A LITERATURE REVIEW OF BIOLOGICS FOR TREATMENT OF ATOPIC DERMATITIS

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INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease primarily affecting children, particularly those under the age of two. The pathogenesis of atopic dermatitis is multifactorial, characterized by intricate interactions among epidermal barrier dysfunction, immune dysregulation, genetic susceptibility, and environmental influences (Figure 1).

In atopic dermatitis, the integrity of epidermal barrier is compromised, characterized by reduced expression of epidermal structural proteins-particularly filaggrin-and a deficiency of lipids, especially long-chain fatty acids, and ceramides. The disease is also marked by immune dysregulation in the skin, which underlies most emerging targeted therapies. Lesional skin shows infiltration predominantly by CD4+ T cells. When exposed to environmental triggers or mechanical scratching, keratinocytes release chemokines (e.g., CCL17, CCL22), the chemotactic factor TSLP, and interleukins (IL-1β, IL-25, IL-33). These mediators subsequently activate skin-resident type 2 lymphocytes and TH2 cells, leading to the secretion of key pro-inflammatory cytokines, including IL-13 and IL-4.TSLP also activates dendritic cells to express OX40 ligand, which engages with T cells to promote the production of IL-4, IL-5, IL-13, and the pruritus-associated cytokine IL-31. Additionally, IL-36 and its receptor IL-36R are expressed in the skin (and bronchial epithelium) and are often upregulated in atopic dermatitis. Signaling pathways involving Janus kinase (JAK) activation and signal transducer and activator of transcription (STAT) proteins play a critical role in disease pathogenesis, perpetuating a chronic inflammatory loop within lesional skin.

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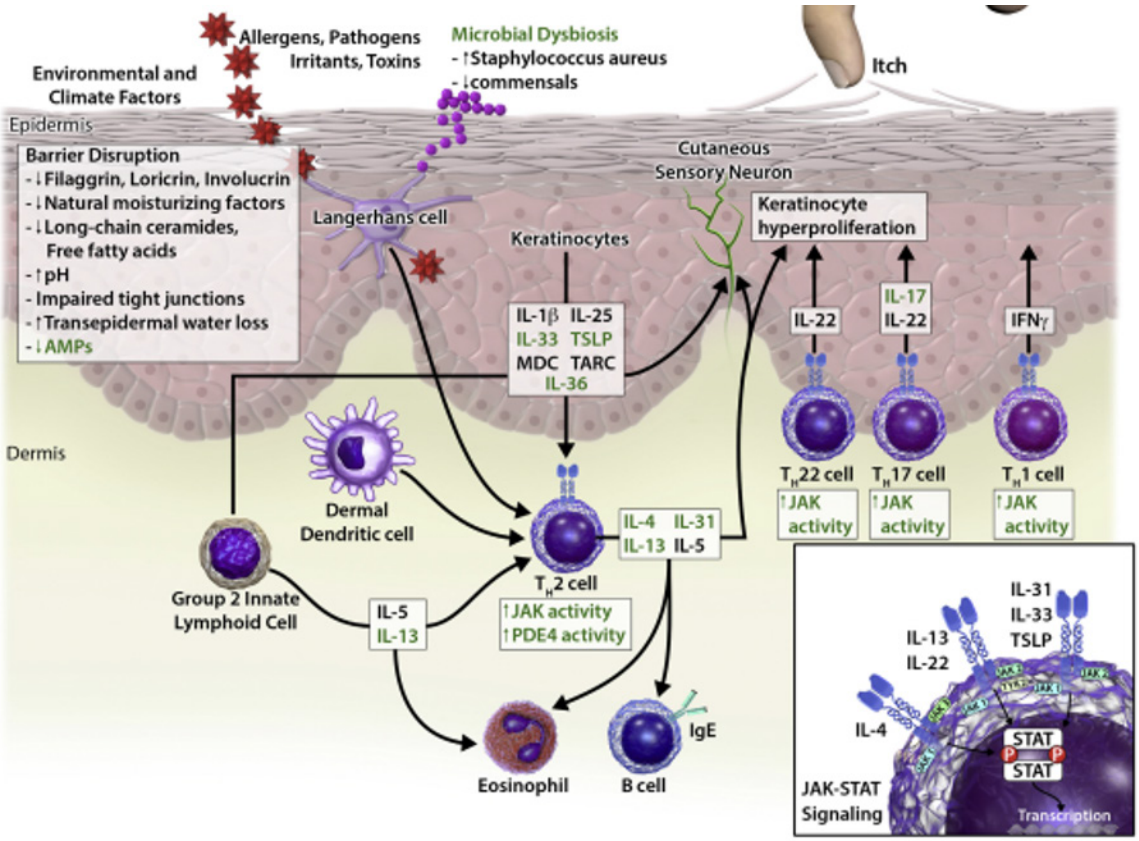

Figure 1. Pathogenesis of atopic dermatitis (Source: N. Puar et al.)

Pruritus in atopic dermatitis is considered a highly characteristic and clinically important feature, as it is not only a consequence of chronic inflammation but also a factor that perpetuates the disease through scratching of lesions. This sensation is primarily detected by unmyelinated C-fibers, which transmit signals to neurons located at the dorsal root ganglion (Figure 2). Exogenous pruritogens from the external environment and endogenous pruritogens released by keratinocytes and immune cells bind to and activate various receptors on pruriceptive sensory neurons, including cytokine receptors, G protein-coupled receptors, and voltage-gated ion channels. Once activated, these receptors trigger action potentials and promote the release of inflammatory mediators. Among them, type 2 cytokines (IL-31, IL-33, and TSLP) can directly stimulate pruriceptive neurons by binding to their respective receptors and activating the JAK-STAT signaling pathway. Activation of the IL-4 receptor alpha (IL-4Rα) on neurons also depends on JAK-STAT signaling. Therefore, targeting these mediators, Th2 cytokines, or their receptors has the potential to both reduce inflammation and suppress pruritus in atopic dermatitis.

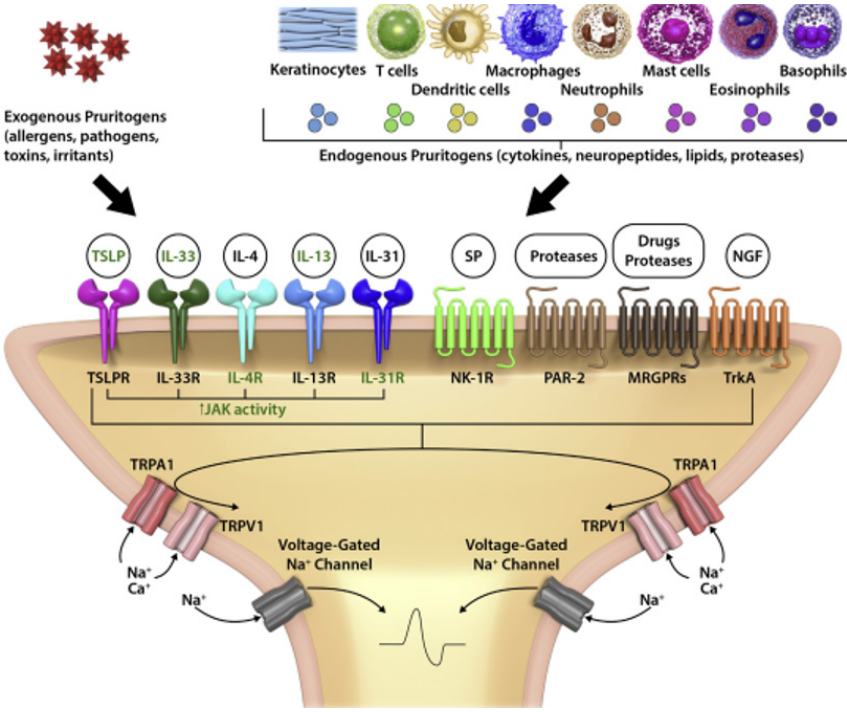

Figure 2. Mechanism of pruritus in atopic dermatitis (Source: N. Puar et al.)

Due to its chronic and relapsing nature, atopic dermatitis significantly impairs patients' quality of life and often requires long-term, multimodal management, including topical agents, systemic therapy, and phototherapy. This is particularly relevant in adults, who may find it challenging to achieve adequate control with topical treatments alone, such as corticosteroids or calcineurin inhibitors. Over time, topical agents may lead to adverse effects and reduced efficacy in severe cases. Consequently, systemic therapy is often necessary to achieve stable disease control, prevent flares, and improve quality of life. However, the long-term efficacy and safety data for conventional systemic agents such as cyclosporine, methotrexate, and azathioprine remain limited, and adverse effects often restrict their use.

Over the past decade, biological therapies have made remarkable advances, offering targeted inhibition of specific inflammatory mediators involved in the pathogenesis of atopic dermatitis. Although only a few biologics have been officially approved for treatment, they represent an auspicious direction for future disease management.

BIOLOGICS FOR TREATMENT OF ATOPIC DERMATITIS

Dupilumab

Dupilumab is the first biologic agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe atopic dermatitis. It is a fully human monoclonal antibody that targets the interleukin-4 alpha receptor (IL-4Rα), thereby inhibiting the signaling of IL-4 and IL-13, two key cytokines involved in the pathogenesis of the disease. Clinical trials have demonstrated that weekly subcutaneous administration of dupilumab at doses of 150 mg or 300 mg significantly improves clinical symptoms in adult patients with moderate to severe atopic

dermatitis, while also reducing serum levels of Th2-related biomarkers, total IgE, and peripheral blood eosinophil counts.

Two randomized, double-blind, placebo-controlled Phase 3 trials (SOLO1 and SOLO2) enrolled 671 and 708 adult patients (aged 18 years or older) with moderate-to-severe atopic dermatitis. Patients were randomized in a 1:1:1 ratio to receive subcutaneous injections for 16 weeks with either: (i) dupilumab 300 mg weekly (after a double loading dose), (ii) placebo, or (iii) dupilumab 300 mg alternating weekly with placebo. Efficacy was assessed using objective clinical endpoints, including EASI, IGA, and SCORAD scores, in all patients treated with dupilumab. Efficacy analyses indicated a dose-dependent response; however, weekly dupilumab 300 mg offered no advantage over administration every two weeks, supporting the approved regimen of 300 mg once every two weeks. Dupilumab has demonstrated sustained efficacy, good tolerability, and long-term safety over 52 weeks, with no dose-limiting toxicities reported in clinical trials. Beyond improving skin lesions, dupilumab provides substantial benefits to patients' quality of life. Clinical improvements are observed as early as one week after treatment initiation, including rapid itch relief, better sleep, enhanced mental health, and improved overall well-being. Among these, itch reduction plays a key role in improving quality of life.

In a 16-week phase 3 trial, adolescents treated with dupilumab monotherapy at 300 mg (≥ 60 kg) or 200 mg (< 60 kg) weekly demonstrated significantly higher response rates compared with placebo: IGA 0/1 (24.4% vs 2.4%), EASI-75 (41.5% vs 8.2%), and pruritus improvement (36.6% vs 4.8%). These findings led to FDA approval of dupilumab for adolescents in March 2019. More recently, a phase 3 dose-finding trial in children aged 6 to < 12 years with severe atopic dermatitis showed that those weighing < 30 kg responded best to 300 mg every 4 weeks (vs 100 mg weekly), while children ≥ 30 kg responded optimally to 200 mg weekly (vs 300 mg every 4 weeks).

In May 2020, the FDA approved dupilumab for children aged 6 to 11 years, with dosing based on body weight. The safety and efficacy of dupilumab have also been described in infants and children aged 6 months to < 6 years with atopic dermatitis. The most common adverse events are localized injection-site reactions. Other reported side effects include conjunctivitis and eosinophilia, generally mild and self-limiting. Some patients developed new-onset or worsening facial erythema that was unresponsive to topical anti-inflammatory agents but improved with increased dupilumab dosing. Psoriasiform dermatitis has also been reported, hypothesized to result from a shift toward Th1/Th17 pathways when Th2 signaling is blocked.

Rituximab

Advances in the knowledge of atopic dermatitis (AD) pathogenesis highlight the central role of T lymphocytes, with B cells also potentially contributing to disease progression. Accordingly, rituximab-a monoclonal antibody targeting CD20 on the surface of B cells-has been considered a potential biologic therapy for AD. Rituximab reduces the number of B cells, thereby decreasing antibody production and the release of inflammatory mediators.

However, current evidence remains limited, derived mainly from case reports and small case series. In one study of six patients receiving intravenous rituximab 1000 mg twice, two weeks apart, all showed improvement in skin symptoms after 4-8 weeks. Conversely, another report of two patients treated with a lower dose (500 mg, two weeks apart) documented slow or absent improvement. Some reports even documented

treatment failure. Thus, the efficacy of rituximab in AD remains controversial, and larger studies are needed to confirm its clinical value.

Ustekinumab

Ustekinumab is a fully human IgG1 monoclonal antibody that specifically binds to the p40 subunit of IL-12 and IL-23, cytokines considered critical in immune-mediated inflammatory diseases. These cytokines promote proliferation of Th17 and Th22 cells, as well as differentiation of naïve T cells into Th1 cells, all of which are implicated in AD pathogenesis alongside the dominant Th2 pathway.

Evidence for ustekinumab in AD is limited and controversial, mostly based on case reports. Puya reported a 21-year-old female patient with severe, treatment-resistant AD who achieved complete clearance of skin lesions and symptoms after 12 months of ustekinumab therapy. Shroff described a 70-year-old woman whose SCORAD decreased from 50 to 0 after 19 weeks, while Fernández-Antón Martínez reported four adult patients with severe AD whose mean SCORAD decreased from 77.8 to 20.2 after 16 weeks. In all these cases, ustekinumab (45 mg) was administered according to the psoriasis regimen, regardless of patient weight.

In contrast, a randomized, double-blind, placebo-controlled phase II trial in 33 patients with moderate-to-severe AD (16 ustekinumab, 17 placebo; crossover at week 16; last dose at week 32) showed higher SCORAD50 responses at weeks 12, 16, and 20 in the ustekinumab group compared with placebo, though the differences were not statistically significant.

In summary, current data suggest that ustekinumab may have potential in AD treatment, but the clinical evidence remains scarce and inconclusive, with no statistically significant efficacy demonstrated in controlled trials. Larger, well-designed studies are required to establish its role.

Omalizumab

Omalizumab is a recombinant monoclonal antibody against the FcεRI, administered subcutaneously. The U.S. FDA has approved this drug for the treatment of severe allergic asthma and chronic spontaneous urticaria. Since atopic dermatitis (AD) may share pathogenic mechanisms with asthma (including elevated serum IgE levels), omalizumab has been considered a potential therapy for severe AD with high IgE levels. Omalizumab promotes polarization of lymphocytes toward type 2 immune responses and suppresses eosinophil-mediated inflammation. Current evidence for omalizumab in AD remains controversial. Its efficacy has mainly been reported in case reports and small case series, with conflicting results. In 2005, Fernandez Anton-Martinez reported nine patients with severe AD treated with 450 mg omalizumab every three weeks; seven of them showed improved quality of life and reduced pruritus. Forman and Garrett described a 41-year-old African-American male with severe AD, previously responsive only to oral corticosteroids, who was successfully treated with a 12-week course of omalizumab. Belloni reported that low-dose omalizumab therapy (10 cycles of 150 mg subcutaneous injections every two weeks) reduced SCORAD by more than 50% in 2/11 (18.2%) patients and by 25 - 50% in 4/11 (36.4%) patients. Omalizumab appeared more effective in patients with concomitant asthma. Zink found a correlation between decreased free IgE levels and clinical improvement in AD when combining topical therapy with omalizumab in ten patients with severe, refractory AD.In contrast, a randomized, double-blind, placebo-controlled trial in 20 adults with AD who received omalizumab (0.016 mg/kg/IgE) for 16 weeks

showed no significant improvement in clinical signs despite substantial changes in IgE levels (reduced free serum IgE, IgE surface expression, and FcεRI, as well as decreased IgE+ cells, but no reduction in FcεRI+ cells in the skin).

The most common side effects of omalizumab are mild, including local injection-site reactions and infections. Anaphylaxis is extremely rare, and there is little to no risk of malignancy. Overall, evidence for omalizumab in AD is inconsistent. The only randomized controlled trial to date failed to demonstrate significant efficacy. Based on limited case series, omalizumab may be useful for severe, refractory AD, particularly in patients with concomitant asthma.

IL-13 Inhibitors

Lebrikizumab is a promising agent that binds soluble IL-13, preventing its interaction with the IL-13α receptor (IL-13Rα) and IL-4Rα. In a phase 2 dose-finding study, lebrikizumab 250 mg every two weeks by subcutaneous injection demonstrated superior efficacy compared with placebo, achieving IGA 0/1 (44.6% vs 15.3%), EASI-75 (60.6% vs 24.3%), and ≥ 4-point improvement in pruritus NRS (70% vs 27.3%). Lebrikizumab was associated with slightly higher rates of injection-site pain (5.3% vs 1.9%) and conjunctivitis (2.7% vs 0%), but lower rates of skin infections compared with placebo.

Tralokinumab is another novel drug that binds IL-13, blocking its interaction with both IL-13Rα1 and IL-13Rα2. In a phase 3, 16-week monotherapy study, adults receiving tralokinumab 300 mg every two weeks achieved IGA 0/1 rates of 15.8% and 22.2% compared with 7.1% and 10.9% in the placebo group. EASI-75 response rates were higher (25% and 33.2% vs 12.7% and 11.4%), as were ≥ 4-point improvements in pruritus NRS (20% and 25% vs 10.3% and 9.5%). Injection-site reactions (7.1% vs 2%) and conjunctivitis (3% vs 1.5%) occurred more frequently than with placebo.

IL-31 Inhibitor

Nemolizumab targets the IL-31 receptor, which is considered a key mediator of pruritus in AD pathogenesis. In a 12-week phase 2a study, patients treated with nemolizumab 0.5 mg/kg every four weeks showed a 59.8% reduction in itch compared with 20.9% in the placebo group. In a 24-week phase 2b dose-finding trial, nemolizumab 30 mg (equivalent to 0.5 mg/kg) every four weeks, combined with topical corticosteroids, significantly reduced sleep disturbance NRS (74.8% vs 43%) and EASI (68.8% vs 52.1%) at week 24. Reported adverse events included elevated creatinine phosphokinase (CPK) and increased rates of mild asthma exacerbations in patients with pre-existing asthma (12.3% with nemolizumab vs 1.8% with placebo).

Other Cytokine and Receptor Targets (OX40, TSLP, IL-33, IL-36, IL-5, Th17/IL-22 Pathway)

GBR 830, an anti-OX40 antibody targeting the Th2 pathway, was administered as two intravenous doses of 10 mg/kg four weeks apart in a phase 2a adult trial. By day 71, GBR 830 significantly reduced epidermal thickness and expression of several mRNA and other biomarkers compared with placebo (67.4% vs 38.2%). Mild side effects were observed; some patients developed skin infections at biopsy sites.

Tezepelumab, a TSLP inhibitor given at 280 mg every two weeks, showed numerical improvement but did not achieve significant EASI-50 differences compared with placebo.

Etokimab, an IL-33 inhibitor, was evaluated in a 16-week study but failed to meet its primary endpoint of significant EASI improvement versus placebo and is no longer pursued for AD.

Mepolizumab (anti-IL-5), *Spesolimab* (IL-36 receptor inhibitor, intravenous every four weeks with future subcutaneous trials planned), and *ARGX112* (anti-IL-22, phase 1 trial) are under investigation.

CONCLUSIONS

Advances in the understanding of AD mechanisms and key immunologic pathways have accelerated the development of targeted biologic therapies. With the emergence of effective agents with fewer side effects, biologics hold promise as an important treatment option for severe, refractory AD. However, only dupilumab has been officially approved by the FDA for moderate-to-severe AD in patients aged six years and older. Future clinical trials of other targeted therapies may provide new and effective options for disease control.

REFERENCES

1. Puar N, Chovatiya R, Paller AS. New treatments in atopic dermatitis. *Annals of Allergy, Asthma & Immunology*. 2021;126(1):21-31. doi:10.1016/j.anai.2020.08.016.
2. Bußmann C, Novak N. Systemic therapy of atopic dermatitis. *Allergol Select*. 2017;1(1):1-8. doi:10.5414/ALX01285E.
3. Megna M, Napolitano M, Patruno C, et al. Systemic Treatment of Adult Atopic Dermatitis: A Review. *Dermatol Ther (Heidelb)*. 2016;7(1):1-23. doi:10.1007/s13555-016-0170-1
4. Werfel T, Heratizadeh A, Aberer W, et al. Update "Systemic treatment of atopic dermatitis" of the S2k guideline on atopic dermatitis. *J Dtsch Dermatol Ges*. 2021;19(1):151-168. doi:10.1111/ddg.14371.
5. Deleanu D, Nedelea I. Biological therapies for atopic dermatitis: An update. *Exp Ther Med*. 2019;17(2):1061-1067. doi:10.3892/etm.2018.6989.
6. Fabbrocini G, Napolitano M, Megna M, Balato N, Patruno C. Treatment of Atopic Dermatitis with Biologic Drugs. *Dermatol Ther (Heidelb)*. 2018;8(4):527-538. doi:10.1007/s13555-018-0258-x.