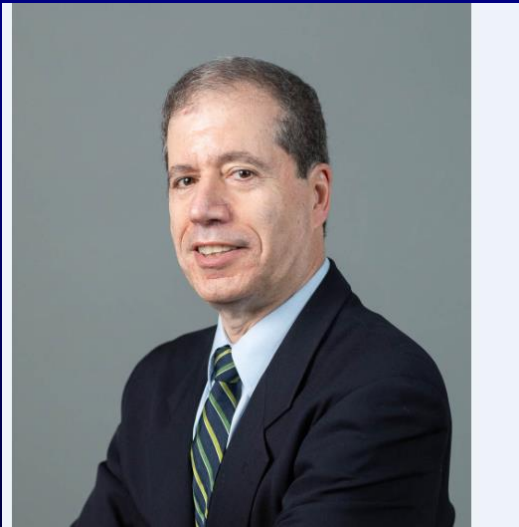


Evolving Therapy of Asthma

Elliot Israel, M.D.
Director of Clinical Research
Pulmonary & Critical Care Division
Division of Allergy and Immunology
Department of Medicine
Brigham and Women's Hospital
Professor of Medicine
Harvard Medical School



Elliot Israel, M.D.



- Johns Hopkins University School of Medicine
- Medicine Residency – Johns Hopkins Hospital, New York Hospital/Cornell
- Pulmonary/Critical Care Fellowship - BWH
- Allergy & Immunology Fellowship - BWH
- Professor of Medicine@ HMS
- Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research
- Clinical focus: Severe Asthma
- Research focus:
 - Clinical and Translational Research related to severe asthma
 - Pharmacogenetics of asthma therapy
 - Innovative trial design in asthma
 - Asthma in disadvantaged communities

Disclosures

- AB Science Consultant
- Amgen Consultant
- Arrowhead Pharmaceuticals Consultant
- AstraZeneca Consultant and Clinical Research Support
- Avillion Consultant and Clinical Research Support
- Circassia Clinical Research Support
- Cowen Consultant
- GlaxoSmithKline Consultant
- Gossamer Bio Clinical Research Support
- Merck Consultant
- Novartis Consultant
- PPS Health Consultant

Disclosures (Con't)

- Regeneron Consultant
- Sanofi Consultant
- TEVA Consultant and Clinical Research Support

Objectives

- Understand new NAEPP and GINA guidelines for the treatment of asthma
- Review biologics and their use
 - T2 and non-T2 inflammation
 - Mechanisms
 - Effects on biomarkers
 - Indications and precision medicine
- Understand how to identify high risk asthma

Definition of Asthma

Chronic inflammatory disorder of the airways

Characterized by:

- Airflow limitation,
 - reversible either spontaneously or with treatment
- Airway inflammation
- Increased responsiveness to a variety of stimuli

Rule of 2's for Lack of Control and Escalation of Medications

- Lack of Control
 - Nighttime awakenings >2/mo
 - SABA use for sxs (not pre-exercise) >2/wk
 - Sx >2 wk
 - ACT / ACQ ≤ 20 / > 1.5
 - Lung function Reduced by >20%
 - Exacerbations >2/yr

Control on ACT or ACQ

- ACT
 - 20 or more
 - MCID is 3
- ACQ
 - ≤ 1.0
 - A 0.5 change is felt to be enough to make a change in therapy
 - Therefore 1.5 is inadequately controlled

30 year old with h/o of occasional asthma using prn albuterol comes in c/o increased symptoms and has an ACT of 18. You should:

- a. Start low dose regular ICS
- b. Give them an ICS and tell them to use it every time they need to use their reliever
- c. Tell them to use combination ICS/formoterol whenever they have symptoms

Major Change in 2021 Update

- The use of as needed inhaled corticosteroids with a short-acting beta-agonist or a long-acting beta agonist (formoterol ONLY) in almost all severity levels

Additional NAEPP Updates

- LAMA can be used in addition to ICS/LABA for some potential additional control
- Allergy shots can be used in mild-moderate asthma but not severe asthma
 - SLIT is not recommended for asthma a
- Indoor allergen mitigation not that effective
 - For those with documented allergy to indoor substances
 - Pest control provides some benefit
 - Multi-strategy dust control provides some benefit

Additional NAEPP Updates

- FeNO can be used as an adjunctive measure to assist in diagnosis of asthma but should not be relied on primarily
- FeNO can be used as an adjunctive measure to follow patients Type 2 inflammation
 - Levels NAEPP recommends are >50 in adults and >35 in kids
 - Need to be aware that allergic rhinitis can produce increased FeNO w/o asthma

Additional NAEPP Updates

- Recommends against bronchial thermoplasty and if done should be performed in the context of a trial or clinical registry

Major Change in 2021 Update

- The use of as needed inhaled corticosteroids with a short-acting beta-agonist or a long-acting beta agonist (formoterol ONLY) in almost all severity levels

SMART Therapy

- Formoterol/Budesonide *when combined with regular bid use,* reduces exacerbations but is NOT APPROVED IN THE USA
- This approach HAS BEEN ENDORSED by the NAEPP 2020 update as reliever therapy for Step 3 and 4 therapy (moderate and moderate/severe)



AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma In Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 [■]
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA [▲] or PRN concomitant ICS and SABA [▲]	Daily and PRN combination low-dose ICS-formoterol [▲]	Daily and PRN combination medium-dose ICS-formoterol [▲]	Daily medium-high dose ICS-LABA + LAMA and PRN SABA [▲]	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA [*] and PRN SABA or Cromolyn, [*] or Nedocromil, [*] or Zileuton, [*] or Theophylline, [*] and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA, [▲] or daily low-dose ICS + LTRA, [*] and PRN SABA or Daily low-dose ICS + Theophylline [*] or Zileuton, [*] and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA [▲] or Daily medium-dose ICS + LTRA, [*] or daily medium-dose ICS + Theophylline, [*] or daily medium-dose ICS + Zileuton, [*] and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA, [*] and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy [▲]			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

NAEPP 2021 Update Medication Progression

		Step 1	Step 2	Step 3	Step 4	Step 5	
		INTERMITTENT	PERSISTENT				
≥ 12 years old	CONTROLLER	None	<div style="border: 1px solid black; padding: 2px; display: inline-block;">Preferred</div> Low-dose ICS	None	Low-dose ICS/formoterol	Medium-dose ICS/formoterol	Medium- to high-dose ICS/LABA + LAMA
	PRN RELIEVER	SABA	SABA	ICS & SABA (concomitant)	ICS/formoterol (up to 12 puffs per day)		“SABA”

GINA (Global Initiative for Asthma)

- GINA recommends ICS/formoterol as reliever therapy for ALL asthma severity including intermittent asthma
 - “This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk”

Type 2 Biologics (Ab Therapy)

Anti-IgE

Anti-IL5

Anti-IL4/13

Tezepelumab

Definition of Type 2 Immunity

- Immune response involving the innate and the adaptive arms of the immune system to promote barrier immunity on mucosal surfaces
- Cells
 - T helper 2 (T^H2) CD4+ T cells and B cell production of the immunoglobulin E (IgE) antibody subclass.
 - Innate response includes ILC 2 innate lymphoid cells, eosinophils, basophils, mast cells and interleukin-4 (IL-4)-and/or IL-13-activated macrophages.
- Associated with IL-4, IL-5, and IL-13.

45 yo female on high dose ICS/LABA has had 2 steroid requiring exacerbations in the past year. She does not c/o of reflux and has no evidence of sinusitis or aspirin sensitivity. Her ACT is 19. Eosinophils 350. FeNO 30. IgE 300. Skin tests positive to dust. You would add on:

- Tiotropium
- Anti-Ige
- Anti-IL5
- Anti-IL4/13
- Anti-TSLP

Anti-IgE

- For poor control on high dose ICS/LABA or equivalent Step 5 therapy
- Qualifications – IgE 30 to 700 and a positive skin test or RAST to an inhalant allergen
- Efficacy – reduces exacerbations by $\frac{1}{4}$ to $\frac{1}{2}$
 - FEV1 increases 4%
 - Not all patients respond
- Toxicity – rare anaphylaxis
 - Had been question about increased rate of cancer
 - Large observational study does not suggest

Anti-IL5 Drugs

- Mepolizumab and Reslizumab bind to IL5 itself and reduce eosinophils by blocking IL5
- Benralizumab binds to the IL5 receptor and also activates NK cells
 - Blocks IL5 signaling
 - Directly toxic to eosinophils
- All indicated for eosinophilic moderate-severe asthma

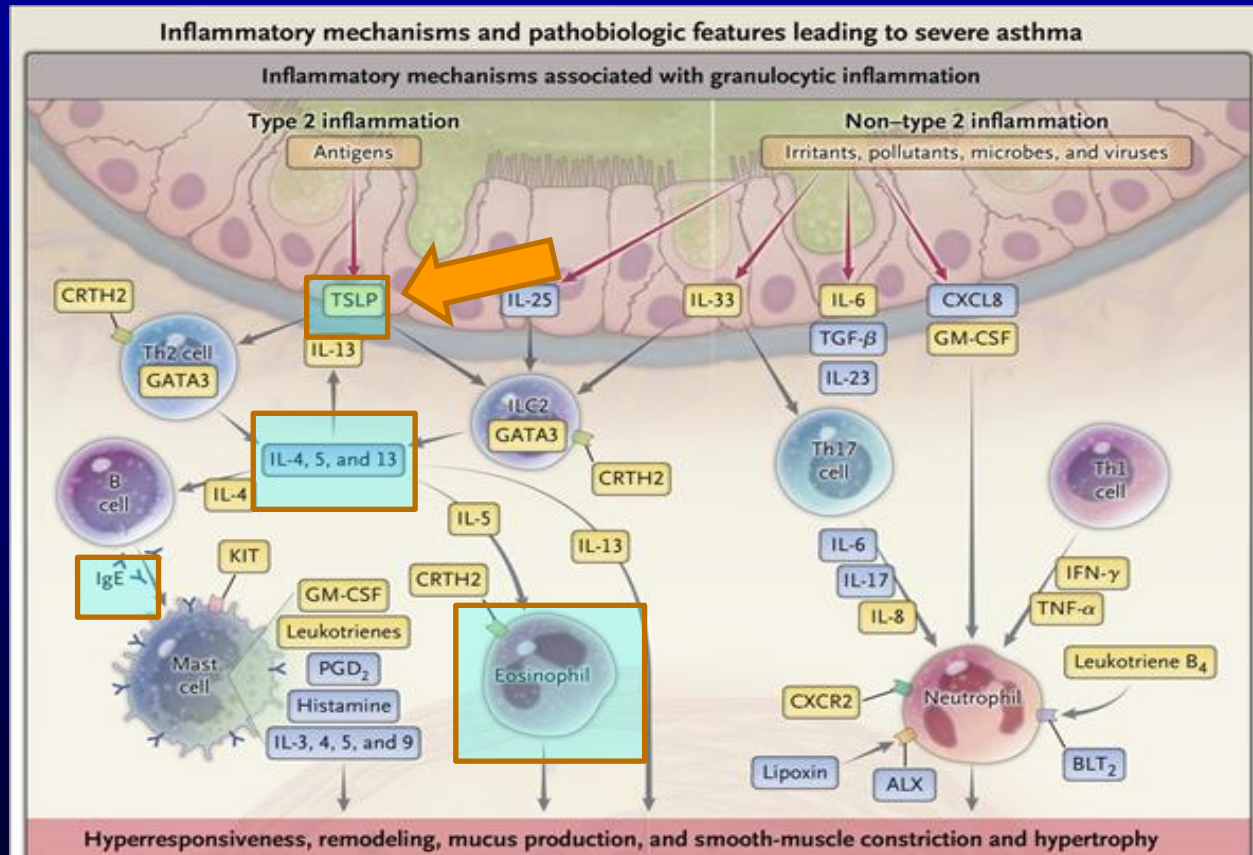
Anti-IL5 (Mepolizumab, Reslizumab, Benralizumab)

- Reduce eosinophils
- Reduce exacerbations by $\geq 50\%$ in patients with ≥ 2 exacerbations/year and h/o blood eosinophils
- Variable effect on FEV₁ and symptoms
- Use in patients with persistent exacerbations despite compliance with high dose ICS/LABA and blood eosinophils ≥ 300 (?150)

Dupilumab

- Blocks IL4 and IL13 receptor
- Reduces exacerbations by 60-70% in patients with 1 or more exacerbations with eosinophils >300
- Reduces FeNO quickly and IgE gradually
- In some patients eosinophils initially rise and then gradually come down
 - Conjunctivitis mostly in patients treated for eczema

Type 2 Inflammatory Targets



• Israel & Reddel, NEJM, 2017

Tezepelumab

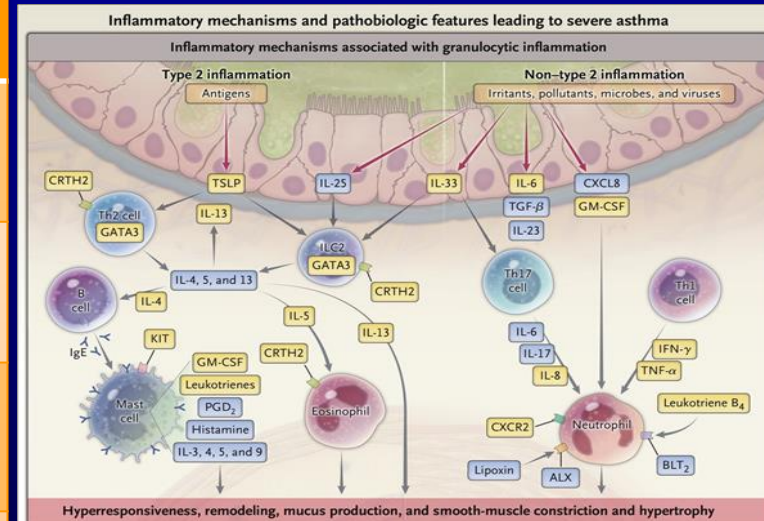
- Binds to TSLP and prevents interaction with TSLP receptors
- Reduces exacerbations by 60-70% in patients with 2 or more exacerbations and appeared effective even in those with low eosinophils
- Reduces eosinophils and FeNO quickly and IgE gradually

OCS-Sparing Effects (Regardless of Baseline Eosinophils)

- Effective
 - Mepolizumab
 - Benralizumab
 - Dupilumab
- Did not Show Effectiveness in Pivotal Trial
 - Tezepelumab
- Not tested
 - Reslizumab

Effect of the Biologics on Biomarkers in Severe Asthma

	Omalizu mab	Mepoliz umab	Resliz mab	Benralizu mab	Dupilu mab	Tezepe lumab
IgE	++++ ^X	=	=	=	+ [#]	+ [#]
FeNO	+ [#]	=	=	=	+	++
Eosinophils	+ [#]	+++	+++	++++/+ +++	-/+ [*]	++
^X Reduction in free IgE (commercial assays detect TOTAL igE) [#] Gradually reduced [*] Eosinophils may rise especially in those with high baseline eosinophils						



Effects on Co-Morbidities

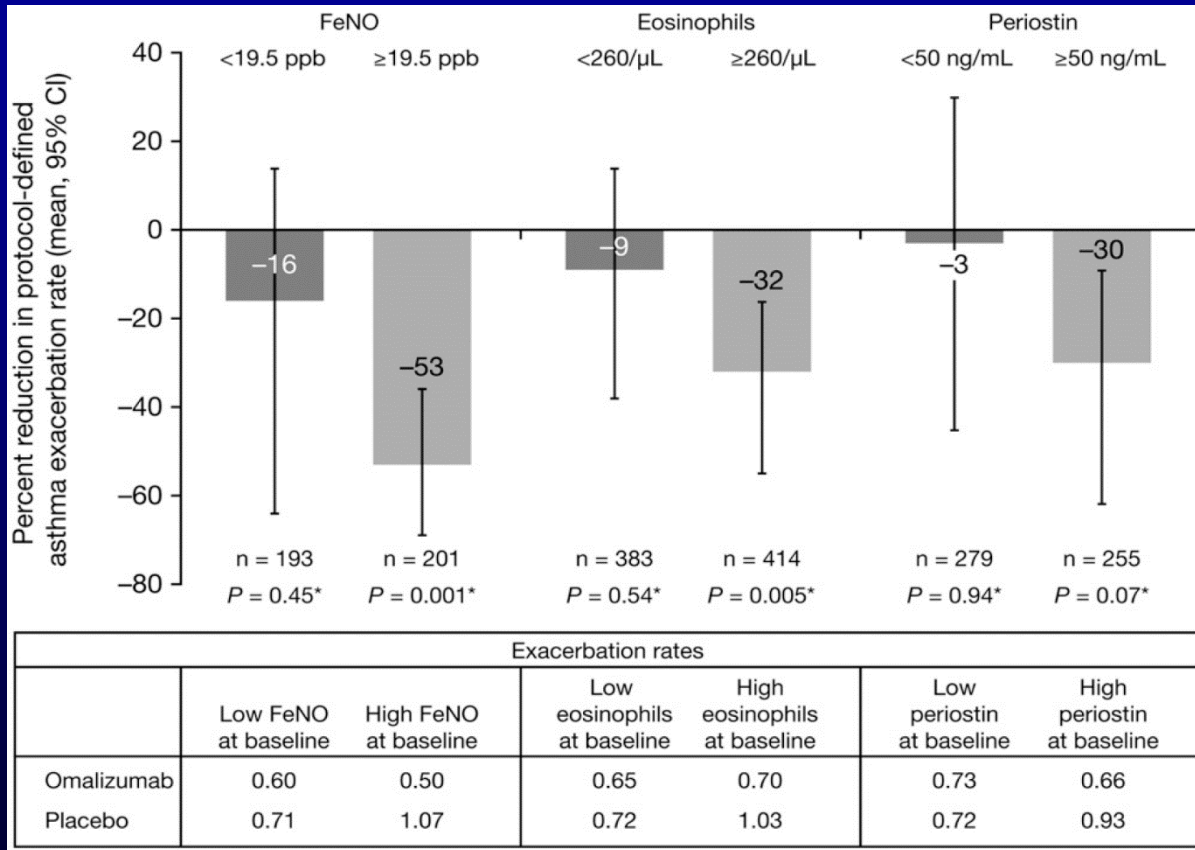
- Nasal Polyps
 - Omalizumab
 - Mepolizumab
 - Dupilumab
- Chronic Idiopathic Urticaria
 - Omalizumab
- Atopic Dermatitis
 - Dupilumab



WHO RESPONDS?



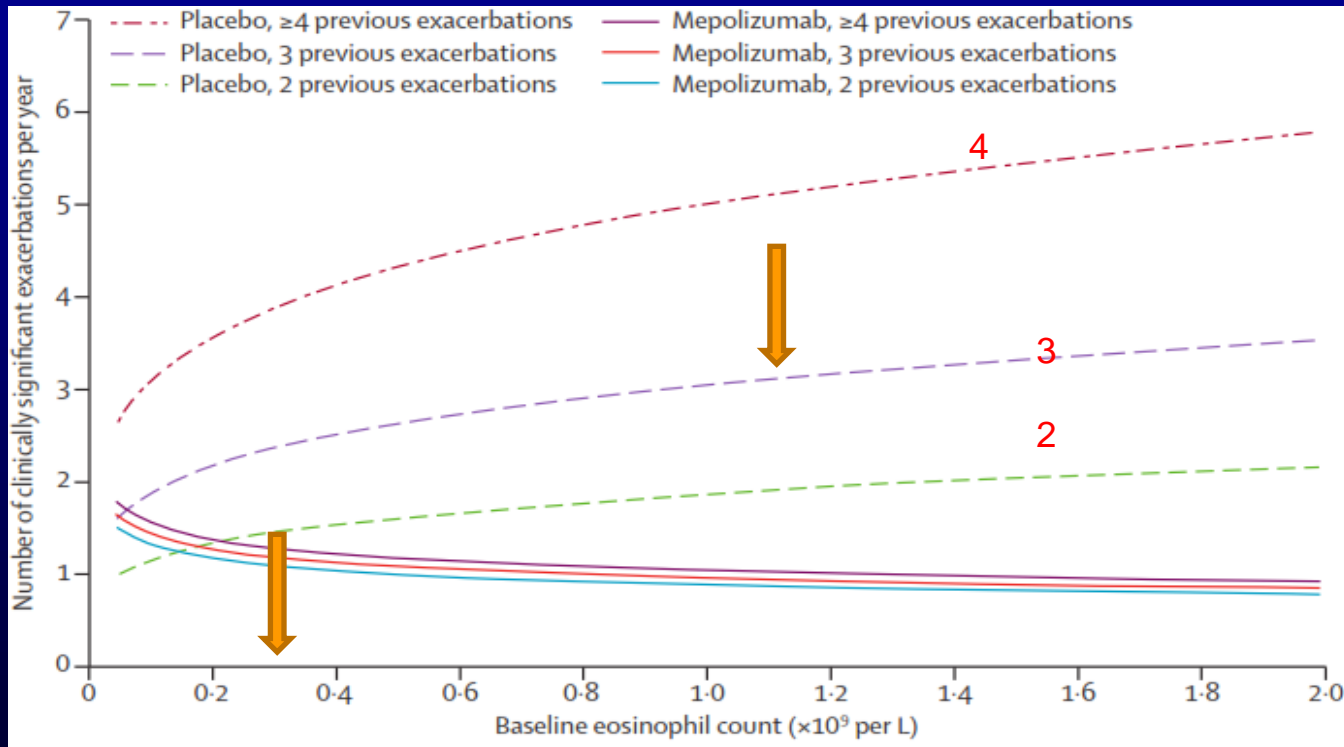
FeNO Best Predictor of Response to Omalizumab in Pre-selected Pts



Hanania, Am J Respir Crit Care Med, 2013



Modeling Suggests that Mepo's Greatest Effect is on Patients with 3 or more Exacerbations or Very High Eosinophils



Pavord, Lancet, 2012

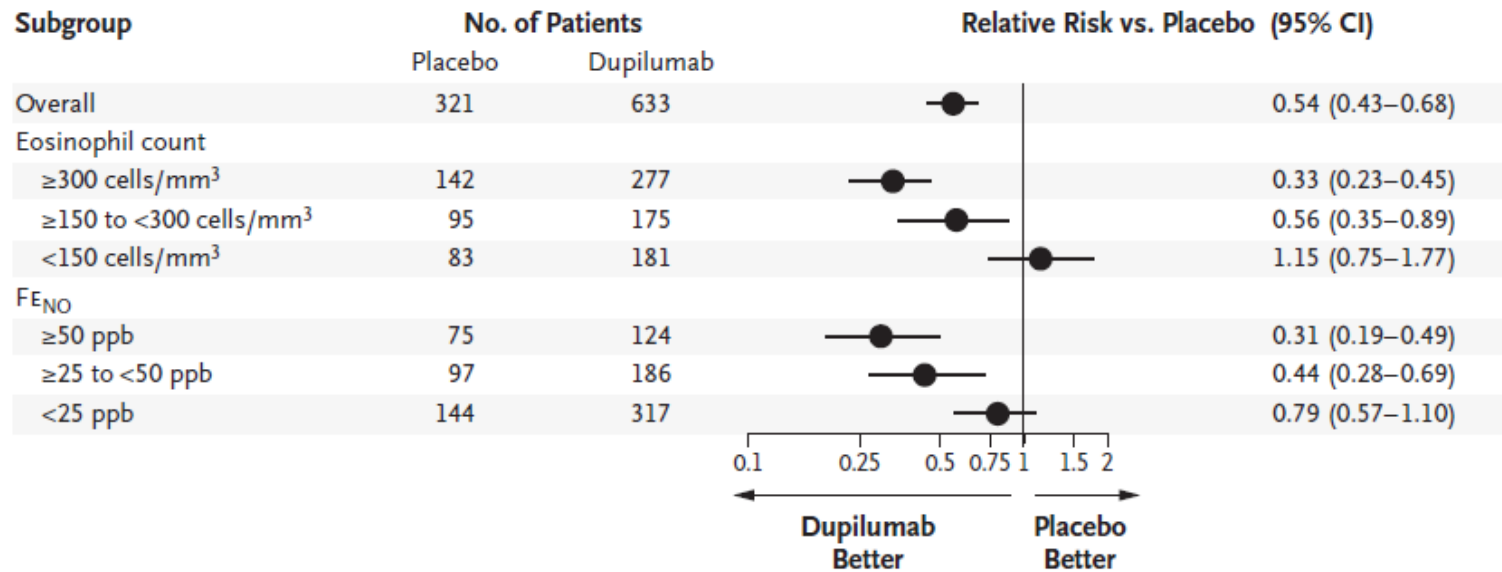


FeNO is NOT a predictor of response to anti-IL5 drugs



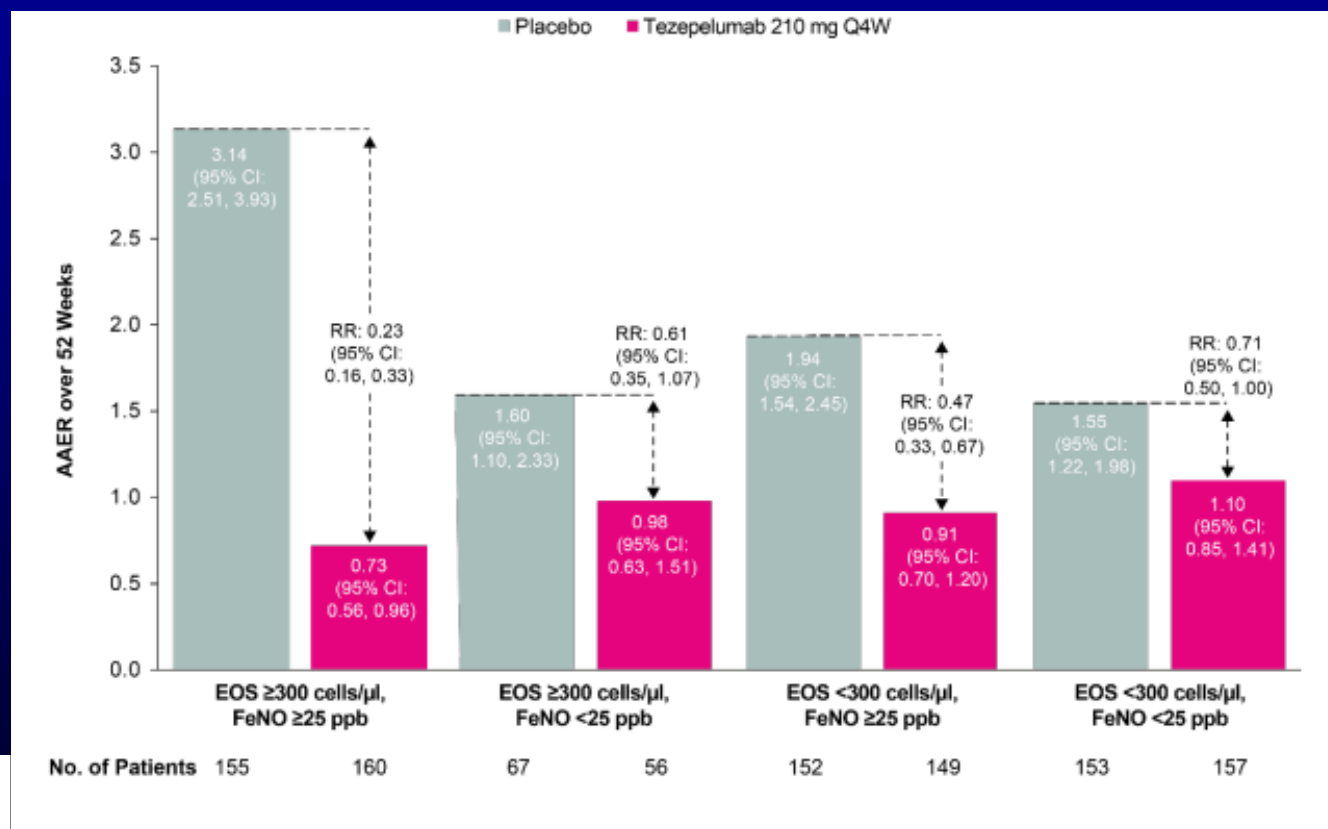
FeNO or Eosinophils Predict Reduced Exacerbations w/ Dupilumab

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo



Castro et al , NEJM, 2018

Tezepelumab is Less Effective in Combined Low Eos/Low FeNO



Menzies-Gow, NEJM, 2021



Biomarkers of Patients Likely To Respond

ALL PATIENTS STUDIES HAD TO HAVE ≥ 1 -2 EXACERBATIONS AT BASELINE AND BD BY $\geq 12\%$

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Eosinophils	++	+++	+++	+++	+++	+++
FeNO	++	0	0	0	+++	+++
Low Eos/Hi FeNO	?	0	0	0	++	++
Low Eos/Low FeNO	0	0	0	0	0	+/-



Neutrophilic or Non-Type 2 Asthma

- More than half of asthma patients have asthma that involves inflammation mediated by Type 2 cytokines (IL4,5, and 13) \cong IgE/Eosinophils
 - Forty to 50% of severe asthmatics may have neutrophilic or paucigranulocytic inflammation
 - May be less responsive to steroids
- May respond to azithromycin



Use of Exhaled Nitric Oxide

- Level of ≥ 30 ppb is consistent with persistent eosinophilic inflammation
- Markedly reduced by use of ICS
- Persistently high FeNO despite therapy is c/w non-compliance or pathobiology resistant to therapy
- May be a good predictor of response to therapy for patients considered for biologic aimed at Type 2 process (Anti-IgE/IL4/IL13/Tezepelumab)

Definition of “High-Risk”

- Newly diagnosed asthma
- On daily prednisone prior to admission
- ≥ 2 E.D. visits in last 6 months
- ≥ 1 prior hosp’ns in last 12 months
- Ever intubated for asthma
- Severe psychosocial problems
- Drug addiction
- Lower socio-economic status

Points to Remember

- Rules of two's for initiation of controller and for step up
- NAEPP prn ICS/SABA for Step 2 and maintenance and reliever ICS/formoterol for Step 3 and 4
- IgE >30 or Eos \geq 300 (150) may be candidates for biologics especially with 2 or more exacerbations per year
- Pts on OCS candidates for biologics regardless of eosinophil count but not yet shown for tezepelumab
- High FeNO alone does not predict response to anti-IL5 and FeNO is suppressed by ICS
- High risk patients



Severe Asthma Program



State of the Art Multidisciplinary
Evaluation and Treatment of Patients
with Severe Asthma

- Pulmonary
- Allergy
- ENT
- GI
- Psychiatry
- Alternative Medicine

• severeasthma@bwh.harvard.edu or 1 844 BWH-LUNG