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Dupilumab Efficacy and Safety as an Add-On Therapy in Uncontrolled Asthma Patients: A Systematic Review

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A B S T R A C T

Asthma is a heterogeneous chronic inflammatory condition affecting the lung. Standard treatment, a high-dose inhaled corticosteroid (ICS) and long-acting bronchodilator (LABA), effectively manages asthma in most individuals. However, 5%-10% of individuals with asthma were ineffective with those treatments. Recent RCTs suggested that Dupilumab posed potential as an add-on therapy. This systematic review aims to support the efficacy (the annualized rate of severe asthma exacerbation and increase in FEV1) and the safety of Dupilumab as an add-on therapy in uncontrolled asthma patients. We used "(Asthma) AND (Dupilumab)" as keywords on PubMed and ScienceDirect. We included only RCT design studies comparing the efficacy and safety of Dupilumab with a placebo in uncontrolled asthma patients. The placebo was ICS and LABA or oral glucocorticoids. This paper included five RCTs with 3400 participants, and their quality was assessed using Critical Appraisal Tools Program (CASP) tools. We conducted a meta-analysis to calculate the pooled risk ratio (RR). In addition, we used Mantel-Haenszel with 95% confidence intervals for dichotomous data. Furthermore, we used a random-effects model to count for interstudy heterogeneity. Then, we processed data using Revman 5.4. Dupilumab as an add-on therapy significantly showed a consistent effect in lower the annualized rate of severe asthma exacerbation (RR= 0.46; 95% CI 0.36- 0.58; p=0.007) and increased FEV1 compared to placebo. In addition, the most common adverse effect of using Dupilumab were injection site reaction, upper respiratory tract infections, and eosinophilia. In conclusion, Dupilumab is safe and well-tolerated as moderate-to-severe uncontrolled asthma add-on therapy

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory affecting the airways caused by airway hyperresponsiveness after exposure to triggers or allergens. It results in bronchoconstriction and airflow obstruction. Its symptoms are breathlessness, chest tightness, wheezing, and cough (Farne *et al.*, 2017; Harb and Chatila, 2017; GINA, 2021). Symptoms due to airflow obstruction may resolve either spontaneously or with asthma therapy. However, patients can experience exacerbations, an increase in the severity of a disease or its signs and symptoms in a certain period (Rothe *et al.*, 2018). Based on World Health Organization (WHO) survey data from 2002 to 2003, the prevalence of asthma patients among young adults (18-45 years old) in 70 countries was 177,496 (Global Asthma Network, 2018; Syfridiana and Herawati, 2021). Furthermore, asthma is still one of Indonesia's top ten diseases causing illness and death. Based on Basic Health Research in 2018, the prevalence of asthma in Indonesia was 2.4% of the total population of Indonesia. The highest asthma prevalence was in DI Yogyakarta (4.59%), East Kalimantan (4.0%), and Bali (3.9%) (Kemenkes RI, 2019).

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The long-term goals of asthma management are symptom control and risk reduction. The treatment includes medication, risk factors modification, and non-pharmacological therapies. Controller medication is vital in controlling asthma and preventing exacerbation in chronic asthma. There are five steps of treatment for chronic asthma. The higher the step, the more medication to manage chronic asthma (Fig.1) (GINA, 2021).

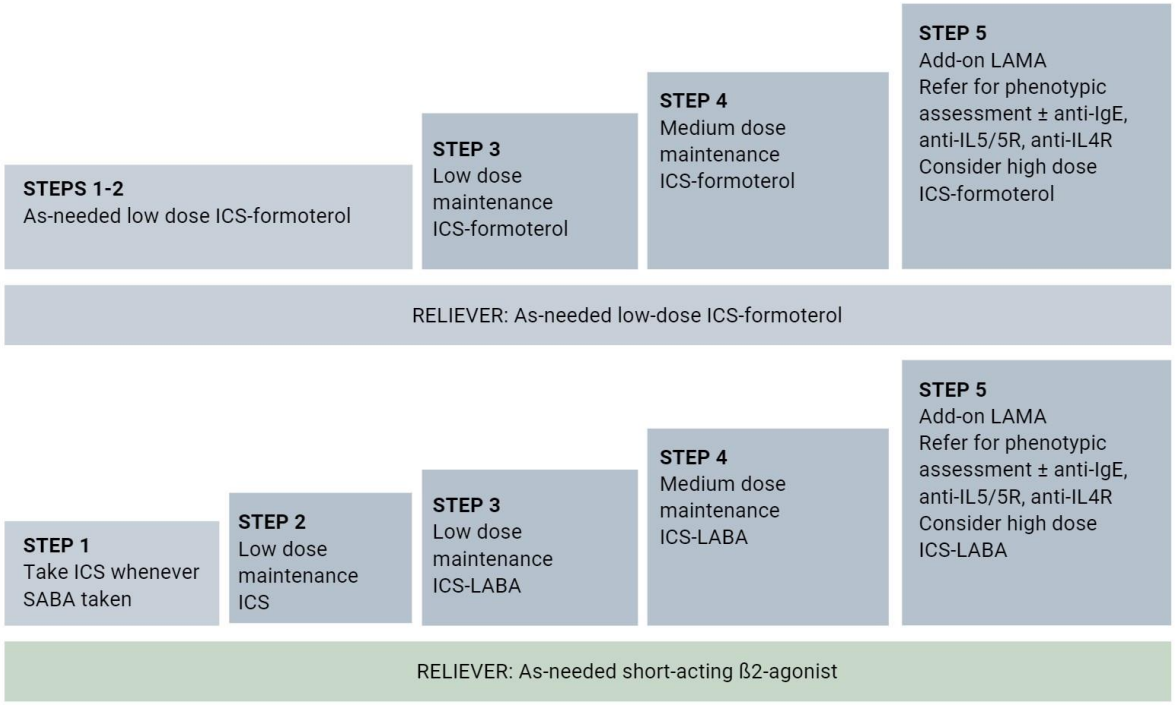

Figure 1. Asthma treatment strategy adapted from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021

Standard treatment, a high-dose inhaled corticosteroid (ICS) and long-acting bronchodilator (LABA), effectively manages asthma in most individuals. There were no data in Indonesia, but to the authors' knowledge, 5%-10% of individuals with asthma were ineffective with those treatments. They require add-on therapy (in step 5; Fig.1). Patients with severe uncontrolled asthma tend to have a poor quality of life (QOL), more extended hospitalization, and impaired lifestyle compared to well-controlled asthmatic patients. In addition, they experience adverse effects from oral corticosteroids (Rogliani *et al.*, 2020; Ricciardolo, Bertolini, and Carriero, 2021).

In the last decade, advanced research has led to new asthma treatments. This new therapy is a biological therapy indicated for uncontrolled severe asthma patients. Most of these therapy target inflammation molecules from the type two inflammation pathway (Rogliani *et al.*, 2020). There is currently a limited medication option in step 5 for uncontrolled, moderate to severe asthma patients. Omalizumab is an anti-IgE available in Indonesia, but only for persistent asthma patients with a positive skin test or reactive to perennial aeroallergen (in vitro) (FDA, 2017b). Also, Dupilumab is

the first biological therapy to target IL-4 and IL-13 type 2 cytokines. As a result, it reduces eosinophil levels.

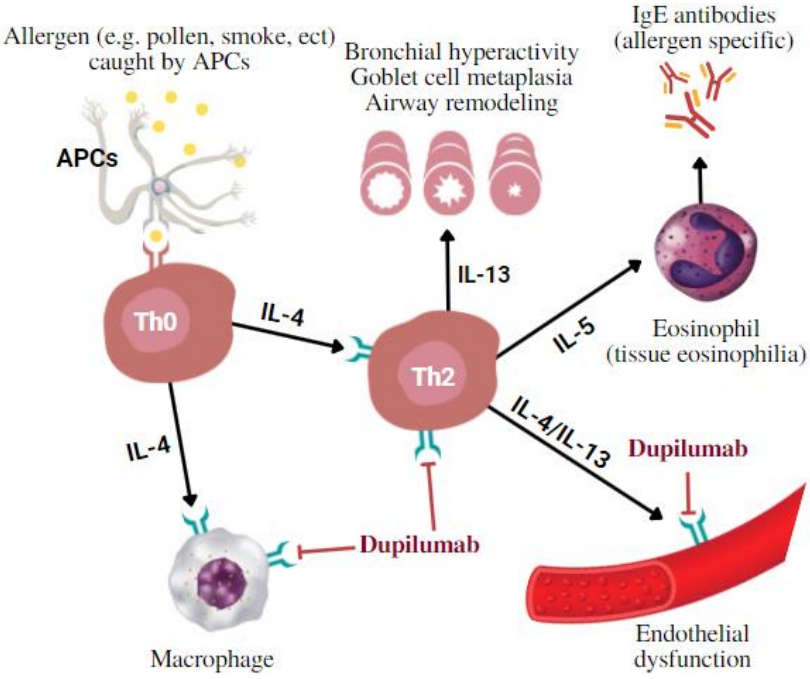

Figure 2. immunopathological pathway of Th-2 mediated asthma (modified from Hammad *et al.* (2021)(Harb and Chatila, 2017; Papi *et al.*, 2018)

T-helper2 (Th-2) lymphocytes can mediate the Th-2 immune response that precipitates asthma. Evidence states that elevated expression of Th2 cytokines, such as IL-4, IL-5, and IL-13, can drive allergic asthma (Ricciardolo, Bertolini, and Carriero, 2021). IL-4 promotes the synthesis of IgE and primes blood vessels for eosinophil extravasation by acting on IL-4R (Papi *et al.*, 2018). Meanwhile, IL-13 induces the production of iNOS in airway epithelial cells and metaplasia of goblet cells. In addition, it causes bronchial hyperactivity (Fig.2) (Papi *et al.*, 2018). Therefore, these molecules are essential for managing T2 allergic asthma (Ricciardolo, Bertolini, and Carriero, 2021). Preliminary simulation of Th-2 lymphocytes with the aid of several inflammatory cytokines, causing the expression of the CCR-4 chemokine receptor and secretion of different inflammatory interleukins, such as IL-4, IL-5, IL-9, and IL-13. As Th-2 lymphocytes migrate from surrounding lymph nodes to the airways, they induce chemotaxis and activation of inflammatory cells. In addition, it causes mast cells and eosinophils production that are liable for bronchial asthma symptoms over a long period (Zayed *et al.*, 2019). The prevalence of eosinophilic asthma is about 50% in asthmatic adults. In addition, recent findings suggest that patients with corticosteroid withdrawal also have eosinophilic inflammation. Therefore an IL-4/IL-13 inhibitor that can lower the eosinophilic levels is essential to target therapy (Papi *et al.*, 2018).

Dupilumab is a monoclonal antibody derived from humans, acting as an IL-4/IL-13 inhibitor. It targets the α subunit of the IL-4 and IL-13 receptors. It forms a high affinity to IL-13- and IL-4-binding type II heterodimeric complex (Fig.2) (Harb and Chatila, 2017, 2020). Thus, it blocks the signal transduction of the Th-2-mediated immune response (Ricciardolo, Bertolini, and Carriero, 2021).

A systematic review and meta-analysis of randomized clinical trials conducted in 2018 supported Dupilumab use in patients with uncontrolled asthma (Zayed *et al.*, 2019). The addition of Dupilumab in moderate-to-severe asthma therapy was associated with a reduced risk of asthma exacerbation and improved FEV_1 without an increased risk of an adverse event (Zayed *et al.*, 2019). Dupilumab injection was approved by the US Food and Drug Administration on Mar 28, 2017, to treat adults with uncontrolled moderate-to-severe eczema (atopic dermatitis) (FDA, 2017a). Dupilumab is available in Indonesia. Therefore, updated evidence with more recent trials is required to support its use in uncontrolled asthma therapy.

In this systematic review, we updated published systematic reviews and meta-analyses (Zayed *et al.*, 2019). This paper analyzes the efficacy (the annualized rate of severe asthma exacerbation and increase in FEV_1 from baseline) and safety of Dupilumab as an add-on therapy compared to a placebo in patients with moderate-severe uncontrolled asthma.

METHOD

Literature search, data source, and selection of study

Electronic literature searching was performed independently and separately by two authors (EE and PBD) using PUBMED and ScienceDirect with keywords (Asthma) AND (Dupilumab). The authors searched studies conducted from January 2013 to Feb 15, 2022. Collected studies were screened, and duplicates were removed using Mendeley Reference Manager. All included studies met the inclusion criteria: RCTs that compare the efficacy and safety of Dupilumab with a placebo in uncontrolled asthma patients with inhaled ICS and LABA or requiring oral glucocorticoids to control their symptoms. We excluded post hoc analysis and non-RCT studies.

Article quality assessment

Two authors (EE and PBD) assessed the studies' quality using the Critical Appraisal Program (CASP) tools (CASP, 2020) and journal reputation. The CASP checklist contains three parts consisting of several questions. Part A assesses the validation of research results. In addition, part B assesses research results. Furthermore, part C assesses whether the research results can be applied or used by readers. For the CASP checklist, articles were considered good quality because there were at least ten "yes" answers.

Outcomes

The primary efficacy outcome was the annualized rate of severe asthma exacerbations with criteria: a reduction of ≥30% in morning peak expiratory flow (PEF) from baseline on two consecutive days, at least six additional reliever inhalations (salbutamol or albuterol or levalbuterol) in 24 hours relative to baseline on two consecutive days, asthma exacerbation requiring systemic glucocorticoid treatment, an increase in inhaled glucocorticoids of at least four times the most recent dose, or hospitalization for asthma. The secondary outcome was the change in forced expiratory volume at 1s (FEV_1) between baseline and the most prolonged follow-up duration (12–24 weeks).

The authors also assessed safety outcomes and adverse events. Furthermore, we analyzed descriptively and narratively all included studies.

Statistical Analysis

We conducted a meta-analysis to calculate the pooled risk ratio (RR). In addition, we used Mantel-Haenszel with 95% confidence intervals for dichotomous data. Furthermore, we used a random-effects model to count for interstudy heterogeneity. Then, we processed data using Revman 5.4.

Ethical Clearance

This systematic review extracted data from accessible published articles, so ethical clearance is not applicable.

RESULT

A keyword search of two electronic databases, PubMed and ScienceDirect, resulted in 497 articles. The first screening based on title and abstract resulted in 52 relevant articles. Then, 52 papers were further reviewed and assessed for eligibility. Finally, this paper reviewed five RCT papers that compared Dupilumab with placebo in patients with severe uncontrolled asthma (Fig.3) (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021). Table 1 summarizes the details of the five included studies.

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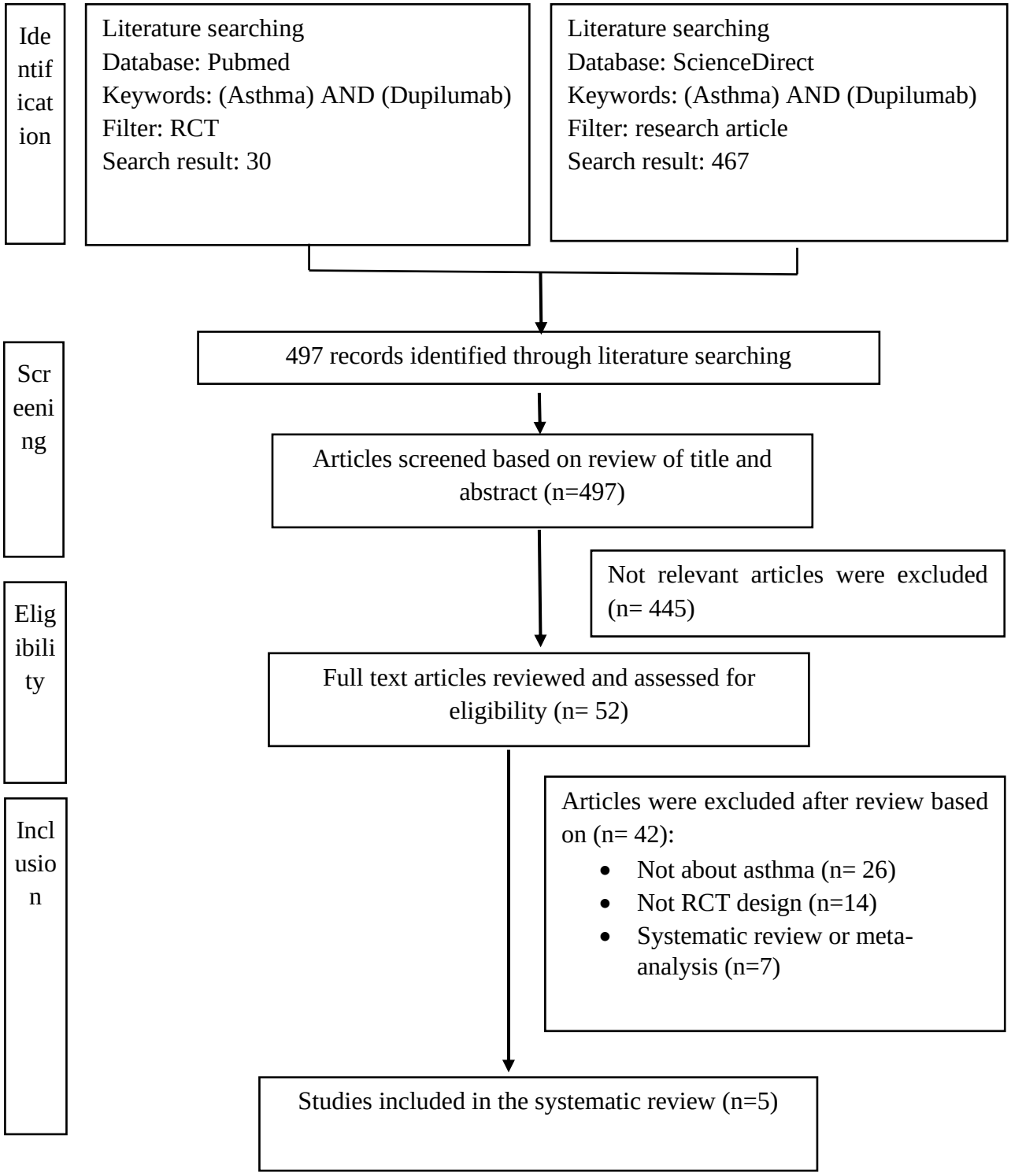

Figure 3. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of Literature Search and Studies Selection (Page *et al.*, 2021)

Quality of Articles

Assessment of articles with the CASP checklist showed that all five RCTs (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021) in included studies had good quality (5; 100%) (Fig.4). All studies were randomized, double-blind, and analyzed based on the

intention-to-treat principle. All outcomes were mentioned and measured statistically with *p* and confidence intervals (CI).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Wenzel, *et al* 2013	+	+	+	+	+
Wenzel, *et al* 2016	+	+	+	+	+
Castro, *et al* 2018	+	+	+	+	+
Rabe, *et al* 2018	+	+	+	+	+
Bacharier, *et al* 2021	+	+	+	+	+
Low risk of bias: +; uncertain risk of bias: ?; high risk of bias: −					

Figure 4. Risk of bias summary of included studies

All five RCTs included in this review were randomized and double-blinded with different Dupilumab doses, with the most frequently used dose of Dupilumab 200-300 mg every two weeks. Other dosages included 300 mg every week and 200-300 mg every four weeks. Thus, all baseline characteristics in these five included studies were similar. The meta-analysis of the primary outcome (the annualized rate of severe asthma exacerbation) was carried out using data from four studies only because the authors could not obtain the raw data from Rabe's study (2018). This statistical analysis found that Dupilumab as an add-on therapy significantly showed a consistent effect in lower the annualized rate of severe asthma exacerbation (RR= 0.46; 95% CI 0.36- 0.58; *p*=0.007) (Figure 5).

Figure 5. Forest plot of an annualized rate of severe asthma exacerbation

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Table 1. The Characteristics of Included Studies

Author (year)	Method	Patient or population	Intervention	Control	Outcomes		
					The annualized rate of severe asthma exacerbation	**Change in FEV1 from baseline**	**Adverse events**
Wenzel, S. *et al* (2013)	RCT (randomized, double-blind, placebo-controlled, parallel-group, phase 2A study)	Adults (18-65 years old), persistent, moderate-to-severe asthma, elevated blood eosinophil count (≥300 cells per microliter), or an elevated sputum eosinophil level (≥3%). In addition, inhaled glucocorticoids (medium to high dose) and LABAs could not control the symptoms. LABAs in the study were fluticasone ≥250 µg and salmeterol 50 µg twice daily or equivalent. (intervention=52; control=52)	Subcutaneous injections of Dupilumab (300 mg) once weekly for 12 weeks	Placebo	Dupilumab vs placebo: odds ratio 0.08; 95% confidence interval [CI], 0.02 to 0.28; $p<0.001$	Dupilumab vs. placebo, difference 0.27 (0.11 to 0.42) $p<0.001$	Injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently in Dupilumab than with a placebo
Wenzel, S. *et al* (2016)	RCT (randomized, double-blind, placebo-controlled, parallel-group, pivotal phase 2b clinical trial)	Adults (aged ≥18 years) with an asthma diagnosis for ≥12 months treated with medium-to-high-dose inhaled corticosteroids (twice daily) plus a long-acting β2 agonist (LABA) for at least one month before the screening. The LABA in the study was fluticasone propionate ≥250 µg or equivalent.	Subcutaneous Dupilumab 200 mg every two weeks (n=150)	Placebo (n=158)	**≥1 severe exacerbation event during the 24-week treatment period:** Risk reduction of 0.269 (0.157-0.461; $p=0.0002$)	**In overall population:** FEV1 increased significantly at week 12 ($p<0.0001$) **In ≥300 eosinophils/ µL subgroup:** FEV1 increased significantly at week 12 ($p=0.0008$) **In <300 eosinophils/ µL subgroup:** FEV1 increased significantly ($p=0.0034$)	Upper respiratory tract infection (14% in Dupilumab group vs. 18% in placebo), injection-site erythema (13% in Dupilumab group vs. 8% in placebo), and headache (10% in Dupilumab group vs. 13% in placebo)
			Subcutaneous Dupilumab 300 mg every two weeks (n=157)	Placebo (n=158)	**≥1 severe exacerbation event during the 24-week treatment period:** Risk reduction of 0.265 (0.157-0.445; $p=0.0001$)	**In overall population:** FEV1 increased significantly at week 12 ($p=0.0002$) **In ≥300 eosinophils/ µL subgroup:** FEV1 increased significantly at week 12 ($p=0.0063$) **In <300 eosinophils/ µL subgroup:** FEV1 increased significantly ($p=0.0086$)	
			Subcutaneous	Placebo	**≥1 severe**	**In overall**	

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			Dupilumab 200 mg every four weeks (n=154)	(n=158)	**exacerbation event during the 24-week treatment period:** Risk reduction of 0.415 (0.260-0.664; *p*=0.0093)	**population:** FEV1 increased significantly at week 12 (*p*=0.0304) **In ≥300 eosinophils/ µL subgroup:** FEV1 increased not significantly at week 12 (*p*=0.2774) **In <300 eosinophils/ µL subgroup:** FEV1 increased not significantly (*p*=0.0795)	
			Subcutaneous Dupilumab 300 mg every four weeks (n=157)	Placebo (n=158)	**≥1 severe exacerbation event during the 24-week treatment period:** Risk reduction of 0.599 (0.396-0.907; *p*=0.1380)	**In overall population:** FEV1 increased significantly at week 12 (*p*=0.0048) **In ≥300 eosinophils/ µL subgroup:** FEV1 increased significantly at week 12 (*p*=0.0212) **In <300 eosinophils/ µL subgroup:** FEV1 increased not significantly (*p*=0.1231)	
Castro *et al*. (2018)	RCT (phase 3, randomized, double-blind, placebo-controlled, parallel-group trial)	Patients ≥ 12 years old and had physician-diagnosed asthma ≥ 1 year. In addition, respondents were treated with medium-to-high-dose inhaled glucocorticoid plus up to two additional controllers (e.g., a long-acting β2-agonist or leukotriene-receptor antagonist). The inhaled glucocorticoid was fluticasone propionate at a total daily dose of ≥500 µg or equipotent equivalent.	Subcutaneous Dupilumab 200 mg (loading dose of 400 mg) or 300 mg (loading dose of 600 mg) every two weeks for 52 weeks	Placebo (1.14 ml or 2 ml)	**Dupilumab 200 mg vs placebo:** 47.7% lower rate of exacerbations with Dupilumab than with placebo (*p*<0.001) **Dupilumab 300 mg vs placebo:** 46.0% lower rate of exacerbations with Dupilumab than with placebo (*p*<0.001)	**Dupilumab 200 mg vs placebo (at week 12):** Dupilumab 0.32 L vs. placebo 0.18 L (difference, 0.14 L; *p*<0.001) **Dupilumab 300 mg vs placebo (at week 12):** Dupilumab 0.34 L vs. placebo 0.21 L (difference, 0.13 L; *p*<0,001)	There were injection-site reactions (15.2% in the 200 mg Dupilumab subgroup vs. 5.4% in the placebo group, and 18.4% in the 300 mg Dupilumab subgroup vs. 10.3% in the placebo group), eosinophilia (4.1% in Dupilumab group vs. 0.6% in the placebo group). In addition, severe adverse events (8.2% in the Dupilumab group and 8.4% in the placebo group) include pneumonia (0.3% in the Dupilumab group and 0.3% in

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							the placebo group).
Rabe *et al.* (2018)	RCT (international, randomized, double-blind, placebo-controlled, phase 3 trial)	Patients ≥ 12 years old, had physician-diagnosed asthma ≥ 1 year, receiving regular systemic glucocorticoids in the previous six months. During the four weeks before the screening, treated with high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of >500 µg or equipotent equivalent) in combination with up to two controllers (i.e., a long-acting β2-agonist or leukotriene-receptor antagonist) for at least three months	Subcutaneous Dupilumab (at a dose of 300 mg, after receiving a 600-mg loading dose on day 1) every two weeks for 24 weeks	Placebo	There was a reduction rate of severe asthma exacerbations by 59% (95% CI, 37 to 74) in the Dupilumab group vs. placebo.	Higher FEV1 in the Dupilumab group than in the placebo group at week 24 by a least-squares mean value of 0.22 liters (95% CI, 0.09 to 0.34)	Viral upper respiratory tract infection (9% in the Dupilumab group vs. 19% in the placebo group), injection-site reaction (9% in the Dupilumab group vs. 1% in the placebo group)
Bacharier, *et al* (2021)	RCT (multinational, randomized, placebo-controlled, phase 3 trial, Liberty Asthma VOYAGE (Evaluation of Dupilumab in Children with Uncontrolled Asthma)	The samples were children from 6 to 11 years old and physician-diagnosed with moderate-to-severe asthma (using GINA guidelines). Respondents had at least a 3-month history of receiving either a medium-dose inhaled glucocorticoid combination with a second controller. Or Respondents received high-dose inhaled glucocorticoid alone or in combination with a second controller at a dose that had been stable for at least one month.	Subcutaneous Dupilumab (273 patients) (dose of 100 mg for those weighing ≤30 kg and 200 mg for >30 kg) every two weeks for 52 weeks.	Volume-matched placebo (135 patients) every two weeks for 52 weeks.	Dupilumab 0.31 (95% CI, 0.22-0.42) vs. placebo 0.75 (95% CI, 0.54- 1.03). Significant relative risk reduction: 59.3%; 95% CI, 39.5 to 72.6; p<0.001)	Predicted prebronchodilator forced expiratory volume in 1 second (ppFEV1) at week 12: significant mean difference (mean difference, 5.2 percentage points; 95% CI, 2.1 to 8.3; p<0.001) between Dupilumab (10.5±1.01 percentage point) and placebo group (5.3±1.4 percentage points)	Viral infection of the upper respiratory tract (12.2% with Dupilumab and 9.7% with placebo), eosinophilia (5.9% on Dupilumab vs. 0.7% on placebo), parasitic infections (2.6% in the Dupilumab group)

DISCUSSION

Efficacy of Dupilumab as add-on therapy in uncontrolled asthma patients

The first RCT by Wenzel et al. (2013) showed that a subcutaneous injection of Dupilumab 300 mg once a week lowered annualized rate of severe asthma exacerbation compared to placebo in adult patients with persistent, moderate, and severe asthma (odds ratio 0.08; 95% confidence interval [CI], 0.02 to 0.28; p<0.001) (Wenzel *et al.*, 2013). Furthermore, Wenzel et al. (2016) investigated various subcutaneous Dupilumab regimens (200 mg every two weeks, 300 mg every two weeks, 200 mg every four weeks, and 300 mg every four weeks) for 24 weeks compared to placebo in adults. The results revealed a significant reduction in exacerbation events in three regimens (200 mg every two weeks, 300 mg every two weeks, and 200 mg every four weeks) but not 300 mg every four weeks. The results align with the RCT by Castro

et al. (2018), which assessed the efficacy of subcutaneous Dupilumab 200 mg and 300 mg every two weeks but in a more extended follow-up period (52 weeks). That study showed a significant reduction of annualized exacerbation by 47.7% and 46.0%, respectively (Castro *et al.*, 2018). Another RCT in 2018 also assessed the efficacy of Dupilumab 300 mg with a loading dose of 600 mg on day one. The study also showed a reduction in severe asthma exacerbations by 59% (95% CI, 37 to 74) (Rabe *et al.*, 2018). Moreover, the newest RCT by Bacharier et al. (2021) also focused on evaluating the efficacy of Dupilumab in children (6-11 years old), with dosage varied based on the child's weight. A child with ≤30 kg body weight received 100 mg of Dupilumab every two weeks, while samples >30 kg received 200 mg every two weeks for 52 weeks. This systematic review and meta-analysis found that the annualized rate of severe asthma exacerbations in the Dupilumab group was lower than in the placebo group (RR 0.46; 95% CI 0.36- 0.58; p=0.007). Previous systematic review and meta-analysis in 2018 also showed a similar result to this paper, despite not including the children population (aged 6-11 years old) (Zayed *et al.*, 2019).

Dupilumab has a complex mechanism and is associated with eosinophil count in reducing severe asthma exacerbation, as mentioned by Zayed et al. (2018). Dupilumab can potentially suppress asthma exacerbation by blocking both IL-4 and IL-13, reducing eosinophil production (IL-4 mediated), mucous production, and preventing airway remodeling (IL-3 mediated, unrelated to the eosinophilia-associated Th-2 response) (Zayed *et al.*, 2019). This notion is supported by findings of a significant reduction of severe asthma exacerbations annual rate and an improvement in FEV1 in asthma patients receiving Dupilumab compared to placebo, regardless of their eosinophil count.

The effect of Dupilumab may be dose-dependent, as demonstrated by Castro *et al.* (2018), one of the RCTs included in this systematic review. Higher and more frequent Dupilumab doses, either 200 mg every two weeks or 300 mg every two weeks, are required to prevent the annualized rate of severe asthma exacerbations (Castro *et al.*, 2018). However, there is still too little RCT conducted to assess the dosing effect on the Dupilumab efficacy. Therefore, we conducted a meta-analysis in this current study that includes all doses given in the RCT studies.

The secondary outcome of this meta-analysis was the change in FEV_1. Dupilumab 300 mg once a week, 200 mg every two weeks, and 300 mg every two weeks significantly showed the consistent result in the increase of FEV_1 (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021) (5;100%). However, Dupilumab 200 mg or 300 mg every four weeks showed no significant increase in FEV_1 (Wenzel *et al.*, 2016). It might be due to the low frequency of doses.

Safety of Dupilumab

The most common adverse events of Dupilumab subcutaneous reported were injection site reactions (Wenzel *et al.*, 2013, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018), upper respiratory tract infections

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(Wenzel *et al.*, 2016; Castro *et al.*, 2018; Rabe *et al.*, 2018; Bacharier *et al.*, 2021), and eosinophilia (Castro *et al.*, 2018; Bacharier *et al.*, 2021). All five studies in this meta-analysis (5;100%) showed no significant differences in any adverse events between Dupilumab and the control group.

CONCLUSION

Dupilumab as add-on therapy in patients with uncontrolled asthma significantly lowered the annualized rate of severe asthma exacerbations and increased FEV1 in all five included studies. The most common adverse effects of using Dupilumab were injection site reaction, upper respiratory tract infections, and eosinophilia. Thus, this review concludes that using Dupilumab in uncontrolled asthma patients is beneficial and well-tolerated.

Although all studies included in this systematic review have a low risk of bias, it still can't point out the best dose of Dupilumab for add-on therapy in moderate-to-severe uncontrolled asthma patients. Moreover, RCT studies assessing Dupilumab efficacy and safety in the Indonesian population are still lacking. Thus, there should be more RCT studies (with more samples for achieving generality), especially in Indonesia, to determine the optimal dose.

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12230

APLIKASI PERAWATAN LUKA DENGAN MENGGUNAKAN ENZYMATIK THERAPY: ALOE VERA DALAM MANAJEMEN LUKA DIABETES
8391

FAKTOR YANG BERPENGARUH TERHADAP KEJADIAN POSTPARTUM BLUES
7717

PENGALAMAN SEKSUALITAS PEREMPUAN PASCA TAH BSO (TOTAL ABDOMINAL HYSTERECTOMYBILATERAL SALPINGO OOPHORECTOMY)
7569

Lactation in Al-Quran Perspective
6733

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