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Original Article

Efficacy and safety of anti-interleukin-5 therapy in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized, controlled trials

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KEYWORDS
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Abstract *Background:* Anti-interleukin-5 (IL-5) therapy has been proposed as a novel treatment option for patients with chronic obstructive pulmonary disease (COPD). However, its efficacy for preventing COPD exacerbation remains unclear.
Methods: A literature review was conducted to August 26th 2019. Only randomized controlled trials (RCTs) that investigated the clinical efficacy and adverse effects of anti-IL-5 therapy were included in the meta-analysis. The primary outcome was the risk of COPD exacerbation.

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Results: A total of 3 articles containing 5 RCTs were included in the study. Overall, 2837 and 1442 patients received anti-IL-5 therapy (mepolizumab, n = 865; benralizumab, n = 1972) and placebo, respectively. In the pooled analysis, anti-IL-5 therapy was associated with a lower risk of COPD exacerbation compared with the placebo (rate ratio, 0.92; 95% CI, 0.86—0.97, I^2 = 0%). In addition, no significant differences in the changes in SGRQ scores and FEV_1 from baseline were found between the anti-IL-5 therapy and placebo (SGRQ, mean difference, −0.86, 95% CI, −1.92 − 0.19, I^2 = 0%; FEV_1, mean difference, 0.01, 95% CI, −0.01 − 0.03, I^2 = 0%). Anti-IL-5 therapy had a similar risk of any adverse event (risk ratio, 1.02; 95% CI, 0.99—1.05), an event leading to treatment discontinuation (risk ratio, 1.04; 95% CI, 0.72 −1.48) and any serious adverse events (risk ratio, 0.93; 95% CI, 0.85—1.01) when compared with the placebo.
Conclusion: Anti-IL-5 therapy was associated with a lower rate of COPD exacerbation compared with placebo. In addition, anti-IL-5 therapy was well tolerated for COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive airway and/or alveolar disease, which has become a great threat to public health.[1–3] For patients with COPD, acute exacerbations of COPD can have a number of adverse effects on patients, including increased hospitalizations, impaired quality of life, accelerated loss of lung function and increased mortality.[4] Therefore, how to reduce these acute episodes is a major goal in the management of COPD. However, the Informing the Pathway of COPD Treatment study[5] showed that even when receiving triple therapy with long-acting muscarinic agonists (LAMAs), long-acting β2-agonists (LABAs) and inhaled corticosteroids, or dual therapy with LAMA/LABA, approximately 50% of patients still experienced an exacerbation within a 1-year period. Therefore, there is an urgent need to develop advanced pharmacotherapy that specifically targets COPD patients at risk of frequent exacerbations.

In COPD patients, airflow obstruction is primarily caused by neutrophils and macrophages, which are predominant in airway inflammation, however there is an elevation of eosinophils in 20—40% of patients.[6] In addition, the eosinophil count was found to be negatively correlated with the forced expiratory volume in 1 s (FEV_1).[7] Moreover, eosinophilic inflammation is also associated with increased episodes of acute exacerbations, and severe exacerbations requiring hospital admission.[8] The proliferation, maturation, and activation of eosinophils and eosinophilic airway inflammation are mainly modulated by interleukin-5 (IL-5).[9] Therefore, anti-IL-5 therapy has been proposed as a novel treatment option for patients with eosinophilic COPD.

Over the last decade, 3 anti-IL-5 pathway—directed therapies, including mepolizumab and reslizumab that target IL-5, and benralizumab that binds to the IL-5 receptor, have been developed. Their efficacy in reducing the exacerbation rate in patients with severe eosinophilic asthma (SEA) have been demonstrated in many randomized controlled trials (RCTs),[10–14] so these agents have been approved by the FDA as an adjunctive treatment for SEA. In contrast to SEA, limited studies[15–18] have investigated the use of anti-IL-5 therapies for the treatment of COPD, but the efficacy of anti-IL-5 in COPD patients remains unclear. In addition, no consistent results were found in 2 recent large RCTs.[15,16] Pavord et al.[16] found that 100 mg mepolizumab was associated with a lower annual rate of moderate or severe exacerbations compared with placebo among patients with eosinophilic COPD. In contrast, Criner et al. observed no significant difference in terms of the annualized COPD exacerbation rate ratios, between any dose of benralizumab and a placebo.[15] To clarify this controversial issue, the present meta-analysis was conducted to assess the clinical efficacy and the safety of anti-IL-5 therapies in patients with COPD.

Methods

Study search and selection

A literature review was conducted using the following databases: PubMed, Embase, Web of Science, EBSCO, Cochrane Library, Ovid Medline, Embase, and Proquest to August 26th 2019. The following search terms were used: "chronic obstructive pulmonary disease", "COPD", "mepolizumab", "reslizumab", "cinqair", "cinqaero", "benralizumab" and "fasenra". Only RCTs that investigated the clinical efficacy and adverse effects of anti-IL-5 therapies were included in the meta-analysis. Two authors (Lan SH & Chang SP) were responsible for searching and examining the risk of bias in each study; this was assessed using the Cochrane Risk of Bias Assessment tool.[19] When they had different opinions, a third author (Lai CC) helped resolve the issue. Data, including the year of publication, study design, study location and duration, demographic characteristics of COPD patients, regimen of the study drug, outcomes and adverse events, were extracted from each included study. This study was registered with PROSPERO (registered ID: 154375) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Definitions and outcomes

The primary outcome of the current study was the risk of moderate or severe COPD exacerbation. Secondary outcomes included changes in lung function from baseline in trough FEV_1, the change from baseline in St. George's Respiratory Questionnaire (SGRQ) scores, and the risk of adverse events.

Statistical analysis

Review Manager software (The Cochrane Collaboration 2008, Copenhagen) was used to develop a random-effects model and to derive the pooled estimates and their associated 95% confidence intervals (CIs). The rate ratio was used to evaluate the exacerbation rates per patient per year. Risk ratios were used to estimate the dichotomous outcomes, such as death and safety. Mean differences were used for continuous variables, such as the FEV_1 and SGRQ scores. The degree of heterogeneity was evaluated using Q statistics generated from the χ^2 test. The proportion of statistical heterogeneity was assessed using the I^2 measure. Heterogeneity was considered as significant when the p-value was <0.10 or the I^2 value was $>50\%$.

Results

The search results generated a total of 265 records; 148 records were excluded because of duplication and 108 records were defined as irrelevant following a title/abstract screen. A total of 9 articles were identified for a full-text review of eligibility, and only 3 articles[15–17] containing 5 RCTs were enrolled for the meta-analysis (Fig. 1). The risk of bias in each study is shown in Fig. 2 and most domains were classified as low risk.

Study characteristics and study quality

All 5 RCTs (NCT01227278, METREX, METREO, GALATHEA and TERRANOVA) in the 3 articles[15–17] were multinational and multicenter studies (Table 1). In the NCT01227278 trial,[17] 100 mg benralizumab was compared with a placebo. In the METREX and METREO trials, 100 or 300 mg mepolizumab for 52 weeks was used as the study drug.[16] In the GALATHEA and TERRANOVA trials, 10, 30 or 100 mg benralizumab for 56 weeks was used as the study drug.[15] In the NCT01227278 trial,[17] only COPD patients with sputum eosinophils >3% were enrolled. In the METREO trial, only COPD patients with an eosinophilic phenotype (eosinophil count $\geq 150/mm^3$ at screening or $\geq 300/mm^3$ at any point in the previous year) were enrolled.[16] In the GALATHEA and TERRANOVA trials, only patients with baseline eosinophil counts $\geq 220/mm^3$ were enrolled.[15] Overall, 2837 patients received anti-IL-5 therapies, and 1442 patients received placebo (Table 2). Among the 865 patients who received mepolizumab, 640 received 100 mg and 225 received 300 mg. Among the 1972 patients who received benralizumab, 377, 779 and 816 received 10, 30 and 100 mg benralizumab, respectively. Across the 5 studies, the mean age of patients was 63–66 years and males comprised 58–72% of the patients. Current smokers comprised 25–42% of patients and the predicted FEV_1 was 42–50% and 1.2–1.4 L. The mean number of exacerbations was 2.3–2.7 in the previous year in 4 of the RCTs[15,16] but only 1.6 in the NCT01227278 trial.[17]

The risk of COPD exacerbation rate

Overall, anti-IL-5 therapy was associated with a lower risk of COPD exacerbation compared with the placebo (rate ratio, 0.92; 95% CI, 0.86–0.97, $I^2 = 0\%$; Fig. 3) following a pooled analysis of the 5 RCTs.[15–17] While we analyzed of the effect of each anti-IL-5 agent, only mepolizumab was associated with a lower risk of COPD exacerbation compared with the

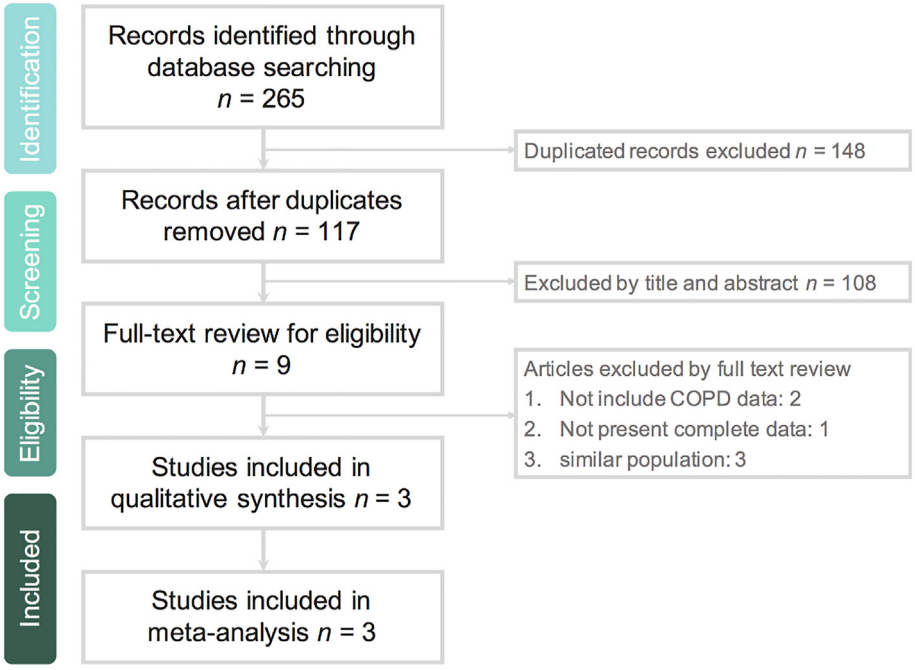

Figure 1. The algorithm of study selection.

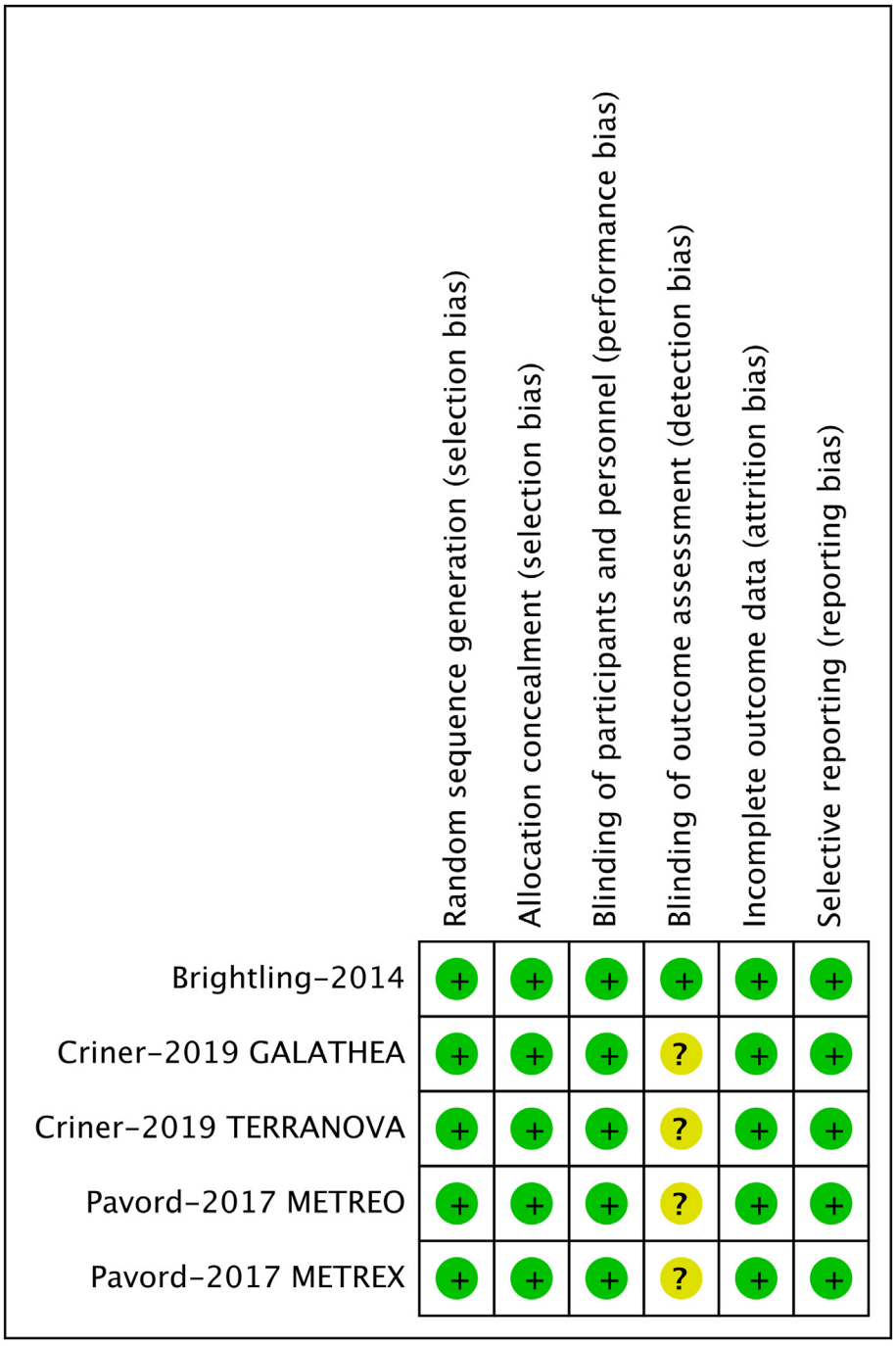

Figure 2. Risk of bias in each domain.

placebo (rate ratio, 0.92; 95% CI, 0.85—1.00, I^2 = 0%; Fig. 3). Although benralizumab was found to be associated with a lower risk of COPD exacerbation when compared with the placebo, the difference was not statistically significant (rate ratio, 0.91; 95% CI, 0.80—1.05, I^2 = 35%). In the subgroup analysis according to each agent with different dose and the blood eosinophil count, the lower risk of COPD exacerbation for anti-IL-5 therapy compared with the placebo was found statistically significant in two condition — using 100 mg of anti-IL-5 therapy with either mepolizumab or benralizumab (rate ratio, 0.92; 95% CI, 0.85—0.99) and blood eosinophil count $\geq$ 300 per cubic millimeter (rate ratio, 0.89; 95% CI, 0.80—0.98) (Table 3).

Change of health-related quality of life

In the pooled analysis of 5 clinical trials,[15–17] there were no significant differences in terms of changes from baseline measured for health-related quality of life using the SGRQ scores, between anti-IL-5 therapy and the placebo (mean difference, −0.86, 95% CI, −1.92-0.19, I^2 = 0%; Fig. 4). In the subgroup analysis, benralizumab was associated with an improved SGRQ score (mean difference, −1.45, 95% CI,

Table 1 Characteristics of included studies.

Author, year	Clinical trial	Study design	Study sites	Study period	Randomization	Administration of study drug	Study population	Eosinophil count
Brightling et al., 2014	NCT01227278	randomized, double-blind, placebo-controlled, phase 2a study	26 sites in 7 countries	2010—2013	1:1 ratio to receive), benralizumab (100 mg) or placebo	subcutaneous injections of benralizumab every 4 weeks for the first 3 doses, then every 8 weeks over 48 weeks	moderate-to-severe COPD, ≥ 1 exacerbation of COPD, and within the previous year, have received high-dose ICS	Sputum eosinophil count of $\geq$3%
Pavord et al., 2017	METREX	randomized, placebo-controlled, double-blind, phase 3 trial	117 sites in 16 countries	2014—2017	1:1 ratio to receive mepolizumab (100 mg) or placebo	subcutaneous injections of mepolizumab every 4 weeks for 52 weeks	$\geq$2 moderate exacerbations or ≥ 1 severe exacerbation in previous year	Not limited
Pavord et al., 2017	METREO	randomized, placebo-controlled, double-blind, phase 3 trial	168 sites in 15 countries	2014—2017	1:1:1 ratio to receive mepolizumab (100 mg), mepolizumab (300 mg) or placebo	subcutaneous injections of mepolizumab every 4 weeks for 52 weeks	$\geq$2 moderate exacerbations or ≥ 1 severe exacerbation in previous year	Blood eosinophil count $\geq$150/mm^3at screening or $\geq$300/mm^3 at any point in the previous year
Criner et al., 2019	GALATHEA	randomized, double-blind, placebo-controlled, phase 3 trial.	409 sites in 17 countries	2014—2018	1:1:1 ratio to receive benralizumab (30 mg), benralizumab (100 mg) or placebo	subcutaneous injections of benralizumab every 4 weeks for the first 3 doses, then every 8 weeks over 48 weeks	Moderate to very severe COPD, mMRC ≥ 1, $\geq$2 moderate exacerbations or ≥ 1 severe exacerbation in previous year	Blood eosinophil counts $\geq$ 220/mm^3
Criner et al., 2019	TERRANOVA	randomized, double-blind, placebo-controlled, phase 3 trial.	356 sites in 26 countries	2014—2018	1:1:1:1 ratio to receive benralizumab (10 mg), benralizumab (30 mg), benralizumab (100 mg) or placebo	subcutaneous injections of benralizumab every 4 weeks for the first 3 doses, then every 8 weeks over 48 weeks	Moderate to very severe COPD, mMRC ≥ 1, $\geq$2 moderate exacerbations or ≥ 1 severe exacerbation in previous year	Blood eosinophil counts $\geq$ 220/mm^3

Table 2 Demographic feature of enrolled patients.

Author, year	Clinical trial	Study group	No of patients	Age, yr	No (%) of male sex	No (%) of current smoker	Percent of predicted FEV1 (%)	FEV1, liters	No of exacerbation in previous year
Brightling et al., 2014	NCT01227278	Benralizumab, 100 mg	51	63 ± 8	35 (69)	17 (33)	44 ± 16	1.3 ± 0.5	1.6 ± 1.0
		Placebo	50	65 ± 8	29 (58)	21 (42)	50 ± 18	1.4 ± 0.6	1.6 ± 1.0
Pavord et al., 2017	METREX	Mepolizumab, 100 mg	417	66 ± 9	257 (62)	106 (25)	45 ± 15	1.2 ± 0.5	2.5 ± 1.2
		Placebo	419	65 ± 9	263 (63)	116 (28)	44 ± 15	1.2 ± 0.5	2.5 ± 1.2
	METREO	Mepolizumab, 100 mg	223	65 ± 9	132 (59)	55 (25)	47 ± 15	1.3 ± 0.5	2.7 ± 1.4
		Mepolizumab, 300 mg	225	65 ± 9	158 (70)	71 (32)	45 ± 16	1.3 ± 0.5	2.7 ± 1.5
		Placebo	226	66 ± 9	156 (69)	63 (28)	46 ± 15	1.3 ± 0.5	2.6 ± 1.4
Criner et al., 2019	GALATHEA	Benralizumab, 30 mg	382	66 ± 8	270 (71)	140 (37)	42 ± 12	1.2 ± 0.4	2.3 ± 1.2
		Benralizumab, 100 mg	379	66 ± 8	262 (70)	129 (34)	44 ± 12	1.2 ± 0.4	2.3 ± 1.2
		Placebo	359	66 ± 9	260 (72)	115 (32)	43 ± 13	1.2 ± 0.5	2.4 ± 1.4
	TERRANOVA	Benralizumab, 10 mg	377	65 ± 8	252 (67)	108 (29)	44 ± 12	1.2 ± 0.4	2.3 ± 1.0
		Benralizumab, 30 mg	397	66 ± 9	269 (68)	108 (27)	43 ± 12	1.2 ± 0.4	2.2 ± 1.0
		Benralizumab, 100 mg	386	65 ± 8	250 (65)	108 (28)	43 ± 12	1.2 ± 0.4	2.3 ± 1.0
		Placebo	388	65 ± 8	253 (65)	118 (30)	43 ± 12	1.2 ± 0.4	2.3 ± 1.0

−2.84 to −0.06, I^2 = 0%) but no significant difference was observed for mepolizumab (mean difference, −0.07, 95% CI, −1.88− 1.74, I^2 = 0%; Fig. 4).

Change in FEV_1

In the pooled analysis of 5 clinical trials,[15–17] lung function, as measured by the changes from baseline pre-bronchodilator FEV_1, was found to be better in patients receiving anti-IL-5 therapy compared with those receiving a placebo (mean difference, 0.01, 95% CI, −0.01 − 0.03, I^2 = 0%), however the difference was not statistically significant (Fig. 5). Similar findings were observed in the subgroup analysis for benralizumab (mean difference, 0.01, 95% CI, −0.02 − 0.05, I^2 = 21%) and mepolizumab (mean difference, 0.01, 95% CI, −0.03 − 0.04, I^2 = 17%; Fig. 5).

The risk of adverse events

Anti-IL-5 therapy had a similar risk of i) any adverse event (risk ratio, 1.02; 95% CI, 0.99−1.05), ii) an event leading to treatment discontinuation (risk ratio, 1.04; 95% CI, 0.72−1.48) and iii) any serious adverse events (risk ratio, 0.93; 95% CI, 0.85−1.01) when compared with the placebo (Fig. 6). In addition, anti-IL-5 therapy was associated with a similar risk of death when compared with the placebo (risk ratio, 0.94; 95% CI, 0.69−1.30). Similarity in terms of the risk of adverse events was also observed between mepolizumab or benralizumab and the placebo.

Discussion

The present meta-analysis was based on 5 RCTs from 3 previous articles.[15–17] It investigated the efficacy and adverse events of 2 anti-IL-5 treatments (mepolizumab and benralizumab) for COPD patients. Overall, patients who were treated with anti-IL-5 therapy had a lower annual rate of COPD exacerbations compared with patients who received a placebo. However, only patients with mepolizumab had a reduced COPD exacerbation rate compared with patients with placebo. Although patients who received benralizumab showed a lower risk of COPD exacerbation compared with placebo, the difference was not statistically significant. The inconsistent findings observed between benralizumab and mepolizumab could be explained by the following reasons: i) the inclusion criteria for each study within the current meta-analysis were different, which could result in a large heterogeneity among study populations, such as baseline lung function, the risk of exacerbation, and eosinophil count; and ii) the regimens of mepolizumab and benralizumab were varied. To overcome these deficits, we did a further subgroup analysis and the positive effect of anti-IL-5 for reducing COPD exacerbation was demonstrated in the patients receiving 100 mg of anti-IL-5 therapy or with blood eosinophil count $\geq$300 per cubic millimeter. Although some residual confounding factors still exist, the overall positive effect of anti-IL-5 therapy reducing COPD exacerbations remains consistent across the meta-analysis. Therefore, the findings suggest that 100 mg anti-IL-5 therapy could be considered as an add-on treatment for COPD patients with blood eosinophil count

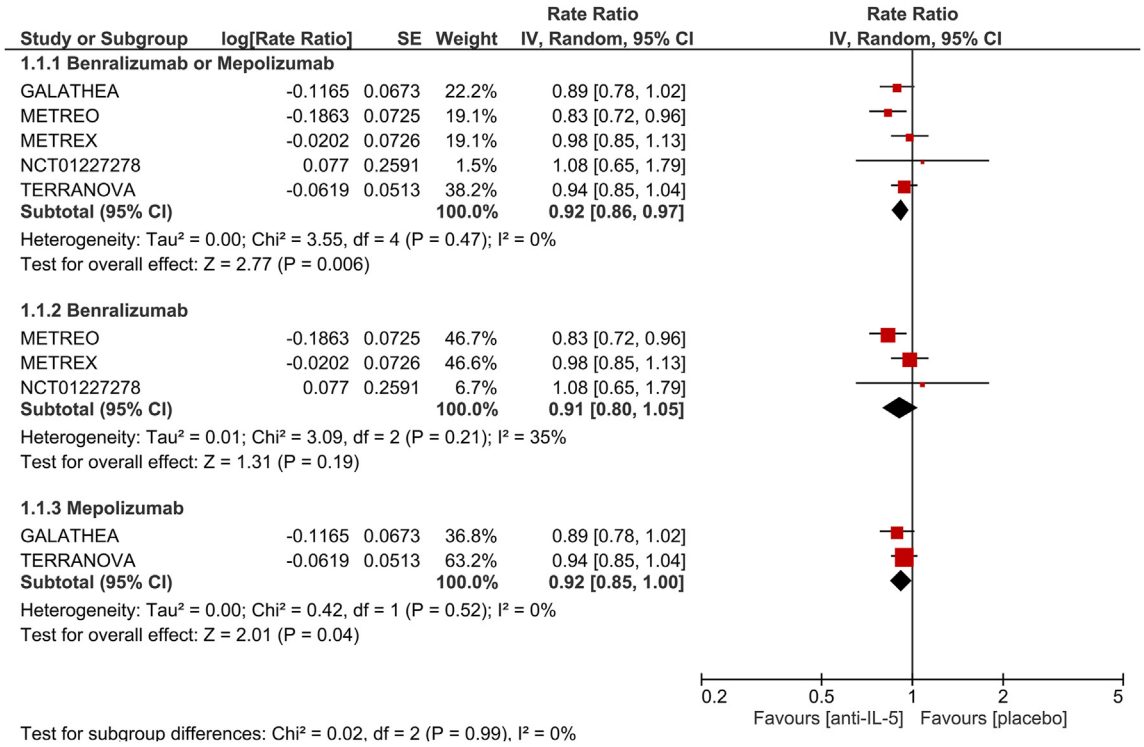

Figure 3. Association of anti-IL-5 with rate of moderate or severe exacerbation.

Table 3 Subgroup analysis of the risk of COPD exacerbation among anti-IL-5 and placebo group according to dosage and blood eosinophil counts.

	No of study	No of anti-IL-5 group	No of placebo group	Rate ratio	95% CI
Drug					
Mepolizumab, 100 mg	2	650	648	0.92	(0.82, 1.03)
Mepolizumab, 300 mg	1	225	226	0.86	(0.70, 1.06)
Benralizumab, 10 mg	1	377	388	0.85	(0.71, 1.02)
Benralizumab, 30 mg	2	776	747	0.94	(0.83, 1.07)
Benralizumab, 100 mg	2	765	747	0.91	(0.82, 1.02)
Dosage of mepolizumab or benralizumab					
10 mg	1	377	388	0.85	(0.71, 1.02)
30 mg	2	776	747	0.94	(0.83, 1.07)
100 mg	3	1415	1395	0.92	(0.85, 0.99)
300 mg	1	225	226	0.86	(0.70, 1.06)
Blood eosinophil count					
$<$150 per cubic millimeter	3	960	529	1.01	(0.91, 1.13)
150 $-$ $<$300 per cubic millimeter	3	1245	633	1.01	(0.92, 1.12)
$\geq$300 per cubic millimeter	3	1662	880	0.89	(0.81, 0.96)

$\geq$300 per cubic millimeter to help reduce their risk of exacerbation.

Compared with the placebo, the current meta-analysis did not find that there was a significant improvement in SGRQ scores following anti-IL-5 therapy. However, it was found that benralizumab was associated with a significant improvement in SGRQ score compared with placebo. In contrast, there was no significant difference between mepolizumab and the placebo with regard to an improvement in SGRQ scores. Additionally, this pooled analysis of 5 RCTs[15–17] revealed a consistent trend of anti-IL-5 therapy being associated with increased improvements in FEV_1 compared with the placebo. However, these differences were not statistically significant. A similar trend was also observed in the subgroup analysis of benralizumab and mepolizumab.

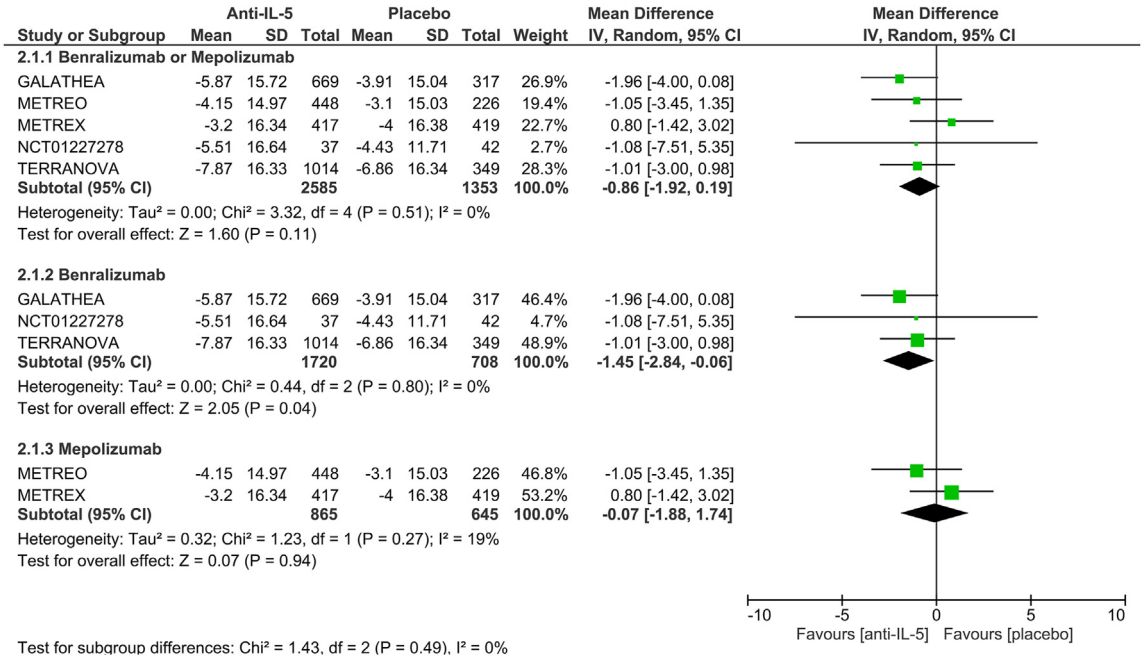

Figure 4. Association of anti-IL-5 with change of St. George's Respiratory Questionnaire total score.

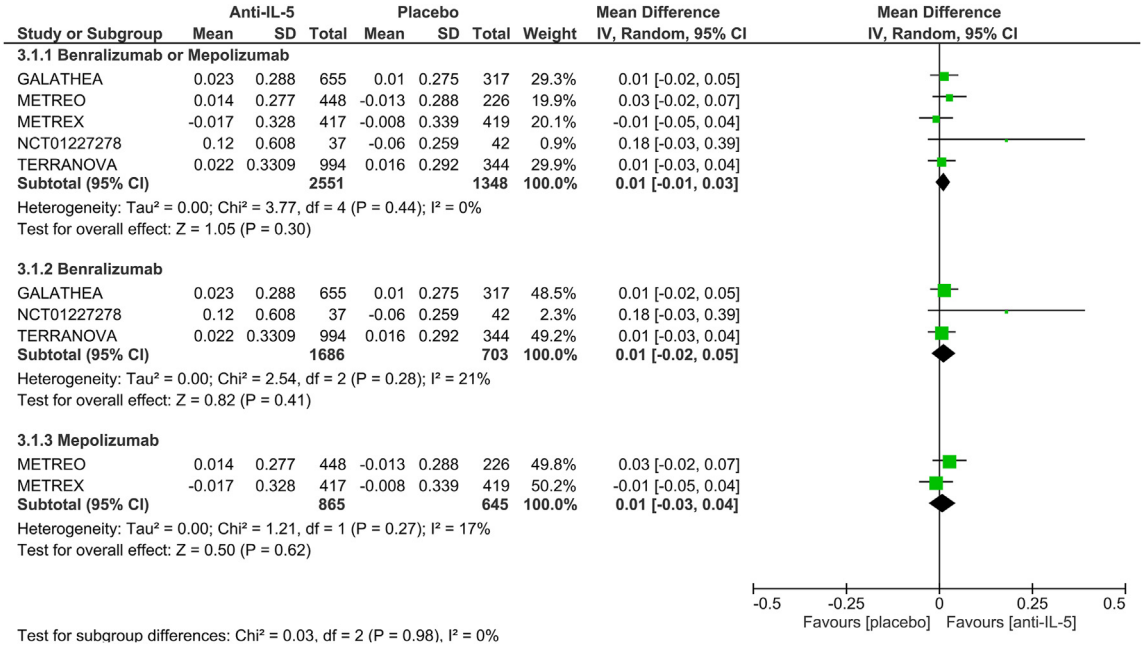

Figure 5. Association of anti-IL-5 with change of FEV_1.

In the present meta-analysis, the risk of treatment emergent adverse events, serious adverse events and events leading to treatment discontinuation, among patients receiving anti-IL-5 therapy were comparable with those receiving placebo. In addition, the overall all-cause mortality was only about 3%. This safety data is consistent with previous reports of Phase 3 trials[11,13,14,20] for anti-IL-5 therapy, including benralizumab and mepolizumab, for asthma. This suggests that anti-IL-5 therapy (benralizumab and mepolizumab), was well tolerated in COPD patients.

The current meta-analysis had several limitations. The aim of the study was to determine the overall effect of anti-IL-5 therapy on COPD; however, the COPD severity and baseline COPD therapy varied among the studies, so the population examined in the meta-analysis was too heterogeneous to draw any conclusions about the general COPD population. Second, in accordance with the Cochrane handbook, 2 or 3 intervention groups were combined into a single intervention group regardless of the different intervention dosages and administration

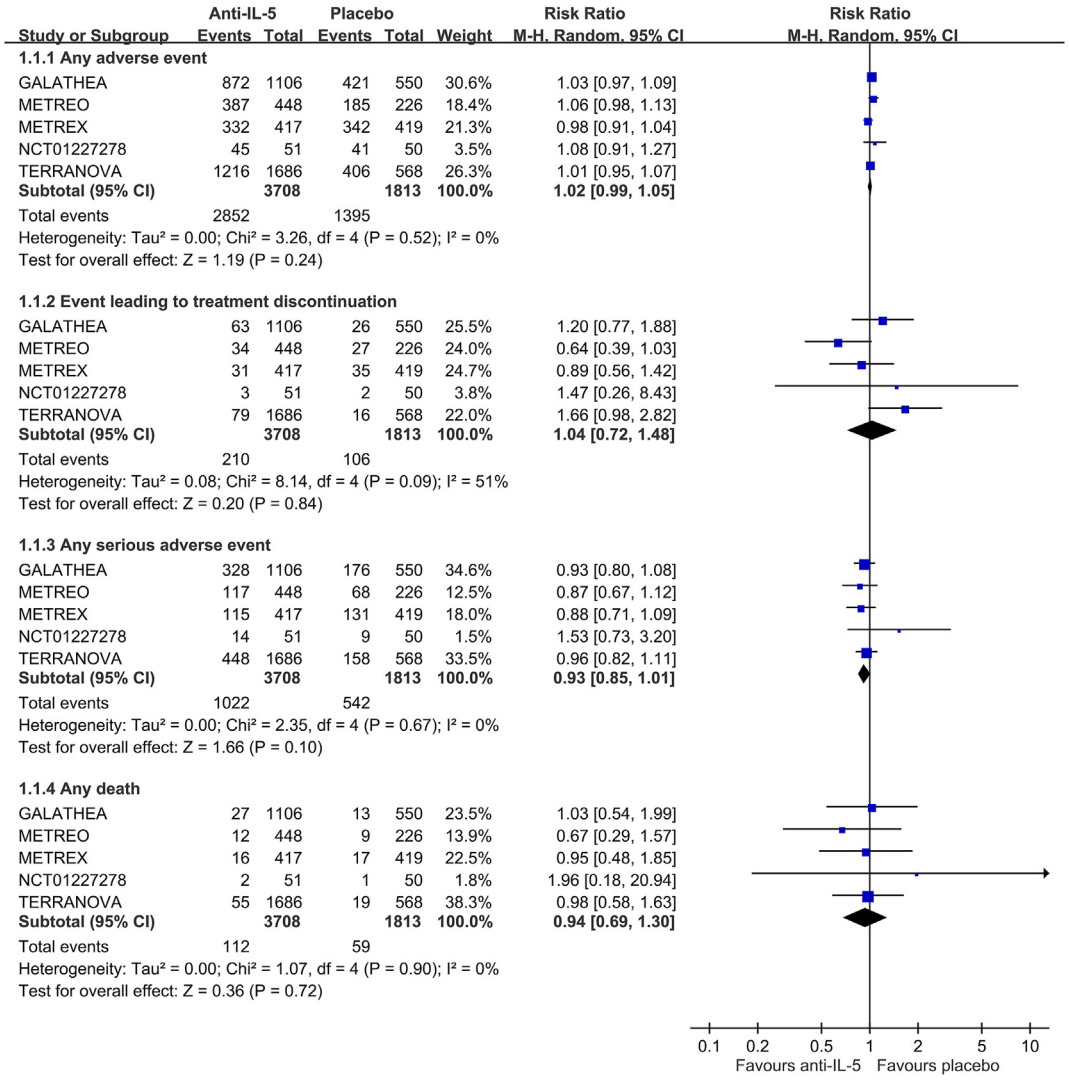

Figure 6. The risk of adverse events with anti-IL-5.

routines in this meta-analysis. However, the effect of different agents with different dosage remains one possible concern. Among the studies[15–17] included in meta-analysis, the dose of benralizumab ranged from 10 to 100 mg and the doses of mepolizumab included 100 mg and 300 mg. In addition, the dose-response of each anti-IL-5 drug could be different. Although we did subgroup analysis according to different anti-IL-5 agents and different dosage, the number of studies and patients in each subgroup were limited. Further research is needed to clarify these issues.

Conclusion

The present meta-analysis indicates that anti-IL-5 therapy is associated with a lower rate of COPD exacerbation compared with placebo, even though anti-IL-5 therapy was not associated with a better quality of life or lung function compared with the placebo. In the subgroup analysis, COPD patients with blood eosinophil count $\geq$300 per cubic millimeter get more benefit at anti-IL-5 therapy. In addition, anti-IL-5 therapy was generally as well tolerated as the placebo. Therefore, anti-IL-5 therapy can be considered as an adjunct therapy for COPD patients.

Ethic approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

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Authors' contribution

SHL, SPC, YHW, CYW and CCL assessed the eligibility of studies for inclusion in the meta-analysis. SHL, SPC, YHW, CYW, CCH, CHC, YHH, YSL, and CCL were all directly involved in the acquisition of data for analysis. All statistical analyses were performed by YHW. CCL and CYW wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the manuscript, ensuring that questions related to the accuracy or integrity of any part of the manuscript were appropriately investigated and resolved.

Declaration of competing interest

The authors declare that they have no competing interest.

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None.

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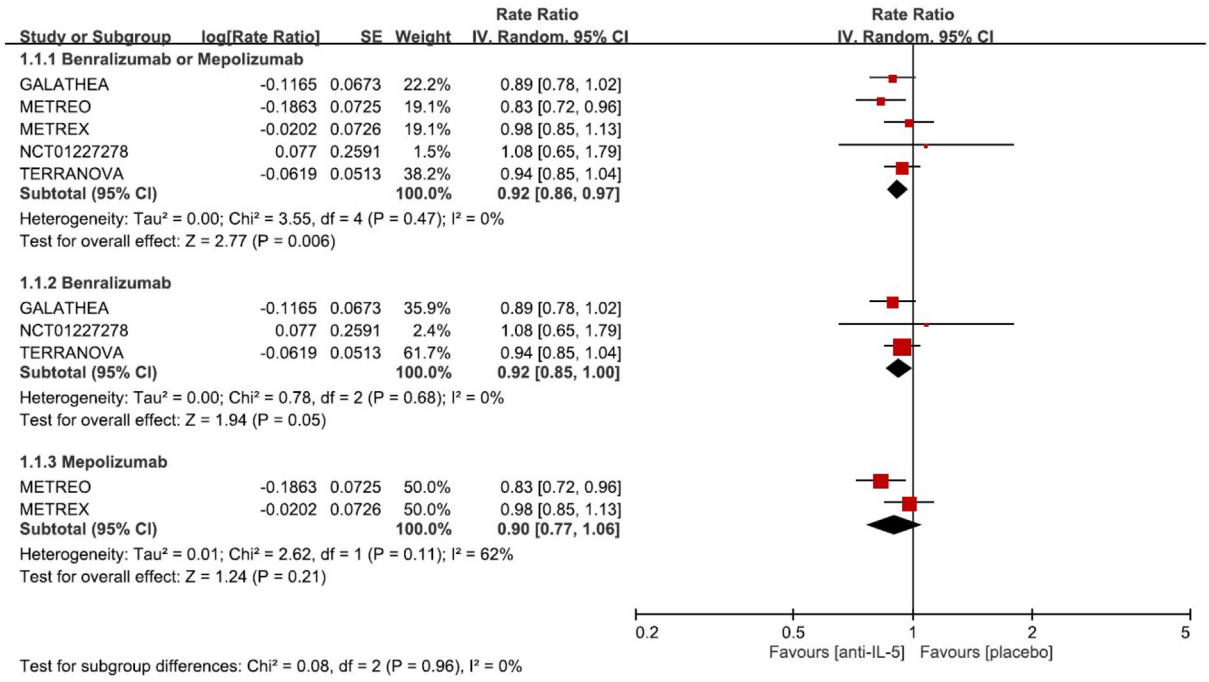
Fig. 3



	Corrected version
Page 3 Results The risk of COPD exacerbation	While we analyzed of the effect of each anti-IL-5 agent, only benralizumab was associated with a lower risk of COPD exacerbation
Page 4	Although mepolizumab was found to be associated with a lower risk of COPD exacerbation when compared with the placebo, the difference was not statistically significant (rate ratio, 0.90; 95 % CI, 0.77—1.06, $I^2 = 62$ %).

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