Immunological Targeting Approach for the Management of

MODERATE-TO-SEVERE ASTHMA

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by an educational grant from Sanofi Genzyme and Regeneron Pharmaceuticals.

Immunological Targeting Approach for the Management of Moderate-to-Severe Asthma

PROGRAM CHAIR

Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF (PROGRAM CHAIR)
Associate Professor of Medicine,
Director, Airway Clinical Research Center
Pulmonary, Critical Care and Sleep Medicine
Houston, TX

FACULTY PRESENTERS

Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF (PROGRAM CHAIR)
Associate Professor of Medicine,
Director, Airway Clinical Research Center
Pulmonary, Critical Care and Sleep Medicine
Houston, TX

Mario Castro, MD, MPH
Chief, Pulmonary, Critical Care and Sleep Medicine
Vice Chair for Clinical and Translational Research
Director, Frontiers: Univ Kansas Clinical & Translational Science Institute
Director, Rainbow Clinical Trials Science Unit
University of Kansas School of Medicine
Kansas City, KS

Diego J. Maselli, MD FCCP
Associate Professor of Medicine
Division of Pulmonary Diseases & Critical Care
University of Texas Health Science Center at San Antonio
Director, Respiratory Care, University Health System
Director, Severe Asthma Program, University Health System
San Antonio, TX

Hassan M. Nasir, DO
Regional Dean at LECOM
Chief of Staff at Larkin Community Hospital
Sunny Isles, FL

Mark Rumbak, MD
Professor of Medicine
University of South Florida
Tampa, FL

Michael Wechsler, MD
Professor of Medicine
Director, NJH Cohen Family Asthma Institute
Department of Medicine
National Jewish Health
Denver, CO

PROGRAM OVERVIEW

This program will review current and emerging therapies for the management of moderate-to-severe uncontrolled asthma.

TARGET AUDIENCE

This CME initiative is designed to meet the educational needs of pulmonologists, allergists, immunologists, and otolaryngologists involved in the healthcare of patients with moderate-to-severe uncontrolled asthma.

LEARNING OBJECTIVES

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

- Review the molecular basis for the pathophysiology of moderate-to-severe asthma and the corresponding targeted biologic therapies
- Describe the current medical committee guidelines and their application in clinical practice for the management of patients with moderate-to-severe asthma
- Discuss the clinical trials data of biologic therapies as add-on treatments in the maintenance setting for patients with moderate-to-severe asthma

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Purpose: This program would be beneficial for nurses involved in the care of patients with moderate-to-severe asthma.
Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Faculty Member	Disclosures
Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF	Served on the Speakers Bureau for AstraZeneca and worked as a consultant for GlaxoSmithKline, Boehringer Ingleheim, Genentech, Novartis, Sanofi, Regeneron and AstraZeneca, Teva and Amgen. He has also done contracted research for GlaxoSmithKline, Boehringer Ingleheim, Sanofi, Genentech, Novartis and Gossamer
Mario Castro, MD, MPH	Royalties paid by Elsevier, serves on the Speakers Bureau for AstraZeneca, Genentech, GlaxoSmithKline, Regeneron, Sanofi and Teva, works as a consultant for Genentech, Teva, Sanofi-Aventis and Novartis, and receives Pharmaceutical Grant Funding from AstraZeneca, GlaxoSmithKline, Pulmatrix, Sanofi-Aventis and Shinogi
Diego J. Maselli, MD FCCP	Consulting for GlaxoSmithKline, AstraZeneca, Novartis, Sanofi/Regeneron and serving on the Speakers Bureau for GlaxoSmithKline, AstraZeneca, Sanofi/Regeneron and Sunovion
Hassan M. Nasir, D.O.	No relationships to disclose
Mark Rumbak, MD	No Relationships to disclose
Michael Wechsler, MD	Consulting for GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, Regeneron, Genentech, Amgen, Cohero, Teva and Equillium, and has provided contracted research for AstraZeneca and Sanofi Regeneron

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

The reviewer of this activity has nothing to disclose.

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Immunological Targeting Approach for the Management of MODERATE-TO-SEVERE ASTHMA

Program 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
  a. Change in understanding: A shift toward disease mechanisms
  b. Phenotyping and biomarkers
  c. Inflammatory pathways
  d. Whiteboard animation: immune cells, inflammatory cytokines underlying pathology of asthma
  e. Causes of uncontrolled asthma and triggers
  f. 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. Investigating the patient with poor symptom control or/and exacerbations despite treatment
  d. Emerging targets for severe T2-high asthma
  e. 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)
  f. Whiteboard Animation: inflammatory targets and agents: IgE, IL-4/13, and IL-5 inhibitors
  g. Factors affecting therapeutic selection
  h. Shared decision-making

IV. Conclusions and Q/A

Immunological Targeting Approach for the Management of Moderate-to-Severe Asthma

Program Chair:

Nicola A. Hanania, MD, MS, FRCP(C), FCCP, FACP, FERS, ATSF

Associate Professor of Medicine,

Director, Airways Clinical Research Center

Baylor College of Medicine

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Disclosures

- Please see Program Overview for specific speaker disclosure information.
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Learning Objectives

- Explain the molecular basis of the pathophysiology of moderate-to-severe asthma and the corresponding targeted biologic therapies
- Describe the current medical committee guidelines and their application in clinical practice for the management of patients with moderate-to-severe asthma
- Discuss the clinical trials data of biologic therapies as add-on treatments in the maintenance setting for patients with moderate-to-severe asthma

Asthma: An Introduction

Burden of Asthma in the United States

~25 million Americans have asthma

In 2016:

More than 11 million people reported having $\geq$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). (www.cdc.gov/asthma/asthmadata.htm). Accessed 9/24/2020.

Multiple Unmet Medical Needs in Asthma

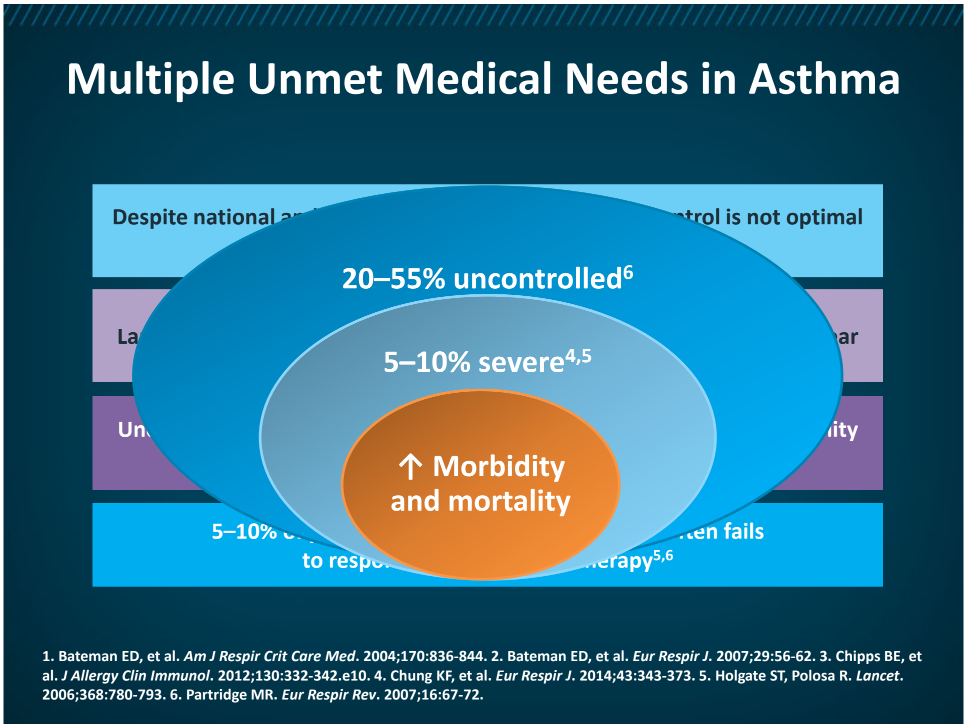
Despite national and international guidelines, asthma control is not optimal with current standard-of-care treatment[1,2]

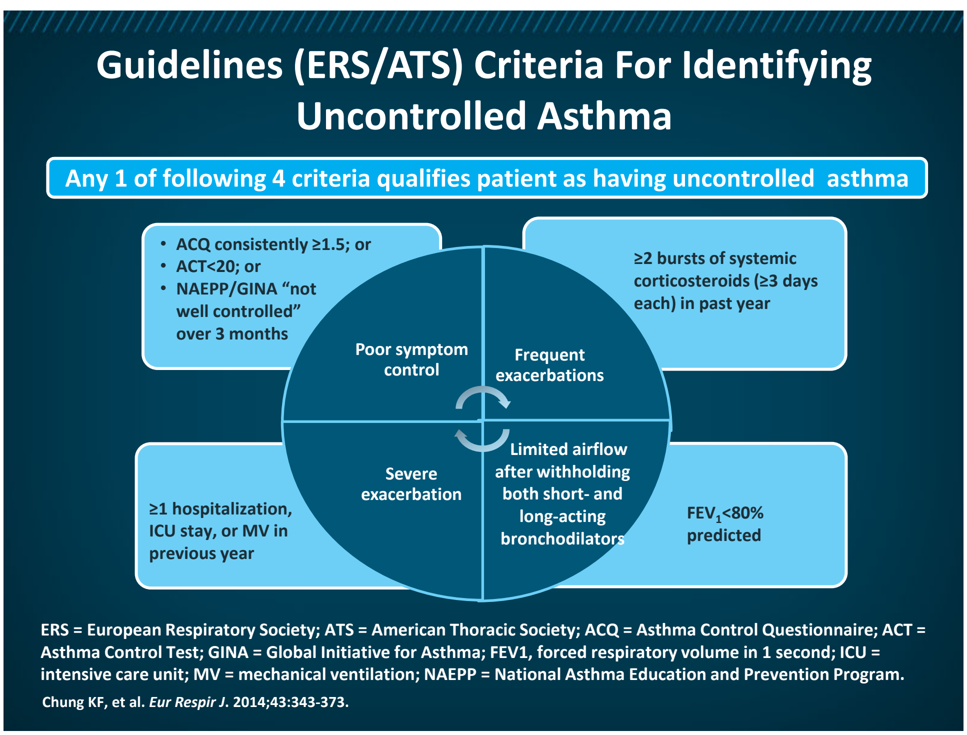
Large number of hospitalizations for people with severe asthma every year

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
Despite national a
trol is not optimal
20–55% uncontrolled[6]
5–10% severe[4,5]
↑ Morbidity and mortality
La
ar
Un
ity
5–10% o
ten fails
to respo
herapy[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.


Guidelines (ERS/ATS) Criteria For Identifying Uncontrolled Asthma
Any 1 of following 4 criteria qualifies patient as having uncontrolled asthma
• ACQ consistently ≥1.5; or
• ACT<20; or
• NAEPP/GINA "not well controlled" over 3 months
Poor symptom control
Frequent exacerbations
≥2 bursts of systemic corticosteroids (≥3 days each) in past year
Severe exacerbation
≥1 hospitalization, ICU stay, or MV in previous year
Limited airflow after withholding both short- and long-acting bronchodilators
FEV1<80% predicted
ERS = European Respiratory Society; ATS = American Thoracic Society; ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; GINA = Global Initiative for Asthma; FEV1, 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 >12 Years of Age and Adults

Components of severity		Classification of Asthma Severity (Youths ≥12 of age 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/per year	≥2/per year
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects (TRAEs)	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.		

ATAQ = Asthma therapy Assessment Questionnaire; SABA = short-acting beta$_2$-agonist; N/A = not applicable.

Adapted from Asthma Care Quick Reference. (www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf). Accessed 9/24/2020.

Who Has Severe Asthma?

Asthma in patients ≥6 years old who required either:

ICS = inhaled corticosteroids, LABA = long-acting β_2-agonist; GERD = gastroesophageal reflux disease.

AAAAI. Available at: https://www.aaaai.org/conditions-and-treatments/library/asthma-library/severe-asthma. Accessed Oct 1, 2020.

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- High-dose ICS + LABA or leukotriene modifier/theophylline

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Who Has Severe Asthma?

Asthma in patients ≥6 years old who required either:

- High-dose ICS + LABA or leukotriene modifier/theophylline
- Systemic corticosteroids for ≥50% of the year

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- Or, asthma that is "uncontrolled" despite these therapies

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- Other clues: nocturnal awakenings and impaired lung function

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- 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)

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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

Patient with respiratory symptoms
Are symptoms typical of asthma?

Detailed history/examination for asthma
Support for asthma diagnosis?

Spirometry/PEF with reversibility test
Support for asthma diagnosis?

Treat for asthma

Identify asthma type/severity

Consider alternative diagnosis

PEF = peak expiratory flow.

Adapted from GINA 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.

Pathogenesis Primer and Treatment Approaches for Uncontrolled and 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 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?

Observable characteristics (Phenotype)

What are the potential drivers of disease?

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

BMI = body mass index; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E

Holgate ST, et al. *Nat Rev Dis Primers*. 2015;1:15025.

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

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  - Frequent exacerbation

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- **Asthma course**
  - Frequent exacerbation
- **Biomarkers**
  - T2-inflammation
    - Sputum/blood eosinophils
    - FeNO
    - IgE/atopy
  - Absence of T2-inflammation
    - Blood/sputum neutrophils

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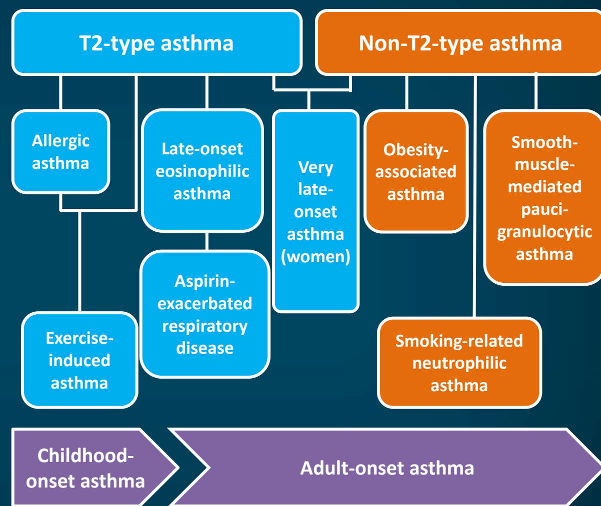

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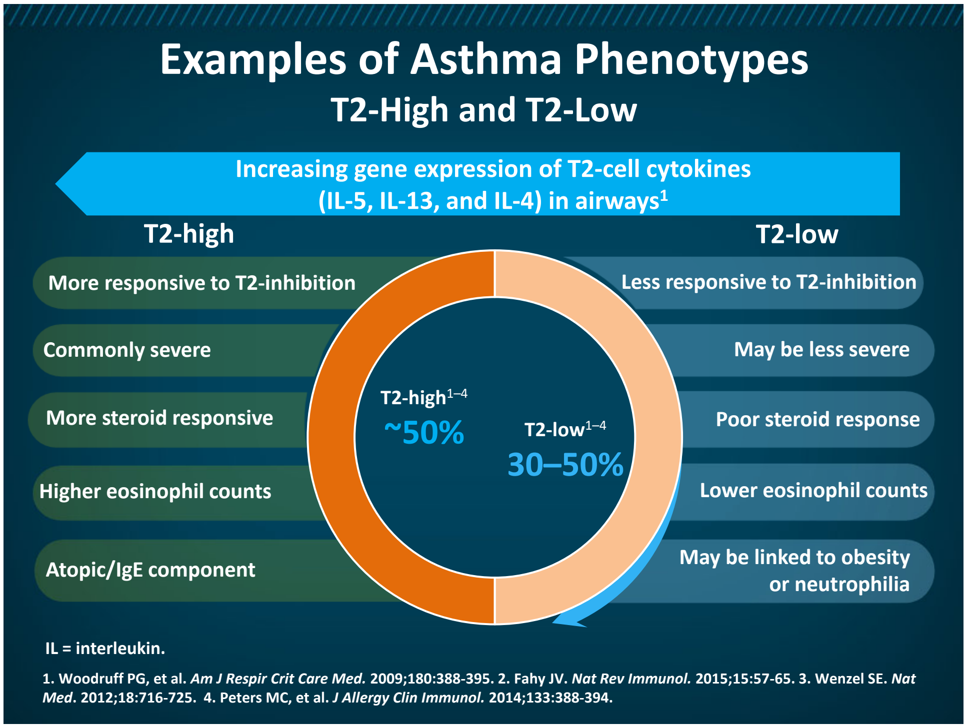
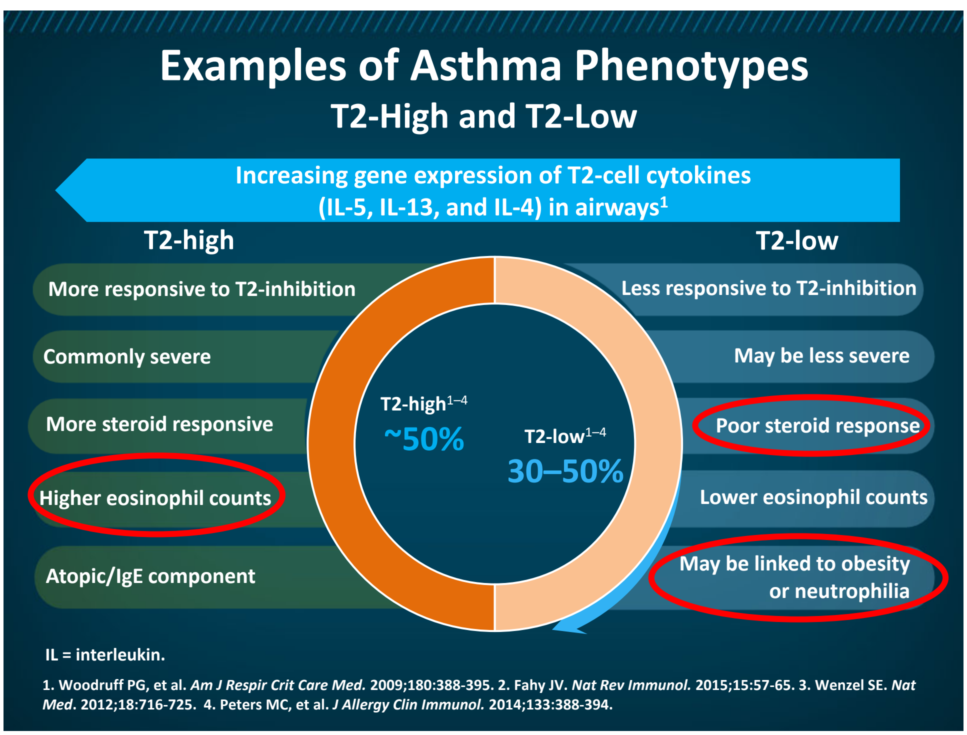
Comparison of Type 2 Inflammation Biomarkers in Asthma

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

T2 = T-helper cell type 2; 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
Increasing gene expression of T2-cell cytokines
(IL-5, IL-13, and IL-4) in airways[1]
T2-high
T2-low
More responsive to T2-inhibition
Commonly severe
More steroid responsive
Higher eosinophil counts
Atopic/IgE component
T2-high[1–4]
~50%
T2-low[1–4]
30–50%
Less responsive to T2-inhibition
May be less severe
Poor steroid response
Lower eosinophil counts
May be linked to obesity
or neutrophilia
IL = interleukin.
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.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Whiteboard Presentation

Please scan the QR code below to view a brief depiction exploring underlying pathology of Asthma

Common Causes of Uncontrolled Asthma

Nonadherence to therapy[1]	Incorrect inhaler technique[1]	Comorbidities and psychosocial factors[1]	Ongoing exposure to asthma triggers[1]

1. GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.
2. Bourdin A, et al. *Clin Exp Allergy*. 2012;42:1566-1574.

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]

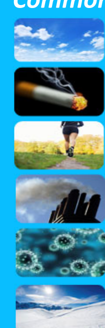
1. GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.
2. Bourdin A, et al. *Clin Exp Allergy*. 2012;42:1566-1574.

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) (https://acaai.org/asthma/types-asthma/allergic-asthma) and (https://acaai.org/asthma/types-asthma/nonallergic-asthma). Accessed 9/25/2020.

Treating the Whole Patient

Comorbidities Commonly Associated With Asthma

Comorbidities

- More health-care 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.

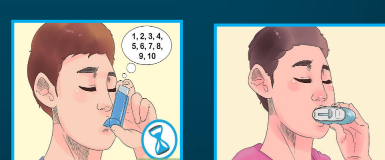
Boulet LP. *Eur Respir J*. 2009;33:897-906. Galli E, et al. *Allergy Asthma Proc*. 2007;28:540-543. Porsbjerg C, Menzies-Gow, A. *Respirology*. 2017;22:651-661. Sundh J, et al. *Respir Med*. 2017;132:154-160.

Proper Inhaler Technique

Poor inhaler technique leads to:

- Poor asthma control
- Increased risk of exacerbations
- Increased adverse effects

- 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



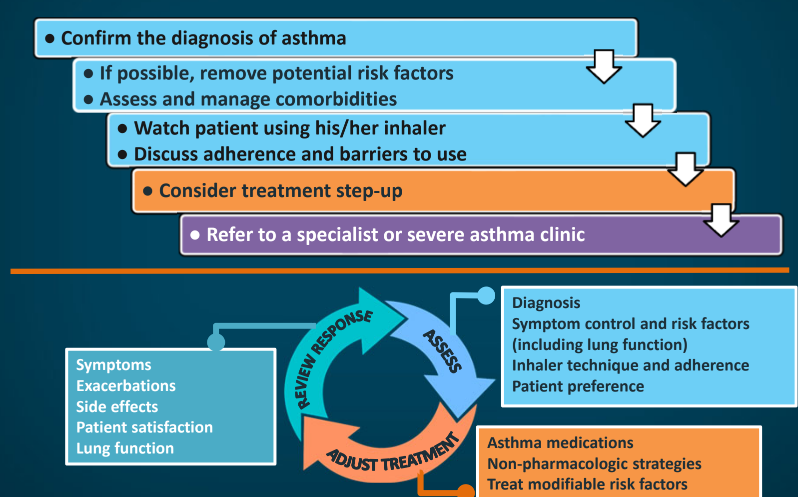
GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.

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 (pMDI), prescribe a spacer or valved holding chamber • Avoid multiple different 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

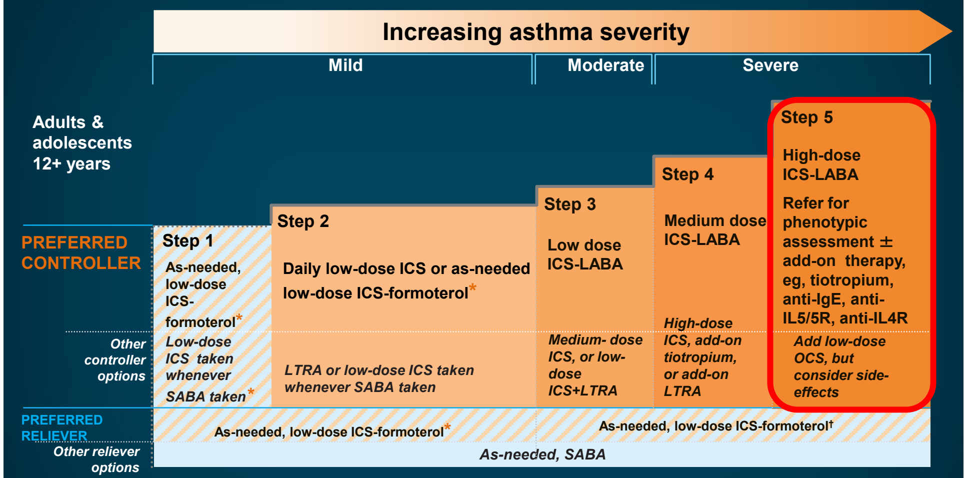
GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.

GINA Recommends Control-Based Asthma Management Strategy
Continuous Team-Based Process



GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.

GINA 2020: Stepwise Treatment Approach



*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; SABA = short-acting β_2 agonist.

Adapted from GINA. 2020. (https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf). Accessed 9/24/2020.

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-5 receptor	SIROCCO/CALIMA/ ZONDA	≥12 years	SC	Q4W/Q8W	COPD
Dupilumab	IL-4 receptor†	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	SC	Q2W/Q4W	Atopic dermatitis

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

DP2 = prostaglandin D2; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily; SC = subcutaneous; EGPA = eosinophilic granulomatosis with polyangiitis; HES = hypereosinophilic syndrome.

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

Whiteboard Presentation

Please scan the QR code below to view a brief depiction exploring Current Inflammatory Targets; Monoclonal Antibodies for IgE, IL-4, IL-5, and IL-13

Case 1: Brittany

- 32-year-old woman with a history of eczema and childhood asthma, improved and not requiring meds in her teenage years, but symptoms returned and have been present since her mid-20s
  - Using rescue inhaler 3-4 times/day for cough/wheezing/shortness of breath
  - No nighttime awakenings
- Taking ICS/LABA and LAMA (technique good on assessment)
  - Leukotriene-receptor modifier and antihistamines and nasal steroid for allergies
- Already addressed/completed all environmental control measures
- Labs
  - FEV_1 = 62% (postbronchodilator) with 8% improvement
  - IgE = 390 IU/mL
  - FeNO = 28 ppb
  - Perennial allergen testing: + mold, oak, ragweed, cat dander, and dust mites
  - CBC normal, absolute eosinophil count of 100 cells/microliter

Which biologic(s) would be most appropriate for Brittany?

GINA: Identifying Patients and Selecting Biologic

Type 2 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:

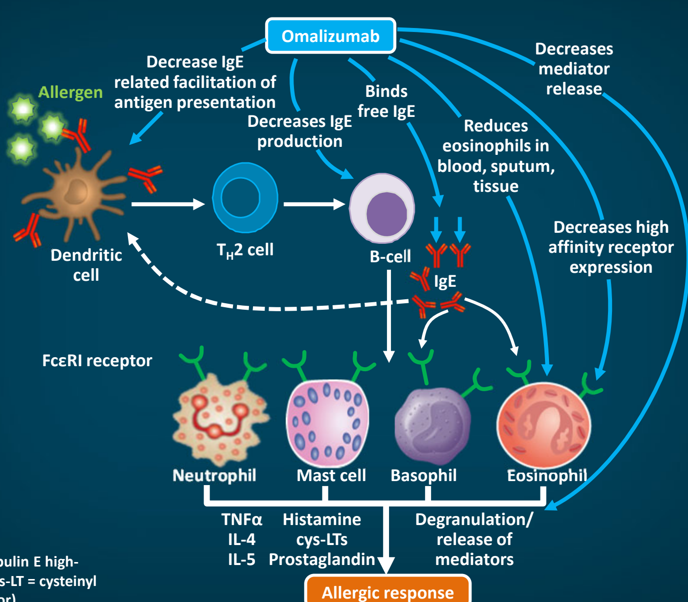
- Ages ≥6 years
- Severe allergic asthma
- Sensitization on skin-prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

Predictors of good response:

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

GINA. 2019 Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 9/25/2020.

Targeting IgE



FcεRI = immunoglobulin E high-affinity receptor; cys-LT = cysteinyl leukotriene (receptor).

Adapted from Edwards M, et al. *Eur Res J*. 2017;49:1602448. Holgate S, et al. *Resp Med*. 2009;103:1098-113.

Omalizumab

- For patients with asthma uncontrolled despite high-dose ICS and LABA and who are adherent to therapy and demonstrate good inhaler technique
- Mechanism of action
  - Inhibits serum IgE by binding to its constant region, preventing interaction with high- and low-affinity IgE receptors
- Efficacy
  - **Reduces free serum IgE by >95%**
  - Results in reduction of receptor density on the mast cells or basophils, leading to decreased allergen-stimulated mediator response
- Administration
  - Always done in healthcare setting by trained healthcare staff

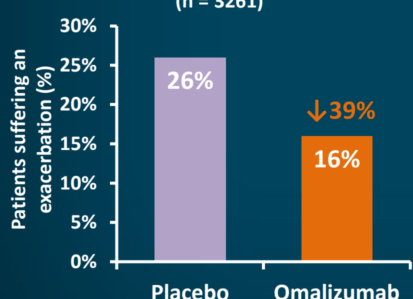
Al Said A, et al. *Ther Adv Chronic Dis*. 2017;8:31-45.

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

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

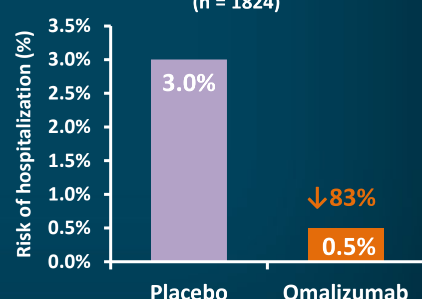
Exacerbations

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.

Case 2: Brian

- 56-year-old man with adult-onset asthma diagnosed 5 years ago
- Presence of nasal polyps, no significant allergy symptoms, no GERD
- Intermittent dyspnea and wheezing with nonproductive cough, worse over the last 6-9 months
  - No changes at home: no pets; environmental measures controlled at home
- Compliant with ICS/LABA/LAMA and good inhaler technique
- Labs
  - IgE = 12 IU/mL
  - FeNO = 22 ppb
  - Allergens negative
  - CBC with absolute eosinophil count of 400 cells/microliter

Which biologic(s) would be most appropriate for Brian?

GINA: Identifying Patients and Selecting Biologic

Type 2 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:

- Ages ≥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-IL5 or anti-IL5R therapy if:

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

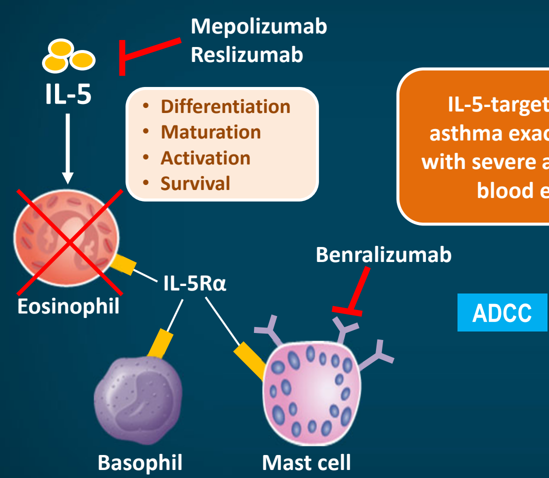
Predictors of good response:

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

*Baseline IgE levels do not predict likelihood of response.

GINA. 2019 Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 9/25/2020.

Targeting IL-5



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

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.

Mepolizumab

- Mechanism of action
  - Selectively inhibits eosinophilic inflammation
  - Reduces the number of eosinophils in sputum and blood
- Efficacy
  - May lead to reduction in exacerbations and need for treatment with systemic glucocorticoids
- Safety
  - Adverse events: nasopharyngitis, headache, URTI, sinusitis

- **Approved as add-on maintenance therapy for severe eosinophilic asthma**
- **Subcutaneous dosing is 40 mg Q4W for ages 6–11 years and 100 mg Q4W for ages ≥12 years.**

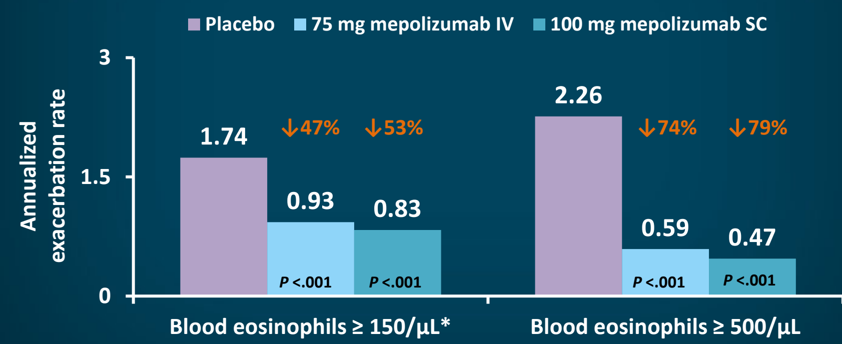
URTI = upper respiratory tract infection.

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207. Mepolizumab (Nucala®) PI 2019. www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed 9/25/2020.

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

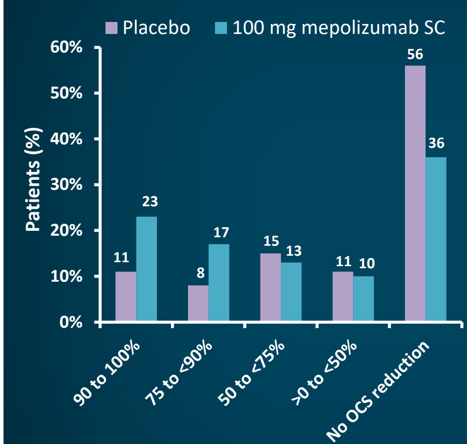


*Eosinophil count ≥150/µL at screening or ≥300/µL within previous year.

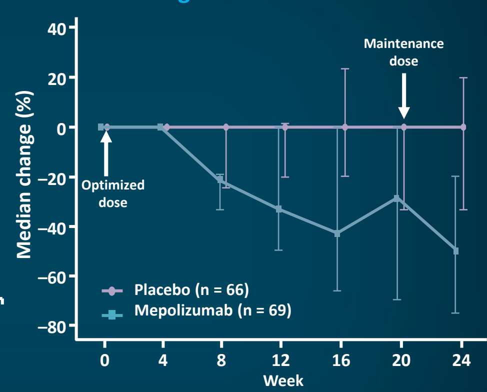
Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207.

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.

Reslizumab

- Indicated as add-on maintenance treatment for severe asthma of eosinophilic phenotype
- Mechanism of action
  - IL-5 antagonist reslizumab binds to the alpha chain of the IL-5 receptor on the eosinophil surface, inhibiting the proliferation of eosinophils
- Adverse events
  - Most common includes oropharyngeal pain

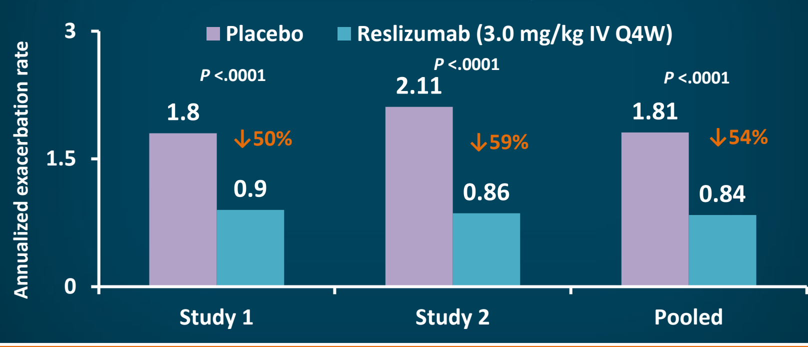
Approved as add-on maintenance therapy for patients ≥18 years old with severe eosinophilic asthma; dosing at 3 mg/kg IV Q4W

Hom S, Pisano M. *P T*. 2017;42:564-568. Reslizumab (Cinqair®) PI 2020 (www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf). Accessed 9/25/2020.

Reslizumab in Moderate-to-Severe Eosinophilic Asthma

2 multicenter trials involving 953 patients ≥12 years with eosinophilic asthma (≥400 cells/µL) inadequately controlled by medium-to-high dose ICS-based therapy

Reduced exacerbation rate vs placebo



Lung function, asthma control, and QoL were also significantly improved in both studies

QoL = quality of life.

Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Benralizumab

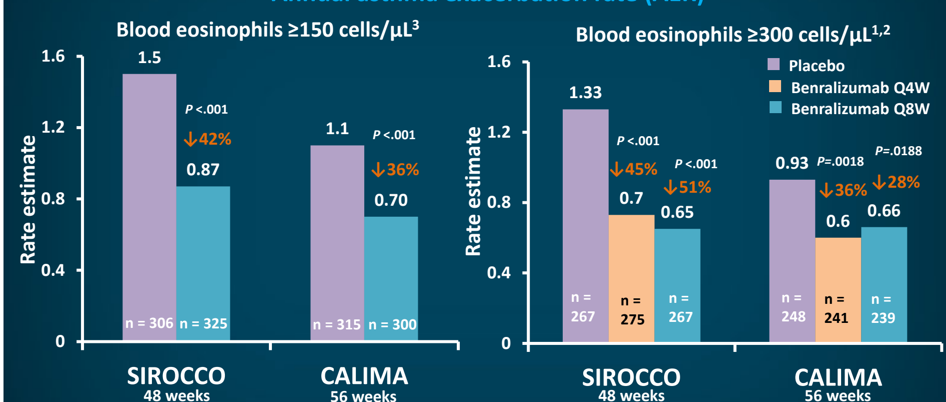
- Humanized IgG1κ mAb
- Indicated for add-on maintenance treatment of patients ≥12 years of age with severe asthma and with eosinophilic phenotype[1]
- WINDWARD program
  - Six phase 3 studies included in the program to evaluate the safety and efficacy of benralizumab[2]
    - SIROCCO
    - CALIMA
    - ZONDA
    - BORA
    - BISE
    - GREGALE

1. Benralizumab (Fasenra®) PI 2019. (www.azpicentral.com/fasenra/fasenra.pdf). Accessed 9/25/2020. 2. Pelaia C, et al. *Drug Des Devel Ther*. 2018:12:619-628.

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])

Annual asthma exacerbation rate (AER)

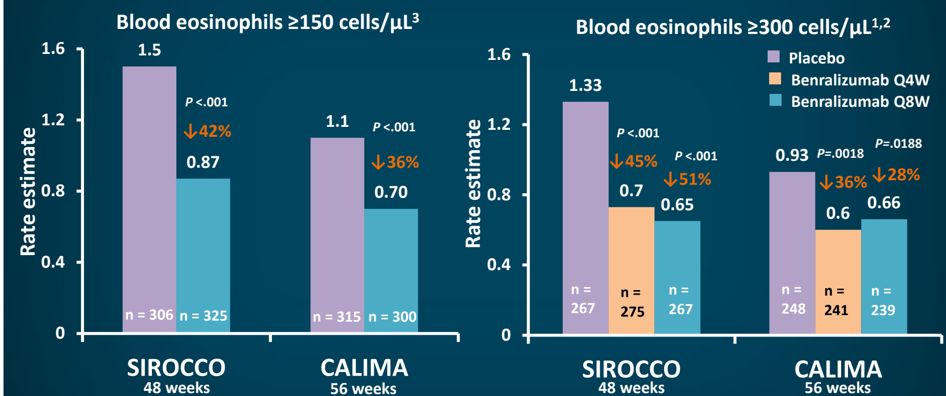


1. Bleecker ER, et al. *Lancet.* 2016;388:2115–2127. 2. FitzGerald JM, et al. *Lancet*. 2016;388:2128-2141. 3. Goldman M, et al. *Curr Med Res Opin*. 2017;33:1605-1613. 4. FitzGerald JM, et al. *Lancet Respir Med.* 2018;6:51-64.

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])

Annual asthma exacerbation rate (AER)



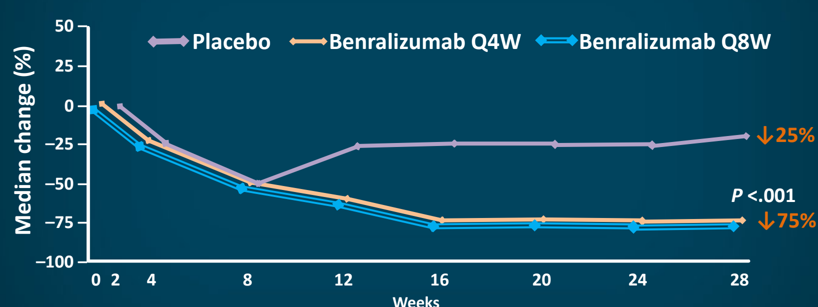
Pooled analysis: Benralizumab ↓AER, ↑FEV_1, and improved symptoms; subanalyses suggested OCS use and nasal polyposis were associated with ↑ response.[4]

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

OCS dose reduction



Annual 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.

Case 3: Barry

- 21-year-old with severe asthma
- 3 exacerbations within the past year
- Medications
  - ICS/LABA/LAMA, prednisone 20 mg q day
- Labs
  - FeNO = 30 ppb
  - CBC with absolute eosinophil count of 300 cells/microliter

Which biologic(s) would be most appropriate for Barry?

GINA: Identifying Patients and Selecting Biologic

Type 2 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:

- Ages ≥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-IL5 or anti-IL5R therapy if:

- Ages ≥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-IL4 if:

- Ages ≥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:

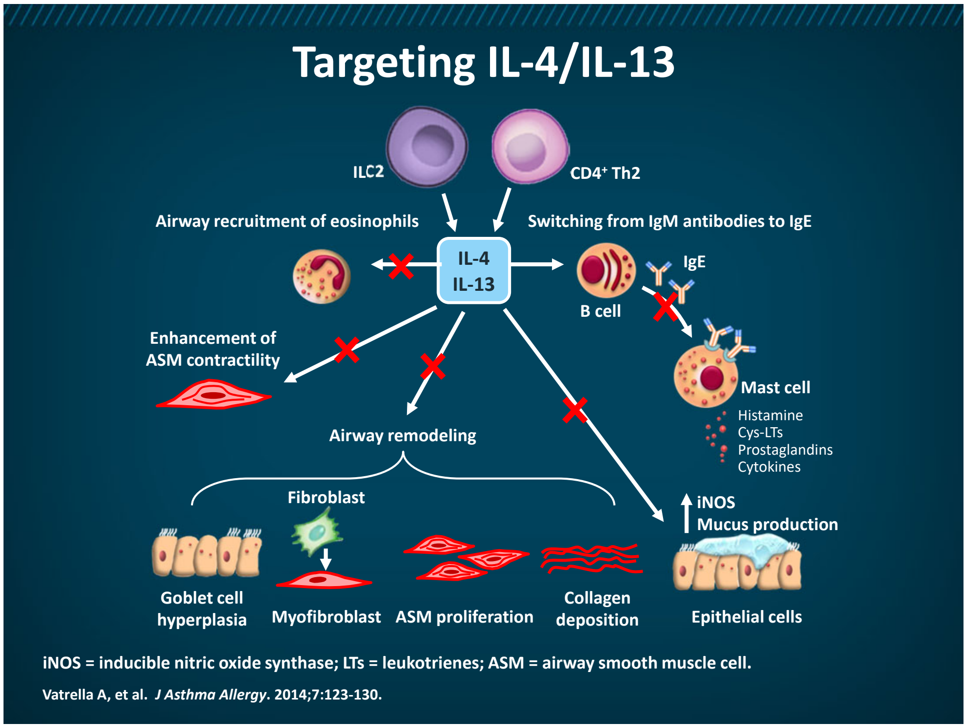
- Higher blood eosinophils
- Higher FeNO

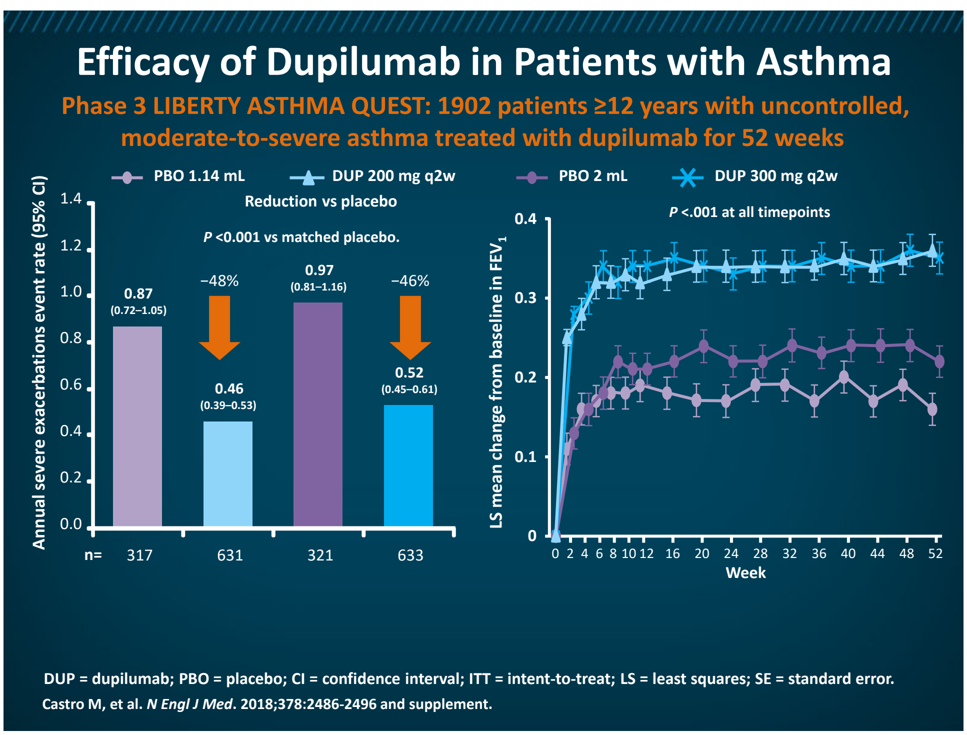
May also be used to treat:

- Moderate-to-severe atopic dermatitis
- Nasal polyps

*Baseline IgE levels do not predict likelihood of response.

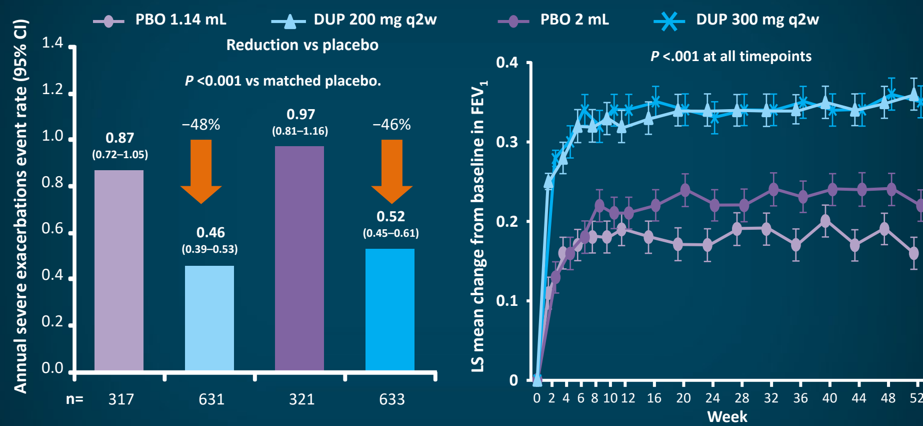
GINA. 2019. Difficult-to-treat severe asthma in adolescents and adult patients: diagnosis and management (https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf). Accessed 9/25/2020.


Targeting IL-4/IL-13
ILC2
CD4+ Th2
Airway recruitment of eosinophils
Switching from IgM antibodies to IgE
IL-4
IL-13
IgE
B cell
Enhancement of
ASM contractility
Mast cell
Histamine
Cys-LTs
Prostaglandins
Cytokines
Airway remodeling
Fibroblast
iNOS
Mucus production
Goblet cell
hyperplasia
Myofibroblast
ASM proliferation
Collagen
deposition
Epithelial cells
iNOS = inducible nitric oxide synthase; LTs = leukotrienes; ASM = airway smooth muscle cell.
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 ≥12 years with uncontrolled,
moderate-to-severe asthma treated with dupilumab for 52 weeks
PBO 1.14 mL
DUP 200 mg q2w
PBO 2 mL
DUP 300 mg q2w
Reduction vs placebo
P <0.001 vs matched placebo.
Annual severe exacerbations event rate (95% CI)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.87
(0.72–1.05)
−48%
0.46
(0.39–0.53)
0.97
(0.81–1.16)
−46%
0.52
(0.45–0.61)
n=
317
631
321
633
P <.001 at all timepoints
LS mean change from baseline in FEV1
0.4
0.3
0.2
0.1
0
0 2 4 6 8 10 12 16 20 24 28 32 36 40 44 48 52
Week
DUP = dupilumab; PBO = placebo; CI = confidence interval; ITT = intent-to-treat; LS = least squares; SE = standard error.
Castro M, et al. N Engl J Med. 2018;378:2486-2496 and supplement.

Efficacy of Dupilumab in Patients with Asthma

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



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

DUP = dupilumab; PBO = placebo; CI = confidence interval; ITT = intent-to-treat; LS = least squares; SE = standard error.

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

Dupilumab in Patients With Uncontrolled Asthma, Efficacy by Subgroup

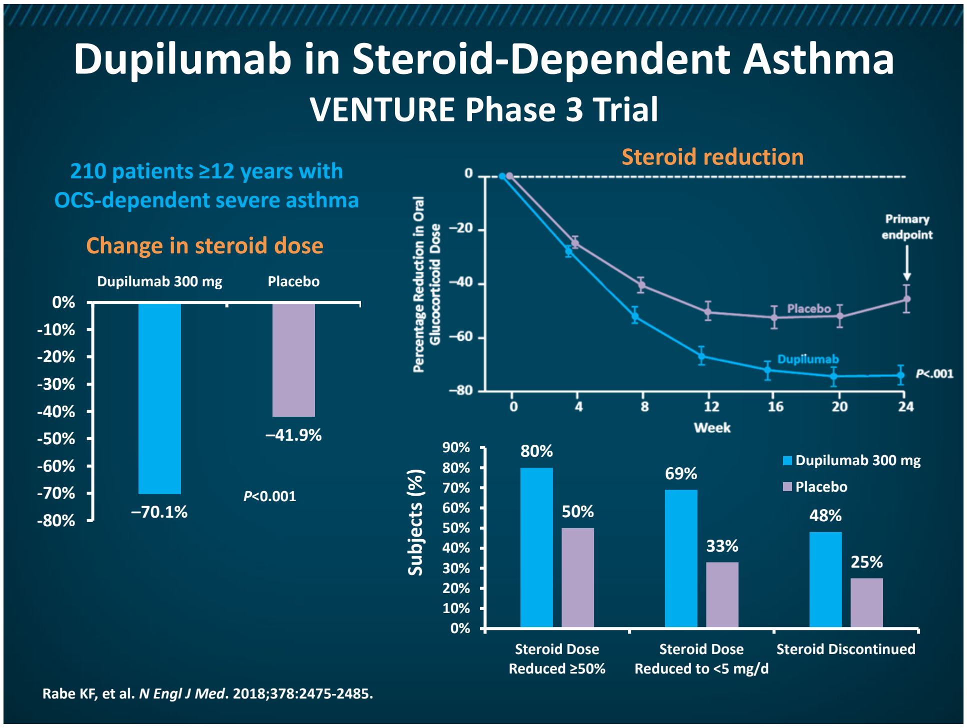
LIBERTY ASTHMA QUEST Phase 3 Trial

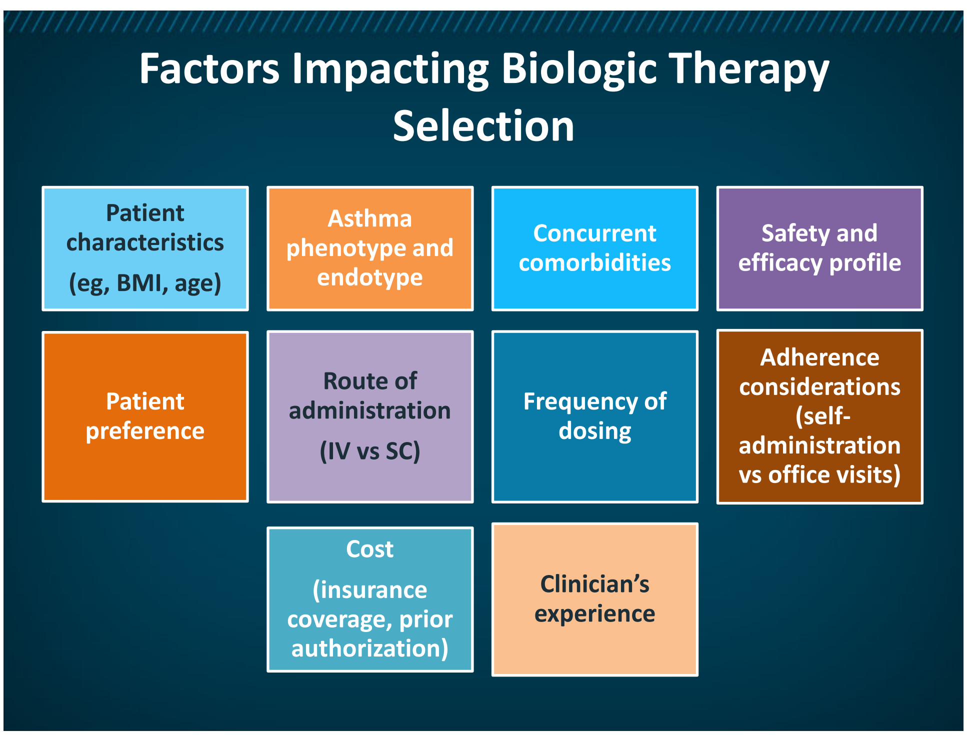
Subgroup	PBO	DUP 200 mg Q2W	RR vs PBO (95% CI)	PBO	DUP 300 mg Q2W	RR vs PBO (95% CI)
Overall	317	631	0.52 (0.41–0.66)	321	633	0.54 (0.43–0.68)
Eosinophil count (cells/mm³)						
≥300	148	264	0.34 (0.24–0.48)	142	277	0.33 (0.23–0.45)
≥150–<300	84	173	0.64 (0.41–1.02)	95	175	0.56 (0.35–0.89)
>150	85	193	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)

0.1 0.25 0.5 0.75 1 1.5 2 — Dupilumab better ← → Placebo better

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 ≥12 years with OCS-dependent severe asthma
Change in steroid dose
Dupilumab 300 mg
Placebo
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
−70.1%
−41.9%
P<0.001
Steroid reduction
Percentage Reduction in Oral Glucocorticoid Dose
0
−20
−40
−60
−80
Primary endpoint
Placebo
Dupilumab
P<.001
0
4
8
12
16
20
24
Week
Subjects (%)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
80%
50%
69%
33%
48%
25%
Dupilumab 300 mg
Placebo
Steroid Dose Reduced ≥50%
Steroid Dose Reduced to <5 mg/d
Steroid Discontinued
Rabe KF, et al. N Engl J Med. 2018;378:2475-2485.


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

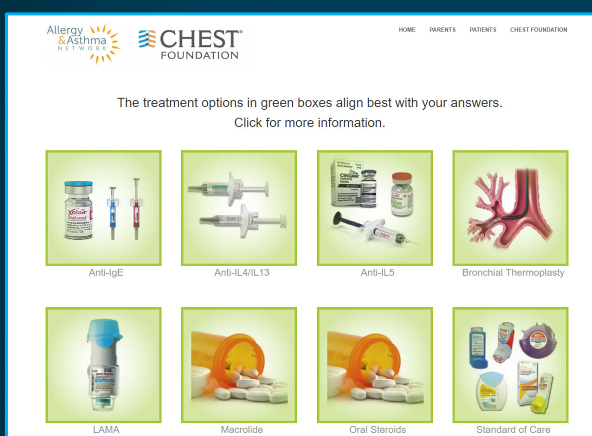
Treatment
- Frequency and route
- Safety and side effects
- Long-term effectiveness
- Unawareness and fear

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: SDM Tool



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

http://asthma.chestnet.org/sdm-tool/

SDM = shared decision-making.

CHEST Foundation (http://asthma.chestnet.org/sdm-tool/). Accessed 9/25/2020.

Treatment of T2-Low Asthma

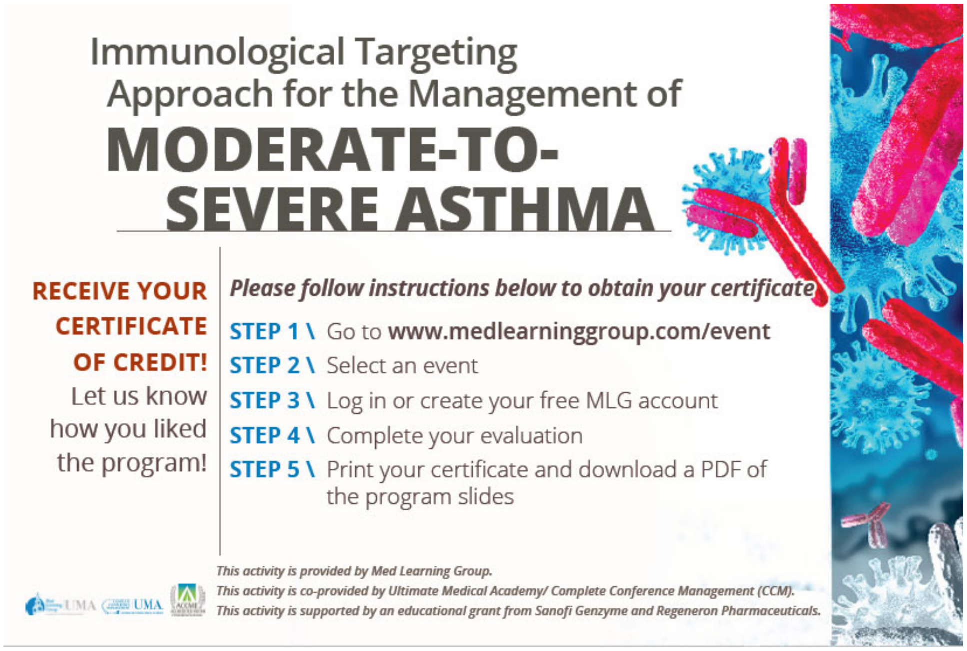
~40% to 50% of asthma patients **do not** have type 2 inflammation

- 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 quality of life** in various severe asthma cohorts
  - Five 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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Thank You!

Moderate-to-Severe Asthma: Identification, Diagnosis and Management

Resource	Address
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Nanda A, et al. Asthma in Adults. *Med Clin North Am*. 2020;104(1):95-108.	https://pubmed.ncbi.nlm.nih.gov/31757240/
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Zayed Y, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma*. 2019;56(10):1110-9.	https://pubmed.ncbi.nlm.nih.gov/30273510/
Zein J, et al. Asthma over the Adult Life Course: Gender and Hormonal Influences. *Clin Chest Med.* 2019;40(1):149-61.	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