VIRTUAL CME SATELLITE SYMPOSIUM

Targeted Management of ASTHMA: Using Phenotypes and Biomarkers to Individualize Treatment

MONDAY, OCTOBER 18, 2021

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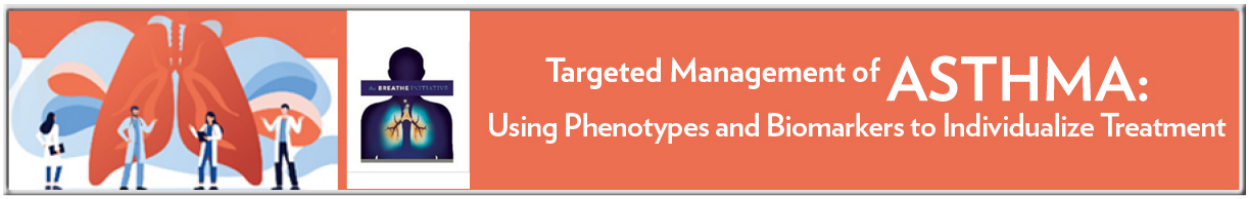

Agenda

I. Asthma: An Introduction
   a. Burden of asthma in the US
   b. Unmet medical needs
   c. Assessment of asthma control; who is at risk?
   d. Diagnosis and misdiagnosis

II. Pathogenesis and Etiology
   a. Change in understanding: A shift toward disease mechanisms
   b. Phenotyping and biomarkers
   c. Inflammatory pathways
   d. Causes of uncontrolled asthma and triggers
   e. Comorbidities

III. Evidence-Based Medical Treatment Recommendations and Targeted Treatment
   a. GINA - Assessing asthma severity – focus on moderate-to-severe
   b. Stepwise approach to treatment
   c. Simulation cases 1 and 2
   d. Investigating the patient with poor symptom control or/and exacerbations despite treatment
   e. Emerging targets for severe T2-high asthma
   f. Pharmacologic treatment options and monitoring response
      i. Biological targeted monoclonal antibodies targeting IL-5 and IgE – clinical trial data (omalizumab, mepolizumab, reslizumab, and benralizumab)
      ii. Biological targeted monoclonal antibodies targeting IL-4/IL-13 – clinical trial data (dupilumab)
      iii. Investigational - tezepelumab
   g. Factors affecting therapeutic selection
   h. Shared decision-making

IV. Conclusions and Q/A

Targeted Management of Asthma: Using Phenotypes and Biomarkers to Individualize Treatment

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PROGRAM OVERVIEW

This live virtual activity will cover the treatment and management of patients with moderate to severe asthma.

TARGET AUDIENCE

This activity is intended for U.S.-based pulmonologists and other health care providers involved in the care of patients with moderate-to-severe asthma

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Utilize predictive biomarkers and clinical presentation to determine the phenotypes and endotypes of patients with asthma
- Evaluate patients with severe asthma for symptom control and identify patients who require step-up therapy to minimize systemic steroid use and reduce emergency room visits
- Develop individualized treatment plans for the management of moderate-to-severe asthma in pediatric and adult patients by incorporating updated guideline recommendations, clinical trial data, and patient-specific factors

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Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

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Targeted Management of Asthma: Using Phenotypes and Biomarkers to Individualize Treatment

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Learning Objectives

- Utilize predictive biomarkers and clinical presentation to determine the phenotypes and endotypes of patients with asthma
- Evaluate patients with severe asthma for symptom control and identify patients who require step-up therapy to minimize systemic steroid use and reduce emergency department visits
- Develop individualized treatment plans for the management of moderate-to-severe asthma in pediatric and adult patients by incorporating updated guideline recommendations, clinical trial data, and patient-specific factors

Asthma: An Introduction

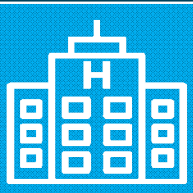
Diego J. Maselli, MD FCCP

Burden of Asthma in the United States

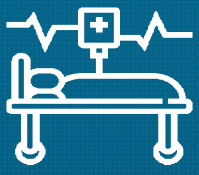
≈25 million Americans have asthma

In 2016:

More than 11 million people reported having ≥1 **asthma exacerbation** in previous year



Almost 1.8 million **emergency room visits**



≈189,000 **hospitalizations**

More than 3400 **deaths**

Centers for Disease Control and Prevention (CDC). 2021 (www.cdc.gov/asthma/asthmadata.htm).

Multiple Unmet Medical Needs in Asthma

Despite national and international guidelines, asthma control is not optimal with current standard-of-care treatment[1,2]

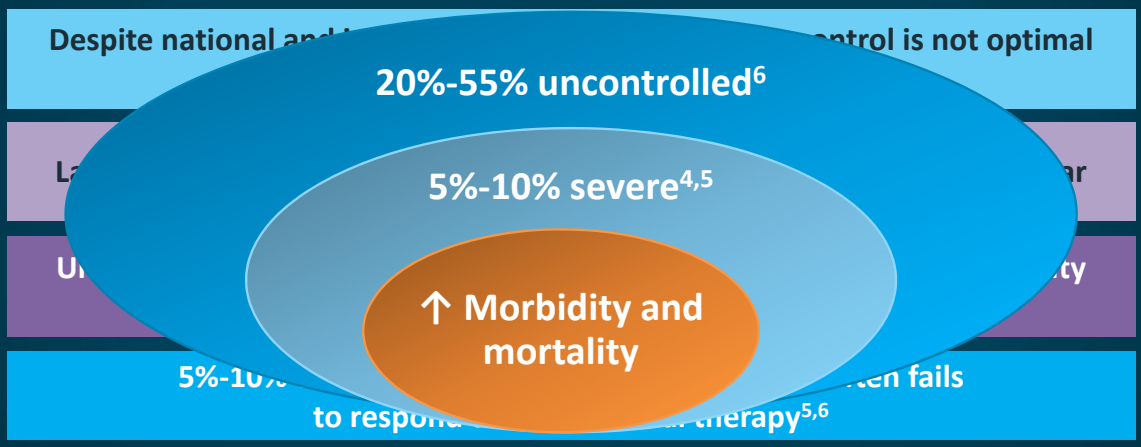
Large number of hospitalizations for people with severe asthma every year

Uncontrolled asthma is associated with significant morbidity and mortality and a high economic burden[3]

5%-10% of patients have severe asthma[4,5] that often fails to respond to conventional therapy[5,6]

1. Bateman ED, et al. *Am J Respir Crit Care Med*. 2004;170:836-844. 2. Bateman ED, et al. *Eur Respir J*. 2007;29:56-62. 3. Chipps BE, et al. *J Allergy Clin Immunol*. 2012;130:332-342.e10. 4. Chung KF, et al. *Eur Respir J*. 2014;43:343-373. 5. Holgate ST, Polosa R. *Lancet*. 2006;368:780-793. 6. Partridge MR. *Eur Respir Rev*. 2007;16:67-72.

Multiple Unmet Medical Needs in Asthma



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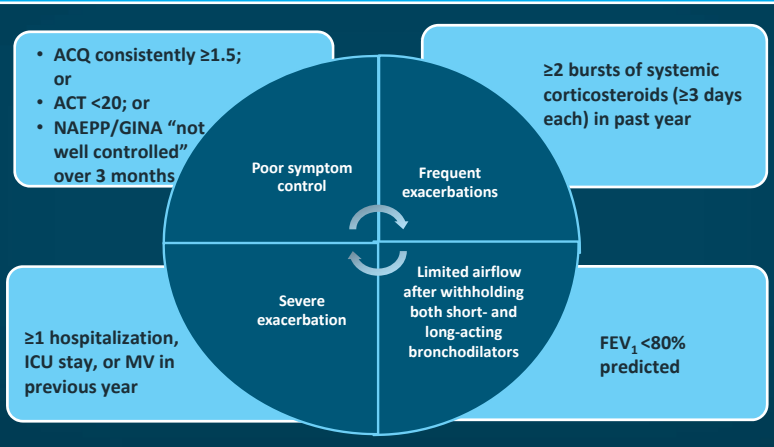
Guideline (ERS/ATS) Criteria for Identifying Uncontrolled Asthma

Any 1 of the following 4 criteria qualifies patient as having uncontrolled asthma



ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ATS = American Thoracic Society; ERS = European Respiratory Society; GINA = Global Initiative for Asthma; FEV_1 = forced respiratory volume in 1 second; ICU = intensive care unit; MV = mechanical ventilation; NAEPP = National Asthma Education and Prevention Program.
Chung KF, et al. *Eur Respir J*. 2014;43:343-373.

NAEPP: Assessment of Asthma Control Patients Aged >12 Years and Adults

Components of severity		Classification of Asthma Severity (Youths Aged ≥12 and Adults)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1-3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptom control	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60%-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires • ATAQ • ACQ • ACT	• 0 • ≤0.75 • ≥20	• 1-2 • ≥1.5 • 16-19	• 3-4 • N/A • ≤15
Risk	Exacerbations	0-1/year	≥2/year	≥2/year
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related AEs	Medication side effects vary in intensity from none to very troublesome. Intensity levels do not correlate to specific levels of control but should be considered in overall assessment of risk.		

AE = adverse event; ATAQ = Asthma Therapy Assessment Questionnaire; N/A = not applicable; SABA = short-acting β_2-agonist.
Adapted from Asthma Care Quick Reference. 2012 (www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf).

Who Has Severe Asthma?

Asthma in patients aged ≥6 years who required either:

- **High-dose ICS + LABA or leukotriene modifier/theophylline**
- **Systemic corticosteroids for ≥50% of the year**
- **Or, asthma that is "uncontrolled" despite these therapies**
- **Other clues: nocturnal awakenings and impaired lung function**

Must confirm that symptoms of "uncontrolled" asthma are not caused by confounding factors (GERD, poor compliance/poor inhaler technique)

GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist.
American Academy of Allergy, Asthma, & Immunology (AAAAI). 2019 (www.aaaai.org/conditions-and-treatments/library/asthma-library/severe-asthma).

Our Understanding of Asthma Is Changing
Focus Shifting Toward Disease Mechanisms

Previous approach

Patients with similar observable clinical characteristics have been grouped and treated similarly

The challenge

- Many patients may not respond or be controlled on therapy that is considered to be the standard of care
- "One size **doesn't** fit all"

Evolving understanding

Clinical differences in treatment response are related to underlying variations in multiple mechanisms

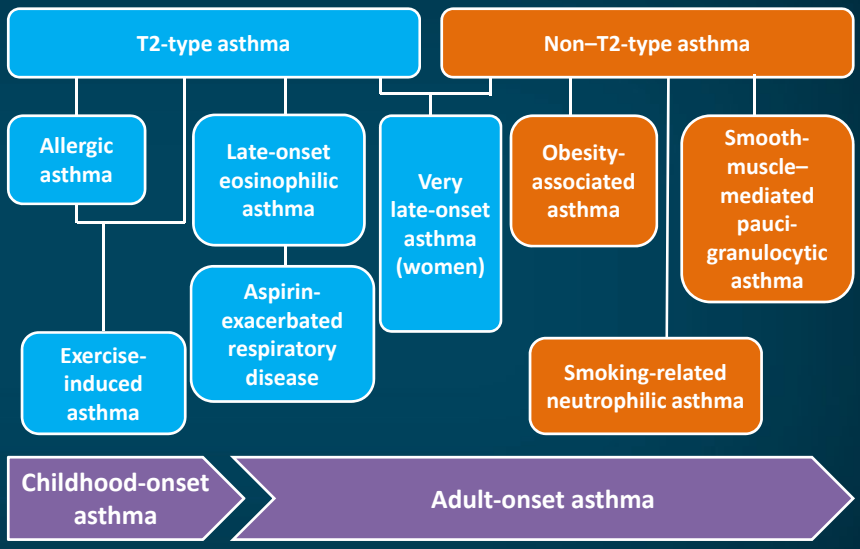
What can be observed and measured clinically?	What are the potential drivers of disease?
Observable characteristics (Phenotype)	Pathophysiological mechanism (Endotype)

The heterogeneity in treatment response has inspired discussion of a precision approach to care that tailors treatment to the patient

Muraro A, et al. *J Allergy Clin Immunol*. 2016;137:1347-1358. Lötvall J, et al. *J Allergy Clin Immunol*. 2011;127:355-360.

Approach to Asthma Phenotyping

- **Age at onset**
  - Early onset likely to be atopic/allergic
  - Later onset more heterogeneous
- **Patient exposures/triggers and host characteristics**
  - Age
  - Smoking, other exposures
  - BMI
  - Infection triggers
- **Asthma course**
  - Frequent exacerbation
- **Biomarkers**
  - T2 inflammation
    - Sputum/blood eosinophils
    - FeNO
    - IgE/atopy
  - Absence of T2 inflammation
    - Blood/sputum neutrophils



BMI = body mass index; FeNO = fractional exhaled nitric oxide; Ig = immunoglobulin; T2 = type 2.
Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

Comparison of Type 2 Inflammation Biomarkers in Asthma

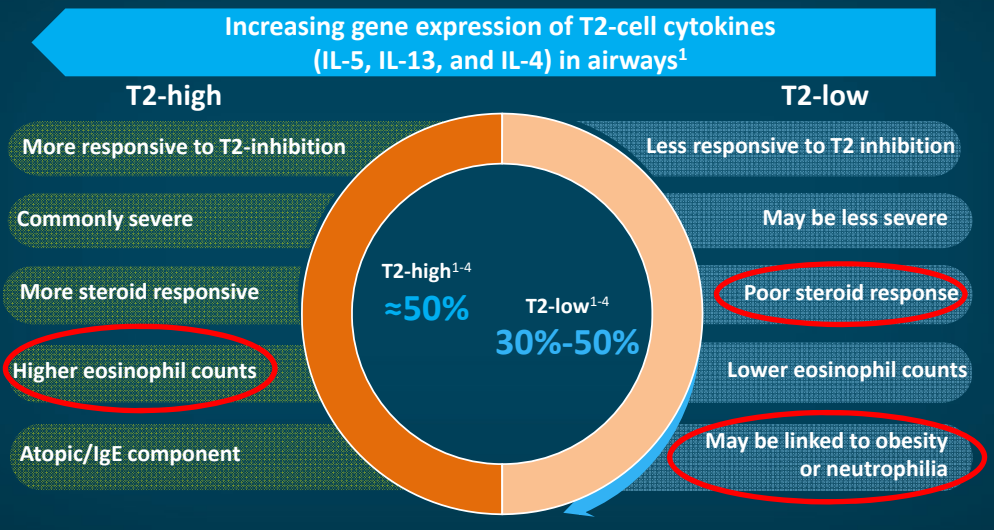
Biomarker	T2 Levels			Limitations
	Low	Medium	High	
Total IgE (IU)	<30	31-149	>150	Affected by age; poor predictor of response rate to biologic therapy. Does not correlate well with asthma severity. Elevations are not specific to asthma (also elevated in atopic dermatitis, allergic bronchopulmonary aspergillosis, etc)
Blood eosinophils (cells/µL)	<150	151-399	>400	Affected by weight, allergen exposure, steroids, and infection; optimal cutoff value varies by therapy. Elevations are not specific to asthma (also in allergic rhinitis, drug reactions, etc)
Sputum eosinophils (%)	—	—	≥3	Semi-invasive; confined to research settings
FeNO (ppb)	<25	26-49	>50	Affected by age, weight, sex, smoking, and respiratory infections

ppb = parts per billion

Parulekar AD, et al. *Curr Opin Pulm Med*. 2016;22:59-68. Peters MC, et al. *Curr Allergy Asthma Rep*. 2016;16:71.

Examples of Asthma Phenotypes

T2-High and T2-Low



1. Woodruff PG, et al. *Am J Respir Crit Care Med*. 2009;180:388-395. 2. Fahy JV. *Nat Rev Immunol*. 2015;15:57-65. 3. Wenzel SE. *Nat Med*. 2012;18:716-725.
4. Peters MC, et al. *J Allergy Clin Immunol*. 2014;133:388-394.

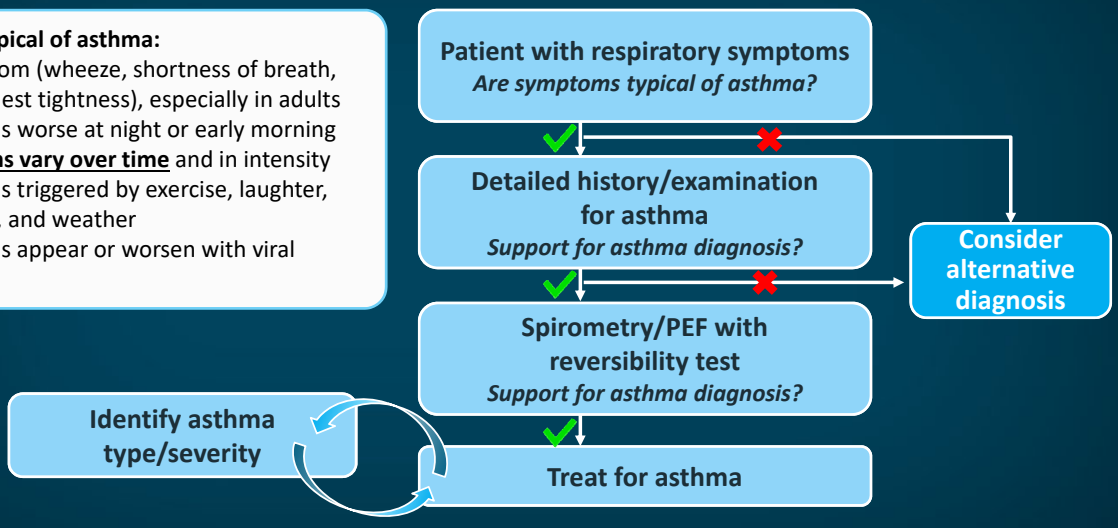
A Guideline-Based Approach to Asthma Management

Nicola A. Hanania, MD

Diagnosis of Asthma Is Based on Characteristic Pattern of Respiratory Symptoms

Features typical of asthma:

- ≥1 symptom (wheeze, shortness of breath, cough, chest tightness), especially in adults
- Symptoms worse at night or early morning
- **Symptoms vary over time** and in intensity
- Symptoms triggered by exercise, laughter, allergens, and weather
- Symptoms appear or worsen with viral infection



PEF = peak expiratory flow.

Adapted from GINA. 2020 (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf).

Common Causes of Uncontrolled Asthma

Nonadherence to therapy[1]

Incorrect inhaler technique[1]

Comorbidities and psychosocial factors[1]

Ongoing exposure to asthma triggers[1]

Understanding a patient's adherence to therapy is always a prerequisite when assessing severe asthma[2]

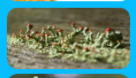
1. GINA. 2020 (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). 2. Bourdin A, et al. *Clin Exp Allergy*. 2012;42:1566-1574.

Managing Allergic and Non-Allergic Triggers of Asthma

Common allergic triggers

House dust mite

Pollen



Mold

Ragweed

Cockroach

Pet dander

Common non-allergic triggers

Ozone

Cigarette smoke

Exercise

Diesel particles

Respiratory infection (viral or bacterial)

Cold air

Diagnostic testing

Allergy skin tests

Blood tests (RAST)—allergen-specific IgE

RAST = radioallergosorbent test.

NAEPP. *J Allergy Clin Immunol*. 2007;120(5 suppl):S94-S138. American College of Allergy, Asthma & Immunology (ACAAI). 2021 (https://acaai.org/asthma/types-of-asthma/allergic-asthma) and (https://acaai.org/asthma/types-asthma/nonallergic-asthma).

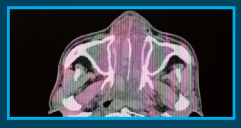
Treating the Whole Patient

Comorbidities Commonly Associated With Asthma

Atopic dermatitis

GERD

Vocal cord dysfunction



Rhinosinusitis/ nasal polyposis

OSA

Obesity

Comorbidities

- More healthcare utilization
- Increased frequency/ severity of exacerbations
- More severe asthma
- Increased systemic inflammation
- Greater reductions in HRQoL

Identification and treatment of comorbid conditions is critical

OSA = obstructive sleep apnea; HRQoL = health-related quality of life.

Boulet L-P. *Eur Respir J*. 2009;33:897-906. Galli E, et al. *Allergy Asthma Proc*. 2007;28:540-543. Porsbjerg C, Menzies-Gow A. *Respirology*. 2017;22:651-661. Sundh J, et al. *Respir Med*. 2017;132:154-160.

GINA 2020: Stepwise Treatment Approach

Increasing asthma severity

Mild | Moderate | Severe

Adults and adolescents 12+ years

	Step 1	Step 2	Step 3	Step 4	Step 5
PREFERRED CONTROLLER	As-needed, low-dose ICS-formoterol*	Daily low-dose 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 (eg, tiotropium, anti-IgE, anti–IL-5/-5R, anti-IL-4R)
Other controller options	*Low-dose ICS taken whenever SABA taken**	*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 options	*As-needed, SABA*				

*Off-label use; not FDA approved for this indication. †Patients prescribed maintenance and reliever therapy.

BDP = beclomethasone dipropionate; HDM SLIT = house dust mite sublingual immunotherapy; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid.

Adapted from GINA. 2020 (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf).

Simulation Case 1: Brittany

- 12-yo girl with severe asthma that developed early in life
- Biological parents were both heavy smokers; severe asthma diagnosed at 1 year old
- Adopted at 3 by a non-smoking family
- Allergies: pollens, cats, tree nuts (family has one cat at home), reports nasal stuffiness and occasional post nasal drip
- Current medications:
  - Fluticasone 2 puffs in the morning and evening
  - Cetirizine
  - Albuterol inhaler and nebulization as rescue
- Patient/parents report that she is compliant with meds
- Multiple exacerbations each year requiring systemic steroids and rescue albuterol, but not requiring hospitalization
- Parents are concerned that her asthma is not controlled and want to explore new options

Audience Response Question

A nasal inhaled steroid and montelukast 5mg once/day at night are started for Brittany. What should happen with her other two daily medications?

A. Continue both medications in their current regimens
B. Continue both medications, but reduce the dose of both
C. Continue fluticasone; stop cetirizine
D. Stop both fluticasone and cetirizine

Simulation Case 1: Labs

- IgE = 285 IU/mL
- Specific IgE: sensitization to cat, dust mite and grass pollen
- FeNO = 45 ppb
- CBC with absolute eosinophil count of 350 cells/microliter
- FVC: 92%
- FEV1: 70%
- FEV1/FVC: 76%

CBC = complete blood count; LAMA = long-acting muscarinic antagonist.

Audience Response Question

Given her eosinophil count and other biomarkers, Brittany is started on dupilumab. Which of the following is true about this agent?

A. It targets the IL-5 receptor
B. It is also approved for atopic dermatitis
C. It is generally not useful in steroid-dependent asthma
D. It is only approved for patients 18 years and older

Targeted Therapies for Severe Asthma

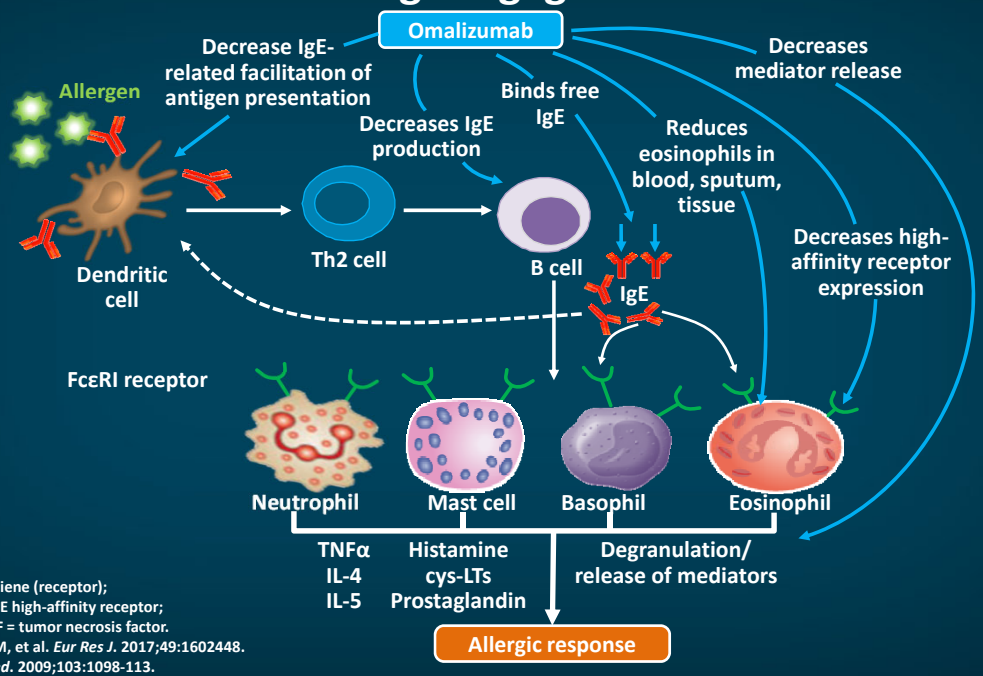
Biologic	Target	Key Trials	Administration			Approved or Studied in Other Diseases
			Age	Route	Frequency	
Omalizumab	IgE	Study 008/009/ALTO	≥6 years	SC	Q2W/Q4W	**Urticaria** Nasal polyps Food allergy
Mepolizumab	IL-5	MENSA/SIRIUS	≥6 years	SC	Q4W	**EGPA** **HES** COPD Nasal polyps
Reslizumab	IL-5	BREATH trials	≥18 years	IV	Q4W	Sinusitis Eosinophilic esophagitis
Benralizumab	IL-5R	SIROCCO/CALIMA/ ZONDA	≥12 years	SC	Q4W/Q8W	COPD
Dupilumab	IL-4R†	LIBERTY QUEST LIBERTY VENTURE SOLO1/SOLO2 CHRONOS	≥12 years	SC	Q2W	**Atopic dermatitis** **Rhinosinusitis with nasal polyps** Eosinophilic esophagitis Peanut allergy Grass allergy COPD
Tezepelumab*	TSLP	PATHWAY	≥18 years	SC	Q2W/Q4W	Atopic dermatitis

*Investigational: phase 3 studies ongoing. †Inhibits IL-4 and IL-13 signaling pathways.

COPD = chronic obstructive pulmonary disease; DP2 = prostaglandin D2; EGPA = eosinophilic granulomatosis with polyangiitis; HES = hypereosinophilic syndrome; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; R = receptor; SC = subcutaneous; TSLP = thymic stromal lymphopoietin.

Prescribing information (PI) for first 5 agents. Corren J, et al. *N Engl J Med.* 2017;377:936-946.

Targeting IgE



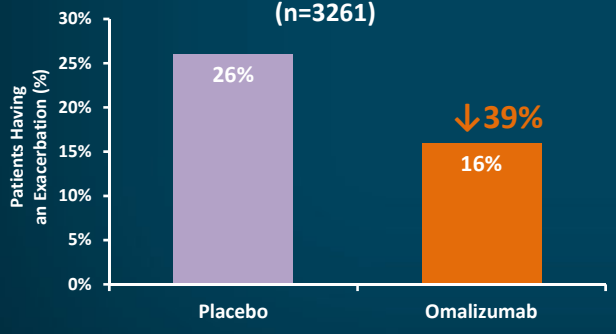
cys-LT = cysteinyl leukotriene (receptor);
FcεRI = immunoglobulin E high-affinity receptor;
Th2 = T helper 2 cell; TNF = tumor necrosis factor.
Adapted from Edwards M, et al. *Eur Res J.* 2017;49:1602448.
Holgate S, et al. *Resp Med.* 2009;103:1098-113.

Efficacy of Omalizumab (Anti-IgE) in Moderate-to-Severe Allergic Asthma (Cochrane Review)

Meta-analysis of 25 studies (N=6382) comparing omalizumab with placebo through June 2013

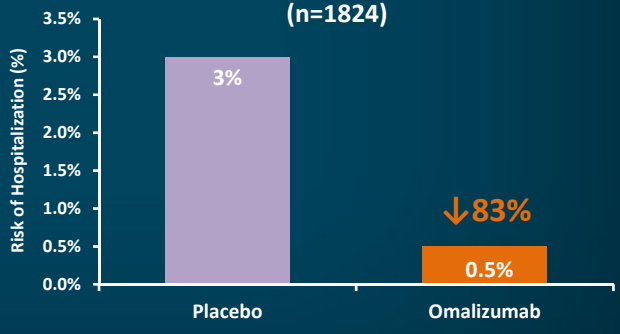
Exacerbations

Absolute reduction over 16-60 weeks (n=3261)



Hospitalizations

Absolute reduction over 28-60 weeks (n=1824)



Omalizumab-treated patients also significantly more likely to completely withdraw ICS

Normansell R, et al. *Cochrane Database Syst Rev*. 2014;1:CD003559.

Simulation Case 2: Steve

- 42-yo man with asthma diagnosed 4 years ago
- Long-standing rhinosinusitis and nasal polyps
- Allergy work-up negative, no GERD
- Intermittent dyspnea and wheezing; nonproductive cough
  - This has worsened over the past 6–9 months
- Nothing changed at home: no pets; environmental measures controlled at home
- Compliant with ICS/LABA/LAMA

Audience Response Question

Which of the following is true about proper inhaler technique in asthma care?

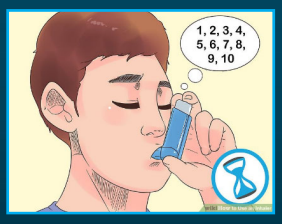
A. Around 10% of patients use their inhaler incorrectly
B. Inhaler technique almost always remains consistent over time
C. Many patients receive inadequate direction; many healthcare providers cannot demonstrate correct inhalers use
D. Inhaler technique should only be assessed on the first few visits

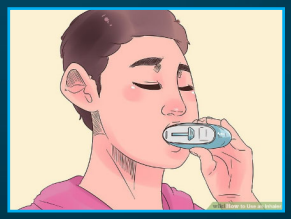
Proper Inhaler Technique

Poor inhaler technique leads to:

- Poor asthma control
- Increased risk of exacerbations
- Increased AEs

- Up to 70%-80% of patients are unable to use their inhaler correctly
- Many patients received inadequate education on inhaler technique
- Many healthcare providers are unable to demonstrate how to use the inhalers they prescribe
- Patients' inhaler technique has been shown to deteriorate over time
- Assess proper inhaler technique at multiple visits and prior to concluding that a given therapy is ineffective





GINA. 2020 (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf).

Keeping the Team Involved—Provide Hands-on Inhaler Skills Training: 4 Cs

Choose
• Choose an appropriate device before prescribing. Consider medication options, arthritis, patient skills, and cost. For ICS by pressurized metered-dose inhaler, prescribe a spacer or valved holding chamber • Avoid multiple inhaler types if possible
Check
• Check technique at every opportunity—"*Can you show me how you use your inhaler at present?*" • Identify errors with a device-specific checklist
Correct
• Give a physical demonstration to show how to use the inhaler correctly • Check again (up to 2-3 times) • Re-check inhaler technique frequently, as errors often recur within 4-6 weeks
Confirm
• Can you demonstrate correct technique for the inhalers you prescribe? • Brief inhaler technique training improves asthma control

GINA. 2020 (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf).

Simulation Case 2: Labs

- IgE = 12 IU/mL
- FeNO = 30 ppb
- CBC with absolute eosinophil count of 850 cells/microliter
- FVC: 90%
- FEV1: 65%
- FEV1/FVC: 72%

Audience Response Question

Which of the following would you try at this point?

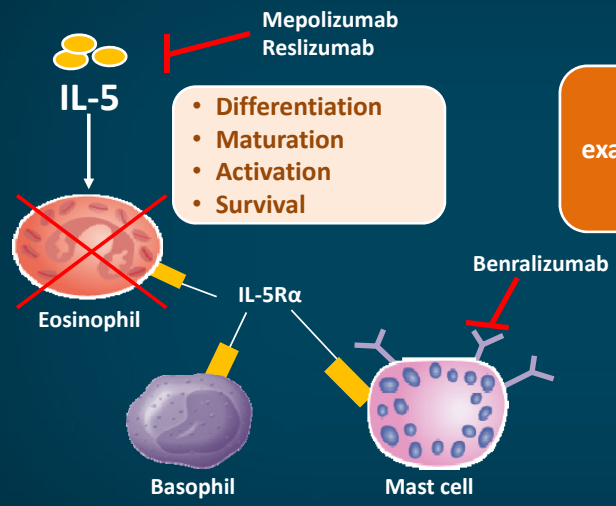
A. IgE therapy
B. Anti-IL5 or anti-IL5R therapy
C. Anti-IL4R therapy
D. B or C

Audience Response Question

The patient is started on an anti-IL-5 biologic. Which of the following would be a be a predictor of good response with this class of agents?

A. Child-onset asthma
B. High IgE
C. Co-existing atopic dermatitis
D. High eosinophils with recent exacerbation(s)

Targeting IL-5



IL-5–targeted agents decrease asthma exacerbations in patients with severe asthma who have high blood eosinophil levels

ADCC

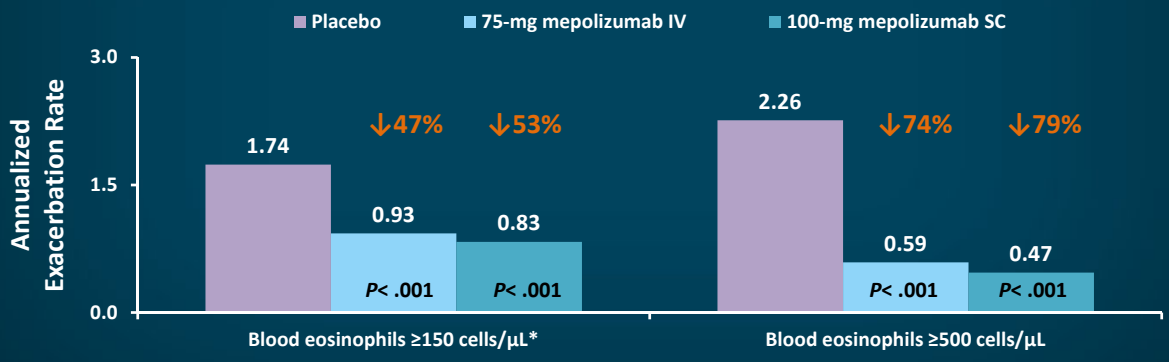
ADCC = antibody-dependent cell-mediated cytotoxicity.

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207. Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Efficacy of Mepolizumab in Severe Eosinophilic Asthma

576 patients aged ≥12 years with severe, eosinophilic asthma received mepolizumab add-on therapy to ICS + ≥1 controller regimen

Reduced exacerbation rate vs placebo

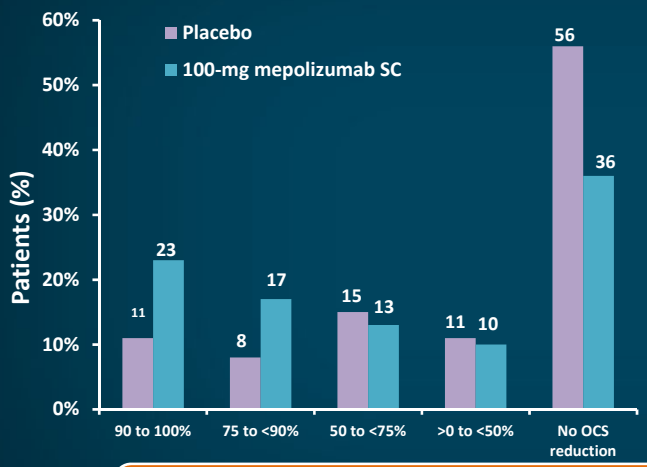


*Eosinophil count ≥150 cells/µL at screening or ≥300 cells/µL within previous year.

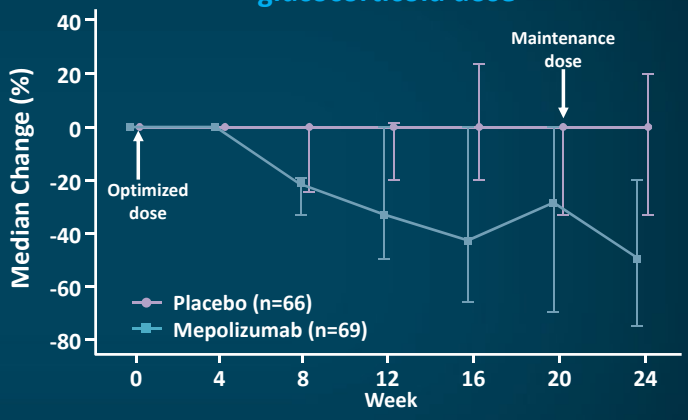
Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207.

Steroid Reduction With Mepolizumab

Reduction in OCS dose



Change from baseline in glucocorticoid dose



Overall OCS dose was reduced by 50% with mepolizumab vs no reduction with placebo (*P*= .007)

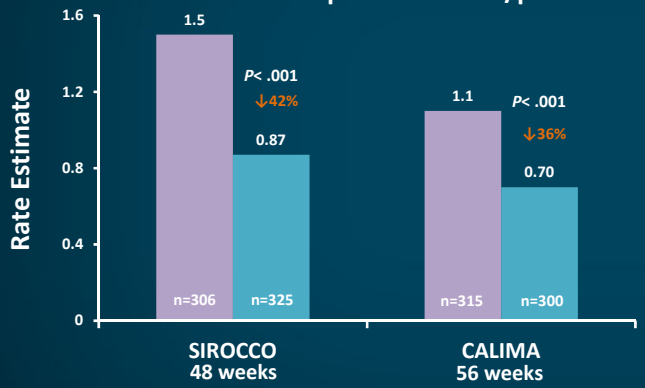
Bel EH, et al. *N Engl J Med*. 2014;371:1189-1197.

Efficacy of Benralizumab in Severe Uncontrolled Asthma

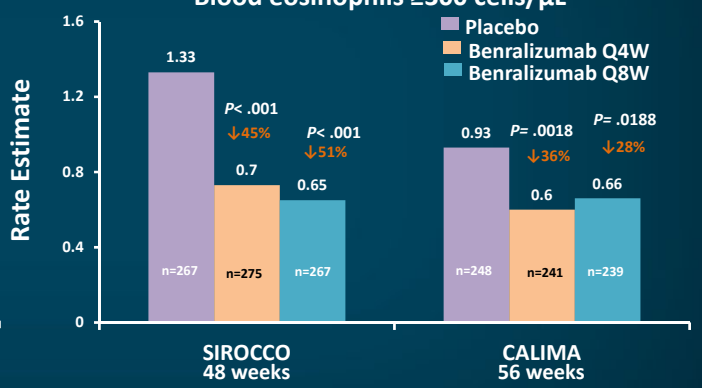
Benralizumab (30 mg Q4W or Q8W) as add-on therapy to high-dose ICS/LABA (SIROCCO[1]) or medium- to high-dose ICS/LABA (CALIMA[2])

Annualized asthma exacerbation rate

Blood eosinophils ≥150 cells/μL[3]



Blood eosinophils ≥300 cells/μL[1,2]



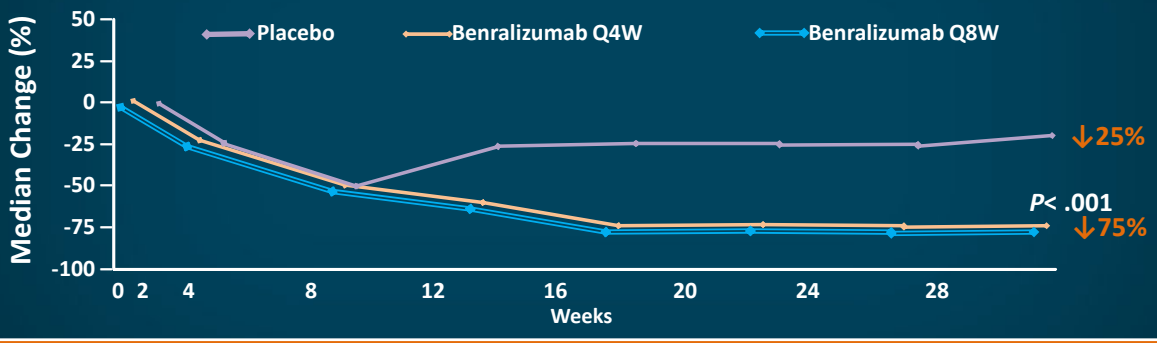
Pooled analysis: Benralizumab ↓annualized exacerbation rate, ↑FEV_1, and improved symptoms; subanalyses suggested OCS use and nasal polyposis were associated with ↑ response[4]

1. Bleecker ER, et al. *Lancet*. 2016;388:2115-2127. 2. FitzGerald JM, et al. *Lancet*. 2016;388:2128-2141. 3. Goldman M, et al. *Curr Med Res Opin*. 2017;33:1605-1613.
4. FitzGerald JM, et al. *Lancet Respir Med*. 2018;6:51-64.

OCS-Sparing Effect of Benralizumab in Patients With Severe Eosinophilic Asthma: ZONDA Phase 3 Trial

220 patients aged ≥18 years with severe asthma currently on OCS-based therapy were randomized to receive placebo or benralizumab for 28 weeks

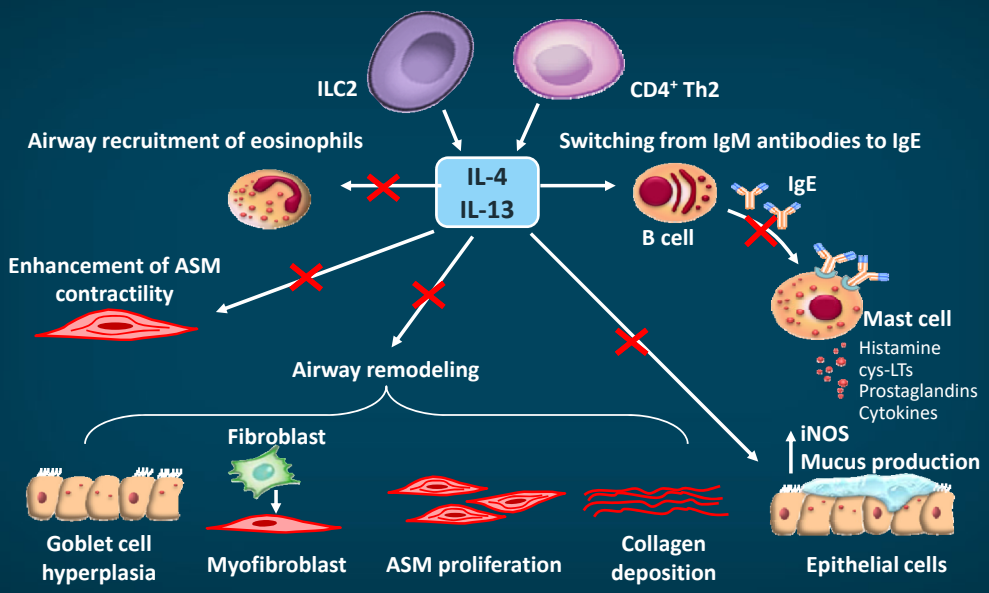
OCS dose reduction



Annualized exacerbation rate and time to first asthma exacerbation also improved in both benralizumab groups vs placebo

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

Targeting IL-4/IL-13

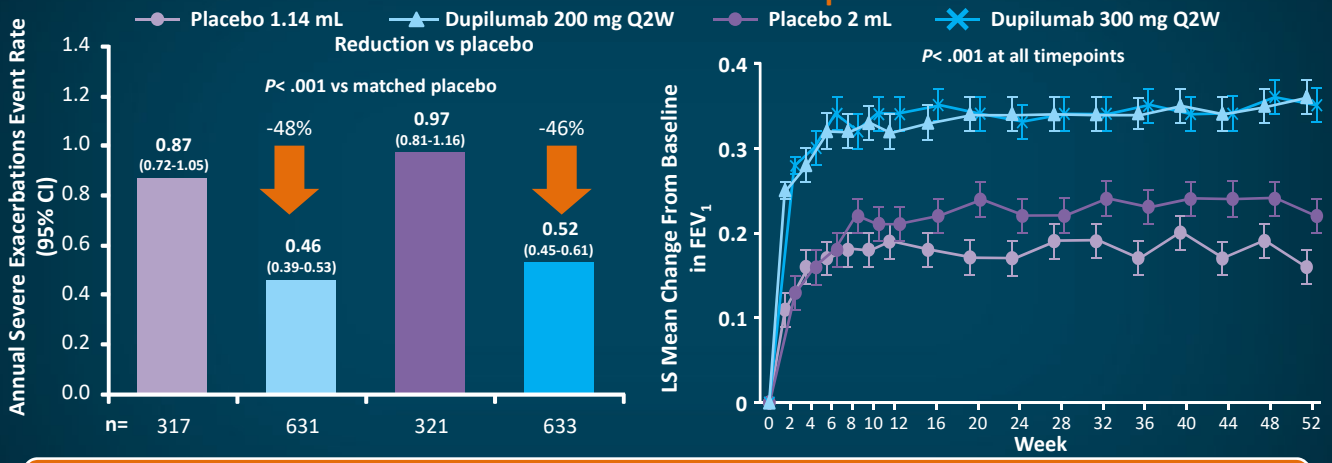


ASM = airway smooth muscle cell; ILC2 = innate lymphoid type 2; iNOS = inducible nitric oxide synthase.

Vatrella A, et al. *J Asthma Allergy*. 2014;7:123-130.

Efficacy of Dupilumab in Patients With Asthma

Phase 3 LIBERTY ASTHMA QUEST: 1902 patients aged ≥12 years with uncontrolled, moderate-to-severe asthma treated with dupilumab for 52 weeks



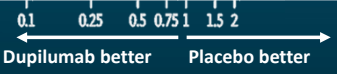
Dupilumab Q2W was more consistent and efficacious at improving time to first exacerbation, asthma control scores, QoL, and FeNO values across patient subgroups

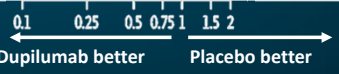
Castro M, et al. *N Engl J Med*. 2018;378:2486-2496 and supplement.

Dupilumab in Patients With Uncontrolled Asthma, Efficacy by Subgroup

LIBERTY ASTHMA QUEST Phase 3 Trial

Subgroup	Placebo	Dupilumab 200 mg Q2W	RR vs Placebo (95% CI)	Placebo	Dupilumab 300 mg Q2W	RR vs Placebo (95% CI)
Overall	317	631	0.52 (0.41-0.66)	321	633	0.54 (0.43-0.68)
Eosinophil count (cells/μL)						
≥300	148	264	0.34 (0.24-0.48)	142	277	0.33 (0.23-0.45)
≥150-<300	84	173	0.64 (0.41-1.02)	95	175	0.56 (0.35-0.89)
<150	85	193	0.93 (0.58-1.47)	83	181	1.15 (0.75-1.77)
FeNO (ppb)						
≥50	71	119	0.31 (0.18-0.52)	75	124	0.31 (0.19-0.49)
≥25-<50	91	180	0.39 (0.24-0.62)	97	186	0.44 (0.28-0.69)
<25	149	325	0.75 (0.54-1.05)	144	317	0.79 (0.57-1.10)





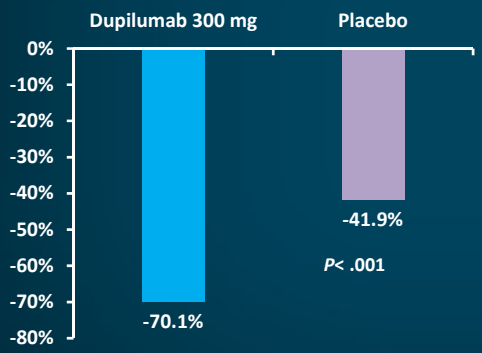
RR = relative risk.

Castro M, et al. *N Engl J Med*. 2018;378:2486-2496.

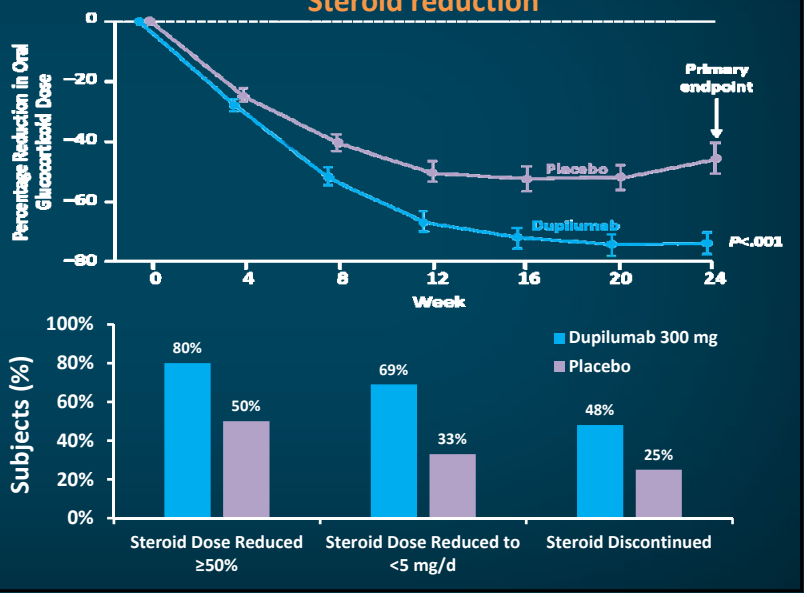
Dupilumab in Steroid-Dependent Asthma
VENTURE Phase 3 Trial

210 patients aged ≥12 years with OCS-dependent severe asthma

Change in steroid dose



Steroid reduction



Rabe KF, et al. *N Engl J Med*. 2018;378:2475-2485.

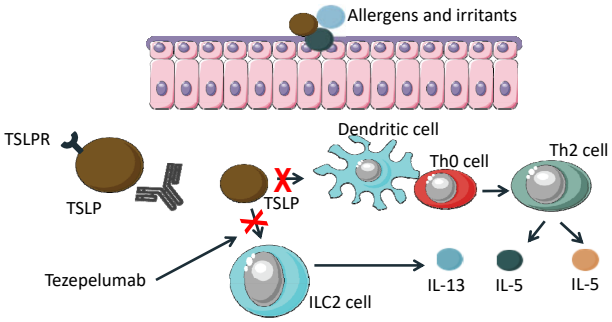
Dupilumab in Children Aged 6-11 Years*
52-Week LIBERTY ASTHMA VOYAGE Phase 3 Trial

- 408 children aged 6-11 years with uncontrolled "broad type 2 inflammatory asthma" (eosinophils ≥150 cells/µL or FeNO ≥20 ppb)
- Dupilumab (vs placebo):
  - 65% reduced rate of severe attacks (0.24 vs 0.67 events/year; *P*< .0001)
  - 59% average reduction over 1 year (0.31 vs 0.75 events/year; *P*< .0001)
- Improved FEV_1pp at 12 weeks; maintained through 52 weeks
- Safety comparable with known profile
- US and EU submissions anticipated Q1 2021

*Dupilumab is not FDA approved for asthma in children aged <12 years.
FEV_1pp = percent predicted FEV_1.
Dupixent press release. 2020 (https://www.sanofi.com/en/media-room/press-releases/2020/2020-10-13-07-00-00).

Tezepelumab* Is an Anti-TSLP mAb

- TSLP is a cytokine predominantly secreted by epithelial cells[1]
- TSLP plays a role in allergic inflammation[2,3]
  - Levels of TSLP correlate with severity of disease symptoms in asthma[4]
- Tezepelumab functionally antagonizes the action of TSLP at its receptor (TSLPR), thereby reducing its pro-inflammatory activity[5,6]



Characterization of tezepelumab was performed using bioassay inhibition of TSLP-induced proliferation of a stable mouse BAF cell-line expressing functional human TSLPR.

*Tezepelumab is not FDA approved.

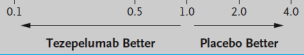
1. Corren J, et al. *N Engl J Med*. 2017;377:936-946. 2. Soumelis V, Liu YJ. *Springer Semin Immunopathol*. 2004;25:325-333. 3. Soumelis V, et al. *Nat Immunol*. 2002;3:673-680. 4. Ying S, et al. *J Immunol*. 2005;174:8183-8190. 5. Gauvreau GM, et al. *N Engl J Med*. 2014;370:2102-2110 and appendix. 6. Verstraete K, et al. *Nat Commun*. 2017;8:14937.

NAVIGATOR: Tezepelumab in Adults and Adolescents With Severe, Uncontrolled Asthma

- Human mAb that binds specifically to TSLP
- Study participants: patients received medium- to high-dose ICS and ≥1 additional controller medication, with or without oral glucocorticoid
- Design: patients randomized to receive tezepelumab (210 mg) or placebo SC every 4 weeks for 52 weeks

Primary endpoint: annualized rate of asthma exacerbations over a period of 52 weeks

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

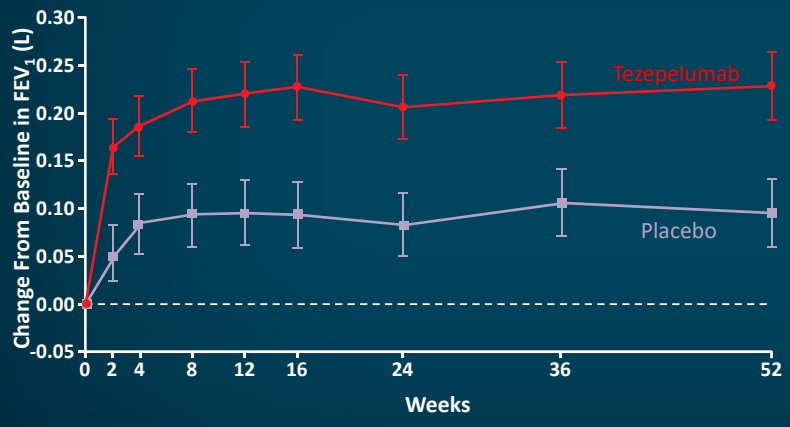


*Tezepelumab is not FDA approved.

Menzies-Gow A, et al. *N Engl J Med*. 2021;384:1800-1809.

NAVIGATOR: Secondary Endpoint and Safety Findings

Change from baseline to week 52 in prebronchodilator FEV_1



Safety findings

- 77.1% of the patients in the tezepelumab group and 80.8% of those in the placebo group reported an AE

Most common AEs

- Nasopharyngitis, URTI, headache, and asthma

*Tezepelumab is not FDA approved.

Menzies-Gow A, et al. *N Engl J Med*. 2021;384:1800-1809.

The Choice of Biologic in Severe Asthma

Diego J. Maselli, MD FCCP

GINA: Identifying Patients and Selecting Biologic

T2 airway inflammation if:

Meets ≥1 of the following criteria while on high-dose ICS (before OCS):

- Blood eosinophils ≥150 cells/µL
- FeNO ≥20 ppb
- Sputum eosinophils ≥2%
- Asthma is clinically allergen driven
- Need for maintenance OCS

Start with anti-IgE therapy if:

- Aged ≥6 years
- Severe allergic asthma
- Sensitization on skin prick testing or specific IgE
- Total serum IgE* and weight within dosage range
- Exacerbations in the last year

Predictors of good response:

- Blood eosinophils ≥260 cells/µL
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

Start with anti–IL-5 or anti–IL-5R therapy if:

- Aged ≥12 or ≥18 years
- Severe eosinophilic asthma
- Exacerbations in the last year
- Blood eosinophils ≥300 cells/µL

Predictors of good response:

- Higher blood eosinophils
- More exacerbations in previous year
- Adult-onset of asthma
- Nasal polyps

Start with anti–IL-4 if:

- Aged ≥12
- Severe eosinophilic asthma or need for maintenance OCS
- Exacerbations in last year
- Blood eosinophils ≥150 cells/µL or FeNO ≥25 ppb

Predictors of good response:

- Higher blood eosinophils
- Higher FeNO

May also be used to treat:

- Moderate-to-severe atopic dermatitis
- Nasal polyps

*Baseline IgE levels do not predict likelihood of response.

GINA. 2019 (https://ginasthma.org/ wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf).

Factors Impacting Biologic Therapy Selection

- Patient characteristics (eg, BMI, age)
- Asthma phenotype and endotype
- Concurrent comorbidities
- Safety and efficacy profile
- Patient preference
- Route of administration (IV vs SC)
- Frequency of dosing
- Adherence considerations (self-administration vs office visits)
- Cost (insurance coverage, prior authorization)
- Clinician's experience

Common Patient Concerns for Treatment Selection

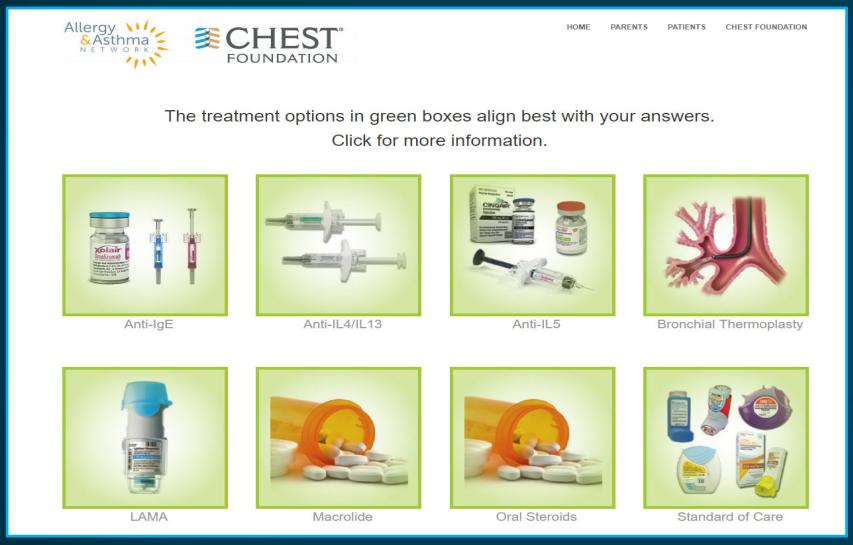
Treatment
- Frequency and route
- Safety and side effects
- Long-term effectiveness
- Unawareness and fear

Patient
- Perceived ineffectiveness
- Perceived need for control
- Time demands and scheduling conflicts

Socioeconomic
- Financial burden
- Insurance coverage

If these concerns are not addressed, they can impact adherence and outcomes

CHEST Foundation: Shared Decision-Making Tool



- Patient identifies his/her preferences and values
- Clinician provides patient's biomarkers
- This narrows down patient's personalized options

CHEST Foundation (http://asthma.chestnet.org/sdm-tool).

Treatment of T2-Low Asthma

≈40%-50% of patients with asthma **do not** have type 2 inflammation

- Severe, uncontrolled asthma without evidence for type 2 inflammation referred to as "type 2 (T2)-low asthma"
- Potential targets for T2-low asthma:
  - IL-17 indirectly recruits neutrophils
  - IL-8 chemoattractant for neutrophils
  - Macrolide antibiotics
- Bronchial thermoplasty

Fajt ML, Wenzel SE. *Allergy Asthma Immunol Res*. 2017;9:3-14.

Summary Points

- Addressing **modifiable risk factors** can improve symptom control in many patients with severe asthma
- Phenotyping and endotyping using clinical, physiologic, and biologic biomarkers will allow for a more precise approach to severe disease
- Growing number of treatment options available for patients with severe asthma
- Clinical trials have shown that several targeted biologic therapies can **improve symptoms, decrease exacerbations, and improve QoL** in various severe asthma cohorts
  - 5 biologic therapies are FDA approved to treat severe T2-high asthma
  - Other biologic agents and small-molecule antagonists are in late-stage clinical development
- Coordinated **multidisciplinary care** is essential for the optimization of outcomes for patients with severe asthma

Thank You!

Targeted Management of Asthma: Using Phenotypes and Biomarkers to Individualize Treatment

TOOLKIT

Moderate to Severe Asthma: Identification, Diagnosis, and Management

Resource	Address
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Zein J, et al. Asthma over the adult life course: gender and hormonal influences. *Clin Chest Med.* 2019;40(1):149-161.	https://pubmed.ncbi.nlm.nih.gov/30691709/

Resources and Societies

Resource	Address
Allergy and Asthma Network	https://allergyasthmanetwork.org/
American Academy of Allergy, Asthma, and Immunology	https://acaai.org/asthma
American Association for Respiratory Care	https://www.aarc.org/
American Lung Association	https://www.lung.org/lung-health-diseases/lung-disease-lookup/asthma
Association of Asthma Educators	https://www.asthmaeducators.org/
Asthma and Allergy Foundation of America	https://www.aafa.org/
Centers for Disease Control and Prevention	https://www.cdc.gov/asthma/default.htm
Global Initiative for Asthma (GINA) Guidelines	https://ginasthma.org/gina-reports/