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Conversations in **PULMONOLOGY**

Individualize and Reassess: Biologics for Severe Asthma





Faculty

Njira Lugogo, MD

Professor of Internal Medicine Division of Pulmonary & Critical Care Medicine Asthma Program Director University of Michigan Ann Arbor, MI





- Njira Lugogo has disclosed the following financial relationship:
 - Consultant: AstraZeneca, Sanofi, Teva, Regeneron, GSK, Amgen, NIOX, Genentech
 - Advisor: AstraZeneca, Sanofi, Teva, Regeneron, GSK, Amgen, NIOX, Genentech
 - Speaker: AstraZeneca, GSK
 - Contracted Research: Amgen, GSK, Genentech, AstraZeneca, Teva, Regeneron, Sanofi
 - All her disclosures are related to respiratory

Faculty, planners, and guest patient(s) (if applicable) for this educational activity not listed in the Summary of Individual Disclosures above have no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

All relevant financial relationships and potential conflicts of interest have been mitigated.

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Learning Objectives



Discuss the relationship between pathophysiology, phenotypes/endotypes, and biological agent treatment targets in asthma

Individualize the selection of biologic agent for patients with severe asthma based on phenotype, comorbidities, and SDM Assess treatment response to biologic therapy using quantitative measures, noting the relationship between persistent symptoms and common comorbidities



Pre-test Questions



Pre-AB1: Which of the following characteristics is the best predictor for response to anti-IL-5 therapy in a patient with severe asthma?

- A. IgE > 30 IU/mL
- B. Blood eosinophils > 1500 cells/ μ L
- C. Comorbid eosinophilic esophagitis
- D. Fractional exhaled nitric oxide (FeNO) > 50 ppb

Pre-AB2: Which of the following characteristics in a patient with severe asthma suggests high risk for exacerbations?

- A. IgE > 150 IU/mL
- B. Blood eosinophils > 400 cells/ μ L
- C. Need for high-dose ICS/LABA/LAMA
- D. Comorbid atopic conditions (e.g., allergy, atopic dermatitis)



Pre-AB3: 33 y/o male with severe asthma has been referred for evaluation for biologic therapy. Reports daily symptoms and SABA use.

PMH: Asthma (3 exacerbations in past year), eosinophilic esophagitis

Meds: High-dose ICS/LABA/LAMA, albuterol prn, PPI

Labs: Blood eosinophils 320 cells/µL, IgE 120 IU/mL, FeNO 65ppb, negative allergy testing.

Which biologic would be most appropriate to initiate?

- A. Benralizumab
- B. Dupilumab
- C. Omalizumab
- D. Reslizumab



Pre-AB4: 40 y/o female returns for follow-up after starting biologic agent 12 months ago.

Reports asthma symptoms are well controlled. No exacerbations in past year.

- **PMH:** Severe asthma, seasonal allergies.
- Meds: High-dose ICS/LABA, mepolizumab
- FEV1 80% predicted. ACT score 23.

The patient asks if he can reduce or stop any medications. What would you recommend?

- A. Continue biologic and current inhaler therapy
- B. Continue biologic, change inhaler to albuterol (rescue)
- C. Discontinue biologic, continue inhaler at current dose
- ⁹ D. Continue biologic, change inhaler to medium-dose ICS/LABA

Pre-AB5: Please rate your overall level of confidence in your responses to the previous questions.

- A. Very confident (4)
- B. Confident (3)
- C. Somewhat confident (2)
- D. Not at all confident (1)



Pre-AB6: How confident are you in your ability to adjust biologic therapy with respect to response in patients with severe asthma?

- A. Very confident (4)
- B. Confident (3)
- C. Somewhat confident (2)
- D. Not at all confident (1)

Pre-AB7: How often do you consider biomarkers when assessing patients with severe asthma for biologic therapy?

- A. Always (4)
- B. Often (3)
- C. Rarely (2)
- D. Never (1)



Pre-AB8: Which of the following describes your perspective regarding the selection and use of biologic treatments for asthma? (choose all that apply)

- A. Overwhelmed by the breadth of literature and lack of clear guidelines
- B. Worried about long-term efficacy and safety of biologic agents
- C. Hopeful that asthma might be a disease that can be treated to remission
- D. Empowered by the number and variety of biologic treatments available



Inflammation, Patient Characterization, Targets, and Treatments



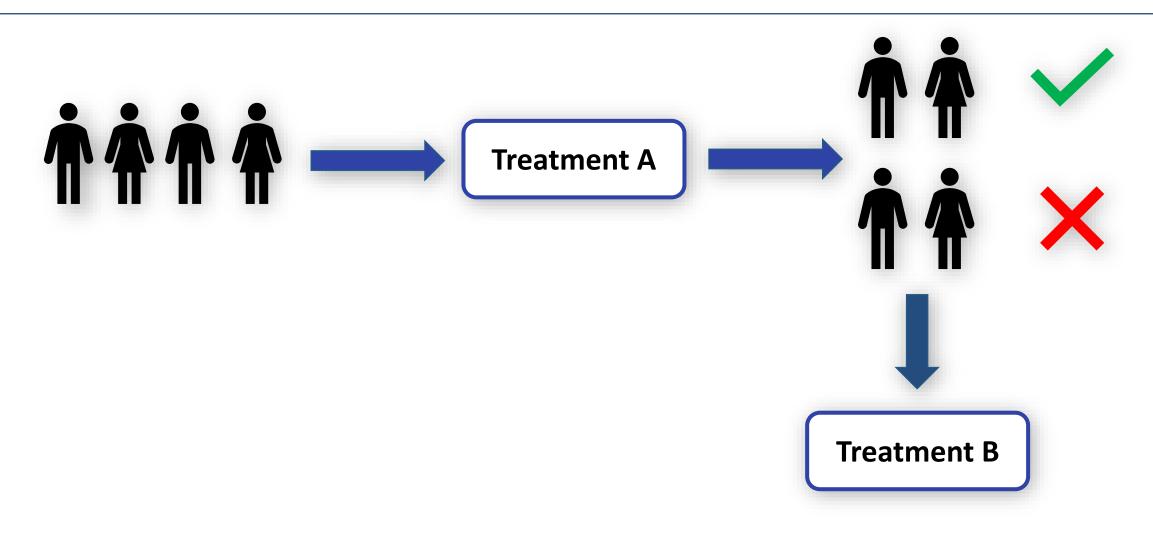
Definitions of Severe Asthma

- Difficult-to-treat asthma:
 - Asthma with uncontrolled symptoms/frequent exacerbations due to modifiable factors or untreated coexisting conditions
- Severe asthma:
 - Requires high-dose ICS + LABA or systemic corticosteroids for ≥ 50% of the year OR asthma that is "uncontrolled" despite these therapies
 - Other components:
 - ≥ 2 exacerbations/year OR 1 requiring hospitalization or ICU
 - FEV1 <80%

Chung KF, et al. *Eur Respir J*. 2014;43:343-373.; Brusselle GG, et al. *N Engl J Med*. 2022;386(2):157-171; GINA. Global Strategy for Asthma Management and Prevention; 2021. Available at: www.ginaasthma.org

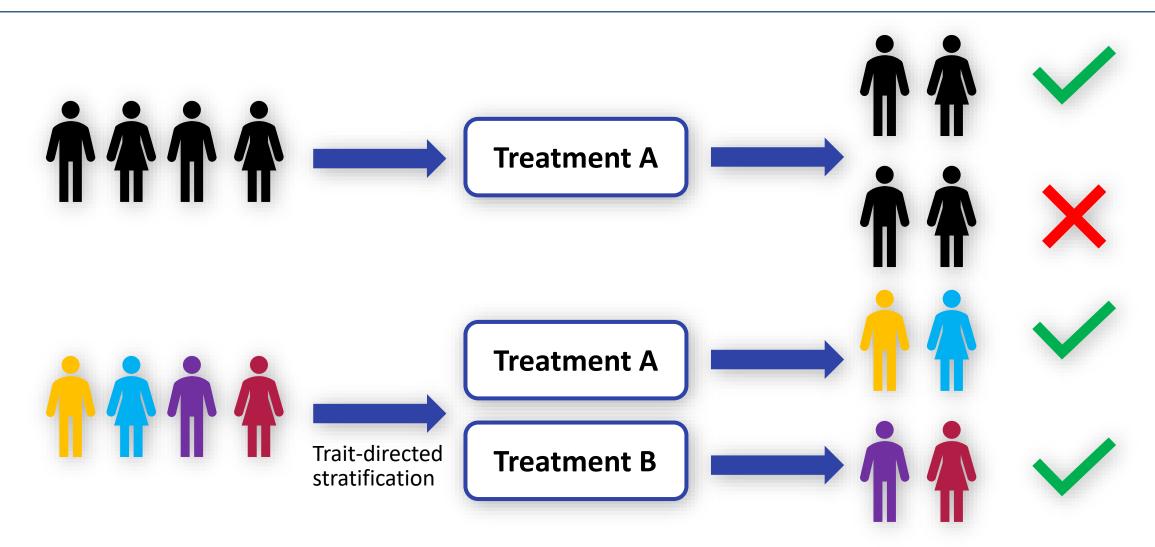
Previous Approach to Asthma Treatment





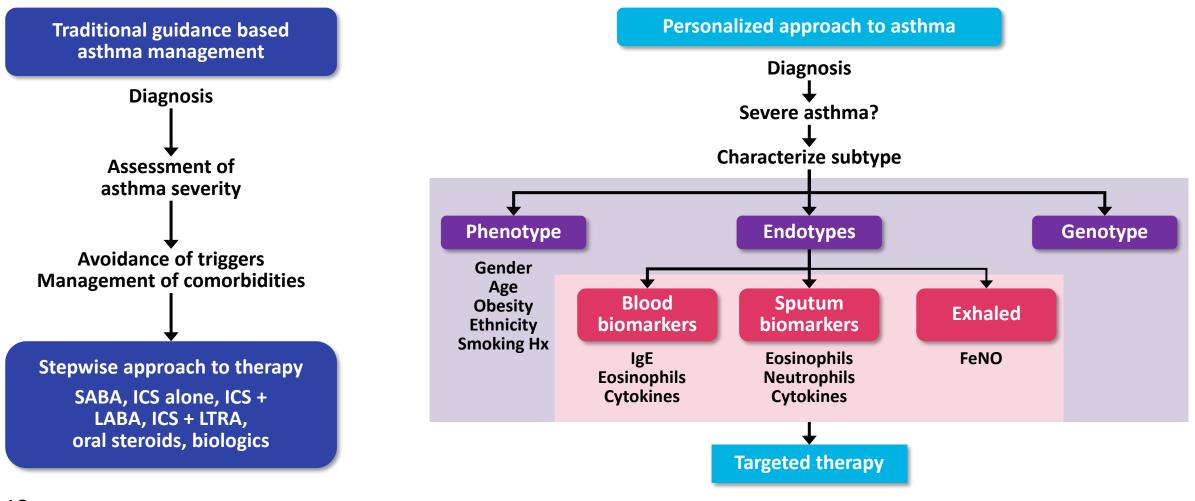
New Approach to Asthma Treatment





Approach to Severe Asthma Therapy





Dunn & Wechsler. Clin Pharmacol Ther. 2015 Jan;97(1):55-65



Biomarkers in Severe Asthma

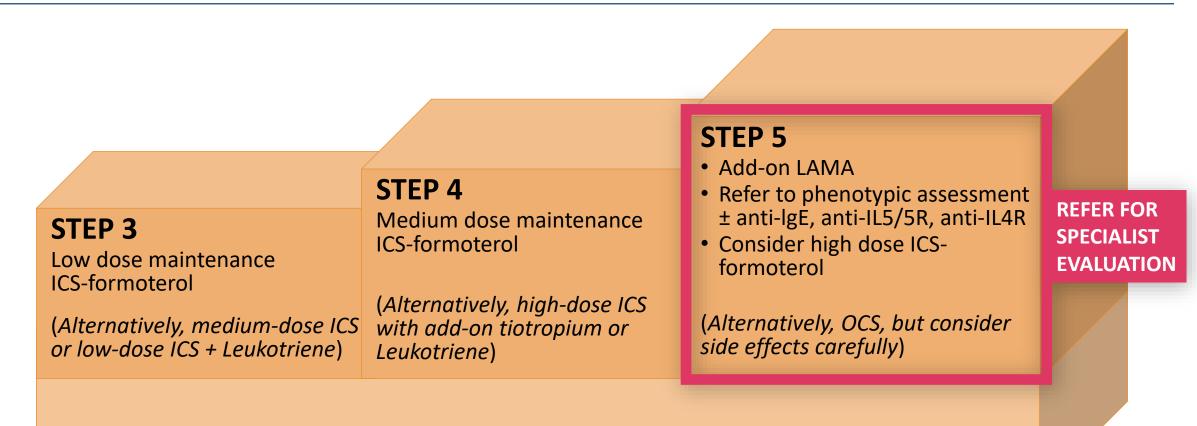
Biomarker	T2 Levels			Limitations
	Low	Medium	High	Littitations
Total IgE (IU/mL)	< 30	31-149	> 150	Affected by oral steroidsNot well-correlated with asthma severity or outcomes
Blood eosinophils (cells/μL)	< 150	151-399	> 400	 Decreased by OCS; slight reduction possible by ICS Elevations can be seen in other conditions Highly predictive of exacerbation risk
Sputum eosinophils (%)	—	—	≥3	 Confined to research settings
FeNO (ppb)	< 25	26-49	> 50	 Suppressed by ICS; less affected by OCS Affected by age, smoking, and respiratory infections Indicator of disease progression > exacerbation risk
Allergy testing in vitro or in vivo	-	+	+++	 Availability, variability from region to region

May repeat biomarkers up to 3 times (when asthma worsens or before oral steroids)

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

Step 5: Focus on Biologics and Move Away From Systemic Corticosteroids



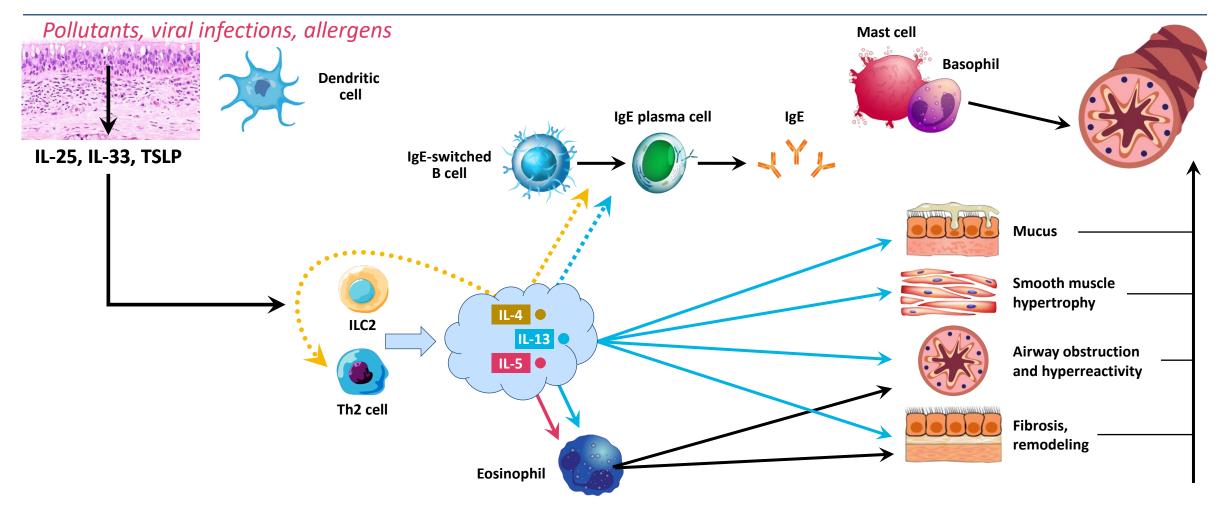


RELIEVER: As-needed low-dose ICS-formoterol OR As-needed short-acting beta agonist

GINA 2021, Box 3-4Bii: Starting asthma treatment in adults and adolescents



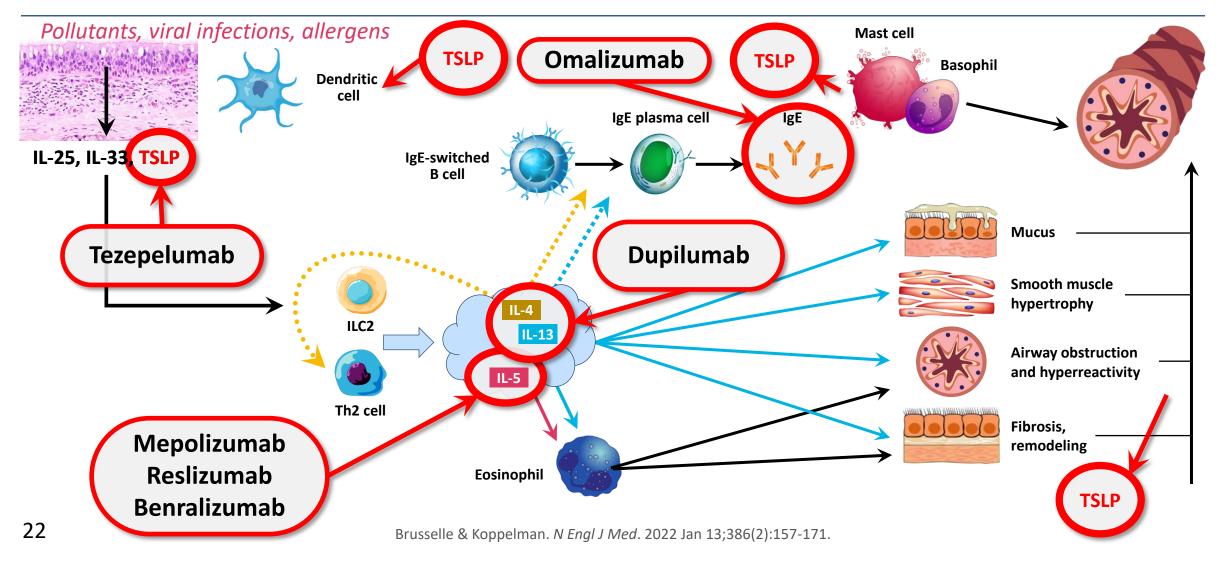
Effects of Type 2 Inflammation



Brusselle & Koppelman. N Engl J Med. 2022 Jan 13;386(2):157-171.



Effects of Type 2 Inflammation



Overview of Biologics in Severe Asthma



Biologic	Target	Treatable Traits	Approved For	
Omalizumab	lgE	IgE level (30-700 IU/ml) + perennial allergies	Moderate-to-Severe Asthma AND Chronic spontaneous urticaria, chronic rhinosinusitis w/nasal polyps, food allergy	
Mepolizumab	IL-5	Eosinophilic phenotype (> 150 cells/µL)	vere Asthma AND PA, HES, chronic rhinosinusitis with nasal polyps	
Reslizumab	IL-5	Eosinophilic phenotype (> 400 cells/µL)	Severe Asthma	
Benralizumab	IL-5R	Eosinophilic phenotype (> 150 cells/µL)	Severe Asthma	
Dupilumab	IL-4R	Eosinophilic phenotype (> 150 cells/μL)	Moderate-to-Severe Asthma AND Atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis	
Tezepelumab	TSLP	No specific biomarker threshold	Severe Asthma	

Brusselle & Koppelman. N Engl J Med. 2022 Jan 13;386(2):157-171.

Overview of Biologics in Severe Asthma



Biologic	Target	Treatable Traits	Approved For					
Omalizumab	nab IgE IgE Ievel (30-700 IU/ml) Moderate-to-Severe Asthma AND Chronic spontaneous urticaria, ch							
Меро	 Blood eosinophils are variable Dupilumab has indication for OCS-dependent asthma Mepolizumab/benralizumab/tezepelumab demonstrated to 							
	olizumak	o/benralizumab/teze	pelumab demonstrated to					
Meg	olizumak	o/benralizumab/teze	pelumab demonstrated to					

N Engl J Med. 2017;376:2448-58; Kavanaugh J et al. Chest. 2020:159(2):496-506; Sher LD et al. Chest. 2022;162(1):46-55.

Efficacy and Safety of Biologics in Moderate-To-Severe Asthma



Efficacy

- Multiple clinical studies:
 - ↑ Quality of life
 - Exacerbations
 - ER visits
 - Hospitalizations
 - ✤ Steroid requirements

Safety

- Very low incidence of side effects in trials (< 3%), including:
 - Headache
 - Nasopharyngitis
 - Injection-site reactions
 - Ocular effects (dupilumab, in atopic dermatitis patients)
 - Rare anaphylactic reactions

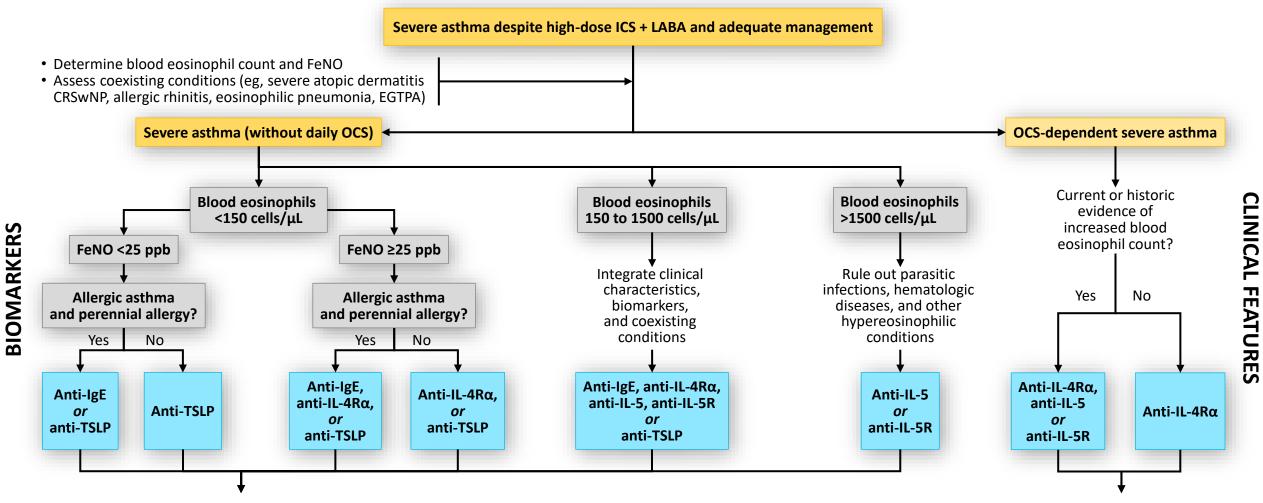
Maselli DJ, et al. *J Asthma Allergy*. 2016 Aug 31;9:155-62; Maselli DJ, et al. *Ther Clin Risk Manag*. 2018;14:2059-2068; Brusselle GG, et al. *N Engl J Med*. 2022 Jan 13;386(2):157-171; Fasenra (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019; Nucala [package insert]; Philadelphia, PA; GlaxoSmithKline LLC; September 2019; Cinqair. [package insert] West Chester, PA; Teva Respiratory, LLC; February 2020; Wechsler ME, et al. Respir Res. 2020; 21: 264; Dupixent. [Package insert]. Tarrytown, NY; Regeneron Pharmaceuticals, Inc; January, 2021; Xolair. South San Francisco, CA; Genentech USA, Inc; November 2020.



Selection of Biologic Therapies in Severe Asthma



Algorithms For Selecting Biologics

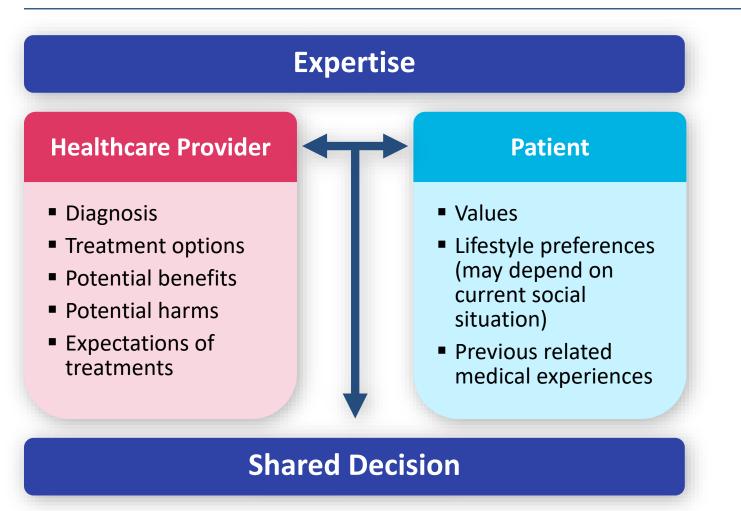


Brusselle G et al. N Engl J Med 2022; 386:157-71.

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Shared Decision Making Is Essential When Selecting Biologics





- Psychological benefits
 - Improved patient knowledge and understanding of risks
 - More active involvement
 - Less indecision
 - Improved understanding of patient goals/values
- Clinical benefits
 - Improved adherence
 - Better outcomes
- Health care resources benefits
 - Less healthcare resource utilization
 - Lower health care costs
 - Lower use of invasive options

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ARS Question 1 Case 1: Mr. Flannagan

- 62 y/o male with persistent asthma symptoms.
- PMH: Adult-onset severe asthma, nasal polyps s/p resection 2 years ago.
- 3 exacerbations in last year.
- Meds: High-dose ICS/LABA/LAMA, 10 mg prednisone daily, albuterol prn.
- **FEV1:** 60% predicted, 24% reversibility.
- ACT score: 8.
- Biomarkers: Blood eosinophils 280 cells/μL, FeNO 50 ppb, IgE 250 IU/mL.
- Negative allergy testing.

ARS-AB10: Which biologic would you consider for this patient?

- A. Anti-IgE (omalizumab)
- B. Anti-TSLP (tezepelumab)
- C. Anti-IL-4/IL-13 (dupilumab)
- D. Anti-IL-5 (benralizumab, mepolizumab, reslizumab)



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ARS Question 2 Case 2: Ms. Nguyen

- 42 y/o female with persistent asthma symptoms.
- PMH: Adult-onset severe asthma, chronic rhinosinusitis with nasal polyps.
- 4 exacerbations in past year.
- **Meds:** High-dose ICS/LABA, albuterol prn.
- **FEV1:** 58% predicted, 10% reversibility.
- ACT score: 13.
- Biomarkers: Blood eosinophils 1500 cells/μL, FeNO 20 ppb, IgE 35 IU/mL.
- Negative allergy testing.

ARS-AB11: Which biologic would you consider for this patient?

- A. Anti-IgE (omalizumab)
- B. Anti-TSLP (tezepelumab)
- C. Anti-IL-4/IL-13 (dupilumab)
- D. Anti-IL-5 (benralizumab, mepolizumab, reslizumab)



ARS Question 3 Case 3: Ms. Roberts

- 28 y/o female with persistent asthma symptoms.
- PMH: Childhood-onset severe asthma. Triggered by smoke, poor air quality.
- 2 exacerbations in past year.
- Meds: High-dose ICS/LABA/LAMA, albuterol prn.
- **FEV1:** 75% predicted, 24% reversibility.
- ACT score: 10.
- Biomarkers: Blood eosinophils 225 cells/μL, FeNO 65 ppb, IgE 250 IU/mL.
- Negative allergy testing.

ARS-AB12: Which biologic would you consider for this patient?

- A. Anti-IgE (omalizumab)
- B. Anti-TSLP (tezepelumab)
- C. Anti-IL-4/IL-13 (dupilumab)
- D. Anti-IL-5 (benralizumab, mepolizumab, reslizumab)





Practical Management of Biologic Therapy



- Use a **systematic** approach to each assessment:
 - Identify treatable traits (pulmonary, extrapulmonary)
 - Define treatment targets (patient and clinician)
 - Identify expected outcomes
 - Temper patient expectations (if necessary)
 - Define length of initial treatment trial (usually 4-6 months)
 - Monitor systematically and compare outcomes to targets
 - Regular follow-up intervals
 - Assess exacerbations, as well as PFTs, symptoms, medication use, triggers, etc.
 - Symptom Questionnaires (ACT, AIR-Q, ACQ)



- Clinically relevant, measurable, and modifiable traits
- May include genetic, biomarker, phenotypic, psychosocial, environmental, or behavioral factors that impact disease control or prognosis

Pulmonary

- Airflow limitation (PFTs)
- Eosinophilic airway inflammation
- Exacerbations
- Pulmonary infection
- Bronchiectasis

Extrapulmonary

- Upper airway disease (allergic rhinitis, rhinosinusitis, nasal polyps, vocal cord dysfunction)
- Obstructive sleep apnea
- GERD
- Obesity
- Atopic dermatitis



Defining Clinical Response to Biologic Therapy

Exacerbations

 Most biologics result in a 30%–55% reduction in severe asthma exacerbations¹

OCS sparing

Biologics show an OCS reduction¹

Achieving control

A modest change in ACQ/ACT is expected¹

Lung function improvement

- Not all patients experience improvements in FEV¹
- Expect the improvement in range of 114–320 mL (pre-bronchodilator), depending on the drug and individual patient factors^{2–4}

Achieving control

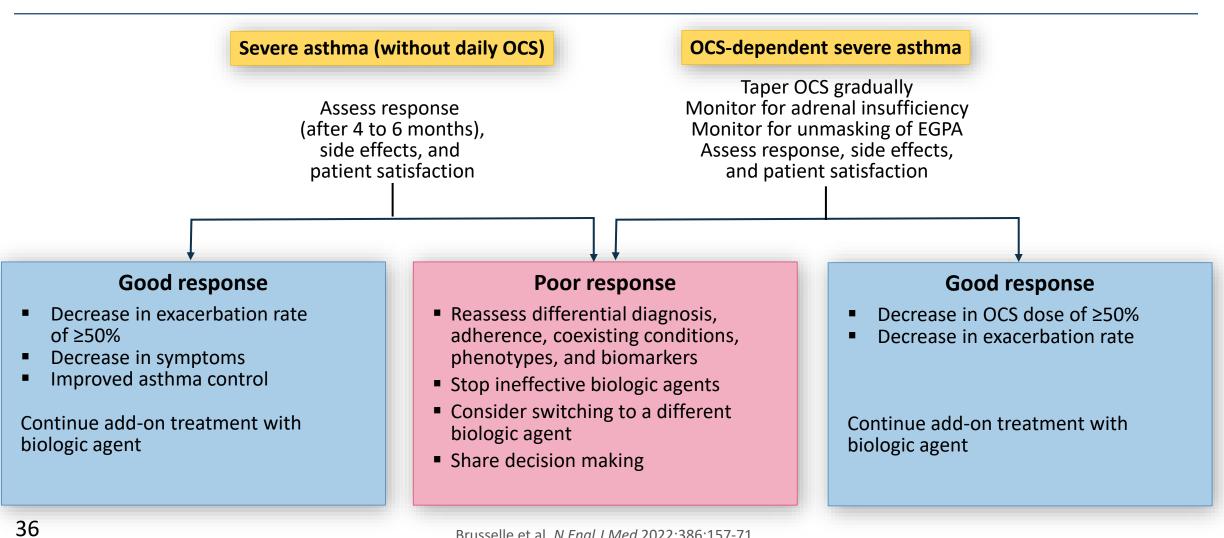
- Reduced ICS dose¹
- Assess side effects, affordability and patient satisfaction¹
- Reevaluate patients every 3–6 months¹

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); OCS, oral corticosteroid(s)

1. GINA 2019. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (Accessed 10 September 2019); 2. Nair P, et al. *N Engl J Med* 2017;376:2448–58; 3. Bel E, et al. *N Engl J Med* 2014;371:1189–97; 4. Rabe K, et al. *N Engl J Med* 2018;378:2475–85

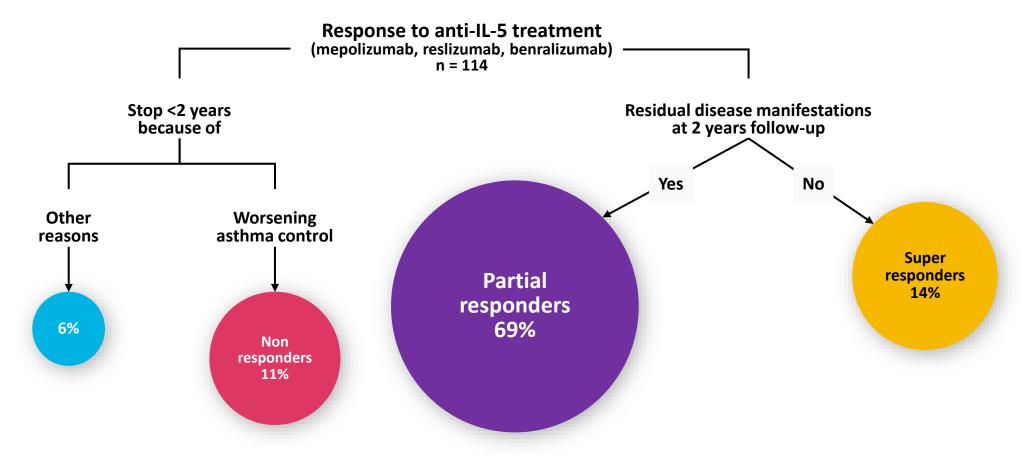
Assessing Response to Biologic Therapy







Response to Biologics Is Heterogenous



NP, nasal polyps; OR, odds ratio; BMI, body-mass index Eger K et al. *J Allergy Clin Immunol Prac.*2021;9(3):1194-1200.

Residual Disease in Partial Responders



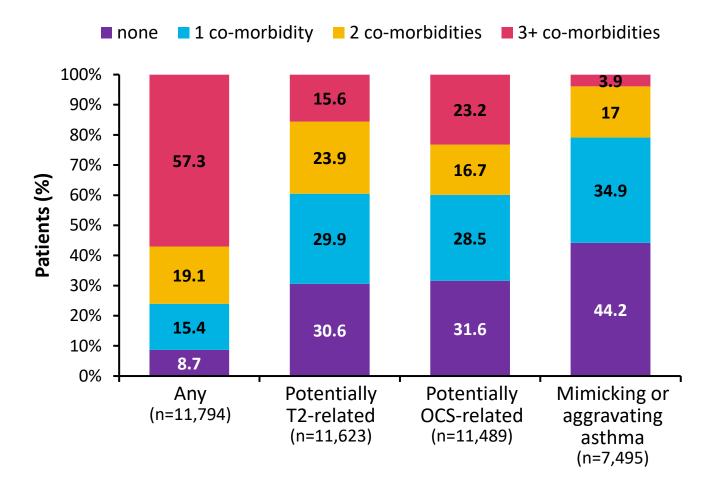
Clinical characteristics		Lung function	
ACQ score ≥1.5	<mark>48%</mark>	FEV ₁ <80%	<mark>59%</mark>
Surrogate Inflammation markers	S	Comorbidities	
Chronic OCS 32%		Sinonasal disease	<mark>58%</mark>
≥1 OCS burst 24%		Atopic disease 23%	
FeNO >50 26%		AI 10%	

ACQ, Asthma Control Questionnaire; OCS, oral corticosteroids; AI, adrenal insufficiency.

Eger K et al. J Allergy Clin Immunol Prac. 2021;9(3):1194-1200.



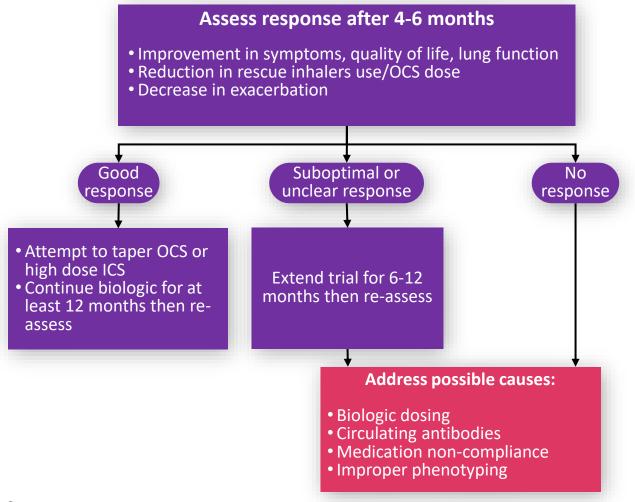
Impact of Comorbidities in Severe Asthma



- Analysis of International Severe Asthma Registry (N = 11,821)
- Clear relationship between number of comorbidities and extent of asthma outcome impairment
- Comorbidities were generally associated with OCS use and higher exacerbation rates, with variable impact on lung function and asthma control
- Chronic rhinosinusitis with nasal polyps was particularly associated with more exacerbations and OCS use



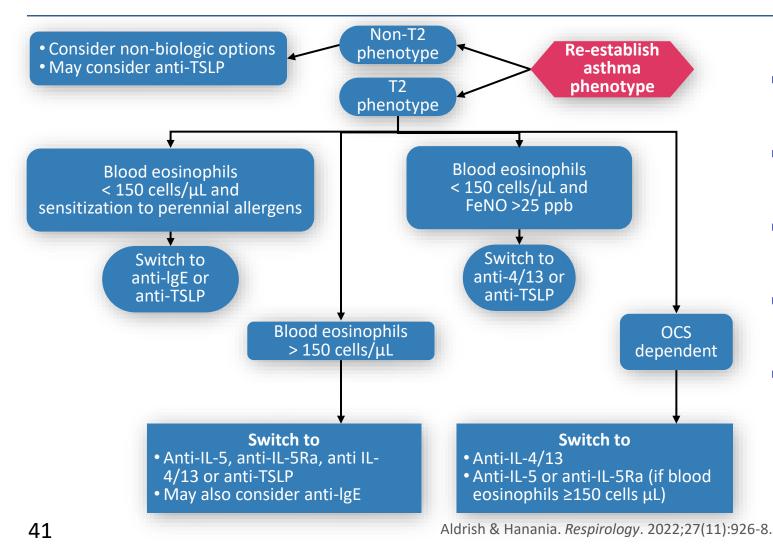
Assessing Biologic Response: A Proposed Algorithm



- No well-defined criteria for assessing biologic response
- Review asthma symptoms, exacerbations, OCS/ICS dose, lung function, and QoL
- Maintain biologic for 4–6 months before re-evaluation
- If response is intermediate or unclear, consider 6–12 month extension
- When response is suboptimal, assessment of biomarkers is recommended



Assessing Biologic Response: A Proposed Algorithm



- No well-defined criteria for assessing biologic response
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ARS Question 1 Case 1: Mr. Flannagan, Cont'd



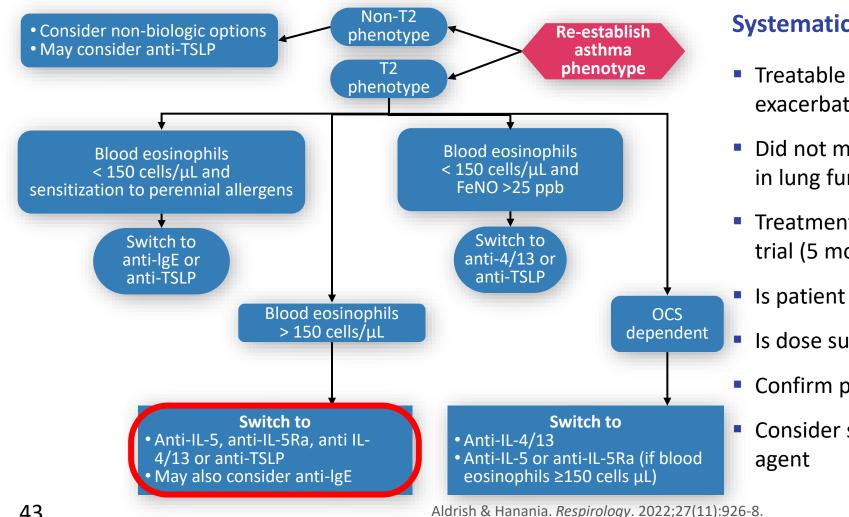
- 62 y/o male with persistent asthma symptoms.
- PMH: Adult-onset severe asthma, nasal polyps s/p resection 2 years ago.
- 3 exacerbations in last year.
- Meds: High-dose ICS/LABA/LAMA, 10 mg prednisone daily, albuterol prn.
- FEV1: 60% predicted, 24% reversibility.
- ACT score: 8.
- Biomarkers: Blood eosinophils 280 cells/μL, FeNO 50 ppb, IgE 250 IU/mL.
- Negative allergy testing.
 - Treated with benralizumab.
 - After 5 months, symptoms are unchanged. ACT score 7. FEV1 60% predicted. Continues to require OCS.

ARS-AB13: What would you recommend now?

- A. Maintain current therapy for 1 year
- B. Switch to anti-IgE agent (omalizumab)
- C. Switch to anti-TSLP agent (tezepelumab)
- D. Switch to anti-IL-4 agent (dupilumab)
- E. Switch between anti-IL-5 agents (mepolizumab, reslizumab)
- F. Repeat evaluation for environmental triggers, adherence, and allergies



Managing Biologic Nonresponse



Systematic assessment:

- Treatable traits: Airflow limitation, exacerbations, OCS use, eosinophilia
- Did not meet targets: No improvement in lung function, symptoms, or OCS use
- Treatment duration sufficient for initial trial (5 months)
- Is patient taking medication as prescribed?
- Is dose sufficient?
- Confirm phenotype/endotype?
- Consider switch to anti-IL-5 or anti-TSLP

ARS Question 2 Case 2: Ms. Nguyen, Cont'd



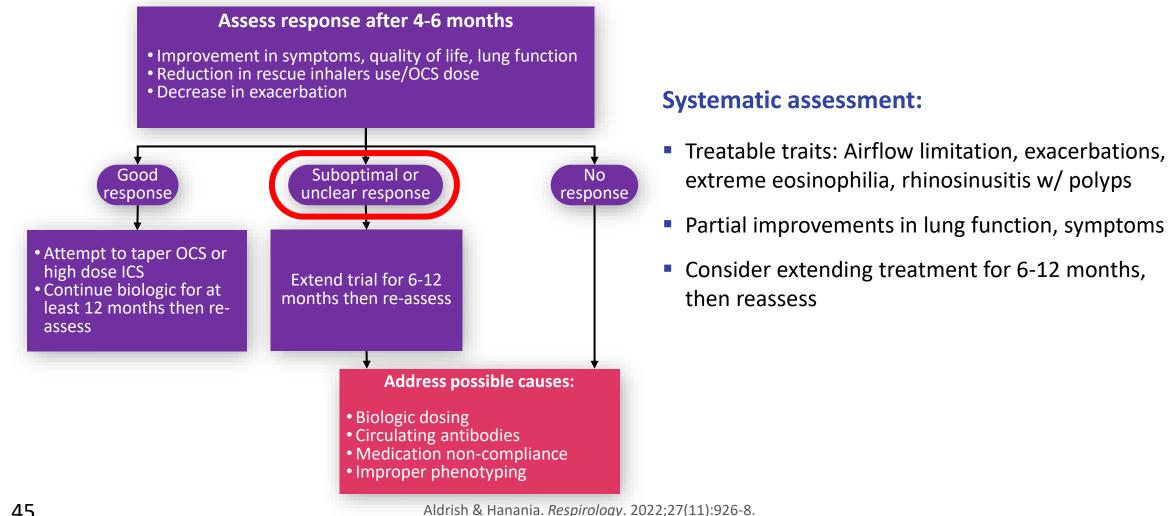
- 42 y/o female with persistent asthma symptoms.
- PMH: Adult-onset severe asthma, chronic rhinosinusitis with nasal polyps.
- 4 exacerbations in past year.
- Meds: High-dose ICS/LABA, albuterol prn.
- FEV1: 58% predicted, 10% reversibility.
- ACT score: 13.
- Biomarkers: Blood eosinophils 1500 cells/µL, FeNO 20 ppb, IgE 35 IU/mL.
- Negative allergy testing.
 - Treated with mepolizumab.
 - After 6 months, patient reports improved but residual symptoms. ACT score 18. FEV1 62% predicted.
 - No OCS and no exacerbations.

ARS-AB14: What would you recommend now?

- A. Start OCS taper
- B. Switch to alternative biologic
- C. Maintain current therapy and add LAMA
- D. Maintain current therapy and re-evaluate in 6-12 months
- E. Add therapy for rhinosinusitis with polyps and/or refer for surgical consultation

Managing Biologic Partial Response





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ARS Question 3 Case 3: Ms. Roberts, Cont'd



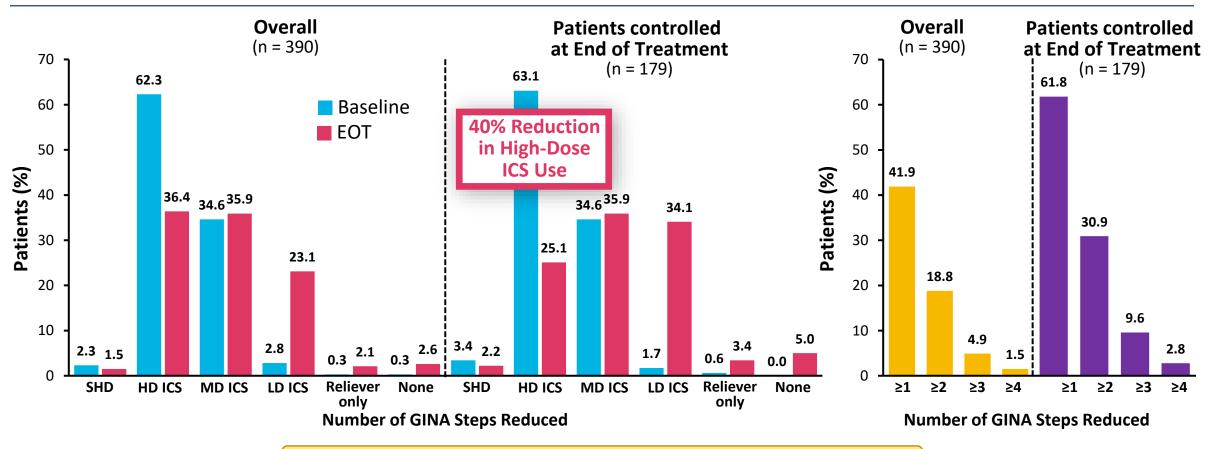
- 28 y/o female with persistent asthma symptoms.
- PMH: Childhood-onset severe asthma. Triggered by smoke, poor air quality.
- 2 exacerbations in past year.
- Meds: High-dose ICS/LABA/LAMA, albuterol prn.
- FEV1: 75% predicted, 24% reversibility.
- ACT score: 10.
- Biomarkers: Blood eosinophils 225 cells/μL, FeNO 65 ppb, IgE 250 IU/mL.
- Negative allergy testing.
 - Treated with dupilumab.
 - After 1 year, all symptoms well controlled. ACT score 23. No exacerbations in >12 months.
 - Patient asks if she can reduce or discontinue any therapies.

ARS-AB15: What would you recommend?

- A. Hold biologic, reduce dose of ICS/LABA
- B. Continue biologic and current inhaler therapy
- C. Continue biologic, change inhaler to albuterol (rescue)
- D. Hold next dose of biologic, continue inhaler at current dose
- E. Continue biologic, change inhaler to medium-dose ICS/LABA



Withdrawal of Background Therapy Post-Biologic



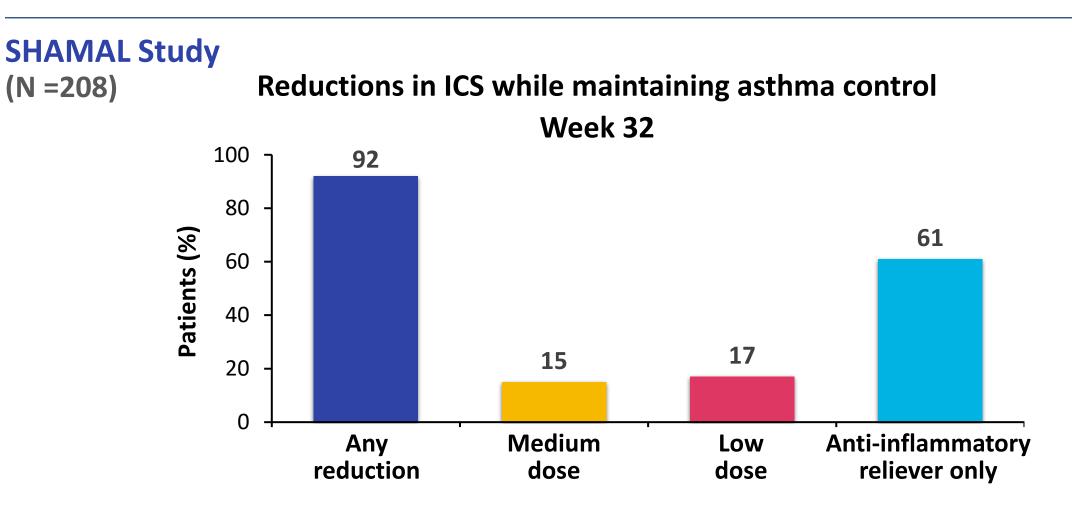
Asthma control: ACQ-6 <1.5 and no recent clinically significant exacerbations

SHD, supra-high dosage; HD, high dose; MD, medium dose; LD, low dose; ICS, inhaled corticosteroids.

Louis R et al. J Allergy Clin Immunol Pract. 2023;11(6):1759-70.

Can We Reduce Maintenance Medications?





Jackson DJ et al. Lancet. 2024;403(10423):271-81.



- ACAAI, American Academy of Asthma, AAAAI, and ATS (endorsed by EUFOREA)
- Consensus paper with expert opinion criteria for asthma remission
 - In the prior 12 months (all criteria must be present):
 - No exacerbations requiring medical visit/care and/or systemic corticosteroids
 - No missed work/school due to asthma-related symptoms
 - Stable/optimized PFTs, measured 2+ times
 - Use of controller medication, with ICS no more than low-medium (based on GINA)
 - ACT > 20 | AirQ <2 |ACQ < 0.75 for all measurements, measured 2+ times</p>
 - Reliever therapy utilization no more than once per month

Blaiss M et al. Consensus of an ACAAI, AAAAI, and ATS Workgroup on Definition of Clinical Remission in Asthma on Treatment. *Ann Allergy Asthma Immunol.* (article in press, accessible online annallergy.com).



Post-test Questions



Post-AB1: Which of the following characteristics is the best predictor for response to anti-IL-5 therapy in a patient with severe asthma?

- A. IgE > 30 IU/mL
- B. Blood eosinophils > 1500 cells/ μ L
- C. Comorbid eosinophilic esophagitis
- D. Fractional exhaled nitric oxide (FeNO) > 50 ppb

Post-AB2: Which of the following characteristics in a patient with severe asthma suggests high risk for exacerbations?

- A. IgE > 150 IU/mL
- B. Blood eosinophils > 400 cells/ μ L
- C. Need for high-dose ICS/LABA/LAMA
- D. Comorbid atopic conditions (e.g., allergy, atopic dermatitis)



Post-AB3: 33 y/o male with severe asthma has been referred for evaluation for biologic therapy. Reports daily symptoms and SABA use.

PMH: Asthma (3 exacerbations in past year), eosinophilic esophagitis

Meds: High-dose ICS/LABA/LAMA, albuterol prn, PPI

Labs: Blood eosinophils 320 cells/µL, IgE 120 IU/mL, FeNO 65ppb, negative allergy testing.

Which biologic would be most appropriate to initiate?

- A. Benralizumab
- B. Dupilumab
- C. Omalizumab
- 53 D. Reslizumab



Post-AB4: 40 y/o female returns for follow-up after starting biologic agent 12 months ago.

Reports asthma symptoms are well controlled. No exacerbations in past year.

PMH: Severe asthma, seasonal allergies.

Meds: High-dose ICS/LABA, mepolizumab.

FEV1 80% predicted. ACT score 23.

The patient asks if he can reduce or stop any medications. What would you recommend?

- A. Continue biologic and current inhaler therapy
- B. Continue biologic, change inhaler to albuterol (rescue)
- C. Discontinue biologic, continue inhaler at current dose
- D. Continue biologic, change inhaler to medium-dose ICS/LABA

Post-AB5: Please rate your overall level of confidence in your responses to the previous questions.

- A. Very confident (4)
- B. Confident (3)
- C. Somewhat confident (2)
- D. Not at all confident (1)

Post-AB6: After completing this activity, how confident are you in your ability to adjust biologic therapy with respect to response in patients with severe asthma?

- A. Very confident (4)
- B. Confident (3)
- C. Somewhat confident (2)
- D. Not at all confident (1)

Post-AB7: After completing this activity, how often do you intend to consider biomarkers when assessing patients with severe asthma for biologic therapy?

- A. Always (4)
- B. Often (3)
- C. Rarely (2)
- D. Never (1)



Post-test Question 8

Post-AB9: About how many patients with severe asthma do you see on a weekly basis?

- A. None
- **B**. 1-5
- **C**. 6-10
- **D**. 11-15
- **E**. 16-20
- **F**. > 20



Q&A