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Società Italiana per le Malattie Respiratorie Infantili **SIMRI**

Farmaci biologici per l'asma grave in terapia: un update

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DIPARTIMENTO AD ATTIVITA' INTEGRATA MATERNO INFANTILE
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Responsabile Prof.ssa Francesca Santamaria

Severe Asthma
Definition

Guidelines	Definition	High Dose Therapy	Poor control	Exacerbations
WHO Consultation on Severe Asthma 2010	It is uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity	No	Yes	Yes
ERS/ATS 2020	Asthma that requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy	Yes	Yes	Yes
BTS 2016	It is defined as persistent symptoms (SABA 3/w) and/or frequent asthma attacks (2/y) despite treatment with high-dose therapies or continuous or frequent use of oral steroids	Yes	Yes	Yes
GINA 2023	It is uncontrolled despite adherence with maximal optimized therapy (Step 4 or Step 5) and treatment of contributory factors, or that worsens when high dose treatment is decreased	Yes	Yes	Yes

Terminology

Uncontrolled asthma

Poor symptom control:

Frequent symptoms

and/or

Frequent exacerbations (≥ 2/yrs requiring OCS) or serious exacerbations (≥1/yrs requiring hospitalization)

Many may have mild asthma, i.e. could be well-controlled with low dose ICS, if taken regularly

Difficult-to-treat asthma

Uncontrolled despite prescribing of medium- high dose ICS + second controller (LABA or LRTA or Tiotropium)

Contributory factors: incorrect inhaler technique, poor adherence, comorbidities or incorrect diagnosis.

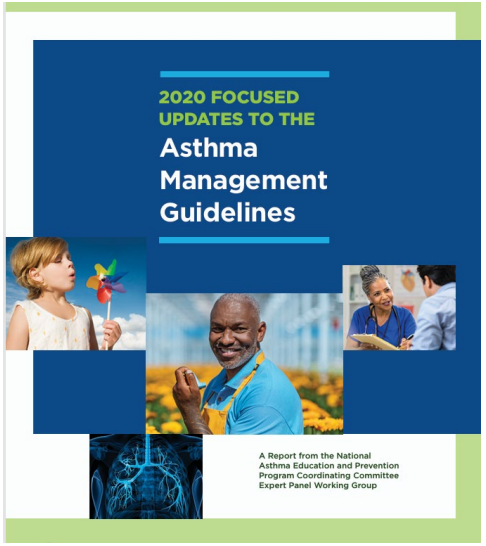
Not difficult patients!

Severe asthma:

Uncontrolled despite adherence with maximal therapy and management of contributory factors, or that worsens when high dose therapy is decreased.

Severe Asthma

National Asthma Education & Prevention Program (NAEPP) 2020



Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years

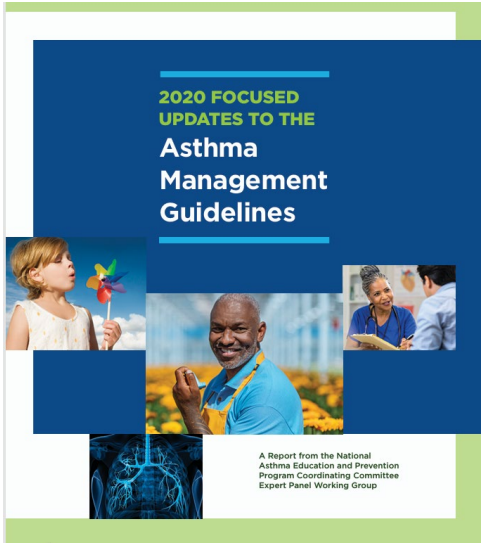
	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, 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 Omalizumab**▲	

Global Initiative for Asthma (GINA) 2024

ASTHMA TREATMENT STEPS FOR CHILDREN 6–11 YEARS

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever (MART)	Refer for expert advice, OR medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART)	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)		*Daily leukotriene receptor antagonist (LTRA†), or low dose ICS taken whenever SABA taken**	*Low dose ICS + LTRA†*	*Add tiotropium or add LTRA†*	*As last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)				

National Asthma Education & Prevention Program (NAEPP) 2020



Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	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)**	

Global Initiative for Asthma (GINA) 2024

ASTHMA TREATMENT STEPS FOR ADOLESCENTS 12+ yrs & ADULTS

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2
As-needed-only low dose ICS-formoterol

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

STEP 1
Take ICS whenever SABA taken*

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*

Medium dose ICS, or add LTRA†, or add HDM SLIT

Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only

Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects

Severe Asthma

Patients of any age

with persistent symptoms
or exacerbations (OCS ≥2/y – hospitalization ≥ 1/y)

despite correct inhaler technique and good aderence with step 4 treatment

despite treatment of comorbidities and elimination of risk factor

and in whom other controller options
have been considered

Refer for phenotypic assessment

Add-on biologic therapy

Biologic Medicines

✓ Medicines whose active principle is a substance produced or extracted from a biological system.

✓Hormones, enzymes, blood derived products, serums and vaccines, immunoglobulins, allergens, monoclonal antibodies = **biological medicines**

www.aifa.gov.it

Highly complex production techniques

Recombinant DNA technology

Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes

Monoclonal antibody methods

Carson, Nat Biotechnol 2005

T2-high Asthma Phenotype in children

Criteria for identifying T2-high phenotype

Biologic Type 2-targeted treatment

Anti IgE: Omalizumab

Anti IL5/IL5R: Mepolizumab - Reslizumab – Benralizumab

Anti IL4R: Dupilumab

Anti TSLP (Thymic stromal lymphopoietin): Tezepelumab

The Choice Of Add-on Type 2-targeted Therapy

Review response to an initial trial of Therapy

OUTLINE

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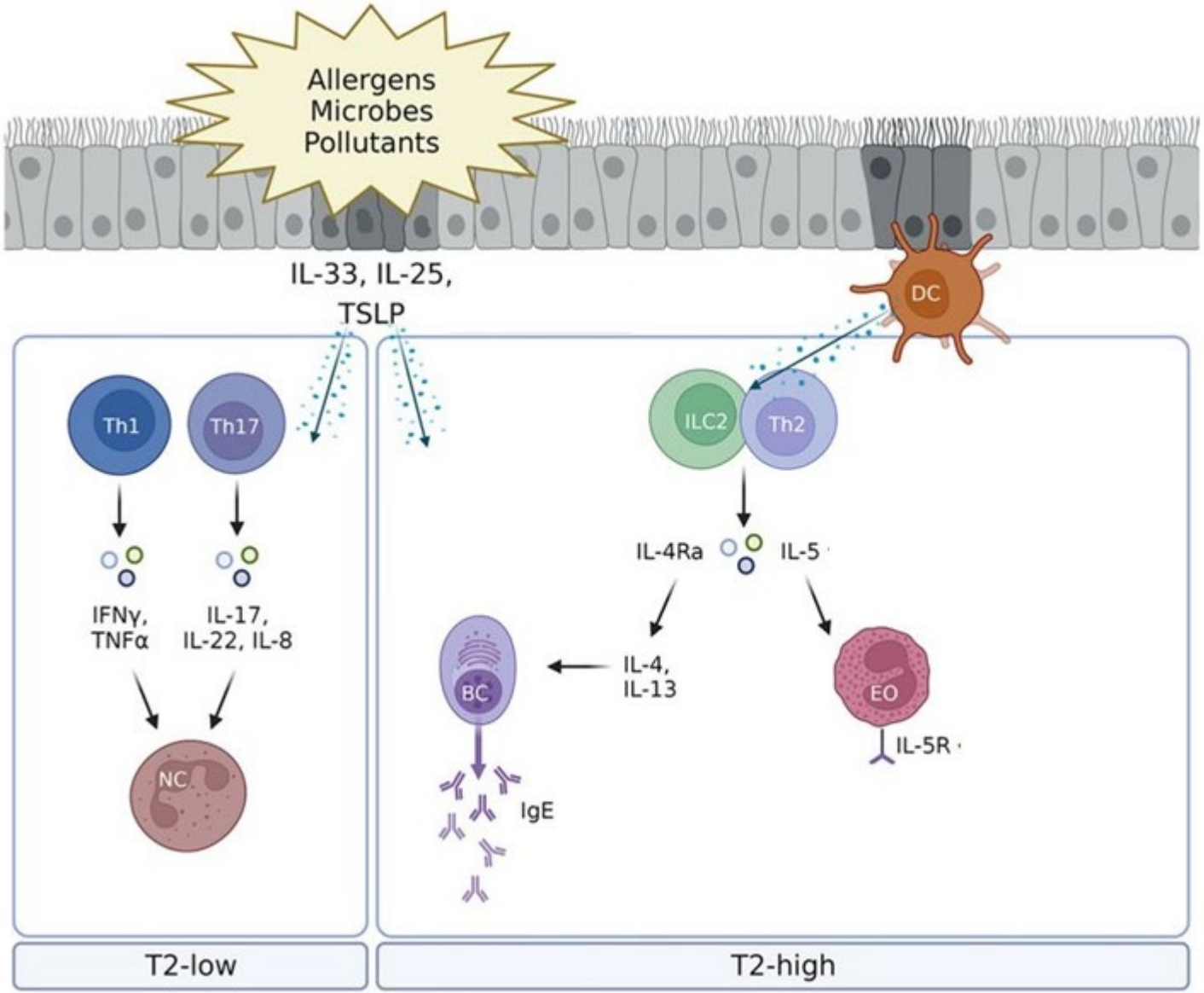
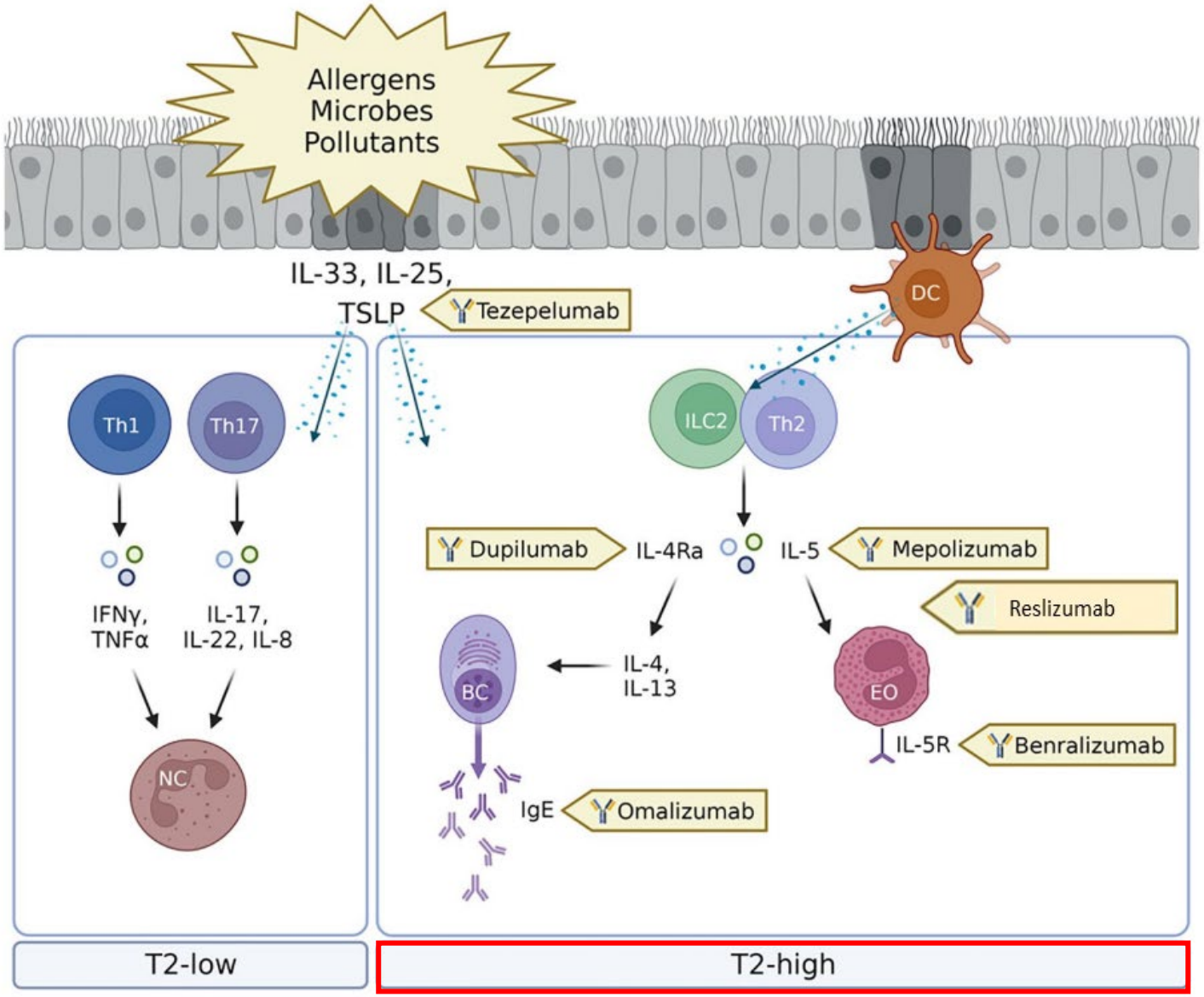
Airway epithelium interactions with environmental factors & Molecular Phenotypes of Severe Asthma



van Dijk YE et al . Pediatric Drugs 2023

T2-high phenotype
& Biologic treatment



van Dijk YE et al .
Pediatric Drugs 2023

Criteria for identifyng Type 2 inflammation

↑ EOS

Blood eosinophils ≥ 150/ µl

and/or

Sputum eosinophils ≥ 2%

and/or

↑ FeNO

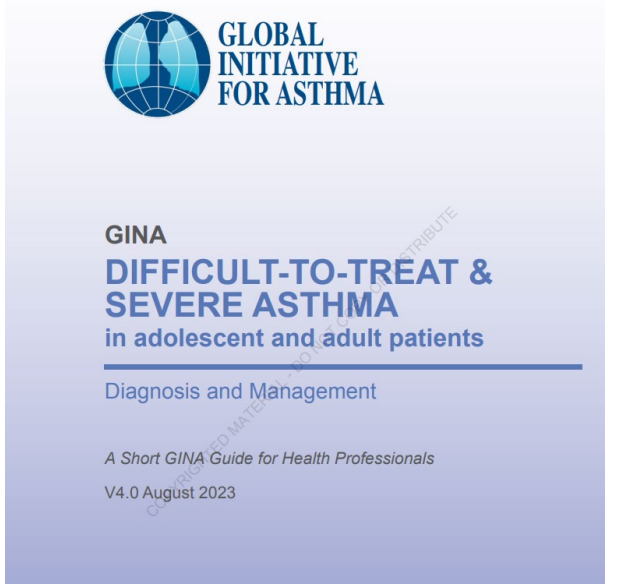
FeNO ≥ 20 ppb

and/or

↑ Total/ Specific IgE

Clinically allergen-driven asthma

OCS Suppression



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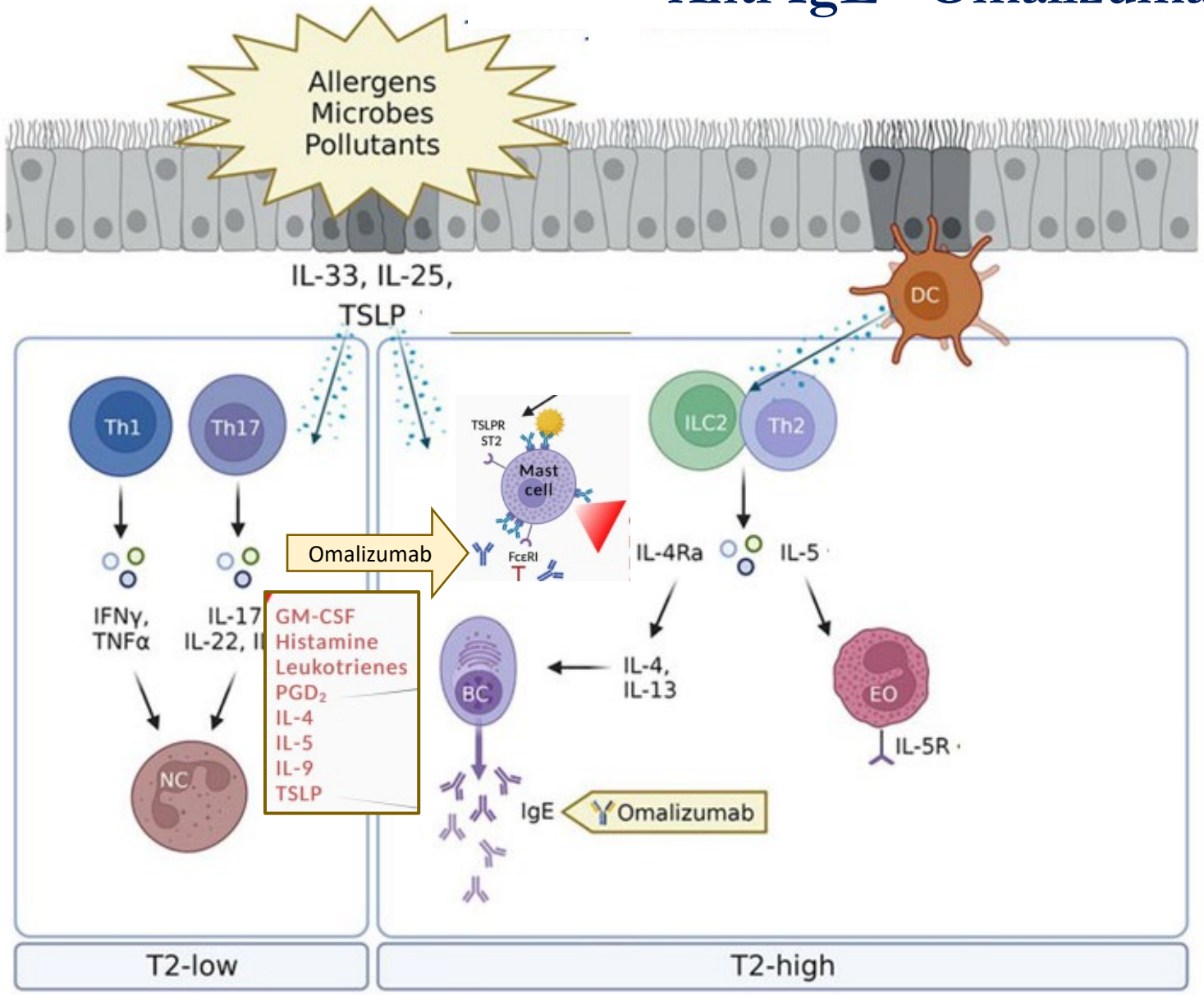
Biologic Type 2-targeted treatment

Anti IgE - Omalizumab



Omalizumab

humanized monoclonal antibody

The first approved biologic for asthma (2003) [and in children aged 6–11 years since 2009]

Mechanism of action

It binds to circulating free IgE preventing it from binding to antigen-presenting cells, mast cells, and basophils

Indications

Severe confirmed IgE-dependent allergic asthma with:

- ✓ Total serum IgE level is 30–1500 IU/mL
- ✓ Raised specific IgE to at least one perennial aeroallergen

Dosage

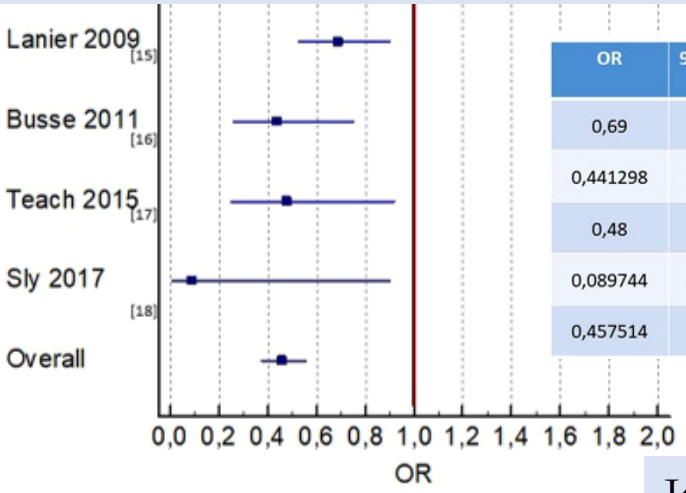
Subcutaneous injection every 2–4 weeks.

Dose is established by a nomogram obtained from total serum IgE levels and body weight (kilograms)

Omalizumab (OM)

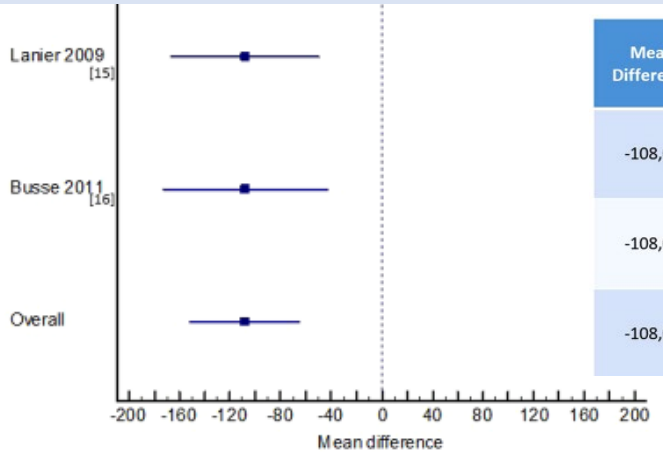
humanized monoclonal anti-IgE antibody

Exacerbation rate was reduced in OM vs placebo



OR	95% IC Low	95% IC High
0,69	0,53	0,9
0,441298	0,258824	0,752417
0,48	0,25	0,92
0,089744	0,008927	0,902174
0,457514	0,375495	0,55745

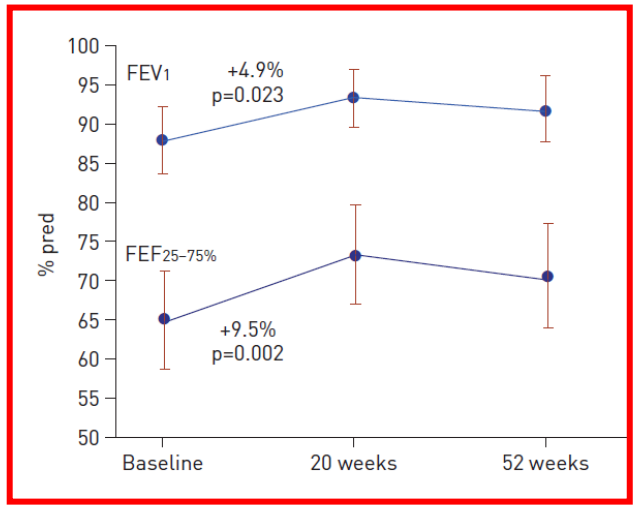
Required dosage of ICS was reduced in OM vs placebo group



Mean Difference	IC-H	IC-L
-108,00	-165,99	-50,01
-108,00	-172,73	-43,27
-108,00	-151,19	-64,81

Improvement of FEV1 after starting treatment of OM

Study	FEV_1 Measurement	Findings*	*p* Value
RCTs			
Milgrom *et al.*,[9] 2001	FEV_1	Baseline, OMA vs Pbo: 1797.1 vs 1855.2 mL Wk 24, OMA vs Pbo: 1891.0 vs 1883.5 mL	NR
Busse *et al.*,[19] 2011	% of predicted FEV_1	Baseline, OMA vs Pbo: 92.9 ± 18.7% vs 92.2 ± 17.6% Week 48, OMA vs Pbo: 92.6 ± 0.60% vs 91.7 ± 0.64% Difference, OMA vs Pbo at wk 48: 0.92 (95% CI, −0.81 to 2.64)	0.30
RWS			
Brodlie *et al.*,[17] 2012	FEV_1 in all patients	Baseline, 2100 mL (median) At 16 wk, 2250 mL (median)	0.1
	FEV_1 in patients <12 y	Baseline, 1800 mL (median) At 16 wk, 2100 mL (median)	0.0058
Odajima *et al.*,[15] 2015 Odajima *et al.*,[20] 2017	% of predicted FEV_1	Baseline, 90.3 ± 19.3% Wk 24, 89.7 ± 23.1% End of treatment, 89.2 ± 15.8%	NR
Deschildre *et al.*,[14] 2013 Deschildre *et al.*,[18] 2015	% of predicted FEV_1	Baseline, 88% (95% CI, 83.8–92.2%) 1 y, 92.1% Mean improvement to 1 y, 4.9% (95% CI, 0.69, 9.19%) 2 y, 89.9% (95% CI, 86.7–93.0%)	0.023 0.38
Campbell *et al.*,[13] 2008	% of predicted FEV_1	Before OMA, 71% ± 15% vs after OMA, 81% ± 15%	0.0004



Fenu G Frontiers in Pediatrics. 2023
Corren J Allergy Asthma Proc. 2017
Deschildre A ERJ. 2013/2015

T2-high Asthma Phenotype in children

Criteria for identifying T2-high phenotype

Biologic Type 2-targeted treatment

Anti IgE: Omalizumab

Anti IL5/IL5R: Mepolizumab - Reslizumab – Benralizumab

Anti IL4R: Dupilumab

Anti TSLP (Thymic stromal lymphopoietin): Tezepelumab

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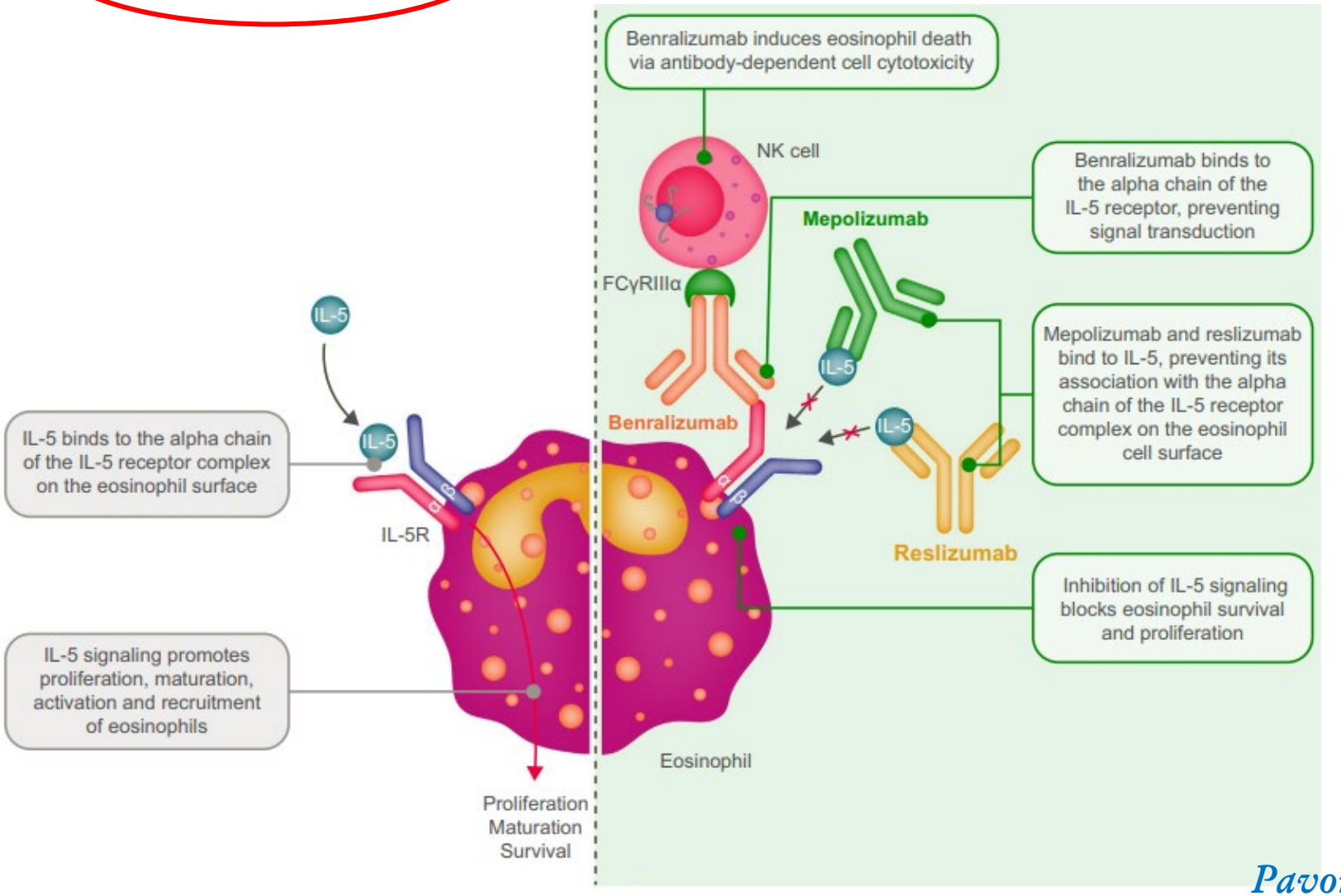
Biologic Type 2-targeted treatment

Anti IL5/IL5R

Mepolizumab – Reslizumab – Benralizumab



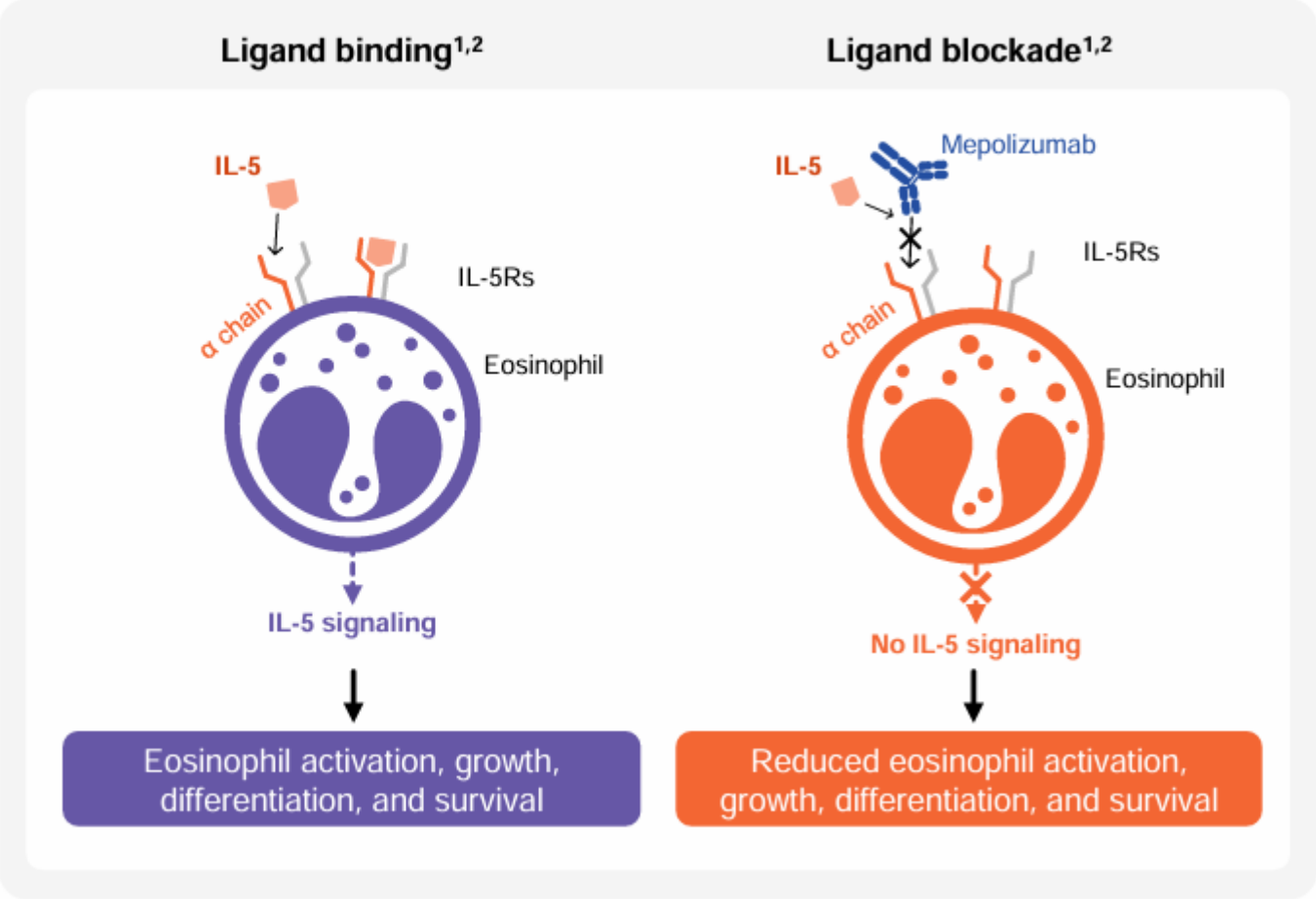
Pavord ID et al. Allergy, 2022

Mepolizumab

Recombinant humanized monoclonal antibody (IgG-1k)

Mechanism of action

It binds human IL-5 with high affinity and specificity



Mepolizumab binds with **high affinity and specificity** to the **IL-5 ligand**, preventing its binding to the IL-5R complex and **inhibiting IL-5 signaling**[1,2]

The most established effect of **IL-5 signaling inhibition** is the reduction of the **proliferation**, **activation**, and **survival** of **eosinophils**[1,2]

Mepolizumab

Recombinant humanized monoclonal antibody

Mechanism of action

It binds human IL-5 with high affinity and specificity

Indications

Severe asthma and eosinophilic phenotype:

- ✓ blood eosinophils ≥150 cells/μL at screening
- ✓ or ≥300 cells/μL within 12 months of enrollment

Dosage

Subcutaneous injection every 4 weeks.

Dose:

for adults and children aged ≥ 12 years → 100 mg

for children aged 6–11 years → 40 mg

Holguin F ERS/ATS guideline. Eur Respir J 2020
Hillson K Pediatr Pulmonol 2024
www.fda.gov
www.aifa.gov

Mepolizumab

Recombinant humanized monoclonal anti-IL5 antibody

The MUPPITS-2 multicenter RCT (290 patients aged 6–17 years) → a significant reduction in the number of asthma exacerbations in mepolizumab group vs placebo [0.96 (95% CI 0.78–1.17) and 1.30 (1.08–1.57), respectively, p = 0.027

Effects on lung function in children less conclusive

Effects on airway remodeling less investigated (at any age)

Higher cost than other antiasthma strategies?

Maglione M, Borrelli M. Children 2024
Jackson DJ. Lancet 2022

Mepolizumab in Severe Pediatric Asthma: Certainties and Doubts through a Single-Center Experience and Review of the Literature

Maglione, Borrelli et al. Children 2024

A case series of children and adolescents with

- Early onset of asthma
- Multiple allergens sensitization
- Blood eosinophilia and high fractional exhaled nitric oxide
- Poor response to long-term maintenance treatment *(medium/high dose inhaled corticosteroids ± other controllers)*
- Comorbidity (obesity; insulin resistance; nasal polyposis)

	Case 1	Case 2	Case 3	Case 4
Age at asthma onset	3 years	12 years	8 months	2 months
Allergic sensitization	House dust mites, cat dander, *Olea europaea*, *Parietaria judaica*	Grass pollen, Artemisia, *Olea europaea*, *Parietaria judaica*	House dust mites, cat/dog dander, cow's milk proteins, egg	House dust mites, *Alternaria*, *Olea europaea*, *Parietaria judaica*
Symptom burden	Weekly cough, dyspnea, and night awakenings. Frequent asthma attacks requiring systemic steroids, extra ICS, and bronchodilators.	Daily chest tightness, cough, exercise-induced dyspnea. Frequent asthma attacks requiring systemic steroids, extra ICS, and bronchodilators.	Monthly exacerbations with frequent need for systemic steroids, extra ICS, and bronchodilators.	Exacerbations requiring systemic steroids twice a month. Weekly night awakenings due to respiratory symptoms.
Comorbidity	Obesity, insulin resistance	Nasal polyposis	-	Obesity, insulin resistance
Treatment at referral	Budesonide (640 µg/d) + Formoterol (18 µg/d)	Budesonide (640 µg/d) + Formoterol (18 µg /d) + Montelukast (10 mg)	Budesonide (640 µg /d) + Formoterol (18 µg/d) + Montelukast (10 mg)	Beclomethasone (200 µg/d) + Formoterol (12 µg/d) + Omalizumab (450 mg/14 d)
Age at mepolizumab	14 years	16 years	10 years	14 years

Mepolizumab in Severe Pediatric Asthma: Certainties and Doubts through a Single-Center Experience and Review of the Literature

Maglione, Borrelli et al. Children 2024

A case series of children and adolescents with

- Early onset of asthma
- Multiple allergens sensitization
- Blood eosinophilia and high fractional exhaled nitric oxide
- Poor response to long-term maintenance treatment *(medium/high dose inhaled corticosteroids ± other controllers)*
- Comorbidity (obesity; insulin resistance; nasal polyposis)

After 12 months treatment with s.c. mepolizumab

- Improvement of Asthma Control Test
- Reduction of blood eosinophilia
- Decrease of asthma exacerbations

	Case 1		Case 2		Case 3		Case 4	
	Baseline	12 Months	Baseline	12 Months	Baseline	12 Months	Baseline	12 Months
Blood eosinophils, cells/μL (%)	1490 (13)	140 (1.3)	1470 (19)	100 (1.4)	420 (8.2)	80 (1.8)	530 (6)	70 (0.8)
Decrease in eosinophil count post-mepo (%)	−91		−93		−81		−86	
FEV_1, L (% pred)	3.7 (125)	3.1 (89)	3.3 (84)	3.0 (86)	1.5 (94)	1.5 (89)	1.6 (37)	4.3 (99)
$FEF_{25–75}$, L/s (% pred)	2.5 (67)	2.9 (73)	3.7 (84)	2.8 (65)	1.3 (64)	0.9 (44)	0.7 (16)	4.2 (87)
Total serum IgE (IU/mL)	1900	1800	234	250	1980	1980	1560	403
FeNO	143	117	53	55	68	33	38	12
ACT score	12	18	15	20	18	21	8	15
No. of exacerbations/year	18	7	20	9	17	5	18	8

T2-high Asthma Phenotype in children

Criteria for identifying T2-high phenotype

Biologic Type 2-targeted treatment

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Anti TSLP (Thymic stromal lymphopoietin): Tezepelumab

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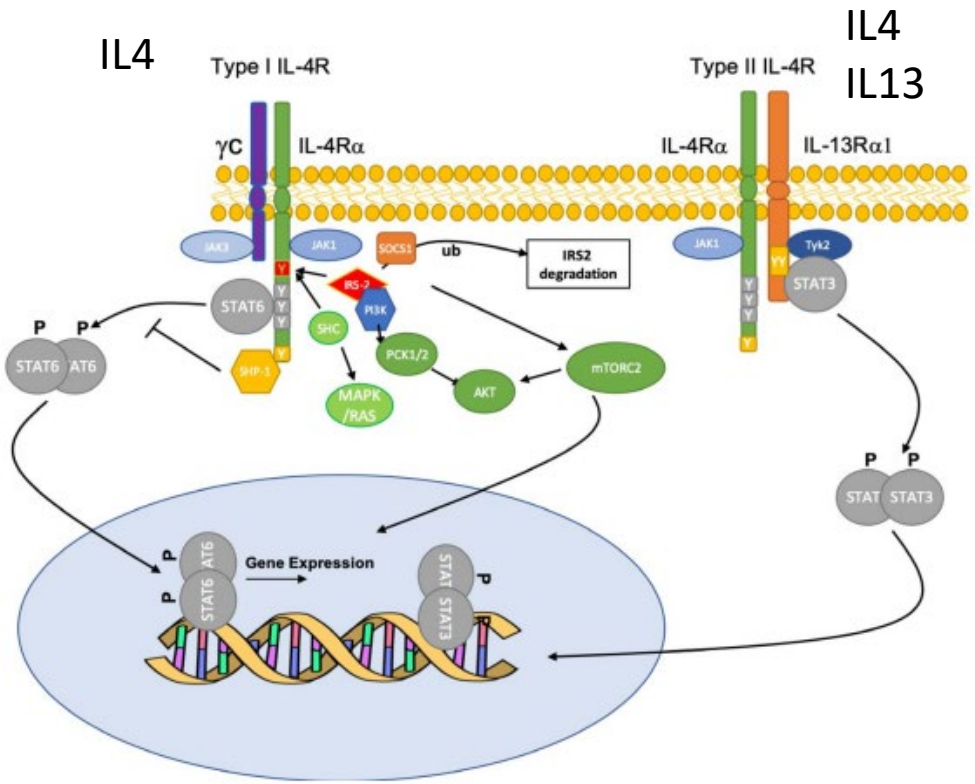
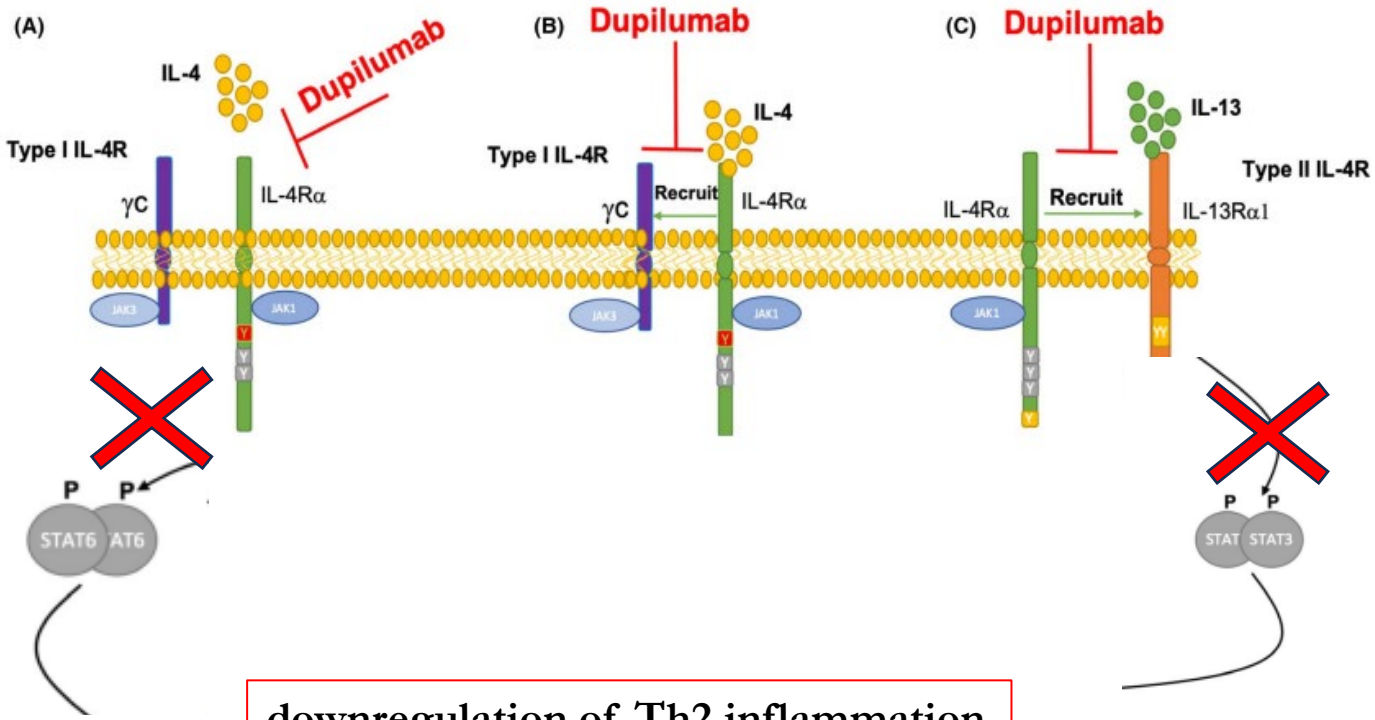
Biologic Type 2-targeted treatment

Anti IL4R

Dupilumab





downregulation of Th2 inflammation

Harb H et al. Clin Exp Allergy 2019

Dupilumab

Recombinant humanized monoclonal anti- IL-4Rα antibody

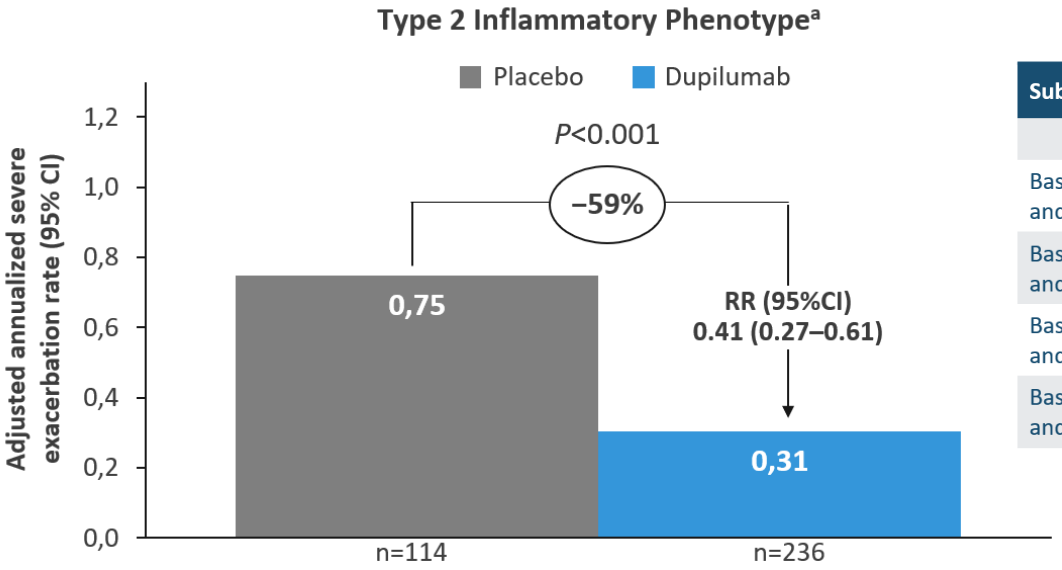
Dosage for children aged 6–11 years

Weight	Dose
15-30 Kg	100 mg every 2 weeks Or 300 mg every 4 weeks
30-60 Kg	200 mg every 2 weeks Or 300 mg every 4 weeks
≥ 60 Kg	200 mg every 2 weeks

Dupilumab

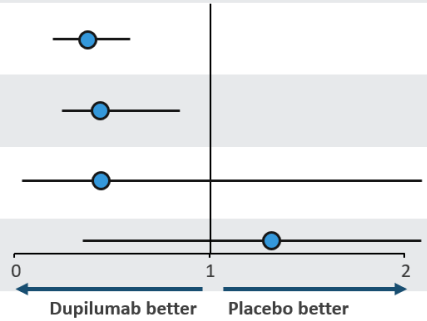
Dupilumab Phase 3 VOYAGE Study - Children aged 6 to 11 years with uncontrolled, moderate-to-severe asthma and Type 2 fenotype

Significant reduction in the annualized rate of severe asthma exacerbations in dupilumab group vs placebo



Type 2 Inflammatory Phenotype[a]

Subgroups	Patients, n		Relative Risk vs Placebo (95% CI)[b]
	Dupilumab	Placebo	
Baseline EOS ≥150 cells/µL and baseline FeNO ≥20 ppb	128	56	0.351 (0.204 to 0.605)
Baseline EOS ≥150 cells/µL and baseline FeNO <20 ppb	89	48	0.473 (0.262 to 0.851)
Baseline EOS <150 cells/µL and baseline FeNO ≥20 ppb	13	6	0.449 (0.051 to 3.989)
Baseline EOS <150 cells/µL and baseline FeNO <20 ppb	35	21	1.295 (0.357 to 4.690)



Bacharier LB *N Engl J Med.* 2021

Dupilumab

The EXCURSION open-label 52-week extension study

It demonstrated that the long-term use of dupilumab was well tolerated in children with an acceptable safety profile

It showed showing similar results about rate of exacerbation

Bacharier LB. *ERS* 2022

T2-high Asthma Phenotype in children

Criteria for identifying T2-high phenotype

Biologic Type 2-targeted treatment

Anti IgE: Omalizumab

Anti IL5/IL5R: Mepolizumab - Reslizumab – Benralizumab

Anti IL4R: Dupilumab

Anti TSLP (Thymic stromal lymphopoietin): Tezepelumab

The Choice Of Add-on Type 2-targeted Therapy

Review response to an initial trial of Therapy

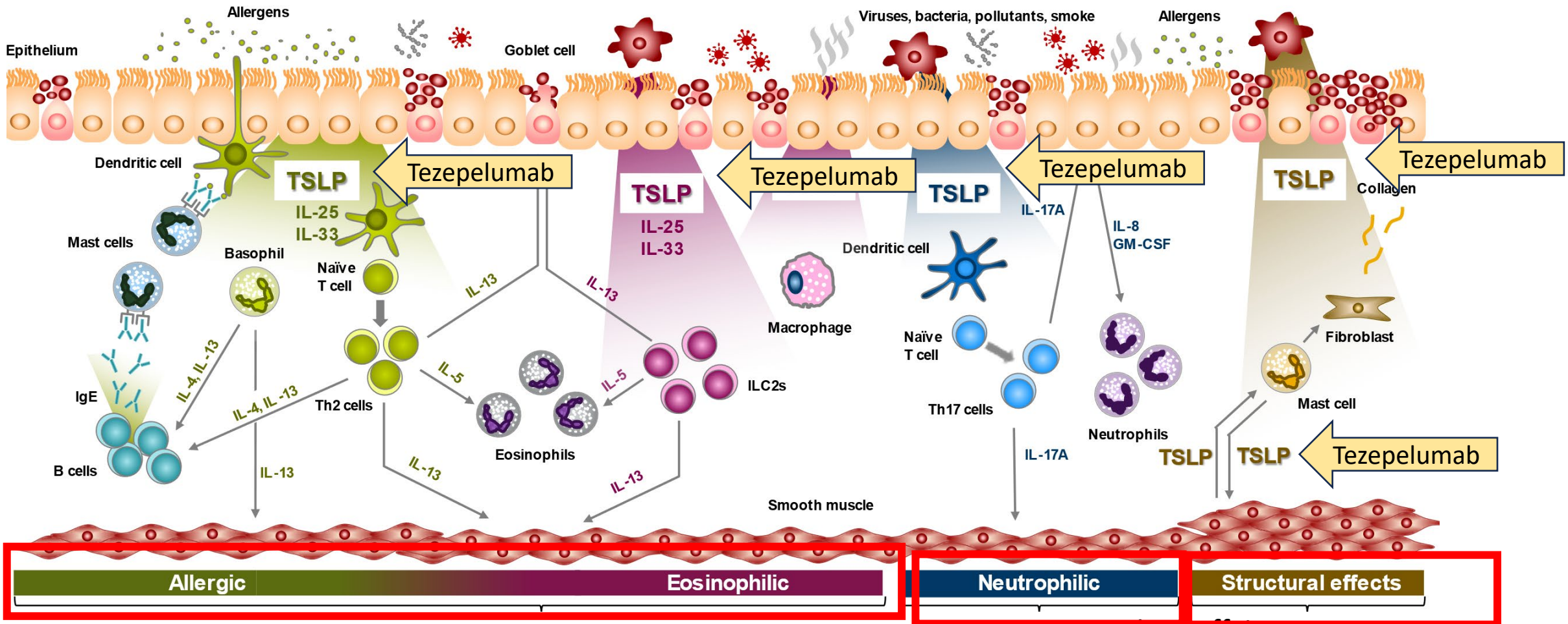
OUTLINE

Biologic Type 2-targeted treatment

Anti TSLP (Thymic stromal lymphopoietin)

Tezepelumab

TSLP Acts Across the Spectrum of Asthma Inflammation



By Medical Affairs AstraZeneca

Tezepelumab

Recombinant humanized monoclonal antibody

Mechanism of action

It blocks the activity of TSLP

Indications

Severe asthma - no biomarkers threshold

Dosage

Subcutaneous injection 210 mg every 4 weeks.

Tezepelumab

Recombinant humanized monoclonal anti-TSLP antibody

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial.

Patients 12 to 80 years of age were randomly assigned to receive tezepelumab (210 mg) or placebo subcutaneously every 4 weeks for 52 weeks.

Menzies-Gow, *NEJM* 2021

Tezepelumab

Recombinant humanized monoclonal anti-TSLP antibody

The annualized rate of asthma exacerbations was significantly lower with Tezepelumab vs placebo in uncontrolled asthma, regardless biomarkers

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

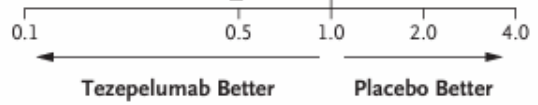


Figure 1. Annualized Rate of Asthma Exacerbations over a Period of 52 Weeks in the Overall Population and According to Baseline Biomarker Category or Allergic Status.

Menzies-Gow, *NEJM* 2021

Tezepelumab

Recombinant humanized monoclonal anti-TSLP antibody

Significant improvements in FEV1 and scores on the ACQ-6, AQLQ(S)+12

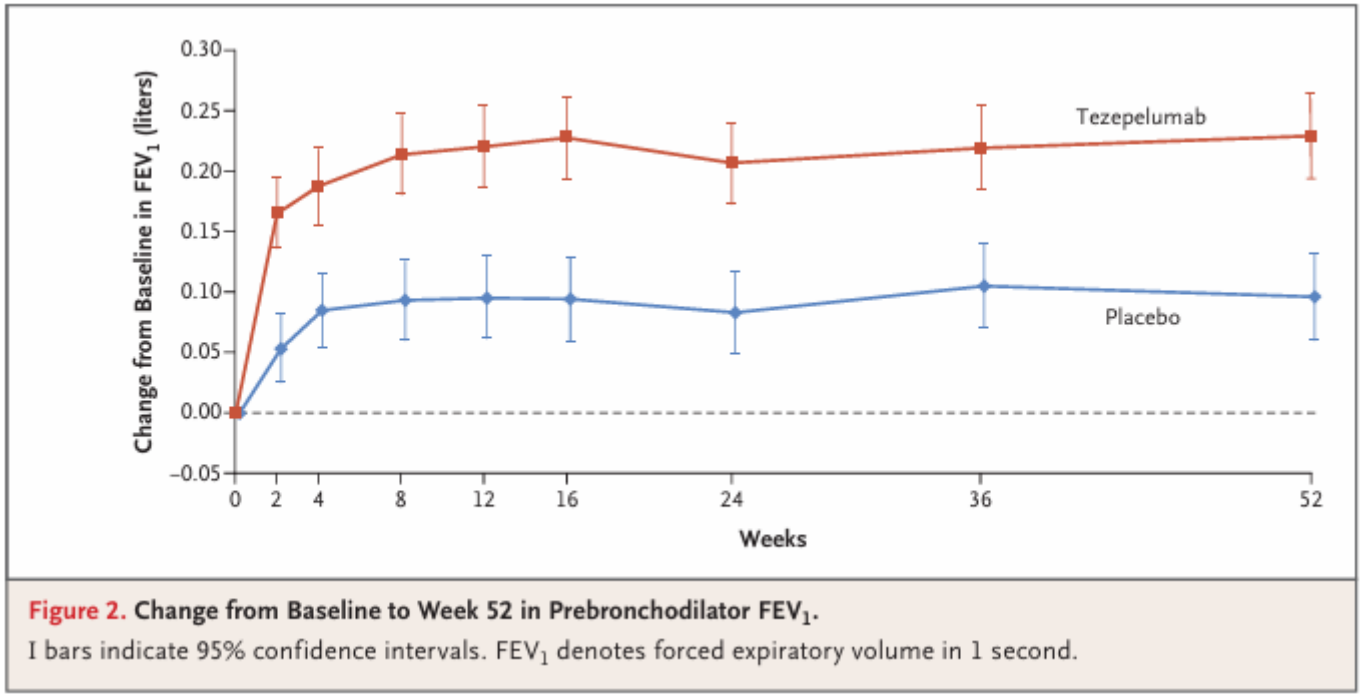


Figure 2. Change from Baseline to Week 52 in Prebronchodilator FEV_1.
I bars indicate 95% confidence intervals. FEV_1 denotes forced expiratory volume in 1 second.

Menzies-Gow, *NEJM* 2021

Tezepelumab

La nostra esperienza

♂ Asma allergico ed obesità (+arco aortico bovino) - proviene da altro centro

Età 11 aa OMA per 3 anni → MEPO

Follow up: OSAS (lieve);
Bcscopia/BAL/CT (neg)

Età 15 anni

Clinica: Frequenti riacutizzazioni severe + dispnea quotidiana
ACT 9
Terapia: Mepo (1 aa) + LABA/CSI; TIOTROPIUM; steroide orale 1vv/mese

IgE totali	IgE specifiche	EOS	FENO	FEV_1	FEF_{25-75}
528 UI/l	*D. pter/farinae; Poa pratensis*	140 cell	38 ppb	76% pred	49% pred

TEZEPELUMAB

data	FENO	FEV_1	FEF_{25-75}	ACT
3 mesi	18 ppb	96% pred	75% pred	23
6 mesi	5 ppb	96% pred	79% pred	23
8 mesi	9 ppb	83% pred	74% pred	23

A 9 mesi dall'inizio Tezepelumab

- Non più riacutizzazioni (no steroide orale)
- Sospende LABA/CSI
- Mantiene tiotropium

Tezepelumab

Recombinant humanized monoclonal anti-TSLP antibody

FUTURE GOALS

A Study to Investigate the Efficacy and Safety of Tezepelumab Compared With Placebo in Children 5 to < 12 Years Old With Severe Asthma (HORIZON)

ClinicalTrials.gov ID NCT06023589

T2-high Asthma Phenotype in children

Criteria for identifying T2-high phenotype

Biologic Type 2-targeted treatment

Anti IgE: Omalizumab

Anti IL5/IL5R: Mepolizumab - Reslizumab – Benralizumab

Anti IL4R: Dupilumab

Anti TSLP (Thymic stromal lymphopoietin): Tezepelumab

The Choice Of Add-on Type 2-targeted Therapy

Review response to an initial trial of Therapy

OUTLINE

The Choice Of Add-on Type 2-targeted Therapy

Eligibility criteria

Predictors of asthma response

Type 2 comorbidities (atopic dermatitis, nasal polyposis)

Cost

Dosing frequency

Delivery route (IV or SC; potential for self-administration)

Patient preference

The Choice Of Add-on Type 2-targeted Therapy

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Predictors of asthma response

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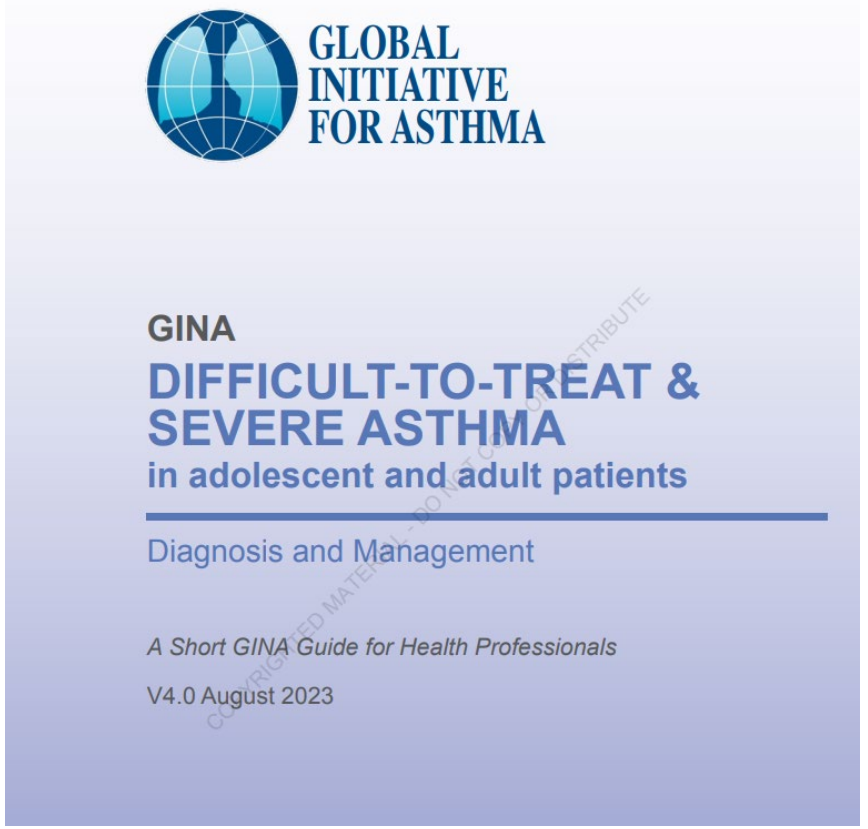

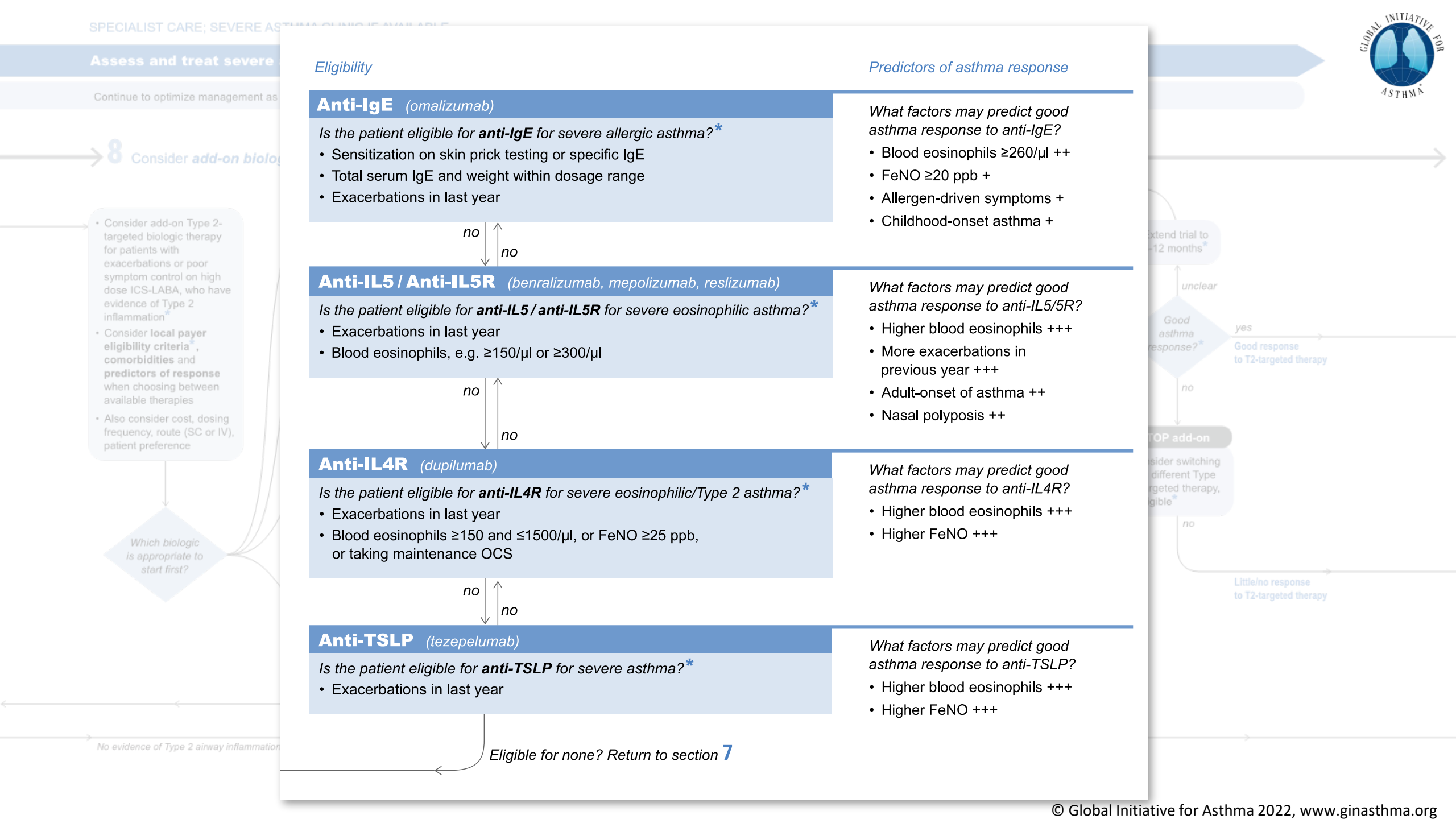

The Choice Of Add-on Type 2-targeted Therapy

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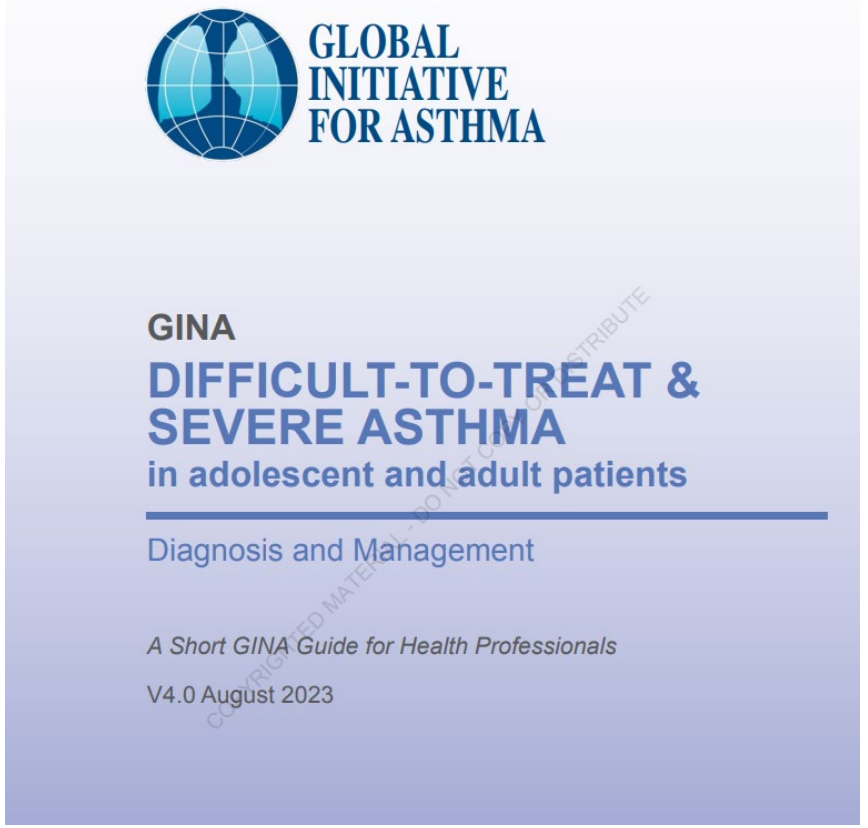


Biologic Type 2-targeted Treatment

Asthma and more……

Therapy	Indication AIFA 	Age
Omalizumab	Severe Asthma	Children ≥ 6 ys/Adult
	Chronic spontaneous urticaria	Children ≥ 12 ys/Adult
	Chronic rhinosinusitis with nasal polyposis	Only adult
Mepolizumab	Severe Asthma	Children ≥ 6 ys/Adult
	Chronic rhinosinusitis with nasal polyposis	Only adult
	Eosinophilic granulomatosis with polyangiitis (EGPA)	Children ≥ 6 ys/Adult
	Hypereosinophilic syndrome (HES)	Only Adult
Dupilumab	Severe Asthma	Children ≥ 6 ys/Adult
	Atopic dermatitis	Children ≥ 6 ys/Adult
	Chronic rhinosinusitis with nasal polyposis	Only adult
Tezepelumab	Severe Asthma	Children ≥ 12 ys/Adult

The Choice Of Add-on Type 2-targeted Therapy

Eligibility criteria

Predictors of asthma response

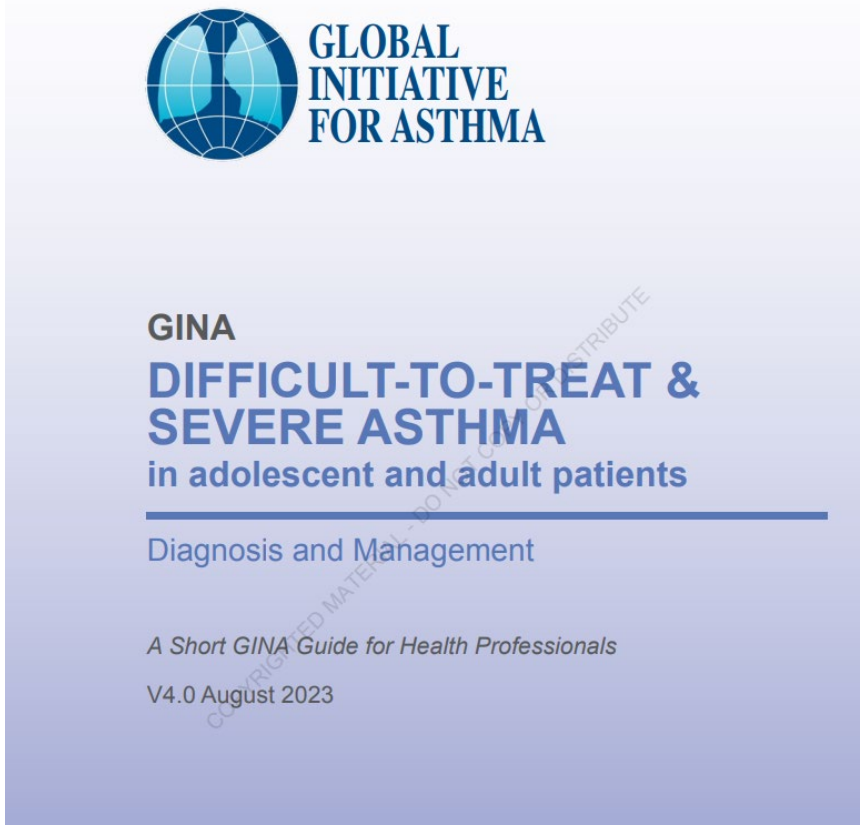
Type 2 comorbidities (atopic dermatitis, nasal polyposis)

Cost

Dosing frequency

Delivery route (IV or SC; potential for self-administration)

Patient preference

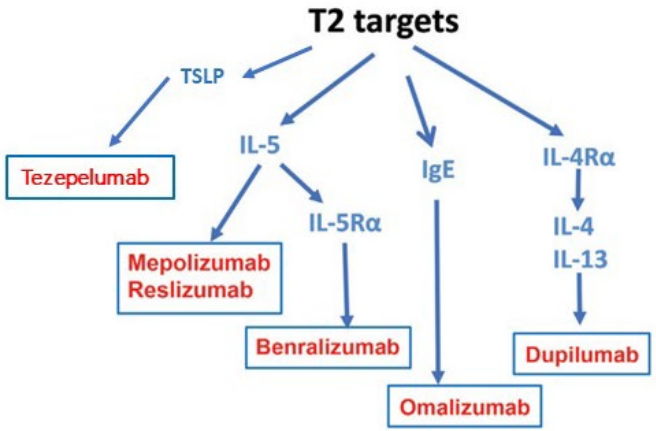


Biologics and costs in children

Classe	Nome	Costo
Anti-IgE	Omalizumab*	369 €/fl Costo/anno 4.450- 28.800 €
Anti-IL5	Mepolizumab	Fl 40 mg: 717 € Costo/anno 8604 € Fl 100: 1792 € Costo/anno 21.000 €
Anti-IL4R	Dupilumab	PENNA PRERIMEPITA e SIRINGA PRERIEMPITA 150 mg/ml: 1.003 € Costo/anno circa 13.000 €
Anti-TSLP	Tezepelumab	Fl 210 mg: 700 € Costo/anno circa 9.000 €

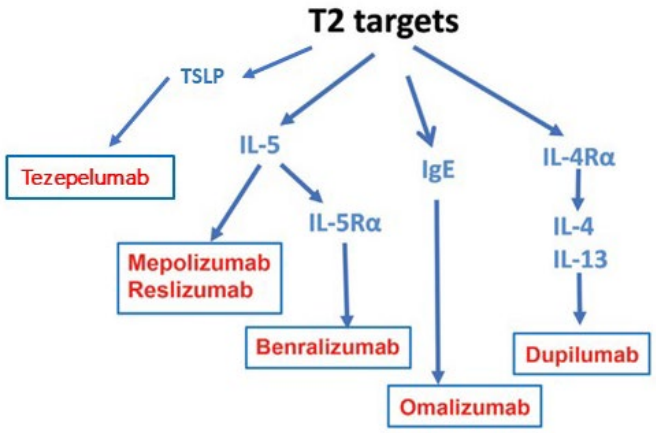
*Dose varia da 75 mg ogni 4 settimane a 375 mg ogni 2 settimane

BIOLOGICAL THERAPY FOR SEVERE ASTHMA IN CHILDREN



	AIFA	EMA	FDA
Omalizumab	≥ 6 years	≥ 6 years	≥ 6 years
Mepolizumab	≥ 6 years	≥ 6 years	≥ 6 years
Dupilumab	≥ 6 years	≥ 6 years	≥ 6 years
Reslizumab	///	///	≥ 18 years
Benralizumab	///	///	≥ 12 years
Tezepelumab	≥ 12 years	≥ 12 years	≥ 12 years

BIOLOGICAL THERAPY FOR SEVERE ASTHMA IN CHILDREN



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Dupilumab	≥ 6 years	≥ 6 years	≥ 6 years
Reslizumab	///	///	≥ 18 years
Benralizumab	///	///	≥ 12 years
Tezepelumab	≥ 12 years	≥ 12 years	≥ 12 years

Review response to an initial trial of add-on Type 2-targeted therapy

For add-on biologic therapy after 3-4 months - For ongoing care every 3-6 months

Assess:

Asthma: symptom control, frequency and severity of exacerbations, lung function

Type 2 comorbidities (nasal polyposis, atopic dermatitis)

Medications: treatment intensity (including dose of OCS), side-effects, affordability

Patient satisfaction

Review response to an initial trial of add-on Type 2-targeted therapy

Unclear response

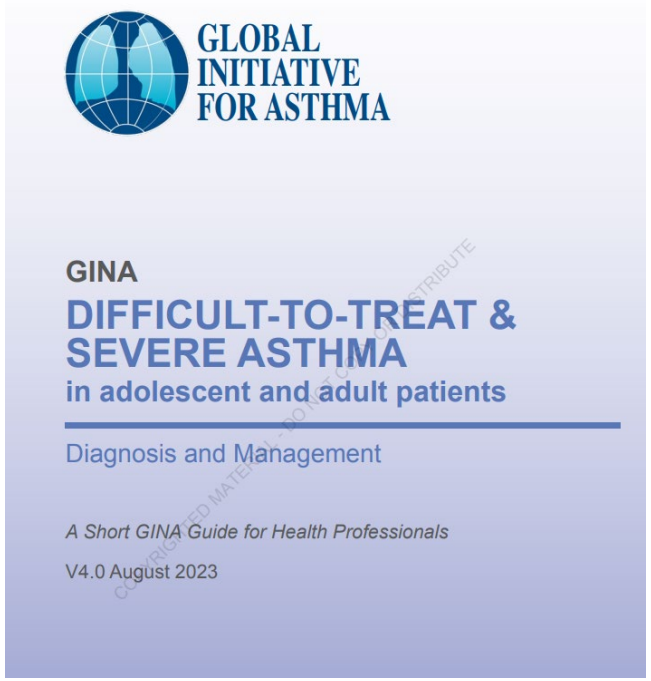
Consider extending the trial to 6-12 months

No response

Stop biologic therapy

Consider switching to a trial of a different Type2-targeted therapy

Consider biomarkers and response of any comorbid Type 2 conditions



Review response to an initial trial of add-on Type 2-targeted therapy

Good response

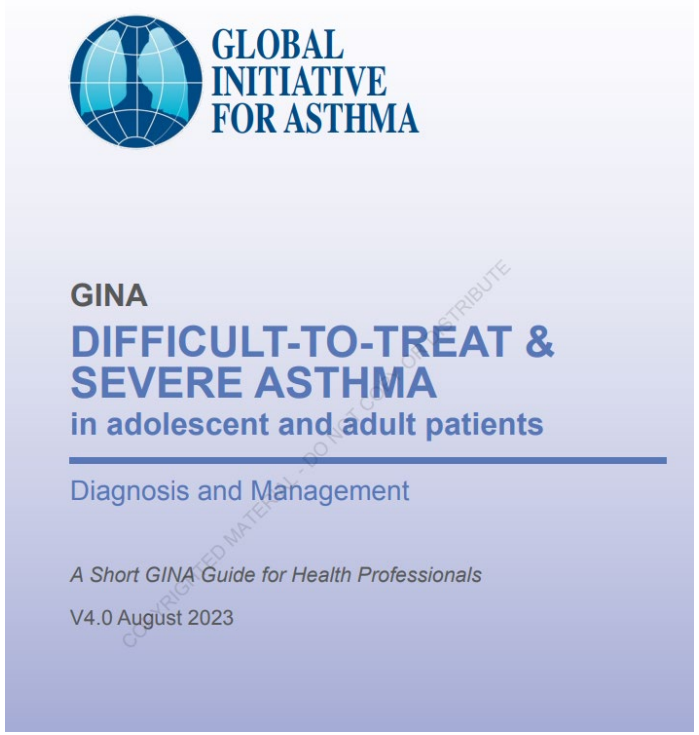
OCS → gradually decrease or stop

Inhaled treatment → reduce ICS (after 3-6 m)

– continue medium dose

Attention
Adrenal insufficiency

Biologic treatments→ trial of until after at least 12 months



JEM Journal of Experimental Medicine

REVIEW

Characteristic	Omalizumab	Mepolizumab	Dupilumab	Tezepelumab
Mechanism	Anti-IgE	Anti-IL5	Anti-IL4Rα	Anti-TSLP
Indication	Severe asthma	Severe asthma	Severe asthma	Severe asthma
Drug form	Prefilled syringe	Prefilled syringe, autoinjector pen	Prefilled syringe, autoinjector pen	Prefilled syringe
Licensed patient age	≥6 yr	≥6 yr	≥6 yr	≥12 yr
Safety concerns	Injection site reactions (2–10%), hypersensitivity reactions (<1%)	Injection site reactions (2–10%), hypersensitivity reactions (<1%), shingles (rare), helminth infection (rare)	Injection site reactions (2–10%), hypersensitivity reactions (<1%), hypereosinophilia (3%), conjunctivitis, helminth infection (rare)	Injection site reactions (2–10%), hypersensitivity reactions (<1%), pharyngitis, arthralgia, back pain
Typical patient group	Allergic asthma, childhood onset	Eosinophilic asthma, adulthood onset	Eosinophilic or allergic asthma, childhood or adulthood onset	Eosinophilic or allergic asthma, adulthood onset, type 2 low asthma
Key biomarker(s) for response	Serum IgE (for dosing)	Raised blood eosinophils	Raised blood eosinophils and FeNO	Raised blood eosinophils and FeNO
Co-existing conditions treated by biologic	Chronic spontaneous urticaria, allergic rhino-conjunctivitis	ABPA, EGPA, chronic rhinosinusitis with nasal polyposis	Chronic rhinosinusitis with nasal polyposis, atopic dermatitis (eczema)	Chronic rhinosinusitis with nasal polyposis

Howell I, 2023

JEM Journal of Experimental Medicine

REVIEW

Characteristic	Omalizumab	Mepolizumab	Dupilumab	Tezepelumab
Mechanism	Anti-IgE	Anti-IL5	Anti-IL4Rα	Anti-TSLP
Effect on blood eosinophil	↓	↓↓	↑ (returns to baseline after 1 yr)	↓
Effect on FeNO	↓	None	↓↓	↓↓
Effect on serum IgE	None	None	↓	↓
Effect on exacerbations	↓	↓↓	↓↓	↓↓
Effect on FEV1	None	↑	↑↑	↑↑
Oral steroid sparing	No	Yes	Yes	No (trial ongoing)

Howell I, 2023

Conclusions

- ✓ The introduction of biologics as add-on therapy for severe asthma has revolutionized severe asthma management
- ✓ The biologic therapy paved the way for precision medicine (*the right treatment to the right patient*) in children and adolescents
- ✓ One particular area of therapeutic advance has been in reducing the need for OCS therapy
- ✓ The current development of other biologics such as the anti-TSLP (and the anti-IL-33) antibody represents further development as they blocks the effect of these alarmins, TSLP and IL-33, produced by epithelial cells interacting with environmental factors such as allergens, pollutants, and infectious agents
- ✓ There is an urgent need for head-to-head comparisons of different biologics in patients eligible for more than one biologic
- ✓ More data on efficacy and long-term safety are need in the paediatric population

GRAZIE