Atopic dermatitis: an expanding therapeutic pipeline for a complex disease

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Abstract | Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a complex pathophysiology that underlies a wide spectrum of clinical phenotypes. AD remains challenging to treat owing to the limited response to available therapies. However, recent advances in understanding of disease mechanisms have led to the discovery of novel potential therapeutic targets and drug candidates. In addition to regulatory approval for the IL-4Ra inhibitor dupilumab, the anti-IL-13 inhibitor tralokinumab and the JAK1/2 inhibitor baricitinib in Europe, there are now more than 70 new compounds in development. This Review assesses the various strategies and novel agents currently being investigated for AD and highlights the potential for a precision medicine approach to enable prevention and more effective long-term control of this complex disease.

Atopic disorders
A group of disorders having in common a genetic tendency to develop IgE-mediated allergic reactions. These are atopic dermatitis, food allergy, allergic rhino-conjunctivitis and allergic asthma.

Rhino-conjunctivitis
An atopic disorder of the eyes and nose as the clinical manifestation of an allergic reaction to environmental allergens.

Biologic therapies
Therapeutic approach using antibodies or other biological and recombinant products typically directed against pathway-related structures.

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https://doi.org/10.1038/s41573-021-00266-6

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. About 80% of disease cases typically start in infancy or childhood, with the remainder developing during adulthood. Whereas the point prevalence in children varies from 2.7% to 20.1% across countries, it ranges from 2.1% to 4.9% in adults. The disease displays a high heterogeneity in its natural course and individual trajectories are unpredictable. AD is characterized by sensitive and dry skin, localized or disseminated eczematous lesions usually accompanied by a severe itching sensation. The heterogeneous clinical phenotype varies by age, severity and ethnic background. AD has a significant impact on the quality of life of the patients and their relatives and represents an important socio-economic burden with an average yearly total (direct and indirect) cost per patient of €15,000 (REFS 7–9).

AD belongs to the spectrum of the atopic disorders, including food allergy, allergic asthma and allergic rhino-conjunctivitis, which are relevant comorbidities. Immunoglobulin E (IgE)-related allergic reactions to environmental allergens represent the common aspect of atopic diseases. Recently, cardiovascular and neuropsychiatric disorders have also been reported to be relevant comorbidities to AD, although the mechanisms underlying these associations remain elusive.

So far, however, AD has primarily been considered as merely a skin disorder in which local anti-inflammatory therapy of the disease flares should be the first-line approach. Such topical therapies include various topical corticosteroids (TCSs), the topical calcineurin inhibitors tacrolimus and pimecrolimus and more recently the phosphodiesterase 4 (PDE4) inhibitor crisaborole. For the more severe forms of AD, besides the use of ultraviolet light, current therapeutic guidelines suggest ciclosporin A, methotrexate, azathioprine and mycophenolate mofetil.

The approvals of the anti-IL-4Ra antibody dupilumab (2016, FDA/2017, EMA) and more recently of the small-molecule Janus kinase inhibitor baricitinib (2020, EMA) and the anti-IL-13 antibody tralokinumab (2021, EMA) have provided first-in-class representatives of different therapeutic strategies for the treatment of moderate to severe forms of AD. Dupilumab and tralokinumab are examples of targeted biologic therapies that specifically address a distinct immune pathway and its cytokines or receptors, whereas baricitinib exemplifies a more wide-ranging approach using small molecules that interact with multiple signal transduction pathways linked to several cytokine receptors and immune pathways. Despite these recent developments, the current therapeutic armamentarium remains very limited and disease management still follows a ‘one-size-fits-all’ paradigm. In particular, the high incidence of AD in the paediatric population, the highly fluctuating and unpredictable course of disease and the limited armamentarium of approved drugs with an adequate benefit-risk ratio represent major challenges in the field. To address this, a better understanding of the mechanisms that underlie the epidermal barrier dysfunction and the sequence of immune responses that underlie the chronic inflammatory reaction is needed, which would ideally...
Fig. 1 | A multidimensional model of atopic dermatitis. A high-level schematic view of the complex interactions that underlie the immunological heterogeneity of atopic dermatitis (AD). This multidimensional disease model generates an ‘immunological march’, which can schematically and tentatively be dissected in several, potentially overlapping phases: first, an asymptomatic preclinical phase (phase 0); second, activation of skin innate immunity (phase 1), rapidly followed by activation of the adaptive immune response (phase 2) starting with a core T helper 2 (TH2) response accompanied by IgE sensitization to environmental allergens, and a widening of the adaptive immunity with TH1, TH17 and TH22 responses. This widening of the immune response paves the way for the development of atopic and non-atopic comorbidities (phase 3). Each putative phase offers opportunities for preventive and targeted therapeutic intervention, including disease modification. In this scenario, the composition of the skin microbiome and the itch–scratch cycle potentially have a crucial role in directing the adaptive immunity and the development of sensitization to self proteins, atopic and non-atopic comorbidities.

Translate into optimized long-term, disease-modifying management of this chronic disorder.

In the past two decades, significant progress has been made in our understanding of the complex phenotype and mechanisms that underlie AD16, offering multiple new potential targets for pharmacological intervention17. More than 70 new compounds are in development and this Review will assess those that are being investigated in clinical trials. The variety of targets and strategies offers significant potential for a precision medicine approach to the management of AD.

Therapeutic strategies and targets

The pathophysiology of AD has been discussed in detail elsewhere18. The disease exhibits a wide spectrum in its clinical phenotype, mirroring a complex and multidimensional interaction between components that represent potential fields of preventive and therapeutic interventions (Fig. 1; Box 1): first, the environmental and exposomal factors16,21 (which will not be addressed in this Review); second, the skin microbiome22–26; third, the epidermal barrier27–28; and fourth, the immune and inflammatory responses29, which cause, fifth, the itch–scratch cycle29. These interactions develop on a particular genetic30 and yet-to-be-explored epigenetic background. This is accompanied by a dynamic of the immune response (‘immunological march’) with a potential systemic impact of the inflammatory reaction, that is, secondary involvement of other organs. The main cellular and soluble components involved in the pathophysiology of AD represent the key targets of current efforts in pharmacological intervention (Fig. 2). Moreover, the complexity of the immune pathways that operate in AD offers the opportunity to explore the potential of bispecific or trispecific antibodies.

For practical purposes, disease severity remains the basis for the treatment algorithm in the current guidelines31–35. The spectrum of AD has been divided into mild, moderate and severe forms, and cut-off points using the scoring tools for the assessment of severity and efficacy as well as patient-reported outcomes (see Box 2) have been defined36,37. Depending on the individual patient’s natural and unpredictable course of the disorder, its management has two main goals: the rapid and efficacious treatment of acute flares and the far more challenging control of the disease in the long term. Thus, besides efficacy, the long-term safety profile is a key aspect of any new compound in a clinical development programme.

Modulating the skin microbiome

Several distinct strategies to restore or modulate the composition of the skin microbiome have been proposed38–40. Microbiome transplantation and bacterial replacement
Bacteriotherapy
Therapeutic approaches using living bacteria to influence the microbiome composition.

Pruritus
Sensation of itching generated at the level of sensory neurons and leading to scratching as a mechanical response.

Cationic host defence peptides
Short peptides with a net positive charge with antibacterial, antifungal and/or antiviral properties.

are currently being explored with several topical products in clinical development (MSB-01, DB-001), but results from proof-of-concept studies are not yet available. Skin from patients with AD presents significant differences in the microbiome compared with healthy individuals, in whom Roseomonas mucosa was found to be the most representative Gram-negative bacteria44. A product combining three strains of R. mucosa (FB-401) has been developed and explored, with its therapeutic activity likely consisting of activation of tissue repair and anti-inflammatory activity via Toll-like receptor 5 (TLR5) and tumour necrosis factor receptor (TNFR)45. In a phase I/IIa study in 30 patients (10 adults and 20 children), 60% of the adult patients showed 50% reduction in the Scoring of Atopic Dermatitis (SCORAD), while 90% of the paediatric patients achieved Eczema Area Severity Index (EASI) 50 and 30% achieved EASI90 (see the press release from Forte Bioscience in Related links). A phase II study in children, adolescents and adults is ongoing.

Following the same strategy of bacteriotherapy, topical application of a lyophilized strain of Staphylococcus hominis A9 (ShA9) with the dual activity of killing Staphylococcus aureus and inhibiting the production of S. aureus-derived toxins, allowed the microbiome to recover. While well tolerated, ShA9 also induced a modest improvement of skin lesions as measured by EASI and SCORAD46.

Nitric oxide is an important mediator with beneficial metabolic and potential anti-inflammatory properties. Nitrosomonas eutropha (B244) is an ammonia-oxidizing bacterium able to produce nitric oxide, which is in clinical development for AD. In a phase IIa randomized controlled trial (RCT) in adults, B244 given as a spray induced a significant improvement of the pruritus. A similar effect on itching was reported in an open-label phase Ib paediatric trial (see the press release from AOBiome in Related links). Unfortunately, results on the clinical response of the inflammatory reaction are not available. A phase Ib dose selection trial is currently ongoing.

Decolonization of S. aureus can be achieved by the niclosamide ATX201, which inhibits bacterial growth. In a phase II trial, a 2% cream formulation showed significant histological and transcriptional modifications, suggesting a dual impact on the barrier function and the inflammatory reaction47.

Antimicrobial cationic host defence peptides48 are interesting candidates to control the overgrowth of S. aureus in AD. Omiganan pentachloride (CLS-001) is a synthetic antimicrobial cationic peptide in clinical development as a potential topical agent for controlling dysbiosis49.

Several microbiome modulators for oral application are currently in phase I (EDP1815, STMC-103H and KBL697). Future strategies will likely be based on a better understanding of the mechanisms that underlie the modulation of the skin microbiome by bacterial quorum sensing on the one hand and host immune responses on the other (Box 1).

Despite significant interest in the therapeutic potential of modulating the microbiome in general, and in strategies aiming to correct the dysbiosis assumed to be instrumental in AD in particular, it remains unclear whether high colonization with S. aureus consistently impacts the immune system and the inflammatory reaction independently of other factors such as the age of the patient, the course and duration of the disease, or epigenetic mechanisms regulating gene–gene and gene–environment interactions. There may be a window of opportunity for interventions that target the skin microbiome, potentially at an early stage of the disease in infancy. Identifying the best time point for intervention may be of crucial importance to improve disease and potentially restore an optimal adaptive immune response against S. aureus.

**Targeting the epidermal barrier function**
One of the clinical hallmarks of AD is dry, sensitive and highly permeable skin. This phenotypic characteristic is due to disturbance of epidermal barrier function (Box 1) owing to a dual mechanism1,2,11: first, a genetic origin with mutations in genes encoding functionally important structures such as filaggrin (FLG); and second, an inflammatory origin with key mediators such as IL-13 negatively impacting epidermal barrier function.

There are two approaches to restore the epidermal barrier function in AD: first, the development of products specifically addressing the biochemical alterations, although the lack of understanding of the functional genetics of the multiple structures involved in these defects represents a major hurdle; and second, effective control of the underlying inflammatory reaction.
**Targeting the innate immune response**

The role of the innate immune system in the early phase of AD was demonstrated using animal models and is likely of clinical relevance in infancy. The aryl-hydrocarbon receptor (AhR) is a ligand-activated transcriptional factor with a Janus-faced role in physiology and the pathophysiology of several skin disorders including AD. It exerts pro- and anti-inflammatory activities, depending on the cell type, the micromilieu and the ligand, that is, exogenous and endogenous metabolites and agents. As it is expressed in keratinocytes and resident epidermal dendritic cells (DCs), AhR represents an ideal target for a topical pharmacological approach. Interestingly, coal tar has been shown to bind to AhR and to restore the expression of filaggrin, as shown by immunohistochemistry and transcriptomic analysis. Tapinarof (also known as benvitimod) is a natural AhR agonist that significantly reduces inflammatory responses both in animal models and in human skin when used topically. In a phase IIB trial, the best results were obtained with a 1% cream, with 53% of the patients reaching the primary end point of Investigator Global Assessment (IGA) 0/1 versus 28% in the placebo group. These data suggest that this compound represents a promising new option for topical therapy of both AD and psoriasis, another chronic inflammatory skin disorder.

Mutations or variants of genes such as SPINK5 favour the development of allergen-independent, nonspecific inflammation, providing a pro-T helper 2 (Th2) micromilieu by virtue of keratinocyte-derived alarmins such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-25. Given their key role in initiation of the skin-derived immune response, alarmins are interesting therapeutic targets. The anti-TSLP antibody tezepelumab (AMG 157) has shown convincing results in patients with severe and uncontrolled allergic asthma. By contrast, a phase IIa study in patients with AD showed 64.7% of patients reaching the EASI50 end point versus 48.2% in the placebo group. However, the interpretation of these data is difficult as all patients were allowed to use TCSs.

Because of its pleiotropic biological activities, targeting IL-33 represents another interesting strategy to affect early mechanisms within the innate immune response. Five different biologics are currently in clinical development. In a proof-of-concept study with a single application of the anti-IL-33 antibody etokimab (ANB020) in 12 patients with moderate or severe AD, 33% of patients reached the primary end point EASI75 and 83% reached EASI50. Interestingly, this improvement lasted for up to 140 days after the single dose. Etokimab inhibited direct, as well as CXCR1-dependent, neutrophil migration in vitro. Whether this observation is relevant for later phases of AD in which neutrophils are only rarely seen in the inflammatory infiltrate remains to be explored. However, in a larger phase IIa study (ATLAS study) with 300 adult patients, the primary end point was not reached (see the press release from AnaptysBio in Related links). Astegolimab (MSTT1041A/AMG282), MEDI3506 and REGN3500 are additional anti-IL-33 antibodies in proof-of-concept studies for which the results are not yet available.

IL-1α is a proinflammatory cytokine released by keratinocytes after injury and by skin dysbiosis. As one of the first and most important mediators in anti-gen presentation and induction of the inflammatory cascade, IL-1α has been considered as a therapeutic target in AD. The anti–IL-1α antibody bermekimab (MABp1) was initially developed for oncological indications and recently for hidradenitis suppurativa. In an open-label phase IIa study in eight patients, the safety profile of bermekimab was acceptable, and results for the highest dose indicated promising efficacy, with 39% of patients reaching the status of clear or almost clear (IGA 0/1) as well as a strong reduction in itching, with 68% improvement in the pruritus numerical rating scale (NRS) (see results under NCT03496974).

IL-36 is another player in the innate immune system that is upregulated in the skin of psoriasis as well as AD. Interestingly, in a mouse model, colonization with *S. aureus* induces IL-36R- and IL-1R-dependent inflammation. Therefore, the anti-IL-36R antibody...
Disease dimensions
Schematically, atopic dermatitis (AD) recognizes several dimensions: the clinical signs (erythema, oedema/induration/population, excoriation, lichenification, oozing and dryness); the symptoms (pruritus/itching and related sleeplessness) and the patient-reported outcomes (PROs) of quality of life and disease control.

These dimensions serve as the basis for objective and subjective assessment instruments from which the end points used in clinical trials are derived. The Harmonising Outcome Measures for Eczema (HOME) initiative has established a core outcome set of tools and end points to be used in clinical trials and are discussed in detail elsewhere. For regulatory purposes, the end points based on clinical signs are typically considered as primary efficacy end points while PROs are secondary end points.

Established instruments for assessment and derived end points

Clinical signs

- The validated Investigator Global Assessment (vIGA) is a simple objective measure providing an overall evaluation. It uses a 5-point scale (clear = 0; almost clear = 1; mild = 2; moderate = 3; severe = 4). The efficacy end point based on vIGA, IGA 0/1 gives the percentage of patients reaching the status of clear (rated as 0) or almost clear (rated as 1) and a minimum 2-grade improvement. IGA 0/1 is mandatory for the FDA as primary end point for phase III trials. It is currently not accepted by the EMA as a primary end point.

- The Eczema Area Severity Index (EASI) considers the average severity of individual clinical signs (see above) (0–3 scale) and surface involved in four body regions (head and neck, trunk, upper and lower extremities), the maximum being 72 points. Clinical end points based on EASI: the percentage change in EASI from baseline and the percentage of patients reaching 75 percentage (EASI 75% improvement from baseline are the most currently used end points. The more stringent EASI90 is almost equivalent to the above-mentioned IGA 0/1.

- The Scoring of Atopic Dermatitis (SCORAD) is based on the intensity of clinical signs (0–3 scale) and the disease extent (involved surface according to the rule of 9). The maximum points are 103. It also considers itch and sleeplessness as subjective symptoms and is evaluated by visual analogue scales. The latter two items are excluded in the so-called objective SCORAD (oSCORAD), the maximum points being 83. Clinical end points based on SCORAD: the percentage change in SCORAD from baseline is frequently used in clinical trials. SCORAD 75 is defined as the percentage of patients experiencing an improvement of at least 75% from the baseline value.

There is good correlation between the various scoring tools that are used to stratify patients according to severity. Mild forms are defined as vIGA = 2; EASI < 7 or SCORAD < 25; moderate forms are defined as vIGA = 3; 7 < EASI < 21 or 25 < SCORAD < 50; severe forms are defined as vIGA = 4; EASI > 21 or SCORAD > 50. The cut-off points to define moderate to severe forms are defined as IGA ≥ 3; EASI ≥ 16 or SCORAD ≥ 50.

Of note, using these instruments is felt to be complex and time consuming by most practitioners outside of the trial setting. A simple tool for daily record keeping is still lacking.

Symptoms

In the Peak Pruritus Numerical Rating Scale (PP-NRS-11), the patient rates their peak itch sensation during the previous 24 h on a 0–10 scale. A decrease of at least 4 points is considered a clinically relevant end point. This tool correlates weakly with objective tools such as EASI and vIGA.

Quality of life

- The Dermatology Life Quality Index (DLQI) is a validated and widely used 10-item questionnaire with paediatric versions (0–3 and 4–16 years). A variation of 4 points is considered a clinically meaningful end point.

- The Patient-Oriented Eczema Measure (POEM) is a validated tool in which the patient self-assesses how many days they experienced seven distinct items (itch, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, dryness of the skin) during a period of 1 week. The maximum score is 28 points. There is good correlation with other PROs.

Disease control

Long-term control is a key aspect in the management of AD. Only recently, two similar instruments have been developed.

- The 7-item Recap of Atopic Eczema (RECAP) validated in adults and children. There is good correlation with POEM and other PROs.

- The 6-item Atopic Dermatitis Control Tool (ADCT) validated for adults.

Targeting the adaptive immune response

The heterogeneity of the clinical phenotype of AD most probably reflects the highly complex pathophysiology. The underlying ‘march of the adaptive immune system’ starts from antigen presentation and affects various pathways, ultimately offering distinct therapeutic options. Besides T2 immune polarization, whereby IgE, IL-4, IL-5 and IL-13 and/or their receptors are potential targets, multiple other mediators — some of them more related to psoriasis such as IL-17, IL-23, IL-36 or IL-22 — are the subjects of clinical development strategies.

Antigen presentation. Antigen presentation has a crucial role in the generation and maintenance of the various pathways of the adaptive immune response, ultimately leading to inflammation. Strategies that aim to modulate the responding T cells are an attractive option, provided that they avoid harmful immunosuppression.OX40 is a costimulatory molecule and member of the TNF receptor family (TNFRSF4). It is transiently expressed on T cells upon activation and contributes to clonal expansion, survival and memory formation. Initial studies with antibodies directed against OX40 (GBR 830 and KHK4083) or its ligand OX40L (KY1005) expressed on DCs have shown promising results. In a phase Ia trial, intravenous GBR 830 was well tolerated and significantly improved the lesions with an EASI50 in 78% of patients who received the antibody, compared with 38% in the placebo group. The antibody also improved the gene signatures in the skin. Similarly, in a phase Ib trial, KHK4083 resulted in a 74% reduction in the EASI score, and the IGA 0/1 was reached in 35% of the patients. Results from the phase Ib trial from both agents are pending.

Interesting results were also seen in a phase Ia study using the non-depleting anti-OX40L biologic KY1005. This antibody inhibits the effector T cell (T eff cell) response and maintains regulatory T cell (T reg cell) activity. A low-dose regimen resulted in a mean percentage change of EASI from baseline of 80.1% versus 49.4% in the placebo group. IGA 0/1 was reached in 44% of those who received KY1005 versus 8% in the placebo group (see the Kyman press bulletin in Related links).

As it is assumed that affecting the OX40–OX40L interaction affects not only the core T eff response but also other T cell subsets, this strategy has interesting
therapeutic potential along the dynamics of the immune response. It may potentially be highly relevant for mechanisms involved in the putative immunological march underlying the individual course of the disease. However, since antigen presentation is also an important step in antitumoural defence, the long-term safety profile of drugs that affect the OX40–OX40L interaction will be key, particularly in older patients in whom the incidence of unrecognized and diagnosed tumours is significantly higher. On the other hand, the long-term data should also demonstrate whether this strategy has the potential for disease modification, at least in a yet-to-be-defined subgroup of patients.

**T_{h2} cytokines and their receptors.** A T_{h2} immune response is considered the core pathway leading to cutaneous inflammation in AD. IL-4, IL-13 and IL-5 or their respective receptors are the focus of drug development strategies that aim to modulate the T_{h2} response^{80,81}.

Dupilumab binds to IL-4Ra, the chain common to the type I (IL-4Ra/IL-2Rγ) and type II (IL-4Ra/IL-13Ra1) receptors for IL-4 and IL-13 (REFS 81,82). It is approved for AD in many countries and real-world data support the efficacy reported in the phase III programme in adults^{83,84}. As AD is a typical disease of childhood, a focus is now placed on the ongoing staggered paediatric investigational programmes, the most advanced being in the USA and the EU where dupilumab is now approved for children aged 6 years and older. Studies exploring the pharmacokinetics, safety and efficacy in children aged 6 months to 6 years are ongoing to provide for the first time an option for systemic therapy in this important population.

CBP-201 is another IL-4Ra antagonist with interesting results in a phase Ib study in 31 patients. Although the mode of action is theoretically similar to that of dupilumab, it seems to have a faster onset of action. After only 4 weeks of therapy, IGA 0/1 was seen in up to 50% of patients receiving CBP-201 versus 13% in the placebo group. The mean reduction in EASI from baseline was 74% versus 33% in the placebo group. There were no safety signals reported and a dose-finding phase Ib study is ongoing. AK120 is another antibody directed against IL-4Ra currently in phase Ib studies in healthy subjects and patients with moderate-to-severe AD.

ASLAN004 is a fully humanized antibody directed against IL-13Ra1, thereby blocking the binding of IL-4 and IL-13 to the type II receptor (IL-4Ra/IL-13Ra1). Owing to the more selective binding compared with dupilumab, ASLAN004 may provide the option of a low-dose regimen and a better safety profile. An interim data analysis from a phase Ib study showed that the compound is well tolerated and provided promising efficacy data, with 67% of the patients achieving EASI75 versus 0% in the placebo group (see the ASLAN press release in Related links).

Whereas IL-4 seems to be more relevant for the central part of the T_{h2} pathway^{85}, IL-13 has been identified as the key T_{h2} cytokine mediating the skin inflammation in AD^{86,87}. Two antibodies that specifically target IL-13 are in late-stage clinical development. Tralokinumab, which was recently backed by a positive opinion from the EMA (EMA/CHMP/202204/2021), is a fully humanized antibody targeting IL-13 that blocks its binding to both IL-13Ra1 and IL-13a2 receptor chains^{88,89}. In the phase III pivotal monotherapy studies, at week 16, tralokinumab showed superiority to placebo, with IGA 0/1 being reached in 16% (ECZTRA1) and 22% (ECZTRA2) of the patients receiving the antibody versus 7% and 11% in the respective placebo groups. Similarly, EASI75 was reached in 25% and 33% of patients receiving treatment in the two trials versus 13% and 11% receiving placebo, respectively. Interestingly after re-randomization at week 16 followed by maintenance treatment, the clinical response further improved, with IGA 0/1 being reached in 51% (ECZTRA1) and 59% (ECZTRA2) of the patients^{90}. This suggests that tralokinumab develops its full potential at a later time point. In the pivotal studies with dupilumab, 11% of the patients developed eye disorders (for example, conjunctivitis, keratoconjunctivitis and keratitis); this adverse event of special interest (AEIS) has been attributed to its IL-13 blocking activity^{91}. Higher rates were described in long-term studies and in real-world reports^{92-94} but interestingly not in asthma^{95}. The mean rate of eye disorders for both ECZTRA1 and ECZTRA2 studies with tralokinumab at week 16 was 7.6% versus 3% in the placebo group. Data from long-term drug exposure will provide more information in this regard.

Lebrikizumab is another fully humanized anti-IL-13 antibody that does not block the binding of the cytokine to the receptor but instead impairs the heterodimerization of IL-4Ra and IL-13Ra1, thereby inhibiting signal transduction^{96,97}. Lebrikizumab does not affect the binding of IL-13 to the IL-13Ra2 receptor chain, the biological role of which remains unclear^{98}. In a phase Ib dose-finding study, the best clinical response for the primary end point (percentage change in EASI) was obtained with 250 mg. In this group, 72% improvement was shown versus 41% in the placebo group^{99}. The efficacy was mirrored by a rapid improvement in the pruritus NRS. The rate of conjunctivitis was low and the drug was otherwise well tolerated.

The importance and efficacy of targeting the T_{h2} cytokines IL-4 and IL-13 and their receptors is now well recognized. Among the drugs considered above, dupilumab recently received an approval extension for the paediatric population in AD. Dupilumab is also approved for atopic comorbidities such as allergic asthma and nasal polyposis, clearly conferring a broad therapeutic profile to this compound. It is still unclear which role the anti-IL-13 strategy plays in allergic asthma and other atopic comorbidities and whether tralokinumab, lebrikizumab and ASLAN004 will be able to efficiently treat dupilumab partial responders and non-responders. The distinct modes of action of dupilumab (blocks IL-4 and IL-13 binding to the type I and type II receptors with no interaction with IL-13Ra2 chain), tralokinumab (blocks binding of IL-13 to IL-13Ra1 and IL-13a2 chains), lebrikizumab (blocks the association of type II receptor subunits after binding of IL-13, no interaction with IL-13Ra2 chain) and ASLAN004 (blocks the binding of IL-4 and IL-13 on the type II receptor, no interaction...
Eosinophilic asthma

Subtype of asthma characterized by strong eosinophilic infiltration of the lung and elevated eosinophil count in the blood.

Aeroallergens

Airborne structures potentially causing allergic reactions. Pollen and fungal spores are typical aeroallergens.

Exotoxins

Products produced or released by the lysis of bacteria that can impact on other bacteria and/or the host.


can impact on other bacteria by the lysis of bacteria that typical aeroallergens. Pollen and fungal spores are causing allergic reactions. eosinophilic infiltration of the characterized by strong subtype of asthma Eosinophilic asthma

Immunoglobulin E. A significant part of the sensitization process leading to the generation of IgE responses against environmental allergens (including food allergens) as well as against self proteins correlates with cutaneous inflammation and overall severity. Moreover, provocation tests with food allergens as well as with aeroallergens induce exacerbation in a subgroup of AD patients. These observations imply a role for IgE-bearing antigen-presenting epidermal DCs such as Langerhans cells in the capture and presentation of allergens to T cells. Hence, it is intriguing that strategies aimed at depleting IgE with the anti-IgE biologic omalizumab failed to show convincing results in proof-of-concept studies and single cases. However, clinical improvement was shown in a small series of patients using omalizumab and/or immunoadsorption. The Atopic Dermatitis Anti-IgE (ADAPT) study was designed to verify the hypothesis that IgE may instead have a role in the paediatric population. Indeed, using weight-adapted doses of omalizumab in children with high total serum IgE, there was a significant difference in the change from baseline for the objective SCORAD as primary end point compared with the placebo group. Similar results were obtained for the EASI score. These encouraging efficacy data were confirmed by reduced use of TCSs as well as improved quality of life in the omalizumab-treated group.

Another approach is to inhibit IgE synthesis by targeting IgE-committed B cells expressing a membrane form of IgE (mIgE). Anti-CεmX (FB825) is directed against IgE-committed B cells and lymphoblasts by apoptosis. This approach would lead to long-term reduction in IgE-mediated reactions in allergic individuals, including patients with AD. The phase IIa study is ongoing.

Although increased IgE serum level is a hallmark of a T_{h}2 immune response and specific IgE to at least one allergen can be found in the vast majority of AD patients, its role in this disorder and the strategies aimed to target IgE are still a matter of debate. The lack of efficacy may be due to a limited ability of the approved doses of biologics such as omalizumab to neutralize the high levels of total IgE typically seen in polysensitized patients with AD. In this case, the use of anti-IgE strategies would be more meaningful in those patients with oligosensitization and specific IgE directed against a few but clinically relevant allergens for a given individual patient. Another explanation could be that IgE-mediated allergic reactions to environmental allergens become irrelevant after a long disease duration, particularly in adults.

IL-22 and its receptor IL-22R. Besides T_{h}2 cytokines, IL-22 is an important part of the transcriptomic signature in AD. This cytokine is induced by staphylococcal exotoxins in numerous inflammatory cells, including T_{h}1 and T_{h}17 cells. Circulating IL-22 correlates with the severity of AD and appears as a key driver in the inflammatory reaction. In keratinocytes, IL-22 exerts multiple biological activities, including their proliferation and downregulation of filaggrin expression. Thus, targeting IL-22 or its receptor seems an attractive therapeutic approach in AD. In a first proof-of-concept study, the anti-IL-22 antibody fezakinumab was designed to block the biological activity of IL-22 in AD with less impact on the IL-20R1–IL-20R2 receptor complexes. Thus, targeting IL-22R1 is an appealing strategy to block the biological activity of IL-22 in AD with less impact on the biological activity of IL-20 and IL-24. This is the strategy followed by the antibody LEO 138559 directed against IL-22R1, which is currently in phase I studies.

The psoriasis pathway: IL-23 and IL-17. Besides being the core pathway in psoriasis, there is increasing evidence that the IL-23–IL-17 axis as well as IL-36 (see above) may have a role, at least in some AD subtypes such as the so-called intrinsic form and in Asian patients. Two studies have been initiated using the anti-IL-17A antibody secukinumab in patients with moderate to severe AD. In a placebo-controlled randomized phase II investigator-initiated study in patients, this compound did not show clinical efficacy or induce any significant changes in several mechanistic investigations such as epidermal thickness, changes

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in the composition of the cellular infiltrate or analysis of the transcriptomic signatures\(^{126}\). Another phase IIa study with 22 patients was completed but the results are not available. As part of the same pathway, IL-23 is another candidate for intervention in AD. A proof-of-concept study exploring the putative efficacy of the anti-IL-23 antibody risankizumab has been initiated.

**Restoring T\(_{reg}\) cell function.** Similar to autoimmune disorders, it is assumed that in allergic diseases such as AD, T\(_{reg}\) cells do not properly exert their dampening activity, allowing immune polarization. A strategy aimed at enforcing the T\(_{reg}\) cell limb of the immune system would restore tolerance and repress chronic inflammation. The pegylated recombinant human IL-2 (rhIL-2; LY3471851) has been designed to target the IL-2 receptor complex on T cells leading to activation and proliferation of T\(_{reg}\) cells. Besides systemic lupus erythematosus, ulcerative colitis and psoriasis, LY3471851 is currently in a phase Ib trial to test its safety and tolerability as well as the hypothesis that this compound could restore tolerance and improve AD.

**Phosphodiesterase 4.** In the early 1980s, increased PDE4 activity was described as one of the first candidate targets for the therapy of allergic disorders including AD\(^{126,127}\). Meanwhile, PDE4 inhibitors are known to have a wide spectrum of interesting therapeutic effects related to downregulation of inflammatory cytokines involved in pulmonary, neurological, rheumatoid, gastrointestinal and dermatological disorders\(^{126}\). In contrast, the oral PDE4 inhibitor apremilast is already approved for the therapy of psoriatic arthritis, ulcerative colitis, and psoriasis, LY3471851 is currently in a phase Ib trial to test its safety and tolerability as well as the hypothesis that this compound could restore tolerance and improve AD.

Although the highest dose showed an interesting effect on the pruritus score, the absolute change in EASI from baseline was not significant when compared with placebo and thereby not superior to pimecrolimus (NCT01037881). Further ongoing phase II studies include the new PDE4 inhibitors Hemay-808 and PF-07038124, for which results are not yet available.

**Histamine H4 receptor.** Four types of histamine receptor (H1R–H4R) have been described, all of which are G protein-coupled receptors\(^{127}\). H1R in the brain is involved in internal clock modulation, while in the skin, it induces pruritus but also has immunomodulatory activities. H2R is mainly localized in the gastrointestinal tract and other organs, where it regulates smooth muscle relaxation. H3R is localized in the central nervous system, where it regulates the synthesis of histamine. H4R exerts immunoregulatory activities on leukocytes and represents an interesting target for immunomodulation.

After the reference compound JNJ-7777120, further selective H4R antagonists\(^{138}\) have been introduced into clinical development for distinct indications such as neurological disorders\(^{139,140}\), asthma\(^{141,142}\), and for inflammatory skin disorders, including AD\(^{143–146}\). While H4R antagonism alone seems promising in reducing the scratching reaction in animal models of skin inflammation, it only improves inflammation in combination with H1R antagonism\(^{147}\). Conversely, conflicting data were reported from a phase IIa study of the H4R antagonist adrofarn (formerly ZPL-389); a modest but significant improvement in the SCORAD was shown, but the reduction in pruritus was not significant\(^{148}\). A phase Ib dose-ranging study with adrofarn was terminated and the programme was suspended. LEO 152020 is another oral H4R antagonist currently in phase I.

**T cell migration.** Antigen-specific T\(_{h}2\) cells represent a numerically important component of the dermal and epidermal infiltrates in AD. By the production of a large variety of mediators, T cells contribute to the generation of a dynamic and disease-specific inflammatory microenvironment with a strong impact on epidermal barrier function. T cells are recruited by locally
produced chemotactic mediators, and inhibition of their migration represents an appealing strategy. Prostaglandin D2 and its receptor (PGD2/CXTH2) play an important role in the generation of inflammation. CRTH2 is preferentially expressed on T_{h}2 cells and, as shown in vitro and in animal models, has an important role in T_{h}2-mediated inflammation of AD by directing their migration into the skin. However, both CRTH2 antagonists fenviprant (QAW039) and temapiprant (OC000459) failed to significantly improve AD in phase II studies.

Like CRTH2, the C-C chemokine receptor 4 (CCR4/CD194) is a hallmark of memory T_{h}2 cells and binds to the chemokines RANTES, MCP1, CCL22/MDC and CCL17/TARC. These mediators are produced in high amounts in AD and correlate with the severity of AD. Hence, blocking CCR4 is an interesting option for reducing inflammation in AD. In preclinical experiments, RPT193, a small-molecule CCR4 antagonist, selectively blocks the recruitment of T_{h}2 cells in allergic diseases. In these animal models, the activity was similar to that of an anti-IL-13 antibody (see information in Form 8-K from Rapt Therapeutics in Related links). First reports from a phase I study showed no serious adverse events in 64 healthy subjects after single and multiple dosing (see the press release from RAPT Therapeutics in Related links). Phase II studies are exploring the efficacy and safety of a single dose in AD as well as in asthma and other allergic disorders.

Another approach to target inflammatory infiltration is to block the emigration of activated T cells from lymphatic sites and the migration of epidermal DCs to the lymph nodes. This goal can be reached by modulation of their receptors for sphingosine 1-phosphate (S1P), the active terminal derivative of sphingosine metabolism. S1P acts via gradients in circulatory fluids and has been reported to be increased in various conditions such as multiple sclerosis and neurodegeneration, pneumonia, psoriasis, asthma, and more recently in AD. The multiple biological activities of S1P are mediated by five distinct G protein-coupled receptors (S1PR1–5), which are differently expressed in various tissues. Whereas DCs express S1PR1, S1PR3 and S1PR4, T cells display S1PR1 and S1PR4 (REFS 164–166) and represent ideal targets for compounds able to modulate their expression on immune cells and thereby prevent lymphocyte migration from lymphatic tissue and reduce the pool of peripheral lymphocytes able to migrate into inflammatory tissues without broad immunosuppression. This strategy has been successfully developed with the S1PR1, 3–5 agonist fingolimod and the S1PR1,5 agonist siponimod, which are both approved for the therapy of multiple sclerosis. Although they act initially as S1PR agonists, they promote receptor internalization and so are functional antagonists in the longer term.

Etrasimod (APD334) is a next-generation S1PR agonist that induces sustained internalization of the S1PR1 receptor. In the phase IIb ADVISE trial, etrasimod achieved the primary end point validated IGA (vIGA) 0/1 in 36.8% versus 13% in the placebo group. Of note, the study included a high proportion of patients with a moderate form of AD. As soon as at week 4, significant changes in peak pruritus NRS (PP-NRS) and the secondary end point EASI75 were observed (see press statement in Related links). Interestingly, the drug did not induce adverse events such as cardiovascular toxicity commonly seen with this class of compound. Etrasimod was overall well tolerated, opening the door for the phase III programme. SCD-044, LC51-0255, BMS-986166 and KT-474 are other selective S1PR1 agonists that aim to affect lymphocyte trafficking and are currently in development for AD and/or psoriasis and other autoimmune disorders.

For dermatological disorders such as AD, compounds of molecular weight <500 Dalton, optimally and stably formulated in a cream or ointment basis, can potentially penetrate the epidermal barrier and directly act on cutaneous inflammation. The topical application of the prototypical S1PR agonist fingolimod (mol. wt 343) has been reported to reduce allergic inflammation in animal models of skin disorders. With its molecular weight of 443.5, the highly selective S1PR1 agonist AKP-111 has entered clinical development in dermatology as a topical formulation for psoriasis and AD with the potential to be a first-in-class S1PR1 modulator in these indications. Although the phase I trial generated promising results for psoriasis, no reports are currently available with regard to its use in AD. Besides the major impact on the segregation of T cells, the biological activity of S1P and its receptors on innate immunity, epidermal keratinocytes and on DCs remain interesting elements to be considered in explaining the mode of action of this class of compounds in AD.

Targeting the key symptom: itch–scratch cycle

The mechanisms that underlie itching sensation are complex, involving multiple mediators that initiate the activation of peripheral sensory neurons. They offer a number of potential targets for pharmacological intervention. As neurons express receptors for IL-4 and IL-13, the early improvement of itch upon targeted therapy with dupilumab, tralokinumab or lebrikizumab supports the assumption of a direct effect of these drugs on nerve endings. IL-31 is a prominent pruritogenic cytokine produced by infiltrating T_{h}2 cells in AD and correlates with disease severity. It signals through the heterodimerization of IL-31Ra and the oncostatin M receptor-β (OSMRβ). Targeting IL-31 and its receptor is a focus of strategies to better control itching. In a phase Ia study, the anti-IL-31Ra antibody nemolizumab led to a significant decrease in the pruritus sensation, but the overall clinical inflammation as evaluated by the body surface area (BSA), EASI and IGA scorings did not improve significantly at this time point. In the 52-week long-term extension of this study, the efficacy towards itching was confirmed while achieving clinical improvement in a dose-independent fashion. However, the concomitant use of TCSs and the lack of placebo arm in this extension study makes the interpretation challenging. In another phase II study, the expected early improvement in itching was captured.
by the decrease in PP-NRS (69% versus 34%), IGA 0/1 was reached in 33% of the patients versus 12% in the placebo group at week 16 but not at later time points, presumably owing to large background consumption of TCSs. The overall efficacy in pruritus in combination with TCSs was further confirmed in a phase III study over 16 weeks with a decrease of 43% versus 21% in the placebo group as measured by the visual analogue scale score. The EASI score showed a moderate improvement of 46% with nemolizumab versus 33% in the placebo group. Of note, nemolizumab generated promising results in prurigo nodularis, a highly pruritic skin disorder assumed to be related to AD.

Vixarelminab (KPL-716) is a fully human antibody that targets the other receptor subunit for IL-31, OSMRβ. In a repeated-single-dose phase Ib study over 12 weeks in AD, vixarelminab induced a rapid and sustained reduction in pruritus with 53% of the patients having a >4-point reduction in the pruritus score versus 26% in the placebo group. However, there was no significant effect on EASI or SCORAD.

Substance P is involved in the initiation and transmission of itch through the neurokinin 1 receptor (NK1R) and the Mas-related G protein-coupled receptor (MRGPRS). NK1R was expressed in the central nervous system and on various other cell types. Overexpression of substance P and NK1R induces itching skin disorders including AD, suggesting that this signalling pathway could be pharmacologically targeted to control itching sensation and neurogenic inflammation. Serlotipant is a NK1R antagonist that has shown efficacy in reducing pruritus in a phase II study in patients with treatment-refractory prurigo nodularis. However, in another large phase II study (ATOMIK study; 484 participants) and in patients with AD, the drug missed the primary end point of change in worst itch NRS from baseline (NCT02975206). In a phase III study with 375 patients, another novel NK1R antagonist tradipitant (VLY-686) (EPIONE study), phase III study with 375 patients, another novel NK1R antagonist tradipitant (VLY-686) (EPIONE study), missed the primary end point of reduction in pruritus. However, reduction of 50% in SCORAD from baseline was noticed in mild forms of AD.

The P2X purinoreceptors 3 (P2XR3) are cation channels expressed in sensory neurons that are activated by extracellular ATP and exert an important role in peripheral irritation, pain sensation, coughing but potentially also in itch. The selective P2X3 antagonist BLU-5937 is in development to treat chronic cough and pruritus. A phase Ia study (the BLUEPRINT trial) has recently been initiated to explore the effects of this drug on pruritus in patients suffering from AD. The topline results are expected by the end of 2021.

Current data obtained from trials of drugs targeting either T₃,₂ inflammation (such as dupilumab) or more specifically the pruritus in AD may help to provide a temporary answer to one of the most debated questions in AD research: is it the itch that rashes or the rash that itches? Currently available data suggest that in AD, itching is a result of inflammation. However, this conclusion may not be generalized for a number of itchy skin disorders such as prurigo nodularis in which targeting itch remains promising.

**The broad approach with JAK inhibitors**

The JAK family of tyrosine kinases includes four members: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Depending on their dose-dependent selectivity for one or several JAKs, the JAK inhibitors (JAKi) exert a broad immunopharmacological impact because they block the signal transduction pathways of multiple type I (hematopoietic family) and type II (interferon) cytokine receptors. These include heterodimeric receptors involved in distinct types of immune response but also colony-stimulating factor and hormone receptors. Currently, there are more than 90 patented JAKi, many of which are in clinical development for various indications such as rheumatoid arthritis and inflammatory bowel diseases. Recently, JAKi were used successfully in treating the cytokine storm generated by the SARS-CoV-2 virus. As the receptors for T₃,2 and T₃,22 cytokines involve downstream JAK–STAT signalling, JAKi represent interesting compounds for the therapy of AD.

With regard to their respective selectivity, JAKi approved for AD or in clinical development for this indication can be classified into three main categories: the non-selective (pan-)JAKi (delgocitinib, cerdulatinib, jakitinib, CEE321); the dual inhibitors (baricitinib, ruxolitinib, brepocitinib, ATI-1777); and the selective JAK1 inhibitors (upadacitinib, abrocitinib, SHR0302). Besides psoriasis and psoriatic arthritis, alopecia areata and vitiligo, AD is the major dermatological indication for topical and systemic JAKi.

**Topical JAK inhibitors.** Delgocitinib (JTE-052/LEO 242549) is a first-generation, non-selective JAK inhibitor that, upon topical and oral application, was shown to improve allergic contact sensitization and AD-like inflammation in animal models. After successful phase III studies, topical delgocitinib ointment was approved in 2020 for moderate to severe AD in Japan. While its clinical development in a cream basis (LEO 24249) has been suspended in the USA and the EU, the development of this product is being focused on chronic hand eczema.

Owing to its particular activity against all JAKs and the spleen tyrosine kinase (SYK), cerdulatinib was initially developed as a systemic therapy for haematological malignancies. Besides T cell activation, SYK is a crucial signalling molecule for the high-affinity receptor for IgE (FcεRI) expressed on epidermal Langerhans cells and inflammatory dendritic epidermal cells. Therefore, simultaneous targeting of JAKs and SYK by cerdulatinib appears to be an appealing strategy for topical pharmacological intervention in AD. In a phase Ib study with cerdulatinib gel in mild to moderate AD, the compound significantly reduced epidermal thickness, decreased inflammatory DCs and strongly impacted on the inflammatory signature in the transcriptomic analysis. The mean change in EASI score as well as significantly decreased itch show that cerdulatinib could be a promising alternative to TCSs and topical calcineurin inhibitors.

Ruxolitinib is a dual JAK1/JAK2 inhibitor that has advanced in the phase III programme (TRuE AD1 and...
AD2 studies) as a cream for mild to moderate forms of AD. In a phase II study, this compound provided a significant therapeutic benefit with 72% change (16% for placebo) from baseline of EASI and an IGA 0/1 of 38% versus 8% in the placebo group. As a common feature of all JAKi, there was a rapid (within 36 h) and sustained reduction in the itch sensation. Interestingly, ruxolitinib also has potential for vitiligo and for cutaneous lupus.

The other topical JAKi, that is, brepocitinib (JAK1/TYK2), jaktinib (pan-JAKi), ATI-1777 (JAK1/JAK3), CEE321 (pan-JAKi) and SHR0302 (JAK1) are currently in clinical development (TABLE 1) and results are not yet available.

**Systemic JAK inhibitors.** Baricitinib is a first-in-class oral JAK inhibitor directed against JAK1/JAK2 approved in the EU in 2020 for adult patients with moderate to severe AD. In this population, the primary end point IGA 0/1 was reached in 17% versus 5% for placebo (BREEZE-AD1 study) and 14% versus 5% in the placebo group (BREEZE-AD2 study). With regard to the onset of action, most patients reported a significant improvement within a few days as shown by PP-NRS. In a pooled safety analysis of the cumulative data from eight studies with 2,531 patients (2,247 patient-years with median duration of 310 days) there were no signals for serious or opportunistic infections. Viral infections such as herpes simplex and eczema herpeticum as well as headache were more frequent than in the placebo group, and there were only two venous thrombosis events reported. Interestingly, unlike selective JAKi (see below), there was no increase in acne under baricitinib. The paediatric programme is currently ongoing.

Signalling of receptors for factors involved in haematopoiesis, such as GM-CSF, G-CSF, EPO or leptin, is crucially dependent on JAK2 homodimers. Thus, the quest for JAK1-selective compounds resulted in the development of second-generation inhibitors such as upadacitinib and abrocitinib, for which the regulatory approvals are expected before the end of 2021. Of note, the JAK1-selective inhibitor SHR0302 is currently in development as a topical application for mild-to-moderate forms as well as for oral application for moderate-to-severe forms of AD. In their respective phase III programmes, upadacitinib (approved since 2019 for rheumatoid arthritis) and abrocitinib demonstrated significant improvement in severity and pruritus as well as in patient-related outcomes (PROs). In the monotherapy pivotal trials (Measure Up 1 and 2), upadacitinib showed significant results at week 16 for the primary end point IGA 0/1 (REF. 279), along with an early reduction in pruritus and improvement of 4 or more points in the PP-NRS score at week 16. The safety profile was comparable to that seen in patients with rheumatoid arthritis with this compound. Acne, upper respiratory tract infections and nasopharyngitis were the most common treatment-emergent adverse events. The other JAK1-selective JAKi abrocitinib showed similar significant results in phase III studies. In the pivotal mono-therapy studies (JADE-MONO-1 and JADE-MONO-2), the primary end point IGA 0/1 was reached. A recent comparative study of abrocitinib with dupilumab and placebo, confirmed that abrocitinib and dupilumab were significantly more efficacious than placebo. Abrocitinib was superior to dupilumab in itch response after 2 weeks but not for other secondary end points. For both abrocitinib and upadacitinib, the rates of discontinuation in the phase III trials owing to an adverse event were lower than in the placebo groups. As AD is the most common inflammatory skin disorder in children, the compounds may be of particular interest for the severe forms in this population and data from the ongoing paediatric programmes are eagerly awaited.

In terms of efficacy, JAKi have the potential to become game changers in the standard of care for some patients with AD, and their benefit–risk ratio in the AD population seems acceptable. As JAK2 is linked to the receptors of cytokines assumed to be instrumental in AD such as IL-13, IL-22, IL-5 and IL-31, one would assume that blocking JAK2 would provide added value in terms of efficacy compared with the more specific JAK1 inhibitors. However, the phase III data of the dual JAK1/JAK2 inhibitor baricitinib suggest a lower efficacy than the more JAK1-specific inhibitors abrocitinib and upadacitinib. A number of mutually non-excluding explanations can be discussed at this current stage of knowledge: owing to the overall tissue inflammatory burden expected in moderate to severe forms of AD where almost the complete skin surface is affected, the JAK1/JAK2 inhibitor baricitinib is underdosed compared with rheumatoid arthritis where the burden of the inflammatory reaction on the joints is more limited and the drug is not taken as a monotherapy but in combination with other anti-inflammatory compounds. Another possible explanation for this discrepancy could be related to the inhibition of the biological activity of the JAK2-associated receptor for IL-10, a well-recognized cytokine with anti-inflammatory properties and a key mediator in tolerance induction. With regard to the long-term safety of dual inhibitors, the latter aspect may also be of relevance in the context of mechanisms involved in antitumour defence. A direct extrapolation from the short- and long-term safety data in rheumatoid arthritis and other disorders where JAKi have been used so far should be considered with caution, since the target populations are different, that is, patients with rheumatoid arthritis are older than patients with AD, they may have additional comorbidities requiring multiple other medications and therefore have a higher risk of drug–drug interactions. At this stage of development of topical and oral JAKi, the number of patients and the data related to extended drug exposure remain limited. It is not yet clear whether, for comparable efficacy, JAK1 inhibitors display distinct safety profiles between themselves and compared with dual inhibitors. Comparative safety analysis extracted from post-authorization safety studies and/or real-world registries will be key to fully evaluate the safety profile of the different JAKi in AD.

**Other inhibitors**

Another approach to affect inflammation is to inhibit the tropomyosin receptor kinases (TRKs), which bind neurotrophins known to aggravate skin inflammation. Another approach to affect inflammation is to inhibit the tropomyosin receptor kinases (TRKs), which bind neurotrophins known to aggravate skin inflammation.
| Strategy                        | Drug type and mode of application | Agent/company                  | Mode of action/target | Clinical development phase in atopic dermatitis | Clinical trial ID       |
|--------------------------------|-----------------------------------|--------------------------------|-----------------------|-------------------------------------------------|-------------------------|
| Modulating the microbiome     | Bacterial strains — topical       | B244 (AOBiome)                | Nitric oxide donor    | IIb                                             | NCT04490109             |
|                                |                                   | ShA9 (NAID)                   | Targeted microbiome transplant | I/IIa                                           | NCT03151148             |
|                                |                                   | FB-401 (Forte Biosciences)    | Bacterial replacement, anti-inflammation via TLR5 and TNFR activation | IIb                                             | NCT04504279             |
|                                | Small molecule — topical          | CLS-001/omiganan (Cutaneous Life Sciences) | Cell membrane enhancer | II                                              | NCT02456480             |
|                                |                                   | ATx201/niclosamide (Union Therapeutics) | Protonophore activity | II                                              | NCT04339985             |
|                                | Bacterial strains — oral          | EDP1815 (Evelo)               | Modulation of systemic inflammation | Ib                                              | NCT03733353             |
|                                |                                   | STMC-103H (Siolta therapeutics) | Immunomodulation via microbiome manipulation | Ib                                              | NCT03819881             |
| Targeting the innate immune response | Small molecule — topical          | Tapinarof/benvitimod (Dermavant) | AhR agonist          | IIb                                             | NA                      |
|                                | Biologic — injection              | Tezepelumab (Amgen/AstraZeneca) | TSLP                  | Ila                                             | NCT02525094             |
|                                |                                   | Etokimab (AnaptysBio)         | IL-33                 | Ila                                             | NCT03533751             |
|                                |                                   | REGN3500 (Regeneron)         | IL-33                 | Ila                                             | NCT03738423             |
|                                |                                   | Astegolimab (Genentech)      | IL-33                 | Ila                                             | NCT03747575             |
|                                |                                   | MEDI3506 (MedImmune)         | IL-33                 | Ila                                             | NCT04212169             |
|                                |                                   | Bermekimab (Janssen)          | IL-1α                 | Ila                                             | NCT03496974             |
|                                |                                   | Spesolimab (Böhringer Ingelheim) | IL-36R              | Ila                                             | NCT03822832             |
| Targeting the adaptive immune response | Biologic — injection              | GBR 830/ISB 830 (Glennmark/Ichnos) | OX40                 | IIb                                             | NCT03568162             |
|                                |                                   | KHK4083 (Kyrin)              | OX40                  | IIb                                             | NCT03703102             |
|                                |                                   | KY1005 (Kymbra/Sanofi)       | OX40L                 | Ila                                             | NCT03754309             |
|                                |                                   | Dupilumab (Regeneron/Sanofi) | IL-4Rα                | Approved globally, staggered paediatric programme ongoing | NCT03346434             |
|                                |                                   | CBP-201 (Connect Biopharma)   | IL-4Rα                | IIb                                             | NCT04444752             |
|                                |                                   | AK120 (Akesobio)             | IL-4Rα                | Ib                                              | NCT04256174             |
|                                |                                   | ASLAN004 (ASLAN)             | IL-13Ra1              | Ib                                              | NCT04090229             |
|                                |                                   | Tralokinumab (LEO Pharma)    | IL-13                 | Approved in EU, staggered paediatric programme ongoing | NCT03526861             |
|                                |                                   | Lebrikizumab (Allmiral/Lilly) | IL-13                 | III, staggered paediatric programme ongoing     | NCT04250350             |
|                                |                                   | Benralizumab (AstraZeneca)    | IL-5Rα                | II                                              | NCT04605094             |
|                                |                                   | Omalizumab (Novartis)        | IgE                   | II                                              | NCT02300701             |
|                                |                                   | FB825/anti-CemX (LEO Pharma/Oneness Biotech) | mlgE                | Ila                                             | NCT04413942             |
|                                |                                   | Fezakinumab (ILI)            | IL-22                 | Ila                                             | NCT01941537             |
|                                |                                   | LEO 138559 (LEO Pharma)      | IL-22R1               | Ila                                             | NCT03514511             |
|                                |                                   | Secukinumab (Novartis)       | IL-17A                | Ila                                             | NCT02594098, NCT03568136 |
|                                |                                   | Risankizumab (AbbVie)        | IL-23                 | Ila                                             | NCT03706040             |
|                                |                                   | LY3471851 (Lilly)            | rhIL-2 to T<sub>reg</sub> cells | Ib                                              | NCT04081350             |
| Strategy | Drug type and mode of application | Agent/company | Mode of action/target | Clinical development phase in atopic dermatitis | Clinical trial ID |
|----------|----------------------------------|---------------|----------------------|-----------------------------------------------|------------------|
| Targeting the adaptive immune response (cont.) | Small molecule — oral | Adriforant (Novartis) | H4R | Iib | NCT03517566 |
| | | LEO 152020/JW1601 (LEO Pharma) | H4R | I | NCT04203836 |
| | | RPT193 (RAPT Therapeutics) | CCR4 | Ila | NCT04271514 |
| | | Etrasisod (Arena Pharma) | S1PR1, S1PR4, S1PR5 | Iib | NCT04162769 |
| | | SCD-044 (Sun Pharma) | S1PR1 | Ila | NCT04664485 |
| | | LC51-0255 (LG Chem) | S1PR1 | I | NA |
| | | BMS-986166 (Bristol Myers Squibb) | S1PR1 | Ila | NCT03038711 |
| | Small molecule — topical | AKP-19 (Akaal Pharma) | S1PR1 | Iib | NA |
| | | Lotamilast (RVT-501/E6005) (Dermavant) | PDE4 | Ila | NCT03394677, NCT02950922 |
| | | Difamilast (OPA-15406/MM36) (Otsuka) | PDE4 | Iib | NCT02945657 |
| | | LEO 29102 (LEO Pharma) | PDE4 | I | NCT01037881 |
| | | Roflumilast (AstraZeneca) | PDE4 | Iib; pharmacokinetics and efficacy in paediatrics | NCT04156191 |
| Targeting itching | Small molecule — oral | Hemay-808 (Tianjin Hemay Pharmaceutical) | PDE4 | I | NCT04352595 |
| | | PF-07038124 (Pfizer) | PDE4 | Ila | NCT04664153 |
| | | BEN2293 (BenevolentAI) | TRK | I/II | NCT04737304 |
| | | HY209 (Shaperon) | GPCR19 | Ila | NCT04530643 |
| | | VTP-38543 (Vitae Pharma) | Liver X receptor-β | I/II | NCT02655679 |
| | | ALX 101 (Ralexar) | Liver X receptor | Ila | NCT03859986 |
| Inhibiting Janus kinases | Small molecule — topical | Nemolizumab (Galderma) | IL-31 | III | NCT03989349, NCT03859943 |
| | | Vixarelimab (Kiniksa Pharma) | OSMRβ | Ila/b | NCT03816891 |
| | | Serloptitant (Menlo) | NK1R | I | NCT02975206 |
| | | Tradipitant (Vanda) | NK1R | II | NCT03568331 |
| | | BLU-5937 (Bella) | P2X3 | I | NCT04939195 |
| | | Delgocitinib (Japan Tobacco/LEO) | Pan-JAK | Iib in EU, approved in Japan | NCT03725722 |
| | | RUxolitinib (Incyte) | JAK1/JAK2 | III | NCT03745638, NCT03745651 |
| | | Cerdulatinib (RVT/DMVT502) (Dermavant) | Pan-JAK/SYK | Iib | NA |
| | | Brelocitinib (Pfizer) | JAK1/TYK2 | Iib | NCT03903822 |
| | | ATI-1777 (Aclaris) | JAK1/JAK3 | I | NCT04598269 |
| | | CEE321 (Novartis) | Pan-JAK | I | NCT04612062 |
| | | Jaktinib (Suzhou Zeigen Biopharma) | Pan-JAK | Ila | NCT04539639 |
| | | SHR0302 (Reistone Biopharma) | JAK1 | II | NCT04717310 |
| | Small molecule — oral | Baricitinib (Lilly) | JAK1/JAK2 | Approved in EU for adults, staggered paediatric programme ongoing | NCT03952559 |
| | | Upadacitinib (AbbVie) | JAK1 | III, staggered paediatric programme ongoing | NCT03646604 |
| | | Abrocitinib (Pfizer) | JAK1 | III, staggered paediatric programme ongoing | NCT03627767 |
| | | SHR0302 (Reistone Biopharma) | JAK1 | II | NCT04162899 |

AhR, aryl-hydrocarbon receptor; BTK, Bruton tyrosine kinase; CCR4, C-C chemokine receptor 4; GPCR19, G protein-coupled receptor 19; H4R, type 4 histamine receptor; IL-4Ra, α-chain of the IL-4 receptor; IL-5Ra, α-chain of the IL-5 receptor; IL-13Ra1, α1 chain of the IL-13 receptor; IL-22R1, IL-22 receptor 1; JAK, Janus kinase; NK1R, neurokinin 1 receptor; NA, not applicable; OSMRβ, oncostatin M receptor-β; OX40L, OX40 ligand; PDE4, phosphodiesterase 4; P2X3, purinoreceptor 3; rhIL-2, recombinant human IL-2; S1PR1, sphingosine 1-phosphate receptor 1; Treg cell, regulatory T cell; TRK, tropomyosin receptor kinase; TSLP, thymic stromal lymphopoietin.
A topical gel formulation of the TRK inhibitor BEN2293 has been developed and is currently in a phase I/II proof-of-concept study for mild to moderate forms of AD.

Tauroxycholic acid (HY209) is an agonist of G protein-coupled receptor 19. In an animal model of AD, HY209 reduced $T_h2$ inflammation via inhibition of nuclear factor κB (NF-κB) and p38 kinase. Typical biomarkers of AD such as TSLP and CCL17/TARC were also significantly decreased, as was serum IgE. HY209 is considered an interesting compound for the therapy of AD and is currently being tested in a phase II trial using a topical gel formulation.

AD is characterized by a disturbed epidermal barrier and chronic inflammation. Interestingly, liver X receptors (LXRα and LXRβ) are ligand-activated nuclear transcription factors that are involved in the regulation of epidermal barrier function and exhibit suppressive effects on skin inflammation, and are therefore potential targets for pharmacological intervention in AD. A comparative transcriptomic analysis of skin biopsy samples from a phase I/II study using a topical cream formulation including the penetration enhancer Transcutol P and the LXRβ agonist VTP-38543 (in patients with mild to moderate AD), revealed increased mRNA expression of important epidermal structural proteins (loricrin and filaggrin) as well as improvement of epidermal hyperplasia. However, the compound did not significantly downregulate markers of inflammation. Although the drug was well tolerated (primary end point reached: number of patients with treatment-related adverse events), the results in terms of clinical improvement (secondary end points) assessed by percentage change in body surface area, percentage change in SCORAD and EASI, were not promising. Moreover, the effects observed were not dose-dependent (NCT02655679). ALX 101 is another LXRβ agonist currently being tested in a phase Ib study using a gel formulation in patients with moderate AD. Results are not yet available.

Towards precision medicine for AD

Scientific rationale

New and broadly effective compounds such as JAKi have exhibited unprecedented efficacy. However, although patients expect that such new compounds provide full clinical response in a monotherapy regimen, the phase III trials with these compounds have highlighted the variability of the clinical response. Clearly, as for rheumatoid arthritis, JAKi are not the ‘one-size-fits-all’ approach for AD. This is certainly the case for the JAK1/JAK2 inhibitor baricitinib, for which the identification of the good-responder population is an unmet need. Patients have high expectations with regard to efficacy, and physicians aim to prescribe therapies for long-term control of the disorder. Although AD is not life-threatening, it has a profound impact on patient quality of life and that of their relatives. The steadily increasing number of new drugs in development for AD has indicated the potential for precision medicine to generate an optimized benefit–risk ratio, particularly in age ranges where safety issues are of crucial interest such as in paediatric patients, as well as in the elderly, where drug–drug interactions represent another potential threat.

There are multiple factors that contribute to the high heterogeneity of the age of disease onset in patients with AD, the variations in the clinical phenotype (particularly in different ethnic backgrounds) and the different risks for early development of an ‘atopic march’ with atopic comorbidities (that is, allergic rhinitis and asthma), neuropsychiatric comorbidities (anxiety, depression) or later non-atopic comorbidities (cardiovascular disorders). These factors, which include diverse environmental influences, a complex genotype, microbiome-derived signals and a dynamic immune response, also underline the highly variable therapeutic response and adverse events to established and new compounds for AD therapy. Lessons from the history of previous drug development programmes in patient populations with complex phenotypes (for example, trastuzumab in breast cancer or mepolizumab in allergic asthma) have shown that compounds that failed to meet the primary end points in phase II or phase III studies in the classic one-size-fits-all approach may still be promising candidates in certain subgroups of patients. This is probably relevant for AD, in which phenotype and/or endotype-based stratification for selection of potential treatment responders with an optimal risk–benefit ratio represents an attractive strategy.

A better understanding of the biochemical and functional consequences of the genetically driven epidermal barrier dysfunction would enable the design of new skin care products that are better adapted to address the individual needs of a patient, to correct and improve the sensitive and permeable skin in AD. An early precise determination of the genetic and/or environmental risk factors leading to the emergence of AD in infancy as well as the risk of developing an atopic march (that is, atopic comorbidities such as allergic asthma) bears the tremendous potential of a disease-modifying prevention strategy early in life. The same holds true for the early identification of patients at risk of developing non-atopic comorbidities such as cardiovascular or neuropsychiatric disorders, offering unique opportunities for prevention and risk mitigation strategies.

Strategies for implementation

Understanding a complex disorder such as AD in its full phenotypic and mechanistic spectrum in order to apply a precision medicine approach is a challenging goal. It requires systematic analysis of a wide cohort of representative patients including all age and severity ranges, ideally at a global level. To reach this ultimate goal, longitudinal ‘regulatory grade’ patient registries linked to high-quality biorepositories collecting microbiome, cellular and fluid blood samples as well as skin tissue and/or non-invasive tape-strip specimens are crucial. Such integrated technological platforms would allow the construction of a multidimensional model of the underlying mechanisms and facilitate the discovery of new drug targets more specifically adapted to the distinct phases of the epithelial events and the dynamic immune response. This systematic approach would...
also foster the identification, validation and regulatory qualification of predictive and prognostic biomarkers for innovative molecular taxonomy and companion diagnostics accompanying drug development programmes for tailored targeted therapeutics \textsuperscript{185–247}.

\textbf{Outlook}

As the skin is easily accessible for local therapy, treatment guidelines historically evolved following the established dogma that topical anti-inflammatory therapy is prioritized for mild to moderate forms of AD, while systemic approaches, potentially associated with a higher risk of adverse reactions, are reserved for moderate to severe cases. Progress in our understanding of the manifold epithelial and immunological pathways leading to AD has contributed to the discovery of a remarkable number of therapeutically interesting pathways and targets. Translational efforts to convert this knowledge into drug discovery have paved the way for an impressive number of preclinical and clinical development programmes. Consequently, there is now an expanding pipeline for the therapy of this complex disorder.

However, the current drug discovery and development strategies still follow the above-mentioned dogma, which may neglect potential preventive and therapeutic approaches. Besides considering solely the severity of disease, these alternative approaches could rely on stratification of the AD population according to other dimensions such as phenotypic information, for example, age, age of onset, duration of disease, ethnic background as well as endotypic hallmarks provided by validated biomarkers. Identification of the window of opportunity according to the age of the patients for intervention in the skin and gut microbiome would allow a differential approach using the numerous compounds aimed at correcting the dysbiotic constellation in AD. Sticking to arbitrary cut-off points in the severity scales to define whether a patient deserves systemic therapy may lead to underestimation of the overall systemic impact of inflammation in the skin and a driving force for comorbidities. Thereby, undertreatment of some individuals at high risk of developing atopic and non-atopic comorbidities as well as the missed opportunity to prevent them by an adequate pharmacological intervention may be substantial.

An area that has an escalating impact on drug development in dermatology is the increasing influence of third-party payers, particularly the health technology assessment agencies in Europe and more recently countries such as Japan. Hence, cost-effectiveness and market access issues tend to become a new hurdle and threat for drug discovery by disincentivizing innovation and hampering patient access. For example, despite its approval by the EMA in March 2020, the topical PDE4 inhibitor crisaborole has never been launched in Europe. Although approved in Japan, the termination of the clinical development in Europe of the JAK inhibitor degronitinib is another example of the deleterious impact of such cost-effectiveness considerations on innovative drug development. While market access aspects become an integral part of the clinical development strategies for pharmaceutical companies, cost-effectiveness should not be the only consideration for third-party payers when it comes to the evaluation of the added value of a new compound. Instead, real-world data and experience, the unmet needs from the patient's (with increased literacy) perspective and their advocacy efforts deserve more attention in this context.

In summary, a better understanding of the mechanisms underlying AD has illuminated both the complexity and the systemic impact of this disorder and supported the development of a comprehensive pipeline of new compounds for disease management. For systemic therapy, biologics with a slow but pathway-specific mode of action are now competing with small molecules such as JAKi with fast but broader activity. Although biologics may be more adapted for long-term control and potentially disease modification in AD, JAKi provide rapid relief in pruritus and inflammation but, while well tolerated, their benefit–risk ratio remains a significant issue for pharmacovigilance. If applied early in the natural course of the disorder, some of these products even have the potential to be disease modifiers in that they could impact on the atopic march and other comorbidities.

Published online 20 August 2021
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