

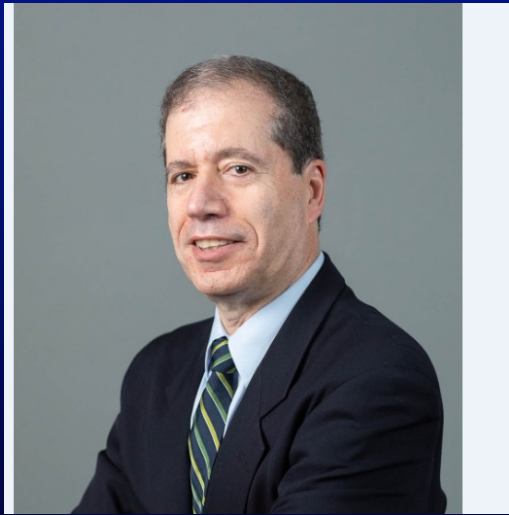
Evolving Guidelines for the Management of Asthma

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- 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
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- Circassia Clinical Research Support
- Cowen Consultant
- GlaxoSmithKline Consultant
- Gossamer Bio Clinical Research Support
- Merck Consultant
- Novartis Consultant
- PPS Health Consultant

Disclosures (Con't)

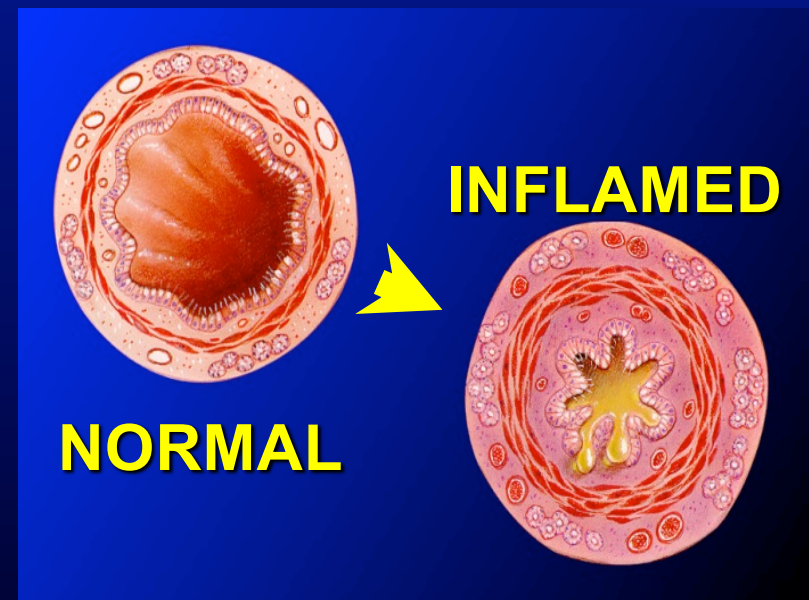
- Regeneron Consultant
- Sanofi Consultant
- TEVA Consultant and Clinical Research Support

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



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

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

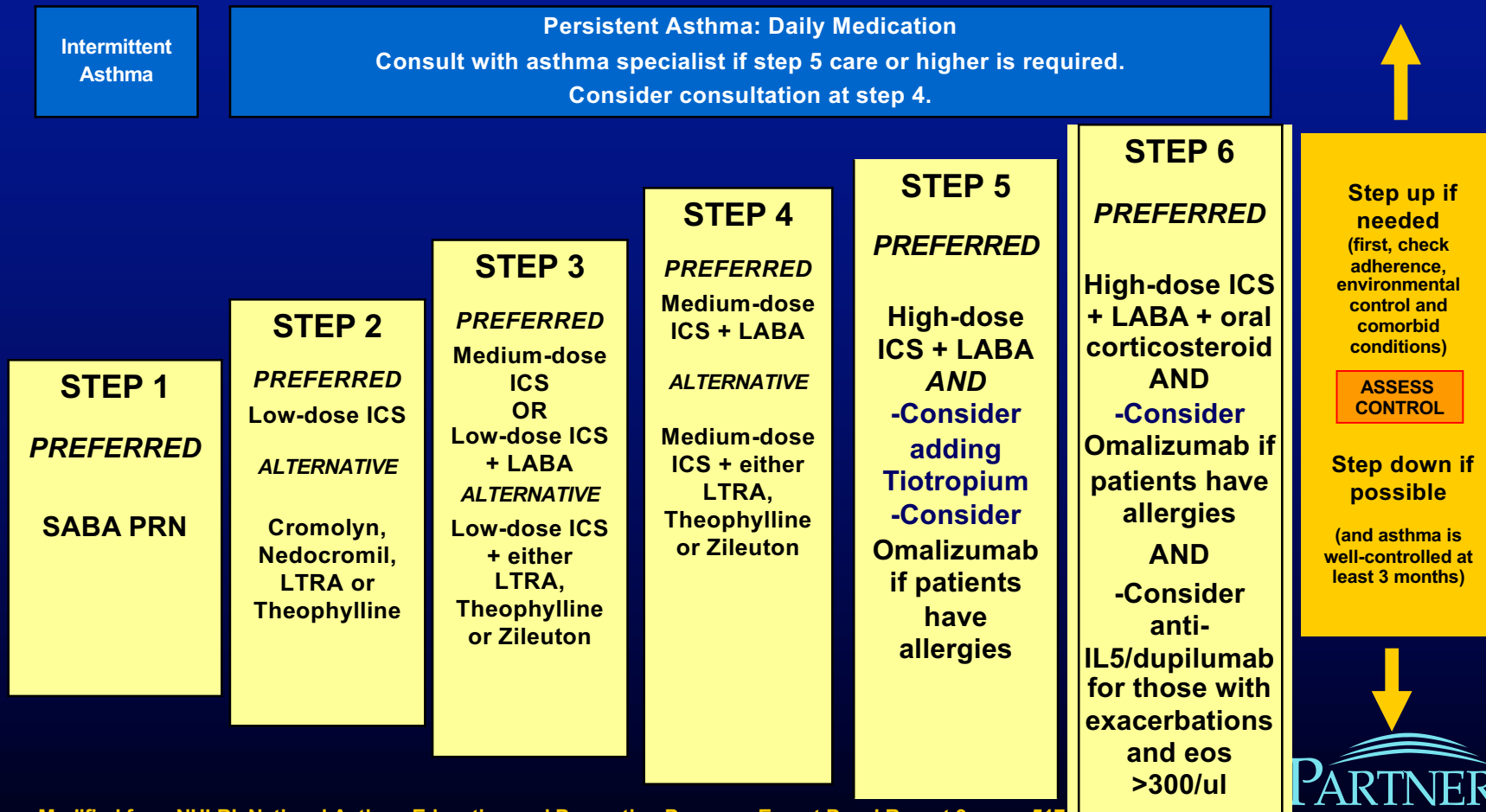
Montelukast

- Black box warning about depression and suicidality

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 fast-acting. It cannot be used with ICS/salmeterol (Advair, Wixela, etc)

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.

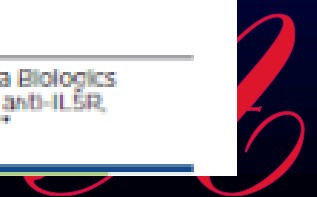


Major Change in 2021 NAEPP Update

- 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

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 2020 Update

		Step 1	Step 2		Step 3	Step 4	Step 5
		INTERMITTENT	PERSISTENT				
≥ 12 years old	CONTROLLER	None	<i>Preferred</i> Low-dose ICS	<i>Preferred</i> 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 beta₂-agonist; LAMA: long-acting muscarinic antagonist; PRN: as needed; SABA: short-acting beta₂-agonist.

Consider Biologics if not controlled

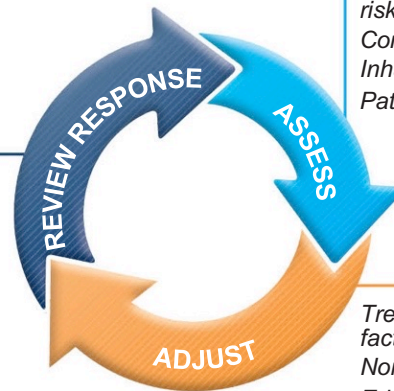
GINA (Global Initiative for Asthma)

- 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”

Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
 Assess, Adjust, Review response

Symptoms
 Exacerbations
 Side-effects
 Lung function
 Patient satisfaction



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

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

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

STEP 1

As-needed low dose ICS-formoterol *
 Low dose ICS taken whenever SABA is taken †

STEP 2

Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
 Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

STEP 3

Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

STEP 4

Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

STEP 5

High dose ICS-LABA
 Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

Add low dose OCS, but consider side-effects

PREFERRED RELIEVER

Other reliever option

As-needed low dose ICS-formoterol *

As-needed short-acting β_2 -agonist (SABA)

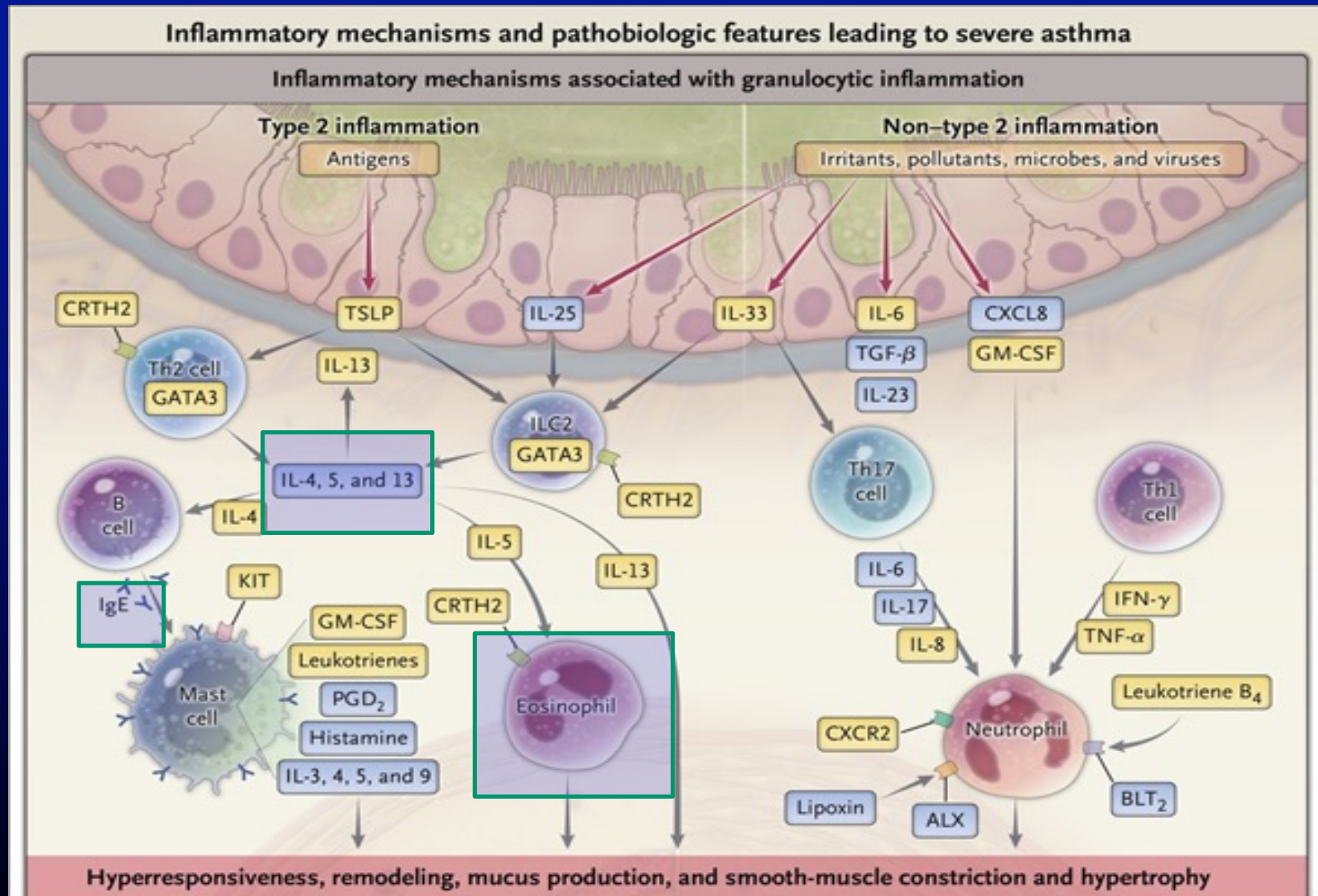
* Off-label; data only with budesonide-formoterol (bud-form)
 † Off-label; separate or combination ICS and SABA inhalers

‡ 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 FEV₁ >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 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

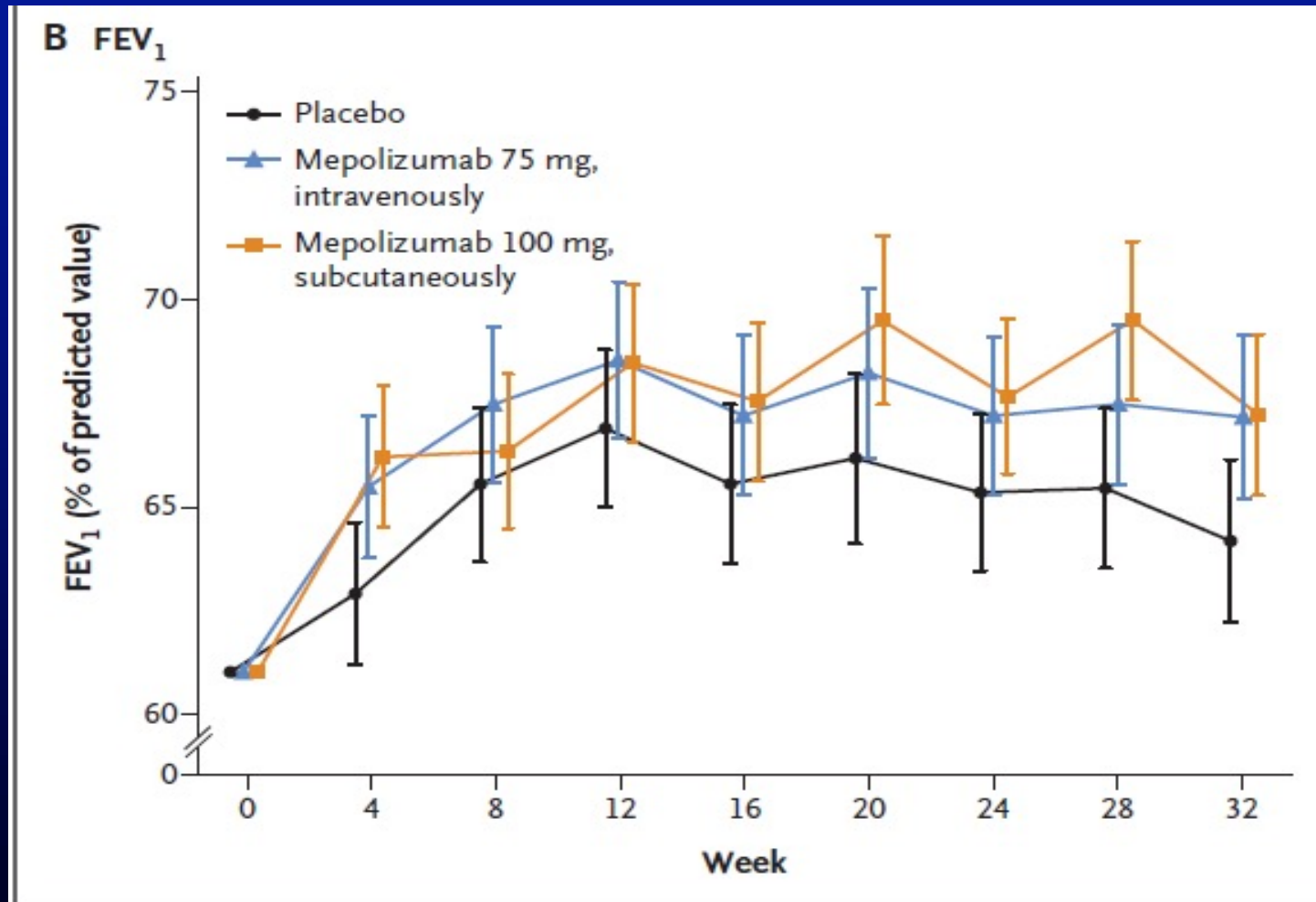
Effect of Anti-IgE on Biomarkers

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

Anti-IL5 Drugs

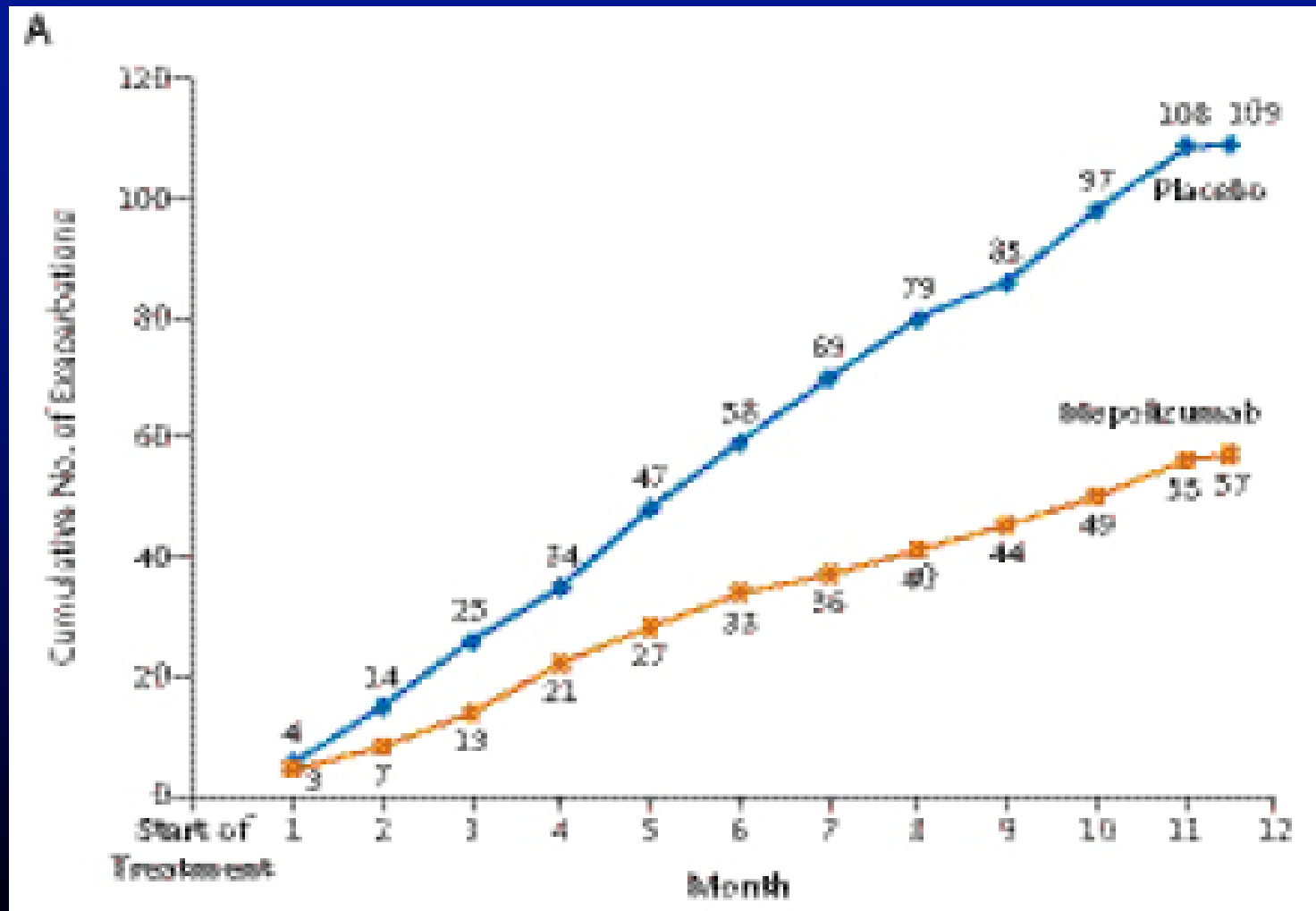
- Mepolizumab and Reslizumab bind to IL5 itself and reduce eosinophils by blocking IL5
- Benralizumab binds to the IL5 receptor and fixes complement
 - Blocks IL5 signaling
 - Directly toxic to eosinophils
- Except for reslizumab (which is administered IV) they are administered SC every month (mepo)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

Mepolizumab Increased FEV₁ by ~100cc



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

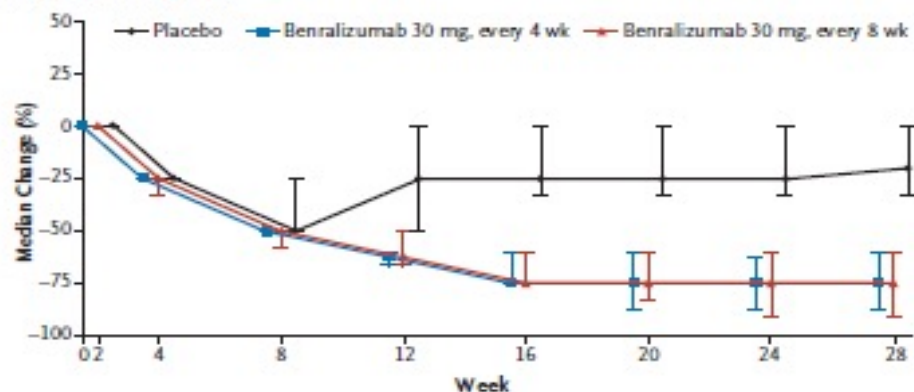
Generally a 50% reduction in exacerbations



•Haldar, NEJM, 2009

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

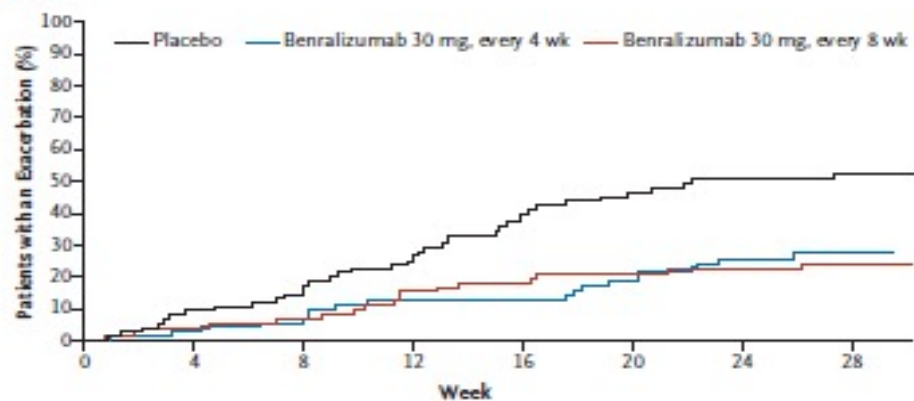
A Change from Baseline in Oral Glucocorticoid Dose



No. at Risk

Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

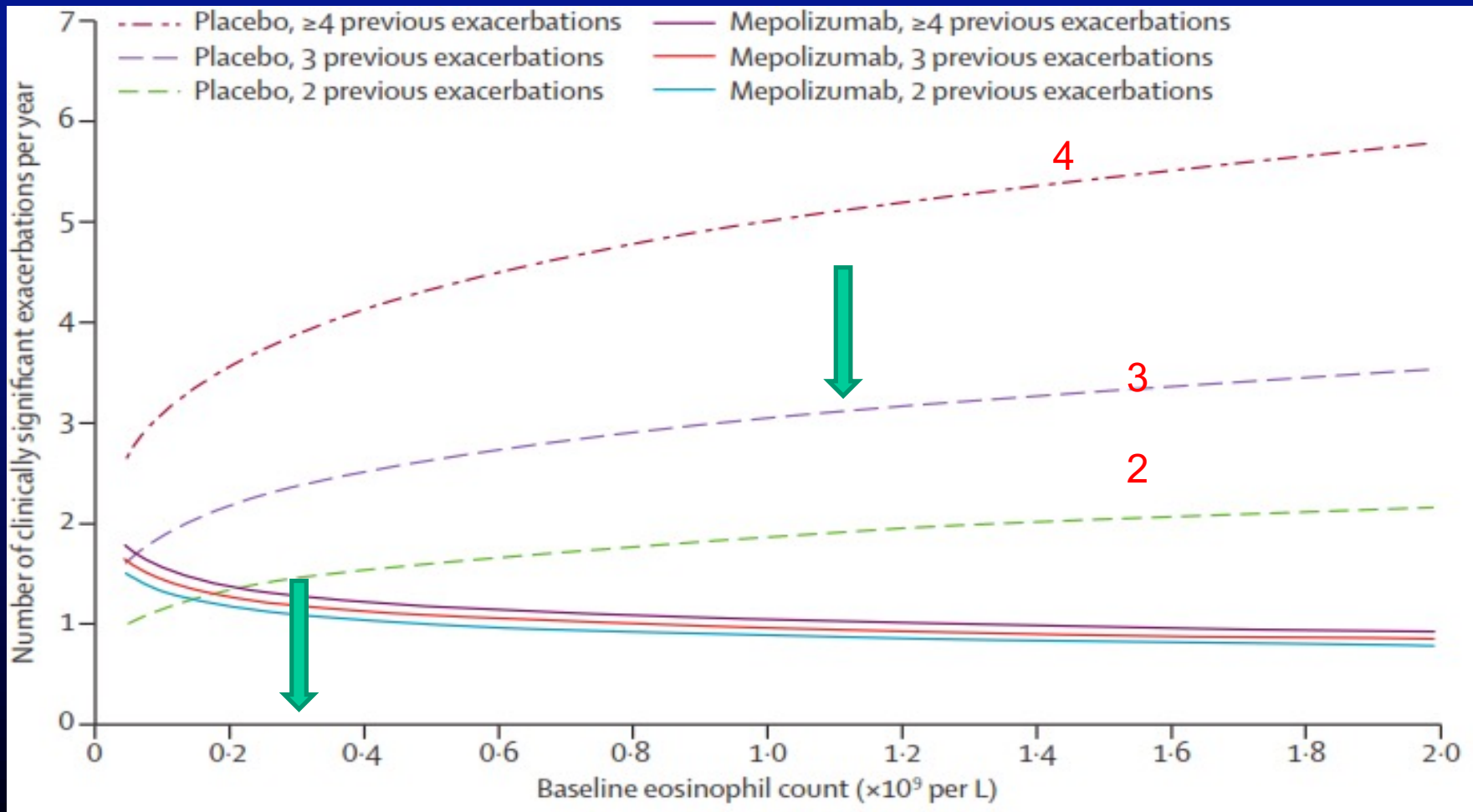
B Time to First Asthma Exacerbation



No. at Risk

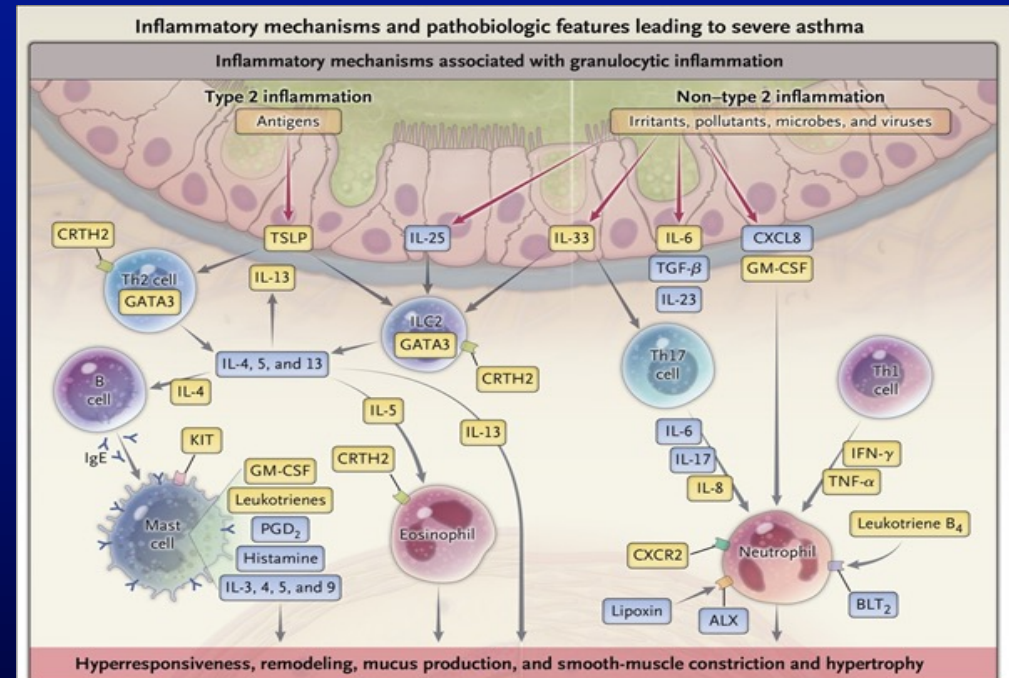
Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

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

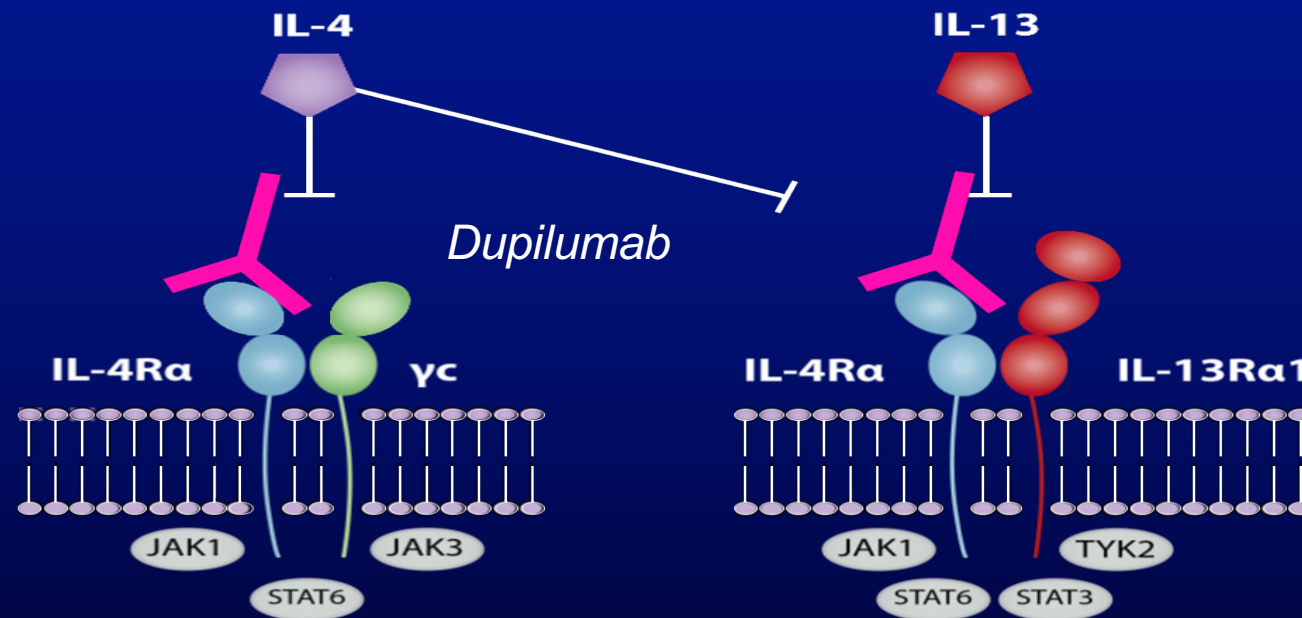


Effect of IL5-active drugs on Biomarkers

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



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



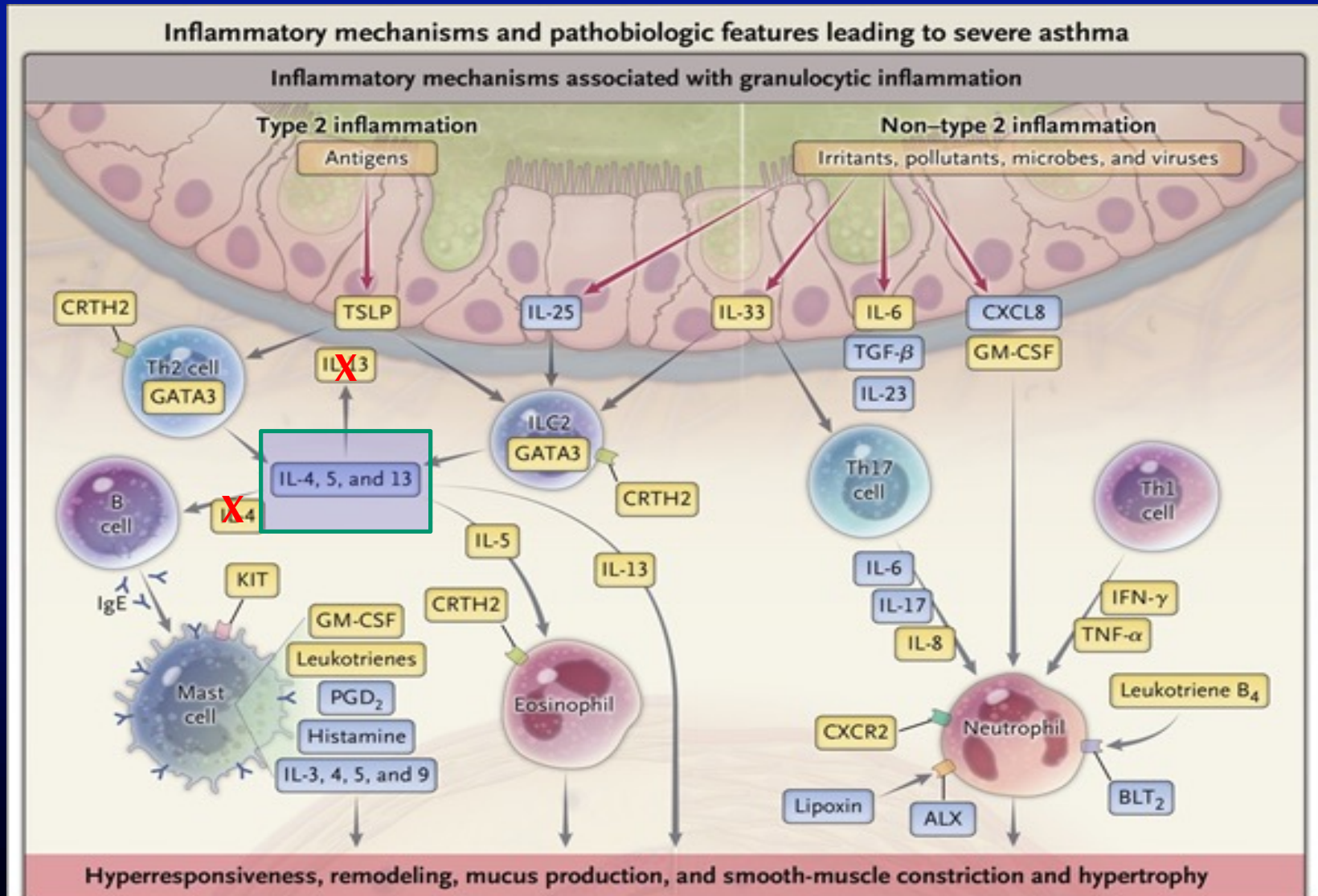
Type I Receptor

B cells, T cells, Monocytes,
Eosinophils, Fibroblasts

Type II Receptor

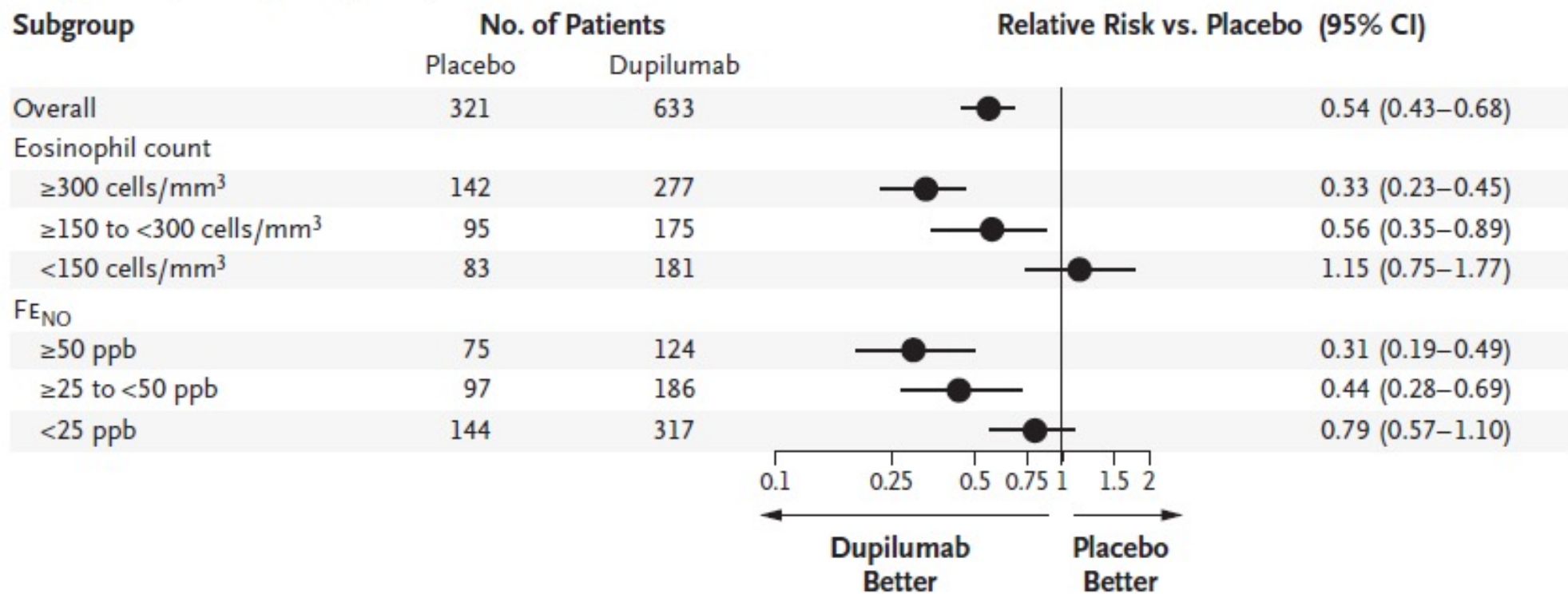
Epithelial cells, Smooth muscle
cells, Fibroblasts, Monocytes,
Activated B cells

Type 2 & Non-Type 2 Inflammation



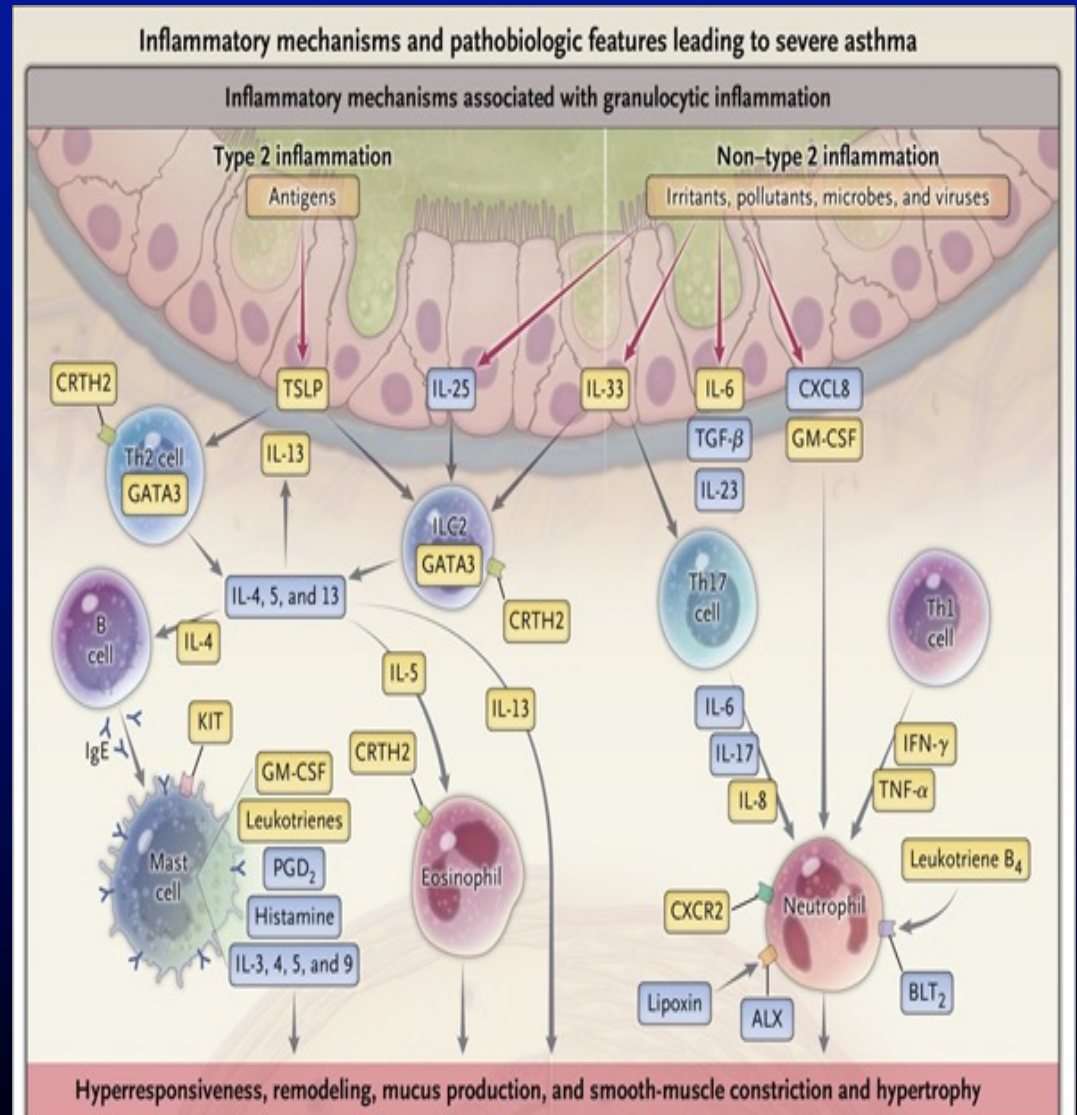
Patients with Greater T2 Markers Had Reduced Asthma Exacerbations w/ Dupilumab

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



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
<p>[^]Free IgE reduced but not detected by commercial assays [*]Eosinophils may rise especially in those with high baseline eosinophils</p>					

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 \geq 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

Answer #1

- D
- Regular low dose ICS plus PRN SABA or ICS triggered by SABA use are equally recommended
- GINA recommends prn ICS/formoterol but that is not recommended by NAEPP until Step 3

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

Answer Question #2

- C
- – 2 or more exacerbations in the context of eosinophils ≥ 300 AND failure on Step 5 therapy identify patients most likely to have a reduction in exacerbations



Severe Asthma Program



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

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

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