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Dupilumab efficacy and safety in patients with moderate to severe asthma: A systematic review and meta-analysis

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Background: Dupilumab is a human monoclonal antibody directed against the alpha subunit of the interleukin-4 receptor and inhibits the signaling of IL-4 and IL-13. It is approved for treating asthma and other type-2 inflammatory diseases. There is a conflict in the literature regarding the safety and efficacy of dupilumab. Thus, we aimed to assess the safety and efficacy of dupilumab in patients with moderate to severe asthma.

Methods: Six databases (PubMed, Embase, Scopus, Web of Science, Cochrane library, and clinicaltrials.gov registry) were searched until January 2022. We included randomized controlled trials that compared dupilumab with the

placebo in moderate to severe asthma patients. We extracted the data at 12 and 24 weeks and analyzed them using review manager 5.4.

Findings: Thirteen trials were included. Dupilumab significantly improved the forced expiratory volume in 1 s, asthma control questionnaire score, the fraction of exhaled nitric oxide level, and immunoglobulin E level at 12 and 24 weeks ($p < 0.05$). However, it was associated with increased blood eosinophils at 12 and 24 weeks. Dupilumab was generally a safe agent for asthmatic patients. It showed no significant difference compared with the placebo regarding most adverse events.

Conclusion: Dupilumab improves pulmonary function and reduces local and systemic inflammatory markers with minimal adverse events in patients with moderate to severe asthma.

KEYWORDS

asthma, dupilumab, monoclonal antibody, systematic review, meta-analysis

1 Introduction

Worldwide, asthma affected approximately 262 million people and caused 461,000 deaths (JL Murray, 2020). It is a major non-communicable disease that affects children and adults of both sexes, with a higher incidence in females (Wu et al., 2019). The disease prevalence has both genetic and environmental factors (Arrieta et al., 2015; Chen et al., 2017). Despite high-dose treatment, nearly more than 25% of the patients have uncontrolled asthma (JL Murray, 2020). In addition, those patients are at increased risk for respiratory function impairment, frequent asthmatic exacerbation, hospitalization, medical and societal costs, and poor quality of life (Bellin et al., 2015; Fleming et al., 2015).

Bronchial asthma is a disease of the air conducting system. It is characterized by a long-term airway inflammatory process even if the patient is in an asymptomatic period (Robinson et al., 1992). Major symptoms include cough, chest tightness, shortness of breath, and reversible episodic wheezes resulting from airway inflammation and hyperresponsiveness (Wu et al., 2019). The inflammatory process of asthma is mediated by helper T-2 cells and eosinophils in addition to the released cytokines, including interleukins (IL); IL-4, IL-5, and IL-13 (Robinson et al., 1992; Fahy, 2015). Interleukin-4 (IL-4) is one of the most important pro-inflammatory mediators in asthma. It mediates essential functions in asthma, including induction of the IgE isotype switch, expression of vascular cell adhesion molecule-1 (VCAM-1), and promotion of eosinophil transmigration across the endothelium, mucus secretion, and differentiation of T helper type-2 lymphocytes leading to cytokine release which causes asthma symptoms (Steinke and Borish, 2001). So, inhibiting the main ILs as IL-4 receptors will reduce the signaling and activity of the asthma inflammatory process, enhancing the pulmonary function and reducing the systemic and local inflammatory mediators.

Traditional pharmacological treatments are classified into controller medication and rescue medication. This comprises long-acting beta-agonists (LABA), inhaled corticosteroids, or leukotriene modifiers that interfere with the inflammatory process and prevent progression into irreversible airway remodeling (Newman, 2004; Chauhan and Ducharme, 2014; Wu et al., 2019). Dupilumab is a human monoclonal antibody directed against the alpha subunit of the interleukin-4 receptor and inhibits the signaling of IL-4 and IL-13 (Le Floc'h et al., 2020). The literature revealed significant improvement in clinical outcomes of asthmatic patients (Castro et al., 2018; Bachert et al., 2019; Castro et al., 2020; Bacharier et al., 2021). The effect of dupilumab starts early after the beginning of the treatment course. Most studies reported that it is maintained to the end of the follow-up periods of different RCTs up to 52 weeks. Moreover, it is approved for treating asthma and other type-2 inflammatory diseases in adults and adolescents. The global initiative for asthma (GINA) 2022 report (Reddel et al., 2022) suggests using anti-IL-4 receptors such as dupilumab in the management of patients with severe eosinophilic/type-2 asthma (step 5). This is suitable for patients of ≥6 years old, adolescents, and adults. However, other literature works revealed discrepancies regarding its efficacy (Wenzel et al., 2016; Weinstein et al., 2018; Laidlaw et al., 2021; Wechsler et al., 2021). This may be explained by different dosage regimens or comorbidities with asthma. Hence, in this systematic review and meta-analysis, we aimed to solve this contrast by evaluating the safety and efficacy of dupilumab in patients with moderate to severe asthma.

2 Materials and methods

2.1 Study design

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic

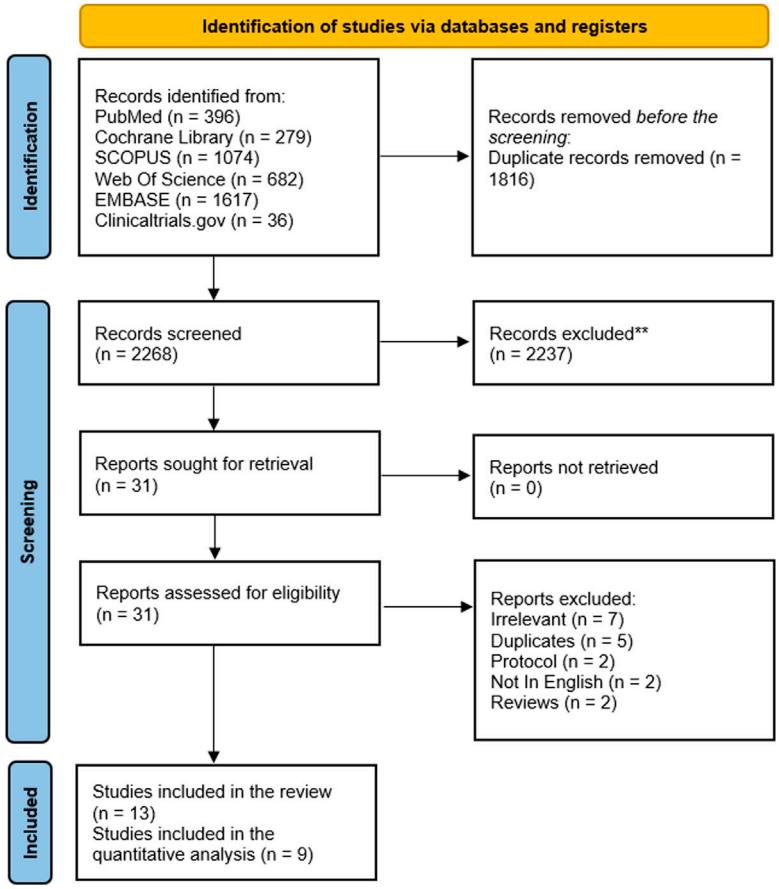

FIGURE 1
PRISMA flow diagram of the included studies.

Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021) and the Cochrane Handbook of Systematic Review and Meta-analysis of Interventions (Higgins, 2019).

2.2 Search strategy

Six databases (PubMed, Embase, Scopus, Web of Science, Cochrane library, and clinicaltrials.gov registry) were used for literature search from inception until January 2022. We used the following keywords (Dupilumab, SAR231893, SAR-231893, Dupixent, REGN668, REGN-668, and Asthma*).

2.3 Inclusion and exclusion criteria

Human-based, English-written randomized controlled trials (RCTs) were included with no restriction on age, sex, settings, or publication dates. The included RCTs compared dupilumab with the placebo in moderate to severe asthma patients. Exclusion criteria included protocols, non-English–written studies, conference abstracts, book chapters, review articles, observational studies, and non-human studies.

2.4 Study selection and data extraction

We used the EndNote X8 version for citation management and duplicate removal. The full text of the eligible studies in the non-open access journals were obtained through academic institution access or by contacting authors requesting full texts of their studies.

The authors selected the studies according to two steps; first, we performed the title and abstract screening, and second, full-text screening to identify studies that fulfill our inclusion criteria. We manually screened the reference list in the included studies and citations of the identified articles. Four independent authors performed each step, and a discussion with the supervisor solved any disagreements.

Four authors extracted the following data (I) summary of included studies, including study design, NCT numbers,

TABLE 1 Summary of the included studies.

Study ID	Study design	NCT	Participants details	Intervention period	Follow-up period	Primary outcomes
Bacharier et al. (2021)	RCT	NCT02948959	- Children of 6–11 years old - Had moderate to severe asthma according to GINA guidelines	- 52 weeks - After week 12, home administration was allowed	-	Percentage of predicted prebronchodilator forced expiratory volume in 1 s
Castro et al. (2018)	RCT	NCT02414854	- Patients of 12 years or older - Had uncontrolled, moderate to severe asthma for ≥1 year, according to GINA guidelines	52 weeks	12 weeks	The annualized rate of severe asthma exacerbations and the absolute forced expiratory volume in 1 s
Castro et al. (2020)	Post-hoc analysis	NCT02414854	- Patients of 12 years or older - Had uncontrolled, moderate to severe asthma for ≥1 year, according to GINA guidelines	52 weeks	12 weeks	The annualized rate of severe asthma exacerbations and the absolute forced expiratory volume in 1 s
Corren et al. (2019)	Post-hoc analysis	NCT02414854	- Patients of 12 years or older - Had uncontrolled, moderate to severe asthma for ≥1 year, according to GINA guidelines	52 weeks	12 weeks	The annualized rate of severe asthma exacerbations and the absolute forced expiratory volume in 1 s (according to allergic asthma presence)
Corren et al. (2021)	Post-hoc analysis	NCT02414854	- Patients of 12 years or older - Had uncontrolled, moderate to severe asthma for ≥1 year, according to GINA guidelines	52 weeks	12 weeks	The annualized rate of severe asthma exacerbations and the absolute forced expiratory volume in 1 s (according to Eosinophil's count)
Tohda et al. (2020)	Post-hoc analysis	NCT02414854	- Japanese patients of 12 years or older - Had uncontrolled, moderate to severe asthma for ≥1 year, according to GINA guidelines	52 weeks	12 weeks	The annualized rate of severe asthma exacerbations and the absolute forced expiratory volume in 1 s (in Japanese only)
Bachert et al. (2020)	RCT	- NCT02912468 - NCT02898454	- Adults of 18 years or older - Had CRSwNP and had corticosteroids for 2 years or previous sinonasal surgery - 50% of these patients had asthma	24 weeks 52 weeks	24 weeks 12 weeks	Bilateral nasal polyp score and nasal congestion or obstruction score
Laidlaw et al. (2021)	Post-hoc analysis	- NCT02912468 - NCT02898454	- Adults of 18 years or older - Had CRSwNP and had corticosteroids for 2 years or previous sinonasal surgery - 50% of these patients had asthma	24 weeks 52 weeks	24 weeks 12 weeks	Bilateral nasal polyp score and nasal congestion or obstruction score. (Longer follow-up)
Rape et al. (2018)	RCT	NCT02528214	- Patients of 12 years or older - Had asthma for ≥1 year, according to GINA guidelines, and received glucocorticoids for 6 months	24 weeks	12 weeks	Percentage reduction in the glucocorticoid dose
Wechsler et al. (2021)	RCT	NCT03387852	- Patients of 18 to 70 years old - Had asthma for ≥1 year, according to GINA guidelines, and received glucocorticoids and LABA for ≥3 months	12 weeks	20 weeks	Event indicating a loss of asthma control
Weinstein et al. (2018)	Post-hoc analysis	NCT01854047	- Adults of 18 years or older - Had asthma for ≥1 year, according to GINA guidelines	24 weeks	16 weeks	Change in forced expiratory volume in 1 s according to perennial allergic rhinitis presence)
Wenzel et al. (2016)	RCT	NCT01854047	- Adults of 18 years or older - Had asthma for ≥1 year, according to GINA guidelines	24 weeks	16 weeks	Change in forced expiratory volume in 1 s
Wenzel et al. (2013)	RCT	NCT01312961	- Patients of 18 to 65 years old - Had persistent, moderate-to-severe asthma for ≥1 year and had ≥300 cells/μl eosinophil in blood or ≥3% in sputum	12 weeks	8 weeks	Occurrence of an asthma exacerbation

GINA; Global Initiative for Asthma, CRSwNP; chronic rhinosinusitis with nasal polyps, LABA; long-acting beta-agonist, RCT; randomized controlled trial.

participants' details, intervention period, follow-up period, primary outcomes, and (II) baseline characteristics of included studies, including study arms, sample size, age, sex, forced expiratory volume in 1 s (FEV1) reversibility, history of nasal polyposis, history of smoking, and allergic conditions. Another three authors extracted the outcomes of interest.

2.5 Outcomes

2.5.1 Primary outcomes

2.5.1.1 Efficacy outcomes

FEV1 change per liter, Asthma Control Questionnaire (ACQ) change.

2.5.1.2 Safety outcomes

Any treatment-emergent adverse events, any treatment-emergent adverse events leading to permanent discontinuation.

2.5.2 Secondary outcomes

2.5.2.1 Efficacy outcomes

Fraction of exhaled nitric oxide (FeNO) change, blood eosinophil change, and IgE changes all at 12 and 24 weeks.

2.5.2.2 Safety outcomes

Any adverse events, any adverse events leading to permanent discontinuation, serious adverse events, serious treatment-emergent adverse events, any adverse events leading to death, any treatment-emergent adverse events leading to death, nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, headache, erythema, injection-site reaction, cough, allergic rhinitis, bronchitis, influenza, urinary tract infection, back pain, sinusitis, and eosinophilia.

2.6 Quality assessment

The risk of bias was assessed according to the Cochrane risk of bias tool, using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins et al., 2011). It includes seven main domains, namely, random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases.

2.7 Statistical analysis

We used Review Manager (Version 5.4) to analyze the data. We used the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous data and mean difference (MD) and 95% CI for continuous data. The data were pooled under a random-effect model. Heterogeneity among the studies was examined using Cochrane's p values and I^2. We considered the data heterogeneous when chi-square $p < 0.1$ and $I^2 > 50\%$. We used a sensitivity analysis by leaving one out method to overcome heterogeneity. According to the Cochrane Handbook, we could not assess the publication bias as all outcomes were reported in less than 10 studies. The efficacy outcomes were pooled at different time points, 12 and 24 weeks. In addition, we performed a subgroup analysis according to the treatment regimen. This includes the following groups: 100–200 mg of dupilumab every 2 weeks, 200 mg dupilumab every 2 weeks, 200 mg dupilumab every 4 weeks, 300 mg dupilumab every 2 weeks, and 300 mg dupilumab every 4 weeks.

3 Results

3.1 Summary of study selection and general characteristics of included studies

A total of 2,268 studies were retrieved from different databases after duplicate removal. Of them, only 31 studies were eligible for full-text assessment. According to our inclusion and exclusion criteria, we included 13 RCTs (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Weinstein et al., 2018; Bachert et al., 2019; Castro et al., 2020; Corren et al., 2020; Tohda et al., 2020; Bacharier et al., 2021; Corren et al., 2021; Laidlaw et al., 2021; Wechsler et al., 2021) in our systematic review; of them, nine trials were eligible for our meta-analysis (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Weinstein et al., 2018; Bachert et al., 2019; Bacharier et al., 2021; Laidlaw et al., 2021; Wechsler et al., 2021). Figure 1 shows the PRISMA flow diagram of our meta-analysis.

We included data of 4,482 patients. Of them, 726 (16.2%) were smokers. A total of 1,092 patients (24.4%) had a history of polyposis, while 2,558 patients (57%) had a history of allergic conditions. The mean age of our population was 45 years old. Most of them were females (59.2%). The mean FEV1 reversibility at baseline was 21.2%. The follow-up periods ranged from 12 to 52 weeks. Tables 1, 2 show the summary and baseline characteristics of the included population.

3.2 Results of the quality assessment

All the included studies revealed a low risk of bias regarding all the assessed domains of the Cochrane risk of bias tool, except for other bias domains. It was put at a high risk as all of the included studies were funded by the drug manufacturer. In addition, in the trial by Wechesler et al. (Laidlaw et al., 2021), data about the allocation process were unclear. Figure 2 shows the summary of the quality assessment.

3.3 Analysis of the outcomes

3.3.1 Change in clinical characteristics after 12 and 24 weeks

3.3.1.1 Change in FEV1 (L) at week 12

This outcome was reported by five trials (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Laidlaw et al., 2021; Wechsler et al., 2021). Dupilumab significantly improved the absolute (dose-independent) FEV1 (L) at week 12 among 2,198 patients in this group compared with 1,450 patients in the placebo group; MD = 0.14, 95% CI = 0.11, 0.16, $p < 0.01$. This outcome was homogeneous $p = 0.47$, $I^2 = 0\%$. The subgroup analysis of different dupilumab doses did not reveal any significant difference between all subgroups $p = 0.57$ (Figure 3).

As for dupilumab 200 mg q2w, two trials reported this outcome (Wenzel et al., 2016; Castro et al., 2018). They revealed a significant improvement in FEV1 (L) compared with the placebo; MD = 0.16 (95% CI = 0.11, 0.20), $p < 0.01$. This subgroup pooled data were homogeneous; $p = 0.33$, $I^2 = 0\%$.

Regarding the 300 mg dupilumab q2w, five trials reported this outcome (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Laidlaw et al., 2021; Wechsler et al., 2021). Dupilumab significantly improved the FEV1(L) compared with the placebo; MD = 0.14, 95% CI = 0.09, 0.18, $p < 0.01$. This subgroup pooled data were homogeneous; $p = 0.32$, $I^2 = 14\%$.

3.3.1.2 Change in FEV1 (L) at week 24

This outcome was reported by five trials (Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Weinstein et al., 2018; Laidlaw et al., 2021). Dupilumab significantly improved the absolute (dose-independent) FEV1 (L) at week 24 among 2,144 patients in the treatment group compared with 1,445 patients in the placebo group; MD = 0.13, (95% CI = 0.11, 0.16), $p < 0.00001$. This outcome was homogeneous; $p = 0.66$, $I^2 = 0\%$. The subgroup analysis revealed no significant difference between them, $p = 0.34$ (Figure 4).

In the dupilumab 200 mg q2w subgroup, two included trials (Wenzel et al., 2016; Castro et al., 2018) revealed a significant improvement in FEV1 in the dupilumab group; MD = 0.17 (95% CI = 0.12, 0.21), $p < 0.00001$. This subgroup pooled data were homogeneous; $p = 0.84$, $I^2 = 0\%$.

As for 200 mg dupilumab q4w, it significantly improved the FEV1 compared with the placebo; MD = 0.12 (95% CI = 0.03, 0.22), $p = 0.01$. This subgroup data were homogeneous; $p = 0.6$, $I^2 = 0\%$.

In four trials (Castro et al., 2018; Rabe et al., 2018; Weinstein et al., 2018; Laidlaw et al., 2021), the dupilumab 300 mg q2w regimen revealed a significant improvement in FEV1 compared with the placebo; MD = 0.11 (95% CI = 0.07, 0.15), $p < 0.00001$. This subgroup data were homogeneous; $p = 0.54$, $I^2 = 0\%$.

3.3.1.3 Change in ACQ at week 12

This outcome was reported in five trials (Wenzel et al., 2013; Wenzel et al., 2016; Bacharier et al., 2021; Laidlaw et al., 2021; Wechsler et al., 2021). They revealed a significant reduction in the absolute ACQ score at 12 weeks In the dupilumab group compared with the placebo; MD = −0.74 (95% CI = −1.20, −0.28), $p = 0.001$. The overall analysis revealed heterogeneity $p < 0.01$, $I^2 = 96\%$. The subgroup analysis revealed no significant difference between all subgroups, $p = 0.11$ (Figure 5).

Regarding the 300 mg q2w regimen reported by four trials (Wenzel et al., 2013; Wenzel et al., 2016; Laidlaw et al., 2021; Wechsler et al., 2021), the dupilumab revealed a significant reduction in the ACQ score compared with the placebo; MD = −1.34 (95% CI = −2.42, −0.26), $p < 0.01$. This subgroup data were heterogeneous; $p < 0.001$, $I^2 = 98\%$. The sensitivity analysis could not solve this heterogeneity.

3.3.1.4 Change in ACQ at week 24

This outcome was reported in four trials (Wenzel et al., 2013; Castro et al., 2018; Bachert et al., 2019; Bacharier et al., 2021). They revealed that dupilumab significantly reduced the absolute ACQ score at 24 weeks Compared with the placebo; MD = −0.43 (95% CI = −0.67, −0.19), $p = 0.0005$. The pooled analysis was heterogeneous; $p < 0.001$, $I^2 = 88\%$. The subgroup analysis revealed no significant difference between subgroups, $p = 0.68$ (Figures 6A,B). As for 300 mg q2w, dupilumab revealed a significant reduction in ACQ at 24 weeks Compared with the placebo; MD = −0.53 (95% CI = −1.04, −0.02), $p = 0.04$. This subgroup pooled data were heterogeneous; $p < 0.001$, $I^2 = 94\%$. To solve this heterogeneity, we excluded Castro et al. (2018). After sensitivity analysis, there was a significant ACQ score reduction in the dupilumab group compared with the placebo; MD = −0.77 (95% CI = −1.07, −0.47), $p < 0.001$. The subgroup analysis was homogeneous; $p = 0.19$, $I^2 = 42\%$.

3.3.2 Change in biomarkers of asthma after 12 and 24 weeks

3.3.2.1 Change in FeNO (ppb) at week 12

Six trials (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Bacharier et al., 2021; Wechsler et al., 2021) reported this outcome. Dupilumab significantly reduced the FeNO (ppb) compared with the placebo; MD = −17.58 (95% CI = −21.87, −13.29), $p < 0.001$. The pooled analysis was heterogeneous $p = 0.005$, $I^2 = 62\%$. The subgroup analysis revealed no significant difference between those regimens regarding the dupilumab efficacy, $p = 0.84$ (Supplementary Figure S1).

Regarding the 200 mg q2w regimens, the pooled two trials (Wenzel et al., 2016; Castro et al., 2018) revealed no significant reduction in the FeNO (ppb) compared with the placebo; MD = −22.25 (95% CI = −44.73, 0.23), $p = 0.05$. The pooled analysis was heterogeneous, $p = 0.01$, $I^2 = 84\%$.

TABLE 2 Baseline characteristics of the study population.

Study ID	Study arm	Sample	Age, year	Sex, male	FEV1 reversibility %	Nasal polyposis history	Former smoker	Allergic condition
Bacharier et al., 2021	Dupilumab 100–200 mg q2w	273	8.9 ± 1.7	175 (64.1)	21.56 ± 22.43	—	—	—
	Placebo	135	8.9 ± 1.6	87 (64.4)	15.63 ± 16.33	—	—	—
Castro et al., 2018, Castro et al., 2020, Corren et al., 2019, Corren et al., 2021	Dupilumab 300 mg q2w	633	47.7 ± 15.6	239 (37.8)	26.29 ± 21.73	145 (22.9)	116 (18.3)	524 (82.8)
	Placebo	321	48.2 ± 14.7	103 (32.1)	25.73 ± 17.65	80 (24.9)	67 (20.9)	266 (82.9)
	Dupilumab 200 mg q2w	631	47.9 ± 15.3	244 (38.7)	27.39 ± 22.79	141 (22.3)	126 (20.0)	509 (80.7)
	Placebo	317	48.2 ± 15.6	119 (37.5)	25.06 ± 18.76	73 (23.0)	59 (18.6)	266 (83.9)
Laidlaw et al., 2021 and Bachert et al., 2020	Dupilumab 300 mg q2w	258	34.78 ± 16.01	210 (49.1)	—	428 (100)	—	—
	Placebo	170			—		—	—
Rape et al., 2018	Dupilumab 300 mg q2w	103	51.9 ± 12.5	41 (40)	—	33 (32)	24 (23)	10 (10)
	Placebo	107	50.7 ± 12.8	42 (39)	—	38 (36)	17 (16)	10 (9)
Tohda et al., 2020	Dupilumab 300 mg q2w	41	47.2 ± 18.2	13 (31.7)	20.11 ± 17.54	8 (19.5)	4 (9.8)	36 (87.8)
	Placebo	17	51.4 ± 12.9	5 (29.4)	21.55 ± 17.95	7 (41.2)	6 (35.3)	13 (76.5)
	Dupilumab 200 mg q2w	37	49 ± 16	19 (51.4)	20.63 ± 19.64	12 (32.4)	10 (27.0)	33 (89.2)
	Placebo	19	47.1 ± 16.9	8 (42.1)	21 ± 11.44	2 (10.5)	6 (31.6)	18 (94.7)
Wechsler et al., 2021	Dupilumab 300 mg	75	51.3 ± 12.7	34 (45)	13.32 ± 11.76	—	14 (19)	66 (88)
	Placebo	74	47 ± 11.4	27 (36)	15.58 ± 15.84	—	17 (9)	67 (91)
Weinstein et al. 2018- with PAR	Dupilumab 300 mg q2w	84	45 ± 13.2	34 (40.5)	—	—	20 (23.8)	53 (63.9)
	Dupilumab 200 mg q2w	73	46.6 ± 14.6	24 (32.9)	—	—	17 (23.3)	54 (75)
	Placebo	84	47.9 ± 12.9	34 (40.5)	—	—	18 (21.4)	59 (71.1)
Weinstein et al. 2018- without PAR	Dupilumab 300 mg q2w	43	48.8 ± 11.5	8 (18.6)	—	—	9 (20.9)	21 (51.2)
	Dupilumab 200 mg q2w	52	55.6 ± 10.5	14 (26.9)	—	—	9 (17.3)	29 (55.8)
	Placebo	56	51.9 ± 13.2	12 (21.4)	—	—	13 (23.2)	30 (56.6)
Wenzel et al., 2013	Dupilumab 300 mg q2w	52	37.8 ± 13.2	26 (50)	—	—	—	—
	Placebo	52	41.6 ± 13.1	26 (50)	—	—	—	—
Wenzel et al., 2016	Dupilumab 200 mg q4w	154	47.9 ± 13.1	67 (43·5)	—	21 (13·9)	34 (22·2)	100 (66·2)
	Dupilumab 300 mg q4w	157	47.9 ± 13.1	57 (36·3)	—	31 (20·0)	38 (24·2)	99 (63·9)
	Dupilumab 200 mg q2w	157	51 ± 13.4	54 (36·0)	—	25 (16·8)	32 (21·3)	99 (66·4)
	Dupilumab 300 mg q2w	150	47.5 ± 12.4	54 (34·4)	—	30 (19·5)	36 (22·9)	94 (61·0)
	Placebo	157	49 ± 12.7	54 (34·2)	—	18 (11·7)	34 (21·5)	102 (66·2)

PAR; perennial allergic rhinitis, FEV1; forced expiratory volume in 1 s. Data are reported as mean ± standard deviation or number (percentage).

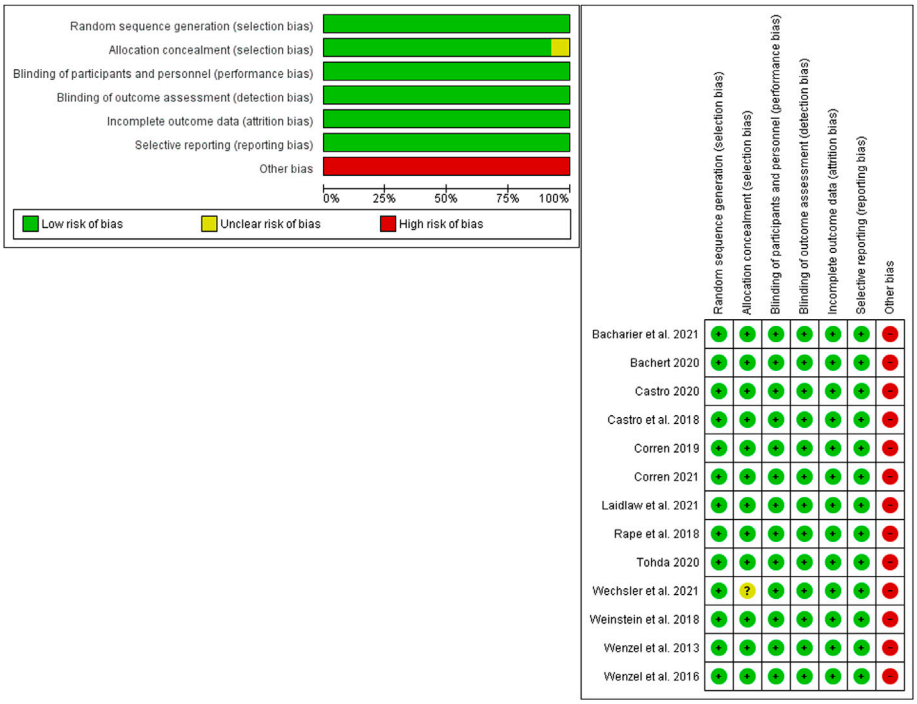

FIGURE 2
Summary and graph of risk of bias assessment results for the included studies.

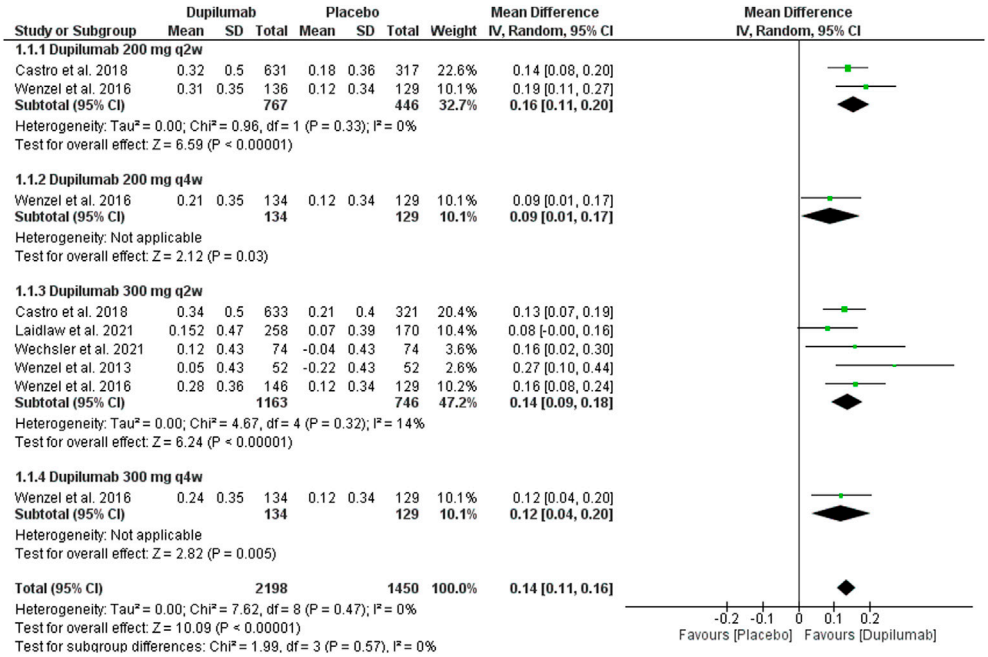

FIGURE 3
Results of the FEV1 change at the 12th week.

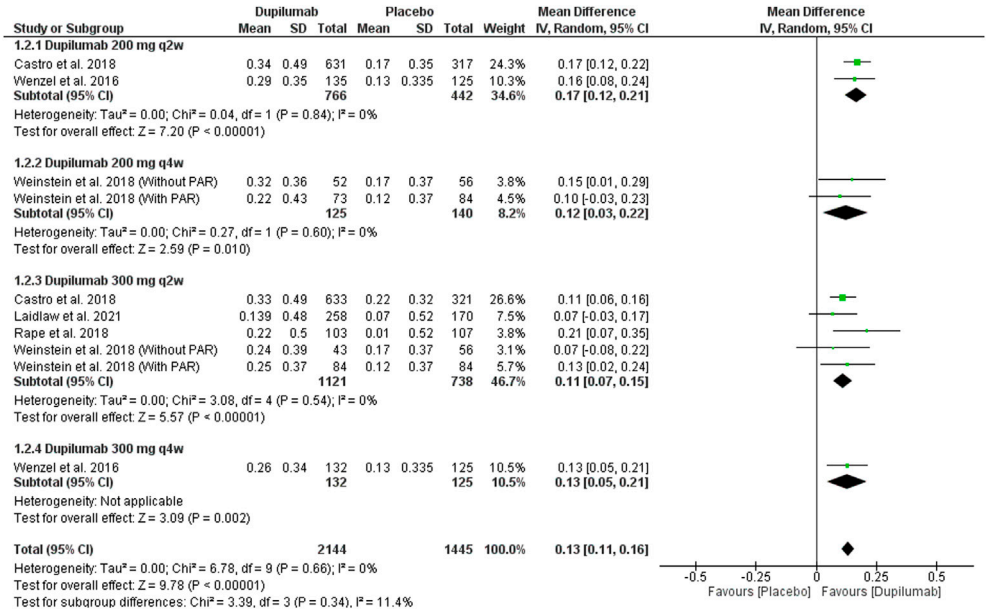

FIGURE 4
Results of the FEV1 change at the 24th week.

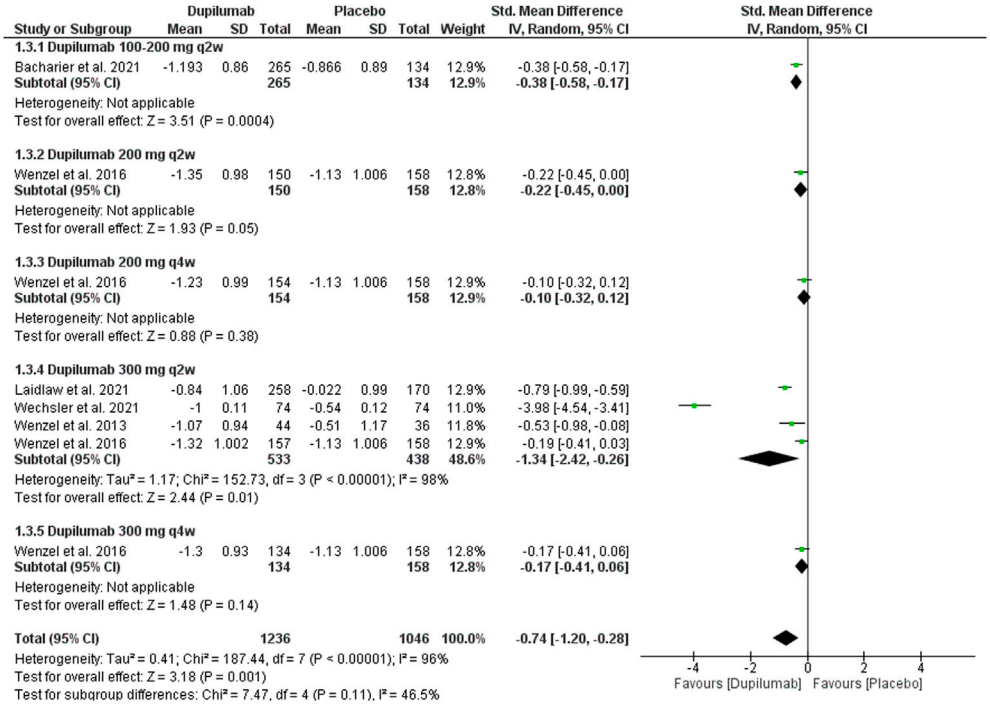

FIGURE 5
Results of the ACQ change at the 12th week.

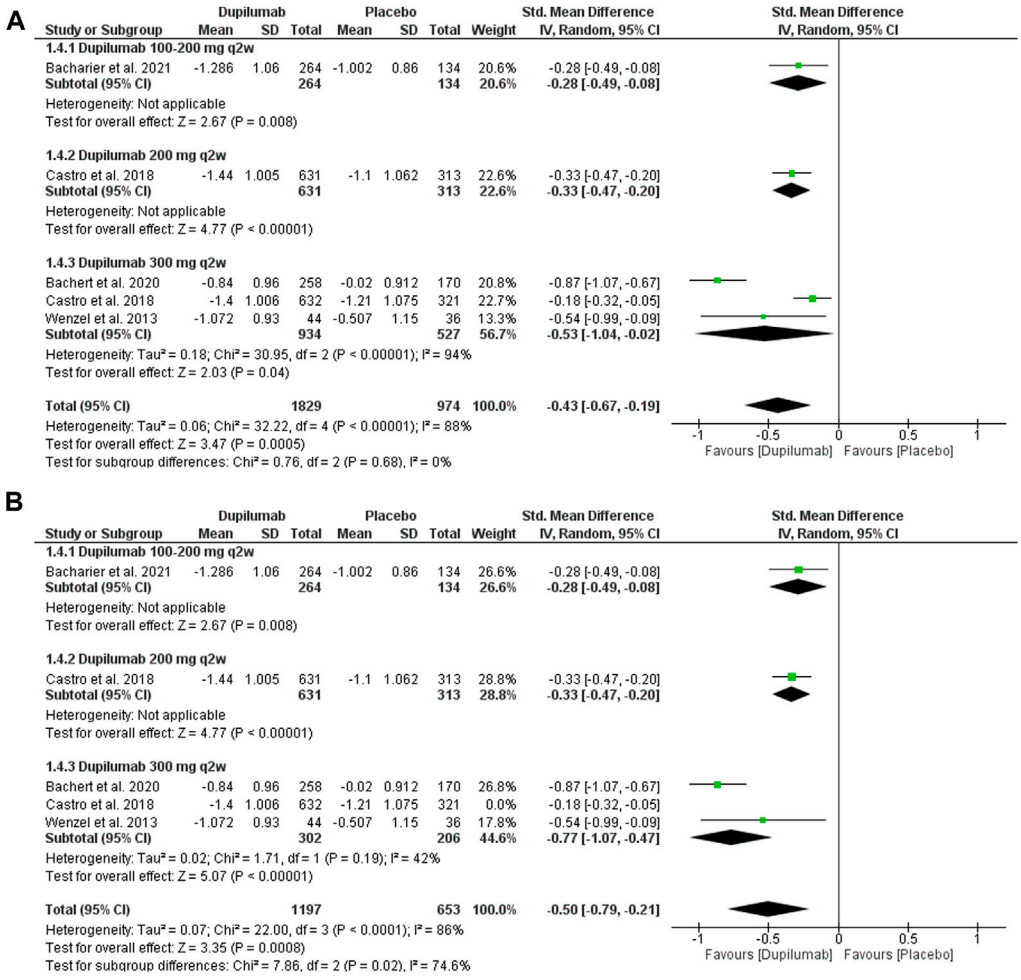

FIGURE 6
Results of the ACQ change at the 24th week. **(A)** Before sensitivity analysis. **(B)** After sensitivity analysis.

Five trials (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Wechsler et al., 2021) evaluated the 300 mg q2w regimen. Dupilumab significantly reduced the FeNO (ppb) compared with the placebo; MD = −19.56 (95% CI = −27.21, −11.90), $p < 0.001$. The pooled analysis was heterogeneous, $p = 0.004$, $I^2 = 74\%$. We could not resolve this heterogeneity by sensitivity analysis.

3.3.2.2 Change in FeNO (ppb) at week 24

Four trials reported this outcome (Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Bacharier et al., 2021). At the week 24, dupilumab significantly reduced the FeNO (ppb) compared with the placebo; MD = −19.50 (95% CI = −24.74, −14.25), $p < 0.001$. The pooled analysis was heterogeneous, $p = 0.001$, $I^2 = 71\%$. The subgroup analysis revealed no significant difference between them, $p = 0.88$ (Supplementary Figures S2A,B).

Two trials (Wenzel et al., 2016; Castro et al., 2018) reported the 200 mg q2w regimen. They reported a significant reduction in the FeNO (ppb) in the dupilumab group compared with the placebo group; MD = −21.61 (95% CI = −40.37, −2.85), $p = 0.02$. The pooled analysis was heterogeneous, $p = 0.01$, $I^2 = 83\%$.

In addition, three trials (Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018) reported the 300 mg q2w revealing that the dupilumab significantly reduced the FeNO compared with the placebo; MD = −21.18 (95% CI = −33.97, −8.38], $p = 0.001$. The pooled analysis was heterogeneous, $p = 0.0009$, $I^2 = 86\%$. We solved this heterogeneity by exclusion of Wenzel et al. (2016); $p = 0.21$, $I^2 = 36\%$. The pooled analysis of subgroup remained significant; MD = −13.34 (95% CI = −18.67, −8.00), $p < 0.001$.

3.3.2.3 Change in blood eosinophils (cells/mm^3) at week 12

This outcome was reported in four trials (Wenzel et al., 2013; Castro et al., 2018; Bacharier et al., 2021; Wechsler et al., 2021). The placebo group showed significantly lower serum eosinophil

TABLE 3 Details of the adverse events results of the included studies.

Outcome	Number of studies	Significance			Heterogeneity	
		RR	95% CI	*p*-value	*p*-value	I2 (%)
Any adverse events	5	0.98	[0.95, 1.02]	0.44	0.75	0
Any treatment-emergent adverse events	3	1.07	[0.97, 1.18]	0.15	0.53	0
Any adverse events leading to permanent discontinuation	5	1.01	[0.68, 1.49]	0.98	0.49	0
Any treatment-emergent adverse events leading to permanent discontinuation	2	1.29	[0.67, 2.46]	0.45	0.81	0
Serious adverse events	4	1.01	[0.76, 1.35]	0.93	0.63	0
Serious treatment-emergent adverse events	2	1.25	[0.72, 2.17]	0.42	0.89	0
Any adverse events leading to death	4	1.04	[0.28, 3.81]	0.96	0.47	0
Any treatment-emergent adverse events leading to death	2	1.3	[0.06, 26.92]	0.87	-	
Upper respiratory tract infection	6	0.82	[0.68, 0.99]	**0.03**	0.91	0
Viral upper respiratory tract infection	5	0.88	[0.59, 1.31]	0.52	0.16	39
Influenza	3	0.92	[0.46, 1.84]	0.81	0.11	55
Nasopharyngitis	5	0.94	[0.73, 1.22]	0.66	0.51	0
Sinusitis	4	0.82	[0.47, 1.45]	0.5	0.3	19
Bronchitis	4	0.81	[0.66, 1.00]	0.05	0.71	0
Injection-site reaction	7	1.73	[1.37, 2.19]	**0.0001**	0.21	28
Eosinophilia	2	10.73	[2.59, 44.43]	**0.001**	0.67	0
Headache	6	0.89	[0.71, 1.11]	0.3	0.72	0
Allergic rhinitis	3	0.68	[0.35, 1.33]	0.26	0.12	53
Cough	2	0.57	[0.17, 1.96]	0.37	0.22	35
Urinary tract infection	2	0.66	[0.42, 1.05]	0.08	0.35	0
Back pain	2	1.25	[0.78, 1.99]	0.35	0.43	0
Erythema	2	1.1	[0.70, 1.72]	0.68	0.35	0

RR; risk ratio, CI; confidence interval.
Bold values mean the results show statistical significance.

levels than the dupilumab group, which showed an increase in their levels; MD = 133.05 (95% CI = 97.46, 168.64), $p < 0.001$. The pooled analysis was homogeneous; $p = 0.41$, $I^2 = 0\%$. The subgroup analysis showed no significant difference between each group; $p = 0.51$, $I^2 = 0\%$ (Supplementary Figure S3).

In three trials (Wenzel et al., 2013; Castro et al., 2018; Wechsler et al., 2021), the dupilumab 300 mg q2w showed a significant increase in eosinophil levels in the dupilumab group; MD = 168.27, (95% CI = 76.12, 260.41), $p = 0.0003$. The pooled data were homogeneous; $p = 0.23$, $I^2 = 33\%$.

3.3.2.4 Change in blood eosinophils (cells/mm^3) at week 24

This outcome was reported in two trials (Castro et al., 2018; Bacharier et al., 2021). Similarly, in the 24th week, the changes in the placebo group were significantly lower than those in the dupilumab group; MD = 94.66 (95% CI = 54.92, 134.40), $p < 0.001$. The pooled analysis was homogeneous; $p = 0.87$, $I^2 = 0\%$. The subgroups of different dupilumab regimens did not show a significant difference; $p = 0.87$ (Supplementary Figure S4).

3.3.2.5 Change in IgE (IU/ml) at week 12

This outcome was reported in three trials (Wenzel et al., 2013; Castro et al., 2018; Wechsler et al., 2021). The dupilumab significantly reduced the IgE levels compared with the placebo; MD = −149.27 (95% CI = −176.39, −122.16), $p < 0.001$. The pooled data were homogeneous; $p = 0.34$, $I^2 = 11\%$. The subgroups did not show a significant difference between both regimens; $p = 0.18$ (Supplementary Figure S5).

3.3.2.6 Change in IgE (IU/ml) at week 24

This outcome was reported by three trials (Castro et al., 2018; Bachert et al., 2019; Bacharier et al., 2021). Dupilumab significantly reduced the IgE levels at the 24th week compared with the placebo; MD = −210.28, (95% CI = −365.02, −55.55), $p = 0.008$. The pooled analysis was heterogeneous, $p < 0.001$, $I^2 = 98\%$. The subgroup analysis revealed no significant difference between dupilumab regimens, $p = 0.55$ (Supplementary Figure S6).

3.3.3 Safety profile of dupilumab

The adverse events of dupilumab were reported by most of the included trials. Compared to the placebo, dupilumab revealed

a significantly higher incidence of upper respiratory tract infections (URTI), injection-site reaction, and eosinophilia, $p < 0.05$ (Table 3; Supplementary Figures S7, S14).

On the other hand, there was no significant difference between dupilumab and placebo groups ($p \geq 0.05$), regarding the following outcomes; any adverse events, any treatment-emergent adverse events, any adverse events leading to permanent discontinuation, any treatment-emergent adverse events leading to permanent discontinuation, serious adverse events, serious treatment-emergent adverse events, any adverse events leading to death, any treatment-emergent adverse events leading to death, viral upper respiratory tract infection, influenza, bronchitis, nasopharyngitis, sinusitis, headache, allergic rhinitis, cough, urinary tract infection, back pain, and erythema.

3.4 Qualitative synthesis

Four trials (Castro et al., 2020; Corren et al., 2020; Tohda et al., 2020; Corren et al., 2021) were included in our qualitative synthesis. In their 2020 trial, Corren et al. (2020) assessed the efficacy of the dupilumab during a treatment period of 52 weeks in 1,902 patients (allergic and eosinophilic asthma). They found dupilumab reduced asthma exacerbation and the inflammatory biomarkers and FEV1 improvement in both types of asthma. Moreover, in a 2021 trial by Corren et al. (2021), they assessed the same outcomes in patients with more than one, two, or three exacerbations in the year before the trial. In addition, they classified patients in different subgroups according to the baseline blood eosinophils, FeNO, and inhaled corticosteroid doses. Corren et al. (2021) in a 2021 *post hoc* analysis reported similar results to their previous 2020 trial. Another *post hoc* analysis by Castro et al. (2020) investigated how dupilumab affects lung function in total participants and according to inflammatory biomarker levels. They concluded that dupilumab enhances lung function results, especially in patients with increased type-2 inflammatory biomarkers. Tohda et al. (2020), in their 2020 trial, evaluated the efficacy of dupilumab in the Japanese subpopulation of the QUEST trial (114). They found dupilumab reduced asthma exacerbation and the inflammatory and improved FEV1 in the Japanese population of QUEST, indicating the significance of dupilumab in different ethnic groups.

4 Discussion

Our pooled data of 13 RCTs found that dupilumab significantly improved the FEV1 at the 12th and 24th weeks. In addition, it reduced FeNO levels, IgE levels, and ACQ scores of asthmatic patients at the 12th and 24th weeks. However, it was associated with an increase in blood eosinophils at the 12th and 24th weeks. Dupilumab was generally a safe agent for asthmatic patients. It showed no significant difference compared with the placebo regarding all adverse effects, except for upper respiratory tract infection, injection-site reaction, and eosinophilia, which had a significantly higher incidence in the dupilumab group. Furthermore, those findings seem to be dose-independent as there was no significant difference between different subgroups.

Those results were consistent with most of the results of these trials (Wenzel et al., 2013; Wenzel et al., 2016; Castro et al., 2018; Rabe et al., 2018; Weinstein et al., 2018; Bachert et al., 2019; Castro et al., 2020; Corren et al., 2020; Tohda et al., 2020; Bacharier et al., 2021; Corren et al., 2021; Laidlaw et al., 2021; Wechsler et al., 2021) and with previous meta-analyses (Edris et al., 2019; Xiong et al., 2019; Zayed et al., 2019). However, Weinstein et al. (2018) trial reported that the 200 mg q2w dupilumab regimen was associated with a statistically insignificant improvement in FEV1 compared with the placebo in patients with perennial allergic rhinitis (PAR). But this was different in non-PAR patients, whereas dupilumab 200 mg/2 weeks regimen significantly increased FEV1 by 0.15 L compared to the placebo. In contrast, the 300 mg q2w dupilumab regimen showed no significant difference regarding FEV1 compared with the placebo. This indicates the importance of classifying asthmatic patients according to their medical conditions or comorbidities and the importance of the choice of treatment regimens. Moreover, similar results were found regarding the annualized rate of severe exacerbations.

The effect of dupilumab starts early after the beginning of the treatment course and is maintained to the end of the follow-up periods of different RCTs up to 52 weeks, as reported by most of our included studies. In addition, it is reported that dupilumab reduced the annualized rate of severe asthma exacerbations by 47%, especially when added to inhaled corticosteroids and other controllers compared with the placebo (Castro et al., 2018).

Asthmatic children require special attention as uncontrolled asthma affects pulmonary functions and limits the airflow, leading to COPD in adulthood (Tagiyeva et al., 2016; McGeachie, 2017). However, the protective role of dupilumab against COPD development or restoring normal pulmonary growth and function is still unclear. Similarly, the role of the different treatment doses and duration is still a query. Although there was no significant difference between different regimens of dupilumab in our trial, we think that the actual effect may be detected in the long-term course of treatment beyond our follow-up periods.

Furthermore, Bacharier et al. (2021) reported that 78% of children using dupilumab as an add-on therapy experienced an exacerbation-free period during the 52 weeks of treatment, compared with 60% of children in the placebo group. Those patients required less use of systemic corticosteroids. This is a critical indicator of efficacy and safety, especially among pediatric asthmatic patients, as they avoided the long-term use of corticosteroids with their subsequent complications.

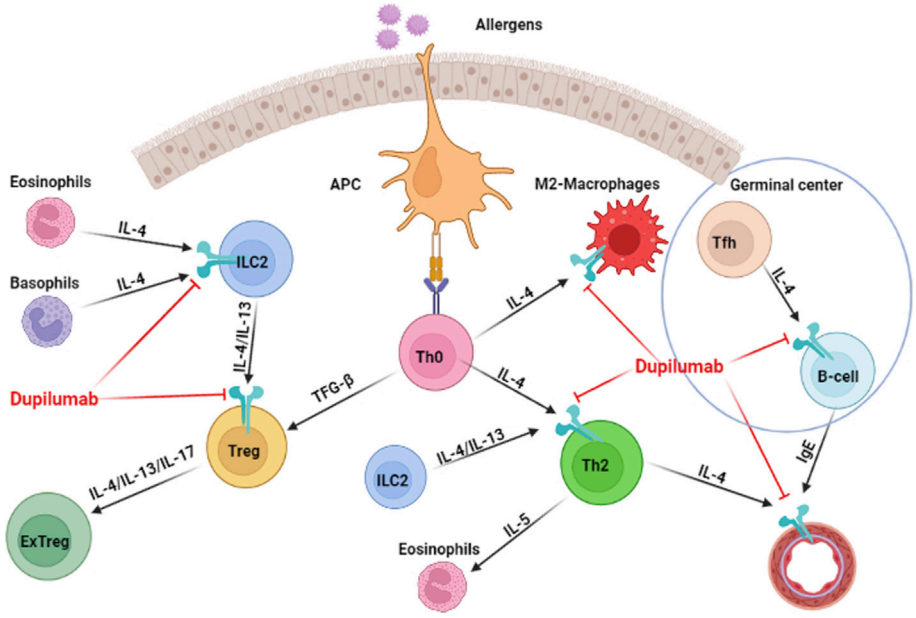

FIGURE 7
Mechanism of action of dupilumab through different sites.

IL-13 promotes the activity of NO-synthase with increased NO levels. This indicates NO's role as a biomarker of asthmatic activity and could be correlated to the levels of IL in the airway mucosa (Chibana et al., 2008; Barranco et al., 2017). Our results were consistent with these mechanisms. We observed that dupilumab significantly reduced the local and systemic inflammatory biomarkers such as FeNO and IgE. This confirms the role of dupilumab in the inflammatory process signaling and activity. In addition, those biomarkers may be used as a screening test for the response to dupilumab and other agents targeting the type-2 inflammatory pathway.

On the other hand, our pooled analysis revealed a relatively higher serum eosinophilic count in the dupilumab group compared with the placebo. This increase seems to be transient at the beginning of dupilumab treatment in adults (Castro et al., 2018) and children (Bacharier et al., 2021). During the inflammatory process, the IL-4 and IL-13 produce eotaxin and vascular cell adhesion molecule, which stimulates eosinophils' migration to targeted tissues. Dupilumab blocks this sequence of events retaining eosinophils in the circulation (Barthel et al., 2008; Tozawa et al., 2011). Moreover, Rabe et al. (2018) explained the increase in blood eosinophil levels due to different corticosteroid dosages between both study arms as glucocorticoids reduce the levels of blood eosinophils. In the dupilumab group, the dose of the glucocorticoids was reduced compared with that in the placebo group. This seems to be responsible for eosinophilia. In addition, the elevation of blood eosinophil levels was not associated with clinical consequences; it was only a laboratory finding, as reported by Castro et al. (2018). Nevertheless, we think dupilumab is still effective in treating asthma, as it significantly reduces the key inflammatory mediators. However, it causes eosinophilia but of no significant role in the efficacy of the dupilumab against inflammation.

The literature lacks the exact mechanism of action of dupilumab either *in vivo* or *in vitro* studies (Harb and Chatila, 2020). Dupilumab is a human monoclonal antibody directed against the alpha subunit of the interleukin-4 receptor and inhibits the signaling of IL-4 and IL-13 (Le Floc'h et al., 2020). Dupilumab acts on the alpha subunit of IL-4 receptor and prevents the binding of the IL-4 to type 1 receptor. In addition, it may inhibit the protein assembly of the type-2 receptor complex. This process may be explained by the inhibition of binding of IL-13 to IL-13 receptor, which is needed for the mobilization of the IL-4 alpha receptor. Moreover, the binding of IL-4 and 13 to their targeted receptors conducts a series of events leading to the recruitment of the other receptors subunits (Harb and Chatila, 2020). Dupilumab has different sites of action, which are fundamental for the Th2 inflammatory process of various diseases. Apart from inflammatory cells, it can also act on endothelium, reducing the cellular recruitment and vascular permeability for those cells (Harb and Chatila, 2020) (Figure 7).

Viral infections have been shown to exacerbate asthma symptoms. Few data exist on COVID-19 immunological responses in biologic-treated asthmatics, and using biological agents during the COVID-19 pandemic is still debatable. A

multicenter study by Eger et al. (2020) revealed that biologic-treated asthmatics were highly vulnerable to COVID-19 infection and had a higher severity than the general population. In contrast, other studies (Klimek et al., 2020; Patruno et al., 2020; Bhalla et al., 2021; Grieco et al., 2021; Tanabe et al., 2021; Ungar et al., 2022a; Ungar et al., 2022b) reported that dupilumab is a safe agent to use during the COVID-19 pandemic and may reduce the severity of COVID-19 symptoms. However, the role of biological agents on the COVID-19 response is still unclear, so each patient should be carefully assessed, and the patient should be involved in considering the therapy's benefits and hazards.

Regarding the other adverse events, all the included studies reported similar incidence of adverse events in both dupilumab and placebo regarding most adverse events. The injection-site reaction was increased with dupilumab treatment in addition to upper respiratory tract infection. This points to the importance of reaching an explanation of those inflammatory conditions in a drug that is thought to reduce inflammation. This may be due to different mechanisms related to the treatment regimen, duration, or the associated add-ons; however, it is not reported. Reaching an explanation of such adverse events is essential to avoid them and to reach more efficient results while manufacturing those agents.

The heterogeneity of some outcomes is the main limitation of this meta-analysis. This heterogeneity might be due to some of the included studies including asthmatic patients associated with other type-2 inflammatory diseases. The dupilumab regimens were not reported in multiple studies, so we could not have a definite conclusion about all regimens. Also, some of the included studies were *post hoc* analyses; thus, we could not pool these data when the results were reported in the original one. In addition, we could not conduct an age-dependent analysis of the efficacy of the dupilumab on different outcomes to determine the best age group to benefit from the targeted medication. There was no data beyond 52 weeks of treatment, and we could not determine the least period for the most effective results. Also, the pediatric population needs special care to detect the least effective dose to avoid the toxic doses. Other trials comparing dupilumab with the placebo and other drugs are needed. We suggest further RCTs that assess the safety and efficacy of dupilumab according to the biomarker level of type-2 inflammation, types of asthma, and age groups. Furthermore, a network meta-analysis to compare dupilumab with other standard treatments is recommended to show the best option for asthmatic patients.

5 Conclusion

Dupilumab improves pulmonary function and reduces local and systemic inflammatory markers with minimal adverse events in patients with moderate to severe asthma. Those effects seem to be dose-independent as there was no significant difference between different regimen subgroups.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Author contributions

MSZ, AGE, YAM, and MAB: Conceptualization. MSZ, AAE, and MAB: Methodology. AM, MAZ, DA, NTA, KFA, and KJA: Data collection. ABE, NTA, YSH, AA, HA, MA, AT, and YMH: Screening. ABE, YAM, MAB, ME, ASM, HA, and AAA: Data extraction. AGE, MAZ, ASM, and ME: Risk of bias. MSZ, ME, and AMF: Analysis. AMF, AGE, YAM, AM, DA, KFA, KJA, and MA: Writing - Original Draft Preparation. YSH, AA, AAE, AT, YMH, MMA, and AAA: Writing - Review & Editing. MSZ, AAE, and MMA: Supervision. All authors reviewed the manuscript and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.992731/full#supplementary-material

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