Hot Issues in Respiratory Medicine

: Appropriate Biologics Selection in Severe Asthma

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Contents

Severe asthma

- **Severe asthma** is defined as “asthma”

that is uncontrolled, despite adherence with maximal optimized high-dose inhaled corticosteroids with LABA treatment and management of contributory factors,

or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.

- High-dose inhaled corticosteroid ?

  - GINA guidelines: more than 800 µg beclometasone,
  - ATS and ERS guidelines: more than 1600 µg beclomethasone

⇒ **Most widely used definition in setting the indication for biological therapies**

Celeste Porsbjerg et al. Lancet 2023;401: 858-73.

Assessment of severe asthma

Difficult-to-treat asthma

- **Poor asthma control despite high-dose ICS and second controller**
- **Caused by treatment barriers or triggers**

Systematic assessment

Diagnosis and endotype

- Confirm the diagnosis, whether current symptoms are due to asthma, assess asthma control, and assess **inflammatory endotype**

Treatment barriers

- Check **adherence, inhaler technique**, and possible need' for asthma education

Triggers

- Exposures (smoking, allergens, occupational exposures)
- Comorbidities

Severe asthma

- **Poor asthma control**
- **Caused by an insufficient response to current standard treatments**

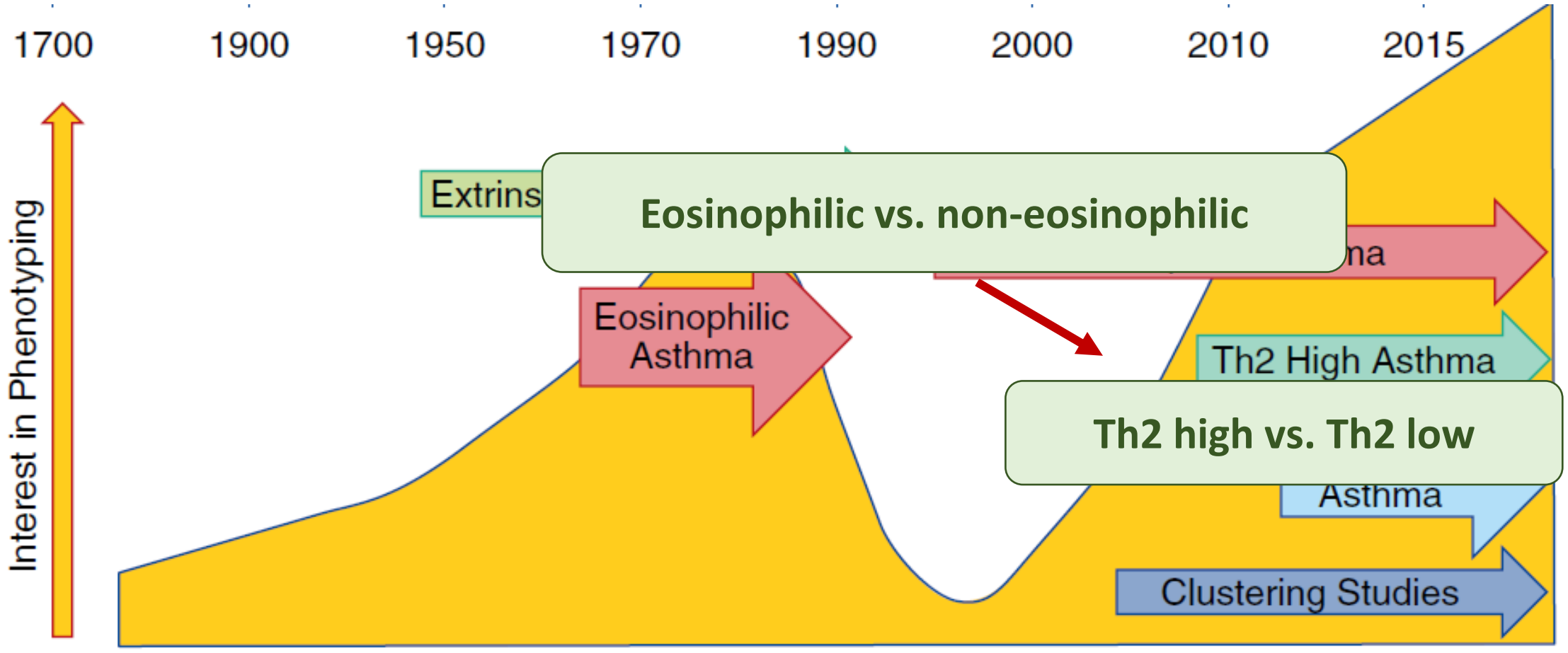
Celeste Porsbjerg et al. Lancet 2023;401: 858-73.

Accessible treatment options of severe asthma

Possible specialised treatments for uncontrolled severe asthma						
	Anti-IgE	Anti-IL-5/5R	Anti-IL-4/13	Anti-TSLP	Azithromycin	Bronchial thermoplasty
Eligibility	• Sensitised to perennial allergens, allergen driven disease and • Exacerbations or • mOCS use	• Blood eosinophilia (>0·15 or 0·3) and •Exacerbations or • mOCS use	B-eos 0·15–1·5, or FeNO >25 ppb and •Exacerbations or • mOCS use	• No phenotype requirements • Exacerbations or • mOCS use	• Exacerbations	• Exacerbations • mOCS at most 10 mg of prednisolone per day • Adults only • FEV_1 >60%
Possible predictors of good response	• B-eos >0·26 • FeNO >20 ppb • Allergen driven asthma	• Higher blood eosinophils • More exacerbations • CRSwNP	• Higher blood eosinophils • Higher FeNO • CRSwNP	• Higher blood eosinophils • Higher FeNO	• Colonisation with *Haemophilus influenzae*	NA
Effective also in	• Chronic spontaneous urticaria • CRSwNP	• CRSwNP • EGPA • HES	• CRSwNP • Atopic dermatitis	NA	• Bronchiectasis	NA

Celeste Porsbjerg et al. Lancet 2023;401: 858-73.

Timeline in the understanding of asthma and phenotype



Am J Respir Crit Care Med Vol 192, Iss 6, pp 660–668, Sep 15, 2015

Inflammatory phenotype in asthma

	Th2-high	Th2-low
Prominent inflammatory type in sputum	Eosinophil	Neutrophil Mixed-granulocytic Pauci-granulocytic
Relevant pathways	IL-4, IL-5, IL-13	IL-17 (?)
Approved biologics	Omalizumab (IgE) Dupilumab (IL-4, IL-13) Benralizumab (IL-5) Mepolizumab (IL-5) Reslizumab (IL-5)	-
Selection of investigational biologics (pathway)	Tezepelumab (TSLP) CSJ117 (TSLP)	
	Astogolimab (IL-33)	CJM112 (IL-17A)
	GSK3772847 (IL-33)	

Allergologie select, Vol. 5/2021 (96-102)

T2-high asthma

Biomarker in type 2 inflammation

- **Allergic asthma**

  - Allergic sensitization to aeroallergens (skin prick test or specific IgE)

  - Symptoms of allergic rhinoconjucvitis

- **T2 biomarkers**

  - FeNO more than 25 ppb (20 ppb in GINA)

  - Blood eosinophils equal or more than 300 cells/μL (150 cells/μL in GINA)

  - Sputum eosinophils equal to or more than 3% (2% in GINA)

* Detectable biomarkers of Th2 high inflammation

: **IgE, FeNO, blood eosinophil >> sputum eosinophil, periostin**

Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated July 2022. https://ginasthma.org/gina-reports/. Accessed August 22, 2022.
Celeste Porsbjerg et al. Lancet 2023;401: 858-73.

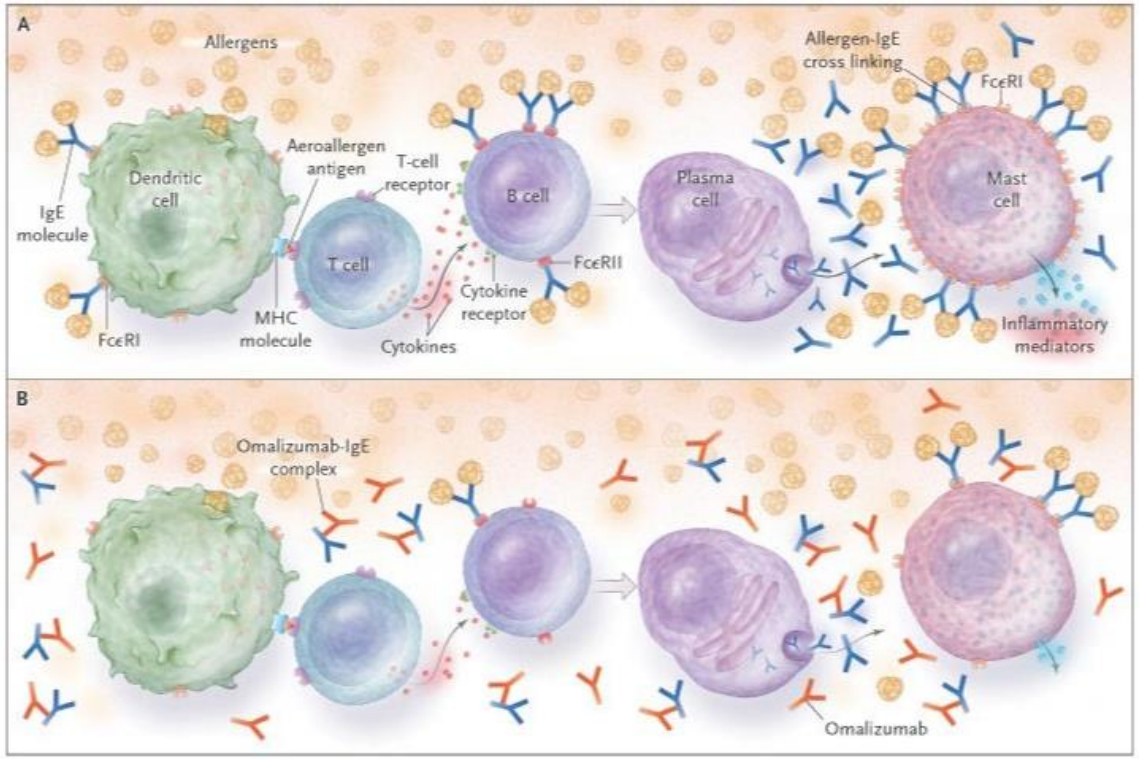
Biologics for pts. at GINA step 5

GINA step 5

Consider add-on biologic therapy (anti-IgE, anti-IL-5/5-Ra, anti-IL-4-Ra, anti-TSLP) for patients with frequent exacerbations or poor symptom control despite high-dose ICS/LABA

Which biologic is appropriate to start first?			
Anti-IgE *(omalizumab)*	**Anti-IL-5/Anti–IL-5R** *(benralizumab, mepolizumab, reslizumab)*	**Anti–IL-4R** *(dupilumab)*	**Anti-TSLP** *(tezepelumab)*
*Is the patient eligible for **anti-IgE** for severe allergic asthma?** • Sensitization on skin prick testing or specific IgE • Total serum IgE and weight within dosage range • Exacerbations in last year	*Is the patient eligible for **anti–IL-5/IL-5R** for severe eosinophilic asthma?** • Exacerbations in last year • Blood eosinophils, eg, ≥150/µL or ≥300/µL	*Is the patient eligible for **anti–IL-4R** for severe eosinophilic/type 2 asthma?** • Exacerbations in last year • Blood eosinophils ≥150/µL and ≤1500/µL, or FeNO ≥25 ppb, or taking maintenance OCS	*Is the patient eligible for **anti-TSLP** for severe asthma?** • Exacerbations in last year

Anti-IgE monoclonal antibody: omalizumab



- 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

- **Route of administration and dose**

  : **SC**, 75 to 375 mg every 2 to 4 wk according to BW and level of serum total IgE

- Patient year of age: ≥ 6
- **Indication**

  - Severe allergic asthma
  - Chronic idiopathic urticaria

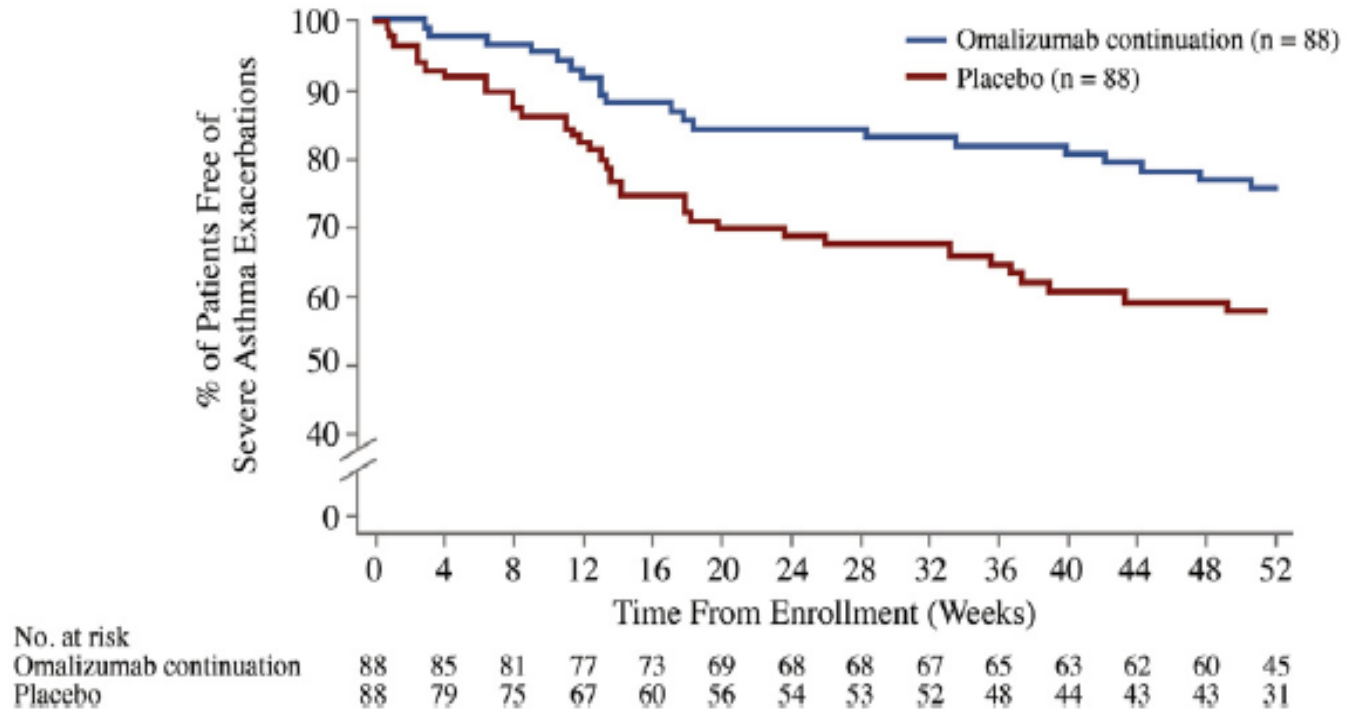
- **Safety concerns**

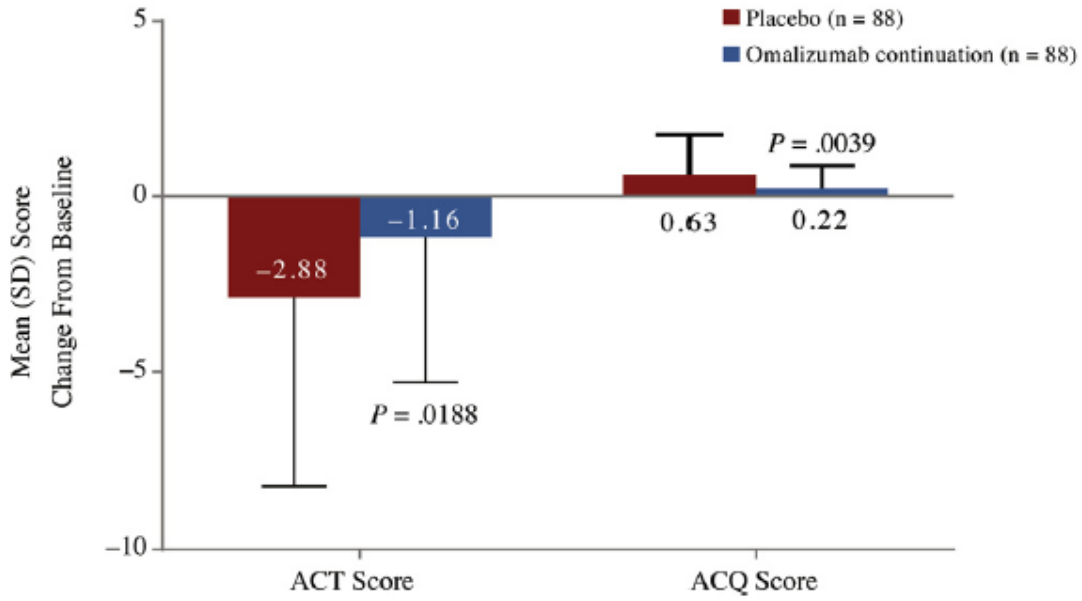
  - Hyper eosinophilic conditions (e.g. EGPA)
  - Serum sickness
  - Abrupt discontinuation of OGs

N Engl J Med 2006; 354:2689-2695

Omalizumab reduced asthma exacerbation

- Randomized, double-blind, placebo-controlled withdrawal study
- Subjects with moderate-to-severe persistent asthma receiving long-term omalizumab
- Study outcome: any protocol-defined severe asthma exacerbation, time to first protocol-defined severe asthma exacerbation, and changes in Asthma Control Questionnaire and Asthma Control Test scores

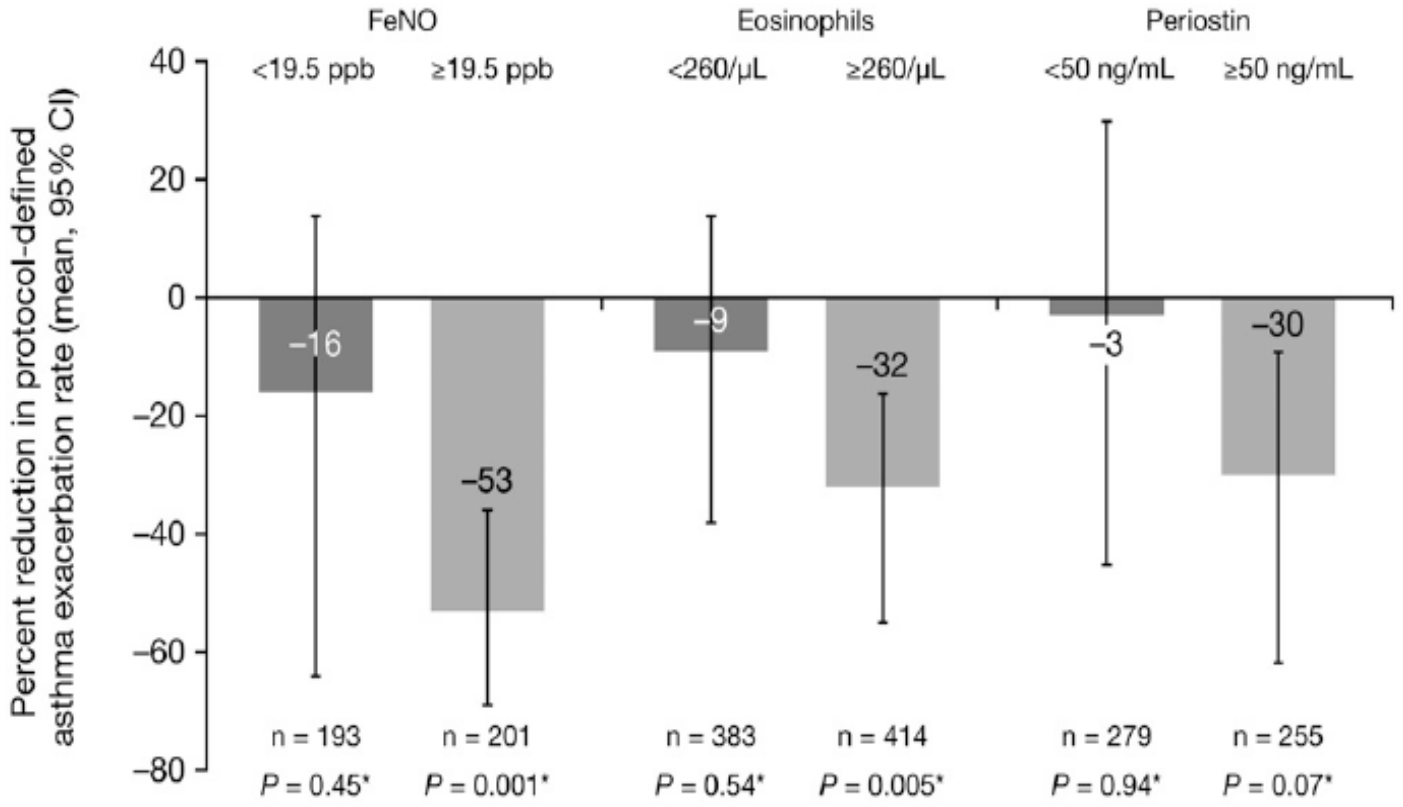




J Allergy Clin Immunol 2017;140:162-9

Biomarkers of omalizumab in the EXTRA study

- EXTRA omalizumab study enrolled patients (aged 12–75 yr) with uncontrolled severe persistent allergic asthma.
- Evaluate treatment effects as number of protocol-defined asthma exacerbations during 48-wk in relation to FENO, blood eosinophils, and serum periostin at baseline.
- Patients were divided into low- and high-biomarker subgroups.

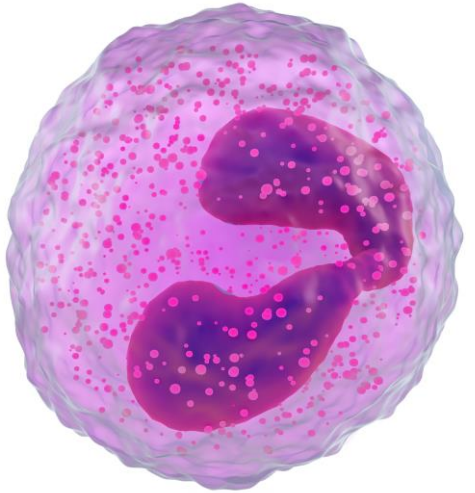


Am J Respir Crit Care Med.2013; 187(8): 804–811

Eosinophilic phenotype in severe asthma

- From the analysis of NHANES data, **69% of adult patients with asthma** had eosinophilic asthma (blood eosinophil cutoff point of ≥150 cells/µL).
- Untreated eosinophilic asthma can lead to serious consequences

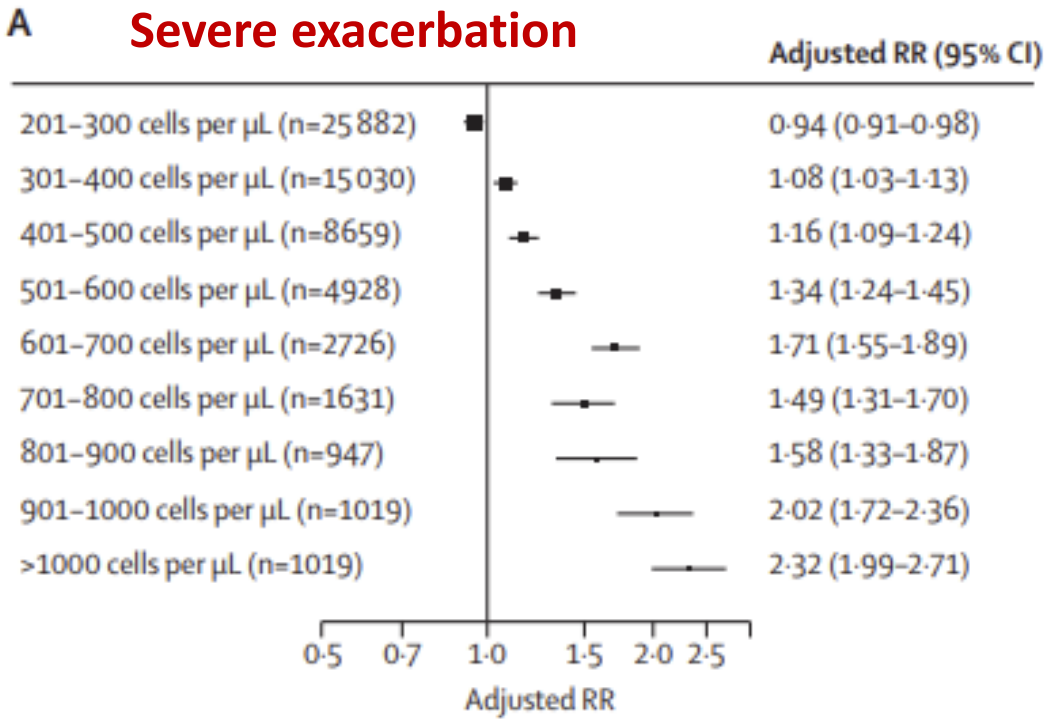
  - Airway smooth muscle contraction
  - Progressive airway damage and poor control
  - Airway hyperresponsiveness
  -Airway remodeling

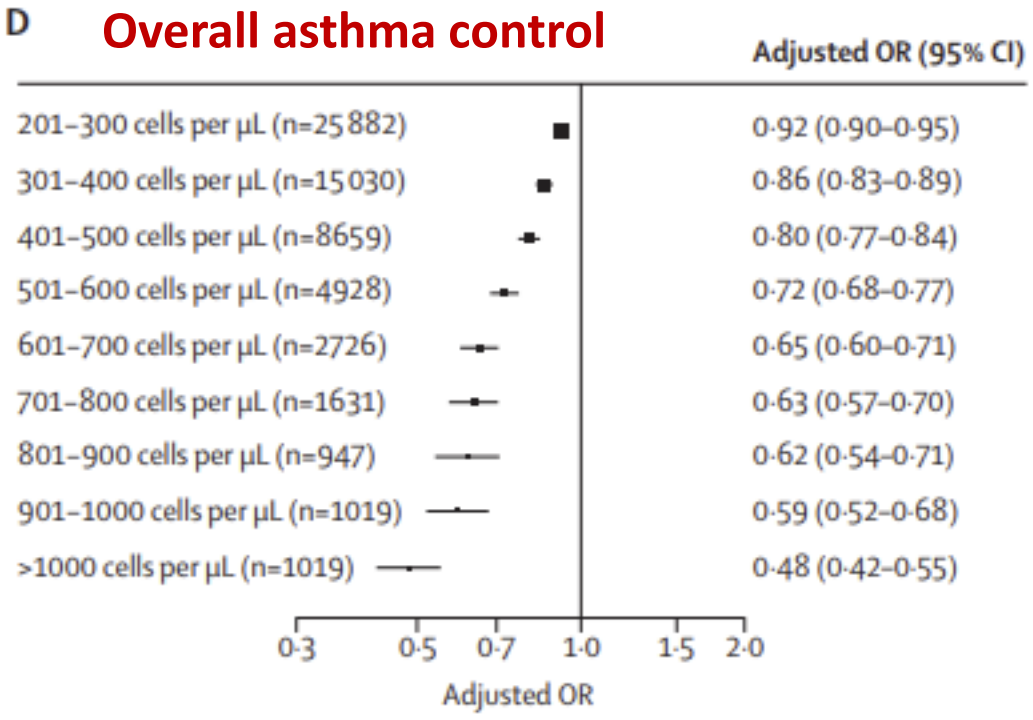


Ann Allergy Asthma Immunol. 2016;116:37-42.
ERJ Open Res. 2015;1:1-11.
Cell Mol Life Sci. 2007;64:1269-1289.

Blood eosinophil count and prospective annual asthma disease burden

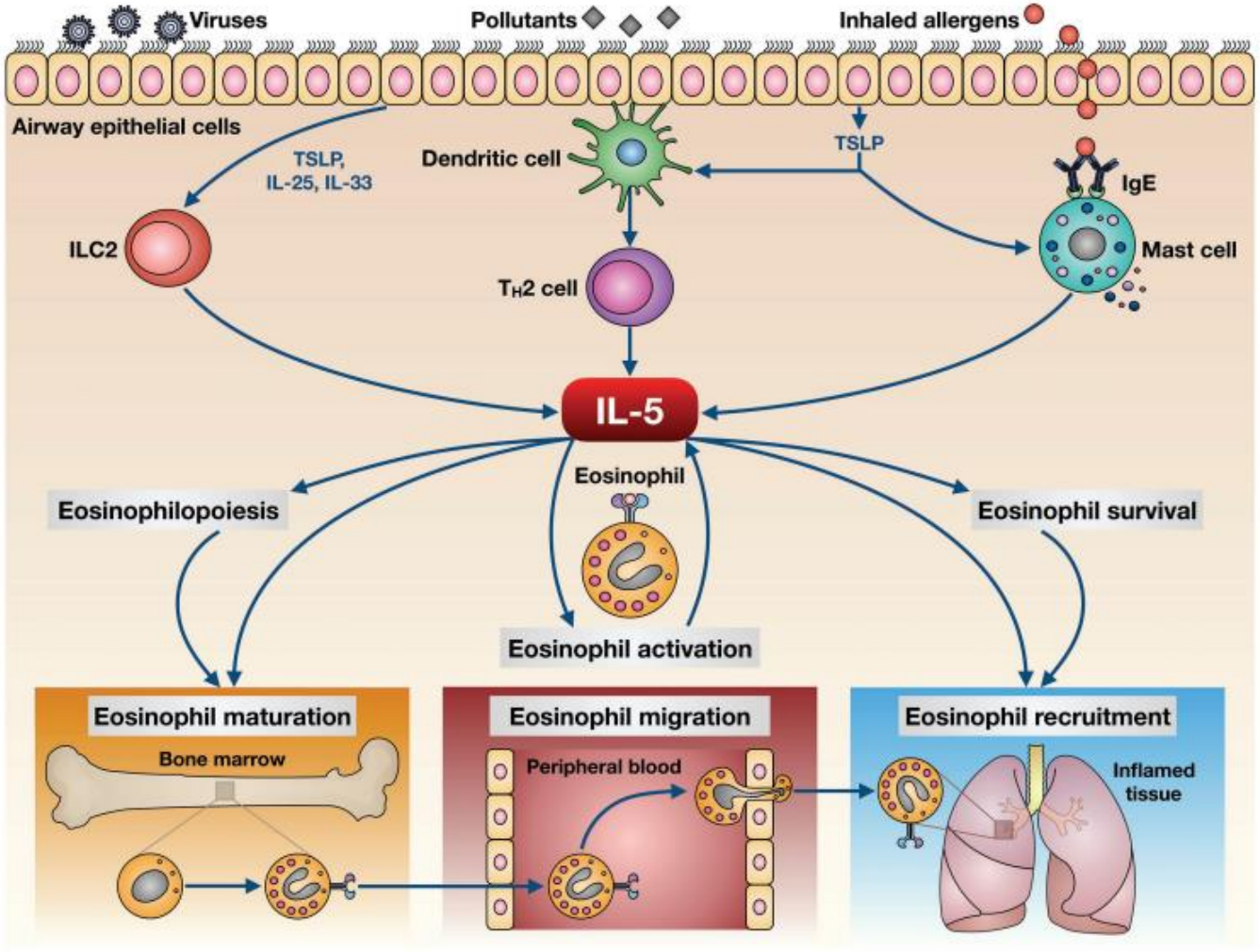
- Cohort study to identify primary care patients with asthma aged 12–80 years with 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count.
- Compare the exacerbation rates and asthma control for patients with 400 cells per µL of cut off value of blood eosinophil counts
- 20 929 (16%) of 130 248 patients had blood eosinophil counts greater than 400 cells per µL





Lancet Respir Med 2015; 3: 849–58

Antibody against IL-5/IL-5R
: mepolizumab/reslizumab/benralizumab



- IL-5 inhibition

  : mepolizumab, reslizumab

- Block of IL-5 receptor

  : benralizumab

N Engl J Med 2006; 354:2689-2695
Front. Physiol. 10:1514.

Mepolizumab

- **Route of administration and dose**
  - Adults and adolescents: SC; 100 mg every 4 wk
  - Children, ages 6–11 yr: SC; 40 mg every 4 wk
- Patient year of age: ≥ 6
- **Indication**
  - Severe eosinophilic asthma
  - EGPA, hyper eosinophilic Syndrome
- **Safety concerns**
  - Helminthic infections
  - Hypersensitivity reactions
  - Abrupt discontinuation of OGs
  - Herpes zoster infections (rare)

N Engl J Med 2006; 354:2689-2695

Mepolizumab for the treatment of severe eos asthma

Endpoints	DREAM				MENSA			SIRIUS		MUSCA	
	Placebo	Mepo 75mg IV	Mepo 250mg IV	Mepo 750mg IV	Placebo	Mepo 75mg IV	Mepo 100mg SC	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC
Annualized rate of exacerbations	2.40 (0.11)	1.24 (0.12)	1.46 (0.11)	1.15 (0.12)	1.75	0.93	0.83	2.12	1.44	1.21	0.51
% reduction, mepo vs. placebo	-	52	61	48	-	47	53	-	32	-	58
Lung function change	60 (38)	121 (38)	140 (37)	115 (37)	86	186	183	-4	111	56	176
Difference from placebo	-	61	81	56	-	100	98	-	114	-	120
SGRQ total score change	-	-	-	-	-9.0	-15.4	-16.0	-3.1	-8.8	-7.9	-15.6
Difference from placebo	-	-	-	-	-	-6.4	-7.0	-	-5.8	-	-7.7

J Allergy Clin Immunol Pract 2021;9:1121-32

Reslizumab

- **Route of administration and dose**

  : IV; 3 mg/kg every 4 wk

- Patient year of age: ≥ 18
- **Indication**

  - Severe eosinophilic asthma

- **Safety concerns**

  - Helminthic infections
  - Abrupt discontinuation of OGs
  - Herpes zoster infections (rare)

N Engl J Med 2006; 354:2689-2695c

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts

- Two duplicate, multicentre, double-blind, parallel-group, RCT phase 3 trials.
- Subjects: aged 12–75 years, asthma was inadequately controlled by medium-to-high doses of inhaled corticosteroid-based therapy and who had **blood eosinophils of 400 cells per µL or higher** and **one or more exacerbations in the previous year**.
- Primary outcome: efficacy and safety of reslizumab in patients with inadequately controlled, moderate to-severe asthma
- Of 2597 patients screened, 953 were randomly assigned to receive either reslizumab (3.0mg/kg) (n=477 [245 in study 1 and 232 in study 2]) or placebo (n=476 [244 and 232])

	Study 1				Study 2				Pooled data			
	Placebo	Reslizumab	Rate ratio (95% CI)*	p value	Placebo	Reslizumab	Rate ratio (95% CI)*	p value	Placebo	Reslizumab	Rate ratio (95% CI)*	p value
Primary endpoint												
Frequency of CAEs												
Patients with ≥1 CAE	132 (54%)	92 (38%)	..	..	105 (45%)	59 (25%)	..	..	237 (50%)	151 (32%)	..	..
Adjudicated CAE rate (events per patient per year)												
All episodes	1·80	0·90	0·50 (0·37 to 0·67)	<0·0001	2·11	0·86	0·41 (0·28 to 0·59)	<0·0001	1·81	0·84	0·46 (0·37 to 0·58)	<0·0001
Episodes requiring systemic corticosteroids for ≥3 days	1·60	0·72	0·45 (0·33 to 0·62)	<0·0001	1·66	0·65	0·39 (0·26 to 0·58)	<0·0001	1·54	0·66	0·43 (0·33 to 0·55)	<0·0001
Episodes requiring hospital admission or ER treatment	0·21	0·14	0·66 (0·32 to 1·36)	0·257	0·05	0·03	0·69 (0·29 to 1·65)	0·402	0·12	0·077	0·66 (0·38 to 1·16)	0·510

Lancet Respir Med 2015; 3: 355–66

Benralizumab

- **Route of administration and dose**

  : SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 자

- Patient year of age: ≥ 12

- **Indication**

  - Severe eosinophilic asthma

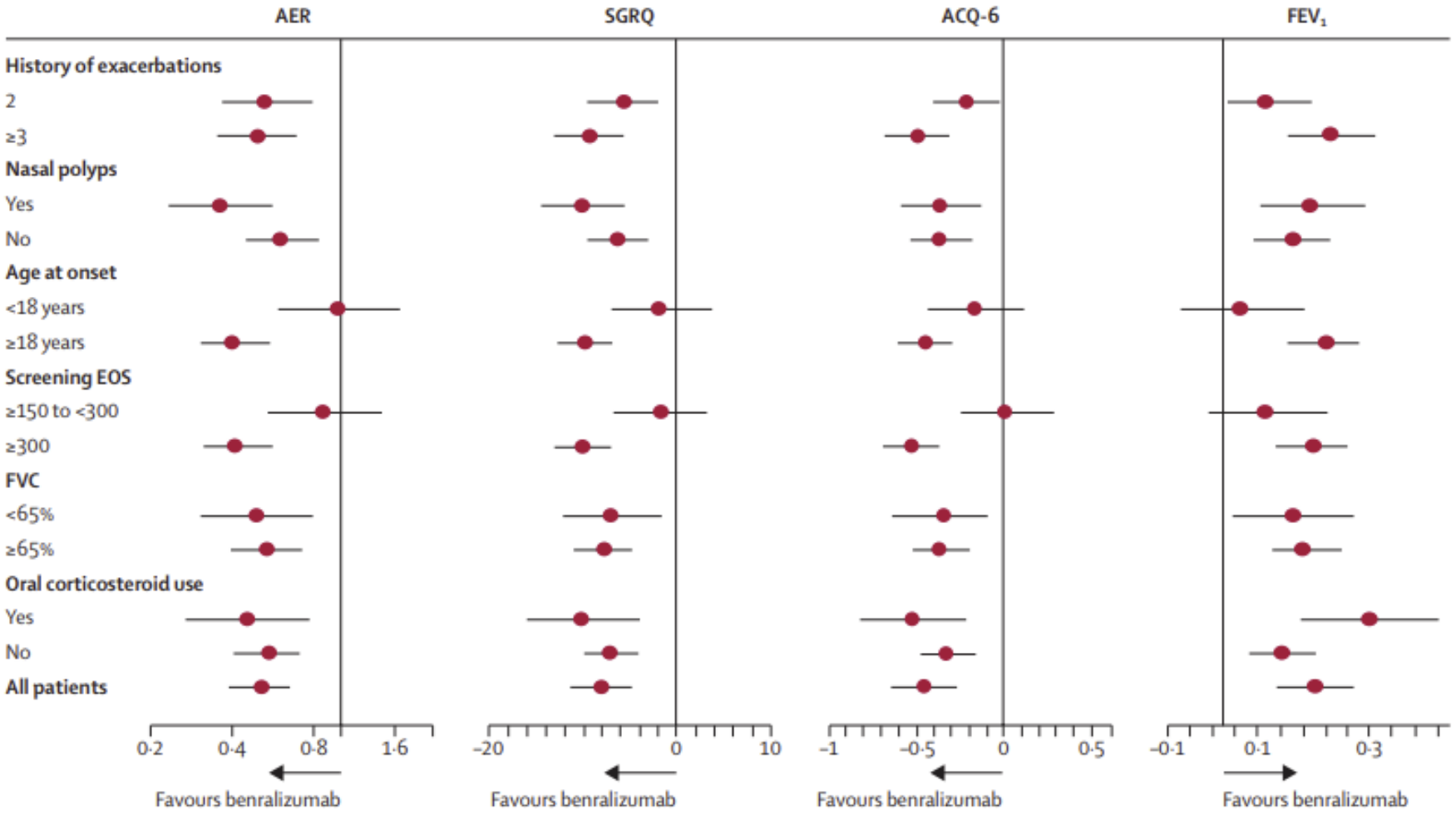
- **Safety concerns**

  - Helminthic infections
  - Hypersensitivity reactions
  - Abrupt discontinuation of OGs

N Engl J Med 2006; 354:2689-2695

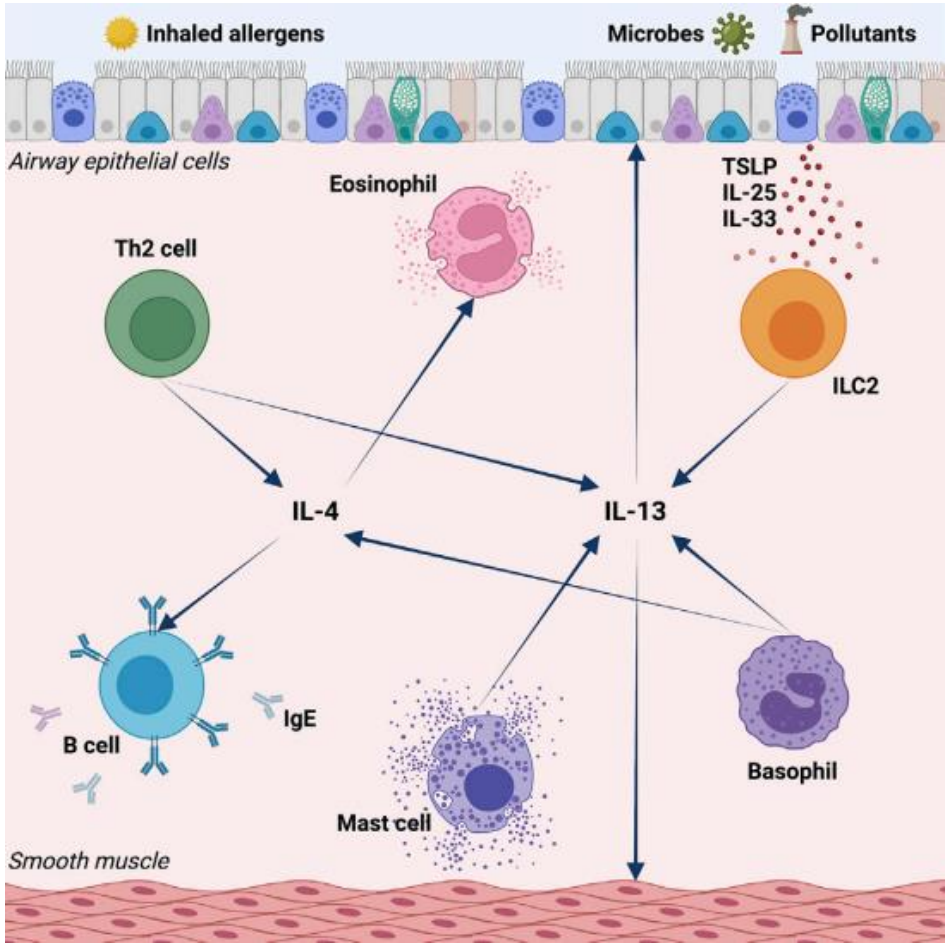
Benralizumab in severe eosinophilic asthma

- RCT of adults (aged 18–75 years) with severe eosinophilic asthma with **at least 2 exacerbations in the previous year** & **blood eosinophil counts of at least 150 cells per µL**
- Receive benralizumab at 30 mg every 8 weeks (first three doses given 4 weeks apart) or matched placebo for 24 weeks.



Lancet Respir Med 2021; 9: 260–74

Antibody against IL-4R: Dupilumab

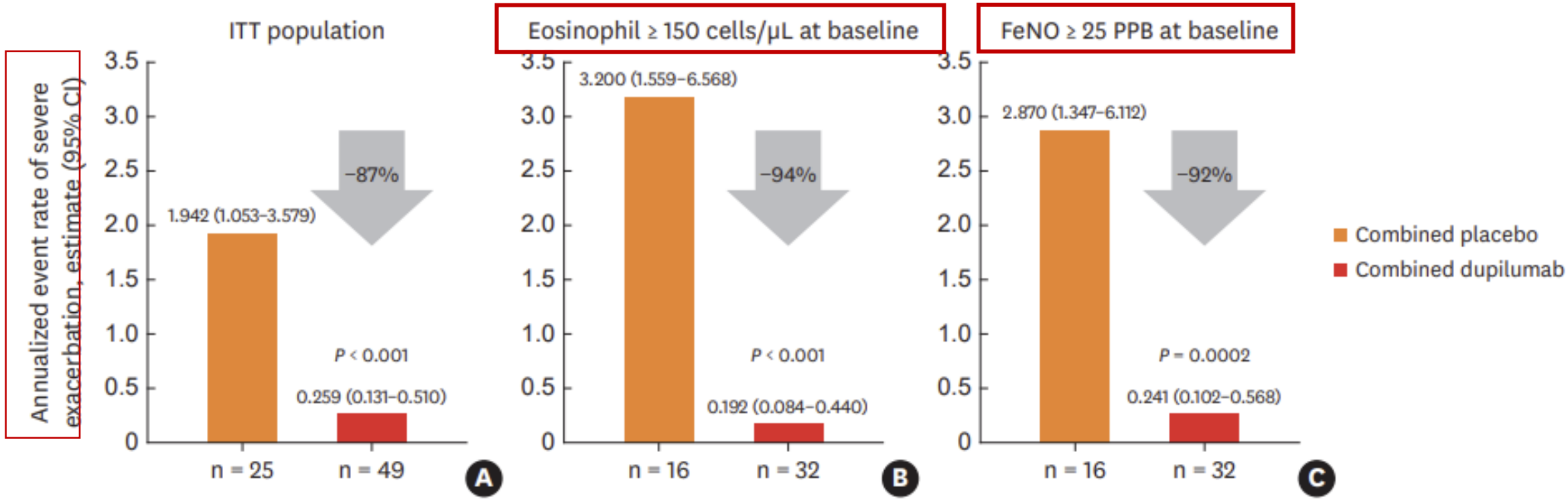


- **Route of administration and dose**
  - Adults and adolescents SC; initial dose of 400 mg, followed by 200 mg every 2 wk
  - Glucocorticoid dependent pts or pts with concomitant mod-to-severe atopic dermatitis
    : initial dose of 600 mg, followed by 300 mg every 2 wk
  - Children, ages 6–11 yr: SC; dose depends on BW
- Patient year of age: ≥ 6
- **Indication**
  - Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA),
  - OG-dependent asthma;
  - CRS with nasal polyposis, moderate-to-severe atopic dermatitis
- **Safety concerns**
  - Helminthic infections
  - Hypersensitivity reactions
  - Abrupt discontinuation of OGs
  - Hyper eosinophilic conditions (e.g., EGPA)

N Engl J Med 2006; 354:2689-2695
Front. Pharmacol. 13:851940.

Effect of dupilumab in Korean pts: LIBERTY ASTHMA QUEST sub analysis

- Of the 1,902 patients enrolled in the LIBERTY ASTHMA QUEST study, a phase-3, randomized, double-blind, placebo-controlled, parallel-group study on dupilumab, 74 (4%) were Korean.
- Outcome: annual rate of severe exacerbation, pre-BD FEV1. asthma control, asthma related QOL, type 2 inflammation marker



Allergy Asthma Immunol Res 2022; 14(2): 182-195.

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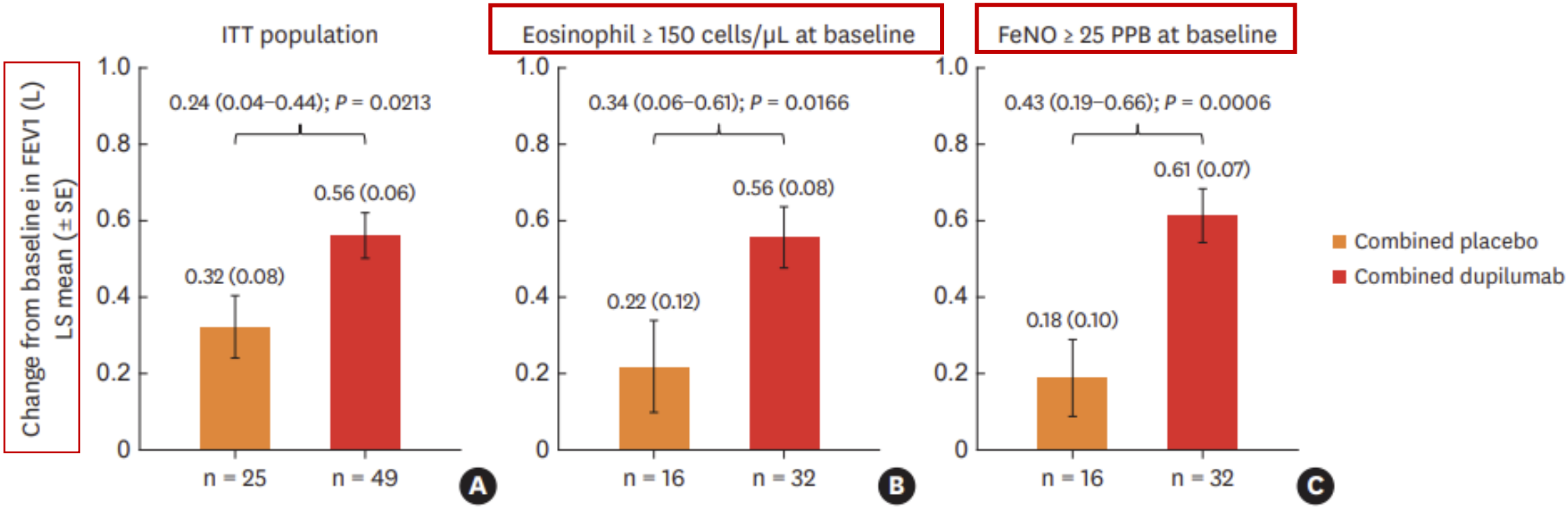

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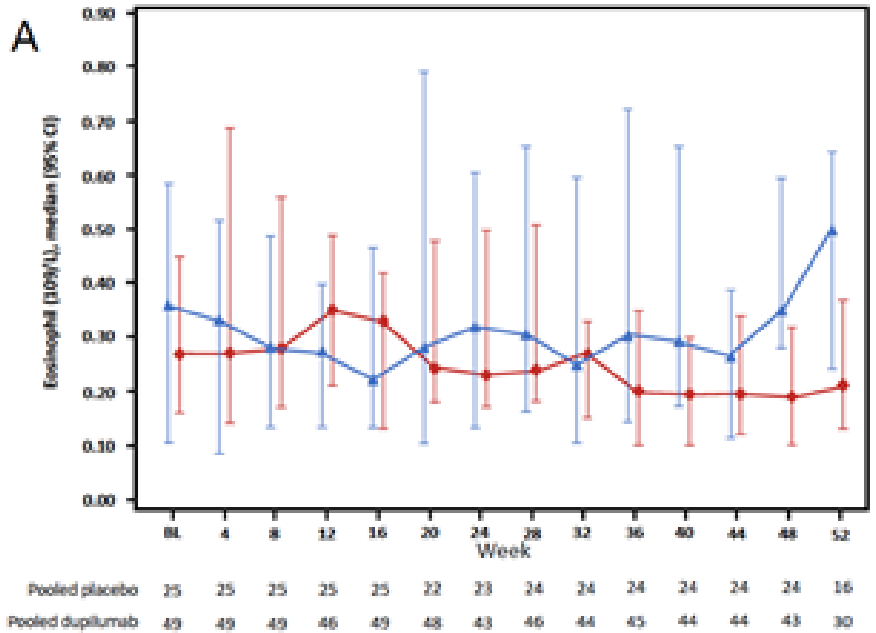
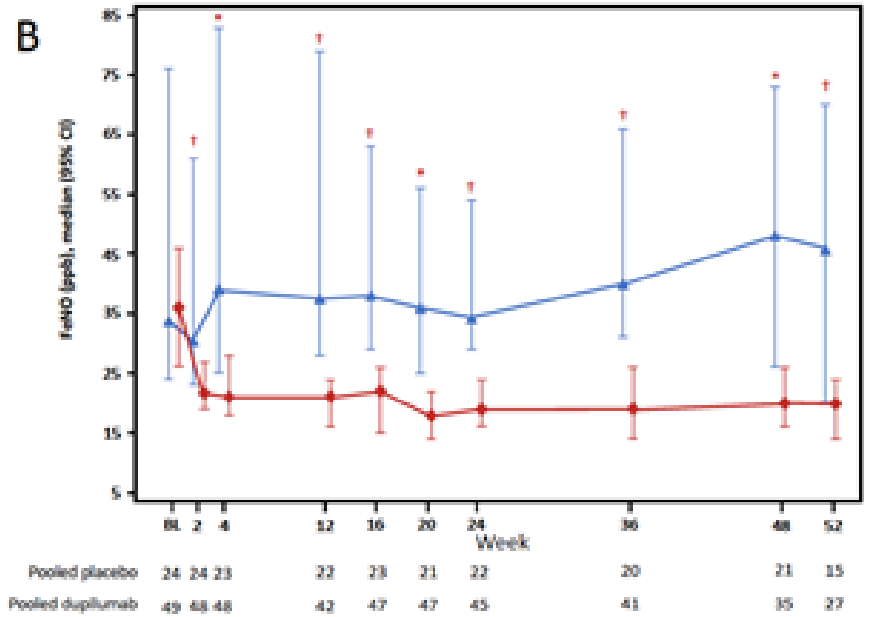
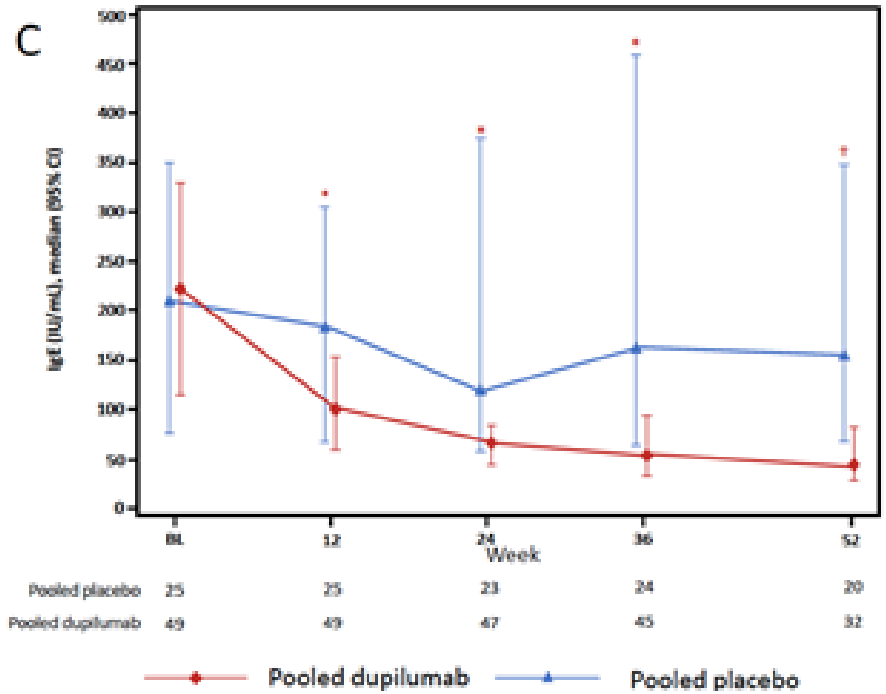




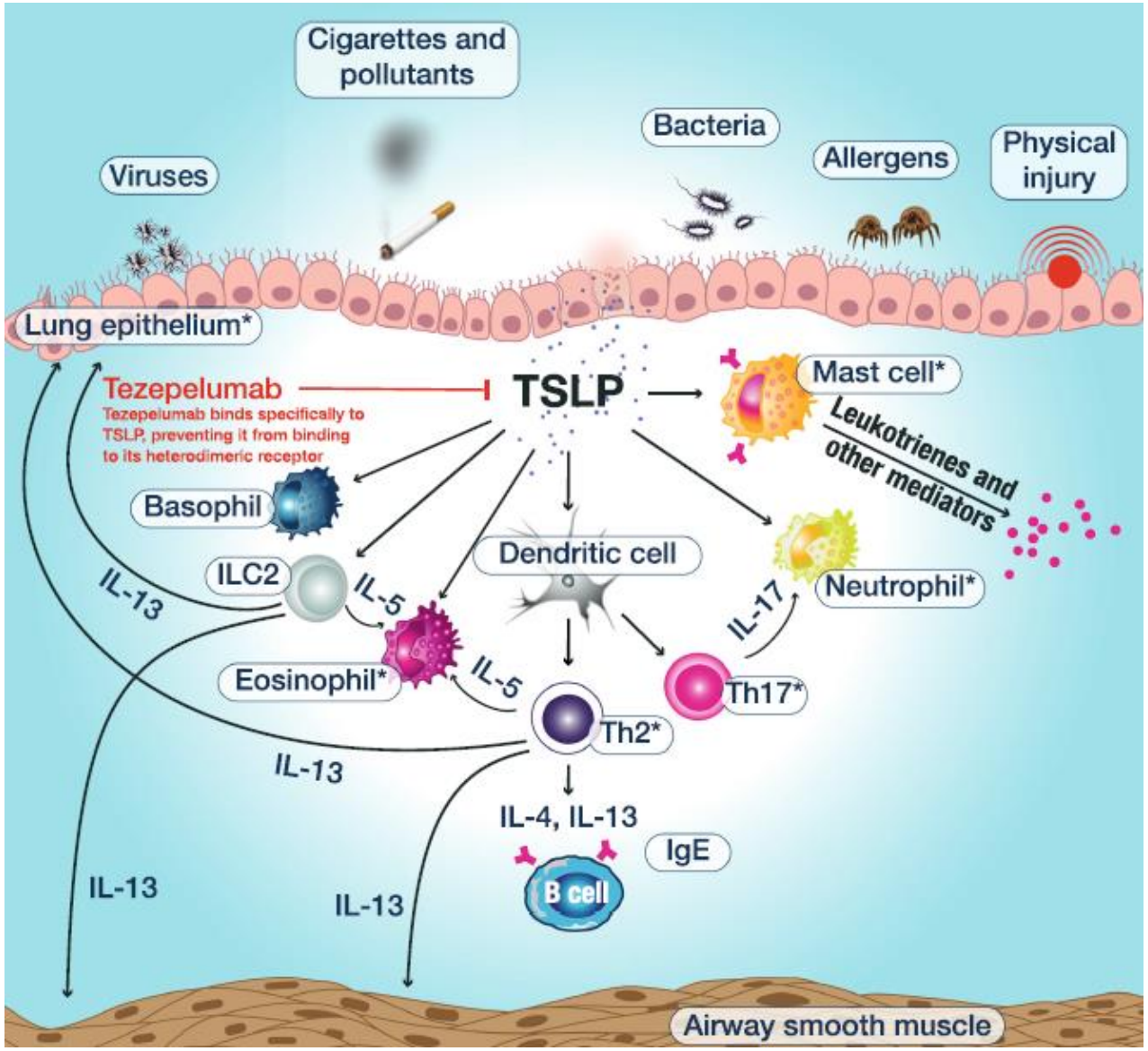


Dupilumab apply

→ benefit for decrease the level of FeNO, IgE

Allergy Asthma Immunol Res 2022; 14(2): 182-195.

Anti epithelial cytokine antibody: tezepelumab

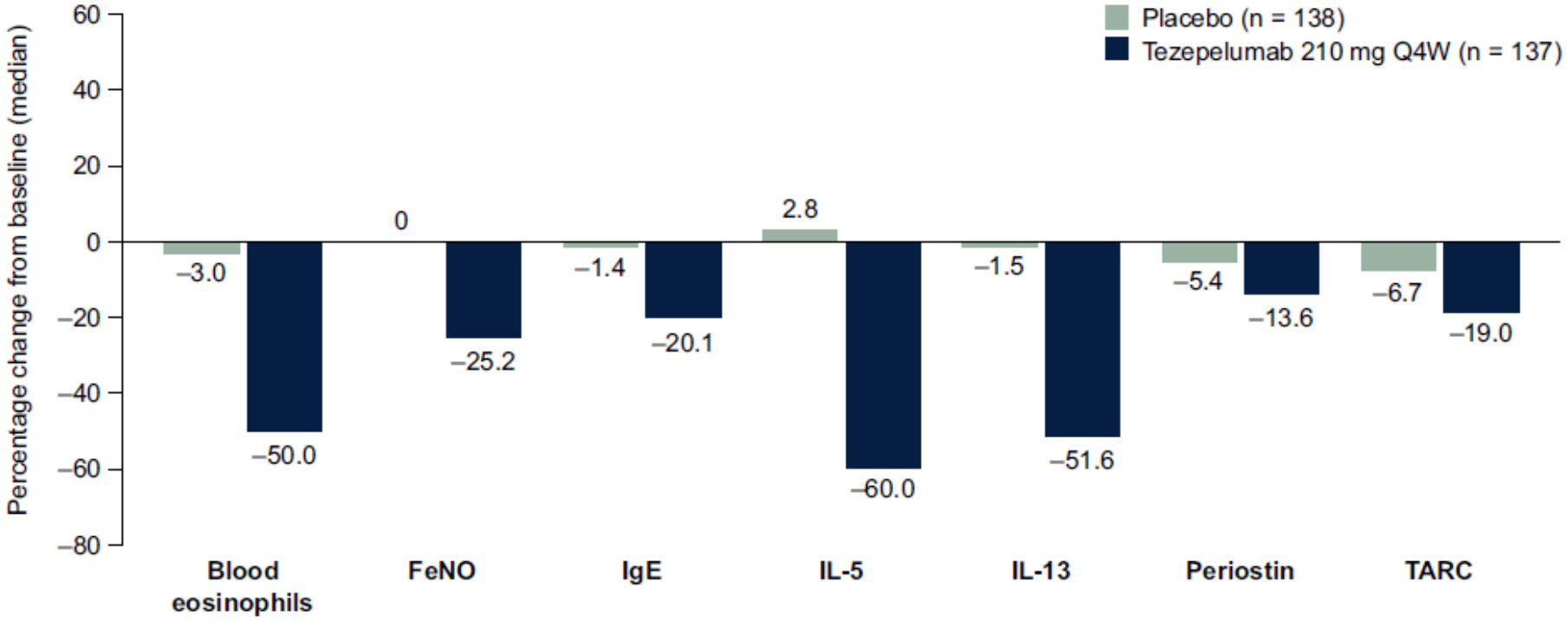


- Human monoclonal antibody
- Block the activity of thymic stromal lymphopoietin, an epithelial cytokine.
- Epithelial-derived cytokine implicated in the initiation and persistence of airway inflammation in response to airborne triggers
- Key regulator of downstream inflammatory pathways in the airway, both T2 mediated and non-T2 mediated, as well as of other related processes such as epithelial barrier function

N Engl J Med 2006; 354:2689-2695c
Respiratory Research (2020) 21:265

Type 2 biomarker levels and response to tezepelumab in severe asthma

- Adults with severe, uncontrolled asthma (*n* = 550) were randomized to tezepelumab (70 mg or 210 mg every 4 weeks, or 280 mg every 2 weeks) or placebo for 52 weeks.
- Blood eosinophil count, fractional exhaled nitric oxide (FeNO), and serum total immunoglobulin (Ig)E, interleukin (IL)-5, IL-13, periostin, thymus and activation-regulated chemokine (TARC), and TSLP were measured at baseline and over 52 weeks.



Allergy. 2022; 77: 1786-1796.

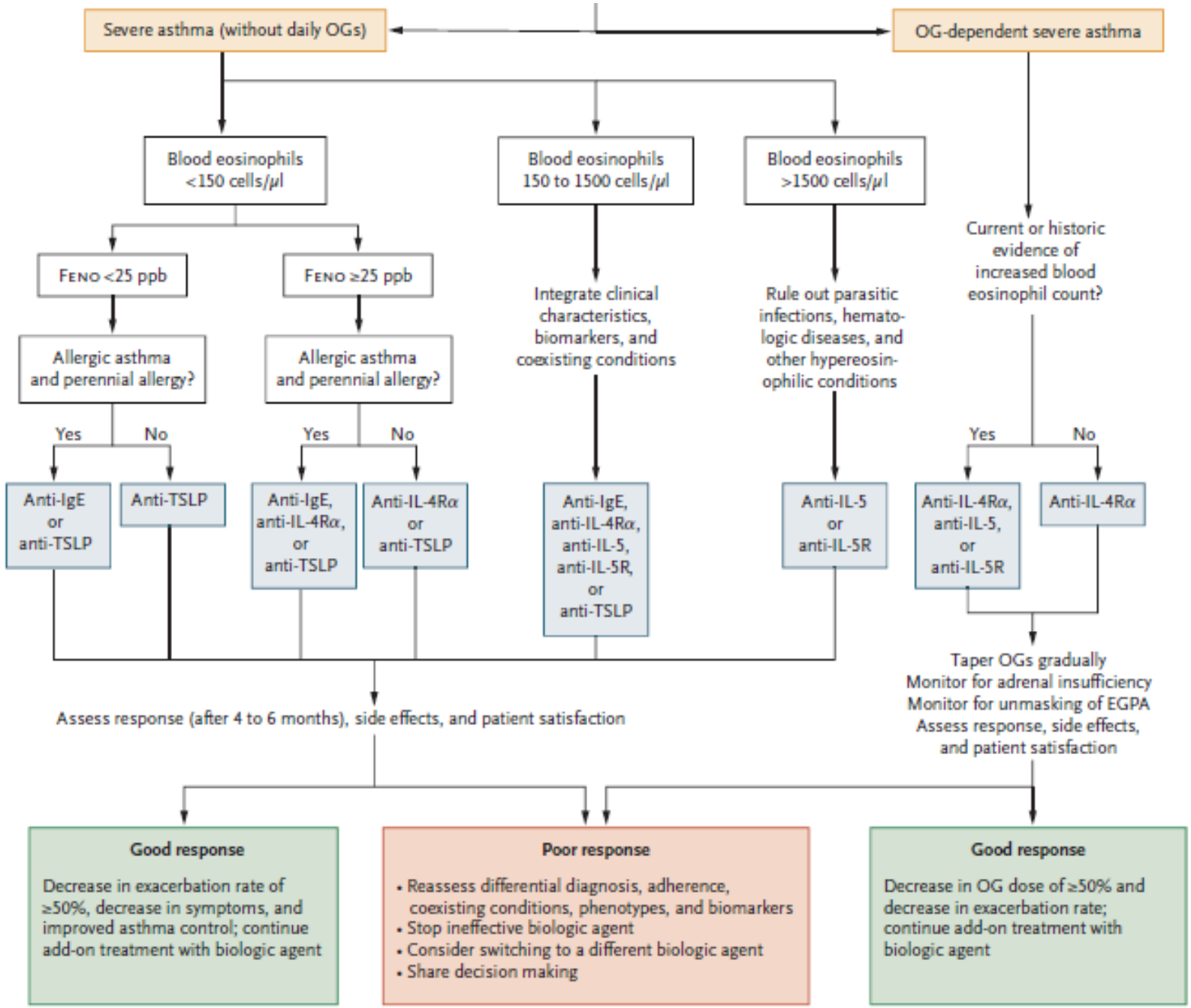
Phenotype : OG dependent

Biomarker : blood eosinophil

Biomarker : blood eosinophil

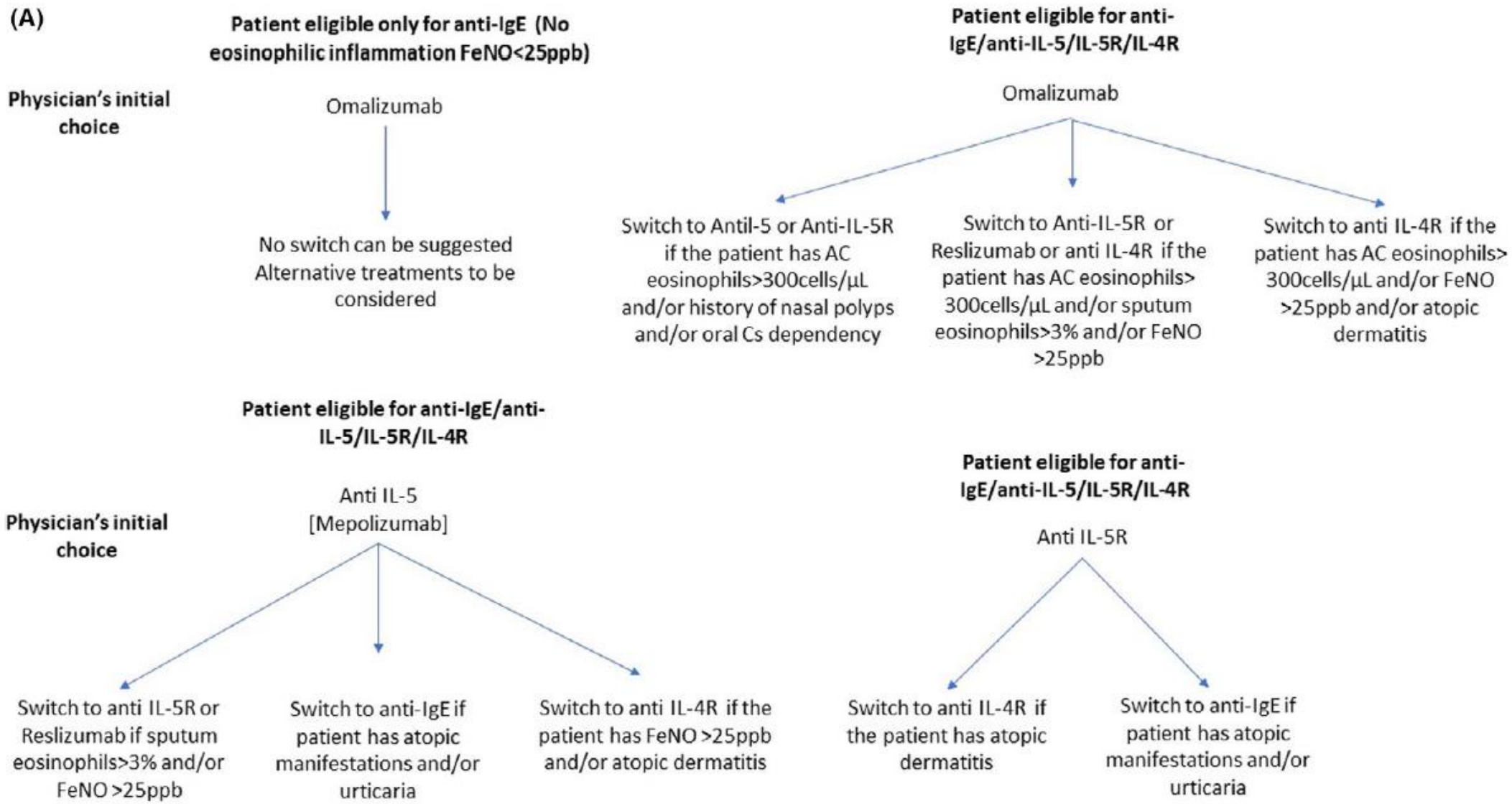
Phenotype : allergic

Biomarker : total IgE



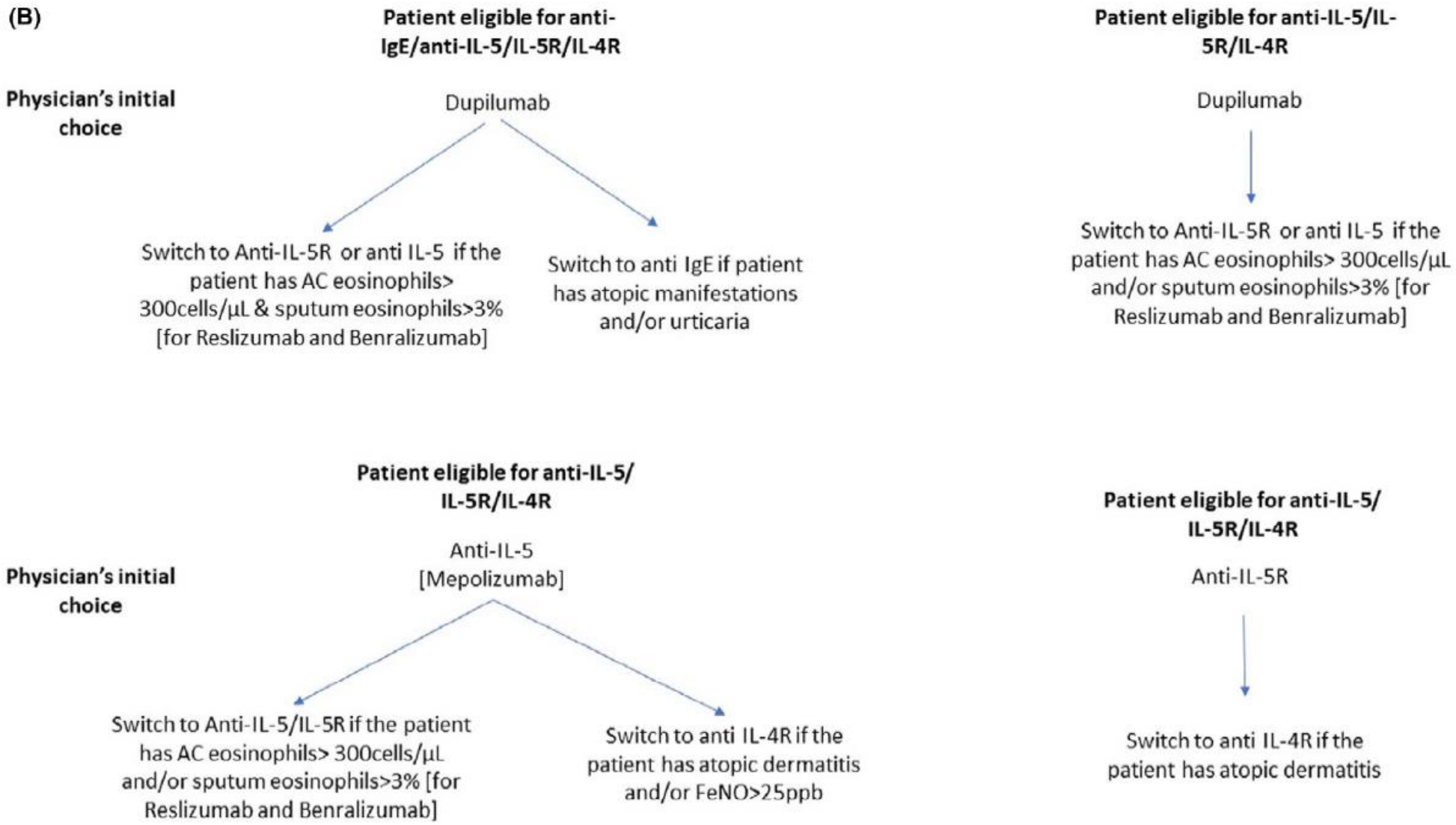
N Engl J Med 2006; 354:2689-2695c

When the first choice is not proven to be the best -1



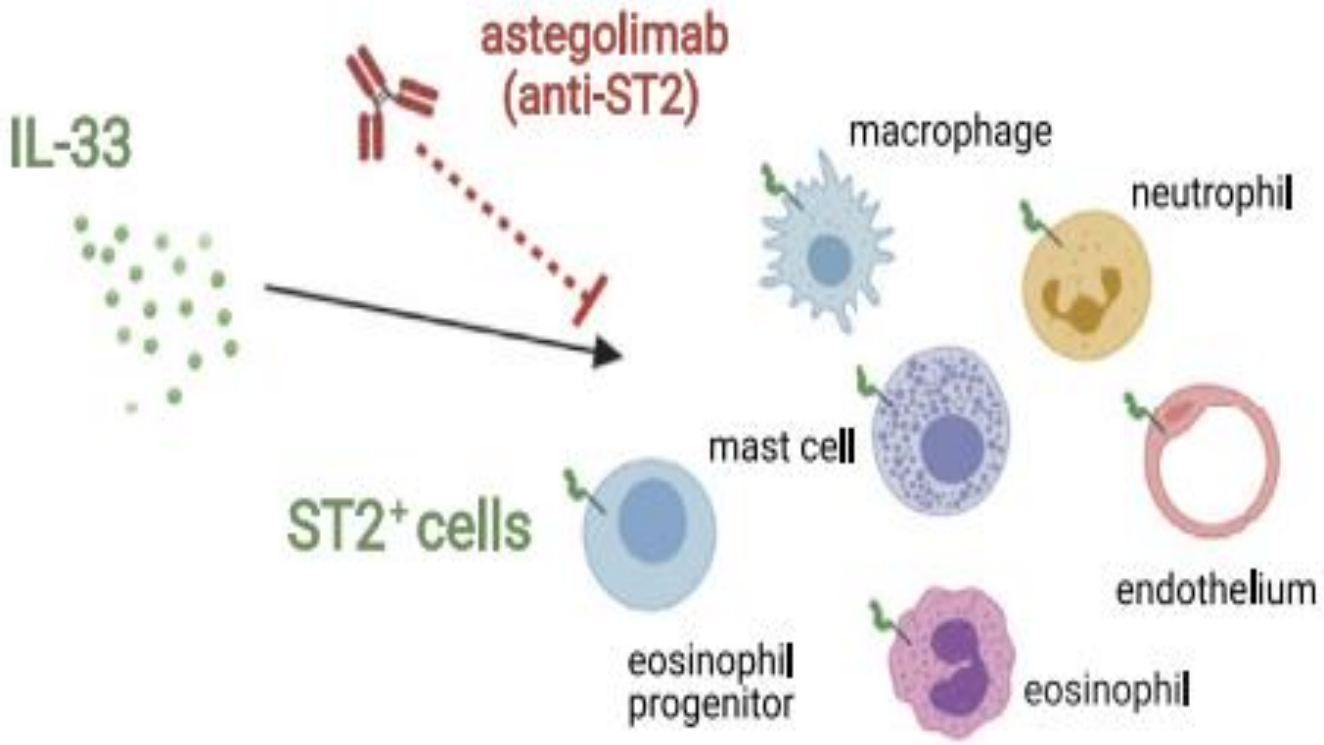
Clin Exp Allergy. 2021;51:221–227.

When the first choice is not proven to be the best -2



Clin Exp Allergy. 2021;51:221–227.

Anti IL-33 receptor: astegolimab

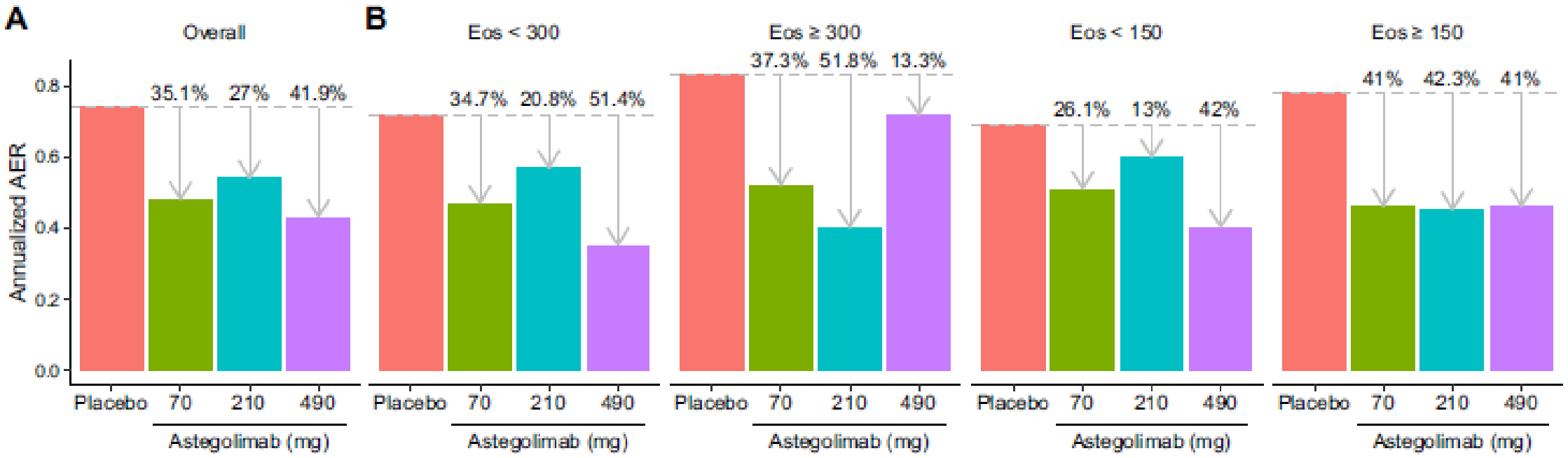


Astegolimab, a human IgG2 mAb, selectively inhibits the IL-33 receptor, ST2.

N Engl J Med 2006; 354:2689-2695c
Respiratory Research (2020) 21:265

Astegolimab, an anti-ST2, as a potential biologic agent

- Double-blind, placebo-controlled, dose-ranging study (ZENYATTA [A Study to Assess the Efficacy and Safety of MSTT1041A in Participants With Uncontrolled Severe Asthma])
- 502 adults with severe asthma to subcutaneous **placebo or 70-mg, 210-mg, or 490-mg doses of astegolimab** every 4 weeks.
- The primary endpoint : annualized asthma exacerbation rate (AER) at week 54.
- Enrollment caps ensured 30 patients who **were eosinophil-high (>300 cells/mL)** and 95 patients who were **eosinophil-low (<300 cells/mL)** per arm.



J Allergy Clin Immunol 2021;148:790-8.)

T2-low asthma

Difficulties in managing Th2 low asthma

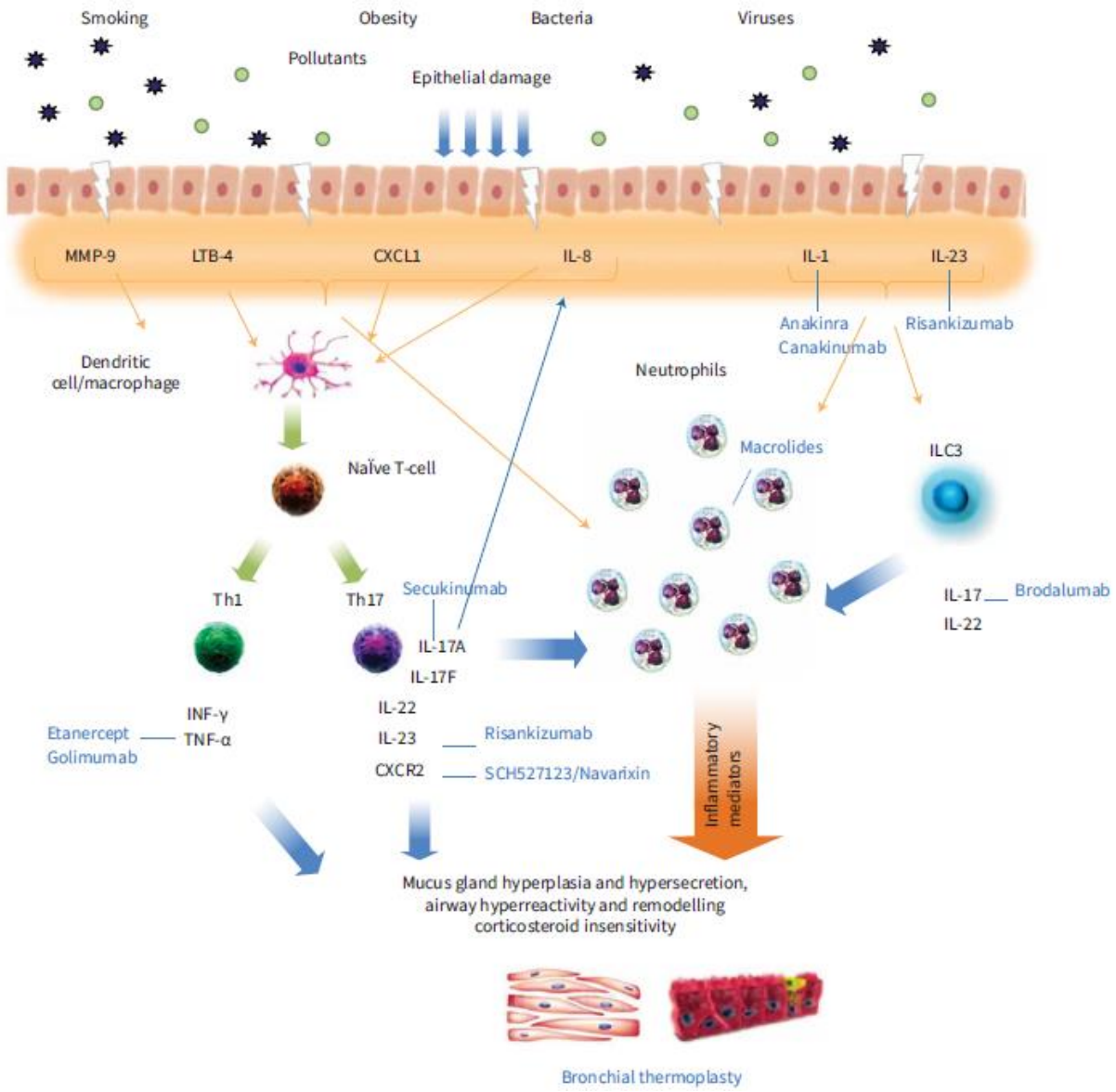
- The therapeutic approach of T2-low asthma is a problem urgently.

  - firstly because these patients have poor response to steroids

  - secondly because they are not candidates for the newer targeted biologic agents

ERJ Open Res 2021; 7: 00309-2020.

Therapeutic approach of T2 low asthma



- Study population : severe, neutrophilic asthma
- Potential biomarkers
  - IL-1
  - IL-8
  - IL-17
  - PDE4
- On-going biomarkers
  - SCH527123/navarixin
  - Brodalumab
  - PRL-554 CHF6001 (inhaler)
  - Etanercept, golimumab
  - Anakinra

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Summary

- Severe asthma: uncontrolled state with good adherence and fully standard treatment
- Differentiation between “**difficult-to –treat asthma**” vs. “**severe asthma**”
- **Th2 high asthma** vs. **Th2 low asthma**
- **Biomarker** of Th2 high asthma: IgE, FeNO, blood eosinophil >> sputum eosinophil, periostin
- Approved biologics: omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, Tezepelumab
- Guidance to appropriate biologics : phenotype, endotype (inflammatory phenotype, biomarker)
- Switching between biologics in severe asthma patients
- Th2 low asthma – biomarker, biologics

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