從A到Z線上藥學論壇

From A to Z online webinar series

嚴重性氣喘生物製劑療法：

綜觀生物製劑帶給病患的改善

林口長庚紀念醫院 胸腔內科系 呼吸道疾病科

張博瑞 醫師

Po-Jui Chang, MD, PhD*

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*** National Heart and Lung Institute, Imperial College London**

處方用藥請參考衛生福利部核准仿單說明書




Difficult-to-treat Asthma

(poor control despite med/high-dose ICS+2nd controller or mOCS

Alternative diagnosis

Non-Asthma:
Bronchiolitis
Hypersensitivity penumonitis
Upper airway disease
COPD
Vocal cord spasm

Compliance / Technique

Severe Asthma

Comorbidity

Sinusitis/Allergic rhinitis
GERD
Aspirin sensitive
Emotional
Pre-menstruation
Occupational
ABPA

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2
As-needed 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-IL4R, anti-TSLP**

RELIEVER: As-needed low-dose ICS-formoterol

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

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-IL4R, anti-TSLP**

RELIEVER: As-needed short-acting beta$_2$-agonist

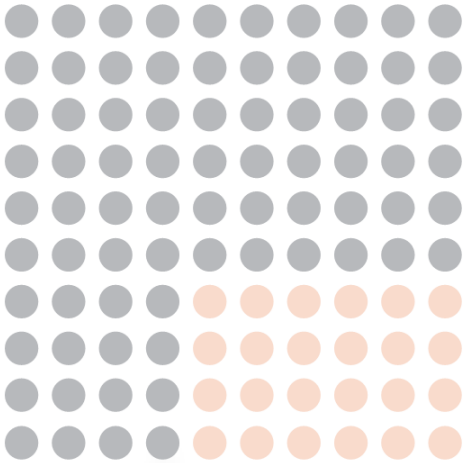
Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	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 LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

High resource consumption and unmet need for

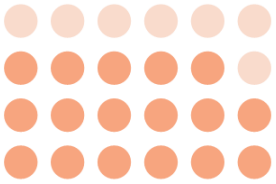
Prevalence: how many people have severe asthma?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



24%

high intensity treatment
= high dose ICS-LABA or medium dose ICS-LABA +OCS

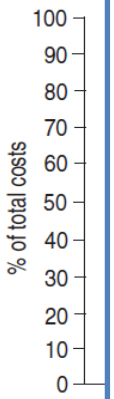


17%

difficult-to-treat asthma
= high intensity treatment + poor symptom control

3.7%

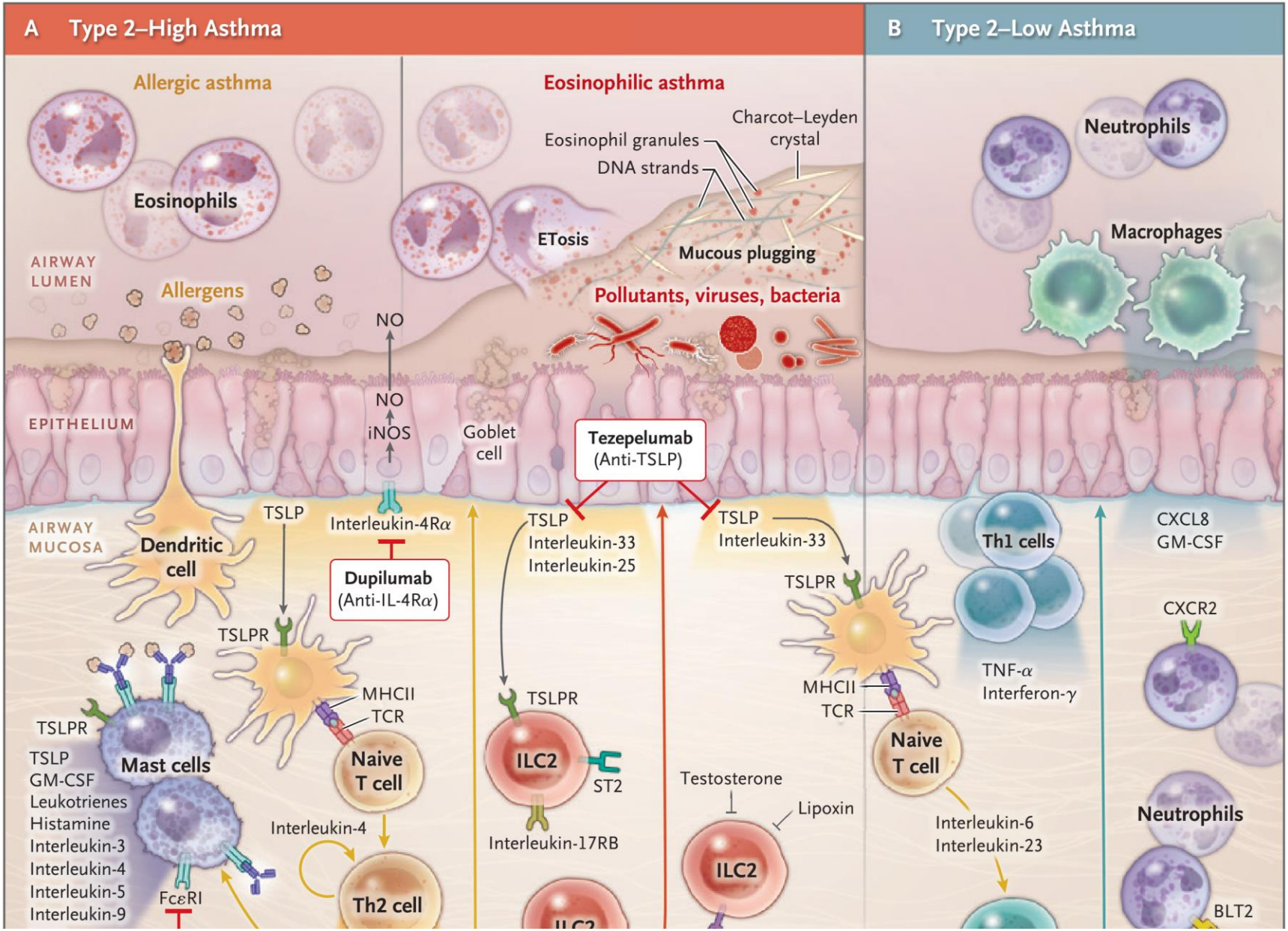
severe asthma
= high intensity treatment + poor symptom control + good adherence and inhaler technique



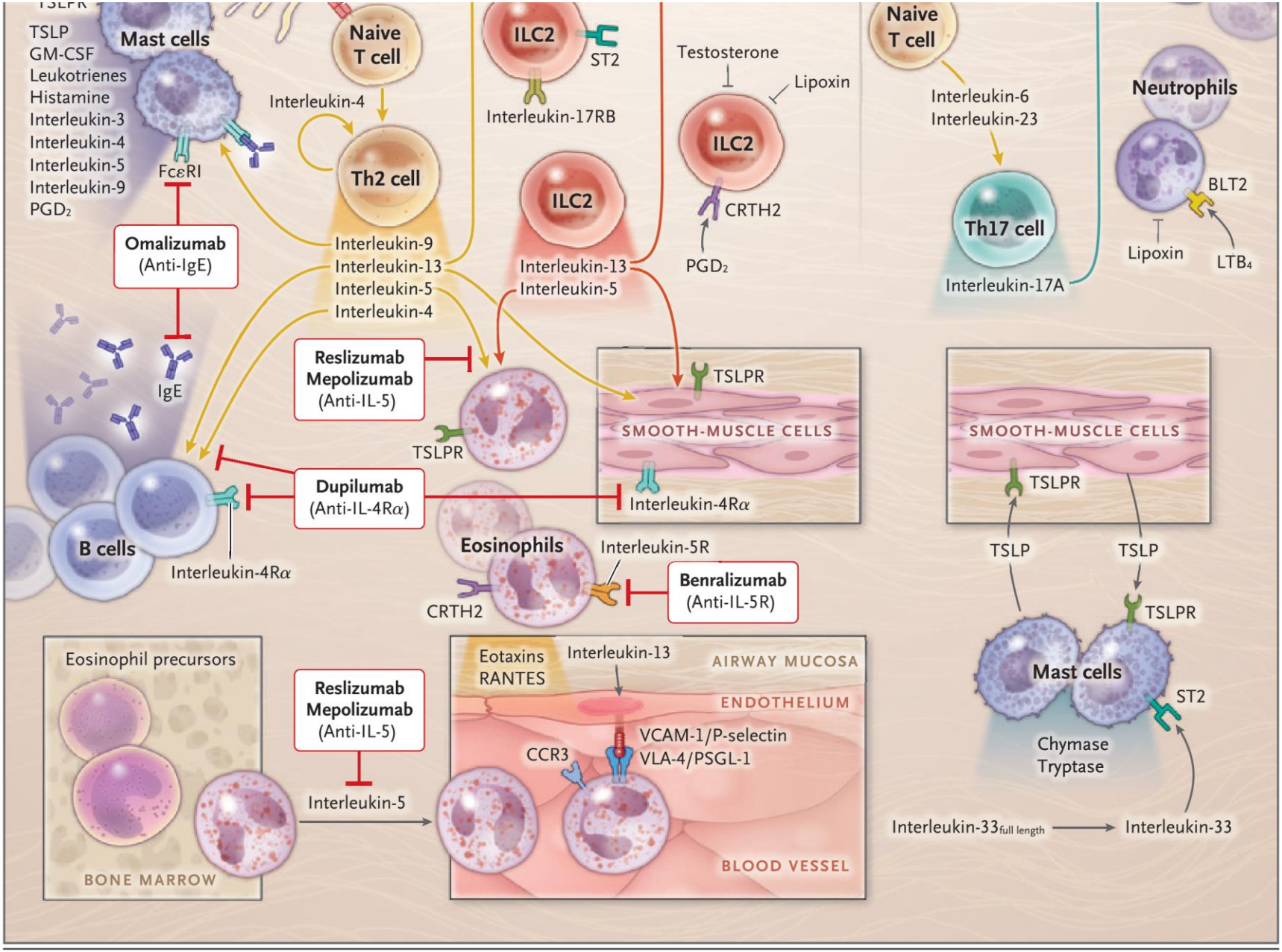
These data are from a Dutch population survey of people ≥18 years with asthma[2]

Barnes PJ *et al. Eur Respir J*. 1996

Moore WC *et al. J Allergy Clin Immunol*. 2007



N Engl J Med. 2022 Jan 13;386(2):157-171



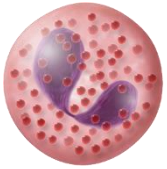
N Engl J Med. 2022 Jan 13;386(2):157-171

Identification of asthma with refractory or underlying Type 2 inflammation

The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high dose ICS or daily OCS:

Blood EOS ≥150 cells/µL

FeNO ≥20 ppb



Sputum EOS ≥2%

Clinically allergen-driven asthma

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

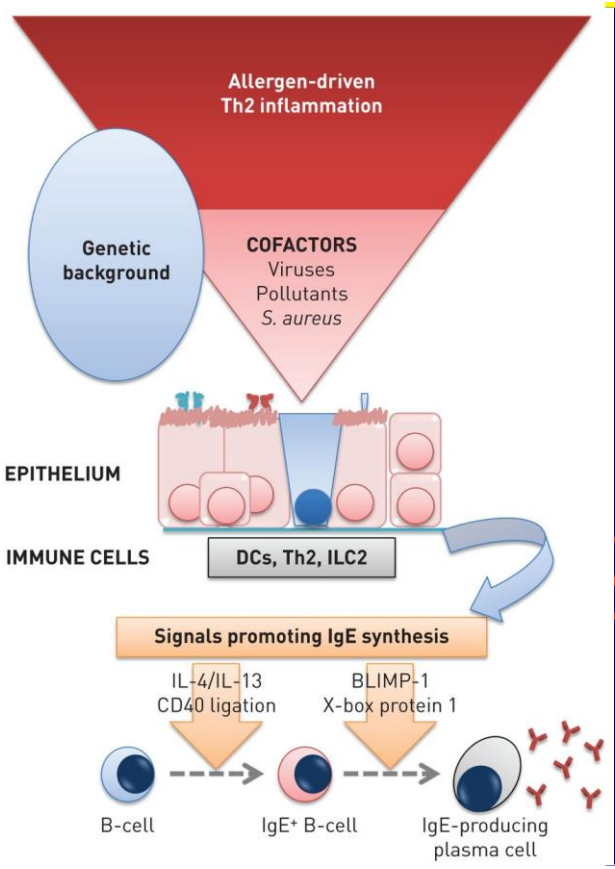
Biologic agents approved by the FDA (and available in Taiwan) for treatment of severe asthma

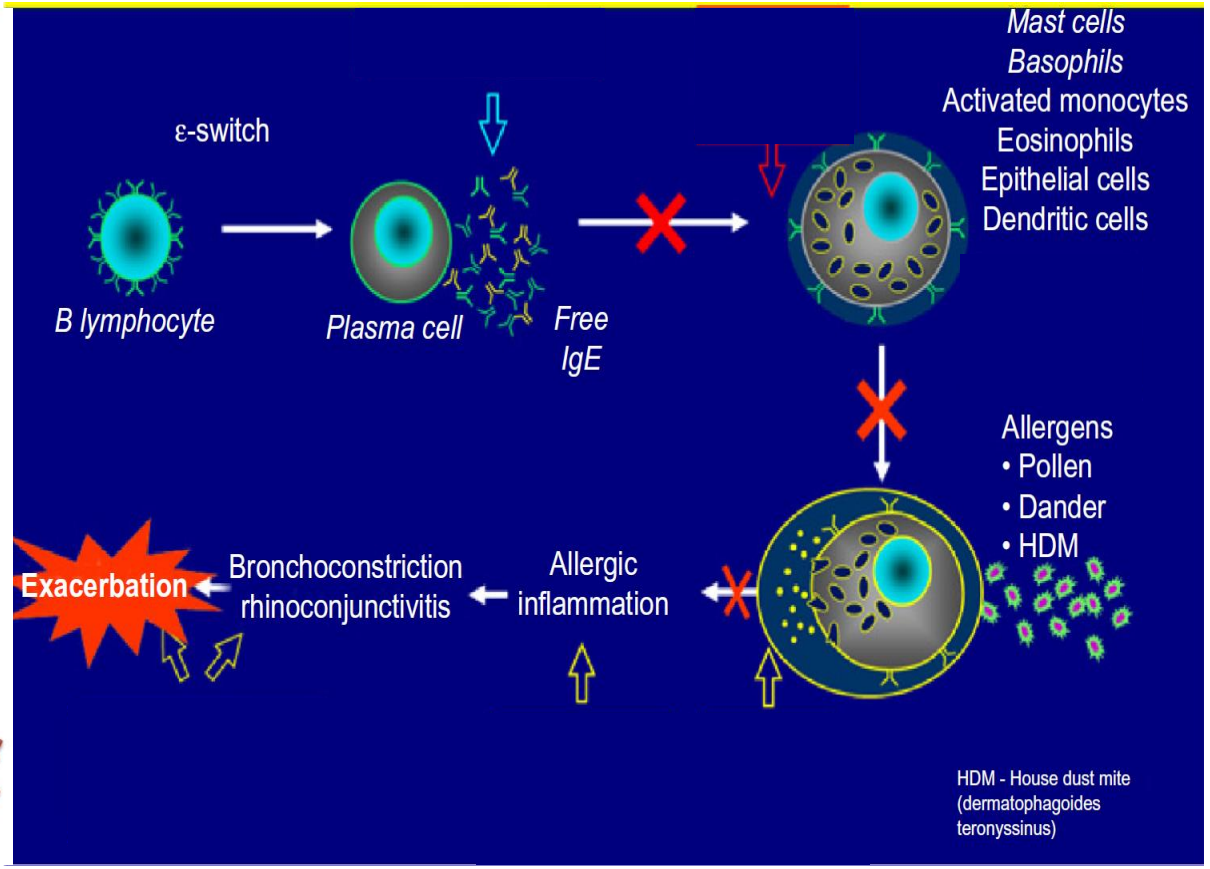
Table 1. Biologic Agents Approved by the Food and Drug Administration for the Treatment of Severe Asthma.*

Biologic Agent (Therapeutic Target and Mechanism of Action)	Route of Administration and Dose†	Forms	Indication	Patient Yr of Age†	Efficacy	Safety Concerns
Benralizumab (interleukin-5Rα; antibody binds to interleukin-5Rα on eosinophils and basophils, depleting them through antibody-dependent, cell-mediated cytotoxicity)	SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma	≥12	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs
Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, inhibiting interleukin-4 and interleukin-13 signaling in hematopoietic cells [e.g., B cells, CD4+ helper T cells, and eosinophils], epithelial cells, and airway smooth-muscle cells)	Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-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 body weight‡	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis	≥6	Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis
Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5)	Adults and adolescents: SC; 100 mg every 4 wk Children, ages 6–11 yr: SC; 40 mg every 4 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome	≥6	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare)
Omalizumab (IgE; 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)	SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE	Prefilled syringe	Severe allergic asthma; other indication: chronic idiopathic urticaria	≥6	Reduced exacerbations, reduced symptoms, small effect on FEV_1; improved quality of life	Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients)

N Engl J Med. 2022 Jan 13;386(2):157-171

Severe allergic asthma

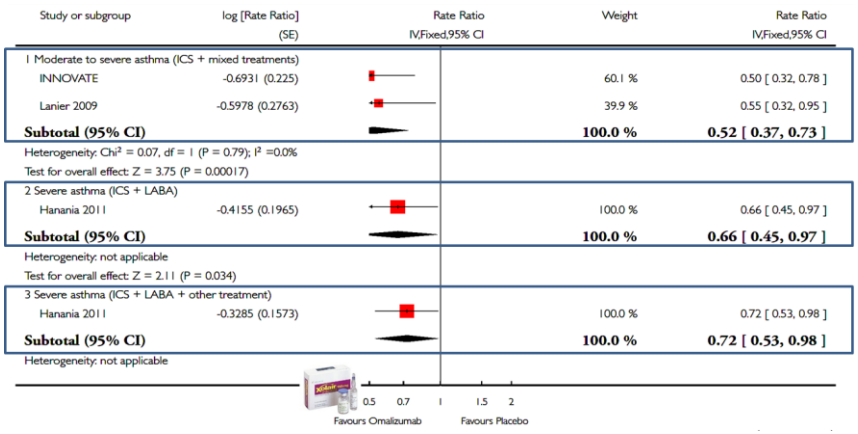




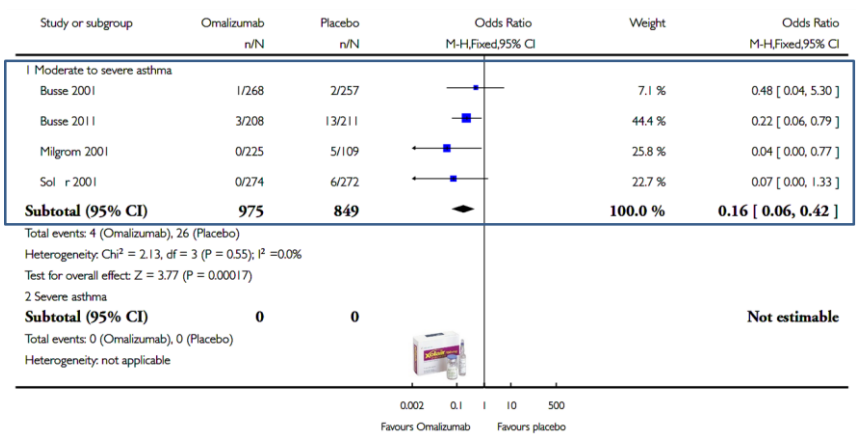
Froidure A *et al. Eur Respir J*. 2016 Jan;47(1):304-19
Incorvaia C *et al. Drug Des Devel Ther*. 2014 Feb 7;8:197-207

Clinical efficacy of omalizumab in severe allergic asthma

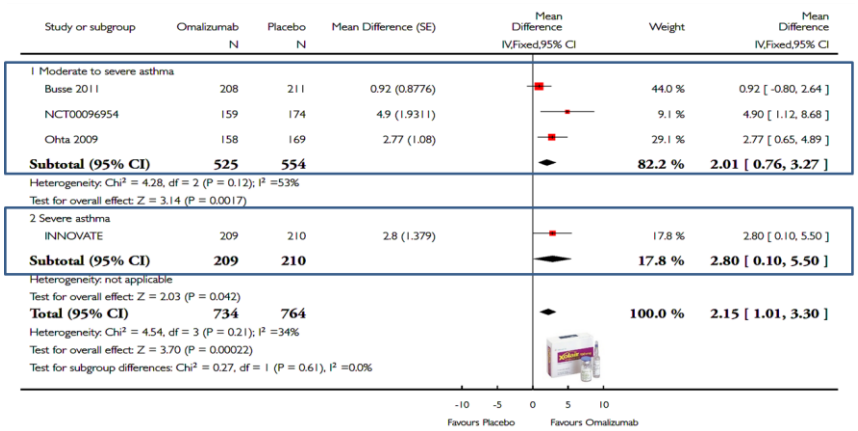
Exacerbations requiring oral steroids



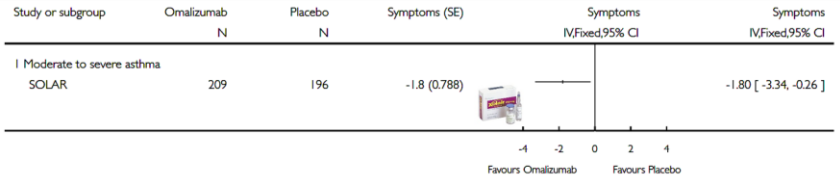
Hospitalisations



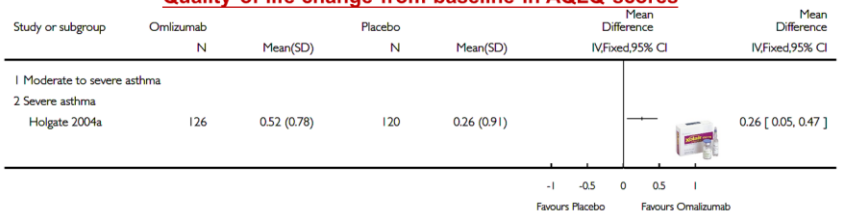
Change of FEV_1 predicted



Mean change in Wasserfallen asthma score



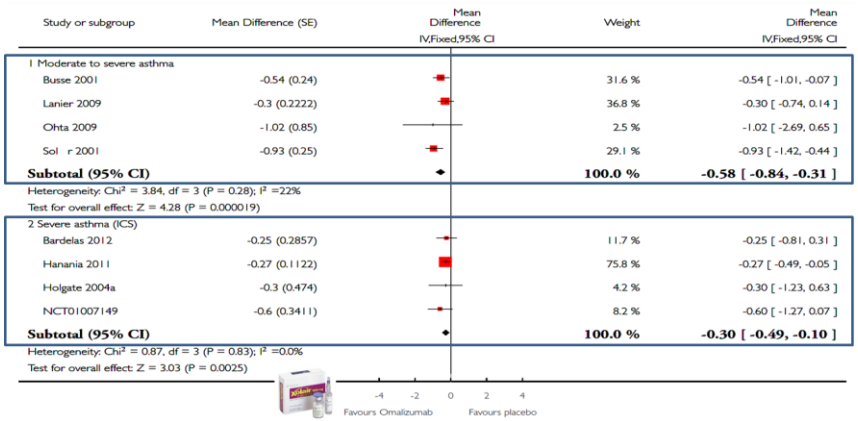
Quality of life change from baseline in AQLQ scores



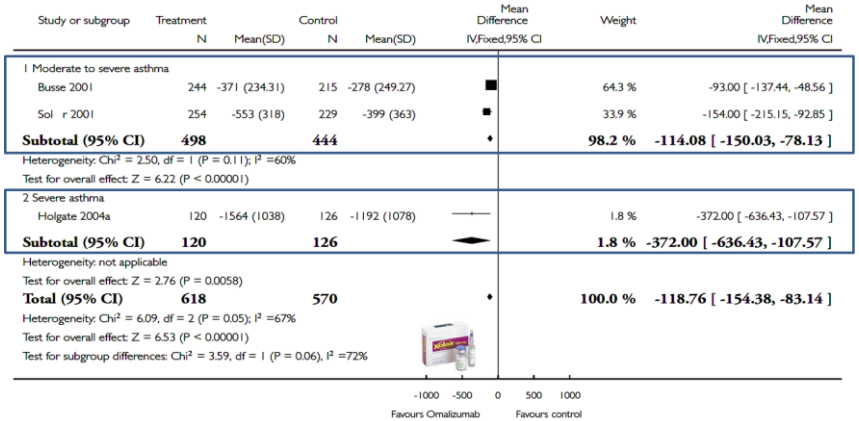
Normansell R *et al. Cochrane Database Syst Rev*. 2014 Jan 13;1:CD003559

Clinical efficacy of omalizumab in severe allergic asthma

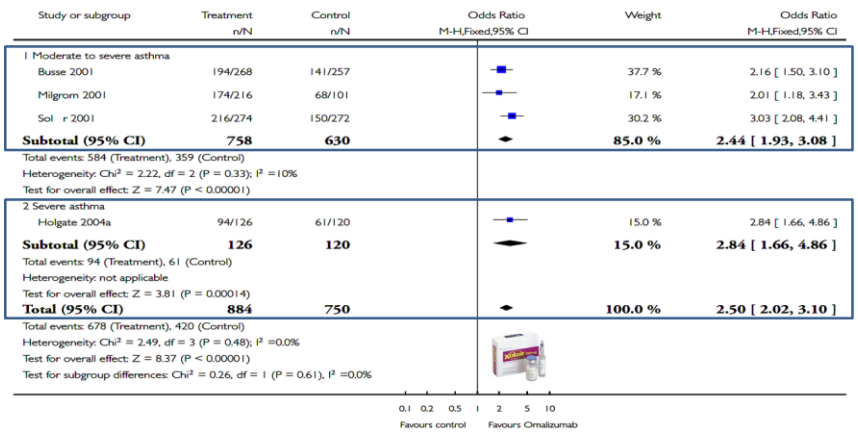
Rescue medication



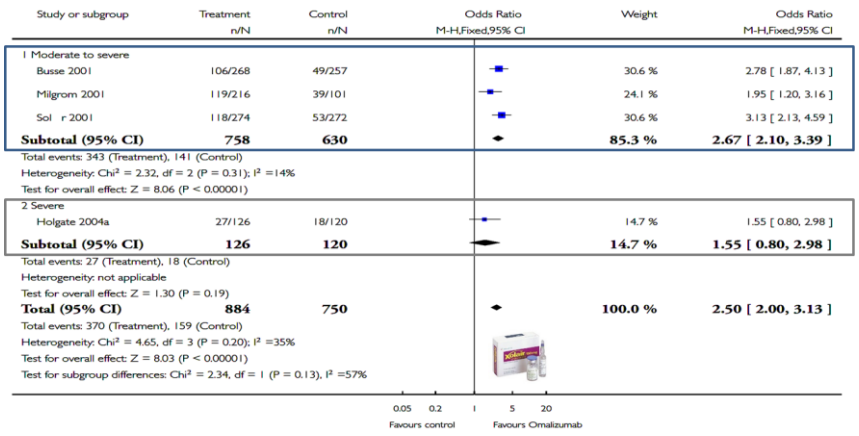
Mean change in steroid consumption (BDP equivalent)



> 50% reduction in inhaled steroid usage

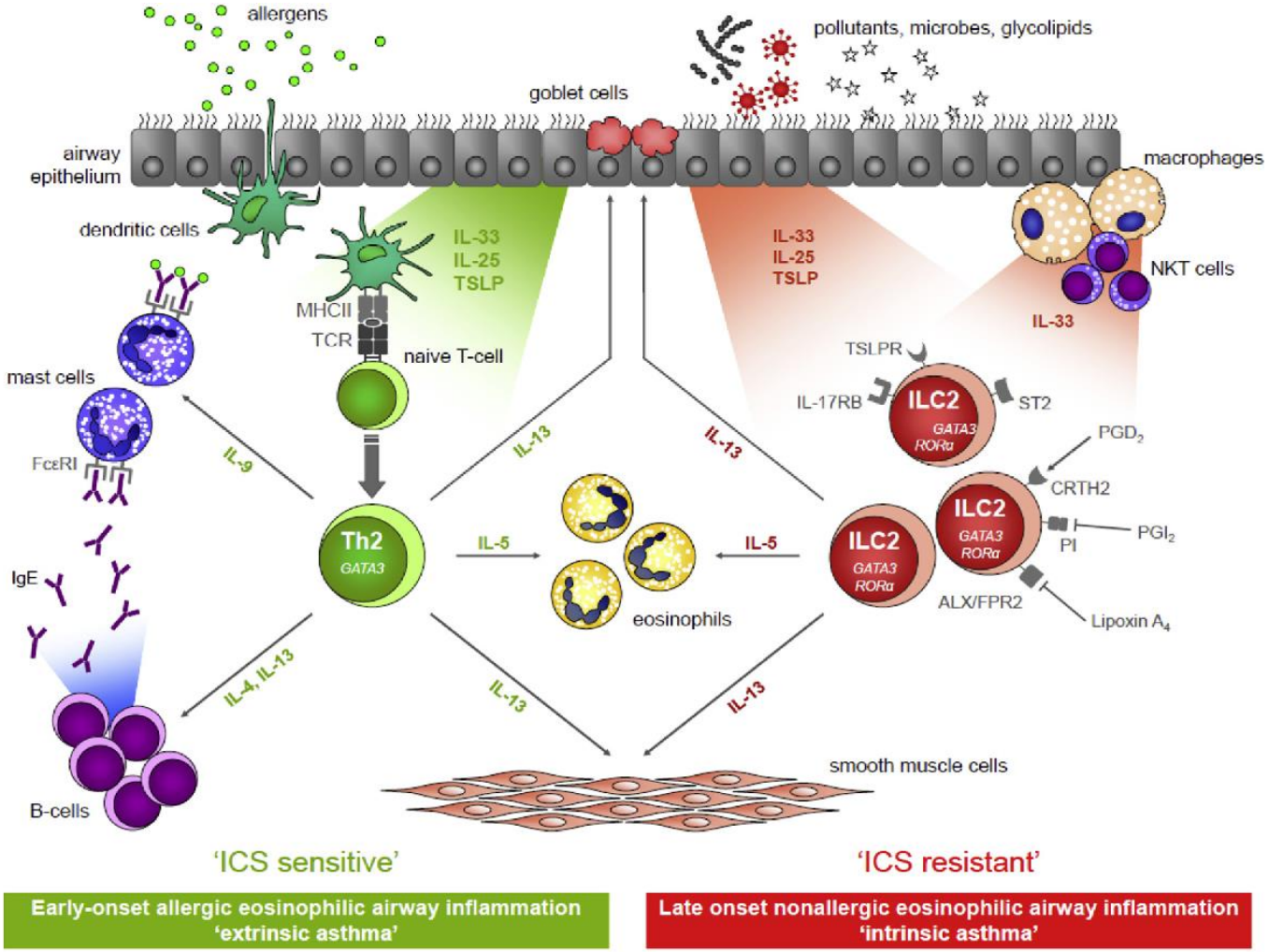


Number of participants achieving complete inhaled steroid withdrawal



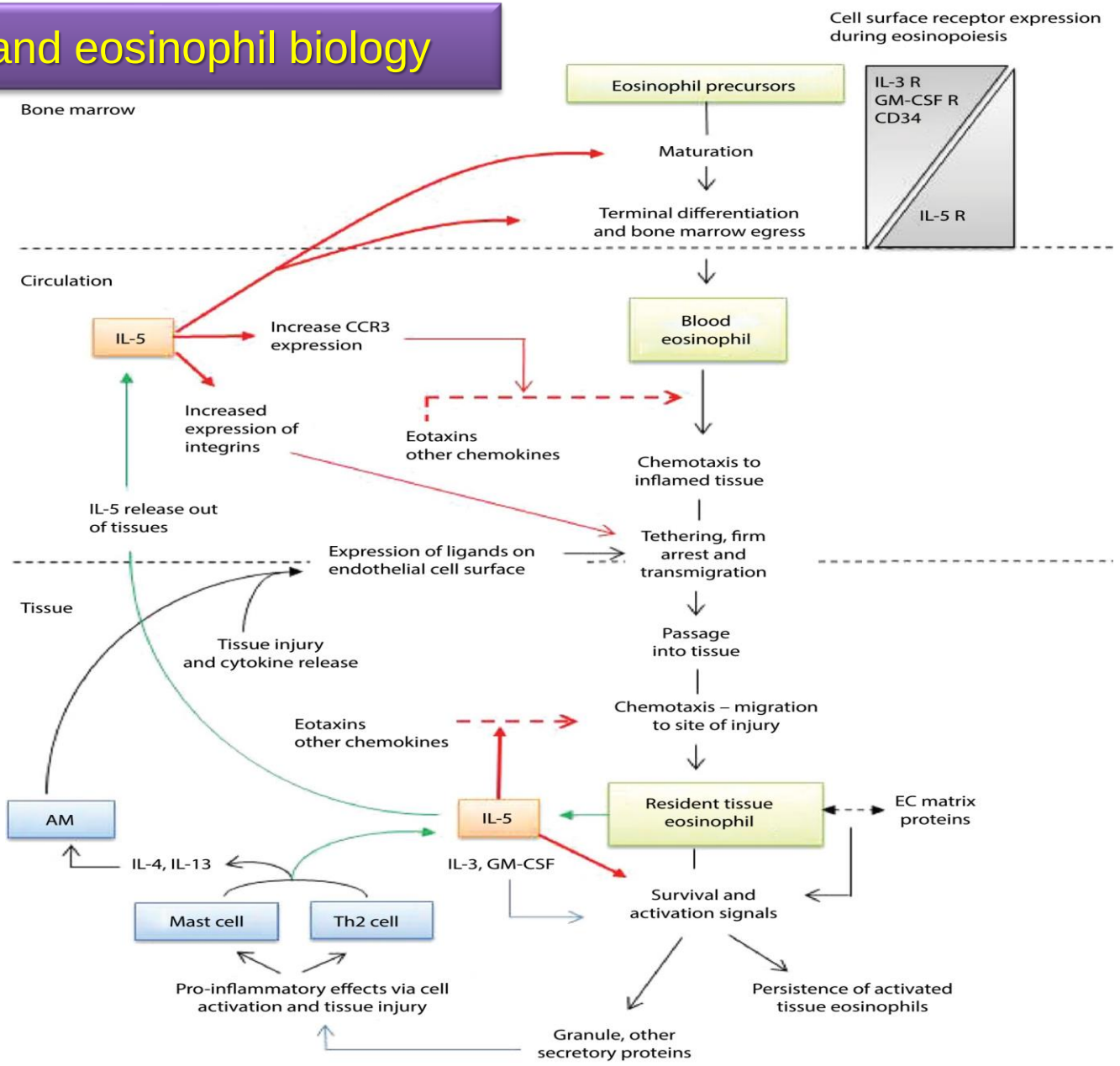
Normansell R *et al. Cochrane Database Syst Rev*. 2014 Jan 13;1:CD003559

Severe eosinophilic asthma



Chest. 2017 Dec;152(6):1276-1282

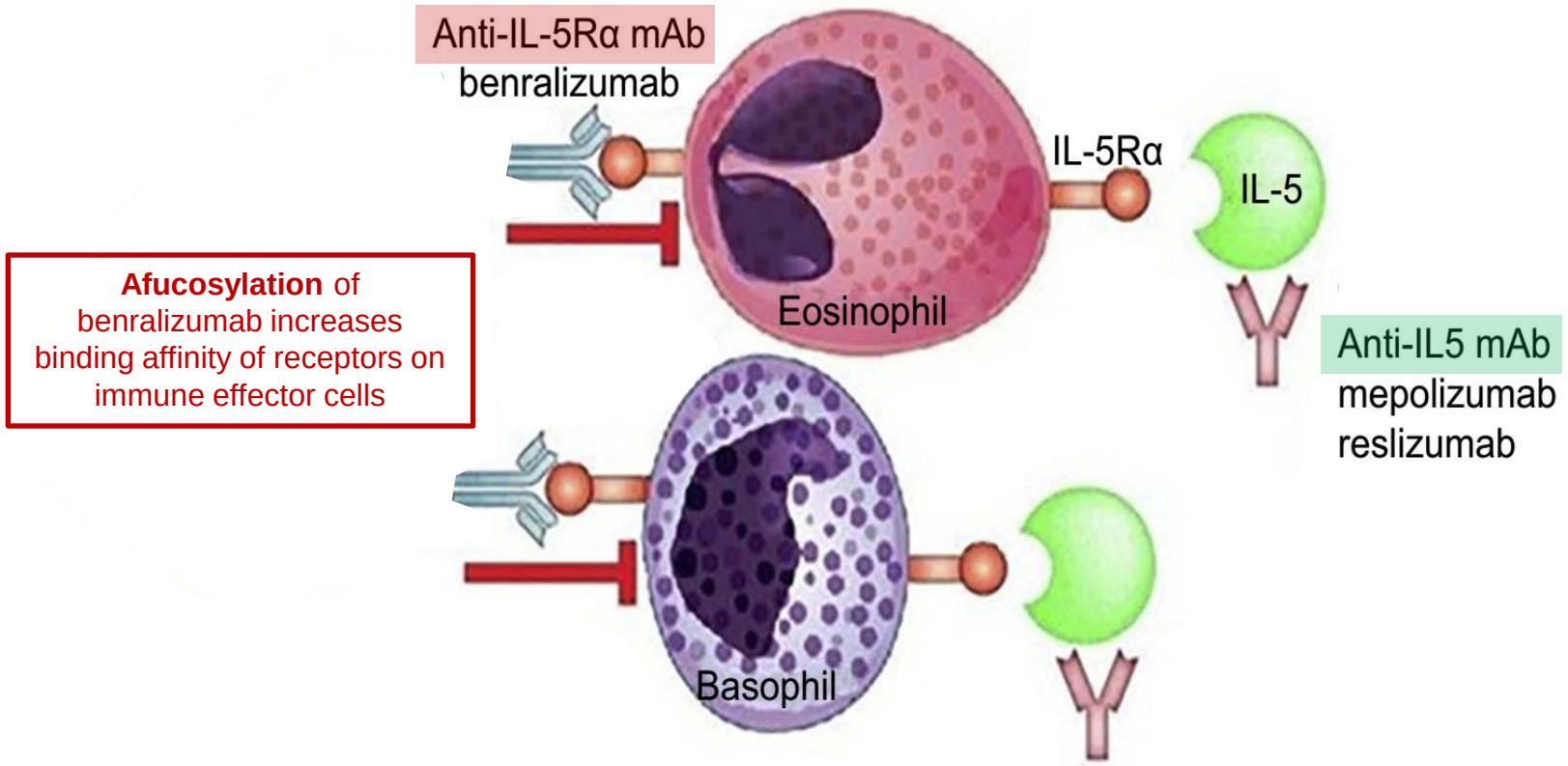
IL-5 and eosinophil biology



Haldar P *et al. Biologics*. 2017 Jun 27;11:81-95

Anti-IL5 vs anti-IL5Rα monoclonal antibodies:
Similar but different mechanism

ADCC
(antibody-dependent cell-mediated cytotoxicity)

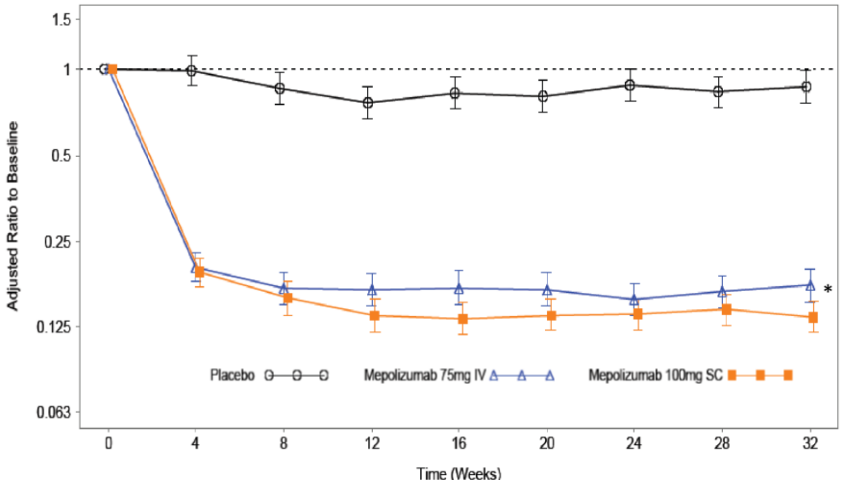


Afucosylation of benralizumab increases binding affinity of receptors on immune effector cells

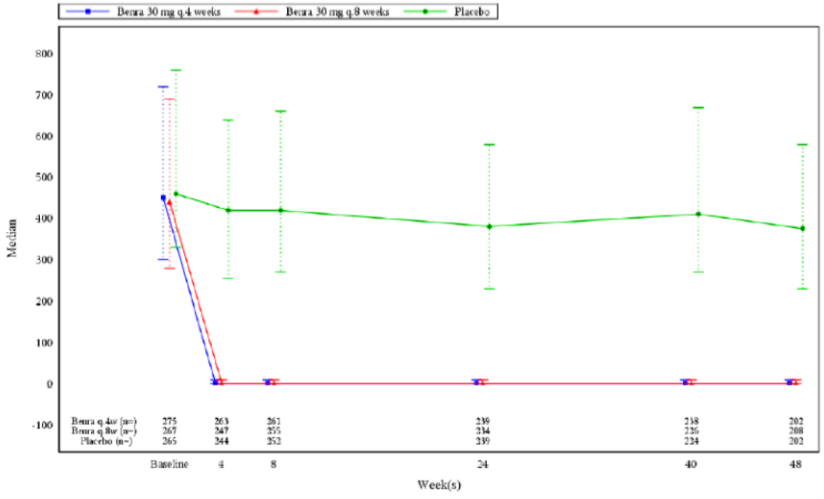
Mkorombindo T *et al. Int J Chron Obstruct Pulmon Dis*. 2019 Aug 7;14:1779-1787

Benralizumab depletes blood eosinophils in severe eosinophilic asthma

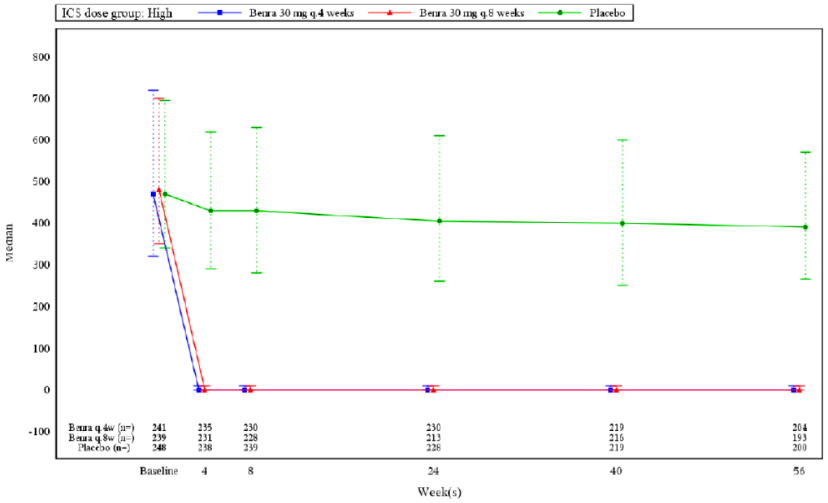
Mepolizumab [MENSA]



Benralizumab [SIROCCO]



Benralizumab [CALIMA]

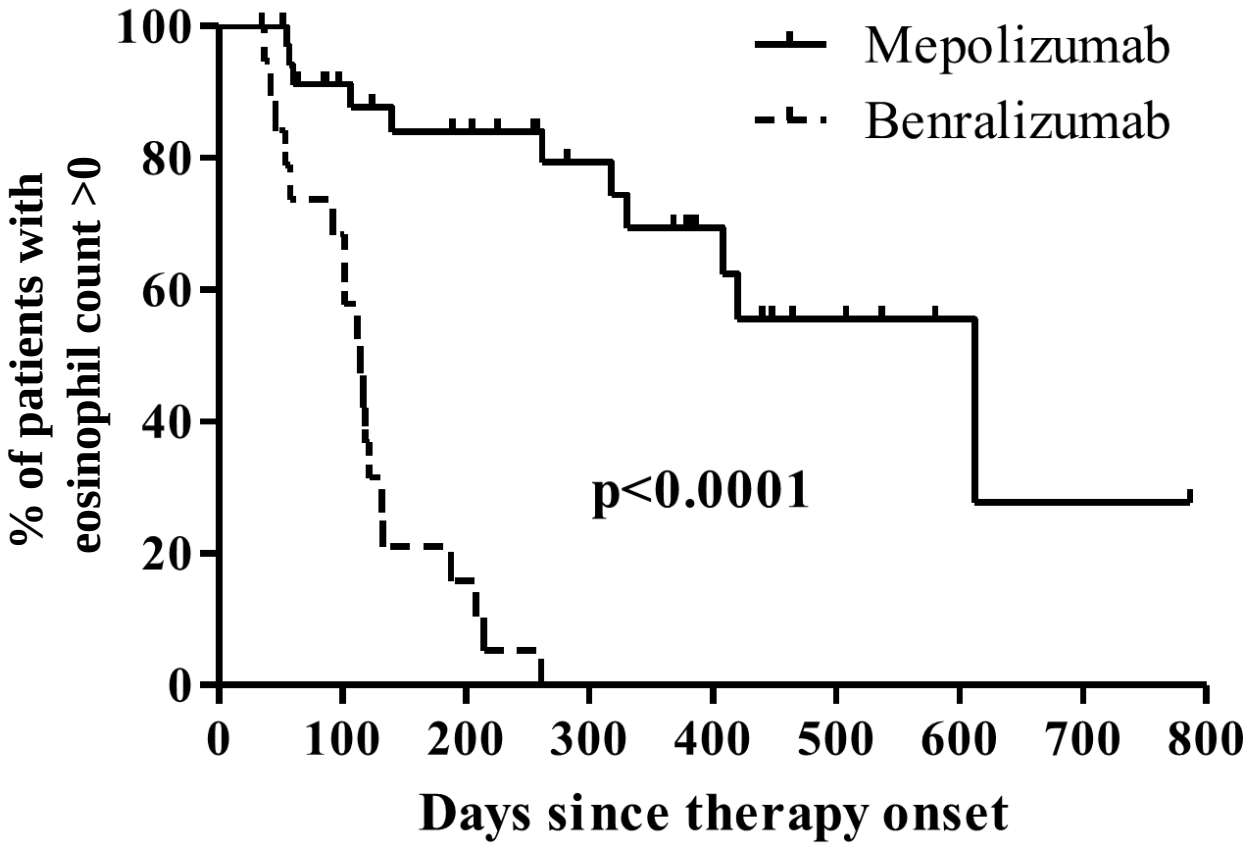


Ortega HG *et al. N Engl J Med*. 2014;371(13):1198-1207; FDA Clinical pharmacology and biopharmaceutics review(s) for Fasenra; Ghassemian A, et al. Allergy Asthma Clin Immunol. 2021 Jan 6;17(1):3

Superior effect in suppressing blood eosinophils in severe eosinophilic asthma treated with benralizumab vs mepolizumab

100% of patients receiving benralizumab vs **69%** receiving mepolizumab achieved undetectable eosinophil counts post-therapy (*p* <0.0001)

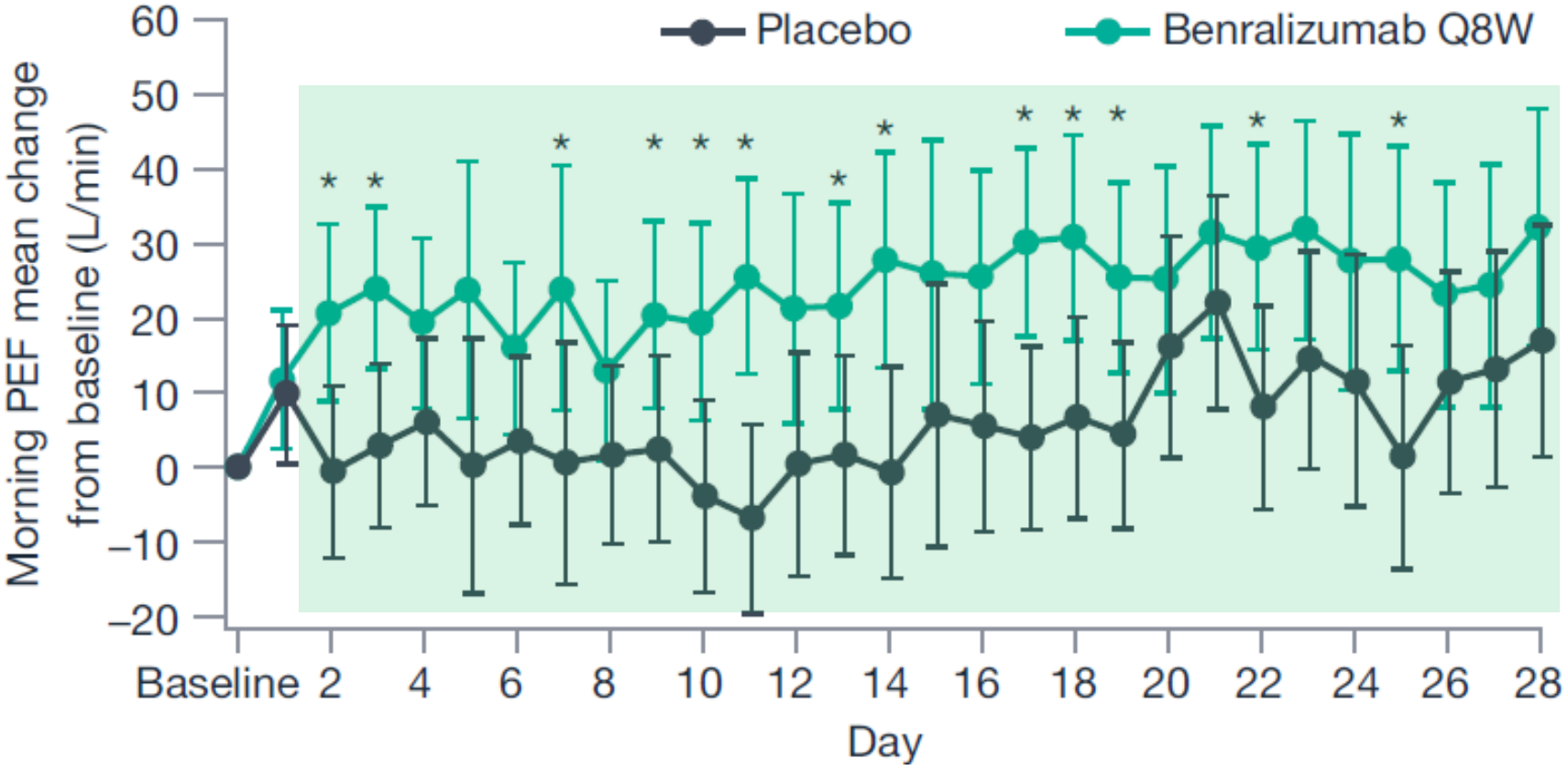
- Retrospective study
- Patients with **severe eosinophilic asthma** (mean Eos : 571/µL) approved for either IL-5 agent (36 mepolizumab; 19 benralizumab)
- The last detectable eosinophil count for each patient prior to start of therapy compared to the highest eosinophil count noted after therapy for ≥30 days



Ghassemian A, *et al. Allergy Asthma Clin Immunol*. 2021 Jan 6;17(1):3

Rapid improvement of PEF with benralizuamab in severe eosinophilic asthma [ZONDA]

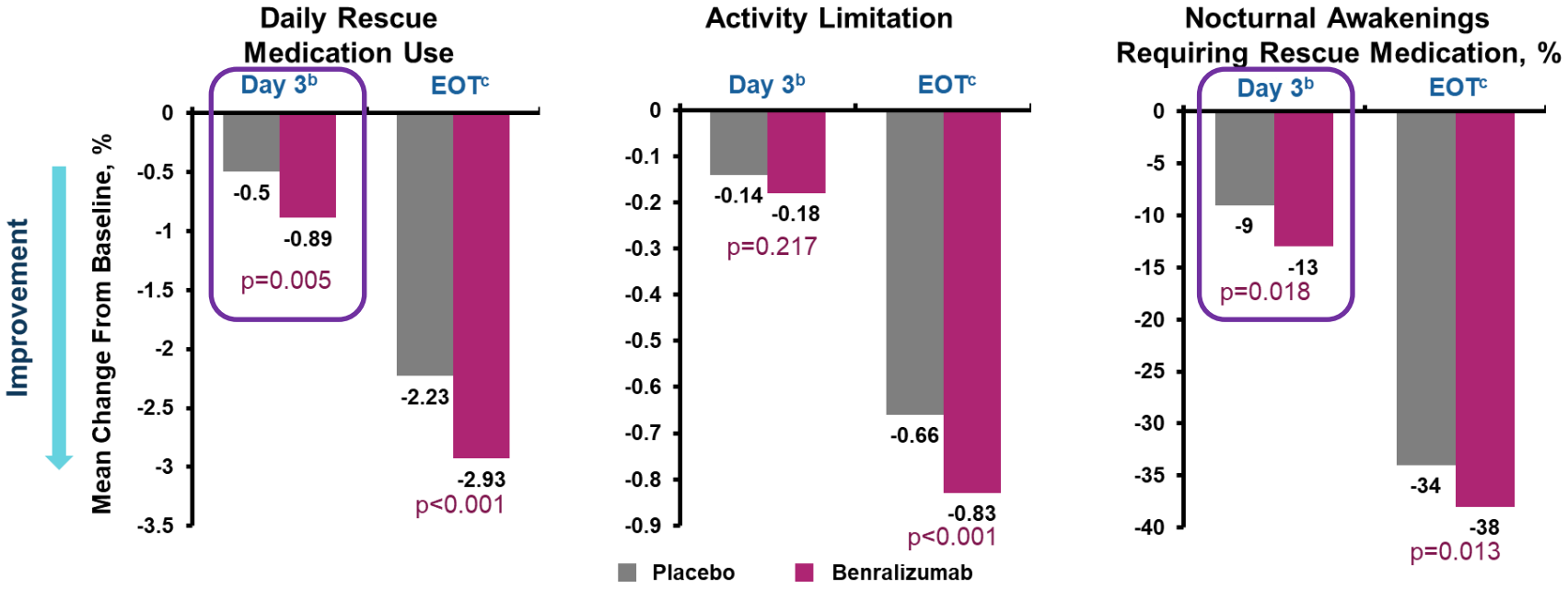
Benralizumab improves PEFR in severe eosinophilic asthma as early as early as 2 days after treatment



Lugogo NL *et al*. Poster presentation at ATS 2018 [Poster # A101]

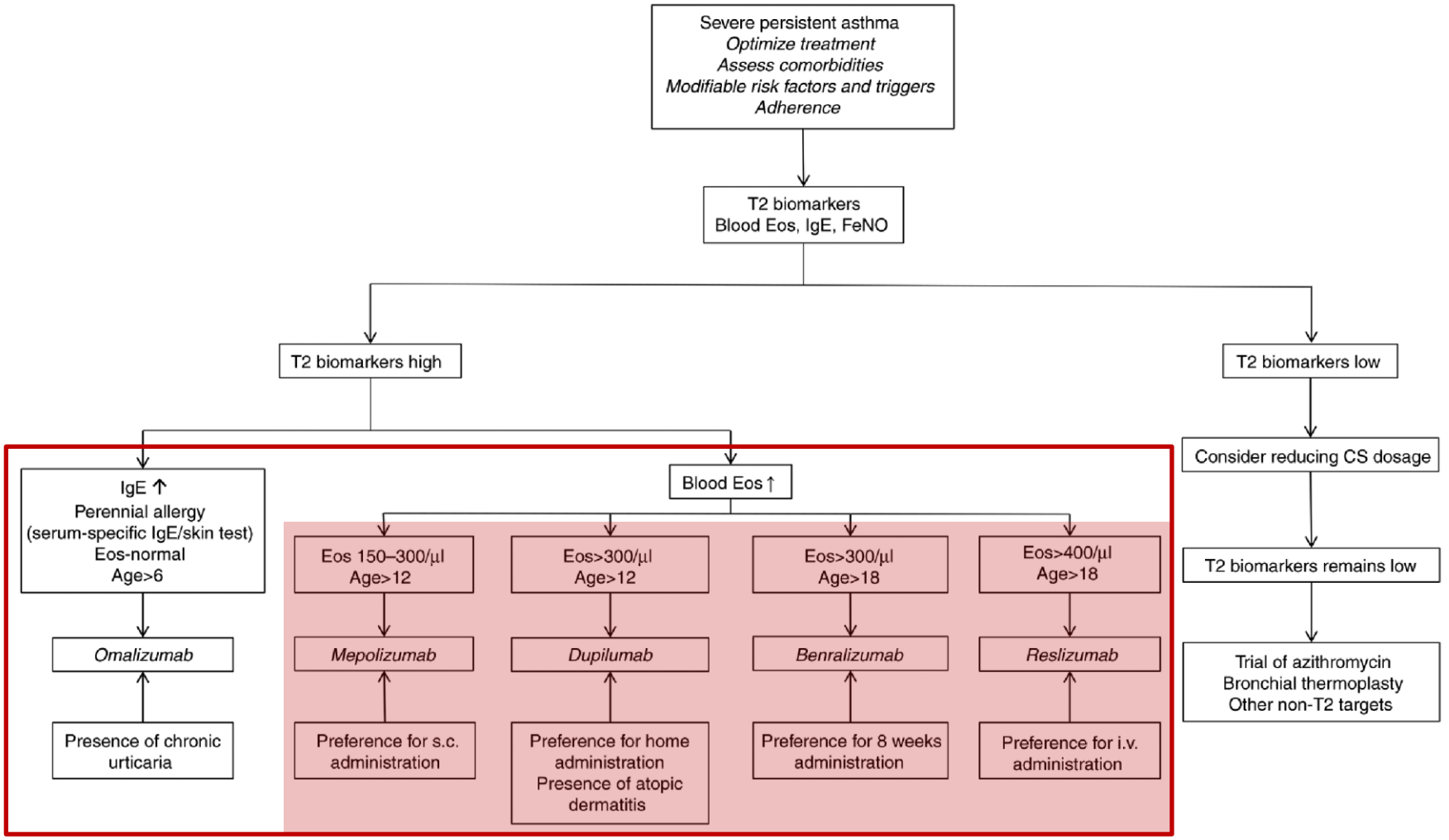
Rapid improvement of patient-reported ouctoms with benralizuamab in severe eosinophilic asthma
[SIROCCO & CALIMA]

Benralizumab significantly reduced rescuer use and nocturnal symptoms as early as 3 days (eosinophils ≥300 cells/µl)



Results as reported in patient daily diaries

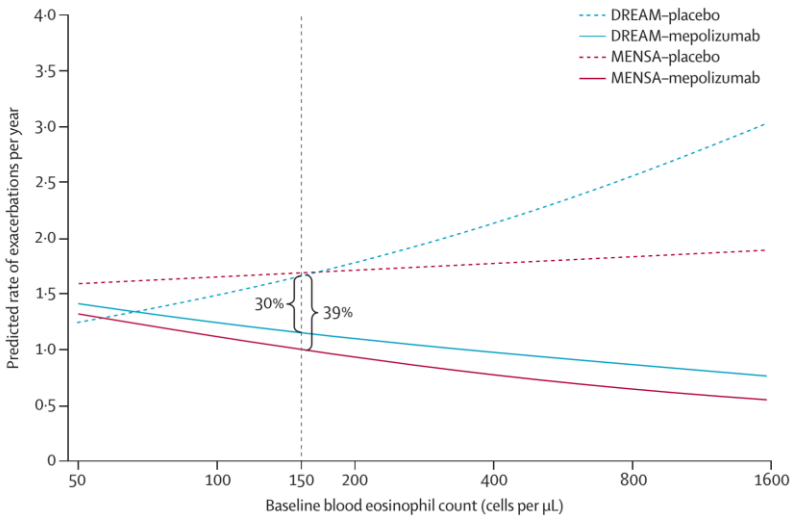
Biologic treatment for severe asthma with ↑ T2 inflammation: Overlapped eligibility



Exp Ther Med. 2021 Nov;22(5):1263

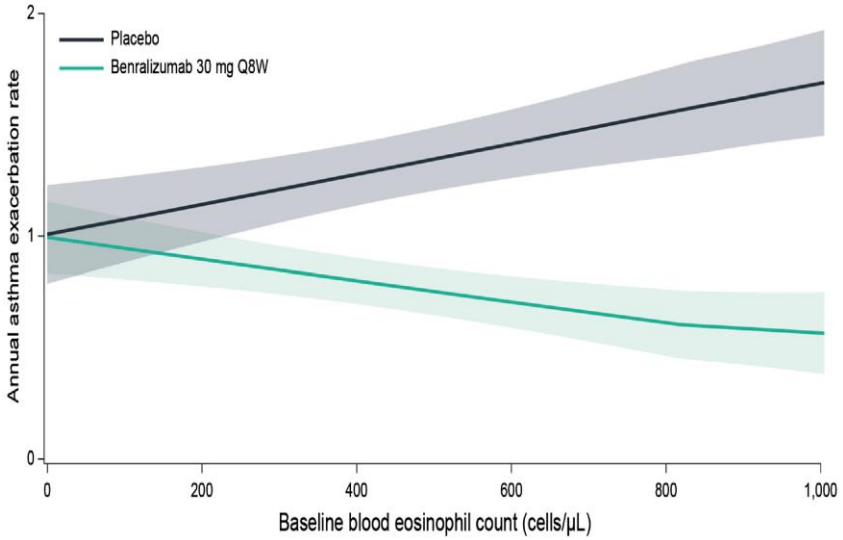
Blood eosinophil count as predictor of response to ALL T2 biologics in severe asthma

Mepolizumab



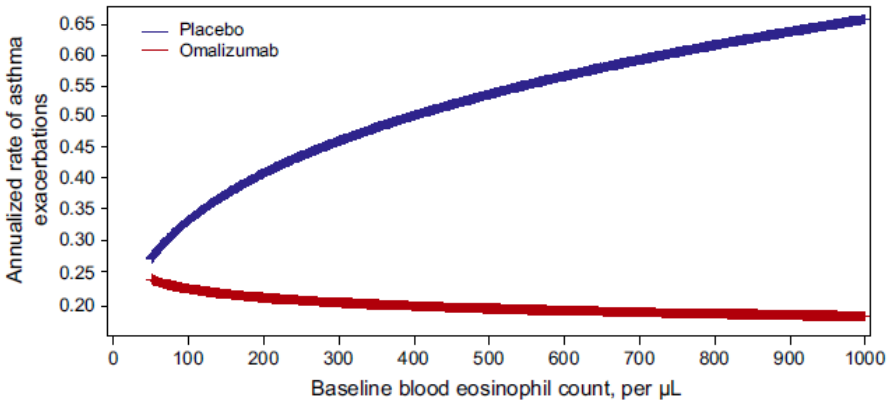
Ortega HG *et al. Lancet Respir Med*. 2016 Jul;4(7):549-556

Benralizumab



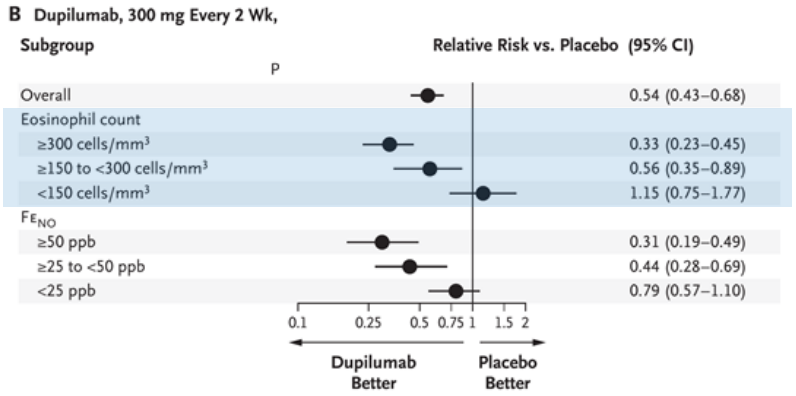
Jackson DJ, *et al. Adv Ther*. 2020 Feb;37(2):718-729

Omalizumab



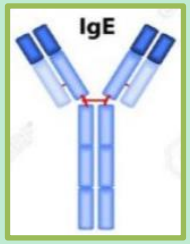
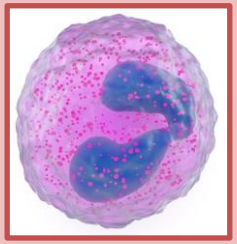
Casale TB *et al. Allergy*. 2018 Feb;73(2):490-497

Dupilumab



Castro M *et al. N Engl J Med*. 2018 Jun 28;378(26):2486-2496

Determining phenotypes based on clinical characteristics and biomarkers

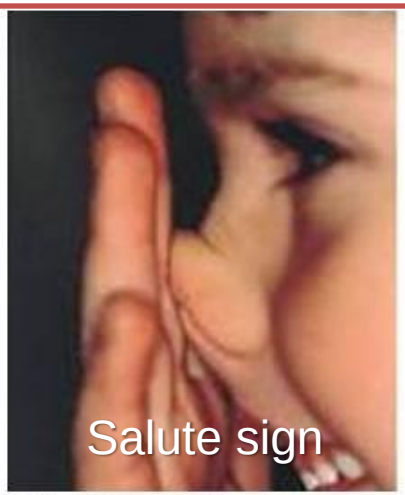
Phenotype	Characteristics
Allergic asthma 	Early-onset asthma Symptoms triggered by allergies Seasonal variations in exacerbations and degree of symptoms Associated with strong family history of asthma
Eosinophilic asthma 	Late-onset asthma Comorbid condition: severe sinus disease, nasal polyps, and aspirin sensitivity Frequent exacerbations requiring healthcare use May require oral corticosteroid maintenance therapy for symptom control

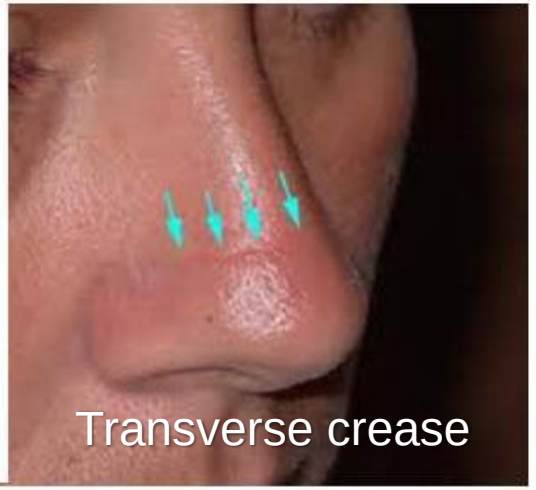
Opina MT *et al. Curr Allergy Asthma Rep*. 2017 Feb;17(2):10

Presence of atopy

Identification by *history taking*, *appearance*, and *in vitro assay*

Allergic appearance

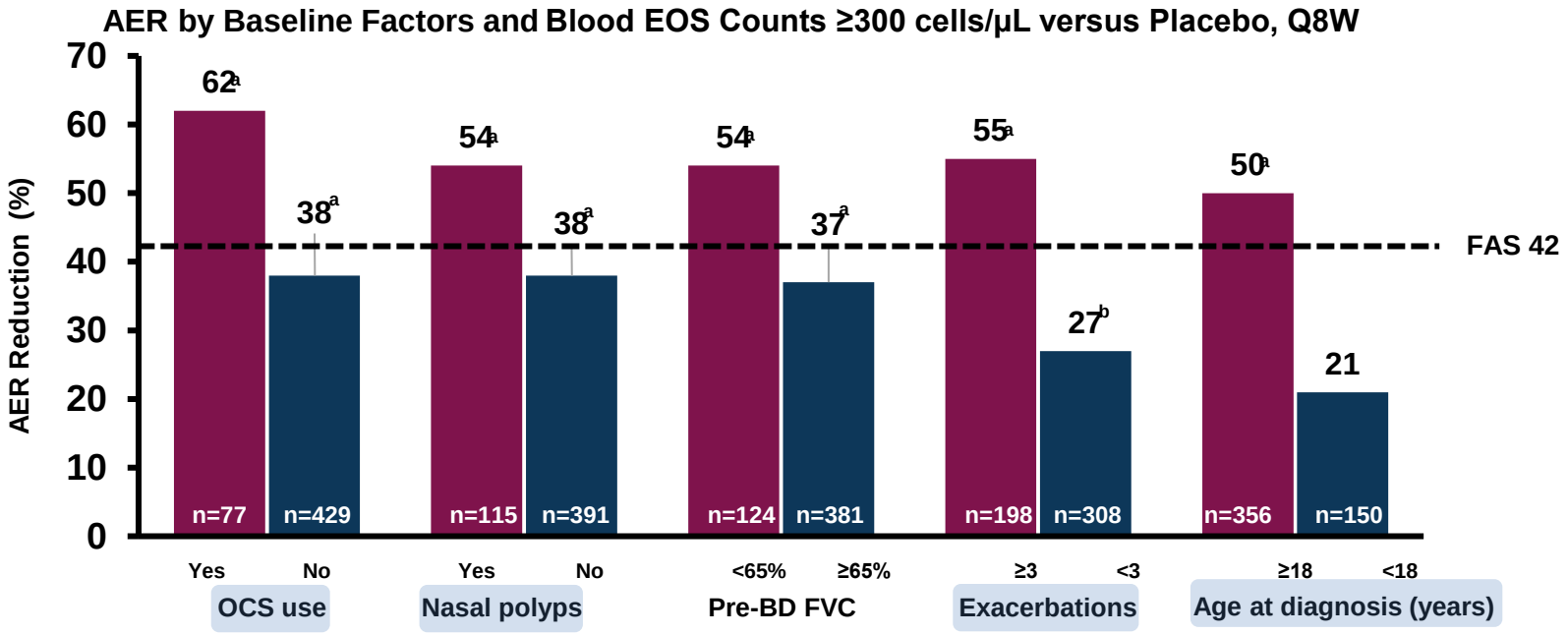




http://theallergist.wordpress.com

Better efficacy of anti-IL5 biologics in severe eosinophilic asthma with common characteristics

Exacerbation Rate Reduction by Baseline Factors and Blood EOS Counts (Pooled SIROCCO and CALIMA; High-Dosage ICS/LABA, ≥300 EOS)



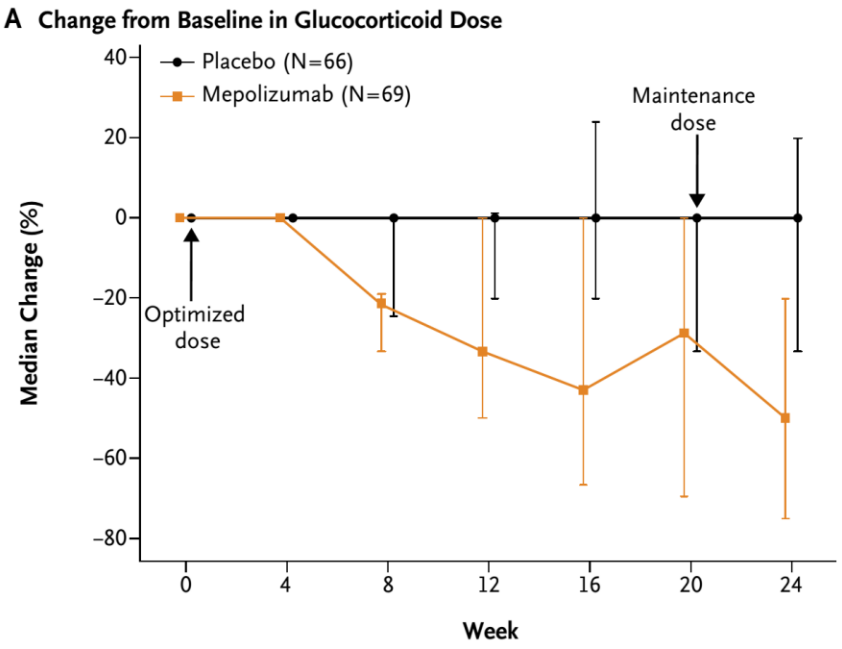
- There was an enhanced reduction in AER in patients with any key baseline characteristic and high blood EOS counts (≥300 cells/μL) relative to the FAS

Bleecker ER et al. Poster presented at: ATS International Conference; May 18-23, 2018; San Diego, CA. Poster 16840.

Comparison of reduced OCS dose between mepolizumab and benralizumab in OCS-dependent severe asthma

Mepolizumab [SIRIUS]

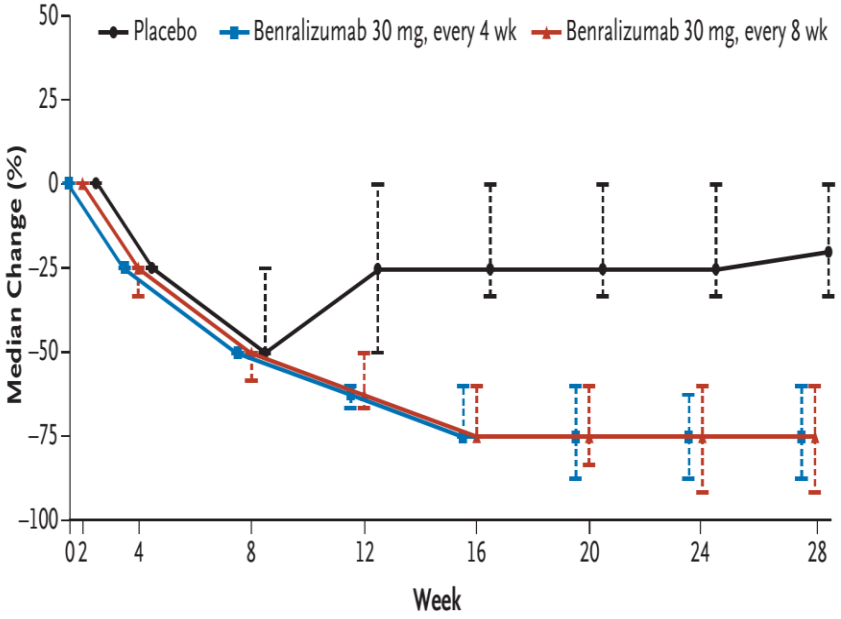
Percentage reduction from baseline in the glucocorticoid dose (**50%** vs 0; *p*=0.007)



Bel EH *et al. N Engl J Med*. 2014 Sep 25;371(13):1189-97

Benralizumab [ZONDA]

Percentage reduction from baseline in the glucocorticoid dose (**75%** vs 25%; *p<0.001*)



Nair P *et al. N Engl J Med*. 2017 Jun 22;376(25):2448-2458

Comorbidities as factors for selecting biologics for severe asthma

Patients with the following diseases may also benefit from certain biologics, independent of asthma

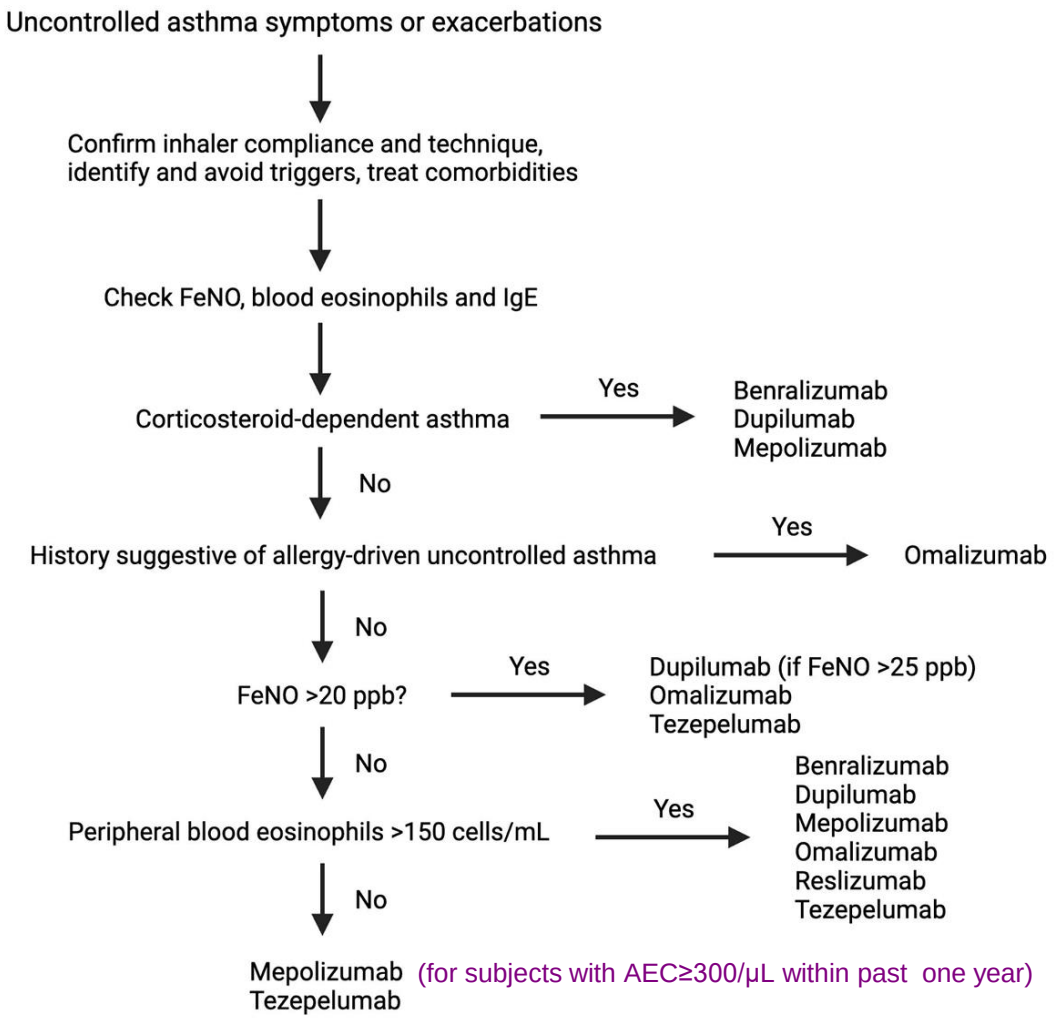
CRSwNP: Dupilumab, omalizumab, mepolizumab

AD: Dupilumab

CSU: Omalizumab

EGPA: Mepolizumab

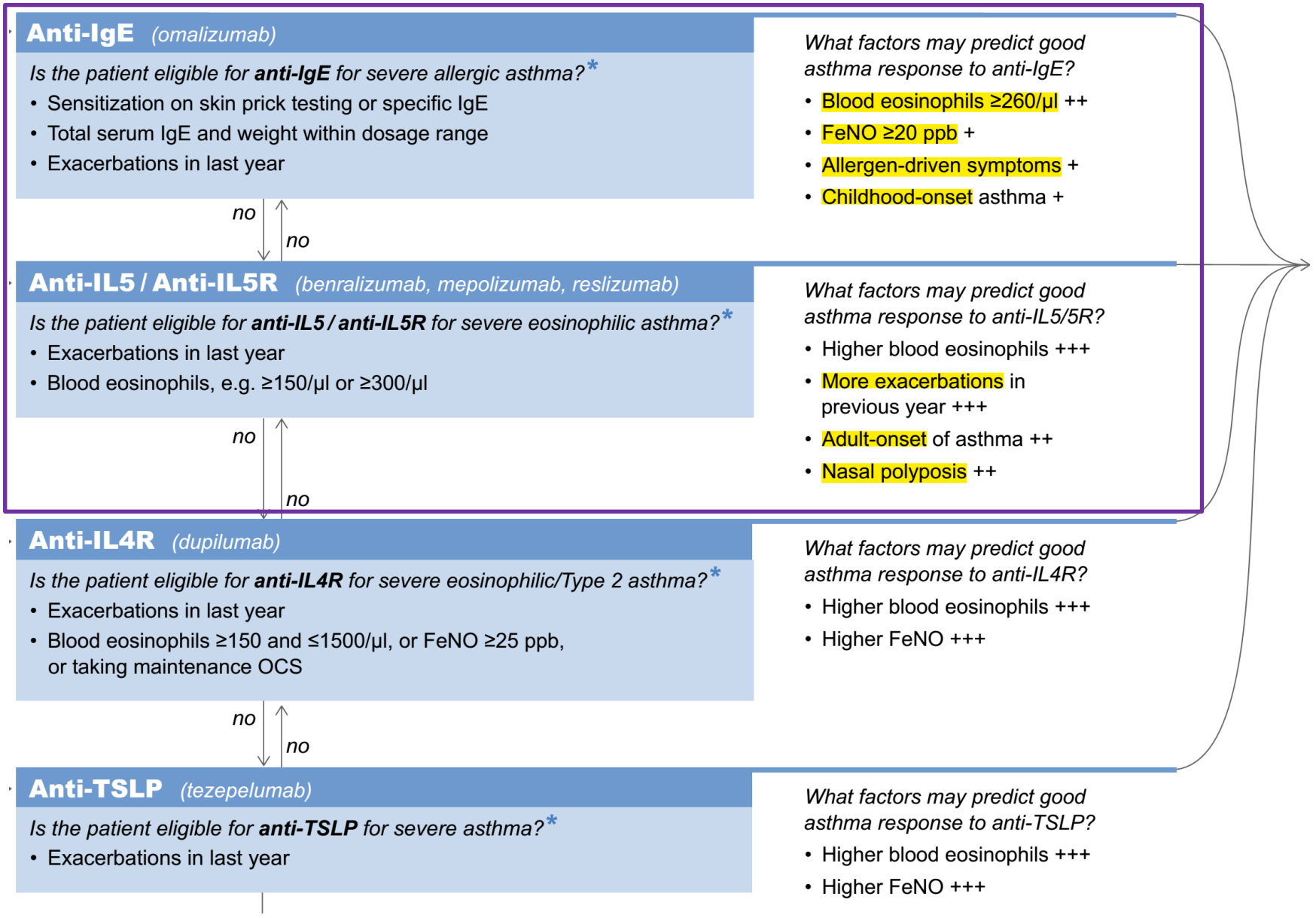
HES: Mepolizumab



CRSwNP: chronic rhinosinusitis with nasal polyps
AD: atopic dermatitis
CSU: chronic spontaneous urticaria
EGPA: eosinophilic granulomatosis with polyangiitis
HES: hyper-eosinophilic syndrome

J Inflamm Res. 2022 Jan 11;15:241-249

Predictors of response to specific biologics beyond eligible criteria



For severe asthma requiring long term regular administration of biologic agents with <u>several choices</u>…

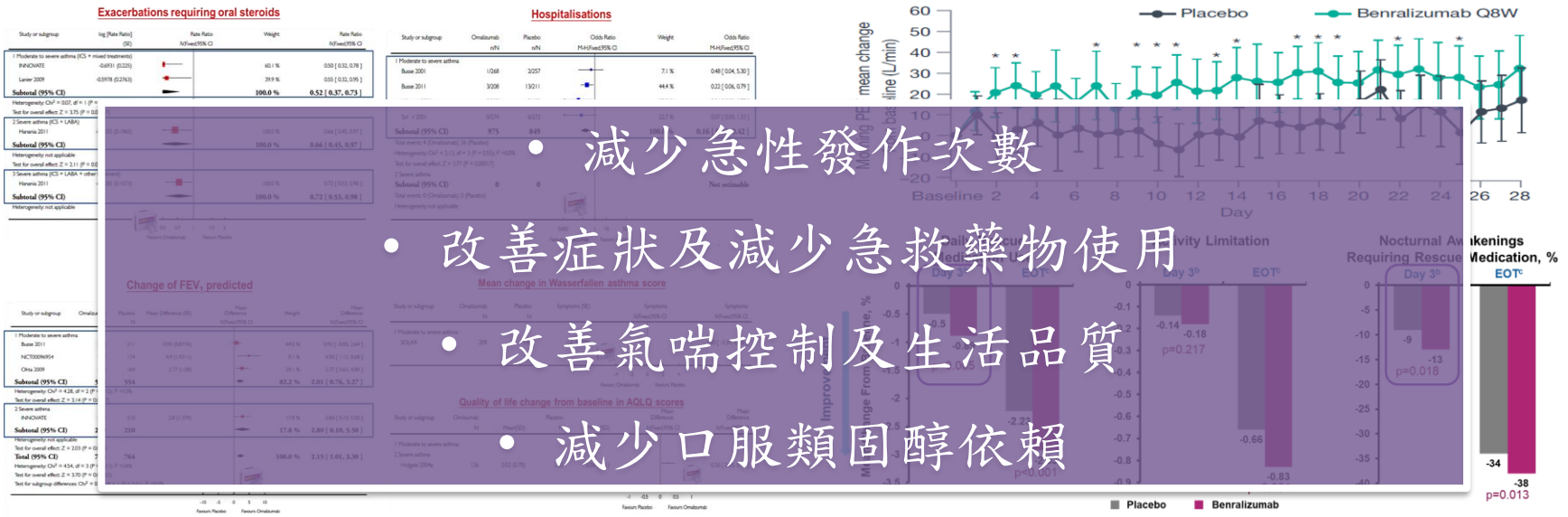
Which will be preferred?

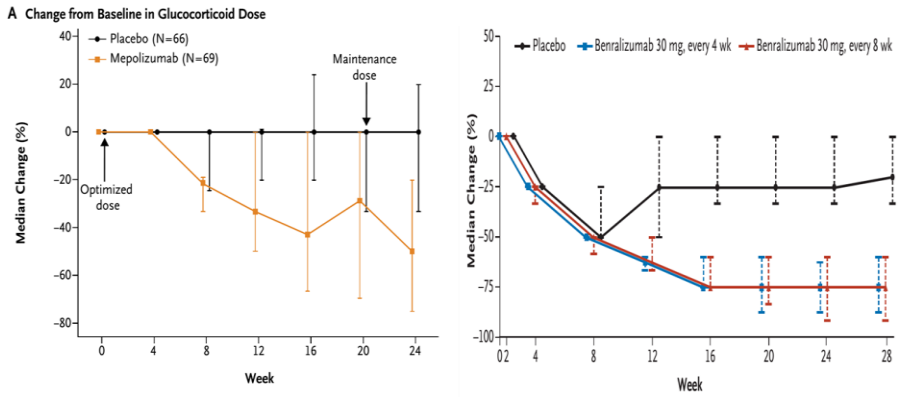
Omalizumab:1-4 vials sc q2w or q4w

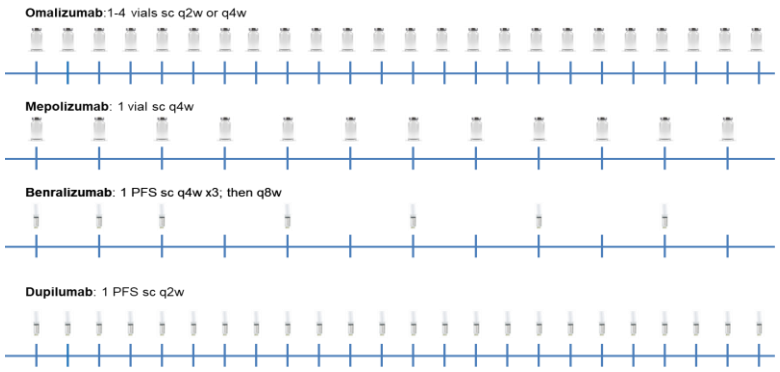
Take home messages

綜觀生物製劑帶給嚴重氣喘病患的改善

- 減少急性發作次數
- 改善症狀及減少急救藥物使用
- 改善氣喘控制及生活品質
- 減少口服類固醇依賴







Thanks for Your Attention!! Po-Jui Chang 張博瑞 Email: playchang5478@gmail.com