Disease Severity of Patients with High Blood Eosinophil Counts Treated for COPD Exacerbation with or Without Oral Corticosteroids

Marjan Kerkhof[1], Isha Chaudhry[1], Janwillem Kocks[2], Ian Pavord[3], David Halpin[4], Omar Usmani[5], Tamsin Morris[6], Marianna Alacqua[7], David Price[1,8]

[1]Observational and Pragmatic Research Institute, Singapore; [2]University of Groningen, Groningen, The Netherlands; [3]Nuffield Department of Medicine and Oxford Respiratory NIHR BRC, University of Oxford, Oxford, United Kingdom; [4]Royal Devon and Exeter NHS Trust, Exeter, United Kingdom; [5]Imperial College London, London, United Kingdom; [6]AstraZeneca, Luton, United Kingdom; [7]AstraZeneca, Cambridge, United Kingdom; [8]University of Aberdeen, Aberdeen, United Kingdom

Abstract

Rationale: Patients with chronic obstructive pulmonary disease (COPD) with elevated blood eosinophil counts (BEC) have greater response to oral corticosteroids (OCS) than those with lower BEC (*Chest* 2016;150:320–28). We aimed to compare disease severity and medication characteristics of COPD patients with BEC ≥250 cells/µL who were treated with OCS (with or without antibiotics) with patients treated with antibiotics only for an exacerbation.

Methods: Combined UK electronic medical records from the Optimum Patient Care Research Database and the Clinical Practice Research Datalink 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. Records for these patients were extracted for 1 year prior to the exacerbation (baseline), and patients were followed for 6 weeks. Clinical and medications characteristics with a standardized mean difference >10% between treatment groups (OCS with or without antibiotics vs. antibiotics only) for patients with BEC ≥250 cells/µL were identified.

Results: Of 9,910 patients with COPD who had BEC recorded on the day of COPD exacerbation, 3,594 (36%) had BEC ≥250 cells/µL. Of these patients, 72.2% were treated with OCS with or without antibiotics for a COPD exacerbation, and 27.8% were treated with antibiotics only. OCS-treated patients had more exacerbations in the baseline period than patients treated with antibiotics only (mean ± standard deviation: 2.6 ± 2.2 vs. 1.8 ± 2.3, respectively). Compared with patients treated with antibiotics only, a greater percentage of OCS-treated patients experienced breathlessness, as measured by the modified Medical Research Council dyspnea scale, and substantial airflow obstruction, as indicated by percent predicted forced expiratory volume in 1 second. In addition, a greater percentage of OCS-treated patients exhibited severe disease symptoms and greater exacerbation risk as indicated by Global Initiative for Chronic Obstructive Lung Disease group D classification, and by their treatment with triple therapy (inhaled corticosteroids, long-acting muscarinic antagonists, and long-acting β_2-agonists).

Conclusion: COPD patients with BEC ≥250 cells/µL treated with OCS for an exacerbation have more severe disease than patients treated with antibiotics only.

Rationale

- Approximately 30–60% of patients with chronic obstructive pulmonary disease (COPD) have blood eosinophil concentrations ≥2%[1–4]
- Blood eosinophil counts may be a useful biomarker to guide treatment decisions, as greater counts have been associated with better response to corticosteroid treatment[5,6]
- Bafadhel et al. reported that patients with blood eosinophil concentrations ≥2% at onset of an outpatient-managed exacerbation responded to prednisolone (oral corticosteroids [OCS]), whereas those with eosinophil concentrations <2% had a greater rate of treatment failure with OCS than with placebo[7]
- To follow up on this finding, the BLood eosinophil counts in guiding ANti-inflammatory treatment of COPD exAcerbations (BLANCA) study was designed to evaluate whether blood eosinophil counts measured during exacerbations can be used as a biomarker to identify specific clinical phenotypes of COPD exacerbations that respond to OCS treatment in a real-life setting

Aim

In this analysis of BLANCA data, we compared baseline disease severity and medication use for patients with COPD and blood eosinophil counts ≥250 cells/µL treated with OCS with or without antibiotics vs. patients treated only with antibiotics.

Methods

Study Design

- BLANCA 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 selected from the databases for this analysis met the following criteria:
  - ≥1 exacerbation treated in a primary care setting with OCS and/or antibiotic prescriptions (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
- For patients with multiple eligible exacerbations, the most recent exacerbation was selected for this analysis
- 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.
- From these data, we identified clinical and medication characteristics that demonstrated a relevant difference between treatment groups (OCS with or without antibiotics vs. antibiotics only) for patients with blood eosinophil counts ≥250 cells/µL
- A relevant difference was defined as a significant difference with a standardized mean difference (SMD) >0.1

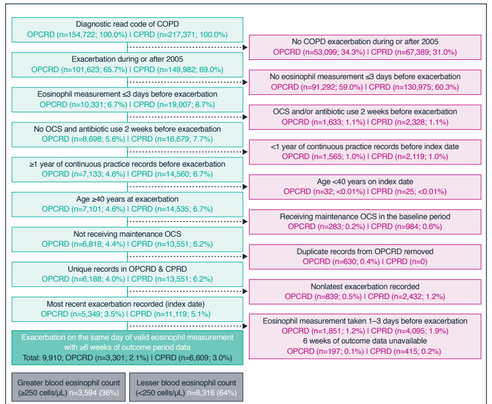
Statistical Methods

- Differences between treatment arms for baseline demographics and other patient characteristics were quantified with the SMD
- All SMD values >0.1 were statistically significant (p<0.05). Therefore, p-values are not presented.

Results

- A total of 9,910 patients met inclusion criteria (**Figure 1**)
- Baseline patient demographics were similar between groups receiving OCS with or without antibiotics vs. antibiotics only (**Table 1**)
- Baseline comorbidities were similar between treatment groups; hypertension and depression/anxiety were the most prevalent comorbidities across both treatment cohorts (**Table 1**)
- Of patients who experienced any exacerbations, 72% were treated with OCS (with or without antibiotics) and 28% were treated with antibiotics only
- At exacerbation, 36% of patients overall had elevated blood eosinophil counts (≥250 cells/µL)
- A greater percentage of patients with blood eosinophil counts ≥450 cells/µL at exacerbation were treated with OCS compared with patients with blood eosinophil counts <450 cells/µL (77% vs. 72%, respectively)
- Very high blood eosinophil counts (≥650 cells/µL) were more common for patients treated with OCS than for patients treated with antibiotics only (5.2% vs. 3.3%, respectively; **Figure 2**)

Figure 1. Patient Selection Process



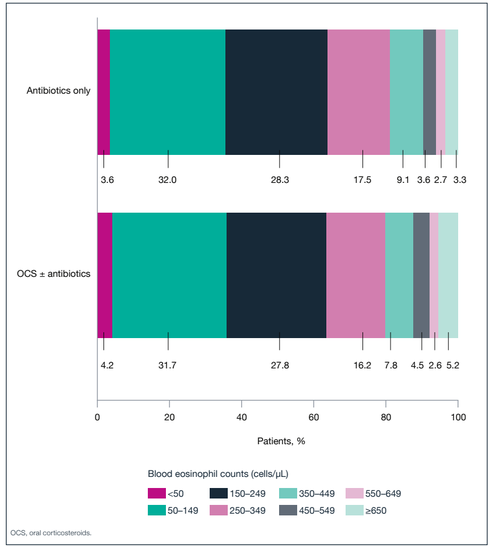
COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; OCS, oral corticosteroids; OPCRD, Optimum Patient Care Research Database.

Table 1. Demographics and Clinically Relevant Baseline Characteristics of Patients with Blood Eosinophil Counts ≥250 cells/µL

	Antibiotics only (n=998)	OCS with or without antibiotics (n=2,596)	SMD
Age at index date [years], mean (SD)	70.4 (10.4)	71.2 (10.2)	0.074
Female, n (%)	456 (45.6)	1,210 (46.6)	0.018
Body mass index, n (%)			
Nonmissing	952 (95.4)	2,496 (96.1)	
Underweight (<18.5 kg/m²)	40 (4.2)	117 (4.7)	
Normal (18.5–<25 kg/m²)	304 (31.9)	824 (33.0)	0.039
Overweight (25–<30 kg/m²)	305 (32.0)	797 (31.9)	
Obese (≥30 kg/m²)	303 (31.8)	758 (30.4)	
Smoking status closest to index date, n (%)			
Nonmissing	988 (99.0)	2,568 (98.9)	
Nonsmoker	131 (13.3)	340 (13.2)	0.018
Current smoker	299 (30.3)	746 (29.0)	
Ex-smoker	558 (56.5)	1,482 (57.7)	
Baseline comorbidities, n (%)			
Active asthma[a]	148 (14.8)	408 (15.7)	0.025
Pneumonia	27 (2.7)	56 (2.2)	0.036
Active rhinitis[b]	22 (2.2)	49 (1.9)	0.022
Eczema	54 (5.4)	142 (5.5)	0.003
Nasal polyps	0 (0.0)	10 (0.4)	0.088
Gastroesophageal reflux	180 (18.0)	483 (18.6)	0.015
Depression/anxiety	366 (36.7)	969 (37.3)	0.014
Sleep disorders	49 (4.9)	82 (3.2)	0.089
Obstructive sleep apnea	8 (0.9)	13 (0.5)	0.006
Cardiovascular disease[c]	104 (11.1)	276 (11.3)	0.002
Heart failure	40 (4.3)	104 (4.3)	0.028

OCS, oral corticosteroids; SD, standard deviation; SMD, standardized mean difference.
[a]Defined as the presence of asthma diagnostic or monitoring code after the second COPD diagnosis code.
[b]Defined as the presence of a rhinitis diagnostic code in the year before the index date.
[c]Diagnosis of coronary heart disease and/or stroke and/or peripheral arterial/vascular disease and/or heart failure and/or diseases of the aorta.

Figure 2. Blood Eosinophil Counts at Exacerbation (n=9,910)

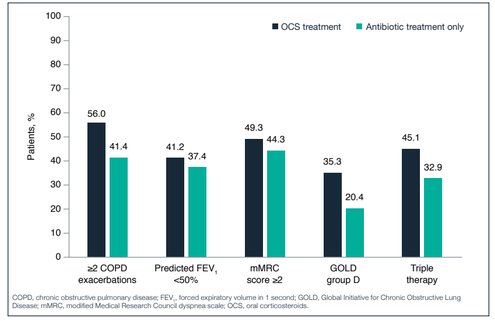


OCS, oral corticosteroids.

Baseline Disease Severity

- Compared with patients treated with antibiotics only, patients treated with OCS with or without antibiotics represented a population with more severe disease (**Figure 3**), as evidenced by:
  - More frequent COPD exacerbations
  - Reduced FEV_1
  - Increased dyspnea (per the modified Medical Research Council dyspnea scale)
  - Greater likelihood of classification in Global Initiative for Chronic Obstructive Lung Disease group D (2017), indicating greater symptom severity and exacerbation risk
  - Greater likelihood of being treated with triple therapy, defined as inhaled corticosteroids/long-acting β_2-agonists/long-acting muscarinic antagonists

Figure 3. Measures of Baseline Disease Severity for Patients with COPD and Baseline Eosinophil Counts ≥250 cells/µL Treated with OCS with or Without Antibiotics or Antibiotics Only for an Exacerbation



COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale; OCS, oral corticosteroids.

Conclusions

- When measured during a COPD exacerbation, blood eosinophil counts were ≥250 cells/µL for 36% of patients with COPD
- 72% of patients who experienced exacerbations were treated with OCS with or without antibiotics
- A greater percentage of patients with COPD and blood eosinophil counts ≥250 cells/µL treated with OCS with or without antibiotics had more severe disease, experienced more frequent prior exacerbations, and were more often treated with triple therapy before exacerbation vs. patients treated with antibiotics only

References

1. Singh D, et al. *Eur Respir J*. 2014;44:1697–700.
2. Pascoe S, et al. *Lancet Respir Med*. 2015;3:435–42.
3. Barnes NC, et al. *Eur Respir J*. 2016;47:1374–82.
4. Roche N, et al. *Am J Respir Crit Care Med*. 2017;195:1189–97.
5. Tsiligianni I, Kaplan AG. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1889–91.
6. Bafadhel M, et al. *Lancet Respir Med*. 2017;5:747–59.
7. Bafadhel M, et al. *Eur Respir J*. 2014;44:789–91.

Acknowledgments and Disclosures

This analysis was funded by AstraZeneca. **Marjan Kerkhof**, **Isha Chaudhry**, and **David Price** are employees of the Observational and Pragmatic Research Institute, which conducted this study and paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Meda; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva Pharmaceuticals; and Zentiva, a Sanofi company. **Janwillem Kocks** received grants and/or personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Mundipharma, and Teva Pharmaceuticals. **Ian Pavord** received grants, fees, and/or sponsorship from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Gerentech, GlaxoSmithKline, Knopp, Merck, Novartis, Regeneron, Sanofi, and Teva Pharmaceuticals. **David Halpin** has received fees and/or sponsorship from Altana, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. **Omar Usmani** has received fees and/or funding from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Edmond Pharma, GlaxoSmithKline, Mundipharma, Napp, Novartis, Pearl Therapeutics, Roche, Sandoz, Takeda, UCB, Vectura, and Zentiva. **Tamsin Morris** and **Marianna Alacqua** are employees of AstraZeneca. **David Price** has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; and has received payment from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia, Singapore, and United Kingdom) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment. Editorial support was provided by **Joanne M. Faysal**, MS, of JK Associates, Inc., and **Michael A. Nissen**, ELS, of AstraZeneca. This support was funded by AstraZeneca.

Presented at the American Thoracic Society (ATS) International Conference, May 17–22, 2019, Dallas, TX, United States