Review

The role of interleukin-13 in the management of atopic dermatitis: an expert consensus panel

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Abstract

Atopic dermatitis is a chronic inflammatory skin condition driven by immune dysregulation, with interleukin-13 playing a central role in its pathogenesis. Recent advances in targeted biologic therapies have shown promising results in treating moderate-to-severe atopic dermatitis. A comprehensive literature review of PubMed and Google Scholar was conducted to identify studies related to interleukin-13 inhibition in atopic dermatitis. An expert panel reviewed and graded the evidence using Strength of Recommendation Taxonomy criteria and utilized a modified Delphi process to formulate consensus statements on the role of interleukin-13 inhibitors. Based on selected literature, the panel developed 14 consensus statements, all receiving unanimous approval. Key findings include the rapid efficacy, sustained benefits, and favorable safety profiles of interleukin-13 inhibitors. Differences between available interleukin-13 inhibitors included pain of injection, speed of onset, durability of efficacy, and number of injections needed to maintain efficacy. Interleukin-13 plays a pivotal role in atopic dermatitis pathogenesis, driving inflammation, pruritus, and barrier dysfunction. Targeted therapies, including interleukin-13 inhibitors, provide rapid, durable, and safe options for managing moderate-to-severe atopic dermatitis. This consensus highlights interleukin-13 inhibition as a cornerstone in advancing atopic dermatitis treatment strategies, offering improved patient outcomes and quality of life.

Introduction

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin condition characterized by significant immune system dysregulation. A growing body of evidence highlights the central role of type 2 helper T-cell (Th2) cytokines, particularly interleukin (IL)-13, in the pathogenesis of AD.[1,2] IL-13 contributes to hallmark features of AD, such as skin barrier dysfunction, pruritus, and inflammation, by activating downstream signaling pathways, including the Janus kinase (JAK)-signal transducer and activator of transcription pathway.[3,4] These insights have spurred the development of biologic therapies targeting IL-13, offering new therapeutic options for patients with moderate-to-severe AD.

This manuscript aims to summarize the current understanding of IL-13's role in AD and evaluate the clinical efficacy and safety of IL-13 inhibitors, emphasizing lebrikizumab and tralokinumab, which specifically target IL-13. Using a systematic review of the literature and a consensus-driven approach by an expert panel, this study provides evidence-based recommendations for the use of

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IL-13 inhibitors in managing AD. The findings underscore the rapid onset of action, sustained efficacy, and favorable safety profiles of these targeted therapies, positioning IL-13 inhibitors as promising treatment modalities for this chronic and burdensome disease.

Capsule summary

The role of IL-13 in atopic disease is clear, with IL-13 playing a central role in atopic dermatitis pathogenesis and influencing inflammation, pruritus, and skin barrier dysfunction. An expert consensus panel developed ten consensus statements on the role of IL-13 inhibition in atopic disease to help guide clinical decision-making. IL-13 inhibitors, such as lebrikizumab and tralokinumab, demonstrate rapid onset of action, with benefits observed as early as week two. Long-term efficacy and safety of IL-13 inhibitors are supported by clinical trials, with sustained symptom improvement over 104 weeks. Lebrikizumab exhibits the lowest incidence of injection site reactions and a favorable safety profile compared to other IL-13 inhibitors. IL-13 inhibitors are effective for patients with inadequate responses to dupilumab or JAK inhibitors, broadening treatment options.

Methods

Literature search and study selection

A comprehensive literature search of PubMed and Google Scholar was completed on November 15, 2024, using the key words “atopic dermatitis,” “IL-13 inhibition,” “biologics,” “lebrikizumab,” “tralokinumab,” and “dupilumab” along with the Boolean term “AND” for English-language original research articles, systematic reviews and meta-analyses without date restrictions. This study did not require Institutional Review Board approval. Articles were screened for relevance to the role of IL-13 in atopic dermatitis. Eight experts were selected for their expertise in the management of atopic dermatitis and were asked to participate in a panel. The articles that met inclusion criteria were distributed to the panelists, and each member of the panel reviewed the selected studies and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[5] These levels included level 1 (good-quality patient-oriented evidence), level 2 (limited-quality patient-oriented evidence), or level 3 (other evidence such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[5]

Development of consensus statements

The panel convened on December 13, 2024, to review and discuss the studies to create consensus statements for the role of IL-13 in atopic disease with guidance on utilizing novel biologic therapies. To reach a consensus for each statement, a modified Delphi process was utilized, requiring supermajority approval for adoption of a recommendation through multiple rounds of real-time voting.[6] This method is regularly utilized to create expert recommendations in dermatology.[7-9] Consensus statements were assigned to a strength of recommendation of A (recommendation based on consistent and good-quality patient-oriented evidence), B (recommendation based on inconsistent or limited-quality patient-oriented evidence), or C (recommendation based on consensus, opinion, disease-oriented evidence or case reports.) Notably, even the strength of C can be considered a strong recommendation for adoption.

Results

Literature search and study selection

The literature search resulted in over 400 articles that met search criteria. After a comprehensive screening process, 20 articles and four publicly presented posters were selected as relevant to the research questions. These were distributed to the panelists for review and evaluation prior to the roundtable discussion.

Levels of evidence designation

For the 20 articles and four posters evaluated, the panel assigned level 1 evidence to 14 articles and four posters, level 2 evidence to four articles, and level 3 evidence to two articles (Table 1).

Consensus statements

The panel developed 14 consensus statements regarding the role of IL-13 in atopic disease. All statements received a unanimous (8/8) vote for adoption. SORT criteria were utilized to assign a strength to each statement and recommendation (Table 2).

Statement 1: IL-13 plays a pivotal role in atopic dermatitis. (SORT level A)

Interleukin-13 (IL-13) plays a pivotal role in atopic dermatitis, as evidenced by multiple studies highlighting its central involvement in the pathogenesis of the disease. IL-13 is a key cytokine in type 2 T-helper (Th2) cell-mediated inflammation, which is characteristic of atopic dermatitis (AD). It is overexpressed in the lesional skin of AD patients, contributing to various pathological features of the disease, including skin barrier dysfunction, pruritus, and chronic inflammation.[1,2]

IL-13 exerts its effects by binding to the IL-13 receptor, which is composed of IL-13Rα1 and IL-4Rα. This interaction leads to the activation of downstream signaling pathways, such as the JAK-signal transducer and activator of transcription pathway, which are crucial for the inflammatory response in AD. Studies have shown that IL-13 reduces the expression of key epidermal barrier proteins like filaggrin, thereby compromising the skin barrier and facilitating allergen penetration and microbial colonization.[3,4] Additionally, IL-13 has been implicated in the recruitment of inflammatory cells, including

Table 1. *SORT Criteria Level of Evidence for Articles Relevant to the Role of Interleukin-13 in Atopic Dermatitis.*

Article Title	Author, Year	Level of Evidence
Tralokinumab Efficacy and Safety, with or without Topical Corticosteroids, in North American Adults with Moderate-to-Severe Atopic Dermatitis: A Subanalysis of Phase 3 Trials ECZTRA 1, 2, and 3	Blauvelt A et al, 2022[10]	1
Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies	Davis DMR et al, 2024[11]	3
Systemic Immunomodulatory Treatments for Atopic Dermatitis: Living Systematic Review and Network Meta-Analysis Update	Drucker et al, 2024[12]	2
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	Guttman-Yassky E et al, 2020[13]	1
Clinical measures of improvement in atopic dermatitis are correlated with reductions in relevant biomarkers in patients treated with lebrikizumab [poster]	Guttman-Yassky E et al, 2024[14]	1
Lebrikizumab treatment results in rapid improvement of atopic dermatitis disease cytokines and pathways [poster]	Guttman-Yassky E et al, 2023[15]	1
Lebrikizumab reduces systemic inflammation in serum of patients with moderate-to-severe atopic dermatitis [poster]	Guttman-Yassky E et al, 2023[16]	1
Lebrikizumab Improves Quality of Life and Patient-Reported Symptoms of Anxiety and Depression in Patients with Moderate-to-Severe Atopic Dermatitis	Lio PA et al, 2024[17]	1
Injection site reactions after dupilumab or tralokinumab for atopic dermatitis	Martora et al, 2024[18]	2
Safety and Efficacy of Lebrikizumab in Adolescent Patients with Moderate-to-Severe Atopic Dermatitis: A 52-Week, Open-Label, Phase 3 Study	Paller AS et al, 2023[19]	1
Matching-Adjusted Indirect Comparison of the Long-Term Efficacy Maintenance and Adverse Event Rates of Lebrikizumab versus Dupilumab in Moderate-to-Severe Atopic Dermatitis	Rand K et al, 2024[20]	2
Patients with Moderate-to-Severe Atopic Dermatitis Maintain Stable Response with No or Minimal Fluctuations with 1 Year of Lebrikizumab Treatment	Silverberg JI et al, 2024[21]	1
Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis	Silverberg JI et al, 2023[22]	1
Lebrikizumab improves atopic dermatitis and quality of life in patients with moderate-to-severe atopic dermatitis previously treated with dupilumab: results from the ADapt trial [poster]	Silverberg JI et al 2024[23]	1
Lebrikizumab Provides Rapid Clinical Responses Across All Eczema Area and Severity Index Body Regions and Clinical Signs in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis	Simpson EL et al, 2024[24]	1
Tralokinumab Efficacy Over 1 Year in Adults with Moderate-to-Severe Atopic Dermatitis: Pooled Data from Two Phase III Trials	Simpson EL et al, 2023[25]	1
Safety of tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled phase II and phase III trials	Simpson EL et al, 2022[26]	1
Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE).	Simpson EL et al, 2018[27]	1
The Impact of Lebrikizumab on Vaccine-Induced Immune Responses: Results from a Phase 3 Study in Adult Patients with Moderate-to-Severe Atopic Dermatitis	Soung J et al, 2024[28]	1
Safety of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: An Integrated Analysis of Eight Clinical Trials	Stein Gold L et al, 2023[29]	1
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)	Wollenberg A et al, 2021[30]	1
Comparison of Old and New Systemic Treatments for Moderate to Severe Atopic Dermatitis	Yim HJ, 2024[31]	3
Stable Response and Sustained Improvement of Itch and Sleep Symptoms in Patients with Atopic Dermatitis Treated with Lebrikizumab over 52 Weeks	Yosipovitch G, 2024[32]	1
The efficacy and safety of IL-13 inhibitors in atopic dermatitis: A systematic review and meta-analysis	Zhang Y et al, 2022[33]	2

T cells and eosinophils, to the skin, further exacerbating the inflammatory milieu.[34,35]

The clinical relevance of IL-13 in AD is underscored by the efficacy of targeted therapies. Biologics such as dupilumab, which blocks IL-4 and IL-13 signaling, and tralokinumab and lebrikizumab, which specifically target IL-13, have shown significant clinical benefits in patients with moderate-to-severe AD. These treatments have been associated with improvements in skin lesions, pruritus, and overall disease severity, highlighting the critical role of IL-13 in the disease's pathophysiology.[36,37]

Lebrikizumab, the newest IL-13 inhibitor approved for atopic dermatitis, demonstrated significantly improved clinical outcomes compared to placebo in the pivotal ADvocate1 and ADvocate2 trials.[19,22,38,39] In ADvocate1, 43.1% of patients in the lebrikizumab group achieved

Table 2. *Consensus Statements and Recommendations for the Role of Interleukin-13 in Atopic Dermatitis.*

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
IL-13 plays a pivotal role in atopic dermatitis.	A	8/8
IL-13 inhibitors are associated with limited side effects as compared to traditional systemic immunosuppressants (methotrexate, azathioprine, cyclosporine, mycophenolate and systemic steroids) and JAK inhibitors in patients with atopic dermatitis.	A	8/8
IL-13 inhibition works well for atopic dermatitis of the head and neck.	A	8/8
IL-13 targeted therapies work quickly for atopic dermatitis with a statistically significant benefit as early as week 2 for both itch and skin clearance.	A	8/8
Responses to IL-13 targeted therapies are sustained over time.	A	8/8
Patients with inadequate response to dupilumab may effectively respond to IL-13 inhibitors.	A	8/8
Treatment with IL-13 inhibitors improves the quality of life of atopic dermatitis patients as early as week 4.	A	8/8
Treatment with IL-13 inhibitors does not impact the effectiveness or safety of nonlive vaccines.	A	8/8
Treatment with IL-13 inhibitors does not increase the risk of serious or opportunistic infections.	A	8/8
Conjunctivitis, which is usually mild to moderate, is a potential side effect of IL-4/IL-13 and IL-13 inhibitors.	A	8/8
There have not been reports of treatment-related facial erythema or migratory polyarthralgias in patients treated with lebrikizumab to date.	A	8/8
Inhibition of IL-13 can normalize and/or improve serum markers associated with atopic dermatitis.	A	8/8
Considering the availability of safe and effective treatments, the use of systemic steroids for atopic dermatitis should be discouraged.	A	8/8
Rate of injection site reactions is lower in patients treated with lebrikizumab than dupilumab and tralokinumab.	A	8/8

the primary endpoint (IGA [Investigator's Global Assessment] (0,1) or EASI [Eczema Area and Severity Index]-75 at week 16) compared to 12.7% in the placebo group. In ADvocate2, the corresponding figures were 33.2% and 10.8%, respectively. EASI-75 responses were also significantly higher in the lebrikizumab groups in both trials.[22,38]

Tralokinumab, the earliest IL-13 inhibitor, also demonstrated efficacy in atopic dermatitis with 15.8% achieving IGA 0,1 at week 16 compared to 7.1% of placebo-treated subjects in Ecztra1. In Ecztra2 the corresponding numbers were 22.2% versus 10.9% in the placebo arm.[30]

Given this, IL-13 clearly plays a central role in the immunopathogenesis of atopic dermatitis, driving key aspects of the disease, including barrier dysfunction, inflammation, and pruritus. The therapeutic success of IL-13-targeted treatments further supports its pivotal role in AD, making it a crucial target for current and future therapeutic strategies.[6,34,36]

Statement 2: IL-13 inhibitors are associated with limited side effects as compared to traditional systemic immunosuppressants (methotrexate, azathioprine, cyclosporine, mycophenolate, and systemic steroids) and JAK inhibitors in patients with atopic dermatitis. (SORT level A)

IL-13 inhibitors, such as tralokinumab and lebrikizumab, have demonstrated a favorable safety profile in the treatment of moderate-to-severe atopic dermatitis (AD).[10,26,27] Clinical trials and systematic reviews have shown that these biologics are associated with fewer adverse effects compared to traditional systemic immunosuppressants like methotrexate, azathioprine, cyclosporine, mycophenolate, and systemic corticosteroids. Traditional immunosuppressants are known for their broad immunosuppressive effects, which can lead to significant long-term adverse effects, including nephrotoxicity, hepatotoxicity, and increased risk of infections.[11,31,40]

In contrast, IL-13 inhibitors target specific pathways involved in the pathogenesis of AD, resulting in a more targeted therapeutic approach with fewer systemic side effects. For instance, a systematic review and meta-

analysis highlighted that IL-13 inhibitors were well-tolerated, with the most common adverse event being mild conjunctivitis, which was significantly less severe than the adverse effects associated with traditional systemic treatments.[12,33] Additionally, the American Academy of Dermatology guidelines emphasize the safety and efficacy of these newer biologics, recommending them over traditional systemic immunosuppressants for long-term management of AD.[11]

When compared to JAK inhibitors, IL-13 inhibitors also exhibit a more favorable safety profile. JAK inhibitors, while effective, are associated with higher rates of adverse events such as infections, acne, and laboratory abnormalities like elevated creatine phosphokinase levels.[41-43] The sequential monitoring system study demonstrated that patients on IL-13 inhibitors had lower rates of outpatient infections and acne compared to those on JAK inhibitors.[41] Given this, it is clear that IL-13 inhibitors offer a safe alternative for managing moderate-to-severe AD, particularly for long-term use.

Statement 3: IL-13 inhibition works well for atopic dermatitis of the head and neck. (SORT Level A)

Atopic dermatitis of the head and neck can be a challenging and cosmetically sensitive area to treat. IL-13 inhibition is effective for treating atopic dermatitis of the head and neck, with a favorable safety profile. In analysis of data from the ADvocate1 and ADvocate2 trials, lebrikizumab-treated patients achieved EASI 100 rapidly and at significantly higher proportions than placebo-treated patients in the head/neck (15.4% versus 3.8%; p B 0.001) by week four.[24]

Notably, dupilumab, an IL-4/IL-13 inhibitor, has been associated with facial erythema in a subset of patients, which can be a significant concern in this sensitive area.[44-46] With use of tralokinumab, an IL-13 specific inhibitor, treatment-related facial redness, including case reports of intense facial erythema and desquamation, has also been reported in the literature.[47] In contrast, lebrikizumab, another specific IL-13 inhibitor, has not been reported to exhibit this side effect to date, making it a useful option for patients with head and neck AD.[22,33,48,49]

Statement 4: IL-13 targeted therapies work quickly for atopic dermatitis with a statistically significant benefit as early as week two for both itch and skin clearance. (SORT level A)

IL-13 targeted therapies, such as lebrikizumab and tralokinumab, have demonstrated rapid efficacy in treating atopic dermatitis (AD). Clinical trials have shown that these therapies provide statistically significant improvements in both itch and skin clearance as early as week 2. For instance, in the ADvocate1 and ADvocate2 phase 3 trials, lebrikizumab significantly reduced pruritus and improved EASI scores within the first two weeks of treatment.[22,38] Similarly, tralokinumab has shown early and sustained improvements in clinical outcomes, with significant reductions in itch and skin lesions observed by week 2.[50,51]

The rapid onset of action of IL-13 inhibitors is particularly beneficial for patients with moderate-to-severe AD, who often experience severe and persistent symptoms. The early improvements in pruritus and skin clearance not only enhance patient quality of life but also reduce the overall disease burden. These findings are supported by systematic reviews and meta-analyses, which confirm the efficacy and safety of IL-13 inhibitors in achieving quick and meaningful clinical responses in AD patients.[13,33]

Overall, the evidence strongly supports the use of IL-13 targeted therapies for their rapid and significant benefits in managing atopic dermatitis, particularly in reducing itch and improving skin clearance within the first two weeks of treatment.[22,38,50]

Statement 5: Responses to IL-13 targeted therapies are sustained over time. (SORT level A)

Responses to IL-13 targeted therapies are sustained over time, as demonstrated by clinical trials evaluating lebrikizumab and tralokinumab.

For lebrikizumab, the ADvocate1 and ADvocate2 trials provide robust evidence of its long-term efficacy. These phase 3 trials demonstrated that lebrikizumab maintained significant improvements in atopic dermatitis symptoms over 52 weeks. Specifically, 71.2% of patients treated with lebrikizumab every 2 weeks (Q2W) and 76.9% of patients treated every 4 weeks (Q4W) maintained an Investigator's Global Assessment (IGA) score of 0 or 1, with similar sustained improvements in EASI scores.[39] Further extending these findings, the 104-week data from the long-term extension studies indicate that the benefits of lebrikizumab are durable. Patients who continued on lebrikizumab therapy maintained high response rates, with 66% to 81% achieving IGA 0 or 1 and 83% to 89% maintaining EASI-75 at week 104.[21,39,52] Additionally, indirect comparative analyses suggest that lebrikizumab may offer maintenance benefits that are comparable or potentially superior to dupilumab in achieving and sustaining clear or almost clear skin, as assessed by IGA 0/1. Similar long-term efficacy was observed for EASI-75 responses, with no significant differences in overall adverse event rates between the therapies.[20]

For tralokinumab, the ECZTRA 1 and ECZTRA 2 trials provide comprehensive data on its long-term efficacy. These phase 3 trials showed that tralokinumab maintained significant improvements in AD symptoms over 52 weeks. In patients who achieved the primary endpoints at week 16, IGA 0/1 responses were maintained at week 52 by 55.9% of patients rerandomized to tralokinumab Q2W and 42.4% of patients rerandomized to tralokinumab once every four weeks. Additionally, the ECZTEND open-label extension trial demonstrated that tralokinumab provided sustained control of AD symp-

toms over two years, with 82.5% of participants achieving EASI-75 after two years of treatment.[25,53]

These studies collectively highlight the sustained efficacy of IL-13 targeted therapies, such as lebrikizumab and tralokinumab, in managing moderate-to-severe atopic dermatitis over extended periods. These findings are supported by robust clinical trial data, including 104-week outcomes, demonstrating that patients can achieve and maintain significant improvements in disease severity and quality of life over extended periods. The long-term data supports their use as effective and durable treatment options for patients with this chronic condition.

Statement 6: Patients with inadequate response to dupilumab may effectively respond to IL-13 inhibitors. (SORT level A)

Patients with moderate-to-severe atopic dermatitis who exhibit an inadequate response to dupilumab, a broader inhibitor of IL-4 and IL-13, may effectively respond to IL-13 inhibitors such as lebrikizumab and tralokinumab. Clinical trials and real-world studies have demonstrated that these IL-13 targeted therapies can provide significant clinical benefits for patients who do not respond adequately to dupilumab.

A multicentric, multinational retrospective cohort study found that tralokinumab was effective in achieving treatment goals in a large proportion of patients, including those who had an inadequate response to dupilumab.[54] The study included adult patients with moderate-to-severe atopic dermatitis who were treated with tralokinumab. Among the 194 patients included, a significant portion had previously been treated with dupilumab.[54]

Additional analysis from the open-label, Phase 3b, 24-week ADapt trial (NCT05369403) found that lebrikizumab provided meaningful improvements in skin (including face and hand) clearance, itch, and quality of life in patients with moderate-to-severe AD who were previously treated with dupilumab, with 57% of patients achieving EASI 75 at 16 weeks, similar to the 55.4% response seen in the Advocate 1 and 2 trials.[23]

Statement 7: Treatment with IL-13 inhibitors improves the quality of life of atopic dermatitis patients as early as week four. (SORT level A)

Evidence from clinical trials supports the rapid improvement in quality of life for atopic dermatitis patients treated with IL-13 inhibitors such as lebrikizumab and tralokinumab. In the ADvocate1 and ADvocate2 phase 3 trials, lebrikizumab demonstrated significant improvements in the Dermatology Life Quality Index (DLQI) in week four. These trials showed that patients treated with lebrikizumab experienced a statistically significant reduction in DLQI scores compared to placebo, indicating enhanced quality of life.[38] Of note, week four was the first time that data was collected on quality-of-life metrics, with clinical experience mirroring the fact that meaningful improvements in quality of life occur much sooner than four weeks for many patients.

Additionally, lebrikizumab significantly reduces patient-reported symptoms of anxiety and depression, which are common comorbidities in AD patients. These improvements were observed early in the treatment course and were sustained over time. The reduction in anxiety and depression symptoms was assessed using validated scales such as the Hospital Anxiety and Depression Scale, showing meaningful clinical improvements. Furthermore, the improvements in quality of life were mediated by significant reductions in pruritus and sleep interference, which are critical factors affecting the daily lives of AD patients. The rapid onset of action of lebrikizumab in alleviating itch and improving sleep quality contributed to the overall enhancement of patient well-being.[17,32]

Similarly, tralokinumab has shown early and sustained improvements in measures of quality of life. In the ECZTRA 1 and ECZTRA 2 trials, tralokinumab treatment resulted in significant improvements in DLQI scores by week four, which were maintained through week 16 and beyond. These findings were corroborated by a systematic review and meta-analysis, which reported that IL-13 inhibitors significantly improved DLQI scores in patients with moderate-to-severe AD.[33,50]

The rapid onset of action of these IL-13 inhibitors is further supported by improvements in other patient-reported outcomes, such as pruritus and sleep interference, which are closely linked to quality of life. For instance, in the phase 2b trial of lebrikizumab, significant improvements in pruritus numeric rating scale (NRS) scores were observed as early as day two, with continued improvement through week 16.[13] These early improvements in pruritus and sleep contribute to the overall enhancement of quality of life for AD patients.

Statement 8: Treatment with IL-13 inhibitors does not impact the effectiveness or safety of nonlive vaccines. (SORT level A)

Results from a 30-week, randomized, placebo-controlled trial demonstrated that tralokinumab did not impair the immune response to the Tetanus, diphtheria, and acellular pertussis and meningococcal conjugate vaccines. Specifically, the noninferiority of tralokinumab versus placebo for immune response to Tetanus, diphtheria, and acellular pertussis (91.9% versus 96.1%) and meningococcal (86.0% versus 84.2%) vaccines was established at week 16. This indicates that tralokinumab treatment does not negatively affect the efficacy of these vaccines.[55]

Similarly, the effect of lebrikizumab treatment on nonlive vaccine immune responses was investigated in a 16 week, randomized, placebo-controlled phase 3 study that found that lebrikizumab treatment did not negatively impact immune response for Tetanus, diphtheria, and acellular pertussis or meningococcal conjugate vaccines.[28] In addition, recent recommendations from a systematic review and Delphi consensus panel of allergists

regarding both live and nonlive vaccine use with dupilumab, an IL-4/IL-13 inhibitor, found no data to suggest safety or efficacy concerns with administration of live vaccines with concomitant dupilumab use.[56]

Statement 9: Treatment with IL-13 inhibitors does not increase the risk of serious or opportunistic infections. (SORT level A)

The safety profile of IL-13 inhibitors, such as lebrikizumab and tralokinumab, has been extensively studied in clinical trials and systematic reviews. These studies consistently demonstrate that IL-13 inhibitors do not significantly increase the risk of serious or opportunistic infections in patients with moderate-to-severe atopic dermatitis.

A systematic review by Braddock et al assessed the potential risks associated with modulating IL-13 and IL-4 signaling, including the risk of infections. The review found no evidence from clinical trials suggesting an increased risk of serious infections with IL-13 inhibition.[57] This comprehensive analysis included data from multiple clinical trials and concluded that IL-13 inhibitors are generally safe, with no significant increase in infection rates compared to placebo.

Additionally, a systematic review and meta-analysis by Zhang et al evaluated the efficacy and safety of IL-13 inhibitors in atopic dermatitis. The analysis included seven randomized controlled trials involving 2,946 patients and found that both lebrikizumab and tralokinumab were well-tolerated. The study reported no significant increase in the incidence of serious or opportunistic infections in patients treated with IL-13 inhibitors compared to those receiving placebo.[33]

Furthermore, the review by Foerster and Molęda highlighted that prolonged IL-13 inhibition in several thousand patients did not uncover any non-redundant functions of IL-13 in immune defense, suggesting that IL-13 inhibitors do not compromise the immune system's ability to prevent serious infections.[58]

When comparing IL-13 inhibitors to JAK inhibitors, the risk of herpes infections is notably lower with IL-13 inhibitors. A systematic review and meta-analysis by Alves et al found that JAK inhibitors, such as baricitinib, abrocitinib, and upadacitinib, significantly increase the risk of herpes zoster infections compared to placebo.[59] The incidence of herpes zoster infection was 2.53% with JAK inhibitors, whereas IL-13 inhibitors did not show a similar increase in herpes infection rates.[60] This difference underscores the safer infection profile of IL-13 inhibitors relative to JAK inhibitors.

The available evidence strongly supports that treatment with IL-13 inhibitors does not increase the risk of serious or opportunistic infections, making them a safe option for managing moderate-to-severe atopic dermatitis. Additionally, IL-13 inhibitors have a lower risk of herpes infections compared to JAK inhibitors, further supporting their favorable safety profile.

Statement 10: Conjunctivitis, which is usually mild to moderate, is a potential side effect of IL-4/IL-13 and IL-13 inhibitors. (SORT level A)

Dupilumab, an interleukin-4 and interleukin-13 inhibitor, has been associated with an increased incidence of conjunctivitis in patients with atopic dermatitis. In a study by Napolitano et al, 10.42% of patients treated with dupilumab developed conjunctivitis, with the majority experiencing mild to moderate severity.[60] Similarly, Akinlade et al reported that dupilumab-treated patients in atopic dermatitis trials had a higher incidence of conjunctivitis compared to placebo, with most cases being mild to moderate.[61]

Additionally, interleukin-13 inhibitors such as lebrikizumab and tralokinumab have also been linked to an increased risk of conjunctivitis. Zhang et al found that these inhibitors were associated with a higher incidence of conjunctivitis compared to placebo in patients with moderate to severe atopic dermatitis.[33] Wollenberg et al also reported a higher incidence of conjunctivitis in tralokinumab-treated patients compared to placebo, with most cases being mild and transient.[62]

The American Academy of Dermatology guidelines also acknowledge conjunctivitis as a common adverse event with both dupilumab and tralokinumab, recommending conservative management with artificial tears and ophthalmology referral for severe cases.[11]

Statement 11: There have not been reports of treatment related facial erythema or migratory polyarthralgias in patients treated with lebrikizumab to date. (SORT level A)

Available data published in an integrated analysis of 8 clinical trials on the safety of lebrikizumab in adults and adolescents with moderate-to-severe atopic dermatitis did not report treatment-related facial erythema or migratory polyarthralgias in patients treated with lebrikizumab to date. The most frequently reported treatment-emergent adverse events were conjunctivitis and injection site reactions, with no mention of facial erythema or migratory polyarthralgias.[29] Additionally, the FDA's adverse reactions table for lebrikizumab lists common adverse events such as conjunctivitis, injection site reactions, and herpes zoster, but does not include facial erythema or migratory polyarthralgias.[48] These findings are consistent across multiple studies, indicating that facial erythema and migratory polyarthralgias have not been observed as treatment-related adverse events in patients treated with lebrikizumab.

Notably, dupilumab, an IL-4/IL-13 inhibitor, has been associated with facial erythema in a subset of patients, which can be a significant concern in this sensitive area.[44-46] Tralokinumab-related facial redness, including case reports of intense facial erythema and desquamation, has been reported in the literature.[47] There are limitations to comparisons of these agents, as head-to-head trials have not been accomplished, and the duration of use of medications since approval varies greatly.

Statement 12: Inhibition of IL-13 can normalize and/or improve serum markers associated with atopic dermatitis. (SORT level A)

Inhibition of IL-13 has been shown to normalize and improve serum markers associated with atopic dermatitis, demonstrating a significant therapeutic benefit. IL-13 is a key cytokine involved in the pathogenesis of AD, driving inflammation and skin barrier dysfunction.

Lebrikizumab, an IL-13 inhibitor, has demonstrated dose-dependent efficacy in reducing serum periostin, total IgE, and other chemokines, further supporting the role of IL-13 in AD pathophysiology.[63] Emerging data has shown improvement in disease related cytokines as early as week 4.[15,16]

Tralokinumab, another IL-13 inhibitor, has been shown to significantly reduce type 2 inflammatory biomarkers such as thymus and activation-regulated chemokine, periostin, and serum immunoglobin E levels in patients with moderate-to-severe AD. Clinical trials have demonstrated that tralokinumab treatment leads to substantial improvements in the transcriptomic profile of lesional skin, with marked reductions in the expression of genes associated with Th (T helper) 2, Th1, and Th17/Th22 pathways, and increased expression of epidermal differentiation and barrier genes.[14,63,64]

The clinical pharmacology of these IL-13 inhibitors underscores their ability to inhibit IL-13-induced responses, including the release of proinflammatory cytokines and chemokines, which are critical in the inflammatory cascade of AD. The normalization of serum markers and improvement in skin barrier function with IL-13 inhibition provide a robust therapeutic strategy for managing moderate-to-severe AD, as evidenced by multiple clinical trials and FDA-approved treatments.[46,48,65] Overall, the inhibition of IL-13 has been consistently shown to improve key serum markers and clinical outcomes in AD, making it a valuable target for therapeutic intervention in this chronic inflammatory condition.

Statement 13: Considering the availability of safe and effective treatments, the use of systemic steroids for atopic dermatitis should be discouraged. (SORT level A)

Systemic corticosteroids, such as prednisone, hydrocortisone, and celestone, are generally not recommended in managing atopic dermatitis according to clinical guidelines and expert recommendations.[40,66-72]

Under certain circumstances, systemic corticosteroids can be considered for isolated short-term use only. For example, if a short course of corticosteroids is needed as a bridge while the patient awaits insurance approval for definitive therapy. However, even short-term use of oral corticosteroids has been associated with increased risk for sepsis, venous thromboembolism, and fractures in adults[73] as well increased risk for diabetes mellitus, hypertension, and venous thromboembolism in pediatric populations.[74] Their use should be limited if at all practically feasible for the patient. Systemic corticosteroids should also be avoided in patients under 12 years of age owing to adverse effects on growth.[66]

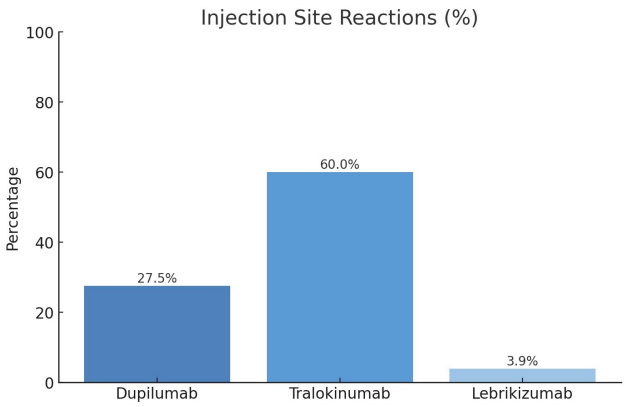

Figure 1. *Reported data on injection site reactions for dupilumab, tralokinumab, and lebrikizumab.*

Data reproduced from Martora et al[67] (dupilumab and tralokinumab) and Stein Gold et al[28] (lebrikizumab).

Despite their ability to rapidly alleviate symptoms, use of systemic corticosteroids is not appropriate for maintenance therapy, and their use is typically reserved for exceptional cases owing to potential adverse effects and the risk of severe rebound flares upon discontinuation.[31,75]

Statement 14: Rate of injection site reactions is lower in patients treated with lebrikizumab than dupilumab and tralokinumab. (SORT level A)

Injection site reactions (ISR) are clinically relevant and important to patient care. Of all IL-13 and IL-4/IL-13 inhibitors, lebrikizumab has the lowest injection site pain.[76] In pivotal trial data, differences in ISR were seen between dupilumab and tralokinumab, with 27.52% (90/327) of patients experiencing ISR with dupilumab versus 60% (39/65) with tralokinumab.[18] In two phase 3 trials of dupilumab versus placebo, Solo 1 and Solo 2, ISR rates were 3% when administered every other week and 9% when administered weekly in Solo 1, and 6% and 5%, respectively, in Solo 2.[77] Emerging data for lebrikizumab found lower rates of ISR in 2.9% (35/1251) of patients treated with 250 mg administered every other week and 3.6% (87/2415) of patients when looking at all lebrikizumab trials to date.[78] Additional data from phase 2 and 3 clinical trials has shown that only 3.1% of lebrikizumab patients had ISR including bruising and only 0.9% reported injection site pain.[29] (Figure 1). In addition, the rate of ISRs falls dramatically after the first 16 weeks with treatment with lebrikizumab.[22,29,48,49,76]

In the experience of some of the participating experts, some patients who experience ISR with tralokinumab, particularly with pain, can be switched to lebrikizumab with marked clinical improvement in pain. Given this, switching from tralokinumab to lebrikizumab in patients with ISR may lead to improved tolerance and decreased pain.

Conclusion

This systematic review and consensus study reaffirms the pivotal role of IL-13 in the pathogenesis of atopic dermatitis and highlights the transformative potential of IL-13-targeted therapies. The evidence demonstrates that IL-13 inhibitors, such as lebrikizumab and tralokinumab, offer rapid, durable, and safe treatment options for patients with moderate-to-severe AD. These therapies not only reduce disease severity and pruritus but also improve quality of life and minimize systemic side effects compared to traditional immunosuppressants. Furthermore, the findings suggest IL-13 inhibitors as viable options for patients with inadequate responses to dupilumab or JAK inhibitors.

As the field of dermatology continues to evolve, the integration of biologic therapies into clinical practice represents a paradigm shift in the management of atopic dermatitis. Future research should focus on long-term outcomes, combination therapies, and biomarker-driven patient stratification to optimize the use of IL-13 inhibitors and further enhance therapeutic outcomes. By bridging the gap between immunological insights and clinical application, this consensus statement provides a robust framework for advancing the care of patients with this challenging condition.

Potential conflicts of interest

Atanaskova-Mesinkovska has received personal fees from Lilly, Concert, Pfizer and grants from Lilly, Pfizer, Concert, and AbbVie and is involved with the National Alopecia Areata Foundation and American Hair Research Society. Michael Cameron has served as a consultant for Abbvie, Apogee, Arcutis, Bristol Myers Squibb, CorEvitas Atopic Dermatitis Registry, CorEvitas Alopecia Areata Registry, Dermavant Sciences, Eli Lilly, Evelo, Galderma, Incyte, Journey Medical, Leo Pharma, Regeneron, Sanofi, Sun, Union Therapeutics, Verrica; a promotional speaker for Abbvie, Amgen, Bristol Myers Squibb, Dermavant Sciences, Eli Lilly, Incyte, Journey Medical, Leo Pharma, Pfizer, Regeneron, Sanofi, Ortho Pharmaceutical, Verrica; and an investigator for Abbvie, Alumis, Apogee, Incyte, Eli Lilly, Novartis, Sanofi, and Sun Pharma. Theodore Daly has served as a speaker and/or consultant for Lilly (Olumiant), Pfizer (Cibinqo, Litfulo, Eucrisa), Abbvie (Rinvoq), and Boehringer-Ingelheim (Spevigo). Lawrence Eichenfield has served as a consultant, advisor, speaker or researcher for AbbVie Inc., Amgen Inc., Attovia, Apogee, Arcutis Biotechnology, Bausch Health, Bristol-Myers Squib, Castle Biosciences, Corvetas, Dermavant,, Dermata, Forte Biosciences, Inc., Galderma Laboratories, L.P., Incyte Corporation, LEO Pharma, Inc., Lilly, Novartis, OrthoDerm, Pfizer, Inc., Regeneron Pharmaceuticals, Inc., Sanofi, T-Rex, and UCB Pharma, Inc. Dawn Merritt has served as an investigator for Aclaris, Incyte, Lilly, Novartis, Regeneron, Sanofi; Speaker Bureaus: Abbvie, Almirall, Amgen, Biofrontera, BMS, Lilly, OrthoDermatologics, Pfizer, Sun, UCB, and is or has been on the advisory Board for BMS, Biofrontera, Pfizer, Sun, and UCB. Lisa Swanson serves as a speaker for AbbVie, Arcutis, Dermavant, Galderma, Incyte, Janssen, Lilly, Pfizer, Sanofi-Regeneron, and Verrica. Additionally, she has held consulting roles (including advisory boards) with AbbVie, Alphyn, Arcutis, Boehringer Ingelheim, Castle, Dermavant, Galderma, Incyte, Janssen, Leo, Lilly, Novan, Pfizer, Sanofi-Regeneron, and Verrica. Mark Lebwohl is an employee of Mount Sinai and receives research funds from Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen, Pfizer, Sanofi-Regeneron, and UCB. He is also a consultant for Almirall, AltruBio Inc., Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica.

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