Biologics Therapies For Severe Asthma

Kenneth Miller MEd, MSRT, RRT-ACCS, AE-C, FAARC

Clinical Educator

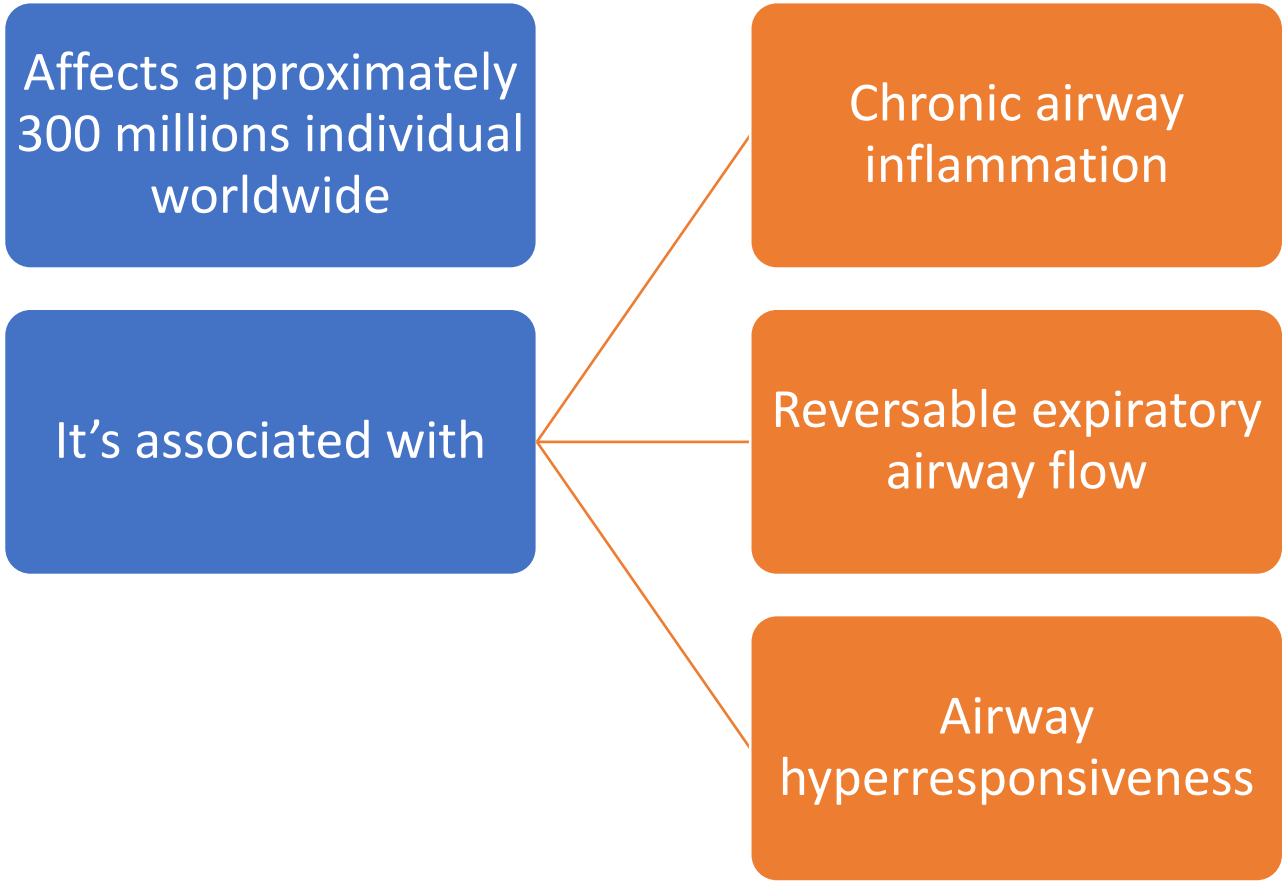
Respiratory Care Services

Lehigh Valley Health Network

Learning Objectives

- Describe the prevalence of asthma
- Define refractory or severe asthma
- Describe the immunologically response in severe asthma
- Review the different biological therapies currently available for the management of severe asthma

The Prevalence of Asthma



Severe Asthma

- Defined as:
  - Poor adherence to inhaled glucocorticoids
  - Poor inhaler technique
  - Continued exposure to triggers and exposures
  - Control remains poor despite addressing the above

Prevalence of Severe Asthma

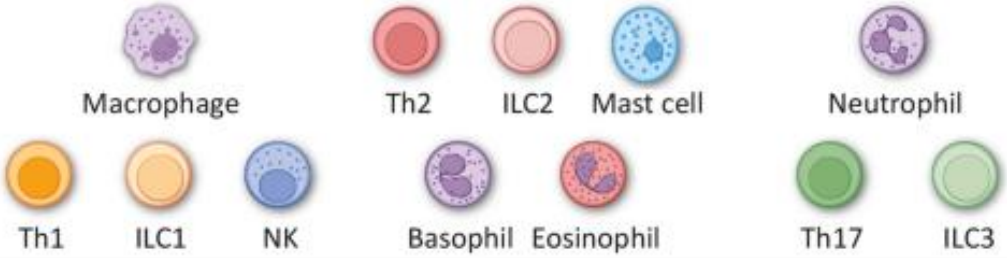
- 10% of adults and 2.5% of children are classified to have severe asthma
- Results in:
  - A reduction in the quality of life
  - Increased healthcare utilization
  - Missed workdays or school days
  - Increase hospitalization
  - Death

These Patients Experience

- Frequent exacerbations
- Repetitive oral steroid burst
- High dose and frequent LABAs and inhaled steroids administration
- Increased medication side effects:
  - Tremor
  - Tachycardia
  - Thrush
  - Cushing syndrome

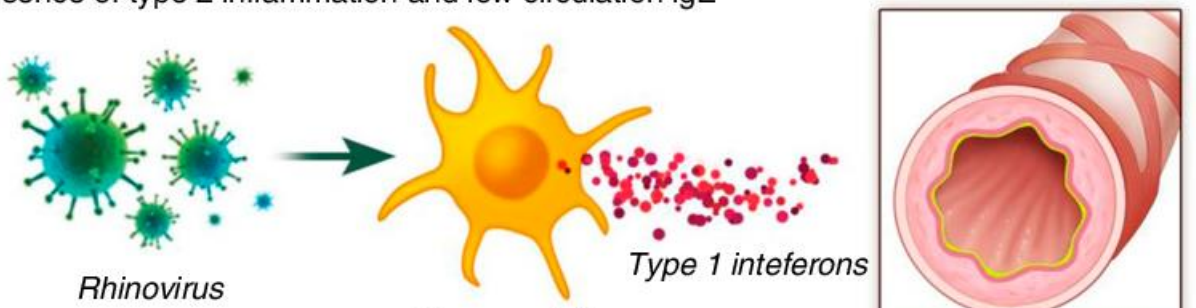
Etiology of Severe Asthma

- Heterogeneous biologically
  - Type 2 high inflammation
    - eosinophilic airway inflammation
    - Interleukins 4
      - Increases secretion of lymphocyctes
    - Interleukins 5
      - Promotes proliferation, activation, and survival of eosinophils
    - Interleukin 13
      - Induces smooth muscle contraction and stimulates nitric oxide synthases in the bronchial cells

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells			
Key cytokines	IFNγ, TNF, IL-6, IL-12, IL-18, IL-2	IL-4, IL-5, IL-13, IL-31	IL-17, IL-6, IL-22, IL-23
Function	• Antitumor activity • Cellular immunity: antiviral/antibacterial • Suppression of type 2	• Humoral immunity: antiparasitic helminths • Neutralizes toxins • Regulates wound repair and regeneration • Suppression of type 1	• Regulation of intestinal epithelial barrier • Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	• Ankylosing spondylitis • Atherosclerosis • Autoimmune gastritis • Diabetes mellitus • Hashimoto thyroiditis • Inflammatory bowel disease • Multiple sclerosis • Rheumatoid arthritis • Sarcoidosis	• Allergy • Anaphylaxis • Type 2 asthma • Atopic dermatitis • Chronic obstructive pulmonary disease with type 2 inflammation • Chronic rhinosinusitis with nasal polyps	• Ankylosing spondylitis • Multiple sclerosis • Psoriasis • Rheumatoid arthritis • Uveitis

Healthy Airway

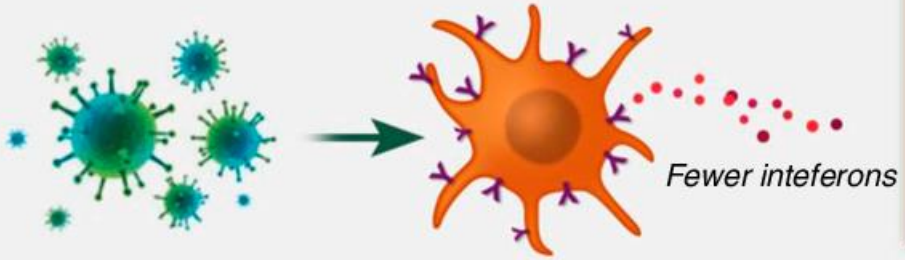
- Absence of type 2 inflammation and low circulation IgE

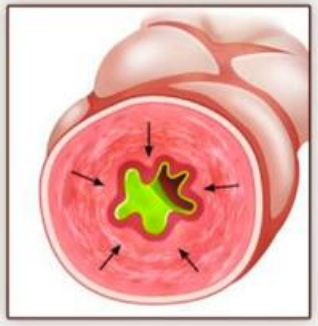


Airway protected from viral infection

Asthmatic Airway

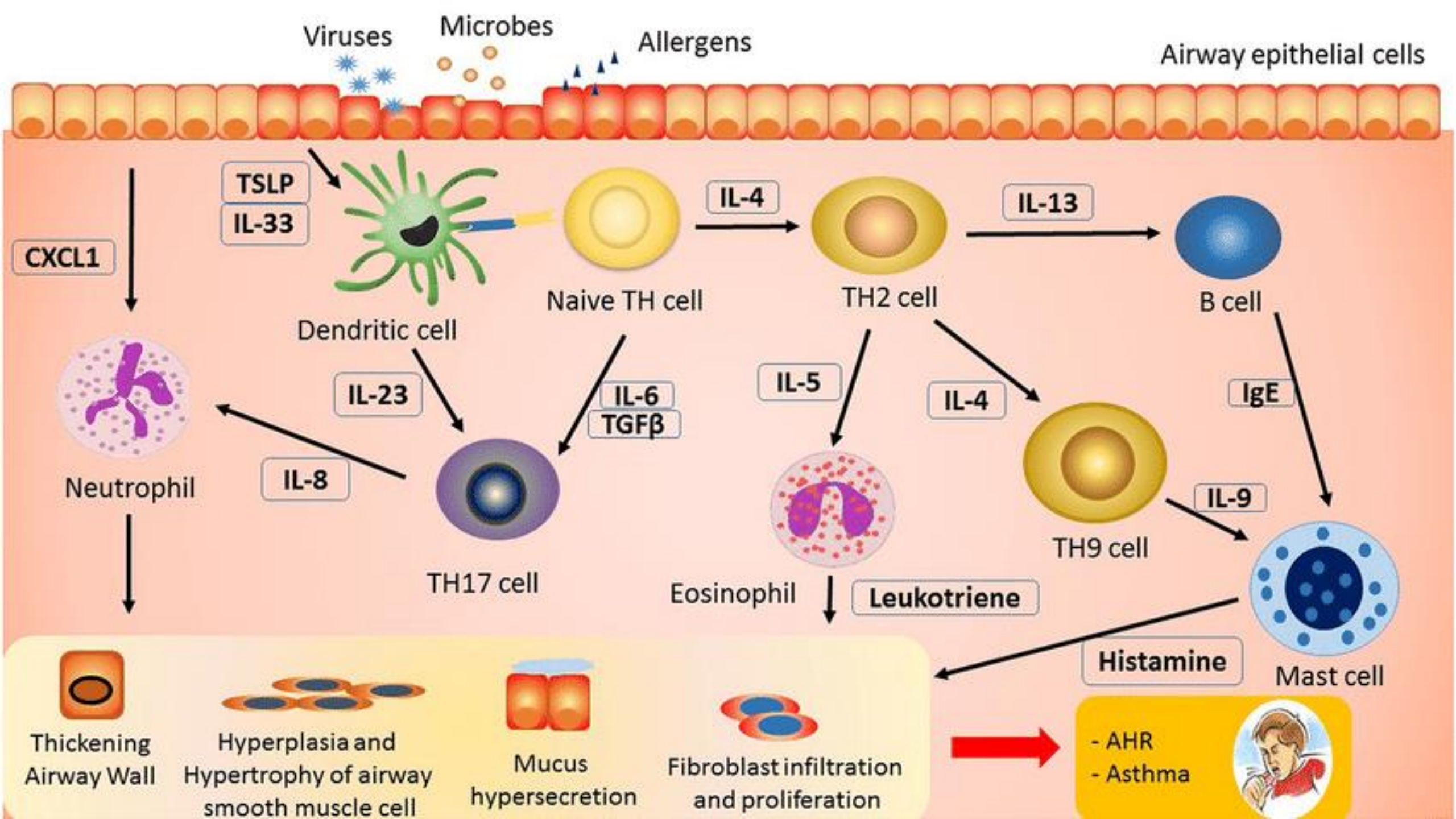
- Presence of type 2 inflammation
- IgE arming of Plasmacytoid Dendritic Cells





Airway susceptible to viral infection

Type 2 asthma	• More severe asthma • Airway and systemic eosinophilia • Responsiveness to corticosteroids • Responsiveness to inhibitors of type 2 inflammation
Non-type 2 asthma	• Less severe asthma • Absence of airway and systemic eosinophilia • Lack of responsiveness to corticosteroids • Lack of responsiveness to inhibitors of type 2 inflammation


Viruses
Microbes
Allergens
Airway epithelial cells
TSLP
IL-33
CXCL1
Dendritic cell
Naive TH cell
IL-4
TH2 cell
IL-13
B cell
IgE
IL-23
IL-6
TGFβ
IL-5
IL-4
IL-8
Neutrophil
TH17 cell
Eosinophil
TH9 cell
IL-9
Leukotriene
Histamine
Mast cell
Thickening Airway Wall
Hyperplasia and Hypertrophy of airway smooth muscle cell
Mucus hypersecretion
Fibroblast infiltration and proliferation
- AHR
- Asthma

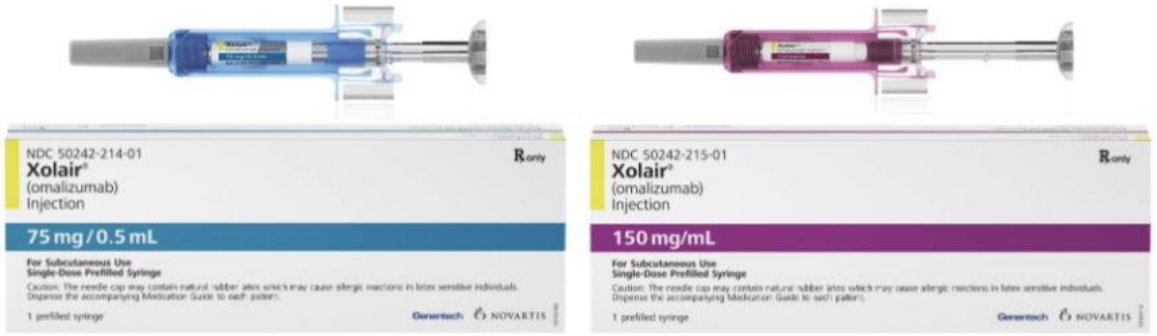
Severe Asthmatics

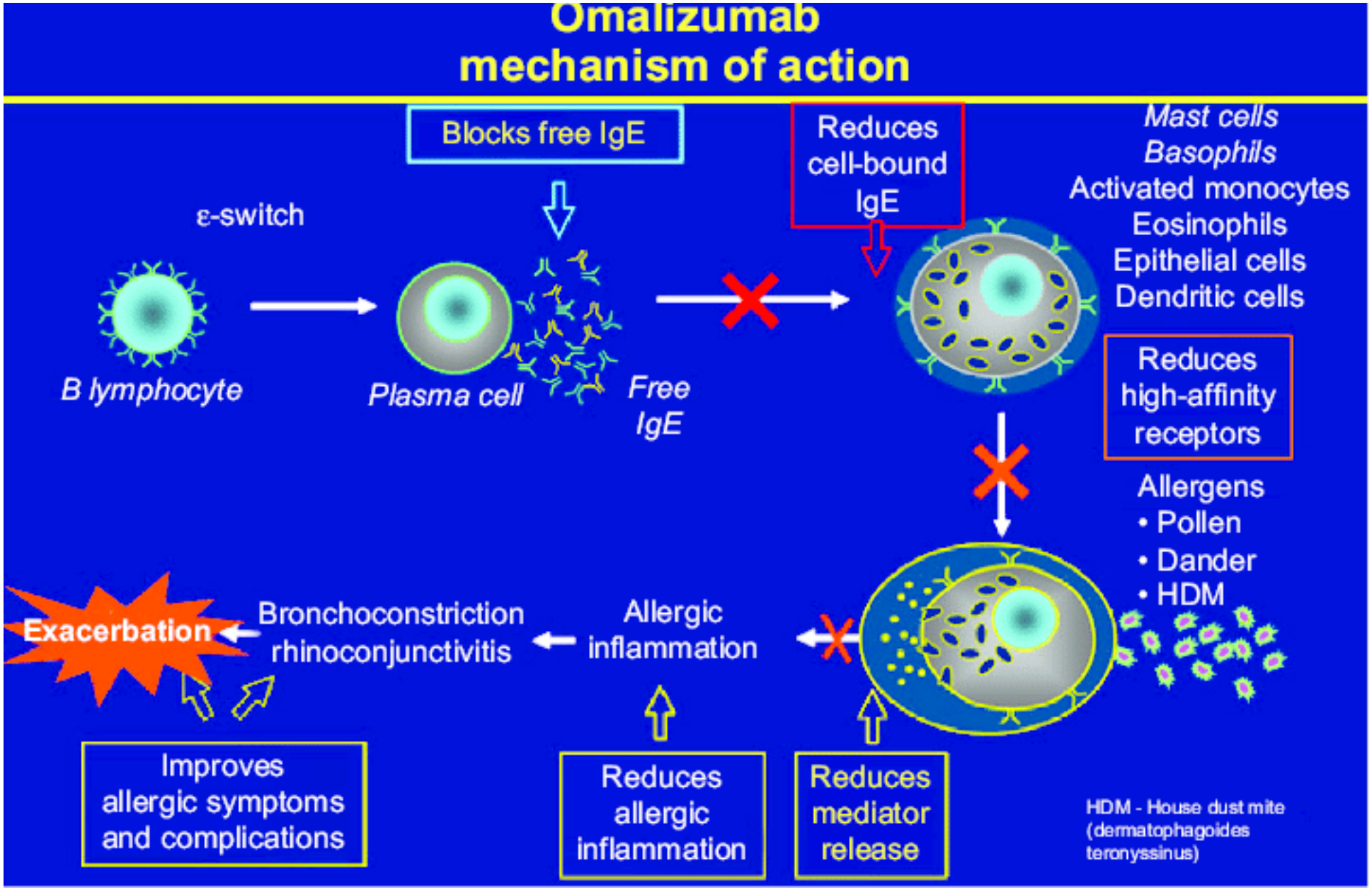
Airway eosinophilia persists despite the administration of inhaled or oral glucocorticoids

No evidence of a reduction in FENO

Anti-IgE Monoclonal Antibody

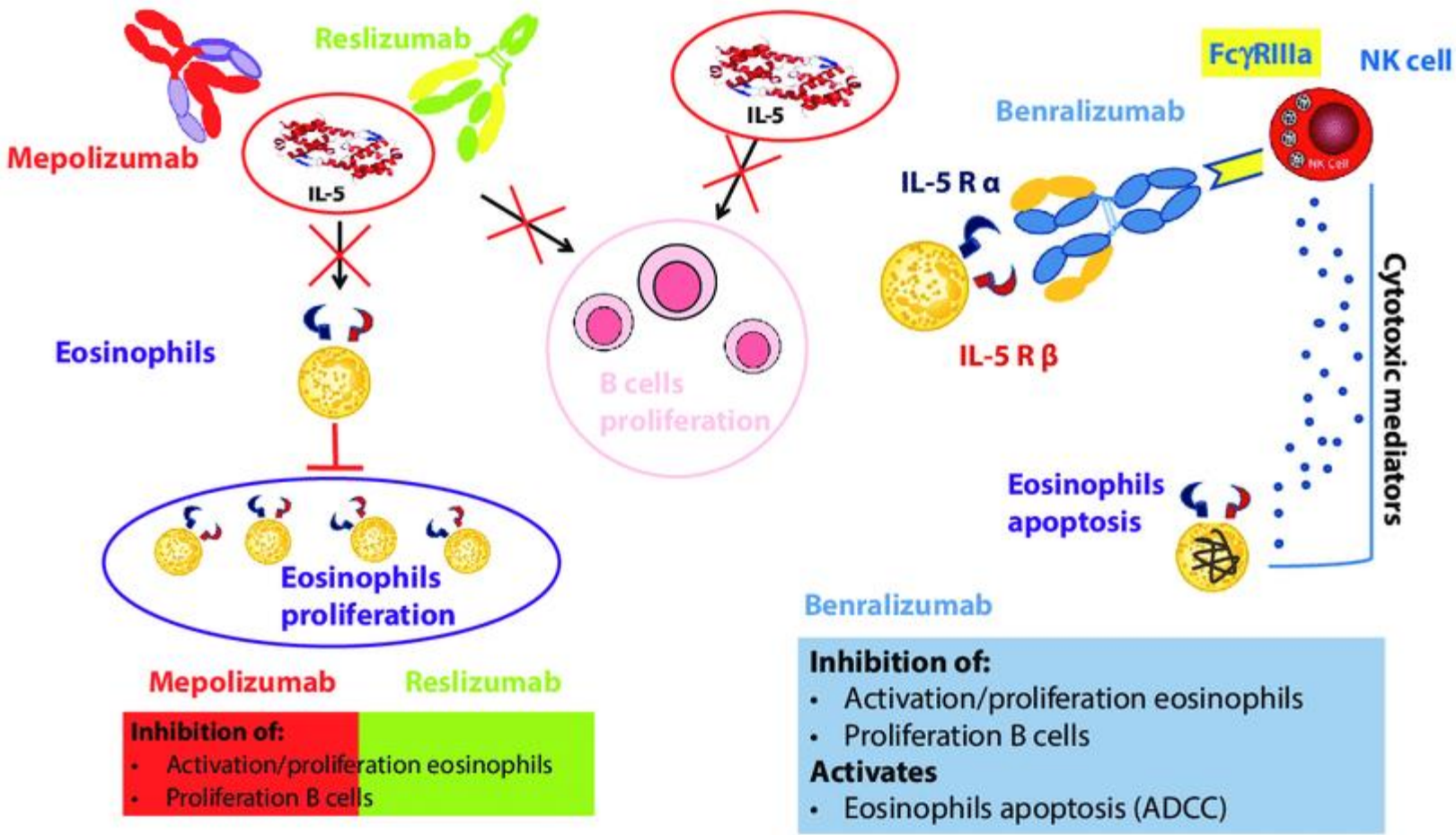
- Goal is to reduce free IgE levels in serum and inhibit the binding of IgE to the mast cells and basophils
- Omalizumab(75 to 375mg) monthly via prefilled syringe




Omalizumab
mechanism of action
Blocks free IgE
ε-switch
B lymphocyte
Plasma cell
Free IgE
Reduces cell-bound IgE
Mast cells
Basophils
Activated monocytes
Eosinophils
Epithelial cells
Dendritic cells
Reduces high-affinity receptors
Allergens
• Pollen
• Dander
• HDM
Exacerbation
Bronchoconstriction rhinoconjunctivitis
Allergic inflammation
Improves allergic symptoms and complications
Reduces allergic inflammation
Reduces mediator release
HDM - House dust mite (dermatophagoides teronyssinus)

Antibodies Against Interleukin -5&5R

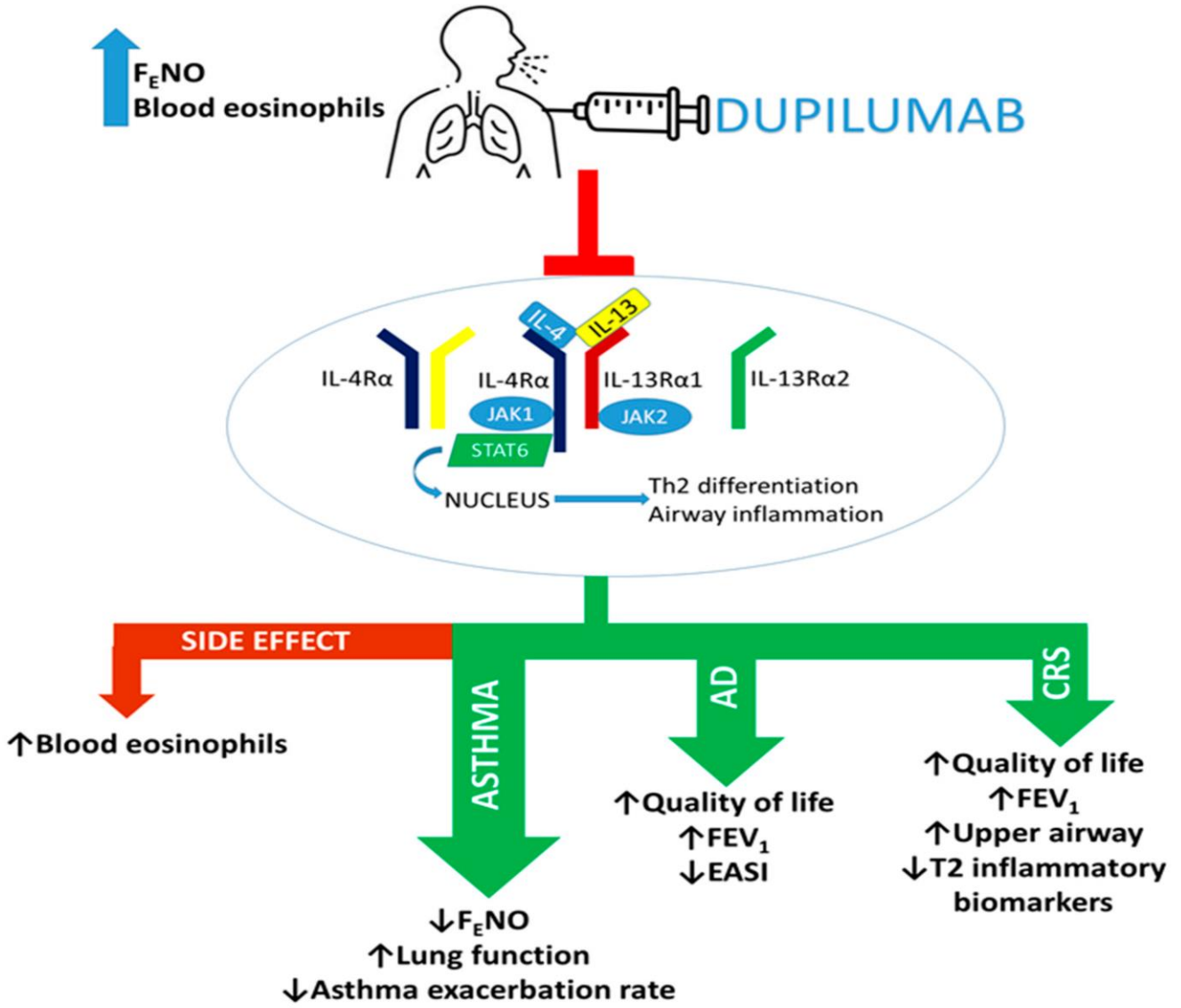
- Depletes eosinophilic binding to the interleukin 5 receptor
- Reduces an alpha subunit of interleukin 5R
- Mepolizumab/Reslizumab/Benralizumb
  - 100mg monthly
  - 50% reduction in asthma exacerbations
  - Increased FEV1



ADCC, antibody-dependent cell cytotoxicity; IL-5Rα, α subunit of the IL-5 receptor; IL-5Rβ, β subunit of the IL-5 receptor; NK, natural killer.

Anti-Interlukin-4 Receptor Antibody

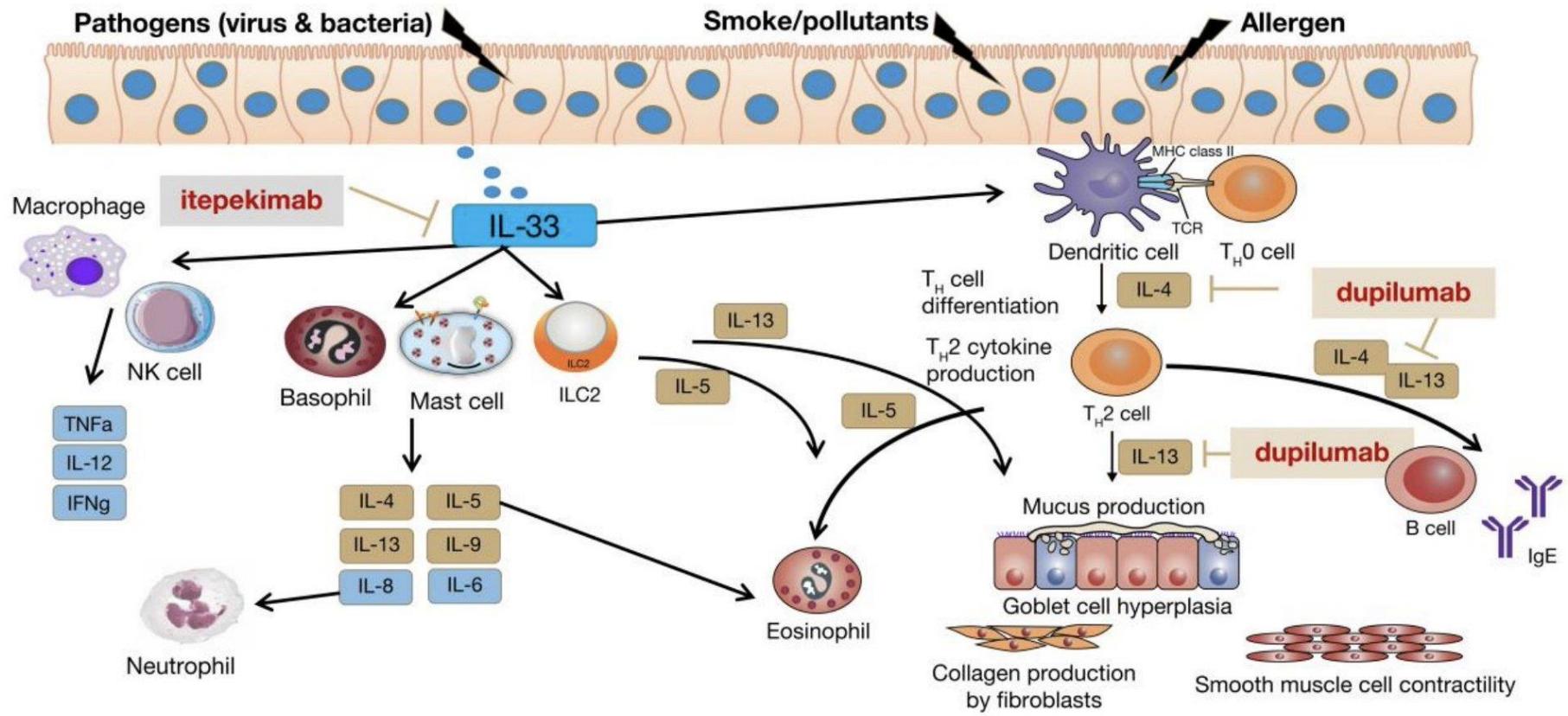
- Inhibits the signaling of interleuckin-4 and-13
- Dupilumab
- Reduction
  - Exacerbations
  - ER visits
  - Hospitalizations


F_ENO
Blood eosinophils
DUPILUMAB
IL-4
IL-13
IL-4Rα
IL-4Rα
IL-13Rα1
IL-13Rα2
JAK1
JAK2
STAT6
NUCLEUS
Th2 differentiation
Airway inflammation
SIDE EFFECT
↑Blood eosinophils
ASTHMA
↓F_ENO
↑Lung function
↓Asthma exacerbation rate
AD
↑Quality of life
↑FEV_1
↓EASI
CRS
↑Quality of life
↑FEV_1
↑Upper airway
↓T2 inflammatory biomarkers

Anti-Epithelial Cytokine Antibodies

- Blocks interleukins -25 & -33 from the airway epithelial cells
- Itepekimab 300mg every two weeks

Figure S1. Mechanism of Action of Interleukin-33.



Adapted from Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Nat Rev Drug Discov 2016;15:35-50.

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Safety of Itepekimab for Moderate-to-Severe Asthma

PHASE 2, MULTICENTER, RANDOMIZED TRIAL

296 Adults with moderate-to-severe asthma

Itepekimab	Itepekimab + Dupilumab	Dupilumab	Placebo
N=73	N=74	N=75	N=74

Every 2 wk for 12 wk

Event indicating loss of asthma control	Itepekimab	Itepekimab + Dupilumab	Dupilumab	Placebo
	16 Participants	20 Participants	14 Participants	30 Participants
	22%	27%	19%	41%
OR (95% CI) as compared with placebo	0.42 (0.20–0.88)	0.52 (0.26–1.06)	0.33 (0.15–0.70)	

Itepekimab led to a lower incidence of loss of asthma control than placebo and improved lung function.

M.E. Wechsler et al. 10.1056/NEJMoa2024257

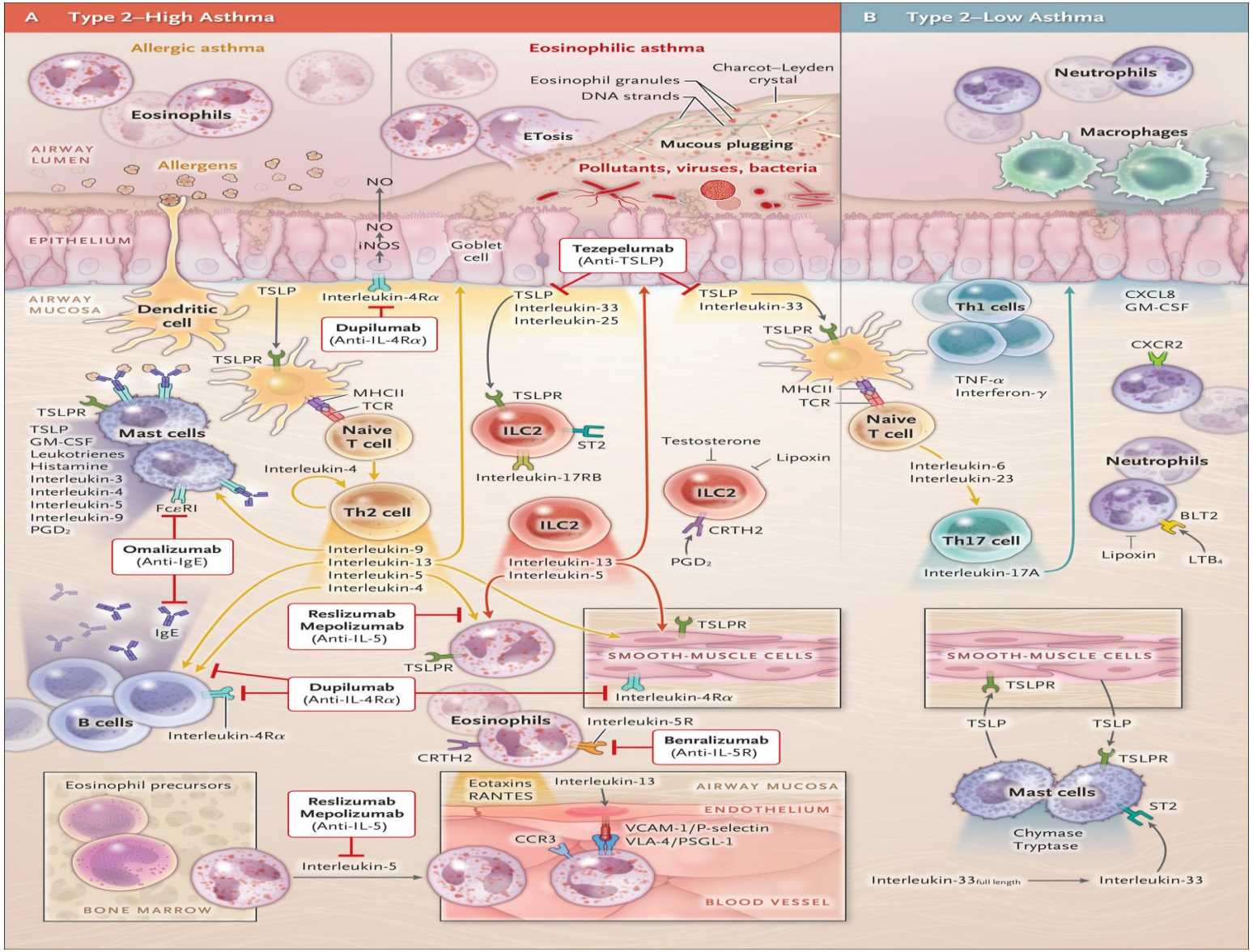

A Type 2–High Asthma
B Type 2–Low Asthma
Allergic asthma
Eosinophilic asthma
Eosinophils
Eosinophil granules
DNA strands
Charcot–Leyden crystal
ETosis
Mucous plugging
AIRWAY LUMEN
Allergens
Pollutants, viruses, bacteria
NO
NO
iNOS
EPITHELIUM
Goblet cell
Tezepelumab (Anti-TSLP)
AIRWAY MUCOSA
Dendritic cell
TSLP
Interleukin-4Rα
Dupilumab (Anti-IL-4Rα)
TSLPR
TSLP
Interleukin-33
Interleukin-25
TSLP
Interleukin-33
TSLPR
MHCII
TCR
Naive T cell
TSLPR
TSLP
GM-CSF
Leukotrienes
Histamine
Interleukin-3
Interleukin-4
Interleukin-5
Interleukin-9
PGD2
Mast cells
FcεRI
Omalizumab (Anti-IgE)
IgE
Interleukin-4
Th2 cell
Interleukin-9
Interleukin-13
Interleukin-5
Interleukin-4
TSLPR
ILC2
ST2
Interleukin-17RB
ILC2
Interleukin-13
Interleukin-5
Testosterone
Lipoxin
ILC2
CRTH2
PGD2
Th1 cells
TNF-α
Interferon-γ
Naive T cell
Interleukin-6
Interleukin-23
Th17 cell
Interleukin-17A
CXCL8
GM-CSF
CXCR2
Neutrophils
BLT2
Lipoxin
LTB4
Neutrophils
Macrophages
Reslizumab Mepolizumab (Anti-IL-5)
TSLPR
SMOOTH-MUSCLE CELLS
Interleukin-4Rα
Dupilumab (Anti-IL-4Rα)
B cells
Interleukin-4Rα
Eosinophils
Interleukin-5R
CRTH2
Benralizumab (Anti-IL-5R)
SMOOTH-MUSCLE CELLS
TSLPR
TSLP
TSLP
TSLPR
Mast cells
ST2
Chymase
Tryptase
Interleukin-33full length
Interleukin-33
Eosinophil precursors
BONE MARROW
Reslizumab Mepolizumab (Anti-IL-5)
Interleukin-5
Eotaxins
RANTES
Interleukin-13
AIRWAY MUCOSA
ENDOTHELIUM
CCR3
VCAM-1/P-selectin
VLA-4/PSGL-1
BLOOD VESSEL

Table 1. Biologic Agents Approved by the Food and Drug Administration for the Treatment of Severe Asthma.*

Biologic Agent (Therapeutic Target and Mechanism of Action)	Route of Administration and Dose†	Forms	Indication	Patient Yr of Age†	Efficacy	Safety Concerns
Benralizumab (interleukin-5Rα; antibody binds to interleukin-5Rα on eosinophils and basophils, depleting them through antibody-dependent, cell-mediated cytotoxicity)	SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma	≥12	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs
Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, inhibiting interleukin-4 and interleukin-13 signaling in hematopoietic cells [e.g., B cells, CD4+ helper T cells, and eosinophils], epithelial cells, and airway smooth-muscle cells)	Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-to-severe atopic dermatitis, initial dose of 600 mg, followed by 300 mg every 2 wk Children, ages 6–11 yr: SC; dose depends on body weight‡	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis	≥6	Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis
Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5)	Adults and adolescents: SC; 100 mg every 4 wk Children, ages 6–11 yr: SC; 40 mg every 4 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome	≥6	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare)
Omalizumab (IgE; antibody binds to Fc part of free IgE, inhibiting binding of IgE to FcεRI on mast cells and basophils and FcεRII on dendritic cells and eosinophils)	SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE	Prefilled syringe	Severe allergic asthma; other indication: chronic idiopathic urticaria	≥6	Reduced exacerbations, reduced symptoms, small effect on FEV_1; improved quality of life	Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients)
Reslizumab (interleukin-5; antibody binds to circulating interleukin-5)	IV; 3 mg/kg every 4 wk	IV infusion	Severe eosinophilic asthma	≥18	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; improved quality of life	Helminthic infections, abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.3% of patients)
Tezepelumab (TSLP)	SC; 210 mg every 4 wk	Prefilled syringe	Severe asthma	≥12	Reduced exacerbations, reduced symptoms, improved lung function; improved quality of life	Pharyngitis, arthralgia, back pain

* CRS denotes chronic rhinosinusitis, EGPA eosinophilic granulomatosis with polyangiitis, EMA European Medicines Agency, FcεRI high-affinity receptor for the Fc region of IgE, FcεRII low-affinity receptor for the Fc region of IgE, FDA Food and Drug Administration, FEV_1 forced expiratory volume in 1 second, interleukin-4Rα interleukin-4 receptor α, interleukin-5Rα interleukin-5 receptor α, IV intravenous, OGs oral glucocorticoids, SC subcutaneous, and TSLP thymic stromal lymphopoietin.

† Information on dose and age is for patients with severe asthma as the main indication.

‡ For pediatric patients, ages 6 to 11 yr, with a body weight of 15 kg to less than 30 kg, the recommended dose of dupilumab is 100 mg every 2 wk or 300 mg every 4 wk; for children with a body weight of 30 kg or more, the dose is 200 mg every 2 wk.

Choosing Initial Biological Therapy

- Assess number of yearly flare-ups
- Biomarkers
  - Blood eosinophil level
  - FENO
  - Serum IgE levels
- FEV1
- Quality of life assessment
- Route of administration
- Subcutaneous or intravenous
- Coexisting conditions

Table 2. Choice of Monoclonal Antibody Treatment of Severe Asthma According to Patient Characteristics.*

Characteristic	Anti-IgE Antibody	Anti–Interleukin-4R Antibody	Anti–Interleukin-5 or Anti–Interleukin-5R Antibody
Indication	Severe allergic asthma	Severe type 2 asthma	Severe eosinophilic asthma
Age group	Children, adolescents, and young adults	Children, adolescents, and adults	Adults
Onset	Childhood	Childhood or adulthood	Adulthood
Allergy	Prerequisite: IgE sensitization to perennial allergen	Irrespective of allergy	Irrespective of allergy
Dominant biomarker	Serum total IgE (for dosing)	Increased FENO	Increased blood eosinophil count
Serum total IgE	Serum total IgE and weight within dose range, according to local eligibility criteria	Irrespective of total IgE	Irrespective of total IgE
Blood eosinophil count†	Slightly better response with increased count	>150 to <1500/μl†	Prerequisite: increased counts (according to local eligibility criteria), >150 to 300/μl†
FENO†	Slightly better response if increased FENO	Better response if FENO >25 ppb	Irrespective of FENO
Coexisting conditions	Allergic rhinitis, CRS with nasal polyposis, chronic urticaria	Atopic dermatitis, CRS with nasal polyposis	CRS with nasal polyposis
Exacerbations in previous yr	According to local criteria	According to local criteria	High frequency (≥2), as specified by local criteria

* In December 2021, the anti-TSLP antibody tezepelumab was approved by the FDA for the add-on maintenance treatment of adults and pediatric patients 12 years of age or older who have severe asthma, with no phenotype (e.g., allergic or eosinophilic) or biomarker limitation within its approved label (Fig. S2 in the Supplementary Appendix). FENO denotes fractional exhaled nitric oxide, and ppb parts per billion.

† Blood eosinophil counts and FENO values are for patients with severe asthma who are not receiving maintenance oral glucocorticoid therapy.

Asthma Assessment

1. **In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

2. **During the past 4 weeks, how often have you had shortness of breath?**

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
○	○	○	○	○

3. **During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?**

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
○	○	○	○	○

4. **During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair® or Primatene Mist®)?**

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
○	○	○	○	○

5. **How would you rate your asthma control during the past 4 weeks?**

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
○	○	○	○	○

6. **In the past 4 weeks, how much did your asthma limit your usual activities or enjoyment of everyday life?**

Not at all	A little	Moderately	Quite a lot	Extremely
○	○	○	○	○

7. **In the past 4 weeks, how often did your asthma limit you in performing your usual daily activities, including housework, work, school or social activities?**

Never	Rarely	Sometimes	Very Often	Always
○	○	○	○	○

8. **In the past 4 weeks, how often did your asthma keep you from socializing?**

Never	Rarely	Sometimes	Very Often	Always
○	○	○	○	○

9. **In the past 4 weeks, how often did you feel fed up or frustrated because of your asthma?**

Never	Rarely	Sometimes	Very Often	Always
○	○	○	○	○

10. **In the past 4 weeks, how often did your asthma leave you too tired to do work or daily activities?**

Never	Rarely	Sometimes	Very Often	Always
○	○	○	○	○

Other Factors

- Insurance coverage
- Cost
- Patient preference
- Self or health care personnel administration

Monitoring of Effectiveness of Therapy

- 4–6-month treatment assessment
- Review of assessment symptoms and quality of life
- Monitor number of oral steroid use
- Side effects
- Patient compliance
- Review of biomarkers
- Use of health care system
    - Provider visits, ED visits, hospitalizations

Side Effects of Biological Therapy

- Irritation at the injection site.
- Cold-like symptoms.
- Headaches.
- Joint pain.
- Sore throat
- Sinus infection.
- Fatigue.
- Conjunctivitis.
- Weaken ability to fight infections

Cost of Biologicals

- $374,000 per QALY for dupilumab
- $325,000 per QALY for omalizumab
- $344,000 per QALY for mepolizumab
- $391,000 per QALY for reslizumab
- $371,000 per QALY for benralizumab
- The cost of Xolair per patient is variable and depends on the patient's weight and immunoglobulin E (IgE) level.
  - This can vary from a small patient with a low IgE level requiring a single monthly 150-mg vial of Xolair, with an annual average wholesale price (AWP) of $12,586, to a patient who is heavier and/or with a higher IgE level receiving 375 mg every 2 weeks, equating to a cost (on the high end) of approximately $81,809 annually.

Conclusion

Biological agents for asthma are efficacious add-on therapies.

Significantly reducing exacerbations rates and improving the patient's quality of life.

There are a plethora of side effects associated with biological drugs

Biological drugs are very expensive.

More head to trials need to be conducted to optimize patient outcomes.