NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń



KONIECZNY, Julia and HANYPSIAK, Maciej. Dupilumab in Type 2 Inflammatory Diseases: Current Evidence and Emerging Therapeutic Applications – A Narrative Review. Journal of Education, Health and Sport. 2026;95:76627. https://doi.org/10.12775/JEHS.2026.95.76627

ARTICLE TIMELINE
Received: 12.10.2026.
Accepted: 19.10.2026.
Published: 12.11.2026.

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2026.

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Dupilumab in Type 2 Inflammatory Diseases: Current Evidence and Emerging Therapeutic Applications – A Narrative Review

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Abstract

Background.

Dupilumab is a fully human monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα), thereby inhibiting signaling mediated by interleukin-4 (IL-4) and interleukin-13 (IL-13). Since the initial approval for moderate-to-severe atopic dermatitis, its therapeutic indications have expanded substantially and currently include several diseases characterized by type 2 inflammation.

Aim.

The aim of this narrative review was to summarize the current evidence regarding the mechanism of action, established clinical applications, efficacy, safety, and emerging therapeutic indications of dupilumab.

Material and methods.

A narrative literature review was performed using PubMed/MEDLINE, Web of Science, supplemented by clinical guidelines and regulatory documents from the U.S. Food and Drug Administration and European regulatory authorities published between 2017 and 2026.

Results.

Dupilumab has demonstrated clinically relevant efficacy in wide range of dieseases including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis. eosinophilic chronic obstructive pulmonary disease, chronic spontaneous urticaria, bullous pemphigoid, and allergic fungal rhinosinusitis. Inhibition of IL-4Rα results in attenuation of type 2 inflammatory signaling, although the clinical treatment response vary between diseases.

Conclusions.

Dupilumab has evolved into a broadly applicable biologic targeting a shared immunological pathway across multiple inflammatory diseases. Its expanding indications emphasize the clinical importance of type 2 inflammation as a therapeutic target. Further studies are required to define optimal patient selection, long-term effectiveness, treatment duration, biomarkers of response, and the role of dupilumab in combination or sequencing with other targeted therapies.

Key words: dupilumab; IL-4; IL-13; IL-4Rα; type 2 inflammation; atopic dermatitis; asthma; eosinophilic esophagitis; chronic rhinosinusitis with nasal polyps; biologic therapy

1. Introduction

The type 2 inflammation represents a central immunological pathway in a broad spectrum of chronic inflammatory diseases affecting the skin, respiratory tract, gastrointestinal tract, and other organs. Its principal mediators include interleukin-4, interleukin-5, and interleukin-13, which contribute to immunoglobulin E production, eosinophilic inflammation, epithelial

dysfunction, mucus hypersecretion, tissue remodeling, and pruritus. The recognition of type 2 inflammation as a common pathogenic mechanism has led to the development of targeted biological therapies [1].

Dupilumab is a fully human monoclonal antibody directed against the alpha subunit of the interleukin-4 receptor. By binding IL-4Rα, dupilumab inhibits signaling mediated by both IL-4 and IL-13, two cytokines that play a central role in type 2 immune responses. This mechanism provides a biological rationale for the efficacy of dupilumab across several apparently distinct diseases [2, 3].

The drug was initially approved in 2017 for the treatment of moderate-to-severe atopic dermatitis [4]. Since then, randomized clinical trials have established its efficacy in asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and prurigo nodularis. More recently, the therapeutic development of dupilumab has expanded to additional diseases, including eosinophilic chronic obstructive pulmonary disease, chronic spontaneous urticaria, bullous pemphigoid, and allergic fungal rhinosinusitis [5].

The growing number of indications makes dupilumab an important example of a mechanism-based therapeutic strategy in modern medicine. Rather than targeting individual symptoms or organ-specific pathways, treatment is directed against a shared immunological pathway that may contribute to disease expression in different tissues.

The aim of this review is to provide an updated overview of the mechanism of action and clinical applications of dupilumab, with particular emphasis on established indications, recently approved applications, efficacy, safety, and remaining therapeutic challenges.

2. Research materials and methods

This narrative review was based on a literature search of PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The search strategy included combinations of the following terms: “dupilumab”, “IL-4Rα”, “IL-4”, “IL-13”, “type 2 inflammation”, “atopic dermatitis”, “asthma”, “chronic rhinosinusitis with nasal polyps”, “eosinophilic esophagitis”, “prurigo nodularis”, “chronic obstructive pulmonary disease”, “chronic spontaneous urticaria”, “bullous pemphigoid”, and “allergic fungal rhinosinusitis”.

Priority was given to randomized controlled trials, phase 2 and phase 3 clinical trials, systematic reviews, meta-analyses, international clinical guidelines, and regulatory documents. Earlier publications were retained when they provided important information concerning the mechanism of action or pivotal clinical development of dupilumab. Publications available up to 2026 were considered for the updated version of the review.

3. Research results

3.1. Mechanism of Action

Dupilumab is a fully human IgG4 monoclonal antibody that binds to IL-4Rα. This receptor subunit is shared by the type I and type II IL-4 receptor complexes. Type I receptors

predominantly mediate IL-4 signaling, whereas type II receptors can mediate signaling induced by both IL-4 and IL-13 [6].

IL-4 and IL-13 are central mediators of type 2 inflammation. Their signaling contributes to differentiation and activation of Th2 lymphocytes, IgE production, eosinophilic inflammation, epithelial barrier dysfunction, mucus production, tissue remodeling, and activation of sensory pathways associated with pruritus.

By binding IL-4Rα, dupilumab inhibits both IL-4- and IL-13-dependent signaling. This mechanism explains why a single biological agent can exert therapeutic effects in diseases involving different organs but sharing a common type 2 inflammatory component [6-7].

Importantly, dupilumab does not directly neutralize circulating IL-4 or IL-13. Instead, it prevents these cytokines from signaling through IL-4Rα-containing receptor complexes. This distinguishes dupilumab mechanistically from biological agents targeting individual cytokines such as IL-5 or IgE. Although IL-4Rα blockade provides a shared mechanistic rationale for dupilumab across multiple indications, the clinical response depends on the contribution of IL-4- and IL-13-mediated pathways to the pathophysiology of each disease. Consequently, the efficacy of dupilumab should not be assumed to be uniform across different inflammatory conditions, and clinical outcomes must be evaluated using disease-specific endpoints [6, 8-9].

3.2. Established Clinical Applications

3.2.1. Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin disease characterized by epidermal barrier dysfunction, pruritus, and immune dysregulation. Type 2 cytokines, particularly IL-4 and IL-13, play a central role in both the initiation and maintenance of inflammation [10].

Clinical trials have demonstrated that inhibition of IL-4Rα produces significant improvements in skin lesions, pruritus, disease severity, and quality of life [11-12]. Dupilumab has also been associated with reductions in Staphylococcus aureus colonization and improvements in sleep disturbances related to atopic dermatitis [12].

In the study conducted by A.S. Pale et al., the impact of dupilumab therapy on the occurrence of infections associated with AD in children was investigated. The study involved 162 patients aged 6 months to 5 years old with moderate-to-severe forms of atopic dermatitis, divided into two groups. The study group consisted of 83 patients who received dupilumab at a dose of 200 mg if the child's weight was ≥5 kg to <15 kg, and 300 mg if the child weighed ≥15 kg to <30 kg. The monoclonal antibody was administered subcutaneously every 4 weeks for a 16-week treatment period. A control group of 79 patients received an equivalent placebo at the same intervals. Both groups simultaneously received low doses of topical corticosteroids as an add-on treatment. The study showed that the group treated with dupilumab was less susceptible to bacterial skin infections compared to the placebo group (RR 0.09, 95% CI 0.01–0.67; $p = 0.019$), which is a significant factor in the pathogenesis of AD. The use of monoclonal antibody therapy also significantly reduced the need for administration of systemic anti-infective drugs

compared to the placebo group (RR 0.52, 95% CI 0.30–0.89; p = 0.019), thereby protecting the patients' physiological microbiota and avoiding the occurrence of potential side effects [13].

In another study conducted by J.F. Merola et al., in phase IV of the randomized, double-blind trial – called DUPISTAD – the impact of dupilumab therapy on sleep quality was investigated. The study involved 188 patients over 18 years old with moderate-to-severe forms of atopic dermatitis inadequately treated with standard treatment regimen, with sleep disturbances assessed with the Numeric Rating Scale (NRS) as ≥ 5 and with severity of the eczema assessed with Eczema Area and Severity Index (EASI) as ≥ 12. These patients were divided in a 2:1 ratio into a group of 127 individuals receiving dupilumab via subcutaneous injection at a dose of 300 mg every 2 weeks for the 12-week study period, and a group of 61 patients receiving an equivalent placebo. The study allowed for the use of the topical corticosteroids as an add-on treatment [13].

The study demonstrated a significant improvement in sleep NRS in the dupilumab group compared to the control group according to the Least Squares Method (LSMD) by −15.5% (95% CI −24.1 to −6.9) by the end of the 12th week, resulting in a 47.7% improvement in sleep compared to 33.0% in the placebo group (P < 0.001). Furthermore, a significant reduction in itching was observed in patients treated with monoclonal antibody compared to the placebo group (LSMD 27.9% (95% CI −38.0 to −17.8), P < 0.001) [14].

These findings highlight the multidimensional effects of dupilumab in atopic dermatitis, extending beyond the improvement of inflammatory skin lesions to include pruritus, sleep disturbance, and infection-related outcomes. Nevertheless, the magnitude of benefit may vary according to baseline disease severity, age, concomitant topical treatment, and the outcome measure used. The therapeutic effect is particularly relevant in patients with moderate-to-severe disease inadequately controlled with topical therapy [15-16]. Importantly, dupilumab has become a long-term treatment option across both adult and pediatric populations [15, 17].

The efficacy of dupilumab in atopic dermatitis also illustrates a broader principle: inhibition of type 2 inflammation may improve not only visible inflammatory lesions but also symptoms such as pruritus and sleep impairment, which have a substantial effect on quality of life [11].

3.2.2. Asthma

Asthma is a heterogeneous inflammatory disease. A substantial proportion of patients with severe asthma exhibit type 2 inflammation characterized by eosinophilia, increased IL-4 and IL-13 activity, and elevated fractional exhaled nitric oxide [18].

Dupilumab is used as an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or in patients with oral corticosteroid-dependent disease. Randomized clinical trials have demonstrated reductions in severe exacerbations and improvements in lung function [19].

A study conducted by Wenzel et al. involved 776 patients aged ≥18 years with asthma diagnosed according to the Global Initiative for Asthma (GINA) criteria for at least 12 months. All

participants were treated with inhaled glucocorticoids at a medium or high dose and a long-acting β2-agonist. Patients were randomly assigned in a 1:1:1:1:1 ratio to five groups: four groups received subcutaneous dupilumab at doses of 200 mg or 300 mg every 2 or 4 weeks, while the fifth group received a placebo. The study period lasted 24 weeks. The final results indicated that dupilumab improved lung function and reduced the severity of severe asthma exacerbations in patients with uncontrolled, chronic asthma, regardless of baseline blood eosinophil levels (which were also considered during the study) and demonstrated a favorable safety profile. The most common adverse effects associated with the use of the monoclonal antibody compared to placebo were upper respiratory tract infections (occurring in 33–41% of patients compared to 35% in the placebo group) and reactions at the injection site (13–26% vs. 13%) [20].

Particularly important is the corticosteroid-sparing effect observed in patients with severe glucocorticoid-dependent asthma [21]. The clinical response is generally more pronounced in patients with evidence of type 2 inflammation, although treatment effects are not determined by a single biomarker. Blood eosinophil counts and fractional exhaled nitric oxide may help identify patients more likely to benefit from IL-4/IL-13 pathway inhibition [22-23]. In clinical practice, dupilumab should be selected according to the patient's clinical phenotype, exacerbation history, corticosteroid dependence, and evidence of type 2 inflammation rather than on the basis of a single biomarker. Its role is that of an add-on maintenance biologic, and it should not replace inhaled controller therapy or be used to treat acute asthma exacerbations [23].

3.2.3. Chronic Rhinosinusitis with Nasal Polyps

Chronic rhinosinusitis with nasal polyps is frequently associated with type 2 inflammation, eosinophilic infiltration, increased IL-4 and IL-13 activity, and substantial impairment of quality of life [24].

In the multicenter, randomized, double-blind studies LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, 276 qualified patients were included, with 143 assigned to study group that received dupilumab every 2 weeks. The remaining 133 patients were assigned to control group that was receiving placebo. The study included individuals aged ≥18 years with bilateral nasal polyps and symptoms of chronic sinusitis despite nasal corticosteroid therapy during the previous two years, those with contraindications to corticosteroid therapy, or those who had undergone sinus surgery [25].

In the SINUS-24 study, patients were divided into two groups in a 1:1 ratio - group A, treated every 2 weeks with 300 mg of dupilumab, and group B, treated with a corresponding dose of placebo. Both groups underwent therapy for 24 weeks. In the SINUS-52 study, patients were divided into three groups in a 1:1:1 ratio - group A, treated every 2 weeks with 300 mg of dupilumab for 52 weeks; group B, treated with the same treatment regimen for the first 24 weeks, followed by 300 mg of dupilumab every 4 weeks; and group C, which received corresponding doses of placebo. All three groups underwent therapy for 52 weeks [25].

The study showed that after the treatment with the dupilumab a significant improvement in the Nasal Polyps Score (NPS) and a reduction in nasal cavity and sinus occupancy compared to the placebo group was achieved, while the condition of patients treated with standard therapy worsened both at week 24 and at week 52. Patients continuously treated with dupilumab in the SINUS-52 study maintained a steadily increasing improvement up to week 52. In contrast, there was a deterioration in disease symptoms in patients who discontinued dupilumab treatment after week 24 in the SINUS-24 study, indicating the need for continuous treatment [25].

The restoration of olfactory function represents a clinically important effect because anosmia is one of the symptoms most strongly affecting patients with severe CRSwNP. The clinical relevance of dupilumab in CRSwNP is reflected not only in reductions in nasal polyp burden but also in improvements in nasal obstruction, olfactory function, and disease-related quality of life. Treatment response should therefore be assessed using a combination of objective measures and patient-reported outcomes, while decisions regarding treatment duration should be individualized [26-27].

3.2.4. Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is one of the most frequently diagnosed inflammatory esophageal diseases (right after gastroesophageal reflux disease), occurring in both children and adults [28]. EoE symptoms significantly impact patients' quality of life, causing dysphagia and food impaction, and in pediatric patients, abdominal pain, vomiting, leading to stunted growth and weight gain. In treatment, patients are often required to follow elimination diets due to the suspicion that food allergens may trigger inflammatory reactions through the activation of Th2 lymphocytes, which secrete interleukins 4, 5, and 13, affecting the production and migration of eosinophils to the esophagus, potentially leading to disease progression (Fig. 1) [29-30]. In 2022, the FDA approved dupilumab as the first medication dedicated to patients suffering from EoE, showing an impact on specific mechanisms of the disease's pathogenesis [31]. The drug was approved for patients aged ≥12 years with a body weight of at least 40 kg, and at the beginning of 2024, the FDA extended the approval to include patients aged 1-11 years weighing at least 15 kg [32-33].

FDA approval of dupilumab for patients aged 1-11 years with eosinophilic esophagitis was based on data from the phase 3 EoE KIDS clinical trial, which included 102 patients. After 16 weeks of therapy, 66% of children receiving the higher dose of dupilumab (dosing regimen dependent on body weight) achieved disease remission and an eosinophil count of ≤6 in a high-power field, compared to 3% of patients in the placebo group. Histological remission was also achieved at week 52 in 8 out of 15 (53%) pediatric patients in the placebo group who were subsequently given dupilumab, indicating significant therapeutic benefits associated with the drug and justifying the expansion of FDA recommendations [33-35].

In EoE, histological remission and symptomatic improvement should be considered complementary outcomes rather than interchangeable measures of treatment success. The assessment of dupilumab efficacy should therefore incorporate esophageal histology,

dysphagia-related symptoms, and relevant functional outcomes, taking into account that improvements in symptoms and tissue inflammation may not occur to the same extent [36].

3.2.5. Prurigo Nodularis

Prurigo nodularis is a chronic pruritic dermatosis characterized by intensely itchy nodules and a self-perpetuating itch–scratch cycle. Type 2 inflammatory pathways contribute to disease pathogenesis [37].

The PRIME and PRIME2 phase 3 trials demonstrated significant improvements in pruritus and reduction of skin lesions in patients treated with dupilumab. These findings established IL-4Rα blockade as an effective targeted approach in a disease in which severe pruritus is the dominant clinical problem [37].

3.2.6. Eosinophilic Chronic Obstructive Pulmonary Disease

One of the most important developments after preparation of the original manuscript was the emergence of dupilumab as a treatment option for a selected population of patients with COPD characterized by an eosinophilic inflammatory phenotype [38].

The evidence supporting dupilumab in eosinophilic COPD is particularly relevant to patients who continue to experience exacerbations despite optimized inhaled maintenance therapy. In this population, dupilumab is used as an add-on treatment rather than as a replacement for established COPD management. Patient selection should take into account blood eosinophil counts, exacerbation history, background therapy, and the eligibility criteria applied in the pivotal clinical trials [38-39].

This indication is particularly important conceptually because it demonstrates that the therapeutic relevance of IL-4/IL-13 signaling extends beyond diseases traditionally regarded as allergic. The identification of an eosinophilic/type 2 inflammatory phenotype may therefore provide a rationale for targeted biological treatment in COPD [38-39].

The results of clinical trials in eosinophilic COPD should not be extrapolated to all patients with COPD, because the disease is heterogeneous and the evidence for dupilumab applies to a selected inflammatory phenotype. Further research is needed to clarify long-term outcomes, treatment persistence, and the characteristics of patients most likely to obtain a clinically meaningful benefit [38-39].

3.2.7. Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is a heterogeneous inflammatory disorder characterized by recurrent wheals, angioedema, or both, occurring without an identifiable external trigger [40, 43]. Dupilumab represents an additional targeted treatment option for selected patients whose symptoms remain inadequately controlled despite H1-antihistamine therapy. Its clinical role

should be interpreted in the context of the available treatment alternatives, previous biologic exposure, and the eligibility criteria specified in the applicable regulatory label [40-42].

Clinical assessment should focus on disease activity, symptom control, angioedema burden, and health-related quality of life [44]. Because the evidence base and approved patient populations may differ between jurisdictions, regulatory status and treatment recommendations should be verified separately for the United States and the European Union [41-42]. Long-term follow-up is also important for determining the durability of response and the need for continued treatment [41, 43].

3.2.8. Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disease in which autoantibody-mediated mechanisms coexist with inflammatory processes involving eosinophils and type 2 immune pathways. This biological complexity provides a rationale for investigating IL-4Rα blockade as a targeted therapeutic strategy. However, mechanistic plausibility alone is insufficient to establish clinical efficacy, and the evidence should be interpreted in relation to the design, endpoints, and limitations of the relevant clinical studies [44].

The regulatory status of dupilumab for bullous pemphigoid differs between jurisdictions. As of October 2026, the indication is included in the United States prescribing information, whereas the application to extend the European Union marketing authorization was withdrawn in June 2026. Accordingly, dupilumab should not be described as an established, EU-approved indication for bullous pemphigoid. Further evidence is needed to define its comparative effectiveness, optimal place in treatment, and long-term benefit–risk profile [41, 45].

3.2.9. Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a distinct inflammatory phenotype of sinonasal disease characterized by type 2 inflammation, hypersensitivity to fungal antigens, and the accumulation of eosinophilic mucin. Dupilumab has emerged as a targeted treatment option for selected patients with this condition, expanding the potential role of IL-4Rα blockade beyond conventional chronic rhinosinusitis with nasal polyps [46].

The indication for AFRS was included in the United States prescribing information in 2026. However, this regulatory development should not be interpreted as equivalent to authorization in the European Union [41, 47]. Future studies should clarify the durability of clinical response, the optimal duration of therapy, and the role of dupilumab in relation to surgery and other established treatment approaches [46].

3.3. Safety and Adverse Events

Dupilumab generally has a favorable safety profile compared with many systemic immunosuppressive therapies. Common adverse events vary according to indication but may include injection-site reactions, conjunctivitis or other ocular adverse events, upper respiratory tract symptoms, eosinophilia, herpes viral infections, and gastrointestinal symptoms [41, 48].

Transient increases in peripheral blood eosinophil counts may occur, particularly in patients with asthma and other eosinophilic diseases. Ocular adverse events are particularly relevant in patients treated for atopic dermatitis [41, 48].

The safety profile of dupilumab should be interpreted in an indication-specific context, because the frequency and clinical relevance of adverse events may differ between patient populations and treatment settings. Particular attention should be paid to ocular adverse events in patients treated for atopic dermatitis, transient or clinically significant eosinophilia in selected patients with respiratory disease, and hypersensitivity reactions [41, 48].

The expanding number of indications also emphasizes the importance of disease-specific safety monitoring. Although dupilumab does not produce broad immunosuppression, clinicians should remain alert to clinically significant eosinophilia, ocular complications, hypersensitivity reactions, and other indication-specific adverse events [41, 49].

Long-term safety assessments should also consider treatment discontinuation, concomitant medications, comorbidities, and adverse events that may be too uncommon to be adequately characterized in randomized clinical trials [15, 41].

4. Discussion

Despite the substantial clinical development of dupilumab, several questions remain unanswered.

First, biomarkers capable of reliably predicting treatment response remain an important area of research. Blood eosinophils and fractional exhaled nitric oxide may provide useful information in respiratory diseases, but no single biomarker adequately predicts response across all indications [50].

Second, the optimal duration of treatment remains uncertain in several diseases. The recurrence of symptoms after treatment discontinuation observed in some inflammatory conditions suggests that dupilumab often controls rather than permanently eliminates the underlying disease process [51-52].

Third, the increasing number of available biologics creates questions regarding treatment selection and sequencing. In diseases such as severe asthma, several targeted therapies may be appropriate depending on the inflammatory phenotype.

Finally, the expansion of dupilumab into diseases such as COPD, CSU, bullous pemphigoid, and allergic fungal rhinosinusitis emphasizes the need for long-term real-world evidence

addressing effectiveness, safety, adherence, treatment persistence, and cost-effectiveness [51-52].

Several limitations should be considered when interpreting the available evidence. Clinical trials differ in eligibility criteria, disease severity, background treatment, follow-up duration, and definitions of treatment response, which limits direct comparisons between indications. Furthermore, evidence derived from randomized controlled trials may not fully reflect the clinical complexity of patients with multiple comorbidities or those receiving several concomitant therapies.

Another important limitation is the unequal maturity of the evidence base across indications. While several established applications are supported by multiple randomized trials and substantial clinical experience, newer applications require additional data on long-term effectiveness, safety, treatment persistence, and comparative benefit relative to alternative therapies. Real-world studies may help address these questions, although their findings must be interpreted in light of potential confounding, selection bias, and differences in clinical practice [51-52].

Future research should prioritize the identification of clinically useful predictive biomarkers, the evaluation of treatment strategies in patients with overlapping inflammatory diseases, and the development of evidence-based approaches to treatment duration, discontinuation, and sequencing. Comparative studies and health-economic evaluations will also be important for defining the most appropriate use of dupilumab within an increasingly complex landscape of targeted therapies [50-52].

5. Conclusions

Dupilumab has become an important targeted therapy for multiple diseases associated with type 2 inflammation. By inhibiting IL-4Rα-mediated signaling, it addresses a shared immunological pathway implicated in disorders affecting the skin, respiratory tract, and gastrointestinal tract. Its established clinical applications demonstrate that targeting this pathway can produce meaningful benefits across distinct disease phenotypes, although the magnitude and nature of treatment response vary between indications [6, 50].

The expanding therapeutic scope of dupilumab should be interpreted in the context of indication-specific clinical evidence and regulatory requirements. Established applications must be distinguished from newer indications for which long-term experience, comparative effectiveness, or evidence in specific patient populations remains limited. Regulatory approval in one jurisdiction should not be assumed to confer an equivalent indication in another [41, 47].

Future research should focus on improving patient selection, validating predictive biomarkers, clarifying the optimal duration and sequencing of treatment, and establishing long-term benefit–risk profiles in both established and emerging indications. Comparative effectiveness studies and real-world evidence will be particularly important for determining how dupilumab should be positioned among other targeted therapies [51-52]. Ultimately, its clinical value will

depend not only on the breadth of its indications but also on the ability to identify patients most likely to achieve sustained, clinically meaningful benefit.

Disclossure

Supplementary Materials: Not applicable.

Author Contributions:

Conceptualization: J.K., M.H.;

Methodology: J.K., M.H.;

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Visualization: J.K., M.H.;

Supervision: J.K., M.H.;

Project administration: J.K., M.H.

All authors have read and agreed to the published version of the manuscript.

AI Statement:

Artificial intelligence tools, specifically the Gemini (Google AI Pro) and Grammarly (https://www.grammarly.com), were used only for linguistic and stylistic refinement as well as grammar correction and organizational assistance under complete human supervision in order to support academic English editing, improve clarity and readability of the manuscript, and assist with language refinement. No AI tools were used for data fabrication, generation of scientific results, interpretation of findings, or autonomous scientific decision-making. All scientific analysis, interpretation of the literature, conclusions, and final editorial decisions were performed by the authors themselves, who take full responsibility for the content of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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