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ORIGINAL RESEARCH

Relationship Between Blood Eosinophils and Systemic Corticosteroid Therapy in COPD Exacerbation

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Purpose: To assess the relationship between the duration of systemic corticosteroid therapy and blood eosinophil counts in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).

Patients and Methods: This study included 292 patients with acute COPD exacerbations treated with daily intravenous injections of 40 mg/day methylprednisolone at the Department of Respiratory Medicine, Anhui No.2 Provincial People's Hospital, Hefei, China. The study subjects were divided into two groups – (1) a low-dose group (n = 136) that included patients treated with methylprednisolone for less than or equal to 5 days and (2) a high-dose group (n = 156) that included patients treated with methylprednisolone for more than 5 days. The blood eosinophil counts were analyzed for both the patient groups, and an optimal cut-off value was calculated to distinguish between the two groups. The study endpoints were readmission or deaths within 30 days or 180 days and re-infections within 90 days after hospital discharge.

Results: The mean blood eosinophil counts in the low- and high-dose groups were 0.15×10^9/L ($0.11–0.23 \times 10^9$/L) and 0.08×10^9/L ($0.04–0.12 \times 10^9$/L), respectively ($P < 0.01$). Receiver operating characteristic (ROC) curve analysis showed that the cut-off value for the blood eosinophils to distinguish the two patient groups was 0.115×10^9/L with a sensitivity and specificity of 72.8% and 72.4%, respectively. The number of readmissions between the two groups at 30 days and 180 days after hospital discharge did not show any significant differences ($P = 0.292$, $P = 0.398$). The follow-up data showed significantly higher rate of re-infections in the high-dose group (24/136) within 90 days after hospital discharge compared to the low-dose group (9/156) ($P = 0.018$).

Conclusion: In patients with acute exacerbations of COPD, blood eosinophil counts of $\geq 0.115 \times 10^9$/L were associated with effective response to corticosteroid therapy in ≤5 days.

Keywords: chronic obstructive pulmonary disease, exacerbation, corticosteroid, eosinophils

Introduction

The acute exacerbations of chronic obstructive pulmonary disease (COPD) are associated with significantly high mortality rates and adverse effects on the quality of life.[1] These effects can be circumvented by the use of oral or intravenous corticosteroids.[2] However, systemic corticosteroids are associated with adverse effects such as osteoporosis, adrenal insufficiency, elevated blood sugar levels, and sepsis.[3] Therefore, it is critical to determine the best timing and dosage of systemic corticosteroids for improving the treatment outcomes with significantly lower adverse effects. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 guidelines recommend treatment of patients with acute exacerbations of moderate to severe COPD with 40 mg/day methylprednisolone for 5 days.[4] However, COPD is an heterogeneous disease and some patients may require prolonged duration of methylprednisolone treatment for resolving the acute exacerbations of COPD. Patients with eosinophilic COPD show association between airway inflammation and the elevated number of eosinophils. Several studies have shown that blood eosinophil counts is a promising biomarker for patients with eosinophilic COPD.[5,6] The response of patients with high blood eosinophil counts to treatment with systemic corticosteroids is significantly higher than those with low blood eosinophil counts.[7] A randomized controlled study by Bafadhel et al, reported that subjects

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with low blood eosinophil counts did not benefit from systemic corticosteroid therapy.[8] These data suggested that corticosteroid treatment should be based on the blood eosinophil counts for patients with acute exacerbations of COPD to reduce adverse effects due to unnecessary exposure to the corticosteroids.[9] However, the blood eosinophil values and patient backgrounds can vary significantly. Hence, standardized eosinophil cut-off values and the corresponding corticosteroid doses are not currently available. Therefore, in this study, we performed retrospective analysis of the clinical data from hospitalized COPD subjects with acute exacerbations to assess whether the effective therapeutic dose of corticosteroids correlates with blood eosinophil counts, thus providing new ideas for optimizing corticosteroid treatment regimens using blood eosinophil counts.

Materials and Methods

Study Design and Participants

This study consecutively enrolled 297 patients with acute exacerbations of COPD that were admitted for treatment at the Department of Respiratory Medicine, Anhui No.2 Provincial People's Hospital between January 2020 and December 2020. The inclusion criteria were as follows: (1) age ≥ 40 years; (2) verified diagnosis of COPD by medical experts based on a stable disease condition. The acute exacerbations were classified according to the consensus definition proposed by the Global Initiative for Chronic Obstructive Lung Disease committee.[10] The exclusion criteria included (1) life expectancy less than 30 days; (2) presence of bronchial asthma, eosinophilia, allergic diseases, parasitic infections, and other diseases that are known to increase blood eosinophil counts; and (3) treatment with systemic corticosteroids 48 hours before admission. Finally, 292 patients were included in the study.

All the patients with moderate-to-severe acute exacerbations were treated with intravenous injections of 40 mg methylprednisolone once a day after admission. The duration of treatment with methylprednisolone was determined by assessing the symptoms and signs of the individual patients. The administration of methylprednisolone was discontinued if a patient showed improvement in dyspnea, bronchospasm, or other respiratory symptoms. Otherwise, the treatment was continued. The study subjects were classified into high- and low-dose groups based on the number of days of methylprednisolone administration. The subjects using methylprednisolone for more than 5 days were classified as the high-dose group (n=136). Those using methylprednisolone for less than 5 days were classified as the low-dose group (n=156). General clinical information and laboratory data was also collected from the study subjects. The general clinical data included gender, age, smoking history, comorbidities, modified British Medical Research Council (mMRC) classification, and the history of acute exacerbations in the previous year. The laboratory data included absolute blood neutrophil and eosinophil counts, and blood C-reactive protein levels at the time of admission in the emergency room or the ward. The endpoints included readmission from acute exacerbations of COPD within 30 days and 180 days of hospital discharge, and all types of infections requiring antibiotic treatment within 90 days of hospital discharge.

The study complied with the Declaration of Helsinki guidelines. Ethics Committee of the Anhui No.2 Provincial People's Hospital approved the experimental protocols and waived the requirement for patient consent to collect, analyze, and publish data because of the retrospective and anonymous nature of this study.

Statistical Analysis

Statistical analysis was performed using the SPSS 24.0 software (IBM Corp., Armonk, NY, USA). Continuous variables conforming to a normal distribution were expressed as means ± SD, whereas those conforming to a non-normal distribution were expressed as median (interquartile ranges). Categorical variables were expressed as absolute numbers and percentages. Mann Whitney U non-parametric test was used to compare data between two groups with uneven variance and non-normal distribution. The differences between categorical variables were measured using the χ^2 or the Fisher exact tests. Receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC) values were used to analyze the diagnostic accuracy of the blood eosinophil counts. Youden index was used to calculate the sensitivity and specificity of the optimal cut-off point for blood eosinophil counts. COX proportional hazards regression models were constructed to evaluate the association between the duration of methylprednisolone treatment and the risk of readmission within 30 or 180 days after hospital discharge, and re-infections within 90 days after hospital discharge. In

the COX proportional hazards regression models, potential confounding factors such as age, history of acute exacerbation in the previous year, and heart failure were adjusted before analysis. $P < 0.05$ was considered as statistically significant.

Results

Basic Characterization of the Study Subjects

This study enrolled 297 subjects. Two subjects were excluded because of incomplete clinical information. Three subjects (one in the low-dose group and two in the high-dose group) were excluded because follow-up was not conducted after hospital discharge. Finally, this study included 292 subjects including 136 cases in the low-dose group and 156 cases in the high-dose group. The flowchart of the patient selection strategy in this study is shown in Figure 1. The mean age for patients in the low-dose and the high-dose groups was 77 (68–82) years and 78 (72–83) years, respectively. The low-dose and the high-dose groups included 98 (72.1%) and 125 (80.1%) males, respectively. The patients in the two groups did not show any statistically significant differences in gender and age ($P > 0.05$). The patients in the high-dose group showed significantly higher incidence of congestive heart failure than the low-dose group ($P = 0.011$), but the differences between the two groups regarding comorbidities such as coronary heart disease ($P = 0.367$), type 2 diabetes ($P = 0.306$), and cerebrovascular disease ($P = 0.998$) were statistically insignificant. Moreover, the two groups of patients did not show any statistically significant differences in smoking history ($P = 0.645$), current smoking history ($P = 0.539$), mMRC classification ($P = 0.288$), and history of acute exacerbations in the previous year ($P = 0.368$).

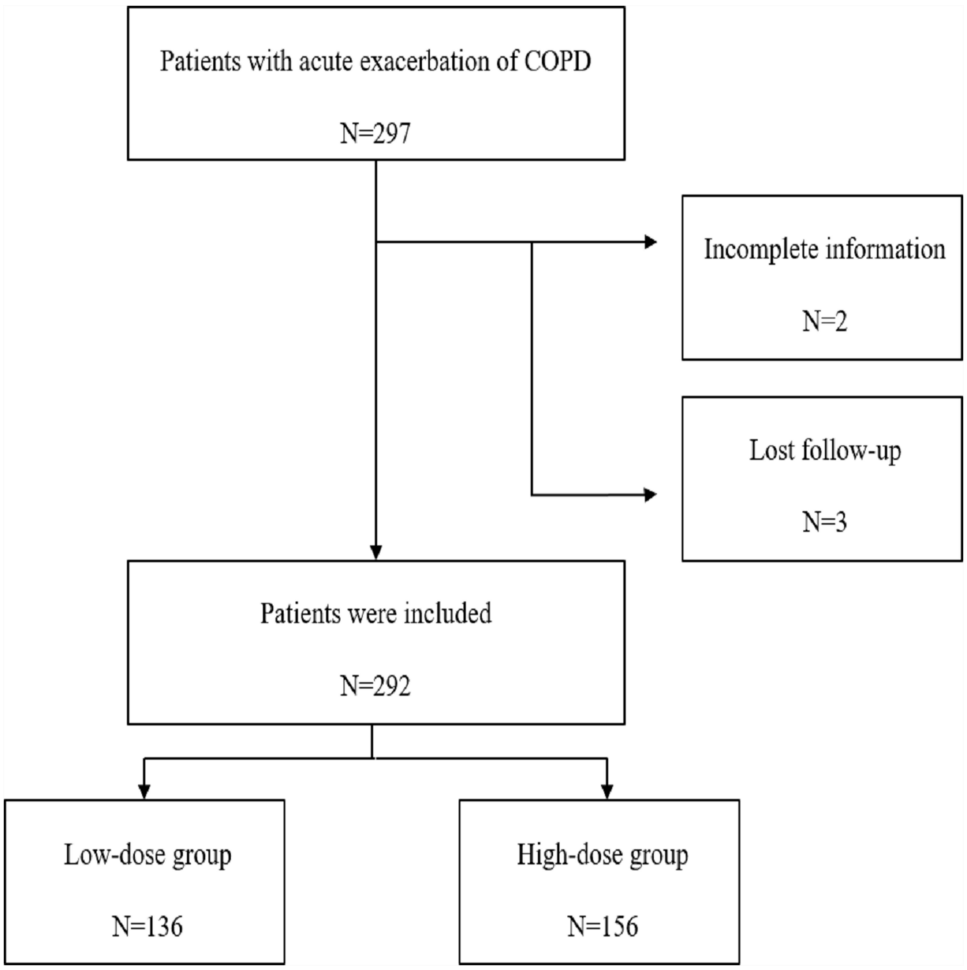

Figure 1 Flowchart of subject selection.

Blood Neutrophil, Eosinophil, and c-Reactive Protein Levels Vary Significantly Between the Low- and High Corticosteroid Dose Groups of Patients with Acute COPD Exacerbations

However, the levels of neutrophils, eosinophils, and C-reactive protein were significantly different between the low-dose and high-dose groups. The absolute neutrophil counts for patients in the low-dose and high-dose groups were 4.53×10^9/L (2.91–6.34) and 6.55×10^9/L (4.44–9.17) (P <0.001; Table 1), respectively. The c-reactive protein levels for patients in the low-dose and high-dose groups were 12.9 mg/L (3.6–50.4) and 25.8 mg/L (5.7–92.1) (P=0.007; Table 1), respectively. The absolute eosinophil counts for patients in the low-dose and high-dose groups were 0.15×10^9/L (0.11–0.23) and 0.08×10^9/L (0.04–0.12) (P <0.001; Table 1), respectively.

The Efficacy of Corticosteroid Treatment is Associated with the Blood Eosinophil Counts in the Patients with Acute COPD Exacerbations

The receiver operating characteristic (ROC) curves constructed for analyzing the diagnostic accuracy of the blood eosinophil counts correlating with the efficacy of corticosteroid treatments are shown in Figure 2. The area under the ROC curve (AUC) value was 0.75 (95% CI 0.693–0.807). The cut-off value for the blood eosinophil counts to distinguish the high- and low-dose groups was 0.115×10^9/L. The sensitivity and specificity values at this cut-off point were 72.8% and 72.4%, respectively.

Patients Treated Longer with Methylprednisolone are Associated with Significantly Higher Risk of Re-Infections

The readmission rates at 30 days and 180 days after discharge were not statistically significant between the low- and high-dose groups (P=0.292, P=0.308, respectively). The multi-parameter adjusted COX regression analysis showed that the low dose of

Table 1 Clinicopathological Characteristics of Study Subjects

Variables	Low-Dose Group (n=136)	High-Dose Group (n=156)	P value
Age (years)[a]	77(68–82)	78(72–83)	0.092
Male, n (%)	98(72.1)	125(80.1)	0.130
Smoking			
Past, n (%)	85(62.5)	94(60.3)	0.645
Current, n (%)	67(49.3)	83(53.2)	0.539
Comorbidities			
Coronary heart disease, n (%)	31(22.8)	43(27.6)	0.367
Heart failure, n (%)	33(24.3)	60(38.5)	0.011*
Type 2 diabetes, n (%)	12(8.8)	9(5.8)	0.306
Cerebrovascular disease, n (%)	39(28.7)	45(28.8)	0.998
mMRC≥2, n (%)	91(66.9)	114(73.1)	0.288
History of acute exacerbations in the previous year, n (%)	51(37.5)	67(42.9)	0.368
Blood test parameters			
Neutrophil counts ($\times10^9$/L)	4.53(2.91–6.34)	6.55(4.44–9.17)	<0.001*
Eosinophil counts [a] ($\times10^9$/L)	0.15(0.11–0.23)	0.08(0.04–0.12)	<0.001*
C-reactive protein[a] (mg/L)	12.9(3.6–50.4)	25.8(5.7–92.1)	0.007*

Notes: [a]Medians with interquartile ranges; *P <0.05.

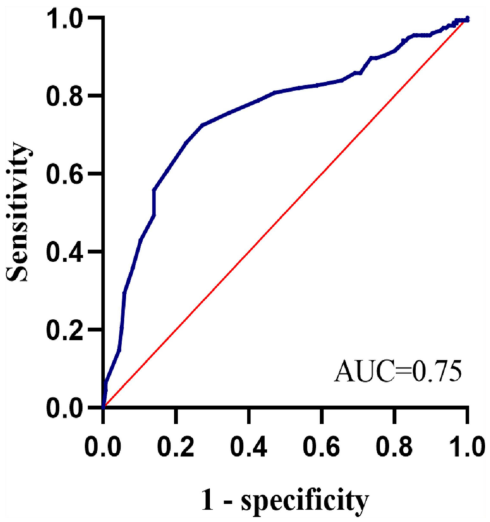

Figure 2 ROC curve analysis shows the cut-off value of blood eosinophil counts to classify the study subjects into high- and low-dose groups.

methylprednisolone was not associated with the risk of readmission at 30 days (HR = 0.372, 95% CI 0.072–1.929, *P*=0.372) and 180 days (HR = 0.810, 95% CI 0.499–1.314, *P*=0.393). At 90 days after discharge, 9 patients in the low-dose group and 24 patients in the high-dose group reported infections due to various causes (*P* = 0.018) (Table 2). The multi-parameter adjusted COX regression analysis showed that the high dose of methylprednisolone was associated with significantly higher risk of re-infection at 90 days (HR = 2.379, 95% CI 1.099–5.152, *P*=0.028).

Discussion

In this retrospective study, we analyzed clinical data of patients hospitalized with acute exacerbations of COPD and found that patients requiring methylprednisolone treatment for shorter period of time (≤5 days) were associated with higher blood eosinophil counts than those that required longer treatment. The optimal cut-off point for the blood eosinophil counts to distinguish the high- and low-dose groups of patients was 0.115×10^9/L. The low-dose group did not show any significant decrease in the readmission rates at 30 and 180 days post-discharge compared to the high-dose group. However, the rate of re-infections at 90 days post-hospitalization were significantly reduced in the low-dose group compared to the high-dose group.

COPD patients in both the stable and acute exacerbation states are treated with corticosteroids, which are non-specific anti-inflammatory medications.[11,12] Patients with stable COPD are treated with inhaled corticosteroids to improve lung function and prevent acute exacerbations. The use of systemic corticosteroids during acute COPD exacerbations decreased the incidence of treatment failure and the time of hospitalization.[13] Blood eosinophil counts are used as biomarkers to guide the therapy of patients with stable COPD. Eosinophilic inflammation is observed in patients with eosinophilic COPD and asthma, but the underlying mechanisms in the two different groups of patients are unclear.[14] In patients with acute COPD exacerbations, the exact relationship between blood eosinophil counts and the dose of corticosteroid therapy is not well described. Our analysis showed that patients with acute COPD exacerbations showed

Table 2 Follow-Up Data of Study Subjects

Variables	Low-Dose Group (n=136)	High-Dose Group (n=156)	P value
Readmission within 30 days, n (%)	2 (1.5)	6 (3.8)	0.292
Readmission within 180 days, n (%)	28 (20.6)	40 (25.6)	0.308
Reinfection within 90 days, n (%)	9 (6.6)	24 (15.4)	0.018*

Note: *P <0.05.

better response to corticosteroid therapy in less than or equal to 5 days when the blood eosinophil counts were higher than 0.115×10^9/L. However, further prospective multi-center large cohort studies are needed to confirm the cut-off value.

Leuppi et al performed a randomized controlled multicenter trial to compare the efficacy of a 5-day versus 14-day therapy in 314 COPD patients with severe acute exacerbations with 40 mg/day of prednisone daily, and showed that readmission rates at 180 days for both the groups were similar.[15] Li et al performed a randomized multicenter prospective study of 228 COPD patients with severe acute exacerbations and similar blood eosinophil counts and showed that individualized systemic corticosteroid strategy for 5 days with larger daily dose of corticosteroids (greater than 60 mg of prednisone) was more effective than a fixed-dose of 40 mg/day of prednisone for 5 days.[16] Our results showed that the treatment response with 40 mg/day of methylprednisolone for ≤5 days was comparable with the response with 40 mg/day of methylprednisolone for ≥5 days. Furthermore, we observed significant statistical differences in the blood eosinophil counts between patients that responded to treatment with 40 mg/day of methylprednisolone within 5 days and patients that required longer treatment time. The relationship between blood eosinophil counts and the response times of COPD patients treated with methylprednisolone for 1–5 days or for more than 5 days has not been reported before this study. However, we did not further investigate if the blood eosinophil counts were different in COPD patients treated with methylprednisolone for 1–5 days and those treated for more than 5 days and whether methylprednisolone treatment could be more carefully individualized further. Therefore, further studies are needed to answer these questions.

The follow-up data regarding the side-effects of systemic corticosteroid use showed that 24 patients in the high-dose group and 9 patients in the low-dose group reported infections within 90 days after hospital discharge. This difference between the two groups was statistically significant. There are two plausible causes for this effect. Firstly, a meta-analysis by Pavord et al reported that the risk of developing pneumonia was higher in COPD patients with <2% blood eosinophil counts.[17] This suggested that the risk of infection was higher in COPD patients with low blood eosinophil counts. Secondly, Waljee et al performed a population-based cohort study in the United States and reported that short-term use of systemic corticosteroids was associated with increased the risk of adverse events including re-infections.[18] Therefore, assessing the reasonable dose of systemic corticosteroid based on blood eosinophil counts is required to reduce the risk of re-infections. We did not observe any new cases of diabetes mellitus in both the groups. This was because the follow-up period was shorter and not sufficient to develop these adverse effects.

The results of our study also showed that the blood eosinophil counts were lower in COPD patients belonging to the high-dose group. This is related to the fact that COPD patients with low blood eosinophil counts are less responsive to corticosteroid therapy and tend to be given higher doses of corticosteroids over the course of previous treatments. However, the use of high doses of corticosteroids in COPD patients with low blood eosinophil counts did not improve treatment success and resulted in an increased risk of infection, fracture, and venous thromboembolism.[17,18] A randomized trial by Bafadhel et al grouped COPD patients based on the usage of corticosteroids and reported that patients with >2% blood eosinophil counts responded well to treatment with corticosteroids, whereas, patients with <2% blood eosinophil counts did not show significant benefits from treatment with corticosteroids.[8] Another multicenter randomized controlled trial by Sivapalan et al classified 218 hospitalized COPD patients into study and control groups. On day one, all the study subjects were administered with 80 mg of methylprednisolone. Then, day 2 onwards, subjects in the study group with blood eosinophils $\geq0.3\times10^9$/L were administered with 37.5 mg of prednisolone daily for up to 4 days, whereas those with blood eosinophil counts $<0.3\times10^9$/L were not administered prednisolone. The control group subjects were administered 37.5 mg of prednisolone for 4 days. The study results did not show any differences between the two groups regarding the number of readmissions 30 days after discharge.[19] This trial differed from our trial because the treatment decision was based on the blood eosinophil counts obtained after the first day of methylprednisolone treatment. Although treatment with methylprednisolone affects blood eosinophil counts, the corticosteroid treatment was halted if the blood eosinophil counts was below 0.3×10^9/L on day 1 after methylprednisolone use in the study by Sivapalan et al because it was concluded that continued corticosteroid use was not necessary when blood eosinophil counts were significantly low. However, the need for corticosteroid therapy based on blood eosinophil counts needs to be confirmed by larger cohort randomized controlled trials. Furthermore, in our study, COPD patients in the high-dose group showed significantly higher absolute blood neutrophil counts and C-reactive protein levels, and significantly higher incidence of cardiac dysfunction than the low-dose group. This may be due to the fact that the causative

factors in the high-dose group of patients were mainly infectious, while the exacerbation causative factors in some patients in a low inflammatory state may be due to cardiac insufficiency or other comorbidities.[20]

This study has several limitations. Firstly, this was a retrospective, single-center study that did not follow a standardized procedure. Furthermore, the effects of factors such as diet and other medications on the blood eosinophil counts were not adjusted in the multi-parameter Cox regression analysis. Secondly, some patients with a clear history of COPD did not undergo assessment of pulmonary function during this analysis. Therefore, the clinical information on the status of pulmonary function was incomplete for the study cohort and was not included in the analysis. This may have partially influenced the study results. Finally, some study subjects showed high sputum eosinophil counts but low blood eosinophil counts. Therefore, errors due to inconsistency between sputum and blood eosinophil counts cannot be excluded.

Conclusion

In patients with acute COPD exacerbations, treatment times of corticosteroid therapy were associated with blood eosinophil counts. Patients with blood eosinophil counts of more than 0.115×10^9/L showed better treatment response than those with lower blood eosinophil counts. Further prospective studies are required to confirm the cut-off value of the blood eosinophil counts for optimizing corticosteroid therapy in patients with acute COPD exacerbations.

Disclosure

The authors declare that they have no conflicts of interest.

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