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Approach to asthma exacerbations including those occurring in patients treated with asthma biologics

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Disclosures

- **Speaker's Honoraria:** AstraZeneca, Boehringer Inglehiem, Aerocrine, Chiesi, Novartis, Sanofi, Regeneron and GSK.
- **Advisory Panels:** Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp, Sanofi, Regeneron.
- **Sponsorship:** Boehringer Ingelheim, GSK, AstraZeneca, Chiesi and Napp.

Introduction

- Definition and epidemiology
- Eosinophilic airway inflammations as a detectable ‘treatable trait’ closely associated with exacerbations
- Heterogeneity of exacerbations and the prospect of a precision medicine approach to treatment
- Exacerbations occurring on biologic treatment.

An exacerbation is more than just an exasperation

- Mortality
- Health care and societal costs
- Irreversible loss of lung function
- High risk of recurrence
- Opportunity for intervention

? Lung attack

? Asthma attack

Severe asthma exacerbations

Among patients with severe asthma:

- >50% have at least one urgent care visit per year[1]
- 54% have ≥3 OCS bursts per year[1]
- Nearly 25% have had a near fatal event in the past[1]
- 34% were hospitalized at least once in a 12-month period[2]
- 19% missed at least one day of work or school in the previous 2 weeks compared to patients with moderate (13%; p<0.001) or mild asthma (12%; p<0.001)[3]

BBC NEWS

Saturday, 17 November, 2001, 00:36 GMT

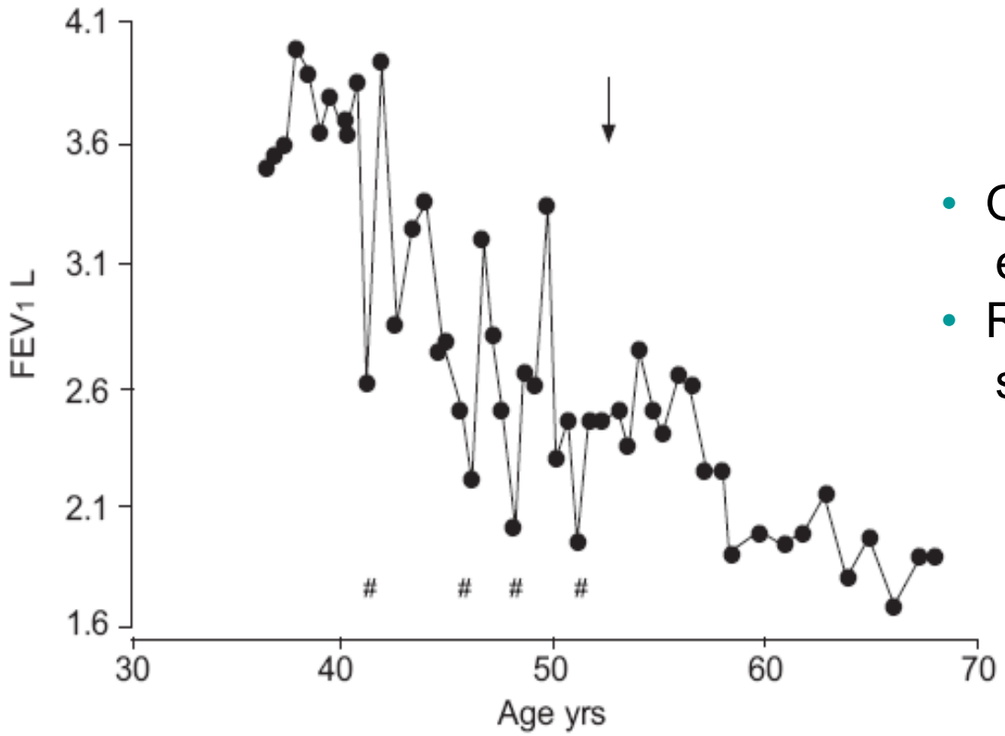
Four Weddings star found dead

Four Weddings and a Funeral star Charlotte Coleman has died aged 33, after suffering a massive asthma attack.

Permission to use photo obtained from PA Images; London UK

[1]Moore et al. J Allergy Clin Immunol 2007;119:405-13
[2]Carvalho-Pinto et al. Resp Med 2012;106:47-56;
[3]Dolan et al. Ann Allergy Asthma Immunol 2004;92:32-39

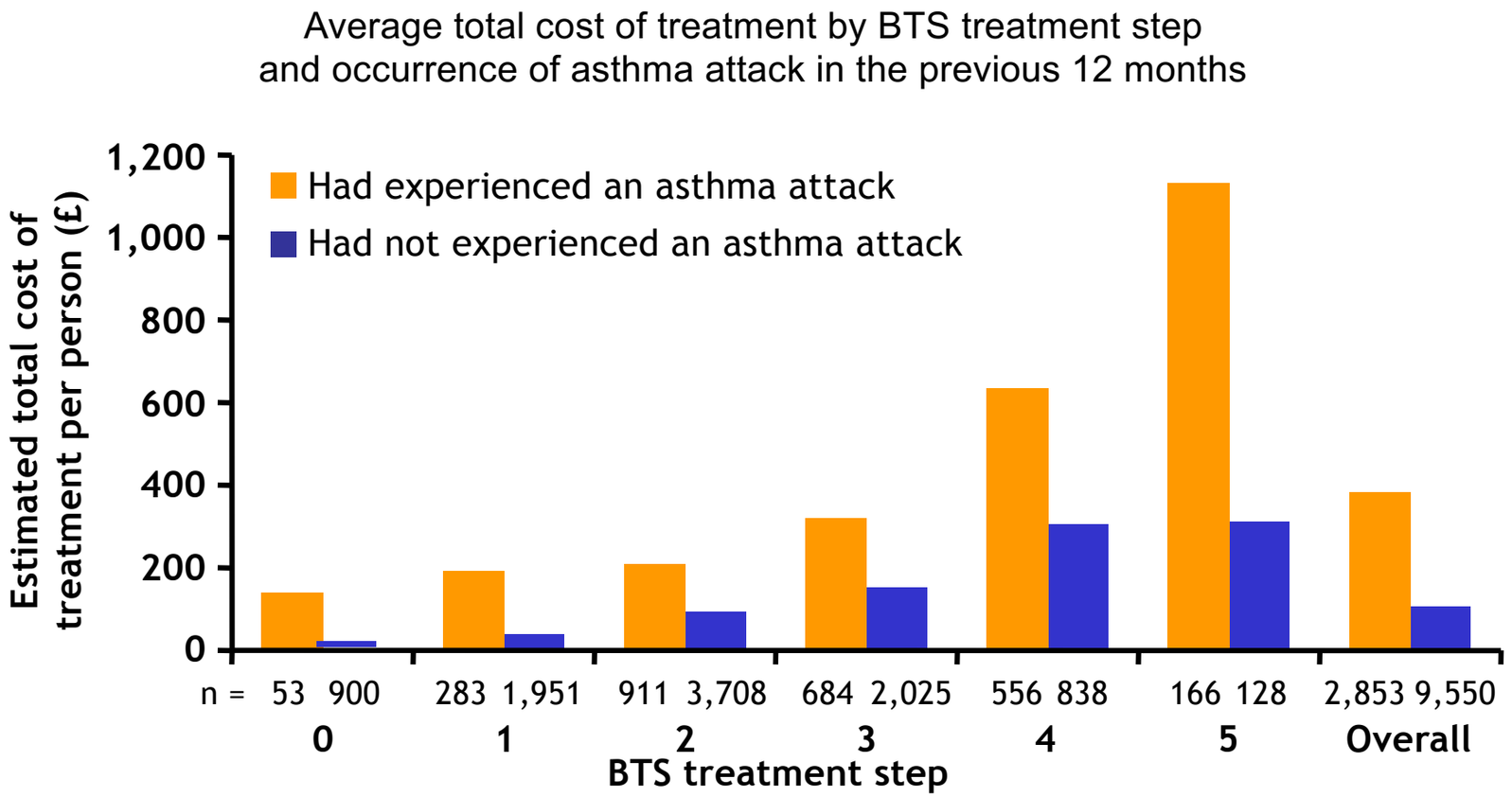
Irreversible loss of lung function with asthma attacks



- One attack/year caused 30 ml excess loss in FEV_1/year
- Roughly equivalent to decline seen with smoking

Bai et al. Eur Resp J 2007;30:452-56

Asthma attacks contribute to substantial healthcare and societal costs



BTS = British Thoracic Society

1. Asthma UK Asthma Audit, 1999; 2. Barnes PJ, et al. Eur Respir J 1996;9:636–42.

Defining exacerbations

ATS/ERS consensus 2009 - Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice

- Severe exacerbations – *"events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma".*
- Moderate exacerbations – *"events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation".*

AJRCCM, Vol 180, 2009

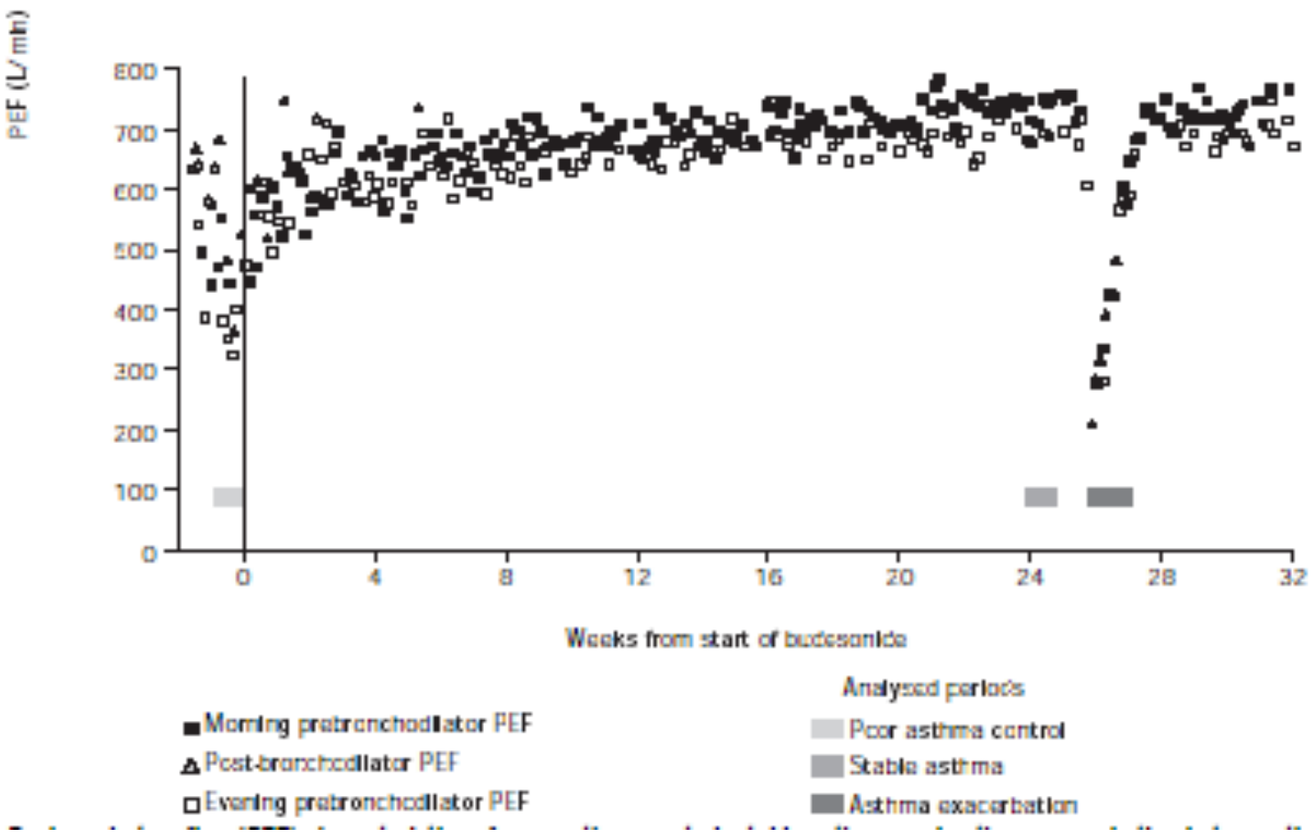
Types of exacerbations

ARTICLES

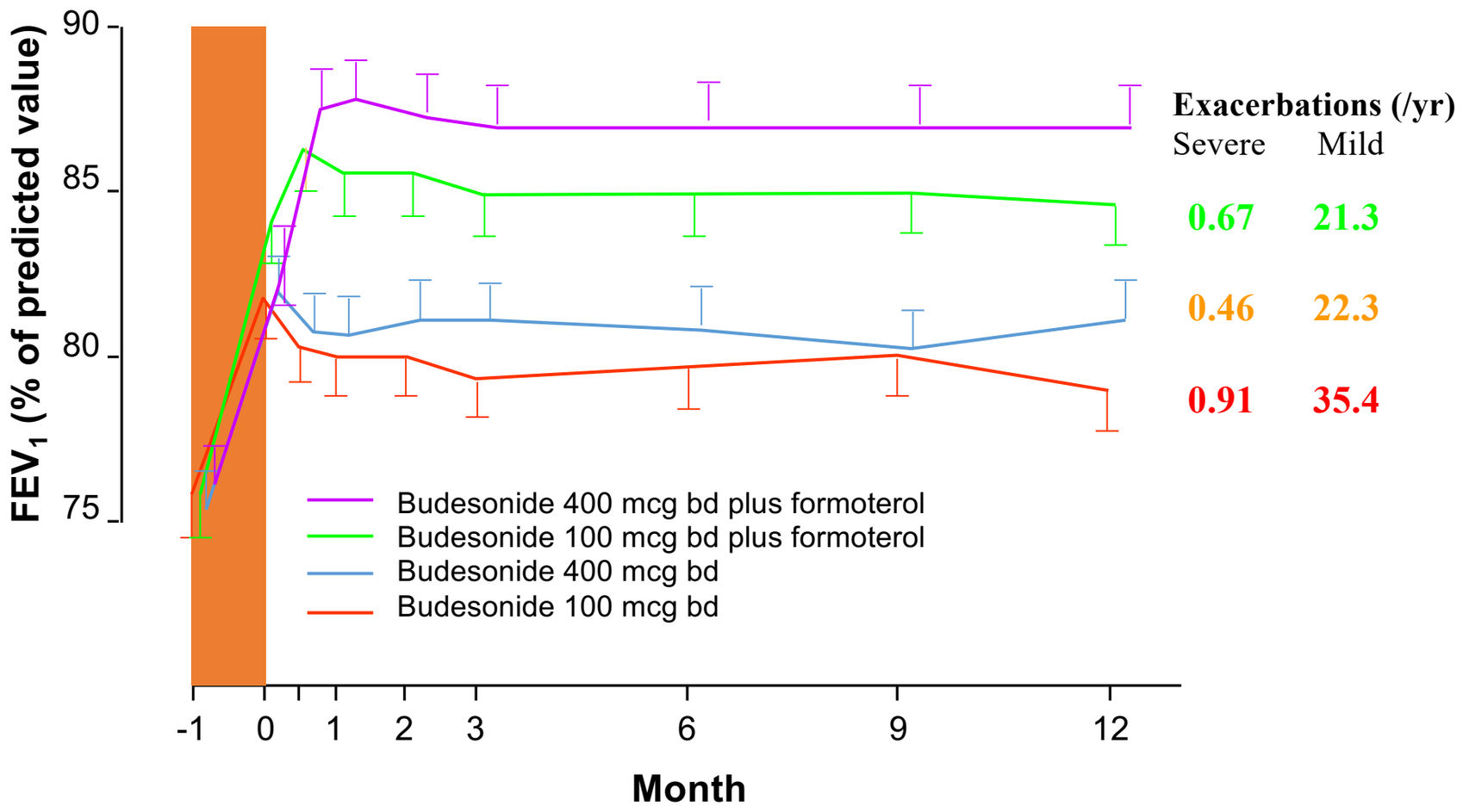
Differences between asthma exacerbations and poor asthma control

Lancet 1999; **353:** 364–69

Helen Reddel, Sandra Ware, Guy Marks, Cheryl Salome, Christine Jenkins, Ann Woolcock

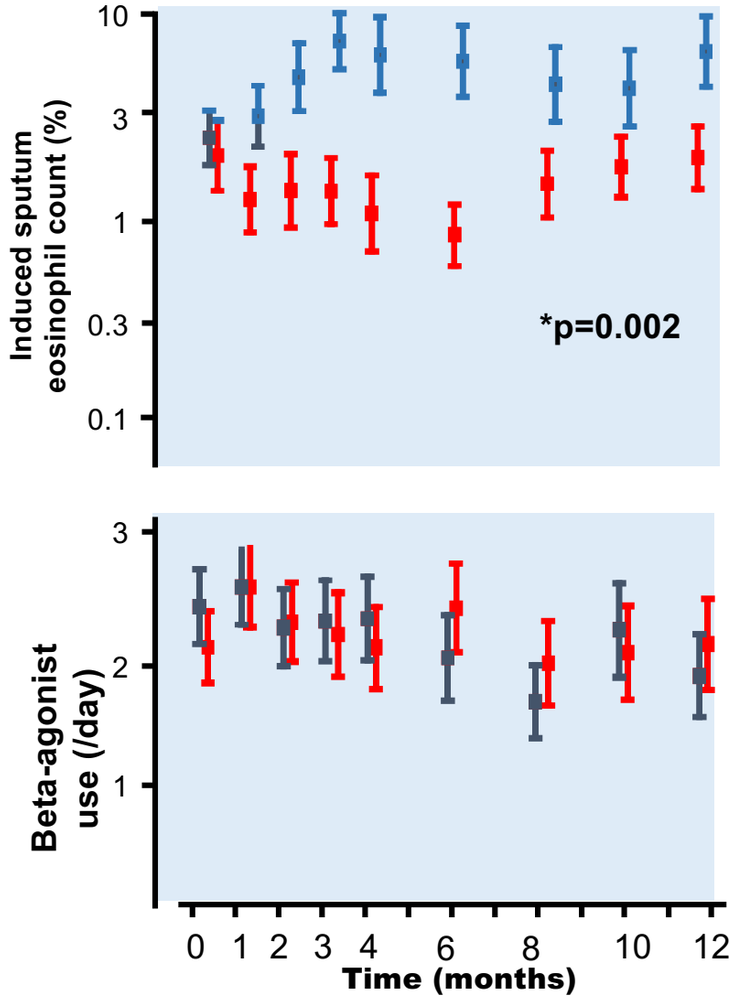


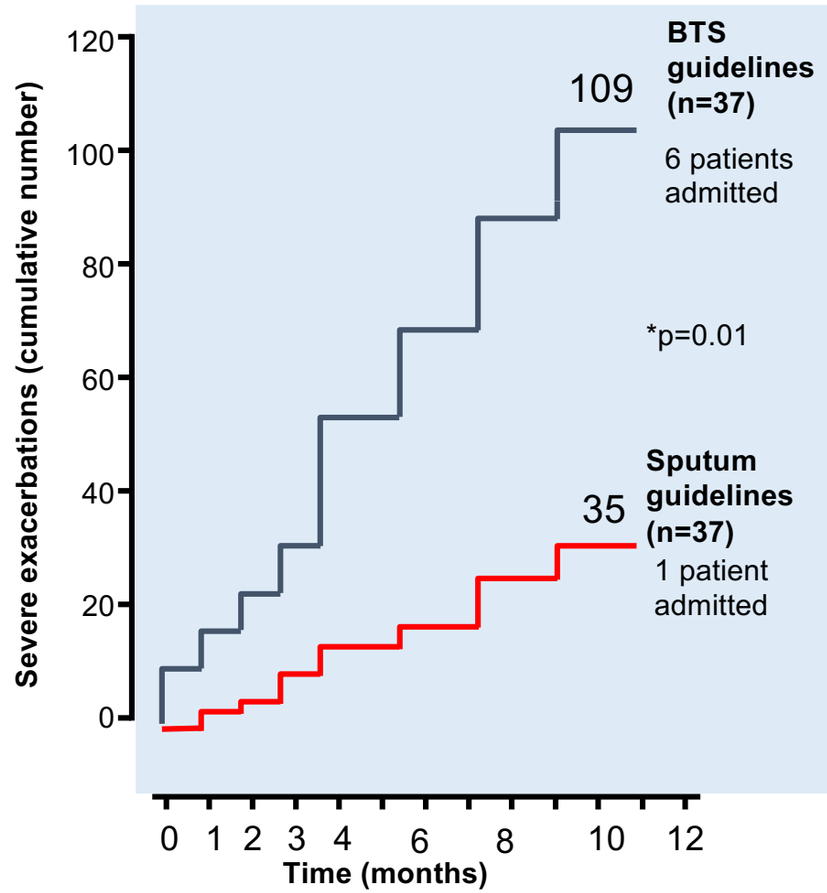
The FACET study



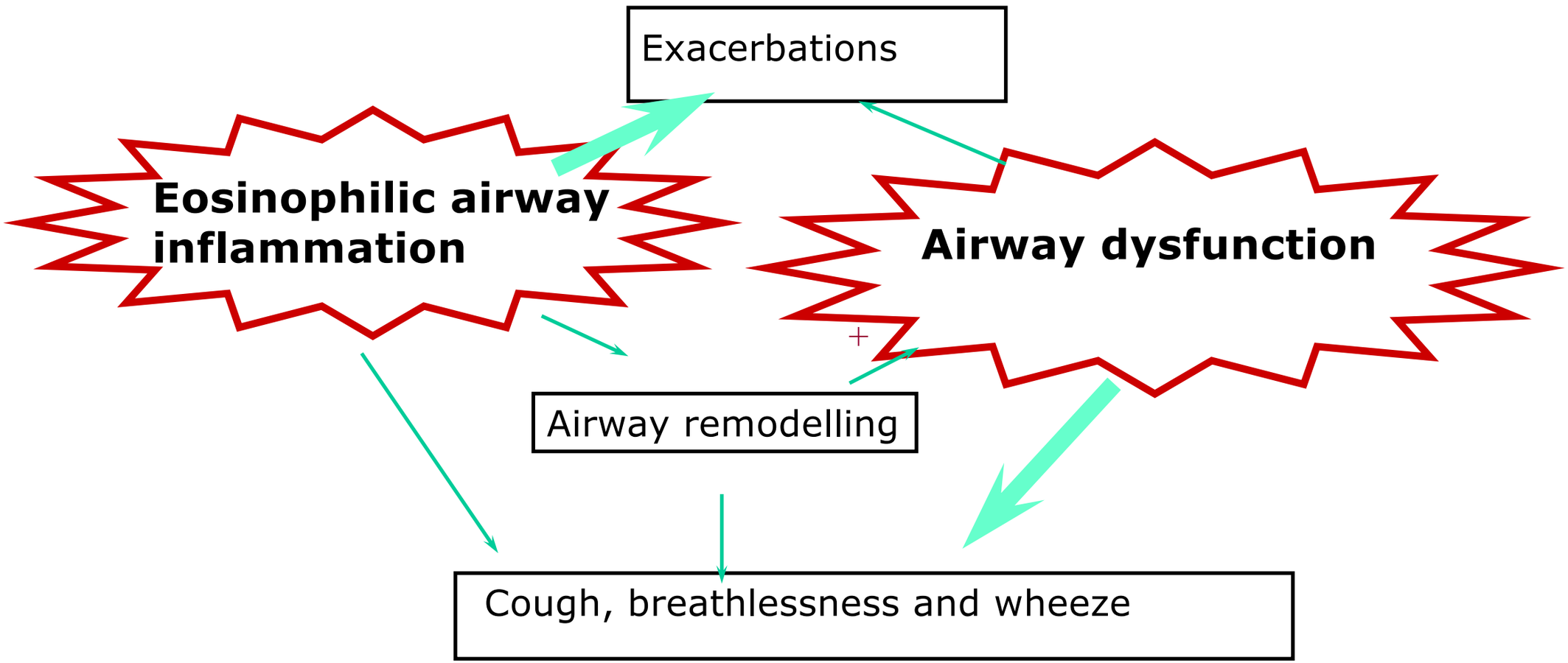
Pauwels et al New Engl J Med 1997;337:1405-1411

Traditional vs inflammation-guided management



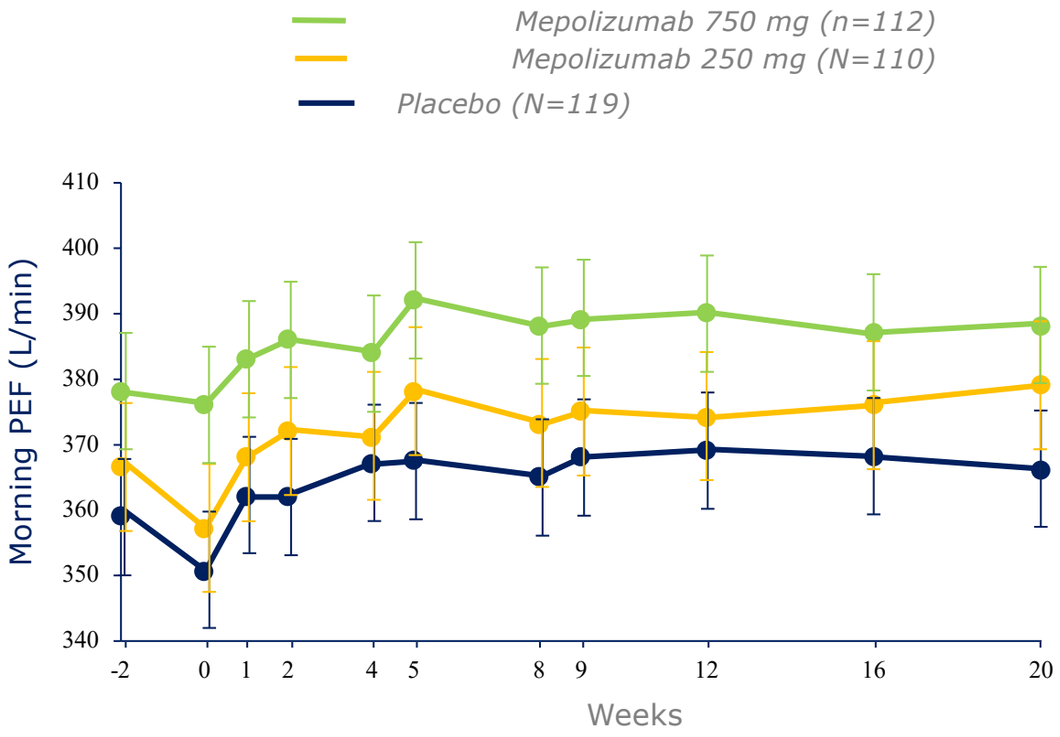


Green et al. Lancet 2002;360:1715-21

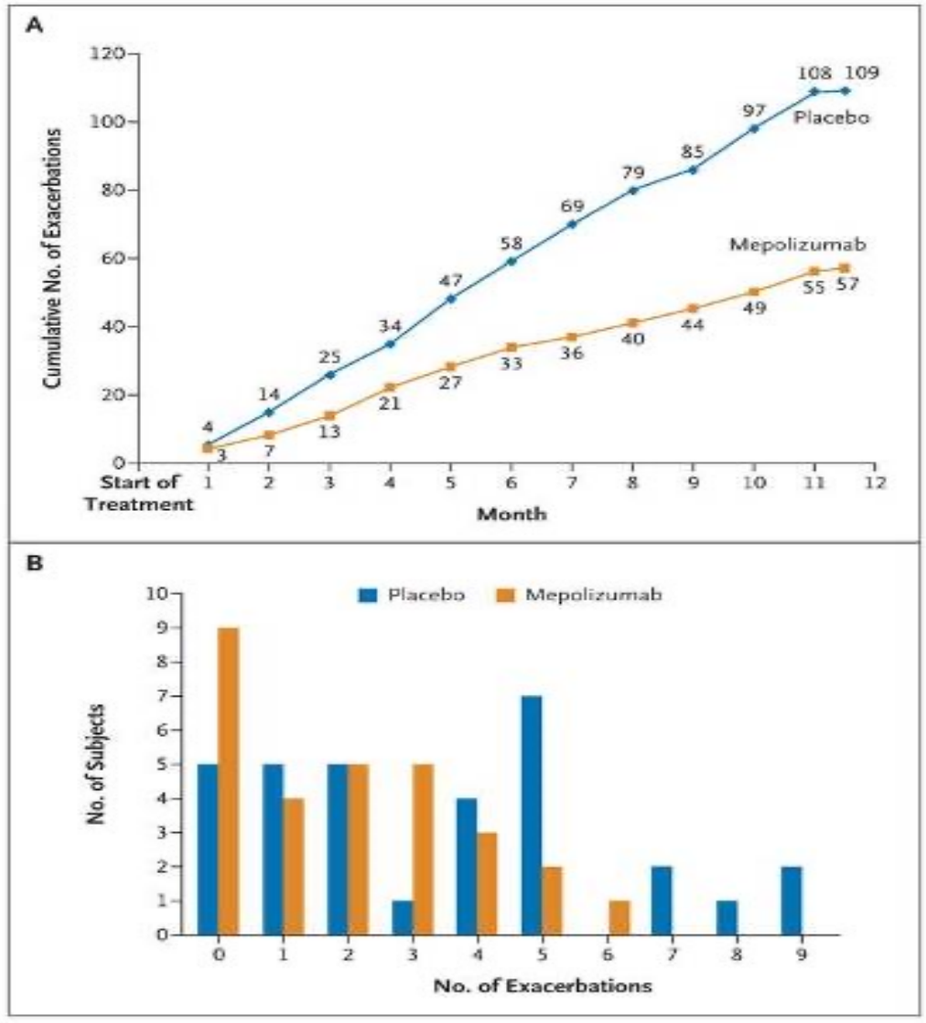


Shaw et al. Lancet Resp Med 2021

Mepolizumab (anti-IL-5): effect in 'asthma' and eosinophilic airways disease

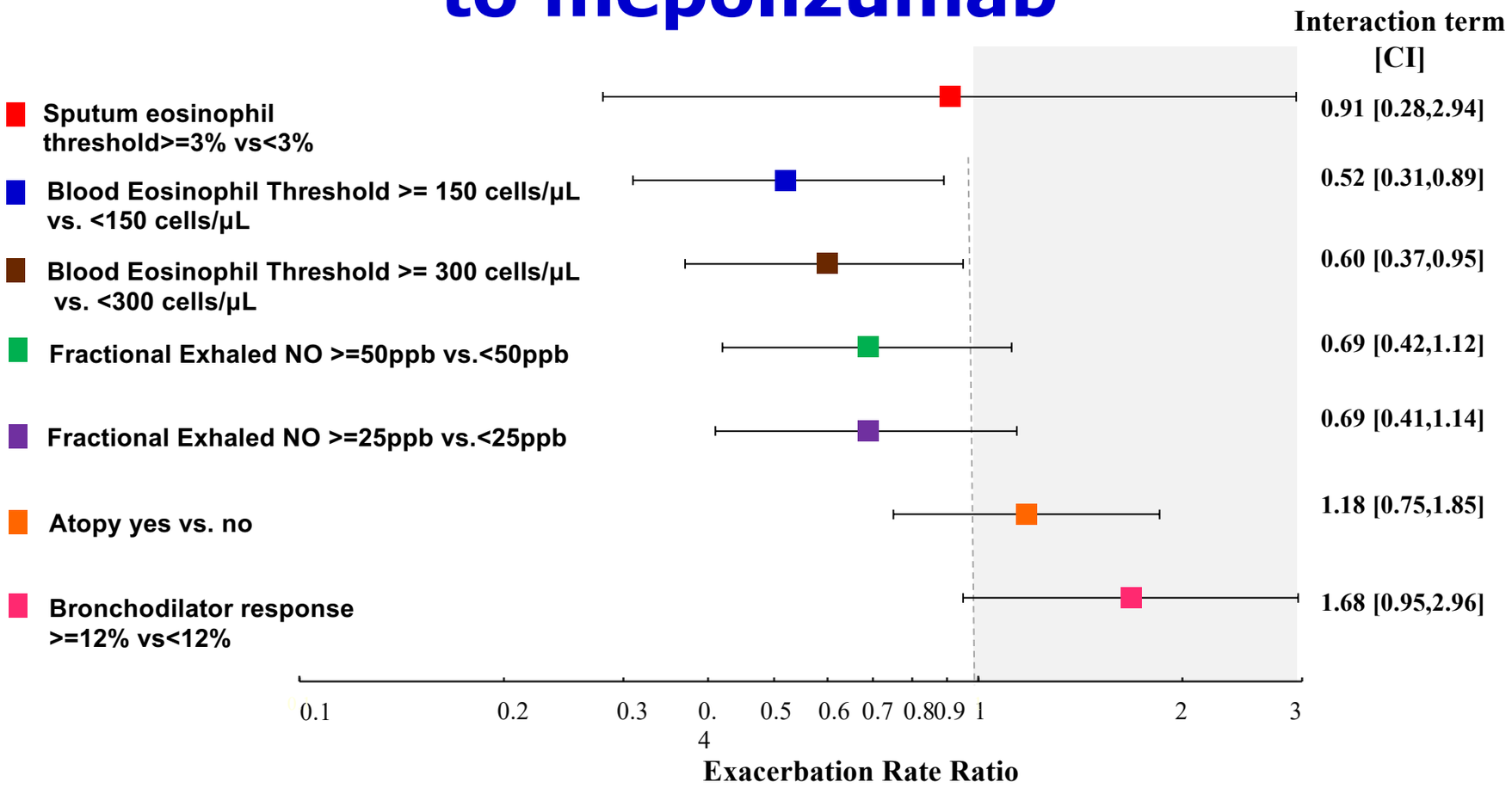


Flood-Page et al. AJRCCM 2007;176:1062-71



Haldar et al. NEJM 2009;360:973-84

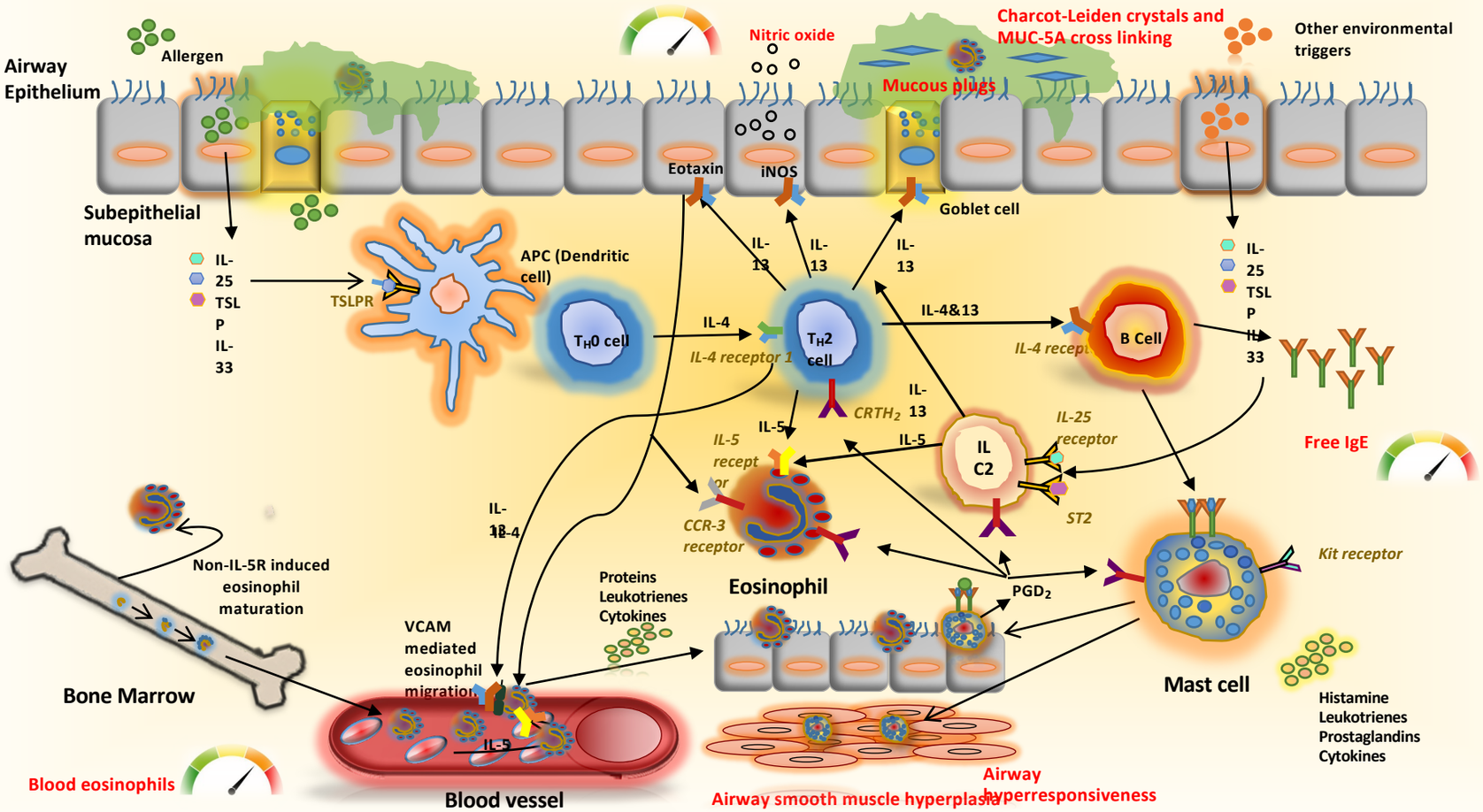
DREAM: predictors of response to mepolizumab



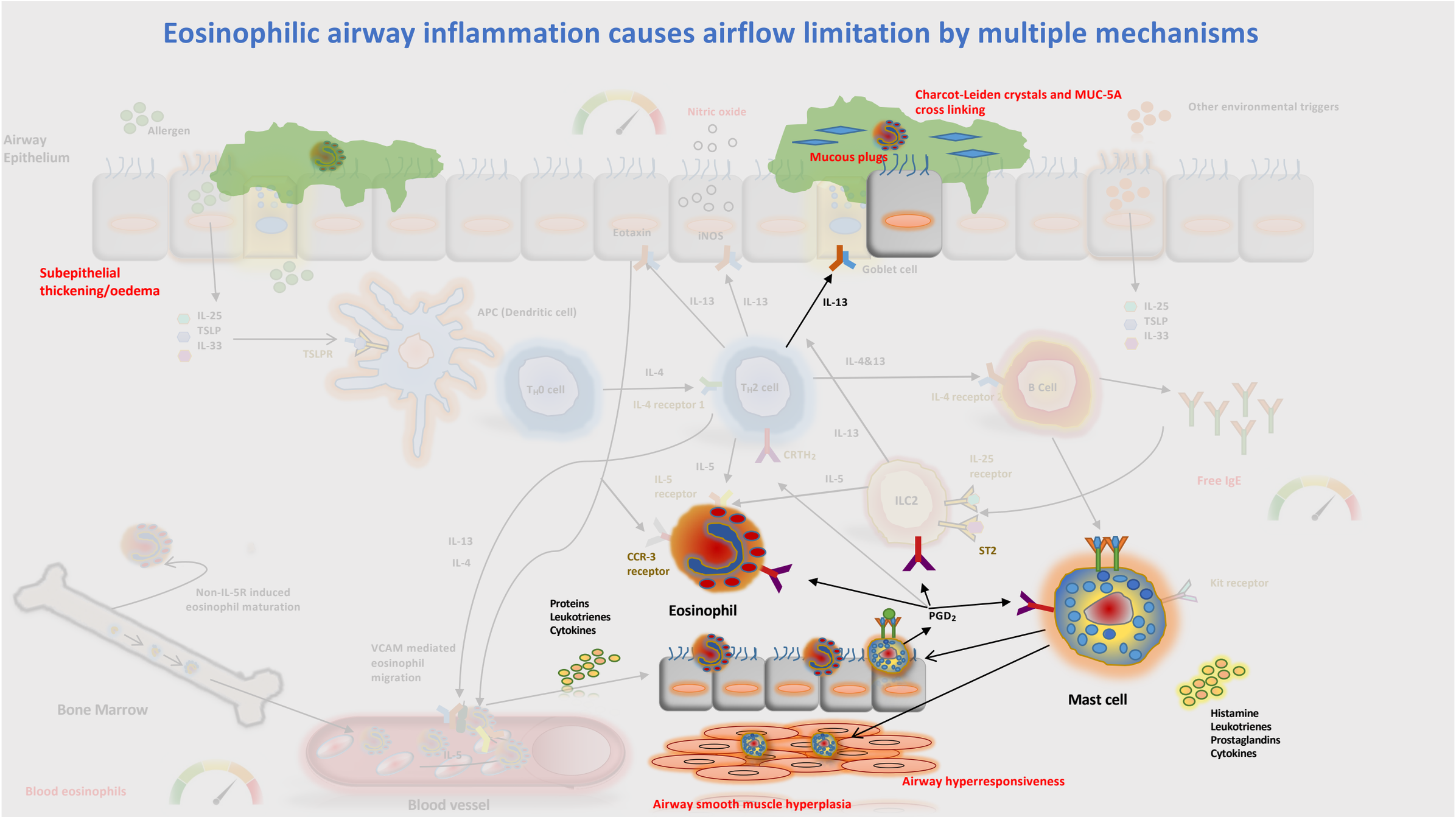
- A post hoc analysis of exacerbation reduction ratios compared 7 biomarkers above and below the listed threshold when measured at baseline

Adapted from GSK data on file; DNG# 2016N275692_00GSK, Supplement to Pavord et al. Lancet. 2012;380(9842):651-659. GSK data on file: RF/NLA/0153/16

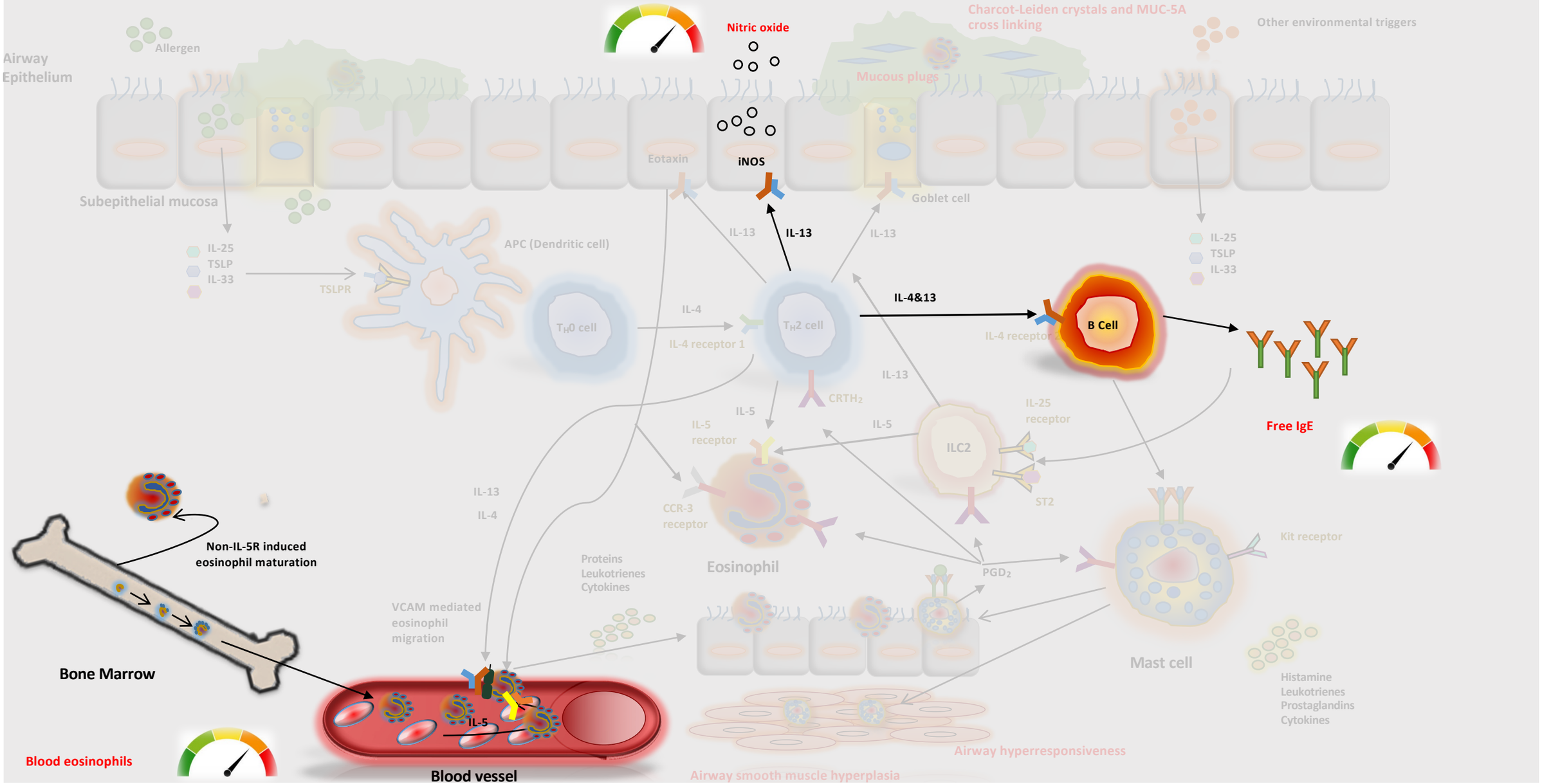
Type-2 airway inflammation



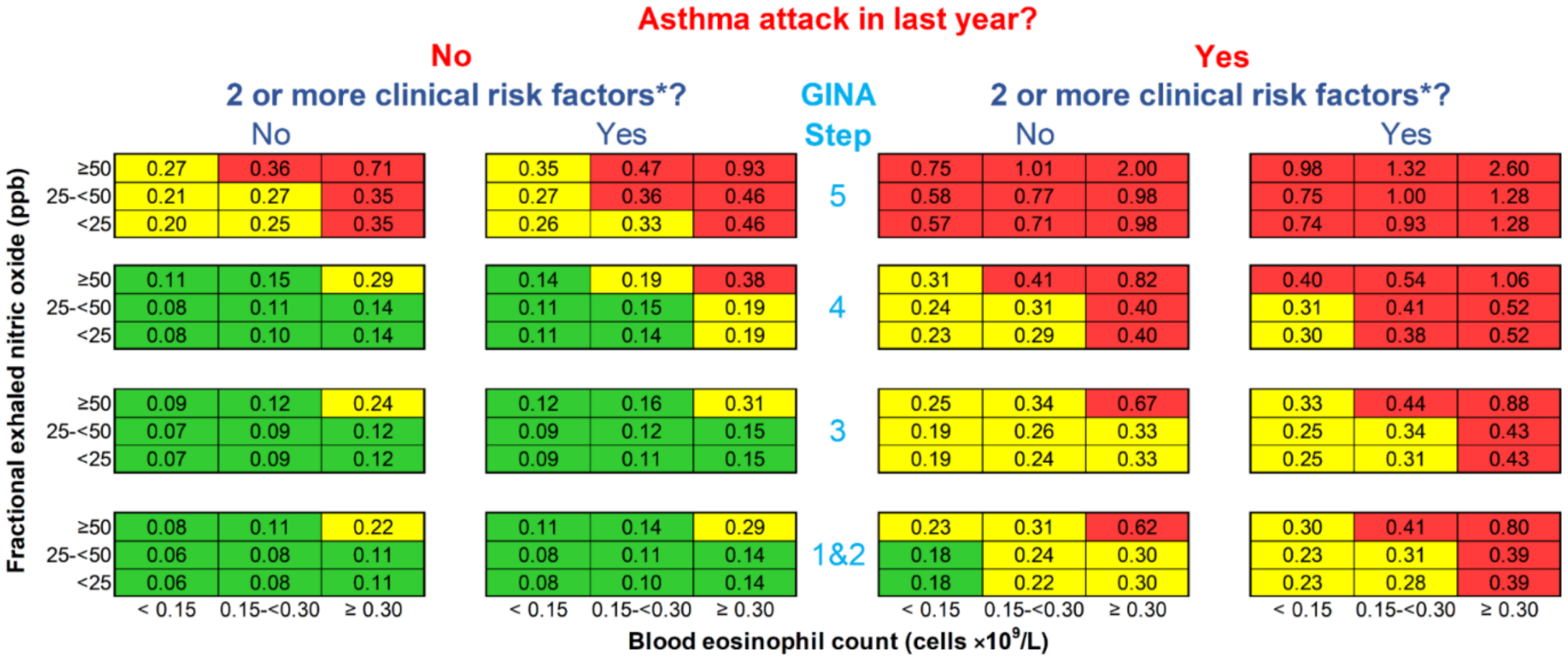
Eosinophilic airway inflammation causes airflow limitation by multiple mechanisms



Eosinophilic airway inflammation is detectable with clinically accessible biomarkers

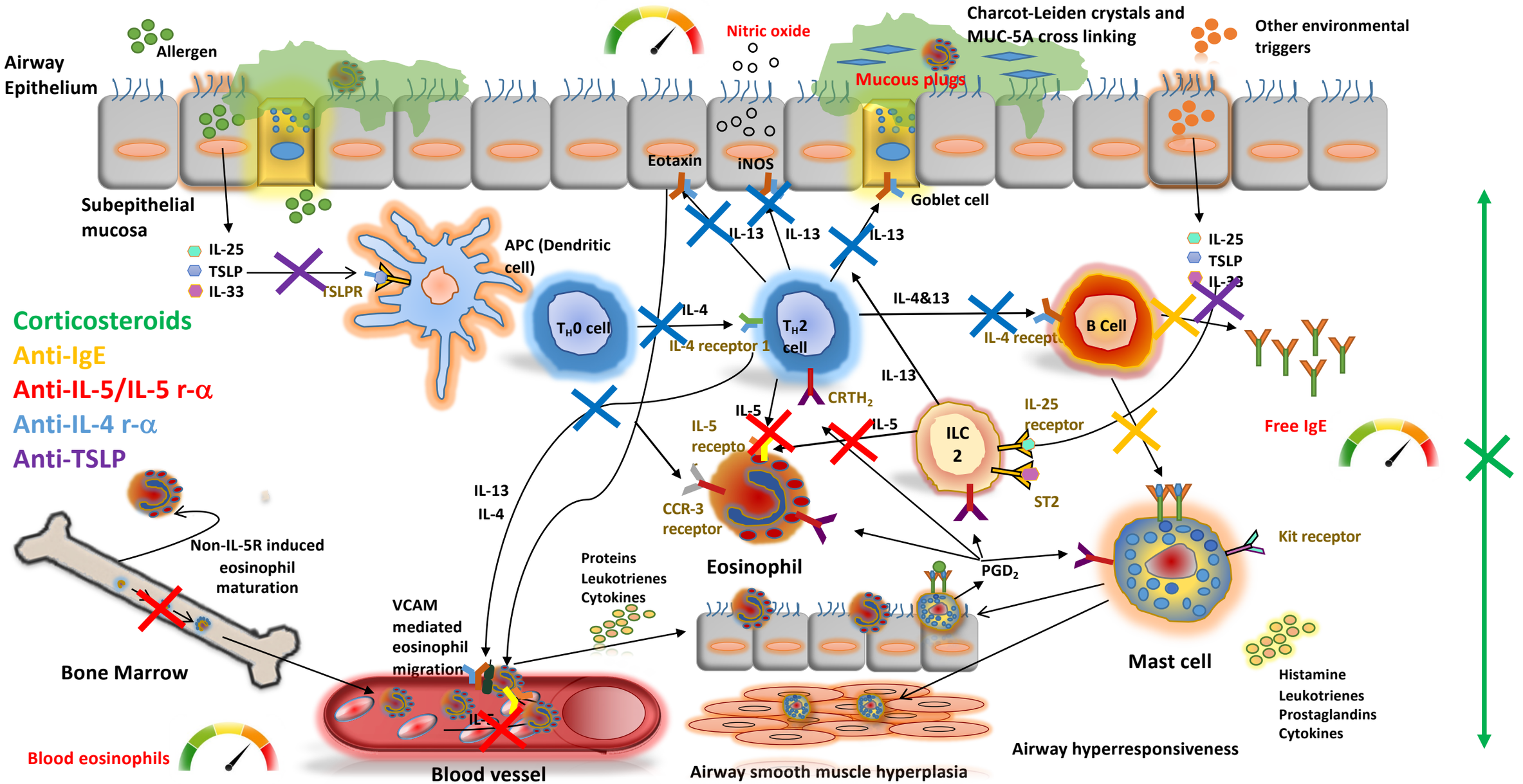


The Oxford Risk of Asthma attaCk scaLE (ORACLE)

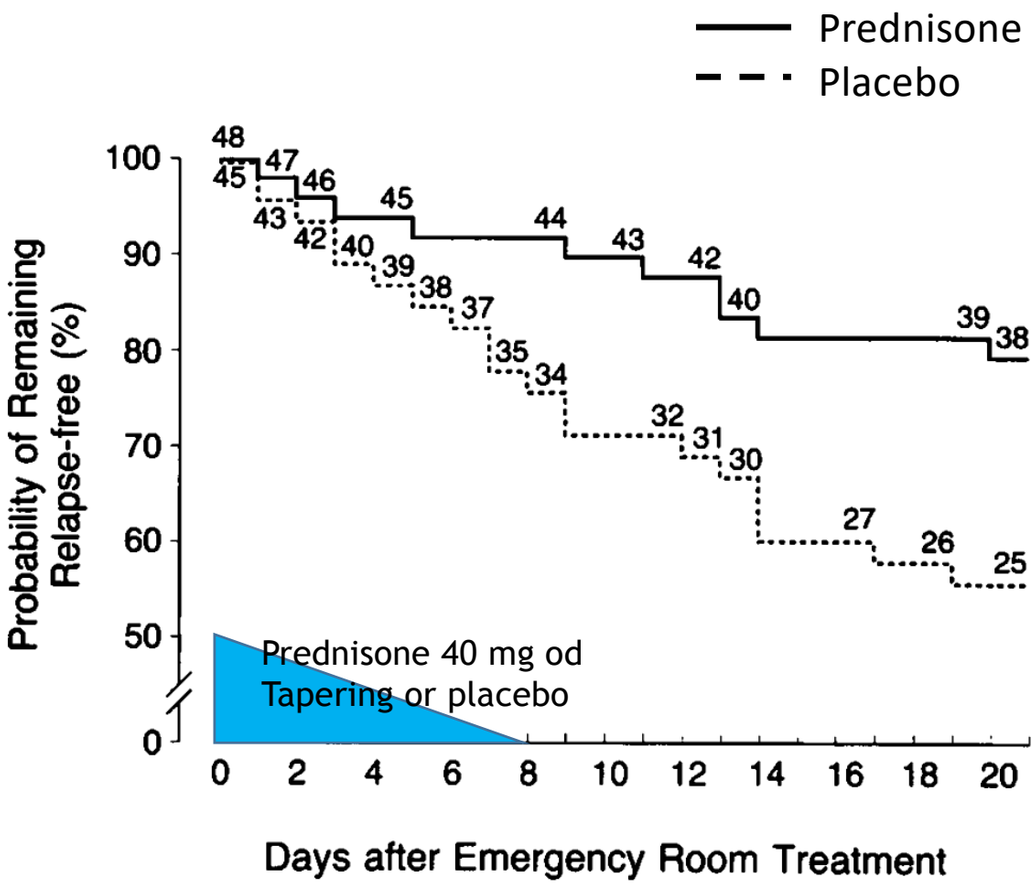


Couillard et al. Thorax 2022

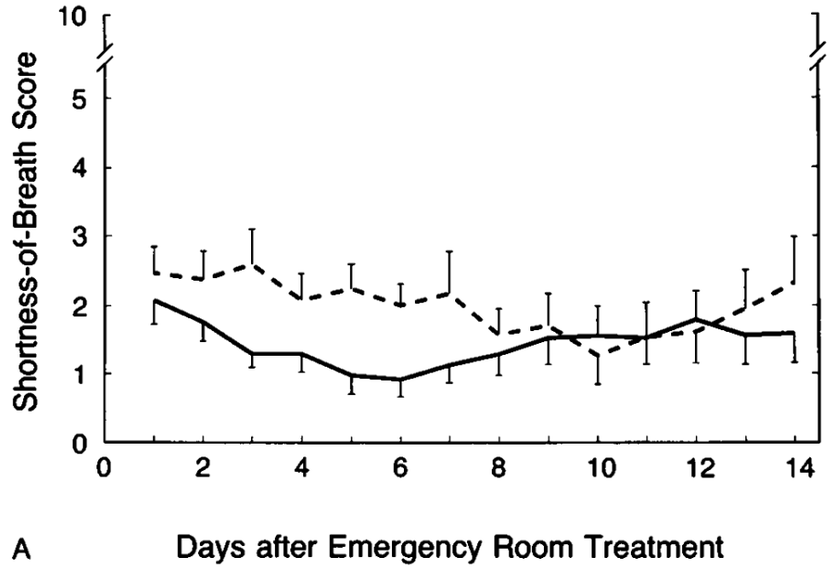
Targeted anti-inflammatory therapies work at different levels

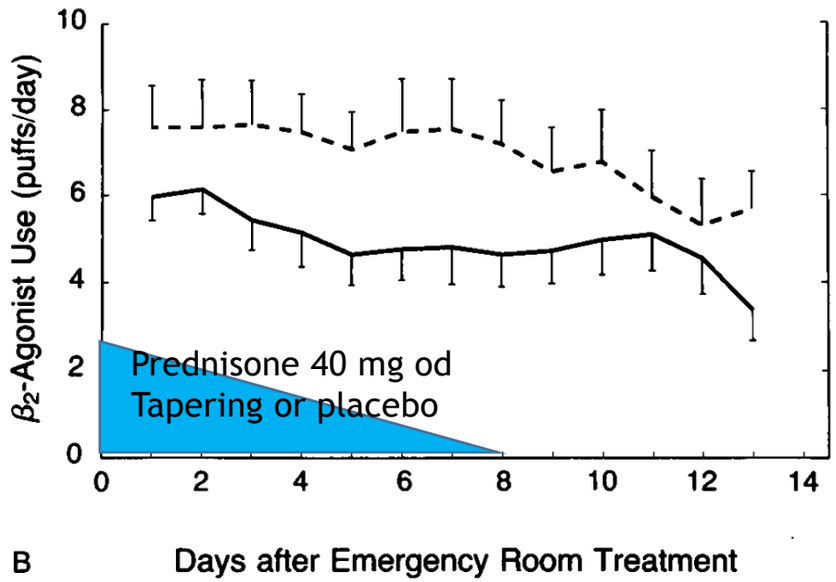


The use of OCS to treat acute severe asthma



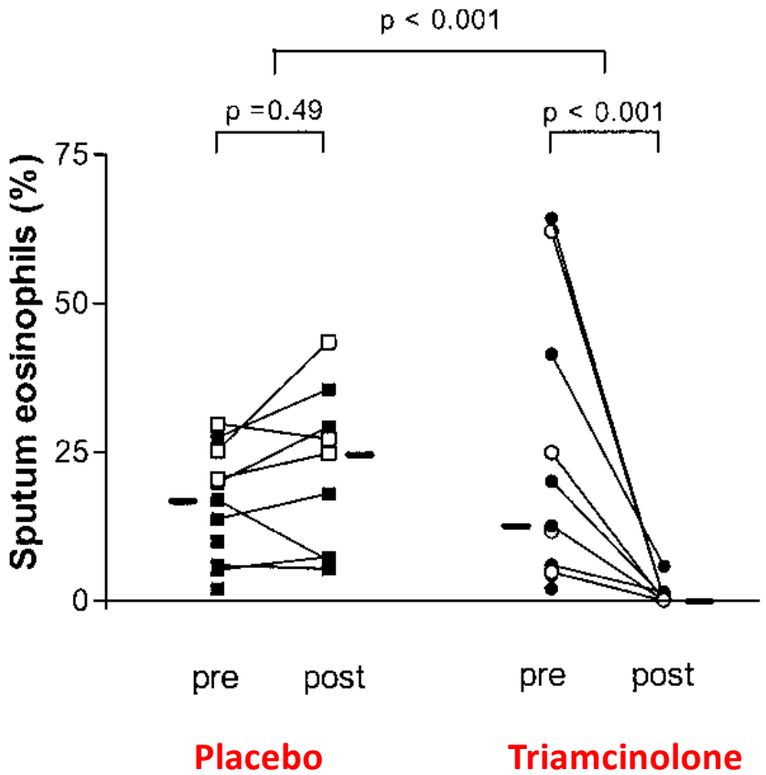
- Only 20% taking ICS on discharge

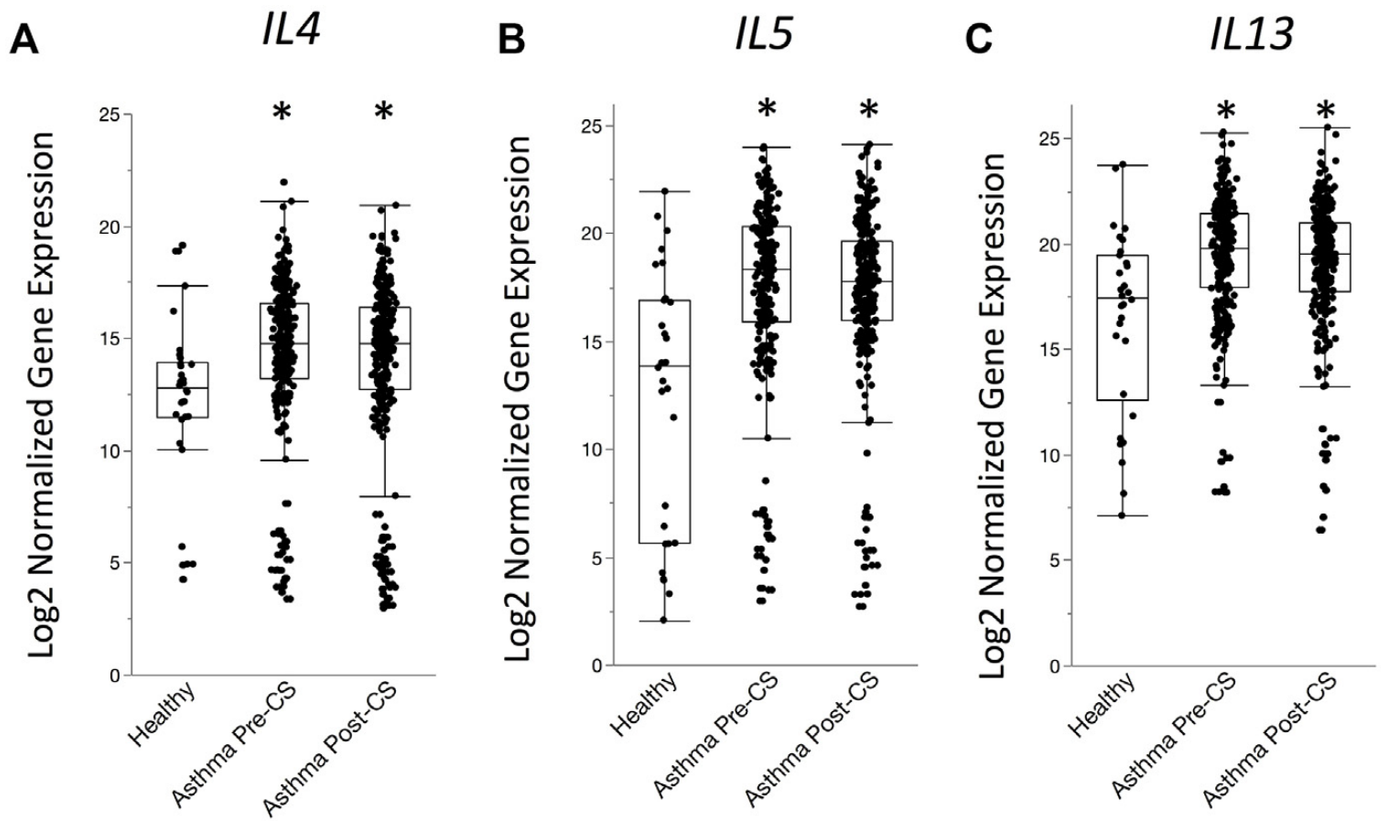




Chapman et al. NEJM 1991;324:788-94

IM triamcinolone reduces eosinophilic airway inflammation but has no effect on airway type-2 cytokine gene expression





Ten Brinke et al. AJRCCM 2004;170:601-5

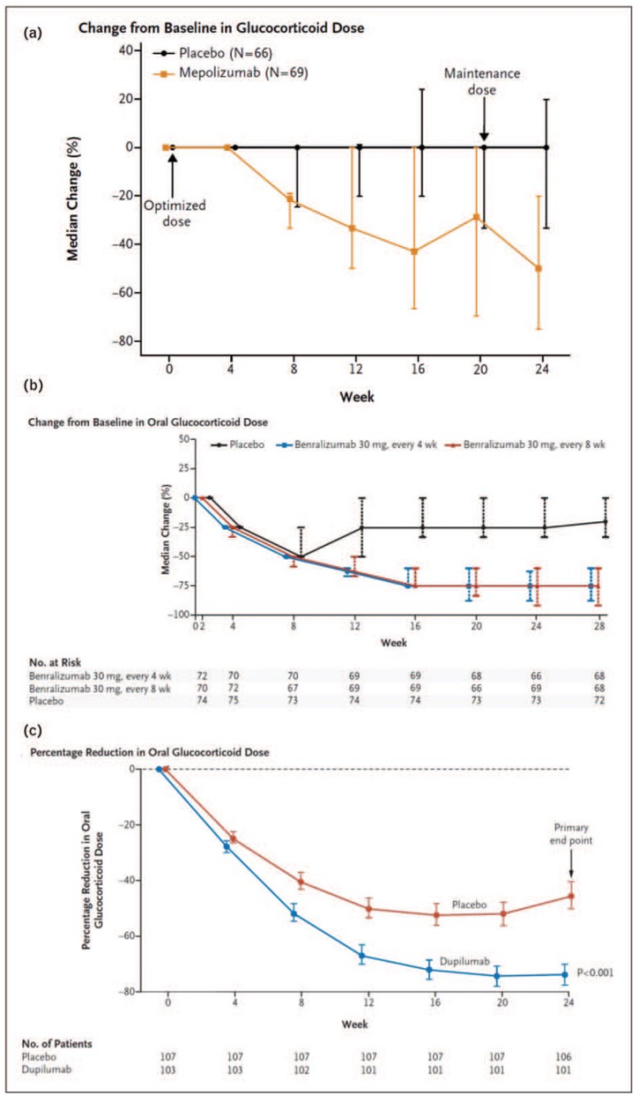
Peters et al. JACI 2019;143:104-13

The effect of corticosteroids and biologics on clinical measures and biomarkers

	Effect on clinical measures					*Effect on biomarkers*			
	FEV_1	Symptoms	Exac	OCS sparing	Type 2 comorbidities*	Sputum eos	Blood eos	FeNO	IgE
Anti-IL-5	+	+	++	++	+	↓↓	↓↓	↔	↔
OCS	+	+	++	NA	++	↓↓	↓↓	↓	↔
ICS	+	+	++	++	0	↓↓	↔/↓	↓↓	↔

Bl, blood; eos, eosinophils; Exac, exacerbations; Sp, sputum. * Rhinosinusitis, nasal polyposis, atopic dermatitis . **free IgE

OCS sparing effect of type 2 biologic therapies



Sirius[1]

Zonda[2]

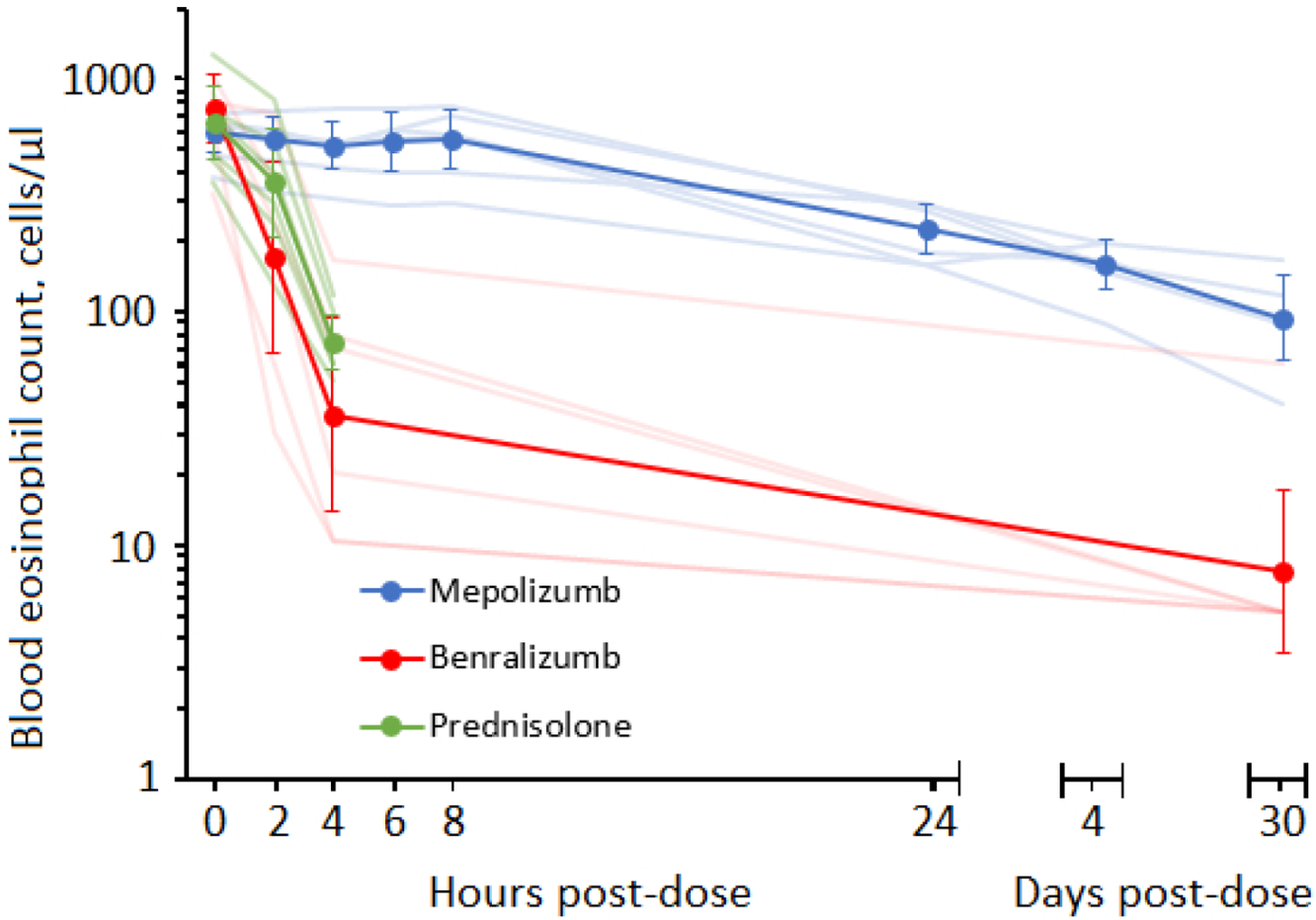
Venture[3]

Biologic	% reduction in OCS dose with active and placebo	Change in pre-bronchodilator FEV1 active – placebo (ml)	% reduction in exacerbations
Mepolizumab	50 vs 0	114	32
Benralizumab*	75 vs 25	113	55
Dupilumab	70.1 vs 41.9	220	59

* 8 weekly dosing

[1]*Bel et al. NEJM 2014; 371:1189-1197*
[2]*Nair et al. NEJM 2017; 376:2448-2458*
[3]*Rabe et al. NEJM 2018;378:2475-85.*

Benralizumab depletes blood eosiniophils as quickly as prednisolone



Moran et al. AJRCCM 2020

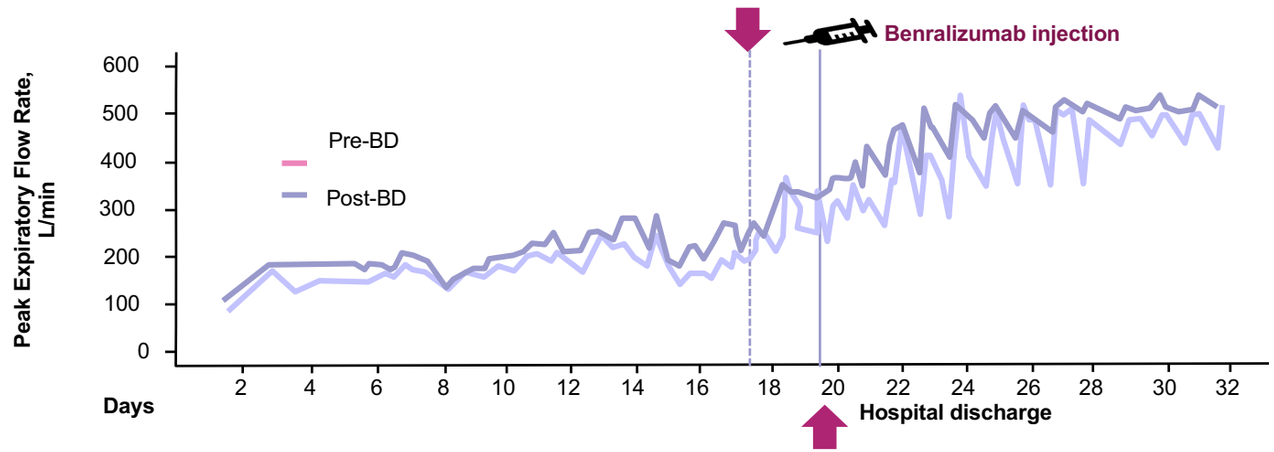
Case Report: Rapid Clinical Improvement With Benralizumab in Acute Asthma Attack

Patient Assessment

A 52-year-old male patient with a history of central serous retinopathy (CSR) with complete visual loss after treatment with an oral steroid for nasal polyps presented with an acute asthma attack

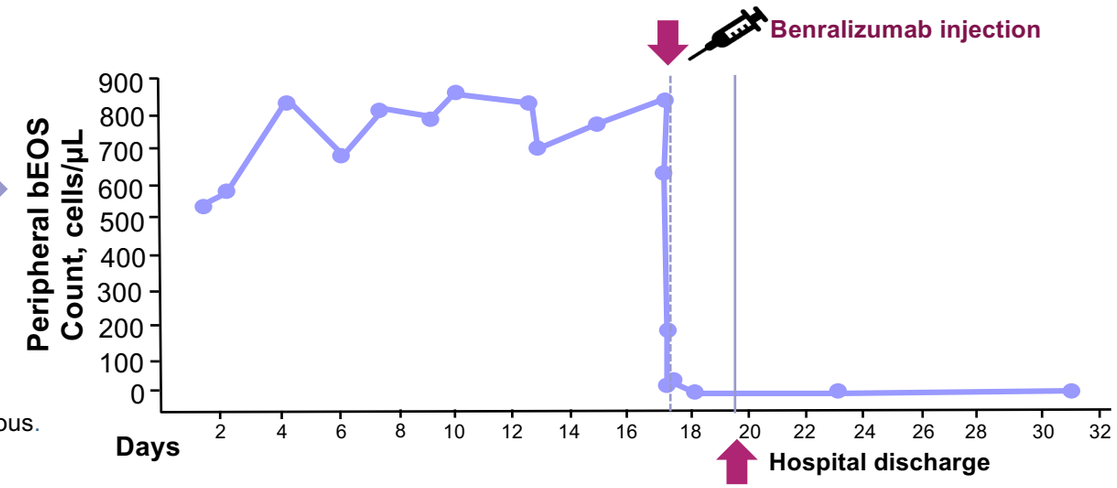
- Treatment with systemic corticosteroids was contraindicated due to CSR and treatment with benralizumab was initiated

Rapid improvement achieved 19 hours after benralizumab treament (post-BD, 270 to 370 L/min)



Diagnostics tests

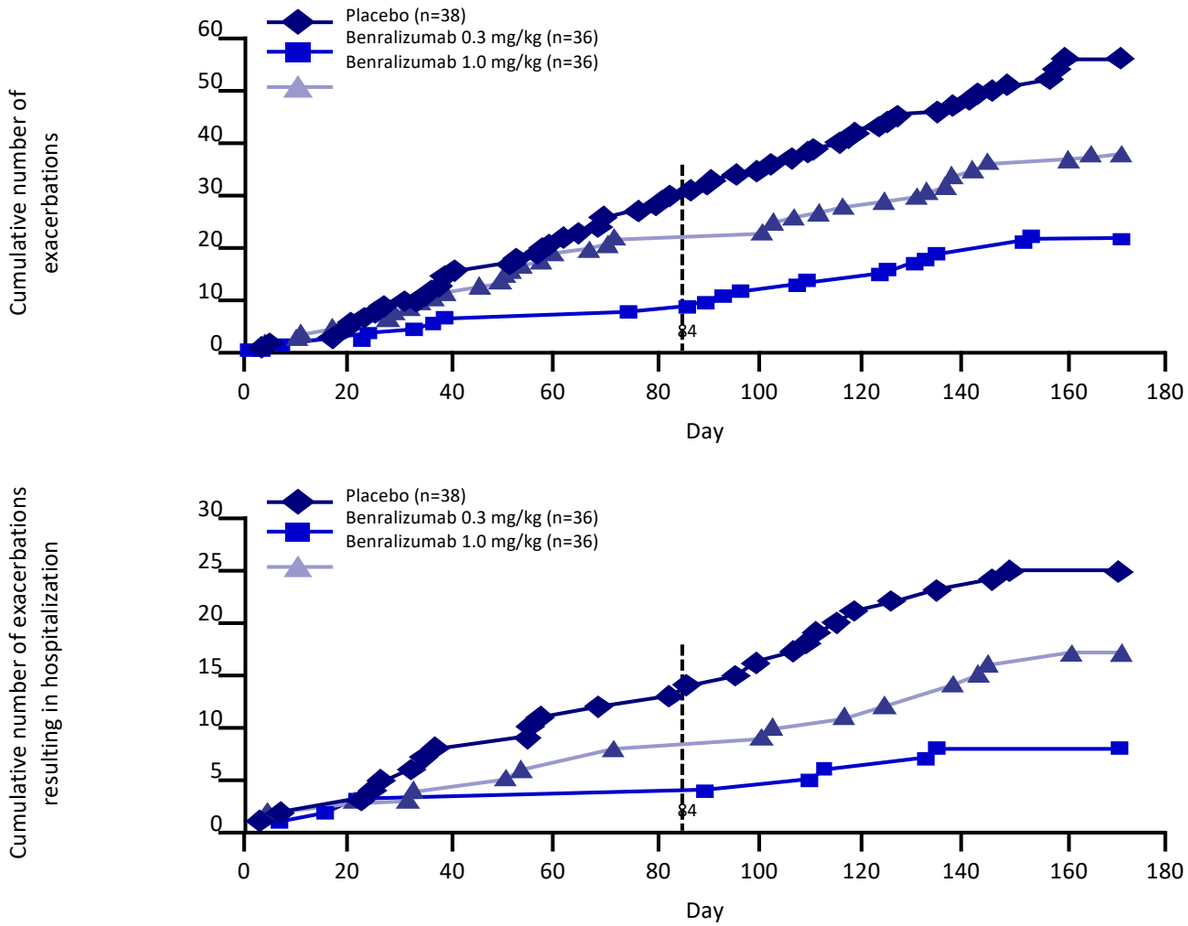
4 hours after administering benralizumab 30 mg SC: **bEOS** decreased from **840 to 10 cells/µL**



BD = bronchodilator; bEOS = blood eosinophils; CSR = central serous retinopathy; SC = subcutaneous.

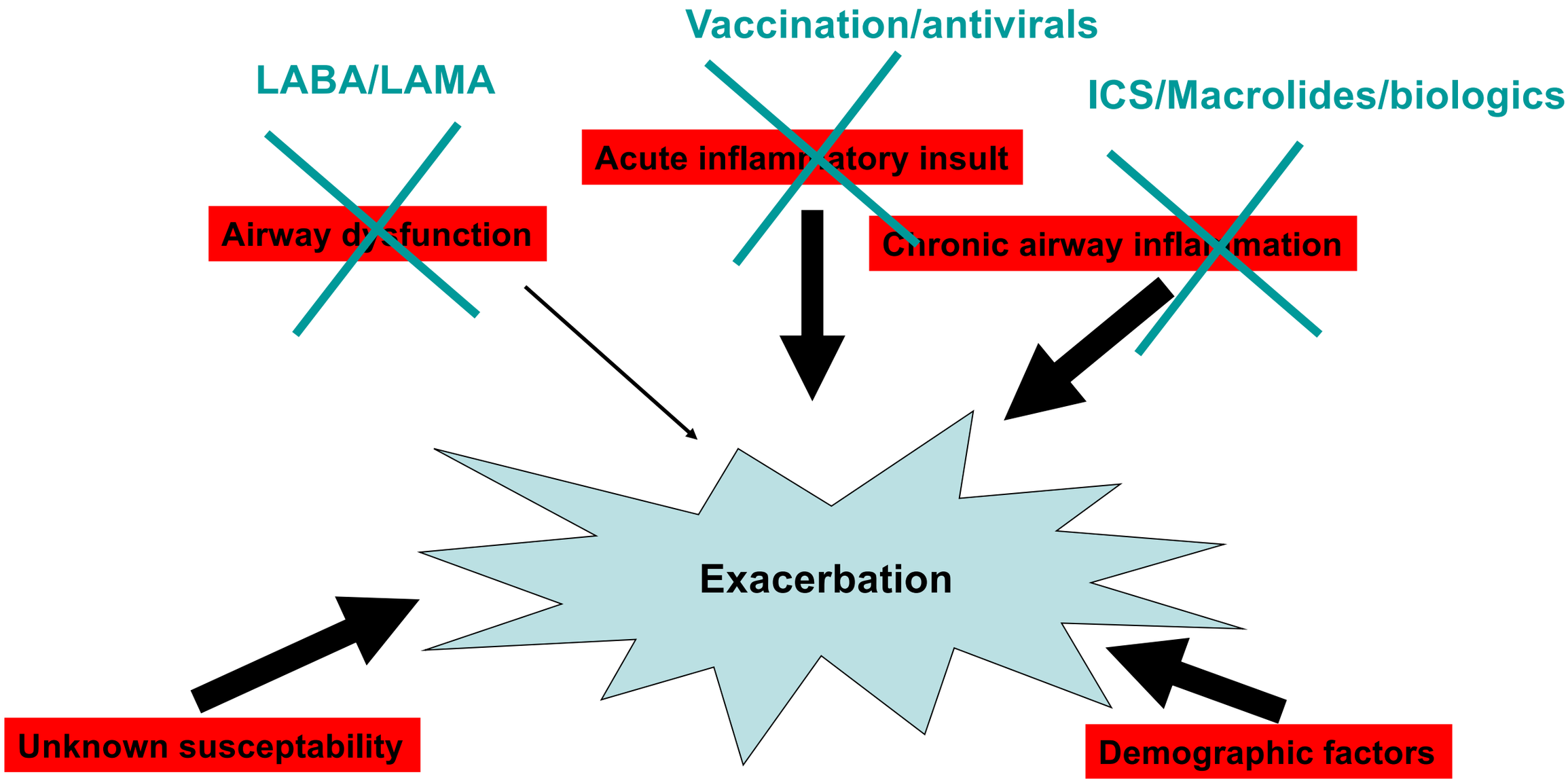
Ramakrishnan S at al. Am J Respir Crit Care Med. 2020;201:1441-1443.

Can we eliminate OCS use entirely? Benralizumab and acute attacks of airway disease

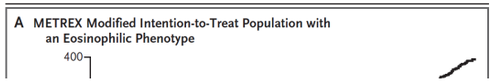


Nowak et al. Am J Emerg Med 2015;33:14-20

Exacerbations: the perfect storm



Mepolizumab (anti-IL-5) in COPD



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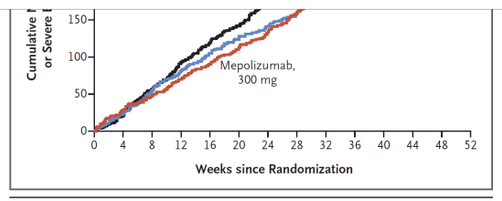
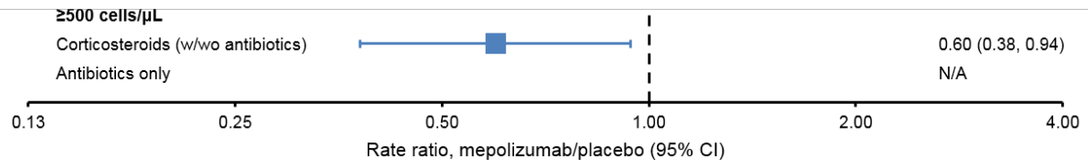
DUPIXENT® (DUPILUMAB) DEMONSTRATES POTENTIAL TO BECOME FIRST BIOLOGIC TO TREAT COPD BY SHOWING SIGNIFICANT REDUCTION IN EXACERBATIONS IN PIVOTAL TRIAL

First and only biologic to demonstrate clinically meaningful and statistically significant reduction (30%) in exacerbations compared to placebo

First and only biologic to show rapid and significant improvement in lung function (160 mL in FEV_1) compared to placebo (77 mL in FEV_1)

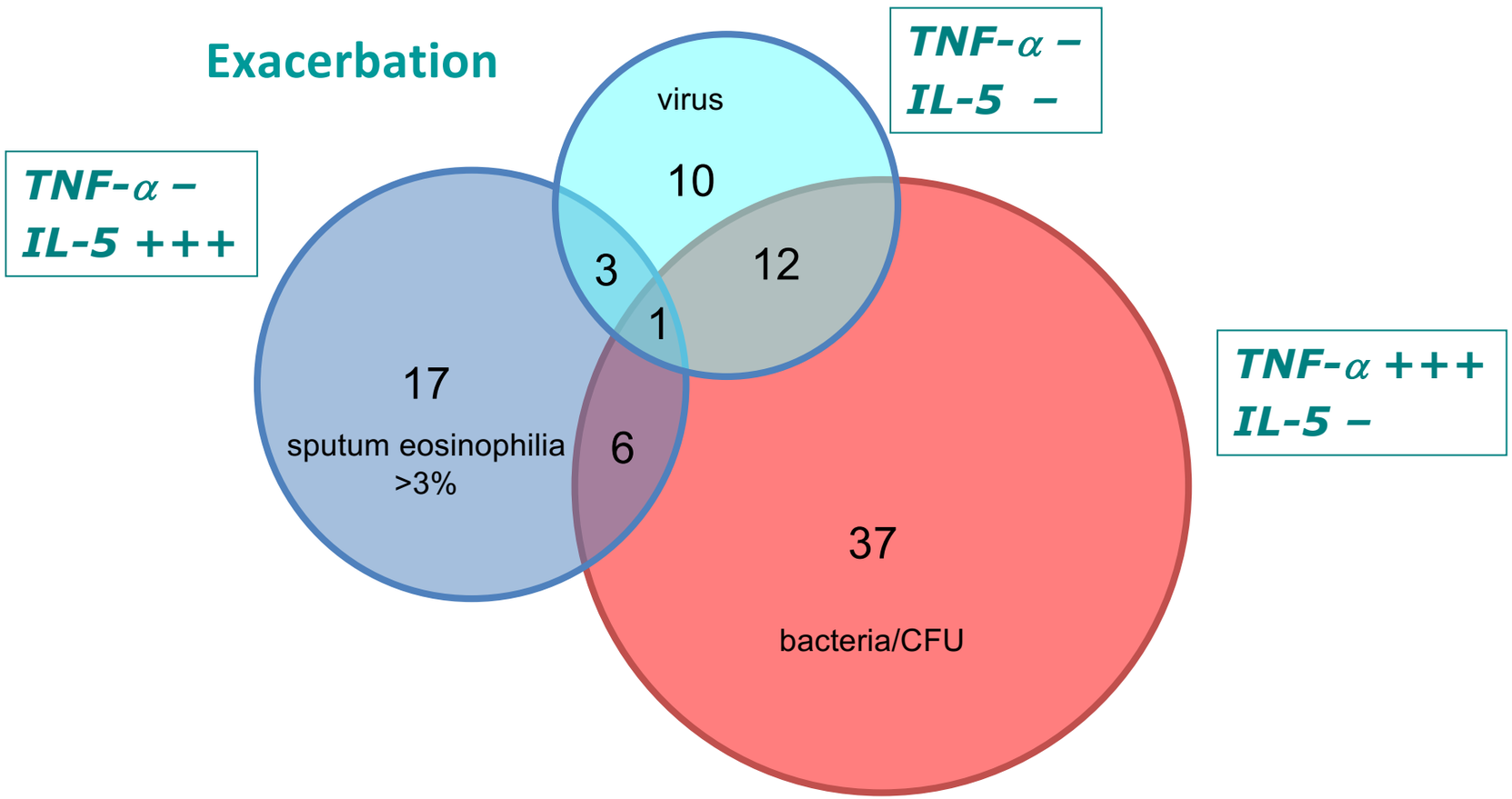
First and only biologic to demonstrate significant improvements in quality of life and respiratory symptoms





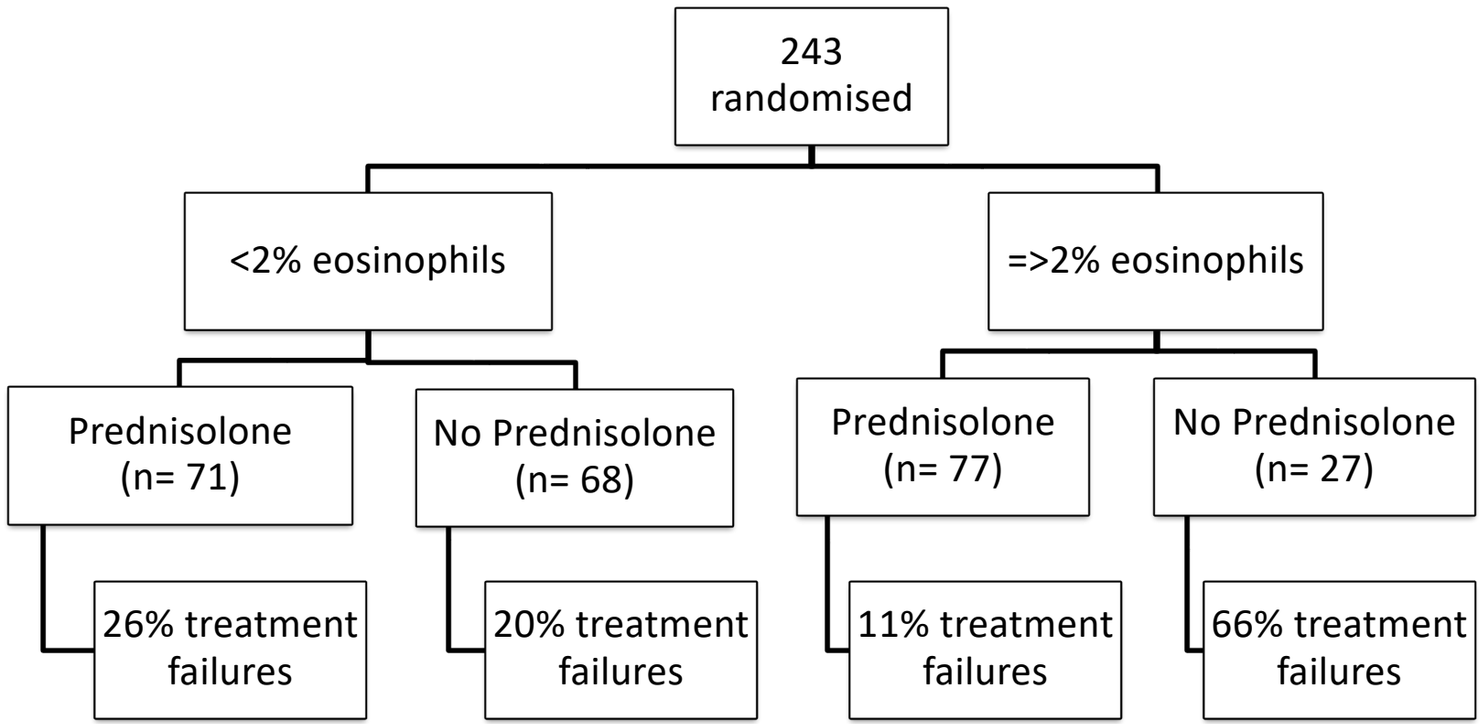
Pavord et al. NEJM 2017;377:1613-1629

Exacerbation heterogeneity in COPD. They look the same clinically but have distinct biology



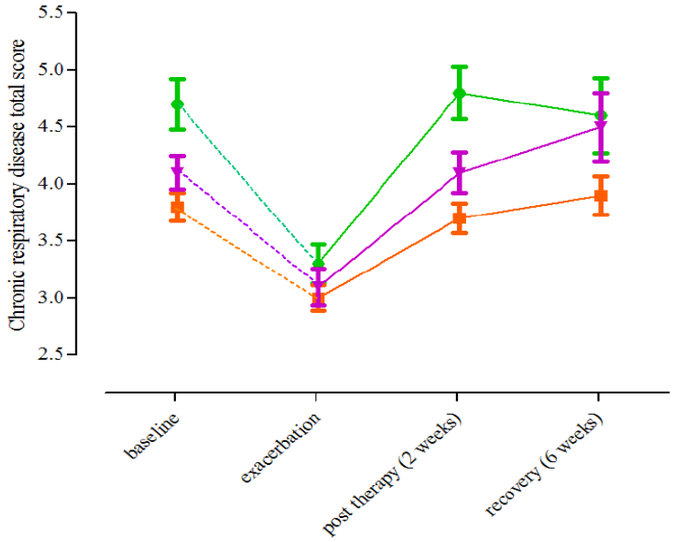
Adapted from: Bafadhel et al. Am J Respir Crit Care Med 2011;184:662-71

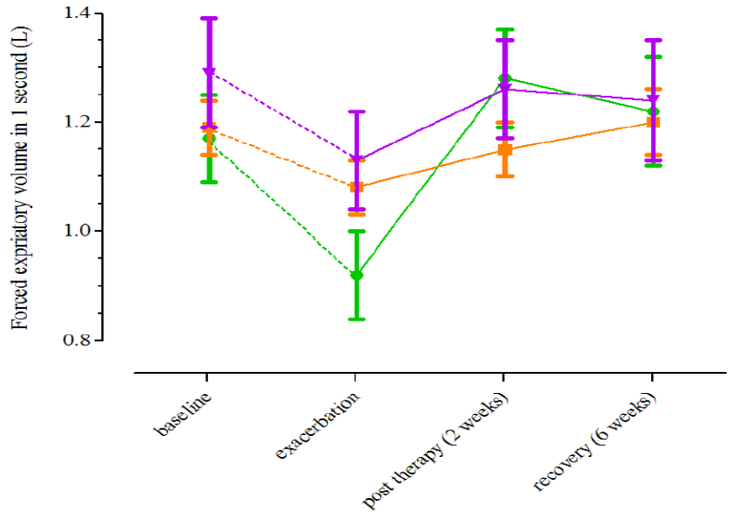
Blood eosinophil directed management of COPD exacerbations: a meta-analysis

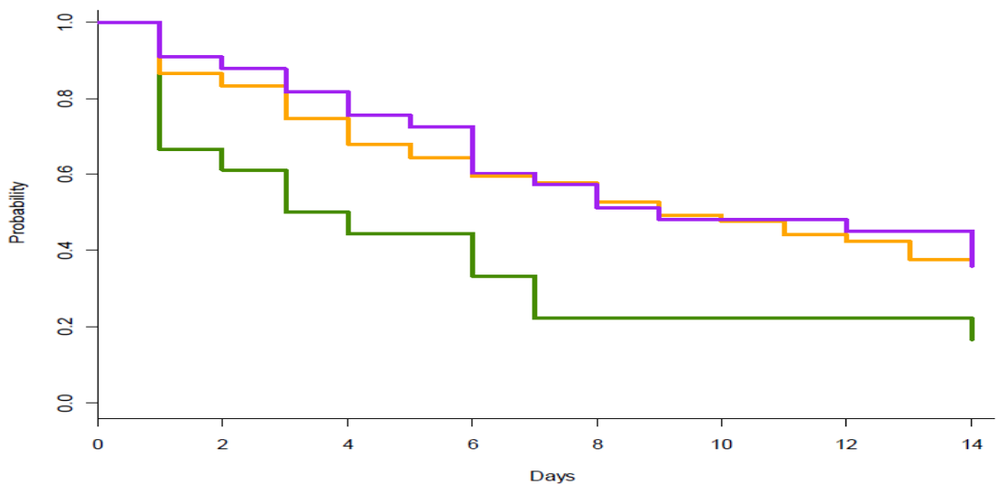


Bafadhel et al. Eur Respir J 2014;44:789-791

Eosinophilic exacerbations: bad but steroid responsive. Non-eosinophilic: long and shallow







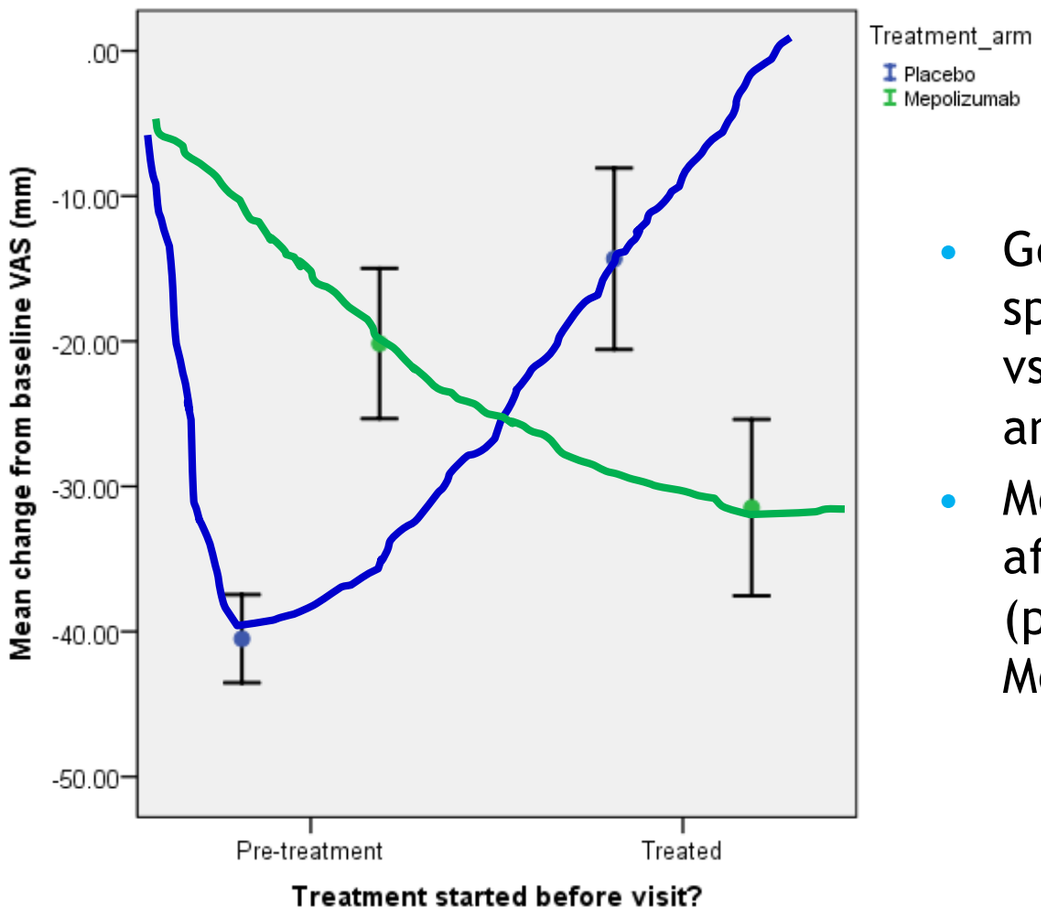
Sp Eos >3% treated with prednisolone
Sp Eos <3% treated with placebo
Sp Eos <3% treated with prednisolone

Bafadhel M et al. Am J Respir Crit Care Med 2011

Exacerbations occurring on biologics

- Are they long and shallow?
- Are pathology and mechanisms different?
- Should we adopt a different management approach?

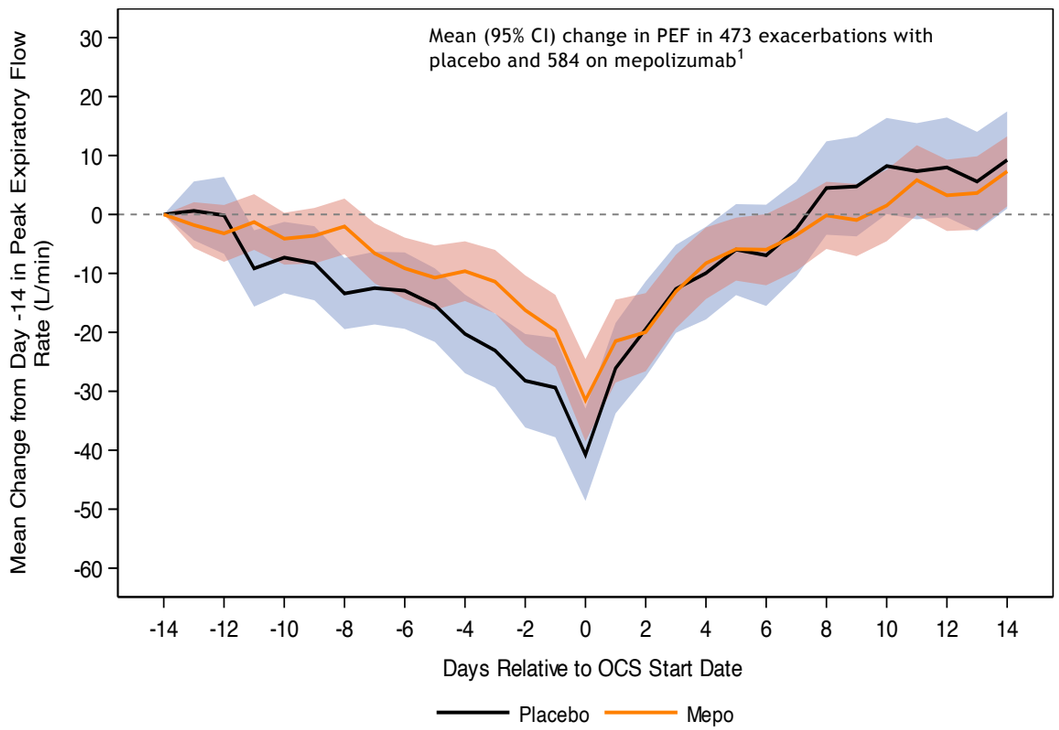
Characteristics, pathology and potential treatment response of on mepolizumab exacerbations

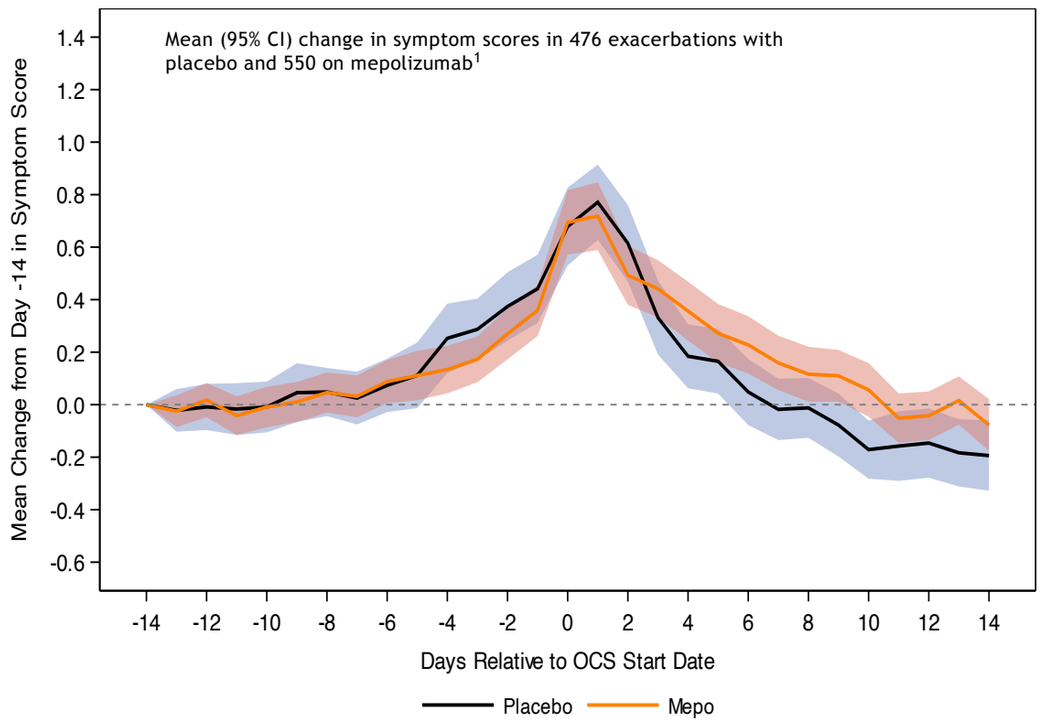


- Geometric mean exacerbation sputum eosinophil count 5.4 vs 2.6 (p=0.03) with placebo and mepolizumab
- Mean change in symptom VAS after prednisolone 15 vs 3 mm (p=0.03) before and after Mepolizumab

Shrimanket et al. ERJ 2018
Haldar et al . NEJM 2009;360:973-84

On mepolizumab exacerbation profiles





Shrimanker et al. AJRCCM 2019

The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study

P Jane McDowell, Sarah Diver, Freda Yang, Catherine Borg, John Busby, Vanessa Brown, Rahul Shrimanker, Ciara Cox, Christopher E Brightling, Rekha Chaudhuri, Ian D Pavord, Liam G Heaney on behalf of the Medical Research Council: Refractory Asthma Stratification Programme (RASP-UK Consortium)

Sputum at exacerbation [n=59 of 96, (61%)]	
Sputum neutrophil percentage ≥65%	n = 28 (47.5%)
Sputum eosinophil percentage ≥2%	n = 28 (47.5%)
Sputum neutrophils ≥65% & eosinophils ≥2%	n = 3 (5.1%)

- Neutrophilic events significantly more likely to have either a detectable pathogenic virus or specific bacteria* in sputum at exacerbation (odds ratio 5; p=0.036)

  *$\geq 10^6$ copies /mL *[Strep Pneumoniae, Haemophilus Influenzae, Moraxella catarrhalis]*

50% exacerbations events were eosinophilic

– despite very low blood eosinophils [70 (50, 90) cells/µL]

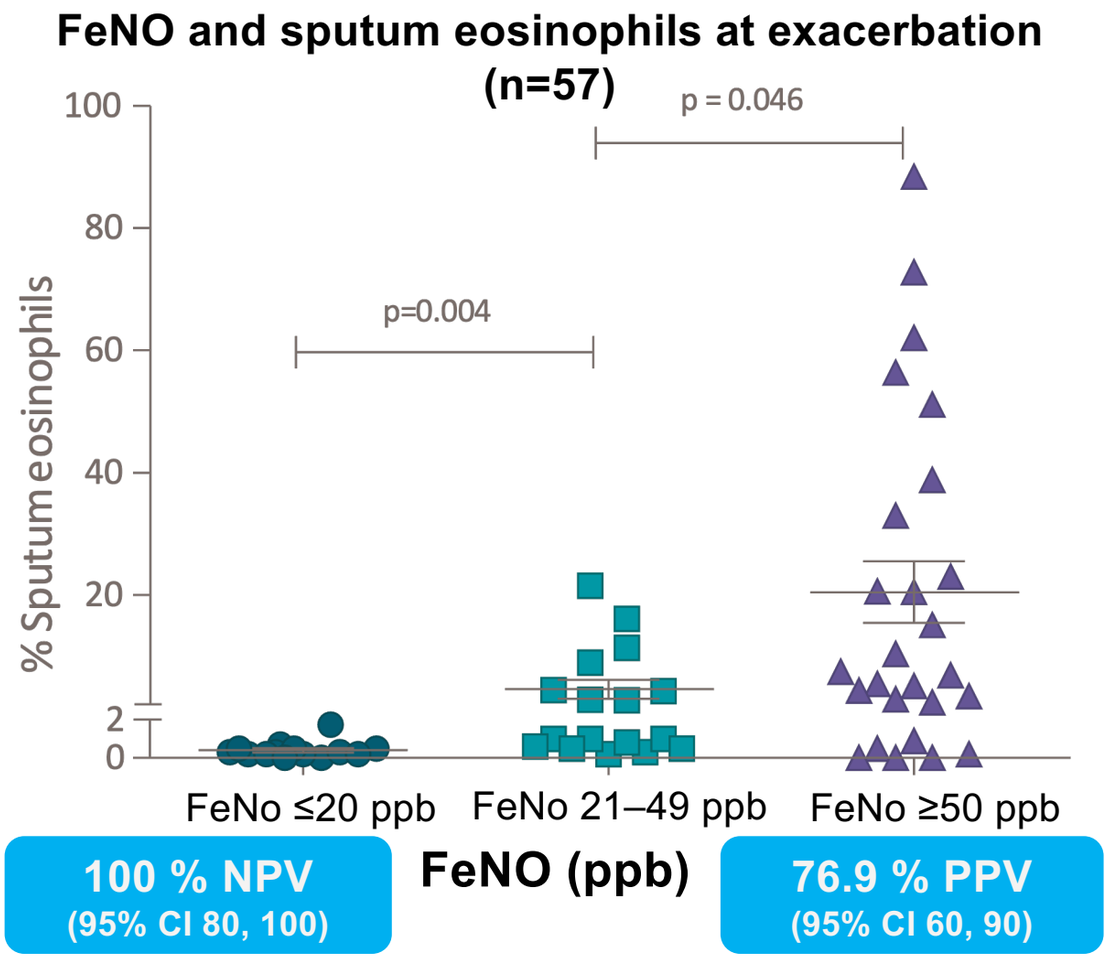
50% were neutrophilic

– broadly mutually exclusive events

- Inflammatory phenotype between baseline and exacerbation was consistent in 70% of patients with repeated exacerbations

(1) McDowell et al. Lancet Respir Med 2021;S2213-2600(21)00004-7 [online ahead of print] (2) Bafadhel M, et al. Int J Chron Obstruct Pulmon Dis. 2015;10:1075-1083

Can we differentiate inflammatory phenotype using FeNO?

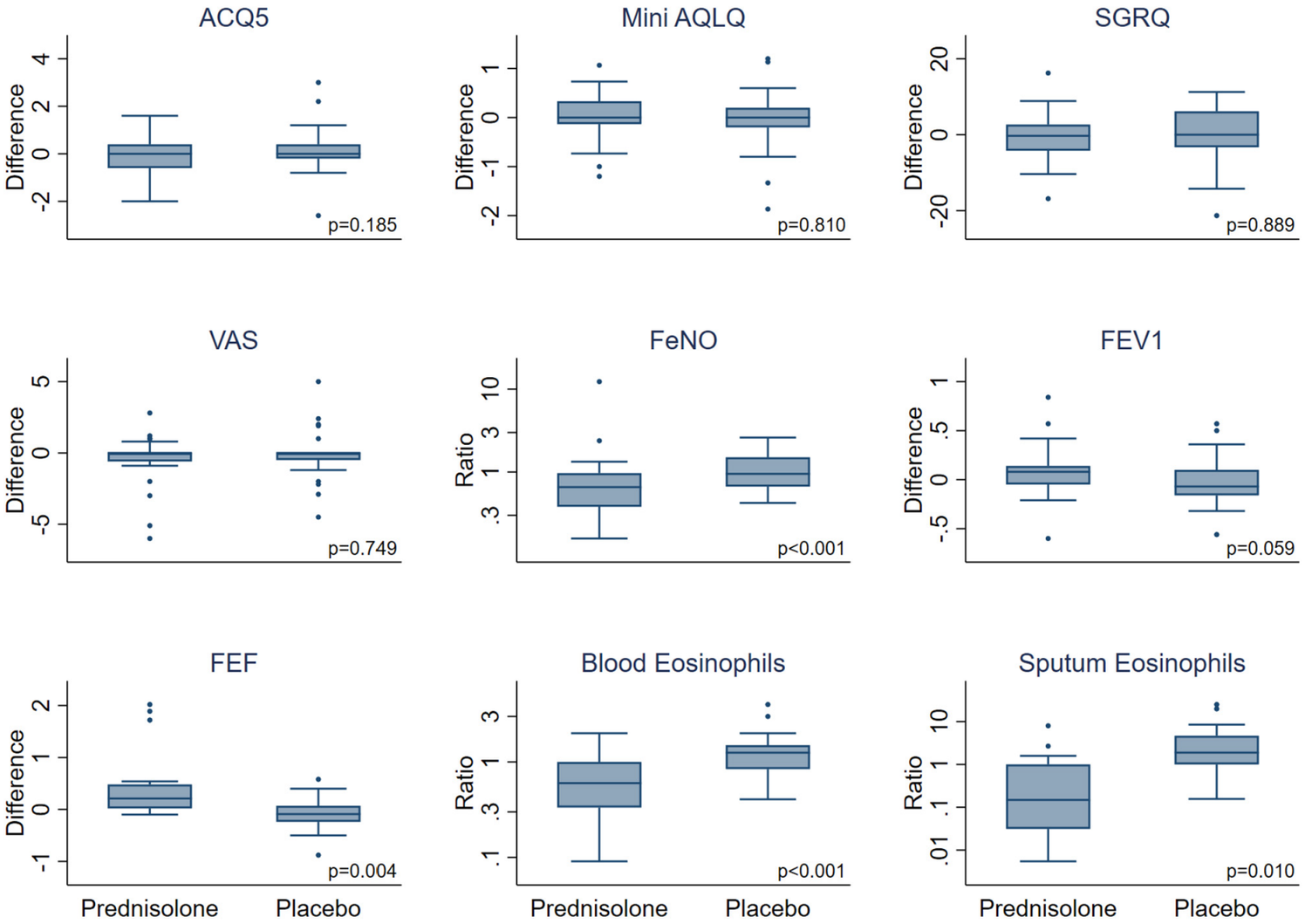


FeNO is a valuable tool in determining inflammatory phenotype when:

- FeNO low ≤20 ppb (25% of exacerbations)
- FeNO high ≥50 ppb (46% of exacerbations)

FeNO is a useful biomarker in 71% of exacerbations **on mepolizumab**

Is there a response to prednisolone in patients taking anti-IL-5 (mepolizumab)?



Yang et al. JACI in practice 2022;10:2925-32

Conclusions

- Asthma biologics reduce exacerbations related to eosinophilic airway inflammation
- They have a big effect on exacerbations and other outcomes if this is the ‘only show in town’.
- Residual exacerbations events are likely to be heterogeneous
- FeNO might be a useful method to characterise them and direct corticosteroid treatment
- Further studies are needed to establish whether on biologic exacerbations are need different non-corticosteroid management approaches.

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