Evolving Guidelines for the Management 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

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S MEN'S
Department of Medicine ine

HARVARD
MEDICAL SCHOOL
Global and Continuing Education

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)

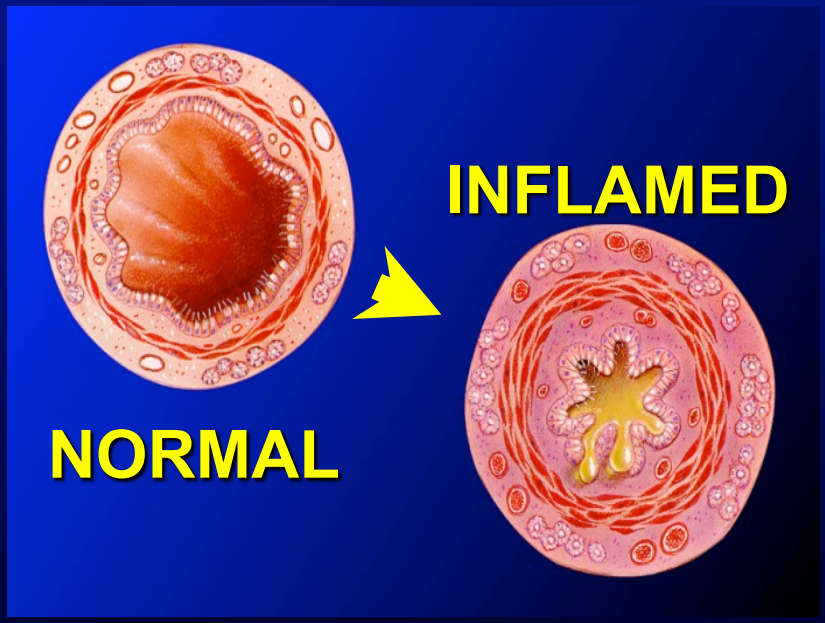
• Regeneron	Consultant
• Sanofi	Consultant
• TEVA	Consultant and Clinical Research Support

GOALS

- Review NAEPP update for asthma management
- Review the new biologics, their use, and effects

Inflammatory Changes in Chronic Asthma

- Mucus secretion
- Inflammatory cell infiltration
- Edema
- Smooth muscle constriction & hypertrophy
- BM thickening and subepithelial collagen



Goal of Asthma Therapy: Achieve Control

Reduce Impairment

- Prevent chronic and troublesome symptoms
- Require infrequent use of inhaled SABA (≤2 days/week)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels
- Meet patients' expectations of, and satisfaction with, asthma care

Reduce Risk

- Prevent recurrent exacerbations
- Minimize need for emergency department visits or hospitalizations
- Prevent progressive loss of lung function
- Provide optimal pharmacotherapy, with minimal or no adverse effects

PARTNERS ASTHMA CENTER

NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm. Accessed 2.8.07.

Rule of 2's for Severity and Control

- Mild Persistent or 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
- Severe
  - Failure to achieve control on high dose ICS and another controller or requirement of these medications to achieve control

PARTNERS ASTHMA CENTER

Recent Changes

Approved Super long-acting beta-agonist combinations (Once a day)

- Fluticasone furoate 100 or 200 with vilanterol 25
  - Combined long-acting ICS and super-long acting (LA)BA.
  - Only approved in 18 yo and above
- Dose equivalency
  - 1 puff 100/25 qd = 1 puff bid FP250/Salm 50 BID
  - 1 puff 200/25 qd = 1 puff bid FP500/Salm50 BID
- ICS/LAMA/LABA once a day now approved in asthma

PARTNERS ASTHMA CENTER

Montelukast

- Black box warning about depression and suicidality

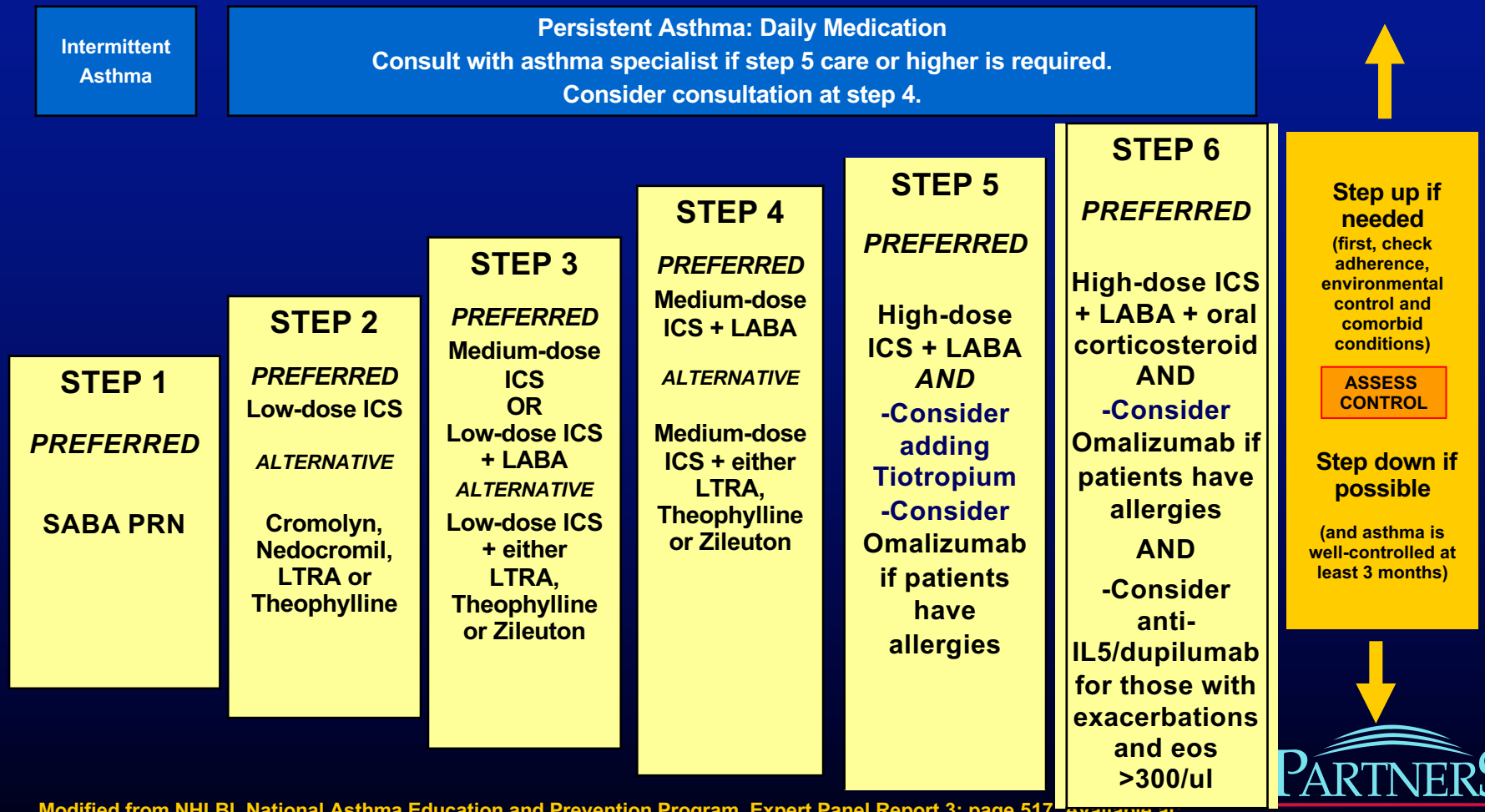
PARTNERS ASTHMA CENTER

SMART Therapy

- Formoterol/Budesonide ***when combined with regular bid use***, reduces exacerbations but is **NOT APPROVED BY THE USA FDA**
- This approach HAS BEEN ENDORSED by the NAEPP 2020 update for Steps 3 and 4
- This only applies to ICS/formoterol combinations since formoterol is fact-acting. It cannot be used with ICS/salmeterol (Advari, Wyxela, etc)

PARTNERS ASTHMA CENTER

PRE-2020 NAEPP Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age



Modified from NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3: page 517. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm. Accessed 2.8.07.

PARTNERS ASTHMA CENTER

Major Change in 2021 NAEPP 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
- Formal recommendation of adding LAMA to ICS/LABA for Step 5

PARTNERS ASTHMA CENTER

AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	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 2020 Update

		Step 1	Step 2		Step 3	Step 4	Step 5
		INTERMITTENT	PERSISTENT				
≥12 years old	CONTROLLER	None	*Preferred* Low-dose ICS	*Preferred* 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"

Highlighted items are areas of change from the 2007 NAEPP Guidelines.
ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; PRN: as needed; SABA: short-acting beta$_2$-agonist.

Consider Biologics if not controlled

GINA (Global Initiative for Asthma)

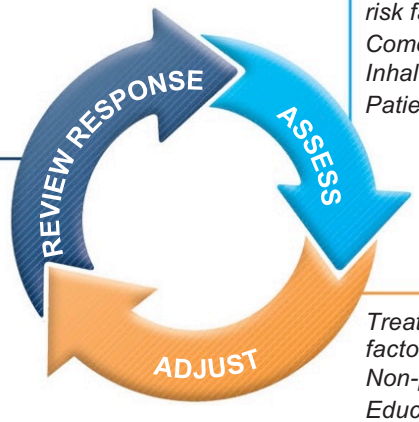
- GINA recommends ICS/formoterol as reliever therapy for ALL asthma severity including intermittent asthma
  - — “This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk”

PARTNERS ASTHMA CENTER

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2 -agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

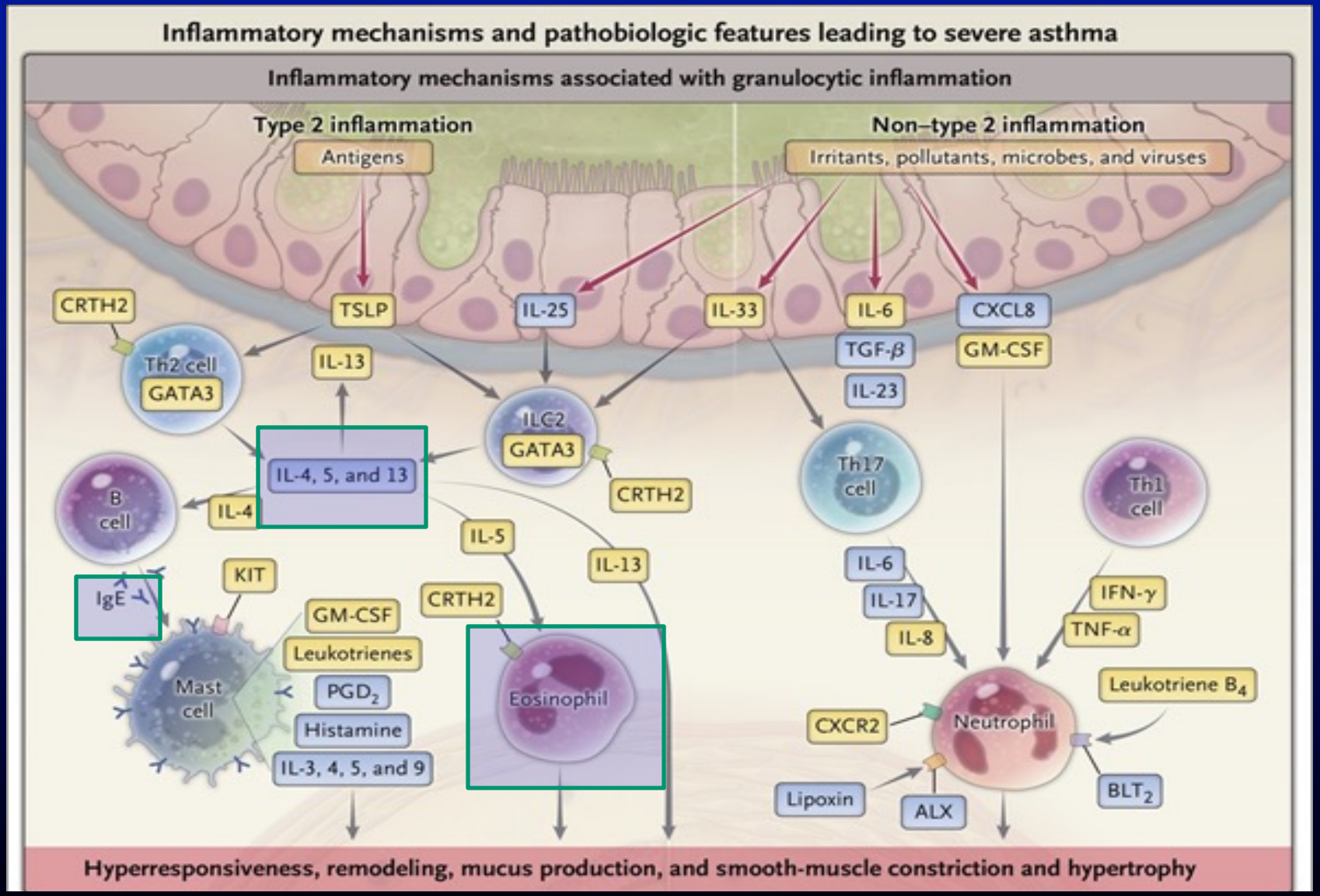
Evolving Information on Biologics and Severe Asthma

-Anti-IgE

-IL5 Modifiers

-Anti-IL4/IL13

Type 2 Inflammatory Targets



•Israel & Reddel, NEJM, 2017

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 inahalant allergen
- Efficacy – reduces exacerbations by ¼ to ½
  - FEV1 increases 4%
  - Not all patients respond
- Toxicity – rare anaphylaxis
  - Had been question about increased rate of cancer
  - Large observational study does not suggest

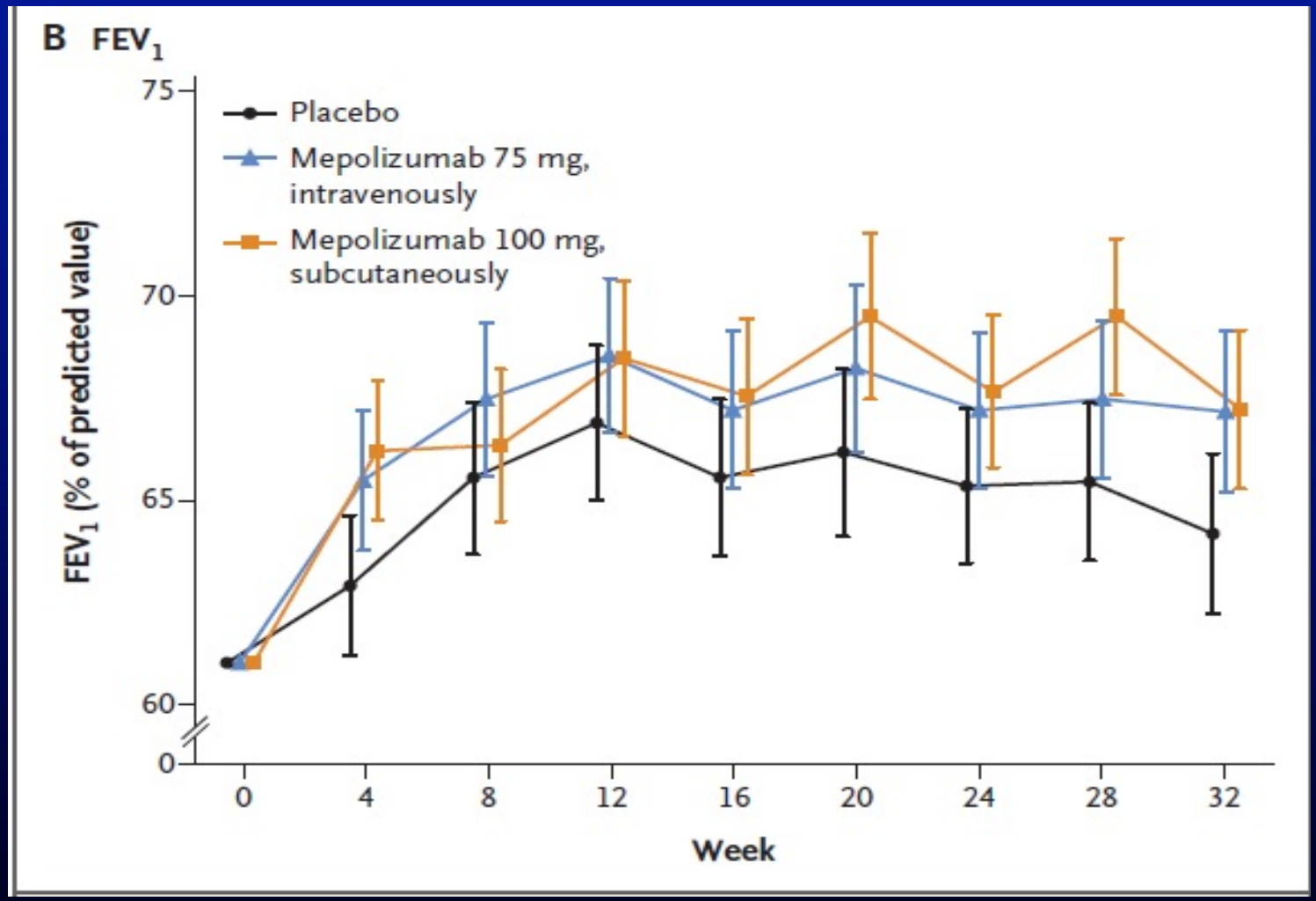
Effect of Anti-IgE on Biomarkers

- Eosinophils =
- IgE – all bound but commercial assays do not detect change
- FeNO – mild reduction

Anti-IL5 Drugs

- Mepolizumab and Reslizumab bind to IL5 itself and reduce eosinophils by blocking IL5
- Benralizumab binds to the IL5 receptor and fixes complement
  - Blocks IL5 signaling
  - Directly toxic to eosinophils
- Except for reslizumab (which is administered IV) they are administered SC every month (mepo) and every 2 mo (benralizumab) with available home injectors

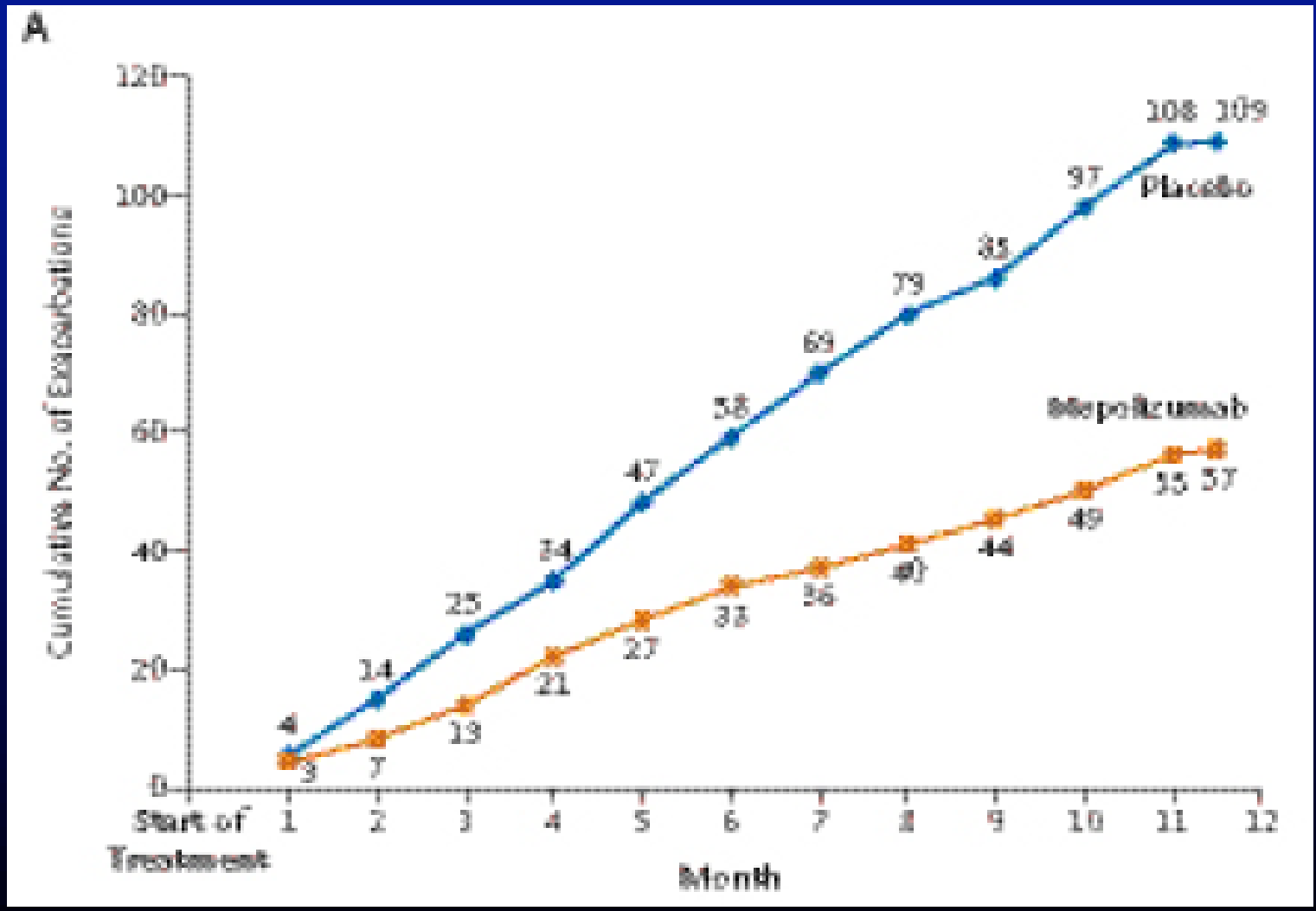
Mepolizumab Increased FEV_1 by ~100cc



Ortega, NEJM, 2014

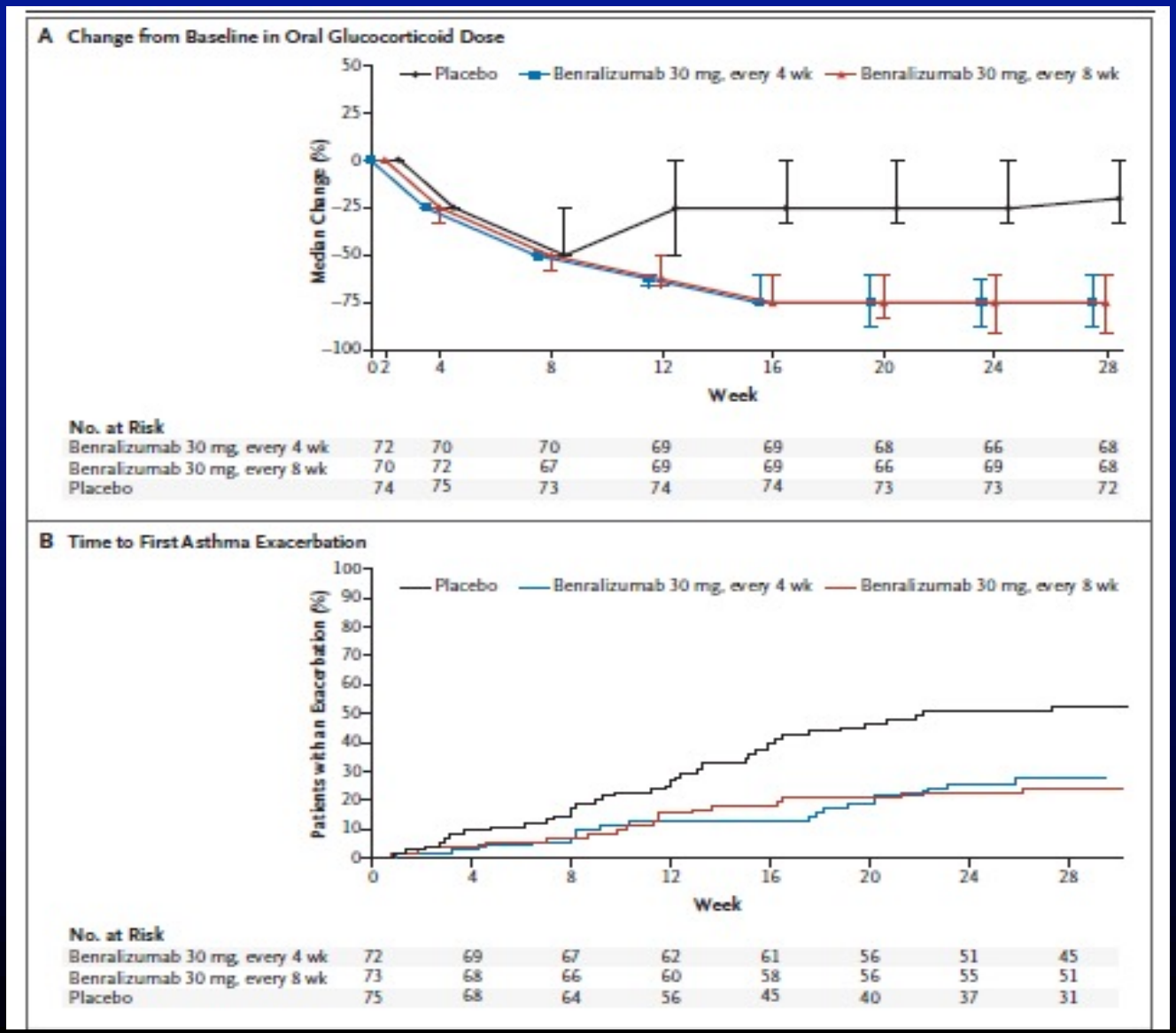
Exacerbations w/ Anti-IL5 Rx in Patients w/ Sputum Eosinophils

Generally a 50% reduction in excacerbations



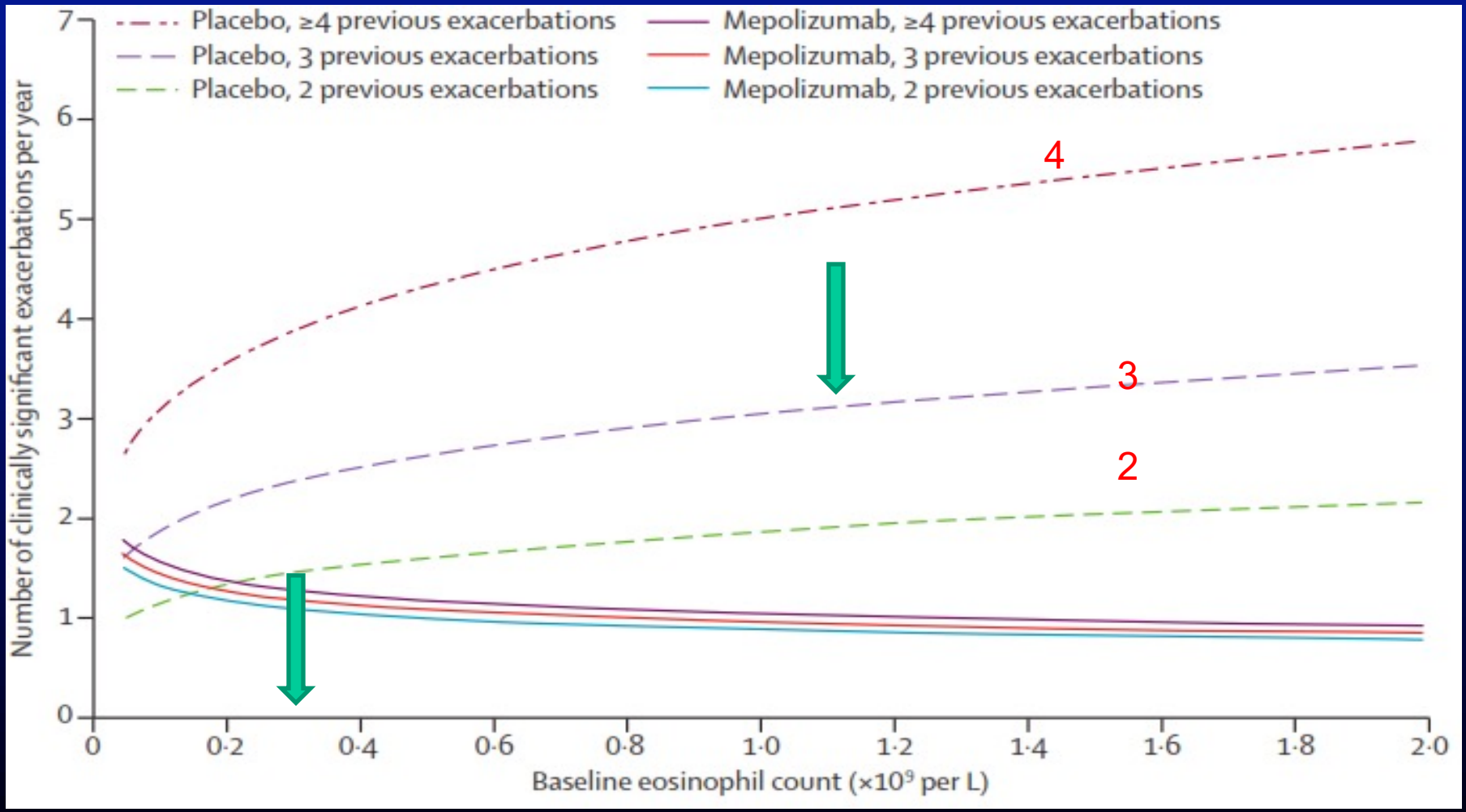
•Haldar, NEJM, 2009

OCS Sparing
Benralizumab(0.32-0.39 HR for time to 1st exacerbation)



Nair, NEJM, 2017

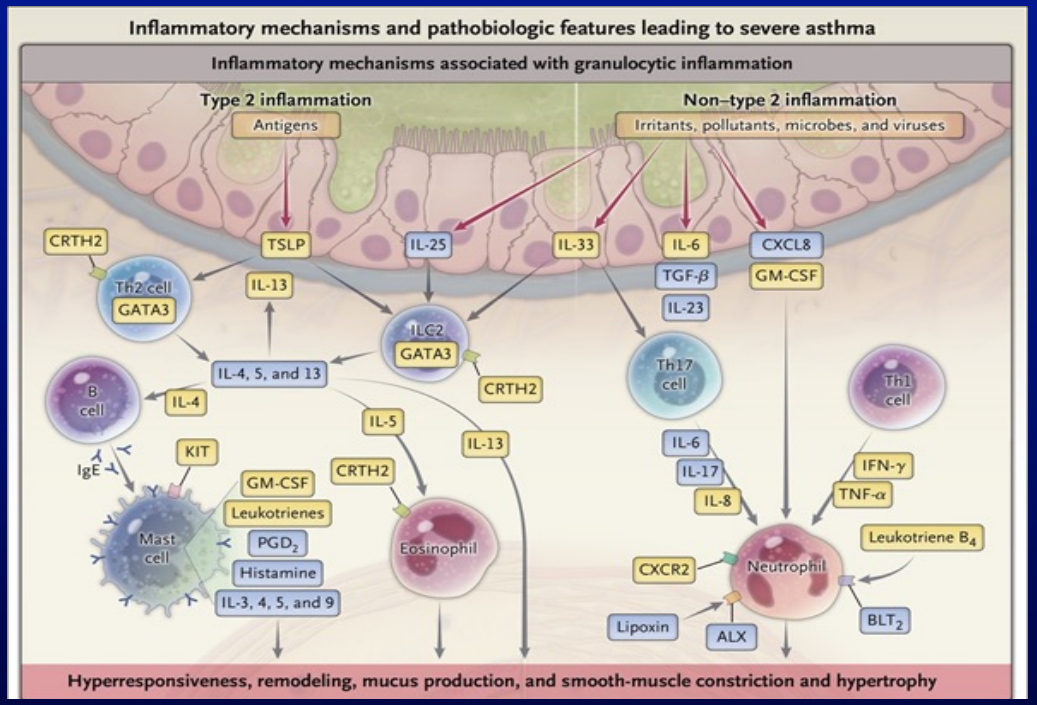
Modeling Suggests that Mepo's Greatest Effect is on Patients with 3 or more Exacerbations or Very High Eosinophils



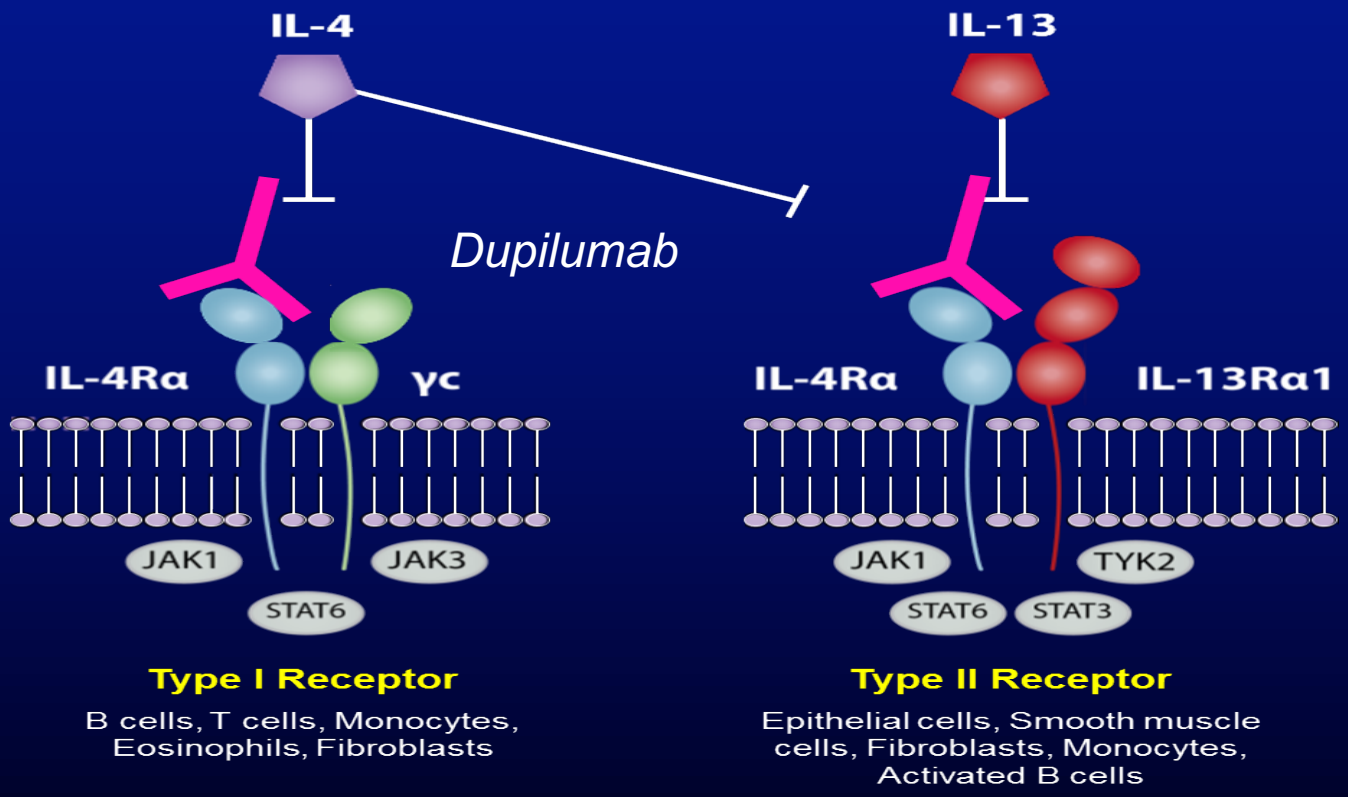
Pavord, Lancet, 2012

Effect of IL5-active drugs on Biomarkers

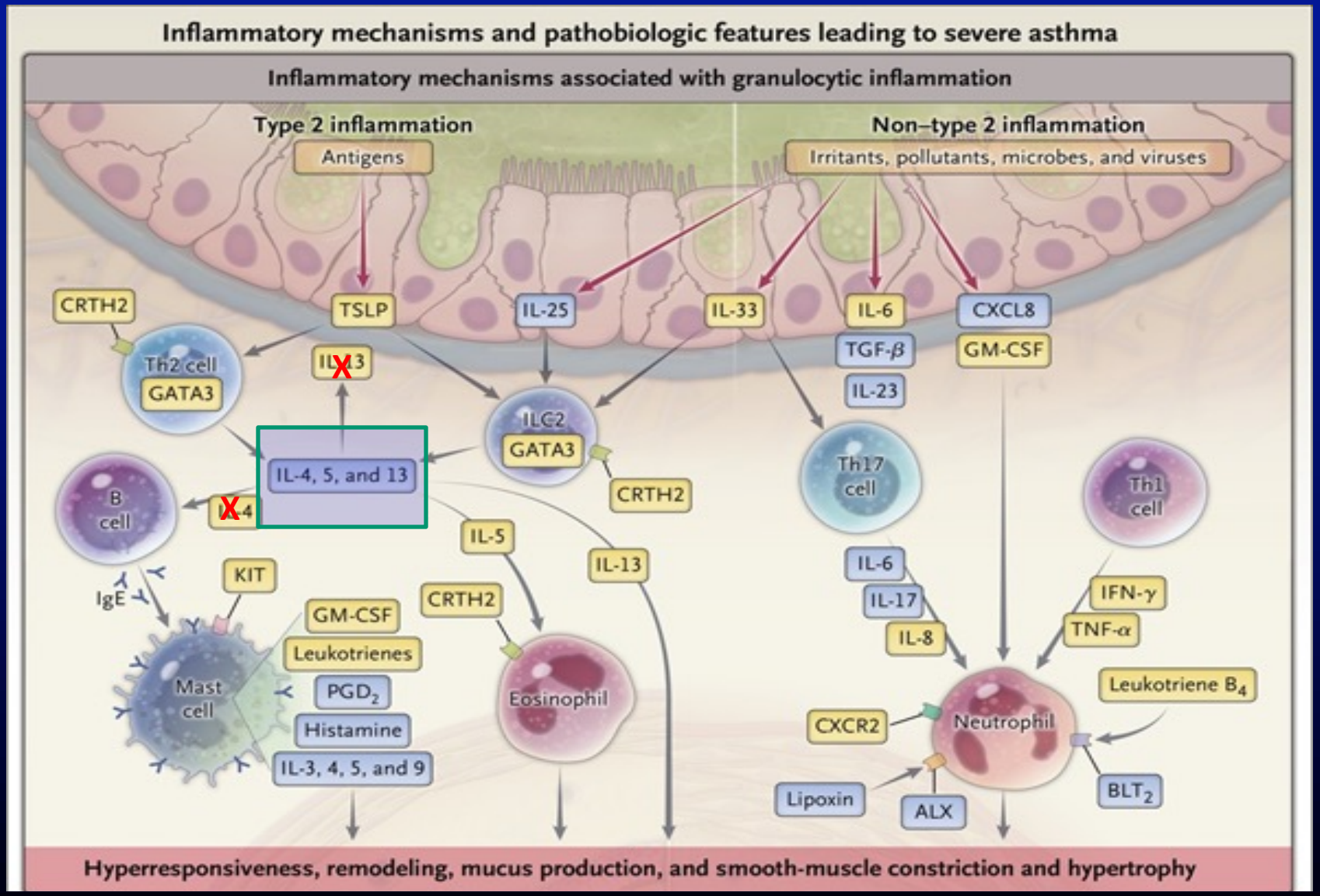
- Eosinophils
  - Rapidly reduced (days to week)
  - Recover within weeks after discontinuation
- IgE – unchanged
- FeNO - unchanged



Blocking IL-4Ralpha (Dupilumab) Blocks both IL4 and IL13



Type 2 & Non-Type 2 Inflammation

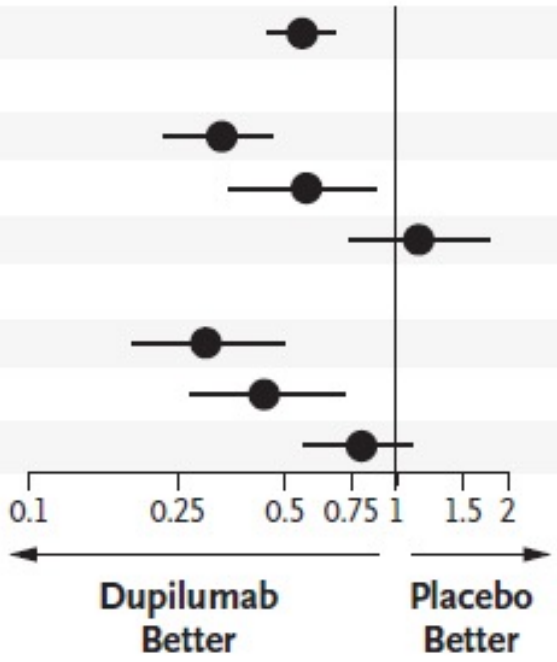


Israel & Reddel, NEJM, 2017

Patients with Greater T2 Markers Had Reduced Asthma Exacerbations w/ Dupilumab

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

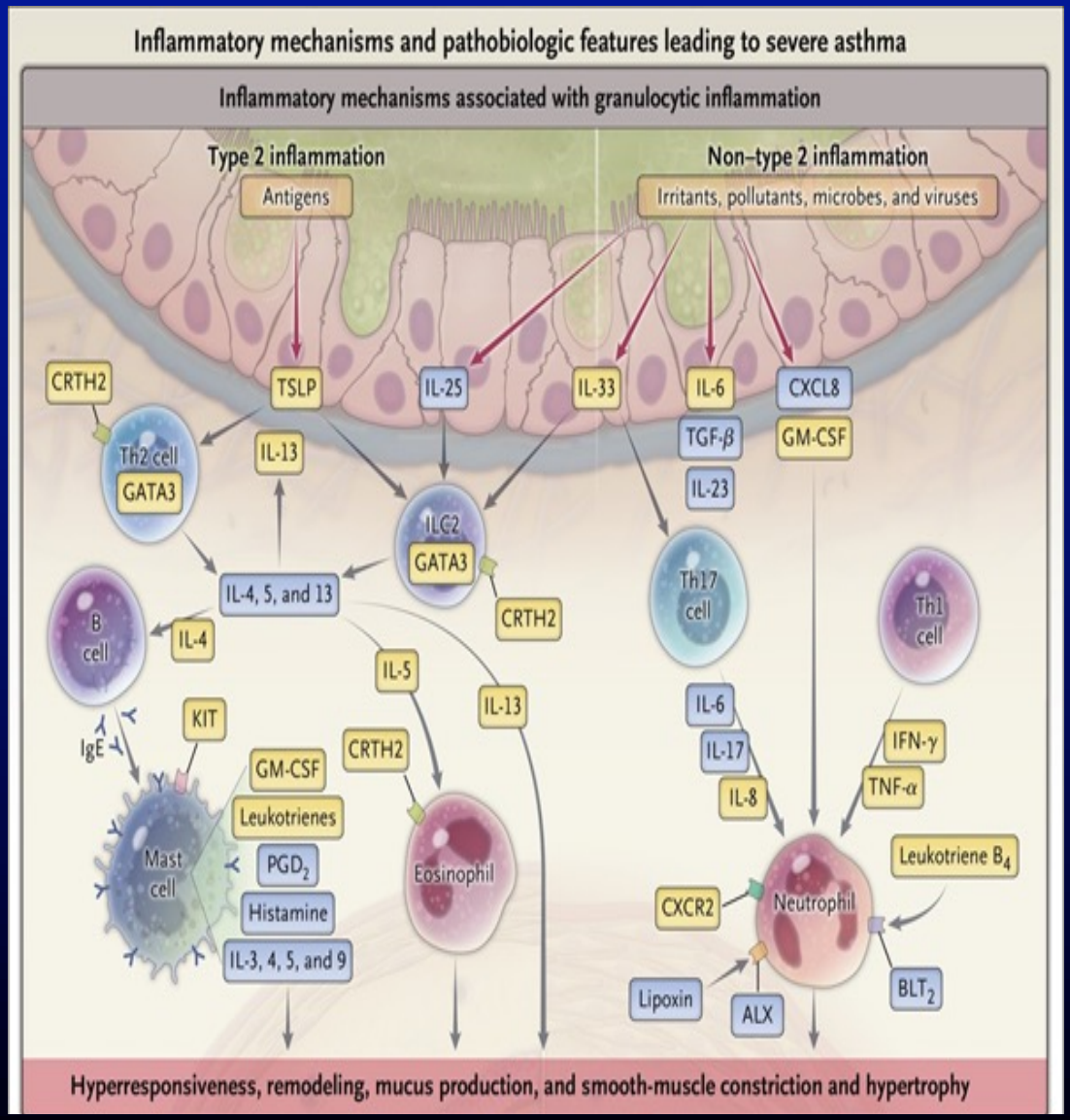
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm^3	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm^3	95	175	0.56 (0.35–0.89)
<150 cells/mm^3	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Castro et al. NEJM 2018

Dupilumab Effect on Biomarkers

- IgE
  - Reduced over time
- Eosinophils
  - Increase at least temporarily
  - 4-5% > 3000 cell/ul
- FeNO
  - Decreases 10-40%



Characteristics of Biologics

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
Exacerbations	+	++	++	++	++
Lung Fx	+/-	+	+/++	+	+/++
IgE	+++^	=	=	=	+
FeNO	+	=	=	=	++
Eosinophils	+	+++	+++	+++/++++	-/+*
Lowest age	6	6	18	12	12
Frequency	2-4 wks	4 wks	IV 4 weeks	8 wks after first months	2 wks

^Free IgE reduced but not detected by commercial assays
***Eosinophils may rise especially in those with high baseline eosinophils**

Summary of Use of Drugs Active on Type 2 Pathway

- Effectiveness shown for patients with 2 or more exacerbations
  - Generally patients with >300 eosinophils or currently 150 with a h/o eosinophils >300
  - Most effective for exacerbations
  - Some effect on symptoms and FEV1

KEY POINTS

- Rule of 2's for determining asthma control
  - ACT <20, ACQ ≥1.5
- LAMA addition at Step 5
- NAEPP suggests SMART for Steps 3 and 4 and prn ICS/SABA for Step 2

- T2-active biologics reduce exacerbations in those with exacerbations and evidence of T2 inflammation
  - Generally 2 or more exacerbations a year
  - Generally eosinophils >300
    - Not necessary on those on chronic oral corticosteroids
  - Allow oral corticosteroid reduction
- Dupilumab is effective in those with eosinophils and those with elevated FeNO
  - Also allows OCS reduction
  - Temporary rise in eosinophils

Question #1

According to the NAEPP which of the following is recommended for mild persistent asthma (Step 2)?

A. Low dose ICS and as needed SABA
B. PRN ICS/formoterol
C. PRN ICS used together with PRN SABA
D. A and C

Question #2

Which of the following is NOT recommended as a necessary for consideration of anti-IL5 therapy?

a. Persistent symptoms on high dose ICS/LABA or two types of asthma controllers
b. Eosinophils ≥300
c. 3 or more exacerbations

Severe Asthma Program

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

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

1-844-BWH-LUNG

severeasthma@bwh.harvard.edu.