



The show must go on: an update on clinical experiences and clinical studies on novel pharmaceutical developments for the treatment of atopic dermatitis

Tatjana Honstein and Thomas Werfel

Purpose of review

This review reports on published clinical studies (full publications) with novel therapeutic agents on the treatment of atopic dermatitis with a focus on the last 2 years.

Recent findings

Atopic dermatitis is a T-cell driven complex inflammatory skin disease. The secretion of cytokines involving not only particularly Th2 but also Th17 and Th22 cell subsets provides a broad spectrum of potential therapeutical targets. A couple of studies on atopic dermatitis with new therapeutical antibodies that target not only the Th2 cytokines IL-4, IL-13, IL-31 but also additional targets, such as TSLP, IL-22 or IL-33, and innovative small molecules binding to the histamine-4 receptor, the phosphodiesterase-4, the aryl hydrocarbon receptor or downstream molecules like Janus kinases have recently been published with promising results on symptoms and signs of atopic dermatitis.

Summary

Applications of newly developed drugs in clinical studies or already in daily practice show a substantial progress in the treatment of moderately to severely affected patients with atopic dermatitis not responsive to standard topical treatments with corticosteroids or topical calcineurin inhibitors alone. Moreover, novel treatment approaches generate new knowledge about (anti)inflammatory effects of immune modulations in atopic dermatitis and the heterogeneity of patient subgroups, which may stimulate further innovations in this field.

Keywords

atopic dermatitis, biologicals, small molecules, systemic therapy, topical therapy

INTRODUCTION

Atopic dermatitis is one of the most common inflammatory skin diseases with multiple negative consequences for the overall physical and mental health and social interactions resulting in reduced quality of life. The systematic analysis of individuals suffering from atopic dermatitis confirmed that the most stressful symptom is severe itch (pruritus) with a reported prevalence of chronicity of 87–100% in atopic dermatitis [1,2]. It is well known that atopic dermatitis is a T-cell driven disease characterized by the overexpression of the key type cytokines IL-4 and IL-13 activating intracellular JAK-STAT pathways via their receptors. Activated STATs subsequently translocate into the cell nucleus and regulate the expression of type 2 cytokine-related target genes [3,4]. In the following overview, recent studies on new drugs that inhibit the binding or

signal transmission of atopic dermatitis-typical cytokines or those directly counteract pruritus in atopic dermatitis are presented.

SYSTEMIC THERAPY IN ATOPIC DERMATITIS

Table 1 summarizes novel substances for the treatment of atopic dermatitis with clinical studies

Division of Immunodermatology and Allergy Research, Department for Dermatology, Allergy and Venereology, Hannover Medical School, Hannover, Lower Saxony, Germany

Correspondence to Dr Tatjana Honstein, Hannover Medical School (MHH), Hannover, Lower Saxony, Germany. Tel +49 511 532 5054; e-mail: Honstein.tatjana@mh-hannover.de

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KEY POINTS

- Dupilumab approved for the treatment of atopic dermatitis in 2017 showed efficacy and safety of dupilumab also in recent registry studies (real world data).
- Novel antibodies address cytokine type 2 targets like IL-13 or IL-31 with promising results published from larger phase 2 studies and proof-of-concept studies showed possible efficacies of anti-TSLP, anti-IL-22 or anti-IL-33 antibodies.
- The histamine-4 receptor antagonist adirforant is a promising candidate for oral therapy of atopic dermatitis having shown efficacy in a proof-of-concept study and a couple of oral JAK inhibitors have already been studied with success in larger phase II or even phase III studies.
- The topical PDE4 inhibitor crisaborole, which is already approved in the USA for the treatment of atopic dermatitis is mildly effective. In addition to tapinarof, a modulator of the aryl hydrocarbon receptor in particular topical JAK inhibitors are currently being examined in clinical studies with promising first results and possibly stronger efficacy in atopic dermatitis.

published as full articles between 2018 and April 2020, which are summarized in this review.

TARGETING THE IL-4 RECEPTOR α CHAIN WITH DUPILUMAB FOR THE TREATMENT OF ATOPIC DERMATITIS: WHAT IS NEW?

Dupilumab enables a targeted therapy inhibiting the action of the key type 2 cytokines IL-4 and IL-13 to their receptors by binding to the common α chain of their receptors. Following successful clinical trials in adults, the antibody was approved in the

USA and the EU for the treatment of severe-to-moderate atopic dermatitis by the Food and Drug Administration (FDA) and the EMA in adults in 2017. The key studies showed efficacy of a reduction of the skin score EASI by 75% ('EASI75') after 16 weeks [5], respectively 1 year [6] in approximately two-thirds of the study patients.

Clinical studies often do not reflect the situation in 'real world' where there is a need of treating patients with comorbidities, which are often defined as exclusion criteria in study settings. Therefore, data coming from disease-specific independent registries have gained increasing interest during the last years. The German registry for adult patients with atopic dermatitis was started more than 5 years ago and follows patients at least 2 years. The registry data show that after approval in the EU, dupilumab displaced cyclosporine and other immunosuppressing drugs and is now used as first-line systemic therapy in Germany in the majority of patients with atopic dermatitis. EASI75 was achieved in 57% of patients participating in the German registry after 3 months and in 52% after 6 months of patients, which is slightly less than in the placebo-controlled studies but overall also indicates a very good responsiveness to the antibody in 'real world' [7,8^{*}]. These data were confirmed by a registry from the Netherlands showing EASI-75 in 62% of all patients after 16 weeks. In addition severity-related serum biomarkers (TARC, PARC, periostin, and IL-22), eotaxin-1, and eotaxin-3 were determined in this registry study and shown to decrease significantly during dupilumab treatment [9].

More recently, the application of dupilumab was also clinically evaluated for pharmacokinetics, long-term safety and efficacy in adolescents in a phase III study, which led to the FDA and EMA approval for this patient group. A significant change in EASI75 was seen in approximately 40% of

Table 1. Studies with novel systemic drugs for atopic dermatitis published January 2018 to April 2020

Substance	Target molecule	Application mode	Published clinical studies until April 2020
Dupilumab	IL-4 receptor, IL-13 receptor	Subcutaneous injection	Phase III
Lebrikizumab	IL-13	Subcutaneous injection	Phase II
Tralokinumab	IL-13	Subcutaneous injection	Phase II
Nemolizumab	IL-31 receptor	Subcutaneous injection	Phase II
Fezakinumab	IL-22	Intravenous injection	Phase II
Etokinab	IL-33	Intravenous injection	Phase II
Adirforant	Histamine 4 receptor	Oral	Phase II
Baricitinib	JAK 1/JAK 2	Oral	Phase III
Upadacitinib	JAK 1	Oral	Phase II
Abrocitinib	JAK 1	Oral	Phase II
Gusacitinib	JAK/SYK	Oral	Phase II

adolescent patients, patients with a lower placebo response in this age group compared with adults [10¹⁰]. The effect of the drug was sustained in an open label trial extension of 1 year [11]. Treatment was well tolerated – as seen before in adults only the incidence of conjunctivitis and injection site reactions were significantly higher in the dupilumab-treated group compared with placebo control.

Other phase III studies, which led to approval of dupilumab by health authorities addressed allergic asthma bronchiale and polyposis nasi, which may now be treated ‘in label’ as stand alone indication or in combination with atopic dermatitis.

As itch has an important impact on the burden of disease effects, all data on pruritus were reanalysed from all placebo-controlled phase III studies with dupilumab recently [12¹²]. It was shown that across all phase III trials, dupilumab treatment showed rapid and sustained improvements in the magnitude of itch, starting with first dose. Responses on itch progressively increased and were sustained up to 1 year.

In terms of the risk of skin infections with herpes viruses or bacteria during therapy with dupilumab, a meta-analysis of study data from four controlled studies with 2706 patients came to a clear result [13]. Treatment with dupilumab reduces the risk of developing eczema herpeticum by about 2/3 [risk ratio (RR) 0.34; 95% confidence interval (CI) 0.14–0.84]. No association was found for overall herpes recurrence during treatment with dupilumab (RR 1.16; 95% CI 0.78–1.74). Interestingly, the same evaluation also calculated a significant overall reduction in skin infections (RR 0.54; 95% CI 0.42–0.70), whereas dupilumab had no effect on overall (i.e. nonskin) infections in atopic dermatitis patients (RR 0.98; 95% CI 0.83–1.16). The result on severe herpes infection was recently confirmed by a comprehensive analysis of seven placebo-controlled clinical trials involving 2932 patients. Here, clinically important herpes virus infection rates (mainly eczema herpeticum) were markedly reduced after dupilumab treatment with a RR of 0.31 [14].

In clinical studies, 11% of patients treated with dupilumab experienced inflammatory eye symptoms at 16 weeks and 47% at 52 weeks. The inflammatory symptoms in the eye varied. Often conjunctivitis or blepharoconjunctivitis with inflammatory changes in the corneal limbus was observed, rarely in combination with keratitis. The severity was usually mild to moderate but in a few patients, it can be severe. Risk factors for the occurrence of inflammatory eye diseases are high severity of atopic dermatitis, a higher age, and a longer disease history. Both worsening and newly

developed eye diseases have been reported during therapy with dupilumab, which usually disappear after discontinuation of medication. Interestingly, this side effect is only observed in patients with atopic dermatitis and not in patients with allergic asthma bronchial or in patients with polyposis nasi treated with dupilumab [15,16]. Numerous mechanisms have been discussed for atopic dermatitis-related ocular symptoms induced by dupilumab. One of them is that the availability of the therapeutic antibody at the conjunctiva may be reduced as it cannot diffuse as well as it is increasingly eliminated via nFcR-dependent mechanisms. This means that with simultaneously increased systemic availability of free IL-4 and IL-13 under the blockade of their receptors, these two cytokines could have stronger effects in loco [17].

Another more recently described side effect is nonpruritic facial rash appearing after the injection of dupilumab sometimes remaining for a couple of days [18,19]. Rosacea-like reactions associated with the administration of dupilumab suggested that Th2 inhibition by dupilumab might support the lesions via increased IL-17 inflammation [20]. In two patients who developed itchy and painful facial flushing during dupilumab treatment, itraconazole led to improvement of the symptoms [21].

It was speculated that Th1-associated or Th 17-associated inflammatory diseases might be induced or aggravated during the therapy with a Th2 blocker like dupilumab. So far, a few case reports or case histories have been published on patients developing arthritis or polyarthralgia during therapy with dupilumab [22,23]. It is not possible to decide if there was a causal relation or if this was coincidental.

TARGETING IL-13 FOR THE TREATMENT OF ATOPIC DERMATITIS WITH TRALOKINUMAB OR LEBRIKIZUMAB

IL-13 is a central therapeutical target of Th2-driven diseases. It has many common functional properties to IL-4 as it binds to IL-13R α containing the same α subunit of the heterodimeric IL-4 receptor. In contrast to dupilumab, the anti-IL-13 antibody tralokinumab and lebrikizumab do not bind to the receptor but neutralize the IL-13 cytokine directly. Moreover, IL-13 has no stimulating effects on T lymphocytes in contrast to IL-4. Interestingly, the binding sites of tralokinumab and lebrikizumab are located at opposite side of the IL-13 molecule, which leads to different blocking effects: Although lebrikizumab blocks the binding of IL-13 exclusively to the IL-13R α 1, tralokinumab also inhibits the binding of IL-13 to IL-13R α 2 [24]. The latter receptor molecule is considered to function mainly as a negative

regulator of IL-13 functions although a few observations support the notion that it may also be involved in stimulating cells (mainly fibroblasts) after internalization of the receptor together with its ligand. A recently published study based on deeply sequenced transcriptomes of 147 atopic dermatitis patients and their in-depth analysis showed a disease-specific molecular signature characterized by a dominant IL-13-signaling pathway and poorly detectable IL-4 [25].

A phase IIb study in a randomized, placebo-controlled group of 204 individuals with severe-to-moderate atopic dermatitis demonstrated the efficacy and safety of tralokinumab. The treatment was administered subcutaneously with different doses for 3 months. The best improvements were observed in the highest dosing group receiving 300 mg antibody. Seventy-three percent of these patients showed a reduction of 50% of the skin severity score EASI ('EASI50') compared with 52% in the placebo group and 43% compared with 16% showed a reduction of 75% ('EASI75'). A positive development of the numerical evaluation scale for itching and the dermatological quality of life index could also be documented. Additionally, a treatment response by means of biomarkers in the blood (DPP4, periostin, TARC, and IgE) was also observed. Upper respiratory tract infections and headache were the most common adverse events. So far, there were fewer treatment-associated cases of conjunctivitis in tralokinumab trials compared with dupilumab trials but of course no head-to-head comparisons are available so far [26]. Tralokinumab also met all primary and secondary endpoints in three phase III studies for the treatment of moderate-to-severe atopic dermatitis in adults, which have so far been communicated in press releases and on conferences.

In a proof-of-concept study with the anti-IL-13 antibody lebrikizumab a significant, but not very pronounced improvement of the eczema score was observed after 12 weeks of monthly treatment [27]. Responses in the placebo group were so high that possible therapeutic effects of the antibody may have been partially masked by topical corticosteroids, which could be applied by the patients in this study. Steroid effects were avoided more in a recent phase II trial with lebrikizumab, and the results of the antibody were more convincing than in the first study [28]. After 16 weeks EASI75 was observed 24% of the study patients in the placebo group compared with 43%, 56 or 61% after the application of 125 mg lebrikizumab every 4 weeks, 250 mg every 4 weeks or 250 mg every 2 weeks. Conjunctivitis as treatment emergent adverse event was observed in 2.6% of all patients in the treatment groups and not in the placebo group.

TARGETING IL-31 RA FOR THE TREATMENT OF ATOPIC DERMATITIS WITH NEMOLIZUMAB

Three therapeutical targets for atopic dermatitis discussed in this overview are directly involved in inducing itch in addition to cytokine type 2-skewed inflammatory responses: IL-31, TSLP, and histamine. Effects of IL-31 are discussed in detail by Topal *et al.* [29] in this issue of *Current Opinion in Allergy & Clinical Immunology*. IL-31 acts via a complex of IL31RA and the oncostatin M receptor β , which is expressed in immune and epithelial cells and on sensory nerves. Interestingly, this antibody was recently successfully applied also in patients suffering from very high pruritus in prurigo nodularis in a placebo-controlled phase II study [30].

Following a well performing phase I study, nemolizumab was tested in patients with moderate-to-severe pruritic atopic dermatitis in a phase II study. The initial evaluation of a study of 12 weeks on 216 patients showed major effects on the reduction of pruritus [31]. Patients from this study entered an extension regimen and continued treatment for another 52 weeks [32]. The study endpoint showed a solid improvement in visual analogue scale (VAS) value for pruritus between 73 and 90% from baseline. During extension, the change in EASI score was also markedly reduced between 69 and 79%. The overall Dermatology Quality of Life Index (DLQI) score decreased progressively in patients receiving nemolizumab. The most common treatment-related adverse effects were exacerbation of atopic dermatitis, upper respiratory tract infections, nasopharyngitis, peripheral edema, elevated blood creatine phosphokinase levels, and injection site responses, usually of mild-to-moderate intensity. An additional dose-adjustment study was performed in 226 adult participants [33]. Patients received placebo or 10, 30, 90 mg of nemolizumab applied subcutaneously every 4 weeks for 24 weeks. Efficacy was determined with EASI, IGA, and NRS pruritus scores compared with the placebo group and it turned out that the 30 mg dose led to best efficacy showing significant reduction not only of pruritus but also of clinical signs (measured by EASI) already after 16 weeks.

TARGETING THYMIC STROMAL LYMPHOPOIETIN FOR THE TREATMENT OF ATOPIC DERMATITIS WITH TEZEPELUMAB

Like IL-31, the epithelial cytokine thymic stromal lymphopoietin (TSLP) has both inflammatory and direct itch-inducing effects, thus representing a further interesting target structure for the treatment of atopic dermatitis. A first proof-of-concept study

with the anti-TSLP antibody tezepelumab led to mild rather clinical effects. There was a trend of improvement of the skin compared with placebo but the primary study objective, and itch reduction was not significant at all visits in this placebo-controlled study. It is possible that topical corticosteroids allowed in the placebo group were responsible for a relatively high placebo effect in this study [34[■]]. The antibody is currently further investigated with another study design.

TARGETING IL- 22 FOR THE TREATMENT OF ATOPIC DERMATITIS WITH FEZAKINUMAB

IL-22 is expressed by T lymphocytes and is mainly expressed on epithelial cells, but not on immune cells. Significantly increased expression levels of IL-22 and of IL-22-producing cells in serum and skin make it a possible therapeutic target for biologicals. In a first phase IIa trial the IL-22-specific antibody fezakinumab was administered intravenously every 14 days for 10 weeks in patients with atopic dermatitis [35[■]]. After 12 weeks, a significant, but overall not very high therapeutic effect was seen with a reduction of the eczema score SCORAD by 14 points in the treatment group and by 8 points in the placebo group. In differentiated subgroup analysis, the therapeutic effect was more pronounced in severely affected patients with a reduction of the SCORAD by 22 points versus 10 points in the placebo group after 12 weeks and 27 points versus 12 points after 20 weeks.

Lesional and nonlesional skin from patients treated with fezakinumab was further investigated using transcriptomic and immunohistochemistry analyses [36]. Baseline median IL-22 mRNA expression was used to stratify for high and low IL-22 expression groups. Much stronger mean transcriptomic improvements were seen with fezakinumab in the IL-22-high drug-treated group than in the respective IL-22-high placebo-treated group, the IL-22-low groups showing significant downregulations of molecules related to TH1, TH2, TH17, and TH22 pathways.

TARGETING IL-33 FOR THE TREATMENT OF ATOPIC DERMATITIS WITH ETOKIMAB

Interleukin-33 is mainly produced by keratinocytes in the skin and has substantial effects on in a lymphoid cells and T cells in cutaneous inflammation, as discussed in further detail by Topal *et al.* [29] in this issue of *COAI*. In a first-in-class phase 2a study of etokimab (ANB020), an IgG1 anti-IL-33 monoclonal antibody was tested in patients with atopic dermatitis [37[■]]. Twelve adult patients with moderate-to-severe atopic dermatitis received a single intravenous systemic

administration of etokimab. More than 80% of them achieved EASI50 and 33% EASI75 at day 29 after administration. The authors describe significant reduction in skin neutrophil infiltration after etokimab compared with placebo upon skin challenge with house dust mite and inhibition of neutrophil migration to skin interstitial fluid *in vitro*.

TARGETING THE HISTAMINE 4 RECEPTOR WITH ADRIFORANT FOR THE TREATMENT OF ATOPIC DERMATITIS

The histamine (H)-4 receptor is expressed not only on afferent (sensitive) nerve fibers but also on many inflammatory cells. Therefore, its blockade promises a dual mechanism of action: direct decrease of itching and reduction of inflammatory activity. In a number of in-vitro models, a function of the H4-receptor in Th2-polarized and also in Th-17 inflammation was shown suggesting that the receptor might be a therapeutic target structure in atopic dermatitis and possibly also in psoriasis [38[■]]. In an in-vivo murine model of atopic dermatitis (ovalbumin-induced eczema by epicutaneous sensitization in wild-type versus H4 receptor knock out mice), it was shown that in the absence of the H4-receptor eczema reactions were significantly weaker in the knock-out model. Moreover, an antagonist against the H4-receptor was able to suppress skin reactions in the mouse model *in vivo* [38[■]].

A first proof-of concept study in humans with atopic dermatitis with the H4-receptor antagonist JNJ-39758979 had to be stopped and unblinded for safety reasons (two cases of severe neutropenia). Numerical improvements in median EASI and itch scores were observed with the study drug at week 6, although the primary endpoint was not met probably to premature study discontinuation [39].

In a phase IIa proof-of-concept study on 98 patients with atopic dermatitis with the orally administered, high-affinity H4 receptor antagonist adriforant (ZPL3893787), significant effects on the visible lesions of eczema with a 50% reduction in EASI were seen, with lower effects on itching. Side effects, especially on neutrophils or other cells in blood counts, did not occur with this compound [40[■]]. The principle of H4-receptor blockade is a promising approach that is now investigated in larger phase IIb study with adriforant.

TARGETING JANUS KINASES FOR THE TREATMENT OF ATOPIC DERMATITIS WITH BARICITINIB, UPADACITINIB, ABROCITINIB, OR GUSACITINIB

In addition to receptor or cytokine blockade on the extracellular portions via antibodies, it is possible to

inhibit signal transmission of cytokine receptors with Janus kinase inhibitors acting in the intracellular part of receptors. JAK inhibitors are small molecules, which can be applied orally or topically, which is a theoretical advantage over the application of therapeutic antibodies particularly in children.

Baricitinib is a selective and reversible inhibitor of Janus kinases 1 and 2, which was already approved for the treatment of rheumatoid arthritis by the FDA and EMA. A first 'full publication' was published for a phase II study in atopic dermatitis with baricitinib in 2018 [41[¶]]. Here 124 patients with moderate-to-severe atopic dermatitis were treated orally in two doses or with placebo in combination with topical corticosteroids. A 50% reduction in eczema score ('EASI50') was achieved in 61% of patients under the higher dose of 4 mg after 16 weeks of baricitinib compared with 37% in the placebo group; the therapeutic effect was significant only after 4 weeks. Itching and sleeping disturbances were also significantly reduced in the treatment group. The drug significantly improved eczema severity measured by EASI75 score by 16% of the highest dose subjects compared with 4.8% of the placebo group.

The results of two phase III studies with a total of more than 1200 subjects treated with baricitinib daily for 16 weeks were recently reported: at week 16, more patients achieved the primary end point of Validated Investigator's Global Assessment of atopic dermatitis (0, 1) on baricitinib compared with placebo in baricitinib 4 mg 16.8% and 2 mg 11.4% compared with placebo 4.8% on the first study and in baricitinib 4 mg 13.8% and 2 mg 10.6% compared with placebo 4.5%. Improvement in itch was achieved as week 1 for 4 mg and week 2 for 2 mg. Improvements in health-related life quality were also reported. Nasopharyngitis, upper respiratory tract inflammation, elevated blood creatine phosphokinase levels and headache were the most common adverse events reported in all treatment groups [42^{¶¶}].

Upadacitinib is a selective, reversible JAK1 inhibitor that blocks Th2 typical IL-4, IL-13, IL-31 cytokine-signaling pathways and was already approved by FDA and EMA for the treatment of rheumatoid arthritis. A randomized, blinded, placebo-controlled phase IIb clinical trial was conducted in 167 atopic dermatitis patients who received orally varying doses of the inhibitor or placebo for 16 weeks. A significant dose-dependent change in EASI of 50, 75% compared with control and positive development of SCORAD, BSA, and POEM was reported. Here were the most adverse effects described as for Baricitinib except for acne.

A saturation plateau was not observed in this study but a steady increase in symptom improvement was observed during the 16 weeks of treatment. Therefore a long-term study was recommended and the testing of higher doses to increase potential efficacy [43[¶]].

The selective JAK1 inhibitor abrocitinib was tested in a blinded, randomized, placebo-controlled phase IIb clinical trial with 267 subjects, who were orally administered different doses of the study drug for 12 weeks daily. EASI75 was achieved by 64.6% in the subgroup getting 200 mg of the drug versus 15.4% participants in the placebo group. A decrease in involved body surface area, the pruritus Numerical Rating Scale (NRS) score and the eczema score SCORAD was observed in all groups. 16.5% of the subjects stopped their participation in this study because of adverse reactions, such as worsening of atopic dermatitis or abdominal pain. One patient had to discontinue treatment because of thrombocytopenia [44[¶]].

Gusacitinib is a potent dual inhibitor of spleen tyrosine kinase (SYK) and Janus kinases (JAK), also known as ASN002. In addition to the Janus kinases, SYK is involved in the modulation of the immune response by controlling the release of cytokines, regulation of dendritic cells and differentiation of keratinocytes [45,46]. A double-blind, randomized, placebo-controlled clinical trial tested different oral doses of the inhibitor in 36 subjects. The 40 mg dose showed the best improvement of sign shown by EASI75 in 71% treated versus 22% untreated patients after 4 weeks. Hundred percent of the subjects in the 40 mg, 83% in the 80 mg, and 22% in the placebo-controlled group achieved EASI50. Additional skin biopsies of volunteers allowed an investigation of RNA expression patterns and showed a shift of the transcriptome towards a healthy phenotype. Serum samples showed a reduction of the inflammatory markers of the Th1, Th2, Th17/22 immune responses and a reduction of E selectin [47[¶],48].

TOPICAL THERAPY: WHAT IS NEW?

Table 2 summarizes novel substances used for topical therapy in atopic dermatitis with phase 2 of phase 3 studies published until April 2020.

TARGETING JANUS KINASES FOR THE TOPICAL TREATMENT OF ATOPIC DERMATITIS WITH RUXOLITINIB OR DELGOCITINIB

JAK inhibitors have the advantage over therapeutic antibodies that they can also be applied topically, and thus, represent an alternative for milder or

Table 2. Studies with novel topical drugs for atopic dermatitis published January 2018 to April 2020

Substance	Target molecule	Application mode	Published clinical studies until April 2020
Ruxolitinib	JAK1/JAK2	Topical	Phase II
Delgocitinib	Pan JAK	Topical	Phase III
Crisaborole	PDE4	Topical	Phase III
Tapinarof	aryl hydrocarbon receptor	Topical	Phase II

localized disease conditions. Ruxolitinib is a selective JAK1 and JAK2 inhibitor. The topical application in a cream was tested a phase 2 study with 307 atopic dermatitis patients. After randomization, subjects were treated with different concentrations of ruxolitinib, the vehicle control or vehicle control with 0.1-containing triamcinolone cream for 8 weeks. All treatments with the inhibitor resulted in a significant improvement of the EASI score compared with the placebo control. More patients achieved EASI 50, EASI 75, EASI 90, and IGA improvement with the 1.5% ruxolitinib ointment than with triamcinolone treatment [49[¶]]. In a separate publication, the data from the same study were shown describing a clinically meaningful reduction in itch and quality of life burden [50]. Application-site pain was the most frequent treatment-related adverse effect.

Delgocitinib is a broader acting kinase inhibitor of TYK2 and other JAK kinases. In a phase III trial, an ointment with delgocitinib was tested on 158 volunteers with atopic dermatitis. After the first 4 weeks, the application of the ointment showed a significant change in EASI, IGA as well as pruritus NRS. The most frequent adverse effect was nasal paronyngitis, followed by acne and eczema herpeticum. The latter was considered treatment-related in 1.9% of cases [51[¶]]. A long-term study with a larger cohort of 330 subjects, duration of 52 weeks and an open label design confirmed the positive results [52]. In addition to studies on adults, a 4-week phase II study was performed in pediatric atopic dermatitis patients. There was a significant improvement of EASI, IGA, and pruritus score compared with the control also in this age group. Here, 50% in the highest dosage treatment group achieved EASI75 compared with 8.6% of the control population [53[¶]].

TARGETING THE ARYL HYDROCARBON RECEPTOR FOR THE TOPICAL TREATMENT OF ATOPIC DERMATITIS WITH TAPINAROF

Another strategy to combat atopic skin disease is the aryl hydrocarbon receptor modulating agent

tapinarof, and recent studies show that the expression of the receptor correlates with the severity of the disease [54]. The aryl hydrocarbon receptor can be activated by various exogenous stimuli, such as molecules present in air pollution [55]. It induces, as a transcription factor, the expression of molecules, such as neurotrophic factor artemin and participates in important cellular processes, such as proliferation, migration, differentiation, and apoptosis [56,57].

Tapinarof is a modulator of the aryl-hydrocarbon receptor that has been used topically for 12 weeks in atopic dermatitis in varying concentrations in a double-blind, placebo-controlled, randomized phase II clinical dose-finding study. Two hundred and forty-seven adolescent or adult subjects received 1 or 0.5% ointment or vehicle control applied it once or twice daily. Sixty percent of the patients with the highest dosage reached EASI75 and only 25% of the control group [58[¶]].

TARGETING THE PHOSPHODIESTERASE-4 RECEPTOR FOR THE TOPICAL TREATMENT OF ATOPIC DERMATITIS WITH CRISABOROLE

Crisaborole is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis. In two pivotal phase III clinical trials in patients aged at least 2 years, crisaborole was superior to vehicle in reducing global disease severity [59]. A crisaborole cream was approved by the FDA for the treatment of atopic dermatitis but not by the EMA so far. The most common treatment-related adverse event is application site pain. In a recent study, the relationship between pruritus and quality of life was quantified using data from the phase III studies with crisaborole [60]. A clear relationship between the Severity of Pruritus Scale SPS, the Dermatology Life Quality Index DLQI, the Children's Dermatology Life Quality Index CDLQI and the Dermatitis Family Impact DFI was shown with these clinical data. Moreover, an independent recent pooled post hoc analysis by race and ethnicity of the two pivotal phase III trials. Across races and

ethnicities, crisaborole demonstrated efficacy for the treatment of mild-to-moderate atopic dermatitis, with a low frequency of treatment-related adverse events [61].

CONCLUSION

During the last years, a number of promising new substances for the treatment of atopic dermatitis were developed. For dupilumab, which was the first antibody approved for the treatment of moderate-to-severe atopic dermatitis, recent 'real world data' from registries confirm efficacy and safety. Novel antibodies address cytokine type 2 targets like IL-13 or IL-31 with promising results published from larger phase 2 studies. Additional proof-of-concept studies showed possible efficacies of anti-TSLP, anti-IL-22 or anti-IL-33 antibodies but here confirming larger phase II studies are needed. Oral drugs for the treatment of atopic dermatitis are highly welcome particularly for the younger population suffering from the skin disease. The histamine-4 receptor antagonist adrioforant showed efficacy in a proof-of-concept study and a couple of JAK inhibitors have already been studied with success in larger phase II or even phase III studies. So far, no increased risk of viral airway infections was noted in controlled phase II or phase III studies of novel systemic drugs for atopic dermatitis – however, generally phase II and phase III studies may be underpowered to detect rare adverse effects of new drugs. Therefore, real world data generated in registries after their approval are highly needed.

It is important that also new topicals for the atopic dermatitis are developed. The topical PDE4 inhibitor crisaborole, which is so far approved in the USA for the treatment of atopic dermatitis is mildly effective. Both tapinarof, a modulator of the aryl hydrocarbon receptor, and topical JAK inhibitors are currently being examined in clinical studies with promising results and possibly stronger efficacy in atopic dermatitis.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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