Economic Outlook for Biologics in Asthma – Are They Cost-Effective?

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Educational Goals

Upon completion of this learning activity, participants should better understand:

- The mechanisms of action of the various biologic agents
- Optimal patient choices when selecting a biologic agent
- Potential future biologic agents that may come to market

Prevalence of Uncontrolled Asthma

- Previous studies have reported a prevalence of uncontrolled asthma ranging from 40–60%, depending on the population studied and the definition of asthma control.

Mintz *Current medical research and opinion* 2009; **25**(10): 2523-31.

Price NPJ primary care respiratory medicine 2014; 24: 14009.

Vietri Journal of occupational and environmental medicine 2014; 56(4): 425-30.

Prevalence of Uncontrolled Asthma

- In patients attending 12 pulmonary and 12 allergy clinics, 53% were not well controlled (mean [SD] Asthma Control Test, 14.3 [3.6] vs 22.4 [1.6] in well-controlled patients).
- Among ICS/LABA users, 56% were not well controlled, which increased with increasing ICS dose
- low-dose ICS 45.7%
- high-dose ICS 59.7%.

Oppenheimer Ann All Asthma Immunol 2021; 126:385-393

Consequences of Uncontrolled Asthma

- Poor asthma control is associated with increased:
  - exacerbation risk,
  - poor health-related quality of life (HRQoL),
  - increased health care utilization (HRU) and costs.

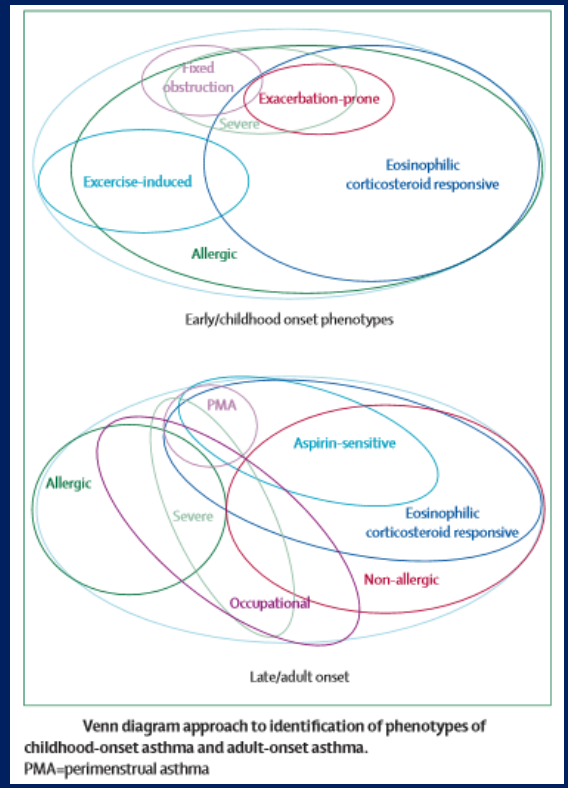
Lee Journal of Asthma 2018; 55(2): 208-19.
Sullivan Journal of Asthma 2017; 54(1): 24-31.
Sullivan Annals of allergy, asthma & immunology 2016; 117(3): 251-7
Sullivan Journal of Asthma 2014; 51(7): 769-78.
Sawicki Journal of Asthma 2010; 47(5): 574-80.
Mintz Current medical research and opinion 2009; 25(10): 2523-31.
Katz Annals of allergy, asthma & immunology 2002; 89(3): 251–8.

- The 20-year cost of asthma in the U.S. is estimated to exceed $963 billion

Yaghoubi Jl Resp Crit Care Med 2019;200:1102-12.

Asthma is a Syndrome

- Evidence indicates asthma is a heterogeneous disorder.[1,2,3]
  - ► Allergic vs nonallergic asthma
  - ► Severity
  - Age of Onset
  - Chronic Airway Obstruction
  - Triggers
    - Viral, Exercise, Occupational Allergens, Irritants
  - Pathobiology
    - Eosinophilic, Neutrophilic and paucigranulocytic asthma
  - Course
    - Early transient, persistent, late onset wheeze



Venn diagram approach to identification of phenotypes of childhood-onset asthma and adult-onset asthma.
PMA=perimenstrual asthma

1) Kontstantellou. Respiratory Medicine. 2015,

2) Wenzel SE. Lancet 2006;368 (9537) 804-813

3) Zedan Pediatrics. 2013; 824

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Assess Control

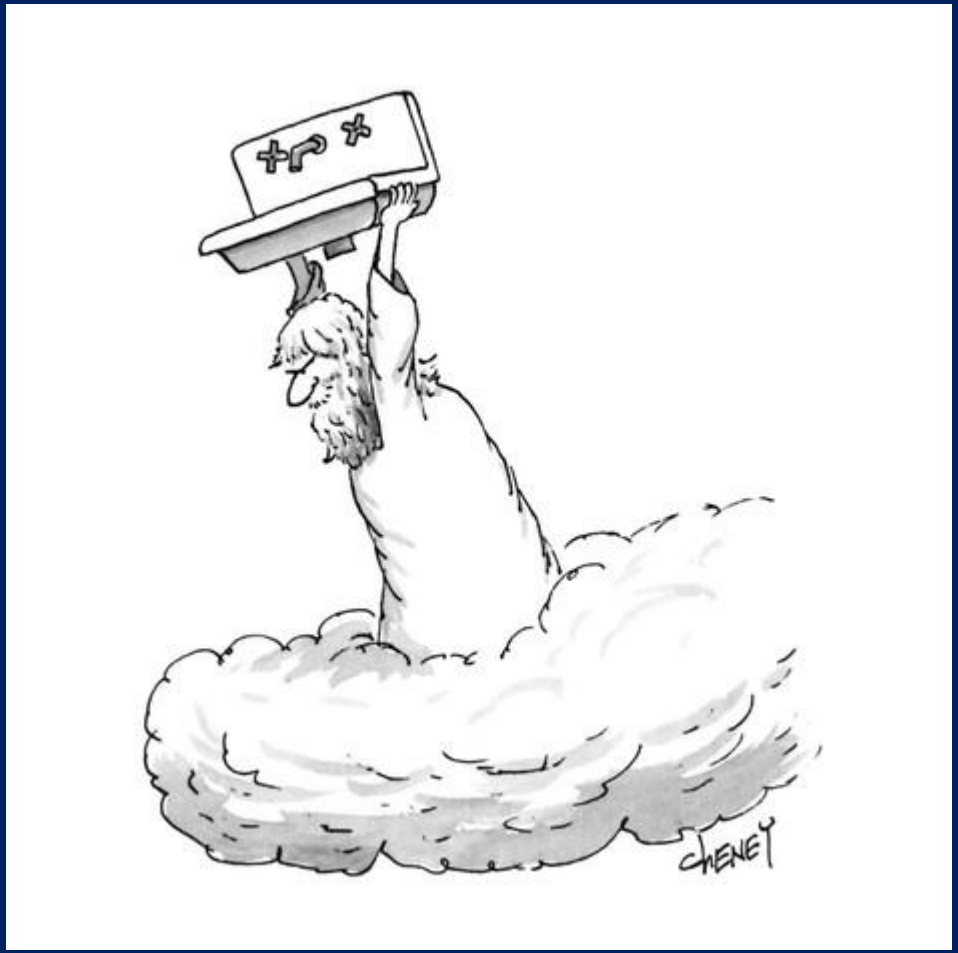
- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

NAEPP 2021

Our Approach to the Severe Uncontrolled Asthmatic:



Step-up Therapy for Children with Uncontrolled Asthma Receiving ICS (BADGER STUDY)

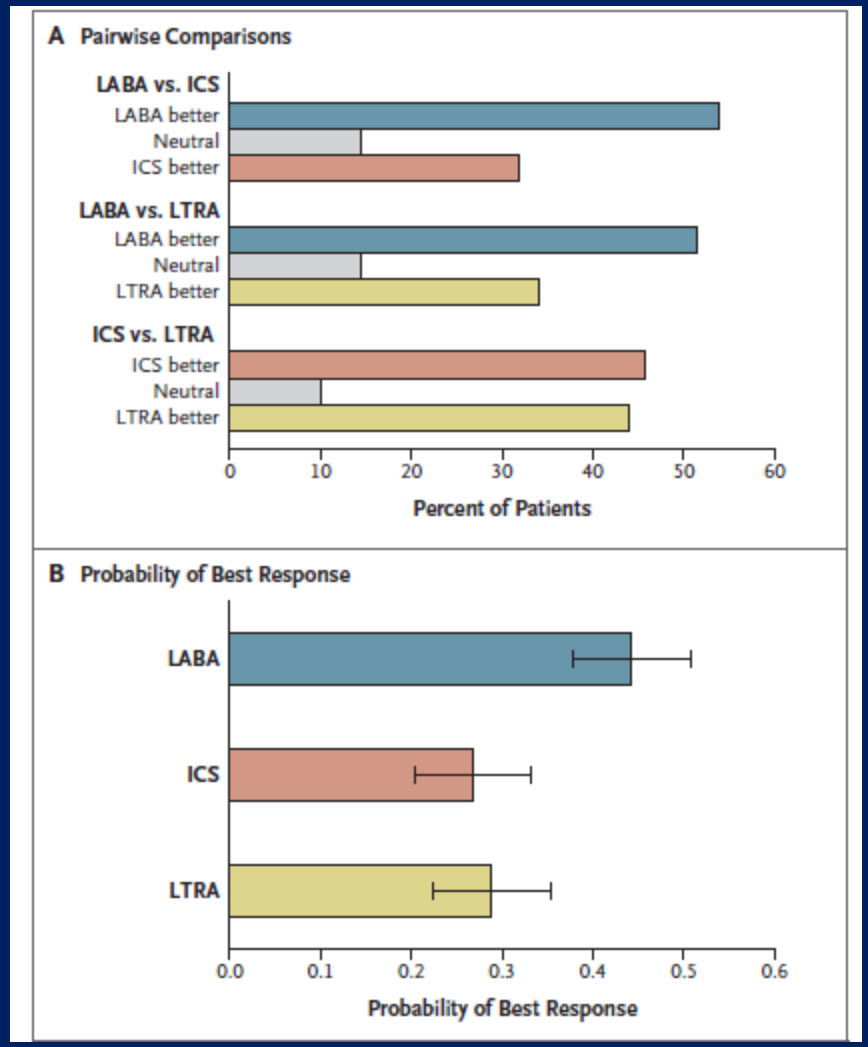
Methods

- randomly assigned 182 children (6 to 17 years of age), who had uncontrolled asthma while receiving 100 µg of fluticasone BID, to receive each of three blinded step-up therapies in random order for 16 weeks:
  - 250 µg of fluticasone twice daily (ICS step-up),
  - 100 µg of fluticasone plus 50 µg of a long-acting beta-agonist twice daily (LABA step-up),
  - 100 µg of fluticasone twice daily plus 5 or 10 mg of Montelukast (LTRA step-up).
- used a triple-crossover design and a composite of three outcomes
  - exacerbations,
  - asthma-control days,
  - FEV1

Lemanske NEJM 2010;362:975-85.

Figure 2. Pairwise Comparison of Three Step-up Therapies and the Overall Probability of Best Response.

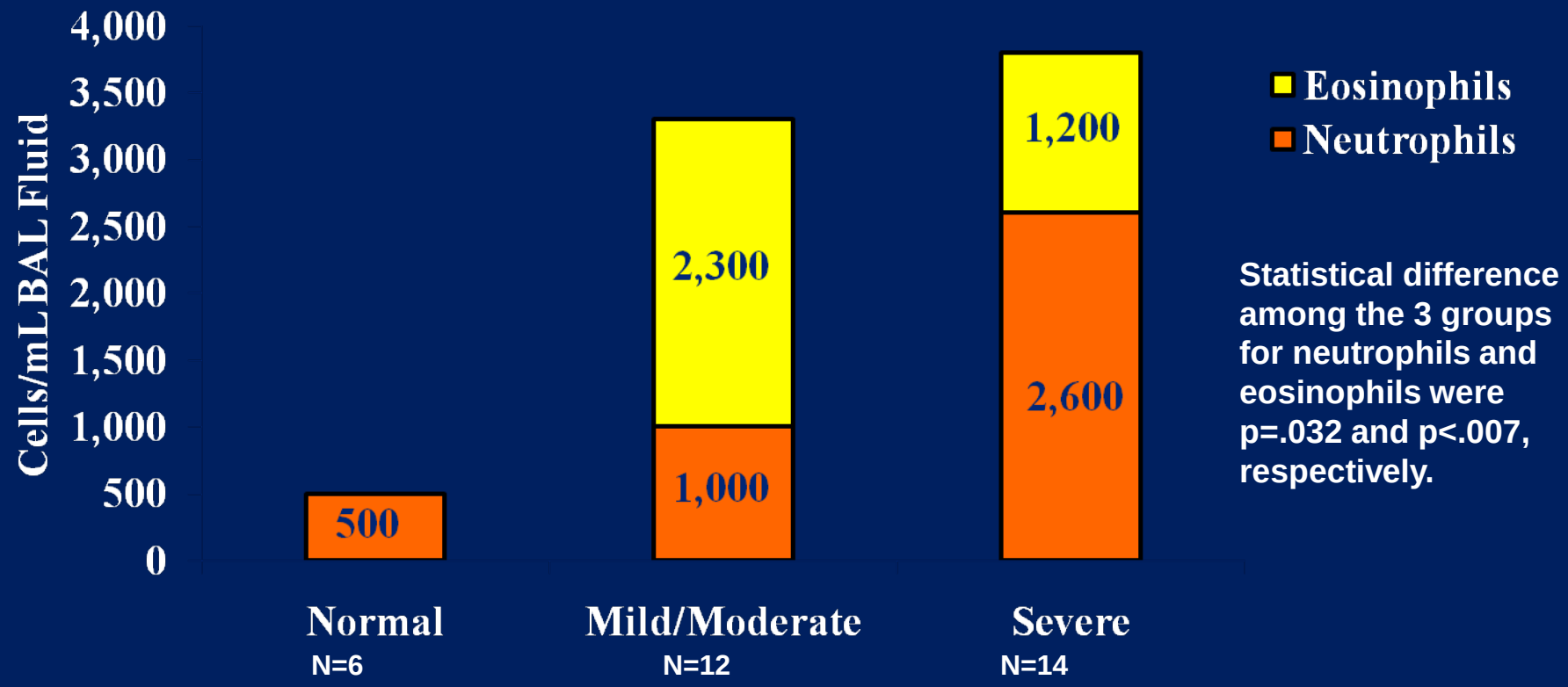
- A differential response occurred in 161 of 165 patients who were evaluated (P<0.001).
- The response to LABA step-up therapy was most likely to be the best response
- Higher baseline ACT scores predicted a better response to LABA step-up (P=0.009).
- White race predicted a better response to LABA step-up,
- African American patients were least likely to have a best response to LTRA step-up (P=0.005).



Lemanske NEJM 2010362:975-85

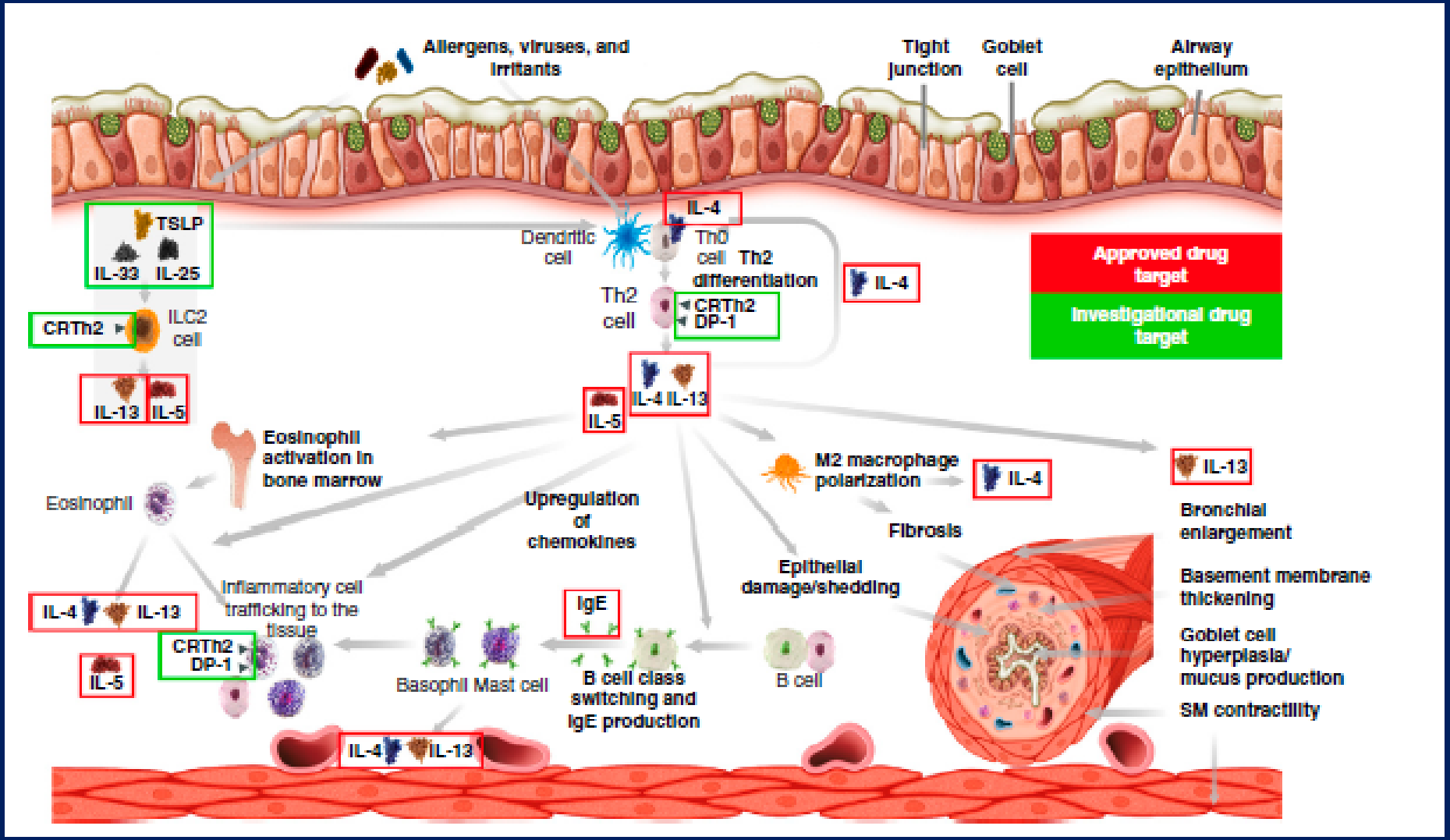
Increased Neutrophilic Inflammation in Severe Steroid-Dependent Asthmatics

BAL Cell Differentials



Statistical difference among the 3 groups for neutrophils and eosinophils were p=.032 and p<.007, respectively.

Wenzel SE et al. *Am J Respir Crit Care Med* 1997;156:737-743.



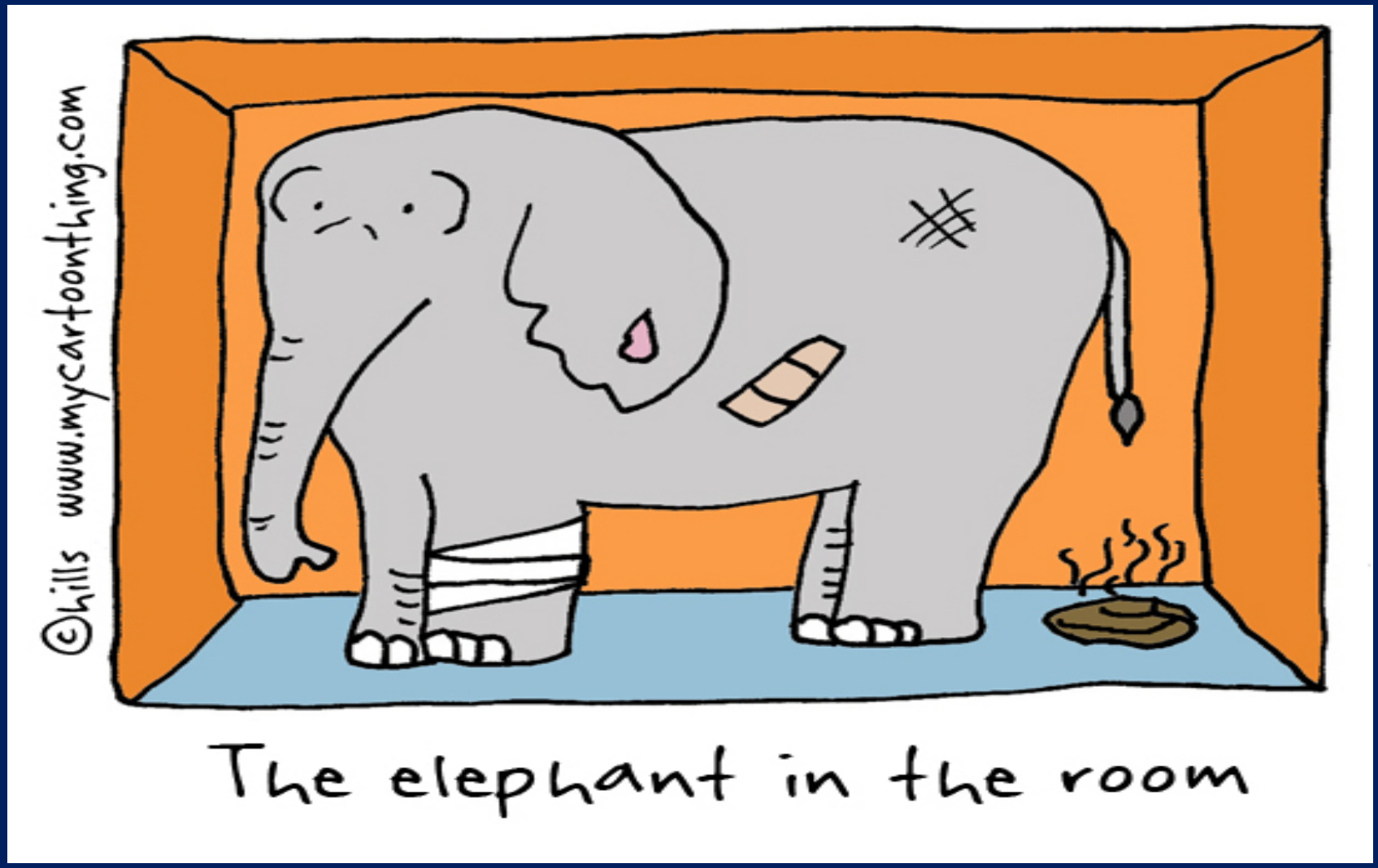
McGregor AJRCCM 2019;191:433-45

Biologic Agents

Drug Name	Mechanism of Action
Omalizumab	Reduces circulating IgE by binding to the constant region of the human immunoglobulin E molecule[47]
Mepolizumab Reslizumab	Binds free IL-5 which reduces airway and systemic eosinophilia.[53,57]
Benralizumab	Binds IL-5 receptor-alpha on eosinophils and basophils.[59]
Lebrikizumab	Binds to circulating IL-13 reducing airway periostin and DPP4[60]
Dupilumab	Inhibits both IL-4 and IL-13 signaling pathways by binding to IL-4 receptor-alpha.[65]
Brodalumab	Anti-IL17 receptor-A which blocks IL-17 and IL-25 pathways.
Infliximab Golimumab	Binds and neutralizes soluble TNF-a, a key regulator of innate immunity and the Th1 response.[67,69]

Draikiwicz + Oppenheimer Immunology and Allergy Clinics 2017

We have to balance Rx costs with outcomes



Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: To biologic or not to biologic?

Table 1
US Food and Drug Administration–Approved Biologics: Target, Cost, and Cost-effectiveness Ratio Estimates[2]

Biologic	Target	Annual WAC, $	Base-case incremental cost-effectiveness ratio, %[a]	Discount from WAC required to achieve cost-effectiveness threshold prices, %[b]
Omalizumab	Anti–IgE	39,048	325,000	66-77
Mepolizumab	Anti–IL-5	37,293	344,000	64-75
Reslizumab	Anti–IL-5	31,637	391,000	67-80
Benralizumab	Anti–IL-5 receptor	30,889	371,000	62-73
Dupilumab	Anti–IL-4 α-receptor subunit	38,110	351,000	62-73

Abbreviations: IL, interleukin; WAC, wholesale acquisition cost.
[a]Annual price excluding loading dose in 1 year of a treatment and excluding administration costs; cost is measured in 2018 US dollars per quality-adjusted life-year gained.
[b]Threshold to achieve an incremental cost-effectiveness ratio between $100,000 and $150,000 per quality-adjusted life-year gained.

Wholesale Acquisition Cost (WAC)

Anderson and Szefler Ann Allergy Asthma Immunol 2019;122:367-72

Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: To biologic or not to biologic?

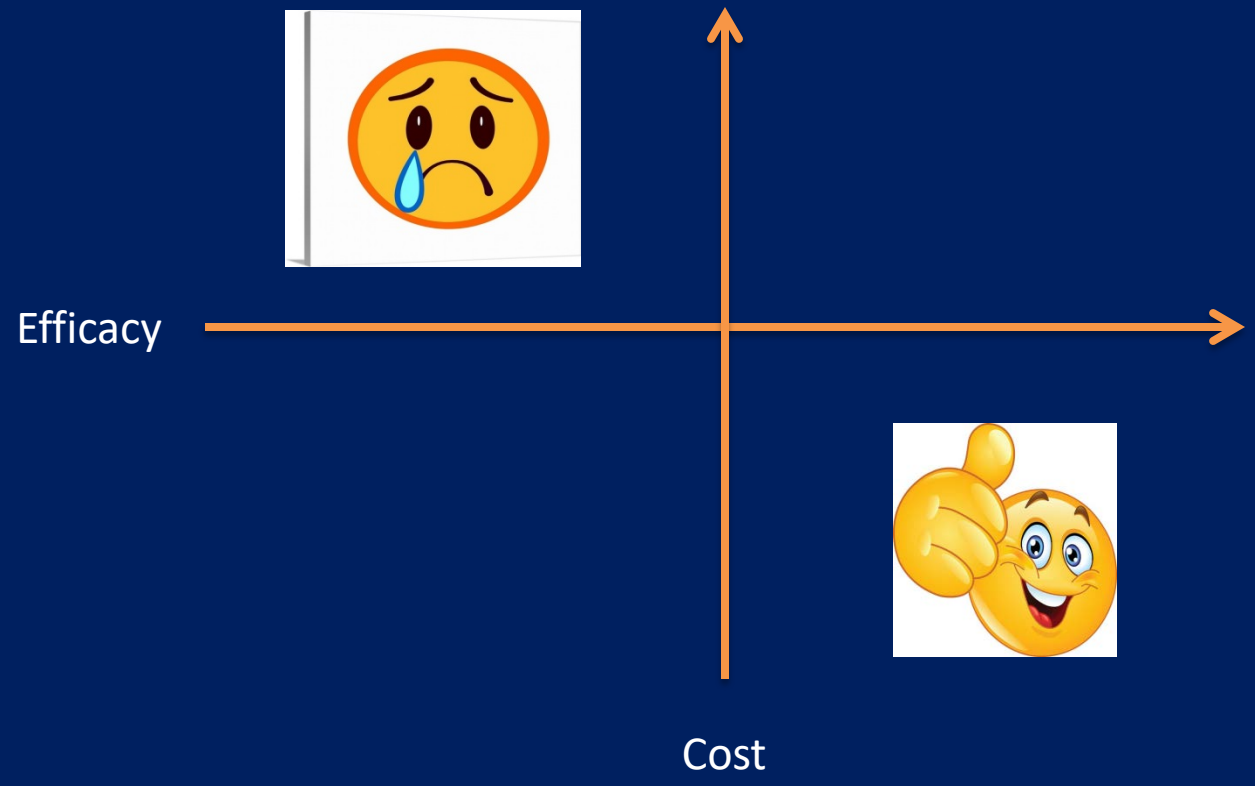
- Current pricing for all biologics exceeds measures of cost-effectiveness.
- To meet available measures indicating cost-effectiveness, prices would have to be reduced by a minimum of approximately 60%.

Conclusion:

Cost effectiveness could be significantly improved if we better understood indicators of those likely to respond to therapy before its initiation, or had knowledge of some early sign of those responding to therapy.

Anderson and Szefler Ann Allergy Asthma Immunol 2019;122:367-72

Cost Effectiveness Analysis



Improving our Precision in Medicine
We are Going to Have to!

https://www.bing.com/images/search?q=precision+medicine&view

Can we improve our choice of patients/Improve the CEA?

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

Mepolizumab significantly reduces the rate of exacerbations in patients with severe eosinophilic asthma.

Methods

- Post-hoc analysis of data from two randomized, double-blind, placebo-controlled studies of at least 32 weeks duration DREAM and MENSA done between 2009 and 2014.

- The primary endpoint in both studies was the annual rate of clinically significant exacerbations
  - defined as worsening of asthma that required the use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences.

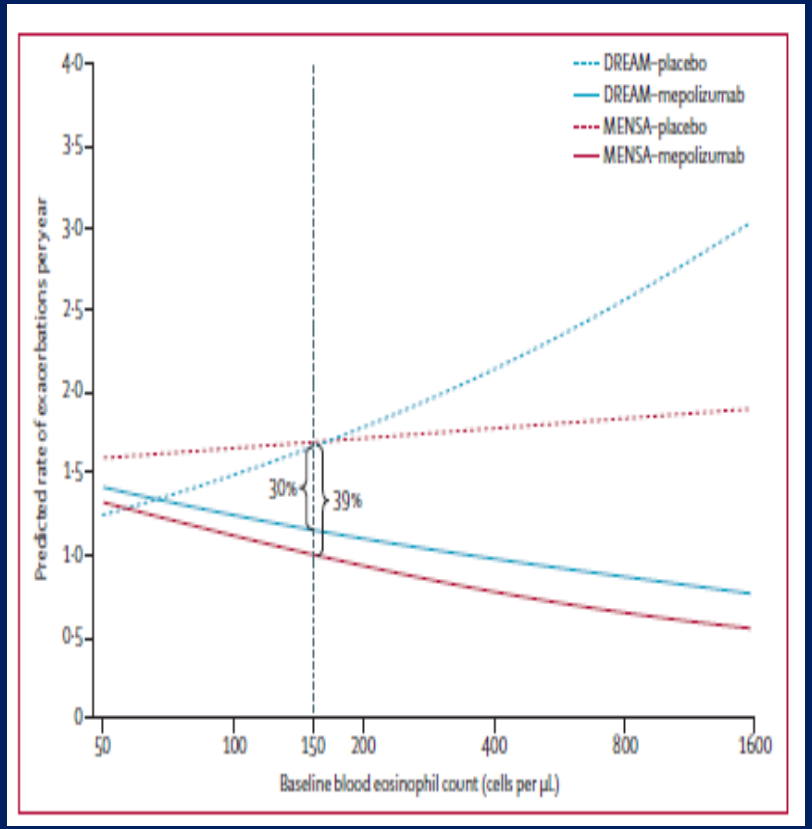
- Subjects were stratified by baseline eo count

Ortega Lancet Respir Med 2016; 4: 549–56

Predicted rate of clinically significant exacerbations per year against baseline blood eosinophil counts

Findings

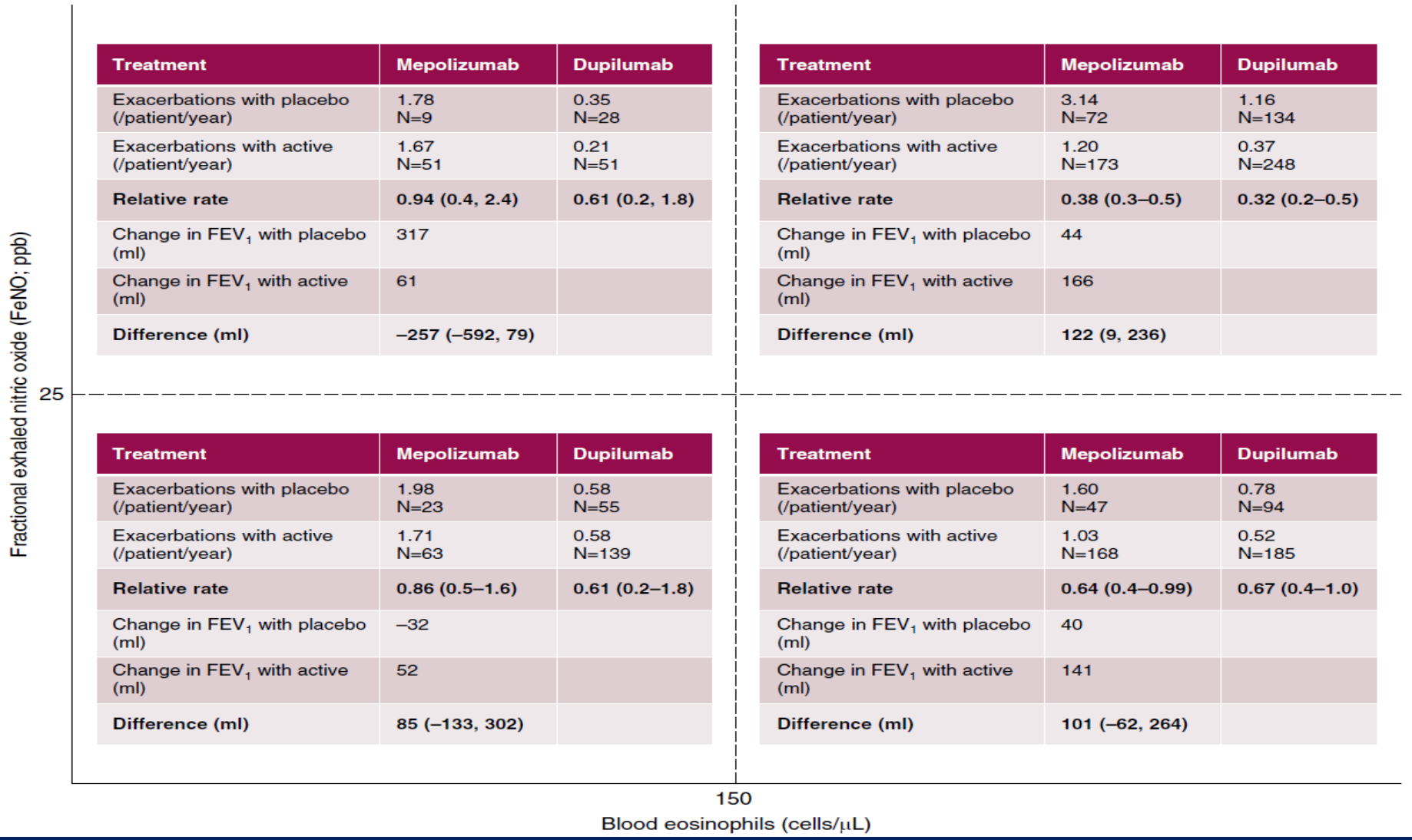
- The overall rate of mean exacerbations per person per year was reduced by 47% on mepo (vs pbo p<0·0001).
- The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline blood eosinophil count of at least 150 cells per µL to 70% with a baseline count of at least 500 cells per µL.
- A baseline count less than 150 cells per µL, predicted efficacy of mepolizumab was reduced.



Ortega Lancet Respir Med 2016; 4: 549–56

Prognostic and Predictive Value of Blood Eosinophil Count, Fractional Exhaled Nitric Oxide, and Their Combination in Severe Asthma: A Post Hoc Analysis

Figure 1. Annualized exacerbation rates



Treatment	Mepolizumab	Dupilumab
Exacerbations with placebo (/patient/year)	1.78 N=9	0.35 N=28
Exacerbations with active (/patient/year)	1.67 N=51	0.21 N=51
Relative rate	**0.94 (0.4, 2.4)**	**0.61 (0.2, 1.8)**
Change in FEV_1 with placebo (ml)	317	
Change in FEV_1 with active (ml)	61	
Difference (ml)	**–257 (–592, 79)**	

Treatment	Mepolizumab	Dupilumab
Exacerbations with placebo (/patient/year)	3.14 N=72	1.16 N=134
Exacerbations with active (/patient/year)	1.20 N=173	0.37 N=248
Relative rate	**0.38 (0.3–0.5)**	**0.32 (0.2–0.5)**
Change in FEV_1 with placebo (ml)	44	
Change in FEV_1 with active (ml)	166	
Difference (ml)	**122 (9, 236)**	

Treatment	Mepolizumab	Dupilumab
Exacerbations with placebo (/patient/year)	1.98 N=23	0.58 N=55
Exacerbations with active (/patient/year)	1.71 N=63	0.58 N=139
Relative rate	**0.86 (0.5–1.6)**	**0.61 (0.2–1.8)**
Change in FEV_1 with placebo (ml)	–32	
Change in FEV_1 with active (ml)	52	
Difference (ml)	**85 (–133, 302)**	

Treatment	Mepolizumab	Dupilumab
Exacerbations with placebo (/patient/year)	1.60 N=47	0.78 N=94
Exacerbations with active (/patient/year)	1.03 N=168	0.52 N=185
Relative rate	**0.64 (0.4–0.99)**	**0.67 (0.4–1.0)**
Change in FEV_1 with placebo (ml)	40	
Change in FEV_1 with active (ml)	141	
Difference (ml)	**101 (–62, 264)**	

Shrimanker AJRCCM 2019;200:1308-12

Real-World Effectiveness and the Characteristics of a “Super-Responder” to Mepolizumab in Severe Eosinophilic Asthma

- How do patients with severe eosinophilic asthma respond to mepolizumab
- in the real world setting and which characteristics are associated with a super response to this therapy?

METHODS:

- Retrospective review of all patients who received at least 16 weeks of treatment with mepolizumab (100 mg subcutaneously) for SEA at a regional asthma center in the UK.
- Clinical data were collected at each 4-week visit.
- At 16, 24, and 52 weeks, patients were classified as “responders” or “non-responders.”
- Responder was defined as ≥50% reduction in exacerbations; for patients whose condition required maintenance OCS, a response was defined as >50%reduction in prednisolone dose.
- Super responders were defined as exacerbation-free and off mOCS at one year.

Kavanagh CHEST 2020; 158(2):491-500

Real-World Effectiveness and the Characteristics of a "Super-Responder" to Mepolizumab in Severe Eosinophilic Asthma

RESULTS:

- Ninety-nine patients were included in the analysis.
- Asthma exacerbations decreased from a baseline of 4.04 +/- 2.57 to 1.86 +/- 2.17 per year at one year (54% reduction; P < .001).
- Sixty-eight patients were receiving maint OCS at the time of commencing mepolizumab.
- By one year, the daily median dose fell from 10 mg (interquartile range, 10 to 15) to 0 mg (interquartile range, 0 to 10; P < .001).
- Fifty-seven percent of them were able to discontinue OCS; 72.7% (95% CI, 63.0 to 80.7) of the patients were classified as responders, and 28.3% (95% CI, 20.2 to 38.0) of the patients were classified as super responders

Kavanagh CHEST 2020; 158(2):491-500

Real-World Effectiveness and the Characteristics of a "Super-Responder" to Mepolizumab in Severe Eosinophilic Asthma

- Baseline characteristics associated with responder and super responder status included:
  - the presence of nasal polyposis (P = .012),
  - lower baseline Asthma Control Questionnaire 6 (P =.006),
  - lower BMI (P = .014),
  - those patients receiving maint OCS, a significantly lower prednisolone dose at baseline (P = .005).

- At 16 weeks, the one-year responder status was correctly identified in 80.8% patients; by 24 weeks, this status rose to 92.9%.

Kavanagh CHEST 2020; 158(2):491-5

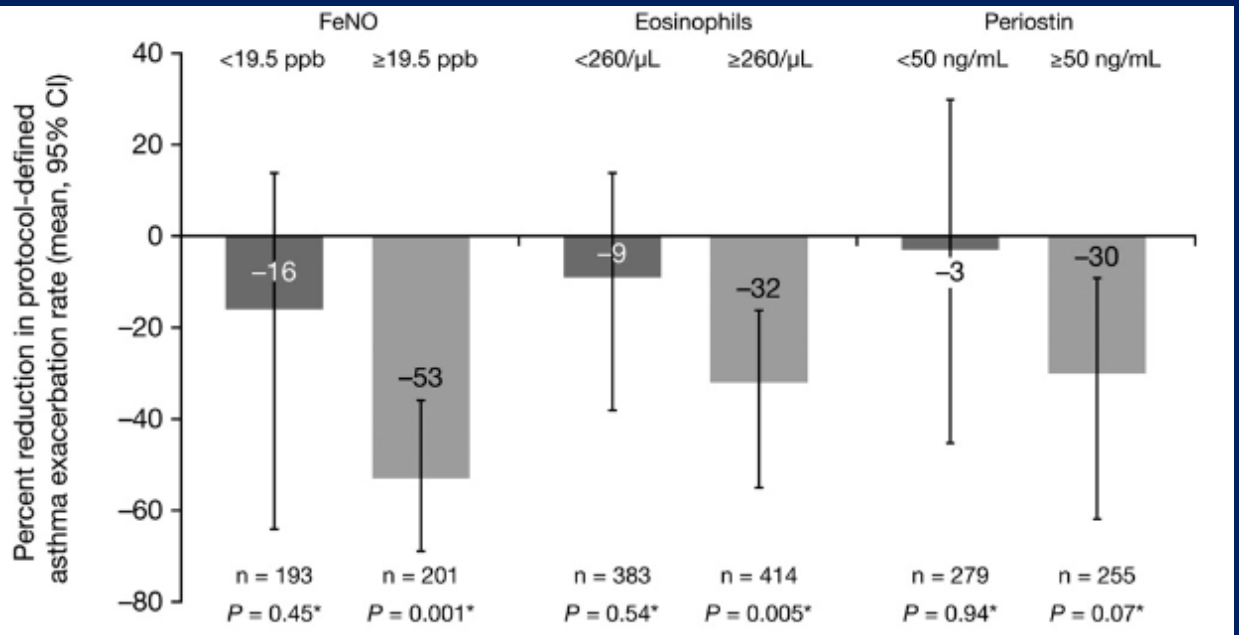
Asthma Therapy - Omalizumab EXTRA Study

- Patients 12-75 years of age with uncontrolled severe persistent asthma were enrolled
  - Need history of severe persistent asthma > 1 year before screening.
    - Uncontrolled despite being on high dose ICS and LABA
  - Randomized 1:1 to receive omalizumab or placebo for 48 weeks.
  - 850 patients enrolled:
    - FENO
    - blood eosinophils
    - serum periostin
  - Primary endpoint was number of observed protocol-defined exacerbations over 48 week trial period
    - Worsening asthma symptoms requiring systemic corticosteroids for >=3 days.

Hanania et al. Am J Respir Crit Care Med 2013;187(8):804-811.

Asthma Therapy - Omalizumab

Th2 low versus Th2 high subgroups



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania Am J Respir Crit Care Med 2013;187(8):804-811.

Cluster Analysis of Inflammatory Biomarker Expression in the International Severe Asthma Registry

Goal:

- characterize biomarker expression in adults with severe asthma.

METHODS:

- Within the International Severe Asthma Registry analyzed data with prespecified thresholds for biomarker positivity and with hierarchical cluster analysis using biomarkers as continuous variables.
  - serum IgE $\geq$ 75 kU/L
  - blood eosinophils $\geq$ 300 cells/ mL
  - FeNO $\geq$ 25 ppb

Denton JACI IP 2021;9:2680-8

FIGURE 3. Graphical representation of the clinical characteristics of the 5 severe asthma clusters relating to biomarkers

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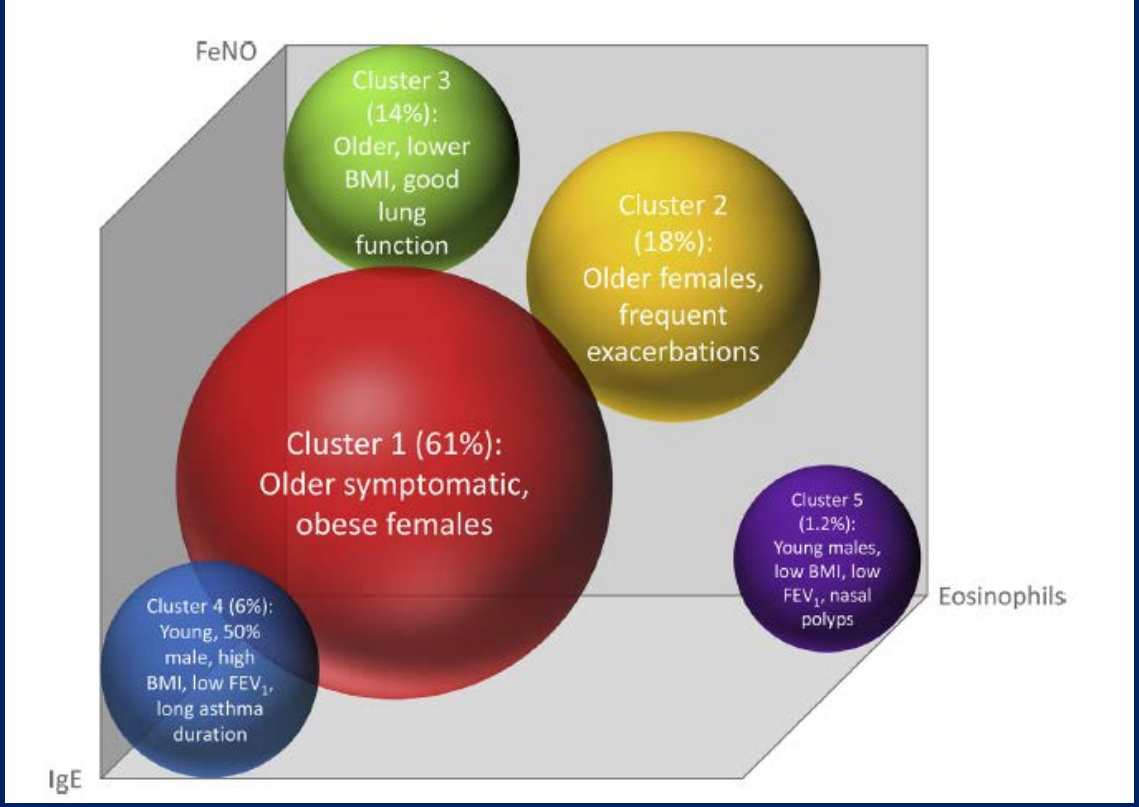


Biomarkers: blood eosinophils ≥300 cells/mL, FeNO ≥25 ppb, total IgE ≥75 kU/L

CONCLUSIONS:

- There is significant overlap of biomarker positivity in severe asthma.
- Distinct clusters according to biomarker expression exhibit unique clinical characteristics, suggesting the occurrence of discrete patterns of underlying inflammatory pathway activation and providing pathogenic insights relevant to the era of monoclonal biologics.
  - Some patients may respond better than others with a specific biologic agent

Denton JACI IP 2021;9:2680-8

Imgflip.com

Pharmacogenomics and Dupilumab

In a humanized mouse model of the IL4Ra-R576 variant, exposure of the mice to fine /ultrafine particles from vehicular exhaust exacerbated allergic inflammation in association with augmented mixed TH2/TH17 airway cell responses, demonstrating the plausibility that interactions between this allele and environmental exposures contribute to asthma morbidity.

Xia JACI 2015; 136:441-53.

Gene-environment interaction between an IL4R variant and school endotoxin exposure contributes to asthma symptoms in inner-city children

Characteristic	Overall	*Q/Q* genotype	*Q/R* genotype	*R/R* genotype	*P* value
n	236	58	107	71	
Age (y), mean ± SD	7.96 ± 1.91	8.00 ± 1.84	7.84 ± 2.01	8.11 ± 1.82	.641
Sex: male, n (%)	122 (51.7)	27 (46.6)	62 (57.9)	33 (46.5)	.216
Self-reported race, n (%)					<.001
White	12 (5.1)	9 (15.5)	3 (2.8)	0 (0.0)	
Black	84 (35.6)	11 (19.0)	33 (30.8)	40 (56.3)	
Hispanic	82 (34.7)	26 (44.8)	44 (41.1)	12 (16.9)	
Other	42 (17.8)	11 (19.0)	19 (17.8)	12 (16.9)	
Mixed	16 (6.8)	1 (1.7)	8 (7.5)	7 (9.9)	

Lai JACI 2018;141:794-6

Effect of IL-4RαR576 polymorphism on response to Dupilumab in Asthma, a Genotype stratified, randomized-placebo controlled trial Investigating Dupilumab's Effect in Asthma by genotype- IDEA

- double-blind, randomized, placebo-controlled parallel-group phase 2 clinical trial.
- Patients will be genotyped and categorized and stratified:
  - 1) the wild type allele (Q576/Q576),
  - 2) heterozygous allele (Q576/R576),
  - 3) homozygous mutant allele (R576/R576); the genotype associated with more severe disease.

- This study addresses fundamental mechanisms by which the IL-4Rα-R576 variant drives the TH2/TH17 disease endotype and the influence of this variant on response to Dupilumab therapy.

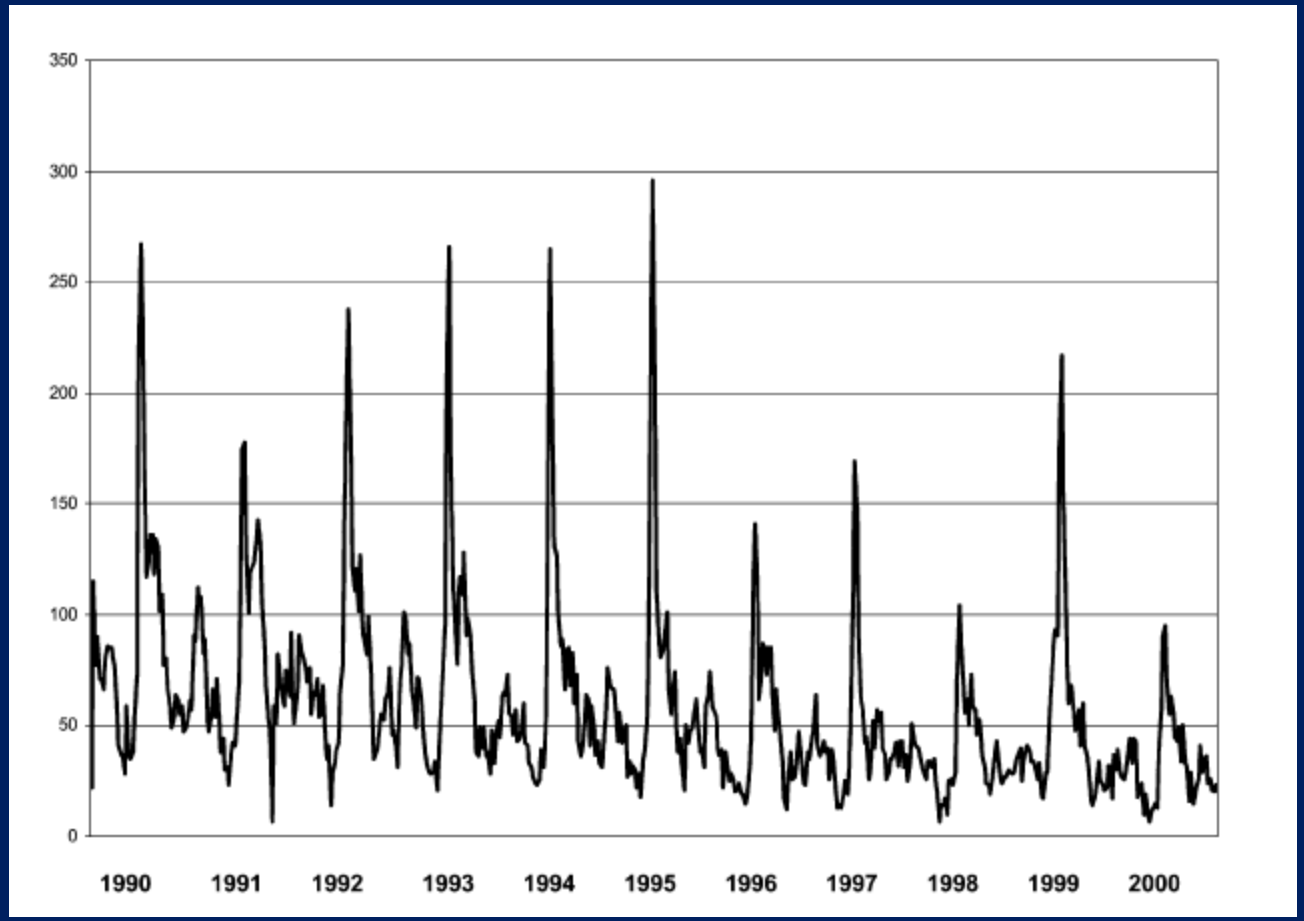
- Asthmatics bearing this endotype will be particularly likely to favorably respond to Dupilumab

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Can we improve our timing of therapy?

FIG 1. Number of hospitalizations of children age 5 to 15 years by week of the year in Ontario from 1990 to 2000.



Johnston N et al. JACI 2005;115:132-8

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

Hypothesis:

- Short-term targeted treatment can potentially prevent fall asthma exacerbations while limiting therapy exposure.

Objective:

- Compared (1) omalizumab with placebo and (2) omalizumab with an inhaled corticosteroid (ICS) boost with regard to fall exacerbation rates when initiated 4 to 6 weeks before return to school.

Methods:

- A 3-arm, randomized, double-blind, double placebo controlled, multicenter clinical trial was conducted among inner-city asthmatic children aged 6 to 17 years with 1 or more recent exacerbations
- Guidelines-based therapy was continued over a 4- to 9-month run-in phase and a 4-month intervention phase.

Teach JACI 2015;136:1476-85

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

Results:

- The fall exacerbation rate was significantly lower in the omalizumab versus placebo arm (11.3% vs 21.0%; OR, 0.48; 95% CI, 0.25-0.92)

- In a pre-specified subgroup analysis, among participants with an exacerbation during the run-in phase, omalizumab was significantly more efficacious than both placebo (6.4% vs 36.3%; OR, 0.12; 95% CI, 0.02-0.64)

Teach JACI 2015;136:1476-85

Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations

- Cost of omalizumab is a limitation, but their findings help identify populations most likely to respond to pre-seasonal treatment.
- For those patients, the reduced cost of treatment for only the fall season to prevent an exacerbation compared with a full year of treatment might be justifiable.
- This suggests a paradigm shift for managing high-risk patients.

Teach JACI 2015;136:1476-85

Comorbidities

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

- I. Executive Summary
- II. Scope and purpose
- III. Introduction
- IV. Methods
- V. How to use these guidelines
- VI. Definition of Severe Asthma
  - Stage 1: Confirm asthma diagnosis and identify difficult-to-treat asthma *
  - Stage 2: Differentiate severe asthma from milder asthma*
  - Stage 3: Determine whether severe asthma is controlled or uncontrolled

Chung ERJ 2014;43:343-73

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  - Stage 2: Differentiate severe asthma from milder asthma*
  - Stage 3: Determine whether severe asthma is controlled or uncontrolled

***consider comorbidities, poor inhaler technique and adherence to rx**

Chung ERJ 2014;43:343-73

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

TABLE 7 Comorbidities and contributory factors

1) Rhinosinusitis/(adults) nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety, depression
3) Vocal cord dysfunction
4) Obesity
5) Smoking/smoking related disease
6) Obstructive sleep apnoea
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
9) Gastro-oesophageal reflux disease (symptomatic)
10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors

Chung ERJ 2014;43:343-73

Chronic Rhinosinusitis (CRS)

- Inflammatory disorder of the nasal mucosa and paranasal sinuses, characterized by at least 12 weeks of symptoms
- US prevalence: 3.0% to 6.4%

de Loos D, et al. *J Allergy Clin Immunol.* 2019;143(3):1207-1214

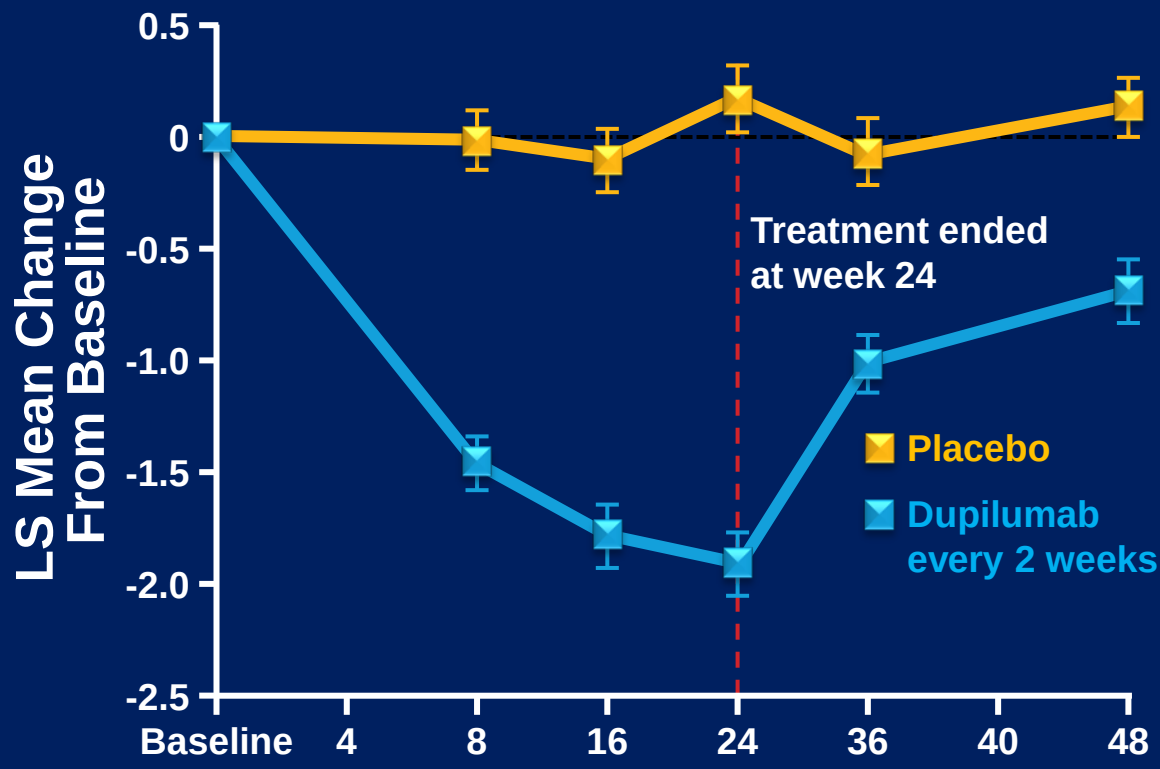
- With significant downstream issues
  - More asthma and allergic rhinitis diagnoses
  - Greater utilization of OCS and macrolides
  - More office and ambulatory care visits
  - Overall healthcare cost burden in the US: $5.7 billion

Bhattacharyya N, et al Laryngoscope. 2019:129:1969–1975

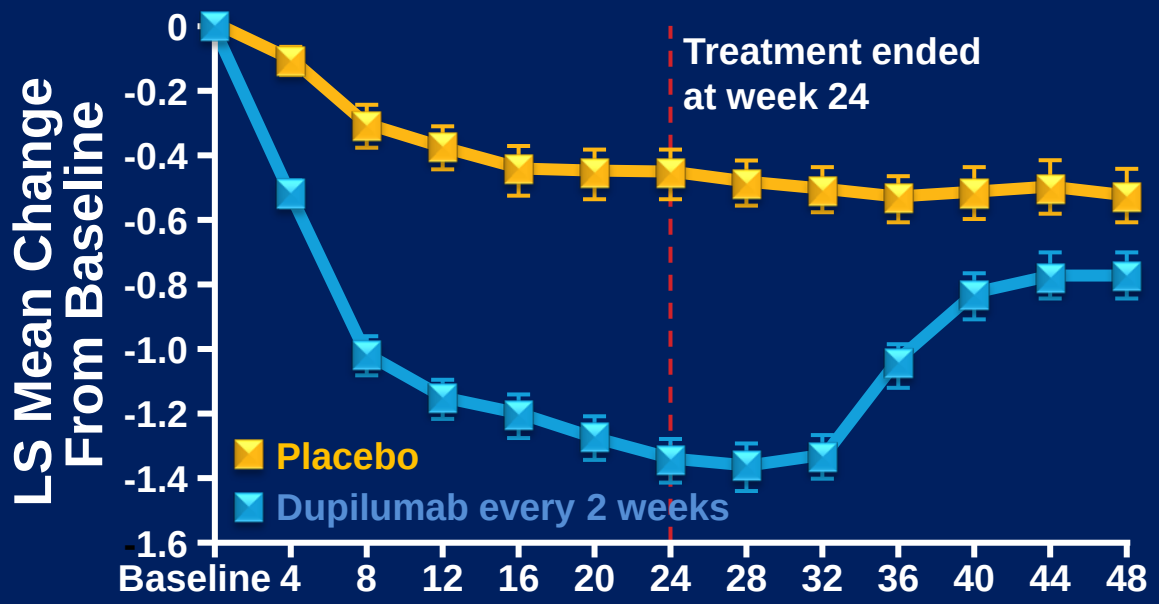
Dupilumab

LIBERTY NP SINUS-24

Nasal polyp score



Nasal congestion or obstruction



Bachert C, et al. *Lancet.* 2019;394(10209):1638-1650.

Phase 3 Investigations of Biologics for CRSwNP *(ClinicalTrials.gov)*

- Omalizumab
  - Phase 3 [NCT03280550, NCT03280537]
  - Open-label extension study ongoing [NCT03478930]
- Benralizumab
  - (ORCHID) [NCT04157335]
- Mepolizumab
  - Phase 3 SYNAPS, [NCT03085797]

ClinicalTrials.gov

Nonadherence: Intentional and Unintentional

Biologic therapy is not a replacement for adherence

Barnes PJ. Chest 2017; 151: 17–20

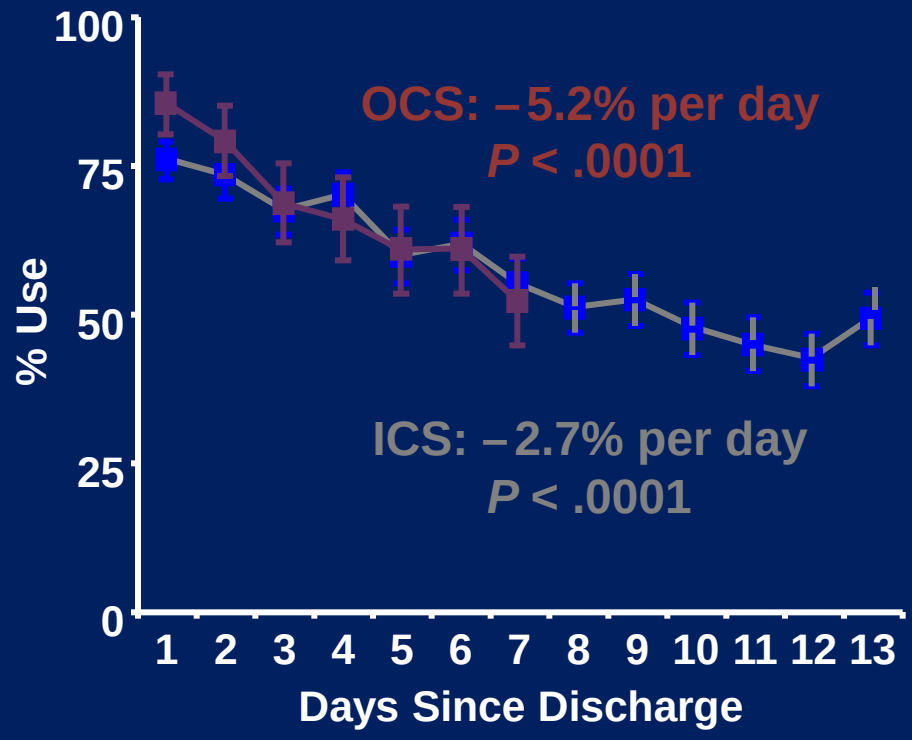
Adherence to Asthma Controller Therapies

- Overall adherence is ≤70%
  - 6%–44% rate of failure to fill initial prescription[1]
  - ICS used as directed <50% of the time, with range of 0%–98%[2]
  - Reported adherence to LTRAs ranges from 18%–68%[3,4]
- In treatment failures, nonadherence should be considered a possible cause

1. World Health Organization 2003. Available at: http://www.who.int/ chronic_conditions/en/adherence_report.pdf. Accessed May 16, 2007. 2. Walders N. *J Pediatr*. 2005;146:177-182. 3. Balkrishnan R. *J Asthma*. 2005;1:35-40. 4. ones C. *J Asthma*. 2003;40:93-101

Adherence - Decline in Corticosteroid Use in Adults After Hospital Discharge

- ICS and OCS use fell to ≈50% by day 7
- Poor ICS adherence in 40.8% of patients 14 days after discharge
- Poor OCS adherence in 27.1% of patients over 7 days



ICS = inhaled corticosteroid; OCS = oral corticosteroid.

Krishnan JA, et al. *Am J Respir Crit Care Med.2004;* 170:1281-1285.

Critical Errors in Inhaler Technique among Children Hospitalized with Asthma

- Conducted a prospective cross-sectional study in a tertiary children's hospital for children 2-16 years of age admitted for an asthma exacerbation, and inhaler technique demonstrations were evaluated in attempt to identify risk factors of improper use.

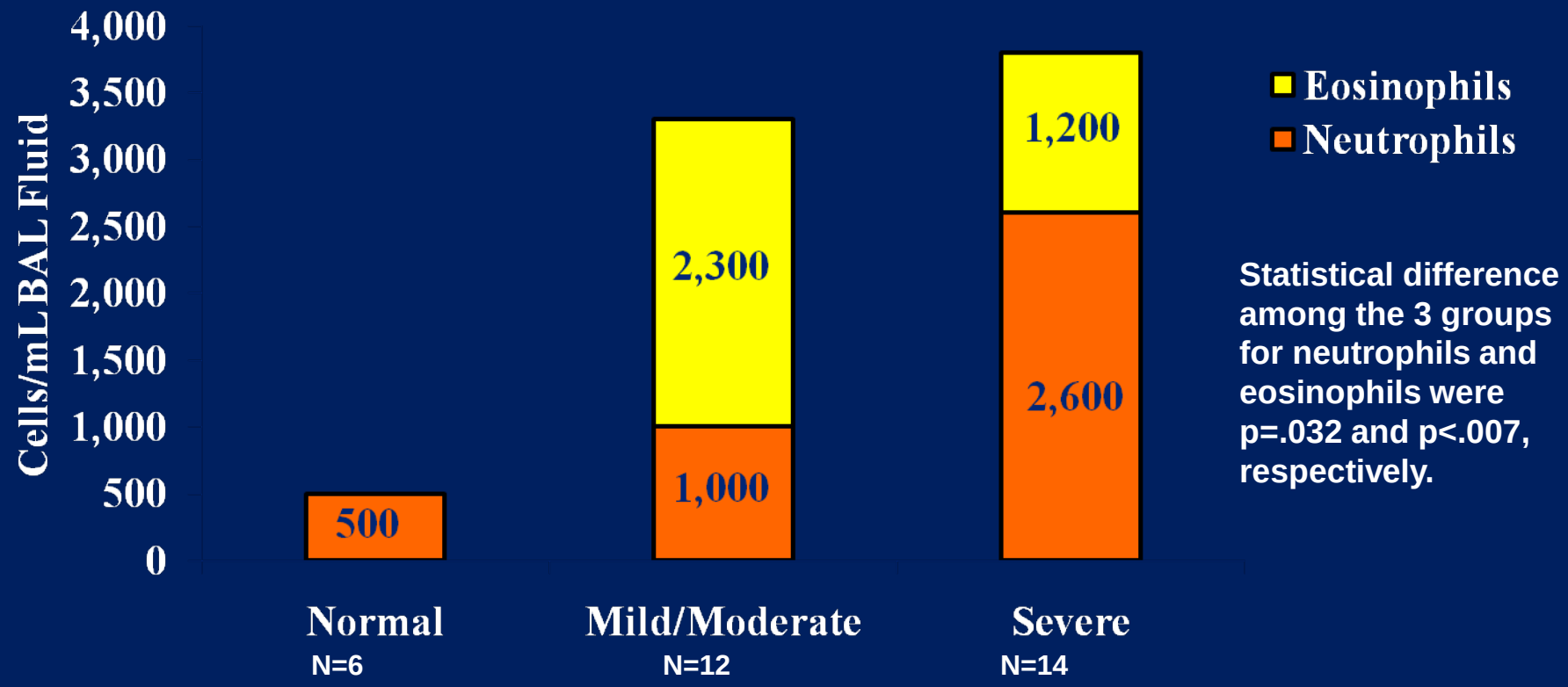
- Of 113 participants enrolled, 42% missed a critical step in inhaler technique.

- More patients missed a critical step when they:
  - used a spacer with mouthpiece instead of a spacer with mask (75% vs 36%)
  - were older (7.8 vs 5.8 years).

Samady JI of Hosp Med 2019

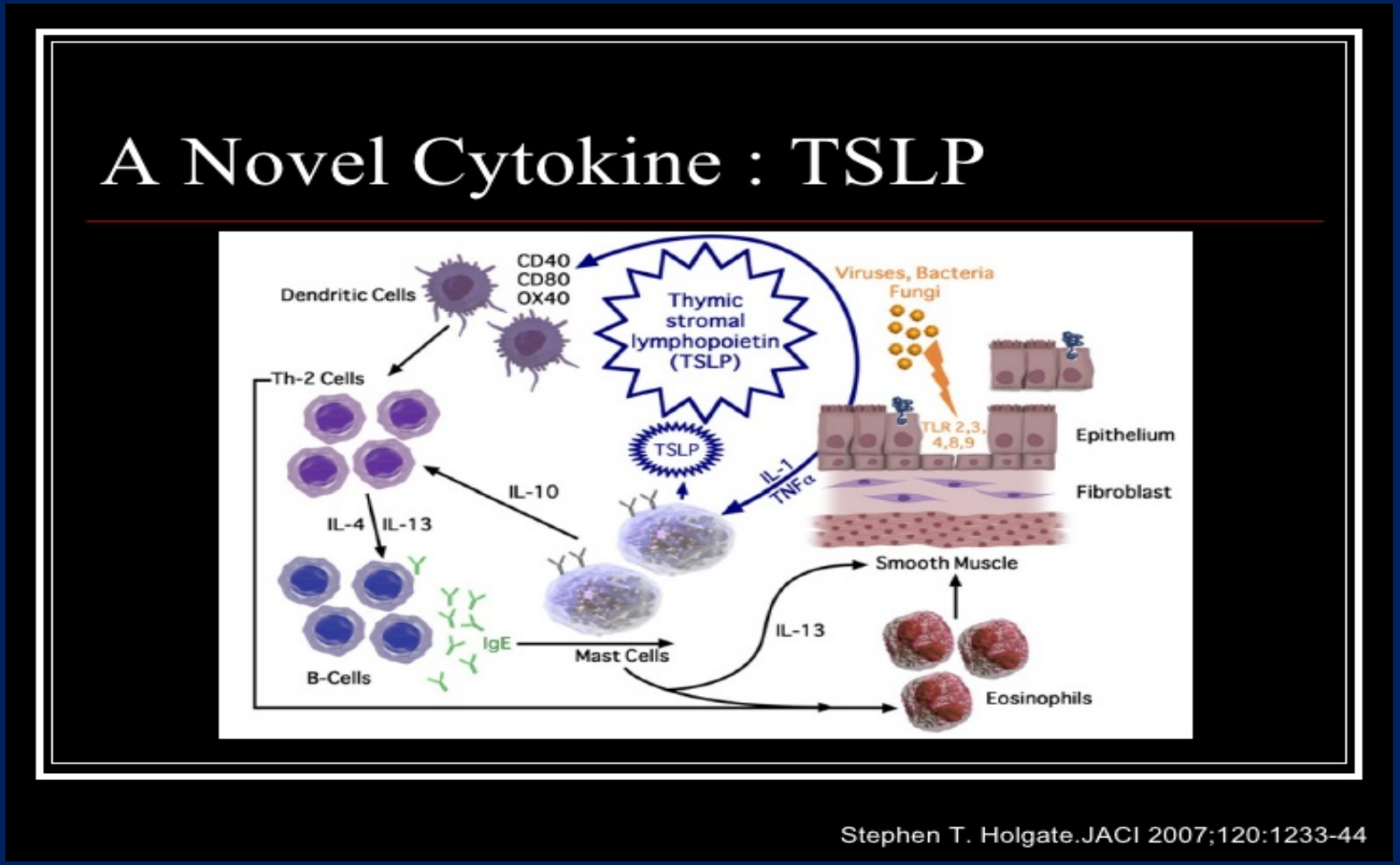
Increased Neutrophilic Inflammation in Severe Steroid-Dependent Asthmatics

BAL Cell Differentials



Statistical difference among the 3 groups for neutrophils and eosinophils were p=.032 and p<.007, respectively.

Wenzel SE et al. *Am J Respir Crit Care Med* 1997;156:737-743.



- Monoclonal antibody directed against thymic stromal lymphopoietin (TSLP).
- As TSLP is a more upstream molecule, secreted by epithelial cells with effector functions on many cells, including eosinophils, mast cells, Th2 cells, basophils and others it is hoped that its blockade will provide efficacy for both the T2 high and low phenotypes.

Tezepelumab in Adults with Uncontrolled Asthma

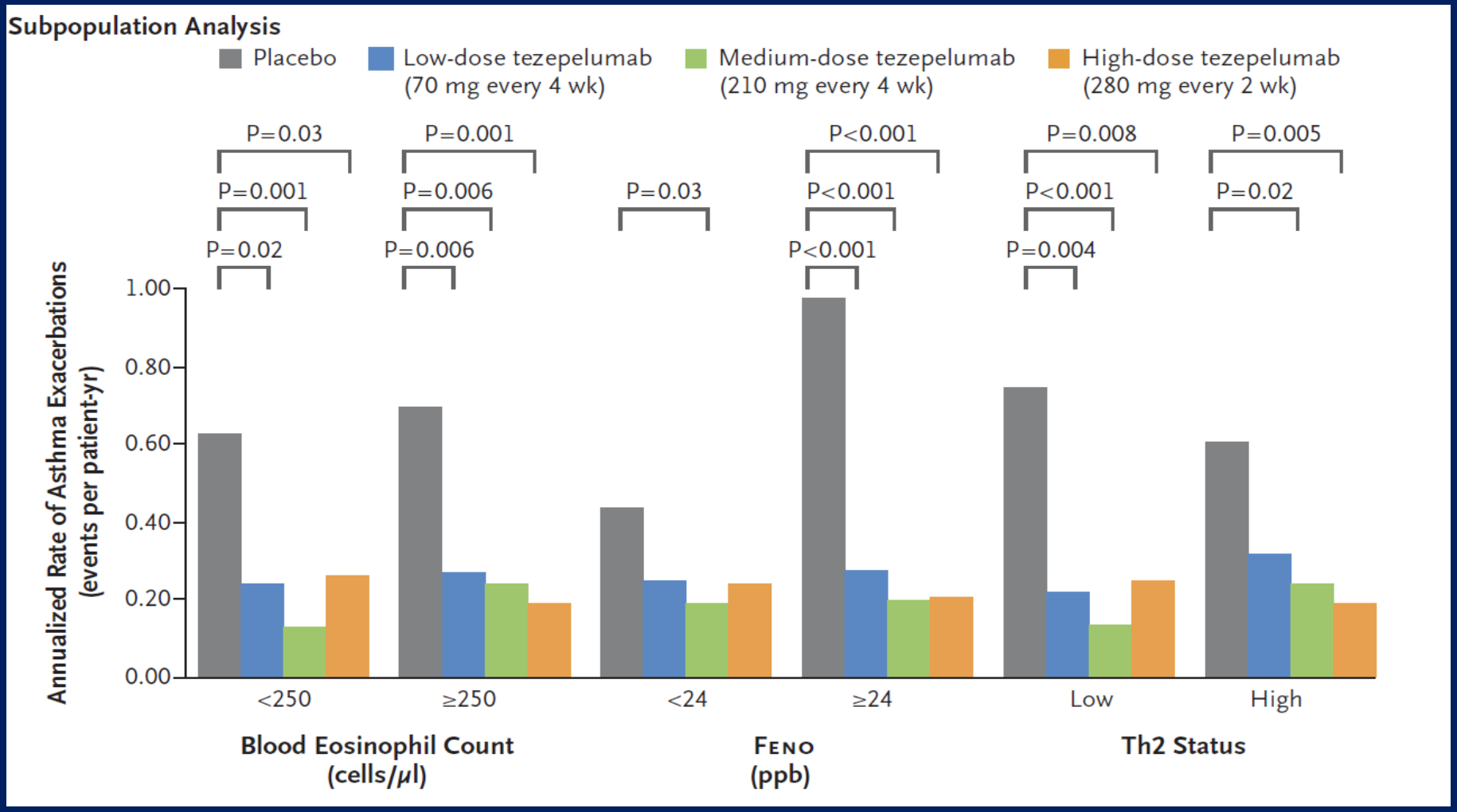
METHODS

- Phase 2, randomized, double-blind, placebo-controlled trial, compared subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period (584 subjects) in subject with breakthrough on ICS/LABA.

- The primary end point was the annualized rate of asthma exacerbations (events per patient-year) at week 52.
- Examined T2-hi and TH-lo population

Corren NEJM 2017;377:936-46

Figure 1. Annualized Rate of Asthma Exacerbations at Week 52, According to Baseline Biomarker Status



Corren NEJM 2017;377:936-46

Tezepelumab in Adults with Uncontrolled Asthma

Conclusion:

- Among patients treated with long-acting beta-agonists and medium-to-high doses of ICS, those who received tezepelumab had lower rates of clinically significant asthma exacerbations vs placebo, independent of BL blood eo counts.

Corren NEJM 2017;377:936-46

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

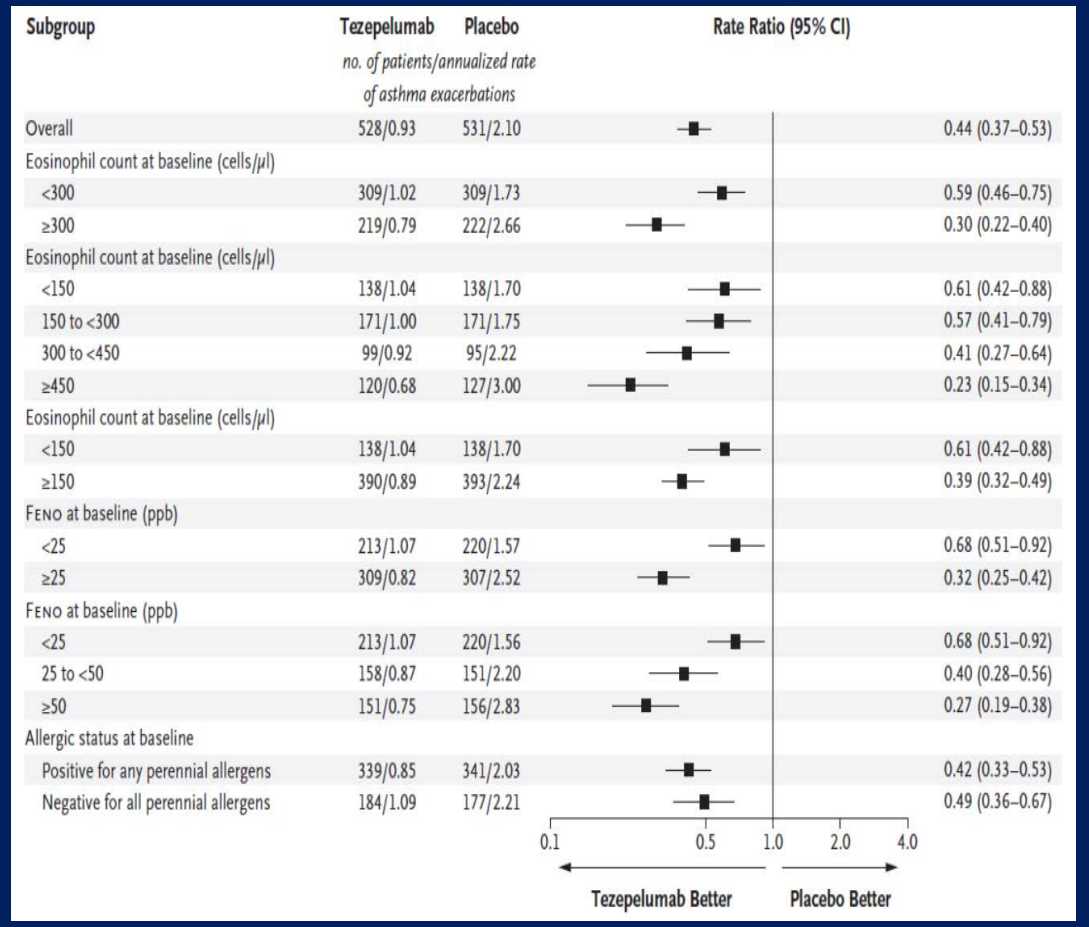
METHODS

- phase 3, multicenter, randomized, double-blind, placebo-controlled trial.
- Patients (12 to 80 years of age) were randomly assigned to receive teze (210 mg) or placebo subcutaneously every 4 weeks for 52 weeks.
- The primary end point was the annualized rate of asthma exacerbations over a period of 52 weeks.
- This end point was also assessed in patients with baseline blood eosinophil counts of less than 300 cells per microliter.
- Secondary end points included the
  - FEV1
  - ACQ–6 (range, 0 [no impairment] to 6 [maximum impairment]),
  - AQLQ (range, 1 [maximum impairment] to 7 [no impairment]),
  - Asthma Symptom Diary (ASD; range, 0 [no symptoms] to 4 [worst possible symptoms]).

Menzies-Gow NEJM 2021;384:1800-9

Figure 1. Annualized Rate of Asthma Exacerbations over a Period of 52 Weeks in the Overall Population and According to Baseline Biomarker Category or Allergic Status.

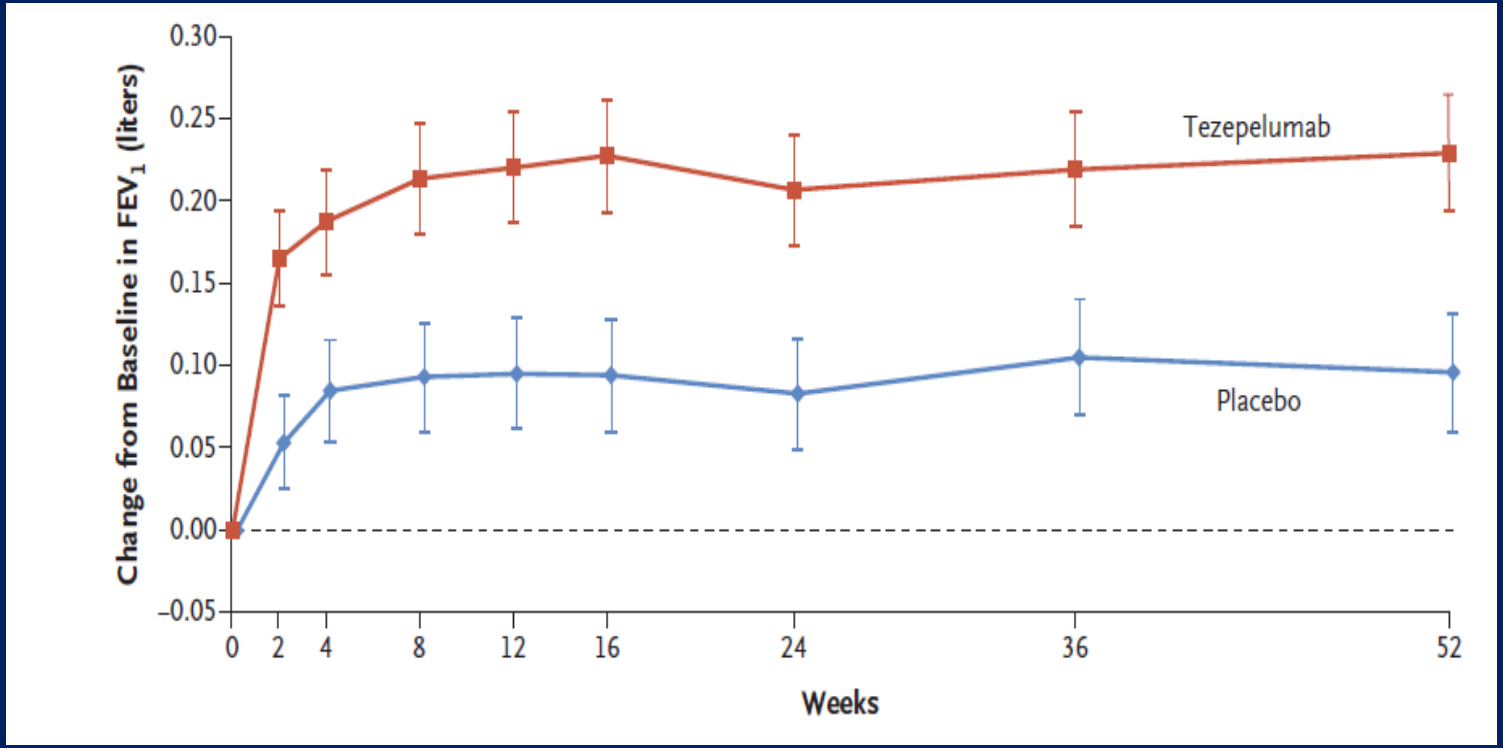
- The annualized rate of asthma exacerbations was:
  - 0.93 (95% confidence interval [CI], 0.80 to 1.07) with teze:
  - 2.10 (95% CI, 1.84 to 2.39) placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001).
- In patients with a blood eosinophil count of less than 300 cells per microliter, the annualized rate was:
  - 1.02 (95% CI, 0.84 to 1.23) with teze
  - 1.73 (95% CI, 1.46 to 2.05) with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001).



Menzies-Gow NEJM 2021;384:1800-9

Figure 2. Change from Baseline to Week 52 in Prebronchodilator FEV1

- At week 52, improvements were greater with teze than with placebo with respect to the prebronchodilator FEV1 :
  - 0.23 vs. 0.09 liters (P<0.001)



Menzies-Gow NEJM 2021;384:1800-9

Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison

Background

- Three anti–IL-5 pathway–directed therapies are approved for use in patients with severe eosinophilic asthma (SEA); however, no head-to-head comparison data are available.

Objective

- Compared the efficacy of licensed doses of mepo, benra and res in patients with SEA, according to baseline blood eos counts.

Methods

- This indirect treatment comparison (ITC) used data from a Cochrane review and independent searches.
- End points included annualized rate of clinically significant exacerbations and change from baseline in ACQ score and FEV_1 stratified by baseline blood eosinophil count.

Busse JACI 2019;143:190-200.

Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison

Results

- Eleven studies were included and all treatments significantly reduced the rate of clinically significant exacerbations and improved asthma control versus placebo in all blood eosinophil count subgroups.

- Mepolizumab reduced clinically significant exacerbations by 34% to 45% versus benralizumab across subgroups (rate ratio ≥400 cells/μL: 0.55 [95% CI, 0.35-0.87]; ≥300 cells/μL: 0.61 [95% CI, 0.37-0.99]; and ≥150 cells/μL: 0.66 [95% CI, 0.49-0.89]; all < .05) and by 45% versus reslizumab in the 400 cells/μL or greater subgroup (rate ratio, 0.55 [95% CI, 0.36-0.85]; = .007).

- Asthma control was significantly improved with mepolizumab versus benralizumab (all subgroups: < .05) and versus reslizumab in the 400 cells/μL or greater subgroup (= .004). Benralizumab significantly improved lung function versus reslizumab in the 400 cells/μL or greater subgroup (= .025).

Busse JACI 2019;143:190-200.

Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review

Methods

- Performed a matching-adjusted indirect comparison (MAIC) of benralizumab versus mepolizumab and reslizumab.
- Benralizumab patient-level data were weighted to match treatment-effect-modifying patient characteristics of comparator trials before indirect efficacy comparisons.

Results

- After matching adjustment, benralizumab and mepolizumab reduced exacerbations versus placebo by 52% and 49%, respectively (rate ratio [RR] 0.94, 95% CI 0.78–1.13; n=1524) and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR 1.00, 95% CI 0.57–1.75; n=1524).

Bourdin ERJ 2018; 52: 1801393

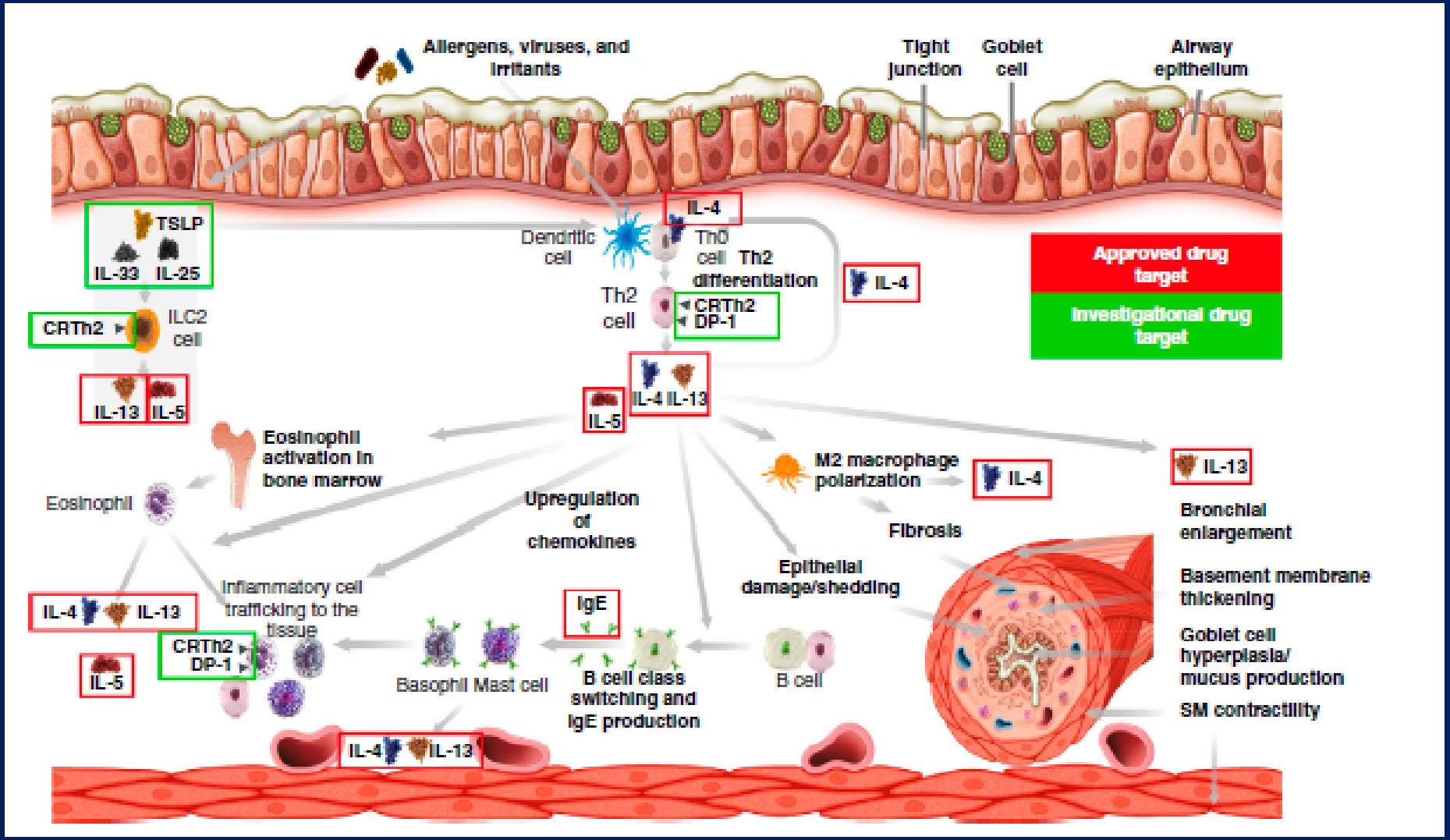
Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review

Results

- Benralizumab and mepolizumab similarly improved pre-bronchodilator forced expiratory volume in 1 s at 32 weeks (difference 0.03 L, 95% CI −0.06–0.12; n=1443).
- Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC. MAIC is a robust way to indirectly compare treatment efficacies from trials with heterogeneous patient populations.
- When baseline patient characteristics were matched across asthma trials, benralizumab and mepolizumab yielded similar efficacy

Bourdin ERJ 2018; 52: 1801393

www.bing.com/images

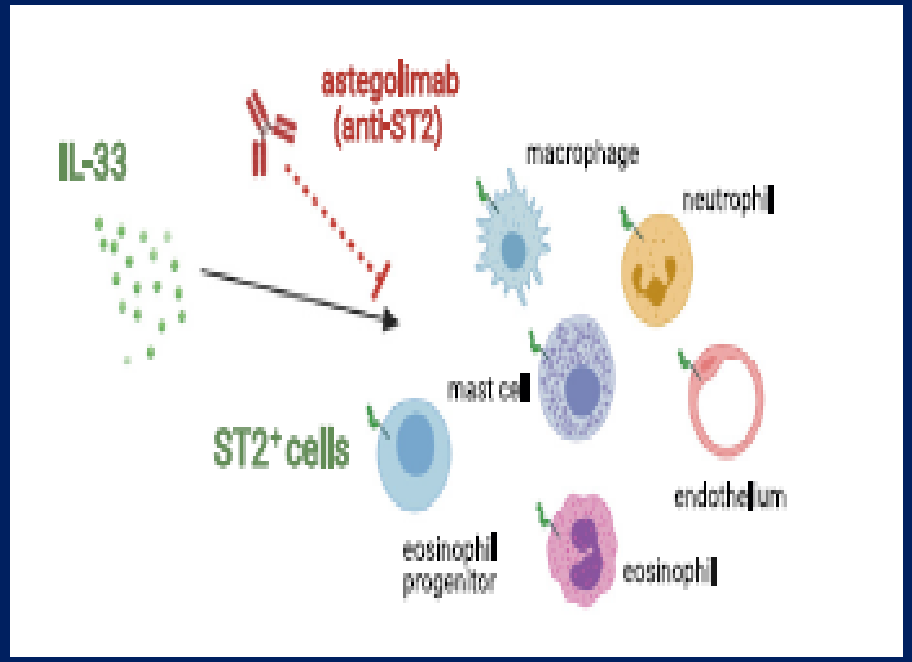


McGregor AJRCCM 2019;191:433-45

Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

Background:

- The IL-33/ST2 pathway is linked with asthma susceptibility.
- Inhaled allergens, pollutants, and respiratory viruses, which trigger asthma exacerbations, induce release of IL-33, an epithelial-derived ‘‘alarmin.’’
- Astegolimab, a human IgG2 mAb, selectively inhibits the IL-33 receptor, ST2.



Kelsen JACI 2021;148:790-8

Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

Methods:

- This double-blind, placebo-controlled, dose-ranging study randomized adults with severe asthma to subcutaneous placebo or 70-mg, 210-mg, or 490-mg doses of astegolimab every 4 weeks.
- The primary endpoint was the annualized asthma exacerbation rate (AER) at week 54.
- Enrollment caps ensured 30 patients who were eosinophil-high (>300 cells/mL) and 95 patients who were eosinophil-low (<300 cells/mL) per arm.

Kelsen JACI 2021;148:790-8

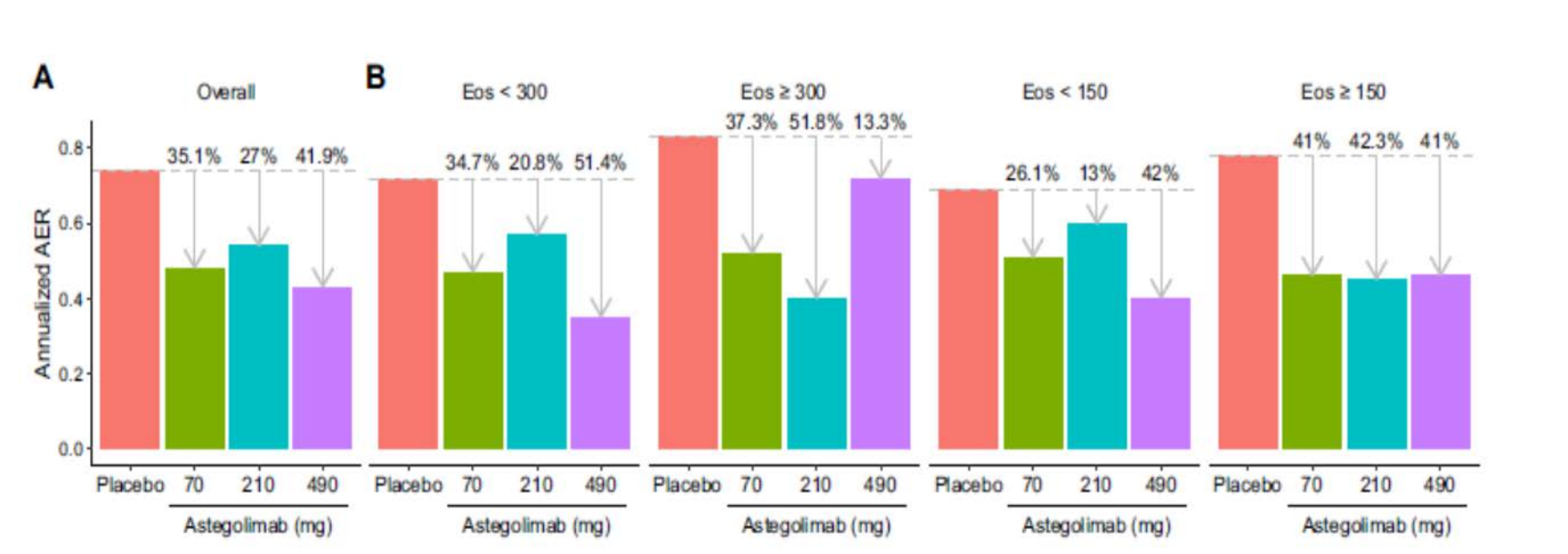
Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

Results:

- Overall, adjusted AER reductions relative to placebo were :
- 43% (P =.005), 490- mg
- 22% (P =.18), 210-mg
- 37% (P =.01) 70-mg doses of astegolimab.
- Adjusted AER reductions for patients who were eosinophil-low were comparable to reductions in the overall population:
  - 54% (P = .002) 490-mg
  - 14% (P = .48), 210- mg
  - 35% (P = .05) 70-mg doses of astegolimab.
- Adverse events were similar in astegolimab- and placebo-treated groups.

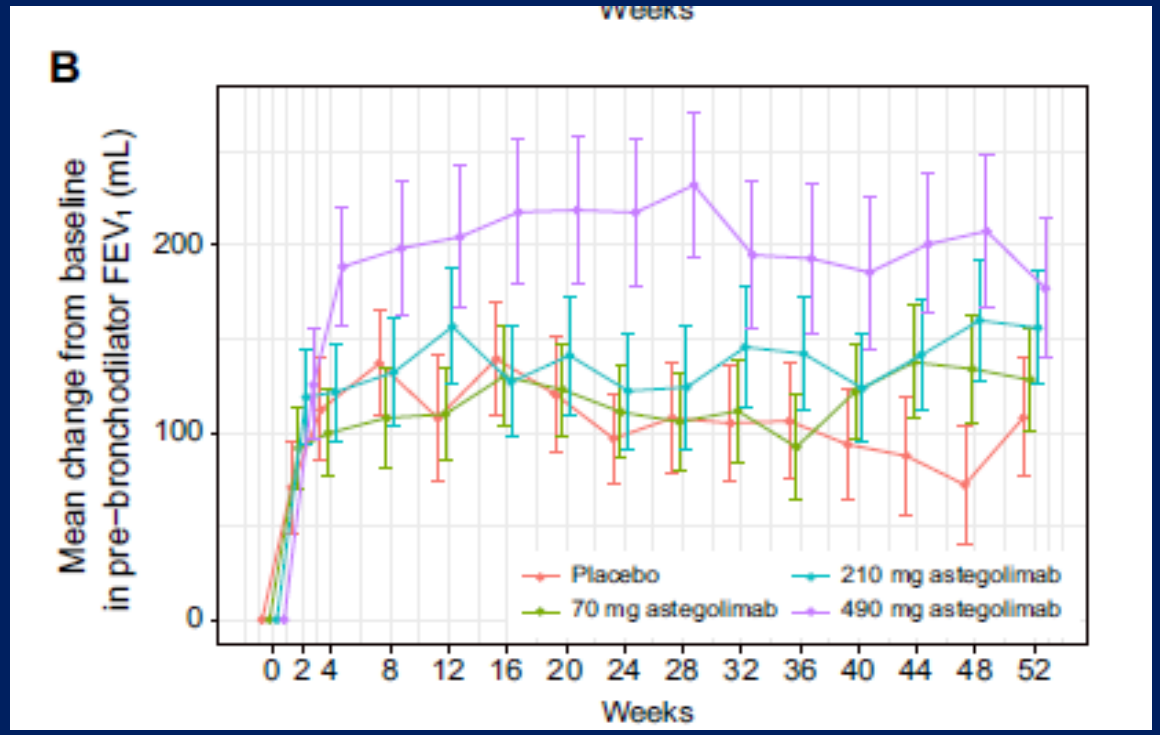
Kelsen JACI 2021;148:790-8

FIG 1. Annualized AERs in the (A) overall population and in (B) patients stratified by baseline eosinophil levels.



Kelsen JACI 2021;148:790-8

Absolute change in FEV1 from baseline to week 54.



Kelsen JACI 2021;148:790-8

Heterogeneity of Paucigranulocytic Asthma: A Prospective Cohort Study with Hierarchical Cluster Analysis

BACKGROUND:

- Asthma, a heterogeneous disease, can be divided into 4 inflammatory phenotypes using induced sputum cell counts:
  - eosinophilic asthma (EA),
  - neutrophilic asthma (NA),
  - mixed granulocytic asthma,
  - paucigranulocytic asthma (PGA).
- Although research has focused on EA and NA, there is little known about PGA.
- OBJECTIVE:
- To study the heterogeneity of PGA and identify possible PGA clusters to guide clinical treatment.

METHODS:

- Patients with PGA were grouped by hierarchical cluster analysis and enrolled into a prospective cohort study to validate the clusters, relative to future risk of asthma exacerbations in a real-world setting.

Deng J Allergy Clin Immunol Pract 2021;9:2344-55

Heterogeneity of Paucigranulocytic Asthma: A Prospective Cohort Study with Hierarchical Cluster Analysis

RESULTS:

- Cluster analysis of 145 patients with PGA identified 3 clusters:
- cluster 1 (n=110, 75.9%) was “mild PGA”
- cluster 2 (n = 20, 13.8%) assoc psychological dysfunction and rhinoconjunctivitis and other allergic diseases”
- cluster 3 (n =15, 10.3%) was “smoking-associated PGA.”
- Cluster 3 had significantly increased risk of:
  - severe exacerbation RR =6.43, P < .01
  - emergency visit (RR = 8.61, P < .03)
  - hospitalization (RR =12.94, P < .01).
- Although PGA can transform into or develop from other phenotypes, 70% were stable over time.

CONCLUSIONS:

- Among 3 identified PGA clusters, cluster 3 had a higher risk of severe exacerbation. PGA heterogeneity indicates the requirement of novel targeted interventions.

Deng J Allergy Clin Immunol Pract 2021;9:2344-55

Original Article

Estimation of Health and Economic Benefits of Clinic Versus Home Administration of Omalizumab and Mepolizumab

Marcus Shaker, MD, MSc[a,b], Aaron Briggs, MD[b], Ahmad Dbouk, MD[b], Emily Dutille, PharmD[a,b], John Oppenheimer, MD[c], and Matthew Greenhawt, MD, MBA, MSc[d] *Lebanon and Hanover, NH; Newark, NJ; and Aurora, Colo*

BACKGROUND:

- Biologic therapy is associated with concerns for therapy-associated anaphylaxis which may limit access to these therapies for patients unable to travel to medical clinics, especially with concerns regard CV19.

OBJECTIVE:

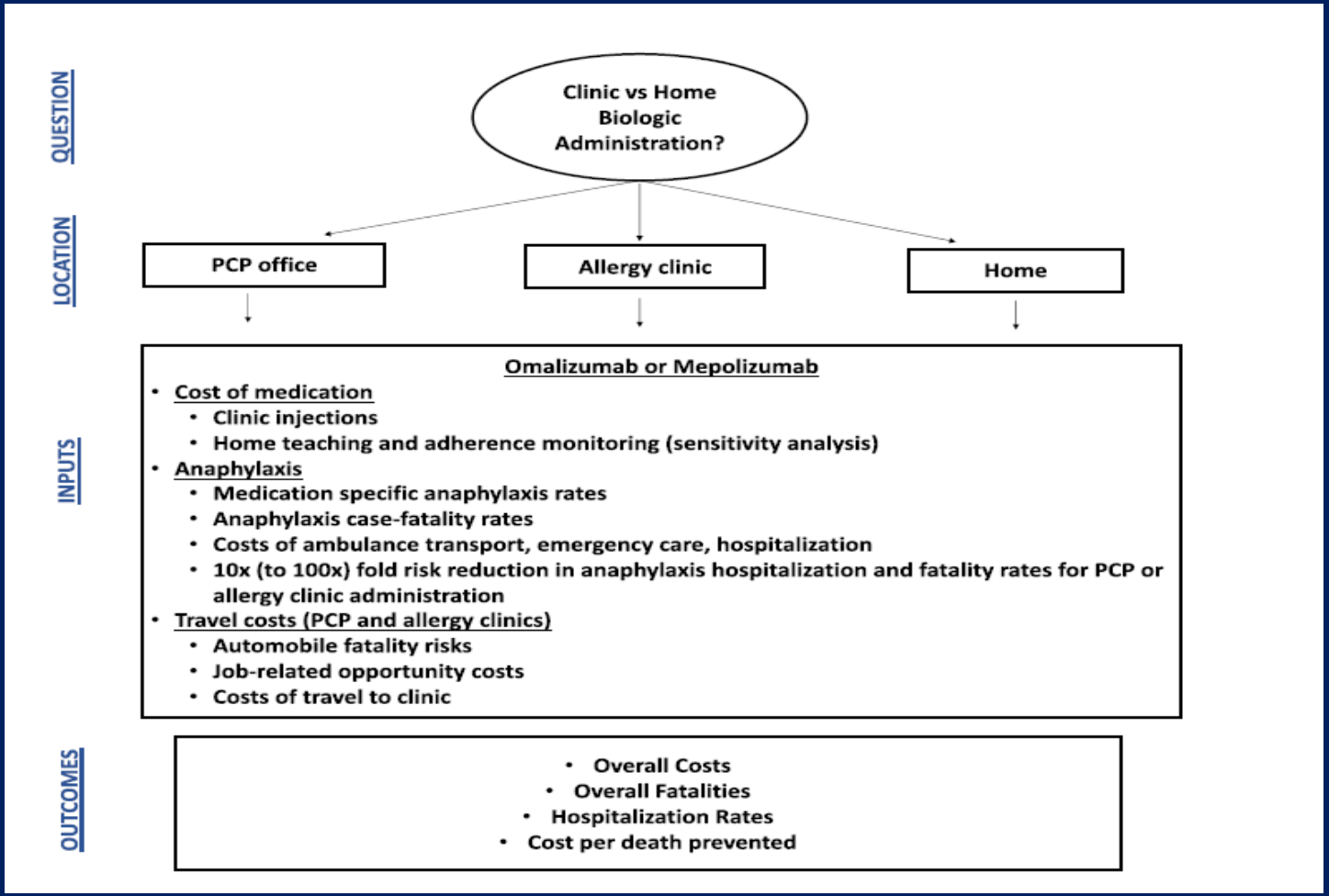
- To characterize the cost-effectiveness of in-clinic versus at-home biologic therapy with omalizumab and mepolizumab.

METHODS:

- Economic evaluation using microsimulations was performed from societal and health care sector perspectives for patients with asthma or chronic spontaneous urticaria receiving omalizumab or mepolizumab in an allergy clinic, primary care provider (PCP) office, or at home over a 1-year period.

Shaker JACI in Pract 2020;8:565-72

FIGURE 1. Evaluation of health and economic benefits of clinic vs home biologic administration



Shaker JACI in Pract 2020;8:565-72

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RESULTS:

- In the omalizumab societal analysis, annual PCP and allergy clinic administration cost $1369.14 (mean) +/–$51.33 (SD) and $1916.68 +/– $40.86, respectively.
- Small reductions in medication-related fatalities with in-clinic administration
- were offset by the potential increase in automobile fatalities resulting from traveling to the allergy clinic (14.6 – 15.0 per million person-years for this strategy).

CONCLUSIONS:

- For many patients, at-home administration of omalizumab may be a cost-effective strategy.

Shaker JACI in Pract 2020;8:565-72

Asthma Patients Who Stop Asthma Biologics Have a Similar Risk of Asthma Exacerbations as Those Who Continue Asthma Biologics

OBJECTIVE:

- There is limited information about outcomes associated with stopping asthma biologics.
- To compare outcomes in people who stopped or continued asthma biologics.

METHODS:

- Identified a cohort of people with asthma who stopped or continued asthma biologics exploring multiple potential confounders.
- Primary outcome used to assess failure of stopping was an increase of 50% or more in the asthma exacerbation rate in the 6 months after discontinuing the biologic compared with the 6-month period before biologic initiation.

Jeffery JACI in Pract 2021;9:2742-50

Asthma Patients Who Stop Asthma Biologics Have a Similar Risk of Asthma Exacerbations as Those Who Continue Asthma Biologics

RESULTS:

- Identified a matched cohort of 1247 stoppers and 1247 people who continued biologic use for at least 18 months.
- In the first 6 months after stopping, 10.2% of stoppers and 9.5% of continuers had an increase of 50% or more in asthma exacerbations.

CONCLUSIONS:

- An increase in asthma exacerbations is infrequently observed in people who stopped asthma biologics and was observed at similar rates as in matched controls who continued asthma biologics

Jeffery JACI in Pract 2021;9:2742-50

Asthma Patients Who Stop Asthma Biologics Have a Similar Risk of Asthma Exacerbations as Those Who Continue Asthma Biologics

Discussion:

- Previous randomized trials with omalizumab and mepolizumab in which a group had their biologic discontinued demonstrated a consistent pattern of a small but statistically significant increase in asthma exacerbations in people randomly assigned to stop the biologic agent.
  - Ledford JACI 2017;140:162-169
  - clinicaltrials.gov/ ct2/show/NCT02555371.

- The findings of this suggest that patients and their doctors who choose to stop biologics appear to be making appropriate decisions.
- Furthermore:
  - this cohort had low estimated ICS/LABA treatment consistency before starting biologic treatment, with an average MPR below 40%*.
  - more than half of the cohort did not experience an exacerbation in the 6 months before index biologic use.

*The medication possession ratio = sum of days supplied for use during the period divided by the number of days in the period

Jeffery JACI in Pract 2021;9:2742-50


We Can
personalize
MEDICINE

Putting All the Data Together in the Real World

- Severe asthma is very costly
- Before use of biologics consider :
  - Non-adherence
  - Treatment of comorbidities
  - Most likely phenotypes to respond
  - Most appropriate time and place to use
  - Appropriate patient selection with consideration of d/c
- Physicians must appropriately use of biologic agents in a personalized medicine approach, otherwise we will bankrupt the system

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