EUROGUIDERM GUIDELINE ON ATOPIC ECZEMA

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## **Antipruritic treatment**

Itch is the most important clinical symptom in AE with particular impact on emotional dimensions of perception as compared to other pruritic dermatoses. Most drugs successfully used in AE patients, because they are targeting the inflammation, will also have a measurable effect on the itch. There is only a limited number of studies that specifically assessed the antipruritic effect of treatment modalities in AE. The treatment of itch in AE requires a multi-dimensional approach treating itch itself, but also the contributing factors, such as the dry skin and skin inflammation.

## Anti-pruritic effect of anti-inflammatory treatment

The anti-inflammatory agents, both topical and systemic ones, reduce skin lesions and significantly relief itch. Although topical corticosteroids do not act as direct antipruritic agents, several studies described the anti-inflammatory effect of topical corticosteroids in AE, in which pruritus was one parameter among others studied.

Topical calcineurin inhibitors relieve pruritus significantly in AE. Itch is completely relieved after the first days of treatment in both adults and children. Topical calcineurin inhibitors appeared to significantly reduce AE itch by 36% compared to vehicle application.<sup>2</sup>

Crisaborole was shown to be effective in reducing itch in mild-to-moderate AE patients. Reszke et al. in their review consider that patients receiving crisaborole 2% ointment experienced pruritus relief at day 29 more commonly than patients receiving vehicle.<sup>3</sup> Furthermore, crisaborole was more likely to provide antipruritic response at the earliest assessment on day 2 and early improvement of pruritus at day 6 than vehicle.<sup>3</sup> However, crisaborole is not available on the European market.

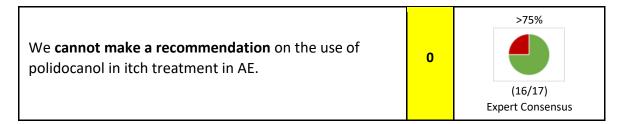
Dupilumab as systemic anti-inflammatory agent showed high effectiveness in reducing itch in AE patients. All the studies confirmed the efficacy of dupilumab in terms of improvement of skin lesions and alleviation of pruritus.<sup>4-7</sup> Similar data exists for other systemic drugs recently licensed for AE treatment, such as tralokinumab, abrocitinib, baricitinib and upadacitinib (see chapters Biologics and JAK-Inhibitors). <sup>8-11</sup>

A meta-analysis of 1505 patients with moderate-to-severe AE revealed that dupilumab started to unveil its antipruritic properties by days 2 and 5 in adults and adolescents, respectively. The response increased over time and was sustained until the end of the studies (up to 1 year).<sup>5</sup>

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## **Anti-prurigitic treatment**

#### Polidocanol

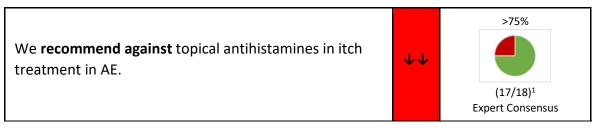


Case series described the efficacy of a combination of the anaesthetic polidocanol and 5% urea.<sup>12</sup> In children with AE, the combination showed a pruritus improvement of 30% in comparison with an emollient.<sup>13</sup> Polidocanol is not licensed for AE in Europe, but OTC products are available.

### Capsaicin

Capsaicin is a naturally occurring alkaloid and the principal pungent of hot chilli peppers. Capsaicin binds to the TRPV1 ion channel, which is present on many itch-mediating C-fibres. Capsaicin has been advocated to be antipruritic in various dermatoses. Concerning AE, experimental studies<sup>14</sup> and case series<sup>15</sup> report on clear itch reduction. However, the practical treatment and updosing are challenging, and no controlled study has been published.

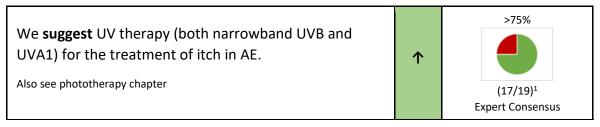
#### **Topical antihistamines**



<sup>&</sup>lt;sup>1</sup> 1 Abstention

5% doxepin cream exhibited antipruritic effects in three controlled studies in AE; one RCT assessed the efficacy of cromoglycate 4% lotion.<sup>2</sup> The meta-analysis of those studies documented that the use of topical antihistamines markedly reduced itch of AE by 27% in patients in comparison with the vehicle. However, topical doxepin therapy is not licensed and not used in any European country due to an increased risk of contact allergy, especially when the treatment exceeds eight days.

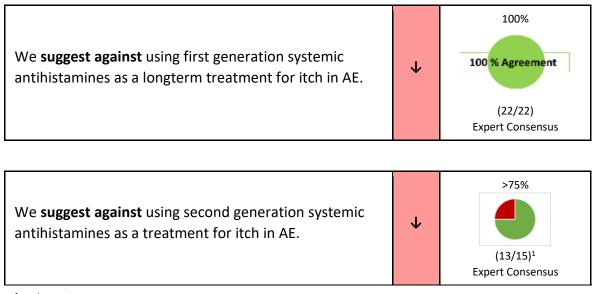
#### **UV** therapy



<sup>1</sup>2 Abstention

UV phototherapy relieves pruritus in AE, which has been demonstrated in several studies. A systematic review of 19 available RCTs suggests the usage of narrowband UVB and UVA1 as the most effective in the treatment of AE, including reduction in itch intensity. A recent study by Jaworek at al. Decumented that narrowband UVB reduces itch in AE patients significantly better than ciclosporine. There is no 'anti-itch-specific' data for UV phototherapy available, which would differ from the general recommendations for UV phototherapy treatment of AE.

#### Systemic antihistamines



<sup>&</sup>lt;sup>1</sup> 1 Abstention

Antihistamines (AH) have been used for decades in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and the majority of them showed only a weak or no effect in decreasing pruritus. A recent Cochrane review did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for AE when compared to placebo. The certainty of evidence for this comparison was of low and moderate quality. It seems that only fexofenadine may lead to small improvement in patient-assessed pruritus (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area. However, these reductions may not be clinically meaningful. In general, AH are safe to use, also for a long period of time. Here is limited data for the antipruritic effect of AH (H1 antagonists) in AE in general, and the effect of both first and second generation AH on pruritus in patients suffering from AE is very limited. The clinical value of systemic antihistamines for the anti-pruritic treatment of AE is not supported.

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Especially the first generation of systemic AH may affect sleep quality and reduce rapid eye movement (REM)-sleep. Therefore, regular long-term use of sedating antihistamines is not recommended. <sup>30-32</sup>

### **Opioid receptor antagonists**

The  $\mu$ -opioid receptor antagonist nalmefene was applied in smaller randomized, controlled studies in AE. A dosage of 10 and 20 mg each once per day showed significant relief of pruritus in three studies. The open-label trials and one double-blind, placebo-controlled study trial, the only orally active  $\mu$ -opioid antagonist naltrexone 25–150 mg per day showed considerable antipruritic effects. The opioid antagonist naltrexone 25–150 mg per day showed considerable antipruritic effects. The benefit-risk ratio is unfavourable.

#### Selective serotonin reuptake inhibitors

We suggest against the use of selective serotonin reuptake inhibitors as itch treatment in AE patients.

100%

Agreement

(20/20)

Expert Consensus

The antipruritic effect of the selective serotonin reuptake inhibitors paroxetine and fluvoxamine was investigated in an open-label trial in dermatological patients. A few patients with pruritus due to AE were included, who responded with considerable reduction in pruritus. In these patients, the pruritus was reduced about half in intensity (maximal antipruritic effect score, 45.0 + /-7.1%). Although the evidence of antipruritic activity of selective serotonin reuptake inhibitors in AE is very low, these agents might be used as second or third line therapy in other types of chronic itch.

Adverse events include constipation, diarrhoea, dizziness, drowsiness, ejaculatory and erectile dysfunction, decreased libido, insomnia, nausea and headache. The risk-benefit ratio of SSRI is highly unfavourable.

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