Biologics for Asthma Management

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GINA – Difficult-to-Treat and Severe Asthma Adults and Adolescents

- Difficult-to Treat: asthma that is uncontrolled despite GINA Step 4 or 5 (med-hi dose ICS with 2nd controller; maintenance OCS)
  - Poor symptom control: frequents symptoms, reliever use, limits in daily activities, nighttime awakenings
  - Frequents exacerbations (≥2/year) requiring OCS, or serious exacerbation (≥1/year) requiring hospitalization
- Severe asthma: asthma that is uncontrolled despite adherence to maximal optimized therapy or asthma that worsens when high dose treatment is stepped down

GINA 2020; www.ginaasthma.org

ERS/ATS Definition of Severe Asthma (ages ≥ 6)

- Uncontrolled asthma defined as at least one of the following
  - Poor Sx control (ACQ ≥ 1.5 or ACT < 20)
  - Frequent severe exacerbations: ≥ 2 bursts of systemic CS for ≥ 3 days each in previous year
  - Serious exacerbations: ≥ 1 hospitalization, ICU stay, or mechanical ventilation in previous year
  - Airflow limitation: < 80% predicted with reduced FEV_1/FVC
- Controlled asthma that worsens on tapering high doses of ICS or systemic CS (or additional biologics)

Chung KF et al. Eur Respir J 2014; 43:343-73.

Severe Asthma: Introduction

- 5-10% of asthma patients have severe disease
  - ↓ QOL
  - ↑ morbidity & mortality
  - ↑ use of healthcare resources
  - 40% reliant on maintenance or frequent OCS
  - GINA Step 5 w/o control
- Biologics act directly to alter asthma immunopathogenesis, rather than downstream airway inflammation & bronchospasm
- 2 major asthma endotypes (subclasses based on pathophysiologic mechanisms)
  - Type 2 cell (T2) – high asthma
  - Type 2 cell (T2) – low asthma
  - Defined on basis of level of expression of T2 cytokines, IL-4, IL-5, and IL-13 produced by T_H2 lymphocytes
  - Biologics most effective in T2 – high endotype

Role of Biologics in Severe Asthma

- For patients with exacerbations or poor symptom control on high dose ICS/LABA who:
  - Have eosinophilic or allergic biomarkers
  - Need maintenance OCS
- Choose agent based on eligibility
  - Trial for 4 months, assess response
  - Extend therapy for another 6-12 and reassess

GINA 2020:www.ginaasthma.org

- Anti-IgE (omalizumab)
  - Severe allergic asthma
  - Sensitization on skin prick testing or specific IgE
  - Exacerbation in past year
- Anti-IL5/Anti-IL5R (mepolizumab, reslizumab, benralizumab)
  - Exacerbation in past year
  - Blood eosinophils ≥300/µl
- Anti-IL4R (dupilumab)
  - Exacerbation in the past year
  - Blood eosinophils ≥150/µl or FeNO ≥ 25 ppb
  - Need for maintenance OCS

Risk Factors for Exacerbation-Prone Asthma

- Environmental Risks
  - Exposure to tobacco smoke (ETS)
  - Air pollution (eg. tobacco smoke, high levels of NO2, diesel fuel)
  - Stress
  - Dietary factors (vitamin D & fish oil)
  - Viral respiratory tract infections (RV, RSV, influenza, metapneumovirus)
  - Allergen exposure in sensitized individuals
  - Microbial organisms
- Personal Risks
  - Established biomarkers (eosinophils, IgE, FeNO)
  - Genetics
  - Comorbid conditions

Denlinger LC et al. JACI: In Practice (2019), in press

T2 – High Versus T2 – Low Endotypes

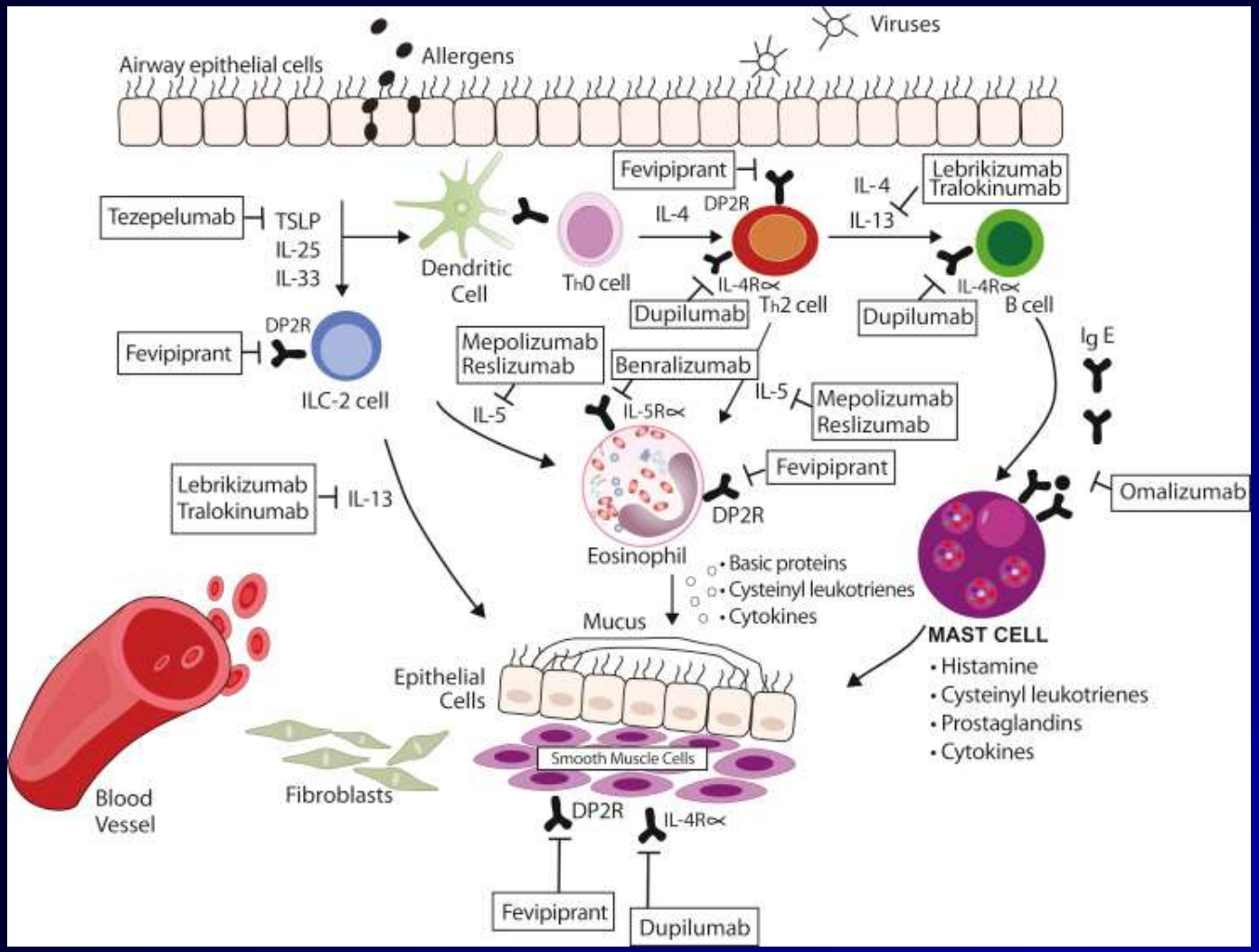
- T2 – high endotype
  - Mediated by type 2 inflammatory pathways, due to effects of cytokines IL-4, IL-5, & IL-13
  - Elevated biomarkers, such as fractional exhaled nitric oxide (FENO), serum IgE, and blood and sputum eosinophil levels

- T2 – low endotype
  - Neutrophilic or pauci-granulocytic inflammation
  - Normal levels of eosinophils both in sputum & in the airway

Pathobiology of T2 – High Asthma

- Genetic susceptibility & exposure to environmental factors (allergens, viruses, pollutants, specific irritants) interact to create airway inflammation
- Interaction of allergies, pollutants, or microbes with the airway epithelium results in release of mediators such as thymic stromal lymphopoietin (TSP), IL-25, & IL-33 & subsequent ↑ production of Type 2 cytokines (IL-4, IL-5, & IL-13)
- Proinflammatory cascade of events results in chemoattraction of mast cells, eosinophils, and basophils, secretion of IgE by B cells, bronchoconstriction, & airway remodeling
- ICS & OCS can suppress T2 – high phenotype, but not in all

Therapeutic Targets for Type 2 Inflammation in Asthma



Krings JG et al. J Allergy Clin Immunol (Pract 2019; 7(5):1379-1392

Biomarkers & Predicting Response to T2 – High Asthma

Biomarker	Tx Expected to Produce Response	Associations
Induced Sputum		
Eosinophils	Anti-IL-5	Exacerbations
	ICS	
IL-13	Anti-IL-13	?
Blood		
Eosinophils	Anti-IL-5	Exacerbations
	Anti-IgE	↓ lung function
	Anti-IL-4/IL-13	Fixed Airway Obs.
	Corticosteroids	
	CRTH 2 Antagonists	
Specific IgE	Anti-IgE	Exacerbations
Exhaled Breath		
FeNO	Anti-IL-5	Exacerbations
	Anti-IgE	↓ lung function
	Anti-IL-13	
	ICS	

Biologics

Agent	Target	Primary Outcomes	Admin	Indications	Biomarkers
Omalizumab	IgE	↓ exacerbations	SC	Allergic asthma Chronic Idiopathic Urticaria (CIU)	Eos–blood FeNO
Mepolizumab	IL-5	↓ exacerbations ↑ asthma control	SC	Eosinophilic asthma	Eos-blood Eos-sputum
Reslizumab	IL-5	↓ exacerbations	IV	Eosinophilic asthma	Eos-blood
Benralizumab	IL-5Rα	↓ exacerbations	SC	Eosinophilic asthma	Eos-blood
Dupilumab	IL-4Rα/ IL-13-Rα1	↓ exacerbations ↑ lung function	SC	Atopic dermatitis Type 2-high asthma	Eos-blood FeNO
Fevipiprant*	PD_2 receptor	↑ FEV_1	po	Eosinophilic asthma	Eos-sputum
Tezepelumab*	TSLP	↓ exacerbations ↑ lung function	SC	Type 2-high asthma Type 2-low asthma	Eso-blood FeNO, IgE
Imatinib*	KIT	↓ airway hyperresponsiveness	po	Pauci-Granulocytic Asthma	Serum trypase

Manka LA, et al. *Annals of Allergy, Asthma, Immunology* (2018), doi:10.1016/j.anai.2018.07.033

Anti-IgE

Omalizumab (Xolair®)

- Recombinant, humanized, monoclonal anti-IgE Ab
  - Prevents IgE from binding to cell-surface receptors of mast cells & basophils, inhibiting release of inflammatory mediators → exacerbations
  - Mod-severe persistent asthma in patients ≥ 6 years with positive skin test/RAST inadequately controlled with ICS
  - May have efficacy in non-atopic asthma
  - Chronic idiopathic urticaria in ≥ 12 years who remain symptomatic despite H1 antihistamines
- Dosing (asthma): 75-375mg SQ every 2-4 weeks. Dose and frequency determined by initial total serum IgE levels and body weight. Max 150mg per injection site
- Lab monitoring not required
- Efficacy:
  - ↓ rate of asthma exacerbations & hosp. rates (peds. data)
  - ↓ ICS requirements, ↓ use of SABA
  - ↑lung function, QoL
  - ↓ asthma symptom scores
- Particularly effective in patients with ↑ blood eos & ↑ FeNO
- Assess response in 4-6 months

Omalizumab (Xolair®); Genentech/Novartis

- Use of 75 mg & 150 mg prefilled syringes
- AE
  - Black box warning – anaphylaxis (0.1-0.2%)
    - Appropriate observation after injection
      - 2 hours x first 3 injections, then 30 minutes post injection thereafter
    - Rx for epinephrine auto-injector
    - Administration in a healthcare setting
  - Arthralgia, pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, earache
  - Children 6-11: nasopharyngitis, HA, pyrexia, upper abdominal pain, pharyngitis (strep), otitis media, viral gastroenteritis, epistaxis

Predictors of Positive Response

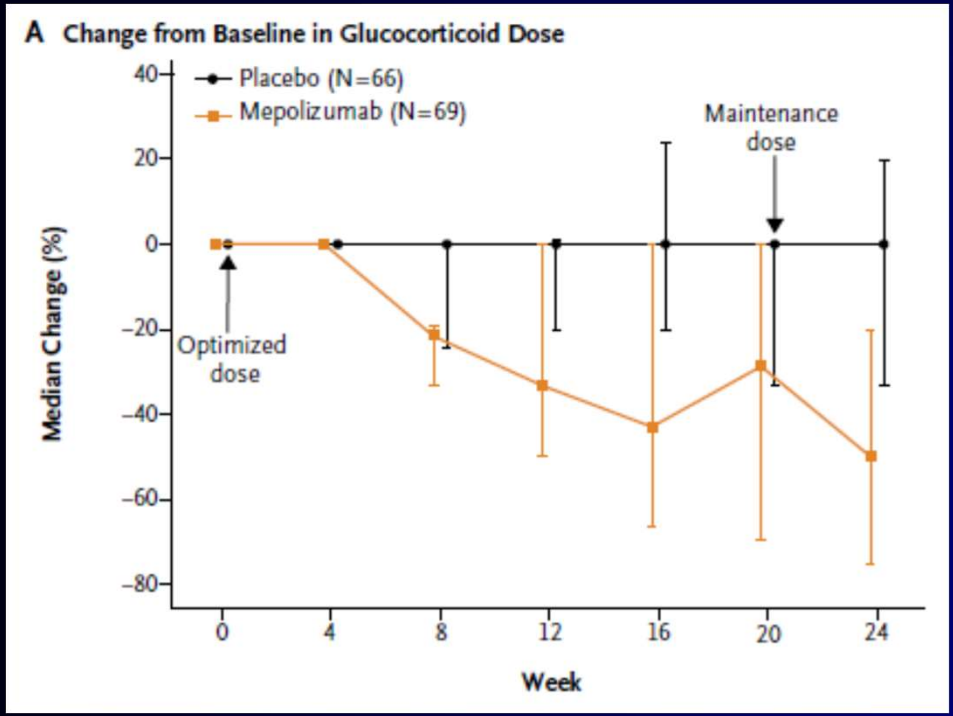
- Blood eosinophils ≥ 260/μl
- FeNo ≥ 20 ppb
- Allergy driven symptoms
- Childhood-onset asthma

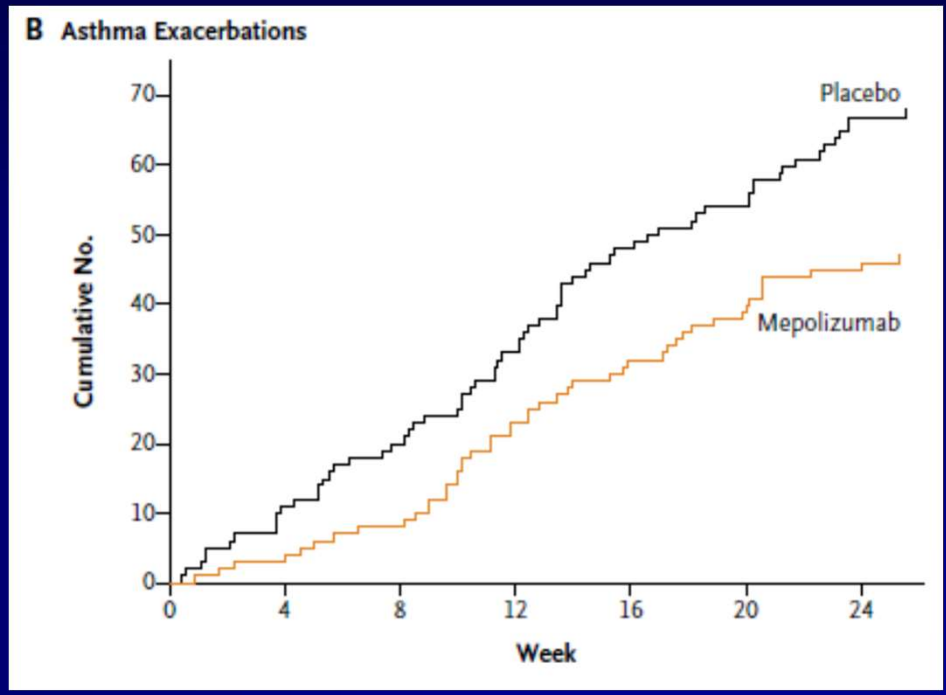
Anti-IL5/Anti-IL5R

Mepolizumab (Nucala®); GSK

- Recombinant, humanized monoclonal anti-IL-5 Ab. Prevents binding of IL-5 to the alpha chain of the IL-5 receptor on eosinophils & basophils
  - IL-5 is critical for maturation, activation & survival of eosinophils
  - Indicated for add-on maintenance treatment of patients (≥ 6 years) with severe asthma of an eosinophilic phenotype
  - Adults with eosinophilic granulomatosis with polyangiitis (EGPA)
- Dosing (asthma): 100 mg SC q 4 weeks if ≥ 12 yrs; 40mg SC q 4 weeks if ages 6-11 yrs
  - Approved for at home administration for patients ≥ 12 yrs
- 100mg prefilled autoinjector or prefilled syringe for ≥ 12 yrs; thigh or abdomen, or upper arm (if administered by caregiver)
- Generally used for patients with ≥ 150-300 blood eos
- Efficacy
  - ↓ frequency of asthma exacerbations
  - Improved lung function, QoL, oral glucocorticoid sparing effect
- AE
  - HA, injection site reaction, back pain, fatigue, nasopharyngitis, hypersensitivity

Efficacy of Mepolizumab





Bel EH, et al. NEJM 2014;371

Reslizumab (Cinqair®); Teva

- IL-5 antagonist monoclonal antibody; binds to IL-5 ligand & blocks signaling of IL5
  - Add-on maintenance treatment for patients (≥ 18 years) with severe asthma of an eosinophilic phenotype (≥400 blood eos)
  - Possible benefit for patients with late onset vs. early onset asthma
- Dosing – IV infusion of 3mg/kg every 4 weeks
- Efficacy
  - ↓frequency of asthma exacerbations
  - Improves lung function, QoL, asthma control
- AE
  - Black box warning – ANAPHYLAXIS (0.3%)
  - Oropharyngeal pain
  - Imbalance in malignancies

Benralizumab (Fasenra™); Astra Zeneca

- IL-5Rα cytolytic monoclonal antibody (binds to IL-5 receptor)
  - Add-on maintenance of patients (≥ 12 years) with severe asthma of an eosinophilic phenotype (≥ 300 blood eos)
  - Potentially minimizes cytokine production
- Dosing – 30mg SQ every 4 weeks x 3 doses, then q 8 weeks
- In-office administration with prefilled syringe of 30mg & 30mg at home administration Fasenra pen (thigh or abdomen, or upper arm)
- Efficacy
  - ↓ frequency of asthma exacerbations, ED visits
  - Glucocorticoid sparing effect
  - Increased efficacy in patients with ≥ 300 eosinophils/µl
- AE
  - HA, pharyngitis , hypersensitivity reactions

Predictors of Positive Response

- Higher blood eosinophils
- Multiple exacerbations in the past year
- Adult-onset asthma
- Maintenance OCS at baseline
- Nasal polyposis

Anti-IL4R

Dupilumab (Dupixent®); Regeneron

- IL-4Rα/IL-13-Rα1 antagonist, monoclonal antibody
  - Blocks IL-4 and IL-13 signaling
  - IL-13 is a component of eosinophil-mediated inflammation in the airway
  - Asthma – add- on maintenance therapy for patients (≥ 12 years) with moderate-severe asthma of an eosinophilic phenotype or with OCS dependent asthma (Th2 high asthma)
  - Atopic dermatitis – patients (≥ 12 yrs) with moderate-severe AD not adequately controlled with topical prescription therapies
  - Chronic rhinosinusitis with nasal polyposis, as add-on maintenance in adults
- Dosing (asthma ≥ 12 yrs)
  - 400 mg SQ (2x200 mg injections at 2 different sites) initially, then 200 mg SQ every other week
  - 600 mg SQ (2x300 mg injections at 2 different sites) initially, then 300 mg SQ every other week
    - Patients requiring concomitant oral corticosteroids or co-morbid AD
- Dosing (AD)
  - Additional info. for adolescents < 60mg or ≥ 60kb

Dupilumab (Dupixent®)

- Prefilled synringes (300mg/2ml and 200mg/1.14ml)
- Efficacy
  - Improved lung function, asthma control
  - Fewer severe exacerbations
  - Potential effect on airway remodeling
  - Higher baseline FeNO, eosinophils > 300 – greater treatment effects
- AE
  - Injection site reactions, oropharyngeal pain, hypereosinophilia
  - Conjunctivitis, keratitis (8-25%)
    - Severe disease (AD), high dose therapy
    - Dupilumab therapy may be discontinued, temporarily stopped or continued based on severity of eye symptoms
    - Counseling: “advise prescriber if any new or worsening eye problems (eye pain or changes in vision)”

Predicators of Positive Response

- Higher blood eosinophils
- Higher FeNO
- May also be used to treat
  - Nasal polyposis
  - Moderate-severe atopic dermatitis

Comparative Efficacy of Biologics

- Allergic, non-eosinophilic asthma – omalizumab
- Eosinophilic, non-allergic asthma
  - Anti IL-5 therapy
    - Mepolizumab – approved for home administration
    - Reslizumab – heavier patients, weight based IV dosing
    - Benralizumab – different MOA, patients who have failed other anti IL-5 tx – approved for home administration
  - Anti IL-4Rα/IL-13-Rα1
    - Dupilumab - approved for home administration, after self-injection training
- Non-Th-2 phenotype
  - No FDA approved therapies
  - Macrolides, bronchial thermoplasty, imatinib
- Minimum 4-12 month trial – duration of Tx under investigation
- Pregnancy exposure registries underway

- **NO EVIDENCE TO GUIDE PRECISE SELECTION OF BIOLOGICS**

Pipeline

- Anti-TSLP (thymic stromal lymphoprotein) – tezepelumab
  - TSLP –initiation and persistence of airway inflammation
  - Patients with severe asthma without an eosinophilic phenotype
  - 70 mg, 210 mg or 280 mg SQ q 2 weeks
  - Reduced asthma exacerbations, improved FEV_1, reduction in blood eos, FeNO, total serum IgE
- CRT_H2 – inhibition of prostaglandin D2 receptor 2
  - Fevipiprant, BID oral medication
  - Reduction in sputum eosinophils, improvement in FEV_1
- Tyrosine kinase inhibition – imatnib (Gleevec®)
  - Oral medication approved for chronic myeloid leukemia
  - Decreased airway hyperresponsiveness, reduced markers of mast cell activation