Dermatology Practical & Conceptual

Interleukin-13 Inhibitors in the Treatment of Atopic Dermatitis: The Role of Tralokinumab

Annunziata Dattola[1], Martina Tolone[2], Emanuele Amore[1], Luigi Bennardo[2], Federica Trovato[1], Simone Amato[1], Teresa Grieco[1], Antonio Giovanni Richetta[1], Giovanni Pellacani[1], Nevena Skroza[3], Steven Paul Nisticò[1,2]

1 Department of Dermatology University of Rome "La Sapienza", Rome, Italy

2 Department of Health Sciences- Unit of Dermatology, Magna Graecia University, Catanzaro, Italy

3 Dermatology Unit 'Daniele Innocenzi', Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino, Latina, Italy

Key words: atopic dermatitis, anti IL13, tralokinumab, biologic therapy

Citation: Dattola A, Tolone M, Amore E, et al. Interleukin-13 Inhibitors in the Treatment of Atopic Dermatitis: The Role of Tralokinumab. *Dermatol Pract Concept*. 2024;14(3):e2024204. DOI: https://doi.org/10.5826/dpc.1403a204

Accepted: April 24, 2024; **Published:** July 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Dr. Dattola Annunziata PhD, Department of Dermatology, La Sapienza of Rome. Phone no: +393208419714. Email: nancydattola@gmail.com

ABSTRACT

Introduction: The advent of biotechnological drugs has significantly changed the management of atopic dermatitis (AD) and the approach to the moderate-to-severe form of this chronic relapsing disease.

Objectives: The aim of our review is to summarize the current literature on anti-interleukin (IL)-13 in atopic dermatitis.

Methods: A literature search was organized and a systematic review was performed to summarize the most recent evidence supporting the efficacy and safety of tralokinumab.

Results: Tralokinumab (anti-IL-13) 300 mg every 2 weeks subcutaneously has proven effective in several clinical trials in adults and adolescents with moderate to severe atopic dermatitis inadequately controlled with other topical or systemic therapies. Tralokinumab was found to be significantly superior in terms of efficacy in reducing Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI) -75, Numeric Pain Rating Scale (NRS) pruritus, and Dermatology Life Quality Index (DLQI) scale numbers. During follow-up, tralokinumab was well tolerated with limited severity of adverse events.

Conclusions: Tralokinumab leads to statistically significant improvements in disease severity and outcome scores. It represents an effective treatment option for adults with moderate to severe AD, but further large-scale studies are needed to verify long-term superiority over other treatments.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic and relapsing inflammatory disease of the skin with a significant economic and social impact. AD prevalence is the highest among inflammatory diseases, affecting adults and children [1]. The onset of AD may occur in early childhood, in the context of the atopic (allergic) march, which starts with AD and food allergy in infants, sometimes associated with asthma in older children, and rhino-conjunctivitis in adolescents. It often persists into adulthood [2]. A senile type of AD, with onset after age 60, was recently added to the classification. [3]. Therefore, AD is considered eczema of all age groups. AD often manifests as a series of acute foci of intensely pruritic eczematous lesions, localized to typical areas such as the flexor compartments of the extremities, but it can have a generalized distribution [4] or sometimes affect only the hands.

The crucial components in the pathophysiology of AD are T helper type 2 (Th2) inflammation and disruption of the skin barrier. Local inflammation is associated with defects in epidermal barrier proteins, including the best-known filaggrin mutations, which promote the interaction between skin-resident immune cells and environmental antigens [5]. The reduction of Lympho-epithelial Kazal-type-related inhibitor (LEKT1) may lead to a rapid degradation of desmogleins, reducing intracellular adhesiveness [6]. Another role has been assigned to skin biofilm, in particular to *Staphylococcus aureus*. This bacterium increases skin inflammation in AD. In moderate to severe cases of AD (20% of AD patients), current therapeutic approaches may range from the use of: phototherapy, corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil and azathioprine. In addition to their limited effectiveness, these approaches can sometimes cause serious side effects [7]. Recent studies elucidating the pathogenesis of AD have identified cytokines involved in the underlying inflammatory cascade, including the central role of interleukin (IL-)13 in the development and maintenance of AD. The first monoclonal anti-interleukin (IL) 4-13 receptor antibody (dupilumab), approved by the US Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD, is widely known for its high efficacy and low side effect profile. It selectively binds to the IL-4/13 receptor [7]. More recently, lebrikizumab and tralokinumab, two selective inhhibitors anti-IL-13, has been developed to manage atopic dermatitis [7,8].

Objectives

The aim of this review was to evaluate the efficacy and safety of tralokinumab, a fully monoclonal antibody that potently and specifically neutralizes IL-13, in the treatment of moderate-to-severe AD, giving the clinician a practical summary.

Methods

Our team performed a literature narrative review of articles on the use of tralokinumab in AD, published in PubMed, Google Scholar, and ClinicalTrials.gov until November 2023. The keywords were: “tralokinumab, IL-13, biological therapy” combined with “atopic dermatitis”.

Results

AD is a combination of skin-barrier dysfunction and immune dysregulation [9]. Studies conducted in mouse models and in humans over time have demonstrated the central role of IL-4 in the pathogenesis of AD [10-12]. However, several studies showed that IL-13 may be of greater importance in the pathophysiology of AD than IL-4 [13]. Mice transgenic for cutaneous IL-13 expression developed an AD-like phenotype. Greater IL-13 expression has been demonstrated in acute and chronic skin lesions in individuals with AD [13–15].

It has also been shown that elevated levels of IL-13, produced by CD4 + and CD8 + T cells as well as mast cells, basophils, and eosinophils [16-19] are responsible for skin inflammation and fibrotic remodeling in AD patients [20]. Further studies demonstrate the role of IL-13 in the dysfunction of the epidermal barrier and in the damage of keratinocytes, both implicated in the pathogenesis of AD. In vitro studies suggest that Th2-type inflammation may result in an acquired filaggrin deficiency [21].

It has also been shown that IL-4 and IL-13 reduce the keratinocyte expression of loricrin, involucrin, keratin 1, keratin 10, hornerin, desmoglein, and desmocollin 1, as well as the lipid composition, important for the constitution and integrity of the skin barrier [22].

Furthermore, IL-13, together with IL-4 and IL-31, appears to stimulate the sensory neurons responsible for peripheral itching. Therefore, it can be considered pruritogenic [23].

Given these reasons, the signal path activated by IL-13 is an excellent candidate for target therapy [24]. Relevant clinical studies on the role of IL-13 in AD are summarized in Table 1.

Tralokinumab (CAT-354) is an IgG4 monoclonal, fully human, IL-13-neutralizing antibody that inhibits its pharmacodynamics. Pre-clinical studies show that binding of tralokinumab to IL-13 prevents the interaction between IL-13 and both IL-13Rα1 and IL-13Rα2 in a concentration-dependent manner [8].

Tollenaere et al demonstrated that CAT-354 is unable to displace IL13 from IL-13Ra2 because of its high affinity.

Table 1. Relevant clinical studies on the role of interleukin-13

Elevated levels of Th2 cytokines contribute significantly to the etiopathogenesis of atopic dermatitis in terms of skin barrier disruption. IL-4 and IL-13 represent crucial factors in the atopic patient immune response [12].
CD8+ T lymphocytes produce pro-inflammatory cytokines in the patient with atopic dermatitis, such as IL-13, IFN-γ, and IL-22. These cytokines contribute to the chronicity of the disease [16].
IL-4 and IL-13 reduce the expression of loricrin, involucrin, keratin-1, keratin-10, hornerin, desmoglein, and desmocollin-1 in keratinocytes. They are also involved in the regulation of lipid composition, which is associated with skin barrier function [22].
IL-13, IL-4, and IL-31 have been shown to be pruritogenic, as they result in stimulation of sensory neurons with induction of peripheral itching [23].

IL = interleukin.

Tralokinumab is not able to regulate this pathway but only IL-13/IL-13Ra1 and IL-13Ra1/IL-13/IL-4Ra complex [25]. Published values for antibody-antigen shape complementarity range from 0.6 to 0.8, where a surface complementarity of 1.0 indicates interfaces with a geometrically perfect fit. This similarity demonstrates the high complementarity of the interface between the antigen-binding fragment of tralokinumab and IL-13 [26,27]. ECZTRA trials 1, 2 and 3 provide evidence to support tralokinumab as a treatment for moderate to severe AD [28-30]. ECZTRA 1 and 2 were identical monotherapy trials that enrolled a total number of 1596 adult patients with moderate-to-severe AD. Patients were randomized into three arms: to either tralokinumab 600 mg and 300 mg subcutaneously (SC) administered every two weeks (Q2W) or to placebo. The primary endpoints were an Investigator Global Assessment (IGA) of 0 or 1 and a 75% improvement in the Eczema Area and Severity Index (EASI 75) at 16 weeks [28].

On the other hand, the ECZTRA 3 trial enrolled 369 adult patients randomized to tralokinumab SC 300 mg Q2W or placebo, with the main difference from ECZTRA 1 and 2 being that topical corticosteroids were allowed as needed. These results are more applicable to real-world use, as systemic therapies are used concomitantly with topical medications. The primary endpoints were the same as ECZTRA 1 and 2. Both studies also assessed the Harmonising Outcomes Measures for Eczema core outcomes: reduction of EASI, Patient-Oriented Eczema Measure, a peak pruritus numerical rating scale, and the Dermatology Life Quality Index [28,31-33]. In ECZTRA 1 and 2, a significantly higher proportion of patients receiving tralokinumab. In both studies, tralokinumab led to improvement of IGA in approximately twice as many patients as placebo (ECZTRA 1: 15.8% versus 7.1%; ECZTRA 2: 22.2% versus 10.9%). EASI 75 was more commonly observed with tralokinumab in ECZTRA 1 (25.0% versus 12.7%) and ECZTRA 2 (33.2% versus 11.4%). In ECZTRA 3, response rates were higher for both tralokinumab and placebo (IGA: 38.9% versus 26.2%; EASI 75: 56.0% versus 35.7%), probably due to the use of topical corticosteroids [28,33]. In the initial 16-week treatment period, the frequency of adverse events was similar between tralokinumab and placebo for all 3 studies.

Conjunctivitis was an adverse event of special interest because it frequently occurs with the use of dupilumab, which also targets the IL-4/IL-13 pathway. Conjunctivitis occurred more frequently in patients receiving tralokinumab in all studies, although most cases were mild or moderate [28,33]. Long-term efficacy was variable in ECZTRA 1 and 2, with approximately half of the patients experiencing response maintenance at 52 weeks. Comparably, maintenance was much higher in ECZTRA 3 [28-30]. Independently of week 16 endpoint, ECZTRA 3 post hoc analysis showed how topical corticosteroids (TCS) in combination with tralokinumab provided a good response over 32 weeks in the management of AD, as evidenced by EASI 75 at week 16 and week 32 (56% versus 70%), respectively. Presumably, there are some patients who need more time to fully benefit from IL-13 treatment. Furthermore, this trial identified a group of "super-responders", who reached EASI 75 or EASI 90 after only 4 weeks of treatment [31,32,34,35]. ECZTRA 7, a randomized, placebo controlled, phase III clinical trial demonstrated the efficacy and safety of tralokinumab plus TCS after 16 weeks in patients not sufficiently controlled with oral cyclosporine or with contraindications to systemic administration [36].

A 16-week real-life experience confirmed the rapid improvement in symptoms and quality of life [1]. Andreas Wollenberg MD et al. sought to evaluate the efficacy and safety of tralokinumab in adults with moderate-to-severe AD. This phase 2b study (NCT02347176) analyzed 204 adults who were randomized 1:1:1:1 to receive placebo or 45, 150 or 300 mg of subcutaneous tralokinumab with concomitant topical glucocorticoids for a total of 12 weeks in alternating weeks [36]. At week 12, co-primary endpoints evaluated the percentage of participants with an Investigator Global Assessment response and, above all, the change from baseline in the Eczema Area Severity Index score. A significant change from baseline in the Eczema Area Severity Index score was observed with 300 mg of tralokinumab versus placebo. A more considerable percentage of participants also achieved an Investigator Global Assessment response (26.7% versus 11.8%). High levels of biomarkers of increased IL-13 activity were observed in participants with the best responses. In addition, improvements in

Table 2. Relevant clinical studies on tralokinumab

ECZTRA 1 and 2 were identical monotherapy studies of1596 adult patients with moderate to severe AD. Patients were randomized into three arms: to tralokinumab 600 mg and 300 mg or to placebo. Patients couldn't use topical corticosteroids during the study. A significantly higher proportion of patients received tralokinumab. In both studies, tralokinumab led to an improvement in IGA in twice as many patients as in the placebo group (ECZTRA 1: 15.8% versus 7.1%; ECZTRA 2: 22.2% versus 10.9%). EASI 75 was achieved more frequently in the groups with tralokinumab in ECZTRA 1 (25.0% versus 12.7%) and ECZTRA 2 (33.2% versus 11.4%). In the initial 16-week treatment period, the frequency of adverse events was similar between tralokinumab and placebo [28].
The ECZTRA 3 trial involved 369 adult patients with AD who were randomized to tralokinumab SC 300 mg Q2W or placebo. Patients could use topical corticosteroids throughout the study. Response rates were higher for tralokinumab than for placebo (IGA: 38.9% versus 26.2%; EASI 75: 56.0% versus 35.7%). In the initial 16-week treatment period, the frequency of adverse events was similar between tralokinumab and placebo. [33,34].
ECZTRA 7 demonstrated the efficacy and safety of tralokinumab and topical CS after 16 weeks in patients with inadequate response or with contraindications to oral cyclosporin. [36].
ECZTEND evaluated long-term safety in patients previously enrolled in other studies. Adverse events were similar for anti-IL-13 and placebo up to 52 weeks. It also demonstrated the efficacy of tralokinumab over 2 years of treatment, with a significant reduction in EASI and DLQI.[38]
ECZTRA 6 is a phase 3, randomized, double-blind, placebo-controlled, 52-week study involving 72 centers in 10 countries. Adolescent patients (12-17 years) with moderate-to-severe form of AD (IGA score ≥3; EASI ≥16) were enrolled, and were randomized to tralokinumab 150 mg, 300 mg, and placebo (initially). The results confirmed the safety and efficacy of anti-IL-13 in the treatment of moderate-severe forms in the adolescent population [40].

AD = atopic dermatitis; CS =corticosteroids; DLQI = dermatology life quality index; EASI = eczema area and severity index; IGA = investigator global assessment; IL = interleukin; SC = subcutaneous.

Dermatology Life Quality Index, SCORAD and Numeric Rating Scale Pruritus (NRS pruritus) were demonstrated in patients taking 300 mg tralokinumab compared to placebo. The most frequent treatment-emergent adverse event reported was upper respiratory tract infection, but in the same percentage (3.9%) in both groups [37].

A new ongoing trial, ECZTEND, assessed long-term safety in patients who were enrolled in previous parent trials. Adverse events were similar for anti-IL-13 and placebo up to 52 weeks. In addition, EZCTEND demonstrated efficacy of tralokinumab for more than 2 years of treatment with a significant reduction of EASI and DLQI [38]. Ewulu et al performed review to investigate the efficacy and safety of tralokinumab also in adolescent population with AD [39]. They concluded that the use of tralokinumab could also be extended to adolescents suffering from moderate-to-severe AD.

A 52-week, randomized, double-blind, placebo-controlled phase 3 study ECZTRA 6 was conducted involving 72 centers in 10 countries that enrolled adolescent patients (12-17 years) with moderate to severe form of AD (IGA score ≥3; EASI ≥16), treated with tralokinumab 150 mg, 300 mg and placebo (initially). Despite some limitations such as low sample size and lack of a placebo group in the maintenance phase, the results confirmed safety and efficacy of anti-IL-13 in the treatment of moderate-to-severe forms in the adolescent population [40]. Merola et al conducted a post hoc analysis focused on the adult population, aged 65 years and older, stratifying data from the phase 3 studies: ECZTRA 1, 2 and ECZTRA 3. The results suggest that tralokinumab is well tolerated and effective in older patients (65 years and older) with moderate-to-severe AD [41]. Relevant randomized clinical trials on the efficacy and safety of Tralokinumab in adults and adolescents with AD are summarized in Table 2.

Conclusions

Tralokinumab represents an innovative therapeutic agent with an excellent efficacy and safety profile, as demonstrated by phase 2 and 3 studies and *post-hoc* analysis. This humanized monoclonal antibody caused an early and sustained response in AD patients, and it demonstrated to be acceptably safe and tolerable, giving significant proof for targeting IL-13 in AD patients. Several drugs to manage AD are currently approved: dupilumab, abrocitinib and upadacitinib. Nevertheless, based on the results of trials, tralokinumab appears to be a promising treatment option for patients with moderate to severe AD. Different from dupilumab, tralokinumab does not currently have an indication for the treatment of AD in the pediatric patients.

Nevertheless, efficacy and a good safety profile of tralokinumab has been demonstrated in adolescents and elderly AD patients.

Our clinical experience also proved that anti IL-13 is an effective drug for severe forms of AD without significant side effects. In particular, ophthalmic side effects, primarily conjunctivitis, were observed less frequently than in patients treated with dupilumab. Despite its induction, tralokinumab

offers long-term superiority over other therapies, based on excellent safety and efficacy profile.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Gargiulo L, Ibba L, Vignoli CA, et al. Tralokinumab rapidly improves subjective symptoms and quality of life in patients with moderate-to-severe atopic dermatitis: a real-life 16-week experience. *J Dermatolog Treat*. 2023 Dec;34(1):2216815. DOI: 10.1080/09546634.2023.2216815. PMID: 37246920.
2. Spergel, Jonathan M, and Amy S Paller. "Atopic dermatitis and the atopic march." The Journal of allergy and clinical immunology vol. 112,6 Suppl (2003): S118-27. doi:10.1016/j.jaci.2003.09.033
3. Tanei R. Atopic dermatitis in the elderly. Inflamm Allergy Drug Targets. 2009 Dec;8(5):398-404. doi: 10.2174/1871528110908050398. PMID: 20025588.
4. Nettis, E et al. "A Multicenter Study on the Prevalence of Clinical Patterns and Clinical Phenotypes in Adult Atopic Dermatitis." Journal of investigational allergology & clinical immunology vol. 30,6 (2020): 448-450. doi:10.18176/jiaci.0519
5. Morelli P, Gaspari M, Gabriele C et al. Proteomic analysis from skin swabs reveals a new set of proteins identifying skin impairment in atopic dermatitis. Exp Dermatol. 2021 Jun;30(6):811-819.
6. Bonnart C, Deraison C, Lacroix M, et al. Elastase 2 is expressed in human and mouse epidermis and impairs skin barrier function in Netherton syndrome through filaggrin and lipid misprocessing. *J Clin Invest*. 2010;120:871–82.
7. Dattola A, Bennardo L, Silvestri M, Nisticò SP. What's new in the treatment of atopic dermatitis? Dermatol Ther. 2019 Mar;32(2):e12787. doi: 10.1111/dth.12787. Epub 2018 Dec 12. PMID: 30548724.
8. May RD, Monk PD, Cohen ES, Manuel D, Dempsey F, Davis NH, Dodd AJ, Corkill DJ, Woods J, Joberty-Candotti C, Conroy LA, Koentgen F, Martin EC, Wilson R, Brennan N, Powell J, Anderson IK. Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. Br J Pharmacol. 2012 May;166(1):177-93. doi: 10.1111/j.1476-5381.2011.01659.x. PMID: 21895629; PMCID: PMC3415647.
9. Silverberg JI, Kantor R. et al. The role of interleukins 4 and /or 13 in the pathophysiology and treatment of atopic dermatitis. *Dermatol Clin*. 2017 Jul;35(3):327-334. doi: 10.1016/j.det.2017.02.005. Epub 2017 Apr 22. PMID: 28577802.
10. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. J Clin Invest. 1994;94(2):870-876. doi:10.1172/JCI117408
11. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. J Invest Dermatol. 2001 Oct;117(4):977-83. doi: 10.1046/j.0022-202x.2001.01484.x. PMID: 11676841.
12. Brandt EB, Sivaprasad U. Th2 Cytokines and Atopic Dermatitis. J Clin Cell Immunol. 2011;2(3):110. doi:10.4172/2155-9899.1000110.
13. Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. Arch Dermatol Res. 2004 Apr;295(11):459-64. doi: 10.1007/s00403-004-0455-6. Epub 2004 Mar 10. PMID: 15014952.
14. Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY. In vivo expression of IL-12 and IL-13 in atopic dermatitis. J Allergy Clin Immunol. 1996 Jul;98(1):225-31. doi: 10.1016/s0091-6749(96)70246-4. PMID: 8765838.
15. Zheng T, Oh MH, Oh SY, Schroeder JT, Glick AB, Zhu Z. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. J Invest Dermatol. 2009 Mar;129(3):742-51. doi: 10.1038/jid.2008.295. Epub 2008 Oct 2. PMID: 18830273; PMCID: PMC4356214.
16. Hijnen D, Knol EF, Gent YY, et al. CD8(1) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN-gamma, IL-13, IL-17, and IL-22. *J Invest Dermatol*. 2013;133(4):973–9.
17. Burd PR, Thompson WC, Max EE, Mills FC. Activated mast cells produce interleukin 13. J Exp Med. 1995 Apr 1;181(4):1373-80. doi: 10.1084/jem.181.4.1373. PMID: 7535336; PMCID: PMC2191950.
18. Li H, Sim TC, Alam R. IL-13 released by and localized in human basophils. J Immunol. 1996 Jun 15;156(12):4833-8. PMID: 8648131.Schmid-Grendelmeier P, Altznauer F, Fischer B, et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. J Immunol. 2002; 169(2):1021-7.
19. Oh MH, Oh SY, Yu J, et al. IL-13 induces skin fibrosis in atopic dermatitis by thymic stromal lymphopoietin. J Immunol. 2011;186(12):7232-7242. doi:10.4049/jimmunol.1100504
20. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, Schneider L, Beck LA, Barnes KC, Leung DY. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2009 Sep;124(3 Suppl 2):R7-R12. doi: 10.1016/j.jaci.2009.07.012. PMID: 19720210.
21. Kim BE, Leung DY, Boguniewicz M, Howell MD. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. Clin Immunol. 2008 Mar;126(3):332-7. doi: 10.1016/j.clim.2007.11.006. Epub 2007 Dec 31. PMID: 18166499; PMCID: PMC2275206.
22. Oetjen LK, Mack MR, Feng J, et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. Cell. 2017;171(1):217-228.e13. doi:10.1016/j.cell.2017.08.006
23. Bieber T. et al. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy*. 2020 Jan;75(1):54-62. doi: 10.1111/all.13954. Epub 2019 Jul 15. PMID: 31230370.
24. Tollenaere MAX, Mølck C, Henderson I, Pollack S, Addis P, Petersen HH, Norsgaard H. et al. Tralokinumab effectively disrupts the IL-13/IL-13Rα1/IL-4Rα signaling complex but not the IL-13/IL-13Rα2 complex. *JID Innov*. 2023 Jul 4;3(5):100214. doi: 10.1016/j.xjidi.2023.100214. PMID: 37554517; PMCID: PMC10405097.
25. Li Y, Li H, Yang F, Smith-Gill S, Mariuzza RA. et al. X-ray snapshots of the maturation of an antibody response to a protein antigen. *Nat Struct Mol Biol*. 2003;10:482–488.
26. Fransson F, Teplyakov A, Raghunathan G, et al. Human framework adaptation of a mouse anti-human IL-13 antibody. *J Mol Biol*. 2010;398: 214–231.
27. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. 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). *Br J Dermatol*. 2021;184(3):437-449.

28. Torres T, Sohrt Petersen A, Ivens U, Bosch Vilaro A, Stinson J, Carrascosa JM. Et al. Matching-Adjusted Indirect Comparison of the Efficacy at Week 32 of Tralokinumab and Dupilumab in the Treatment of Moderate-to-Severe Atopic Dermatitis. *Dermatol Ther (Heidelb)*. doi:10.1007/s13555-024-01143-x
29. Guttman-Yassky E, Kabashima K, Staumont-Salle D, et al. Targeting IL-13 with tralokinumab normalizes type 2 inflammation in atopic dermatitis both early and at 2 years. *Allergy*. doi:10.1111/all.16108
30. Simpson EL, Blauvelt A, Silverberg JI, et al. Tralokinumab Provides Clinically Meaningful Responses at Week 16 in Adults with Moderate-to-Severe Atopic Dermatitis Who Do Not Achieve IGA 0/1. *Am J Clin Dermatol*. 2024;25(1):139-148. doi:10.1007/s40257-023-00817-0
31. Cozzani E, Marzano AV, Caproni M, Feliciani C, Calzavara-Pinton P. Cutaneous Immunology group of SIDeMaST. Bullous pemphigoid: Italian guidelines adapted from the EDF/EADV guidelines. *G Ital Dermatol Venereol.* 2018 Jun;153(3):305-315. doi: 10.23736/S0392-0488.18.06006-6. Epub 2018 Mar 30. PMID: 29600832.
32. Silverberg JI, Toth D, Bieber T, et al. 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. *Br J Dermatol.* 2020; https://doi. org/10.1111/bjd.19573.
33. Silverberg JI, Adam DN, Zirwas M, et al. Tralokinumab plus topical corticosteroids as needed provides progressive and sustained efficacy in adults with moderate-to-severe atopic dermatitis over a 32-week period: An ECZTRA 3 post hoc analysis. *Am J Clin Dermatol.* 2022 Jul;23(4):547-559. doi: 10.1007/s40257-022-00702-2. Epub 2022 Jul 20. PMID: 35857179; PMCID: PMC9334431.
34. Alegre-Bailo A, Sánchez-Gilo A, Marlene-Mendoza NM, Mateos-Rico JJ, Vicente-Martín FJ. et al. Tralokinumab treatment in atopic dermatitis: Depicting super-responders. *J Dermatol.* 2023 Oct 23. doi: 10.1111/1346-8138.17009. Epub ahead of print. PMID: 37870261.
35. Gutermuth J, Pink AE, Worm M, Soldbro L, Bjerregård Øland C, Weidinger S. et al. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). *Br J Dermatol.* 2022 Mar;186(3):440-452. doi: 10.1111/bjd.20832. Epub 2021 Dec 22. PMID: 34698371.
36. Wollenberg A, Howell MD, Guttman-Yassky E, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol.* 2019 Jan;143(1):135-141. doi: 10.1016/j.jaci.2018.05.029.
37. Blauvelt A, Langley RG, Lacour JP, et al. Long-term 2-year safety and efficacy of tralokinumab in adults with moderate-to-severe atopic dermatitis: Interim analysis of the ECZTEND open-label extension trial. *J Am Acad Dermatol.* 2022 Oct;87(4):815-824. doi: 10.1016/j.jaad.2022.07.019. Epub 2022 Jul 19. PMID: 35863467.
38. Ewulu AR, Prajapati S, Feldman SR. et al. The role of tralokinumab in the treatment of atopic dermatitis and future perspectives for adolescents. *Immunotherapy.* 2023 Nov;15(16):1341-1349. doi: 10.2217/imt-2022-0307. Epub 2023 Aug 29. PMID: 37641871.
39. Paller AS, Flohr C, Cork M, et al. Efficacy and safety of tralokinumab in adolescents with moderate to severe atopic dermatitis: The Phase 3 ECZTRA 6 randomized clinical trial. JAMA Dermatol. 2023 Jun 1;159(6):596-605. doi: 10.1001/jamadermatol.2023.0627. Erratum in: *JAMA Dermatol.* 2023 Jun 1;159(6):673. PMID: 37074705; PMCID: PMC10116386.
40. Merola JF, Butler DC, Mark T, Schneider S, Kim Y, Abuabara K. et al. Safety and efficacy of tralokinumab in older adults with moderate-to-severe atopic dermatitis: a secondary analysis. *JAMA Dermatol.* 2023 Oct 1;159(10):1119-1123. doi: 10.1001/jamadermatol.2023.2626. PMID: 37610789; PMCID: PMC10448370.