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Should Eosinophils Direct Therapy in COPD?

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Disclosures

- Consultant: AstraZeneca, GlaxoSmithKline, Circassia, Spiration, Royalty Walters Knue, UpToDate and Boehringer Ingelheim
- Speaker: Sunovion
- Advisory Board: Verona

Learning Objectives

- Discuss the presence of Th2 inflammation
- Describe the range of eosinophil counts in COPD
- Review clinical trial results of inhaled steroids (ICS) in relationship to eosinophil counts

Do You Use Blood Eosinophil Count To Drive Therapy for Your COPD Patients?





Barnes P. Chest 2000

Th2 Eosinophilic Inflammation



Th1 Neutrophilic Inflammation



Barnes, P. J Allergy Clin Immunol, 2015

Learning Objectives

- Discuss the presence of Th2 inflammation
- Know the range of eosinophil counts in COPD.

Do eosinophil counts consistently reflect Th2 inflammation in COPD?

 Review clinical trial results of inhaled steroids (ICS) in relationship to eosinophil counts

What Is A High Blood Eosinophil Count?

- A. > 150 eos/uL
- B. > 200 eos/uL
- C. > 250 eos/uL
- D. > 300 eos/uL
- E. > 350 eos/uL

Normal Eosinophil Count



Blood Eosinophil Counts In COPD



Bafadehl M. Lancet Resp Med, 2017

Do Blood Eosinophils Identify Th2-High COPD Phenotype?

- Speculation: Blood eosinophilia correlates with lung eosinophilia and Th2 inflammation
- 2,499 SPIROMICS subjects with smoking history Low eos <200/uL – 1,262 (50.5% of subjects) High eos >200/uL – 1,237 (49.5% of subjects)

Hastie A. Lancet Resp Med, 2017

Blood Eosinophils Do Not Predict Sputum Eosinophils



Hastie A. Lancet Resp Med, 2017



Blood Eosinophils Do Not Predict Sputum Eosinophils

Blood eos from 50/µL (highest sensitivity) to 500/µL (lowest sensitivity) for correct prediction of sputum eos <1.25% or \geq 1.25%. Maximum sensitivity and specificity observed at blood eosinophil cutoff of 150/µL.

Hastie A. Lancet Resp Med, 2017

Blood Eosinophils Are Not Good Predictor of Sputum Eosinophils

Sputum eosinophilia:

- More severe airflow obstruction
- Worse quality of life
- Greater emphysema and air trapping
- Greater number of exacerbations

Blood eosinophilia:

- More severe airflow obstruction
- No association with COPD exacerbations (cutoffs at 200/µL or 300/µL) or other features
- Do not predict sputum eosinophilia

CAT scores did not differ by blood or sputum eos

Is Blood Eosinophil Count Stable?

210 patients with 2,059 visits

- Followed over 4 years (median)
 - Irrespective of AECOPD and hospitalizations
 - 8.2 stable visits, 4.2 AECOPD-related visits

Blood Eosinophil Count Is Variable





Schumann D. CHEST, 2019

Time Of Day Affects Blood Eosinophil Level



Figure 4 – Using all eosinophil values measured, including those recorded during hospitalizations, there seems to be an eosinophil circadian rhythm, with higher eosinophil values between 6 AM and 12 PM compared with the rest of the day.



Is Blood Eosinophil Count Stable?

Results:

- Eosinophil counts were highly variable
- Circadian variation in eosinophil counts

Is Blood Eosinophil Count Stable?

• Subjects:

308 with COPD and 67 smokers without COPD CHAIN and BODE cohort subjects

Eos over 2 years



Casanova C. Eur Resp J, 2017

Is Blood Eosinophil Count Stable?

- 40.5% of COPD patients had eos oscillating above and below 300
- Eos >300 -

Not a risk factor for AECOPD Better survival (15.8% mortality vs 33.7% over 10.8 years)

Is Blood Eosinophil Count Stable?

- ECLIPSE cohort 51% remained above or below 2% cutoff (measured once a year for 3 years)
- Leicester cohort 65% remained above or below 400/uL

What Is A High Blood Eosinophil Count On A Single Measurement?

- A. > 150 eos/uL
- B. > 200 eos/uL
- C. > 250 eos/uL
- D. > 300 eos/uL
- E. > 350 eos/uL

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Eos And Treatment Response In IMPACT

• Participants

10,333 COPD moderate – very severe History of >1 AECOPD in last year

- Compared Triple Rx (LABA-LAMA-ICS) vs LABA-LAMA and LABA-ICS
- Secondary objective of IMPACT trial Relationship of eosinophil counts to treatment response

Baseline Eos And Exacerbation Rate-IMPACT



Eos And Treatment Response In IMPACT



Eos And Treatment Response In IMPACT: Current Smokers vs Former Smokers



Pascoe S. Lancet Resp Med, 2019

Eos And Exacerbations: Secondary Analysis

Post-hoc analysis of 2 replicate studies Randomized to LABA: Vilanterol 25 ug (n= vs LABA-ICS: Vilanterol + Fluticasone furoate (50 ug, 100 ug, 200 ug) LABA group: More exacerbations with higher baseline eosinophil counts

Pascoe S. Lancet Resp Med 2015



Eos And Exacerbations: Secondary Analysis

Pascoe S. Lancet Resp Med 2015

Eos And Exacerbations: Secondary Analysis



Pascoe S. Lancet Resp Med 2015

Inhaled Steroid Considerations

Endotype - Th2 inflammation

- Eosinophil count (? > 300)
- FeNO (? > 50)

Symptoms

- Intermittent, nocturnal, early am
- Allergen induced

Phenotype

- Acute bronchodilator response
 - (? >12% and > 200 ml)
 - (? >14% and > 400 ml)

Benefits Of ICS In COPD

Clinical benefits of inhaled steroids in COPD

- Improves lung function
- Reduces dyspnea
- Increases exercise duration
- Reduces rate of exacerbations

Adverse Effects Of ICS

- Pneumonia
- Osteoporosis
- Cataracts
- Mycobacterial infections
- Poor diabetes control

- Hoarseness
- Thrush
- Skin thinning
- Ecchymoses

GOLD Symptom & Exacerbation Risk Exacerbation Hist Gategories



mMRC: modified Medical Research Council Dyspnea Scale. CAT: COPD Assessment Test

Treatment of stable COPD

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	Group C LAMA	Group D LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	Group A A Bronchodilator	Group B A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	mMRC $\ge 2 \text{ CAT} \ge 10$

FIGURE 4.1

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

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Treatment of stable COPD

Group D LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300

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GOLD: Eos In COPD

- Repeatability of blood eosinophil counts in primary care appears reasonable
 - Greater variability at higher thresholds
- Differing results of eosinophil count prediction of AECOPD
- "Insufficient evidence to use eosinophil counts to predict exacerbation risk on an individual basis in COPD"

GOLD: Eos and ICS In COPD

- Eosinophil counts predict the magnitude of AECOPD reduction
 - o <100 eos/uL no benefit</p>
 - >300 eos/uL greatest likelihood of benefit
- Eosinophil counts can <u>help</u> clinicians predict response to ICS
 - In conjunction with AECOPD risk, clinical features, and potential adverse effects