ASTHMA BIOLOGICS:

REAL-WORLD EFFECTIVENESS, IMPACT OF SWITCHING

BIOLOGICS, AND PREDICTORS OF RESPONSE

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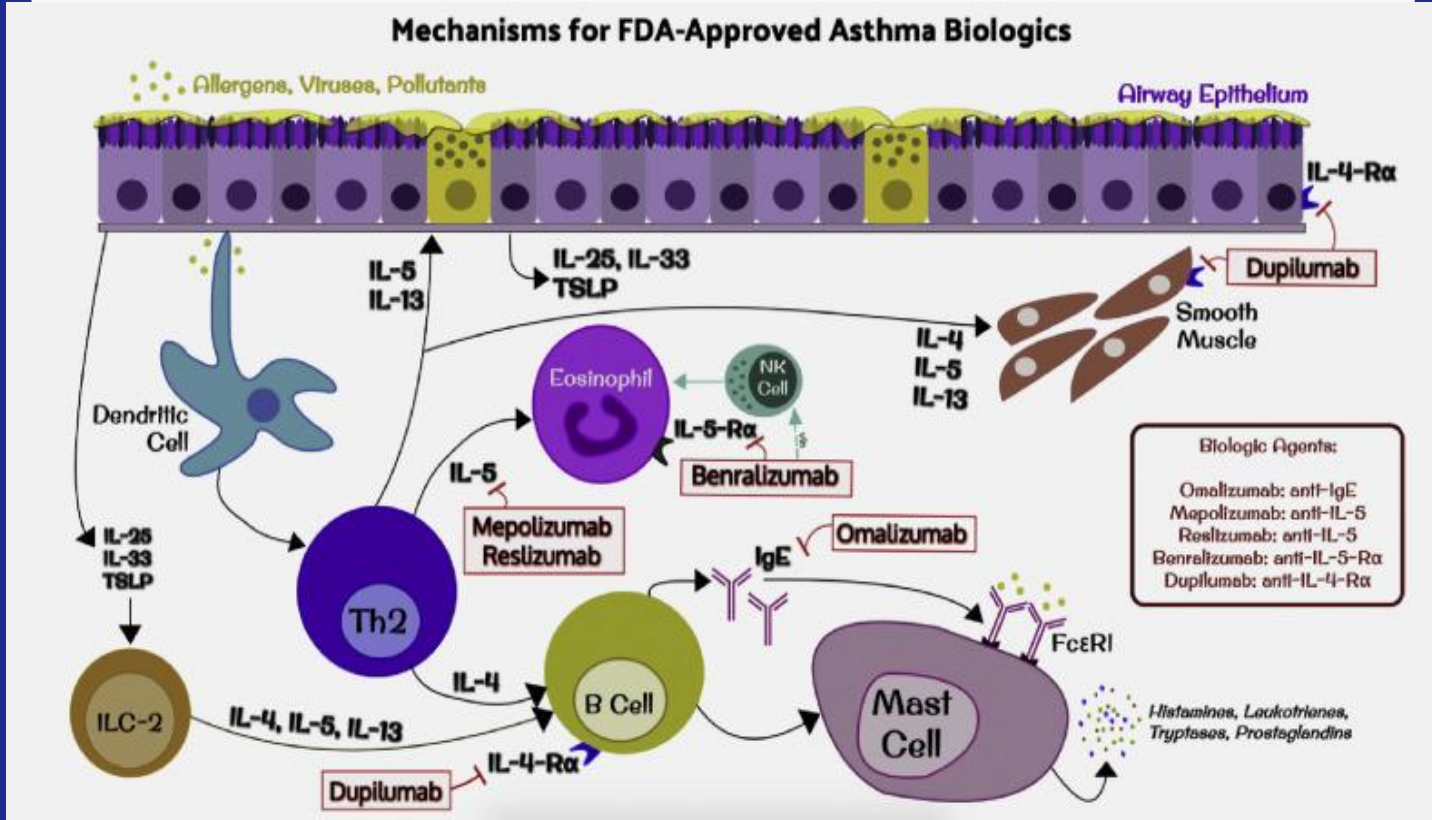

DISCLOSURES

I have no conflicts of interest to disclose in relation to this PowerPoint presentation.

INTRODUCTION

- **Severe asthma:** Classification of patients who warrant high dose ICS + 2nd controller or systemic corticosteroids to establish symptom control
- This diagnosis constitutes a minority of asthma patients, yet comprises the majority of asthma-related morbidity & mortality
- **Variable presentations** of severe asthma contribute to challenges pertaining to medical management
- **Precision medicine:** Groundbreaking treatment & prevention model focused on tailoring therapies to the individual:
    - Genes, lifestyle, and environmental factors are considered
    - Development of biologic therapies has facilitated tremendous growth in this area of interest
- **Purpose of this study:** Assess the efficacy of FDA-approved asthma biologic agents in patients carrying a diagnosis of severe asthma
    - Focuses on the utility of these treatments in the real world: accounting for biomarker profiles & individual comorbidities
    - Investigated factors influencing response to biologics
    - Analyzed the effect of switching biologics

METHODS

- **Retrospective study**→University of Rochester Asthma Center
- Assessed **severe asthma patients**: Jan. 2014-Dec. 2020
- Reviewed clinical characteristics & measures of asthma severity
    - Patient demographics
    - Baseline pulmonary function
    - Medications and underlying comorbidities
    - Exacerbation histories and Asthma Control Test scores
- **Primary outcome:** Change in clinically significant asthma exacerbations 1 yr. pre-biologic vs. 1 yr. into starting it
    - Determined by: Exacerbations necessitating OCS, ED or urgent care visits, or asthma hospitalizations
- **Secondary outcomes:**
    - Decrease in severe exacerbations & maintenance OCS: examined 1 yr into starting biologic
    - Change in prebronchodilator FEV1 & change in ACT score: examined 3-12 months into starting biologic

METHODS

- 112 patients were included
  - 83: previously not on biologics
  - 29: switched to a different biologic d/t inadequate response
- Divided into 2 groups: responders & nonresponders
- **Responders:** defined as individuals meeting ≥1 of the following:
  - ≥50% decrease in clinically significant exacerbations
  - ≥50% decrease in maintenance OCS dose
  - ≥120 mL rise in FEV1 and ≥3-point rise in ACT score
- **Unpaired t-test & contingency chi-square test** evaluated the difference between responders & nonresponders
- **Stepwise logistic regression model** compared patient characteristics across responders & nonresponders
  - Significant associations were included in bivariate analysis
- **Sensitivity analyses:** Created on patients with ≥ 12 mo f/up
- **Subgroup analyses:** Conducted to determine the impact of switching biologic therapies due to suboptimal response

RESULTS

- **Mepolizumab & dupilumab:** Most utilized biologics
- All subjects were on ICS, 44% needed maintenance OCS
- Avg. asthma control test score: 14
- Biologics: switched in 26% of subjects
- Management integrating any biologic:
  - Linked to a **59% decrease in clinically significant exacerbations**
    - Mean 4.5/y in 12 months preceding tx to 1.83/y in 12 months after initiating treatment (p<.001)
  - Associated with a **65% reduction in severe exacerbations**
    - From 1.62/y to 0.57/y (p<.001)
- Biologics **improved mean FEV1** (180 mL, p=.002) & mean ACT score (4 pts, p<.001)
- **Mean mOCS dose reduction** was 54% w/ biologic therapy (prednisone 11 to 5 mg, p=.001)
- 26% of pts needed a greater mOCS dose in spite of the biologic initiated

Table 1
Baseline Patient Characteristics (N = 112)

Mean age, y (range)	57 (28-92)
Female, n (%)	62 (55)
Body mass index, kg/m^2 (range)	32.8 (16.47-59.21)
Race, n (%)	
White	86 (77)
African American	19 (17)
Asian	2 (1.8)
Other	5 (4.5)
Mean blood eosinophil count, cells/μL (range)	624 (0-3400)
Mean blood eosinophil percentage, (range)	7 (0-30)
Mean FEV1 pre-BD, L (range)	2.05 (0.56-3.67)
Mean FEV1 pre-BD, % predicted (range)	69 (25-110)
Mean ACT score (range)	14 (5-25)
Patients with history of asthma related-intubations, n (%)	14 (12.5)
Medications, n (%)	
Inhaled corticosteroids	112 (100)
LABA	96 (86)
LAMA	76 (68)
LTM	81 (72)
Nasal corticosteroids	66 (59)
Theophylline	6 (5)
Patients previously on a biologic, n (%)	29 (26)
Patients on maintenance OCS, n (%).	49 (44)
Mean daily OCS dose, mg (range)	11 (2.5-60)
Comorbidities, n (%)	
GERD	87 (77)
Allergies	69 (62)
Allergic rhinitis	63 (56)
OSA	47 (42)
Depression	40 (36)
Nasal polyposis	23 (20)
Vocal cord dysfunction	16 (14)
Frequent respiratory tract infections	15 (13)
Aspirin allergy	4 (3)

Abbreviations: ACT, asthma control test; GERD, gastroesophageal reflux disease; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTM, leukotriene modifier; OSA, obstructive sleep apnea; OCS, oral corticosteroid; pre-BD, prebronchodilator.

RESULTS

- Compared outcomes: previously **biologic naïve** & those who **switched biologics** d/t tx failure
- Effect size was superior for the group in which the original biologic agent was continued
  - 80% decrease: mean clinically significant exacerbations (5-1, p<.01)
  - 100% decrease: severe exacerbations (2-0, p<.01)
  - Amelioration in ACT score
  - 53% decrease in mOCS dose
- **29 patients needed to switch** from the original biologic to a different one
  - Attributed to inadequate success with improving exacerbation frequency, symptoms, lung function
  - Mepolizumab, omalizumab, benralizumab, & reslizumab→switched to dupilumab, benralizumab, & mepolizumab

Table 2
Response to Biologics in All Patients (n = 112)

Outcomes	Mean baseline	Mean follow-up	*P* value
Rate of clinically significant exacerbations (n = 103)	4.50	1.83	< .01
Rate of severe exacerbations (n = 103)	1.62	0.57	< .01
mOCS-mg prednisone equivalent (n = 50)	11	5	< .01
FEV1 L (n = 77)	2.05	2.23	< .01
FEV1 (% predicted) (n = 77)	69.49	77.39	< .01
ACT score (n = 83)	14	18	< .01

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in 1 second; mOCS, maintenance oral corticosteroid.

Table 3
Response to Biologics in Patients Previously Not on a Biologic (N = 83)

Outcomes	Mean baseline	Mean follow-up	*P* value
Rate of clinically significant exacerbations (n = 74)	5.0	1.0	< .01
Rate of severe exacerbations (n = 74)	2.0	0.0	< .01
mOCS-mg prednisone equivalent (n = 36)	13.7	6.4	< .01
FEV1 L (n = 58)	2.08	2.00	.05
ACT score (n = 56)	13	18	< .01

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in 1 second; mOCS, maintenance oral corticosteroid.

RESULTS

- **Switching biologics:**
  - 40% decrease in clinically significant exacerbations (3.46-2.07, p=.01)
  - Ameliorated FEV1 (330 mL, p=.01) & ACT score (3, p=.04)
  - No clinically significant decrease in severe exacerbations
  - 42% decrease in mOCS dose (not statistically significant)
  - Group that switched from **anti-IL-5** treatment (mepolizumab) to **anti-IL-5R** treatment (benralizumab):
    - Switch appeared efficacious
    - Result was not statistically significant, likely attributed to small sample size involved

Table 4
Response to Biologics in Patients Previously on a Different Biologic (N = 29)

Outcomes	Mean baseline	Mean follow-up	*P* value
Rate of clinically significant exacerbations (n = 28)	3.46	2.07	< .01
Rate of severe exacerbations (n = 28)	1.28	0.78	.09
mOCS-mg prednisone equivalent (n = 14)	8.82	5.07	.16
FEV1 L (n = 19)	1.94	2.27	.01
ACT score (20)	15	18	.04

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in 1 second; mOCS, maintenance oral corticosteroid.

RESULTS

- **Responders vs. Nonresponders**
- **Multivariable stepwise logistic regression model** compared characteristics between the 2 groups
- The groups did not have statistically significant differences in the following parameters:
    - BMI, mean blood eosinophil count, serum IgE, ACT score, mOCS dose, or % of subjects on mOCS
- Features that **increased the likelihood of being a responder:**
    - Higher baseline FEV1 (odds ratio 1.05; p=.01)
    - Eosinophil count ≥500 cells/mL (odds ratio 1.24; p=.02)
    - Hx of GERD: marginally higher likelihood of being a responder (odds ratio 4.55; p=.06)
- Subjects who smoked at some point had a lower chance of being a responder (odds ratio .01; p=.01)
- **Sensitivity analyses** performed on the data arrived at the same conclusions

DISCUSSION

- Utilizing **any biologic agent** was linked to marked improvement in:
  - Asthma exacerbations, OCS dependence, pulmonary function, & asthma symptom control
- 1 in 4 patients on a biologic needed to switch to another one
- Switching biologics led to an improvement in asthma exacerbations, OCS dependence, lung function, ACT score
- Greater degree of improvement in asthma outcomes was observed in biologic-naïve pts compared to those who switched biologics
- Patients previously on a biologic for 1 yr had fewer
  - 1.) baseline clinically significant exacerbations (3.46 vs 5) or
  - 2.) lower baseline mean mOCS dose requirement (8.82 vs. 13.7 mg) than biologic-naïve patients
- **Potential rationale:** Some degree of asthma control was achieved with initial biologic
- **Other rationale:** “Nonresponders” may have a unique pathobiology of severe asthma imparting resistance to targeted biologics
- Suboptimal responders to anti-IL-5 tx (mepolizumab) may experience improvement w/ anti-IL-5R treatment (benralizumab)

DISCUSSION

- **Nonresponders-** higher likelihood of these classifications:
  - Female gender, ever-smoker, lower prebronchodilator FEV1
- **Responders-** higher likelihood of these associations:
  - Never smoker, hx GERD, higher prebronchodilator FEV1, absolute blood eosinophil count > 500 cells/mL
- Prior studies:
  - Did not elucidate an association between presence of GERD & response to biologics- could some have EoE?
  - Showed **FeNO**>25 predicted clinically significant response to dupilumab when switched from a previous biologic
- This study did not corroborate FeNO finding→FeNO data was not accessible for all pts
- **Study limitations:** Not a very diverse cohort, FeNO data only existed for 40% of pts, f/up was < 1 yr for 8% of pts
- Asthma biologics can markedly enhance control of respiratory disease in a real-world context; switching biologics can benefit pts
- Determining factors that predict response to certain biologics will revolutionize precision medicine & optimize severe asthma control

POLL QUESTIONS

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Question 1: In a retrospective study that models a real-world setting, which of the following outcomes would you expect when a patient with severe asthma switches from one biologic to another due to suboptimal response?

A) Switching biologics would not yield improvements in objective measures of lung function such as FEV1 or ACT score.
B) Those who switch biologics experience greater improvement in asthma outcomes compared to previously biologic-naïve patients who initiate biologic treatment.
C) Patients who experience a suboptimal response to anti-IL-5 therapy (mepolizumab) would not be expected to display a favorable response to anti-IL-5R therapy (benralizumab).
D) A reduction in clinically significant exacerbations can occur when patients are switched from one biologic therapy to a different one.

POLL QUESTIONS

Answer: D.

Why D is correct:

-Switching from mepolizumab, omalizumab, benralizumab, & reslizumab to dupilumab, benralizumab & mepolizumab→40% reduction in clinically significant exacerbations

-Lack of success with one biologic does not preclude clinical success with a different one

Why A is incorrect:

-Switching from mepolizumab, omalizumab, benralizumab & reslizumab to dupilumab, benralizumab & mepolizumab→ clinically significant improvements in FEV1 & ACT score

-Patients with severe asthma may encounter significant improvement in pulmonary function & symptom control after switching biologic agents

Why B is incorrect:

-There was greater improvement in asthma outcomes in previously biologic-naïve pts who started a biologic than those who switched biologics due to a suboptimal response

-The original biologic imparted some amelioration of asthma control, or the pathobiology of severe asthma was resistant to targeted biologic therapy

Why C is incorrect:

-Patients with a suboptimal response to anti-IL-5 therapy (mepolizumab) experienced improvement when switched to anti-IL-5R therapy (benralizumab)

-Mepolizumab directly binds to IL-5→reduces production & survival of eosinophils

-Benralizumab targets IL-5Rα →directly leads to cell toxicity→depletes eosinophils as well as other cells carrying the IL-5Rα receptor

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POLL QUESTIONS

Question 2: In this study, "responders" to a particular biologic agent are described as individuals with a ≥50% reduction in clinically significant exacerbations, ≥50% reduction in mOCS dose, or ≥120 mL rise in FEV1 and ≥3-point increase in ACT score. 83 patients who were biologic naïve were started on biologic therapy, while 29 patients were switched from one biologic agent to another. Responders to the new therapy were more likely to have which of the following characteristics?

A) They were more likely to have a higher serum IgE level compared to nonresponders.
B) There were more likely to have a higher baseline FEV1 compared to nonresponders.
C) They were more likely to have a smoking history compared to nonresponders.
D) They were more likely to have an absolute blood eosinophil count ≤ 500 cells/mL compared to nonresponders.

POLL QUESTIONS

Answer: B.

Why B is correct: This study shows that responders are more likely than nonresponders to have a higher baseline FEV1 level

Why A is incorrect: Based on the results of this retrospective study, responders and nonresponders did not differ significantly based on serum IgE level

Why C is incorrect: According to this study, nonresponders are more likely than responders to have a smoking history

Why D is incorrect: Responders are more likely than nonresponders to have an absolute blood eosinophil count ≥ 500 cells/mL

THANK YOU