Symposium 2: State of art: New treatment for moderate to severe atopic dermatitis

# Biologic Treatements in Atopic Dermatitis

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Atopic dermatitis (AD) is chronic inflammatory skin disorder. Prevalence of AD is about 15-20% in of children and 3-5% of adults. Proposed pathogenesis of AD is barrier dysfunction and dysregulation of innate and adaptive immune response to extrinsic and intrinsic genetic factors. About 20% of AD patients, the disease severity is moderate to severe. Although[1,2] treatments of AD are often successful, treatments can be challenging for certain some patients. Due to its recurrent and long term clinical course, AD cause significant impairment in quality of life of patients and their family. With advances in the understanding of immunologic pathway involved in the pathogenesis of AD, biologic agents targeting specific immune-related targets are growing options for the patients with severe or refractory disease (Table1)[3-5].

## Anti-Immunoglobulin E

Eighty percent of all patients with atopic dermatitis show elevated serum levels of total immunoglobulin E (IgE) and specific sensitization to allergens.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that blocks the interaction of IgE with high-affinity Fc $\varepsilon$ RI and downregulates dendritic cell, basophil, and mast cell Fc $\varepsilon$ RI expression[6]. It reduces levels of free IgE in the serum by blocking initial antigen presentation and the additional production of IgE, and also reduces numbers of inflammatory cells. Treatment with the anti-IgE antibody omalizumab demonstrated inconsistent results in some case series. A randomized, placebo-controlled, double-blind clinical trial with omalizumab was completed in 20 patients with severe atopic dermatitis. No significant effect on the severity of dermatitis was shown in this study , although IgE and other immune parameters were significantly reduced[7]. In 28-week open-label trial using omalizumab in 20 adults with moderate-to-severe AD, AD patients without filaggrin mutation responded to omalizumab, whereas those who showed filaggrin mutations did not[8]. These suggest that anti-IgE may have a moderate effect on cutaneous

**Table 1.**

| Target | Biologic Agent | Mechanism | Route | Clinical trial |
|---|---|---|---|---|
| IgE | Omalizumab | Anti-IgE mAb | SC | Phase II ongoing |
| | Ligelizumab | Anti-IgE mAb | SC | Phase II completed |
| | Medi4212 | Anti-IgE mAb( also react with FcχRIIIa) | SC | Phase I completed |
| | XmAb7195 | Anti-IgE mAb,( also react with FcχRIIb) | IV | Phase I ongoing |
| IL-4Ra | Dupilumab (Dupixent) | Anti-IL-4Rα mAb (blocks IL-4 &IL-13 ) | SC | Phase III completed (FDA approved) |
| | Pitakinra | Anti-IL-4Rα mAb (blocks IL-4 & IL-13) | SC | Phase II |
| IL-5 | Mepolizumab | Anti-IL-5 mAb | IV | Phase II completed |
| IL-13 | Lebrikizumab | Anti-IL-13 mAb | SC | Phase III ongoing |
| | Tralokinumab | Anti-IL-13 mAb | SC | Phase II completed |
| IL-12/IL-23 | Ustekinumab(Stellar) | Anti-IL-12/IL-23 mAb | SC | Phase II completed |
| IL-17 | Secukinumab(Cosentyx) | Anti-IL-17a mAb | | Phase II ongoing |
| IL-22 | Fezakinumab (ILV-094) | Anti-IL-22 mAb | SC | Phase II ongoing |
| IL-31Ra | Nemolizumab | Anti-IL-31RA mAb | SC | Phase II completed |
| IL-31 | BMS-981164 | Anti-IL-31 mAb | SC | Phase I |
| TSLP | MEDI9929 (AMG 157) | Anti-TSLP mAb | SC | Phase II |
| JAK Pathway | Tofacitinib (Xeljanz) | JAK 1/3 inhibitor | Topical | Phase II completed |
| (small molecule) | Baricitinib | JAK 1/2 inhibitor | oral | Phase II ongoing |
| | PF-04965842 | JAK 1 inhibitor | oral | Phase Iib |
| PDE-4 | Apremilast | PDE-4 inhibitor | oral | Phase II ongoing |
| (small molecule) | Roflumilast | PDE-4 inhibitor | Topical(cream) | Phase II completed |
| | Crisaborole (Eurisca) | PDE-4 inhibitor | Topical(ointment) | Phase III completed (FDA approved) |
| | E6005 | PDE-4 inhibitor | Topical(ointment) | Phase II completed |
| | OPA-15406 | PDE-4 inhibitor | Topical(ointment) | Phase II completed |
| | DRM-02 | PDE-4 inhibitor | Topical(gel) | Phase II ongoing |
| | LEO29102 | PDE-4 inhibitor | Topical(cream) | Phase II ongoing |
| CRTH2 | Fevipiprant (QAW039) | CRTH2 antagonist | oral | Phase II completed |
| (small molecule) | OC459 (OC000459) | CRTH2 antagonist | oral | Phase II ongoing |
| | BBI-5000 | CRTH2 antagonist | oral | Phase I ongoing |

CRTH2: chemoattractant receptor-homologous molecule expressed on Th2 cells, FcχRIIb: low-affinity Ig Fc gamma receptor subtype IIb (also called CD32), FcχRIIIa: low-affinity Ig Fc gamma receptor subtype IIIa (also called CD16a), JAK:Janus kinase, PDE:phosphodiesterase, SC: subcutaneous

atopic inflammation if this is not amplified by inherited skin barrier defects.

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. Uncertain efficacy of anti-IgE antibody in AD patients group compared to its possible adverse events may limit its use in AD.

## Anti-IL-4 receptor

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[9].

Dupilumab is a fully humananized monoclonal antibody against the shared alpha subunit of the IL-4 and IL 13. Dupilumab improved the inflammatory molecular signature of AD in a dose-dependent manner and the molecular changes paralleled improvements in clinical scores. Significant decreases in mRNA expression of genes, Th2-associated chemokines (CCL17, CCL18, CCL22, and CCL26) were noted at week 4 in dupilumab 300mg group without significant modulation of TH1-associated gene[10]. In phase II study of 4-12 weeks dupilumab treatment, either as monotherapy or in combination with topical corticosteroids, clearly resulted in a significant improvement of eczema area and severity index (EASI) (85% vs 35% in the placebo group in EASI-50); pruritus ( itch score reduction 55.7% vs 15.1% in the placebo), and investigator's global assessment(IGA) (40% vs 7% in the placebo group, had a score of 0 to 1 on the IGA). Dupilumab response was strongly supported by the reduction in the serum levels of the Th2-associated biomarkers, such as thymus and activation-regulated chemokine (TARC), total IgE, and eosinophil counts[11]. A randomized, double-blind, placebo-controlled, dose-ranging phase IIb study in adult patients with moderate to severe atopic dermatitis [Total 380 AD patients were randomly assigned, 300 mg of dupilumab once a week (n=63), 300 mg every 2 weeks (n=64), 200 mg every 2 weeks (n=62), 300 mg every 4 weeks (n=65), 100 mg every 4 weeks (n=65), or a placebo (n=61)] was conducted. The efficacy data was consistent with the results from the four early phase studies. EASI score reduction at week 16 was noticable in all dupilumab regimens versus placebo ($p<0.0001$): 300 mg once a week (−74% ), 300 mg every 2 weeks (−68% ), 200 mg every 2 weeks (−65% ), 300 mg every 4 weeks (−64% ), 100 mg every 4 weeks (−45% ); placebo (−18% ). Nasopharyngitis was the most common adverse event( 28% vs 26%). However, there was an increased rate of herpes viral infections in dupilumab treated patients (8% vs 2% in placebo), with the highest occurrence in the lowest dosage group (12%)[12]. These efficacy data are unique and suggest that dupilumab might even be better than the well known ciclosporin, both in terms of final efficacy and in rapid achievement.

In two randomized, placebo-controlled, phase 3 trials (SOLO 1 and SOLO 2), adults with moderate to severe AD received subcutaneous dupilumab (300 mg) weekly or every other week or placebo for 16

weeks13). At week 16, the primary outcome ( IGA score 0 or 1) occurred in 38% (dupilumab biweekly) and 37% (dupilumab weekly) as compared with 10% (placebo) in SOLO1 and 36% (dupilumab biweekly) and 36% (dupilumab weekly) as compared with 8% (placebo) in SOLO2 ($p<0.001$). Secondary outcome at week 16, EASI 75 were achieved in 51% (dupilumab biweekly) and 52% (dupilumab weekly) as compared with 15% (placebo) in SOLO1 and 44% (dupilumab biweekly) and 48% (dupilumab weekly) as compared with 12% (placebo) in SOLO2 ($p<0.001$). Dupilumab was also associated with improvement of parametes, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.[13)]

In March, 2017, FDA approved dupilumab (Dupixent) for adult patients with moderate to severe AD. A study of dupilumab use in children and adolescents (aged 6-17 years) is currently in progress.

Pitrakinra is a recombinant human IL-4 protein capable of specifically binding to the alpha subunit of the IL-4 receptor. Like dupilumab, it inhibits the downstream signaling pathways of both IL-4 and IL-13 A total of 25 patients were randomized to receive placebo or pitrakinra (30 mg subcutaneously twice daily) for 28 days. Phase II study is ongoing.

## Anti IL-5

An increased number of eosinophils in both peripheral blood and inflammatory infiltrate is a relatively frequent finding in AD. Mepolizumab is a fully humanized monoclonal antibody specifically directed against IL-5, the main factor of eosinophil growth, differentiation, and activation. It presents a high affinity and specificity against free IL-5, preventing it from binding to its receptor on the surface of eosinophils. In a RCT in AD patients (n = 43), two single doses of 750 mg mepolizumab, injected 1 week apart, caused a significant decrease in blood eosinophils and tissue eosinophils. However, clinical improvement was not achieved, possibly due to the relatively short duration of mepolizumab treatment[14)].

## Anti IL-13

IL-4 and IL-13 signal induce the STAT6/JAK1 signaling cascade. Mice genetically modified to express constitutively active STAT6 develop AD-like disease which is reversed by antibodies against either IL-4 or IL-13[15)], suggesting that interfering in this pathway could be efficacious in patients with AD. Downstream signaling of IL-4 and IL-13 has been shown to prevent the induction of innate immune response genes, such as b-defensins and cathelicidin.

Lebrikizumab is a humanized mAb directed against IL-13 that is in phase III trials for AD.

Tralokinumab is a humanized mAb directed against IL-13 that has completed phase IIb study in AD

patients. Tralokinumab 300 mg treatment significantly reduced EASI scores change from baseline: 15.7) vs. placebo (-10.8) and more pts had IGA 0/1 (26% vs. 12%). Tralokinumab 300 mg significantly reduced the number of *Staphylococcus aureus* colonized pts (p=0.015), concentration of serum immunoglobulin E, periostin, and TARC/CCL17, dose-dependently vs. placebo (p< 0.001).

## Anti-IL-22

The T-cell cytokine IL-22 is mainly produced by Th22 and Th17 lymphocytes and mast cells. It induces activation of keratinocytes, which leads to the upregulation of inflammatory mediators in the epidermis and increased epidermal thickening. Th22 cells are increased in AD lesions, and levels reflect disease severity[16].

Fezakinumab (ILV-094) is an mAb directed against IL-22. Phase II study is ongoing

## Anti IL-31 and anti IL-31RA

IL-31 is a cytokine produced by Th2 cell, mast cells, and keratinocytes. The expression of IL-31 is elevated in atopic dermatitis skin and serum levels of IL-31 correlate with disease severity in patients with atopic dermatitis. IL-31 works as a strong inflammatory cytokine on various cells expressing the IL-31 receptor. In mouse models IL-31 induced atopic dermatitis-like lesions and pruritus[17]. Therefore, the cytokine or its receptor are promising targets for the reduction of cutaneous inflammation and itch.

Nemolizumab (CIM331) is an mAb that targets the IL-31 receptor A (IL-31RA). IL-31 acts through a heterodimeric receptor composed of IL-31RA and the oncostatin M receptor (OSMR), which are expressed on keratinocytes, eosinophils, and neurons that coexpress transient receptor potential cation channel vanilloid subtype 1 receptors (TRPV1). It is released by activated Th cells (especially Th2), mast cells, and mononuclear cells and is thought to mediate itch in a number of conditions, including AD, prurigo nodularis, and cutaneous T-cell lymphoma. In phase I/Ib trial with antibodies blocking IL-31 receptor A (CIM331, nemolizumab) single injection reduced pruritus visual-analogue scale(VAS) to about -50% at week4 compared with -20% in placebo[18]. A Phase II, randomized, double-blind, placebo-controlled, 12-week trial with Nemolizumab in adults with moderate-to-severe atopic dermatitis was completed, At week 12, patients who received nemolizumab every 4 weeks, changes on the pruritus VAS were −43.7% in the 0.1-mg group, −59.8% in the 0.5-mg group, and −63.1% in the 2.0-mg group, versus −20.9% in the placebo group (P<0.01)[19].

Anti IL-31 mAb (BMS-981164) are in ongoing clinical studies with patients with AD.

## Anti-Thymic stromal lymphopoetin(TSLP)

Thymic stromal lymphopoetin (TSLP) is a cytokine of the interleukin-7 family mainly produced and secreted by keratinocytes. It produced in response to barrier disruption or innate signals and drives Th2 response. High expression of TSLP was observed acute and chronic atopic dermatitis skin. It promotes the activation of myeloid dendritic cells, favouring lymphocyte activation and a Th2-polarized response with the consequent release of pro-inflammatory cytokines The induction of pruritus with TSLP was described in animal models[20].

MEDI9929/AMG 157 (NCT02525094) is a mAb targeting TSLP. A phase II study evaluating the effects in adults with moderate to severe AD is ongoing.

## Novel target therapy with small molecules

In addition to biologic agents, approaches targeting defined molecules with small molecules have been developed and currently clinical trials for the treatment of AD is in progress.

### 1. Janus Kinase (JAK) inhibitors

The JAK family consists of JAK 1, JAK 2, JAK 3, and tyrosine kinase 2 (Tyk2), all of which have tyrosine kinase activity and, upon activation, activate one or more STAT family members, which subsequently induce cellular gene expression. IL-4, IL-5, IL-13, and TSLP signal through their respective receptors to induce downstream signaling events through the JAK/STAT pathway[9].

JAK inhibitors provide the opportunity to prevent the downstream signaling of multiple Th2 cytokines, and are currently being evaluated in patients with moderate to severe AD[21].

#### 1) Tofacitinib

Tofacitinib is a small molecule that targets the JAK1 and JAK3 enzymes and interferes with the JAK-STAT pathway important for lymphocyte activation. A phase II study with topical ointment has been completed in 69 adult subjects with mild to moderate AD. Preliminary results demonstrate an 81.7 % drop in baseline EASI score after 4 weeks of twice-daily application compared with 29.9 % in the placebo group ($p<0.0001$)[21]. 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[22].

#### 2) Baricitinib

Baricitinib (LY3009104) is a small molecule that inhibits JAK1 and 2 signaling. Phase II trials are currently is ongoing for adults with moderate to severe AD. It is an oral formulation and may also be beneficial for alopecia areata.

#### 3) PF-04965842

PF-04965842 is a JAK1 inhibitor that has completed phase I studies and is recruiting sites for phase IIb studies to test the efficacy of this therapy for adults with moderate to severe AD.

### 2. Phosphodiesterase-4 (PDE-4) inhibitor

Leukocytes from patients with atopic dermatitis have an increased phosphodiesterase activity compared with normal controls contributing to inflammation. PDE-4 is most abundant in keratinocytes. PEDs are responsible for hydrolyzing cyclic adenosine monophosphate (cAMP).

PDE-4 inhibitor will cause accumulation of intracellular cAMP and inhibit cytokine transcription.

#### 1) Apremilast

Apremilast is an oral PDE-4 inhibitor, which has been approved in 2015 for the treatment of psoriasis. Apremilast also resulted in significant improvement of the skin condition in atopic dermatitis. In two open-label studies evaluating the safety and efficacy of apremilast in adult

with AD and/or contact dermatitis, modest improvements observed in EASI and IGA scores[23,24].

Not uncommon minor adverse events are headache, nausea, and diarrhea.

Phase II trials for adults with moderate to severe AD is ongoing.

#### 2) Roflumilast

Roflumilast is a topical PDE4 inhibitor that has completed a phase IIa trial in 20 AD patients. The results demonstrate improvement in the primary endpoint of SCORAD index along with improvement in TEWL. The only statistically significant outcome was reduction in pruritus.

#### 3) Crisaborole (Eucrisa)

Crisaborole (AN-2728) is a boron-containing topical PDE4 inhibitor. In the phase IIa adult study, 68 % experienced a decrease in atopic dermatitis severity index(ADSI) in the crisaborole-treated lesion compared with only 20 % in the vehicle-treated lesion 25). The phase IIa open-label study demonstrated that 70 % of subjects achieved an Investigator's Static Global Assessment (ISGA) score of 0 or 1 (clear or almost clear) with crisaborole 26). Crisaborole 2 % is generally well-tolerated, with the most common adverse events is pain on application site. The common side effects of the oral PDE4 inhibitors (nausea, vomiting, and headache) were not observed with topical medication, and serum drug concentration studies show that it is not absorbed systemically to any significant extent. The drug has completed two phase III trials in children and adults with mild to moderate AD They reported that approximately 32 % of patients achieved a score of 0 or 1 in the ISGA as compared with only 18–25 % of vehicle-treated patients.

The FDA approved crisaborole ointment in December 2016 to treat mild-to-moderate AD patients ≥2 years of age. Cisaborole is a novel non-steroidal topical anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that is applied topically twice daily.

### 3. Chemoattractant receptor-homologous molecule 2 (CRTH2) antagonist

Chemoattractant receptor-homologous molecule 2 (CRTH2, $DP_2$) is one of the two receptors that prostaglandin D2 (PGD2) binds to and it mediates its biological actions. CRTH2 is expressed on Th2 cells eosinophils and basophils. It activate and induces chemotaxis of these cell in response to prostaglandin D2 (PGD2). CRTH2 might have an important role in the recruitment of allergic cell types and in driving Th2 cytokine production. Fevipiprant (QAW039), OC459, and BBI-5000 are oral CRTH2 receptor antagonists in development for the treatment of allergic diseases[27].

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). Fevipiprant is still in development for asthma. OC459 (also known as OC000459) is a daily oral medication currently finishing a phase II trial in adult subjects with moderate to severe AD. BBI-5000 is still in phase I trials in healthy adults, with the expectation that the first indication will be AD.

Current studies with emerging new targeting biologic agents in AD have significant implications for the future treatment paradigm of atopic dermatitis. . Biologic therapies might be efficacious alternative in some refractory AD patients. For the personalized tailored approach of AD, biomarkers, endotypes, and genetic background along with clinical characteristics might guide the choosing biologics. Long term efficacy and safety data is of paramount importance for biologic agents.

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