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REVIEW

Targeting the IL-4/IL-4R Axis in Th2 Inflammatory Diseases: A Review of Clinical Efficacy and Safety

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Abstract: The interleukin-4/its receptor (IL-4/IL-4R) axis has been identified as a pivotal driver of type 2 (Th2) inflammation. Biologics targeting this axis, particularly IL-4 receptor alpha subunit (IL-4Rα) monoclonal antibodies (such as dupilumab), provide revolutionary therapeutic options for multiple Th2 inflammatory diseases by simultaneously blocking IL-4 and interleukin-13 (IL-13) signaling. This review systematically evaluates the clinical application of IL-4/IL-4R-targeted therapies across a spectrum of indications, including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis, and bullous pemphigoid. A substantial body of research, including randomized controlled trials and real-world studies, has demonstrated the efficacy of this therapy in improving disease-specific scores, enhancing lung function, and reducing the risk of acute exacerbations. However, the effectiveness of this treatment exhibits heterogeneity, with some patients developing primary resistance. With respect to safety, the therapy is generally well-tolerated; however, it is associated with a series of characteristic adverse events, including injection site reactions (incidence 8%-22%), disease-specific conjunctivitis (up to 14%-19% in patients with atopic dermatitis), nasopharyngitis, and transient eosinophilia. Future advancements in dynamic biomarker monitoring, bispecific antibody development, and precision dosing strategies hold promise for further optimizing the efficacy-safety balance and expanding therapeutic applications, including in neurodegenerative diseases. The objective of this review is to provide clinicians with a thorough, evidence-based synopsis of the current clinical value and prospects of IL-4/IL-4R-targeted therapies.

Keywords: IL-4/IL-4R axis, dupilumab, Th2 inflammatory diseases, targeted therapy, clinical efficacy and safety

Introduction

Interleukin-4 (IL-4), predominantly synthesized by T helper 2 (Th2) lymphocytes, innate lymphocyte type 2 (ILC2), and follicular helper T cells, serves as a pivotal regulator of Th2 immune responses. It exhibits a dual function in immune regulation, inflammatory response, and tissue repair.[1–5] IL-4 has been shown to act synergistically with interleukin-13 (IL-13) by binding to the α-chain of the IL-4 receptor (IL-4R). The receptor alpha subunit (IL-4Rα) has been found to activate the Janus Kinase - signal transducer and activator of transcription 6 (JAK-STAT6) signaling pathway, induce B cells to immunoglobulin E (IgE) class switching, and promote memory B cell generation.[2,6–8] This process underlies the IgE-mediated type I hypersensitivity reaction in allergic diseases.[9] IL-4 has been shown to drive eosinophil infiltration into inflammatory sites and enhance their degranulation capacity by upregulating the expression of vascular cell adhesion molecule-1 (VCAM-1) and eosinophil chemokines, creating a vicious cycle of Th2 inflammation.[10,11] Furthermore, IL-4 has been shown to inhibit Th1 cell differentiation while promoting M2-type macrophage polarization, thereby constructing a Th2/M2-dominated immunosuppressive microenvironment.[8,12,13] This feature of IL-4 plays a dual role in tumor-associated inflammation and chronic infection.

Aberrant activation or dysregulation of the IL-4 signaling pathway has been observed to be closely associated with a variety of Th2 inflammatory diseases. For instance, in the case of atopic dermatitis (AD), IL-4 has been shown to directly activate cutaneous sensory nerves, thereby initiating the itch-scratch cycle and exacerbating skin barrier dysfunction.[10,14,15] Concurrently, IL-4 and IL-13 activate keratinocytes, fibroblasts, and endothelial cells, promote

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chemokine production, and recruit inflammatory cells such as eosinophils to the skin, thereby exacerbating the inflammatory response.[10,16] In the context of asthma, IL-4 has been demonstrated to induce the production of mucus by airway epithelial cells and smooth muscle cells, thereby increasing airway hyperresponsiveness and leading to airway narrowing and dyspnea.[2,3] Furthermore, aberrant IL-4 signaling has been implicated in the process of eosinophilic inflammatory infiltration in chronic rhinosinusitis with nasal polyps (CRSwNP) and esophageal fibrosis in eosinophilic esophagitis (EoE).[10,17] The resultant inflammation is characterized by the induction of chemokine production in esophageal epithelial cells, the attraction of eosinophils to accumulate in the esophageal mucosa, and the subsequent development of esophageal dysfunction, including dysphagia and chest pain.[10,18] In recent years, genome-wide association studies (GWAS) have further revealed that *IL4R* polymorphisms are significantly associated with Th2-type disease susceptibility, suggesting the centrality of the IL-4/IL-4R axis in disease development.[19,20] A review of epidemiological data shows a global increase in the prevalence of the diseases above. It is estimated that 30–50% of patients exhibit suboptimal responses to conventional therapeutic modalities, underscoring the necessity for targeted interventions that selectively modulate the IL-4 pathway.[21,22]

Glucocorticoids and broad-spectrum immunosuppressive agents (eg, cyclosporine, methotrexate) have been utilized for the management of Th2-type inflammation for an extended period. However, their nonspecific immunosuppressive characteristics result in substantial clinical limitations.[23–25] Prolonged systemic use of glucocorticoids has been demonstrated to result in the development of metabolic disorders, including diabetes and osteoporosis, an elevated risk of infection, and suppression of the hypothalamic-pituitary-adrenal axis.[26] Topical hormones, despite their enhanced safety profile, demonstrate limited efficacy in patients with moderate-to-severe atopic dermatitis and are associated with adverse effects, such as skin atrophy and capillarization.[25,27] Furthermore, approximately 30–40% of patients diagnosed with severe asthma exhibit non-response to high-dose inhaled corticosteroid combined with long-acting beta agonist (ICS/LABA) therapy, and some patients even develop a hormone-resistant phenotype.[28,29] The targeted anti-IgE monoclonal antibodies (eg, omalizumab) have been demonstrated to impede the allergic response, albeit with limitations. Their targeting is confined to the downstream effects of IgE, precluding intervention in the IL-4-driven upstream inflammatory cascade.[30] A more critical issue that must be addressed is the predicament encountered by patients suffering from refractory Th2 disease (eg, CRSwNP or EoE accompanied by multiple comorbidities). These patients often find themselves confronted with the unfortunate circumstance of "no drug available".[31] They are in dire need of more precise and long-lasting targeted therapeutic strategies.

In light of these challenges, the development of biologics targeting the IL-4/IL-4R axis has been undertaken to achieve "cause-level" intervention by specifically blocking the core signaling nodes of Th2 inflammation.[11] In contrast to conventional broad-spectrum immunomodulation, IL-4 inhibitors (eg, anti-IL-4 monoclonal antibody, anti-IL-4Rα monoclonal antibody) selectively impede IL-4 binding to type I/II receptors, consequently diminishing IgE production, eosinophil activation, and tissue fibrosis, while maintaining the functional integrity of other immune pathways.[32] The remarkable effectiveness of dupilumab, the first approved IL-4Rα inhibitor, in the treatment of atopic dermatitis and asthma has not only validated the therapeutic potential of this target but has also catalyzed the development of multifaceted drugs targeting the IL-4 signaling network (eg, bispecific antibodies, gene-silencing technologies).[33] However, as clinical applications have expanded, concerns regarding the heterogeneity of efficacy (eg, primary resistance in some patients), safety risks (eg, conjunctivitis, nasopharyngitis), and the lack of data on the use of IL-4 inhibitors in special populations (children, pregnant females) have gradually emerged.

In order to provide a comprehensive and objective evaluation of the efficacy and safety of IL-4/IL-4R-targeted therapies, this review primarily analyzes published pivotal Phase III randomized controlled trials (RCTs), significant real-world studies (RWS), and relevant meta-analyses. A comprehensive literature search was conducted in major databases, including PubMed, Web of Science, and the Cochrane Library, with a cutoff date of 2025. The core search terms that were utilized in this study included "IL-4", "IL-4Rα", "dupilumab", "Th2 inflammation", and related disease names (eg, "atopic dermatitis", "asthma"). In the context of literature screening, a deliberate emphasis was placed on high-quality, large-sample clinical studies to ensure the reliability and clinical relevance of conclusions. This review aims to systematically evaluate the efficacy and safety of biologics targeting the IL-4/IL-4R axis (represented by dupilumab) as

demonstrated in multiple randomized controlled trials and real-world studies, and to discuss their current clinical positioning and future challenges.

IL-4/IL-4R Signaling Pathway and Targeted Therapeutic Mechanism

Signaling Cross-Talk Between IL-4 and IL-13

IL-4 and IL-13 are classified as Th2-type cytokines, and they share part of the receptor complex. However, the signaling pathways and biological effects of these two cytokines differ significantly.[8,10,34–36] IL-4 is known to act through two receptor complexes. The type I receptor (IL-4Rα/γc) is expressed primarily on hematopoietic cells (eg, T cells, B cells, mast cells). Type I receptors activate JAK1 and JAK3, which mediate the classical functions of IL-4, including B-cell class switching (IgE production), Th2 cell differentiation, and M2-type macrophage polarization.[10,34,35,37] Type II receptors (IL-4Rα/IL-13Rα1) are widely distributed in non-hematopoietic cells (eg, Epithelial cells, fibroblasts, and smooth muscle cells are the target cells for IL-4 and IL-13, and the type II receptor activates JAK1 and Tyrosine Kinase 2 (TYK2), which in turn drive the tissue inflammatory response (eg, mucus secretion, airway hyperresponsiveness) and the fibrotic process.[10,34,35] Although IL-13 is unable to bind to the type I receptor, its high-affinity binding to the type II receptor allows it to dominate in tissue remodeling.[36] This signaling crossover leads to a "complementary-synergistic" network between IL-4 and IL-13 in Th2 inflammation: IL-4 has been shown to play a predominant role in the regulation of immune cells, while IL-13 has been identified as a key factor in the induction of tissue structural changes (Table 1).[38] The phenomenon of IL-4/IL-13 synergy in AD is characterized by a duality of manifestations, including skin barrier disruption, a trait associated with IL-4 dominance, and the presence of chronic pruritus which is commonly linked to IL-13 dominance.[11] Additionally, in CRSwNP, these manifestations are characterized by polyp growth (IL-13-dominated) and eosinophil infiltration (IL-4-dominated).[39] Consequently, monoclonal antibodies that target IL-4Rα, such as dupilumab, can impede the signaling of both IL-4 and IL-13, thereby achieving a dual inhibition of Th2 inflammation (Figure 1).[11,33]

Targets of Action and Drug Types of IL-4 Inhibitors

The molecular interactions characterized by the IL-4/IL-4R axis are the basis for the classification of currently developed IL-4 inhibitors into the following three main categories: The mechanism of action of anti-IL-4 monoclonal antibodies involves the prevention of the interaction with type I and II receptors through a direct binding process with free IL-4.[40] The designated pharmaceutical agent is pascolizumab (a recombinant, humanized, anti-IL-4 monoclonal antibody) that functions by impeding the binding of IL-4 to IL-4Rα through a spatial site-blocking mechanism.[40] Preliminary clinical investigations indicated that the substance could curtail the incidence of acute exacerbations and enhance lung function in

Table 1 Distribution and Functional Differences Between IL-4Rα/γc Complex (Type I Receptor) and IL-4Rα/IL-13Rα1 Complex (Type II Receptor)

Characteristic	Type I Receptor (IL-4Rα/γc)	Type II Receptor (IL-4Rα/IL-13Rα1)
Cellular distribution	Hematopoietic cells (T cells, B cells, mast cells)	Non hematopoietic cells (epithelial cells, endothelial cells, fibroblasts)
Ligand specificity	IL-4 only	IL-4 and IL-13
Signaling pathway	JAK1/JAK3-STAT6 (Rapid immune response)	JAK1/TYK2-STAT6 (Continuous tissue remodeling)
Disease association	Acute allergic reactions (such as IgE mediated urticaria)	Chronic fibrosis diseases (such as asthma airway remodeling)
Therapeutic target value	Inhibit acute inflammation	Reduce chronic tissue damage

Abbreviations: IL-4Rα, Interleukin-4 Receptor Alpha Subunit; γc, Common Gamma Chain; IL-13Rα1, Interleukin-13 Receptor Alpha 1; JAK, Janus Kinase; STAT, Signal Transducer and Activator of Transcription; TYK, Tyrosine Kinase; IgE, Immunoglobulin E.

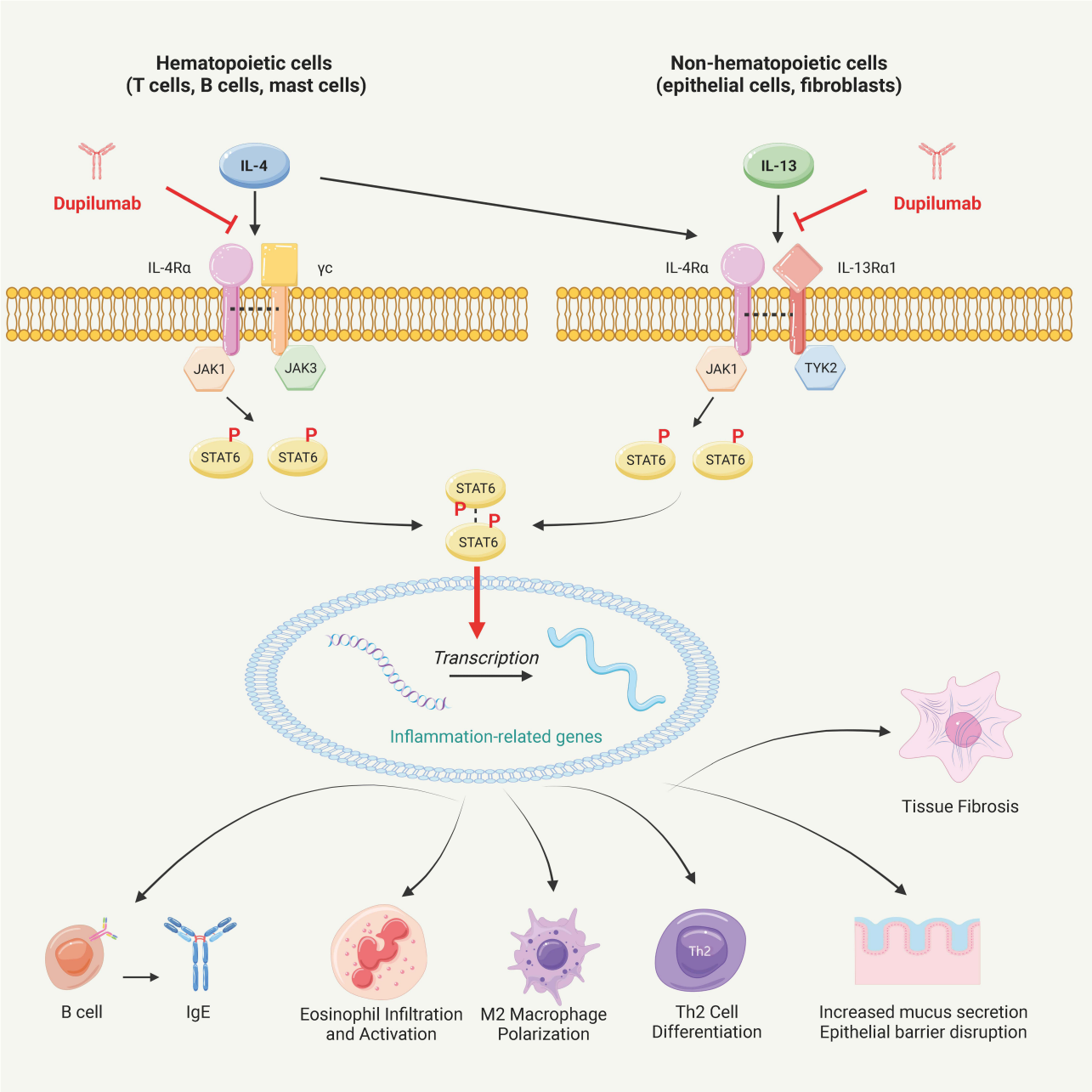

Figure 1 IL-4/IL-13 Signaling Pathway and Mechanism of Targeted Therapy.
Abbreviations: IL-4, Interleukin-4; IL-13, Interleukin-13; IL-4Rα, Interleukin-4 Receptor Alpha Subunit; IL-13Rα1, Interleukin-13 Receptor Alpha Chain 1; JAK1, Janus Kinase 1; JAK3, Janus Kinase 3; TYK2, Tyrosine Kinase 2; STAT6, Signal Transducer and Activator of Transcription 6; IgE, Immunoglobulin E; Th2, T helper type 2 cell.

mild asthma cases.[41] However, further development was precluded due to its brief half-life and constrained efficacy.[41] Its limitations include its inability to inhibit IL-13 signaling, which renders it less effective in diseases that depend on type II receptor-mediated processes. Furthermore, the treatment necessitates frequent administration and often requires patient compliance, which can be a significant challenge.[41]

The anti-IL-4Rα monoclonal antibody is the most critical and commonly used target in IL-4 signaling. The primary mechanism of action involves the inhibition of IL-4 and IL-13 signaling through binding to IL-4Rα, thereby forming a "dual-target inhibition" that has emerged as the most effective clinical strategy to date.[42] The pharmaceutical agent under consideration is dupilumab, a fully human immunoglobulin G4 (IgG4) monoclonal antibody that exhibits high affinity binding to IL-4Rα, thereby impeding IL-4/IL-13-dependent STAT6 phosphorylation and, consequently, the

expression of downstream inflammatory genes, including *CCL26* and *MUC5AC*.[36] The medication has been approved for the treatment of a variety of indications, including moderate-to-severe AD, moderate-to-severe asthma, CRSwNP, EoE, prurigo nodularis (PN), and bullous pemphigoid (BP).[43]

The IL-4 variant antagonist is a genetically engineered, modified IL-4 molecule. It is not an antibody itself, but rather a functionally defective cytokine variant. Its primary mechanism of action is to serve as a "molecular decoy", competitively inhibiting the signaling pathway of native IL-4. A representative drug is pitrakinra, which has been demonstrated to reduce the risk of systemic exposure through localized administration (eg, inhalation in the lungs) and has been shown to reduce airway eosinophil infiltration in asthma models.[44] In an independent randomized, double-blind, placebo-controlled, parallel-group Phase 2a clinical trial, nebulization of 60 mg pitrakinra twice daily resulted in a significant reduction in asthma symptoms.[45] While the topical administration of these substances may enhance safety, it is imperative to optimize stability and tissue penetration.[46] In comparison to monoclonal antibodies targeting IL-4Rα, such as dupilumab, which demonstrate notable efficacy and advancement in development, these drugs exhibit a significantly lower level of success. Furthermore, there are no widely available marketed products in this category. The clinical development timeline of IL-4/IL-4R targeted drugs is detailed in Table 2.

Table 2 Clinical Development Timeline of IL-4/IL-4R-Targeted Therapeutics

Drug Name/Code	Drug Type	Primary Target	Key Development Milestones	Current Status
Pascolizumab	Humanized anti-IL-4 monoclonal antibody	Soluble IL-4	Completed initial clinical studies for mild asthma in the early 2000s.	Development Terminated (due to short half-life and limited efficacy)
Pitrakinra	IL-4 variant antagonist	IL-4Rα (blocks both IL-4 and IL-13 signalling)	A Phase 2a trial in 2007 showed reduction in asthma symptoms.	Development Terminated (Not advanced further, no marketed product)
Dupilumab	Humanized anti-IL-4Rα monoclonal antibody	IL-4Rα (blocks both IL-4 and IL-13 signalling)	First approved for moderate-to-severe atopic dermatitis in 2017; subsequently approved for asthma, CRSwNP, EoE, PN, and BP (2025).	Approved Globally (Core drug, multiple indications)
Stapokibart (CM310)	Humanized anti-IL-4Rα monoclonal antibody	IL-4Rα (blocks both IL-4 and IL-13 signalling)	Initially approved in China for adults with moderate-to-severe atopic dermatitis in September 2024; Approved for CRSwNP in December 2024; Approved for seasonal allergic rhinitis in January 2025.	Approved in China (Indications expanding)
Rademikibart (CBP-201)	Next-generation anti-IL-4Rα monoclonal antibody	IL-4Rα (blocks both IL-4 and IL-13 signalling)	Phase 2 trials demonstrated significant efficacy in atopic dermatitis and eosinophilic asthma.	Phase III
RC1416	Anti-IL-4Rα/IL-5 bispecific nanobodies	IL-4Rα and IL-5	In May 2025, positive results from the Phase Ib trial in moderate-to-severe asthma showed good efficacy, safety, and tolerability.	Phase II

(*Continued*)

Table 2 (Continued).

Drug Name/Code	Drug Type	Primary Target	Key Development Milestones	Current Status
IBI3002	Anti-IL-4Rα/ TSLP bispecific antibody	IL-4Rα and TSLP	Completed Phase I single ascending dose trial; evaluating safety and PK/PD in healthy volunteers and patients with mild-to-moderate asthma.	Phase I
GB12-09	Anti-IL-4Rα/ IL-31R bispecific antibody	IL-4Rα and IL-31R	Preclinical studies showed significant improvement in skin barrier dysfunction and inflammation in a mouse model of AD.	Preclinical Research

Abbreviations: IL-4, Interleukin-4; IL-4R, Interleukin-4 Receptor; IL-4Rα, Interleukin-4 Receptor Alpha Subunit; IL-13, Interleukin-13; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; EoE, Eosinophilic Esophagitis; PN, Prurigo Nodularis; BP, Bullous Pemphigoid; TSLP, Thymic Stromal Lymphopoietin; IL-31R, Interleukin-31 Receptor; PK/PD, Pharmacokinetics/Pharmacodynamics; AD, Atopic Dermatitis.

Clinical Applications of IL-4 Inhibitors

Atopic Dermatitis

IL-4 inhibitors have emerged as a pivotal therapeutic approach for moderate-to-severe AD, effectively modulating the Th2-type immune response by obstructing the IL-4 signaling pathway. This has led to a substantial improvement in the skin inflammation and pruritic symptoms associated with AD.[47,48] At present, the IL-4 inhibitor market is dominated by dupilumab, which is designed to target IL-4Rα and impede the IL-4 and IL-13 signaling pathways. It is approved for use in adult and pediatric patients aged ≥6 months.[49–53] The pivotal clinical trials (SOLO 1/2, CHRONOS) confirmed that a significantly higher proportion of adults treated with 300 mg every 2 weeks achieved Investigator Global Assessment (IGA) 0/1 (lesion clearance/near clearance) and a ≥2-point reduction in IGA scores than the placebo group (SOLO 1: 38% vs 10%; SOLO 2: 36% vs 9%; CHRONOS: 39% vs 12%). The study found that the proportion of patients achieving ≥75% improvement in the Eczema Area and Severity Index (EASI-75) and significant relief of pruritus was higher.[50,54,55] In children aged 6 months to 5 years with severe AD, there was a substantial improvement in response rates after 16 weeks of treatment with IGA ≤1 (14.3% vs 1.6%) and EASI-75 (46.0% vs 6.6%). Furthermore, the adverse event rates were comparable to those of placebo, with no treatment interruptions.[56] The pharmaceutical agent demonstrated a marked enhancement in the quality of life for both patients and caregivers, with generally good tolerability.[57] However, it is imperative to observe for the occurrence of conjunctivitis or injection site reactions, necessitating appropriate monitoring measures.[55]

In a phase 2 trial, rademikibart (CBP-201), one of the investigational drugs, demonstrated significant improvements in EASI score and pruritus compared to placebo. The incidence of adverse events was comparable between the rademikibart treatment group and the placebo group.[58] Stapokibart (CM310) was the first to be approved in China in September 2024 for the treatment of moderate to severe atopic dermatitis in adults who are poorly controlled or for whom topical medications are not indicated.[59] The results from the Phase 3 trial demonstrated the long-term efficacy of stapokibart and its favorable safety profile in adults with moderate to severe AD.[42,60,61]

Concerning prevailing clinical trends, dupilumab continues to be regarded as the prevailing standard of efficacy. However, ongoing research endeavors may lead to advancements in the field, particularly in overcoming existing efficacy limitations. These advancements may be achieved through the optimization of targets (eg, dual inhibition of IL-4/IL-13) and the development of population-specific designs. One notable example of a combination strategy involves the use of IL-4 inhibitors in conjunction with other biological agents. It has been posited that the administration of upatinib or IL-13/IL-31-targeted agents may result in higher remission rates. The employment of biomarkers such as serum thymus activation-regulated chemokine (TARC) has the potential to facilitate the identification of populations that may benefit from treatment. Furthermore, the range of indications is anticipated to expand to encompass patients with infantile AD or comorbid Th2-related diseases, including asthma. In summary, the utilization of IL-4 inhibitors has the potential to enhance the efficacy of AD therapy, leading to increased response rates and a more customized approach to treatment.

However, it is crucial to note that further validation is necessary to ensure the long-term safety, cost-effectiveness, and performance of these treatments in specific populations.

Asthma

In the field of immunology, IL-4 inhibitors have emerged as a promising therapeutic agent for the management of asthma. The efficacy of IL-4 inhibitors has been well-documented in clinical trials, particularly in cases of moderate-to-severe asthma. They have shown notable benefits for patients suffering from elevated eosinophils or those with refractory asthma, highlighting their potential for diverse therapeutic applications.[2,62–65] At present, dupilumab constitutes the primary therapeutic agent. Its pivotal clinical trials, QUEST and VENTURE, demonstrated a 48–66% reduction in severe acute exacerbations and a 130–240 mL improvement in forced expiratory volume in one second (FEV1) over 52 weeks in adult patients with eosinophils ≥150/μL or fractional exhaled nitric oxide (FeNO) ≥ 25 ppb.[63,64,66] In the case of oral hormone-dependent asthma, a combination treatment for 24 weeks led to a 70% reduction in hormone dosage, accompanied by a 59% reduction in the risk of acute exacerbations and a 220 mL improvement in lung function (FEV1).[67] From a safety perspective, the most prevalent adverse effects associated with dupilumab were nasopharyngitis (17.5–25.9%), injection-site erythema (2.2–23.4%), and bronchiolitis (9.3–19.0%). However, the medication was generally well tolerated.[68] In a randomized controlled trial of children aged 6 to 11 years with uncontrolled moderate to severe asthma, those treated with add-on dupilumab demonstrated a reduced incidence of asthma exacerbations and enhanced lung function and asthma control, in comparison with those receiving placebo.[69] Children and their caregivers also experienced significant improvements in quality of life.[70] The most frequently reported adverse events included nasopharyngitis, pharyngitis, and upper respiratory tract infections.[71]

Among the investigational drugs, rademikibart, which targets patients with eosinophilic asthma, demonstrated an increase in FEV1 of approximately 420 milliliters after 24 weeks of treatment, accompanied by a reduced rate of acute exacerbations and milder injection reactions.[72] Concerning the trends in efficacy, biomarkers (eg, blood eosinophils, FeNO) have emerged as key predictors of IL-4/IL-13 inhibitor efficacy.[73,74] Furthermore, the emergence of long-acting agents and combination strategies, such as those targeting IL-5 or thymic stromal lymphopoietin (TSLP), signifies a paradigm shift in the therapeutic landscape for patients with non-eosinophilic asthma or children. These novel approaches aim to overcome the current treatment limitations, thereby offering a promising avenue for advancements in the management of these conditions. Subsequent studies will concentrate on broadening the indication population (eg, hypereosinophilic asthma, pediatric patients) and individualized treatment strategies. The potential of IL-4 inhibitors to further optimize asthma management is predicated on their capacity to co-target multiple inflammatory pathways, such as IL-4/IL-13 with IL-5 or TSLP, or to reduce hormone dependence.

Chronic Rhinosinusitis with Nasal Polyps

In the context of CRSwNP, IL-4 inhibitors have exhibited remarkable therapeutic efficacy, particularly in cases of recurrent or refractory disease.[75,76] At present, dupilumab represents the core therapeutic agent, and its phase III clinical trial (LIBERTY NP SINUS-24/52) demonstrated a substantial decrease in the nasal polyp score (NPS) (≥1) in approximately 75% of patients at 16–24 weeks, in contrast to 39% in the placebo group. A reduction in nasal polyp volume by at least 50% was observed in 60% of patients after 52 weeks of long-term treatment. Concurrently, a decrease in Sino-Nasal Outcome Test 22 (SNOT-22) of nearly 9 points was demonstrated. Furthermore, significant reductions in systemic hormone use and the need for surgery were observed.[75,77,78] The 12-month long-term real-world study continues to support the effectiveness of dupilumab as an add-on therapy in patients with CRSwNP in reducing polyp size and improving quality of life, symptom severity, nasal congestion, and odor.[79] Furthermore, dupilumab demonstrated a more pronounced efficacy in improving objective measures and patient-reported symptoms in patients with uncontrolled severe CRSwNP in combination with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) compared to those not exhibiting these characteristics.[80]

The efficacy of the investigational drug is being enhanced by mechanism optimization and population segmentation. A phase 2 clinical trial demonstrated that stapokibart (CM310) significantly reduced nasal polyp size and relieved nasal congestion compared to placebo. Additionally, the drug decreased considerably type 2-related biomarkers, including

serum TARC and total IgE, as well as tissue eosinophils.[81] Two key directions mark the future of this field. Firstly, there is a push to expand the treatment population to improve accessibility and inclusivity. Secondly, there is a focus on developing precision strategies, which aim to target specific conditions with greater accuracy and precision. The investigation of the utilization of IL-4 inhibitors in pediatric patients afflicted with CRSwNP, comorbid asthma, or atopic dermatitis, and the development of combination therapies (eg, with IL-17 inhibitors) for patients exhibiting hypereosinophilia or non-Th2 types is imperative. The early utilization of biologics to substitute for or postpone surgical interventions and to mitigate the likelihood of subsequent occurrences has emerged as a pivotal clinical concern. Furthermore, precise stratification based on nasal mucosal gene expression or multiple cytokine profiles may obviate overtreatment with pan-Th2 inhibition and enable individualized dosing.

Eosinophilic Esophagitis

IL-4 inhibitors modulate the Th2-type inflammatory response by targeting the IL-4/IL-13 pathway and show significant potential in the treatment of EoE, especially for moderate-to-severe patients in whom conventional therapies (eg, proton pump inhibitors, topical hormones) have failed.[82] Dupilumab, the first biologic to be approved for EoE, is currently available.[82,83] A pivotal phase III trial (LIBERTY EoE TREAT) demonstrated the efficacy of a dual endpoint, which was achieved after 24 weeks of treatment. Histologic remission (esophageal eosinophil counts ≤6/higher magnification field of view) was achieved in approximately 60% of patients, in contrast to only 5% of those in the placebo group. Additionally, patients who underwent weekly treatment with dupilumab exhibited a decrease in dysphagia symptom scores (DSQs) by more than 9.9–12.3 points, in comparison to the placebo group.[82] The long-term extension trial further confirmed that the histologic remission rate improved to more than 75% with a manageable safety profile when treatment was continued for 52 weeks, with the common side effect being injection site reactions (11–14%).[84] Subgroup analyses indicated that dupilumab 300 mg administered once weekly exhibited efficacy and was well tolerated in patients diagnosed with EoE, irrespective of prior corticosteroid utilization, inadequate response, intolerance, and/or contra-indications to corticosteroids.[85] Furthermore, in patients aged 1 to 11 years with active eosinophilic esophagitis, those receiving dupilumab (either dose) exhibited a 55–65% higher rate of histologic remission in comparison to the placebo group.[86] In a series of clinical trials conducted in the context of EoE, the majority of patients administered dupilumab demonstrated histologic, endoscopic, and symptomatic improvement, accompanied by a reduction in esophageal stricture diameter.[87–89]

In terms of efficacy trends, biomarker stratification has become critical. A robust correlation was identified between the levels of blood eosinophils (EOS) and esophageal tissue IL-4/IL-13 expression and the response to treatment. Furthermore, combination therapy strategies for refractory EoE are being investigated, including the use of IL-4 inhibitors in conjunction with anti-IgE drugs (omalizumab) or JAK inhibitors to target multiple inflammatory pathways. In the context of distant complications, such as esophageal fibrosis, dual inhibition of IL-4/IL-13 with pro-fibrotic factors (eg, TSLP) has the potential to represent a breakthrough point. Furthermore, the emergence of noninvasive biomarkers (eg, TARC) is anticipated to supersede the necessity for repeated endoscopic biopsies, thereby facilitating streamlined treatment monitoring.

Prurigo Nodularis

IL-4 inhibitors have emerged as a significant therapeutic option for PN. Dupilumab received FDA approval in September 2022 for the treatment of PN, and in 2023 for adult patients with moderate-to-severe PN in the United Kingdom and China, among other regions. It is particularly indicated for patients with severe or treatment-resistant PN for whom topical therapy is ineffective or contraindicated. A global phase III trial (PRIME/PRIME2) revealed that itch was significantly reduced in 37% of patients after 12 weeks of treatment, in comparison to 22% in the placebo group. Furthermore, sustained relief of itch was increased to 60% at 24 weeks (18% in the placebo group), which was three times more efficacious than the placebo.[90] Concurrently, complete or near-complete clearing of the lesions was achieved by week 24 in 46.4% of patients (17.1% in the placebo group), who experienced a significant improvement,[91] and a higher percentage of patients exhibited an enhancement in their quality of life (DLQI score) (24.8% vs 6.3%).[92] Patients treated with dupilumab demonstrated a significantly faster rate of clinically meaningful symptom improvement

compared to those treated with a placebo.[92] The efficacy of the treatment was further validated in the China 2025 multicenter real-world study. After 12 weeks of treatment in 73 patients with refractory PN, 84.9% achieved a clinically meaningful improvement in PP-NRS ≥ 4 points. By 16 weeks, 46.6% of patients had achieved complete clearance or almost complete clearance of skin lesions (IGA grade 0/1) and demonstrated an improvement in their quality of life index (DLQI) from 16.6 to 6.4 points.[93] However, the existing body of literature on the subject is limited, with only a few case reports addressing the treatment of PN in children. For instance, the 2025 case study documented a substantial alleviation of pruritus in an 11-year-old child diagnosed with allergic rhinitis who received dupilumab treatment within two weeks. The treatment resulted in a reduction in pruritus score (PP-NRS), skin lesion score (IGA), and quality of life (CDLQI) scores of 7, 2, and 10, respectively, after four weeks. Notably, these improvements were sustained at six months following the cessation of drug administration.[94] Another report documented the case of a 9-year-old girl afflicted with intractable nodular itchy rash, who initiated treatment with dupilumab. This treatment resulted in a swift alleviation of pruritus within a fortnight, accompanied by a near-total regression of the lesions after three months.[95]

The future direction of research will center on the exploration of combination therapy strategies, such as the administration of dupilumab in conjunction with JAK inhibitors (upatinib). This approach aims to enhance the control of refractory PN by synergistically inhibiting neuroimmune pathways, such as IL-31-JAK-STAT. Concurrently, the trend of individualized dosing is gaining increasing significance. This is being accompanied by the optimization of patient selection based on the stratification of biomarkers, such as serum TARC, IL-13, and others. The objective of this development is to promote precision treatment.

Bullous Pemphigoid

IL-4 inhibitors for the treatment of BP have recently achieved a significant breakthrough with the FDA's approval of dupilumab in June 2025 as the world's first biologic targeted at BP. This approval is predicated on data from the pivotal LIBERTY-BP ADEPT phase 2/3 clinical trial, the results of which have not yet been made publicly available.[96] A substantial body of research has validated the significant clinical benefits of dupilumab in the treatment of BP. A study of 13 elderly patients (mean age 76.8 years) exhibited 92.3% of subjects achieving disease clearance or a satisfactory response, with 53.8% demonstrating complete resolution and no adverse events.[97] A multicenter study of 103 patients in Spain further substantiated these findings, revealing that 53.4% experienced complete resolution of symptoms within 4 weeks. Furthermore, 70% experienced early relief of pruritus, and more than 80% saw a reduction in corticosteroid dosage. The adverse event rate was only 12.6%.[98] A controlled study confirmed that the time to cessation of new blisters was reduced by 4 days in the combined dupilumab group compared to the hormone-alone group (8 vs The duration of hormone reduction to the minimum dose was advanced by 27 days (121.5 vs 148.5 days). The cumulative dose of hormone was reduced by 24% (18%). The cumulative dose of hormone was decreased by 24% (1898 mg vs 2344 mg), and BPDAI scores and eosinophil/IgE levels were significantly improved.[99] A retrospective study of 146 patients further validated disease control in 87% of patients within 4 weeks, with a total of 35.6% of patients in complete remission within the observation period.[100] All studies reported mild adverse effects, with no serious safety concerns identified.

Future directions in this field are focused on three primary areas of research. Firstly, there is a need to expand the indication population, including cases of pediatric BP and hypereosinophilic subtypes. Secondly, there is a need to explore combination therapy strategies with anti-IgE or JAK inhibitors to attack refractory BP. Thirdly, there is a need to promote biomarker stratification based on serum TARC, IL-13, and eosinophilic counts to achieve individualized dosing. To assess the long-term safety of conjunctivitis, herpesvirus infections, and related conditions, continuous monitoring of real-world data for a period exceeding five years is imperative. This comprehensive approach will facilitate the optimization of therapeutic strategies, thereby contributing to the refinement of BP clinical management (Table 3).

Table 3 Summary of Key Clinical Trials for IL-4/IL-4R Targeted Therapies (Dupilumab)

Indication	Key Phase 3 Trial Name	Patient Population	Primary Endpoint(s)	Key Efficacy Results (vs Placebo)	Common Adverse Events (Higher Than Placebo)
AD	SOLO 1 and 2	Adults with moderate-to-severe AD	IGA score of 0 or 1 and EASI-75 at Week 16	IGA 0/1: 36% vs 9% (p<0.001)	Injection site reactions (8–19%)
				EASI-75: 49% vs 14% (p<0.001)	Conjunctivitis (3–5%)
AD	LIBERTY AD CHRONOS	Adults with moderate-to-severe AD requiring topical corticosteroids	IGA score of 0 or 1 and EASI-75 at Week 16	IGA 0/1: 39% vs 12% (p<0.001)	Conjunctivitis (14–19%)
				EASI-75: 66% vs 23% (p<0.001)	Injection site reactions (15–19%)
Asthma	LIBERTY ASTHMA QUEST	Adults with uncontrolled moderate-to-severe asthma (Blood EOS ≥150/μL or FeNO ≥25 ppb)	Annualized severe exacerbation rate and change in FEV1 at Week 12	Reduction in exacerbations: 48–66% (p<0.001)	Injection site reactions (15–18%)
				Improvement in FEV1: 130–240 mL (p<0.001)	Eosinophilia (4%)
Asthma	LIBERTY ASTHMA VENTURE	Adults with oral corticosteroid-dependent severe asthma	Reduction in OCS dose at Week 24	Reduction in OCS dose: 70% vs 41% (p<0.001)	Injection site reactions (9%)
					Eosinophilia (14%)
CRSwNP	LIBERTY NP SINUS-24/52	Adults with severe CRSwNP	Change in nasal polyp score (NPS) and nasal congestion or obstruction score (NCS) at Week 24/52	Week 24:	More common in the placebo group
				NPS: −1.89 vs 0.17 (p<0.001)	
				NCS: −1.34 vs −0.45 (p<0.001)	
				Week 52:	
				NPS: −1.71 vs 0.10 (p<0.001)	
				NCS: −1.25 vs −0.38 (p<0.001)	
EoE	LIBERTY EoE TREET	Adults and adolescents with active EoE	Histologic remission (peak eosinophil count ≤6/HPF) and change in Dysphagia Symptom Questionnaire (DSQ) at Week 24	Histologic remission: 60% vs 5% (p<0.001)	Injection site reactions (17–22%)
				Difference in DSQ change from placebo group: −9.9 to −12.3 points (p<0.001)	Nasopharyngitis (2–12%)

(*Continued*)

Table 3 (Continued).

Indication	Key Phase 3 Trial Name	Patient Population	Primary Endpoint(s)	Key Efficacy Results (vs Placebo)	Common Adverse Events (Higher Than Placebo)
PN	LIBERTY-PN PRIME & PRIME2	Adults with moderate-to-severe PN	Proportion of patients with ≥4-point improvement in Worst Itch Numeric Rating Scale (WI-NRS) at Week 12/24	WI-NRS (Week 12): 37% vs 22% (p<0.001) WI-NRS (Week 24): 60% vs 18% (p<0.001)	No significant difference compared to the placebo group
BP	LIBERTY-BP ADEPT (Phase 2/3)	Adults with moderate-to-severe BP	Proportion of patients achieving complete remission off steroid therapy at week 36	Data pending publication, based on approval.	Data pending publication, based on approval.

Abbreviations: IL-4, Interleukin-4; IL-4R, Interleukin-4 Receptor; AD, Atopic Dermatitis; IGA, Investigator Global Assessment; EASI-75, 75% improvement in the Eczema Area and Severity Index; EASI, Eczema Area and Severity Index; vs, versus; p, p-value; FEV1, Forced Expiratory Volume in 1 second; EOS, Eosinophils; FeNO, Fractional exhaled Nitric Oxide; ppb, parts per billion; OCS, Oral Corticosteroids; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; NPS, Nasal Polyp Score; NCS, Nasal Congestion Score; EoE, Eosinophilic Esophagitis; HPF, High-Power Field; DSQ, Dysphagia Symptom Questionnaire; PN, Prurigo Nodularis; WI-NRS, Worst Itch Numeric Rating Scale; BP, Bullous Pemphigoid.

Safety Data Analysis

Injection Site Reactions

A comprehensive analysis of pooled data from phase III clinical trials of dupilumab revealed that injection site reactions (ISRs) are prevalent adverse events in its treatment, with an incidence ranging from 8% to 22%. These reactions manifest clinically as localized erythema, pruritus, pain, or the presence of hard nodules, predominantly observed during the initial phase of treatment.[54,55,84,101] Such reactions are typically mild to moderate, and with continued administration, approximately 80% of patients' symptoms gradually decrease or disappear in subsequent injection cycles.[102] At the mechanistic level, recent studies suggest that ISRs may be associated with shifts in the Th1/Th2 and Th2/Th17 immune balance. Elevated local IL-4/IFN-γ ratios and abnormal activation of IL-17A have been evidenced in support of this hypothesis.[103] A variety of preventive strategies are effective in reducing the incidence of this condition. These strategies include active rotation of the injection area, pre-cooling treatment, and post-injection compression.[102]

Conjunctivitis

Dupilumab-associated conjunctivitis (DEC) is an adverse reaction that necessitates focused monitoring, and its incidence is disease-specific: 3%-19% in patients with AD,[55,104,105] 1%-3% in patients with asthma,[106,107] and rare in patients with CRSwNP.[107,108] Mechanistically, the development of DEC may be associated with drug perturbation of the ocular surface immune microenvironment,[104,109] manifesting in clinical symptoms such as ocular redness, ocular itchiness, and increased secretions. A history of previous allergic conjunctivitis or elevated serum total IgE levels has been demonstrated to significantly increase the risk of developing the condition.[107,110,111] First-line management entails the administration of topical glucocorticoid drops, accompanied by monitoring of intraocular pressure. This approach has been shown to resolve symptoms in a significant proportion of patients effectively. However, if exacerbations persist, escalating interventions become necessary.[104,107]

Nasopharyngitis

Nasopharyngitis has been identified as a prevalent adverse event associated with dupilumab therapy across various indications.[49,68,108,112] In adult patients diagnosed with moderate-to-severe AD, nasopharyngitis occurred in 28% (258/318) of cases involving inadequate control of topical therapy following administration.[50] This adverse event consistently

ranked as the most prevalent (≥5%) in a 5-year long-term study.[113] A 17.5% to 25.9% prevalence was observed in the Adult Asthma Study (TRAVERSE),[68] with a notable elevation in eosinophilia, which was significantly higher than in the placebo group.[62] In the Phase II trial of EoE, the prevalence was 17% (placebo 4%),[112] and in patients with CRSwNP, it was 47% (placebo 33%).[108] The prevalence of these conditions was also observed to be high in the pediatric population: nasopharyngitis was the most prevalent condition among children aged 6–11 years with uncontrolled asthma;[71] the 1-year incidence of treatment in children aged 6 months to 5 years with AD was 19.7%.[114] This phenomenon is associated with altered mucosal immune barrier function due to inhibition of the IL-4/IL-13 pathway.

Dupilumab Facial Redness

Dupilumab facial redness (DFR) has been observed in approximately 4% to 43.8% of patients treated with dupilumab, with most cases manifesting 10 to 39 weeks after treatment initiation.[115,116] Retrospective analysis revealed that 52% of patients with DFR had pre-existing head and neck atopic dermatitis involvement at baseline, while 45% exhibited lesions with features different from the primary presentation.[117] The clinical interventions were based on the administration of topical medications, including corticosteroids, calmodulinic nephosphatase inhibitors, and antifungals. The results demonstrated that 54.4% of patients (33 out of 57) exhibited improvement (29 patients) or complete clearance (4 patients). However, 28.1% (16 patients) were found to be ineffective, 14.0% (8 patients) experienced a worsening of symptoms, and ultimately, 11% of patients discontinued treatment due to DFR.[117]

Blood Eosinophilia

Transient peripheral blood eosinophilia was observed in 4% to 25% of patients treated with dupilumab. Some studies have demonstrated that, among patients diagnosed with moderate-to-severe uncontrolled asthma, the incidence of eosinophilia was 4.1% (52/1268) in the dupilumab group, which was significantly higher than the 0.6% (4/649) observed in the placebo group.[63] The difference in the prevalence of this phenomenon was even more pronounced among patients with glucocorticoid-dependent asthma (14% vs 1%).[67] A retrospective study further confirmed that 11.3% of 142 patients with asthma/CRSwNP developed elevated eosinophil counts after medication.[118] It is noteworthy that eosinophilia is also a frequent adverse effect associated with the treatment of herpetic pemphigoid.[100] The mechanism in question has been linked to the inhibition of the IL-4/IL-13 pathway. Dupilumab exerts its inhibitory effect on the migration of eosinophils to tissues by down-regulating the expression of eosinophil chemokines, such as eotaxin-3, VCAM-1, and TARC.[119] It is imperative to acknowledge that persistent significant elevations may induce eosinophilic pneumonia (EP) or eosinophilic granulomatous polyangiitis (EGPA).[120,121] However, studies on chronic sinusitis have indicated a positive correlation between elevated peripheral blood eosinophils and response to dupilumab therapy in patients with Th2 inflammation.[122]

Potential Risk of Malignancy

Several studies have indicated a potential correlation between the administration of dupilumab and an elevated risk of cutaneous T-cell lymphoma (CTCL).[123–125] A cohort study revealed that patients diagnosed with AD who received treatment with dupilumab exhibited a higher prevalence of CTCL compared to those who were not treated (relative risk = 4.59, 95% confidence interval 2.459–8.567, $P < 0.0001$).[124] Moreover, a retrospective study of asthma patients (n = 14,936), matched by propensity score, demonstrated that the risk of lymphoma was significantly elevated in the dupilumab group compared to the inhaled corticosteroid/long-acting beta2-adrenergic agonist (ICS/LABA) control group (hazard ratio = 1.79, 95% confidence interval 1.19–2.71, $P = 0.005$).[125] The underlying mechanism may be related to IL-13 receptor blockade, leading to elevated local IL-13 levels, which in turn drive the progression of CTCL.[126] However, it is imperative to acknowledge that the benign lymphoid tissue proliferative response (with histopathologic features foreign to CTCL) observed in certain patients may be misdiagnosed as malignancy.[127] Moreover, a 5-year AD study revealed an absence of lymphoma occurrences.[113] However, it is essential to note that the current evidence is subject to certain limitations. These limitations include an insufficient sample size, a lack of standardization in treatment duration, and a paucity of long-term follow-up data. Consequently, a causal relationship between the direct induction of lymphoma and dupilumab has not been firmly established. A comprehensive review of

the extant literature reveals an inadequate corpus of studies to substantiate a direct carcinogenic risk associated with the pharmaceutical agent in question.[128]

Other Adverse Reactions

It is important to note that dupilumab treatment has been observed to trigger a variety of adverse reactions in some cases. The prevalence of arthralgia is minimal, with studies of AD in children and adolescents reporting an incidence of 2.2%.[129] A meta-analysis of 34 studies revealed a combined prevalence of 1.74%.[130] A higher prevalence of upper respiratory tract infections has been observed in adults diagnosed with moderate-to-severe AD.[113,131,132] It is important to note that the administration of the drug has been associated with the onset of psoriasis in some cases. A retrospective cohort study spanning three years and encompassing 214,430 patients with atopic dermatitis revealed a significantly higher cumulative prevalence of psoriasis in the dupilumab group compared to the control group (2.86% vs 1.79%).[133] In addition, although rare, cases of hypersensitivity reactions have been reported with IL-4 inhibitor use.[134,135] In such cases, immediate discontinuation of the drug and emergency interventions are required. These interventions may include antihistamines, glucocorticoids, and endotracheal intubation in life-threatening situations. These reactions are associated with altered immune homeostasis due to the inhibition of the IL-4/IL-13 pathway.

Current Challenges and Future Directions

Dynamic Biomarker Monitoring

Dynamic biomarker monitoring is a core strategy to achieve precise management of drug resistance, and its mechanism covers multiple levels of biological response: Following the activation of the IL-4/IL-13 pathway, single-cell sequencing reveals that the expression of CD69 and CD200R1 on the surface of eosinophils is up-regulated.[136,137] These proteins act as cell membrane markers, providing an early warning of drug resistance. Furthermore, the level of phosphorylation of STAT6 and the serum eosinophil chemokine CCL26 can reflect the pathway inhibition status in real time, offering insights into the dynamics of the signaling layer.[138,139] The clinical effect level is manifested as follows: Elevated circulating eosinophil counts and FeNO are significantly associated with the risk of acute asthma exacerbation.[63,140] In Th2 inflammatory diseases, such as asthma and atopic dermatitis, IL-4/IL-13-induced periostin is highly expressed and driven. Inflammation has been demonstrated to be a driving force in the progression of pathological processes.[141,142] In the future, integrating the aforementioned cellular, pathway, and clinical end-effect indicators through machine learning will be necessary to construct dynamic evolution models that accurately predict the risk of drug resistance and guide real-time treatment adjustments.

Combination Targeted Therapy

The strategic direction of combination targeted therapy has been identified as a means to overcome the challenge of drug resistance.[143] TSLP, a pivotal cytokine implicated in allergic and inflammatory diseases, has been shown to trigger the activation of diverse immune cell types, thereby instigating the inflammatory cascade.[144,145] Preclinical studies have demonstrated that the simultaneous blockade of TSLP and IL-4R (ie, the anti-TSLP/anti-IL-4R combination) is significantly more potent than a single agent in a mouse model of asthma.[146] The underlying mechanism of action is believed to originate from a more comprehensive inhibition of the inflammatory network, which is expected to enhance efficacy and reduce the risk of drug resistance. The following findings were reported on the clinical translation front: Firstly, for patients diagnosed with multi-drug resistant severe atopic dermatitis, a combination of dupilumab (IL-4R inhibitor) and baricitinib (JAK inhibitor) achieved significant symptomatic improvement without side effects within three months.[147] Secondly, case reports have demonstrated the efficacy and safety of mepolizumab (anti-IL-5) and omalizumab (anti-IgE) when used in combination with dupilumab in cases of severe asthma, AD, and CRSwNP.[148–152] The safety and efficacy of these combination strategies are currently being systematically evaluated in multiple clinical trials.

Bispecific Antibody Drug Development

Despite the absence of approved bispecific antibodies targeting IL-4Rα, several preclinical and early clinical programs are investigating their therapeutic potential. By concurrently obstructing the IL-4/IL-13 pathway in conjunction with synergistic pathogenic pathways (eg, IL-5/IL-5R, TSLP, or IL-31), a more comprehensive inhibition of the disease can be attained, particularly in patients who have exhibited an inadequate response to monotherapy. In particular, the dual antibodies IL-4Rα/IL-5R have been shown to inhibit eosinophil activation (IL-5) and type 2 inflammation (IL-4/IL-13) synergistically. These antibodies have demonstrated promising efficacy and safety in animal models and have provided a new strategy for the treatment of complex inflammatory diseases.[153] In addition, IL-4Rα/TSLP dual antibodies (eg, IBI3002) synchronously target both type 2 inflammatory pathways and epithelial alerting hormones.[154] Epithelial alerting hormones have a synergistic mechanism that enhances the inhibitory efficacy against atopic dermatitis, asthma, and other diseases.[154] The initial human Phase I trial (single-dose incremental) has been concluded, and the safety and pharmacokinetics/pharmacodynamics are being assessed in healthy individuals and patients with mild-to-moderate asthma. Furthermore, the IL-4Rα/IL-31R dual antibody has been shown to significantly improve skin barrier dysfunction and inflammation (eg, GB12-09 reduces IgE/IL-31 levels and alleviates symptoms in a mouse model of AD) by blocking IL-4/IL-13 and the key mediator of itch, IL-31.[155,156] These innovative dual-antibody architectures are expected to overcome existing therapeutic limitations.

Applications in Central Nervous System Diseases

In the pathological process of Alzheimer's disease, IL-4 plays a pivotal regulatory role by inducing the polarization of microglia towards a neuroprotective M2 phenotype.[157] However, existing therapeutic antibodies have difficulty effectively reaching the brain parenchyma due to the blood-brain barrier (BBB). The emerging delivery technology, focused ultrasound combined with microbubbles (FUS-MB), represents a novel solution to this limitation by reversibly opening the BBB through the acoustic cavitation effect.[158] Preclinical studies are imperative to elucidate the impact of FUS-MB-mediated intracerebral delivery of dupilumab on the modulation of core pathological markers of Alzheimer's disease (eg, Aβ plaque deposition and neuroinflammation), which will catalyze breakthroughs of neuroimmune-targeted therapies in neurodegenerative diseases.

Artificial Intelligence-Driven Precision Medicine

The field of artificial intelligence (AI) has begun to impact the paradigm of drug development and clinical practice profoundly. In the domain of antibody engineering, the IL-4Rα-targeting nanoantibody H5, which was screened through the application of ribosome display technology, has been shown to enhance binding affinity through a combination of AlphaFold2-guided dimerization simulation and GROMACS-driven computer-assisted affinity maturation. The antibody under consideration enables non-invasive delivery, targeting allergic airway inflammation sites. It effectively inhibits the IL-4/IL-13 signaling pathway and downregulates inflammatory markers in human nasal epithelial cells.[159] Within the domain of computational biology, Meta-IL4, a pioneering integrated learning model, integrates base classifiers such as Random Forest and XGBoost with Gaussian process meta-classifiers to predict IL-4-inducing peptides with 90.70% accuracy. This is achieved through the encoding of multi-dimensional peptide sequence features, providing a precise design tool for the development of peptide vaccines that target the activation of Th2 immune responses.[160]

Gene Editing and Cell Therapy

Gene editing techniques, such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9, have been demonstrated to impede the Th2 inflammatory response by silencing the *IL4R*.[161] Future studies could explore the realization of long-lasting Th2 inflammation suppression after hematopoietic stem cell transplantation; however, the risk of off-targeting must be circumvented. In the domain of cellular therapies, chimeric antigen receptor (CAR) T-cell therapies have attained noteworthy success in the clinical management of cancer.[162] Recent studies have demonstrated that the incorporation of IL-4 during antigen activation mitigates CAR-T cell dysfunction and enhances their adaptability at the transcriptomic and epigenetic levels.[163] Consequently, the prospect of engineering CAR-Treg cells that express IL-

Figure 2 Future Directions for IL-4/IL-4R Targeted Therapy.
Abbreviations: IL-4Rα, Interleukin-4 Receptor Alpha Subunit; IL-13R, Interleukin-13 Receptor; TSLP, Thymic Stromal Lymphopoietin; IL-31R, Interleukin-31 Receptor; JAK, Janus Kinase; IgE, Immunoglobulin E; AI, Artificial Intelligence; FUS-MB, Focused Ultrasound with Microbubbles; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; CAR-Treg, Chimeric Antigen Receptor-Regulatory T Cell.

4Rα-targeted chimeric receptors has emerged as a potential avenue for the development of a long-lasting therapeutic strategy for autoimmune diseases (Figure 2).

Conclusion

Recent advancements in the field have led to the development of biologics targeting the IL-4/IL-13 pathway, particularly the IL-4Rα monoclonal antibody dupilumab. These biologics have emerged as a significant breakthrough in the treatment of Th2 inflammatory diseases. A substantial body of clinical evidence has accumulated demonstrating the consistent and substantial efficacy of the therapy across multiple conditions, including AD, asthma, CRSwNP, and EoE. In adult patients diagnosed with AD, approximately 36%-39% achieve clear or almost clear skin, with over half attaining EASI-75 improvement. In patients diagnosed with asthma who exhibit elevated levels of eosinophils, the administration of this medication has been shown to reduce the risk of acute exacerbations by nearly half and to improve lung function significantly. For patients diagnosed with CRSwNP, approximately three-quarters demonstrate objective improvement in polyp scores. The clinical application of the device is supported by precise efficacy data that provide a robust evidence-based foundation.

Regarding safety, this therapeutic modality exhibits a distinctive adverse reaction profile. While the medication demonstrates adequate tolerability, its clinical application necessitates a meticulous approach to common adverse events, including ISRs, nasopharyngitis, conjunctivitis, and DFR. These events occur more frequently in patients with AD. Furthermore, transient increases in blood eosinophil counts, particularly in patients with asthma, necessitate appropriate monitoring and management. According to the available data, this therapeutic modality is principally indicated for patients with moderate-to-severe Th2 inflammatory diseases that are unresponsive to conventional treatments. Among

asthma patients, those with elevated eosinophil counts or elevated FeNO levels have been shown to respond more strongly to therapy.

In the future, this field will continue to face numerous challenges and opportunities. The prevailing challenges in contemporary clinical practice encompass therapeutic heterogeneity and primary resistance in a subset of patients. Addressing these issues requires implementing precision medicine through dynamic biomarker monitoring, including serum TARC and IL-13 levels. Concurrently, exploring combination strategies with other targeted therapies—such as anti-TSLP, anti-IL-5, or JAK inhibitors—holds promise for delivering novel solutions to patients with refractory disease. Long-term innovations, such as the development of bispecific antibodies, the integration of artificial intelligence into drug design, and the application of gene-editing technologies, have the potential not only to enhance therapeutic outcomes but also to expand their range of applications into new domains, including neurological disorders. Nevertheless, it is imperative to undertake extensive research to substantiate their clinical translation.

In summary, the emergence of IL-4/IL-13 pathway inhibitors marks a pivotal paradigm shift in the management of Th2 inflammatory diseases, transitioning from conventional immunosuppressive treatments to a more precise, targeted therapeutic approach. The prevailing clinical decision-making paradigm should be founded upon a comprehensive understanding of the efficacy profiles and safety risks associated with these treatments, to identify target populations for whom they are most beneficial. The future of this field will be determined by the extent to which I deepen my understanding of resistance mechanisms, refine precision stratification, and continuously explore innovative treatment paradigms. These efforts will ultimately result in the provision of more effective and personalized therapeutic options to patients.

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