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Responsiveness to inhaled corticosteroid treatment in patients with asthma–chronic obstructive pulmonary disease overlap syndrome

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ABSTRACT

Background: Inhaled corticosteroid (ICS) is recommended in the management of patients with asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS), but its effectiveness has not been clearly proved.

Objective: To evaluate whether ICS has effects on outcomes of ACOS.

Methods: In this observational 12-year retrospective cohort study involving 125 patients with ACOS from Seoul National University Hospital, the annual rate of decrease in forced expiration volume in 1 second, the incidence rate of severe exacerbation, and overall mortality in an ICS-treated group were compared with those in a non-ICS-treated group.

Results: Of 125 patients with ACOS, 90 and 35 were categorized to the ICS and non-ICS treatment groups, respectively. There were no significant differences between the 2 groups in the annual rate of decrease in forced expiration volume in 1 second (9.61 mL/year in ICS treatment group vs 15.68 mL/year in non-ICS treatment group, $P = .598$). Compared with the non-ICS treatment group, the ICS treatment group did not show a decrease in the risk of severe exacerbation (adjusted incidence rate ratio 1.24, 95% confidence interval 0.44–3.46). Time to death also did not differ between the 2 groups. Even when analyses with propensity score matching were performed, the results were similar.

Conclusion: In the management of ACOS, the use of ICS was not significantly associated with improvements in the annual rate of decrease in forced expiration volume in 1 second, the incidence of severe exacerbations, and overall mortality compared with the non-ICS treatment group.

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Introduction

Asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) occurs when patients with COPD and a history of cigarette smoking have an asthmatic component, although ACOS has not been clearly defined.^{1,2} The definition of ACOS has been simplified into patterns of abnormal airway physiology, which in conjunction with symptoms can be used to facilitate clinical recognition.³ It could be accepted that at a physiologic level, patients with ACOS have 2 characteristics. One is an incompletely reversible airflow obstruction that can be defined by a post-bronchodilator forced expiratory volume for 1 second (FEV₁) to forced vital capacity (FVC) ratio of less than 70%. The other is an increased variability of airflow obstruction, which can be

determined by increased bronchodilator responsiveness or bronchial hyperresponsiveness demonstrated by a bronchial challenge test.³

Clinicians are often faced with ACOS, and the prevalence is reported as up to 25% in adults with obstructive airway diseases.² In the Proyecto Latino-Americano de Investigación en Obstrucción Pulmonar (PLATINO) study of obstructive lung diseases, including asthma, COPD, and ACOS, ACOS was reported in 11.6% of cases. Furthermore, patients with ACOS had more respiratory symptoms, worse lung function, and greater use of respiratory medications, more hospitalizations, and more exacerbations.⁴ However, treatment is based on extrapolation of data derived from studies in patients with asthma or COPD alone owing to a lack of studies in those with coexisting asthma and COPD.^{2,5} Spanish and Canadian guidelines have suggested that inhaled corticosteroid (ICS) treatment could be justified in the management of COPD combined with asthma,^{6,7} and the Japanese Respiratory Society has recommended that ICS should be used in cases of COPD complicated by asthma, regardless of the severity of COPD.⁸ ICS is the most potent and

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effective anti-inflammatory medication in the management of asthma, and its clinical effects include improvement in prevention of exacerbations, hospitalizations, deaths from asthma, and possibly the attenuation of lung function loss in adults.⁹ Conversely, ICS treatment is controversial in COPD, and only medium doses of ICS in fixed combination (ICS plus a long-acting β_2 agonist [LABA] inhaler) are approved by the US Food and Drug Administration to control symptoms and decrease acute exacerbations.¹⁰ The American Thoracic Society and the European Respiratory Society also recommend the addition of ICS to a LABA or long-acting muscarinic antagonist, but only when the FEV₁ is less than 50% predicted or the patient has experienced an acute exacerbation in the past year.¹¹ The effectiveness of ICS in ACOS has not been investigated in a plenary study, and no sufficiently powered studies have been published demonstrating the role of ICS in ACOS.

The present study examined the effects of ICS in patients with ACOS by measuring the rate of decrease in lung function, the incidence rate of severe exacerbation, and overall mortality.

Methods

Study Subjects

An observational retrospective cohort study of patients with ACOS was conducted by analyzing data from Seoul National University Hospital (Seoul, Republic of Korea) from February 2000 through February 2012. ACOS was defined as a post-bronchodilator FEV₁/FVC less than 0.70 and a positive bronchodilator response or positive airway hyperresponsiveness. A positive bronchodilator response was defined as an increase in FEV₁ by at least 200 mL and 12% after inhalation of 200 μ g of salbutamol. Airway hyperresponsiveness was defined as having a provocation concentration that caused a decrease in FEV₁ of 20% or higher than 16 mg/mL.¹² Patients were eligible for inclusion if they were at least 40 years old, had a smoking history of at least 10 pack-years, and had undergone at least 2 spirometric assessments with bronchodilator reversibility testing at an interval of at least 1 $\pm$ 0.25 year.

Patients were excluded if they had alternative respiratory disorders that could have effects on lung function, such as significant bronchiectasis, tuberculosis-destroyed lung, or a history of thoracic surgery.

This study was approved by the institutional review board of Seoul National University Hospital (number 1312-124-547).

Measurement of Outcomes and Variables

Eligible patients were classified into 2 groups according to the use of ICS: an ICS treatment group and a non-ICS treatment group. The ICS treatment group included patients who received at least 1 dose of ICS or ICS–LABA during the follow-up period based on the number of prescription days for each inhaler as detailed in their medical records. The non-ICS treatment group included those who were never prescribed ICS or ICS–LABA during the study period.

The primary outcomes were the annual rate of decrease of FEV₁, the incidence rate of severe exacerbation, and overall mortality during the survey period. The mean follow-up period was 5.7 $\pm$ 2.5 years for the main analysis, and the mean observation duration for mortality was 7.9 $\pm$ 2.4 years. The average number of post-bronchodilator spirometric tests for each patient was 3.44 $\pm$ 1.76 during the study period.

A severe exacerbation was defined as ACOS-related hospitalization. Exacerbations that occurred within 14 days were defined as a single event to allow for a clear distinction between events. A death event was evaluated by linkage analysis between patients' anonymously coded identification data and the data on death from the Korean Ministry of Security and Public Administration.

Patients' demographic and clinical data were carefully reviewed. Drug usage and compliance were calculated by the medication possession ratio (MPR), which measures the percentage of time a patient has access to medication, using a variable duration denominator in the analysis for all patients and a fixed-duration (4 years) denominator in the 4-year analysis.

Statistical Analysis

The χ^2 test and Fisher exact test for comparison of categorical variables and the *t* test and Mann–Whitney *U* test for continuous variables were used to compare the baseline characteristics of the ICS and non-ICS treatment groups. Annual rates of decrease in FEV₁ were analyzed using a random-slope and random-intercept linear mixed model, which was similar to the analysis in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort.¹³ The incidence rates of severe exacerbation were compared between the 2 groups using Poisson regression or, if there was over-dispersion, negative binomial regression analyses. Overall mortality was compared using Kaplan–Meier estimates and Cox proportional hazards regression. Analyses were adjusted by covariates such as age, sex, smoking history (pack-years), body mass index, FEV₁ after bronchodilation (percentage of predicted value), bronchial reversibility (degree of percentage of change in FEV₁ after bronchodilation), and concomitant use of medication (LABA, long-acting muscarinic antagonist, short-acting β_2 agonist, short-acting muscarinic antagonist, and theophylline).

First, multivariable analysis was performed for all eligible patients, and then repeated comparison was performed using only patients matched by propensity score (PS). PS was calculated by logistic regression analysis with available covariates. Second, a sensitivity analysis was performed with the cutoff point set at an ICS MPR of 0.75, and a minimum 4-year follow-up, in the 2 groups: those with an ICS MPR less than 75% (*n* = 69) and those with an ICS MPR of at least 75% (*n* = 19). Incidence rates of severe exacerbation and lung function decrease during the first 4 years between the 2 groups (4-year analysis) were compared. This 4-year analysis was performed because a follow-up of at least 3 years is needed to monitor decreasing lung function and mortality.¹⁴ In fact, the Towards a Revolution in COPD Health (TORCH) trial, in which mortality was the primary outcome, observed participants for 3 years¹⁵ and the Understanding the Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, in which the annual rate of decrease in lung function was the primary end point, evaluated participants for 4 years.¹⁶

All statistical analyses were performed using STATA 13.0 (StataCorp, College Station, Texas). A *P* value less than .05 was regarded as indicating statistical significance.

Results

In total, 331 patients with COPD were screened, each having undergone at least 2 postbronchodilator spirometric assessments with bronchodilator reversibility testing during the study period. Of these, 125 patients who met the inclusion criteria of an ACOS diagnosis were identified, of whom 90 had a record of at least 1 ICS or ICS–LABA combination prescription and 35 were treated only with another medication, such as a LABA, a short-acting β_2 agonist, a short-acting muscarinic antagonist, or theophylline during the survey period (Fig 1). The mean follow-up period was 5.7 $\pm$ 2.5 years for the main analysis. In addition, the analysis was performed in patients who were followed up for at least 4 years (4-year analysis). To evaluate mortality, the mean follow-up duration was 7.9 $\pm$ 2.4 years, because these data were collected from the Korean Ministry of Security and Public Administration beyond the end of the study period. Thirty-one patients were eligible for PS matching in each group.

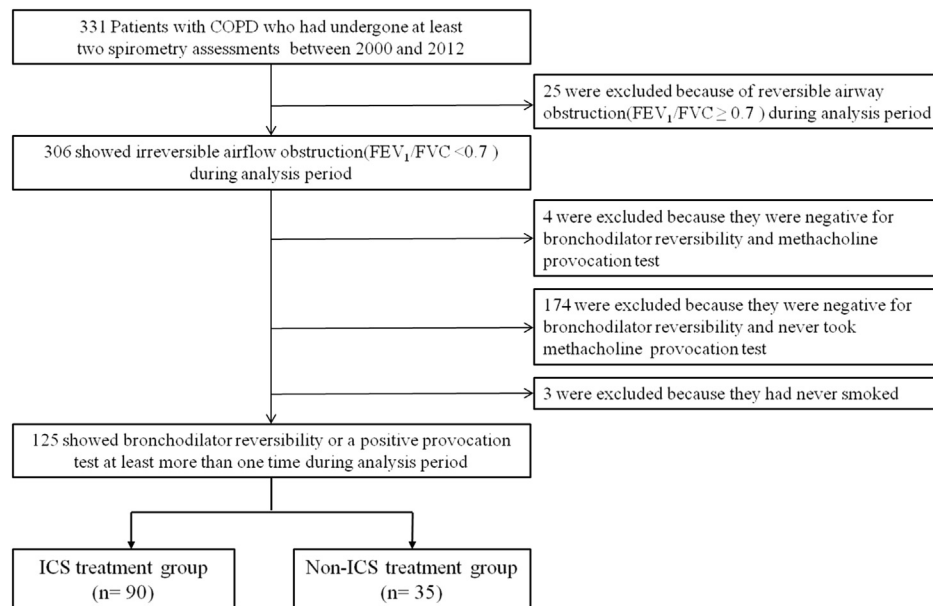


Figure 1. Flowchart of inclusion and exclusion of patients. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

Baseline Characteristics

Baseline characteristics of the enrolled patients were stratified by their usage of ICS or ICS–LABA (Table 1). In total, there were no significant differences in sex, age, smoking history, Global Initiative for Chronic Obstructive Lung Disease stage, pulmonary function after bronchodilator inhalation (FEV₁, FEV₁ percentage of predicted, FVC, FVC percentage of predicted), degree of response to β_2 agonist, and MPR for respiratory medication except for LABA and theophylline between the study groups. During the study period, body mass index, postbronchodilator FEV₁/FVC (percentage), and the MPR for LABA and theophylline were significantly

different between the 2 groups. However, the PS matching (1:1) resulted in 2 cohorts of 31 patients each, with no significant differences observed in characteristics after matching, and PS-matched groups consisted of male patients (Table 1).

Annual Rate of Decrease in FEV₁

Although the adjusted rate of decrease in mean post-bronchodilator FEV₁ was higher in the non-ICS treatment group, there were no significant differences between the 2 groups (9.61 mL/year in ICS treatment group vs 15.68 mL/year in non-ICS treatment group, $P = .598$). After PS matching, there were no

Table 1

Characteristics of 125 patients with asthma–chronic obstructive pulmonary disease overlap syndrome, grouped according to treatment^a

Characteristics	Total dataset			PS-matched dataset		
	ICS (n = 90)	Non-ICS (n = 35)	P value	ICS (n = 31)	Non-ICS (n = 31)	P value
Men	90 (100)	34 (97.1)	.280	31 (100)	31 (100)	—
Age (y)	65.2 ± 7.3	65.0 ± 5.1	.890	66.3 ± 7.2	65.0 ± 5.4	.420
Smoking (PY)	45.5 ± 17.7	48.3 ± 19.4	.427	50.0 ± 20.1	49.1 ± 20.4	.869
BMI (kg/m ²)	22.9 ± 2.8	24.3 ± 3.3	.017 ^b	23.9 ± 2.8	24.2 ± 3.2	.694
GOLD stage						
I	21 (23.3)	8 (22.9)		10 (32.3)	8 (25.8)	
II	42 (46.7)	22 (62.8)	.155	15 (48.4)	18 (58.1)	.786
III	27 (30.0)	5 (14.3)		6 (19.3)	5 (16.1)	
Postbronchodilator spirometry						
FEV ₁ (L)	1.65 ± 0.46	1.76 ± 0.45	.199	1.76 ± 0.49	1.77 ± 0.48	.913
FEV ₁ (% predicted)	62.1 ± 18.1	65.6 ± 15.5	.309	67.5 ± 19.6	65.5 ± 16.2	.663
FVC (L)	3.65 ± 0.65	3.52 ± 0.67	.312	3.45 ± 0.65	3.54 ± 0.65	.578
FEV ₁ /FVC (%)	45.46 ± 10.84	50.11 ± 8.77	.025 ^b	50.55 ± 9.48	49.54 ± 8.37	.661
Initial response to β_2 agonist						
Δ FEV ₁ (mL)	183.11 ± 119.69	175.67 ± 99.5	.814	169.35 ± 124.95	175.48 ± 105.07	.835
Percentage of change	15.1 ± 11.4	12.5 ± 8.6	.240	12.6 ± 9.6	12.5 ± 9.17	.955
Concomitant drugs (MPR)						
LABA	0.05 ± 0.01	0.01 ± 0.00	.038 ^b	0.03 ± 0.01	0.01 ± 0.01	.071
LAMA	0.12 ± 0.02	0.09 ± 0.03	.480	0.10 ± 0.03	0.10 ± 0.04	.971
SABA	0.10 ± 0.01	0.07 ± 0.03	.377	0.06 ± 0.02	0.07 ± 0.03	.927
SAMA	0.15 ± 0.02	0.10 ± 0.03	.239	0.12 ± 0.03	0.10 ± 0.04	.582
Theophylline	0.15 ± 0.02	0.05 ± 0.02	.011 ^b	0.06 ± 0.02	0.05 ± 0.02	.707

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; MPR, medication possession ratio; PS, propensity score; PY, pack-years; SABA, short-acting β_2 agonist; SAMA, short-acting muscarinic antagonist.

^aData are presented as number (percentage) or mean ± SD.

Table 2
Annual rate of decrease in FEV₁ in patients with asthma–chronic obstructive pulmonary disease overlap syndrome in non-ICS and ICS treatment groups during study period^a

	Total dataset (unadjusted)		Total dataset (adjusted)		PS-matched dataset	
	ΔFEV ₁ (mL/y), mean (95% CI)	P value	ΔFEV ₁ (mL/y), mean (95% CI)	P value	ΔFEV ₁ (mL/y), mean (95% CI)	P value
ICS	–7.25 (–34.21 to 5.07)	.521	–9.61 (–20.51 to 1.29)	.598	–12.88 (–34.49 to 8.73)	.972
Non-ICS	–14.57 (–17.91 to 3.40)		–15.68 (–35.41 to 4.06)		–12.37 (–31.15 to 6.41)	

Abbreviations: CI, confidence interval; Δ, change; FEV₁, postbronchodilator forced expiratory volume in 1 second; ICS, inhaled corticosteroid; PS, propensity score.

^aAdjusted by age, sex, body mass index, smoking history (pack-years), postbronchodilator FEV₁ (percentage of predicted), degree of initial response to β₂ agonist (percentage of change in FEV₁), and medication possession ratio of long-acting β₂ agonist, long-acting muscarinic antagonist, short-acting β₂ agonist, short-acting muscarinic antagonist, and theophylline.

significant differences between the study groups (12.88 mL/year in ICS treatment group vs 12.37 mL/year in non-ICS treatment group, $P = .972$; Table 2).

Incidence Rates of Severe Exacerbations

There were 18 individual episodes of severe exacerbation in 125 patients during the study period. Fifteen events occurred in the ICS treatment group, corresponding to an incidence rate of 0.06 per patient-year, whereas only 3 episodes occurred in the non-ICS treatment group, corresponding to a rate of 0.03 per patient-year. However, patients receiving ICS treatment did not have a higher incidence of severe exacerbation (relative risk 1.24, 95% confidence interval [CI] 0.44–3.46). After PS matching, the relative risk between the 2 groups showed no significant differences in the rate of exacerbation (relative risk 1.88, 95% CI 0.37–9.71; Table 3).

Overall Mortality

In total, 4 and 7 patients in the ICS and non-ICS treatment groups, respectively, died during the survey period, and each follow-up period was comprised of 263 and 719 patient-years, respectively. The proportion of survival to 10 years was not significantly different between the 2 groups ($P = .467$). After matching, the proportion of survival between the 2 groups did not differ significantly ($P = .965$). The proportions of survival during the survey period in the ICS and non-ICS treatment groups are shown in Figure 2.

Outcomes According to the MPR of ICS

In the 4-year analysis, after adjusting for differences in covariates, there were no statistically significant differences in the annual rate of decrease in FEV₁ (–17.5 mL/year in those with ICS MPR ≥75%, $n = 13$, vs –26.3 mL/year in those with ICS MPR <75%, $n = 44$, $P = .059$) and the incidence rate of severe exacerbation (ICS MPR ≥75%, $n = 19$, vs ICS MPR <75%, $n = 69$; 2.69, 95% CI 0.94–7.70) between the higher ICS MPR group and the lower ICS MPR group. The average days of prescription of ICS therapy was 291.4 ± 349.8 in those with an MPR less than 75% and $1,394.1 \pm 220.4$ in those with an MPR higher than 75% ($P < .001$) in the 4-year analysis.

Table 3
Incidence rates of severe exacerbation of patients with asthma–chronic obstructive pulmonary disease overlap syndrome

	Total dataset					PS-matched dataset				
	ICS (n = 90)		Non-ICS (n = 35)		IRR ^a for ICS vs non-ICS (95% CI)	ICS (n = 31)		Non-ICS (n = 31)		IRR ^a for ICS vs non-ICS (95% CI)
	n (%)	Rate ^b	n (%)	Rate ^b		n (%)	Rate ^b	n (%)	Rate ^b	
Severe exacerbation	15 (16.7)	0.06	3 (8.6)	0.03	1.88 (0.37–9.71)	4 (12.9)	0.02	2 (6.45)	0.01	1.24 (0.44–3.46)

Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; IRR, incidence rate ratio; PS, propensity score.

^aAdjusted by age, sex, body mass index, smoking history (pack-years), postbronchodilator forced expiratory volume in 1 second (percentage of predicted), degree of initial response to β₂ agonist (percentage of change in forced expiratory volume in 1 second), and medication possession ratio of long-acting β₂ agonist, long-acting muscarinic antagonist, short-acting β₂ agonist, short-acting muscarinic antagonist, and theophylline.

^bIncidence rate (per patient-year).

Overall mortality during 6 years was analyzed, censoring the data analysis at 7 years, and no significant differences were found between the non-ICS and ICS treatment groups ($P = .587$ by log-rank test) or between the ICS treatment group with an MPR less than 50% and that with an MPR of at least 50% ($P = .473$ by log-rank test; Fig 3).

Discussion

In this study, no beneficial effects of ICS treatment were found in patients with ACOS with regard to mortality, decreasing lung function, and exacerbation.

Various COPD guidelines have proposed that ICS should be preferentially considered for use in the management of ACOS. Spanish COPD guidelines have classified patients with ACOS as a mixed COPD–asthma phenotype group and have suggested that ICS associated with a long-acting bronchodilator could be the first option in ACOS.⁶ Japanese COPD guidelines also have proposed ICS as a first-line medication, regardless of the severity of COPD, when patients show asthmatic features, such as paroxysmal dyspnea, wheezing, and cough, occurring predominantly during the night and in the morning.⁸ However, these are not strongly based on evidence, and there are only a small number of retrospective studies supporting the recommendations of these guidelines.

The present results contradict the recommendations of these guidelines. No additional benefits of ICS were observed in patients with ACOS by the annual rate of decrease in FEV₁, incidence rate of severe exacerbation, and overall mortality. Several explanations could account for these differences.

First, it has been argued that the efficacy of ICS is questionable in patients with COPD.¹⁴ ACOS might be within the domain of COPD or it could be 1 of the various COPD phenotypes, although ACOS also has asthmatic features. Therefore, the role of ICS could be less clear in patients with ACOS. Gibson and Simpson³ suggested that the pattern of airway complications and inflammation of ACOS resembles that of COPD regarding the need for oral corticosteroids, presence of chronic bronchitis, bacterial colonization, and increased sputum neutrophils, although some other studies have presented relatively higher sputum eosinophil counts in patients with ACOS.¹⁷ The present results could be explained in terms of

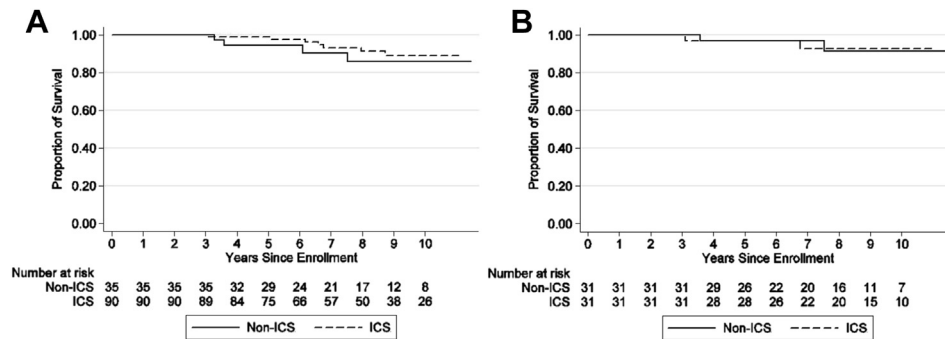


Figure 2. Probabilities of survival in patients with asthma–chronic obstructive pulmonary disease overlap syndrome. (A) Overall dataset ($P = .467$ by log-rank test). (B) Dataset matched by propensity score ($P = .965$ by log-rank test). ICS, inhaled corticosteroid.

these COPD aspects. Regular treatment with ICS does not modify the long-term decrease in FEV₁ or mortality in patients with COPD.^{15,18–23} Although several randomized control trials and meta-analyses have reported that regular treatment with ICS^{15,18,23,24} or ICS–LABA²⁵ decreases the frequency of COPD exacerbation, it does not mean that ICS has a preferential role in COPD treatment because those were placebo-controlled studies and did not compare efficacies with other treatment options. In addition, there are studies showing that ICS has a small role in decreasing exacerbation in patients with COPD. For example, Szafranski et al²⁶ found that ICS or ICS–LABA did not decrease severe exacerbation (use of oral steroids and/or antibiotics and/or hospitalization owing to respiratory symptoms) rates significantly compared with placebo. Until now, the role of ICS in COPD treatment has been controversial.²⁷ Because ACOS is a form of COPD, ICS may play a small role in the treatment of patients with ACOS.

Second, the definition of ACOS in the present study was based on the physiologic characteristics of respiratory function testing according to currently accepted definitions from different reviews and studies. When establishing treatment strategies in ACOS, especially considering ICS use, the inflammatory pattern of the airway could be important because eosinophils are extraordinarily sensitive to the action of corticosteroids. Although positive bronchial reversibility produces greater bronchial eosinophilic inflammation compared with nonreversibility,²⁸ it is uncertain whether patients with ACOS in the present study actually had airway eosinophilia. This is because patient sputum cell count or

bronchoalveolar lavage fluid was not investigated owing to the lack of databases for these examinations during the study period.

Third, this is a retrospective observational study, and these results could have limitations associated with residual confounding by indication or other unknown factors. Because the ICS treatment group was composed of patients who received at least 1 dose of ICS or ICS–LABA, early discontinuation in this group could bias results. Moreover, the number of prescribed drugs taken by each patient could not be accurately evaluated. To address this, the analysis was adjusted with all available influential covariates, including MPR of other respiratory medications during the study period. Furthermore, a matched PS analysis was performed, which is designed to decrease the effects of confounding by indication and balance the covariates in the 2 groups,²⁹ and thus the authors endeavored to overcome some limitations of this analysis. Small sample size can contribute to a lack of statistical power. However, a P value higher than .9 in the annual rate of decrease in FEV₁, overall mortality between the 2 groups, and the graphic overlapping in overall mortality for the long follow-up period could indicate that there is no superiority of ICS treatment in patients with ACOS.

In conclusion, the authors found no beneficial effect on the annual rate of decrease in FEV₁, incidence rates of severe exacerbation, or overall mortality in these patients with physiologically defined ACOS, which contradicts current recommendations. Further prospective studies are needed to identify preferential treatment options and clarify the role of ICS in patients with ACOS.

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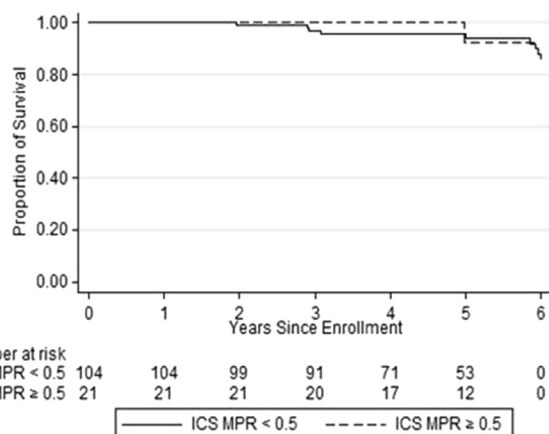


Figure 3. Probabilities of survival between the ICS treatment group with an MPR less than 50% and that with an MPR of at least 50% during 6 years with censoring of the data analysis at 7 years ($P = .473$, log-rank test). ICS, inhaled corticosteroid; MPR, medication possession ratio.

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