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Abstract

Rationale: Small randomized controlled trials have shown that patients with chronic obstructive pulmonary disease (COPD) who had blood eosinophils $\geq 2\%$ achieve better outcomes with oral corticosteroid (OCS) treatment than patients with blood eosinophils $< 2\%$ (*Eur Respir J* 2014;44[3]:789–91). We aimed to verify the relationship between blood eosinophil count (BEC) and OCS treatment success (with or without antibiotics) in a large, real-life, population-based historical cohort study.

Methods: Combined UK electronic medical records from the Optimum Patient Care Research Database and the Clinical Practice Research Datalink (CPRD) were used to select patients with COPD who had BEC recorded on the day of a COPD exacerbation (defined as a prescription for acute OCS with or without antibiotics) and had not received OCS or antibiotic treatment in the 2 weeks prior to the exacerbation. Treatment failure was defined as any of the following in the 6 weeks after the index exacerbation: additional prescription for an acute OCS course or respiratory-related antibiotics or a COPD-related emergency department visit or inpatient hospitalization. In a subpopulation of patients from CPRD with Hospital Episode Statistics (HES) available, hospitalization for COPD exacerbation was studied as an outcome. Logistic regression analyses were performed to estimate adjusted odds ratios with 95% confidence intervals for patients with high BEC vs. low BEC using cut-off points of 250 cells/ μ L (primary outcome) and 150 cells/ μ L (sensitivity analysis). The model tested all demographics and comorbidities as potential confounders and adjusted for the most relevant confounders. Count-response relationship was assessed by comparing associations for incremental categories of BEC with the reference category of BEC ≥ 50 cells/ μ L and < 150 cells/ μ L, as a sensitivity analysis.

Results: This study included 7,152 patients with OCS prescribed for a COPD exacerbation (2,773 with HES). Compared with patients with BEC < 250 cells/ μ L, patients with elevated BEC (≥ 250 cells/ μ L) (36%) had a significantly lower risk of hospitalization for COPD exacerbation. Overall risk of treatment failure was not significantly different between the two groups ($p=0.074$). Patients with BEC ≥ 150 cells/ μ L (64%) had a significantly lower risk of hospitalization and overall treatment failure than patients with BEC < 150 cells/ μ L. There was no count-response relationship for incremental BEC categories > 150 cells/ μ L. Patients with BEC < 50 cells/ μ L had the greatest risk of treatment failure.

Conclusions: BEC ≥ 150 cells/ μ L measured at the time of exacerbation was indicative of OCS treatment success. Very low BEC (< 50 cells/ μ L) was associated with the greatest risk of treatment failure.

Rationale

- Approximately 30–60% of patients with chronic obstructive pulmonary disease (COPD) have baseline blood eosinophil concentrations $\geq 2\%$ ^{1–4}
- Efficacy of inhaled corticosteroids (ICS) to reduce exacerbations has been demonstrated to increase with greater blood eosinophil concentrations (from $\geq 2\%$ to $\geq 6\%$) in clinical trials for patients with COPD^{3,5}
- Small studies suggest that patients with COPD and blood eosinophil concentrations $\geq 2\%$ represent a distinct phenotype and may experience greater response to treatment with oral corticosteroids (OCS) during exacerbations than patients with blood eosinophil concentrations $< 2\%$ ^{6–8}
- A real-world database study of a large population of patients with COPD would strengthen the evidence for the potential role of blood eosinophil counts in predicting patient response to different types of systemic anti-inflammatory treatment during acute exacerbations

Aim

In this analysis, we evaluated whether blood eosinophil counts, measured at time of exacerbation for a large, real-world population of patients with COPD, can be used as a biomarker to identify specific clinical phenotypes of exacerbations that respond to OCS.

Methods

Study Design

- The Blood eosinophil counts in guiding ANti-inflammatory treatment of COPD exAcerbations (BLANCA) study was a historical observational database study
- UK electronic medical records for patients with COPD were selected from the Optimum Patient Care Research Database and the Clinical Practice Research Datalink
- Patients with physician-diagnosed COPD for this analysis met the following criteria:
 - ≥ 1 exacerbation treated in a primary care setting with short-term OCS and/or antibiotics (during or after 2005)
 - ≥ 40 years of age at the date of the COPD exacerbation
 - Blood eosinophil count recorded on the same day as an exacerbation (index date)
 - No OCS and/or antibiotic use during the 2 weeks before the exacerbation
 - Valid continuous data in the baseline year before and for ≥ 6 weeks after the index date (date of COPD exacerbation with eosinophil count on the same day) (see poster #219; Wednesday, May 22, 2019, 9:15–11:15 AM)
- Duplicate records were removed to create a combined data set of unique patients. Records for these patients were extracted for 1 year before (baseline) and 6 weeks after the exacerbation.

Study Objectives

- The primary study objective was to compare treatment failure between patients with blood eosinophil counts ≥ 250 cells/ μ L vs. < 250 cells/ μ L at the time of exacerbation who were prescribed OCS with or without antibiotics
- Secondary study objectives were to:
 - Study eosinophil count–treatment response relationship
 - Compare associations between eosinophil count and treatment response for patients with and without a prescription for inhaled corticosteroid (ICS) maintenance therapy in the past 3 months
 - Study whether changes in blood eosinophil counts from stable state (no exacerbations within 4 weeks) to acute exacerbation state were associated with treatment failure in a subgroup of patients who had a stable-state eosinophil count available within 1 year before the index date
- Study outcomes included:
 - Treatment failure, defined as any of the following during the outcome period (6 weeks following index date):
 - Antibiotics with lower respiratory consultation
 - Short-term course of additional OCS
 - COPD-related accident and emergency attendance or unscheduled hospital attendance/admission recorded in Hospital Episode Statistics (HES)
 - Hospitalization for COPD exacerbation for the subgroup of patients with HES available

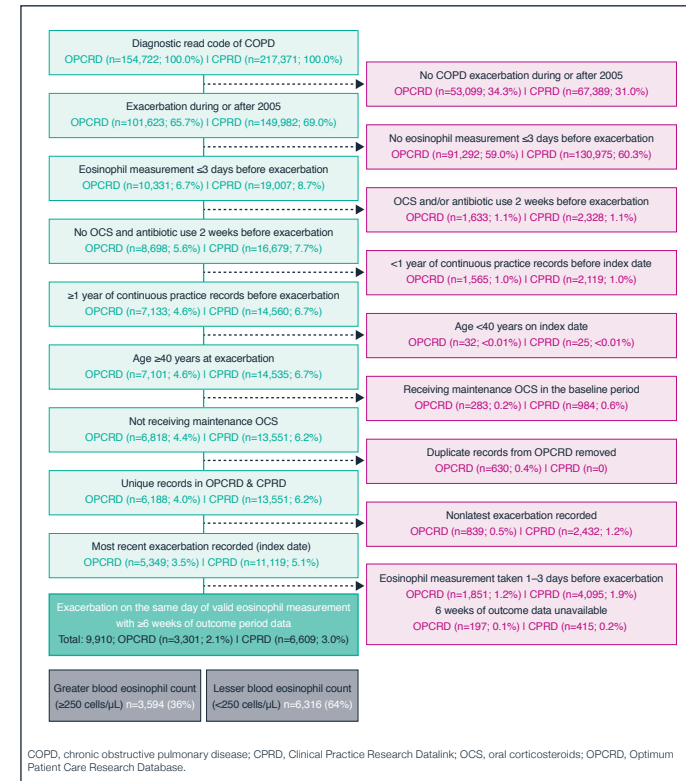
Statistical Methods

- Logistic regression analysis, with odds ratios and corresponding 95% confidence intervals, was performed to estimate the association between blood eosinophil counts and outcomes
- The analysis tested all demographics and comorbidities as potential confounders and adjusted for the most relevant factors

Results

- A total of 9,910 patients met inclusion criteria (Figure 1). Of those:
 - 7,122 (77.5%) had available blood eosinophil counts during stable disease in the previous year, including 2,574 patients with HES data
 - 7,152 (72.0%) were prescribed OCS with or without antibiotics for COPD exacerbations, including 2,773 patients with HES data; 2,758 (27.8%) were prescribed antibiotics only, including 992 with HES data
 - In the OCS-treated cohort, 5,072 patients had available blood eosinophil counts during stable disease in the previous year, including 1,874 with HES data
- Demographics and clinical characteristics were, in general, similar between groups receiving OCS (with or without antibiotics) or antibiotics only (see poster #219; Wednesday, May 22, 2019, 9:15–11:15 AM)

Figure 1. Patient Selection Process



Associations Between Blood Eosinophil Count and Treatment Failure for OCS-Treated Patients

- For OCS-treated patients with COPD, overall treatment failure was 39%; 10% were hospitalized for COPD within 6 weeks of the index exacerbation
- Patients with blood eosinophil counts ≥ 250 cells/ μ L had slightly less treatment failure and fewer hospitalizations for COPD than patients with blood eosinophil counts < 250 cells/ μ L (Table 1; Figure 2)
- This effect was accentuated when a blood eosinophil cut-off of ≥ 150 cells/ μ L was used (Figure 2)
- Patients with eosinopenia (blood eosinophil counts < 50 cells/ μ L) had the greatest risk of treatment failure and hospitalization (Figure 3)
- The relatively low risk of hospitalization for patients with blood eosinophil counts ≥ 250 cells/ μ L was most pronounced for patients not treated with ICS in the last 3 months (Table 2; Figure 4)

- For OCS-treated patients who were very adherent to dual/triple therapy ($n=7,152$; 34.7%), treatment failure rates were comparable across eosinophil groups (Table 3)
- COPD-related unscheduled hospital attendance was more common for patients with blood eosinophil counts < 250 cells/ μ L than for those with blood eosinophil counts ≥ 250 cells/ μ L (odds ratio=0.64 [95% CI: 0.42, 0.99], $p=0.044$)
- Patients with greater increases in blood eosinophil counts from stable state to exacerbation state may have smaller risk of hospital admission (Figure 5), but further investigation is needed to confirm this

Table 1. Treatment Failure Within 6 Weeks for Patients Treated with OCS with or Without Antibiotics

	Blood eosinophil count < 250 cells/ μ L (n=4,556)	Blood eosinophil count ≥ 250 cells/ μ L (n=2,596)
Any treatment failure, n (%)	1,823 (40.0)	983 (37.9)
Any additional antibiotics	391 (8.6)	279 (10.7)
Any additional short-term OCS	1,587 (34.8)	873 (33.6)
Subpopulation with HES, n	1,806	967
Any COPD-related unscheduled hospital attendance, n (%)	206 (11.4)	76 (7.9)
Any COPD-related A&E attendance, n (%)	53 (2.9)	17 (1.8)

A&E, accident and emergency; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; OCS, oral corticosteroids.

Figure 2. Association Between Elevated Blood Eosinophil Counts (≥ 250 and ≥ 150 cells/ μ L) and Treatment Failure and Hospitalization for COPD in OCS-Treated Patients

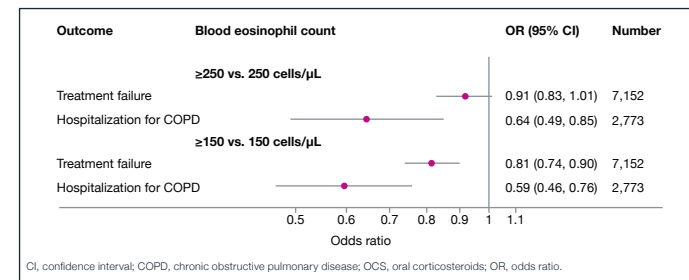


Figure 3. Eosinophil Count–Response Relationship for Treatment Failure and COPD-Related Hospitalization

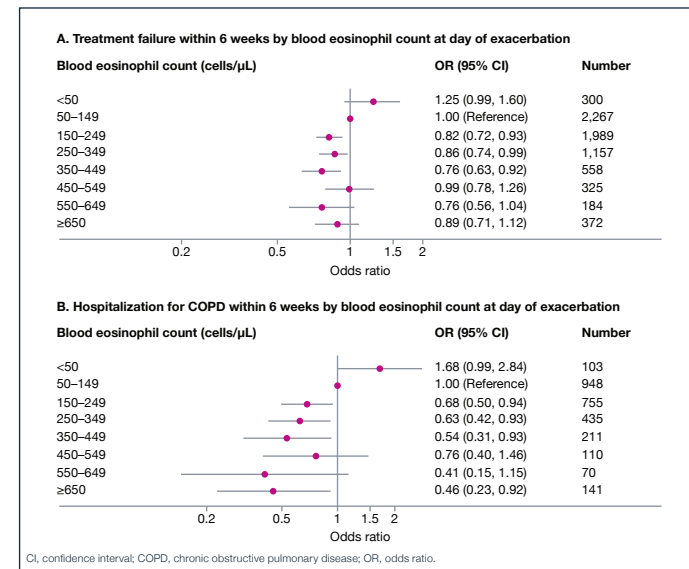


Table 2. Treatment Failure for Patients with and Without ICS Prescriptions in the Previous 3 Months

Treatment failure for OCS-treated patients	ICS		No ICS	
	Blood eosinophil count < 250 cells/ μ L (n=3,129)	Blood eosinophil count ≥ 250 cells/ μ L (n=1,806)	Blood eosinophil count < 250 cells/ μ L (n=1,427)	Blood eosinophil count ≥ 250 cells/ μ L (n=790)
Any treatment failure, n (%)	1,276 (40.8)	700 (38.8)	547 (38.3)	282 (35.8)
Any additional antibiotics	292 (9.3)	292 (9.3)	99 (6.9)	70 (8.9)
Any additional short-term OCS	1,102 (35.2)	621 (34.4)	485 (34.0)	252 (31.9)
Subpopulation with HES, n	1,289	697	517	270
Any COPD-related unscheduled hospital attendance, n (%)	151 (11.7)	61 (8.7)	55 (10.6)	15 (5.6)
Any COPD-related A&E attendance, n (%)	40 (3.1)	11 (1.6)	13 (2.5)	6 (2.2)

A&E, accident and emergency; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

Figure 4. Association Between Elevated Blood Eosinophil Counts (≥ 250 cells/ μ L) and Treatment Failure and COPD-Related Hospitalization, Stratified by ICS Therapy in the Previous 3 Months

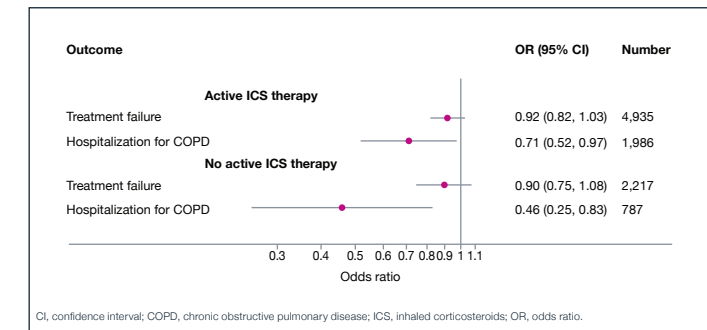


Table 3. Treatment Failure for OCS-Treated Patients with High Adherence to Dual/Triple Therapy

	Blood eosinophil count < 250 cells/ μ L (n=1,591)	Blood eosinophil count ≥ 250 cells/ μ L (n=889)
Any treatment failure, n (%)	657 (41.3)	353 (39.7)
Any additional antibiotics	141 (8.9)	108 (12.2)
Any additional short-term OCS	560 (35.2)	311 (35.0)
Subpopulation with HES, n	667	346
Any COPD-related unscheduled hospital attendance, n (%) ^a	91 (13.6)	32 (9.2)
Any COPD-related A&E attendance, n (%)	27 (4.0)	6 (1.7)

A&E, accident and emergency; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; OCS, oral corticosteroids. ^aOccurrence of a hospital admission for COPD exacerbation in data linked to HES ICD-10 code J44.0 or J44.1; COPD exacerbation in any diagnostic position. A total of 32 (3.4%) patients treated with corticosteroids died in the outcome period.

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