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Targeted therapy for moderate to severe atopic dermatitis

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Atopic dermatitis (AD) is chronic recurrent inflammatory disease of skin. The pathogenesis of AD is multifactorial including genetic and environmental factors. Development and maintenance is caused by an impaired skin barrier, a dysfunctional immune response and individual triggering factors. About 20% to 30% of AD patients, the disease severity is moderate to severe. Treatments for those moderate to severe AD patients can be challenging. AD causes significant impairment in quality of life of patients and their family. Recent progress in understanding the pathogenesis of AD focuses on the key molecules targeting specific immunologic pathways in the development of AD. Clinical trials evaluating targeting agents specifically towards immunologic pathomechanism in AD are ongoing and may provide treatment options for severe or refractory AD patients in the near future

Anti-IL-4 receptor

The Th2 cytokines interleukin (IL)-4 and IL-13 and their downstream effects are prominent in AD.

IL-4 is the key cytokine which promotes Th2 cell differentiation and consequently the produce IL-4 and IL-13, potent stimulators of IgE production by B lymphocytes. Due to the Th2-driven inflammatory characteristics of AD, it is reasonable to assume that inhibition of Th2-related mole-cules reduces inflammation and break the inflammatory downstream.

Dupilumab is a fully humananized monoclonal antibody against the shared alpha subunit of the IL-4 and IL-13. The safety and efficacy of dupilumab was primarily established in 3 placebo-controlled studies with a total of 2,119 adult participants with moderate to severe AD. Dupilumab showed significant clinical improvement of at least 75% from baseline to week 16 in Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), and SCORing Atopic Dermatitis (SCORAD) including pruritus.

Effect of dupilumab was independent of the patient's phenotype (low vs. high IgE or levels of serum thymus- and activation-regulated chemokine, CCL17), proving that dupilumab is effective in both intrinsic and extrinsic AD. Dupilumab treatment was in general well tolerated with few serious adverse events. Side effects such as conjunctivitis and inflam-mation of the cornea were observed about 14% in the dupilumab group. Food and Drug Admin-istration approved dupilumab treatment for adults with moderate to severe AD in March 2017, and European Medicines Agency in 2017. When combined with topical glucocorticoids in the Chronos study, all patients treated with dupilumab reached EASI-50, compared with only half of those receiving topical glucocorticoids plus placebo (p=0.002). Importantly, patients receiving dual therapy with dupilumab used less than half the glucocorticoid therapy required by those patients receiving glucocorticoid plus placebo (p=0.16). Currently, a phase II pharmacokinetic study in pediatric patients 6 to 17 year-old is ongoing.

Anti IL-5

Interleukin-5 (IL-5) is a key cytokine for eosinophilic differentiation and activation and is elevated in lesional skin and in the blood of patients with atopic dermatitis. Mepolizumab, a humanized monoclonal antibody targeting IL-5, did not significantly reduce skin disease severity in patients with atopic dermatitis

Anti IL-13

Tralokinumab is an mAb that targets the cytokine IL- 13. In a double-blind phase IIb study including 204 adults who suffered from moderate to severe AD, tralokinumab demonstrated efficacy in the primary and key secondary end points and had an adverse event profile comparable to placebo. Treatment with tralokinumab for 12 weeks, 150 and 300 mg, significantly reduced the total EASI from baseline compared with placebo. Patients achieving EASI 50, reduction of EASI score by 50%, at week 12 in the tralokinumab 300-mg group was significantly higher compared with placebo (73.4 vs. 51.9%, p = 0.025). The patients were allowed to use topical corticosteroids during the trial.

Lebrikizumab is a humanized mAb that specifically targets IL-13. Clinical trials investigating the effects of lebrikizumab in asthma patients have been terminated due to poor efficacy. However, the data on the 2 phase II studies investigating the drug in adult patients with moderate to severe AD have not been available yet.

Anti-IL-22

It belongs to the IL-10 family of cytokines and induces activation of keratinocytes, which leads to the

upregulation of inflammatory mediators in the epidermis and increased epidermal thickening. Phase II study of Fezakinumab (ILV-094), mAb directed against IL-22, in AD is in progress.

Anti IL-31 and anti IL-31RA

IL-31 is a member of the IL-6 family and related to AD. It is mainly produced by Th2 cells and dendritic cells, mast cells, and monocytes. Studies have indicated a critical role of IL-31 in the pathophysiology of itch.

Nemolizumab, mAb against the IL-31 receptor A, which constitutes the IL-31 receptor in conjunction with the oncostatin M receptor (OSMR). Phase II study of nemolizumab in 264 moderate to severe AD patients shows significantly decreased pruritus. However, reductions of both the EASI and SCORAD severity scores did not achieve the statistical significance possibly due to sample size.

BMS-981164, mAb targeted at circulating IL-31, completed an initial investigation in a phase I study.

Anti-Thymic stromal lymphopoetin(TSLP) and anti-OX40

Thymic stromal lymphopoietin (TSLP) is known as a keratinocyte-derived cytokine that leads to conditioning of skin-derived dendritic cells, ultimately generating a strong TH2 response. TSLP seems to deliver important signals for the overall sensitization mechanisms initiated on contact of allergens in inflamed skin. Increased TSLP production in keratinocytes is facilitated by *Staphylococcus aureus*, a common skin-colonizing microorganism, in AD patients. TSLP has been shown to act as inducer of myeloid dendritic cells, Th2 responses, mast cells, and natural killer T cells, thereby launching cytokine secretion and the development of AD. Influence of TSLP on dendritic cells generates another highly Th2-polarizing signal, the OX40 ligand, which is pivotal in the generation of long-term Th2 memory response, optimal T-cell activation and inflammatory conditions like allergic asthma and AD. TSLP and OX40 are both pivotal cytokines in the activation and Th2 skewing of the immune system in AD

Tezepelumab, an anti-TSLP antibody (MEDI9929/AMG-157), has completed phase 2a trials in 155 patients with moderate to severe AD.

GBR 830 is an OX40 antagonist that exclusively binds and blocks the OX40-mediated signaling in AD. Phase II clinical trial is ongoing.

Anti-Immunoglobulin E

Omalizumab, the humanized anti-IgE antibody approved for the treatment of asthma and chronic urticaria. A randomized, placebo-controlled, double-blind investigation with omalizumab was conducted in 20 patients

with severe atopic dermatitis. No effect on the severity of dermatitis was shown in this small study. In a recent study severely affected patients without mutations in filaggrin mutation responded to omalizumab, whereas those who showed filaggrin mutations did not.

Ligelizumab is an anti-IgE mAb that has higher affinity for IgE than omalizumab and has demonstrated greater reductions in free IgE in AD patients. A phase II trial in adult AD patients with moderate to severe disease has completed enrollment, but results are not available yet.

Targeting Janus Kinase/Signal Transducer and Activator of Transcription Pathways

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling axis has been shown to play a critical role in the dysregulation of immune responses in AD, involving amplification of Th2 cell response, instigation of eosinophils, and suppression of regulatory T cells. JAK/STAT pathway, when activated by IL-4, IL-13, and TSLP, plays an important role in the pathogenesis of AD by upregulating the expression of epidermally derived chemokines and a cascade of pro-inflammatory cytokines as well as downregulating structural epidermal proteins, e.g. filaggrin, involucrin, or loricrin, which are associated with epidermal barrier function.

Baricitinib

Baricitinib is a small molecule inhibiting both JAK1 and JAK2. The drug has been approved for rheumatoid arthritis (RA), and tested in psoriasis, alopecia areata, and other inflammatory or auto-immune conditions, with promising results. Side effects primarily confined to a slightly increased rate of infection, risk of low neutrophils and reduced hemoglobin levels. With the promising results in phase II trial in 124 adult with moderate to severe AD, phase III trial is ongoing.

Tofacitinib

Tofacitinib inhibits JAK1 and JAK3 and in theory interferes with lymphocyte activation and Th2 skewing than the inhibitors also targeting JAK2 which are more involved in Th1 signaling. It is approved for RA, and is in phase III trials for psoriasis. Side effects comprise increased rates of diarrhea, infections, low neutrophils and lymphocytes, and increased levels of creatinine and lipids, and possible increased risk of lymphoma. Oral tofacitinib (5 mg administered in six patients with moderate to severe AD resulted in 66% reductions in Scoring Atopic Dermatitis (SCORAD) index with no serious adverse events.

Upadacitinib

Upadacitinib is a small molecule targeting only JAK1. Studies of upadacitinib in RA and Crohn's disease

has been completed. Positive results were revealed, and the safety profile was modest in-creased rates of infections. Phase IIb placebo-controlled multicenter study to evaluate the safety and efficacy in adult patients with moderate to severe AD was investigated.

PF-04965842

PF-04965842 is a JAK1 inhibitor. Phase II studies and is evaluated for the efficacy and safety for adults with moderate to severe AD. Rates of adverse events were markedly increased in the high-dose group compared to placebo, but it was primarily reports of nausea, headache, and hypertension.

Phosphodiesterase-4 (PDE-4) inhibitor

PDE4 is an enzyme which is increased in AD and in part is responsible for the hydrolyzation of cyclic adenosine monophosphate (cAMP). This consequently diminishes levels of cAMP, which lead to increased transcription of numerous proinflammatory cytokines, and accelerates other intracellular functions. Potential therapeutic use of phosphodiesterase-4 (PDE4) inhibitors in a variety of inflammatory diseases is proved.

Apremilast

Apremilast is an oral PDE4 inhibitor evaluated in two open-label phase II studies and one larger clinical trial for patients with moderate to severe AD. Studies revealed modest reduction of EASI and the IGA score, with the main side effects such as nausea, vomiting, and headache. Compared to placebo treatment, apremilast 30 or 40 mg daily demonstrates mean EASI reductions of −15.01 and −20.60 points, respectively, at 12 weeks, with only 40mg dose being a statistically significant result.

Crisaborole (Eucrisa)

The boron-based benzoxaborole named crisaborole (AN2728) is a small molecule specifically inhibiting PDE4 activity and the first in its class to be approved by the FDA. Data on the previous phase I and II studies showed positive results across a accumulated cohort of 189 subjects with AD as young as 2 years of age. In vehicle-controlled, double-blind studies, AD patients aged over 2 years were enrolled with an Investigator's Static Global Assessment (ISGA) score of mild or moderate for twice-daily application for 28 days. The primary end point of the ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline was achieved in a greater percentage of crisaborole-treated patients than placebo-treated subjects. Crisaborole treatment resulted in a 32.8% and 31.4% improvement of the clinical score (investigator static global assessment) versus 18% and 25.4% in the placebo-treated subjects ($p = 0.0038$ and > 0.0001). Application site adverse events were present in the majority of patients in the treatment group across all trials.

Chemoattractant receptor-homologous molecule 2 (CRTH2) antagonist

Chemoattractant receptor homologues molecule expressed on Th2 cells (CRTH2 or DP2) is a receptor for the ligand prostaglandin D2, which is a product from cyclooxygenase activity. CRTH2 is a transmembrane prostaglandin D2 receptor and is expressed on Th2, but not Th1, cells, eosinophils and basophils and its activation leads to chemotaxis and activation of Th2 cells. CRTH2 antagonists were tested for allergic rhinoconjunctivitis and asthma showing a beneficial effect on clinical symptoms. CRTH2 could be beneficial to AD patients as a means of correcting a skewed Th2 response and reducing eosinophil activity.

Fevipiprant

Fevipiprant(QAW039) has completed a phase II trial. Adults with moderate to severe AD were treated with either Fevipiprant at 450 mg per day or placebo for 12 weeks, with minimal effect on the primary endpoint of change from baseline EASI score (mean -8.65 for QAW039 and -6. for placebo). Its clinical efficacy in AD is not significant.

Timapiprant

In timapiprant study enrolled 142 AD patients, there was no meaningful treatment response. CRTH2 antagonist does not look promising in the adult subset of AD patients with moderate to severe disease.

Histamine-4 receptor antagonist

The role of histamine as an itching-inducing mediator is well known, but the effect of medications that target anti-H1 and anti-H2 receptors in managing itch in patients with AD has often been disappointing. The histamine receptor type 4 (H4R) is expressed on keratinocytes and TH2 cells, and H4 stimulation leads to IL-31 production in human.

Oral administration of an H4R antagonist (JNJ-39758979) to patients with AD significantly reduced pruritus but was terminated because of agranulocytosis in 2 of 27 patients with JNJ-39758979 (300 mg/d). ZPL-389, a H4R antagonist, has completed phase 2 clinical trials for AD with significant improvement in the EASI score.

Neurokine-1(NK-1) Antagonist

Signaling via the NK1 receptor is mediated by several different neuropeptides, the most prominent being substance P (SP), which act as a neurotransmitter and as a neuromodulator. SP and the NK1 receptor are both widely distributed in the brain and the skin where the SP is a key responder to stimuli. In AD

patients, there are high levels of SP associated with increased pruritus. NK1 antagonist might hold the potential to counter the SP-mediated itching in AD patients

Tradipitant (VLY-686 or LY686017)

Tradipitant is a NK1 antagonist that blocks SP. Phase II trial in patients with AD with severe pruritus was investigated. There are no dramatic effects of tradipitant treatment in AD patient.

Serlopitant (VPD-737)

Serlopitant is an oral NK1 antagonist under development exclusively for the treatment of severe chronic pruritus. Placebo-controlled phase II trial involving 257 patients with severe refractory chronic pruritus of various etiologies, 6 weeks of serlopitant at 1 or 5 mg/day were effective than placebo in reducing itch intensity. Study investigating efficacy, safety, and tolerability of serlopitant for treating pruritus in adult AD patients is in progress.

Recent progress in insights into the immunopathogenesis of AD developed novel treatment modalities of AD patients. Emerging therapies directing to TH2 cells and downstream pathway of Th2 axis seem highly promising for the management of severe refractory AD. Novel targeting agents for AD would have significant impact on future treatment paradigm.

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