DOI: https://doi.org/10.61841/7k51ta96 Publication URL: https://nnpub.org/index.php/MHS/article/view/2186

EFFECTS OF INHALED CORTICOSTEROIDS IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE : A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Inhaled corticosteroids aid COPD patients by improving lung function and reducing exacerbations. The combination of ICS and LABA is more effective than LABA alone, indicating that blood eosinophilia influences therapy efficacy. Patients with low peak inspiratory flow may not receive enough delivery, necessitating the use of spacers to enhance inhaler actuation and inspiration timing. This study aims to systematically review the literature on the effects of inhaled corticosteroids in stable COPD in the last 10 years.*

Methods: *This systematic review used the PRISMA 2020 principles and examined full-text English literature published between 2014 and 2024. Submissions without a DOI were not taken into consideration, nor were editorials and review papers from the same publication. Online resources like PubMed, SagePub, and ScienceDirect were used to compile the literature.*

Result: *Initially, our study team gathered over 60,000 papers from reputable websites such as PubMed, SagePub, and ScienceDirect. Only five papers were found to be directly relevant to our ongoing systematic review after a thorough three-level filtering approach. These publications were then selected for further research through full-text reading.*

Conclusion: *ICS is an effective treatment for COPD because it reduces inflammation, improves airway remodelling, and lowers bacterial load. Higher doses are more effective, because budesonide inhalation enhances lung function.*

Keyword: *Effects, inhaled corticosteroids, stable, COPD*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), which is distinguished by significant variation in both clinical presentations and underlying processes, is an ideal target for the implementation of precision medicine therapies.[1] COPD patients at high risk of exacerbation should be treated with inhaled corticosteroids (ICS) and long-acting β2 agonists (LABAs).[2] Clinical research has recently looked at strategies to customize the administration of inhaled corticosteroids (ICS), which seem to help a small percentage of people with COPD.[1] For patients with moderate-to-very severe COPD with a history of exacerbations, fixed-dose inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) combination treatment is successful in improving lung function and minimizing exacerbations.[3] According to intriguing new research, blood eosinophilia predicts that the ICS/LABA combination will be more effective than LABA alone in preventing exacerbations. This suggests that blood eosinophilia may be a useful biomarker for identifying patients who will benefit from this medication.[2] Corticosteroids, whether inhaled or systemic, reduce eosinophil count in proportion to their efficacy. It has been demonstrated that oral and inhaled corticosteroids considerably reduce sputum eosinophils in COPD patients. We postulated that the administration of ICS may also have an impact on blood EOS and that alterations in blood EOS after ICS treatment may be indicative of the medication's long-term effectiveness.[4] It has been suggested that individuals with COPD who exhibit high eosinophilic inflammation in their airways may be the only ones benefiting from ICS.[5] Concerns that the advantages of ICS came at the expense of side effects, such as a markedly elevated risk of pneumonia, drove these investigations.[6]

When employing devices with high inspiratory airflow resistance, patients with COPD and low peak inspiratory flow (PIF) may experience inadequate inhaled drug delivery to the airways. Significantly, compared to metered dosage inhalers (MDIs), dry powder inhalers (DPIs) have a higher flow dependency on fine particle mass, which could affect how well medications are delivered and how well the lungs function.[7] DPIs must generate enough airflow (often 60 L/min or more),[8] yet their airflow resistance is [0.060-0.163 $cmH2O^{0.5}$ $(L/min)^{-1}$]. There can be significant differences in the PIF rate (49-108L/min) amongst devices.[9] While MDIs are less dependent on a patient's ability to generate airflow than DPIs, some patients experience difficulties while using them appropriately, especially when it comes to synchronizing inhalation and device activation. To improve inhaler actuation and inspiration timing, an MDI can be used in conjunction with a spacer, which is a valved holding chamber.[9,10]

This study aims to systematically evaluate the literature on the effect of inhaled corticosteroids in stable chronic obstructive pulmonary disease patients over the past decade.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were strictly followed by the study's author. This was done to ensure that the study complied with all standards. The methodology employed was designed with the express purpose of guaranteeing the precision and reliability of the inquiry's findings.

Criteria for Eligibility

In the last ten years, the effects of inhaled costicosteroid on patients with stable chronic obstructive pulmonary disease have been extensively studied in the literature. Through careful data analysis, this study seeks to shed light on patient treatment strategies and make them better. This work's main goal is to highlight the general significance of the major issues brought up in the literature.

This study employs strict inclusion and exclusion criteria to ensure the quality of the literature included. To be eligible for inclusion, papers must be published in English between 2014 and 2024. Editorials, DOI-free submissions, already published review pieces, and duplicate journal entries are all excluded.

Search Strategy

The keywords used for this research is "effects, inhaled corticosteroids and chronic obstructive pulmonary disease". The Boolean MeSH keywords inputted on databases for this research are: *((("inhaled corticosteroids"[MeSH Terms] OR ("steroids"[All Fields] AND "chronic obstructive pulmonary disease"[All Fields]) OR ("chronic obstructive pulmonary disease"[MeSH Terms] OR ("chronic"[All Fields] AND "obstructive pulmonary disease"[All Fields]) AND ("effects"[MeSH Terms] OR "effects"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])))*

Data retrieval

To determine the relevance of each study, the authors carefully evaluated its abstract and title before conducting this systematic review. Only articles that met the inclusion requirements and had something to do with the goals of the article were taken under consideration for further assessment. A recurring pattern found in several investigations ultimately

produced a definitive answer. The chosen submissions have to be full-text and in English. Only items that satisfied all specified inclusion criteria and had a direct bearing on the study question were included in the extremely thorough review. Research that did not fit these requirements was routinely disregarded, and their conclusions were not looked at. A thorough examination was conducted, considering various information that came to light during the investigation, such as titles, authors, publication dates, places, study methodologies, and parameters.

Quality Assessment and Data Synthesis

The study reported in the title and abstract of each publication was independently assessed by the authors to determine which ones require additional investigation. Examining every article that satisfied the predetermined standards for review inclusion was the next step. The evaluation procedure yielded information that informed the choice to include an article in the review. This criterion served to speed up the process of selecting papers for additional evaluation, enabling a thorough discussion of previous studies and the criteria that made them eligible for the review.

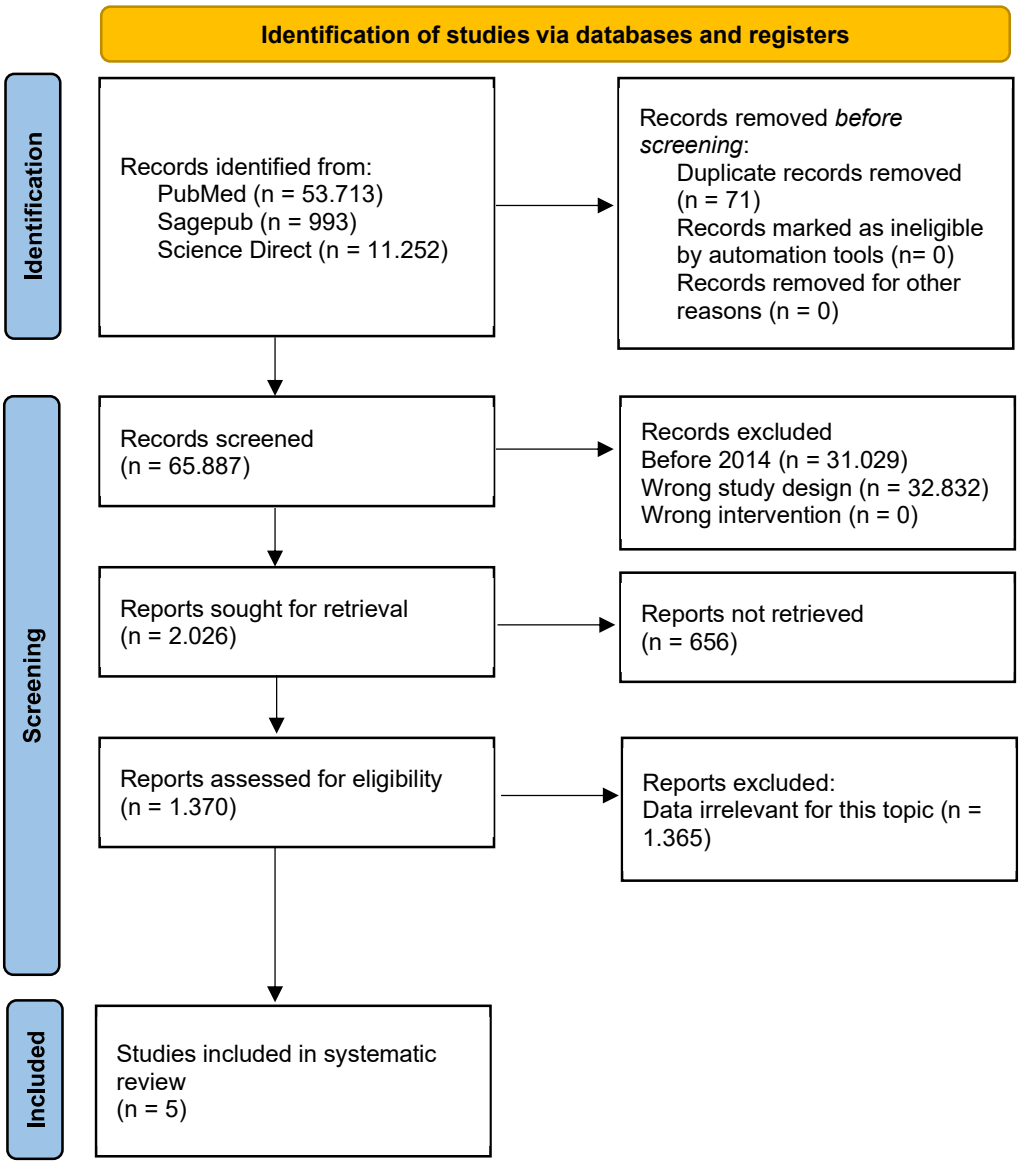

Figure 1. Article search flow chart

RESULT

Our study team first collected more than 60,000 papers from reliable sources like Science Direct, PubMed, and SagePub. Only five papers were found to be directly relevant to our ongoing systematic review after a thorough three-level screening process, and they were selected for further analysis through full-text reading. We have compiled the literature used in this research into Table 1 for ease of presentation.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Cheng et al.[11] (2014)	Taiwan	Randomized Controlled Trial	237 patients	A total of 237 COPD patients were randomly assigned to one of two therapy arms: HD (115) or MD (122). At the end of the research, patients in the HD group had significantly higher FEV1 levels than those in the MD group (103.9±26.6 mL vs. 51.4±19.7 mL, P=0.01). Patients utilizing an HD showed significant improvement in CAT scores compared to those using an MD (HD 13±5 vs MD 16±7, P=0.05). The two groups showed a significant difference in annual rates of acute exacerbations (HD 0.16 vs MD 0.34, P = 0.01). The incidence of pneumonia was comparable across the two groups (HD 0.08 vs MD 0.10, P=0.38).
Soltani et al.[12] (2016)	Australia	Retrospective case control study	34 patients	There were no significant variations in baseline characteristics between the treatment groups. With ICS, vessels and angiogenic factors did not change in the hypervascular reticular basement membrane, but increased in the hypovascular lamina propria (LP), affecting lung air trapping. There was some evidence that ICS treatment reduced VEGF staining in LP arteries, but there was also a large reduction in p-SMAD 2/3 expression.
Contoli et al.[13] (2017)	Italy	Randomized Controlled Trial	60 patients	After a year of treatment with salmeterol + fluticasone, the bacterial load in sputum increased significantly (p=0.005), the microbiological makeup of sputum changed, and the airway load of potentially pathogenic bacteria increased in comparison to salmeterol. Patients with lower baseline blood or sputum eosinophil levels (⩽2%) after inhaled corticosteroid treatment had higher bacterial loads, but not higher baseline eosinophil levels.

Mathioudakis et al.[4] (2019)	United Kingdom	Randomized Controlled Trial	751 patients	EOS change within one year after the introduction of ICS was strongly predictive of treatment response. A suppressed EOS was associated with the treatment effect. Characteristically, in patients with EOS suppression of ≥200 EOS/µL, ICS use was associated with a decelerated FEV1 decline rate, of 32mLs/year, and a 30% reduction in the exacerbation rate. In contrast, in patients experiencing an increase in EOS of ≥200 EOS/µL, ICS use was associated with an accelerated FEV1 decline rate by 37mLs/year and an increased exacerbation rate by 80% ($p<0.0001$). EOS change was not predictive of clinical response with regards to health status evaluated using the Saint George Respiratory Questionnaire.
Huber et al.[7] (2022)	Germany	Randomized Controlled Trial	35 patients	The modified intention-to-treat study included 30 patients (mean age: 66.9 years, mean baseline FEV1: 766 mL, and mean COPD assessment test score: 22.20). After one week of treatment, both BFF MDI and BUD/FORM DPI enhanced the mean [95% confidence interval (CI)] peak FEV1 4 hours post-dose [256 (190, 322) mL and 274 (208, 340) mL, respectively]. There was no clinically significant difference between treatments for any lung function goal. There were no unexpected safety findings.

Cheng et al. found that higher doses of fluticasone improved lung function, reduced COPD symptoms, and decreased acute exacerbations in GOLD II patients. There was no significant difference in the incidence of pneumonia between high-dose and medium-dose groups.[11]

Soltani et al. discovered that inhaled corticosteroids did not significantly alter the number of vessels in the reticular basement membrane, but they moderately increased vascular density in the lamina propria in COPD patients who smoke.[12]

Contoli et al. found that the overall bacterial load increased after a year of therapy with salmeterol/fluticasone (SALM/FP), but there was no link between ICS treatment and specific infections. The SALM/FP group showed no meaningful trend in terms of exacerbation rate reduction compared to the previous year.[13]

According to Mathioudakis et al., the response of ICS treatment on post-bronchodilator forced expiration volume in 1 second (FEV1) declines was significantly predicted by changes in blood eosinophil count. When patients had an EOS

suppression of >200 EOS/µL, ICS medication delayed the mean yearly FEV1 loss; however, when patients had an EOS rise of >200 EOS/µL, the mean FEV1 decrease was accelerated.[4]

After one week of treatment, Huber et al. observed that peak FEV1 improvements were comparable for both budesonide/formoterol fumarate dihydrate MDI (BFF MDI) and budesonide/formoterol fumarate dihydrate DPI (BUD/FORM DPI) within 4 hours post-dose. In both inhalers, the budesonide plasma concentration-time patterns were comparable.[7]

DISCUSSION

Chronic obstructive pulmonary disease (COPD) pathophysiology is based on airway inflammation produced by cigarette smoke and/or indoor/outdoor fume exposure. The presence of inflammation in the airways justifies employing ICS and LABA to treat the condition. Previous research by Ozol et al. demonstrated that ICS treatment reduces neutrophil and interleukin 8 expressions in bronchoalveolar lavage fluid in COPD patients by suppressing Toll-like receptor 4 and lipopolysaccharide-induced interleukin 8 expressions in a dose-dependent manner.[11] Zanini et al. discovered that ICS medication improves airway remodeling by decreasing vascular endothelial growth factor and transforming growth factor-β levels.[14] Cheng et al. found that higher ICS doses (fluticasone 1,000 µg/day) improved COPD patients' lung function, reduced acute exacerbations, and improved symptoms and quality of life compared to medium doses. Most critically, the chance of acquiring pneumonia or other side effects was the same for both treatment groups. Higher doses of ICS were found to be more effective for treating COPD patients.[11] In addition, the study from Soltani et al. in 2016 found that the current investigation examined the effects of ICS on airway vascular remodeling in COPD and discovered that, contrary to our hypothesis, Rbm hypervascularity did not respond to ICS treatment. In contrast, this study discovered that, particularly in the current smoking COPD group, ICS restored the density of LP vessels to normal.[12] This finding was not observed in the ex-smoking COPD sample, but vessel counts at baseline were practically normal.[15]

The impact of a year-long treatment with the inhaled corticosteroid fluticasone (FP) in combination with SALM (a LABA) on sputum microbiological loads was investigated by Contoli et al. in a controlled research. The study discovered that adding FP to SALM enhanced the bacterial load in sputum samples from persons with intermediate COPD and moderate airflow limitation using traditional sputum cultures and molecular methods.[13] The impact of ICS on pulmonary host defense against bacterial infections was investigated in several research. By obstructing essential components of innate antimicrobial activity, such as 1) suppressing macrophage antimicrobial activity, 2) preventing macrophage release of cytokines like TNF and IP-10, 3) downregulating MHC class II molecule expression in macrophages, and lowering adaptive immune responses, FP can impede bacterial clearance..[16,17] Contoli et al.'s work shows that in this clinical situation, long-term ICS treatment resulted in a net increase in the airways' bacterial burden.[13] In contrast, the frequency of respiratory virus detections remained constant. Furthermore, Maria et al. discovered that viral detection is low in patients with stable disease.[14]

Pascoe et al. evaluated blood EOS as a responsive therapeutic biomarker to direct the delivery of ICS in COPD patients in an experimental post hoc trial. The clinical response to ICS in terms of FEV1 drop and frequency of exacerbations was predicted by an increase or decrease in EOS in response to ICS delivery in the ISOLDE cohort.[2,18] An increase in EOS after taking ICS medication revealed a patient category that was sensitive and for whom ICS treatment was less effective than a placebo. This cluster needs more research because it was found in the ISOLDE trial study population with a prevalence of 20%. The fact that patients in this group continue to suffer from an immunosuppressive load even in the absence of benefit from ICS may account for the decreased therapeutic index of ICS. Consequently, patients have an increased risk of recurrent acute respiratory infections, including pneumonia or COPD exacerbations, which precipitate a faster decline in FEV1. What mechanism leads to the increase in EOS in response to ICS is unknown.[4]

Mathioudakis et al. compared EOS while patients were receiving ICS (EOS on ICS) to EOS when patients were not receiving steroids for at least 8 weeks (EOS off steroids) to ascertain if ICS medicine lowers blood EOS. The latter was assessed following the first year of treatment. After a year, the EOS count was substantially lower after ICS treatment than it was at baseline. Of the 68 individuals, 41 (60.3%) had EOS less than 200 cells/µL while taking ICS, but more than 200 cells/µL when off steroids. However, in terms of the frequency of exacerbations, EOS off steroids but not EOS on ICS or EOS change predicted response to ICS. In our investigation, the only factor that predicted the clinical response to ICS in terms of pulmonary function and health status was higher EOS measured when patients were not taking corticosteroids, not EOS while on ICS. When ICS was administered, the number of exacerbations increased by 80% for people whose EOS rise was 200 EOS/µL and decreased by 33% for people whose EOS suppression was -200 EOS/µL.[4] In eosinophilic patients, whose exacerbations are more common and bacterial etiology is less likely, ICS/LABA prevents exacerbations better than LABA alone.[2] Contoli et al. discovered that ongoing ICS treatment did not affect bacterial burdens in this eosinophilic milieu. On the other hand, the low-eosinophil group develops higher airway bacterial load and infectivity, increasing the chance of infective episodes. This group is therefore less likely to benefit from continuous ICS treatment for exacerbation prevention in addition to LABAs. The addition of ICS to LABA resulted in an increased

number of potential pathogen microorganisms (Pneumococcus, Haemophilus, and Moraxhella) in COPD patients with baseline eosinophil levels <2%, which is consistent with data from sputum cell culture.[13]

The effects of budesonide inhalation using various methods on pulmonary function in individuals with COPD were investigated in a recent study by Huber et al. Because an MDI with a spacer has less inspiratory airflow resistance than a DPI, researchers reasoned that it would be more suited for patients with low PIF. Regardless of the treatment approach, the results indicated that patients with a PIF ≥ 40L/min improved more than those with a PIF < 40L/min in terms of lung function across endpoints. The absorption rates of budesonide and formoterol fumarate were similar in both BFF MDI and BUD/FORM DPI, despite their respective well-tolerance. By week 1, there was no discernible difference in the effects on lung function. Overall, there were no appreciable differences in the effectiveness of BFF MDI and BUD/FORM DPI in enhancing lung function for patients with severe to very severe COPD and low PIF according to the delivery method.[7]

CONCLUSION

ICS treatment is an effective treatment for COPD, reducing inflammation caused by cigarette smoke and fume exposure. It improves airway remodeling, reduces acute exacerbations, and reduces bacterial load. Higher doses are more effective than medium doses. Blood EOS (Eosinophil Oxygen) is a responsive biomarker for ICS delivery, and treatment significantly reduces EOS count at one year. Budesonide inhalation through different devices improves lung function, with patients with a PIF ≥ 40L/min experiencing better improvement compared to those with a PIF < 40L/min.

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