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ORIGINAL RESEARCH

Blood eosinophils and inhaled corticosteroids in patients with COPD: systematic review and meta-analysis

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Shih-Lung Cheng[1,2]

[1]Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan; [2]Department of Chemical Engineering and Materials Science, Yuan-Ze University, Taoyuan, Taiwan

Background: COPD is a highly heterogeneous disease. Potential biomarkers to identify patients with COPD who will derive the greatest benefit from inhaled corticosteroid (ICS) treatment are needed. Blood eosinophil count can serve as a predictive biomarker for the efficacy of ICS treatment. The aim of this systematic review and meta-analysis was to assess whether a blood eosinophil count of ≥2% in patients undergoing ICS therapy was associated with a greater reduction in COPD exacerbation rate and pneumonia incidence.

Materials and methods: An electronic search was performed using the keywords "COPD", "eosinophil", and "clinical trial" in the PubMed and EMBASE databases to retrieve articles, up to 2017, relevant to our focus. Data were extracted, and a meta-analysis was conducted using RevMan 5 (version 5.3.5).

Results: Five studies comprising 12,496 patients with moderate-to-very severe COPD were included. At baseline, 60% of the patients had ≥2% blood eosinophils. Our meta-analysis showed a 17% reduction in exacerbation of moderate/severe COPD in patients with ≥2% blood eosinophils undergoing ICS therapy compared to the non-ICS/ICS withdrawal/placebo group. The difference between the two types of treatment was significant (risk ratio [RR], 0.816; 95% CI, 0.67–0.99; P=0.03). Furthermore, the risk of pneumonia-related events was significantly increased in the subgroup with eosinophil count ≥2% undergoing ICS-containing treatments (RR, 1.969; 95% CI, 1.369–2.833; $P<0.001$). There was no significant difference in the subgroup with eosinophil count <2% (RR, 1.29; 95% CI, 0.888–1.879; $P<0.181$).

Conclusion: The results of our meta-analysis suggest that the 2% threshold for blood eosinophils could accurately predict ICS treatment response in patients with COPD, but increased the risk of pneumonia.

Keywords: COPD, inhaled corticosteroid, eosinophil

Introduction

Inhaled corticosteroids (ICSs) can reduce acute exacerbation in patients with COPD having moderate-to-very severe lung function defects and a history of frequent exacerbation.[1–5] However, the risks and benefits of ICS treatment are still controversial, especially the purported increase in pneumonia incidence.[6] Airway eosinophilia is a hallmark inflammatory response for asthma pathogenesis and is now known to be involved in the airway inflammatory process in COPD.[7–9] Eosinophilic COPD is defined using sputum eosinophil counts of ≥3% and has been reported during acute exacerbations in up to 28% of cases.[10] Interestingly, it is seen in ~34%[11] (or 38%[12]) of patients with COPD in stable condition. Airway eosinophilia is an important marker

Correspondence: Shih-Lung Cheng
Department of Internal Medicine, Far Eastern Memorial Hospital, 21 Nanya South Road, Taipei, Taiwan
Tel +886 2 8966 7000 ext 2160
Fax +886 2 7738 0708
Email shihlungcheng@gmail.com

for treatment effectiveness of inhaled and oral corticosteroid therapies in patients with COPD.[12–15]

A diagnostic tool for the measurement and detection of airway eosinophilia is induced sputum assessment.[8] Sputum induction is thought to be a direct and reliable method for evaluating airway inflammation; however, it has several limitations.[16,17] For instance, it is unsuitable for point-of-care testing, requires experience, and has a failure rate of up to 30%.[16,17] Due to these limitations, the search for minimally invasive and easily available methods that can identify and evaluate the status of sputum eosinophilia inflammation in asthma and COPD has been intensified.[10,11,18–21] The use of peripheral blood cell counts is a simple and attractive tool that has potential in clinical practice. The prediction and accuracy of blood eosinophils and sputum eosinophilia in patients with asthma have been assessed and have demonstrated promising results.[21–24] However, limited studies have examined this issue in patients with COPD in a stable condition. One study reported a correlation between bronchial and blood eosinophil counts in 20 patients with COPD and 21 healthy controls.[25] Previous reports have also confirmed that blood eosinophils can serve as a good biomarker for steroid therapy in exacerbating[26] and stable[27,28] patients with COPD. Therefore, blood eosinophil count could be a predictive biomarker to indicate stable or exacerbating status and may indicate the effectiveness of ICS treatment in patients with COPD.

At present, there is still a lack of consensus about the optimal threshold of blood eosinophils for guiding ICS treatment in patients with stable COPD. Hence, the aim of this systematic review and meta-analysis was to investigate the predictive value of blood eosinophil count (cutoff point of 2%) as a biomarker of ICS efficacy in reducing the annual rate of moderate/severe exacerbations for patients with moderate-to-very severe COPD and a history of exacerbations.

Materials and methods

Search strategy and inclusion/exclusion criteria

This systematic review was performed in accordance with the guidelines on "Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare" and "How to Review a Meta-analysis". A comprehensive search was conducted using the terms "COPD", "eosinophil", and "clinical trial" in PubMed and EMBAS to identify relevant studies published up to 2017. All articles identified in the initial database search were screened based on title, abstract, and full text to confirm eligibility and avoid overlapping data. Primary research articles were compared for the following items: studies of ICS treatment and annual rates of moderate/severe exacerbations in patients with COPD with $<2\%$ and $\geq 2\%$ blood eosinophils. Studies involving patients with COPD that had acute exacerbation, preclinical studies, and conference abstracts were excluded from our meta-analysis.

Data extraction

Relevant data were extracted from the eligible publications: the name of the first author, the year of publication, trial name, the number of patients analyzed, inclusion criteria for participants, baseline patient characteristics, treatment regimens, study duration, the annual rate of moderate/severe exacerbations (including time-to-first exacerbations), and pneumonia events. Data on the therapeutic partners for ICS medications were obtained from seven studies from 1 to 3 years. The therapeutic partners included fluticasone propionate, fluticasone furoate, salmeterol+tiotropium, and ICS+long-acting β2-agonist (LABA).

Statistical analysis

To compare patients with COPD with eosinophil counts of $<2\%$ and $\geq 2\%$ in terms of the risk of exacerbation, time-of-first exacerbation, and pneumonia events, the meta-analysis software, "Comprehensive Meta-Analysis" version 2.2.055 (Englewood, NJ, USA) was used. Heterogeneity across studies was assessed by the Cochran's Q statistic test and the I^2 test. I^2 values $\geq 25\%$, 50%, and 75% were considered to reflect mild, moderate, and high degrees of heterogeneity, respectively. A random-effects model was used for pooled outcome measures with $I^2 > 50\%$. The difference in moderate/severe exacerbation rate between both treatment arms was expressed as the risk ratio (RR). The time-to-first exacerbation was expressed as the hazard ratio (HR). The relative risk of pneumonia events was expressed as RR. Data are presented as 95% CIs.

Results

Search strategy and data extraction

From the search using the keywords "COPD", "eosinophil", and "clinical trial" from PubMed and EMBASE, a total of 57 primary articles that were potentially relevant were obtained to determine further eligibility. Of these, 52 articles did not fulfill our inclusion criteria and were excluded. Of the five remaining publications[27,29–32] published from 2015 to 2016, a total of 12,496 patients were included in this meta-analysis/systematic review. The characteristics of the eligible studies are summarized in Table 1. Overall, the total number

Table 1 Summary of five articles from PubMed and EMBASE that were determined eligible using the keywords "COPD", "eosinophil", and "clinical trial" based on systematic review criteria

No	Author	Year	Title	Study arms	Subgroup
1	Barnes et al[29]	2016	Blood eosinophils as a marker of response to ICS in COPD	FP vs placebo	Eos count: <2% and ≥2%
2	Pascoe et al[27]	2015	Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with COPD: a secondary analysis of data from two parallel randomised controlled trials	FP/SAL vs tiotropium	Eos count: <2% and ≥2%
Pascoe et al 2015 (appendix)			FP/SAL with its monocomponents and placebo		
Appendix			FP/SAL with FP and placebo		
3	Pascoe et al[27]	2015	Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with COPD: a secondary analysis of data from two parallel randomised controlled trials	Fluticasone furoate + vilanterol vs vilanterol alone	Eos count: <2% and ≥2%
4	Roche et al[32]	2017	Blood eosinophils and response to maintenance COPD treatment	Indacaterol glycopyrronium vs fluticasone salmeterol	Eos count: <2% and ≥2% <3% and ≥3% <5% and ≥5%
5	Watz et al[31]	2016	Blood eosinophil count and exacerbations in severe COPD after withdrawal of ICS: a post-hoc analysis of the WISDOM trial	ICS continuation vs ICS withdrawal	Eos count: <2% and ≥2%

Abbreviations: Eos, eosinophil; ICS, inhaled corticosteroid; FP, fluticasone propionate; SAL, salmeterol.

of patients included in our study was 12,496. All participants were current or ex-smokers with a mean age of 64 years and were diagnosed with moderate-to-vey severe COPD. The asthma diagnosis was excluded in all trials. The proportion of patients with ≥2% blood eosinophils at baseline ranged from 32% to 75% in seven studies (mean 60%). In total, ICS-containing treatments included 854 patients treated with ICS monotherapy, 5,134 patients treated with ICS+LABA combination therapy; and 1,115 patients treated with ICS+LABA+long-acting muscarinic antagonist (LAMA) triple therapy. Non-ICS/ICS withdrawal/placebo included 4,269 patients treated with non-ICS regimens/placebo and 1,124 patients in withdrawal from ICS+LABA+LAMA triple therapy.

Primary outcome: risk of moderate/severe exacerbation

In the meta-analysis of primary outcomes, seven studies[27,29–32] were pooled for moderate/severe exacerbation RR analysis. Overall, there was no significant difference between ICS-containing treatments and non-ICS/ICS withdrawal/placebo treatments at eosinophil counts of <2% (RR, 1.038; 95% CI, 0.882–1.222; P=0.654), as shown in Figure 1A. ICS-containing treatments in the subgroup with eosinophil counts of ≥2% had a significantly reduced RR of moderate/severe exacerbations than did non-ICS/ICS withdrawal/placebo treatment groups (RR, 0.816; 95% CI, 0.672–0.990; P=0.039), as shown in Figure 1B. The publication bias of pooled risk for moderate/severe exacerbations was minimized by selecting high-quality articles and well-compared systematic review items, whereby either eosinophil counts of <2% or ≥2% had a low risk difference (Figure 2).

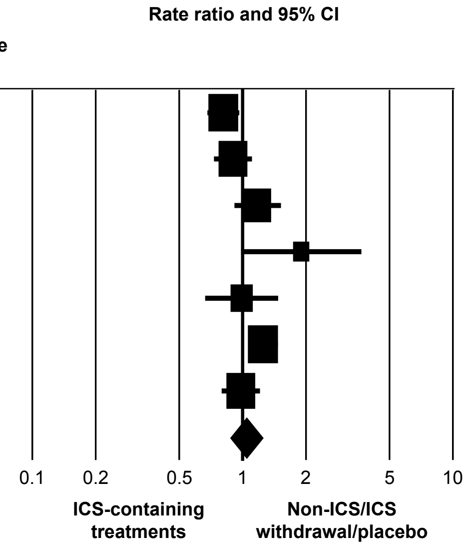
Secondary outcomes: risk of time-to-first moderate/severe exacerbation and pneumonia

ICS-continuing treatment in patients with COPD with baseline blood eosinophil levels ≥2% was associated with reduced risk of moderate/severe exacerbation. The secondary outcomes of the meta-analysis (pooled HRs for time-to-first moderate/severe exacerbation and pooled relative risk of pneumonia events) were significantly higher in the subgroup with eosinophil counts ≥2% with ICS-containing treatments.

Two populations of five studies[29,32] were pooled to analyze the HR for time-to-first moderate/severe exacerbation between ICS-containing treatments and non-ICS/ICS withdrawal/placebo treatments in the subgroup with eosinophil counts <2%, but no significant association was observed (HR, 1.148; 95% CI, 0.743–1.775; P=0.534), as shown in Figure 3A. In the subgroup with eosinophil counts ≥2%, ICS-containing treatments showed a significantly higher association with moderate/severe exacerbation than did non-ICS/ICS withdrawal/placebo treatments (HR, 1.173;

A

Study name	Rate ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Barnes et al, 2016[29]	0.810	0.685	0.957	–2.470	0.013	18.23
Pascoe et al, 2015[27]	0.900	0.737	1.100	–1.030	0.303	16.82
Pavord et al, 2016[30] (INSPIRE)	1.180	0.921	1.512	1.309	0.190	14.83
Pavord et al, 2016[30] (SCO30002)	1.900	0.991	3.643	1.932	0.053	4.91
Pavord et al, 2016[30] (TRISTAN)	0.990	0.668	1.466	–0.050	0.960	9.77
Roche et al, 2017[32]	1.250	1.070	1.460	2.815	0.005	18.71
Watz et al, 2016[31]	0.980	0.800	1.200	–0.195	0.845	16.72
	1.038	0.882	1.222	0.449	0.654	



B

Study name	Rate ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Barnes et al, 2016[29]	0.880	0.694	1.116	–1.054	0.292	14.23
Pascoe et al, 2015[27]	0.710	0.612	0.823	–4.538	0.000	16.39
Pavord et al, 2016[30] (INSPIRE)	0.750	0.606	0.929	–2.638	0.008	14.84
Pavord et al, 2016[30] (SCO30002)	0.820	0.480	1.400	–0.727	0.467	7.59
Pavord et al, 2016[30] (TRISTAN)	0.630	0.501	0.792	–3.959	0.000	14.46
Roche et al, 2017[32]	1.170	1.035	1.323	2.502	0.012	16.89
Watz et al, 2016[31]	0.820	0.683	0.984	–2.129	0.033	15.60
	0.816	0.672	0.990	–2.060	0.039	

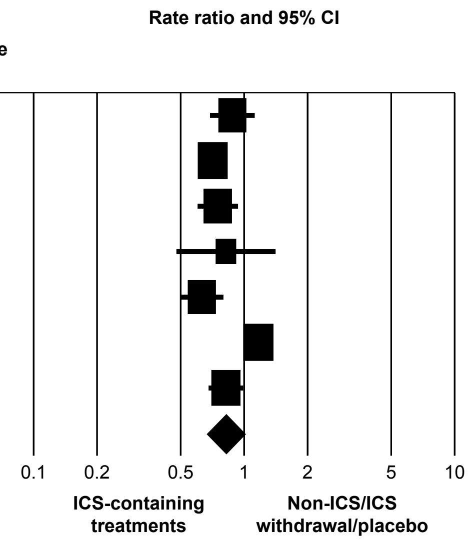


Figure 1 Forest plots of studies comparing the pooled risk ratio for moderate/severe exacerbation in patients with COPD receiving ICS-containing treatment or non-ICS/ICS withdrawal/placebo treatments by subgroup.
Note: (**A**) Eosinophil counts <2% and (**B**) eosinophil counts ≥2%.
Abbreviation: ICS, inhaled corticosteroid.

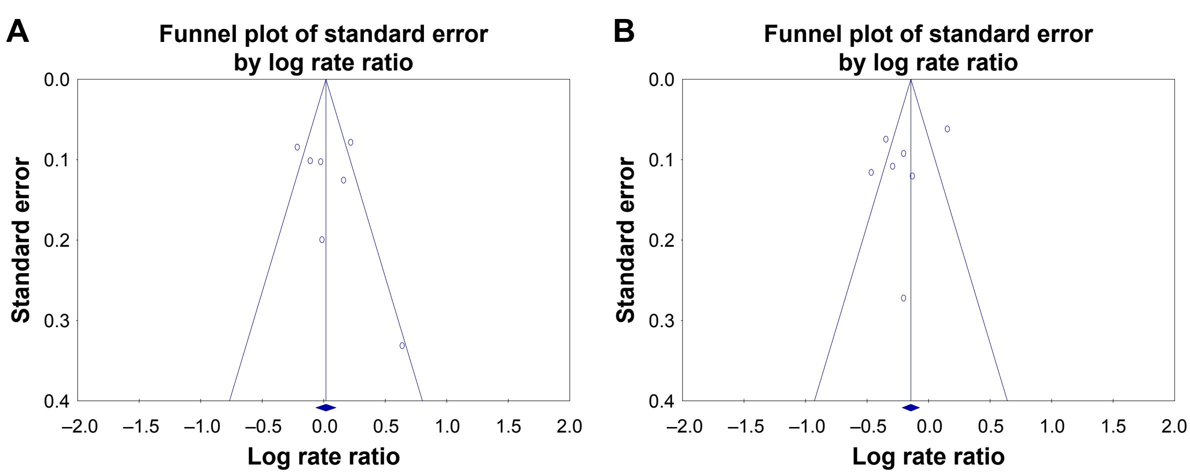
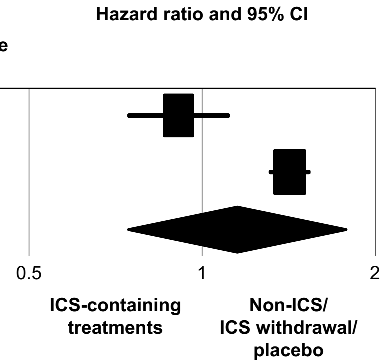


Figure 2 Analysis of publication bias for pooled risk ratio of moderate/severe exacerbation for (**A**) eosinophil counts <2% and (**B**) eosinophil counts ≥2%.

A

Study name	Hazard ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Barnes et al, 2016[29]	0.910	0.743	1.115	–0.912	0.362	47.73
Roche et al, 2017[32]	1.420	1.309	1.540	8.468	0.000	52.27
	1.148	0.743	1.775	0.622	0.534	



B

Study name	Hazard ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Barnes et al, 2016[29]	1.040	0.776	1.393	0.263	0.793	16.13
Roche et al, 2017[32]	1.200	1.056	1.364	2.786	0.005	83.87
	1.173	1.043	1.319	2.657	0.008	

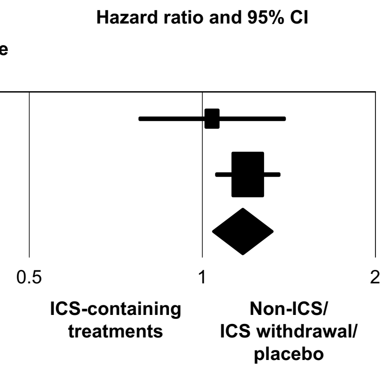


Figure 3 Forest plots of studies comparing the pooled hazard ratio for time-to-first moderate/severe exacerbation in patients with COPD receiving ICS-containing treatment or non-ICS/ICS withdrawal/placebo treatments by subgroup.
Note: (**A**) Eosinophil counts <2% and (**B**) eosinophil counts ≥2%.
Abbreviation: ICS, inhaled corticosteroid.

95% CI, 1.043–1.319; *P*=0.008), as shown in Figure 3B. Although numerous trials have confirmed the efficacy of ICS for the treatment of COPD, ICS may also increase the risk of pneumonia in patients with COPD. Analysis of two populations of five studies[27,32] revealed that the risk of pneumonia events was significantly increased in the subgroup with eosinophil counts ≥2% with ICS-containing treatments (RR, 1.969; 95% CI, 1.369–2.833; *P*<0.001), as shown in Figure 4A. There was no significant difference in the subgroup with eosinophil counts <2% (RR, 1.291; 95% CI, 0.888–1.879; *P*=0.181), as shown in Figure 4B.

Discussion

Summary of main results

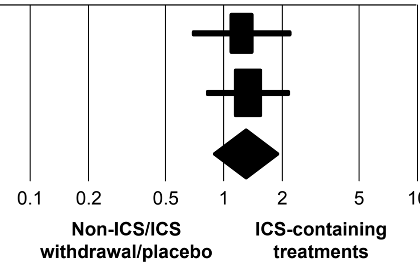
We conducted a systematic review and meta-analysis to investigate the predictive role of baseline blood eosinophil counts as a biomarker of response to ICS in patients with moderate-to-very severe COPD. A total of five studies with 12,496 patients were used for analysis. The cutoff of 2% blood eosinophil counts was utilized to categorize patients in this study, and 60% of patients had ≥2% blood eosinophils at baseline. For patients with ≥2% blood eosinophils, the five studies provided inconsistent results when comparing the efficacy of ICS-containing regimens and non-ICS regimens/ICS withdrawal/placebo treatments at reducing exacerbation risk. In the meanwhile, we excluded the patients treated with other anti-inflammatory agents such as oral steroid or phosphodiesterase type 4 inhibitors at the same time. Our meta-analysis showed a significantly decreased acute exacerbation risk in favor of ICS-containing treatments vs non-ICS/ICS withdrawal/placebo treatments for reducing COPD exacerbations in patients with ≥2% blood eosinophils (RR, 0.81; 95% CI, 0.67–0.99; *P*=0.03).

The characteristics of COPD include chronic inflammation and structural changes in the respiratory tract, which are mediated by inflammatory cells and a complex cytokine network.[33,34] Neutrophils are the predominant cell type involved in airway inflammation in patients with COPD and account for >70% of sputum cells.[35,36] However, ~20%–40% of patients with stable COPD show elevated eosinophil levels (>3%) in sputum.[7] Furthermore, blood eosinophilia (≥2%) has been reported in 50%–70% of patients with COPD.[37] Eosinophils are multifunctional leukocytes characterized by the storage of cytotoxic basic proteins in secondary granules

A

Study name	Events/total: ICS-containing treatments	Events/total: Non-ICS/ICS withdrawal/placebo	Risk ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Pascoe et al, 2015[27]	46/795	14/299	1.236	0.690	2.214	0.711	0.477	41.34
Roche et al, 2017[32]	37/672	26/629	1.332	0.816	2.173	1.148	0.251	58.66
			1.291	0.888	1.879	1.336	0.181	

Risk ratio and 95% CI



B

Study name	Events/total: ICS-containing treatments	Events/total: Non-ICS/ICS withdrawal/placebo	Risk ratio	Lower limit	Upper limit	*Z*-value	*P*-value	Relative weight
Pascoe et al, 2015[27]	104/1,583	13/500	2.527	1.432	4.458	3.200	0.001	41.01
Roche et al, 2017[32]	43/1,004	27/1,044	1.656	1.032	2.659	2.088	0.037	58.99
			1.969	1.369	2.833	3.653	0.000	

Risk ratio and 95% CI

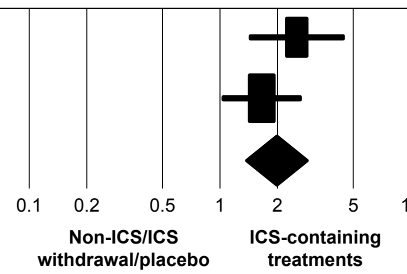


Figure 4 Forest plots of studies comparing the pooled relative risk of pneumonia events in patients with COPD receiving ICS-containing treatment or non-ICS/ICS withdrawal/placebo treatments by subgroup.
Note: (**A**) Eosinophil counts <2% and (**B**) eosinophil counts ≥2%.
Abbreviation: ICS, inhaled corticosteroid.

as well as the production of reactive oxygen species, lipid mediators, and cytokines.[38,39] The release of cytotoxic basic proteins, reactive oxygen species, and lipid mediators is associated with damage to airway epithelial cells.[7,39] During a COPD exacerbation, both absolute and relative eosinophil counts in sputum are significantly increased compared with those during the stable phase.[36] Therefore, eosinophils may contribute to increased airway inflammation during acute exacerbations of COPD.[36] Additionally, blood eosinophilia is associated with a higher risk of COPD exacerbation,[40,41] which may lead to a decline in lung function[7] and increased mortality.[42]

The molecular mechanisms for the anti-inflammatory activity of corticosteroids include repression of activated inflammatory genes, activation of anti-inflammatory genes, and posttranscriptional effects.[43,44] At the cellular level, corticosteroids can inhibit the survival of eosinophils in the airways.[43,45] Leigh et al reported that 4-week treatment with inhaled budesonide (1,600 µg/day) normalized the sputum eosinophil counts in patients with COPD with sputum eosinophilia.[12] In patients without sputum eosinophilia, the sputum eosinophil counts stayed within the normal range after budesonide treatment.[12] Budesonide treatment did not significantly affect the sputum neutrophil counts of all enrolled patients.[12] Similar results were observed in patients with COPD treated with a combination therapy of inhaled fluticasone (200 µg/day) and salmeterol (100 µg/day) for 2 months.[46] In patients with sputum eosinophilia, the percentage of eosinophils in sputum significantly decreased from 8.9% to 1.6% (P=0.003) after treatment with inhaled fluticasone–salmeterol.[46] In contrast, sputum neutrophils remained unchanged after fluticasone–salmeterol combination therapy.[46] Based on currently available data, ICS can significantly suppress eosinophilic airway inflammation, but has less of an effect on neutrophilic airway inflammation, which predominates in COPD.[12,46] There is some evidence suggesting that maintenance treatment with ICS is more effective in patients with COPD with higher eosinophil counts, with regards to reducing exacerbation frequency and improving lung function.[27–31,47,48]

Although asthma and COPD are two different chronic respiratory diseases, a significant proportion of patients aged >40 years present with overlapping conditions.[49] These patients are categorized as having asthma–COPD overlap syndrome (ACOS).[49] A joint project of the Global Initiative for Asthma and the Global initiative for chronic Obstructive Lung Disease (GOLD) provides the clinical description for ACOS:

> ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified in clinical practice by the features that it shares with both asthma and COPD.[49]

However, there is no universally accepted definition of ACOS at present. Previous large-scale studies have revealed that the prevalence rates of ACOS in patients with COPD are between 5.6% and 55%, depending on the diagnostic criteria applied.[50–57] The mixed COPD–asthma phenotype is associated with more respiratory symptoms, increased risk of exacerbation and hospitalization, and worse health-related quality of life compared with the pure COPD phenotype.[53,54,56,58,59] Regarding eosinophils, patients with ACOS show significantly higher sputum and blood eosinophil counts than those with pure COPD.[60] A blood eosinophil count >5% was used as a minor criterion for defining ACOS in a cohort of Spanish patients with COPD.[51]

Several studies suggested that ACOS patients were more likely to benefit from ICS treatment because of sputum eosinophilia.[52,60,61] Kitaguchi et al reported that patients with ACOS showed a significant increase in forced expiratory volume 1 (FEV_1; 32.4%) than did those with pure COPD (12.8%) after being treated with inhaled fluticasone propionate (400 µg/day) for 2–3 months.[60] Moreover, a significant correlation was observed between the increase in FEV_1 and sputum eosinophil counts.[60] In a study conducted by Lee et al, the improvement in FEV_1 was significantly greater in patients with ACOS (240.2±33.5 mL) than that in patients with pure COPD (124.6±19.8 mL) after 3 months of treatment with ICS+LABA (salmeterol 50 µg/fluticasone 500 µg or formoterol 9 µg/budesonide 320 µg twice daily).[61] A Canadian longitudinal cohort study revealed that new use of ICS+LABA was associated with a modestly reduced risk of death or COPD hospitalization in patients with COPD compared with new use of LABA alone (HR, 0.92; 95% CI, 0.88–0.96).[52] A more pronounced reduction in risk was observed in the ACOS subgroup (HR, 0.84; 95% CI, 0.77–0.91).[52]

Based on clinical evidence, the GOLD 2017 guidelines recommend ICS+LABA as the first-line treatment in patients with high blood eosinophil counts and/or ACOS.[62] In a joint project by Global Initiative for Asthma and GOLD, ICS was considered as the initial treatment for ACOS patients, and add-on treatment with LABA and/or LAMA is also usually necessary.[49]

It is still debated whether high eosinophil levels in either sputum or blood are associated with a severe COPD allergic phenotype, including greater exacerbation frequency, and whether blood eosinophils are predictive of sputum eosinophils. Hastie et al reported that high concentrations of sputum eosinophils were a better biomarker than high concentrations of blood eosinophils to identify a patient subgroup with more severe disease, more frequent exacerbations, and increased emphysema by quantitative computer tomography.[63] Further studies should be performed to demonstrate the roles of sputum or blood eosinophil counts in COPD.

The most commonly used cutoff point for blood eosinophil counts in previous studies was 2%[27,29–32] because this level showed high sensitivity for identifying sputum eosinophilia of ≥3%.[10] However, our meta-analysis indicated that the 2% threshold may be too low to accurately identify the group of patients most likely to benefit from ICS treatment. In several studies, the choice of a cutoff point showing the best predictive ability of blood eosinophils was based on the analyses of treatment outcomes, such as COPD exacerbation rate, stratified by a number of possible blood eosinophil levels.[28,31,47,48] In the NCT01009463 and NCT01017952 trials, there was a linear relationship between blood eosinophil count and the RR of annual exacerbation rate for fluticasone furoate–vilanterol vs vilanterol, and a blood eosinophil cutoff of 2.4% was used in the cluster analysis (>2.4% blood eosinophils: RR, 0.68; 95% CI, 0.58–0.79; blood eosinophil count ≤2.4%: RR, 0.94; 95% CI, 0.80–1.11).[47] Results of the WISDOM trial suggested that blood eosinophil counts of ≥4% or ≥300 cells/µL may identify patients with COPD requiring continuation treatment with ICS (triple therapy consisting of fluticasone propionate, salmeterol, and tiotropium).[31] According to the post hoc analysis of the FORWARD trial, the greatest differences in COPD exacerbation rate (reduction: 46%; $P \leq 0.001$) and improvements in FEV_1 (difference: 0.102; $P=0.001$) and St George's Respiratory Questionnaire for COPD score (difference: −5.9; $P \leq 0.001$) between dipropionate–formoterol fumarate and formoterol fumarate were observed in patents with blood eosinophil counts of ≥279.8 cells/µL.[28] A pooled analysis of the LANTERN and ILLUMINATE trials demonstrated that fluticasone–salmeterol was more effective than indacaterol–glycopyrronium at reducing exacerbation risk in patients with COPD with blood eosinophil counts >300 cells/μL (RR, 0.59).[48]

The optimal cutoff points of blood eosinophil counts (2.4%–4% and 279.8–300 cells/μL) obtained from the studies mentioned above[28,31,47,48] might not represent the true predictive ability because of the implicit multiple comparisons with different possible cutoff points. Further randomized studies with a biomarker-stratified design should be performed in order to find the most appropriate cutoff point for blood eosinophils.

Since COPD is a highly heterogeneous disease and several molecular mechanisms are associated with corticosteroid resistance,[43] the combination of blood eosinophil counts with other markers may achieve the best predictive accuracy in predicting treatment response to ICS.[17] Cigarette smoking is not only the primary cause of COPD but also associated with a poor response to ICS.[64] Various mechanisms may be involved in the development of resistance to ICS, in particular, HDAC2 dysfunction.[64–66] Peroxynitrite produced by the reaction of nitric oxide and superoxide anion from cigarette smoke may cause reduced HDAC2 activity and expression, which decreases the efficacy of ICS.[65,66]

A cluster analysis of the patients who may benefit more from fluticasone furoate–vilanterol vs vilanterol identified three separate clusters in 3,255 patients with smoking-related COPD from the NCT01009463 and NCT01017952 trials.[47] Cluster 1 included patients with >2.4% blood eosinophils (n=1,777, 54.6%), cluster 2 included patients with ≤2.4% blood eosinophils and a smoking history of ≤46 pack-years (n=891, 27.4%), and cluster 3 included patients with ≤2.4% blood eosinophils and a smoking history of >46 pack-years (n=587, 18.0%). The RRs of annual exacerbation rates for fluticasone furoate–vilanterol vs vilanterol revealed that the greatest treatment effect of fluticasone furoate–vilanterol was found in cluster 1 (RR, 0.68; 95% CI, 0.58–0.79). Patients in cluster 2 may also benefit from fluticasone furoate–vilanterol treatment (RR, 0.78; 95% CI, 0.63–0.96); however, those in cluster 3 were considered to be non-responders to fluticasone furoate–vilanterol (RR, 1.22; 95% CI, 0.94–1.58). Blood eosinophil count was the most important factor affecting the treatment response to fluticasone furoate–vilanterol, followed by smoking history. The impact of smoking history on ICS treatment in patients with COPD also warrants further investigation.

Limitations of this study

Our meta-analysis was limited to only five studies on the post hoc analyses of eight randomized trials. None of these trials were originally designed to assess the usefulness of blood eosinophils as a biomarker for predicting the response to ICS in patients with COPD. Heterogeneity in study design and patient populations was observed across the eight trials. Randomized withdrawal study design was only utilized in the WISDOM trial.[31] The experimental and active comparator arms were somewhat heterogeneous among trials. The combination therapy of ICS+LABA or ICS+LABA+LAMA was studied in seven trials,[27,30–32] and the results suggest that the therapeutic response to ICS may be influenced by LABA or LABA+LAMA to some degree. The FLAME trial recruited patients with moderate-to-very severe airflow limitation.[32] Five trials involved patients with moderate-to-severe COPD;[27,29,30] however, two trials involved patients with more severe disease (severe-to-very severe COPD).[30,31] Patients without a history of exacerbations could only be enrolled in the SCO30002 trial,[30] while patients who had never smoked were excluded from all trials.[27,29,31,32,67–69] Therefore, our results may not be generalizable to real-world patients suitable for ICS therapy as recommended by the GOLD guidelines.[62] The withdrawal rates in the ICS-containing treatment arms and active comparator/placebo arms were 18.3%–34.5% and 16.6%–41.7%, respectively.[2,32,67–71] The highest withdrawal rates (34.5% in the fluticasone propionate–salmeterol group and 41.7% in the tiotropium group) were observed in the INSPIRE trial, which included patients with severe and very severe COPD.[69] In the INSPIRE,[69] ISOLDE,[70] and TRISTAN 66 trials, significantly higher proportions of patients in the active comparator or placebo arms failed to complete the study than did those in the ICS-containing arms. High withdrawal rates could lead to bias in the estimates of treatment effect because patients who completed the study may be healthier than the population at study entry.

A comprehensive assessment of the relationship between blood eosinophil counts and the treatment effects of ICS regimens is necessary. However, the meta-analysis of other efficacy parameters, such as time to first exacerbation, FEV_1, St George's Respiratory Questionnaire for COPD total score, and mortality was not performed in this study because some of these data stratified by blood eosinophil counts were not presented in the five studies.

Conclusion

Our meta-analysis suggested a modest benefit from ICS-containing treatments vs non-ICS/ICS withdrawal/placebo treatments in reducing the annual rate of moderate/severe exacerbations in patients with COPD with ≥2% blood eosinophils at baseline. However, the incidence of pneumonia risk was also increased in patients with COPD with higher eosinophil counts who used ICS treatment. To be useful in clinical practice, further prospectively designed studies with prespecified criteria for blood eosinophil subgroups of patients with COPD are required to identify the best cutoff point for blood eosinophil count.

Disclosure

The author reports no conflicts of interest in this work.

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