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Asthma inflammatory subtypes and new biologic therapies

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Children with asthma can be challenging to manage in the surgical arena, especially if baseline airways inflammation is not well-controlled. In addition to the familiar corticosteroid inhalers, leukotriene inhibitors, mast cell stabilizers, anti-IGE monoclonal antibody, and bronchodilators, new biologic modulators are appearing on the market. Selection of the appropriate biologic for add-on or replacement therapy depends on the subtype of airways inflammation and age of the patient. This lecture will present a framework for thinking about the characteristics of severe, poorly-controlled asthma in children, when to recommend a biologic medication, and what to expect in benefit and side effects.

«Asthma», as defined by GINA (Global Initiative for Asthma; www.ginasthma.org), is a heterogenous, usually inflammatory disease with respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough. Asthma waxes and wanes over time including variable expiratory limitation. A «biologic» is a noun referring to material isolated from a living organism (plants or animals). The biologic can be a recombinant protein, tissue, gene, or antibody. A «phenotype» is an observable characteristic of an organism produced by gene and environment interactions with each other. An «endotype: is a combination of clinical characteristics with an identifiable mechanistic pathway».

Asthma can be confounded by comorbidities such as dysphagia, gastroesophageal reflux, sinusitis, and congenital anomalies of respiratory and cardiac systems. The level of control of asthma symptoms changes with infection, aspiration, altitude, and air pollution. In the end, the choice of biologic is affected by the degree and quality of the inflammation-eosinophilic, lymphocytic, or neutrophilic or a mix, and whether the drug is approved for the age of the patient.

ERS/ATS (European Respiratory Society/American Thoracic Society) guidelines say that severe asthma requires treatment with a high dose inhaled corticosteroid plus a second controller (either a long-acting beta agonist or a leukotriene antagonist) for the previous year, or systemic corticosteroids for at least 50% of the year, or the condition remains uncontrolled despite these measures. Uncontrolled asthma is defined as at least one of the following: asthma control scores in the not well controlled category, frequent exacerbations requiring at least 2 courses of systemic corticosteroid, at least one hospitalization, ICU stay, or mechanical ventilation in the previous year, or FEV1 < 80% predicted (bronchodilator withheld) along with reduced FEV1/FVC ratio[1].

USFDA-approved biologics are now available and target interleukins (IL) 4, 5 and 13, and IgE[2]. Investigational trials are underway targeting Il-33, Il-25, CRTh2, DP-1, and TSLP. In addition to controlling symptoms and perhaps reducing corticosteroid use, it is hoped that eosinophilic activation, IgE production, epithelial damage, macrophage polarization, bronchial enlargement basement membrane thickening, goblet cell hypertrophy, mucus production, smooth muscle contraction, and fibrosis can be prevented.

Asthma is often referred to as Type 2 or Non-type 2. Both types can result in airways hyperresponsiveness, remodeling, mucus production, smooth muscle constriction and smooth muscle hypertrophy[3]. Mediators of type 2 inflammation include Il-4, 5, 13, CRTH2, TSLP, GM-CSF, leukotrienes, PGD2, and histamine. Mediators of non-type 2 inflammation include Il-6, Il-8, Il-17, IFN-gamma, TNF-alpha, CXCR2, and lipoxin. Allergens stimulate type 2 inflammation. Irritants, pollutants, microbes, and viruses stimulate non-type 2 inflammation. Interestingly it has recently been shown that anti-IgE treatment reduces viral exacerbations of asthma, so there is cross-talk or overlap between the mechanistic pathways[4]. Type 2 or Th-2 asthma begins in childhood, is eosinophilic, often atopic, and corticosteroid-sensitive. Non-

type 2 or Non-Th-2 asthma is mostly identified in adults, and tends to be obesity-related, smoking-related, post-infectious, an inconsistently responsive to corticosteroids.

The lecture will review each of the biologics that have approvals in children, and one that does not. We will discuss the intended mechanisms, indications, pivotal clinical trials, and the emerging limitations and side effects. Omalizumab (anti-IgE Fc region monoclonal antibody)[4-7], mepolizumab[8-10] and reslizumab (anti-Il-5)[11-13], benralizumab (anti-Il-5 receptor alpha chain)[14-19], and dupilumab (IL-4 receptor alpha antagonist)[18,19], will each be featured. The investigational biologics on the horizon will be briefly mentioned.

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Definitions

1. «Biologic» - a noun referring to material isolated from a living organism (plants or animals)--recombinant protein, tissue, gene, antibody
2. Phenotype - an observable characteristic of an organism produced by gene/environment interactions
3. Endotype - a combination of clinical characteristics with an identifiable mechanistic pathway

Objectives

- To review the current management of severe pediatric asthma
- To explore the use of «biologics» approved for children
  - Omalizumab
  - Mepolizumab
  - Benralizumab
  - Dupilumab
- To predic the next medications on the horizon

Is it Asthma?

- Diagnosis
  - www.ginasthma.org: «heterogeneous, usually inflammatory, respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough, varies over time, with variable expiratory limitation»
  - Level of control: impairment by symptoms and lung function, exacerbation prone
  - Confounders and comorbidities: gerd, dysphagia, sinusitis
  - Eosinophilic? Lymphocytic? neutrophilic?
  - Medication trials

Definition of severe Asthma

- Guideline-driven definition:
  - FEV1 < 60% predicted or PEF variable > 30%
  - Applies to patients NOT already on controller

- Broader definition*: at least three of the following:
  - Seen by an asthma specialist within the last two years
  - Persistent symptoms and decreased quality of life
  - On high dose inhaled steroids, with documented good adherence
  - History of previous respiratory failure/intubation/near-fatal episodes
  - Repeated low FEV1 (<70% predicted)

*European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA)

Definition of Severe, Refractory, or Therapy-Resistant asthma and ≤ 6 years of age

- Severe *asthma* REQUIRES treatment with high dose inhaled corticosteroids plus a second controller (either a long-acting beta-agonist or a leukotriene antagonist) for the previous year OR systemic corticosteroids for at least 50% of the previous year to prevent asthma from becoming «uncontrolled» or remains «uncontrolled» despite this therapy
- Uncontrolled asthma is characterized as at least ONE of the following:
  - Poor symptoms control: ACQ consistently > 1.5; ACT < 20 or «not well controlled» by guidelines
  - Frequent severe exacerbations: ≥ 2 systemic corticosteroids in the previous year
  - Serious exacerbations: ≥ 1 hospitalization, ICU, or mechanical ventilation in the previous year
  - Airflow limitation: after appropriate bronchodilator withhold--- FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

Chung KF et al., ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma, Eur Resp J 2014;43:343-37.

NAEPP 2007 Stepwise approach for managing asthma in children.

		Intermittent	Persistent Asthma: Daily medication				
			Step down if possible (and asthma is well controlled at least 3 months)		Assess control	Step up if needed (first check inhaler technique, adherence, environmental control and, comorbid condition)	
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Age 0-4 years	Preferred	SABA prn	Low dose ICS	Medium dose ICS	Medium dose ICS + either LABA or LTRA	High dose ICS + either LABA or LTRA	High dose ICS + either LABA or LTRA and oral corticosteroid
	Alternative		Cromolyn or montelukast				
Age 5-11 years	Preferred	SABA prn	Low dose ICS	EITHER Low dose ICS + either LABA, LTRA, or theophylline OR medium dose ICS	Medium dose ICS + LABA	High dose ICS + LABA	High dose ICS + LABA and oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium dose ICS + either LTRA or theophylline	High dose ICS + either LTRA or theophylline	High dose ICS + either LTRA or theophylline and oral corticosteroid
Age ≥ 12 years	Preferred	SABA prn	Low dose ICS	Low dose ICS + LABA OR medium dose ICS	Medium dose ICS + LABA	High dose ICS + LABA and consider omalizumab for patients with allergies	High dose ICS + LABA + oral corticosteroid and consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low dose ICS + either LTRA, theophylline, or zileuton	Medium dose ICS + either LTRA or theophylline or zileuton		

Each step: patient education, environmental control, and management of comorbidities.
Age ≥ 5 years: steps 2-4: consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

TH-2 High versus TH-2 Low

- TH-2 High Asthma
  - Childhood onset
  - Increased TH-2 cytokines (IL-5 and IL-13)
  - Increased bronchodilator hyper-responsiveness
  - Corticosteroid-sensitive
  - Features of:
    - Atopy/IgE
    - Elevated eNO
    - Blood/sputum/lung eosinophils
    - Serum periostin
- TH-2 Low Asthma
  - Mostly adults, obesity-related, post-infectious, neutrophilic, smoking-related
  - No type 2 cytokine elevations
  - Inconsistent response to corticosteroids

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Biologics

Approved biologics for severe asthma.

Target	Drug	Approval date	Key studies
IgE	Omalizumab (Xolair®)	2002; in younger children 2016	Extra; prose; innovate
IL5	Mepolizumab (Nucala)	2015	Dream; mensa; sirius; musca
	Reslizumab (Cinqair®)*	2016	
IL5R	Benralizumab (Fasenra™)	2017	Sirocco; calima; zonda, bora
IL4Ra	Dupilumab (Dupixent®)	2018	Liberty quest; liberty venture

* Only approved for adults.

Omalizumab

Younger children

Indicated for moderate to severe persistent asthma

Anti-IgE: Omalizumab

- Humanized murine monoclonal antibody-Binds to the Fc portion of human IgE, regardless of specificity, eliminating 95% of circulating IgE
- Indicated in children ≥ 6 years with atopic asthma who are inadequately controlled on medium to high doce ICS
- Studies demonstrate inhaled and oral steroid reductions and fewer urgent care visits and hospitalizations
- Limitations: administered subcutaneously (q2-4 wks);

Side effects: anaphylaxis and bronchospasm common cold symptoms headache fever sore throat pain or discomfort of your ear abdominal pain, nausea, vomiting nose bleeds.

Mepolizumab

Anti-IL-5 approach

- Proof of concept study enrolling adult patients with severe asthma having sputum eos (> 3%) to receive mepolizumab 750 mg IV vs placebo
- Relative risk of exacerbation 0.57 (95% CI 0.32, 0.92; p = 0.02)

Mepolizumab trial: dream

- Compared IV 75 mg vs 250 mg vs 750 mg mepo vs placebo
- Demonstrated 38-52% reduction in clinically significant exacerbations in active treatment compared to placebo

Reslizumab (not approved for children and adolescents)

- Directed against IL-5
- Given intravenously, weight-based dosing (3 mg/kg/every 4 weeks)
- Cut-off eosinophils of 400 cells/μL to select patients for treatment
- Reslizumab reduces asthma exacerbations by approximately 50% (Lancet Respir Med. 2015;3:355-366)
- Reslizumab improved FEV1 within 4 weeks of initiating treatment by 0.270 ± 0.1320 li improvement over placebo in a 16-week trial (Chest. 2016;150:7799-810)
- It also reduced symptoms and a need for rescue short acting beta agonist use was reduced
- When eosinophils < 400 cells/μL, no improvements were noted with reslizumab

Benralizumab

Benralizumab does not impair antibody response to seasonal influenza vaccination in adolescent and young adult patients with moderate to severe asthma: results from the phase IIIb ALIZE trial.

- 3 doses of benralizumab or placebo in 103 12-21 yo on medium to high dose LABA
- Influenza vaccine at dose 3 study drug
- No effect of benralizumab on antibody responses to vaccine

Zeitlin PL, et al. Journal of Asthma and Allergy. 2018;11:181-192.

Dupilumab (approved for moderate to severe asthma)

Dosing and eligibility cut off for different biologics.

Drug	Route/dosing/ frequency	Biomarker cut off
Omalizumab Xolair®	SC (based on serum IgE and weight) Q2W or Q4W	Serum total IgE 30-700 iu/mL (30/1300 for younger children) and sensitized to perennial aeroallergen
Mepolizumab Nucala	SC (100 mg) Q4W	≥ 150 cells/mL at screening or ≥ 300 cells/mL in previous year
Reslizumab Cinqair®	IV (3 mg/kg) Q4W	≥ 400 cells/mL
Benralizumab Fasenra	SC (30 mg) Q8W (first 3 doses every 4 wk)	≥ 300 cells/mL
Dupilumab Dupixent®	SC 200 mg Q2W 300 mg Q2W	≥ 300 cells/mL If on OCS

OCS = Oral corticosteroid dependent.

Comparative key outcome measures of available biologics for children.

Drug	Exacerbation reduction rate vs plac	Change in FEV1 compared with placebo	OCS reduction (drug vs placebo)
Omalizumab Xolair®	23-50*%	< 5% (2-3%)	Real world study: 30-74%
Mepolizumab Nucala	53%	98 mL	50% vs 0
Benralizumab	36% (Q4W)	125 mL (Q4W)	75% vs 25%
Fasenra	45% (Q4W)	106 mL (Q4W)	
	28% (Q8W)	116 mL (Q8W)	
	51% (Q8W)	159 mL (Q8W)	
Dupilumab	48% (200 mg)	210 mL (200 mg)	70% vs 42%
Dupixent®	46% (300 mg)	240 mL (300 mg)	

Overlap of atopic, eosinophilic, and Th2-high asthma phenotypes in children with asthma

- Analysis of NHANES data
- 57% of children (6-17 years old) with asthma are eosinophilic (300/υL)
- 63% of children with asthma are sensitized to at least 1 perennial aeroallergen

	Frequency, %
Both atopic and eosinophilic asthma	47
Frequency of atopic asthma among those with eosinophilic asthma	81
Frequency of eosinophilic asthma among those with atopic asthma	75
Frequency with neither eosinophilic or atopic asthma	26

		Atopic	
		+ (63%)	-
Eosinophilic	+ (57%)	47	10
	-	16	26

Tran T. Annals Allergy Immunol. 2016;116:37-42.

How does omalizumab compare with mepolizumab

- Indirect treatment comparison using a meta-analysis of double blinded randomized controlled clinical trials ≥ 12 weeks duration in patients ≥ 12 years old receiving high dose ICS plus ≥ 1 additional controller
- 2 populations: OVERLAP *(eligible for both)* and TRIAL *(eligible for either monoclonal)*
- For the OVERLAP population, no difference in clinically significant exacerbations (CSE) between mepolizumab and omalizumab
- For the TRIAL population, mepolizumab had an 37% reduction in the rate of CSE compared to omalizumab
- Mepolizumab trials used in this analysis had inclusion criteria of at least 2 exacerbations in the previous year
- For both populations, no differences in effects on lung function and adverse events between mepolizumab and omalizumab

Cockle S, et al. Respir Med. 2017;123:140-148.

Comparison of approved anti-IL5 biologics in patients with severe eosinophilic asthma by blood thresholds

- Indirect treatment comparison using a meta-analysis of double blinded randomized controlled clinical trials of mepolizumab, reslizumab, or benralizumab
- Primary outcome: clinically significant exacerbations
- Compared with placebo, all treatments reduced rate of CSE, asthma control, and lung function in each baseline blood eosinophil count threshold
- In unadjusted analysis without accounting for baseline eosinophil counts, no significant differences between the 3 treatments found
- When accounting for baseline eosinophil count, mepolizumab was associated with significantly greater reductions in exacerbation and greater improvement in asthma control compared with reslizumab or benralizumab

Busse W, et al. J Allergy Clin Immunol. 2018, in press.

Practical issues

- Differential diagnoses of hypereosinophilia
- Omalizumab (Xolair): thick liquid, multiple injections doses of more than 150 mg are divided among more than 1 injection site to limit injections to not exceed more than 50 mg per site
  - Xolair Prefilled Syringe (PFS) is expected to be available in both a 75 mg/0.5 mL and 150 mg/mL dosage strengths soon. The drug is now only available as a 150 mg per vial powder for SQ
- Dupilumab: home administration, conjunctivitis in 10% of atopic dermatitis patients

- Presence of other allergic conditions
- Cost

Summary

- Stablish the diagnosis and severity of the «difficult to treat asthma»
- Characterize the type of severe asthma (clinical and endotype) to be able to monitor treatment outcome; often comprehensive approach
- Available biologics targeting T2 high pathway
- Atopy and eosinophilia are helpful biomarkers
- Children with severe asthma may be more responsive to biologics targeting T2 high inflammation

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Table I. Other biologics and small molecules under development for type 2 inflammation diseases.

Agent	Clinical trial number	Mode of action	Mode of administration	Current clinical phase	Investigated patient populations
Asapiprant[90]		Prostaglandin D2 antagonist	Oral	Preclinical, 3 for allergic rhinitis	Allergic asthma, allergic rhinitis
RPC4046[91]	NCT02098473	IL-13R antagonist/ anti-IL-13 mAb	s.c./i.v.	2 for EoE, 1 in asthma	EoE, moderate to severe asthma
ADC3680/ ADC3608B[92]	NCT01730027	CRTh2 antagonist	Oral	2	Inadequately controlled asthma
AMG-282/ RG6149	NCT01928368, NCT02170337	IL-33 antagonist/ anti-IL-33 mAb	s.c./i.v.	2 for asthma, 1 for CRSwNP	Mild atopic asthma, CRSwNP
ANB020[93]	NCT03469934, NCT02920021	IL-33 antagonist/ anti-IL-33 mAb	s.c./i.v.	2	Severe asthma (eosinophilic phenotype), peanut allergy, AD
SB010[94]	NCT01743768	Anti-GAT3 DNAzyme	Oral	2	Mild asthma
GSK3772847	NCT03207243	IL-33 antagonist/ anti-IL-33 mAb	i.v.	2	Moderate to severe asthma
MK-1029[95]	NCT02720081	CRTh2 antagonist	Oral	2	Persistent asthma uncontrolled by montelukast
SAR440340/ REGN3500	NCT03387852	IL-33 antagonist/ anti-IL-33 mAb	s.c.	2	Moderate to severe asthma
Timapiprant	NCT02002208	CRTh2 antagonist	Oral	2	Severe asthma of eosinophilic phenotype, moderate to severe AD
Fevipiprant	NCT03215758, NCT01785602	CRTh2 antagonist	Oral	3 for asthma, 2 in AD	Uncontrolled asthma, moderate to severe AD
Tezepelumab	NCT03347279	TSLP antagonist	s.c.	3	Inadequately controlled severe asthma
Lebrikizumab[96]	NCT02340234	IL-13R antagonist/ anti-IL-13 mAb	s.c.	Discontinued in asthma, 2 in AD	Uncontrolled asthma with ICS, moderate to severe AD
Tralokinumab[97]	NCT03131648	IL-13R antagonist/ anti-IL-13 mAb	s.c.	Discontinued in asthma, 3 in AD	Uncontrolled asthma, AD

Definition of abbreviations: AD = Atopic dermatitis, CRSwNP = Chronic rhinosinusitis without nasal polyps, CRTh2 = Chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells, EoE = Eosinophilic esophagitis, ICS = Inhaled corticosteroid, mAb = Monoclonal antibody, TSLP = Thymic stromal lymphopoietin.

American Journal of Respiratory and Critical Care Medicine. 2019;199.

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