

Biologics in the Management of Severe Atopic Dermatitis

Mohammed Al Abadie^{1*}, Zinah Sharara^{2*} and Sami Al Abadie^{3*}

¹North Cumbria integrated care NHS Foundation Trust, Clinical Director & Consultant Dermatologist, and UCLAN medical School. United Kingdom.

²National Health Service (NHS), Community Dermatology Clinics (Health Harmonie). United Kingdom.

³Royal School of Wolverhampton. United Kingdom

*Corresponding Author

Professor Mohammed Al Abadie PhD FRCP. North Cumbria integrated care NHS Foundation Trust, Clinical Director & Consultant Dermatologist, and UCLAN medical School. United Kingdom.

Submitted: 2023 Sep 15; Accepted: 2023 Oct 25; Published: 2023 Nov 05

Citation: Abadie M Al., Sharara, Z., Abadie S Al. (2023). Biologics in the Management of Severe Atopic Dermatitis. *Int J Clin Expl Dermatol*, 8(2), 49-55.

Abstract

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, it is presented with heterogeneous clinical phenotypes that can alter by severity, age, and ethnic background. The chronic nature of AD necessitates safer, and newer treatment that is effective in improving quality of life [1]. A new era of therapeutics is in innovation phase including Biologic treatment and it is essential to provide a comprehensive understanding of this modality of treatment. Hence, this review presents an overview of up to date biologics that are approved or are in development for the treatment of AD.

Keywords: Atopic Dermatitis, Biologic Therapy, EASI

Introduction

Treatment of mild dermatitis mostly starts with topical therapies primarily various strength of topical corticosteroids (TCSs), topical calcineurin inhibitors which are tacrolimus and pimecrolimus and the phosphodiesterase 4 (PDE4) inhibitor crisaborole. Management of severe forms of AD is mainly maintained by ultraviolet light and available conventional immunosuppressants which are ciclosporin, methotrexate, azathioprine, and mycophenolate mofetil. An expanded therapeutic pathway has developed with novel therapies as biologics, janus kinase inhibitors and other potential therapeutic agents that mainly target the T helper (Th) 22 and Th17/IL23 pathways among others. Which have provided an advanced milestone of the management of atopic dermatitis [2].

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) and the European Commission (EC) has recently approved 2 biologics for the treatment of moderate-to-severe atopic dermatitis in adult patients who are eligible for systemic therapy [3].

Dupilumab

Dupilumab (Dupixent®) was the first approved biologic treatment for the management of AD. On March 28, 2017, the FDA approved dupilumab. In the UK, this biologics was approved on the 1st August 2018 as an option for the treatment of moderate-to-severe AD in adults only if there is a lack of response to at least 1 other systemic therapy, such as, ciclosporin, azathioprine, methotrexate, or mycophenolate mofetil, or if these immunosuppressants are contraindicated or cannot be tolerated [4, 5].

Dupilumab is a monoclonal IgG antibody that has high affinity to the α -subunit of the interleukin (IL)-4 receptor, thus it inhibit the signaling pathways of type 2 inflammatory cytokines; IL-4 and IL-13 [6]. (figure -1, 2) [7].

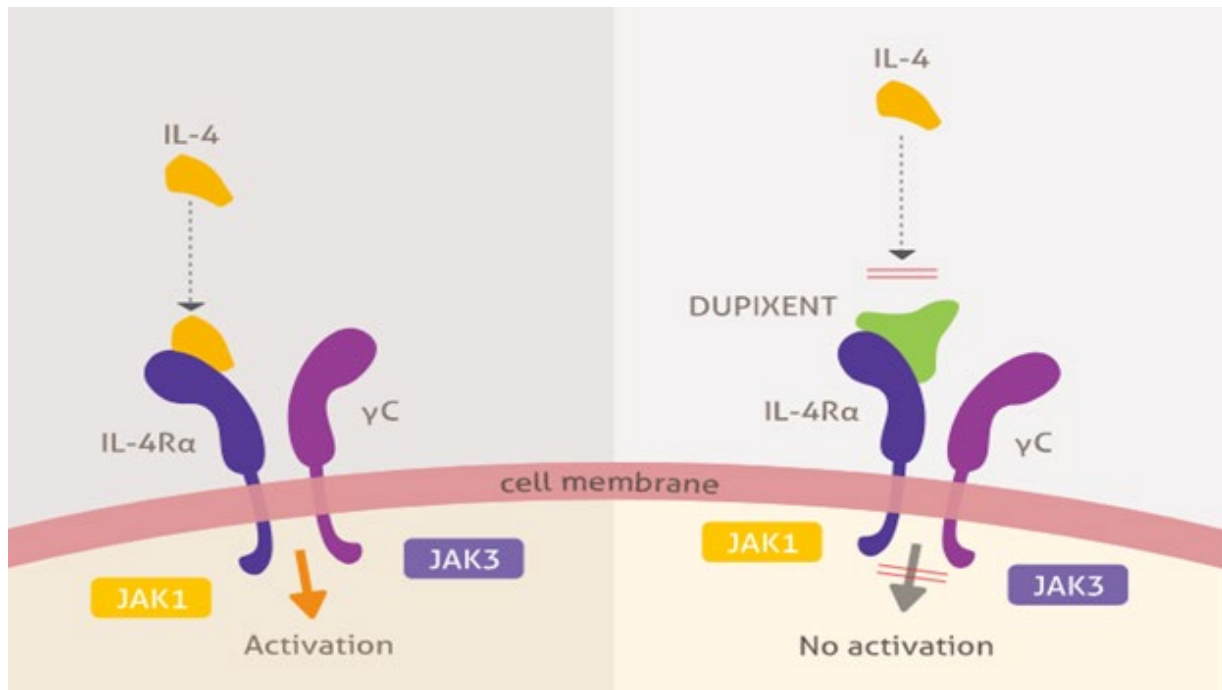


Figure 1: Dupixent® inhibits the signaling of IL-4 via the Type 1 and 2 receptors for IL-4 (adapted from <https://www.dupixent.co.uk>)

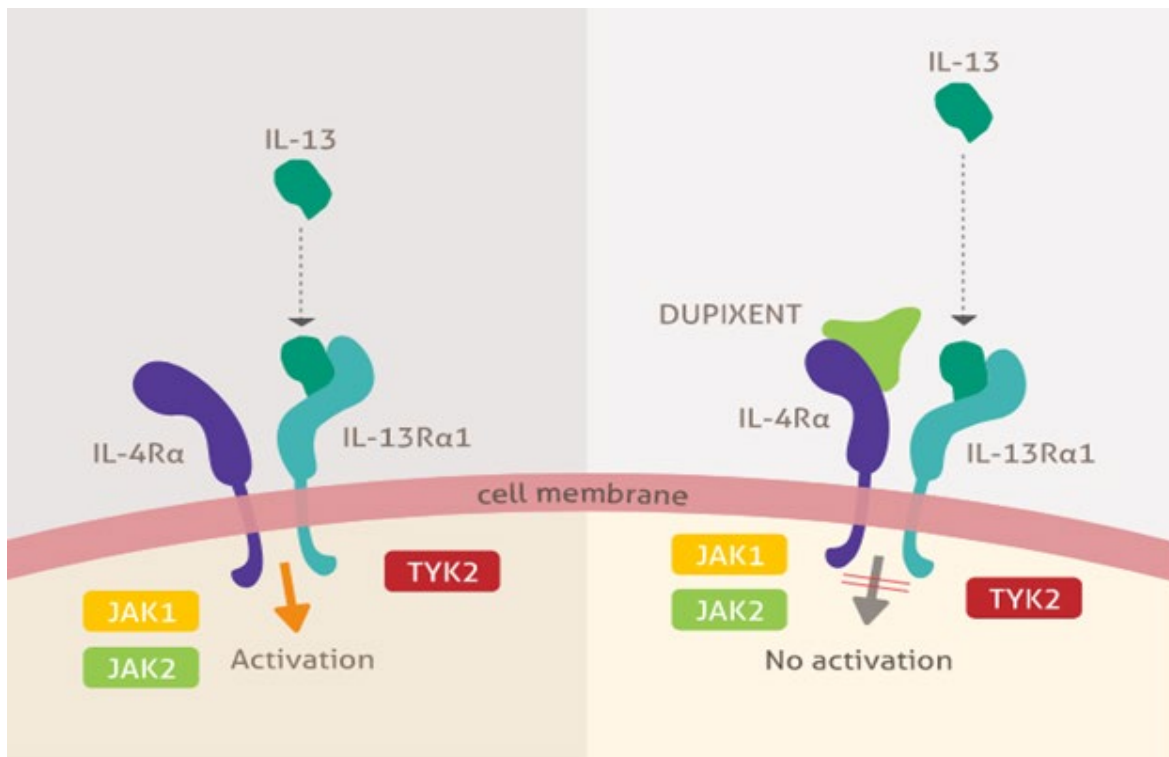


Figure 2 : Dupixent® inhibits IL-13 signaling via the Type 2 receptor for IL-13 (Adapted from <https://www.dupixent.co.uk>)

The efficacy and tolerability of dupilumab have been demonstrated in numerous randomized controlled trials.

In two phase 3 monotherapy trials (SOLO1 and SOLO2), 671 patients with moderate-to-severe AD treated with 300 mg of subcutaneous dupilumab 300 mg or placebo for 16 week in two different regimens; every week (qw) or every other week (q2w), after which 36% of dupilumab treated subjects in the both groups had achieved complete or almost complete symptom clearance compared to 9% in the placebo group. In SOLO 1, the primary outcome occurred in (38%) receiving dupilumab every other week and in (37%) receiving weekly dupilumab, as compared with (10%) improvement in the group receiving placebo. The results were similar in SOLO 2, with the primary outcome occurring in (36%) in both dupilumab regimen which is significantly better as compared with (8%) receiving placebo [8].

In (LIBERTY AD CHRONOS) a randomised, double-blinded, placebo-controlled, phase 3 study, adults with moderate-to-severe atopic dermatitis were administered subcutaneous dupilumab 300 mg once weekly (qw), 300 mg every 2 weeks (q2w), or placebo, in which all subjects were also allowable to apply topical glucocorticosteroids (TCS) and/or topical calcineurin inhibitors (TCI).

After 16 weeks, 39% of the dupilumab treated subjects achieved the coprimary endpoints of IGA 0/1 vs. 12% in the placebo group. EASI-75 was achieved by 64% (dupilumab qw + TCS/TCI) and 69% (dupilumab q2w + TCS/TCI) vs. 23% (placebo + TCS/TCI). On 52-week time, improvement was maintained. The most common side effects of dupilumab treated group were Injection-site reactions and conjunctivitis [9].

Further analysis of the clinical laboratory findings from the above three trials (LIBERTY AD SOLO 1 & 2 and LIBERTY AD CHRONOS), were published to depict the safety of dupilumab. It was concluded that treatment groups had similar results in baseline laboratory parameters and treatment with dupilumab do not require routine laboratory monitoring in clinical practice as there were no clinically meaningful changes observed between treatment groups in any laboratory parameters tested [10].

Recent metanalysis, in which twenty-two randomized studies involving 3303 patients with atopic dermatitis treated by subcutaneous dupilumab for 16 weeks, in which data analysis revealed that the mean reduction in EASI score was 69.6%. The pooled percentages of patients achieving 50%, 75%, and 90% EASI score improvement was 85.1%, 59.8%, and 26.8%, respectively. The most common side effect reported was Conjunctivitis in a proportion of 26.1% [11].

Dupilumab also studied in younger children (≥ 6 months to < 6 years), the safety and efficacy of dupilumab after a single dose was proved. The pediatric patients received either 3 mg/kg or 6 mg/kg BW. The EASI reduction was 44.6% in the 3 mg/kg group and 49.7% in the 6 mg/kg group after 3 weeks. An EASI-75 was achieved by 30% and 20%, respectively. Slightly better responses

were noticed in older than in younger age group. At week 4, all groups showed a diminished response mostly in the low dose group [12].

Tralokinumab

Tralokinumab (Adtralza®) is a fully human IgG4 monoclonal antibody that specifically neutralise IL-13; which is the main cytokine in lesional atopic dermatitis skin. Levels of IL-13 have been correlated with disease severity [13, 14, 15], [1, 3, 4]. skin-barrier function is also impaired by the over-expression of IL-13 cytokine due to the down regulation filaggrin and loricrin among other several proteins essential for skin-barrier function [9]. IL-13 can also promote and amplifies the Type 2 inflammation by recruiting eosinophils and activated T-cells. Moreover IL-13 raises the risk of infection and predisposes the skin to *Staphylococcus aureus* colonization and by decrease the keratinocyte antimicrobial peptide production [16].

Recently, IL-13 cytokine has been found to be the dominant cytokine in lesional atopic dermatitis skin and in addition, levels of IL-13 (mRNA and protein) have been shown to correlate with disease severity [17] [4–6]. IL-13 also promotes the recruitment of eosinophils and activated T-cells, which amplifies the Type 2 inflammation [11]. Furthermore, by reducing the keratinocyte antimicrobial peptide production, IL-13 predisposes the skin to *Staphylococcus aureus* colonization and raises the risk of infection [11].

(anti-IL-13 antibody) Tralokinumab (Adtralza®), an interleukin-13 antibody, was approved by The UK's Medicines and Healthcare products Regulatory Agency (MHRA) and the European Commission (EC) for the treatment of moderate-to-severe atopic dermatitis in adult patients who are eligible for systemic therapy. Tralokinumab specifically neutralizes the biological activity of IL-13, which is an important cytokine driver of type II skin inflammation, by inhibiting its binding to IL-13R α 1 and IL-13R α 2 [18].

Tralokinumab will be available in a 150mg/mL prefilled syringe for subcutaneous injection with an initial dose of 600mg followed by 300mg every other week and it can be used with or without topical corticosteroids.

In a phase 3, controlled trial, subcutaneous tralokinumab 300 mg, every 2 weeks and TCS as needed were administered over 16 weeks., The EASI-75 improvement were: 56•0% vs. 35•7% and IGA 0/1: 38•9% vs. 26•2% for tralokinumab versus placebo respectively. At week 32, in the tralokinumab group, 30.5% of patients achieved IGA 0/1, and 55•8% achieved EASI-75 [19].

In two 52-week, randomized, double-blind, placebo-controlled, phase 3 trials, ECZTRA 1 and ECZTRA 2, adults with moderate-to-severe AD were randomized (3: 1) to subcutaneous tralokinumab 300 mg every 2 weeks (Q2W) or placebo. At week 16, in both trials, patients treated with tralokinumab achieved significant improvement in IGA score of 0/1(15.8% vs. 7.1% in ECZTRA 1)

and (22.2% vs. 10.9% in ECZTRA 2), in regard to EASI 75 it was also more significantly than placebo group (25.0% vs. 12.7% in ECZTRA 1 and 33.2% vs. 11.4% in ECZTRA 2. The majority of week 16 tralokinumab responders did maintain response at week 52 with continued tralokinumab treatment without any other therapy [20].

Conjunctivitis and upper respiratory tract infection were more often reported with tralokinumab than placebo, however Tralokinumab has an acceptable safety profile, and showed side effects in a comparable pattern to placebo in both studies.

In Phase 2 b study, in which patients received 3 doses of Tralokinumab with concomitant topical glucocorticoids, the EASI was evaluated at the end of 12 weeks. 300 mg of tralokinumab significantly improved change from baseline, moreover, SCORAD, DLQI, and pruritus numeric rating scales, were also improved as compared to placebo. Upper respiratory tract infection was the most frequent treatment-emergent adverse in both groups [21].

In a phase 2b randomized, placebo controlled study, tralokinumab was administered each 2 weeks, and by the end of 12 weeks and one daily class III topical corticosteroid cream or ointment from the run-in to end of follow-up, total Dermatology Life Quality Index was significantly improved in the subcutaneous tralokinumab treated subjects as compared to placebo [22].

In a phase 2, double-blind, randomized, placebo-controlled trial that took place over 30 weeks the safety of tralokinumab 300 mg given over 16 weeks was evaluated in relation its effect on immune responses towards Tdap (tetanus/diphtheria/pertussis) and meningococcal vaccines at week 12. tralokinumab was well tolerated when administered concomitantly with the vaccines and demonstrated a safety profile comparable to phase 3 trials [23].

In a phase 1, single-blind, randomized, placebo-controlled, single ascending-dose study assessed the safety, tolerability, pharmacokinetics (PK), and immunogenicity of subcutaneous tralokinumab (150, 300, or 600 mg) in thirty healthy Japanese adults. Injection-site pain was the most common side effect and the severity was shown in dose dependent pattern. A post-hoc pooled population PK modeling analysis, incorporating pharmacokinetic data from this study, demonstrated that Japanese individuals had greater systemic exposure to tralokinumab than non-Japanese individuals. This difference was not clinically relevant [24].

Lebrikizumab

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-4R α and IL-13R α 1, thereby inhibiting signal transduction [25, 26]. Figure (3)

A total of 280 patients; were randomized receive lebrikizumab with three different dosages of (125 mg every 4 weeks (n=73), 250 mg every 4 weeks (n=80), or 250 mg every 2 weeks (n=75) and response were compared to placebo (n=52)

The best clinical response for the primary end point (percentage change in EASI) was achieved with 250 mg of lebrikizumab group. The results showed dose-dependent, statistically significant improvement in the primary end point vs placebo at week 16: 125 mg every 4 weeks (–62.3% [37.3%], P=.02), 250 mg every 4 weeks (–69.2% [38.3%], P=.002), and 250 mg every 2 weeks (–72.1% [37.2%], P<.001). This response was reflected by a prompt improvement in the pruritus NRS.

The side effect was reported in both placebo patients and in lebrikizumab treated subjects and most were mild to moderate and did not lead to discontinuation. The rate of conjunctivitis was low, and the medication was well tolerated [27].

Etokimab

IL-33 is one of the a key cytokine in type 2 inflammation, it has a key role in activation of Th2 and ILC2 by inducing IL-4, IL-5 and IL-13 and modulating mast cell degranulation. IL-33 is highly expressed in skin of atopic dermatitis patients with active disease [28].

Etokimab (ANB020) is a humanized anti-human IL-33 monoclonal antibody. A phase 2a clinical trial in what is called Proof of concept study has resulted in significant improvement in EASI when treated with Etokimab as compared to placebo. Moreover, itch scores (SCORAD), Dermatology Life Quality Index (DLQI scores), and Investigator Global Assessment (IGA) score 0/1 achievement are all proven satisfactory. Side effects were mild and headache in 25% of the etokimab arm versus dizziness in 17% of the placebo group. The medication was well tolerated. In ATLAS trial, which is another phase 2b randomized, double-blinded, placebo controlled, multidose study, 300 patients with moderate-to-severe atopic dermatitis were treated with etokimab (ANB020) for 16 weeks (ClinicalTrials.gov Identifier: NCT03533751). Each of the etokimab dosing regimen failed to meet the primary endpoint at week 16 [29].

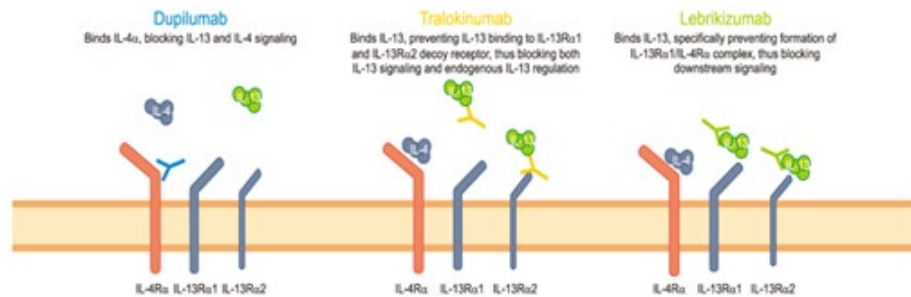


Figure 3: Mechanism of action of Dupilumab, Tralokinumab and Lebrikizumab [30].

Nemolizumab

Nemolizumab has affinity to the α -subunit of the IL-31 receptor, hence inhibiting the action of IL-31, which involve pruritus, pro-inflammatory, and barrier-regulatory function [31].

In a 12-week phase 2 study, 264 patients were evaluated after administration of subcutaneous Nemolizumab (0.1, 0.5, or 2.0 mg/kg BW q4w or 2.0 mg/kg BW q8w) versus placebo. The visual analogue scale (VAS) for pruritus was the primary end point and measured at week 12, and was significant for treatment groups. The most common adverse reactions were exacerbation of AD, nasopharyngitis, and upper respiratory tract infections, however not statistically significant difference with the placebo group [32]. A long-term-extension 64-week study was completed by 153 patients (part B), in which itch reduction from baseline to week 64 was highest in the group receiving 0.5 mg nemolizumab per kg BW (–89.6%); a –73.0% reduction was seen with 0.1 mg/kg nemolizumab, –74.7% with 2.0 mg/kg q4w, and –79.1% with 2.0 mg/kg q8w. The EASI reduction was –68.5%, –75.8%, –78.9%, and –69.3% in the 0.1 mg/kg, 0.5mg/kg, 2 mg/kg q4w, and 2 mg/kg q8w groups, respectively. No new adverse events were noted [33].

In another phase 2 study, patients were randomised to three different doses of Nemolizumab (10, 30 or 90 mg) and were compared to placebo for treatment period of 24 weeks during which, the use of topical steroids was allowed. The study confirmed that 30-mg dosage was most effective. The EASI reduction was more significant in the treatment group than the placebo. Moreover, 36.8% of patients treated with 30 mg Nemolizumab achieved an IGA 0/1 compared to 21.1% of patients in the placebo arm at week 24. Visual scale analysis (VAS) was also used as a measure of peak pruritus and has shown to be reduced significantly in the 30-mg nemolizumab group at week 24 compared to the placebo group. The most common side effect were nasopharyngitis and upper respiratory tract infections [34].

For the above study, further post-hoc analysis was done by researchers on the subpopulation of patients with EASI ≥ 16 who involved 83.9% of all study patients, to compare 30 mg Nemolizumab to placebo. Mean EASI score at week 16 was improved by 68.6% reduction in the Nemolizumab group as compared with 42.6% in the placebo group ($P = 0.002$). Moreover, (EASI 75) and (EASI 90) were achieved more likely and significantly with Nemolizumab treated group than placebo. Other primary end points were analysed, these are IGA success rates (score of 0/1) that proven significantly greater in 30 mg Nemolizumab than the placebo, among other primary end points like reduction in AD-involved BSA, reduction in itch, and sleep improvement [35].

In phase 3, a randomised phase 3, placebo-controlled trial; subcutaneous nemolizumab was evaluated in a dose of 60 mg each 4 weeks until week 16; during which the application of topical therapy was permitted. The mean reduction in EASI in the nemolizumab group was –45.9% vs. –33.2% in the placebo group. The mean pruritus score at baseline was 75 (scale of 0 – 100, with higher scores indicating more pruritus). At week 16, there was a significant reduction in the score for Nemolizumab as compared to placebo group (–42.8% versus –21.4%) [36].

Other monoclonal antibodies are undergoing research in AD:

OX40-OX40L axis blockers have different results, this is achieved by using 2 antibodies:

- 1) GBR 830; a humanized monoclonal antibody against OX40 which is a costimulatory receptor expressed by activated T cells. This approach resulted in improved clinical outcomes in a phase 2a study, and determined significant progressive reductions in Th1, Th2, Th17/Th22 mRNA expression in lesional AD skin [37].
- 2) KHK4083, a fully human anti-OX40 monoclonal antibody, A phase 2 study results has been released and statistically significant improvements of EASI was maintained as compared to the baseline at 16 weeks, the treatment was also effective and safe in a phase 1 study in patients with moderate-to-severe AD [38].

Anti-IL-22 monoclonal antibody: Phase 2a study of fezakinumab,

showed potential effective results compared to placebo, especially in patients with severe AD and particularly in those with high levels of IL-22 [39].

Tezepelumab, anti-TSLP monoclonal antibody, in combination with topical steroids did not show efficacy in adults with moderate to severe AD in a phase 2 study [40].

Conclusion

There are two approved biologics for treatment of atopic dermatitis; dupilumab and tralokinumab, while many other biologics targeting cytokines of type 2 inflammation are in an advanced phase of clinical research. With the unmet needs from the patient's perspective, the application of these medication could influence on the atopic march and other comorbidities. Although biologics are well tolerated, their benefit–risk ratio represents a significant question for pharmacovigilance and further research is mandated to elucidate their safety and effectiveness.

Acknowledgment

Thanks for Hanna Evens for helping with the manuscript.

References

1. Yew, Y. W., Thyssen, J. P., & Silverberg, J. I. (2019). A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *Journal of the American Academy of Dermatology*, 80(2), 390-401.
2. Goh MS, Yun JS, Su JC. Management of atopic dermatitis: a narrative review. *Medical Journal of Australia*. 2022 Jun 20;216(11):587-93.
3. Gov.Uk. Retrieved from <https://www.gov.uk/drug-safety-update/dupilumab-dupixentv-risk-of-ocular-adverse-reactions-and-need-for-prompt-management>.
4. Selondonccg.nhs.uk. 2022. Retrieved from: https://selondonccg.nhs.uk/wp-content/uploads/dlm_uploads/2021/09/Atopic-dermatitis-%E2%80%93-dupilumab-pathway-FINAL-June-2021.pdf.
5. Nice.org.uk. Available from: <https://www.nice.org.uk/guidance/ta534/resources/dupilumab-for-treating-moderate-to-severe-atopic-dermatitis-pdf-82606900940485>.
6. Guttman-Yassky, E., Bissonnette, R., Ungar, B., Suárez-Fariñas, M., Ardeleanu, M., Esaki, H., ... & Hamilton, J. D. (2019). Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology*, 143(1), 155-172.
7. Dupixent Information for Healthcare Professionals [Internet]. Dupixent.co.uk. 2022 [cited 28 March 2022]. Available from: <https://www.dupixent.co.uk/>
8. Simpson, E. L., Bieber, T., Guttman-Yassky, E., Beck, L. A., Blauvelt, A., Cork, M. J., ... & Ardeleanu, M. (2016). Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *New England Journal of Medicine*, 375(24), 2335-2348.
9. Blauvelt, A., de Bruin-Weller, M., Gooderham, M., Cather, J. C., Weisman, J., Pariser, D., ... & Shumel, B. (2017). Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 389(10086), 2287-2303.
10. Wollenberg, A., Beck, L. A., Blauvelt, A., Simpson, E. L., Chen, Z., Chen, Q., ... & Ardeleanu, M. (2020). Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). *British Journal of Dermatology*, 182(5), 1120-1135.
11. Halling, A. S., Loft, N., Silverberg, J. I., Guttman-Yassky, E., & Thyssen, J. P. (2021). Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, 84(1), 139-147.
12. Paller, A. S., Siegfried, E. C., Simpson, E. L., Cork, M. J., Lockshin, B., Kosloski, M. P., ... & Bansal, A. (2021). A phase 2, open-label study of single-dose dupilumab in children aged 6 months to < 6 years with severe uncontrolled atopic dermatitis: pharmacokinetics, safety and efficacy. *Journal of the European Academy of Dermatology and Venereology*, 35(2), 464-475.
13. Newsom, M., Bashyam, A. M., Balogh, E. A., Feldman, S. R., & Strowd, L. C. (2020). New and emerging systemic treatments for atopic dermatitis. *Drugs*, 80, 1041-1052.
14. Wollenberg, A., Blauvelt, A., Guttman-Yassky, E., Worm, M., Lynde, C., Lacour, J. P., ... & ECZTRA 1 and ECZTRA 2 study investigators. (2021). Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British Journal of Dermatology*, 184(3), 437-449.
15. EMA, E. H. (2022). CHMP/559383/2017< https://www.ema.europa.eu/en/documents/assessment-report/imraldi-epar-public-assessment-report_en.pdf>(2017). Accessed April.
16. Bieber, T. (2020). Interleukin-13: targeting an underestimated cytokine in atopic dermatitis. *Allergy*, 75(1), 54-62.
17. Tsoi, L. C., Rodriguez, E., Degenhardt, F., Baurecht, H., Wehkamp, U., Volks, N., ... & Weidinger, S. (2019). Atopic dermatitis is an IL-13–dominant disease with greater molecular heterogeneity compared to psoriasis. *Journal of Investigative Dermatology*, 139(7), 1480-1489.
18. Popovic, B., Breed, J., Rees, D. G., Gardener, M. J., Vinall, L. M. K., Kemp, B., ... & May, R. D. (2017). Structural characterisation reveals mechanism of IL-13-neutralising monoclonal antibody tralokinumab as inhibition of binding to IL-13Rα1 and IL-13Rα2. *Journal of molecular biology*, 429(2), 208-219.
19. Silverberg, J. I., Toth, D., Bieber, T., Alexis, A. F., Elewski, B. E., Pink, A. E., ... & ECZTRA 3 study investigators. (2021). Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *British Journal of Dermatology*, 184(3), 450-463.
20. Wollenberg, A., Blauvelt, A., Guttman-Yassky, E., Worm,

- M., Lynde, C., Lacour, J. P., ... & ECZTRA 1 and ECZTRA 2 study investigators. (2021). Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British Journal of Dermatology*, 184(3), 437-449.
21. Wollenberg, A., Howell, M. D., Guttman-Yassky, E., Silverberg, J. I., Kell, C., Ranade, K., ... & van der Merwe, R. (2019). Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *Journal of Allergy and Clinical Immunology*, 143(1), 135-141.
 22. Silverberg, J. I., Guttman-Yassky, E., Gooderham, M., Worm, M., Rippon, S., O'Quinn, S., ... & Wollenberg, A. (2021). Health-related quality of life with tralokinumab in moderate-to-severe atopic dermatitis: a phase 2b randomized study. *Annals of Allergy, Asthma & Immunology*, 126(5), 576-583.
 23. Merola, J. F., Bagel, J., Almgren, P., Röpke, M. A., Lophaven, K. W., Vest, N. S., & Grewal, P. (2021). Tralokinumab does not impact vaccine-induced immune responses: results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *Journal of the American Academy of Dermatology*, 85(1), 71-78.
 24. Baverel, P., She, D., Piper, E., Ueda, S., Yoshioka, T., Faggioni, R., & Gevorkyan, H. (2018). A randomized, placebo-controlled, single ascending-dose study to assess the safety, tolerability, pharmacokinetics, and immunogenicity of subcutaneous tralokinumab in Japanese healthy volunteers. *Drug Metabolism and Pharmacokinetics*, 33(3), 150-158.
 25. May, R. D., & Fung, M. (2015). Strategies targeting the IL-4/IL-13 axes in disease. *Cytokine*, 75(1), 89-116.
 26. Ultsch, M., Bevers, J., Nakamura, G., Vandlen, R., Kelley, R. F., Wu, L. C., & Eigenbrot, C. (2013). Structural basis of signaling blockade by anti-IL-13 antibody lebrikizumab. *Journal of molecular biology*, 425(8), 1330-1339.
 27. Guttman-Yassky, E., Blauvelt, A., Eichenfield, L. F., Paller, A. S., Armstrong, A. W., Drew, J., ... & Simpson, E. L. (2020). Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA dermatology*, 156(4), 411-420.
 28. Chen, Y. L., Gutowska-Owsiak, D., Hardman, C. S., Westmoreland, M., MacKenzie, T., Cifuentes, L., ... & Ogg, G. (2019). Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. *Science translational medicine*, 11(515),
 29. AnaptysBio. Retrieved from <https://ir.anaptysbio.com/news-releases/news-release-details/anaptysbio-reports-tokimab-atlas-phase-2b-clinical-trial>.
 30. Ahn, J., Choi, Y., & Simpson, E. L. (2021). Therapeutic new era for atopic dermatitis: part 1. *Biologics. Annals of Dermatology*, 33(1), 1.
 31. Nakashima, C., Otsuka, A., & Kabashima, K. (2018). Interleukin-31 and interleukin-31 receptor: new therapeutic targets for atopic dermatitis. *Experimental Dermatology*, 27(4), 327-331.
 32. Ruzicka, T., Hanifin, J. M., Furue, M., Pulka, G., Mlynarczyk, I., Wollenberg, A., ... & Kabashima, K. (2017). Anti-interleukin-31 receptor A antibody for atopic dermatitis. *New England Journal of Medicine*, 376(9), 826-835.
 33. Ruzicka, T., Hanifin, J. M., Furue, M., Pulka, G., Mlynarczyk, I., Wollenberg, A., ... & Kabashima, K. (2017). Anti-interleukin-31 receptor A antibody for atopic dermatitis. *New England Journal of Medicine*, 376(9), 826-835.
 34. Silverberg, J. I., Pinter, A., Pulka, G., Poulin, Y., Bouaziz, J. D., Wollenberg, A., ... & Clucas, A. (2020). Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *Journal of Allergy and Clinical Immunology*, 145(1), 173-182.
 35. Silverberg, J. I., Pinter, A., Alavi, A., Lynde, C., Bouaziz, J. D., Wollenberg, A., ... & Piketty, C. (2021). Nemolizumab is associated with a rapid improvement in atopic dermatitis signs and symptoms: subpopulation (EASI $\geq$ 16) analysis of randomized phase 2B study. *Journal of the European Academy of Dermatology and Venereology*, 35(7), 1562-1568.
 36. Kabashima, K., Matsumura, T., Komazaki, H., & Kawashima, M. (2020). Trial of nemolizumab and topical agents for atopic dermatitis with pruritus. *New England Journal of Medicine*, 383(2), 141-150.
 37. Guttman-Yassky, E., Pavel, A. B., Zhou, L., Estrada, Y. D., Zhang, N., Xu, H., ... & Wolff, G. (2019). GBR 830, an anti-OX40, improves skin gene signatures and clinical scores in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology*, 144(2), 482-493.
 38. Agree, I. AMGEN TO PRESENT NEW, POSITIVE CLINICAL AND REAL-WORLD DATA ACROSS INFLAMMATION PORTFOLIO AT EADV 2022.
 39. Guttman-Yassky, E., Brunner, P. M., Neumann, A. U., Khattri, S., Pavel, A. B., Malik, K., ... & Lebwohl, M. G. (2018). Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *Journal of the American Academy of Dermatology*, 78(5), 872-881.
 40. Matera, M. G., Rogliani, P., Calzetta, L., & Cazzola, M. (2020). TSLP inhibitors for asthma: current status and future prospects. *Drugs*, 80, 449-458.

Copyright: ©2023 Mohammed Al Abadie, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.