Difficult Asthma II

Cased-based discussion

Focus on Advanced Therapies

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Disclosures

Cowl:

None

Khurana:

Grant support – GSK, Sanofi

We will not be discussing off-label use for any drugs or devices

Learning Objectives

- Review heterogeneity in asthma and understand the concept of cluster analysis
- Review the pathophysiologic mechanisms that form the basis for biologics in asthma
- Describe how phenotypes and endotypes can be used to choose targeted therapy in asthma
- Discuss the approach to the patient with severe asthma and choosing the appropriate advanced therapy

Outline

Cowl

- Case
- Overview of pathophysiology, phenotypes and biomarkers

Khurana

- Case
- Selection and efficacy of advanced therapies

Jim: A 38-year-old man with asthma

- Jim is a never-smoker
- Diagnosed with asthma at age 3
- Asthma was mild during childhood and teenage years; worsened in his 20s, following an episode of pneumonia
- Recent 5 ED visits and 2 hospitalizations over past 2 years. Intubated twice in his lifetime.
- He reports daily cough, wheeze and shortness of breath. Asthma control test score is 11.

- Current medications include: Inhaled corticosteroid + long-acting β-agonist (ICS/LABA), long-acting muscarinic antagonist (LAMA), leukotriene modifier (LTM), antihistamine, intranasal corticosteroids, and proton pump inhibitor. He is also currently completing a prednisone taper for acute asthma.

Jim: A 38-year-old man with asthma

- Moved in with his parents two years ago after his first intubation/ICU admission
- His parents own a cat. The entire house is carpeted.
- Allergy skin testing during childhood was positive for multiple environmental allergens. He tried allergy shots (immunotherapy) for 2 years with some improvement.

- Physical Exam:

  Normal vital signs. BMI 26.

  Erythematous nasal mucosa, no polyps or exudate

  No stridor

  Good air movement b/l, clear to auscultation

What will be your next step in evaluating Jim's asthma?

A. Pre- and Post- bronchodilator spirometry
B. Methacholine challenge test
C. High resolution CT chest
D. FeNO

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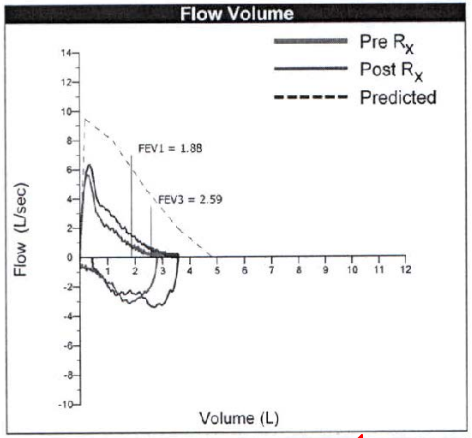
Case continued

Spirometry (BTPS)		Pre Bronchodilator Actual	Predicted	% Pred	CI Range			Post Bronchodilator Actual	% Pred	% Chg
FEV_1	L	1.88	3.86	49	3.14	4.58	A	2.28	59	21
FVC	L	2.97	4.81	62	3.96	5.66	A	3.58	74	21
FEV_1 / FVC	%	63	80	79	70	90	A	64	80	2
FEF_{25-75}	L/s	1.06	3.74	28	2.28	5.20		----	----	----
PEFR	L/s	5.67	9.51	60	7.40	11.62		6.37	67	12
FIF50	L/s	1.52	----	----	----	----		2.53	----	66
MVV	L/m	----	157.3	----	100.5	214.1		----	----	--



Jim: A 38-year-old man with asthma

- You confirm adherence and inhaler technique
- You identify and mitigate triggers
- You optimize management of comorbidities: GERD and CRS

- Asthma remains uncontrolled on current asthma regimen:
  - Inhaled corticosteroid
  - Long-acting beta agonist
  - Long-acting muscarinic antagonist
  - Leukotriene modifier (LTM)
  - Antihistamine
  - Nasal steroids
  - Proton pump inhibitor

What is true regarding the definition of phenotype vs endotype?

A. A phenotype is the inflammatory pathway producing the endotype
B. A phenotype is a collection of clinical characteristics; the endotype is the mechanism producing the phenotype
C. There is one endotype for every phenotype
D. Multiple phenotypes are associated with an endotype

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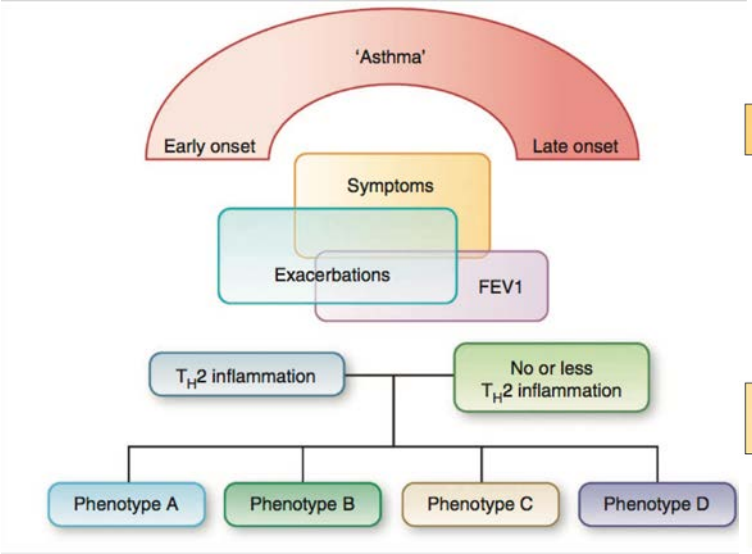
Terminology & Definitions

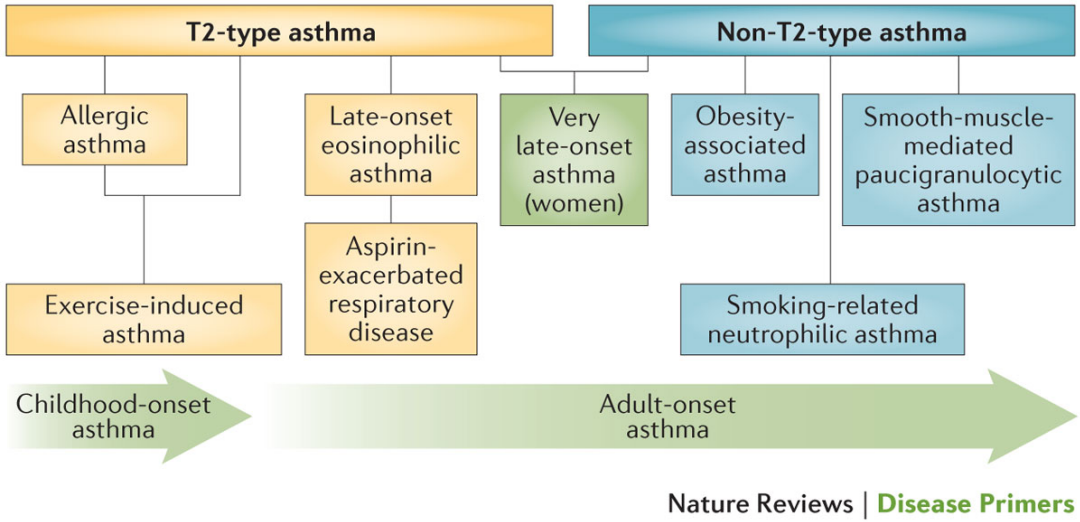
Phenotype: Observable characteristic/traits

Endotype: Distinct pathophysiology that provides insight into mechanism

Biomarker: Measurable indicator of biologic state

Selected asthma sub-phenotypes





Wenzel Nature Medicine 2012
Holgate Nat. Rev. Dis. Primers 2015

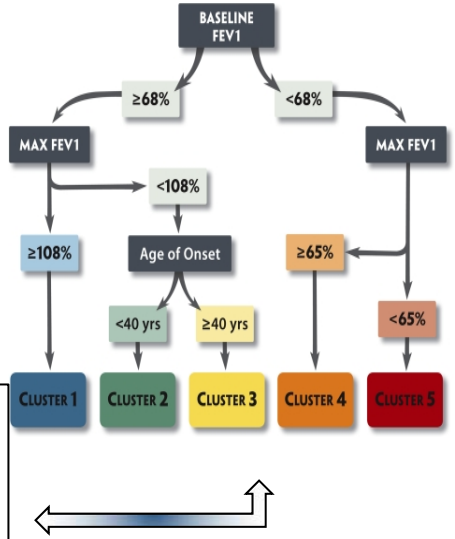
Severe Asthma Research Program (SARP) clusters

726 subjects in Severe Asthma Research Program

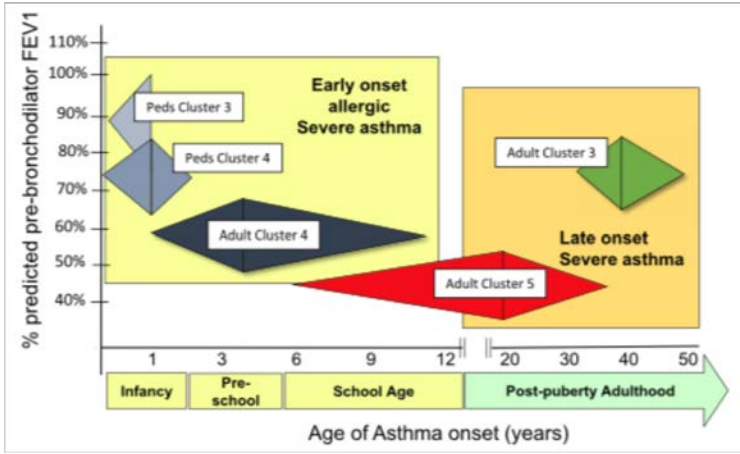
628 total variables reduced to 34 core variables

Unsupervised hierarchical cluster analysis

Five major phenotypes emerged



1. Younger, mild childhood onset, atopic
2. Older, childhood onset, atopic, moderate severity
3. Older women, high BMI, late-onset, non-atopic
4. Severe, earlier onset, reversible obstruction
5. Severe, later onset, fixed obstruction



Moore et al. AJRCCM 2010
Silkoff et al. Clin Chest Med 40 (2019)

What additional information will help guide further treatment for your patient?

A. Allergy testing & IgE level
B. Blood eosinophil count
C. Serum periostin level
D. A and B

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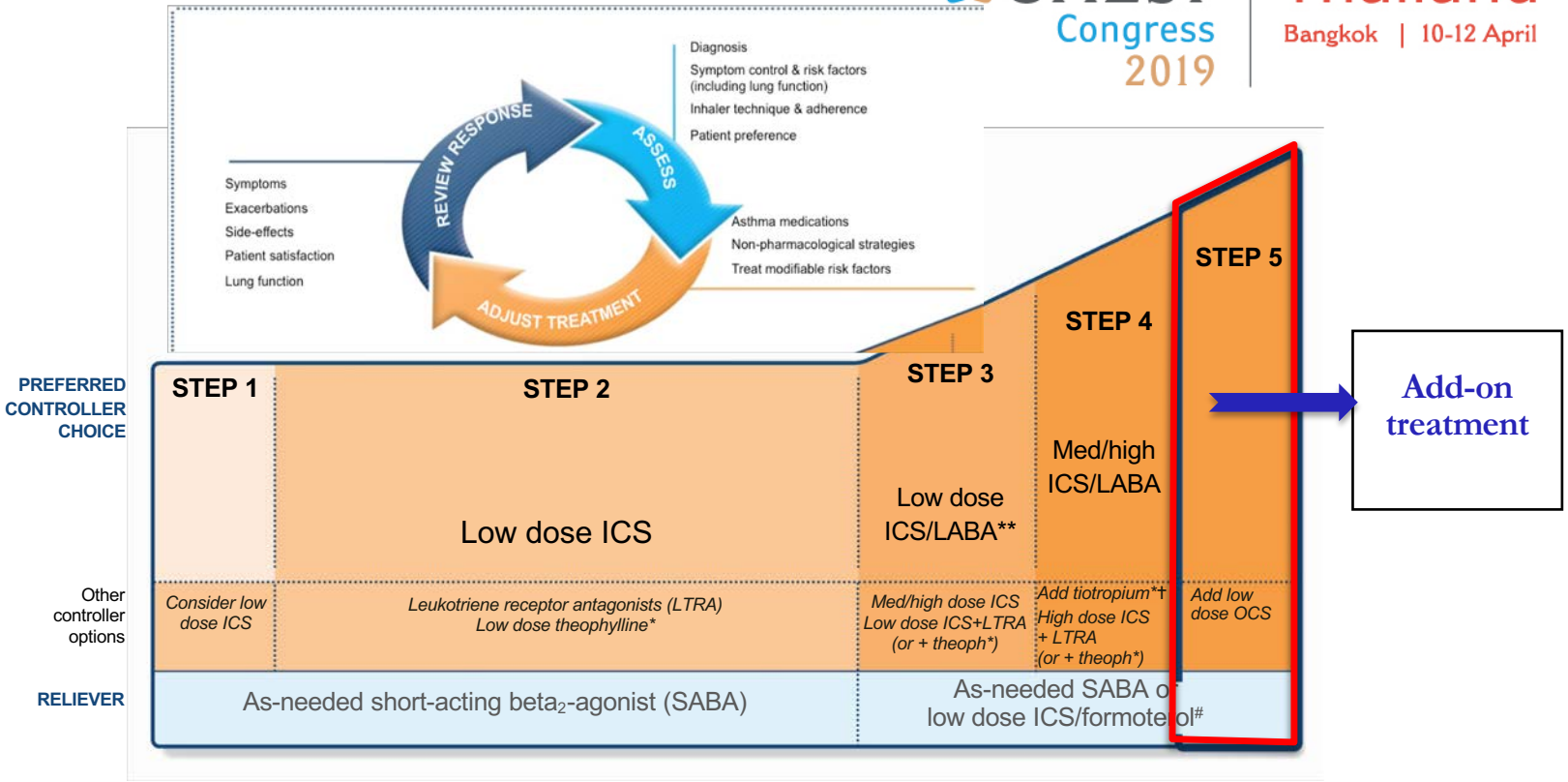
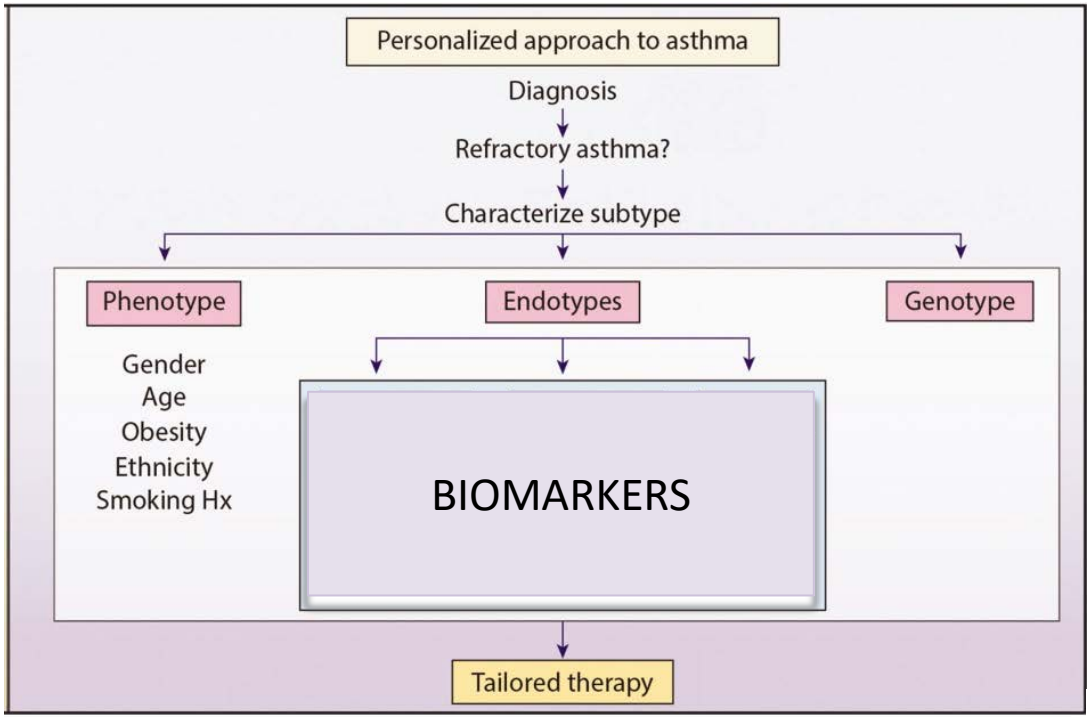


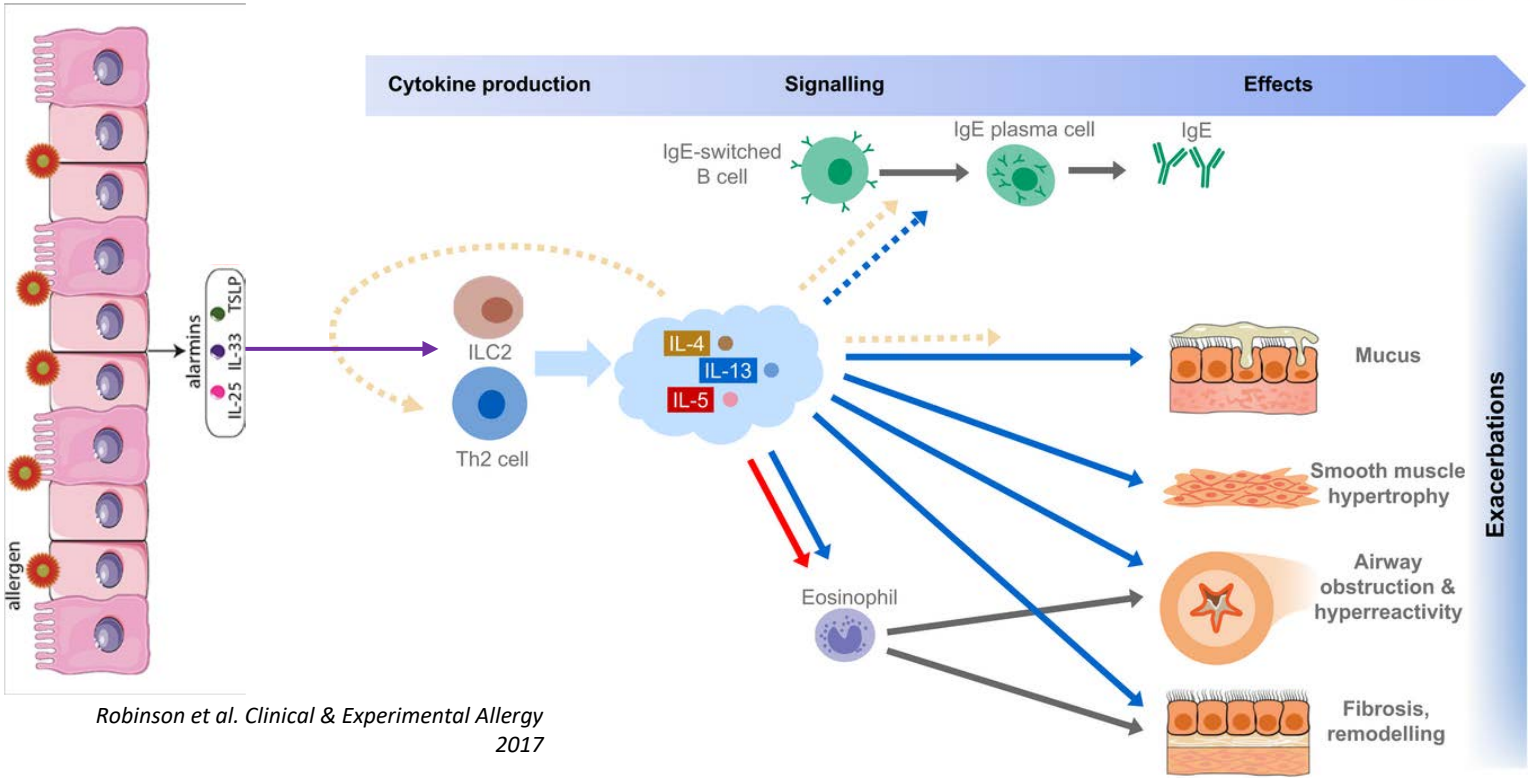
Source: ginaasthma.org

Personalized approach to asthma



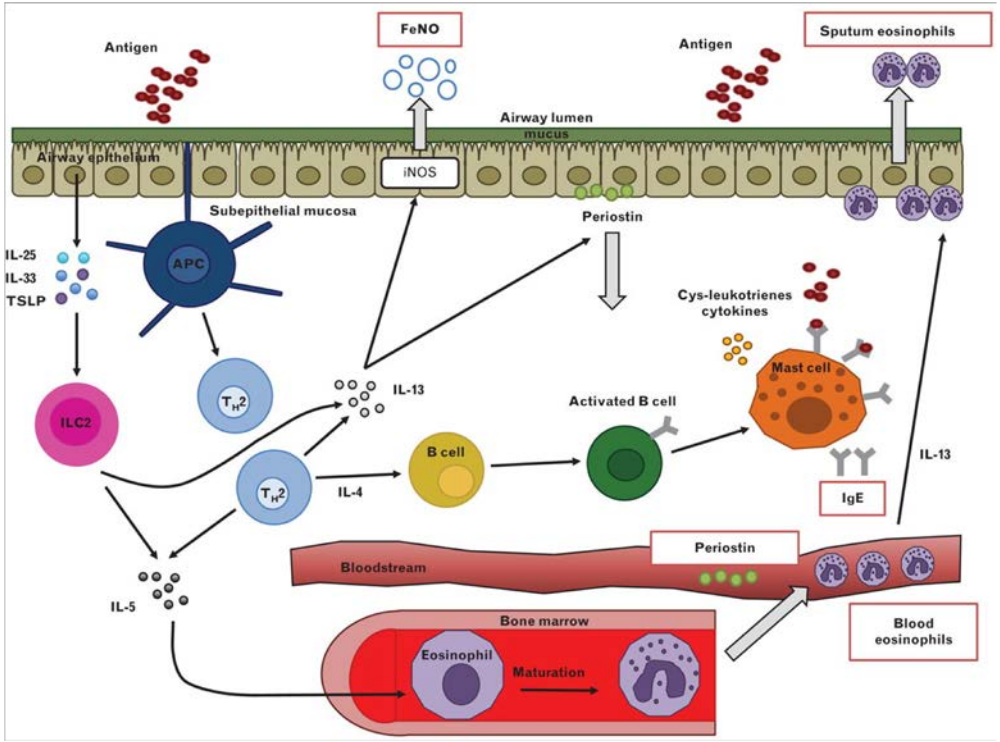
Dunn & Wechsler. Clin Pharmacol Ther 2015

Type 2 inflammation in asthma



Robinson et al. Clinical & Experimental Allergy 2017

Biomarkers in T2 asthma



Biomarker	Characteristics
Sputum Eos	Allergic & Eosinophilic Asthma Increased exacerbations and poor lung function
Blood Eos	Allergic & Eosinophilic asthma Increased exacerbations and poor lung function
IgE	Allergic asthma
FeNO	Indicator of oxidative and nitrative stress Allergic & eosinophilic asthma
Periostin	Potentially allergic & eosinophilic asthma

Parulekar. Curr Opin Pulm Med 2016

Interim summary

- Asthma is a complex heterogeneous condition
- Best understood in terms of underlying phenotypes (observable characteristics) and endotypes (specific biologic mechanisms)
- Biomarkers can provide information about the disease as well as targeted therapy
- Many biomarkers available for Type 2 asthma including sputum eosinophils, FeNO, blood eosinophils, IgE level
- No biomarkers currently available for non-Type 2 asthma and this is an area of great need

Back to our patient…

Jim – A 38-year-old man with severe asthma

- Childhood asthma
- Uncontrolled on ICS, LABA, LAMA, LTM
- Frequent exacerbations
- Moderate airflow obstruction on spirometry with reversibility
- Adherence, triggers, comorbidities addressed and optimized

- Additional diagnostic tests performed

Scenario 1

WBCs	7.7 K/µL
Eos (%)	3.6
Absolute Eos	277 cells/µL
IgE	386 kU/L
FeNO	14 ppb

Multiple positives on blood test for allergies

- Dustmites
- Seasonal molds
- Trees
- Pollen
- Ragweed
- Cats
- Dogs

Which of the following therapies would you add to this patient's current regimen?

A. Mepolizumab
B. Omalizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above

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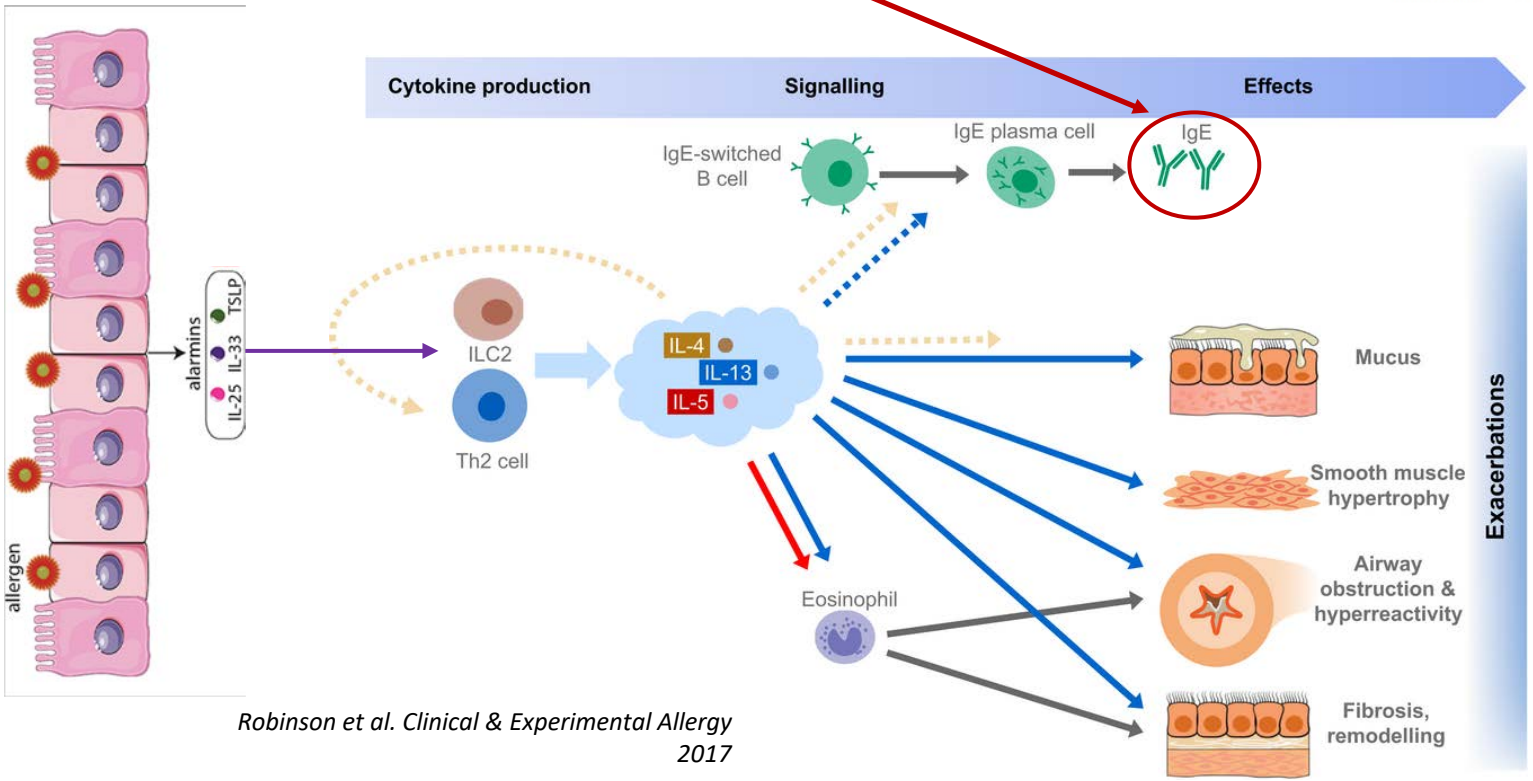
Allergic Asthma - Omalizumab



Robinson et al. Clinical & Experimental Allergy 2017

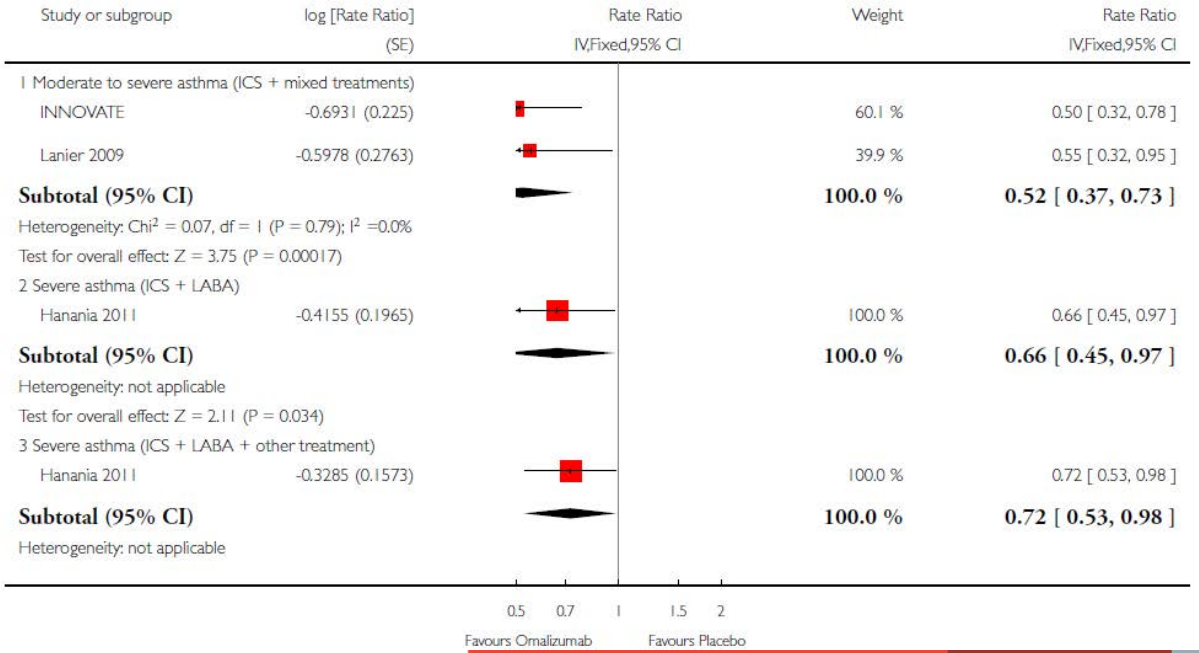
Omalizumab Decreases Asthma Exacerbations

Analysis 1.2. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 2 Exacerbations requiring oral steroids.

Review: Omalizumab for asthma in adults and children

Comparison: 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 2 Exacerbations requiring oral steroids



Cochrane Database Syst Rev. 2014(1):CD003559.

Omalizumab Decreases Hospitalizations

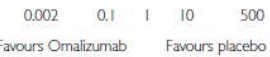
Analysis 1.3. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 3 Hospitalisations.

Review: Omalizumab for asthma in adults and children

Comparison: 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

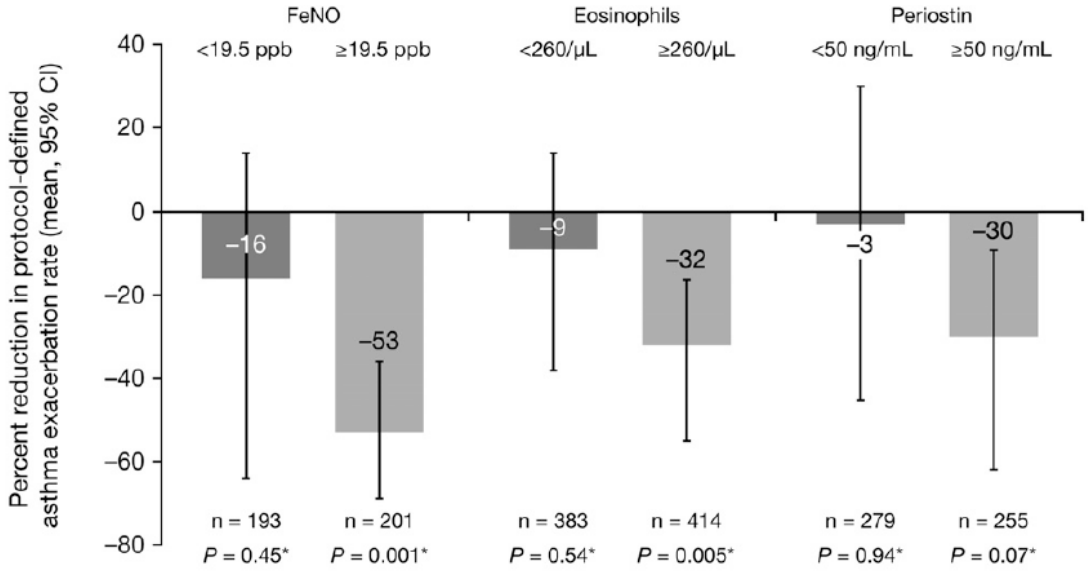
Outcome: 3 Hospitalisations

Study or subgroup	Omalizumab n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate to severe asthma					
Busse 2001	1/268	2/257		7.1 %	0.48 [0.04, 5.30]
Busse 2011	3/208	13/211		44.4 %	0.22 [0.06, 0.79]
Milgrom 2001	0/225	5/109		25.8 %	0.04 [0.00, 0.77]
Sol r 2001	0/274	6/272		22.7 %	0.07 [0.00, 1.33]
Subtotal (95% CI)	**975**	**849**		**100.0 %**	**0.16 [0.06, 0.42]**
Total events: 4 (Omalizumab), 26 (Placebo)					
Heterogeneity: $Chi^2 = 2.13$, $df = 3$ ($P = 0.55$); $I^2 = 0.0\%$					
Test for overall effect: $Z = 3.77$ ($P = 0.00017$)					
2 Severe asthma					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Omalizumab), 0 (Placebo)					
Heterogeneity: not applicable					



Cochrane Database Syst Rev. 2014(1):CD003559.

Biomarkers Predict Response to Omalizumab

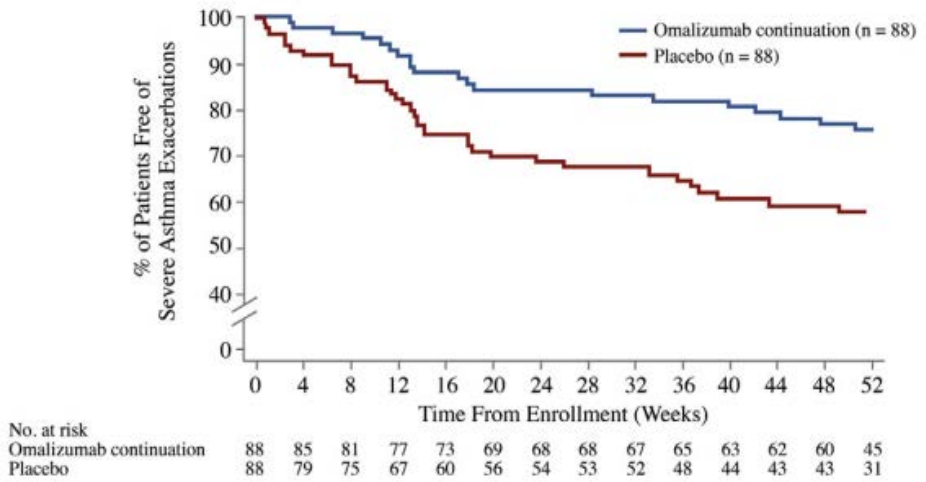


Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

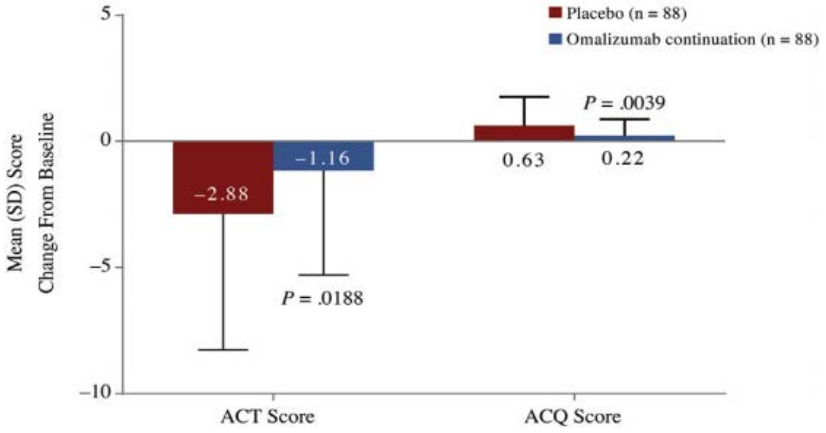
Hanania NA, et al. *Am J Respir Crit Care Med. 2013*

Omalizumab: Duration of Therapy

Time to first exacerbation



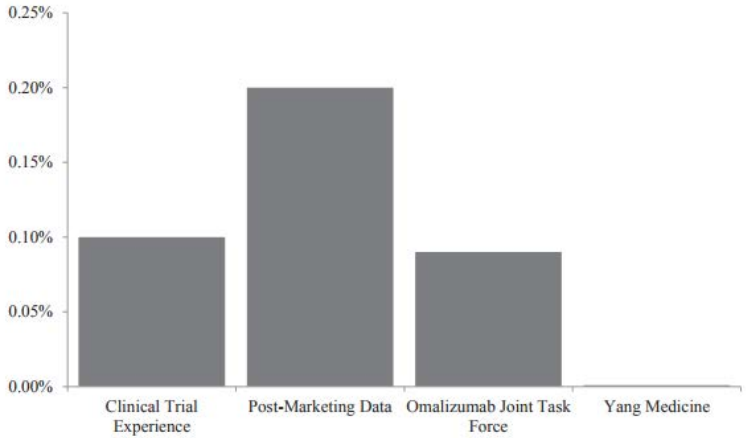
Change in symptoms



Ledford D, et al. A *J Allergy Clin Immunol. 2017;140(1):162-169*

Omalizumab: Safety

	Incidence, *n* (%)				
	Core study (32 weeks)		Extension 1 (96 weeks)	Extension 2 (52 weeks)	Extension 3 (104 weeks)*
Event	Omalizumab (*n* = 174)	Placebo (*n* = 165)	Omalizumab (*n* = 222)	Omalizumab (*n* = 178)	Omalizumab (*n* = 118)
Any AE	136 (78.2)	135 (81.8)	195 (87.8)	134 (75.3)	78 (66.1)
Mild or moderate	120 (69.0)	105 (63.6)	156 (70.3)	115 (64.6)	71 (60.2)
Severe	16 (9.2)	30 (18.2)	39 (17.6)	19 (10.7)	7 (5.9)
Serious AEs	11 (6.3)	11 (6.7)	27 (12.2)	8 (4.5)	5 (4.2)
Treatment-related AEs	6 (3.4)	8 (4.8)	26 (11.7)	4 (2.2)	1 (0.8)



Corren J, et al. *Clin Exp Allergy*. 2009;39(6):788-797.

Harrison RG, et al. *Ann Allergy Asthma Immunol*. 2015;115(1):77-78.

Scenario 2

WBCs	7.7 K/µL
Eos (%)	6.3
Absolute Eos	570 cells/µL
IgE	53 kU/L
FeNO	35 ppb

Blood test for allergies negative

Which of the following therapies would you add to the patient's current regimen?

A. Omalizumab
B. Mepolizumab
C. Dupilumab
D. Lebrikizumab
E. None of the above

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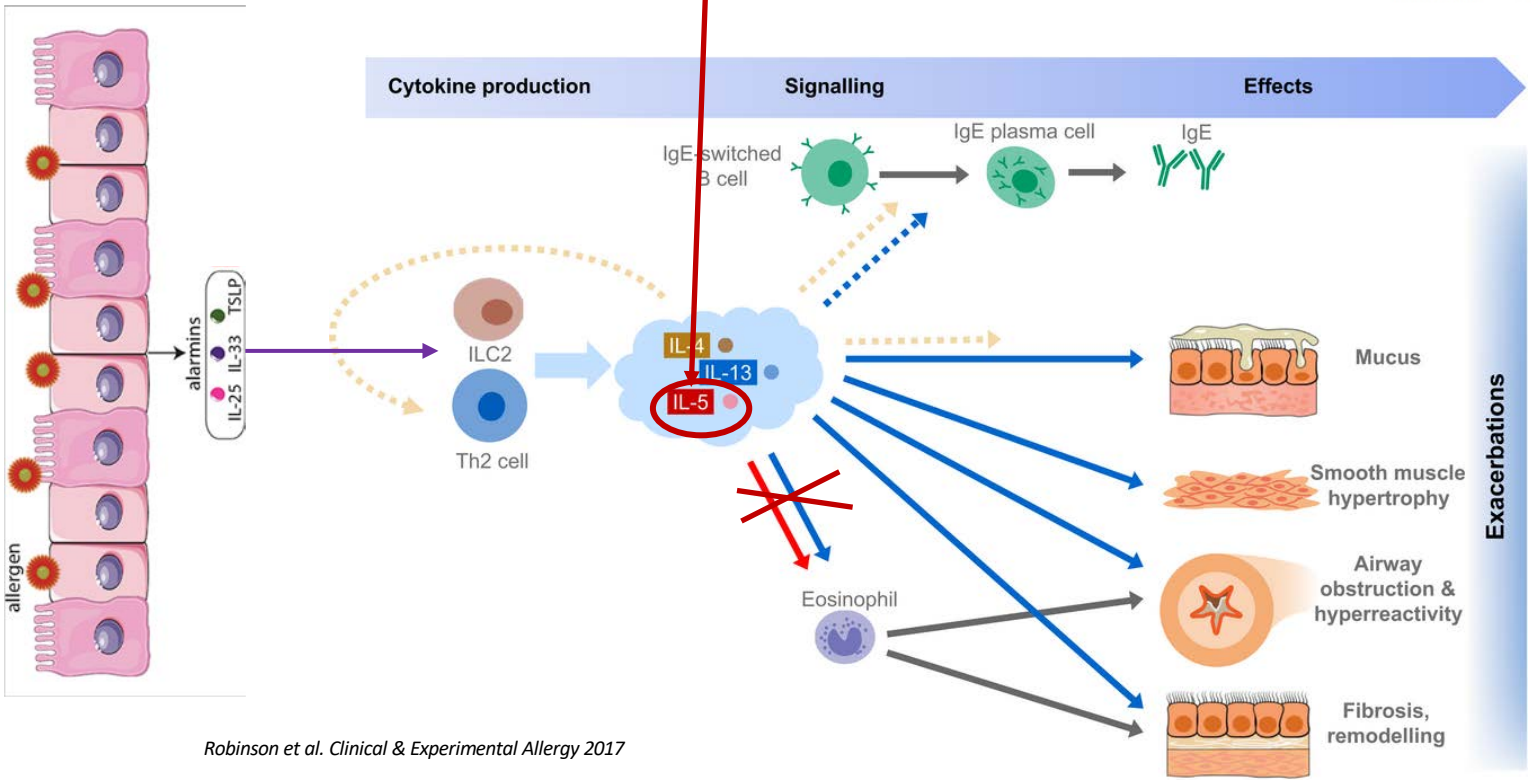
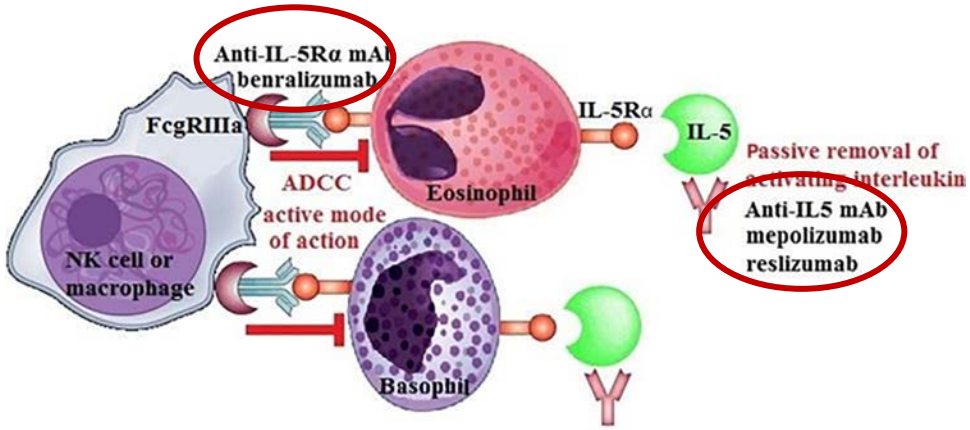
Eosinophilic Asthma: Anti-IL5 Therapy
(mepolizumab, benralizumab, reslizumab)



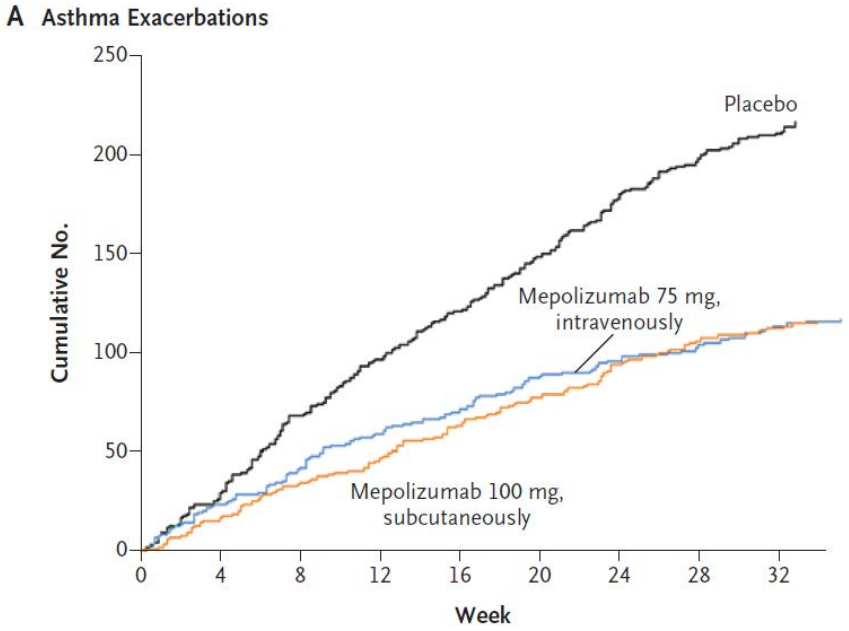
Robinson et al. Clinical & Experimental Allergy 2017

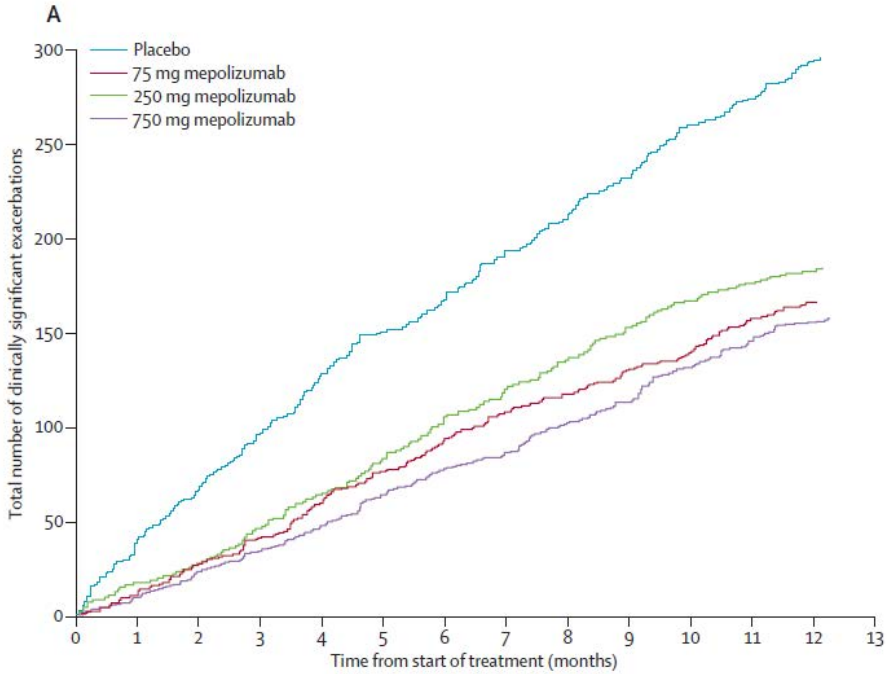
Mechanism of action of anti-IL5 therapies



Tan et al. Journal of Asthma and Allergy 2016:9 71–81

Mepolizumab decreases exacerbation rates in patients with severe eosinophilic asthma

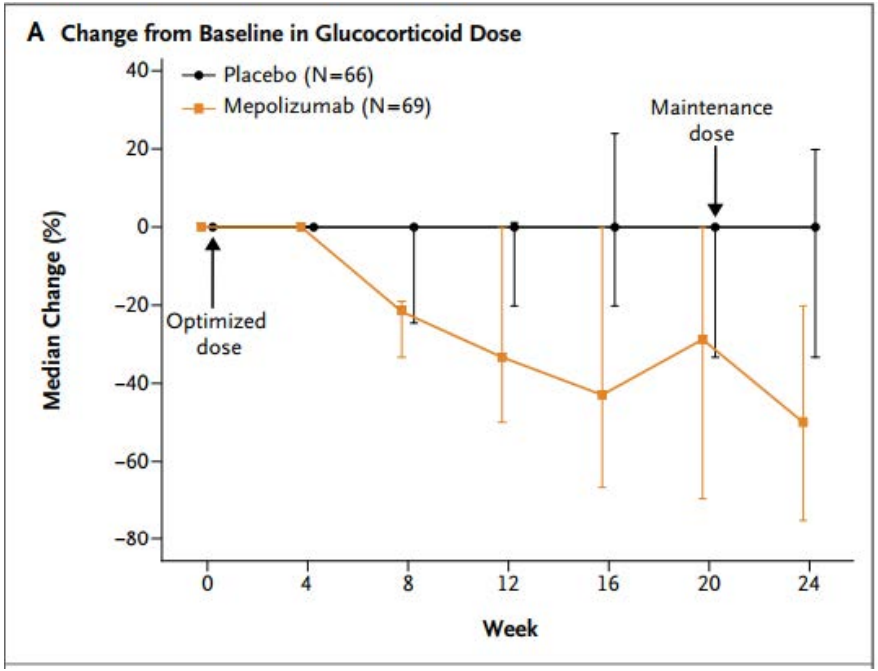


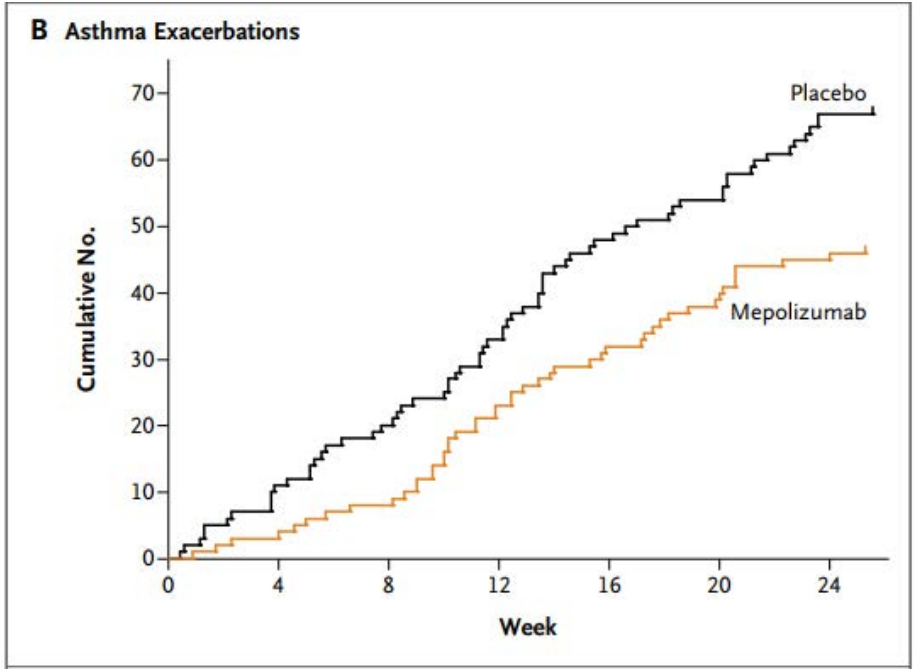


Ortega HG, et al. *N Engl J Med. 2014;371(13):1198-1207.*

Pavord ID, et al. *Lancet. 2012;380(9842):651-659.*

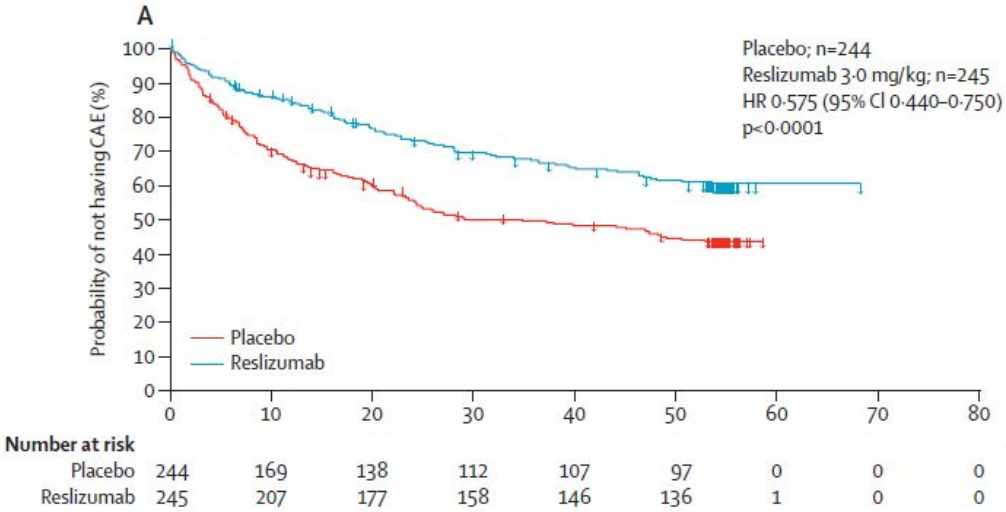
Mepolizumab has a steroid-sparing effect in patients with asthma and blood eosinophilia

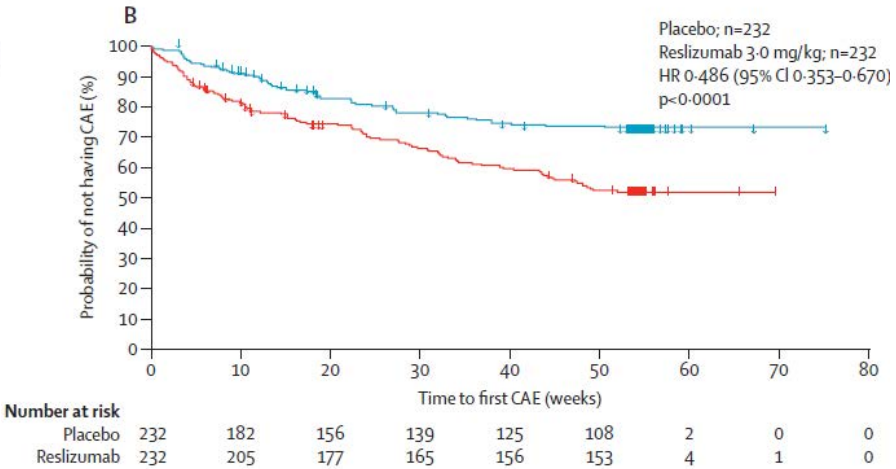




Bel EH, et al. *N Engl J Med. 2014;371(13):1189-1197.*

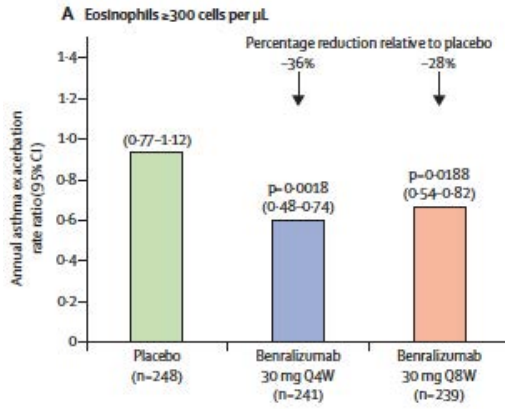
Reslizumab decreases exacerbations in patients with uncontrolled asthma and blood eosinophilia

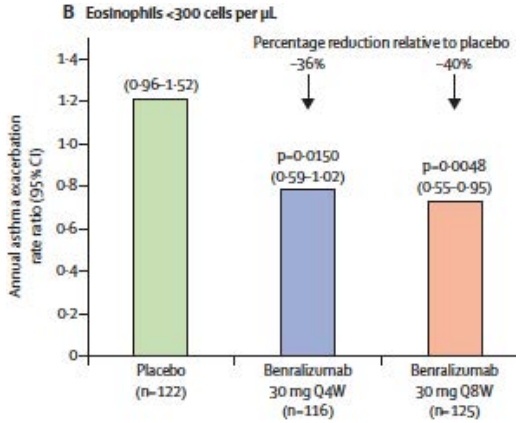


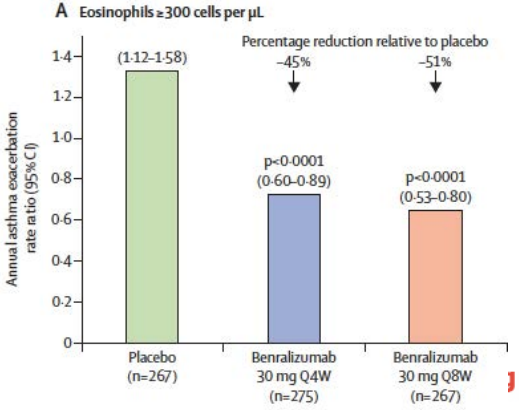


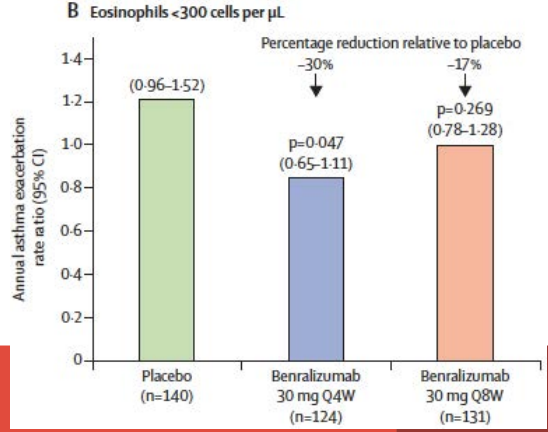
Castro M, et al. *Lancet Respir Med. 2015;3(5):355-366.*

Benralizumab reduces frequency of asthma exacerbations





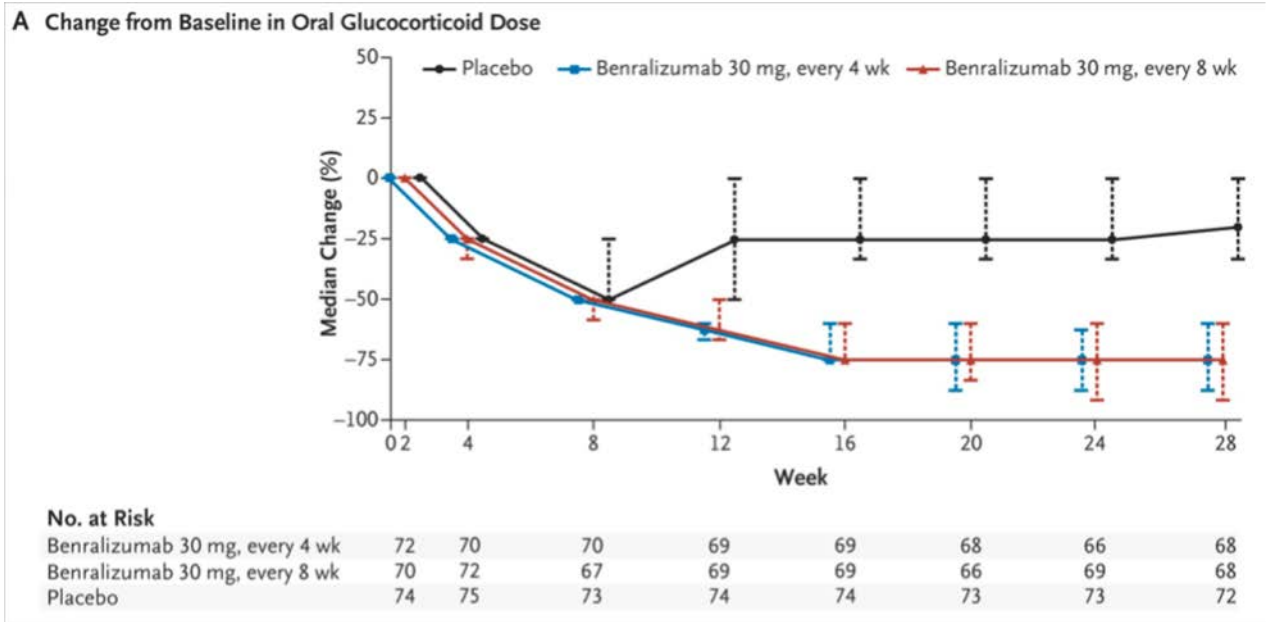




Bleecker ER, et al. Lancet. 2016
Fitzgerald JM, et al. Lancet. 2016

Re

Benralizumab reduces OCS dose in severe asthma



Nair P, et al. N Engl J Med. 2017;376:2448-2458.

Scenario 3

WBCs	5.0 K/µL
Eos (%)	1.2
Absolute Eos	60 cells/µL
IgE	23 kU/L
FeNO	21 ppb

AND

OCS dependent

Which of the following therapies would you consider adding on in this patient?

A. Omalizumab
B. Lebrikizumab
C. Reslizumab
D. Dupilumab
E. None of the above

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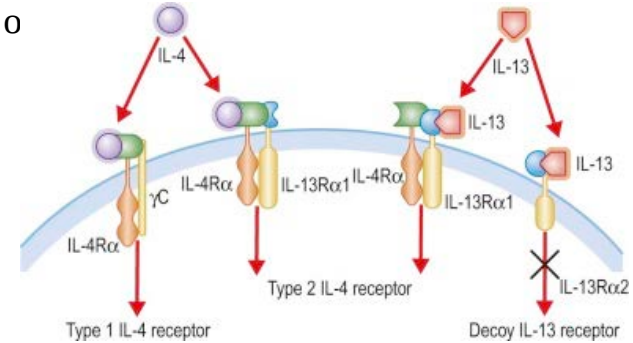
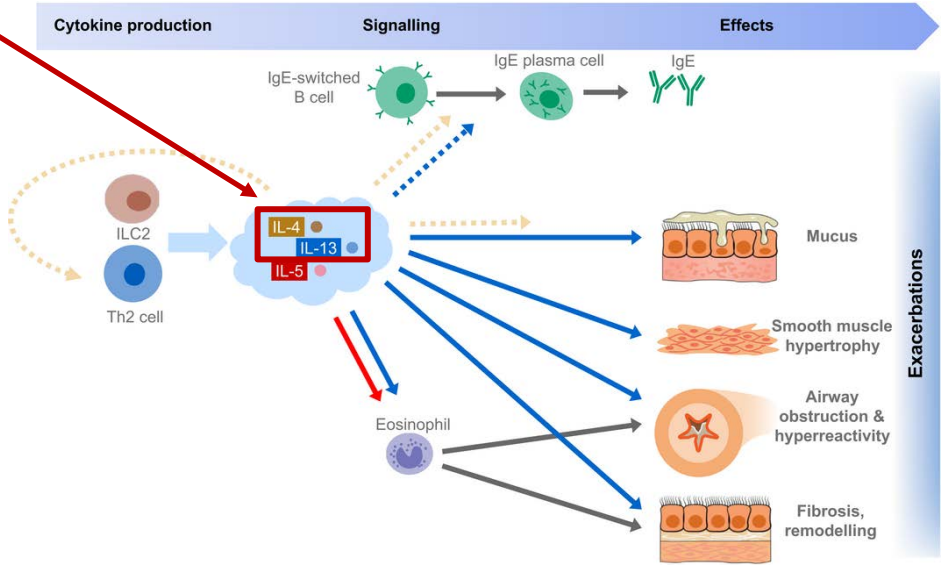
Dupilumab inhibits IL-4/IL-13

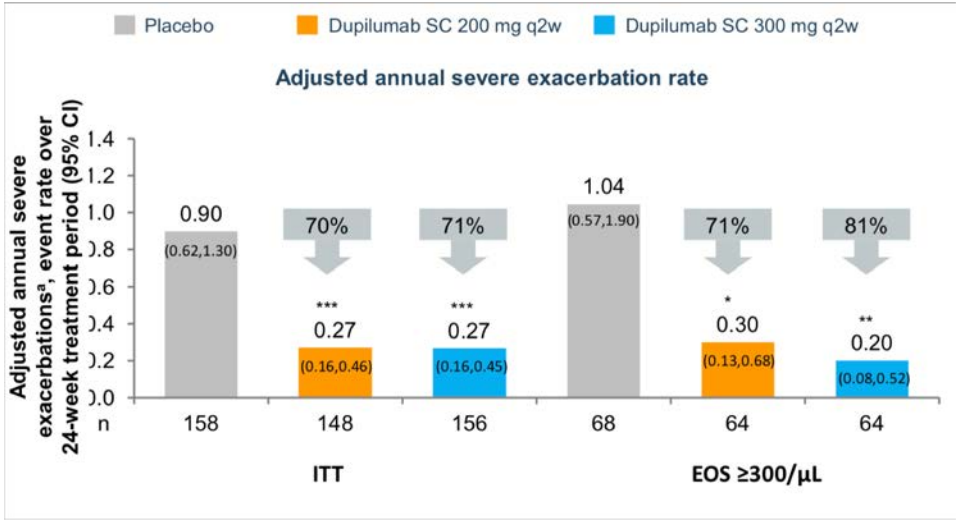
- IL-4 and IL-13 bind to a shared subunit, IL-4Rα
- Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signaling
- IL-4 and IL-13 pathways have unique and o

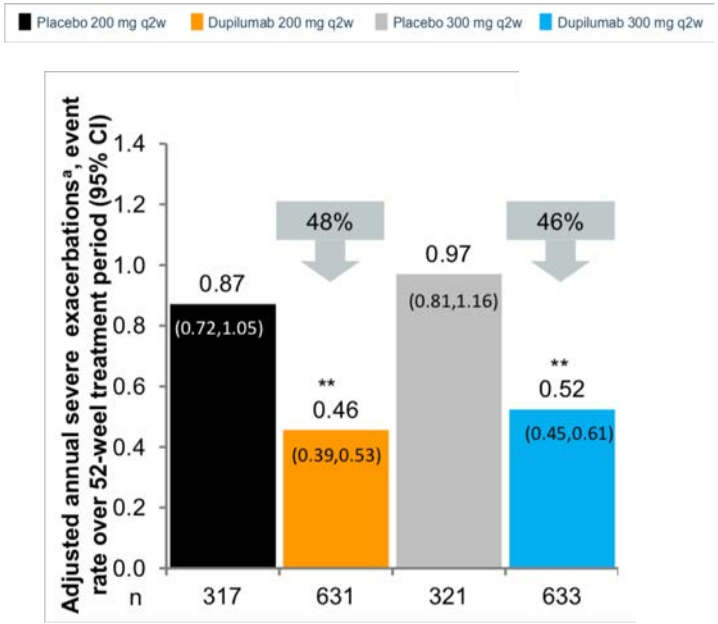




Middleton's allergy essentials
Robinson et al. Clinical & Experimental Allergy 2017

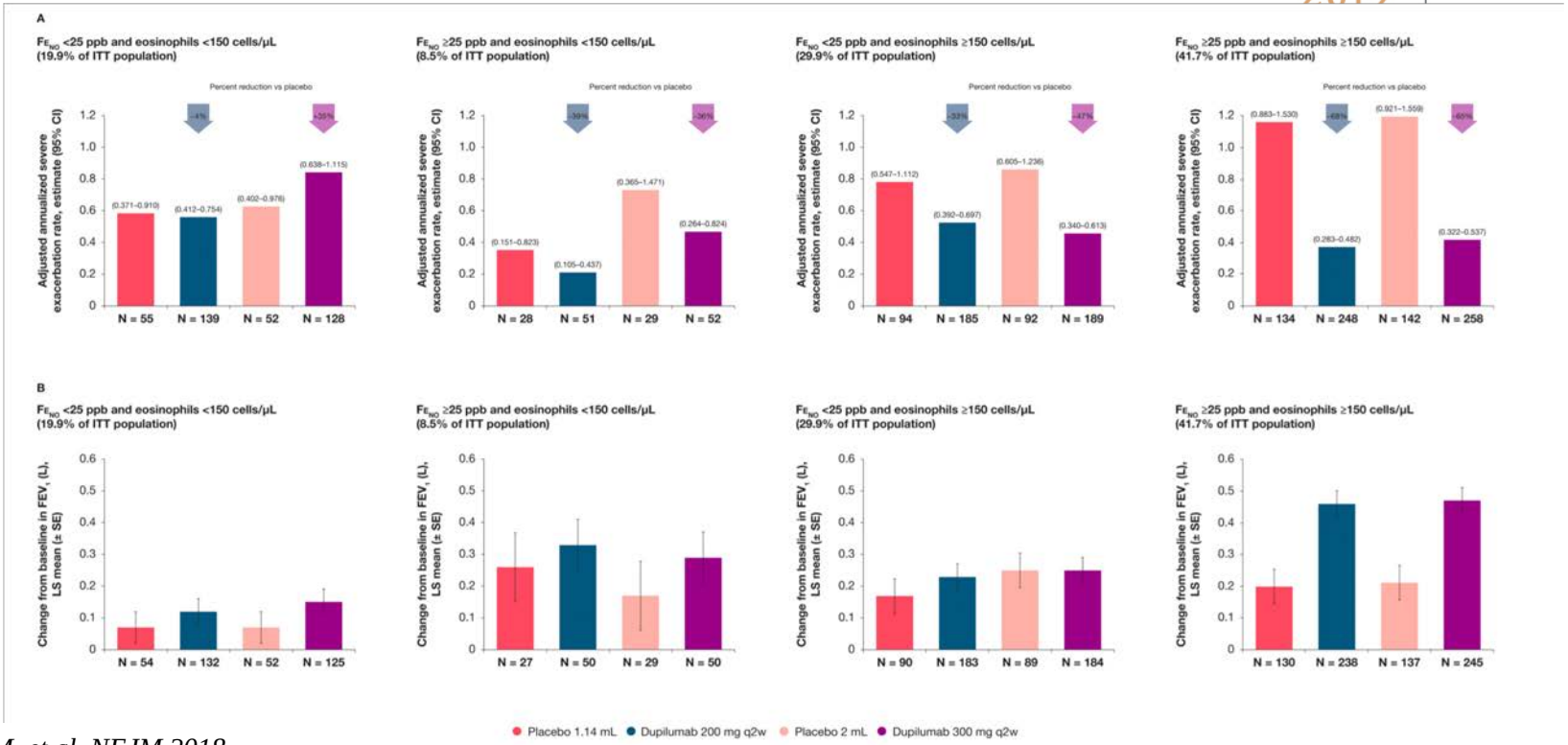
Dupilumab reduces exacerbations in patients with uncontrolled asthma





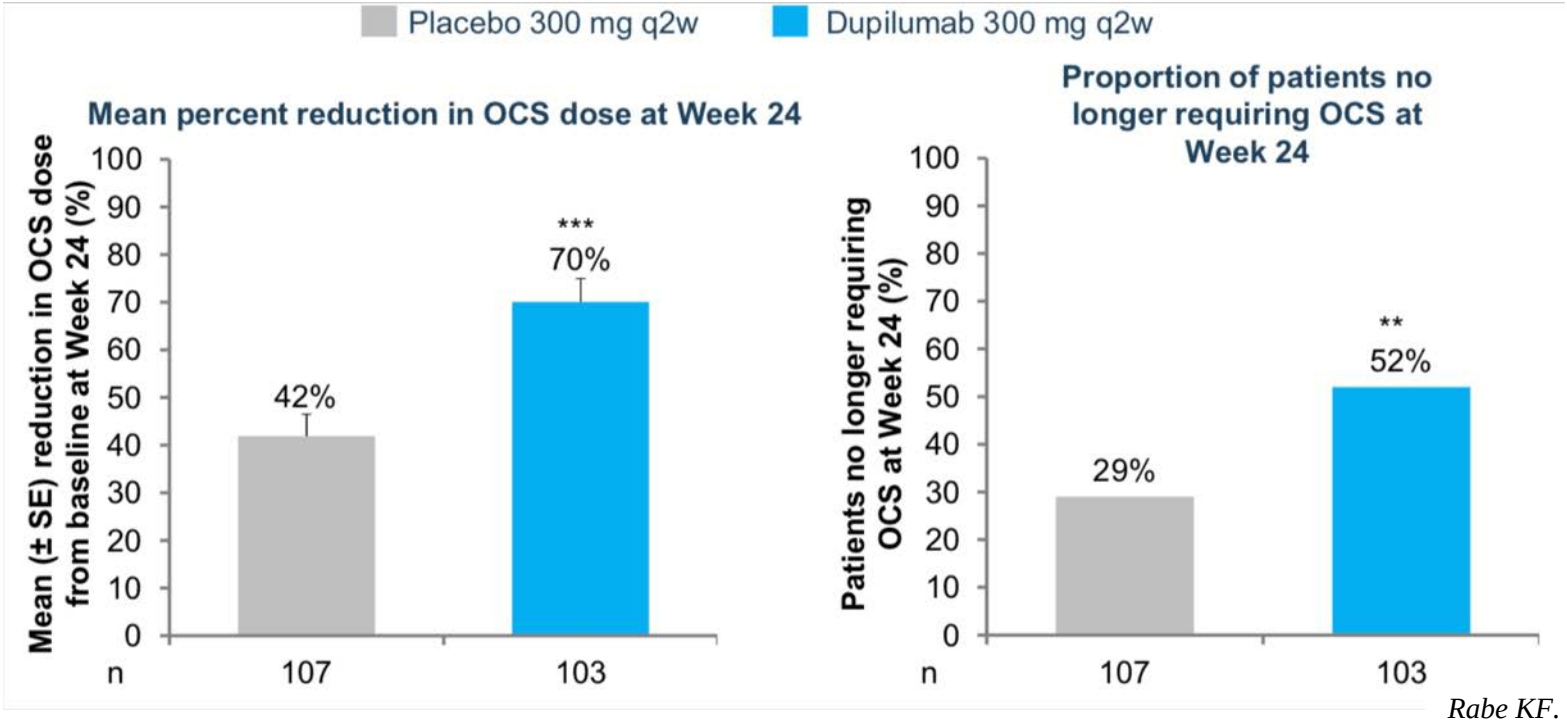
Wenzel S, et al. Lancet
Castro M. et al. NEJM 2018

Effect of dupilumab on exacerbation and lung function by baseline Eos and FeNO



Castro M. et al. NEJM 2018

Dupilumab reduced OCS use



Rabe KF. et al. NEJM 2018

Summary

- Current biologics target patients with a T2 high phenotype
- Biomarkers of T2 inflammation can help to determine which therapies may be most efficacious
- Omalizumab treatment is effective in patients with atopic asthma
- Mepolizumab, benralizumab and reslizumab are effective in patients with eosinophilic asthma
- Dupilumab targets IL-4/IL-13 and is effective in patients with type 2 asthma
- Dupilumab, mepolizumab and benralizumab are effective in OCS-dependent asthma

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