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1

# **Biologics in Asthma**

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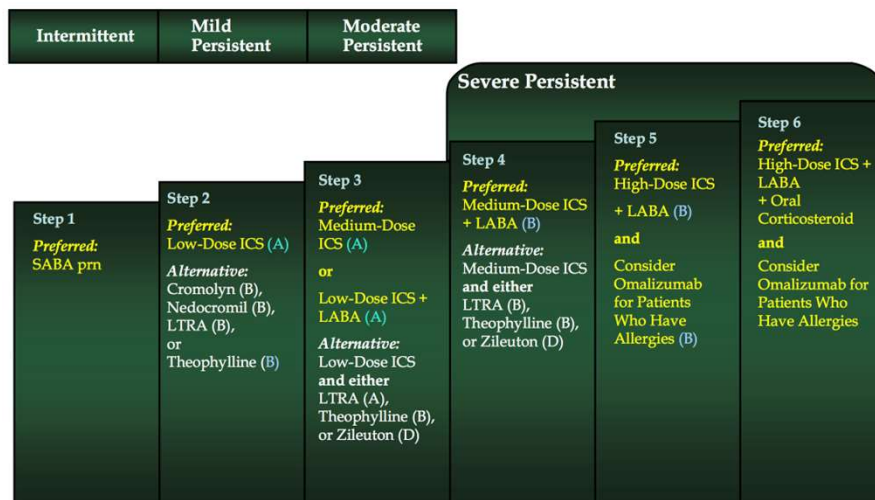
2

## Disclosures

None

3

## Asthma Step-up Protocol



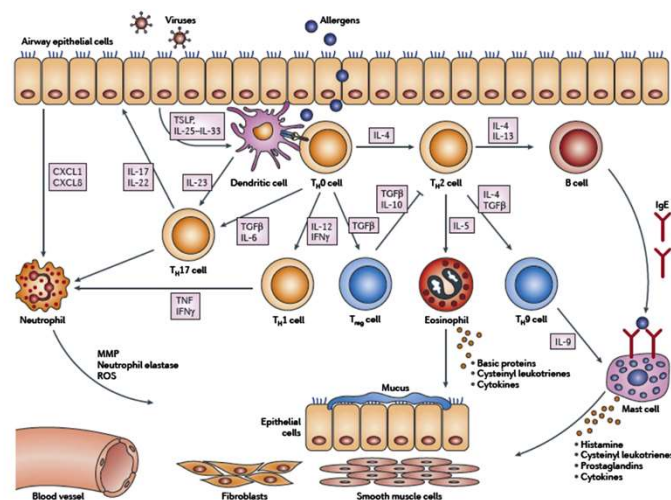
4

## Immunobiology of Asthma

- Allergic asthma – Th2 driven process
  - 50-80% of asthma
- Th2 driven cytokines
  - IL-5
    - growth, maturation and activation of eosinophils
  - IL-4
    - Th2 cell differentiation
    - Isotype switching of B-cells to IgE synthesis
    - Eosinophil recruitment
    - Development of mast cells
  - IL-13
    - IgE synthesis
    - Recruitment of eosinophils and basophils
    - Airway remodeling

5

## TH2 Pathway



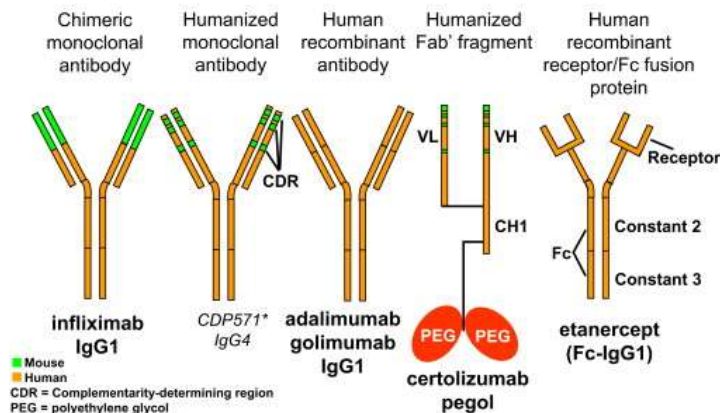
6

## Nomenclature for Monoclonal Antibodies

- Suffix – *mab* is used for monoclonal antibodies
- Animal source:
  - Mouse: *omab*
  - Chimera: *ximab*
  - Humanized: *zumab* (less than 5% mouse)
  - Human: *umab*
- Disease or target class
  - Immune: *lim* (mepoli(m)zumab)
  - Tumor: *tum* (ritu(m)ximab)

7

### TNF Inhibitors



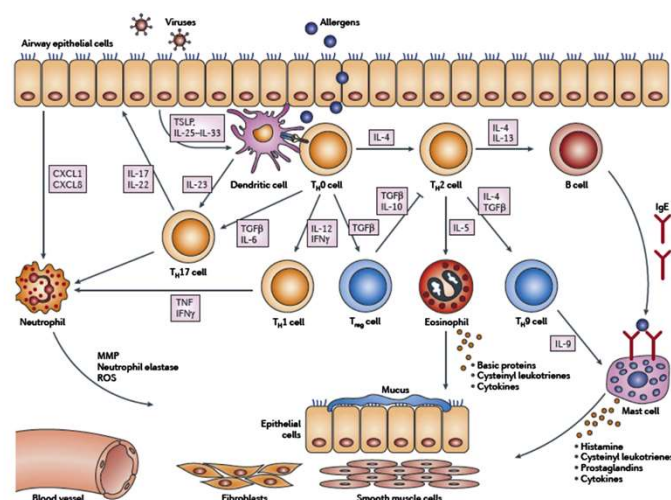
8

## FDA Approved Monoclonal Antibodies in Asthma

- Anti IgE
  - Omalizumab (Xolair)
- Anti IL-5
  - Mepolizumab (Nucala)
  - Reslizumab (Cinqair)
  - Benralizumab (Fasenra)
- Anti IL-4 receptor alpha (IL-4 and IL-13)
  - Dupilumab (Dupixent)
- Anti-TSLP
  - Tezepelumab (Tezspire)

9

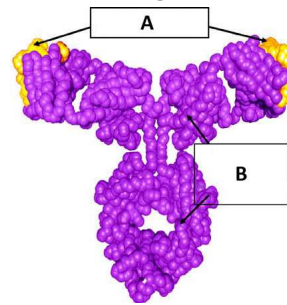
## TH2 Pathway



10

## Omalizumab

- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
- Forms small inert omalizumab/IgE complexes



11

## Effects of Omalizumab

- Decreased eNO
- Decreased airway eosinophils, mast cells, basophils, T&B lymphocytes
- Decreased IgE in bronchial epithelium
- Decreased responsiveness on skin testing

12

## Omalizumab Indications

- Severe persistent asthma
- Chronic urticaria
- Nasal polyps
- Food allergy

13

## Omalizumab Dosing

- Down to 6 years of age (1 year in food allergy)
- Given every 2 or 4 weeks based on weight and IgE level
- Also need to have perennial allergies
- Must be prescribed EpiPen
- First three doses in health care facility then can be dosed at home

14

## Anti IL-5

- Mepolizumab (Nucala)
- Reslizumab (Cinqair)
- Benralizumab (Fasenra) – targets  $\alpha$  chain of IL-5 receptor

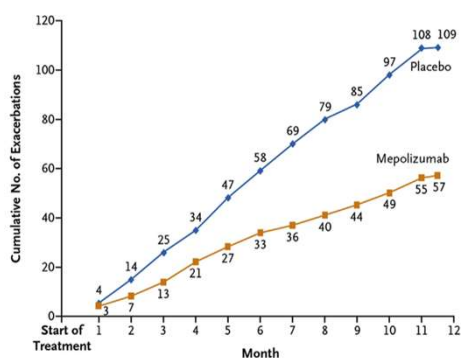
15

## Mepolizumab

- Significant reduction in blood and sputum eosinophils
- Reduction in exacerbation rates
- Other FDA approved indications:
  - Eosinophilic granulomatosis with polyangiitis (EGPA)
  - Hypereosinophilic syndrome
  - Nasal polyps

16

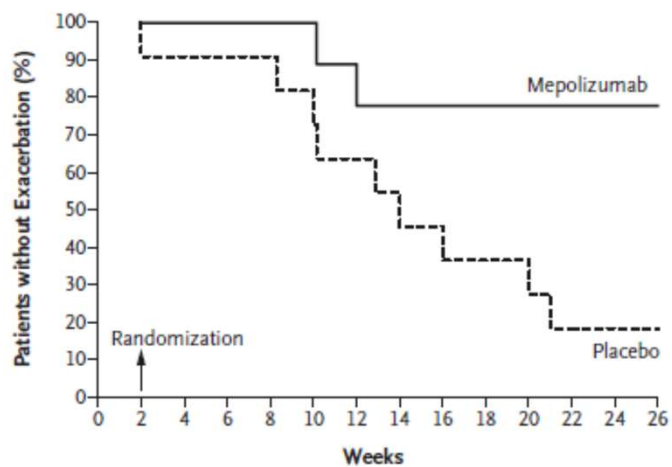




**FIGURE 4.** Mepolizumab and exacerbations of refractory eosinophilic asthma. The cumulative number of severe exacerbations that occurred in each study group over the course of 50 weeks. Adapted from Ref. 40.

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma. Halder et. Al. NEJM 2009

17



Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia. Nair et. al NEJM 2009

18

## Dosing for Anti IL-5

- Eosinophil count above 150 cells/ $\mu$ L (although more benefit if >300)
- Subcutaneous or IV every 4 to 8 weeks depending on the drug
- No EpiPen necessary

19

## Key Differences

Mepolizumab (Nucala)	Reslizumab (Cinqair)	Benralizumab (Fasenra)
6+	18+	6+
Every 4 weeks	Every 4 weeks	Every 8 weeks
40 mg (6-11 yo) 100 mg (12 and up)	Weight based dosing - IV	10-30 mg
No black box warning but possible shingles flares	Black box warning for anaphylaxis	No black box warning
Can be given at home or clinic	Given in infusion clinic	Can be given at home or clinic

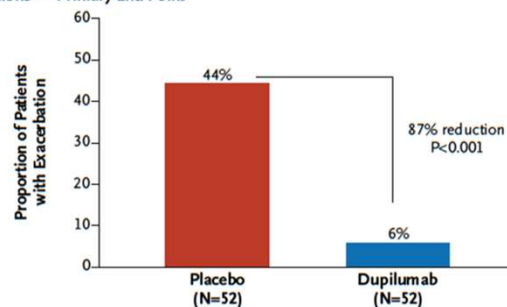
20

## Dupilumab (Dupixent)

- Anti IL-4R $\alpha$  (subunit common to IL-4 and IL-13 receptors)
- Approved for asthma down to age 6 (down to 6 months in atopic dermatitis)
- Other FDA approved indications:
  - Nasal polyps
  - Atopic dermatitis
  - Eosinophilic esophagitis
  - Prurigo nodularis
  - Eosinophilic COPD

21

A Exacerbations — Primary End Point

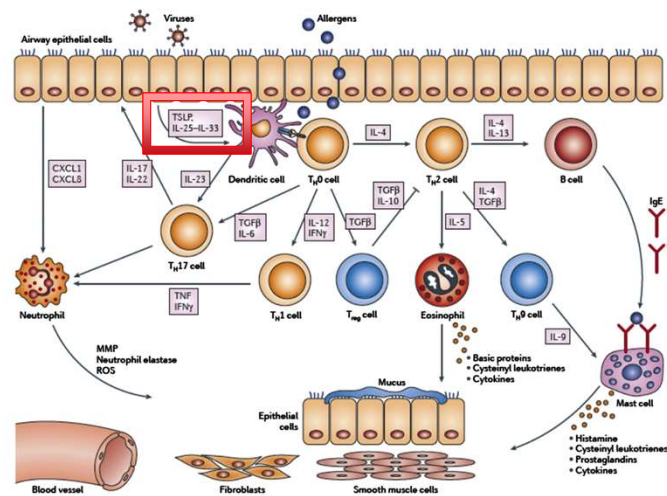


Dupilumab in Persistent Asthma with Elevated Eosinophil Levels. Wenzel et. al NEJM 2013

22

- Anti-TSLP (thymic stromal lymphopoietin)
  - Cell surface alarmin important in maturation/recruitment of T cells, B-cells, neutrophils, mast cells, eosinophils
- Increased TSLP linked to asthma, inflammatory arthritis, eczema and eosinophilic esophagitis

## TH2 Pathway

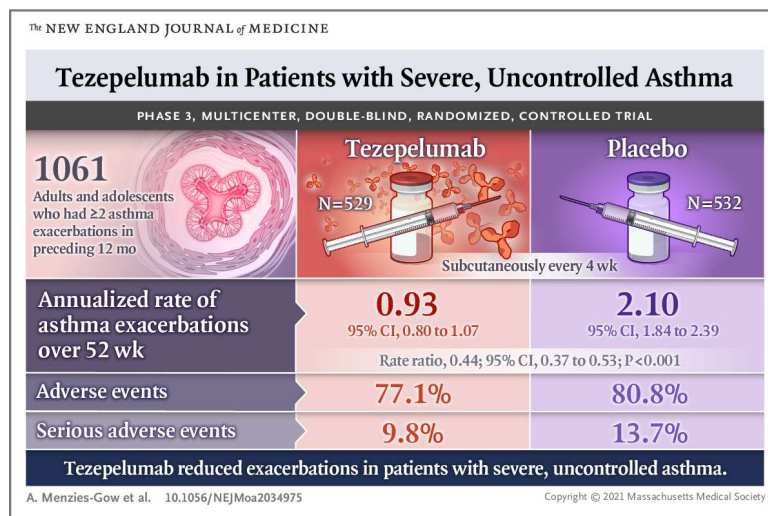


## Tezepelumab

- Reduction of asthma exacerbations in patients with and without elevation in eosinophils
- Improvement of FEV1
- Dosed every 4 weeks
- Down to age 12

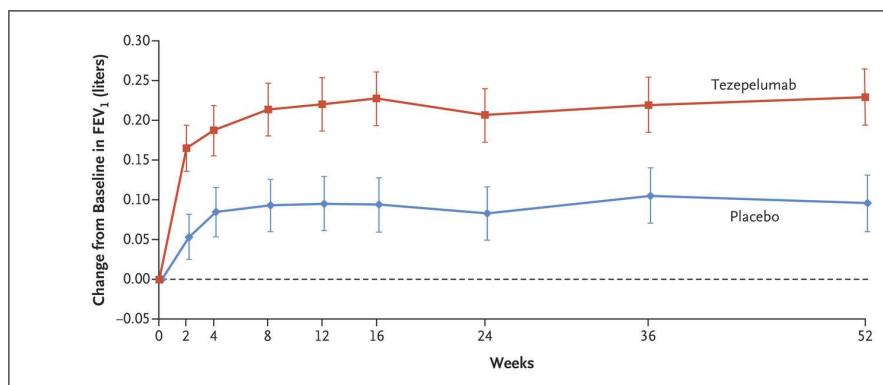
25

## Tezepelumab



26

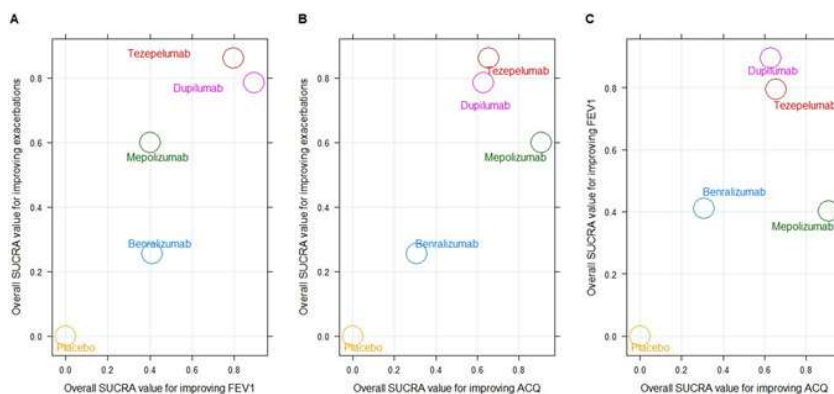
## Tezepelumab



Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma.  
A.Menzies-Gow et. al. NEJM  
May 2021

27

## Comparison via Meta-analysis



Comparative efficacy of tezepelumab to mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: A Bayesian network meta-analysis. Nopsopon et al. J. Allergy Clin Immunol. 2023

28

## Summary



	<b>Xolair</b>	<b>Nucala</b>	<b>Fasenra</b>	<b>Dupixent</b>	<b>Tezspire</b>
Age	6+	6+	6+	6+	12+
Target	IgE	IL-5	IL-5	IL-4 and IL-13	TSLP
Location	First 3 in clinic	Home	Home	Home	Home
Indication	Target weight and IgE + allergy	Eos > 150	Eos > 150	Eos. asthma	Severe asthma
Dosing	2 or 4 weeks	4 weeks	8 weeks	2 or 4 weeks	4 weeks
Side effects	Anaphylaxis	Shingles	Shingles	Conjunctivitis	Minimal

29

## Biologics on the Horizon



- Current biologics at younger age
- New drugs targeting IgE or IL-5
- Anti-IL-33 – An alarmin similar to TSLP
- Anti- $\beta$  chain of GM-CSF, IL-5 and IL-3

30

