Eosinophils in COPD: Myths and reality

Stelios Loukides MD Phd FCCP FERS
ERS educational council
University of Athens Medical School
Conflicts

- AstraZeneca
- Boehringer Ingelheim
- Chiesi
- GlaxoSmithKline
- Elpen
- Menarini
- Novartis
- Sanofi
MCQ 1

Only one of the following is true

A. The most stable phenotype in COPD is the eosinophilic one
B. Biologics targeting IL-5 or IL-5R are effective at a level of > 300 AC eosinophils
C. Blood or sputum eosinophilia are inflammatory variables at ACO defined process
D. In a COPD patient treated with LAMA & LABA and having >2 exacerbations the cut off value for the identification of eosinophilic endotype is 150AC.
MCQ 1

Only one of the following is true

A. The most stable phenotype is the eosinophilic one
B. Biologics targeting IL-5 or IL-5R are effective at a level of > 300 AC eosinophils
C. Blood or sputum eosinophilia are inflammatory variables at ACO defined process
D. In a COPD patient treated with LAMA & LABA and having >2 exacerbations the cut off value for the identification of eosinophilic endotype is 150AC.
Design

- Some introductory remarks. The eosinophil
Eosinophil: A key regulatory cell

**Eosinophil activation pathways**
- Chemoattractant: CCR1, CCR3, C5aR, PAFR, PGDR2, CysLT1R, CysLT2R
- Cytokine and growth factors: IL-2R, IL-3R, IL-4R, IL-5R, GM-CSFR, TGFβR, TSLPR, ST2 (IL-33R)
- Other: SIGLEC-8/F, ILT2/PIR-A, ILTs/PIR-B, EMR1, Fc receptors, TLRs

**Host protective: Defense against mucosal pathogens**
- Cytotoxicity by granule proteins
- Mitochondrial DNA traps
- Respiratory burst
- Nitric oxide release

**Proinflammatory: Tissue damage and remodeling**
- Epithelial cell damage
- Fibrosis
- Airway hyperreactivity

**Immunoregulatory**
- T cells: Antigen presentation, Co-stimulation, Th2 polarization, recruitment
- B cells: IgM production, secretory IgA production, plasma cell survival
- Dendritic cells: Activation, maturation

Travers J et al Mucosal Immunology (2015) 8, 464-475;
Is it different in COPD?

Nixon J et al Pharmacology & Therapeutics, 2016
Eosinophils are multivalent leukocytes that contribute to a variety of immune responses in physiological and pathological conditions.

Eosinophils contribute to protection against parasitic, microbial and viral infections\(^1\)

- Eosinophils are commonly associated with protection against helminths
- Associated with protective response to respiratory viruses
- Interact with dendritic cells to promote immune responses
- In vitro, eosinophils release mitochondrial DNA in response to LPS

Eosinophils contribute to the inflammatory response as:

- Response to allergens\(^2\)
- Tissue repair and remodeling\(^1\)
- Asthma\(^1,2\)
- Eosinophilic oesophagitis\(^1\)
- Hyperosinophilic syndrome\(^1\)
- Increasing evidence now suggests eosinophils are involved in COPD\(^3,4\)
Design

- Some introductory remarks. The eosinophil
- Endotyping
Inflammatory endotypes in COPD: The eosinophilic part

Barnes PJ Allergy, First published: 04 March 2019, DOI: (10.1111/all.13760)
Remodeling in COPD: How eosinophilic it is?
Eosinophils directly modulate alveolar macrophage production of matrix metalloprotease (MMP)-12 through interleukin (IL)-13-dependent mechanisms
Design

• Some introductory remarks. The eosinophil
• Endotyping
• Phenotyping
Microbiome and eosinopenia

Marco Contoli et al. Eur Respir J 2017
Blood and sputum eosinophils in COPD; relationship with bacterial load

Colsum U et al Resp Research 2017
Eosinopenia and Emphysema
Predicting airway eosinophilia

Phenotyping ECOPD: The T2 approach

Bafadhel M et al Am J Respir Crit Care Med. 2011
Asthma-chronic obstructive pulmonary disease overlap: Diagnostic stability and inflammatory characteristics

Patentalakis G et al  Allergy, First published: 11 May 2019, DOI: (10.1111/all.13865)
Design

- Some introductory remarks. The eosinophil
- Endotyping
- Phenotyping
- Outcomes
Eosinopenia in ECOPD

Table 3 The DECAF Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>1</td>
</tr>
<tr>
<td>eMRCD 5a</td>
<td>2</td>
</tr>
<tr>
<td>Eosinopenia (&lt;0.05 x 10⁹/l)</td>
<td>1</td>
</tr>
<tr>
<td>Consolidation</td>
<td>1</td>
</tr>
<tr>
<td>Acidaemia (pH &lt;7.3)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Total DECAF Score</td>
<td>6</td>
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</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II; BAP-65, Blood urea nitrogen, Altered mental status, Pulse >109/min, Age >65 years; CAPS, COPD and Asthma Physiology Score; COPD, chronic obstructive pulmonary disease.

Low and High Blood Eosinophil Counts as Biomarkers in Hospitalized ECOPD

McDonald Mi et al Chest 2019
Exacerbation COPD: outcome

A) Length of stay (days)

<table>
<thead>
<tr>
<th></th>
<th>non-eosinophilic</th>
<th>eosinophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.015</td>
<td></td>
</tr>
</tbody>
</table>

B) Percent in hospital vs. Length of Stay (days)

<table>
<thead>
<tr>
<th></th>
<th>eosinophilic</th>
<th>Non-eosinophilic</th>
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</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.046</td>
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Exacerbation phenotype
Predicting rate of ECOPD: Remains controversial
Selecting the better?

Design

• Some introductory remarks. The eosinophil
• Endotyping
• Phenotyping
• Outcomes
• Stability
## Blood Eosinophils: How stable they are?

### Table 2: Proportion of COPD patients with stable eosinophil counts among stratified by gender, age, eosinophil counts, and smoking status at different time points

<table>
<thead>
<tr>
<th>COPD patients</th>
<th>6 months</th>
<th>9 months</th>
<th>1 year</th>
<th>2 years</th>
<th>4 years</th>
<th>6 years</th>
<th>8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute blood eosinophil count (cells/L)</td>
<td>85%</td>
<td>82%</td>
<td>75%</td>
<td>62%</td>
<td>49%</td>
<td>42%</td>
<td>35%</td>
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<tr>
<td>&lt;0.34 x 10^9 cells/L</td>
<td>95%</td>
<td>93%</td>
<td>90%</td>
<td>86%</td>
<td>80%</td>
<td>77%</td>
<td>75%</td>
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<tr>
<td>≥0.34 x 10^9 cells/L</td>
<td>80%</td>
<td>70%</td>
<td>63%</td>
<td>45%</td>
<td>30%</td>
<td>23%</td>
<td>18%</td>
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<tr>
<td>Age</td>
<td>95%</td>
<td>93%</td>
<td>85%</td>
<td>83%</td>
<td>76%</td>
<td>71%</td>
<td>67%</td>
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<tr>
<td>40-59 y</td>
<td>95%</td>
<td>93%</td>
<td>90%</td>
<td>80%</td>
<td>79%</td>
<td>70%</td>
<td>65%</td>
</tr>
<tr>
<td>60-79 y</td>
<td>93%</td>
<td>90%</td>
<td>85%</td>
<td>76%</td>
<td>70%</td>
<td>65%</td>
<td>60%</td>
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<tr>
<td>80+ y</td>
<td>91%</td>
<td>89%</td>
<td>77%</td>
<td>73%</td>
<td>66%</td>
<td>61%</td>
<td>58%</td>
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<td>Gender</td>
<td>94%</td>
<td>92%</td>
<td>89%</td>
<td>81%</td>
<td>75%</td>
<td>70%</td>
<td>68%</td>
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<tr>
<td>Females</td>
<td>92%</td>
<td>89%</td>
<td>85%</td>
<td>75%</td>
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<td>61%</td>
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<td>95%</td>
<td>90%</td>
<td>88%</td>
<td>81%</td>
<td>72%</td>
<td>69%</td>
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<tr>
<td>No</td>
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<td>90%</td>
<td>88%</td>
<td>79%</td>
<td>72%</td>
<td>69%</td>
<td>62%</td>
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<tr>
<td>Smoking status</td>
<td>96%</td>
<td>93%</td>
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<td>77%</td>
<td>73%</td>
<td>69%</td>
</tr>
<tr>
<td>Non-COPD controls</td>
<td>97%</td>
<td>95%</td>
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<td>88%</td>
<td>80%</td>
<td>74%</td>
<td>71%</td>
</tr>
</tbody>
</table>

**Abbreviation:** COPD = chronic obstructive pulmonary disease, y = years

Oshagbemi OA et al AJRCCM 2017
Stability of the Blood Eosinophilic Phenotype in Stable and ECOPD

210 patients with COPD with >1 visit

2,059 visits
January 2008 to July 2015

1,039 ambulatory visits
1,020 hospitalized visits

Stable COPD
853 visits
7.2 ± 10.2 visits/patient

Moderate AECOPD
204 visits
3.4 ± 2.0 visits/patient

COPD hospitalizations (Severe AECOPD)
312 visits
3.8 ± 2.1 visits/patient

Hospitalizations for other reasons
708 visits
4.6 ± 2.7 visits/patient

Eosinophils (%), Difference from Baseline

Baseline Eosinophils (%)
0 2 4 6 8 10 12 14

COPD acute exacerbation
No
Yes

Schumann DM et al Chest 2019
Design

- Some introductory remarks. The eosinophil
- Endotyping
- Phenotyping
- Outcomes
- Stability
- Treatment decisions
A 56 year old woman was referred to our department. She has COPD [treated with triple therapy ICS, LAMA & LABA]. CAT 10, mMRC 1. FEV1 69% pred, ratio 65%. 1 exacerbation in the last year. No signs of Asthma. Absolute eosinophilic count 150 measured twice, The patient is eligible for:

A. ICS withdrawal
B. Keeping the same treatment strategy
C. None of the above
D. I need further information
A 56 year old woman was referred to our department. She has COPD [treated with triple therapy ICS, LAMA & LABA]. CAT 10, mMRC 1. FEV1 69% pred, ratio 65%. 1 exacerbation in the last year. No signs of Asthma. Absolute eosinophilic count 150 measured twice, The patient is eligible for:

A. ICS withdrawal
B. Keeping the same treatment strategy
C. None of the above
D. I need further information
Eosinophil-guided treatment strategy in COPD
COPD initial treatment: The eosinophilic part?

**INITIAL PHARMACOLOGICAL TREATMENT**

**Group C**
- ≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

**Group A**
- 0 or 1 moderate exacerbations (not leading to hospital admission)

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

**Group B**
- A Long Acting Bronchodilator (LABA or LAMA)

**FIGURE 4.1**

mMRC 0-1 CAT < 10
mMRC ≥ 2 CAT ≥ 10

GOLD 2019
COPD follow up: The eosinophilic part?

**FOLLOW-UP PHARMACOLOGICAL TREATMENT**

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT: ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
   - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   ✓ Place patient in box corresponding to current treatment & follow indications
   ✓ Assess response, adjust and review
   ✓ These recommendations do not depend on the ABCD assessment at diagnosis

---

**DYSPNEA**

- LABA or LAMA
  - LABA + LAMA
    - Consider switching inhaler device or molecules
    - Investigate (and treat) other causes of dyspnea
  - LABA + ICS
  - LABA + LAMA + ICS

**EXACERBATIONS**

- LABA or LAMA
  - LABA + LAMA
    - Consider if eos < 100
      - LABA + LAMA + ICS
        - Roflumilast
          - FEV₁ < 50% & chronic bronchitis
      - LABA + ICS
      - In former smokers
        - Azithromycin
        - LABA or LAMA
          - Consider if eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization
          - Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

*eos = blood eosinophil count (cells/μL)*

* Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization
** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

FIGURE 4.3
The eosinophilic part of the GOLD guidelines

4528 patients from 3 RCT BUD/FOR vs FOR

ICS withdrawal...

12-month, double-blind, parallel-group study - 2485 patients with a history of ≥1 AECOPD in the previous year - FEV₁ < 50% pred.

Triple therapy TIO 18 μg once daily + SALM 50 μg twice daily + FP 500 μg twice daily during a 6-week run-in period

RCT: continued triple therapy vs. withdrawal of fluticasone in three steps over a 12-week period.

Primary end point: time to the first moderate or severe COPD exacerbation
**ICS and eosinophils in COPD: Exacerbations - Wisdom**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Rate ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eosinophils (&lt;2% vs ≥2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2%</td>
<td>1039</td>
<td>1.02 (0.83–1.25)</td>
<td>0.84</td>
</tr>
<tr>
<td>≥2%</td>
<td>1200</td>
<td>1.22 (1.02–1.48)</td>
<td>0.033</td>
</tr>
<tr>
<td>Baseline eosinophils (&lt;3% vs ≥3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3%</td>
<td>1520</td>
<td>1.07 (0.90–1.29)</td>
<td>0.46</td>
</tr>
<tr>
<td>≥3%</td>
<td>729</td>
<td>1.27 (1.06–1.62)</td>
<td>0.053</td>
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<tr>
<td>Baseline eosinophils (&lt;4% vs ≥4%)</td>
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<td></td>
<td></td>
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<td>&lt;4%</td>
<td>1803</td>
<td>1.02 (0.89–1.20)</td>
<td>0.66</td>
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<tr>
<td>≥4%</td>
<td>436</td>
<td>1.63 (1.23–2.14)</td>
<td>0.0025</td>
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<tr>
<td>Baseline eosinophils (&lt;5% vs ≥5%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;5%</td>
<td>1962</td>
<td>1.07 (0.92–1.23)</td>
<td>0.39</td>
</tr>
<tr>
<td>≥5%</td>
<td>277</td>
<td>1.82 (1.20–2.76)</td>
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<tr>
<td>Baseline eosinophils (&lt;6% vs ≥6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6%</td>
<td>2060</td>
<td>1.10 (0.95–1.27)</td>
<td>0.20</td>
</tr>
<tr>
<td>≥6%</td>
<td>479</td>
<td>1.50 (1.24–1.84)</td>
<td>0.011</td>
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</table>

**Baseline eosinophils (mutually exclusive subgroups)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Rate ratio (95% CI)</th>
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</tr>
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<tbody>
<tr>
<td>&lt;2%</td>
<td>1039</td>
<td>1.02 (0.83–1.25)</td>
<td>0.84</td>
</tr>
<tr>
<td>2 to &lt;3%</td>
<td>481</td>
<td>1.16 (0.87–1.55)</td>
<td>0.31</td>
</tr>
<tr>
<td>3 to &lt;4%</td>
<td>283</td>
<td>0.90 (0.62–1.33)</td>
<td>0.69</td>
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<tr>
<td>4 to &lt;5%</td>
<td>159</td>
<td>0.91 (0.61–1.39)</td>
<td>0.11</td>
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<tr>
<td>5 to &lt;6%</td>
<td>93</td>
<td>0.93 (0.63–1.37)</td>
<td>0.0094</td>
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<tr>
<td>≥6%</td>
<td>179</td>
<td>1.49 (0.92–2.43)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Decreased rate ratio with ICS withdrawal**

**Increased rate ratio with ICS withdrawal**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td>2296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eosinophils (&lt;150 cells per µL vs ≥150 cells per µL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 cells per µL</td>
<td>1067</td>
<td>1.08 (0.89–1.32)</td>
<td>0.44</td>
</tr>
<tr>
<td>≥150 cells per µL</td>
<td>1172</td>
<td>1.17 (0.97–1.41)</td>
<td>0.034</td>
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<tr>
<td>Baseline eosinophils (&lt;300 cells per µL vs ≥300 cells per µL)</td>
<td></td>
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<tr>
<td>&lt;300 cells per µL</td>
<td>1791</td>
<td>1.04 (0.89–1.21)</td>
<td>0.59</td>
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<tr>
<td>≥300 cells per µL</td>
<td>448</td>
<td>1.56 (1.14–2.13)</td>
<td>0.0055</td>
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<tr>
<td>Baseline eosinophils (&lt;400 cells per µL vs ≥400 cells per µL)</td>
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<tr>
<td>&lt;400 cells per µL</td>
<td>1952</td>
<td>1.07 (0.92–1.23)</td>
<td>0.39</td>
</tr>
<tr>
<td>≥400 cells per µL</td>
<td>247</td>
<td>1.73 (1.27–2.32)</td>
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**Baseline eosinophils (mutually exclusive subgroups)**

<table>
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<td>1067</td>
<td>1.08 (0.88–1.33)</td>
<td>0.44</td>
</tr>
<tr>
<td>150 to &lt;300 cells per µL</td>
<td>724</td>
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<td>300 to &lt;400 cells per µL</td>
<td>201</td>
<td>1.30 (0.80–2.11)</td>
<td>0.28</td>
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<tr>
<td>≥400 cells per µL</td>
<td>247</td>
<td>1.73 (1.15–2.62)</td>
<td>0.0089</td>
</tr>
</tbody>
</table>

**Decreased rate ratio with ICS withdrawal**

**Increased rate ratio with ICS withdrawal**
A different view of the Isolde study: A different FEV$_1$ decline

**Panel a:**
- Change from baseline pre-bronchodilator FEV1, mL
- FP versus placebo = 3.8 mL·year$^{-1}$, p = 0.616

**Panel b:**
- Change from baseline pre-bronchodilator FEV1, mL
- FP versus placebo = 37.7 mL·year$^{-1}$, p = 0.001

Patients n
- Placebo: 89, 201, 193, 169, 158, 150, 147, 138, 127, 126, 116, 104, 89
- FP: 113, 230, 208, 198, 192, 178, 172, 170, 165, 157, 153, 149, 113

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SUNSET another trial for ICS withdrawal

SUNSET: The eosinophilic sign

D

Blood eosinophils < 300 cells/μL

Exacerbation-free probability

Days

Tiotropium plus Salmeterol/Fluticasone
Indacaterol/Glycopyrronium

Tiotropium plus Salmeterol/Fluticasone
Indacaterol/Glycopyrronium

E

Blood eosinophils ≥ 300 cells/μL

Exacerbation-free probability

Days

Tiotropium plus Salmeterol/Fluticasone
Indacaterol/Glycopyrronium

Tiotropium plus Salmeterol/Fluticasone
Indacaterol/Glycopyrronium

The Impact study: Triple therapy superiority Irrespective of eosinophils?

Lipson D, et al. NEJM 2018
Who drives the eosinophilic inflammation in COPD?

Samy Suissa, and Amnon Ariel Eur Respir J 2018;52:1801848
LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study.

Suissa S et al Lancet Resp Med 2018
ICS recommendations

**Strong support**

- History of hospitalisation(s) for exacerbations of COPD#
- $\geq 2$ moderate exacerbations of COPD per year#
- Blood eosinophils $>300$ cells·$\mu$L$^{-1}$
- History of, or concomitant, asthma

**Consider use**

- 1 moderate exacerbation of COPD per year#
- Blood eosinophils 100–300 cells·$\mu$L$^{-1}$

**Avoid use**

- Repeated pneumonia events
- Blood eosinophils $<100$ cells·$\mu$L$^{-1}$
- History of mycobacterial infection

↑age, ↓BMI,
greater overall fragility,
blood eosinophils $<100$ cells·$\mu$L$^{-1}$,
pts receiving higher ICS doses

Anti-IL-5: Not yet for COPD


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**Blood Eosinophil Count**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients meeting criterion/total no. of patients</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab Group</td>
<td>184/184</td>
<td>190/190</td>
</tr>
<tr>
<td>Placebo Group</td>
<td>236/640</td>
<td>230/645</td>
</tr>
<tr>
<td>≥300 with no historical count ≥300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>≥300 to &lt;500</td>
<td>237/456</td>
<td>235/455</td>
</tr>
<tr>
<td>≥500</td>
<td>112/456</td>
<td>110/455</td>
</tr>
<tr>
<td>&lt;150 with historical count ≥100</td>
<td>53/456</td>
<td>42/455</td>
</tr>
</tbody>
</table>

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The graph shows the percentage of patients with an event over weeks since randomization for different dose groups of Mepolizumab and Placebo.
Benralizumab for COPD

Criner CJ et al NEJM 2019
Eosinophils are multifunctional cells that contribute to both innate and adaptive immunity.

Eosinophils have a critical role in asthma pathogenesis. Still questioning in COPD.

Different cellular and molecular mechanisms drive eosinophilia in COPD.

Eosinophil represents an “ideal” biomarker to optimise steroid therapy (personalised medicine) in asthma –but not yet in COPD.

Still searching their predictive role.

Eosinophilic inflammation improves responses to targeted therapies in asthma but not in COPD.

To be continued…..