



Dupilumab in the Treatment of Moderate to Severe Asthma: An Evidence-Based Review

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ABSTRACT

Background: Asthma affects millions of patients across the globe and also accounts for numerous mortalities every year. The current pharmacologic approach to the treatment of asthma includes the use of glucocorticoids and beta-agonists mainly. However, these conventional therapies have poor controllability of moderate-to-severe asthma and also produce several side effects on their long-term use. These limitations had led to the development of biologics targeting the mediators involved in T helper 2-inflammation associated with the pathogenesis of asthma such as interleukin (IL) 4, IL-5, and IL-13. dupilumab, a fully human monoclonal antibody, an IL-4 receptor alpha-antagonist targeting IL-13 and IL-4 has a potential role in treatment of moderate-to-severe asthma and was approved by the Food and Drug Administration on October 19, 2018. The dual-antagonistic action of dupilumab on IL-4 and IL-13 receptors renders it more efficient in asthma treatment.

Objectives: To review the efficacy and safety profile of dupilumab in the treatment of moderate-to-severe asthma.

Methods: Systematic search was performed via PubMed, Cochrane library, Embase, and ClinicalTrials.gov using the key words *dupilumab*, *moderate-to-severe asthma*, *interleukin*, *IL-13*, *IL-4*, and *monoclonal antibody*. Randomized controlled trials that compared between placebo and dupilumab in patients with uncontrolled asthma were included and observational studies were excluded in this review.

Results: The review of selected literature reveals that addition of dupilumab to conventional therapy improves forced expiratory volume in 1 second and reduces the risk of severe asthma exacerbations in patients. No significant differences in incidence of adverse drug reactions/adverse drug events were observed between dupilumab and placebo groups except higher rates of injection site reactions in the dupilumab group.

Conclusions: Concomitant use of dupilumab with long-acting beta agonists used in combination with inhaled corticosteroids, improves clinical outcomes and quality of life in patients with moderate to severe asthma. Although dupilumab has a promising role in treatment of patients with asthma, it is still in the emerging stage for its acceptance globally. Ongoing studies will help to determine dupilumab's long-term efficacy and safety for its future extensive use.

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Introduction

Asthma, a chronic inflammatory respiratory disease, is among the most common noncommunicable diseases, affecting millions of lives and causing numerous morbidities around the world. According to the World Health Organization, around 100 to 200 mil-

lion people experience asthma, and annual deaths have reached 180,000 worldwide.¹ The severity of asthma ranges from occasional and mild to severe. Although conventional medications like inhaled corticosteroids and long-acting beta agonists (LABAs) are reliable, some types of asthma, especially eosinophilic asthma, does not show effective response due to the poor controllability and side-effects during the long-term use. These limitations have led to the introduction of new classes of medication, such as monoclonal antibodies.²

The immunopathogenesis of asthma demands biological targets on mediators like interleukin that improve forced expiratory

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volume in 1 second (FEV1) outcome and reduces the incidence of severe asthma exacerbation. Dupilumab is the latest drug in the class of monoclonal antibodies for the treatment of moderate-to-severe asthma and was given approval by the Food and Drug Administration on October 19, 2019.³ Dupilumab is a fully human monoclonal antibody, an interleukin (IL)-4 receptor alpha antagonists subsequently inhibiting the IL-4 and IL-13 signaling that contributes to the T helper 2 cell (Th2) inflammation that is linked to the pathogenesis of moderate-to-severe asthma.⁴

Initially, dupilumab was approved for the treatment of moderate-to-severe atopic dermatitis (March 28, 2017).⁴ On October 19, 2018, dupilumab was approved by the Food and Drug Administration for the treatment of asthma after it had exhibited promising results in clinical trials.⁵ It was found to reduce the risk of severe asthma exacerbation and improve FEV1 values.⁵ So, the current approach in treating moderate-to-severe asthma can be significantly improved by the use of dupilumab. Hence this article reviews the significance of dupilumab in the pharmacotherapy of uncontrolled asthma.

Role of IL-4 and IL-13 in asthma

IL-13 and IL-4 are the interleukins that play a vital role in Th2 inflammation associated with the pathophysiology of allergic asthma.⁶ IL-13 and IL-4 are involved in the proliferation of myofibroblasts, bronchial fibroblasts, and airway smooth muscle causing remodeling of the airway.⁷ The activity of IL-13 and IL-4 are interlinked due to the activation of alpha subunits of IL-4 receptors by the duo.⁸ In the majority of patients with asthma, synthesis of immunoglobulin E and eosinophil inflammation are stimulated by the anomalous production of proinflammatory mediators such as IL-5, IL-4, and IL-13 associated with Th2 inflammation.⁹ Whereas IL-13, a pleiotropic cytokine, plays multiple roles in the remodeling of airways, eosinophil recruitment, and mucus production.¹⁰

Role of dupilumab in asthma

Dupilumab is a newer monoclonal antibody drug approved by the Food and Drug Administration that acts by inhibiting IL-4 receptors.¹¹ Although the earlier biologics like lebrikizumab targeting only the IL-13 receptor reduce exacerbations, they were found to be less efficient than dupilumab.¹² The biologics targeting IL-4 receptors have shown improved results by targeting the IL-4 downstream signaling and IL-13 downstream signaling because IL-4 receptors act as a common receptor for both IL-13 and IL-4.¹³

Methodology

Eligibility criteria

Randomized control trials that compared placebo and dupilumab in patients with moderate-to-severe asthma are included in this review. After the initial search, studies that reported outcome parameters such as annualized severe asthma exacerbations, absolute change in FEV1 values, and adverse events were included. The exclusion criteria were:

- Animal studies,
- Studies of nonstandard methods,
- Case reports,
- Lack of adverse drug reaction/adverse drug event data,
- Studies without results, and
- Studies with indications other than asthma.

Study Designs

Study population, timing, and setting

There were no restrictions on type of population participated in the clinical trials. Additionally, there were no restrictions on type of setting. The studies included were published from 2013.

Languages

No restrictions were applied for languages during the literature search. However, the included studies were reported only in English.

Publication status

The included studies were published in scientific journals as well as unpublished ones.

Data source

This review was conducted according to preferred reporting items for systematic review and meta-analysis protocols statement 2015. All relevant studies that assessed the safety and efficacy of dupilumab in the treatment of moderate-to-severe asthma were identified. Two reviewers (KKR and JJA) independently performed a systematic search in PubMed, Cochrane Library, ClinicalTrials.gov, and Embase up to May 30, 2019. The literature was search conducted by using the key words *dupilumab*, *moderate-to-severe asthma*, *interleukins*, and *monoclonal antibody*. Any discrepancies were resolved by a discussion with the third reviewer (TMV).

Study selection

The 2 reviewers (KKR and JJA) independently reviewed the titles and abstracts followed by full text using predefined inclusion criteria. The study selection process and reason for exclusion of studies were mentioned using the preferred reporting items for systematic review and meta-analysis protocols statement flow chart. The predefined inclusion criteria were formed for the extraction of the information from the included studies such as first author name, study design, sample size, dose, duration, and study site. Finally the studies were compared based on the outcomes such as annualized severe asthma exacerbations, absolute change in FEV1 values, and adverse events. The quality assessments of the included studies were conducted by using Cochrane collaborations tool for assessing the risk of bias.

Risk of bias

The quality assessments of included studies were conducted by using the Cochrane Collaboration tool for assessing the risk of bias. Two reviewers (KKR and JJA) performed this quality assessment independently. In case of disagreement, it was resolved by considering the risk of bias concerning predefined inclusion criteria.

Clinical Indication, Dosing, and Pharmacokinetic Parameters of Dupilumab

Initially, dupilumab was approved for the treatment of moderate-to-severe atopic dermatitis.¹⁴ Later, it was also indicated for the treatment of moderate-to-severe asthma, oral corticosteroid-dependent asthma, and elderly patients with eosinophilic phenotype asthma.

Adult dosing

A loading dose of 400 mg or a 600 mg loading dose followed by the administration of 200 mg or 300 mg maintenance dose, respectively, every other week subcutaneously. An initial dose of 600 mg followed by 300 mg given every other week subcutaneously to oral corticosteroid-dependent asthma patients.¹⁵

Pharmacokinetic parameters of dupilumab

Absorption

The bioavailability of dupilumab in the subcutaneous route of administration ranges from 60.7% to 64%. The time taken for dupilumab to attain the maximum plasma concentration was reported as 1 week after the administration of the 600 mg loading dose.¹⁵

Distribution

The volume of distribution of dupilumab in blood was reported as 4.8 L. However, the drug distribution in the central compartment and the peripheral compartment were measured as 2.74 L and 1.38 L, respectively.¹⁵

Metabolism

The exact mechanism of metabolism is not characterized. However, it is suspected to be degraded into small peptides and amino acids via catabolic pathways.¹⁵

Elimination

The weekly and biweekly steady state dose of dupilumab takes around 10 and 13 weeks, respectively, to disintegrate into negligible concentration (<78 ng/mL).¹⁵

Results

Study selection

A total of 592 studies were initially screened. Out of these, 236 studies were included after the exclusion of duplicates. Based on the title review 115 out of 236 studies were selected after the removal of irrelevant studies. The selected studies were further screened based on the abstract and 22 studies were included by removal of case reports, animal studies, and studies with non-standard methods. The full text of the 22 studies was reviewed against the inclusion criteria and out of those, 17 studies were excluded. Finally, 5 studies were included, out of which 4 studies were published in scientific journals and the remaining is unpublished. Additionally, the ongoing studies were selected from ClinicalTrials.gov.

Randomized, Placebo Controlled Trials of Dupilumab

Extensive clinical trial programs have been conducted globally to evaluate the clinical efficacy and safety of dupilumab in patients with asthma. At present, 5 clinical trial studies have revealed that dupilumab has a significant role in the treatment of moderate-to-severe asthma. The efficacy of dupilumab was determined by evaluating the parameters such as FEV1, Th2-associated biomarkers, exhaled nitric oxide, serum biomarkers (ie, thymus and activation-regulated chemokine, immunoglobulin E, chitinase-3-like protein 1, and carcinoembryonic antigen, plasma eotaxin-3), and peripheral blood eosinophil levels.

Five randomized trials that compared dupilumab with placebo in patients with uncontrolled asthma were reviewed in this article. Different dupilumab dosages were used in these clinical trials; 200 to 300 mg every 2 weeks were the most frequently used

doses; other dosages included 300 mg every week and 200 to 300 mg every 4 weeks. Follow-up period ranged from 20 to 64 weeks. A summary of characteristics of included studies are included in Table 1.

Phase IIA trial

NCT01312961 was a randomized double-blind placebo-controlled study conducted at 50 sites in the United States. A total of 104 patients with moderate-to-severe asthma with a blood eosinophil count of at least 300 cells/ μ L were included in this study, out of which 52 were assigned as the placebo group and remaining 52 as the test group. The test group was administered with 300 mg dupilumab, and a single dose of placebo was administered to the placebo group every week subcutaneously for 12 weeks. Follow-up was done for 8 weeks. The parameters measured to determine the dupilumab efficacy included FEV1, peak expiratory flow, 5-item Asthma Control Questionnaire score, fractional exhaled nitric oxide, asthma exacerbations, and morning and evening asthma score. When compared with the placebo group, the dupilumab group showed 87% reduction in the risk of exacerbation of asthma. Dupilumab was associated with a significant increase from baseline in percentage of predicted FEV1 and actual FEV1 at Week 2, which was maintained through Week 12.¹⁶

Phase IIB trials

NCT01854047

This was a randomized double-blind placebo-controlled dose-ranging study conducted at 174 sites in 15 countries. A total of 769 patients were included in this study, out of which 611 were assigned as test group and remaining 158 as a placebo group. A single dose of placebo was administered to placebo group every 2 weeks subcutaneously for 24 weeks. The test group was subjected to dupilumab therapy in such a way that, out of 611 patients, 150, 157, 148, and 156 patients were administered with a dosage of 200 mg every 4 weeks, 300 mg every 4 weeks, 200 mg every 2 weeks, or 300 mg every 2 weeks, respectively, for 24 weeks subcutaneously in addition to stable inhaled corticosteroids. Follow-up was done for 12 weeks. The outcome measures studied include FEV1, 5-item Asthma Control Questionnaire score, fractional exhaled nitric oxide, Asthma Quality of Life Questionnaire, severe asthma exacerbations, and morning and evening asthma scores. The 200 mg every 2 weeks and 300 mg every 2 weeks dupilumab groups had a better result in increasing FEV1 values when compared with the placebo group and other 2 dupilumab groups. Among the test groups, the dupilumab every 2 weeks groups showed the best result in reducing the exacerbation of asthma.¹⁷

NCT02573233

This was a randomized double-blind placebo-controlled parallel group study conducted at 16 sites in 6 countries. A total of 42 patients were included in this study, out of which, 22 were assigned as the placebo group and remaining 20 as a test group. Dupilumab 300 mg every 2 weeks was administered to the test group, and a single dose of placebo was administered to placebo group subcutaneously for 12 weeks. The primary outcome measures include the change from baseline in eosinophil cell count, mucin-stained area, mast cells count (chymase positive), mast cells count (tryptase positive), T-lymphocytes count, and T-helper lymphocytes count in bronchial submucosa. In this study, the data suggest that dupilumab has a significant role in the treatment of patients with asthma, although the official results are yet to be published.¹⁸

Table 1
Characteristics of included studies.

Author name	Study design	Sample size	Dose and duration	Study site	Parameters	ADR/ADE observed	Results
Rabe et al ²⁰	Randomized double-blind	210 Dupilumab (n = 103) Placebo (n = 107)	Dupilumab: 300 mg injection every 2 wk for 24 wk in combination with OCS (prednisone or prednisolone) and stable ICS Placebo: Single-injection every 2 wk for 24 wk in combination with OCS (prednisone or prednisolone) and stable ICS	United States, Argentina, Belgium, Brazil, Canada, Chile, Colombia, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russian Federation, Spain, Ukraine	Percentage reduction of OCS dose at Week 24 as the response variable, and treatment group Baseline eosinophil level, Optimized OCS dose at baseline Change from baseline in pre-bronchodilator FEV1 at Week 12 and 24	Dupilumab: Eosinophilia (1.94%), pneumonia (0.97%), respiratory tract infection (0.97%), asthma (2.91%) Placebo: Asthma 2.80%, asthmatic crisis (0.93%)	Dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing FEV1
Castro et al ¹¹	Randomized, double-blind, placebo-controlled parallel-group study	1902 Dupilumab (n = 1268) Placebo (n = 634)	Dupilumab: 200 mg (loading dose 400 mg) every 2 wk- 631 300 mg (loading dose 600 mg) every 2 wk- 633 Placebo: 1.14 mL- FOR 200 mg- 317 2 mL- FOR 300 mg- 321 52-wk randomized treatment period, and 12-wk posttreatment follow-up period	Argentina, Australia, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Korea, Republic of Mexico, Poland, Russian Federation, South Africa, Spain, Taiwan, Turkey, Ukraine, United Kingdom, United States	FEV1, morning/evening peak expiratory flow forced vital capacity, forced expiratory flow postbronchodilator FEV1, and postbronchodilator slope analysis on FEV1 ECG genetic analysis of DNA/RNA blood eosinophil count	Dupilumab: Total, serious adverse events (8.08%) 200 mg (8.86%) 300 mg Placebo: (8.31%) match for 200 mg (8.72%) match for 300 mg	Dupilumab shows improvements in lung function and asthma control, reductions in severe exacerbations
Wenzel et al ²⁴	Randomized, double-blind, placebo-controlled, dose-ranging study	776 Dupilumab-618 Placebo-158	Dupilumab: 200 mg every 4 wk- 154 300 mg every 4 wk- 157 200 mg every 2 wk- 150 300 mg every 2 wk- 157 over a 24-wk period	Argentina, Australia, Chile, France, Italy, Japan, The Republic of Korea, Mexico, New Zealand, Poland, Russia, South Africa, Spain, Turkey, Ukraine, United States	FEV1 Eosinophil count	Dupilumab: Injection-site erythema (13%) Nasopharyngitis (10%) Influenza (6%) Headache (10%) Bronchitis (10%) Sinusitis (6%) Placebo: Similar to the adverse events of the drug, headache (13%), bronchitis (10%), sinusitis (7%) Dupilumab: Injection-site reactions (29%) Nasopharyngitis (13%) Nausea (8%) Headache (12%) Placebo: Similar to the adverse events of the drug, plus upper respiratory tract infection (17%)	Dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count Dupilumab had a favorable safety profile
Wenzel et al ²⁵	Randomized, double-blind, placebo-controlled, parallel group study	104 Dupilumab (n = 52) Placebo (n = 52)	Dupilumab: 300 mg, subcutaneously, weekly Placebo: weekly 12-wk intervention period 8-wk follow-up period	United States	FEV1 T helper 2-associated biomarkers Exhaled nitric oxide serum biomarkers (thymus and activation-regulated chemokine CCL17, IgE, YKL-40, and carcinoembryonic antigen) plasma eotaxin-3 (CCL26) peripheral-blood eosinophil levels Eosinophil cell count, mucin-stained area, mast cells count (chymase positive), mast cells count (tryptase positive), T-lymphocytes count, T-helper lymphocytes count, serum functional dupilumab concentration, fractional exhaled nitric oxide	Dupilumab: Nausea (15%), injection site erythema (15%), upper respiratory tract infection (15%), back pain (15%), headache (25%) Placebo: Nasopharyngitis (n = 18.18%), cough (n = 9.09%), wheezing (9.09%)	Significant improvements were observed for most measures of lung function and asthma control Dupilumab reduced biomarkers Associated with T helper 2-driven inflammation
NCT02573233	Randomized double-blind, placebo-controlled study	42 Dupilumab (n = 20) Placebo (n = 22)	Dupilumab: 300 mg injection every 2 wk 14-wk intervention period	United States, Canada, Denmark, Germany, Sweden, United Kingdom	Eosinophil cell count, mucin-stained area, mast cells count (tryptase positive), T-lymphocytes count, T-helper lymphocytes count, serum functional dupilumab concentration, fractional exhaled nitric oxide	Dupilumab: Nausea (15%), injection site erythema (15%), upper respiratory tract infection (15%), back pain (15%), headache (25%) Placebo: Nasopharyngitis (n = 18.18%), cough (n = 9.09%), wheezing (9.09%)	Officially not published

ADE = adverse drug event; ADR = adverse drug reaction; CCL17 = Chemokine (C-C motif) ligand 17; CCL26 = Chemokine (C-C motif) ligand 26; ECG = Electrocardiogram; FEV1 = forced expiratory volume in 1 second; ICS = Inhaled corticosteroids; IgE = immunoglobulin E; OCS = Oral corticosteroids; YKL-40 = Chitinase-3-like protein 1.

Table 2

Summary of characteristics of ongoing clinical trials of Dupilumab in Asthmatic patients.

ClinicalTrials.gov identifier	Study design	Sample size	Study site	Interventions	Outcome measures	Study status
NCT02948959	Randomized, double-blind, Placebo-controlled, parallel group study	471 (estimated)	Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Turkey, Ukraine, United States	Drug: Dupilumab Other: Placebo Drug: Asthma controller therapies Drug: Asthma reliever therapies	Change from baseline in pre-bronchodilator % predicted FEV1 AM/PM PEF forced vital capacity FEF 25%-75% Assessment of IgG responses to vaccination during dupilumab treatment Serum dupilumab concentrations	Ongoing
NCT03112577	Randomized, placebo-controlled, parallel panel study	38 (estimated)	United Kingdom	Drug: Dupilumab Placebo drug: Fluticasone propionate	Difference in BAC-induced changes in sputum inflammatory markers in individuals Serum concentration-time profile-maximum plasma concentration Immunogenicity-measurement of antidrug antibodies	Ongoing
NCT03387852	Randomized, double-blind, placebo-controlled, parallel-group, 12-week proof-of-concept study	240 (estimated)	Argentina, Chile, Mexico, Poland, Russian Federation, Turkey, Ukraine, United States	Drug: Dupilumab Drug: Fluticasone or Fluticasone/salmeterol combination Drug: Placebo	Change in FEV1 LOAC events	Ongoing
NCT03782532	Randomized, double-blind, placebo-controlled, parallel-group study	486 (estimated)	China, India	Drug: Dupilumab SAR231893 Drug: Placebo Drug: Asthma controller therapies Drug: Asthma reliever therapies	Change in pre-bronchodilator FEV1, ACQ-5 score, ACQ-7 score, AQLQ	Ongoing
NCT03560466	Open-label, interventional, cohort study	377 (estimated)	Argentina, Brazil, Canada, Chile, Colombia, Hungary, Lithuania, Mexico, Poland, South Africa, Spain, Turkey, United States	Drug: Dupilumab (SAR231893/REGN668) Drug: Asthma controller therapies Drug: Asthma reliever therapies	Change in % predicted FEV1, absolute FEV1, forced vital capacity, FEF Assessment of blood eosinophil count, total IgE	Ongoing
NCT03620747	Open-label, interventional, cohort study	750 (estimated)	Belgium, Canada, France, Germany, Israel, Japan, South Africa, United States	Drug: Dupilumab SAR231893 (REGN668)	Not available	Ongoing

ACQ-5 = 5-item Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BAC = bronchial allergen challenge; FEF = forced expiratory flow; FEV1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; IgG = immunoglobulin G; PEF = peak expiratory flow.

Phase III trials

NCT02528214

This randomized double-blind placebo-controlled study was conducted at 68 centers in 17 countries. A total of 210 patients were included in this study, out of which 103 were assigned as the test group and 107 as the placebo group. The test group was administered with 300 mg dupilumab, whereas the placebo group was administered a single dose of placebo subcutaneously every 2 weeks for 24 weeks in combination with oral corticosteroids and stable inhaled corticosteroids. The efficacy of dupilumab was evaluated by analyzing the parameters such as FEV1, fractional exhaled nitric oxide, severe asthma exacerbations, and reduction in the oral glucocorticoid dose. Dupilumab treatment reduces oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing FEV1 values.¹⁹

NCT02414854

This randomized double-blind placebo-controlled parallel group study was conducted at 321 centers in 22 countries. A total of 1897 patients were included in this study, out of which 634 were assigned as the placebo group and 1263 as the test group. Among

the placebo group, 313 patients were administered with 200 mg placebo and 321 patients with 300 mg placebo subcutaneously every 2 weeks for 52 weeks in combination with stable inhaled corticosteroids. Among the test group, 631 and 632 patients were administered with 200 mg and 300 mg dupilumab subcutaneously every 2 weeks for 52 weeks, respectively, in combination with stable inhaled corticosteroids. Follow-up was done for 12 weeks. The parameters measured include FEV1, peak expiratory flow, 5-item Asthma Control Questionnaire score, fractional exhaled nitric oxide, Asthma Quality of Life Questionnaire score, severe asthma exacerbations, and morning and evening asthma scores. FEV1 increased by 0.32 L in the dupilumab groups of both lower and higher doses than in the placebo group. Annualized rate of severe asthma exacerbations was 47.7% lower with dupilumab than with placebo.²⁰

Safety Profile of Dupilumab

All clinical studies that were completed exhibited adverse events, and the risk of adverse safety outcomes in the 2 treatment groups was not significantly different. However, the dupilumab-treated groups showed a relatively low occurrence of adverse events. In Phase IIB studies, the most prevalent adverse effects

occurred includes injection site-reaction, sinusitis, headache, upper respiratory tract infection, nasopharyngitis, and viral upper respiratory tract infection.¹⁶ The severity of these adverse effects was characterized as mild to moderate. During a Phase IIA clinical trial, no mortality was reported. In Phase IIB studies, similar incidences of adverse effects as in previous clinical trials were reported in addition to bronchitis.¹⁷

In Phase III studies, the dupilumab-treated and placebo groups showed similar incidence of adverse events. Incidence of injection site reaction is higher in the case of patients treated with dupilumab when compared with the placebo group.^{19,20} Among the adverse events reported by dupilumab-treated patients, injection site-reaction had the highest rate of incidence. Patients with moderate-to-severe asthma might be susceptible to increased risk of developing bacterial and viral respiratory tract infections. This necessitates an approach toward the prevention of patients acquiring such comorbidities.

Ongoing Studies

Despite the potential of dupilumab in the treatment of asthma and its marketing, the evaluation of tolerability and safety need to be studied extensively for its efficient use globally. Various clinical trials are underway that focus on particular areas of interest, such as pediatric patients with asthma (NCT03560466²¹ and NCT02948959²²), evaluation of safety in long-term use of dupilumab (NCT03620747²³), evaluation of combination therapy with dupilumab (NCT03387852²⁴ and NCT03112577²⁵), and efficacy and safety study in persistent asthma (NCT03782532²⁶). Summaries of the characteristics of ongoing studies are included in Table 2.

Discussion

Dupilumab, a newer monoclonal antibody drug, has produced robust results in various stages of clinical trials in improving the asthma condition, especially in patients with the eosinophilic phenotype and oral-corticosteroid dependent types. It ameliorates the severity of asthma by improving the FEV1 values while reducing the risk of severe asthma exacerbations. Recent studies reveal that dupilumab is relatively well tolerated and presents itself as a safe molecule, having produced only mild-to-moderate adverse events in the majority of exposed study groups.

Additionally, the recent meta-analysis studies by Zayed et al²⁷ and Xiong et al⁵ highlight the potential of dupilumab in the treatment of moderate-to-severe asthma. However, the clinical trials were limited to a short duration of use. Hence, efficacy and safety profile of dupilumab in its long-term use must be studied extensively. Further, the studies must be extended to pediatric and geriatric patients to gain knowledge about its effect in such vulnerable populations. Various monoclonal antibodies targeting different elements of Th2 inflammation have been approved by the Food and Drug Administration during the study period for the treatment of uncontrolled asthma. Most of these biologics target either IL-4 or IL-13 receptors—which explains the wider treatment effect of dupilumab due to its dual blocking action on both IL-4 and IL-13 receptors. However, extensive and adequately powered clinical trials must be performed to compare the effectiveness of these biologics to establish the best available treatment regimen based on a patient's baseline eosinophil count.

Limitations

Follow-up duration varied among the included studies. The inclusion criteria were inconsistent and varied among the included studies. One study was composed of patients with asthma treated

with only oral glucocorticoids, whereas other studies involved patients with uncontrolled asthma using high-dose inhaled glucocorticoids and LABAs. The included studies differed in the phases of the clinical trials. The review was performed using the included studies in which 2 studies represented Phase III trials, 2 were Phase IIB trials, and 1 was a Phase IIA trial. The dupilumab administration was done in varying doses and frequency across the included studies. Not all studies addressed their outcomes with mention of respective eosinophil count, and the primary outcomes were not homologous among the included studies. A quantitative analysis of primary and secondary outcomes was not performed due to those limitations. Instead, the results are presented in a narrative manner.

Conclusions

The immunological-targeting approach in the treatment of moderate-to-severe asthma paves the way for the discovery of newer monoclonal antibodies. Among the biologics, dupilumab has a promising role in reducing the risk of severe asthma. The addition of dupilumab to conventional therapy, which includes LABAs and glucocorticoids improved the FEV1 values and reduced the rate of risk of severe exacerbations when compared with placebo in patients with moderate-to-severe asthma. The dupilumab and placebo groups have exhibited relatively similar safety profiles except the former showing a higher incidence of injection site-reactions. Future studies focusing on the concerns like the use of dupilumab in vulnerable populations, evaluation of long-term use, and comparison of efficacy with other biologics that may facilitate commercialization and wider acceptance globally.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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