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Inhaled corticosteroids in asthma and chronic obstructive pulmonary disease combined phenotype: when to use and what to expect?

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Abstract

The term "asthma-chronic obstructive pulmonary disease (COPD) combined phenotype" describes patients with persistent airflow limitation and features of both asthma and COPD. There is a lack of data on effective treatments for this group, often excluded from asthma or COPD trials. Inhaled corticosteroids (ICS) are standard for asthma, while bronchodilators are key for COPD. This study is a prospective interventional study that included 43 patients diagnosed with the asthma-COPD overlap phenotype, as per Sin *et al*. criteria, who were treated as COPD previously and followed over 1 year. These patients received additional treatment with a moderate-dose ICS metered-dose inhaler, beclamethasone 800 mcg daily, in addition to their optimal inhaled bronchodilator therapy. Follow-up spirometry, along with reversibility, fractional exhaled nitric oxide (FeNO), and blood investigations like total eosinophil count (TEC) and immunoglobulin E (IgE) were done; sputum eosinophils were measured, and a history of exacerbations was noted. These parameters were compared with baseline values obtained prior to the initiation of ICS to evaluate the impact of the intervention. Among the 43 individuals in the study population, the majority fell within the age group of 60-69 years. The addition of ICS to bronchodilators over a 1-year period resulted in significant improvements in their forced expiratory volume in one second. Additionally, there was a notable reduction in the FeNO level, along with decreases in the TEC, serum IgE levels, and sputum eosinophils. Although the number of exacerbations decreased during the study period in this subgroup, this reduction did not reach statistical significance. Based on these findings, the study suggests that ICS should be considered as an adjunct to inhaled bronchodilators for the management of stable COPD patients exhibiting features of the asthma-COPD combined phenotype.

Key words: asthma-COPD combined phenotype, FeNO, serum IgE, inhaled corticosteroid, total eosinophil count.

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Introduction

The term "asthma-chronic obstructive pulmonary disease (COPD) combined phenotype" is used to collectively describe patients who have persistent airflow limitation along with clinical features consistent with both asthma and COPD. This condition, known as asthma-COPD overlap (ACO) [1,2], has sparked debate due to evidence showing a significant number of patients exhibiting characteristics of both diseases in clinical practice [1]. In 2015, a consensus document jointly developed by the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease proposed a clinical description for patients showing features of both asthma and COPD, naming this entity the ACO syndrome (ACOS) [2-4]. However, this approach to the definition is imprecise because it does not specify how many of these features are necessary or whether they hold equal diagnostic relevance for ACO.

Eosinophilic airway inflammation is consistently observed in ACO. Evidence has emerged using various markers such as eosinophils in induced sputum and peripheral blood, as well as fractional exhaled nitric oxide (FeNO) [5,6]. The presence of eosinophilic airway inflammation in these patients may have therapeutic implications, potentially recommending the use of inhaled corticosteroids [4]. FeNO evaluation in managing ACO patients is a current trend, with an ongoing need for further study. Chen *et al*. found an optimal FeNO cut-off of 22.5 ppb, offering 70% sensitivity and 75% specificity for distinguishing ACO from COPD [7]. Takayama *et al.* suggested combining FeNO>25 ppb with blood eosinophil counts >250 cells/µL for this differentiation [8]. Debate surrounds ACO patients' exacerbation rates and severity. While evidence varies, a prevailing view suggests ACO patients experience more frequent and severe exacerbations, leading to higher mortality and healthcare costs [5,6,9]. This underscores the need for meticulous management to mitigate individual and systemic burdens.

Generally, inhaled corticosteroids (ICS) are pivotal in treating asthma, while inhaled bronchodilators are essential for managing COPD [3,4]. However, there is limited data on effective treatments for ACOS. Clinical studies often exclude ACOS patients,

hindering the application of trial findings to this population. Hence, this study is carried out to explore the changes in forced expiratory volume in the first second (FEV1), bronchodilator reversibility, eosinophilic inflammatory markers like FeNO, blood and sputum eosinophils, serum immunoglobulin E (IgE), and track exacerbation frequency and hospitalizations before and after initiating ICS treatment in ACO phenotype subjects.

Materials and Methods

This study is a prospective interventional study conducted with approval from the institutional ethical committee. A total of 171 stable COPD patients participated in the study. All patients were using inhalers that contained bronchodilators, with the majority relying on short-acting β-agonists delivered *via* metered-dose inhalers (MDIs). None of the participants was using ICS. They underwent screening using a comprehensive set of tests to identify a subgroup with the ACO phenotype, based on the criteria established by Sin *et al*. [10].

Major and minor criteria

The major criteria were:

1. Persistent airflow limitation post-bronchodilator FEV1/forced vital capacity <0.7 in an individual of 40 years of age or older.
2. At least 10 pack years of tobacco smoke or equivalent indoor or outdoor air pollution exposure.
3. Documented history of bronchial asthma before 40 years of age.
4. Bronchodilator reversibility (BDR) >400 mL FEV1.

The minor criteria were:

1. Documented history of allergic rhinitis or atopy.
2. BDR of FEV1 >200mL and >12% from baseline value on 2 or more occasions.
3. Peripheral blood eosinophil count of >300 cells per microlitre.

The presence of 3 major and 1 minor criteria would qualify for the diagnosis of ACO.

Out of 171 screened patients, 125 were diagnosed with COPD alone, and 46 were identified as having the asthma-COPD combined phenotype; however, 3 patients were lost to follow-up.

All stable prediagnosed ACO without any co-morbidities, giving consent to be part of the study, were included. Those subjects who were non-adherent to treatment, unable to perform spirometry, and with significant comorbidities like ischemic heart disease, lung cancer, active infections in the lungs, associated bronchiectasis, chest wall deformities, associated pleural or occupational lung diseases, or eosinophilic lung disorders were excluded from the study.

Hence, 43 subjects were followed up over 1 year. These patients received a moderate dose of ICS (MDI beclamethasone 800 mcg daily) in addition to their optimal inhaled bronchodilator therapy. The history of acute exacerbations was recorded. Follow-up blood investigations, including total eosinophil count (TEC) and IgE levels, and sputum eosinophils were measured at the investigating institute. Follow-up spirometry and reversibility tests were performed according to American Thoracic Society/European Respiratory Society standards [11]. Follow-up FeNO measurements were conducted using the FeNO-HYPAIR device (MEDI SOFT). All assessments were compared with baseline values obtained before initiation of ICS. Data were tabulated and analyzed accordingly.

Statistical analysis was done using Epi Info (CDC, Atlanta, GA, USA) version 7.2.1.0 software. Categorical variables were expressed as frequency and percentage and analyzed with the McNemar test for before-after comparisons. Continuous variables, presented as mean and standard deviation, were analyzed using paired t-tests. A p-value less than 0.05 indicated statistical significance.

Results

Among the 43 ACO patients, 86% (n=37) were male, and 14% (n=6) were female. The largest age group was 60-69 years (46.5%), while the smallest was 30-39 years (4.7%). The mean age of the patients was 59.37 years. Post-medication FEV1 increased from 1206±488 mL (50.4±18.4% predicted) to 1388±567.7 mL (54.56±17.16% predicted); a significant increase of 182.1±237.6 mL (4.16±9.1% predicted) after adding ICS to inhaled bronchodilators in our ACO subjects was observed, with p<0.001 (Table 1). Before ICS treatment, 11.6% of subjects had reversibility ≥400 mL, increasing to 41.9% after ICS with p<0.001 (Table 2).

Table 1. Change in forced expiratory volume in the first second (mL) among asthma-chronic obstructive pulmonary disease overlap patients.

	Baseline	Follow-up
Mean±SD	1206±488 (50.4±18.4% predicted)	1388±567.7 (54.56±17.16% predicted)
Change	182.1±237.6 (4.16±9.1% predicted)	
Change in %	16% (12% in % of predicted)	
p	<0.001 (S)	

SD, standard deviation.

Table 2. Distribution of study subjects according to post-bronchodilator reversibility (mL).

Post bronchodilator reversibility (mL)	Baseline		Follow-up	
	n	%	n	%
<400 mL	38	88.4	25	58.1
≥400 mL	5	11.6	18	41.9
Total	43	100	43	100

McNemar's Test - Chi-square=7.562 with 1 degree of freedom; p=0.006 (S).

After 1 year of treatment with ICS, FeNO levels decreased significantly by 52.53% (p<0.001), TEC decreased by 31.51% (p<0.001), and IgE levels decreased by 9.8% (p=0.030), indicating reduced eosinophil-mediated inflammation (Table 3). Initially, 23.3% of the ACO study population had sputum eosinophils >2.5%. After adding ICS to the bronchodilators, this proportion decreased significantly to 2.3%, p=0.016 (Table 4).

Initially, 79.1% of the study population (n=34) had no exacerbations before ICS treatment, which increased to 88.4% (n=38) after ICS. The proportion experiencing one exacerbation per year decreased from 11.7% (n=5) to 4.6% (n=2), while those with two or more exacerbations decreased from 9.3% (n=4) to 7% (n=3) after ICS. However, these changes were not statistically significant (p=0.494) (Table 5). None of the ACO study population experienced exacerbations requiring hospitalization before or after the addition of ICS.

Discussion

In our study of 43 ACO patients, ages ranged from 33 to 75 years, with the majority (46.5%) aged 60 to 69 years and a mean age of 59.37 years. Our findings contrast with previous studies that included both asthma and COPD patients, which typically found ACO patients to be younger [12-14]. Our study comprised 86% male and 14% female patients, consistent with some previous findings [13,15] that ACO patients are predominantly male, although other studies have reported higher female proportions, likely due to differing study populations that included asthma alongside COPD.

After adding ICS to inhaled bronchodilators in ACO subjects, there was a significant increase in post-bronchodilator FEV1. Studies by Jia-Xi Feng *et al*. and Suh-Young Lee *et al.* showed improvements in pulmonary function parameters, including FEV1, following ICS treatment [16,17]. However, Barnes *et al.* found no significant difference in FEV1 in their study [18].

Prior to ICS treatment, 11.6% of the study population had post-BDR ≥400 mL, which increased significantly to 41.9% after ICS addition. Studies by Barrecheguren *et al.* and Renthlei *et al.* support these findings, indicating a favorable impact of ICS on pulmonary function parameters in ACO patients [13,19]. These findings support our observation of the beneficial impact of adding ICS on pulmonary function parameters in this subset of patients.

Kitaguchi *et al.* observed higher peripheral and sputum eosinophil counts in COPD with asthma [20]. In our ACO study, adding ICS led to a significant reduction in blood eosinophil counts (p=0.001) and a 39.9% decrease in sputum eosinophils. Previous studies by Steven Pasco *et al.* and Takayama *et al.* have shown that eosinophil counts correlate with FEV1 improvements in response to ICS treatment, supporting eosinophils as a biomarker for ICS responsiveness [8,21].

Kobayashi *et al.* found no change in total serum IgE levels with ICS therapy (p=0.004) [22]. In our study of ACO patients, adding ICS led to a significant reduction in serum IgE levels. Feng *et al.* also observed significant reductions in total serum IgE levels following ICS treatment (p<0.05) [16].

FeNO levels in our ACO population decreased significantly by 52.53% after adding ICS. Following ICS therapy, the proportion of ACO patients with FeNO >25 ppb at 50 mL/s decreased from

Table 3. Changes in markers of eosinophilic inflammation after adding inhaled corticosteroids to bronchodilators.

Parameter	Baseline	At 1 year follow-up	Change observed	Change	p
FeNO (ppb)	27.47±30.57	13.09±22.45	14.37±18.68	52.53%	<0.001 (S)
TEC (cells/cumm)	380.7±213.7	211.3±170.7	169.3±239.1	31.51%	<0.001 (S)
IgE (IU/mL)	592.9±729	429±664.4	163.9±479.8	9.8%	0.030 (S)

FeNO, fractional exhaled nitric oxide; TEC, total eosinophil count; IgE, immunoglobulin E.

Table 4. Distribution of study subjects according to the presence of sputum eosinophil (>2.5%).

Sputum eosinophil (>2.5%)	Baseline		Follow-up	
	n	%	n	%
Present	10	23.3	1	2.3
Absent	33	76.7	42	97.7
Total	43	100	43	100

McNemar's Test - Chi-square=5.818 with 1 degree of freedom; p=0.016 (S).

Table 5. Distribution of study subjects according to acute exacerbations.

Acute exacerbations	Baseline		Follow-up	
	n	%	n	%
0	34	79.1	38	88.4
1	5	11.7	2	4.6
2 or more	4	9.3	3	7.0
Total	43	100	43	100

Chi-square=3.182 with 3 degrees of freedom; p=0.494 (NS).

34.9% to 14%. Takayama *et al.* observed higher FeNO levels in ACO patients compared to COPD patients and noted a significant reduction in FeNO levels after ICS treatment [8]. Similarly, Yamaji *et al.* found a significant decrease in FeNO after 12 weeks of ICS treatment in their study of ACO patients [23].

In our ACO study, no patient required hospitalization for exacerbations. However, adding ICS did not significantly reduce the frequency of exacerbations. Similar findings were noted by Izquierdo-Alonso *et al.,* who found no significant differences in exacerbation rates between long-acting β-agonist (LABA) and LABA+ICS treatments [24]. Siddiqui *et al*. observed that COPD patients with higher eosinophil counts experienced more exacerbations, indicating potential benefits from additional ICS therapy in these cases [25].

Conclusions

In patients with ACO, adding ICS to bronchodilators improves post-bronchodilator FEV1 and significantly reduces markers of eosinophilic inflammation like TEC, sputum eosinophils, serum IgE, and FeNO. However, there were no significant reductions in exacerbations observed. Based on these findings, ICS should be considered alongside inhaled bronchodilators for managing stable COPD patients with the ACO phenotype.

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