pruritus associated with genital psoriasis, with a rapid onset of action unfolding within the first 2 weeks of therapy [117, 118].
4.2.3 Brodalumab

Brodalumab is a human mAb that targets the IL-17A receptor and blocks the IL-17 pathway [119]. In the study by Gottlieb et al. [120], the Psoriasis Symptom Inventory (PSI) itch item score was significantly improved with both brodalumab 140 mg and 210 mg versus placebo starting at week 2 (30.5% and 36.1%, respectively, vs. 7.8%; \( p < 0.001 \)). Additionally, brodalumab induced a more rapid antipruritic response when compared with ustekinumab.

4.3 IL-23

IL-23 is a proinflammatory cytokine consisting of two subunits (p19 and p40) and plays an important role in the pathogenesis of psoriasis [121]. It stimulates proliferation of the Th17 lymphocyte population, subsequently producing IL-17A and other proinflammatory cytokines [122].

4.3.1 Ustekinumab

Ustekinumab is a human mAb that targets the shared p40 subunit of the proinflammatory IL-12 and IL-23 cytokines. Its efficacy and safety has been demonstrated in the treatment of psoriasis [123, 124]. In the study by Reich et al. [123], both ustekinumab \(( n = 166)\) and ixekizumab \(( n = 136)\) provided itch alleviation in terms of NRS reduction at week 24. However, patients who experienced at least a 4-point improvement from baseline NRS were more common in the ixekizumab group (85.5% vs. 72.1%; \( p = 0.018 \)).

4.3.2 Risankizumab

Risankizumab is a human monoclonal immunoglobulin (Ig) G antibody that binds with high affinity to the p19 subunit of IL-23 [124]. When compared with ustekinumab \(( n = 40)\), patients receiving risankizumab \(( n = 126)\) were more likely to experience PASI 90 improvement at week 12 (40% vs. 77%; \( p < 0.001 \)), as well as in terms of pruritus (assessed by patients’ assessment of itch).

4.3.3 Guselkumab

Guselkumab is a human IgG1λ mAb that binds to the p19 subunit of IL-23 [125]. The efficacy and safety of guselkumab treatment for psoriasis was demonstrated in three phase III trials (VOYAGE 1, VOYAGE 2, NAVIGATE) [126–128]. Furthermore, Papp et al. [129] revealed that patients receiving guselkumab \(( n = 249)\) experienced higher improvement of itch severity (assessed using the Psoriasis Symptoms and Signs Diary) than in the placebo \(( n = 129)\) and adalimumab \(( n = 274)\) groups \( (p < 0.001) \).

4.3.4 Tildrakizumab

Tildrakizumab is a humanized IgG1κ mAb that also selectively binds to the p19 subunit of IL-23 [130]. Treatment with subcutaneous tildrakizumab was studied in two phase III, double-blind, randomized trials in psoriasis (resURFACE 1 and resURFACE 2 [131]) and proved statistically efficacious compared with placebo and etanercept in terms of PASI improvement. Unfortunately, the aforementioned studies did not directly report on pruritus outcomes. Nevertheless, among currently active clinical trials on the use of tildrakizumab in psoriasis, there are several that will assess the severity of itch with NRS or VAS [132–136], eventually bringing important insight into the actual antipruritic effect of tildrakizumab.

4.4 IL-31

IL-31 is a member of the IL-6 family and its role in the pathogenesis of pruritus has long been studied. It is involved mainly in Th2 lymphocyte-associated inflammation and does not directly induce pruritus, rather contributing to the itch sensation in inflamed skin [137]. The functional IL-31 receptor (IL-31R) consists of two subunits—IL-31RA and the oncostatin M receptor-β (OSMRβ). As IL-31 targets dorsal root ganglia in the spinal cord, keratinocytes, eosinophils, mast cells and basophils [138], it is associated with pleomorphic effects associated with pruritus and the chronic inflammatory process in the skin. Increased levels of IL-31 have been reported in itchy dermatoses such as AD, chronic prurigo, mycosis fungoides, BP and dermatitis herpetiformis [138].

4.4.1 Nemolizumab

Nemolizumab is a humanized mAb against IL-31R, which could alleviate pruritus through IL-31 signaling inhibition [139]. A phase II, randomized, double-blind trial among 211 patients with AD receiving nemolizumab revealed that the active groups were more prone to report pruritus improvement (assessed by VAS) when compared with placebo \(( n = 53; p = 0.002 in the 0.1 mg/kg group, and p < 0.001 in the 0.5 and 2.0 mg/kg groups) [139]. Another phase II study recounted that nemolizumab significantly reduced pruritus and the severity of skin lesions in patients with moderate to severe chronic prurigo [140]; however, it was also associated with AEs, including gastrointestinal (diarrhea and abdominal pain) and musculoskeletal symptoms.

4.4.2 Vixarelimab

Vixarelimab (KPL-716) is a mAB against OSMRβ. It does not directly block IL-31, however it interferes with IL-31
signaling and has proved effective in decreasing pruritus in AD [141]. It is now being studied in a phase II study on chronic pruritic diseases (LP, lichen simplex chronicus, chronic idiopathic pruritus, plaque psoriasis and chronic idiopathic urticaria) [142], and promising results regarding chronic prurigo have been announced recently [143].

4.5 Immunoglobulin E

Ligelizumab is a high-affinity humanized IgG1κ mAb targeting free IgE, basophil FcεRI and surface IgE [144]. It inhibits exocytosis from basophils and mast cells, and generation of mediators and cytokines, thereby attenuating allergic responses. In a recent phase IIb trial, ligelizumab was instigated in patients with chronic spontaneous urticaria [145]. At week 12, ligelizumab provided complete control of urticarial flares in 30%, 51%, and 42% of patients (at doses of 24, 72 and 240 mg administered every 4 weeks, respectively), in contrast to 26% of patients treated with another IgE antagonist (omalizumab 300 mg every 4 weeks) and 0% of patients in the placebo group. Moreover, the weekly Itch Severity Score (ISS7) of 0 at week 12 was achieved by 40%, 48% and 42% of patients receiving ligelizumab, respectively, compared with only 26% of patients in the omalizumab group. Ligelizumab was well tolerated, with upper respiratory tract infections and headaches constituting the main AEs.

5 Janus Kinase Inhibitors

One of the newly identified targets for dermatological treatment are JAKs, which belong to the group of cytoplasmic tyrosine kinases. When activated by various cytokines, colony-stimulating factors, and hormones, JAKs phosphorylate signal transducer and activator of transcription (STAT) factors and affect expression of specific genes [146], e.g. those associated with inflammatory cytokines and growth factors. JAKs contribute to inflammatory diseases, such as rheumatoid arthritis or inflammatory bowel diseases, however certain dermatologic conditions could also benefit from JAK inhibition [147]. There is growing evidence regarding the safety and efficacy of the use of JAK inhibitors in psoriasis, AD, alopecia areata and vitiligo [148].

5.1 Ruxolitinib

Ruxolitinib is a JAK1/2 inhibitor that has been studied in a phase II, double-blind, randomized study in patients with AD [149]. The use of ruxolitinib 1.5% cream twice daily led to 42.5% of patients experiencing minimal clinically important differences in pruritus within 36 h of treatment (13.6% for vehicle; p = 0.01). Further clinical trials are ongoing regarding the antipruritic properties of ruxolitinib in AD (both for adults and children) [150–152], LP [153] and chronic cutaneous graft-versus-host disease (cGvHD) [154]. Additionally, systemic administration of ruxolitinib improved pruritus in the course of myeloproliferative neoplasms (polycythemia vera, essential thrombocytopenia and myelofibrosis) [155–157].

5.2 Baricitinib

Baricitinib is another JAK1/2 inhibitor administered orally [158] and is currently under investigation in several clinical trials in adults and children with AD [159–162]. Its effectiveness in AD was confirmed in one phase II [163] and two phase III studies [158]. An improvement in pruritus was achieved within 1 week in the 4 mg/day group and within 2 weeks in the 2 mg/day group [158]. Moreover, in a phase Ib randomized study among psoriatic patients, all baricitinib treatment groups reported significantly greater mean changes than placebo in the WI-NRS at week 12 [164].

5.3 Tofacitinib

Tofacitinib preferably binds to JAK1 and JAK3, with functional selectivity over JAK2 [165]. Oral tofacitinib demonstrated antipruritic properties in several psoriasis studies [166–171] and CP of unknown origin in patients with rheumatoid arthritis [172], whereas its topical preparation proved effective in both AD [173] and psoriasis [174].

5.4 Abrocitinib

Oral abrocitinib is a selective JAK1 inhibitor with proven efficacy from a phase II, double-blind, randomized study (n = 267) for the treatment of AD in adults [175]. Recently, two clinical trials (JADE Mono-1 and JADE Mono-2) have confirmed its antipruritic properties in adolescent and adult patients with AD (n = 387 and n = 391, respectively) compared with placebo [176, 177]. Moreover, in March 2020, the results of the JADE Compare study [178] were announced, which demonstrated the superiority of abrocitinib (200 mg/day) over dupilumab in achieving a clinically significant reduction in pruritus severity (at least a 4-point reduction assessed using the Peak Pruritus NRS) at week 2 [179].

5.5 Upadacitinib

Upadacitinib is another oral selective JAK1 inhibitor that warrants its improved benefit-to-risk ratio [180]. Guttman-Yassky et al. [181] reported on a phase IIb randomized trial in adult patients with moderate to severe AD receiving upadacitinib monotherapy (n = 126) or placebo (n = 41). Regardless of dose, patients receiving upadacitinib experienced
quick improvement in pruritus (within 1 week), and the improvement in pruritus at week 16 was significantly higher in the active groups than in the placebo group \( (p < 0.001 \text{ for the } 30 \text{ and } 15 \text{ mg/day doses}, \text{ and } p < 0.01 \text{ for the } 7.5 \text{ mg/day dose}) \). Several trials are in progress [182–184], including the evaluation of upadacitinib versus dupilumab [185] and safety aspects in the pediatric population with AD [186].

### 5.6 Delgocitinib

Delgocitinib is a new JAK inhibitor specific for JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK-2) [187]. Treatment with topical delgocitinib proved effective for chronic hand eczema in a phase IIb, double-blind, randomized study [188]. At week 8, there was no difference between the active and placebo groups in terms of the ‘no itching’ status \( (p = 0.09) \). However, a greater proportion of patients with a baseline itch NRS score > 4 points experienced at least a 4-point reduction in NRS at week 8 compared with placebo (55% vs. 24%; \( p = 0.029 \)). Three recent reports have currently elucidated delgocitinib as an effective modality in reducing pruritus in the course of AD, including pediatric subjects [189–191].

### 6 Phosphodiesterase-4 Inhibitors

PDE-4 is an intracellular enzyme that takes apart cyclic adenosine monophosphate (cAMP). PDE-4 inhibition leads to increased cAMP levels, subsequently suppressing the production of various cytokines involved in the inflammatory processes of AD \( \text{(e.g. IL-4, IL-5, IL-13)} \) [192].

Crisaborole is a small molecule containing boron atom that targets PDE-4 [193]. Its effectiveness in AD was observed among adults and children [193, 194]. Patients receiving crisaborole 2% ointment experienced pruritus relief at day 29 (assessed using a 4-point scale; an expected score of 0 or 1 point and a ≥ 1-point reduction from baseline) more commonly than patients receiving vehicle (63% vs. 53%; \( p = 0.002 \)) [194]. Furthermore, crisaborole was more likely to provide antipruritic response at the earliest assessment on day 2 (34.3% vs. 27.3%; \( p = 0.013 \)) and early improvement of pruritus at day 6 (56.6% vs. 39.5%; \( p < 0.001 \)) than vehicle [195], thereby emphasizing its rapid mode of action.

### 7 Tropomyosin-Receptor Kinase A Inhibitors

Tropomyosin receptor kinase A (TrkA) is a surface transmembrane tyrosine kinase serving as a receptor for NGF and contributes to the development of psoriasis and pruritic response [196]. NGF stimulates histamine secretion from mast cells and sensitization of peripheral sensory nerve terminals.

Pegcantratinib (CT327/SNA-120) was utilized topically in patients with psoriasis and revealed no benefit over placebo in terms of improvement of cutaneous lesions [197]. However, among a subgroup of patients \( (n = 108) \) initially complaining of moderate pruritus \( (\text{VAS} \geq 40 \text{ mm}) \), pegcantratinib 0.05%, 0.1% and 0.5% provided mean VAS reductions of 37.1, 31.5 and 36.4 mm, respectively, whereas patients receiving placebo experienced only a 16.1 mm improvement \( (p = 0.0067, p = 0.0523, \text{ and } p = 0.0124, \text{ respectively}) \). Conversely, another study \( (n = 208) \) among psoriatic patients reported clinical improvement in terms of psoriatic lesions but no significant reduction of itch when compared with vehicle \( (4.2 \text{ points according to WI-NRS vs. 3.9 points; } p = 0.362) \) [198]. Recently, Zhong et al. [196] explored the inhibitory properties against the NGF/TrkA pathway of cucurbitacins, which are tetracyclic triterpenes derived from plants (especially the *Cucurbitaceae* family). The authors implied cucurbitacins could be potential precursors of successful antipruritics in the future.

### 8 Ileal Bile Acid Transporter Inhibitors

CP is an important and common symptom in patients with PBC, primary sclerosing cholangitis (PSC) or Allagile syndrome. The complex pathogenesis involves, among others, the role of bile salts, opioids, serotonin, lysophosphatidic acid and autotaxin [199–202]. IBAT inhibitors block the SLC10A2 transporter, decreasing reabsorption of bile acids in the terminal ileum and subsequently reducing enterohepatic recirculation and stimulating fecal excretion of bile acids [203, 204]. These effects are similar to the effects achieved by partial external biliary diversion surgical procedures that interrupt the circulation of bile acids and reduce pruritus.

In a phase II, randomized, crossover trial on linerixibat (GSK2330672; \( n = 22) \), patients with PBC experienced significant pruritus improvement over placebo [205]. Another study reported on 10 PBC patients who were administered odevixibat (A4250) for 4 weeks, of whom four finished the study per protocol and achieved excellent alleviation of pruritus [206]. Two further studies on maralixabat (SHP625) used for 13 weeks in patients with PBC \( (n = 66) \) and children with Allagile syndrome \( (n = 37) \) revealed alleviation of pruritus in the active groups, but the differences over the placebo groups did not reach statistical significance [203, 204].
9 Aryl Hydrocarbon Receptor Agonists

AhR, also termed dioxin receptor, is a ligand-activated transcription factor expressed in all types of skin cells, which binds to environmental polyaromatic hydrocarbons and dioxins, eventually causing oxidative stress [207, 208]. There is high expression of AhR in all epidermal cells and fibroblasts of the skin [209]. AhR maintains skin barrier integrity, regulates innate and adaptive immune responses, impacts the balance of Th17 and T-regulatory cells and is associated with phototoxins and skin carcinogenesis [210–212]. In general, the AhR signaling pathway is linked to several conditions, mainly non-melanoma skin cancers, melanoma, AD, psoriasis, chloracne or vitiligo [207].

Tapinarof (GSK2894512) is a naturally derived stilbene particle that activates AhR, subsequently inducing the expression of barrier genes in keratinocytes and downregulating the Th17 pathway, thereby possessing the potential for alleviating symptoms of AD [211]. In a recent phase II study, 247 patients with AD were randomized to receive tapinar of cream or vehicle for 12 weeks [213]. In addition to achieving improvement in terms of the Investigator’s Global Assessment (IGA) and Eczema Area and Severity Index (EASI), pruritus also improved (according to NRS), with differences between the active and vehicle arms beginning to unveil at week 2.

10 Histamine H4 Receptor Antagonists

Histamine is regarded as a classic mediator of itch and is released from mast cells during inflammation or stimulation by allergens. It induces itch by interacting with histamine receptors on unmyelinated C-fibers [214]. Currently, four types of receptors are described (H1R, H2R, H3R and H4R), with H4R being the most commonly targeted in clinical practice. H4R was cloned in 2000 and is chiefly expressed on hematopoietic cells, possessing relevant properties associated with the activation of mast cells, eosinophils, monocytes, dendritic cells and T lymphocytes [215]. It is an important component influencing the Th2 lymphocyte response, with its stimulation resulting in induction of IL-31 and the signal transduction molecules activator protein 1 (AP-1) [216]. Experimental studies on mice have demonstrated that an H4R antagonist (JNJ-7777120) reduces dermal inflammation and pruritus via reducing tissue cytokines and chemokines and inhibiting chemotaxis [217, 218]. The relevance of the Th2 milieu in the development of AD warranted the possibility of experimenting with H4R antagonists in the human population with this common condition. A phase II, randomized, double-blind study evaluated an H4R antagonist (JNJ-39758979) in patients with moderate AD [219]. Despite alleviation of pruritus, the study was ended prematurely due to safety concerns (agranulocytosis in 2 of 88 patients).

In a recent study [220], another H4R antagonist (adriforant; ZPL-3893787) was instigated orally in 65 AD patients, while 33 patients received placebo. Overall, the baseline maximal pruritus intensity measured by NRS was approximately 7.3 points. At week 8, pruritus was reduced by 3 points in the active group and by 2.7 points in the placebo group (p = 0.25). The beneficial effect on itch reduction might have been partially confounded by the use of rescue medication (such as topical corticosteroids) in the placebo group. Moreover, the EASI excoriation subscore (an indirect indicator of pruritus) revealed improvement from baseline at week 8 (p < 0.05). Further studies (ZEST and ZESTExt) among AD patients are ongoing [221, 222].

11 Miscellaneous Modalities

Based on anecdotal reports in humans, the potential utility of various complementary treatment modalities remains to be elucidated more clearly in the future, e.g. regarding the 755 nm alexandrite laser, botulinum toxin, acupuncture, transcranial magnetic stimulation, extracorporeal shockwave therapy, massage with violet oil, positive verbal suggestions or music therapy [223–231].

Additionally, experimental evidence points towards the growing importance of certain itch-associated signaling pathways that may be targeted in the near future, including the spinal α2/α3 GABA_A receptors, bovine adrenal medulla (BAM) 8-22 and the Mrgr, sodium channels (NaV_1.7, NaV_1.8, NaV_1.9), natriuretic peptides (BNP) and their receptors (NPR-1), gastrin-releasing peptide receptor (GRPR), PAR2 and CCL2/CCR2 [232–242].

12 Conclusions

Regardless of the cause, patients with CP will benefit from the continuously increasing armamentarium of novel therapies. To a large extent, the expected progress is based on the flourishing data on CP pathophysiology, but, in the era of evidence-based medicine, another crucial factor (conscious planning and execution of clinical trials) has to be taken into account. Thereby, therapeutic success, safety and economic issues will be maintained in real-life settings.

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Compliance with Ethical Standards

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