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Treatments for chronic pruritus outside of the box

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Abstract

Patients with chronic pruritus are in desperate need of novel treatment options, as current therapeutic possibilities are often not effective, have a poor level of evidence and are mostly off-label. In recent years, much effort has been put into the identification of potential targets for the treatment of chronic pruritus. More importantly, a number of promising new drugs that are aimed at treating pruritus in different conditions are currently in advanced stages of clinical trials. Here, current pharmacological developments leading to potential new drugs for the treatment of chronic pruritus within various conditions are summarized. Hopefully, these new approaches will result in effective and safe therapies for our patients with chronic pruritus associated with dermatological or non-dermatological diseases in the near future.

KEYWORDS
atopic dermatitis, itch, neurokinin-1, prurigo, urticaria

1 | INTRODUCTION

Chronic pruritus (chronic itch) is not only a very bothersome, but also a very common symptom. The lifetime prevalence of chronic pruritus has been reported to be more than 20% in the general population and reaches more than 50% among patients with skin diseases.[1] Despite this very high prevalence of chronic pruritus and the often dramatic negative impact on the patient's quality of life, available therapeutic options to specifically treat pruritus are sparse. In fact, while an immense number of different pain medication exists, in Europe, there is currently not a single drug approved for the treatment of pruritus. Antihistamines, which are commonly used to treat pruritus, are only approved for the treatment of itch associated with urticaria and are largely ineffective for non-histaminergic itch. A current search in *clinicaltrials.gov* (March 2019) with the term "pain" as condition or disease resulted in 16,188 hits, while a search for "pruritus" or "itch" resulted in 337 registered trials. Despite this lack of available drugs and the small amount of clinical trials investigating anti-itch therapies, the medical need for effective drugs to treat chronic pruritus is huge.

In recent years, research into the pathophysiological mechanisms of pruritus has been intensified and the clinical significance of the symptom is now much more widely recognized in both skin and systemic diseases.[2–5] While all of these efforts have so far not resulted in an approved anti-itch drug, we now know a lot more about the potential targets for the treatment of itch. There are a number of ongoing clinical trials evaluating the potential of novel anti-itch drugs and more and more currently available drugs for other diseases are evaluated in clinical practice for their effects on chronic pruritus.

2 | POTENTIAL TARGETS IN CHRONIC PRURITUS

Histamine is a well-known mediator of itch and there are many drugs available that target the histamine H1 receptor (H1R). However, apart from urticaria, the role of H1R in chronic pruritus is thought to be limited. There is some evidence that the histamine receptors H3 and H4 are also involved in pruritus.[6] In a recently published trial using an H4R antagonist in patients with atopic dermatitis (AD),

TABLE 1 Ongoing clinical trials assessing efficacy on pruritus as predefined readout as listed on clinicaltrials.gov

Target	Name	Application	Indication	Study phase	NCT #
Chronic pruritus on primarily altered skin (IFSI classification group I)					
BTK	Fenebrutinib	oral	Chronic spontaneous urticaria	2	NCT03693625 NCT03137069
H4R	Adriforant	oral	Atopic dermatitis	2	NCT03517566
IgE	Ligelizumab	s.c.	Chronic spontaneous urticaria	3	NCT03580356 NCT03580369
IL-4Rα	Dupilumab	s.c.	Chronic spontaneous urticaria	2	NCT03749135
IL-4Rα	Dupilumab	s.c.	Cholinergic urticaria	2	NCT03749148
JAK	Ruxolitinib	topical	Atopic dermatitis	3	NCT03745651 NCT03745638
JAK/Syk	ASN008	topical	Atopic dermatitis	1	NCT03798561
MOR	Naloxon	topical	Cutaneous T cell-lymphoma	3	NCT02811783
NK1R	Serlopitant	oral	Epidermolysis bullosa	2	NCT02654483 NCT03836001
NK1R	Serlopitant	oral	Atopic dermatitis, psoriasis	3	NCT03540160
NK1R	Tradipitant	oral	Atopic dermatitis	3	NCT03568331
OSMR	KPL-716	s.c.	Urticaria, lichen planus, psoriasis	2	NCT03858634
PDE-4	Apremilast	oral	Psoriasis	4	NCT03553433
Syk	GSK2646264	topical	Chronic spontaneous urticaria Cold urticaria	1	NCT02424799
Chronic pruritus on primarily unaltered skin (IFSI classification group II)					
IBAT	GSK2330672	oral	Primary biliary cholangitis	2	NCT02966834
KOR	Difelikefalin	iv	Uraemic pruritus	2	NCT03802617
KOR	Difelikefalin	iv	Uraemic pruritus	3	NCT03422653
KOR	Difelikefalin	oral	Uraemic pruritus	3	NCT03617536
NK-1	Serlopitant	oral	Chronic Pruritus	2	NCT03841331
OSMR	KPL-716	s.c.	Chronic pruritus	2	NCT03858634
Chronic pruritus with secondary scratch lesions (IFSI classification group III)					
IL-31	Nemolizumab	s.c.	Prurigo	2	NCT03181503
MOR/KOR	Nalbuphine ER	oral	Prurigo	3	NCT03497975
NK-1	Serlopitant	oral	Prurigo	3	NCT03677401
NK-1	Serlopitant	oral	Prurigo	3	NCT03546816
NK-1	Serlopitant	oral	Prurigo	3	NCT03540160
OSMR	KPL-716	s.c.	Prurigo	2	NCT03816891

Note: Trials are listed according to the clinical classification of chronic pruritus.
Abbreviations: BTK, Bruton's tyrosine kinase; H4R, Histamine 4 receptor; IBAT, Ileal bile acid transporter; IgE, Immunoglobulin E; IL-31, interleukin-31; IL-4Rα, IL-4 receptor α; JAK, Janus kinase; KOR, κ-opioid receptor; MOR, μ-opioid receptor; NK1R, Neurokinin-1 receptor; OSMR, Oncostatin M receptor; PDE-4, Phosphodiesterase-4; Syk, spleen tyrosine kinase.

reduction of pruritus was not found to be different to placebo,[7] future investigations using H4R antagonists will have to identify potential anti-pruritic effects of H4 in other settings. In vitro research using cellular approaches as well as investigations in animal models and patient samples have identified a number of other receptors or their respective ligands to be involved in mediating pruritus.

Many of the large number of identified G protein-coupled receptors associated with itch are expressed both in the peripheral and the central nervous system, and it is, as of yet, largely unclear whether the itch-mediating or suppressing effects occur mainly in the periphery or centrally. Some of the receptors are predominantly expressed in the peripheral nervous system and include (apart from H1R and H4R) protease-activated receptors (eg PAR-2), Mas-related G protein-coupled receptors (eg MrgprX1), neurokinin 1 receptor (NK1R), serotonin receptors (eg 5-HT2R), endothelin-1 receptors (eg ET_A), neurotrophin receptors (eg TrkA), bile salt receptor (TGR5) and cannabinoid receptors (eg CB_2). Other itch-related G protein-coupled receptors are primarily expressed in the central nervous system and include gastrin-releasing peptide and μ- and κ-opioid receptors.[8–14] While most of these receptors are involved in inducing

pruritus, cannabinoid and κ-opioid receptors are mainly thought to suppress itch signalling.

In addition to G protein-coupled receptors, a number of cytokines have been associated with pruritus either by direct action on receptors expressed in the peripheral or central nervous system, or indirectly via other mechanisms.[15] Cytokine receptors directly associated with itch are the IL-4 receptor α (IL-4R α), IL-31 receptor, oncostatin M receptor (OSMR) and the thymic stromal lymphopoietin (TSLP) receptor.[8,15] Additionally, some ion channels such as voltage-gated sodium channel (NaV1.7) and the transient receptor potential (TRP) channels TrpV1 and TrpA1 have been shown to be involved in the transmission of itch signals.[16,17]

Although many mediators, receptors and downstream pathways that are associated with itch have been identified in the past, it is largely unknown which of these pathways are specific for certain types of itch and which pathways belong to an existing common pathway of itch. Ongoing and future investigations will enable us to optimize treatment and hopefully to tailor specific itch treatments for individual patients with chronic pruritus.

3 | TARGETS THAT ARE CURRENTLY EXPLORED IN CLINICAL TRIALS

The current guideline on the diagnosis and treatment of chronic pruritus classifies patients with chronic pruritus into three groups, based on their clinical features: (a) Chronic pruritus on primarily altered skin, (b) chronic pruritus on primarily unaltered skin and (c) chronic pruritus with secondary scratch lesions.[18] Depending on the clinical presentation and the underlying aetiology, different therapeutic options may be chosen. In currently ongoing clinical trials, studies are performed in diseases of all three groups (Table 1).

In recent years, there have been many drugs assessed for their efficacy in pruritus in phase 1 and phase 2, and very few also in phase 3 trials. Some of these drugs have failed to show sufficient efficacy for further development, others showed more promising results and are in later stage trials. Excellent reviews highlight the anti-pruritic therapies that have been in development in recent years,[19–22] currently ongoing clinical trials are listed in Table 1. Among the ongoing trials, there are three classes of drugs that are currently in phase 3 trials: a monoclonal anti-IgE antibody (Ligelizumab for the treatment of chronic spontaneous urticaria), opioid receptor blockers (difelikefalin and nalbuphine for the treatment of uraemic pruritus and prurigo respectively) and neurokinin 1-receptor antagonists (tradipitant for the treatment of atopic dermatitis, and serlopitant for the treatment of prurigo and other pruritic diseases).

4 | WHAT CAN WE LEARN FROM PUBLISHED TRIALS AND CASE SERIES?

Chronic pruritus can be a symptom of many dermatological and non-dermatological diseases, and in many of these diseases, the effective therapy of itch is a large unmet medical need. The current European guideline on chronic pruritus recommends treatment algorithms that are specific for the underlying aetiology,[23] although it is often unclear whether the recommended treatment is indeed specific for the respective aetiology or is rather a general anti-pruritic treatment. The current evidence of anti-pruritic efficacy of existing drugs and potential future treatments in systemic diseases are reviewed elsewhere, for example, for uraemic[24] and hepatic pruritus.[25] Controlled clinical trials aimed at showing anti-pruritic efficacy are overall sparse, but are performed more often in recent years. Table 1 provides an overview of currently ongoing trials with pruritus as a predefined outcome parameter. In dermatological diseases, pruritus is a more commonly defined primary treatment goal, both within clinical trials and in real life settings. The following therefore focusses on chronic prurigo and atopic dermatitis, two typical pruritic dermatological diseases.

4.1 | Chronic prurigo

In 2010, Ständer et al published the first case series on 20 patients treated with the neurokinin 1 receptor (NK1R) antagonist aprepitant. Among these 20 patients, 13 were diagnosed with nodular-type chronic prurigo (prurigo nodularis). Patients with prurigo showed an excellent clinical response with a mean pruritus intensity reduction of almost 50%.[26] These very promising results led to the design of an investigator-initiated, placebo-controlled, phase 2 study to test the efficacy of aprepitant in patients with chronic prurigo. In this recently published trial, the 4-week treatment did not result in a significant difference between aprepitant and placebo.[27] Another placebo-controlled trial with a topical formulation of aprepitant also failed to show significant differences between aprepitant or placebo vehicle-treated skin. In this trial, a split-sided approach was chosen with aprepitant on one and placebo vehicle on the other arm. Overall, the patients reported a substantial reduction in pruritus intensity by more than 50% from baseline to day 28 both in aprepitant and placebo vehicle-treated skin, thus failing to show a significant improvement of aprepitant versus placebo.[28] Finally, another NK1R-antagonist, serlopitant, has been assessed for its efficacy in nodular-type chronic prurigo. In this randomized, placebo-controlled multicenter study involving 128 patients with chronic prurigo, significantly better improvement in pruritus has been observed in those patients treated with serlopitant.[29] The promising result of this study has led to a phase 3 trial that is currently conducted in the US and Europe (Table 1).

Apart from these few randomized, controlled trials in chronic prurigo, there are a large number of case reports and case series published. This reflects the current difficulty in effectively treating patients with chronic prurigo. A very recent systematic review provides an overview of evidence-based treatments for prurigo.[30] Additionally, recently published case series indicate a possible role for dupilumab (a monoclonal anti-IL-4Rα-antibody) in the treatment of chronic prurigo. In the four published reports with overall 11 patients with chronic prurigo treated with dupilumab, all patients showed a complete or almost complete control of pruritus.[31–34] It would be interesting to learn from a placebo-controlled trial whether this efficacy can also be seen in a larger patient population.

4.2 | Atopic dermatitis

The pathophysiology of AD is complex and involves many cells, mediators and receptors that have been associated with the induction or maintenance of pruritus. There are excellent reviews that summarize the diverse network of itch mediators in AD and the huge developments in the recent years in the treatment of AD.[13,35,36] The currently most promising published data regarding chronic pruritus in AD are derived from clinical trials with the monoclonal antibodies against IL-4Rα (dupilumab) and IL-31RA (Nemolizumab). Dupilumab has recently been approved for the treatment of patients with AD who require systemic therapy, based on two phase 3 trials showing an excellent efficacy of the drug on signs and symptoms of AD including pruritus.[37] In these trials, and other investigations since the approval of the drug, the reduction in itch intensity after dupilumab treatment has been reported to range from 40% to 60%, and 36%-59% of the patients within the phase 3 trials had a more than 4-point reduction in peak pruritus scores, as measured by a numerical rating scale.[38–40] In general, dupilumab thus leads to a very good reduction of pruritus in patients with AD. Whether the observed effect on pruritus is due to a general reduction of inflammation in the skin of AD patients or whether this a specific anti-pruritic effect of IL-4Rα blockade, for example on sensory nerves, is, as of yet, unclear. Future trials in patients with chronic pruritus not associated with AD could help in clarifying this question.

Interleukin-31 (IL-31) has long been thought to be involved in the pathogenesis of pruritus. While IL-31 does not directly induce an itch response in healthy human skin,[41] it likely contributes to chronic pruritus in inflamed skin. Feld et al have shown, for example, that IL-31, which can be secreted by activated T cells in the inflamed skin of AD patients, can lead to elongation and branching of sensory neurons.[42] While this could be involved in neuronal sensitivity in patients with AD, recent elegant investigations using 3D imaging in whole skin biopsies from AD patients and controls revealed a reduced nerve fibre density in pruritic AD skin,[43] questioning this potential mechanism of IL-31. Nevertheless, a randomized, controlled phase 2 trial assessing the efficacy of the monoclonal anti-IL-31 antibody Nemolizumab, showed a reduction of pruritus of up to 63% along with a still significant but less dramatic reduction of the eczema scores.[44] Even more striking results regarding pruritus are presented in the reports of a long-term extension study using Nemolizumab in patients with AD. Here, an up to almost 90% reduction in itch intensity have been observed after 64 weeks of treatment with Nemolizumab.[45] Therefore, it will be very interesting to learn about the effects of an anti-IL-31 treatment in patients with chronic prurigo. The results of a recently conducted phase 2 trial with Nemolizumab in this indication have not yet published, but the findings from the AD trials indicate that a highly pruritic skin disease such as prurigo may benefit very much from a treatment with Nemolizumab.

In Psoriasis, the phosphodiesterase 4 (PDE4) inhibitor, apremilast, has been shown to provide a rapid improvement in pruritus,[46] and PDE4 has long been thought to be a promising target in pruritus in atopic dermatitis and possibly other forms of chronic pruritus. Surprisingly, a recently published trial with apremilast in patients with atopic dermatitis, however, failed to show effects on pruritus compared to placebo.[47] Topical approaches using PDE4 inhibitors in contrast were successful in suppressing pruritus,[48,49] indicating a potential role for PDE4 expressed by keratinocytes in inducing pruritus in at least a subtype of AD patients. Interestingly, in a single case report, the complete disappearance of a longstanding severe hepatic pruritus was reported in a patient with hand eczema treated with apremilast.[50]

5 | PERSONAL EXPERIENCES

It is good to see that pruritus is more and more within the focus of ongoing and future clinical developments. Nonetheless, not only our future patients require effective relief from pruritus, but also the patients we are seeing today. This can only be accomplished by carefully listening to our patients, thoroughly inspecting their skin, doing all necessary diagnostic tests and procedures and by providing the best treatment we can offer. This means that treatment of our patients is either based on existing evidence or aimed at creating evidence. Wherever possible, we treat an underlying disease or a treatable, aggravating factor of chronic pruritus, according to the guidelines or recommendations of the respective diseases. If this cannot be done, if treatment is not sufficient or if there is no identifiable underlying disease, we follow the current guidelines on the management and treatment of pruritus, which, in most cases, includes treating our patients with gabapentin or pregabalin, or with sertraline or another selective serotonin reuptake inhibitor.[18,23] Additionally, for every patient in our clinics, we check whether there is the possibility of offering the patient participation in an ongoing, well-designed, controlled trial. As outlined above, there are currently a number of clinical trials suitable for patients with chronic pruritus, especially for those with chronic prurigo, and our patients should have the possibility to benefit from participating in one of these. Wherever guideline-recommended treatments fail and no clinical trials are available or suitable, we, together with our patients, have to find effective alternatives for each individual patient, and there is not even one common recommendation on what to do.

Outside of the general recommendations, many of our patients get a short-term relief from pruritus by applying a cream containing 1% menthol and 2% camphor,[51] but additional systemic treatment is always required in these difficult-to-treat patients. Regardless of the underlying cause of pruritus, the most effective treatment in our otherwise treatment-refractory patients is the iv application of the NK1R-antagonist fosaprepitant. A large proportion of our patients report about a cessation or marked improvement of pruritus for a few days to a few weeks after a single infusion. In patients with localized pruritus, especially with notalgia paresthetica, we have good experience with topical 8% capsaicin,[52] and in some patients manipulative physiotherapy, as described by Sahhar et al, has proven beneficial.[53] Other systemic treatments are used only

rarely and are chosen very individually based on the history of the patient, previous treatment, comorbidities and potential underlying mechanism of the chronic pruritus. For example, in some patients with chronic pruritus, eosinophilia can be found in the blood and/or in the skin, without other signs of atopic dermatitis, bullous pemphigoid or other obvious dermatological diseases. Here, targeting eosinophils can be beneficial, and we have successfully treated some patients using different monoclonal anti-IL-5 antibodies.[54,55] Other possible treatments range from JAK inhibition using oral ruxolitinib in patients with severe pruritus associated with polycythaemia vera to anti-IgE treatment with omalizumab in patients with mastocytosis or other suspected mast cell-associated disorders. Other treatment options such as thalidomide, other monoclonal antibodies, methotrexate, azathioprine, mycophenolate mofetil and many more have been described in individual case reports, but are not used in our clinics for the treatment of chronic pruritus.

6 | SUMMARY AND CONCLUSIONS

The treatment of chronic pruritus has long been neglected by scientists, physicians and pharmaceutical companies. More surprisingly, as chronic pruritus poses a tremendous burden on everyday life of those affected, and the available therapeutic options are very limited, have a poor level of evidence and are mostly off-label. Within the last decade, however, much effort has been put into the identification of potential targets for the treatment of chronic pruritus in many different diseases. Furthermore, new drugs are in, or about to enter, phase 3 trials, hopefully resulting in effective and safe therapies for our patients with chronic pruritus associated with dermatological or non-dermatological diseases in the near future.

CONFLICT OF INTEREST

None in association with this review. I have received honoraria as a consultant and/or speaker for Bayer Pharma, Beiersdorf, Celgene, GSK, Menlo Therapeutics, Moxie, Nerre Therapeutics, Novartis, Roche, Sanofi.

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