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POSITION STATEMENT

A position paper on the management of itch and pain in atopic dermatitis from the International Society of Atopic Dermatitis (ISAD)/Oriented Patient-Education Network in Dermatology (OPENED) task force

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Abstract

Atopic dermatitis (AD) is a disease that can have a high impact on quality of life, especially due to itch and skin pain. This paper utilizes expertise from members of the International Society of Atopic Dermatitis (ISAD)/Oriented Patient-Education Network in Dermatology (OPENED) task force to review the epidemiology, pathophysiology and exacerbating factors of itch and pain in atopic dermatitis. General principles of treatment are provided, as well as a more detailed evaluation of topical and systemic therapies. Educational and psychological approaches to itch and pain in atopic dermatitis are proposed, along with expert recommendations for the management of itch and pain in atopic dermatitis.

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Conflict of interest

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory and multifactorial skin disease, with an increasing prevalence. Itch and pain are burdensome AD symptoms. Itch is easily defined as an unpleasant sensation leading to the need to scratch.[1] According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Skin pain is pain that is perceived to be located in the skin.

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Itch is a central and extremely distressing hallmark of AD.[2,3] Its assessment represents an item used to score disease severity in SCORAD (SCORing Atopic Dermatitis) and PO-SCORAD (Patient-Oriented SCORAD). Itch is responsible for two of the cardinal clinical signs of AD (excoriations and lichenification) which are measured by EASI, SCORAD, objective SCORAD and multiple investigator global scales.[4–6] The itch/scratch cycle can worsen and perpetuate skin inflammation in AD. Skin pain, is also a frequently reported accompanying symptom, resulting in profound AD burden.[7,8] From a patient's perspective, itch and pain are the most important symptoms of AD when assessing whether a treatment works or not.[9] Self-assessment of skin hurting in AD patients significantly correlated with AD severity measured by SCORAD. It was also shown that burning or stinging in AD patients significantly correlated with the age of adult patients.[10]

In this position paper, eleven members of the International Society of Atopic Dermatitis (ISAD)/Oriented Patient-Education Network in Dermatology (OPENED) task force designed the process, reviewed the published medical literature, wrote sections, and reviewed, edited and approved the whole manuscript.

Epidemiology, exacerbating factors and itch and pain in AD

Although itch is included in the definition of AD, and is commonly included in diagnostic criteria and outcome measures, the prevalence of itch in patients with AD has been sparsely assessed. Multicentre studies suggest that itch occurs in 86% of tertiary care centre patients with AD.[11,12] Recent research suggests that pain is also common in AD with up to approximately 40% of AD patients reporting skin pain.[7,13] Pain in patients with AD is often associated with scratching and itch.[7]

Many different factors can increase disease activity, itch and pain.[14] Most triggering factors are non-allergic, like sweating, mechanical irritation, such as long nails, clothing, exposure to water, soaps, or chemicals and climactic factors (low humidity and cold temperature).[15,16] Even stress can worsen AD and its symptoms.[17] Food, contact and airborne allergens can also act as triggering factors.[18]

Pathophysiology of pain and itch in AD

Emerging data have the potential to improve our understanding of itch and pain pathophysiology[2,19,20] and improved management. Pain and itch are generally regarded antagonistic as painful stimuli such as scratching suppresses itch. Moreover, inhibition of pain processing by opioids generates itch further supporting their opposing role. Separate specific pathways for itch and pain processing have been described from the skin to the brain, suggesting that pain and itch should be investigated separately on the level of neurons, mediators and mechanisms. However, in addition to broadly overlapping mediators of itch and pain, there is also evidence for overlapping functions in primary afferents: nociceptive primary afferents can provoke itch when activated very locally in the epidermis, and sensitization of both nociceptors and pruriceptors has been found following local nerve growth factor application in volunteers. Thus, also mechanisms that underlie the development of chronic itch and pain including spontaneous activity and sensitization of primary afferents as well as spinal cord sensitization may well overlap to a great extent.[21] In AD, the role of histamine as a pruritogen is highly debated, since H(istamine)-1-receptor blockers are not (or are poorly) effective in the treatment of itch in AD[22,23] and histamine effects may be restricted to acute itch[24]. Consequently, itch is partially or totally related to non-histaminergic nerve fibres.[25] However, experimental and clinical data indicate a relief of itching in eczematous skin lesions, particularly, in AD by antagonism of the H(istamine)4 receptor that is expressed on various inflammatory cells as well as on sensory nerves.[26]

IL-31, a Th2 cytokine, is a very important mediator of itch.[27] Keratinocytic cytokines driving Th2 immunity IL-33[28] and TSLP (thymic stromal lymphopoietin)[29] can directly activate sensory neurons to evoke itch. IL-31, IL-33 and TSLP activate sensory neurons thanks to specific receptors. The Th2 cytokines IL-4 and IL-13 were clearly shown to modulate itch responses.[24] Cytokines that underlie type 1 and/or type 3 immune responses, such as IL-1β, IL-6, TNF-α and IL-17A, have been associated with pain.[30]

Following the activation of specific nociceptive or pruriceptive pathways, a number of overlapping cation channels are activated at the neuronal membrane, including transient receptor proteins TRPA1 and TRPV1 as well as sodium channels Nav1.7 and Nav1.8.[31] This activation induces the release of neuropeptides, especially substance P and CGRP (calcitonin-gene-related peptide) by sensory neurons. These neuropeptides enhance itch and pain by activating mast cell and mononuclear cells through MrgprX1 then the release of the previously cited cytokines.[16,32–34] Agonists of protein-activated receptor PAR-2 agonists provoke enhanced and prolonged itch.[35] In the spinal cord and brain, gastrin-releasing peptide receptor (GRPR) and Mas-related G protein-coupled receptor (Mrgpr) are specialized pathways that can distinctly mediate itch.[31,36]

Several studies suggest that mechanisms of central modulation play an important role in the development and maintenance of chronic itch in AD.[37] Brain imaging research has shown different brain activation patterns in AD patients after pruritic stimulation compared to healthy controls, suggesting central sensitization.

General principles of therapy

AD management often requires a multidisciplinary approach.

The management of itch and pain is mostly based on topical therapy. However, other therapeutic options such as systemic drugs, phototherapy, balneotherapy and control of environmental triggers are available. Topical therapy is time-

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consuming for both the patients and the parents of children with AD, although it may be structured as an opportunity to play, talk and spend time together turning it into a positive occasion. It may be helpful to create a relaxing environment appropriate to the patient's age; use of music, video, games or other media may be helpful.

Topical therapy

There is clear evidence that the use of topical anti-inflammatory agents is an essential therapeutic option that substantially decreases itch in AD.[38] According to information obtained from AD patients, moisturizers were the most frequently used treatment to decrease itch, followed by corticosteroids, antihistamines and calcineurin inhibitors.[39]

Emollients

While some studies showed improvement of itch in AD after emollient use, few have shown effects on pain. We consider protective action of emollients, which prevent formation of potentially painful lesions,[40] as more important than direct pain relief because of their application. It was previously shown that the prevalence of skin pain was significantly increased in AD patients with excoriations.[7] However, it is possible that some AD patients experience the sensation of pain secondary to cutaneous inflammation and/or neurosensory dysfunction.

In one study, emollients were considered by 90.9% of patients with AD as providing relief of itching and by 4.5% as being ineffective.[41] Authors of the Cochrane systematic review on emollients and moisturizers for eczema did not find reliable evidence that one emollient is better than another.[42] Basic therapeutic agents and emollients should not contain any frequent contact allergens or ingredients that are irritating or sensitizing to the patient. Consensus-based European guidelines for treatment of AD stated that emollients should be prescribed in adequate amounts, and these should be used liberally and frequently, in a minimum amount of 250 g/week for adults and up to 100 g/week in young children.[43] The cost of high-quality emollients often restricts their use because they are considered to be non-prescription drugs in many countries and the quantities required are usually high.[43]

Topical corticosteroids

Topical pharmacologic agents of choice are corticosteroids (TCS). TCS are recommended for moderate and severe AD and for patients who do not respond to emollients alone and they are often very effective in reducing itch. The effect on pain in AD is not clear.

Several factors should be considered when choosing a TCS, including patient age, affected areas, extension of the lesions, formulation, cost of medication, duration of treatment, possible side-effects and eventual cortico-phobia. The frequency of application varies upon the TCS used, and it is applied once to twice daily and then tapered progressively with two applications a week on the frequent flared areas for maintenance.[43]

Calcineurin inhibitors (TCI)

Topical calcineurin inhibitors (TCI), pimecrolimus cream and tacrolimus 0.1% and 0.03% ointments, are frequently used AD treatments. They might be especially effective for itch and pain because they induce TRPV1 phosphorylation (activation) on neurons. Several studies have shown interesting effects on itch but pain relief has been poorly studied. Unfortunately, there is no meta-analysis on the effects of TCS and TCI on itch and pain.

The frequency of application is preferably twice a day, and the duration of the treatment is until resolution of the acute phase. The prevention of relapses is possible through an intermittent use of TCI (2–3 times per week) on areas that flare frequently.[44] Therapeutic education should be performed to inform the patient and parents about possible burning and itching during the first applications and/or on very inflamed skin. In some cases, it will be better to start with a TCS to reduce inflammation and then switch to a TCI.

Antimicrobials and antiseptics

Patients with AD may develop cutaneous widespread viral and bacterial infections, which could enhance itch and pain. These infections have to be treated specifically.[45]

New topical therapies

New topical promising therapeutic alternatives have been developed.[23,46]

Topical phosphodiesterase 4 (PDE4) inhibitors are effective in AD reducing inflammation and itching by decreasing the levels of IL-4 and IL-31.[47] In the pooled analysis of the first 4 studies, treatment with crisaborole topical ointment 2% resulted in statistically significant reductions in pruritus severity at the first time point evaluated in both analyses.[48] Significantly more patients experienced early improvement in pruritus with crisaborole than with vehicle (56.6% vs. 39.5%; $P < 0.001$), including at the earliest assessment (day 2, 34.3% vs. 27.3%; $P = 0.013$) in a study focused on itch. Crisaborole is a topical treatment option that can rapidly relieve atopic dermatitis-associated pruritus.[49,50] Novel topical Janus kinase (JAK) inhibitors are also effective on pruritus by acting directly on sensory nerve fibres by blocking the transphosphorylation of cytokine receptors and consequently their activity. They are promising AD treatments. Patients treated with tofacitinib showed significant improvements vs. vehicle across all prespecified efficacy end points and for pruritus at week 4. Significant improvements in pruritus were observed by day 2.[51] Paediatric trials on delgocitinib[52] showed that pruritus scores were significantly improved compared with those in the vehicle group. Improvements in itch were observed with ruxolitinib 1.5% cream: 42.5% of patients who applied it experienced

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minimal clinically important differences in itch within 36 h of treatment (vehicle, 13.6%; $P < 0.01$); near-maximal improvement was observed by week 4[53]. Tapinarof may be an effective treatment for AD modulating the aryl hydrocarbon receptor. The proportion of patients who achieved a minimum 3-point improvement in itch/pruritus with use of the NRI method was also greater at weeks 4 to 12 in all groups treated with tapinarof than in the groups treated with vehicle. The tapinarof and vehicle groups showed a clear separation starting at week 2.[54] The effects of these therapies on itch and pain need to be more studied but anti-Jak is promising treatments. The induction of pain by their application has been noted.

Wet-wrap therapy and bandage

Wet-wrap therapy increases penetration of topical agents, decreases water loss and protects against scratching. It is suggested as a second-line treatment for severe or refractory AD in patients older than 6 months of age. Bandages can be used on a portion or the entire body to improve absorption of the topical agents and to protect against scratching reducing complications (prurigo, lichenification, infection).

UV therapy

The use of artificial UV (ultraviolet) light represents a well-established treatment option[43] and is recommended in patients ≥ 18 years of age, while it may be considered in adolescents > 12 years of age.[55] UV treatment has been demonstrated to be effective in the acute stage (UV-A1) of AD as well as in cases with chronic itch.[56]

A systematic review[57] and guidelines[55] concluded that narrowband UV-B is more effective than treatment with UV-A[58,59] and that narrowband is preferred over broadband UV-B.[60] UV-A1 is more effective than topical steroids[61] and the use of combined UV-A/UV-B.[60] The application of medium-dose UV-A1[60,62] (i.e. max. dose of 65 J/cm^2) and narrowband UV-B is equally recommended for AD.[43] With regard to PUVA options, balneo-PUVA therapy may still be considered as an additional treatment, but with regard to the risk-benefit ratio, it is not as a preferred UV treatment option in AD. UV therapy is one treatment option for AD in acute AD and acute flare-ups of chronic AD, respectively, and can easily be combined with (topical) treatments in the 4-step therapy regimen for AD, except for topical calcineurin inhibitors and systemic immunosuppressants.[43,55]

Therefore, it could be useful to alleviate (chronic) itch but the effects on pain are poorly known.

Systemic treatments of AD

Systemic treatments are indicated in moderate-to-severe AD and refractory forms of disease, in association with the topical treatments.

Cyclosporine A

Cyclosporine can be used from the age of 2 years.[63–65] Cyclosporine reduces the transcription of several itch mediators, such as interleukin (IL)-2 and IL-4.[66] Consequently, it can be used in the treatment of itch in AD. No effect on pain has been shown until now.

Cyclosporine is generally recommended at an initial dose of 2.5 up to 5 mg/kg/day for the first 2 weeks of treatment, with a gradual dosage reduction to 1.5–3 mg/kg/day, for a total treatment period of 6–12 months. Long-term cyclosporine therapy is not recommended for the risk of kidney toxicity.[63–65] Elderly patients with pre-existing renal disease must be treated with special caution.

Dupilumab

Dupilumab is a monoclonal antibody (mAb) which binds to the α-subunit of the IL-4 and IL-13 receptor complex. Significant clinical effects across 3 distinct severity assessment tools were reported: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA) and SCORing Atopic Dermatitis (SCORAD).[67,68] Dupilumab treatment rapidly reduced pruritus (44%–51% reduction on NRS = numeric rating scale) at week 16. No data on pain were provided. Dupilumab treatment is well tolerated but non-infectious conjunctivitis is frequent.

Corticosteroids

Systemic corticosteroids have a limited role in the therapeutic management of AD, with limited beneficial effects on pruritus and pain. Corticosteroids should not be used in children and, in adults, should be reserved in cases of severe AD in particular conditions (such as lack of other possible alternative treatments, or using corticosteroids transiently, as a short-term therapy (up to 1 week), for immediate relief before the beginning of other systemic therapies or phototherapy).[45,69–71]

Methotrexate, azathioprine and mycophenolate mofetil

Methotrexate, azathioprine and mycophenolate mofetil are second-line treatment options of moderate-to-severe AD. Few studies address the impact of methotrexate on itch in AD (and none on pain).[72] Beneficial effects of mycophenolate mofetil on itch in AD patients have been shown[73] but there is no study with azathioprine.

Antihistamines

Antihistamines are frequently used, without any significant difference with placebo. Hydroxyzine represents a common sedating H1-antihistamine choice. However, the possible effects of these drugs should be discussed with the parents and long-term use of sedating antihistamines that is not recommended in children.[45,74,75]

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Table 1 Take-home messages

Take-home messages
• Itch and skin pain are frequently reported by patients with atopic dermatitis.
• Itch and pain have many consequences on the quality of life as well as on the burden and the evolution of atopic dermatitis.
• There is a need to provide effective treatments for atopic dermatitis to alleviate itch and pain.
• These treatments may be topical agents, phototherapy or systemic drugs. In addition, therapeutic patient education should be performed and psychological interventions should be proposed, if necessary.
• Specific efficient treatments for itch or pain have to be added to the global treatment of atopic dermatitis if their effects on itch and pain are not sufficient.

New therapies

The development of new drugs for AD patients is more targeted to itch mediators.[2,23] Nemolizumab is a humanized anti-IL-31 receptor A mAb, that was specifically developed for the treatment of AD-related pruritus. A single nemolizumab subcutaneous injection reduced the pruritus score to approximately −50% at week 4 compared with −20% with placebo in patients with AD.[76] A further study showed that nemolizumab significantly improved pruritus in adults with moderate-to-severe AD by 43.7% (0.1-mg group), 59.8% (0.5-mg group), 63.1% (2.0-mg group) and 20.9% (placebo group).[77] In a 52-week, double-blind extension of the previously described study,[77] pruritus was reduced up to 90% and eczema scores up to 80%.[78]

Anti-IL13 mAbs such as tralokinumab[79] or lebrikizumab[80] are also promising. At week 12, participants treated with 300 mg of tralokinumab demonstrated improvements in SCORAD, Dermatology Life Quality Index and pruritus numeric rating scale (7-day mean) scores vs. placebo.[79] From a phase II randomized controlled trial investigating the efficacy and safety of lebrikizumab in moderate-to-severe AD, dose-dependent responses were reported for per cent change from baseline pruritus VAS at week 20.[80] EASI scoring does not directly assess itch, but indirectly using the item 'excoriations'. At week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks (82.4%) than placebo every 4 weeks (62.3%) while patients receiving a single dose of lebrikizumab showed no statistically significant improvements in EASI-50 (indirectly assesses pruritus by the item 'excoriations') compared with placebo.[80]

In a randomized controlled phase IIa study, promising therapeutic effects of an orally administered histamine 4-receptor antagonist on skin inflammation and itch in adults with moderate-to-severe AD were shown at week 8 of treatment.[26]

Inhibitors of the JAK/STAT signalling axis could also be used as systemic treatments. Baricitinib is effective in moderate-to-severe AD, with an improvement of pruritus (45% change in itch NRS at week 1) and sleep loss.[81] Tofacitinib and upadacitinib have also been evaluated for AD treatment.[51,82]

Because thymic stromal lymphopoietin (TSLP) plays a crucial role in AD and in the pathophysiology of itch in this disease,[29] tezepelumab (a mAb targeting circulating TSLP) might also be a promising drug but the results of the phase 2a study were disappointing, including those on itch reduction.[83]

Itch and pain specific treatments

The treatment of AD itself usually decreases itch and pain. Nonetheless, the soothing effect is frequently not good enough and topical treatments have only local effects, while itch and pain are commonly reported outside lesions by patients. Notably, calcineurin inhibitors have direct effects on neurons[84,85] that explain better effects on pruritus but the possible induction of pain hypersensitivity. Nonetheless, one side-effect of topical calcineurin inhibitors is a burning (painful) sensation, which improves with time. Patient-reported skin pain is an ill-defined, common and burdensome symptom in AD.[7] When using analgesics (including gabapentinoids), the treatment of pain must be adapted to the intensity of pain as well as to the patient age and history and the effects of systemic drugs on pain in AD need to be further evaluated.

Doctors are aware of itch in AD patients but frequently underestimate its intensity and its extent, especially outside lesions. Thanks to recent research, the era of new treatments for AD is coming and most of them have promising effects on itch because they target cytokines such as IL-4, IL-13, IL-31 or TSLP, neurotransmitters such as substance P (tradipitant, serlopitant and others) or opioids as well as phosphodiesterase-4 or the Jak/Stat pathways.[23]

The European Guideline on Chronic Pruritus recently recommended pruritus-relieving measures but without any specificity for AD patients. The evaluation of treatments fighting itch[86] and pain[87] is difficult because there is a considerable placebo effect. Nonetheless, this placebo effect can also be an opportunity for many patients, with an important role of verbal suggestion by healthcare professionals.[86,88] However, convincing antipruritic effects were confirmed in controlled studies and the following treatments are recommended by the guideline: glucocorticosteroids (topical and oral), cyclosporin A, mycophenolate mofetil, dupilumab, tacrolimus ointment, pimecrolimus cream and naltrexone. The authors of the guideline considered that there were equivocal results with antihistamines (topical and systemic), azathioprine, methotrexate, apremilast and interferon γ. They also referenced that antipruritic effects were only shown in case reports for intravenous immunoglobulins, UV-A1–/UV-B 311 nm/PUVA therapy, leucotriene antagonists, capsaicin, infliximab and omalizumab. Gabapentinoids and antidepressants should be also used.

Education and pruritus management

The burden of chronic pruritus in AD is influenced by cultural and individual factors.[89] A multidisciplinary educational

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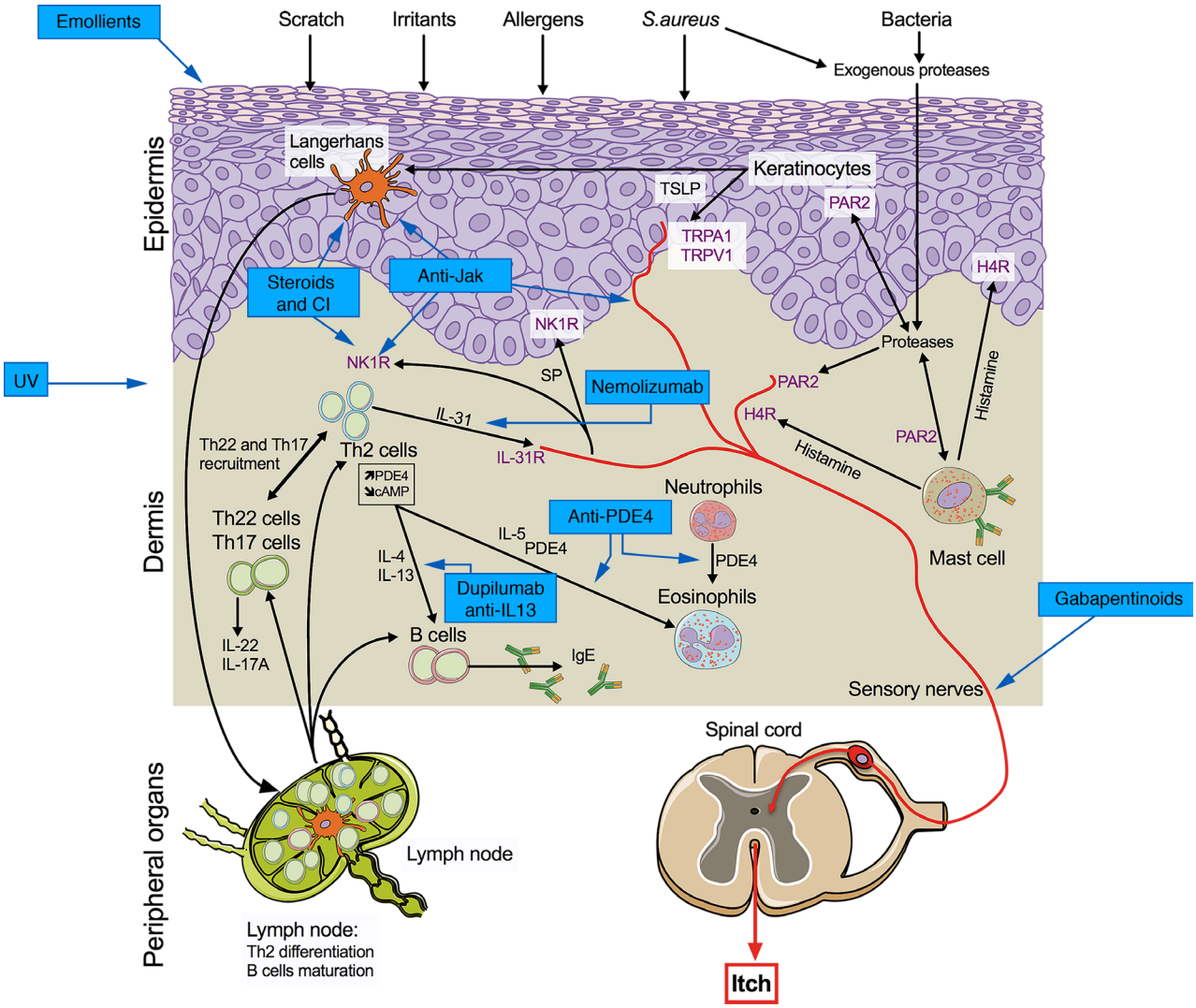

Figure 1 Different receptors for itch and pain relevant for AD and specific medications (inspired from Misery *et al*[23]).

programme approach and behavioural therapy can improve the outcomes.[90–94] Educational programmes were proven to be helpful measures in AD therapy while different models could be used worldwide.[95] Even in adults, a significant improvement of both the disease severity and coping behaviour with respect to itch could be achieved by structured patient education.[96] Approaches on therapeutic education for pruritus and AD are heterogeneous.[91,97,98] Behaviour modifications should also be part of the programme in the intent to break the itch–scratch cycle.[90,99,100]

Psychological approaches

Psychological distress, depression and anxiety, as well as suicidal ideation are enhanced by itch and skin pain.[11,101,102] Among skin diseases, AD has one of the most severe psychological impacts. Itch is a powerful inducer of mental distress, especially in AD patients.[103,104] Skin pain was also demonstrated to be associated with AD burden.[7,101] Unfortunately, dermatologists and other healthcare professionals underestimate the psychological impact of skin diseases, especially itch and skin pain.[105] Several studies suggest that mechanisms of central modulation play an important role in the development and maintenance of chronic itch.[37] Stress is also known to increase AD severity and itch. Therefore, treating the psychological aspects of itch is an important part of the management of chronic itch.

Psychological interventions may be very helpful in AD, especially in relation to severe itch.[37,106–108] Some studies have demonstrated their positive effects on itch and scratching in AD patients.[107] Autogenic training or behavioural treatment, for 12 weeks, improved itch and scratching 1 year after

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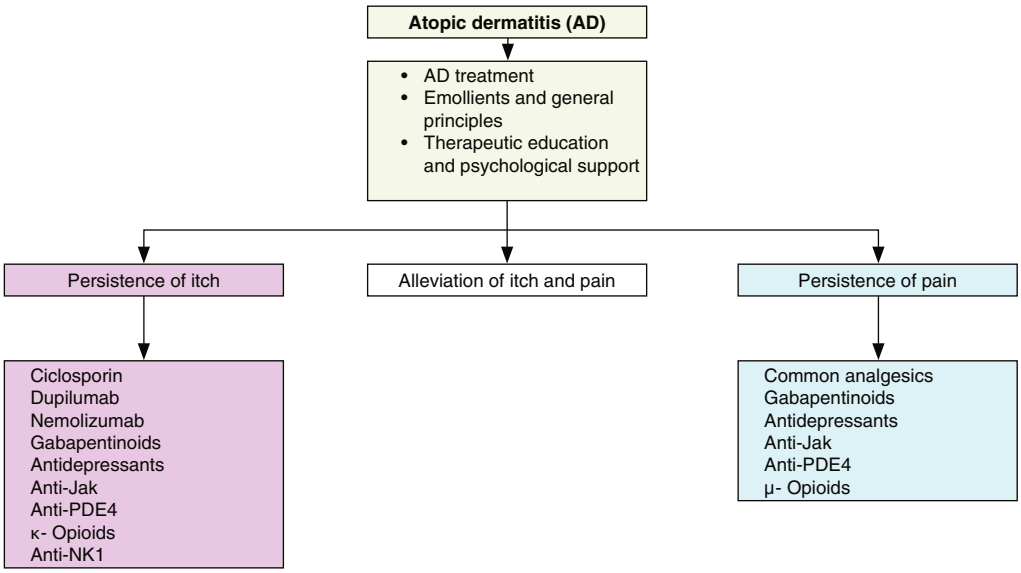

Figure 2 Proposal for a treatment algorithm.
[Correction added on 20 November 2020, after first online publication: Figure has been updated in the version.]

treatment.[109] A one-year multidisciplinary itch-coping programme on itch and scratching significantly decreased itch and scratching, even after the end of the intervention.[110] Relaxation techniques can also be very useful.[111] Studies investigating the effects of psychological interventions on chronic pain patients with other diseases could show very interesting results.[112] Mindfulness meditation is also promising in patients with skin diseases and in reducing pain and itch at the same time (Table 1).[37]

Perspectives

It is exciting to have numerous new therapeutic agents that have been recently approved and in development. Notably, some of the newest and future treatments of AD impact cytokines and neurotransmitters as well as receptors or the associated signalling pathways that are involved in itch and pain pathophysiology (Fig. 1). However, there is still a huge difference of information we were able to deliver concerning the impact of the treatments on itch and pain. We propose a treatment algorithm for the management of itch and skin pain in AD patients (Fig. 2).

This is very satisfying because itch and pain are the main patient sensory complaints. Fortunately, there is ongoing work to build clinical trials with patient prioritized outcomes, and to organize medical management according to a patient-centred model. A holistic approach is obviously essential. Therapeutic patient education and psychological approach would complete the caring patient-doctor relationship based on reciprocity. In any case, it is beneficial to break the itch/scratching cycle.[107,113]

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