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Introduction

Chronic pruritus (CP) is a very common and often debilitating symptom in many dermatological and non-dermatological diseases [1, 2]. In dermatological conditions, CP is not only one of the most common symptoms, but also often the main factor affecting quality of life impairment. For example, 47 % of patients presenting to the emergency dermatological unit of a university hospital in Germany suffered itching [3] and dermatological patients with “very strong” pruritus reportedly have very severely impaired sexual activities and a high rate of suicidal ideation (17.9 % vs. 4.1 % in patients with “mild” pruritus) [4].

In atopic dermatitis (AD) rapid and effective treatment of pruritus is one of the main goals, as most patients suffer from moderate or severe pruritus, leading for example to sleep disturbances in the vast majority of AD patients [5–7]. Within the last years, a number of novel therapeutic options for AD have been introduced or are in late stages of clinical development [8]. Here, we summarize the reported efficacy on pruritus of these novel agents.

Pathogenesis of pruritus in atopic dermatitis

The exact underlying mechanism of pruritus in AD is not yet fully understood. Recent evidence indicates that histamine-independent pruritogens such as interleukin (IL) -31 [9], IL-13 and IL-4 [10] are implicated in CP in AD patients. Interleukin-31 is a cytokine that is predominantly produced by Th2 cells. It evokes itch via a receptor complex on C-fibers that consists of IL-31 receptor A (IL-31RA) and oncostatin M receptor β (OSMRβ). Binding of IL-31 to its receptors activates three pathways: ERK1/2 MAP kinase, PI3K/AKT, and Janus kinase (JAK) 1/2 signaling pathways [11]. In addition, IL-13 and IL-4 are Th2-specific cytokines that are thought to be involved in the pathogenesis of AD. Both cytokines share
the IL-4/IL-13 receptor (formed by IL-4Rα and IL-13Rα2) on sensory neurons and can mediate CP through JAK1/2 signaling. Interleukin-13 also binds with high affinity to the IL-13 Ra2 receptor [12]. Its role in AD is still under investigation but preliminary studies have indicated a possible role of IL-13 Ra2 as a decoy receptor with anti-inflammatory properties [13]. Other pruritogens that have been associated with itch in AD are histamine (via histamine type 1 and 4 receptors), tryptase (via mas-related G protein-coupled receptor X2), IL-33, and thymic stromal lymphopoietin (TSLP) [14]; their clinical relevance in inducing itch in AD, however, remains unclear (Figure 1). Overall, pruritus in moderate and severe AD has been reported to be closely associated with AD severity [5], indicating that similar mechanisms may be responsible for both itch and skin inflammation. However, many AD patients report generalized pruritus which is not restricted to the lesional skin [4], and a subset of patients with mild atopic dermatitis report severe itch [15]. Therefore, other factors than those directly associated with inflammation may contribute to the pathomechanism and severity of pruritus.

**Treatment Approaches**

**Biologics**

**Dupilumab:** Dupilumab is a fully human Immunoglobulin (Ig) G4κ monoclonal antibody that inhibits IL-4 and IL-13 signaling via inhibition of IL-4Rα (Figure 1). A recent analysis of four randomized phase III clinical trials focuses on the effects of dupilumab on pruritus in patients with moderate to severe AD. The authors specifically analyzed the time course (onset, duration, magnitude) of reduction of itch in those patients. Dupilumab treatment led to a rapid and statistically significant improvement vs. placebo in daily peak pruritus (percent change, numerical rating scale [NRS]) as early as day 2 in adult and day 5 in adolescent patients. Furthermore, there was a rapid improvement (defined as patient proportion with at least 3-point improvement from baseline) of itch from day 4 in adult and day 13 in adolescent patients. Over the course of the respective studies, itch intensity was significantly reduced in all studies compared to placebo and showed a progressive reduction over time (Table 1) [16].

**Lebrikizumab:** Lebrikizumab is a humanized monoclonal IgG4κ anti-IL-13-antibody which prevents heterodimerization of the IL-13Ra1/IL-4Ra complex and therefore selectively inhibits IL-13 signaling (Figure 1). Recently, efficacy and safety of lebrikizumab has been explored in adult patients with moderate to severe AD in a phase IIb trial. Subcutaneous lebrikizumab injections showed a dose-dependent clinical efficacy in AD patients compared to placebo during the 16-week treatment phase. In regard to the effect on pruritus, lebrikizumab treatment resulted in a dose-dependent improvement in pruritus NRS score with significant difference for all three dosing options compared to placebo. First differences in NRS score changes of at least four points compared to placebo were observed at day 2 for the high dosed groups, without further statistical analysis [17]. The currently ongoing phase III studies will provide more detailed information on the specific effects on pruritus (Table 1).
Table 1 Overview of pruritus efficacy of novel treatments for atopic dermatitis in adult patients. Data shown for adult patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biologics</th>
<th>JAK-Inhibitors</th>
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<tbody>
<tr>
<td></td>
<td>Dupilumab</td>
<td>Lebrikizumab</td>
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<tr>
<td>Therapeutic target</td>
<td>Interleukin-4-Receptor α</td>
<td>Interleukin-13</td>
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<tr>
<td>Formulation and Dosing (adult patients)</td>
<td>s.c. injection; 300 mg every 2 weeks (LD 600 mg)</td>
<td>s.c. injection; 125 mg every 4 weeks (LD 250 mg); 250 mg every 4 weeks (LD 500 mg); 250 mg every 2 weeks (LD 500 mg)</td>
</tr>
<tr>
<td>Effect on pruritus</td>
<td>Significant effect compared to placebo</td>
<td>Significant effect compared to placebo (all 3 dosing options)</td>
</tr>
<tr>
<td>Mean change from baseline in daily peak pruritus NRS/VAS at week 16</td>
<td>Dupilumab*:−47.4 % (125 mg) −49.6 % (250 mg/4w) −60.6 % (250 mg/2w) Placebo −20.5 %</td>
<td>Lebrikizumab −35.9 % (125 mg) −49.6 % (250 mg/4w) −60.6 % (250 mg/2w) Placebo 4.3 %</td>
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Continued
Pruritus efficacy by atopic dermatitis treatments

### Table 1 Continued.

<table>
<thead>
<tr>
<th>Drug</th>
<th><strong>Biologics</strong></th>
<th><strong>JAK-Inhibitors</strong></th>
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<tbody>
<tr>
<td></td>
<td>Dupilumab</td>
<td>Lebrikizumab</td>
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<tr>
<td>Proportion of patients with meaningful response at week 16</td>
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<td></td>
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<tr>
<td>≥ 4-point improvement in daily peak pruritus NRS scores from baseline</td>
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<tr>
<td>Dupilumab</td>
<td>38.4 %</td>
<td>Lebrikizumab 41.8 % (125 mg) 47.4 % (250 mg/4w) 70.0 % (250 mg/2w)</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.9 %</td>
<td>Placebo 27.3 %</td>
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<tr>
<td>Onset of first significant itch reduction</td>
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<td></td>
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<tr>
<td>Day 2</td>
<td>Not analyzed; first differences compared to placebo at day 2</td>
<td></td>
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<tr>
<td>Changes from baseline of daily peak pruritus in comparison to placebo from week 1 onwards</td>
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<td></td>
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<tr>
<td>Not analyzed</td>
<td>Day 2</td>
<td>Day 1</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions, conjunctivitis</td>
<td>Injection site reactions, herpesvirus infections, conjunctivitis</td>
<td>Injection site reactions, worsening of atopic dermatitis</td>
</tr>
</tbody>
</table>

*Abbr.: IL, Interleukin; LD, loading dose; NRS, numerical rating scale; s.c., subcutaneous; VAS, visual analogue scale.

†Data from patients with dupilumab monotherapy: studies LIBERTY SOLO AD 1 and 2 *study medication/placebo in combination with topical corticosteroid treatment.

NRS and VAS are highly correlated and are thus considered comparable.
Tralokinumab: Tralokinumab is a recombinant human IgG4κ monoclonal antibody targeting IL-13 by prevention of its binding to the IL-13Rα1 and IL-13Rα2 (Figure 1) and has very recently been approved for adults with moderate to severe atopic dermatitis in the European Union. Compared to lebrikizumab, tralokinumab binds a different epitope of soluble IL-13 but also with high affinity. In 2020, first results from phase III trials on tralokinumab monotherapy (ECZETRA 1 and 2) as well as in combination with topical corticosteroid treatment (ECZETRA 3) in patients with moderate to severe AD were published. At week 16, a reduction of weekly average daily peak pruritus (NRS ≥ 4) compared to baseline was achieved in a higher proportion of patients treated with Tralokinumab than compared to the placebo group. In addition, Tralokinumab-treated patients showed higher changes from baseline of daily peak pruritus NRS compared to placebo with significant difference from treatment week 1 onwards (Table 1) [18, 19].

Nemolizumab: Nemolizumab is a humanized monoclonal antibody targeting the IL-31RA (Figure 1) and is applied subcutaneously every 4 weeks. In a recent phase III study, treatment with nemolizumab in conjunction with topical corticosteroids showed an excellent effect on pruritus reduction in patients with moderate to severe AD compared to placebo with topical agents. At week 16, the mean percent change in the VAS score was significantly higher in the nemolizumab group (−42.8 %) as compared to placebo (−21.4 %) [20].

JAK-inhibitors

Baricitinib: Baricitinib is an oral JAK inhibitor with an equally high specificity for JAK-1 and -2 (Figure 1) and a lower specificity for Tyk2 [21]. It is the first of its class that received approval for the treatment of moderate to severe AD. In conjunction with topical corticosteroids, both 2 mg and 4 mg daily treatment with baricitinib resulted in a significant reduction of daily itch (mean NRS compared to baseline) at day 2. At week 16, a significant higher proportion of treated patients with AD (44 % for the 4 mg group, 38 % for the 2 mg group) compared to the placebo group (20 %) showed a clinical significant improvement of itch (defined as change compared to baseline NRS ≥ 4) (Table 1) [22, 23].

Abrocitinib: Abrocitinib is an oral selective JAK-1 inhibitor (Figure 1) and has been investigated as a daily treatment (100 mg and 200 mg 1 x/d) in a phase III trial in adults and adolescents with moderate to severe AD. Here, the proportion of patients who achieved a clinically relevant reduction of the peak pruritus was significantly higher for the abrocitinib treatment groups (57 % for the 200 mg group, 38 % for the 100 mg group) compared to the placebo group (15 %) at week 12 [24]. In another phase III head-to-head trial comparing abrocitinib in both doses to dupilumab, efficacy of abrocitinib was comparable to dupilumab in most endpoints, but was superior (in the 200 mg group) to dupilumab treatment in regard to itch response at week 2 (Table 1) [25].

Upadacitinib: Upadacitinib is an oral inhibitor of JAK-1 and has been shown to be effective in adult patients with moderate to severe AD in two replicate phase III trials (monotherapy) and in a phase III trial as a combination therapy with topical corticosteroids [26, 27]. At week 16, monotherapy with 15 mg or 30 mg 1 x/d resulted in significant improvement of pruritus as well as a significant, clinically relevant reduction of pruritus (defined as improvement compared to baseline NRS ≥ 4) in patients with AD compared to placebo (Table 1) [26]. In comparison to dupilumab treatment in a phase III head-to-head study in adult patients with AD, upadacitinib treatment was found to be superior in terms of improvement of pruritus [28].

Discussion

In a recently published survey of 1,104 patients with AD, pruritus was considered by the vast majority of patients (95.4 %) to be very important in deciding whether or not a treatment is working [29]. Therefore, knowledge of the effects of novel drugs in AD on the improvement of pruritus is important. In recent years, pruritus assessments have become an important outcome parameter in clinical trials in AD. Itch parameters are commonly reported using standardized outcome measures, which makes it possible to compare novel drugs in terms of their effects on pruritus. It is important to note, however, that there are differences between the study designs, for example, in time points of assessment, allowed co-medication, the study population size and study specifics (for example, exclusion of patients with mild AD), so the comparisons presented here should be interpreted with caution. Particularly informative are therefore head-to-head trials, such as those already carried out and published for abrocitinib versus dupilumab and upadacitinib versus dupilumab [25, 28]. It is important to note that this review only describes effects on pruritus characteristics and does not address other efficacy outcomes such as improvement in eczema scores or safety aspects such as overall number of adverse events or suspected unexpected serious adverse reactions. In addition, the pipeline of potential treatments for patients with AD includes further drug candidates that are in earlier stages of development. Of special interest, and not discussed within this review, are novel topical treatment approaches such as the tyrosine kinase 2 (TYK2) inhibitor brepocitinib or the aryl hydrocarbon receptor modulating agent tapinarof [30, 31]. It will be interesting to compare the effects on pruritus of these topical treatments to those of the systemically applied drugs. All of the novel drugs in AD presented in this
review have shown promising data on improving itch, with a very rapid onset of itch relief often being reported. Although it is certainly debatable whether an improvement in pruritus occurring after two rather than ten days is relevant, the overall efficacy in reducing pruritus over the entire treatment period is of great importance to patients.

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Conflict of interest

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References

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