ASTHMA

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SEVERE ASTHMA RESEARCH PROGRAM
Brigham and Women's Hospital
Founding Member, Mass General Brigham

Mass General Brigham
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- 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

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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

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Disclosures (Con't)

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

Objectives

- Understand changes in treatment algorithms for asthma
- 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

Super long-acting beta-agonist combinations for once a day

- Fluticasone furoate 100/vilanterol 25 and 200/25
  - 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 for asthma (FF/umeclidinium/vilanterol)
  - (100/62.5/25 and 200/62.5/25)

NAEPP Major Change in 2021 Update AIR

- 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

- Now Referred to as

AIR (Anti-Inflammatory Relievier)

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)**	

	Step 1	Step 2		Step 3	Step 4	Step 5
	INTERMITTENT	PERSISTENT				
≥12 years old	CONTROLLER	None	Preferred: 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 (con-comitant)	ICS/formoterol (up to 12 puffs per day)		"SABA"

MART
Maintenace and Reliever Therapy

- In Steps 3 and 4 (when regular background therapy is recommended) NAEPP and GINA (Global Initiative for Asthma) recommend MART (Maintenance and Reliever Therapy)
- Previously called SMART (Single Maintenance and Reliever Therapy)
- Both NAEPP and GINA recommend Budesonide/formoterol (160/4.5) as the background maintenance and reliever

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"

Considerations Regarding Single Maintenance and Reliever Therapy (MART) with ICS/LABA

- Formoterol is the preferred LABA due to its rapid onset of action; salmeterol has a slower onset of action and should NOT be used
- FDA package insert warns against using budesonide/formoterol prn
  - Many insurers will not cover the extra inhaler
- Studies of MART were almost exclusively performed with budesonide/formoterol;
  - Theoretically, other ICSs could be effective but they have not been studied

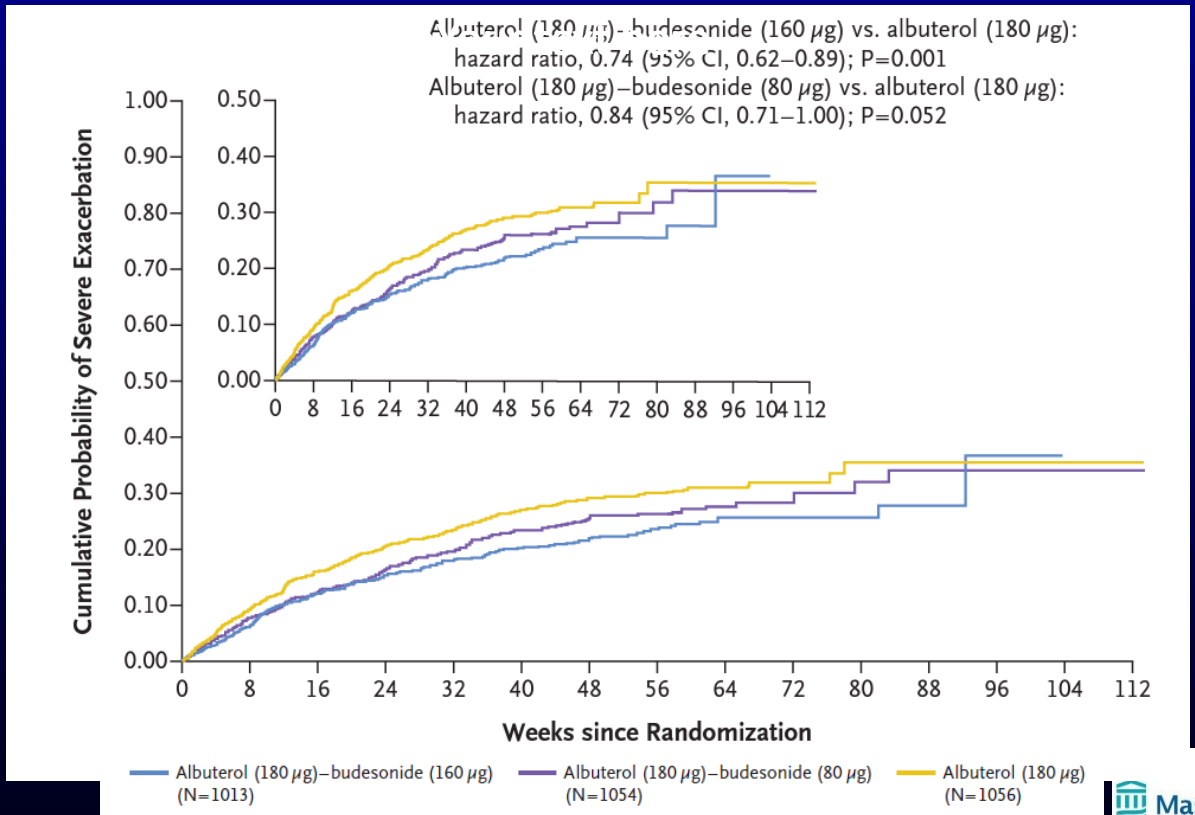
Considerations Regarding Single Maintenance and Reliever Therapy (MART) with ICS/LABA

- In moderate to severe asthma MART was only studied in patients
  - With at least one exacerbation in the past year
  - Who were NOT using nebulizers for reliever medication
  - Who bronchodilated before entering the study

ICS/Albuterol Fixed Combination Introduced in the US as PRN Reliever + ICS

Added to Underlying ICS or ICS/LABA (not on nebulizers)

Reduced Exacerbations by 26% c/w Albuterol Alone (0.15/yr)



•Papi, NEJM, 2022

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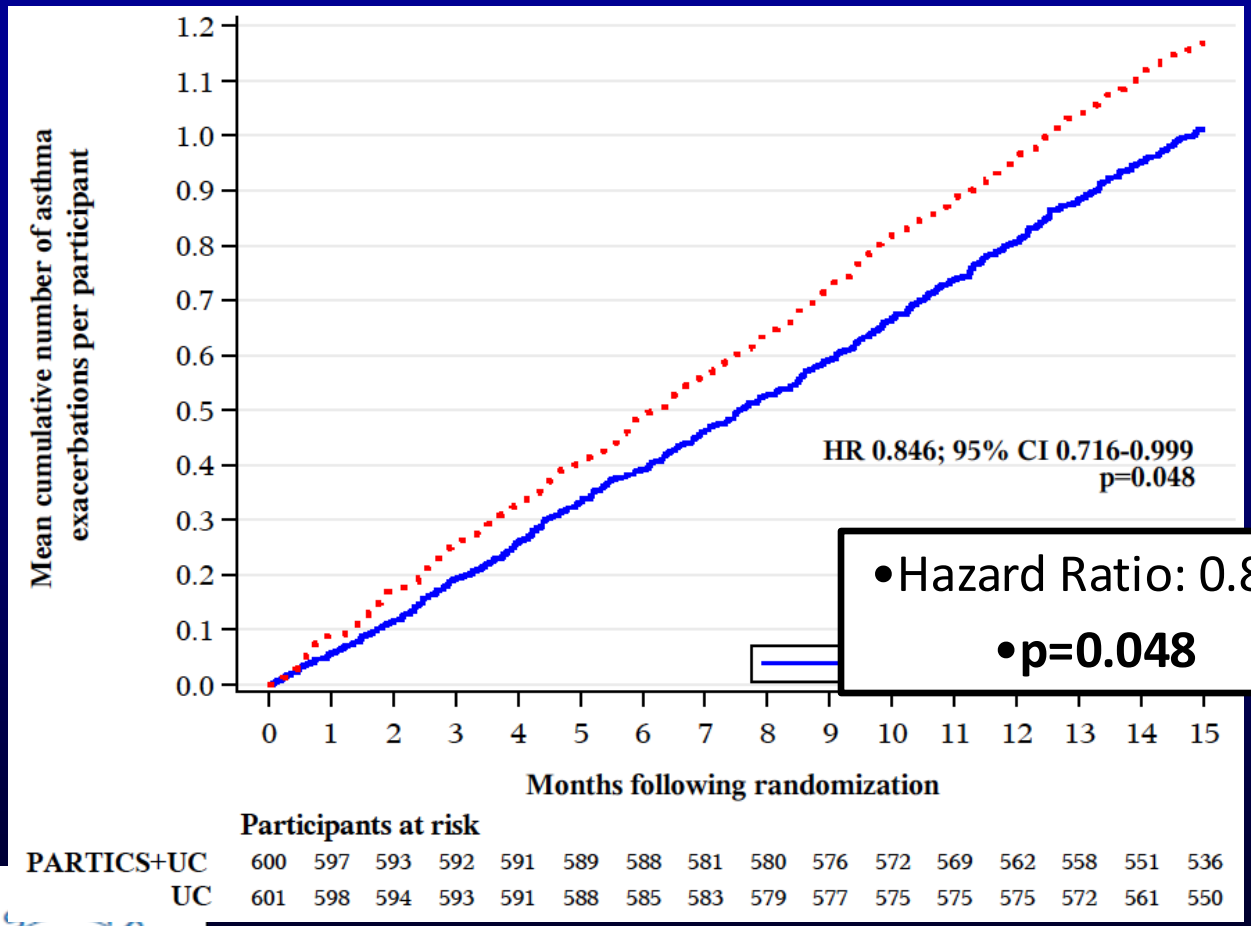
Patient Activated Reliever Triggered ICS
(QVAR 80 puff for puff w/MDI and 5 puffs w/neb)
reduced asthma exacerbations



- Hazard Ratio: 0.846
- **p=0.048**

- Israel et al. NEJM 2022

- **PARTICS**: **P**atient **A**ctivated **R**eliever **T**riggered **ICS**

- **PARTICS** reduced severe exacerbations by 0.13/person/year

- This is **equal or greater** than the reduction in severe exacerbations seen in **MART** studies cited by NAEPP (0.12/patient/year, weighted by sample size and duration)

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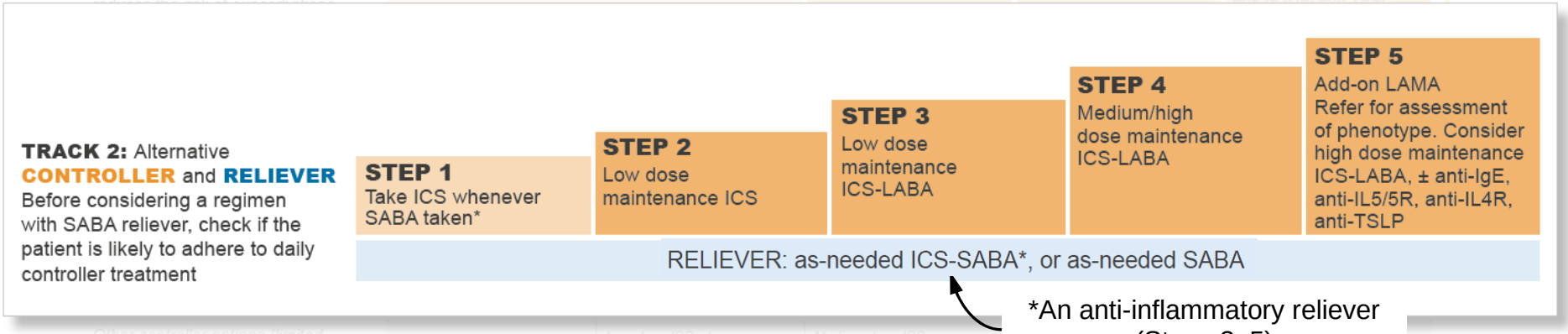
AIR & MART in the US

- Consider in all patients with “persistent symptom”
- If barriers to using ICS/f
  - Regulatory concerns
  - Insurance concerns
  - Unwilingness to change background meds to ICS/f
- Consider
  - Combined ICS/SABA if not using a nebulizer
  - Consider PARTICS (instructing to use ICS every time they use SABA and 5 times with a neb)

GINA HAS NOW INCORPORATED PRN ICS/SABA INTO TRACK 2 RECOMMENDATIONS

GINA 2023 – Adults and adolescents
Track 2



*An anti-inflammatory reliever (Steps 3–5)

Box 3-12 (3/4) Track 2

GINA Differs from NAEPP

- GINA does not recommend MART for those 5-11 years old
- GINA recommends MART at step 5 while NAEPP does not
- GINA advocates using ICS/formoterol instead of SABA as reliever therapy for *all* patients,12 years and older including those with intermittent asthma (it does not recommend ICS/formoterol as reliever therapy in those under 12)

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
  - High levels according to NAEPP are >50 in adults and >35 in kids
  - Need to be aware that allergic rhinitis can produce increased FeNO w/o asthma

Use of Exhaled Nitric Oxide

- 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 / Anti - IL4/IL13

Additional NAEPP Updates

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

Inhaler choice and environmental considerations

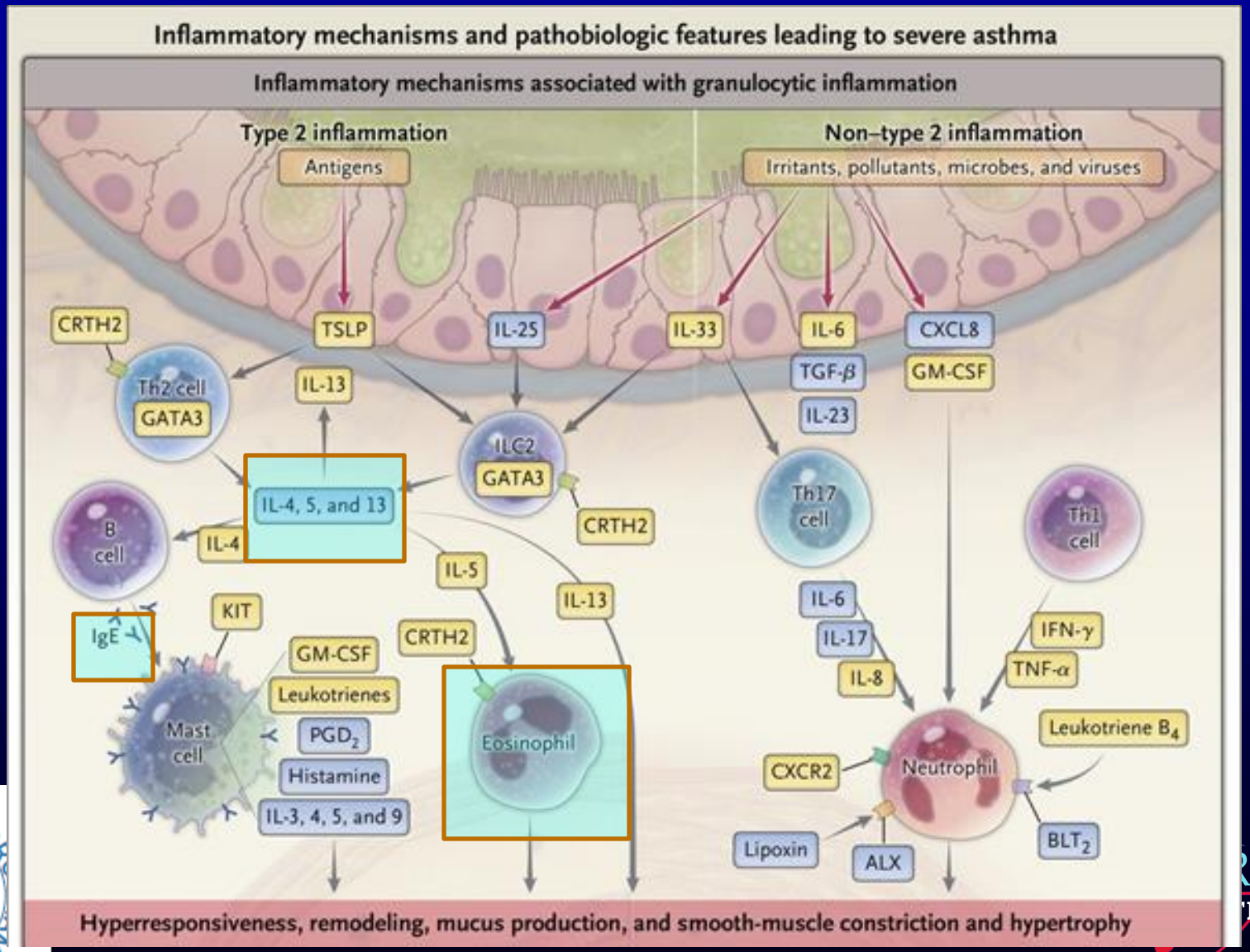
- Inhaled corticosteroids markedly reduce the risk of asthma exacerbations and death
  - But limited availability and access in low and middle income countries
- Many inhaler types available, with different techniques
- Some inhalers are not suitable for some patients. For example:
  - DPIs are not suitable for children ≤5 years and some elderly
  - pMDIs difficult for patients with arthritis or weak muscles
  - Capsule devices are difficult for patients with tremor
- Most patients don't use their inhaler correctly
  - More than one inhaler → more errors
- Incorrect technique → more symptoms → worse adherence → more exacerbations → higher environmental impact
- Propellants in current pMDIs have 25x global warming potential compared with dry powder inhalers
  - New propellants are being developed but not yet approved
- Choice of inhaler is important!

BIOLOGICS

Definition of Type 2 Immunity

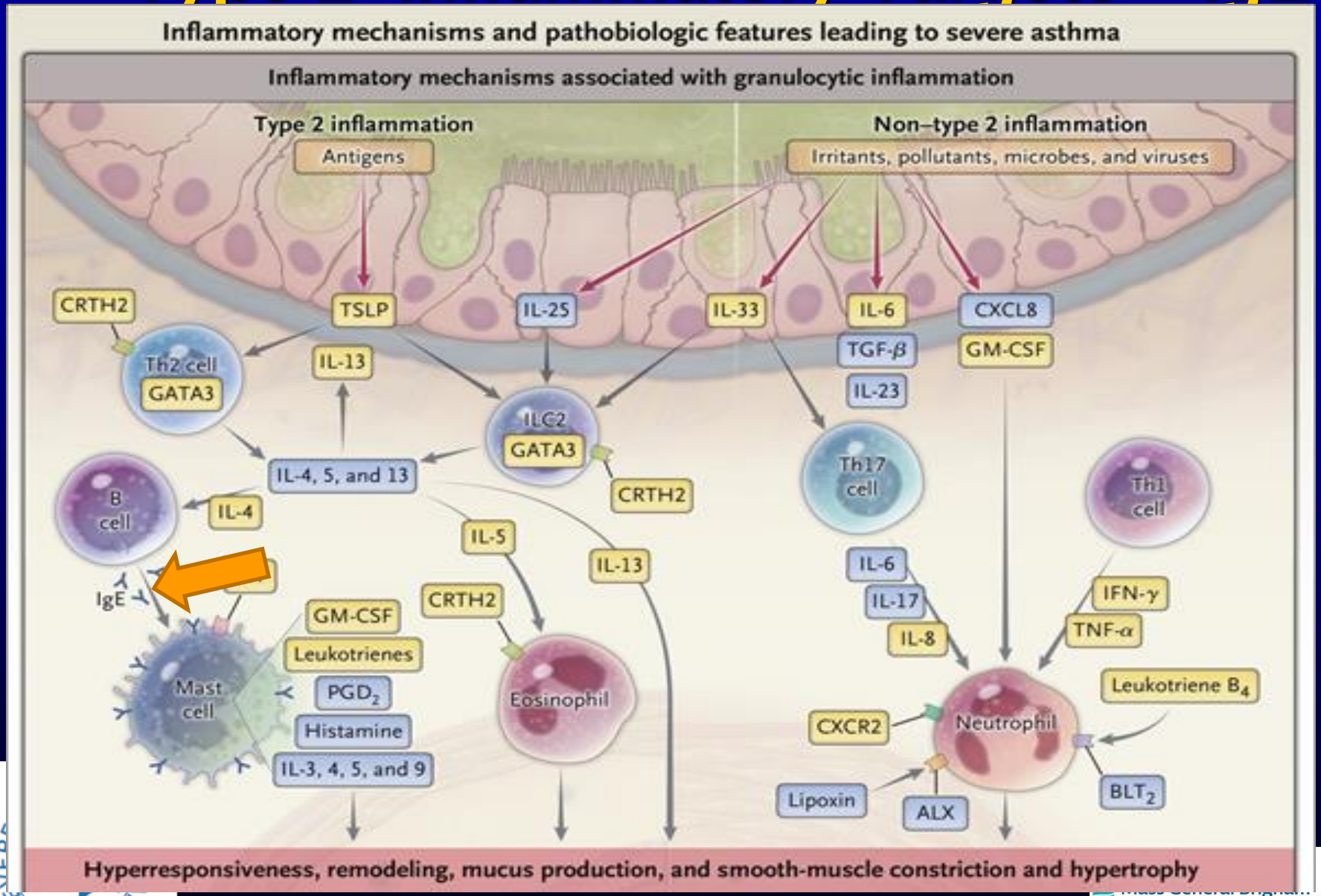
- Immune response involving the innate and the adaptive arms of the immune system to promote barrier immunity on mucosal surfaces
- Cells
  - T helper 2 (T^H2) CD4+ T cells and B cell production of the immunoglobulin E (IgE) antibody subclass.
  - Innate response includes ILC 2 innate lymphoid cells,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

Type 2 & Non-Type 2 Inflammation



Israel & Reddel, NEJM, 2017

Type 2 Inflammatory Targets – IgE



•Israel & Reddel, NEJM, 2017

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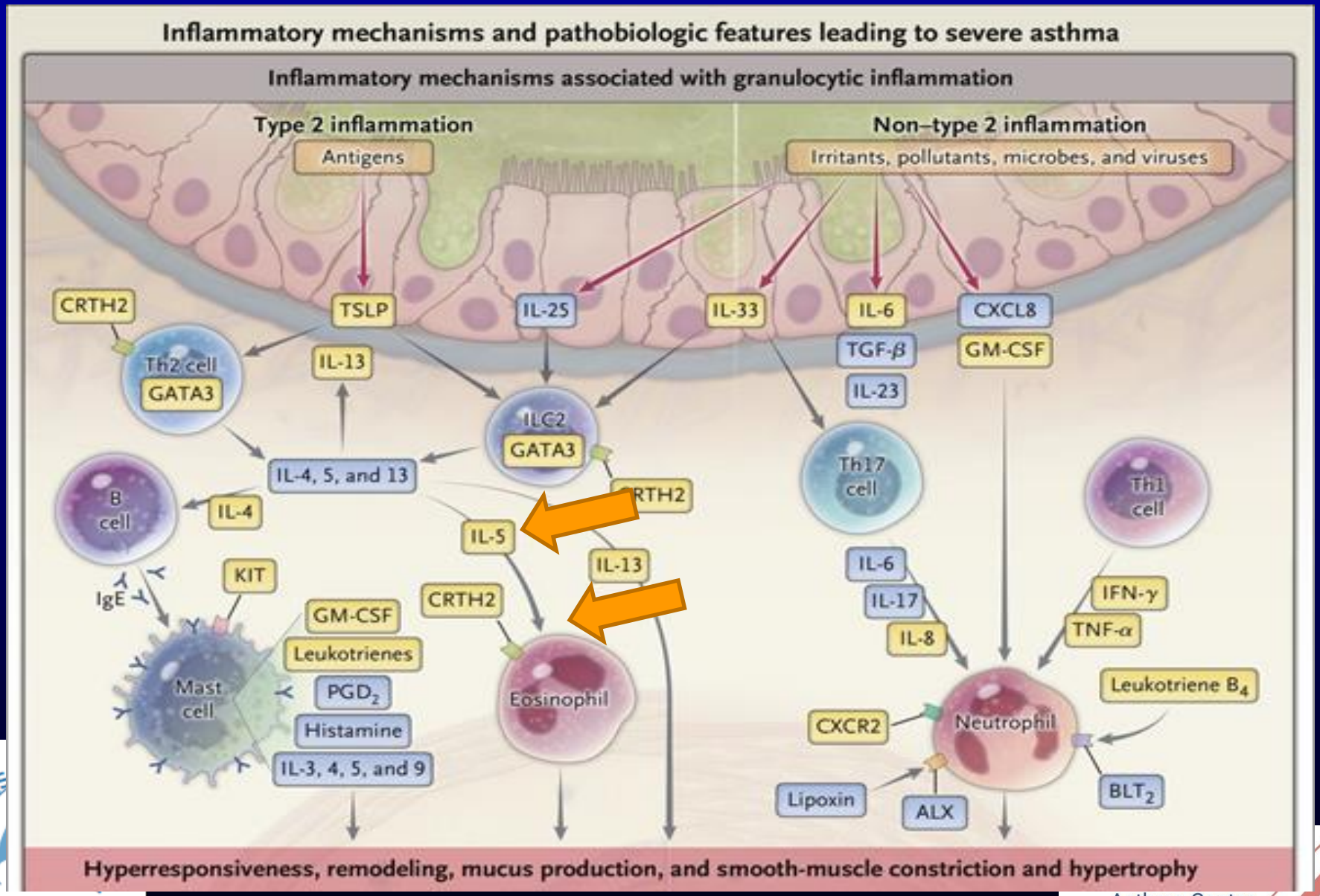
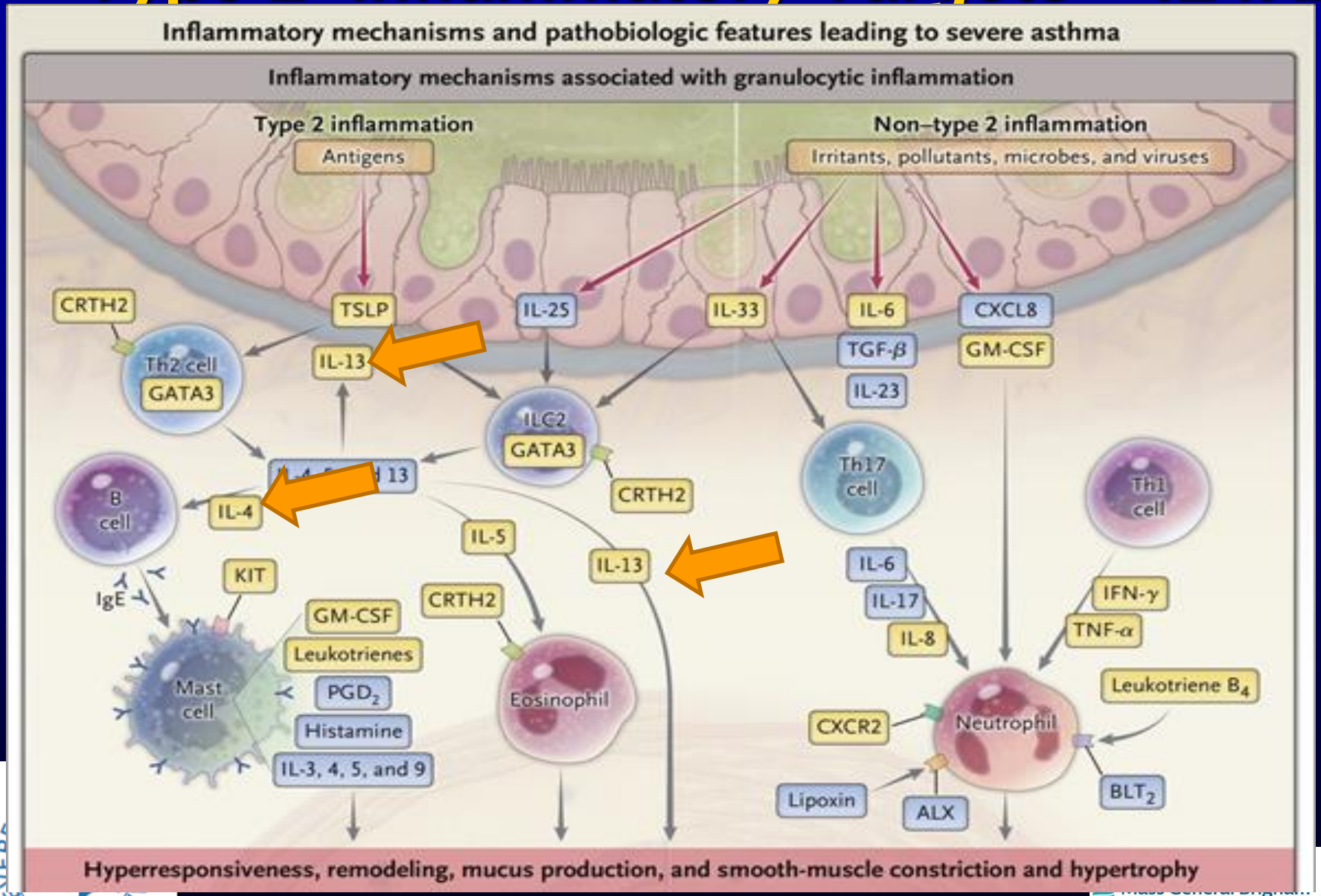
Type 2 Inflammatory Targets – IL5



•Israel & Reddel, NEJM, 2017

Type 2 Inflammatory Targets – IL4RA



•Israel & Reddel, NEJM, 2017

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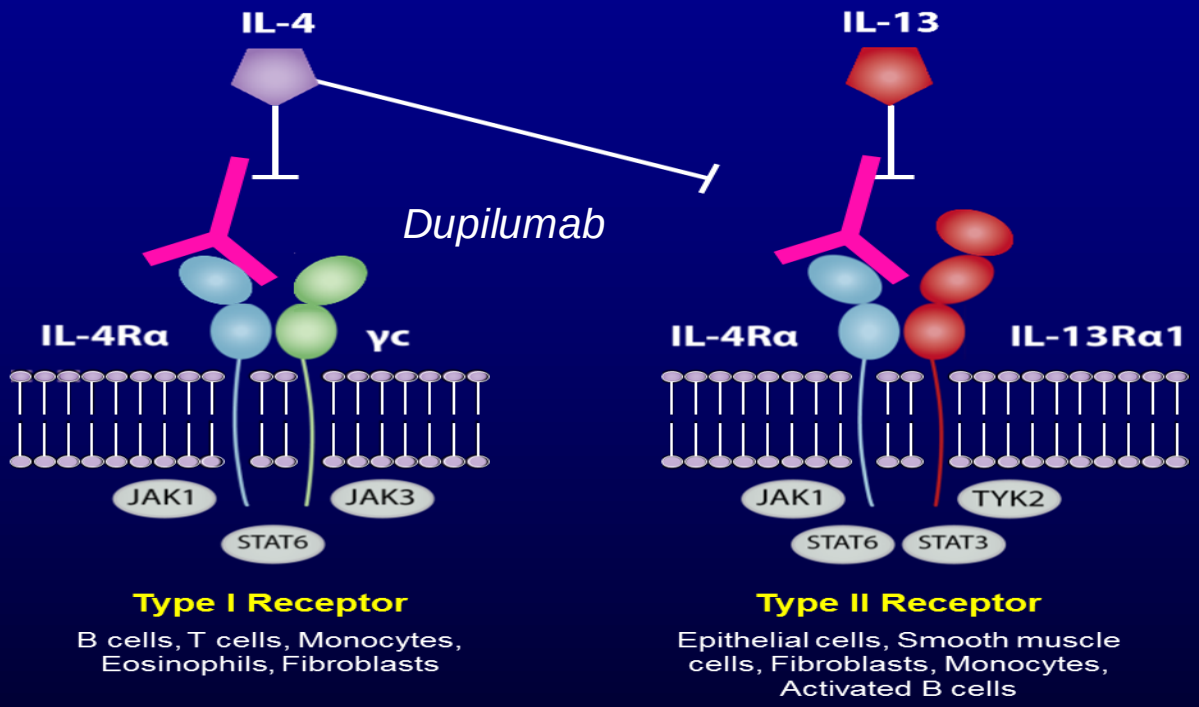
Blocking IL-4Ralpha (Dupilumab) Blocks both IL4 and IL13



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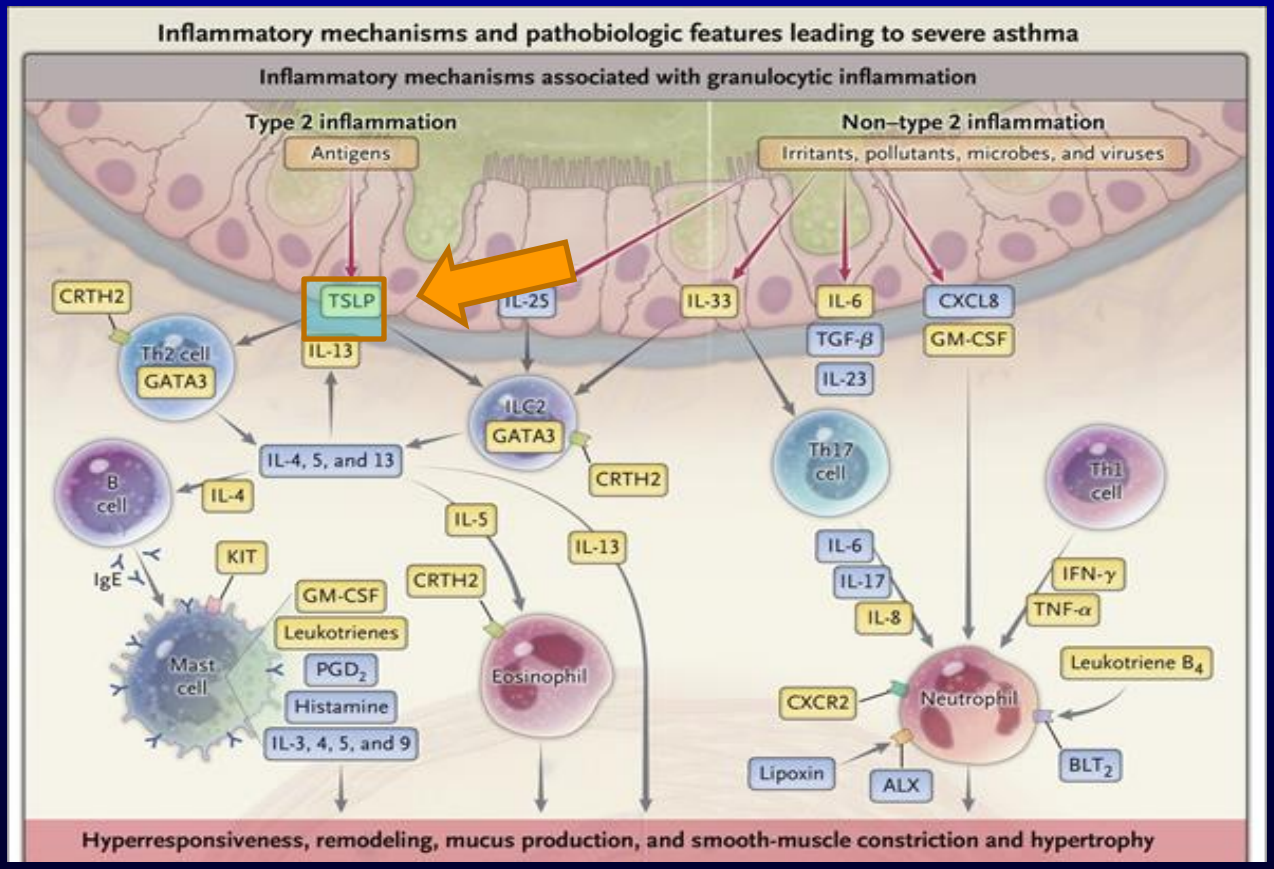
Type 2 Inflammatory Targets - TSLP



•Israel & Reddel, NEJM, 2017

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Outcomes in Patients with Eosinophils ≥300/ul

- (Studies Required 1-2 exacerbations, ≥12% Bronchodilator Response and ACQ ≥1.5 on Study Entry)

	IgE	IL5		IL4RA	TSLP
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
% Reduction in Exacerabation	32	61	~55 (In eos >400/ul)	~35	66	70
FEV1 (cc)	40	202	126	~138	~225	230
ACQ	0.36	~0.48	~0.24	~0.2	~0.4	0.33

OCS-Sparing Effects (Regardless of Blood Eosinophil Count)

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

Administration of the Biologics in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Lowest age	6	6	18	12	6	12
Frequency	2-4 wks	4 wks	IV 4 weeks	8 wks after first months	2 wks	4 wks
Mode	SC	SC	IV	SC	SC	SC
Home Administration	Y	Y	N	Y	Y	Y
Anaphylaxis	0.1-0.3%	NR	0.3%	NR	NR	NR
Additional Notes	-	-	-	-	-Temporary increase in eosinophil - Conjunctivitis	

Effects on Biomarkers

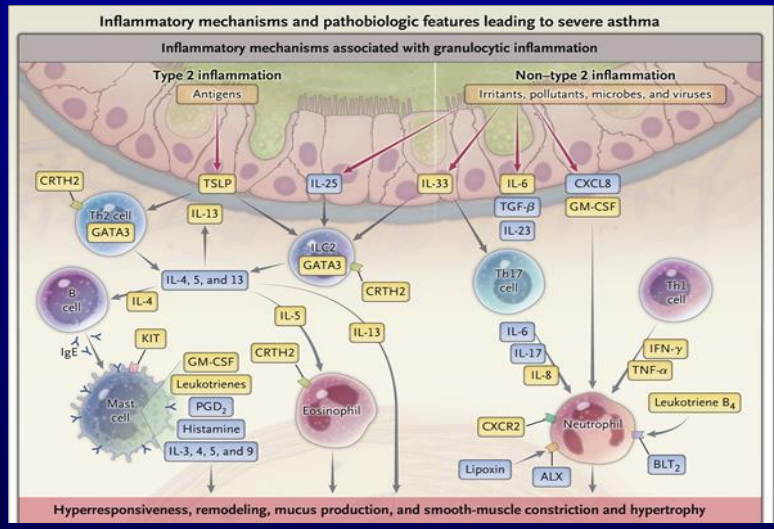
Effect of the Biologics on Biomarkers in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
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



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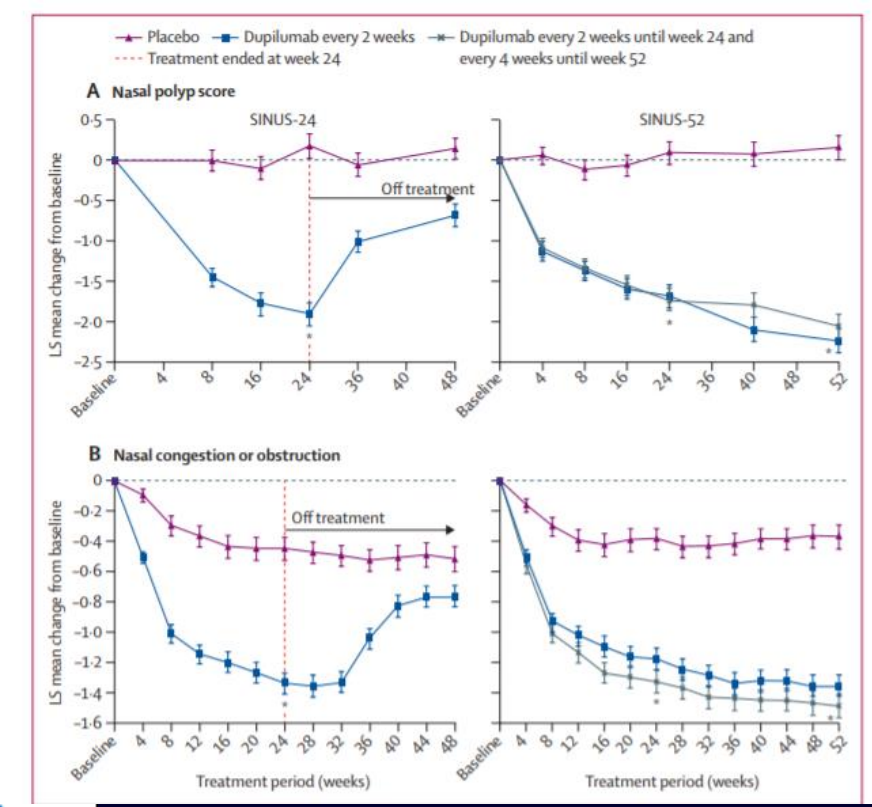
Effects on Co-Morbidities

Dupilumab First Shown Effective in Nasal Polyposis



Now shown for:
-Mepolizumab
-Omalizumab

Bachert, Lancet, 2019

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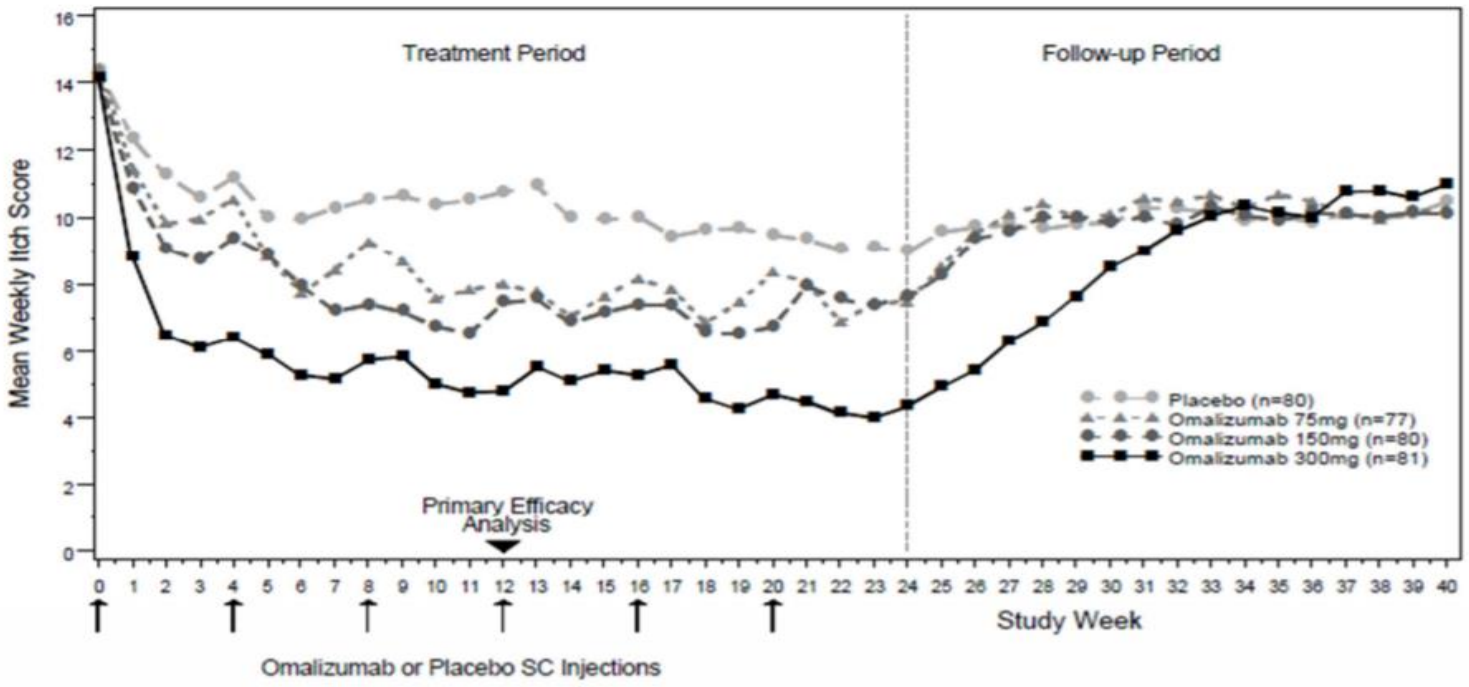
Omalizumab is Effective in Chronic Idiopathic Urticaria

Figure 2. Mean Weekly Itch Severity Score by Treatment Group
Modified Intent to Treat Patients in CIU Trial 1



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Dupilumab is Very Effective in Atopic Dermatitis and Is Approved for that Indication in Age 6 months and above

-Also approved for eosinophilic esophagitis age 12+

-Approved for prurigo nodularis

Biomarkers of Patients Likely To Respond

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

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Eosinophils ≥300 (>150 w/3+ exac)	++	+++	+++	+++	+++	+++
Low Eos/Hi FeNO (FeNO >20-25)	0	0	0	0	++	+++
Low Eos/Low FeNO	0	0	0	0	0	+/-
OCS Dependent (regardless of T2)	N.D.	+	N.D.	+	+	-

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 ¼ to ½
  - FEV1 increases 4%
  - Not all patients respond
- Greatest efficacy in patients with eosinophils >300 or FeNO 20
- Toxicity – rare anaphylaxis
  - Had been question about increased rate of cancer
  - Large observational study does not sugg

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

Anti-IL5 (Mepolizumab, Reslizumab, Benralizumab)

- Reduce eosinophils
- Reduce exacerbations by ≥50% in patients with ≥2 exacerbations/year and h/o blood eosinophils
- Variable effect on FEV_1 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

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
- Effective, but less so, in patients with eosinophils <150 with exacerbations

OCS-Sparing Effects (Regardless of Baseline Eosinophils)

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

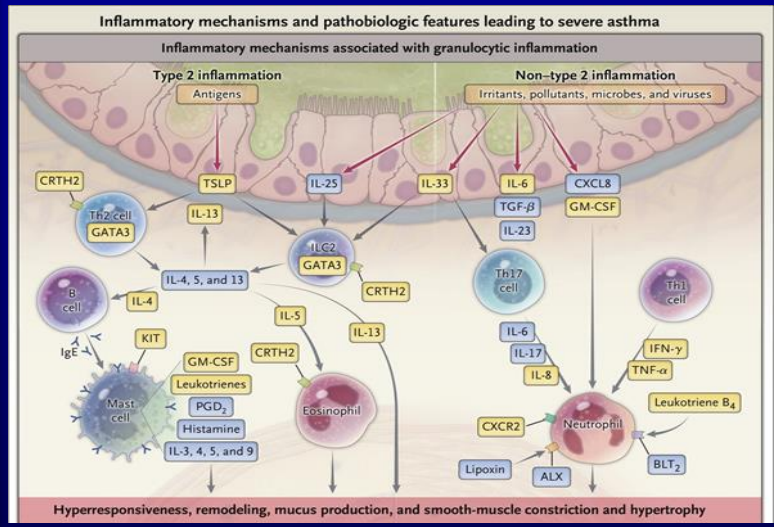
Effect of the Biologics on Biomarkers in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
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
  - Dupilumab
  - Omalizumab
  - Mepolizumab
- Eczema
  - Dupilumab
- Idiopathic Urticaria
  - Omalizumab
- Eosinophilic esophagitis
  - Dupilumab

Biomarkers of Patients Likely To Respond

ALL PATIENTS STUDIES HAD TO HAVE ≥1-2 EXACERBATIONS AT BASELINE AND BD BY ≥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) ⩾ IgE/Eosinophils
- Forty to 50% may have neutrophilic or paucigranulocytic inflammation
  - May be less responsive to steroids
- May respond to azithromycin

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

- MART is recommended in Step 3 and 4 therapy by NAEPP but may have implementation and patient characteristic limitations
- IgE >30 or Eos ≥300 (150) may be candidates for biologics especially with 2 or more exacerbations per year
- Consider co-morbidities in use of biologics
- While tezepelumab is most effective in T2 high asthma it appears to have significant effectiveness in T2 low asthma with high exacerbations
- Pts on OCS candidates for biologics regardless of eosinophil count
- Isolated high FeNO may be responsive to dupilumab or tezepelumab
- ICS suppress FeNO

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 ≥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**

Question #1

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 #1

- 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 exacerbation

Question #2

55F symptomatic on Step 5 therapy with 2 exacerbations in the last year, IgE 300, Eos 100, FeNO 55, RAST negative. Comorbidities include hypertension and atopic dermatitis. Which of the numbered options would you choose?

1. Omalizumab
2. Anti-IL5 therapy
3. Dupilumab
4. Tezepelumab

a. **All of them**
b. **#3 or #4**
c. **#3**
d. **#4**

Answer Question #2

- C

-She has the requisite number of exacerbations and medication use for all of them. However, RAST is negative so not omalizumab. Eos are too low for anti-IL5.

FeNO is high enough for Dupilumab and Tezepelumab but concomitant atopic dermatitis makes dupilumab the preferred choice.

Short List of References

- 2020 Focused Updates to the Asthma Management Guidelines: : A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Cloutier M et al. J All Clin Imm 2020: 146: 1217-1270

- Israel E, Reddel HK. Severe and Difficult to Control Asthma in Adults, N Engl J Med 2017; 377:965-976