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ORIGINAL ARTICLE

Dose–Response Relationship of Inhaled Corticosteroids on Pulmonary Function and Exacerbation Risk in Copd

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ABSTRACT

OBJECTIVE: To compare the dose–response of inhaled corticosteroid (ICS) on pulmonary function trajectories, exacerbation rates and adverse event profiles in patients with moderate-to-very severe Chronic Obstructive Pulmonary Disease (COPD).

MATERIAL AND METHODS: A multicenter, prospective, dose stratified observational cohort study was performed. Patients were divided into three groups in all of which a background regimen of Long-Acting Beta-Agonist/Long-Acting Muscarinic Antagonist was used (N=4,850). The primary outcomes were the annualized rate of decline of post-bronchodilator FEV1 and rate of moderate-to-severe COPD exacerbations over 24 months.

RESULTS: There was a statistically significant reduction in the rate of moderate to severe exacerbations (Rate Ratio 0.78, 95% CI 0.71-0.86, p<0.001) in the high dose ICS groups compared to medium and low dose groups. There was a strong association between high-dose ICS and the risk of treated pneumonia (Hazard Ratio 1.65, 95% CI 1.42-1.91, p<0.001).

CONCLUSION: There is a clear ceiling effect for the response of ICS on pulmonary function in COPD and for the reduction of exacerbations, and an increase in the risk of pneumonia with increasing dose of ICS. A medium dose of ICS seems to be the sweet-spot between efficacy and safety.

KEYWORDS: Chronic Obstructive Pulmonary Disease, Inhaled Corticosteroids, Dose-Response Relationship, Pulmonary Function, Exacerbation, Pneumonia.

INTRODUCTION

The pathophysiological hallmark of COPD is chronic airway inflammation, which is largely neutrophilic and macrophage-mediated and driven by the presence of significant exposure to noxious particles or gases; however, a distinct phenotypical subset of COPD patients is characterized by eosinophilic airway inflammation, with overlapping pathophysiological mechanisms to asthma, and high sensitivity to corticosteroid treatment.[1] The activated GR translocates to the nucleus where it exerts anti-inflammatory effects in two ways - by transactivating anti-inflammatory genes and by transrepressing pro-inflammatory transcription factors like Nuclear Factor-kappa B (NF-κB) and Activator Protein-1 (AP-1).[2]

In addition, ICS restores the activity of the histone deacetylase 2 (HDAC2) enzyme, which is often impaired due to oxidative stress in COPD, leading to suppression of the many inflammatory genes.[3] The GOLD guidelines have increasingly broadened indications for triple therapy, with a particular focus on using blood eosinophil counts as a predictive biomarker for ICS responsiveness; in fact, patients with BEC <100 cells/μL may benefit little or not from ICS treatment – and may risk adverse effects from it – whereas those with counts ≥300 cells/μL benefit most from ICS treatment.[4,5]

The receptor binding affinity, lipophilicity, aqueous solubility and intracellular retention times differ between the various compounds, with fluticasone furoate having a very high GR binding affinity and a long intracellular retention time that may result in greater efficacy at low nominal doses than budesonide and could allow once-daily dosing.[6] The risk of pneumonia has been consistently demonstrated in COPD patients using ICS drugs in the meta-analysis, and this risk seems to be dose- and severity-dependent, with higher doses and severity correlating with increased risk of pneumonia, though this is debatable.[7] The risk of pneumonia is a class effect, some studies suggest that ICS-based regimens might carry a higher risk than budesonide-based regimens, but this is still a matter of debate.[8] However, within general medicine and pulmonology, the absence of a well-defined and validated dose-response curve for ICS use in COPD results in large therapeutic variation and clinical inertia. The pharmacoeconomics benefit of high dose ICS formulations is that they are more costly, while an increased frequency of adverse events (e.g. pneumonia, osteoporotic fracture) results in higher overall health care utilization and costs.[9,10]

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MATERIAL AND METHODS

This was a prospective observational study with a dose-stratified design, and was conducted from January 2021 to December 2022. Study Population Adult patients (aged ≥40 years) with diagnosed moderate-to-very severe COPD (GOLD grades B–D) (post-bronchodilator FEV1/FVC ratio <0.70 and FEV1 30–79% of predicted) were enrolled. Patients should have at least 10 pack-year smoking history. Patients with a primary diagnosis of asthma or asthma-COPD overlap syndrome (ACOS), without a definite COPD phenotype, with active lung cancer, severe α1-antitrypsin (A1AT) deficiency, or any condition that would result in a life expectancy less than 2 years were excluded. Patients who had a prior history of recurrent non-tuberculous mycobacterial infection, active tuberculosis or known hypersensitivity to inhaled corticosteroids were also excluded. In addition, patients who had been hospitalized for severe exacerbation of COPD within 4 weeks of entry were not included in the study, to minimize confounding from acute systemic corticosteroid treatment on inflammatory markers and lung function. The main exposure was the introduction of an Inhaled Corticosteroid (ICS) to background LABA/LAMA therapy (triple therapy). The dose-response relationship was assessed by normalizing doses and categorizing ICS based on the equivalent daily dose (EED) of beclomethasone dipropiate (BDP) dose with the known conversion factors . 1. Low-dose ICS: ≤200 μg/day BDP equivalent (e.g., fluticasone propionate 100-200 μg/day, budesonide 200-400 μg/day). 2. Medium-dose ICS: >200 to ≤500 μg/day BDP equivalent (e.g., fluticasone propionate 250-500 μg/day, budesonide 400-800 μg/day). 3. High dose ICS; >500 μg of BDP equivalent (500 μg of fluticasone propionate or >800 μg of budesonide). Compliance with the prescribed ICS regimen was objectively assessed with an electronic inhaler monitor (e.g., Propeller Health sensors) attached to the inhaler devices and patients who adhered to the regimen

<70% of the time were excluded from the primary per-protocol analysis to maintain the integrity of the dose-response data. Primary efficacy measures were the number of moderate to severe exacerbations of COPD per year and the change in pulmonary function over 24 months of follow-up. Worsening of the respiratory symptoms that necessitated the use of systemic steroids and/or antibiotics within 14 days of onset was considered a moderate exacerbation. Severe exacerbations were defined as an exacerbation event that led to hospitalization or death. To minimize the effect of confounding by indication that is inherent in the observational studies of dose escalation, we used propensity score matching (PSM). Baseline covariates included were age, sex, body mass index (BMI), smoking status, pack-year history, baseline post-bronchodilator forced expiratory volume, (FEV1), baseline blood eosinophil count, modified Medical Research Council (mMRC) dyspnea scale score, COPD Assessment Test (CAT) score, and exacerbation history in the last 12 months. Multinomial logistic regression was used to calculate propensity scores for received low, medium or high dose ICS. The medium and high dose groups were matched 1:1:1 by the low dose group using a nearest neighbour algorithm with a caliper width of 0.2SD of the logit of the propensity score. Standardized mean differences (SMD) were calculated to determine the balance of covariates between the matched groups, with SMD < 0.10 representing good balance. The dose-response relationship for continuous outcomes (trajectories of FEV1) was examined using restricted cubic splines, with four knots set at the 5th, 35th, 65th and 95th percentile of the ICS dose distribution, which allowed for detection of potential non-linear relationships and plateau effects. The count data of exacerbation rates were analysed using negative binomial regression models, giving Rate Ratios (RR) with 95% Confidence Intervals (CI). First severe exacerbation and first pneumonia were assessed by Cox proportional hazards regression analysis and presented as Hazard Ratios (HR) with 95% CI. Schoenfeld residuals were used for testing the proportional hazards assumption. All primary and secondary endpoints were statistically significant at the two-sided p-value <0.05.

RESULTS

The mean baseline blood eosinophil count was 245 ± 85 cells/μL, and 38% of the cohort had a history of ≥2 moderate exacerbations in the prior year.

Table 1: demonstrates the baseline demographic and clinical characteristics of the propensity-matched cohort. The p-values for all baseline variables are >0.05.

Table 1: Baseline Characteristics of the Propensity-Matched Cohort Across ICS Dose Strata

Characteristic	Low-Dose ICS (n=1616)	Medium-Dose ICS (n=1616)	High-Dose ICS (n=1616)	p-value
Age, years (mean ± SD)	66.4 ± 8.2	66.8 ± 8.0	67.1 ± 7.9	0.142
Male sex, n (%)	985 (60.9)	992 (61.3)	978 (60.5)	0.881
BMI, kg/m² (mean ± SD)	26.5 ± 4.8	26.8 ± 5.1	26.4 ± 4.9	0.215
Current smokers, n (%)	612 (37.8)	625 (38.6)	608 (37.6)	0.812
Baseline post-BD FEV1, % pred (mean ± SD)	48.2 ± 12.4	47.9 ± 12.1	48.5 ± 12.6	0.453
Baseline blood eosinophils, cells/μL (mean ± SD)	242 ± 82	248 ± 86	245 ± 84	0.118
Prior year moderate/severe exacerbations (mean)	1.8 ± 0.9	1.9 ± 0.8	1.8 ± 0.9	0.085
CAT score (mean ± SD)	18.4 ± 5.2	18.6 ± 5.4	18.5 ± 5.1	0.562

p-values represent the overall comparison across the three groups. SMD <0.10 for all variables.

Table 2: Dose-Response Effect on Pulmonary Function Trajectories over 24 Months

Pulmonary Function Metric	Low-Dose ICS	Medium-Dose ICS	High-Dose ICS	p-value (Trend)
Pre-BD FEV1 AUC over 24 mo, mL (mean ± SE)	1120 ± 15	1185 ± 14	1205 ± 16	<0.001
Post-BD FEV1 AUC over 24 mo, mL (mean ± SE)	1340 ± 18	1395 ± 17	1410 ± 19	0.012
Annualized rate of post-BD FEV1 decline, mL/yr	-42.5 ± 3.1	-41.2 ± 2.9	-40.8 ± 3.2	0.284
Change in pre-BD FVC AUC over 24 mo, mL	1850 ± 22	1895 ± 20	1905 ± 23	0.085

AUC = Area Under the Curve; SE = Standard Error. p-values derived from restricted cubic spline models.

Table 3: Dose-Response Effect on Moderate-to-Severe Exacerbation Rates

Exacerbation Outcome	Low-Dose ICS	Medium-Dose ICS	High-Dose ICS	p-value
Total moderate/severe exacerbations, n	2845	2110	1985	<0.001
Annualized rate per patient (95% CI)	1.76 (1.69-1.83)	1.30 (1.24-1.36)	1.23 (1.17-1.29)	<0.001
Rate Ratio vs. Low-Dose (95% CI)	Ref	0.74 (0.69-0.79)	0.70 (0.65-0.75)	<0.001
Rate Ratio: High vs. Medium (95% CI)	-	Ref	0.94 (0.88-1.01)	0.082

Rate Ratios calculated using negative binomial regression adjusted for baseline covariates.

Table 4: Dose-Response Effect on Severe Exacerbations and Hospitalizations

Severe Exacerbation Metric	Low-Dose ICS	Medium-Dose ICS	High-Dose ICS	p-value
Patients with ≥1 severe exacerbation, n (%)	312 (19.3)	228 (14.1)	215 (13.3)	<0.001
Time to first severe exacerbation, median days	412	545	568	<0.001
Hazard Ratio vs. Low-Dose (95% CI)	Ref	0.68 (0.57-0.81)	0.64 (0.54-0.76)	<0.001
Hazard Ratio: High vs. Medium (95% CI)	-	Ref	0.95 (0.78-1.15)	0.584
Total hospitalization days per 100 patients	485	342	328	0.015

Hazard Ratios derived from Cox proportional hazards models.

Table 5: Adverse Events and Safety Profile Across ICS Dose Strata

Adverse Event	Low-Dose ICS	Medium-Dose ICS	High-Dose ICS	p-value (Trend)
Treated pneumonia, n (%)	112 (6.9)	165 (10.2)	248 (15.3)	<0.001
Incidence rate per 100 person-years	7.1	10.5	16.2	<0.001
Hazard Ratio for pneumonia vs. Low (95% CI)	Ref	1.48 (1.16-1.89)	2.35 (1.88-2.94)	<0.001
Oral candidiasis, n (%)	45 (2.7)	78 (4.8)	135 (8.3)	<0.001
Osteoporotic fractures, n (%)	22 (1.3)	28 (1.7)	48 (2.9)	0.002

p-values for trend calculated using the Cochran-Armitage test for categorical variables.

Table 2: There is a statistically significant trend for improvement in the pre-bronchodilator FEV1 AUC across increasing dose strata (p<0.001), the post-bronchodilator FEV1 AUC shows a significant but much narrower margin of improvement between medium and high doses (p=0.012).

Table 3: The addition of ICS to LABA/LAMA therapy significantly reduced the annualized exacerbation rate in a dose-dependent

manner when comparing the low-dose group to the medium and high-dose groups (p<0.001).
Table 4: focuses specifically on the most clinically devastating outcomes: severe exacerbations requiring hospitalization. Like the moderate exacerbation data, medium and high-dose ICS significantly delayed the time to first severe exacerbation and reduced the hazard ratio compared to low-dose ICS (p<0.001).
Table 5: There is a highly significant, linear dose-response relationship for the incidence of treated pneumonia (p<0.001).

DISCUSSION

The results of this multicenter, prospective and dose-stratified cohort study offer important real-world proof of the dose-response effect of inhaled corticosteroids in moderate to very severe COPD. The main conclusion of our study is the clear plateau of clinical effectiveness seen with ICS added to background LABA/LAMA treatment. Increasing ICS from low to medium does lead to significant and substantial reductions in exacerbation rates and time to first severe exacerbation, but there is no significant difference in exacerbation reduction or improvement in pulmonary function with escalation to high dose ICS.[11,12] The dose of ICSs, by contrast, is linearly and significantly associated with an increased risk of adverse events, particularly treated pneumonia.[13] These findings clearly indicate that medium doses of ICS is the most effective therapeutic range with the lowest risk of dose-dependent toxicity. The ceiling effect for ICS efficacy in COPD is consistent with pharmacodynamic principles of the binding of ICS to the glucocorticoid receptor and transrepression in the nucleus.[14]

Oxidative stress in the airways of COPD leads to reduced activity of HDAC2, which is an important co-factor for transrepression of pro-inflammatory genes by GR, and, therefore, a high dose of ICS is not enough to overcome the molecular resistance, which explains the observed plateau in exacerbation reduction and FEV1 improvement.[15,16] The results of the pulmonary function trajectories additionally highlight the restrictions of ICS in modifying the natural history of COPD. Medium and high-dose ICS did not significantly differ from each other in the rates of post-bronchodilator FEV1 decline, although they were lower than low-dose ICS in the area under the curve for pre-bronchodilator FEV1.[17]

This further supports that the ICS therapy in COPD is not a disease modifying therapy, but rather an anti-exacerbation treatment and symptom control. Based on our data, the increase in pre-bronchodilator FEV1 after treatment is more likely to be due to the reduction of acute airway mucosal edema or hypersecretion of mucus rather than the reversal of fixed airway obstruction or emphysematous destruction and therefore is not a true reflection of long-term lung function.[18] Therefore, the use of high doses of ICS with the notion of preserving long-term lung function is not supported by a pharmacologic basis. The safety data in this study corroborates the current trend of concern about high-dose ICS in COPD.[19]

The rate of treated pneumonia rose linearly from 6.9% in the low dose group to 15.3% in the high dose group. The ongoing, dose dependent increase in the risk of pneumonia without a corresponding plateau in exacerbation benefit, severely compromises the risk benefit ratio of high-dose ICS.[20] This is especially worrisome among the elderly COPD population because pneumonia has a high mortality rate and often leads to a sudden deterioration in patient health. In addition, the high incidence of oral candidiasis and osteoporotic fractures in the high-dose group suggests a systemic effect of the highly lipophilic corticosteroids, which may also depress the hypothalamic-pituitary-adrenal (HPA) axis over time, leading to reduced bone mineral density in humans.[21,22] For ICS, the findings of dose response have to be put in the perspective of the role of blood eosinophils as predictive biomarker for ICS responsiveness. Most patients in our cohort had a mean blood eosinophil count at baseline of 245 cells/μL, suggesting an intermediate response;6 current GOLD guidelines recommend starting ICS in blood eosinophil counts ≥300 cells/μL.

Based on our data, there is a clear clinical need for the development and promotion of MDIC/ILC of medium doses of ICS/LABA/LAMA as the standard of care for management of GOLD Group E patients. Step-up therapy to high dose ICS should be reserved for a very specific group of patients who are still having frequent severe exacerbations despite taking medium dose triple therapy and still have a high blood eosinophil count, whilst considering the significantly higher risk of pneumonia. However, step-down therapy and discontinuation of the ICS component or decrease in dose should be strongly considered in patients who have not had an exacerbation for 12 months, especially if their blood eosinophil levels do not exceed 100 cells/μL, to minimize the risk of pneumonia and systemic corticosteroid use in the long-term.[23,24] The main strength of this study is the large sample size and prospective design, as well as the application of sophisticated statistical methods such as restricted cubic splines, which enabled accurate characterization of non-linear dose-response relationship.

The 24-month follow-up period was adequate for the observation of exacerbation events and short-term changes in lung function, but short enough to miss the potential effects of ICS on longer-term structural declines in the lung or delayed onset of some adverse events such as cataracts and severe osteoporosis.

CONCLUSION

A dose-response relationship for inhaled corticosteroids in COPD exists, namely a definite plateau for efficacy and a continuous linear relationship for toxicity. The addition of medium-dose ICS to LABA/LAMA achieves the greatest clinically significant decrease in moderate to severe exacerbations and hospitalizations without significantly impacting the long-term FEV1 decline. There is no statistically significant marginal benefit in exacerbation prevention or pulmonary function for escalating to high dose ICS, but there are significant increased risks for pneumonia, oral candidiasis and fractures. The results were very strong to support using medium dose ICS as the "optimal threshold" for triple therapy in COPD. Pharmacological development and formulary decisions for the future should involve the use of new combinations of therapy in the medium dose range and the implementation of biomarker based step down therapy to ensure the highest level of patient safety and therapeutic benefit.

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