BIOLOGICALS IN ASTHMA

Dr. Gunda Jaya Hareesh

Difficult to treat Asthma is that is uncontrolled despite

- medium or high dose ICS with a second controller (usually LABA) (or)
- with maintenance steroids to maintain good symptom control and reduce risk of exacerbations (or)
- Requires high dose treatment TO MAINTAIN GOOD SYMPTOM CONTROL AND REDUCE RISK OF EXACERBATIONS

Inhaled corticosteroid (alone or in combination with LABA)	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400		>400

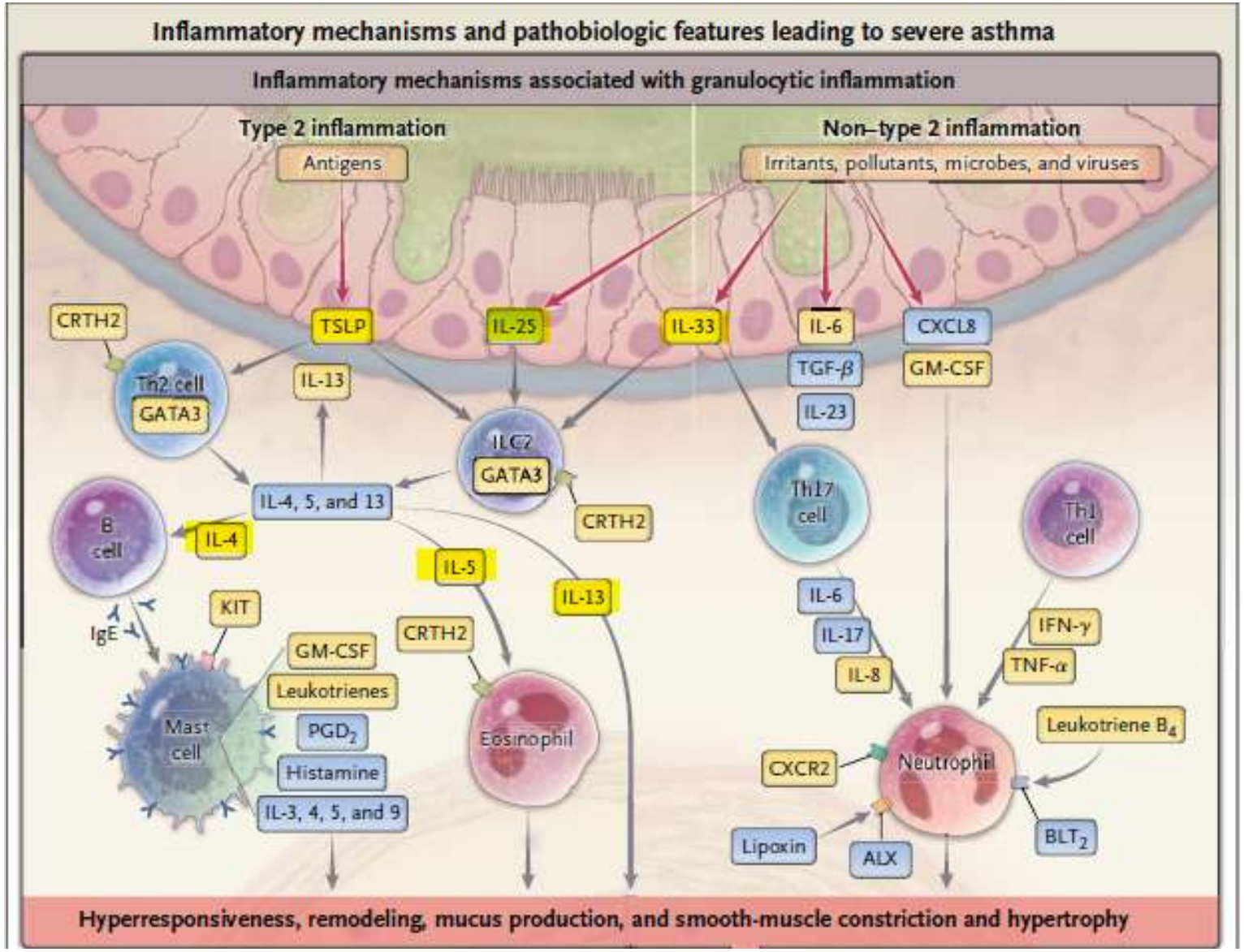
GINA 2024

- Severe Asthma is a subset of difficult-to-treat asthma, characterized by asthma that remains uncontrolled despite adherence with maximal optimized high dose ICS-LABA and treatment of contributory factors or that worsens when high dose treatment is reduced.
- **IT IS A RETROSPECTIVE DIAGNOSIS**

Additional testing in severe asthma

- AEC: to evaluate for eosinophilic lung diseases, to decide biologicals
- Evaluation for ABPA/ABPM
- If omalizumab is being considered: Total IgE, allergy testing for perennial aeroallergens
- Directed testing in case of suspicion - HRCT chest, ANCA, CT sinuses, BNP, Echo

ASSESS THE SEVERE ASTHMA PHENOTYPE



- Persistent T_{H2} inflammation
- Neutrophilic
- Mixed
- Pauli Granulocytic

Elliot et al, N Engl J Med 2017;377:965-76

	Type 2 inflammation	Neutrophilic inflammation	Mixed inflammation	Paucigranulocytic inflammation
Frequency	Very common	Common	Not common	Variable
Causes and contributing factors	Allergens, occupational exposures, ABPA, AERD	Infections, Smoke, Irritants, Pollutants, Glucocorticoids, Occupational	Combination	Glucocorticoid treatment
Features	Early onset, allergies, sinusitis, nasal polyps, Frequent exacerbations	Low lung function Poor response to ICS, Purulent mucus, Bronchiectasis		Fixed and variable obstruction
	IL-4 -> IgE production IL-5 -> Eosinophils IL-13	Th17 -> neutrophils	IL-6 and IL-17 may produce dual Th2 and Th17 response	

Elliot et al, N Engl J Med 2017;377:965-76

Biomarkers used in asthma phenotyping

Markers suggestive of TH2 inflammation

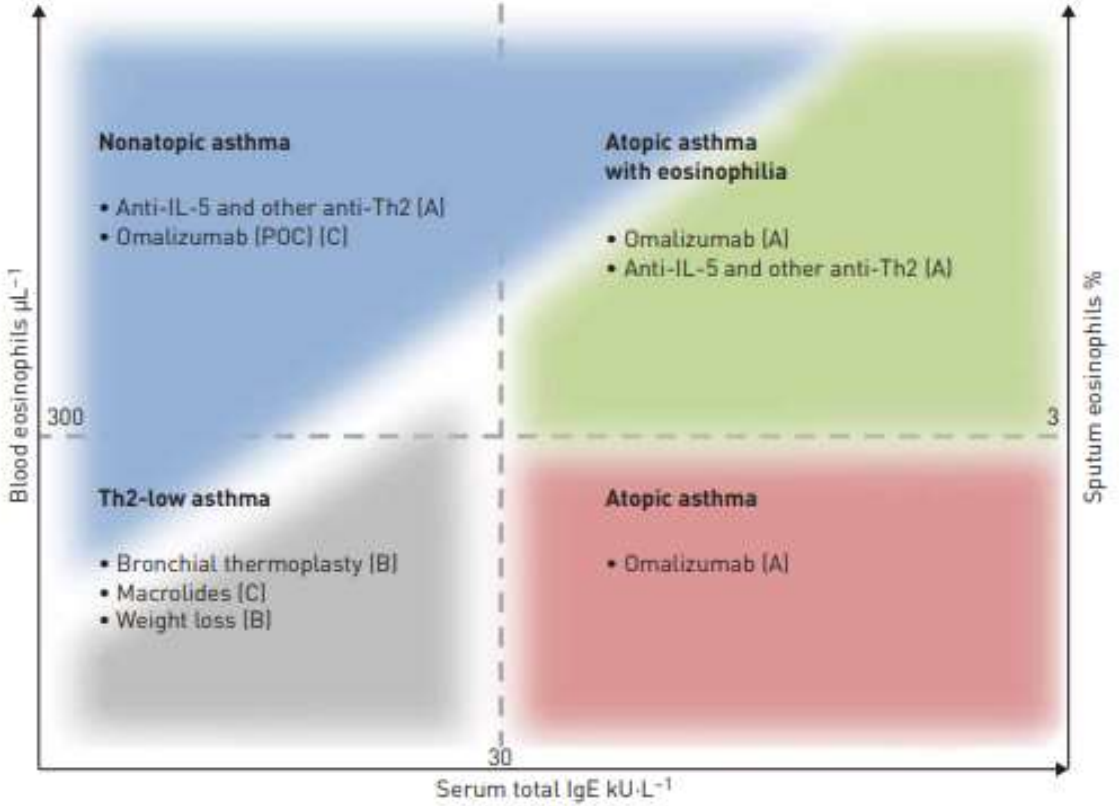
- Blood eosinophils ≥150 cells/µl - Predict responsiveness to corticosteroid therapy

  Predict clinical efficacy of anti IL-5 therapies
- Serum IgE levels – Used a response biomarker for the use of omalizumab in severe allergic asthma
- FeNO ≥20 ppb – High levels predicted those response with biologicals
- Sputum eosinophils ≥2 % - Helps in obtaining better outcome measures if they improve with treatment
- Serum periostin

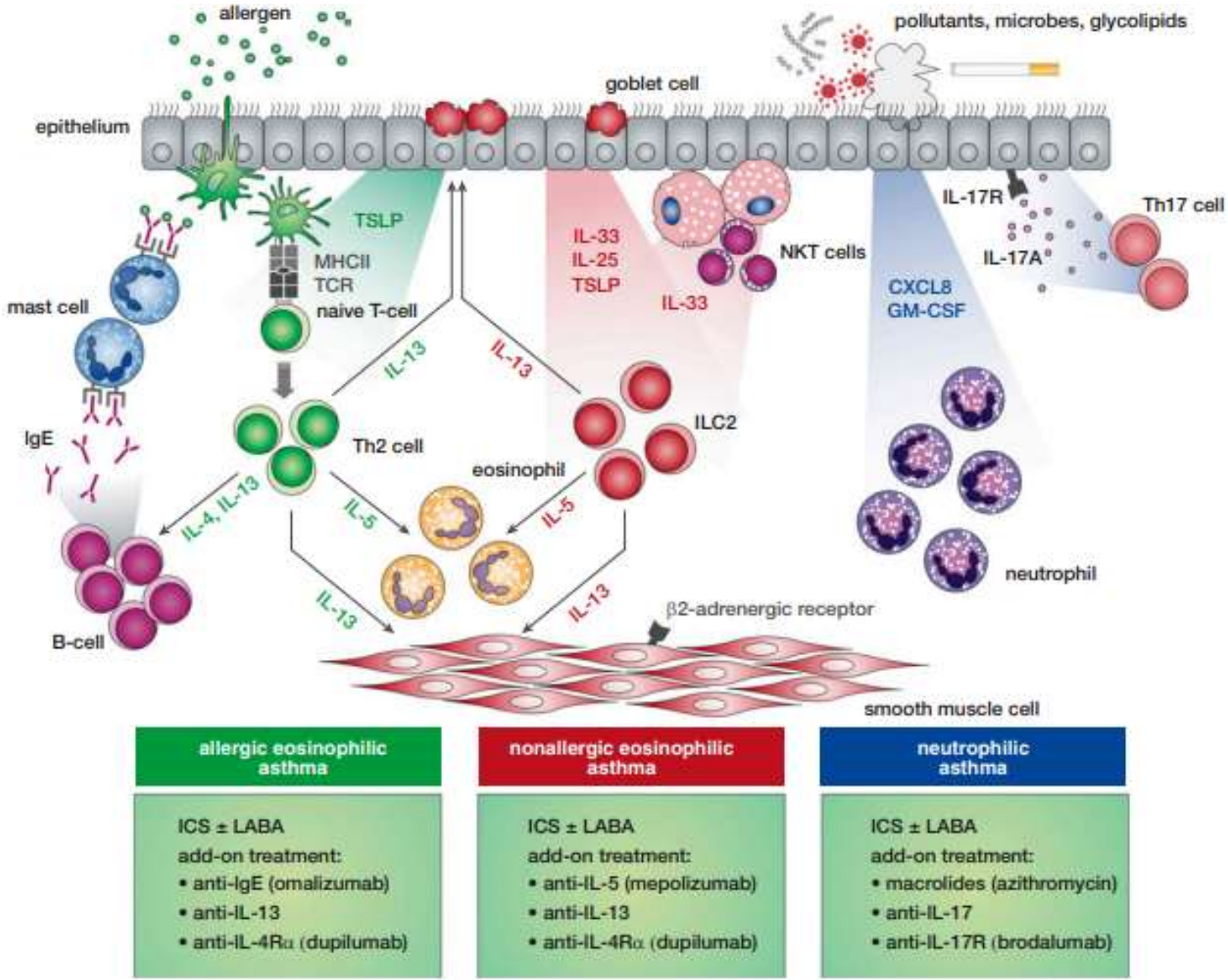
Possibility of refractory type 2 inflammation considered if any are present despite on high dose ICS or daily OCS

Chung KF. Personalized medicine in asthma : time for action Eur Resp Rev 2017;26:170064
GINA 2024

- Atopic asthma – Persistent Th2 inflammation triggered upon exposure to certain allergen. Presence of certain IgE is characteristic with elevated eosinophils and skin prick testing
- Non atopic asthma – late onset, no familial history, frequent association with chronic rhino sinusitis and nasal polyps and aspirin hypersensitivity
- Th2 low asthma – neutrophilic asthma
  IL-17 and IL-33 play role in this



Froidure et al(2015). Asthma phenotypes and IgE responses. European Respiratory journal, 47(1), 304-319



allergic eosinophilic asthma	nonallergic eosinophilic asthma	neutrophilic asthma
ICS ± LABA add-on treatment: • anti-IgE (omalizumab) • anti-IL-13 • anti-IL-4Rα (dupilumab)	ICS ± LABA add-on treatment: • anti-IL-5 (mepolizumab) • anti-IL-13 • anti-IL-4Rα (dupilumab)	ICS ± LABA add-on treatment: • macrolides (azithromycin) • anti-IL-17 • anti-IL-17R (brodalumab)

Brusselle et al Targeting immune pathways for therapy in asthma Ann Am Thorac Soc 2014: 11(5); 322-8

Biologic therapies

- Anti-IgE monoclonal antibody- **Omalizumab**
- Monoclonal antibodies against Interleukin-5- **Mepolizumab/** Reslizumab
- Monoclonal antibodies against Interleukin-5 receptor- **Benralizumab**
- Monoclonal antibodies against Interleukin-4 receptor- Dupilumab
- Monoclonal antibodies against Interleukin-13- Lebrikizumab/ Tralokinumab
- Monoclonal antibodies against TSLP- Tezepelumab
- Monoclonal antibodies against Interleukin-33- Itepekimab
- Monoclonal antibodies against Interleukin-33 receptor- Astegolimab
- Monoclonal antibodies against Non Type 2 cytokine antibodies- Risankizumab/ Brodalumab/Golimumab

Omalizumab- FDA 2003

First biological approved for asthma –

2003 for ≥ 12 yrs and in 2016 for ≥ 6 yrs

Labelled indications:

- **1. Moderate to severe persistent asthma** positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS with total IgE 30-700 IU/L (≥ 12yrs) or 30-1300IU/L(6-11 yrs)
- **2. Chronic idiopathic urticaria(2014)**

- INR – 10000 per 150 mg , for 70 kg patient monthly cost 40000/-

Table 1. Subcutaneous Xolair Doses Every 4 Weeks for Patients 12 Years of Age and Older with Asthma

Pre-treatment Serum IgE	Body Weight			
	30–60 kg	> 60–70 kg	> 70–90 kg	> 90–150 kg
≥ 30–100 IU/mL	150 mg	150 mg	150 mg	300 mg
> 100–200 IU/mL	300 mg	300 mg	300 mg	
> 200–300 IU/mL	300 mg	SEE TABLE 2		
> 300–400 IU/mL				
> 400–500 IU/mL				
> 500–600 IU/mL				

Table 2. Subcutaneous Xolair Doses Every 2 Weeks for Patients 12 Years of Age and Older with Asthma

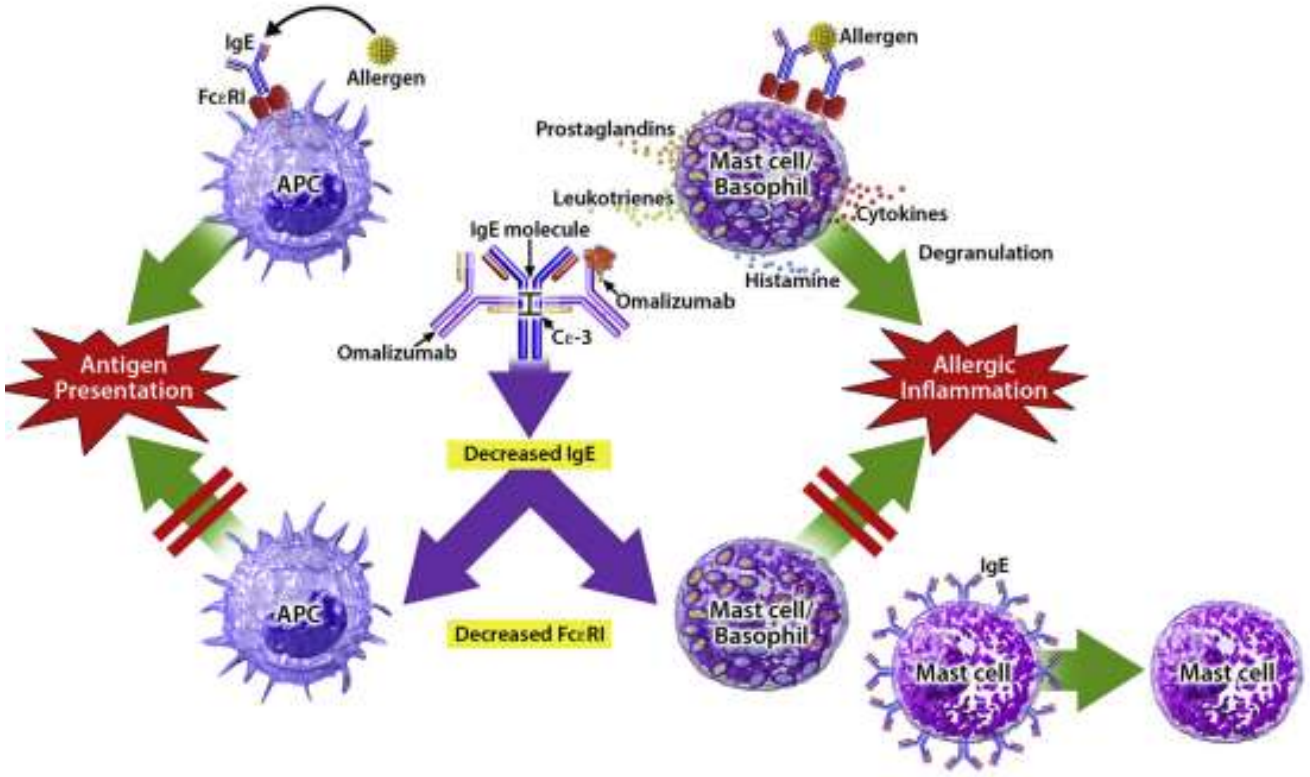
Pre-treatment Serum IgE	Body Weight			
	30–60 kg	> 60–70 kg	> 70–90 kg	> 90–150 kg
≥ 30–100 IU/mL	SEE TABLE 1			
> 100–200 IU/mL				225 mg
> 200–300 IU/mL		225 mg	225 mg	300 mg
> 300–400 IU/mL	225 mg	225 mg	300 mg	
> 400–500 IU/mL	300 mg	300 mg	375mg	
> 500–600 IU/mL	300 mg	375 mg	DO NOT DOSE	
> 600–700 IU/mL	375 mg			

MECHANISM

- Recombinant, humanized IgG1 antibody binding to Fc region of free IgE forming complexes which block IgE binding to high affinity IgE receptor

1. Binding to circulating free IgE – occurs in days
2. Downregulation of high affinity cell surface IgE receptor – takes weeks to months – based on effector cell type.

90% reduction of receptors on basophils and mast cells by 7 an 70 days respectively



Cassale,JACI 2017;139; 1411.21

- Omalizumab reduces free IgE by 96% although total IgE levels increase after first injection due to omalizumab and IgE complex formation (Doroudchi, Ann Allergy,2020; 124; 44-56)
- Plateau of improvement in asthma symptoms and morning peak expiratory flow around 12–16 weeks reflecting the downregulation of FceRI receptors on effector cells.(INNOVATE trial)
- THUS IT WOULD BE BETTER TO ASSESS TREATMENT EFFECTIVENESS AFTER 16 wk TRAIL and assess clinical symptoms and lung function and decide on further continuation

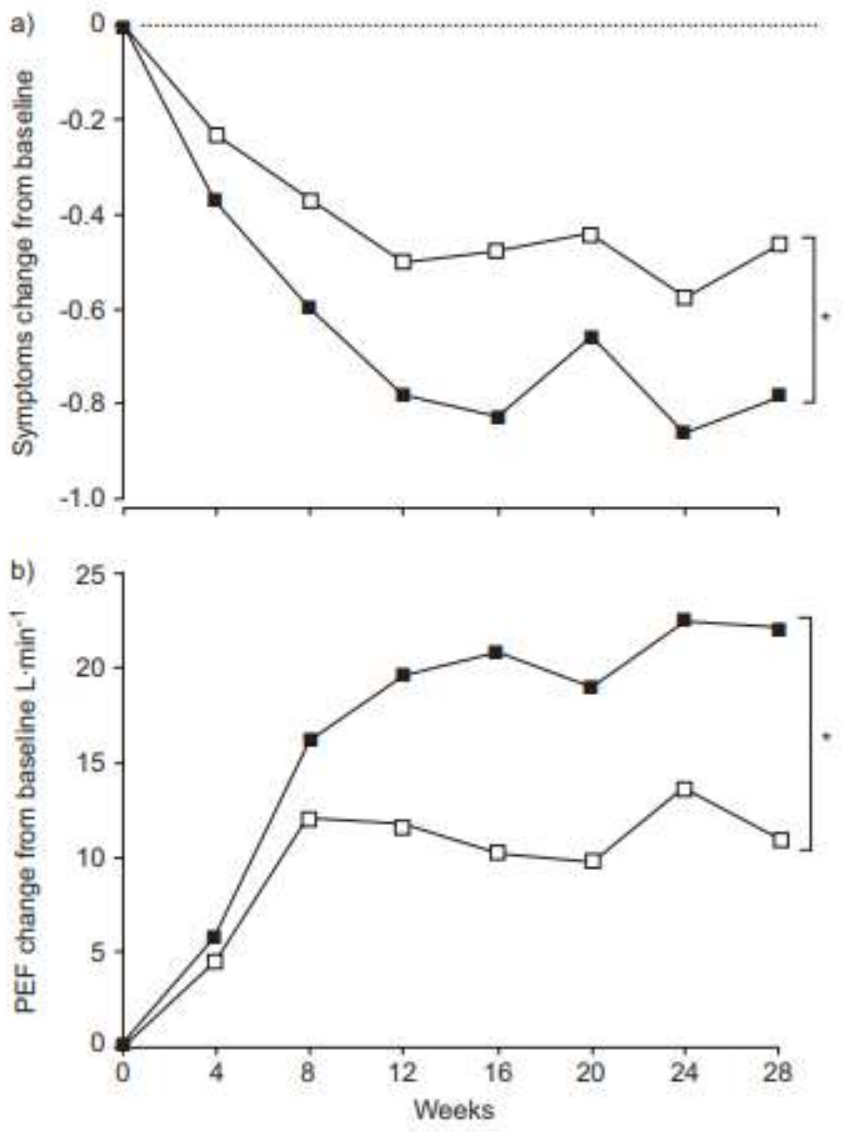


FIGURE 3. Changes in a) symptoms and b) peak expiratory flow (PEF) with time during omalizumab treatment. Changes from baselines are shown as least-squares means. □: placebo, ■: omalizumab. *: $p<0.05$. Data taken from [1].

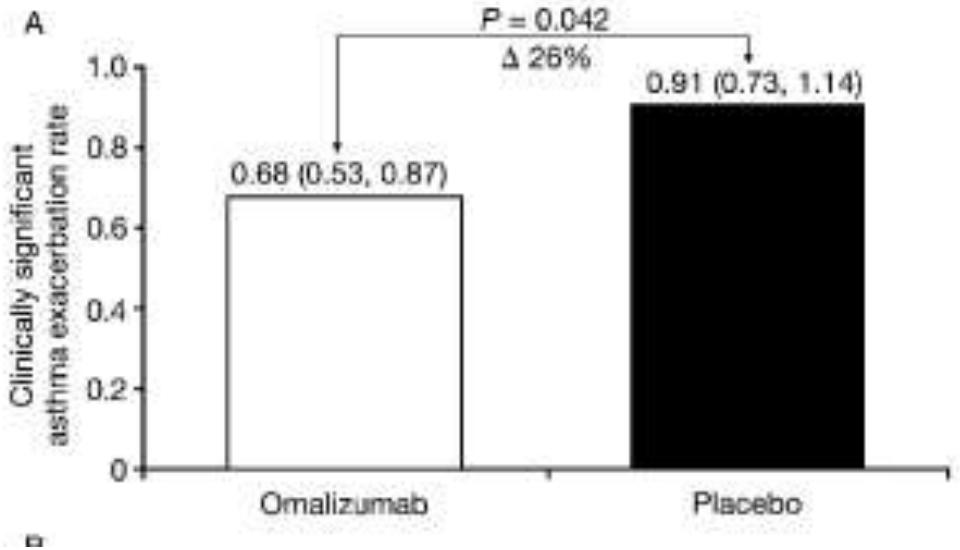
Allergy 2005: 60: 309–316

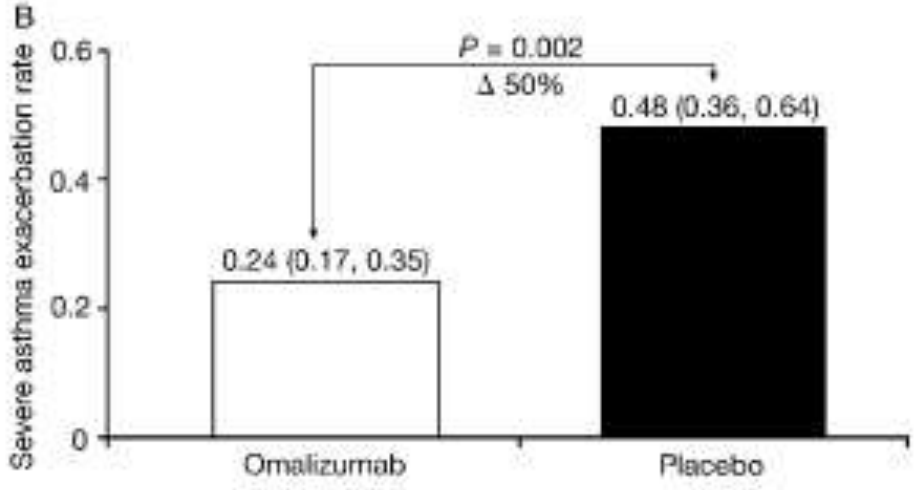
ALLERGY
DOI: 10.1111/j.1398-9995.2004.00772.x

Original article

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE

INNOVATE TRIAL (2005)	Severe persistent allergic asthma with total IgE 30-700 IU/ml and not controlled despite high dose ICS (>1000µg/day BDP) Excluded smokers / ≥10 PY	28 weeks of omalizumab(209 patients) vs placebo(210 patients) **Age – 43.4 vs 43.3** Female – 67.5 vs 65.7 Weight – 81.2 vs 79.2 **FEV1 – 61 % vs 61.6 %** Reversibility – 28.9 % vs 24.5 % Duration – 23.3 yrs vs 22.7 yrs **ICS (µg/day) – 2359 vs 2301**	**Clinically significant asthma exacerbations** **Severe exacerbation** **FEV1 and PEFR**





Clinically significant exacerbation rate
0.68 vs 0.91 (**26% reduction**)
NNT for 1 year - 2.2

Severe exacerbations
0.24 vs 0.48 (**50% reduction**)
NNT for 1 year – 2.2

Failed to achieve significant results in ITT population not accounting for previous exacerbation

rate ratio – 0.806 (p=0.15)

FEV1 improved by 2.8% of predicted (Improvements – 190 ml vs 96 ml)

Treatment arm – used 0.5 puffs/day less as rescue

Also reduced hospitalization rate by 50% and improved asthma QOL

Original Research | 3 May 2011

Annals of Internal Medicine®

Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy: A Randomized Trial FREE

Authors: Nicola A. Hanania, MD, MS, Oral Alpan, MD, Daniel L. Hamilos, MD, John J. Condemi, MD, PhD, Karin E. Rosen, MD, PhD, Mark D. Eisner, MD, MPH, Dennis A. Wong, MD, and William Busse,

EXTRA TRIAL (2011)	**Severe allergic asthma for 1 yr before screening, not controlled on high dose ICS(>500**µg/day fluticasone**) with total IgE 30-700 IU/ml with pre bronchodilator FEV1 40-80%** Excluded current smokers / ≥10 PY, other causes of elevated IgE(ABPA, parasites, Hyper IgE)	48 weeks of omalizumab(427 patients) vs placebo(421 patients) **Age – 43.7 vs 45.3** Female – 61.4 vs 70.1 Weight – 87.9 kg vs 86.2 kg **FEV1 – 65.4 % vs 64.4 %** Duration – 22.8 yrs vs 24.7 yrs	**Protocol defined asthma exacerbation**

Table 2. **Protocol-Defined Asthma Exacerbations Over the 48-Week Treatment Period**

Analysis of Primary End Point	Omalizumab Group (n = 427)	Placebo Group (n = 421)
Frequency of protocol-defined asthma exacerbations, *n (%)*		
0	275 (64.4)	242 (57.5)
1	94 (22.0)	107 (25.4)
2	31 (7.3)	34 (8.1)
3	16 (3.7)	23 (5.5)
≥4	11 (2.6)	15 (3.6)
Rate of protocol-defined asthma exacerbations per patient	0.66	0.88
Incidence rate ratio (95% CI); *P* value	0.75 (0.61–0.92); 0.006	

Incidence rate ratio – 0.75 (0.61-0.92)

SUB – GROUPS

ICS plus LABAs alone (M1) – **IRR 0.66** [0.44 - 0.97]

With 1 additional controller (M2) - **IRR 0.72** [0.53 - 0.98]

With ICS plus LABAs plus maintenance OCS (M3) IRR 0.95

[0.63 -1.43]

PREDICTORS OF RESPONSE TO OMALIZUMAB

- Baseline IgE levels does not predict likelihood of response to omalizumab (Holgate et al, Eur Respir Rev 2007; 16: 104, 78-84)

ARE THERE ANY PREDICTORS FOR TREATMENT

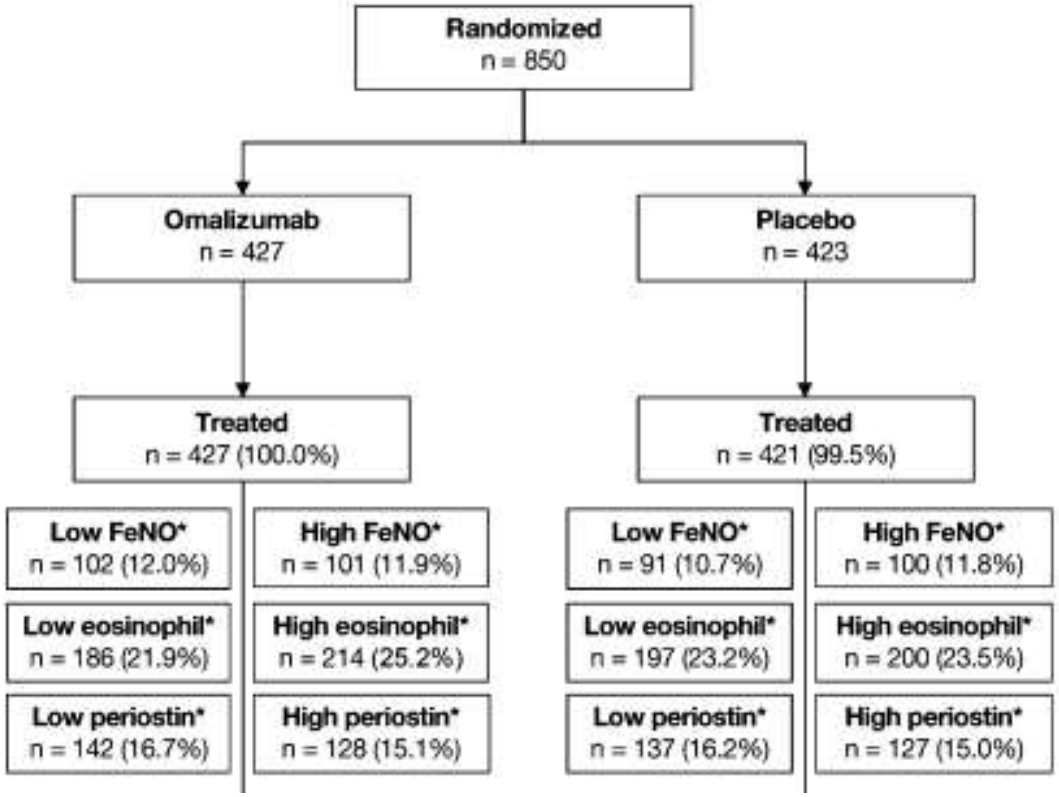
Exploring the Effects of Omalizumab in Allergic Asthma

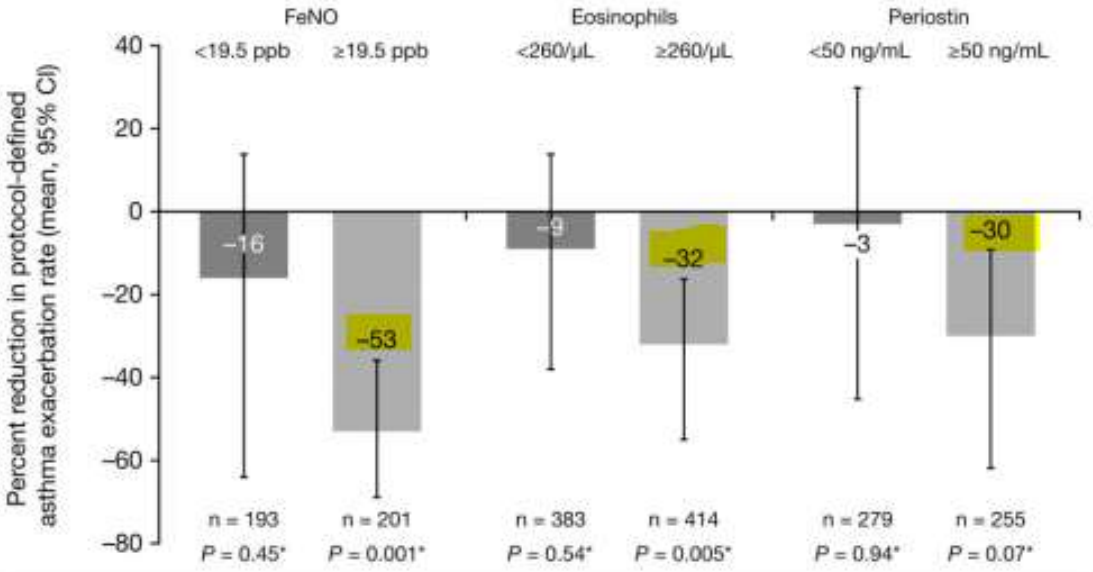
An Analysis of Biomarkers in the EXTRA Study

Nicola A. Hanania[1], Sally Wenzel[2], Karin Rosén[3], Hsin-Ju Hsieh[3], Sofia Mosesova[3], David F. Choy[3], Preeti Lal[3], Joseph R. Arron[3], Jeffrey M. Harris[3], and William Busse[4]

3 biomarker sub groups

1. FeNO -predefined <19.5 and ≥ 19.5 ppb
2. Peripheral eosinophilia <260 and ≥ 260 cells/microl
3. Serum periostin <50 and ≥ 50 ng/ml





Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Reduced the rate of asthma exacerbations -

FeNO (53% vs 16%)

Eosinophils (32% vs 9%)

Periostin (30% vs 3%) – not statistically significant

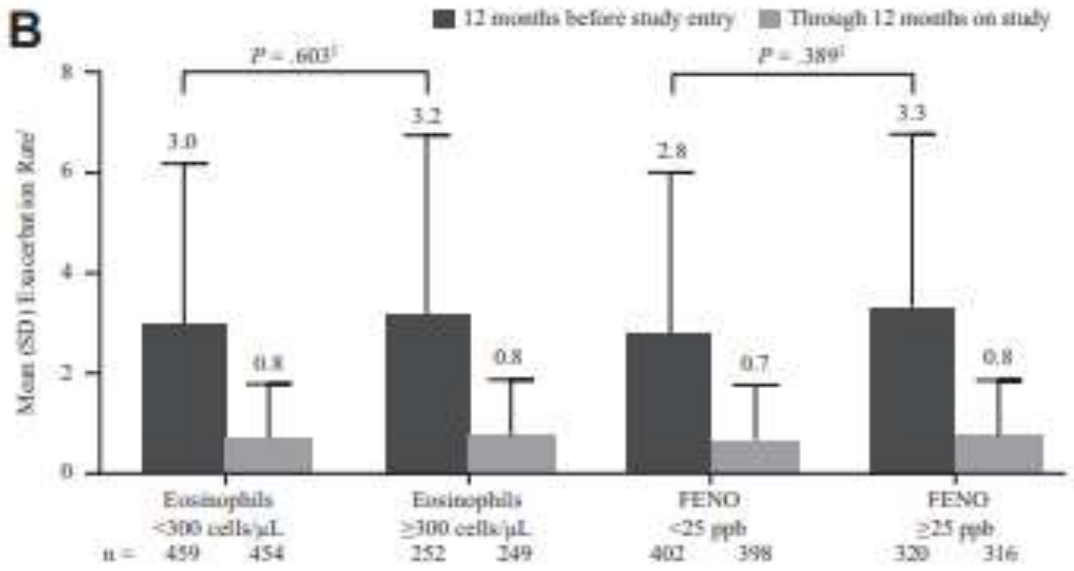
Original Article

Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study

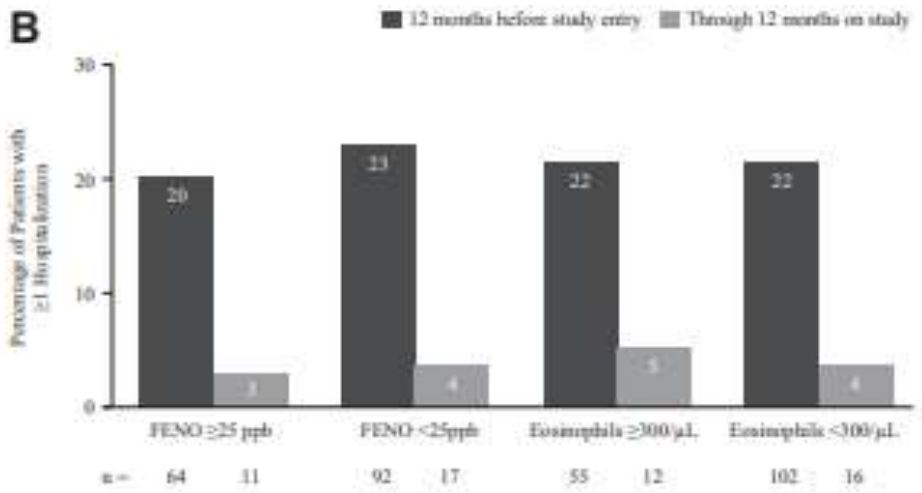
Thomas B. Casale, MD[a], Allan T. Luskin, MD[b], William Busse, MD[c], Robert S. Zeiger, MD, PhD[d,e], Benjamin Trzaskoma, MS[f], Ming Yang, PhD[f], Noelle M. Griffin, PhD[f,*], and Bradley E. Chipps, MD[g] *Tampa, Fla; Madison, Wis; and San Diego, Pasadena, South San Francisco, and Sacramento, Calif*

- Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab – 2019
- Multicenter, prospective, 48-week effectiveness study of omalizumab(n=801)

1. FeNO -<25 and ≥ 25 ppb
2. Peripheral eosinophilia <300 and ≥ 300 cells/microl



Decreased exacerbation rate irrespective of biomarker status



Decreased hospitalization irrespective of biomarker status

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

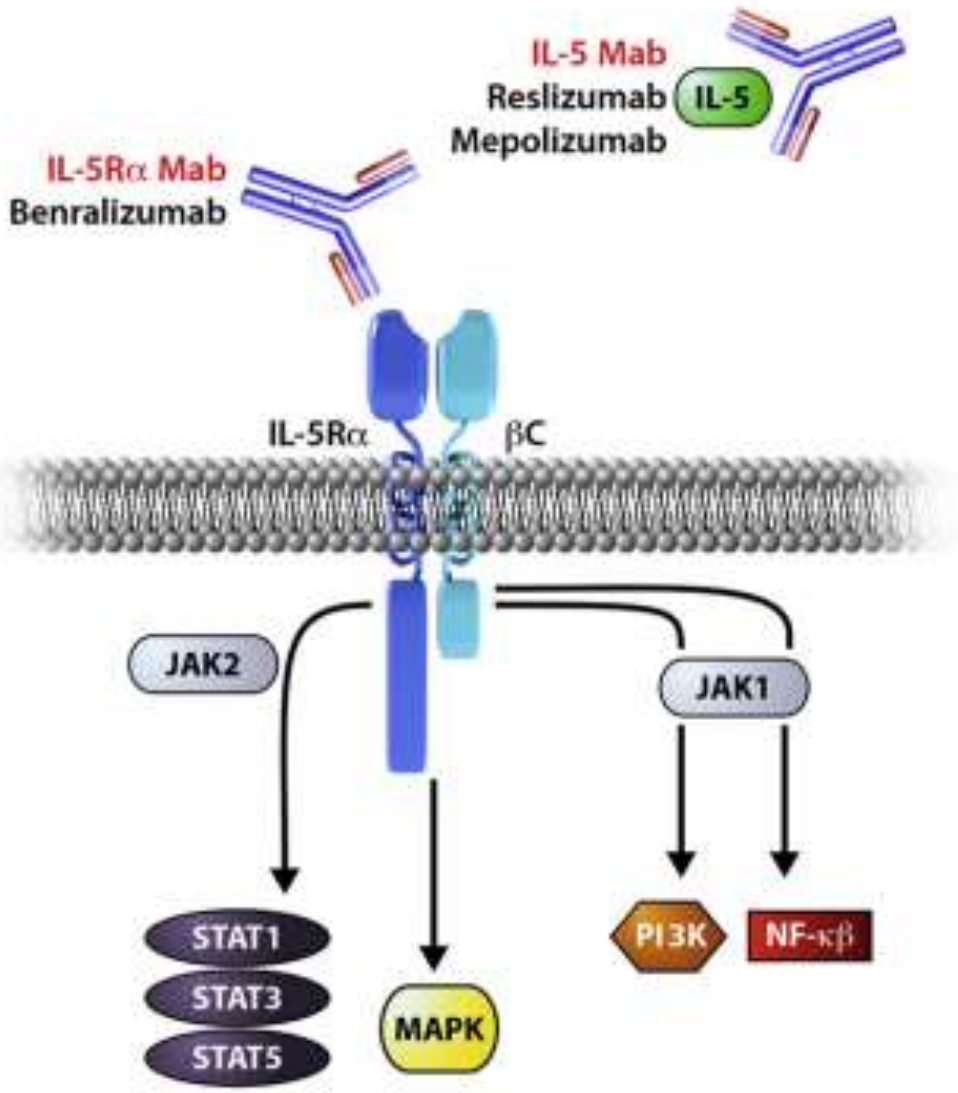
Cochrane Library
Cochrane Database of Systematic Reviews

- 25 RCTs involving 6382 patients of moderate to severe Asthma
- Treatment duration- 8- 60 weeks
- All studies compared Omalizumab versus placebo
- Results:
  - **Exacerbation**- 16 % v/s 26% over 16-60 wks
  - **Hospitalisations**- 0.5 % v/s 3% over 28-60 wks
  - **Reduction in ICS dosage-** 118 mcg BDP equivalent/day
  - No reduction in OCS dose
  - No significant change in in end of treatment FEV1

Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003559.

MEPOLIZUMAB

- Binds to IL-5 and prevents it binding to IL-5 receptor alpha chain on eosinophils and basophils
- Decreased maturation, migration and activation of eosinophils
- Leads to decreased blood and sputum eosinophils



Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

DREAM TRIAL (2012)	12-74 yrs with asthma on high dose ICS with 2 or more exacerbations in previous year and evidence of eosinophilic inflammation 1. Sputum eosinophil ≥ 3% 2. Feno ≥ 50% 3. AEC ≥ 300/µl 4. Prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids. Exclusion – smoker/ ≥ 10PY, parasitic infection	dose ranging study (75mg,250mg,750mg and placebo every 4weekly for 48 weeks) (154, 152, 156, 159) **Age – 50.2 vs 49.4 vs 48.6 vs 46.4** BMI – 28.4 vs 28.3 vs 28.9 vs 28.3 **FEV1 – 60% vs 59% vs 61% vs 59%** **AEC – 250 vs 230 vs 250 vs 280** **Sputum E – 13.9% vs 8.1% vs 5.8% vs 6.8%**	**Clinically significant asthma exacerbations**

Efficacy end points – 52 weeks

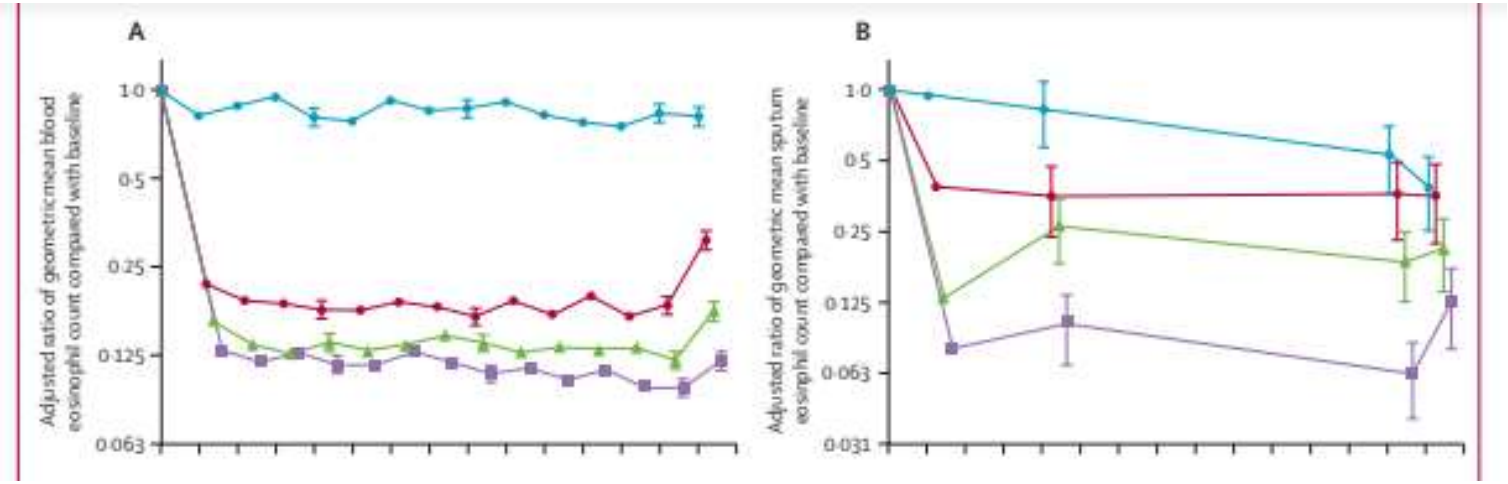
	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Rate of clinically significant exacerbations per patient per year*	2·40 (0·11)	1·24 (0·12)	1·46 (0·11)	1·15 (0·12)
Ratio to placebo	..	0·52 (0·39 to 0·69)	0·61 (0·46 to 0·81)	0·48 (0·36 to 0·64)
Rate of exacerbations requiring admission or visit to emergency department per patient per year*	0·43 (0·24)	0·17 (0·30)	0·25 (0·26)	0·22 (0·26)
Ratio to placebo	..	0·40 (0·19 to 0·81)	0·58 (0·30 to 1·12)	0·52 (0·27 to 1·02)
Rate of exacerbations requiring admission*	0·18 (0·29)	0·11 (0·35)	0·12 (0·32)	0·07 (0·39)
Ratio to placebo	..	0·61 (0·28 to 1·33)	0·65 (0·31 to 1·39)	0·37 (0·16 to 0·88)
Change in prebronchodilator FEV$_1$ from baseline (mL)†	60 (38)	121 (38)	140 (37)	115 (37)
Difference from placebo	..	61 (−39 to 161)	81 (−19 to 180)	56 (−43 to 155)

Exacerbation ratio with placebo

0.52 vs 0.61 vs 0.48

Change in FEV1
61 ml vs 81 ml vs 56 ml (not significant)

Change in sputum and blood eosinophils

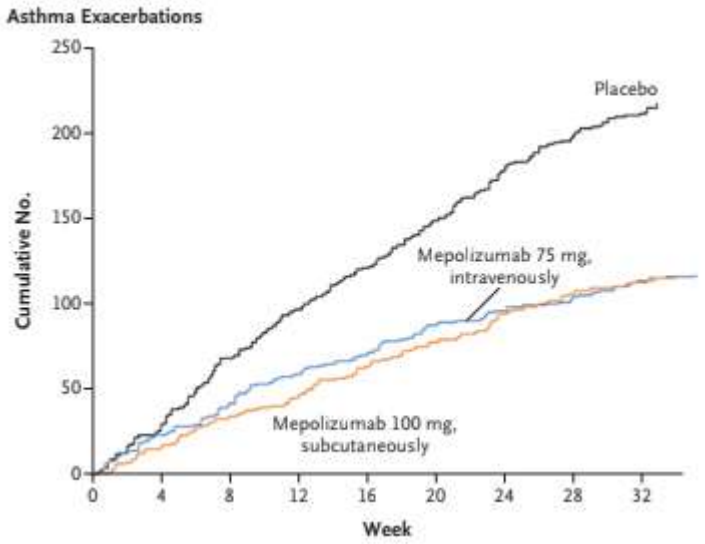


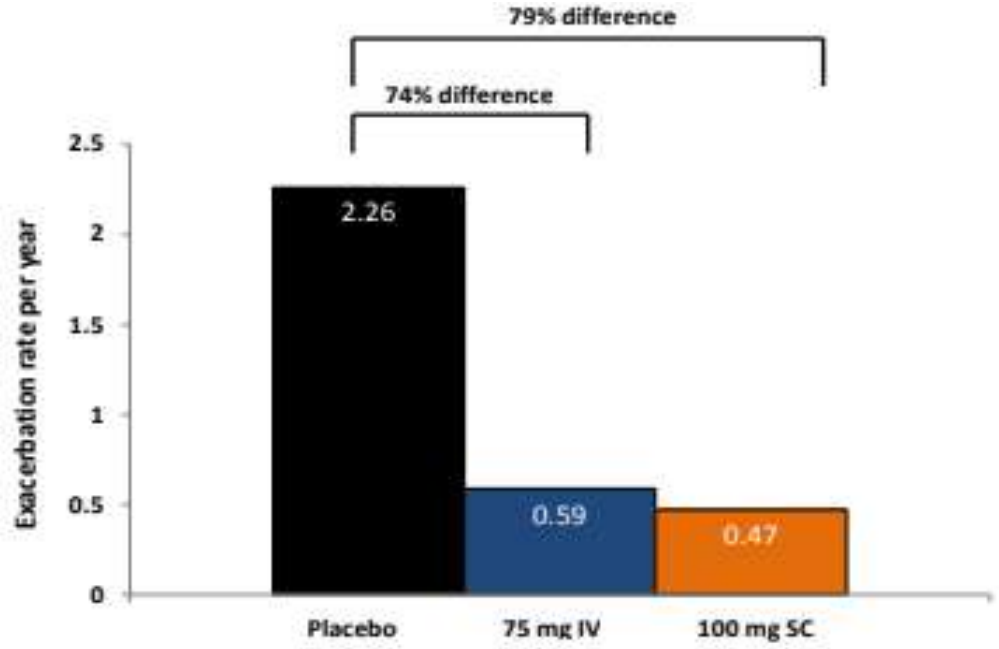
ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

MENSA TRIAL (2014)	**12-82 years on high-dose ICS (≥880 µg/day FP) and LABA ± OCS** **History of ≥ 2 exacerbations requiring systemic steroids** **Eosinophilic inflammation- Blood eosinophil ≥ 150/µl at screening or ≥ 300/µl at least once in last 1 yr**	**Placebo, 75mg intravenous, 100mg subcutaneous every 4 weekly for 32 weeks** (191 vs 191 vs 194) Age – 49 vs 50 vs 51 Female – 56 vs 55 vs 60 BMI – 28 vs 27.7 vs 27.6 Duration – 19.5 vs 19.8 vs 20.5 FEV1 – 62.4 vs 61.4 vs 59.3	**Clinically significant asthma exacerbations**

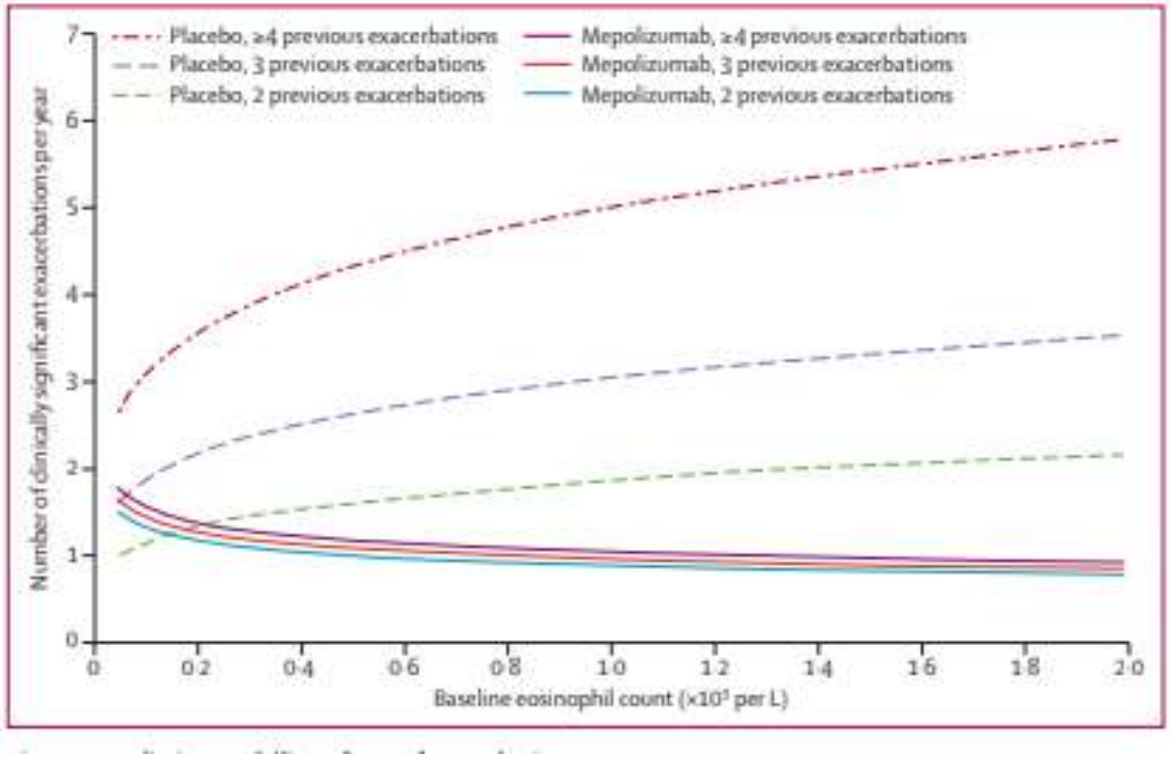


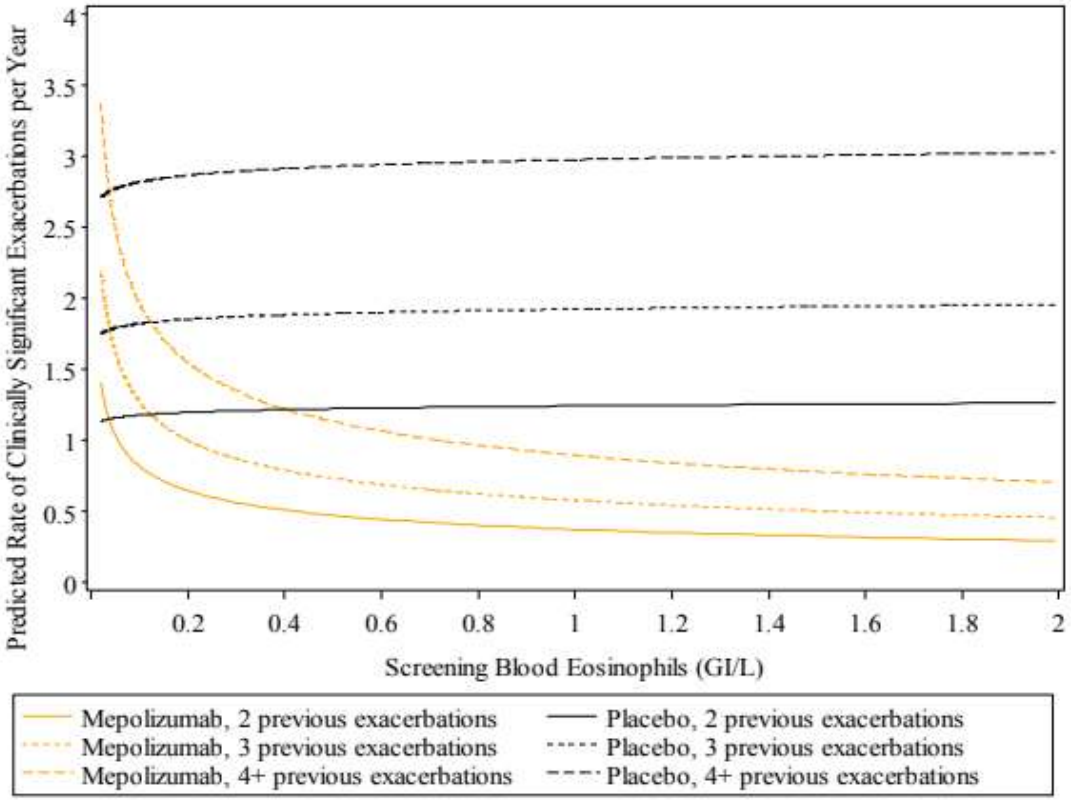


Rate of exacerbations reduced by
47% (28-60) – iv mepolizumab group
53%(36-65) – sc mepolizumab group

Subgroup analysis showed most effective in eosinophil count >500/microliter

Change in FEV1 is 100 ml in iv group vs 98 ml in sc group





Both DREAM and MESNA trail predictive modelling showed exacerbations has been decreased in patients with high eosinophil count and previous history of more exacerbations

THUS HIGH EOSINOPHIL COUNT AND HIGHER SEVERE EXACERBATIONS IN LAST YEAR STRONGLY PREDICTS THE GOOD RESPONSE TO TREATMENT

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

SIRIUS TRIAL (2014)	**6 months of maintenance OCS (5-35 mg prednisolone)** **Eosinophilic inflammation- Blood eosinophil ≥ 150/µl at screening or ≥ 300/µl at least once in last 1 yr**	**Mepolizumab arm 100mg s.c once 4 wk until week 20 (69) vs placebo (66)** Age – 50 vs 50 Female – 64% vs 45% BMI – 27.8 vs 29.5 Duration – 17.4 vs 20.1 **Median OCS – 15 vs 12.5** FEV1 – 63 vs 61 IgE – 117 vs 114 **AEC – 250 vs 230**	**Clinically significant asthma exacerbations**

- Showed that patients with mepolizumab where able to reduce CS dosage by 50%
- 14% discontinued OCS completely

Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

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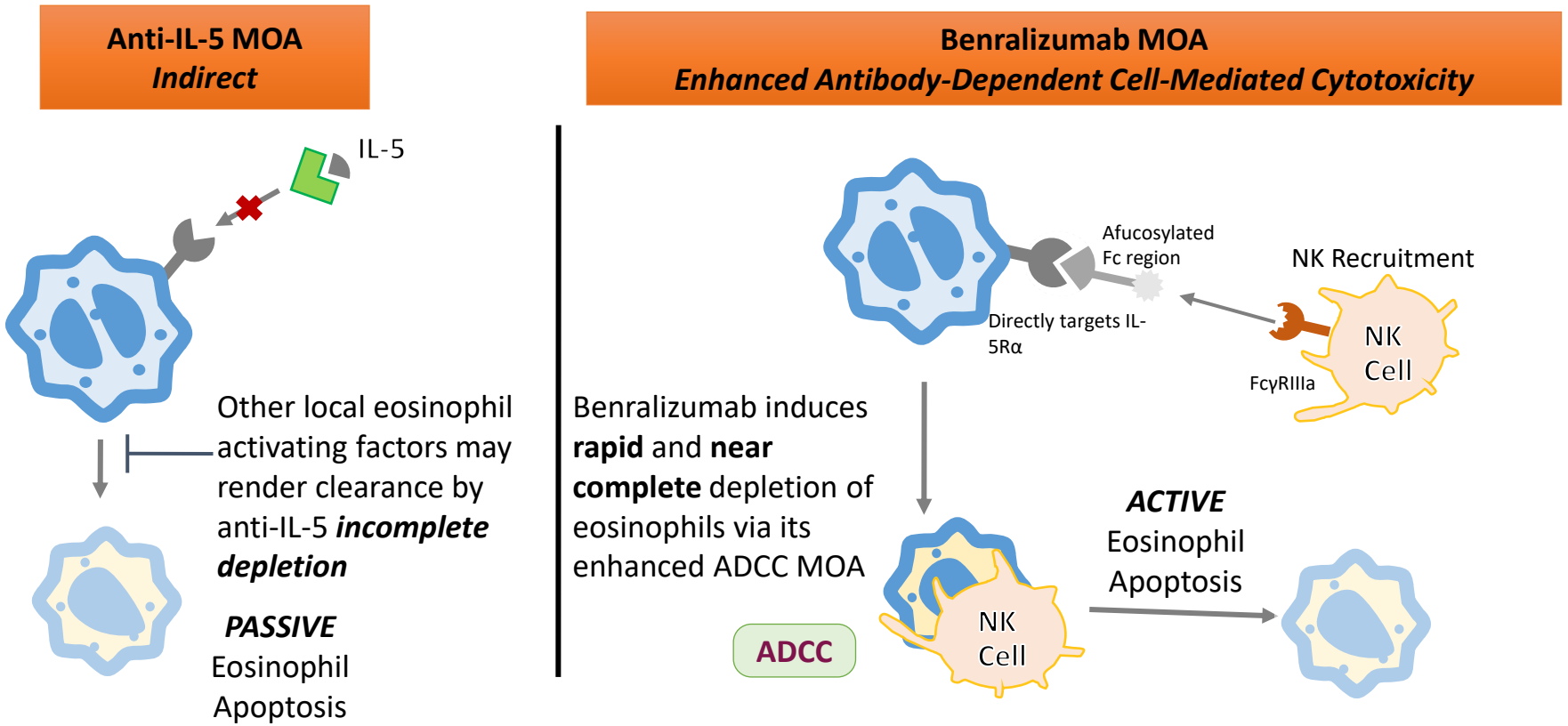
Anti-IL-5 therapies for asthma (Review)

- Included six studies involving a total of 2294 participants
- 2 studies with s.c mepolizumab (n=936) Reduction in clinically significant asthma exacerbations compared to placebo - rate ratio 0.45 (0.36 - 0.55)
- stopping mepolizumab - shorter time to clinically significant exacerbations hazard ratio 1.61(1.17 - 2.22)
- 3 studies (n=1231) pre bronchodilator FEV1 mean difference 0.09L (0.05 to 0.14)
- Found blood eosinophil count decreased by week 4 and 86% decreased by week 12 and is maintained through out the study and stopping results in increase of counts

BENRALIZUMAB

- Humanized, afucosylated against IL-5 receptor α -> Antibody dependent cell mediated **depletion** of eosinophils through NK cells (Unlike mepolizumab which acts passively and reduces the eosinophils)

Mechanism of action of anti IL- 5 therapies



Patterson MF et al. *J Asthma Allergy*. 2015;8:125-134;
Busse WW eal. In: Lee JJ, Rosenberg HF, eds. *Eosinophils in Health and Disease*. London, UK: Academic Press; 2013: 587-591;
Flood-Page P et al. *Am J Respir Crit Care Med.* 2003;167:199-204;

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

SIROCCO TRAIL (2016)	12-75 yr, poorly controlled asthma on medium to high dose ICS-LABA History of $\geq$ 2 exacerbations in last year requiring systemic steroids/increase in dose FEV1 <80%	**Placebo, Benralizumab 30mg every 4 wks, 8 wks (1st 3 doses 4 weekly) for 48 wks (407, 399, 398)** Age – 48.7 vs 50.1 vs 47.6 Female – 66% vs 69% vs 63% BMI – 28.9 vs 29.2 vs 28.2 **Median OCS – 15 vs 12.5** FEV1 – 56.6% vs 57.4% vs 56.1% **AEC – 350 vs 360 vs 325**	**Annual exacerbation rate, FEV1 change**

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

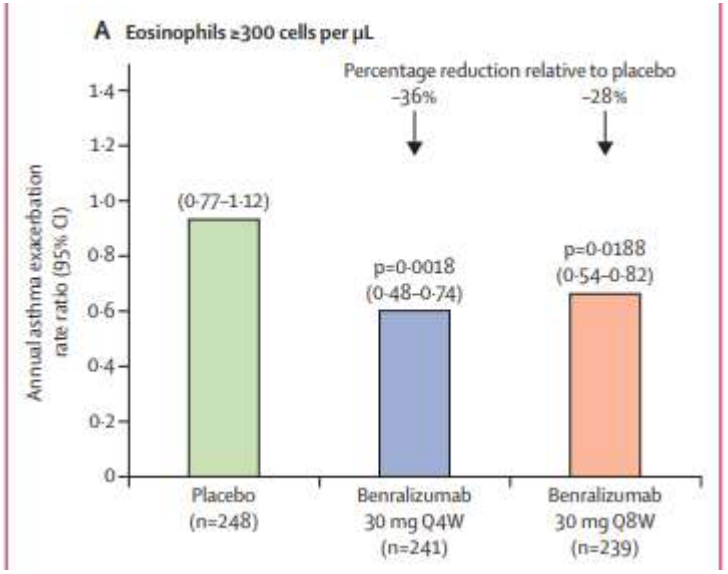
Dr J Mark FitzGerald, MD [a] · Prof Eugene R Bleecker, MD [b] · Prof Parameswaran Nair, MD [c] · Stephanie Korn, MD [d] · Ken Ohta, MD [e] · Prof Marek Lommatzsch, MD [f] · et al. Show more

CALIMA TRIAL (2016)	12-75 yr, poorly controlled asthma on med- high ICS-LABA (≥250µg of FP) for >12 m before enrolment or >3 m of ≥500µg of FP before enrolment History of ≥ 2 exacerbations requiring systemic steroids FEV1 <80% 2 groups: Blood eosinophil ≥ 300/µL, <300/µl	**Placebo, Benralizumab 30mg every 4 wks, 8 wks (1st 3 doses 4 weekly) for 48 wks (440, 425, 441)** Age – 48.8 vs 50 vs 49 Female – 60% vs 64% vs 62% BMI – 28.9 vs 28.7 vs 28.8 **Median OCS – 15 vs 12.5** FEV1 – 58% vs 58.9% vs 57.9% **AEC – 371 vs 370 vs 400** **Duration – 16.2 vs 15.8 vs 16.8 yrs**	**Annual exacerbation rate, FEV1 change**

SIROCCO trail (lancet 2016)

Results:

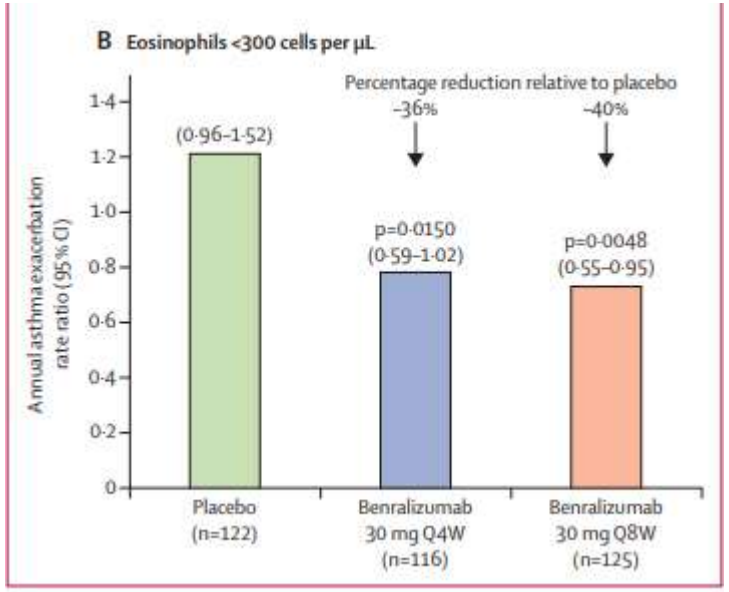
- Both groups reduced AER- 0.55 & 0.49 for 4 wkly and 8 wkly regimen.
- Both groups improved FEV1-106ml & 159ml for 4 wkly and 8 wkly regimen.



CALIMA trial (Lancet 2016)

Results:

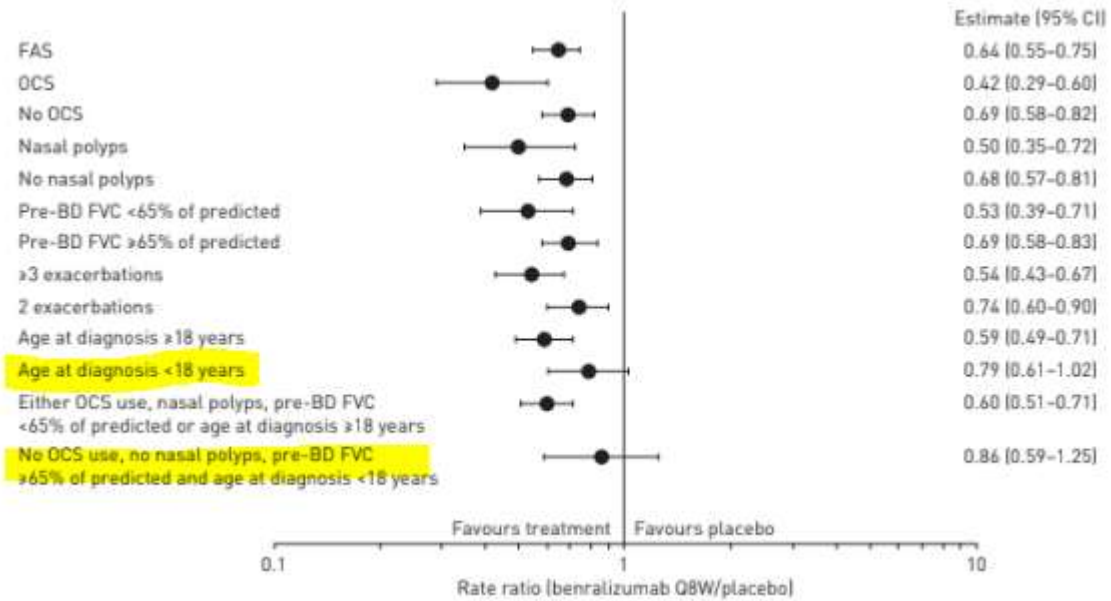
- Both groups reduced AER- 0.60 & 0.66 for 4 wkly and 8 wkly regimen.
- Both groups improved in 4 wkly and 8 wkly regimen.
- AER and FEV1 improvement is significant in patients with ≥300cells/µL

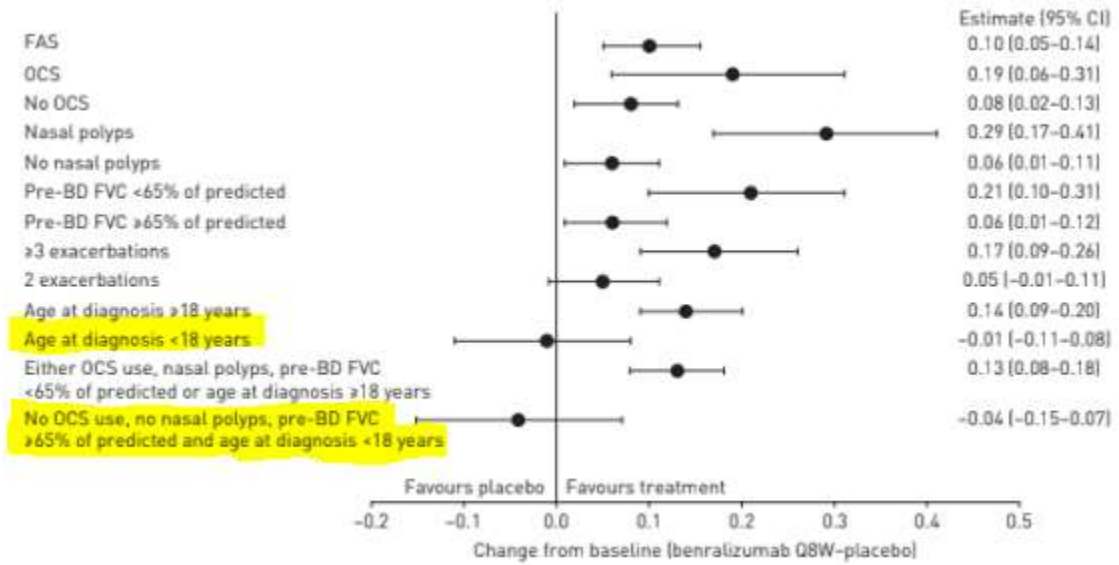


Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma

Eugene R. Bleecker[1], Michael E. Wechsler[2], J. Mark FitzGerald[3], Andrew Menzies-Gow[4], Yanping Wu[5], Ian Hirsch[5], Mitchell Goldman[5], Paul Newbold[6] and James G. Zangrilli[5]

Eur Respir J 2018; 52: 1800936





On exacerbations

On change in FEV1

ORIGINAL ARTICLE

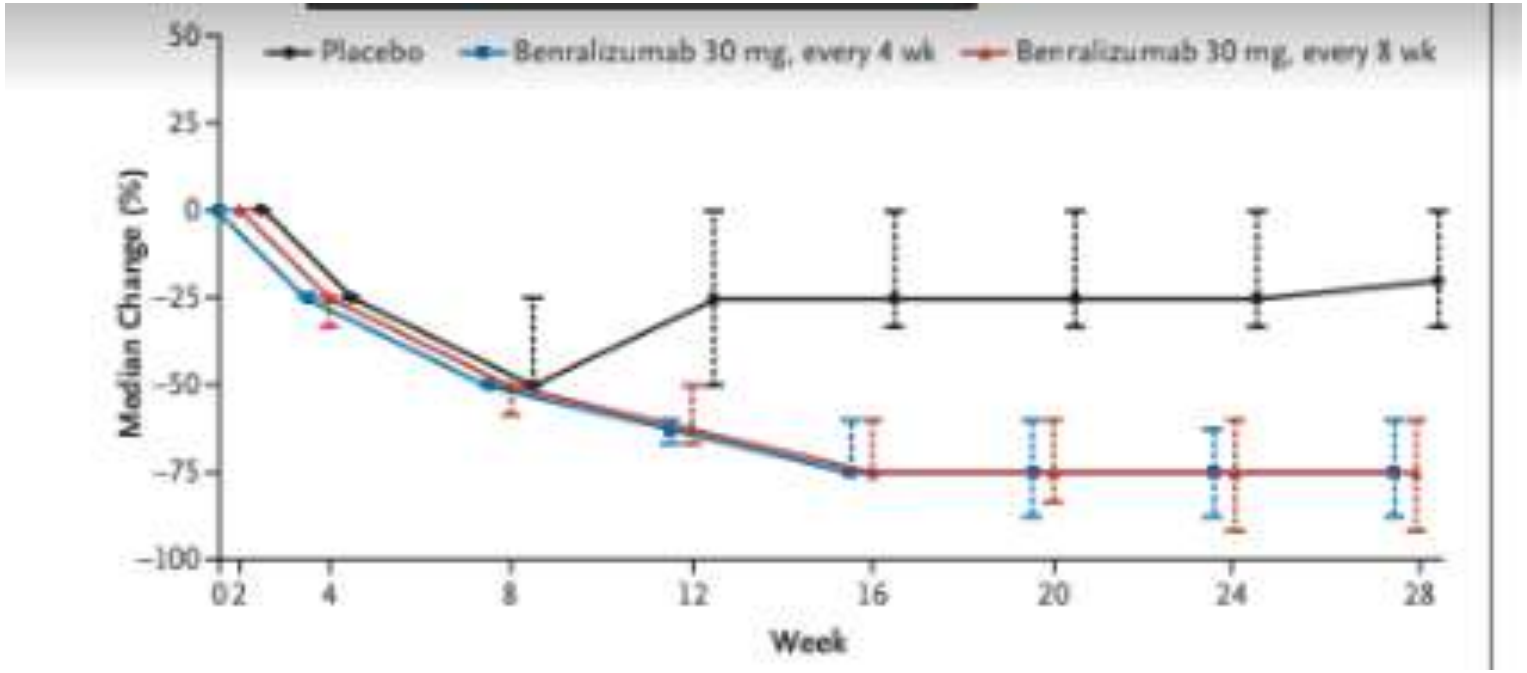
Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

ZONDA TRIAL

- This randomized, double-blind, parallel-group, placebo-controlled trial
- Patients received oral glucocorticoids for at least 6 months and were adjusted to minimal dose to prevent asthma control before randomization
- Inclusion – AEC >150 cells/microL, Uncontrolled asthma on medium to high dose ICS + LABA
- Benralizumab 30 mg Q4W vs Q8W(first 3 doses Q4W)
- Outcome – Primary is reduction in median oral GC dose at 28 weeks

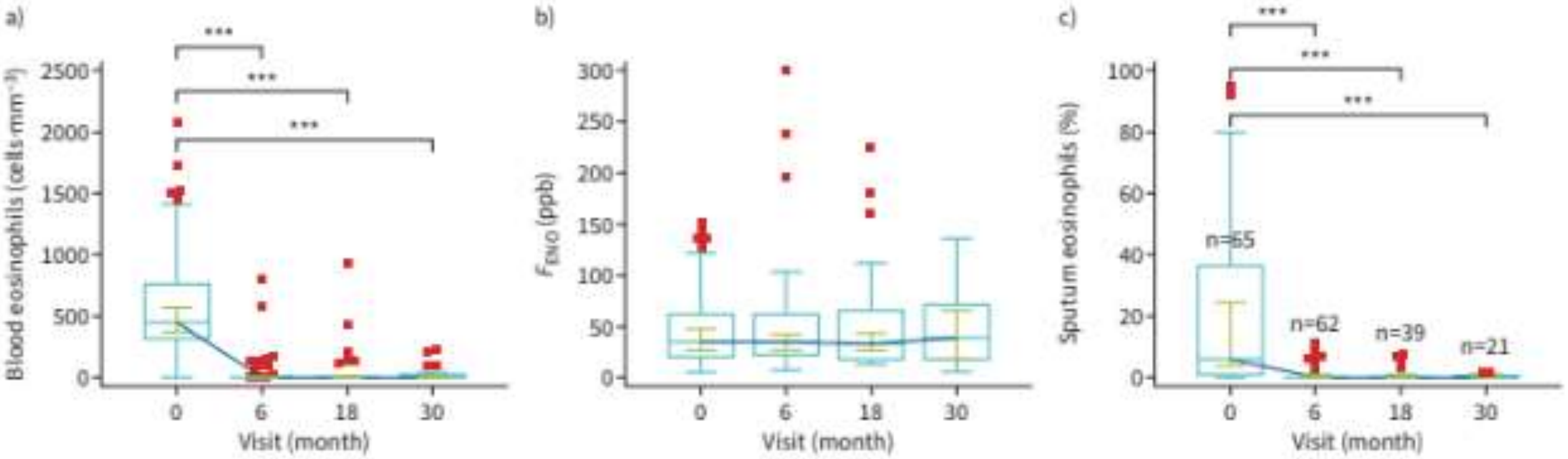
- Median reduction of GC dose from baseline - 25% in placebo vs 7% in each Q4W and Q8W groups
- 100% reduction seen in 19% VS 56% VS 52%



Benralizumab in severe eosinophilic asthma in real life: confirmed effectiveness and contrasted effect on sputum eosinophilia *versus* exhaled nitric oxide fraction – PROMISE

ERJ OPEN RESEARCH
ORIGINAL RESEARCH ARTICLE
F. SCHLEICH ET AL

- Prospective follow up study of 73 patients which were followed for 30 months
- AEC>300 cells/µL with at least 2 exacerbations in last 12 months and FEV1<80%
- Study showed >50% reduction in exacerbation rate and also >50% reduction in maintenance corticosteroid dose consistent to precious studies
- Benralizumab as expected had marked reduction of sputum eosinophil count but with no significant change in FeNO



In this study 81% of participants discontinued benralizumab by 6 months – they didn't have any reduction in exacerbation and didn’t have reduction in OCS dose by half

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Anti-IL-5 therapies for asthma (Review)

- Included five studies involving a total of 3304 participants
- 4 studies (n=3112) Reduction in clinically significant asthma exacerbations compared to placebo - rate ratio 0.59 (n=0.52 – 0.66)
- 4 studies (n=2786) pre bronchodilator FEV1 mean difference 0.11L (0.08L to 0.15L)
- 2 studies (n=2295) mean reduction in blood eosinophils 104 (93 – 116 cells/µL)

Reslizumab

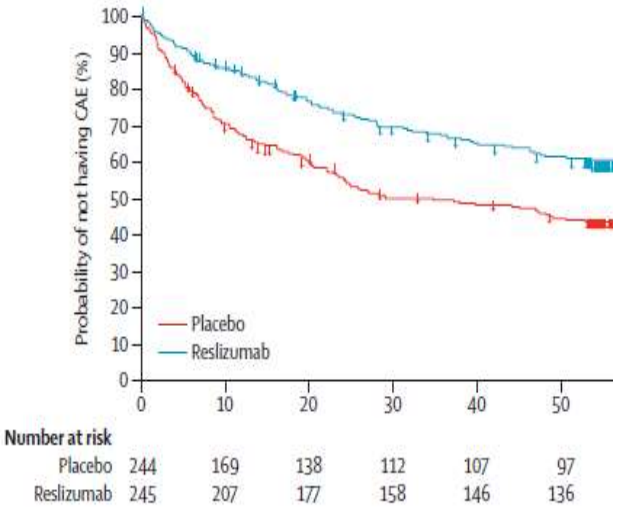
- Reslizumab is a high-affinity, humanized anti-interleukin IL-5 monoclonal (IgG4/k) antibody, which inhibits activity within the IL5 signalling pathway by reducing ligand-receptor interactions and reduces blood and tissue eosinophils in patients with asthma

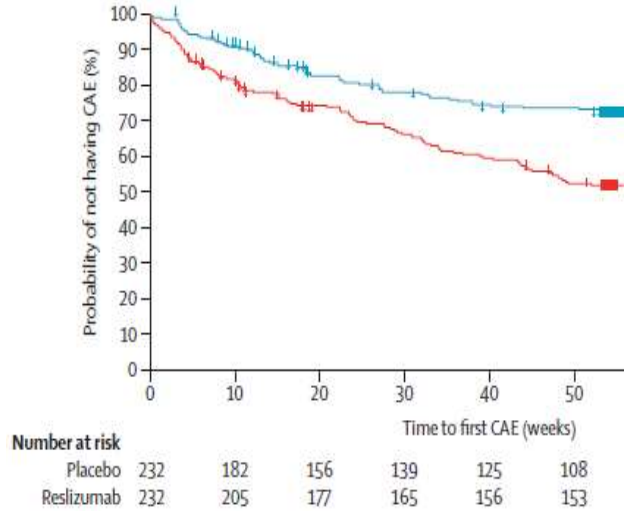
Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

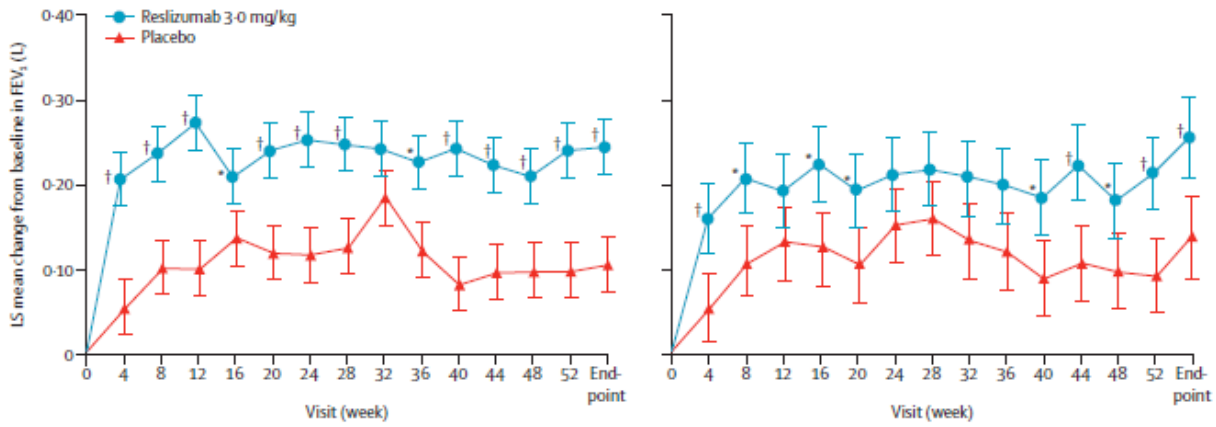
Prof Mario Castro, MD [a] · James Zangrilli, MD [b] · Prof Michael E Wechsler, MD [c] · Prof Eric D Bateman, MD [d] · Prof Guy G Brusselle, MD [e] · Prof Philip Bardin, MD [f] · et al. Show more

Castro et al 2015 (2 Studies)	12-75 yr, poorly controlled asthma on medium-high ICS(≥ 400µg/day) Duration- 1 year History of ≥ 1 exacerbations requiring systemic steroids Eosinophilic inflammation- At least eosinophil ≥ 400/µL during 2-4 week screening	**Placebo vs** IV Reslizumab (3mg/kg) every 4 weeks(13 doses) **(244 & 232 vs 245 & 232)** Age – 49 & 48 vs 48 & 48 Female – 66% & 65% vs 65% vs 62% BMI – 28 & 27 vs 27.7 vs 27 **Mean ICS – 442.1 & 274.2 vs 380.3 & 588.4** FEV1 – 65% & 68% vs 63.6% vs 70.4% **AEC – 624 & 688 vs 696 & 610**	**Annual exacerbation rate, FEV1 change**

- **Conclusion:** Reslizumab group had higher probability of not having exacerbations in both studies compared with placebo.
- Study 1- 61% v/s 44%, Study 2- 73% v/s 52%.
- study 1: rate ratio, 0.50 [95% CI, 0.37-0.67]; study 2: rate ratio, 0.41 [95% CI, 0.28-0.59]







[Original Research Asthma]

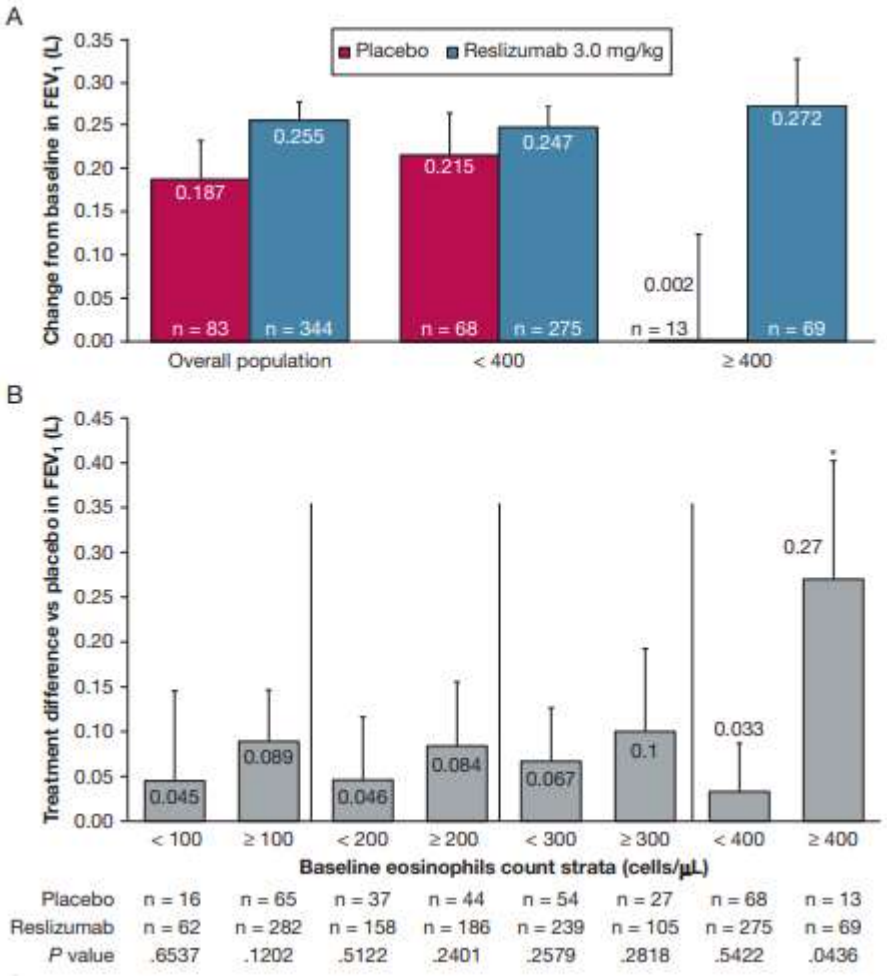
CHEST

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma

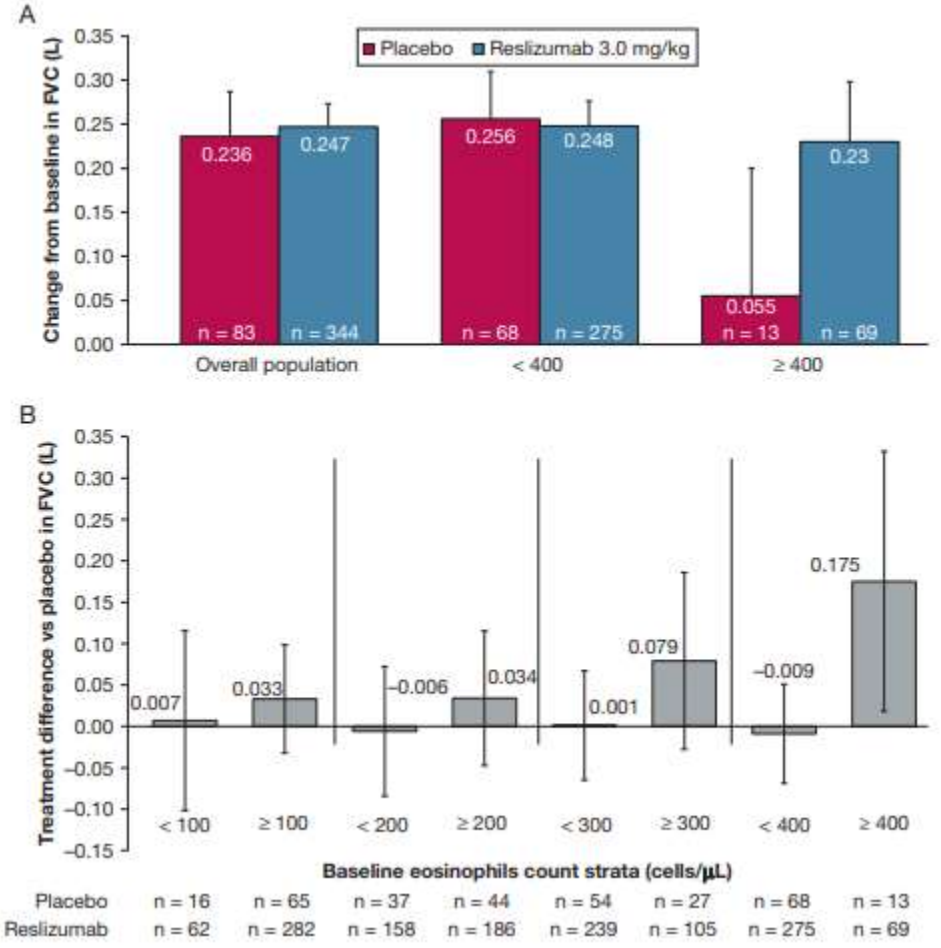
Effects Across a Broad Range of Eosinophil Counts

Jonathan Corren, MD; Steven Weinstein, MD; Lindsay Janka, MS; James Zangrilli, MD; and Margaret Garin, MD

Corren et al (2016)	**18 - 65 years with severe uncontrolled asthma despite on medium dose ICS(≥440µg FP)** No eosinophil cut off and no limit of FEV1	randomly assigned (4:1) to reslizumab 3.0 mg/kg or placebo given intravenously once every 4 weeks(398 and 98 patients respectively) 4 doses Age – 44.9 vs 45.1 Female – 66% vs 55% BMI – 32.3 vs 31.6 **Mean ICS – 615.7 vs 627.8** FEV1 – 66.8% vs 66.5% **AEC – 281 vs 877**	**FEV1 change**



Change in FEV1



Change in FVC

Significant improvement in lung function among patients with eosinophils ≥ 400 cells/µL

Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils

Guy Brusselle [a,*], Matthew Germinaro [b], Sivan Weiss [c], James Zangrilli [b]

[a] Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[b] Teva Pharmaceuticals, Frazer, PA, USA
[c] Teva Pharmaceutical Industries Ltd., Netanya, Israel

CrossMark

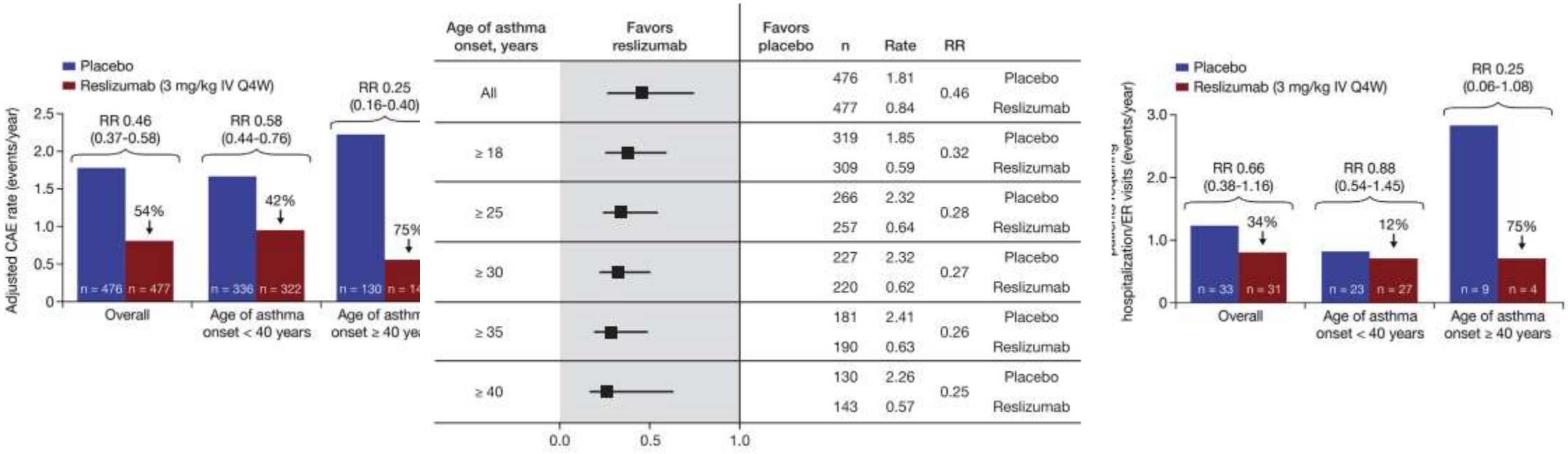
ELSEVIER

- Post hoc analysis of 2 Randomized (1:1 ratio), placebo-controlled, double-blind studies on late onset asthma
- Post hoc analysis is done with strong rationale that presence of different endotypes of eosinophilic asthma based on age of onset
- Reslizumab (3 mg/kg) or placebo administered IV Q4W for 52 weeks
- Patients 12-75 years with inadequately controlled asthma with eosinophils >400 cells/µL
- Outcomes - Frequency of clinical asthma exacerbations, Changes in FEV1

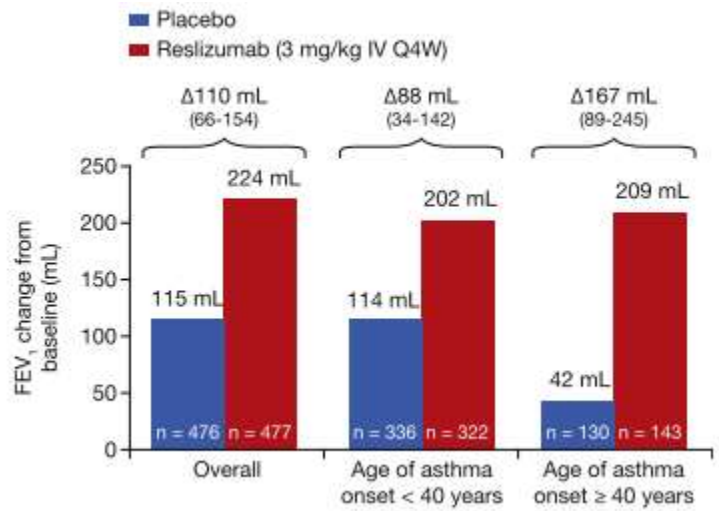
Patient demographics and baseline disease characteristics by age of asthma onset.

	Age of onset <40 years (n = 658)	Age of onset ≥40 years (n = 273)
Age, years, mean (SD)	42 (13)	58 (7)
Male, %	36	41
BMI, kg/m^2, mean (SD)	27.3 (5.9)	27.9 (5.3)
ICS[a] plus LABA, n (%)	545 (83)	221 (81)
Geographical location, n (%)		
USA	86 (13)	18 (7)
Europe	280 (43)	167 (61)
Asia	103 (16)	52 (19)
Other	189 (29)	36 (13)
OCS, n (%)	98 (15)	44 (16)
FEV_1 (L), mean (SD)	2.06 (0.79)	1.84 (0.64)
FEV_1% predicted, mean (SD)	66.5 (2.1)	67.8 (18.7)
ACQ6 score, mean (SD)	2.50 (0.93)	2.46 (0.87)
AQLQ score, mean (SD)	4.27 (1.10)	4.20 (1.02)
ASUI score, mean (SD)	0.65 (0.20)	0.62 (0.19)
Blood eosinophils, cells/μL		
Mean, SD	667 (693)	637 (467)
Median	500	500
Allergic disease by history[b], n (%)	438 (67)	134 (49)
Atopy (specific IgE)[c], n (%)	231 (69)	54 (41)
Chronic sinusitis + nasal polyps[d], n (%)	89 (14)	60 (22)
Number of exacerbations in previous 12 months mean (SD)	1.97 (1.82)	1.99 (1.99)

- Early-onset asthma - driven by atopy - type 2 cytokine expression (including IL-5) with consequential eosinophilia
- Late-onset asthma - the exogenous causes are largely unknown, although some environmental stimuli such as oxidants, microbes - airway epithelial cells - secrete cytokines that activate innate lymphoid type 2 (ILC2) cells to produce IL-5 in an allergen-independent manner
- Also increased number of ILC2 cells producing IL 5 have been found in LO asthma and patients with chronic sinusitis and nasal polyps despite treatment with OCS suggesting ILC2 cells are resistant



Exacerbation-prone, LO asthma with elevated blood eosinophil levels (>400 cells/mL) and inadequately controlled symptoms responded well



Change in FEV1

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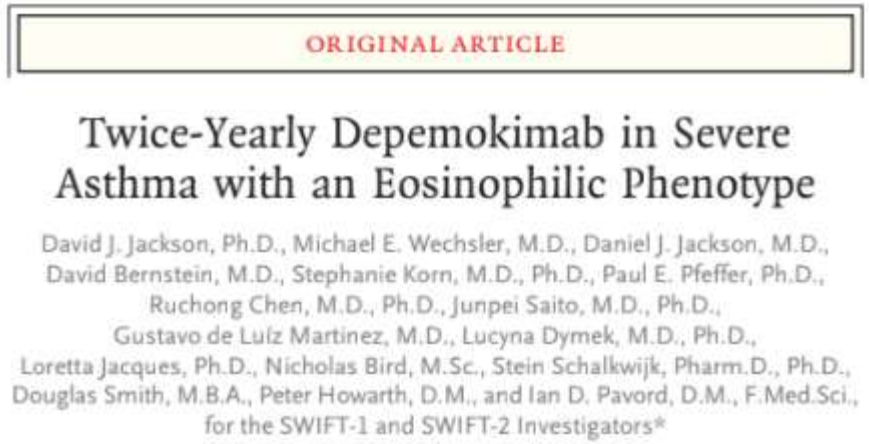
Anti-IL-5 therapies for asthma (Review)

- Included 4 studies (n=1652)
- 2 studies (n=953) reduction in clinically significant exacerbation rate ratio 0.43 (0.33 to 0.55)
- 4 studies (n=1652) pre bronchodilator FEV1 mean difference is 110 ml (70 ml – 150 ml)
- 4 studies (n=1652) Eosinophils mean difference is -476 cells (-499 – -454)



ORIGINAL ARTICLE

Twice-Yearly Depemokimab in Severe Asthma with an Eosinophilic Phenotype

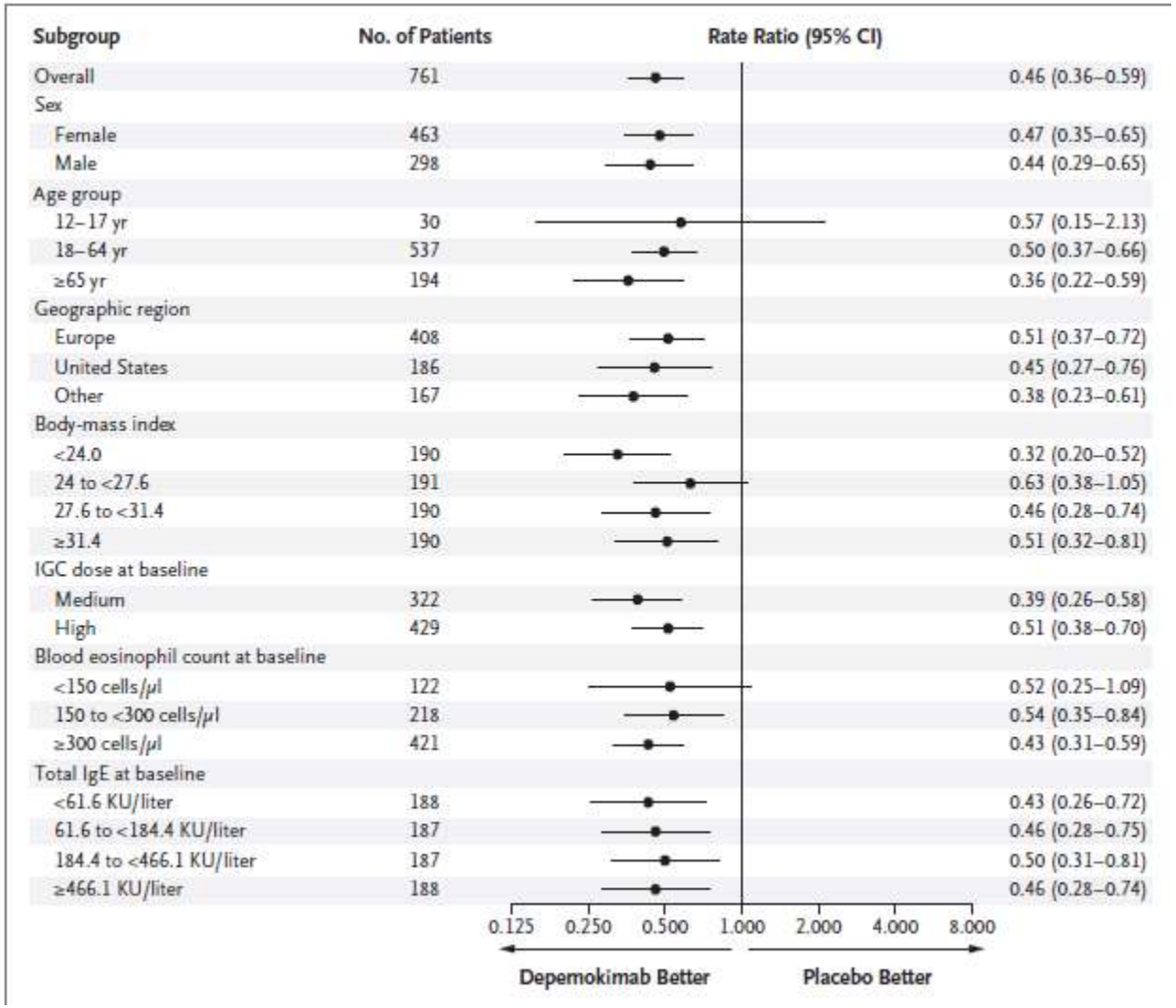
David J. Jackson, Ph.D., Michael E. Wechsler, M.D., Daniel J. Jackson, M.D., David Bernstein, M.D., Stephanie Korn, M.D., Ph.D., Paul E. Pfeffer, Ph.D., Ruchong Chen, M.D., Ph.D., Junpei Saito, M.D., Ph.D., Gustavo de Luiz Martinez, M.D., Lucyna Dymek, M.D., Ph.D., Loretta Jacques, Ph.D., Nicholas Bird, M.Sc., Stein Schalkwijk, Pharm.D., Ph.D., Douglas Smith, M.B.A., Peter Howarth, D.M., and Ian D. Pavord, D.M., F.Med.Sci., for the SWIFT-1 and SWIFT-2 Investigators*

- ultra-long-acting biologic therapy with enhanced binding affinity for interleukin-5 - 6-month dosing

SWIFT 1 & 2 (2024)	12-75 yr, poorly controlled asthma on medium-high ICS(≥ 400µg/day) > 2yrs History of ≥ 2 exacerbations requiring systemic steroids Eosinophilic inflammation- At least eosinophil ≥ 300/µl in last 12 months or at least 150/µl at screening FEV1 ≤ 80%	Depemokimab 100 mg s.c at week 0 and week 26 vs placebo (250 & 252 vs 132 & 128) Age – 54.1 & 53.6 vs 53.6 & 51.2 Female – 58% & 63% vs & 60 % vs 63% FEV1 – 56.6% vs 57.4% vs 56.1% **AEC – 298 & 339 vs 310 & 330**	**Annual exacerbation rate, FEV1 change**

End Point	SWIFT-1			SWIFT-2			Pooled Trials	
	Depemokimab (N=250)	Placebo (N=132)	P Value†	Depemokimab (N=252)	Placebo (N=128)	P Value†	Depemokimab (N=502)	Placebo (N=260)
Primary end point								
Annualized rate of exacerbations at 52 wk (95% CI)	0.46 (0.36 to 0.58)	1.11 (0.86 to 1.43)	<0.001	0.56 (0.44 to 0.70)	1.08 (0.83 to 1.41)	<0.001	0.51 (0.43 to 0.60)	1.11 (0.92 to 1.33)
Rate ratio (95% CI)	0.42 (0.30 to 0.59)			0.52 (0.36 to 0.73)			0.46 (0.36 to 0.59)	
Percent between-group difference in annual rate (95% CI)	58 (41 to 70)			48 (27 to 64)			54 (41 to 64)	
No. of exacerbations‡	120	150		153	167		273	317

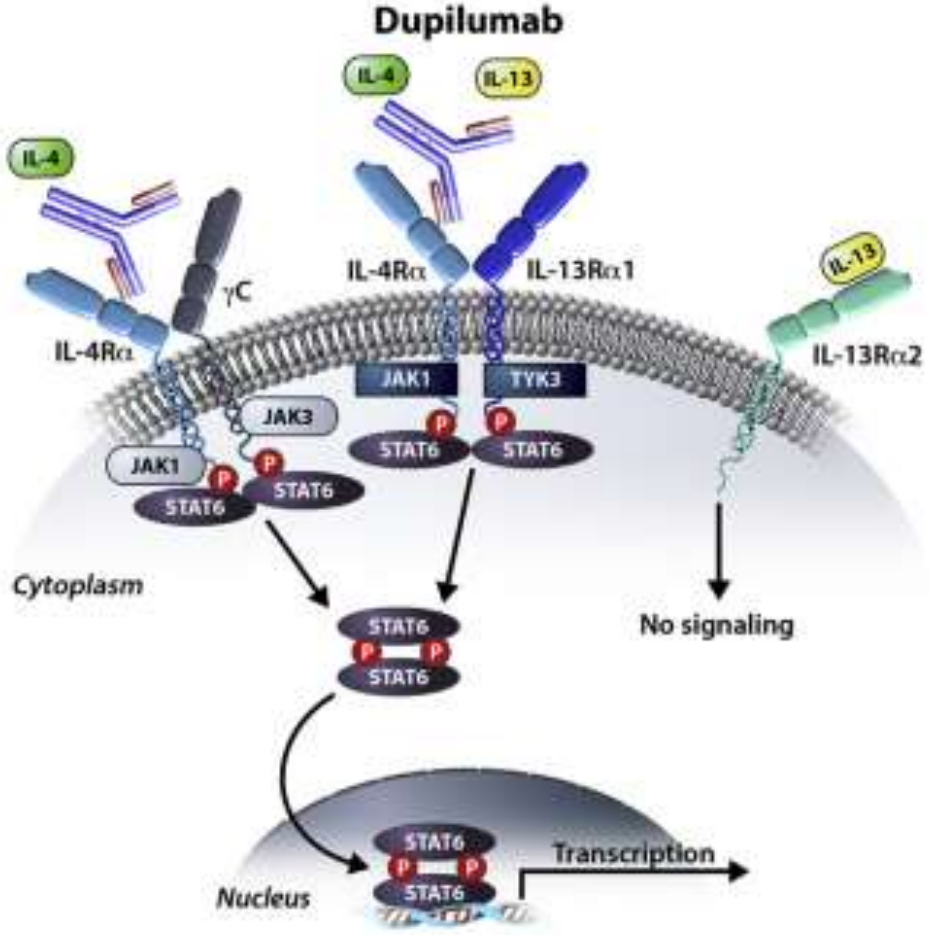
- Reduced exacerbation risk by 54%



- Can work at any levels of IgE, Eosinophil >150
- Also found to have increased time to exacerbation in both SWIFT 1 and SWIFT 2 with hazard ratio – 0.56 (95% CI, 0.40–0.79) and 0.53 (95% CI, 0.38–0.74)

DUPILUMAB

- Dupilumab is a fully humanized monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, which are key and central drivers of type 2 inflammation
- Labelled Indications:
- As an **add-on maintenance** treatment in patients with **moderate-to-severe asthma** aged 12 years and older with an **eosinophilic phenotype** or with oral corticosteroid dependent asthma
- Atopic dermatitis
- Chronic Rhino sinusitis with nasal polyposis



Liberty asthma quest

ORIGINAL ARTICLE

N Engl J Med 2018;378:2486-96.

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

Castro et al	12-75 yr, poorly controlled asthma on medium to high ICS-LABA**(≥500µg FP)** Pre BD FEV1 - <80% History of ≥ 1 exacerbations requiring systemic steroids No eosinophil cut off	Dupilumab 200 mg vs placebo 300mg Vs placebo every 2 wks(2:1:2:1) Duration- 52 weeks Age – 47.9 vs 48.2 & 47.7 vs 48.2 FEV1 – 58.3% vs 58.4% & 58.5 vs 58.3	Annual exacerbation rate, FEV1 change

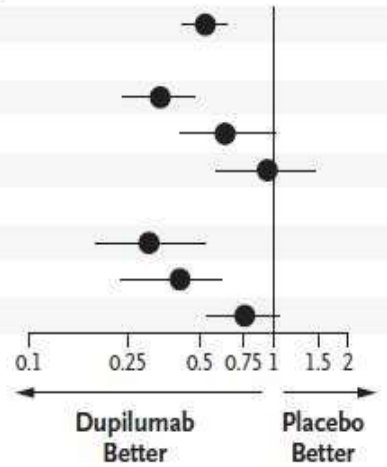
Adjusted AER reduced 47.7% among 200 mg when compared to placebo and 46% among 300 mg when compare to placebo

Among patients with Eosinophils ≥300 cells/µL higher reduction in exacerbations

FEV1 increased by 320 ml vs 180 ml in 200 mg at 12 wks
340 ml vs 210 ml in 300 mg

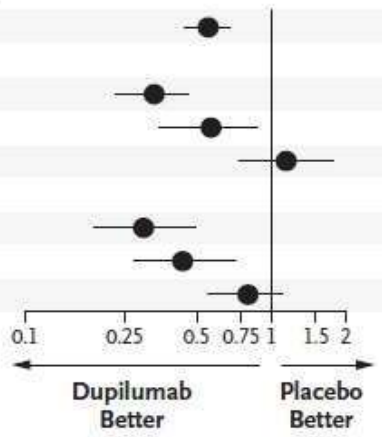
.

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



Dupilumab, 200 mg every2wk

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Dupilumab, 300 mg every2wk

Liberty asthma venture

ORIGINAL ARTICLE
N Engl J Med 2018;378:2475-85.
DOI: 10.1056/NEJMoa1804093

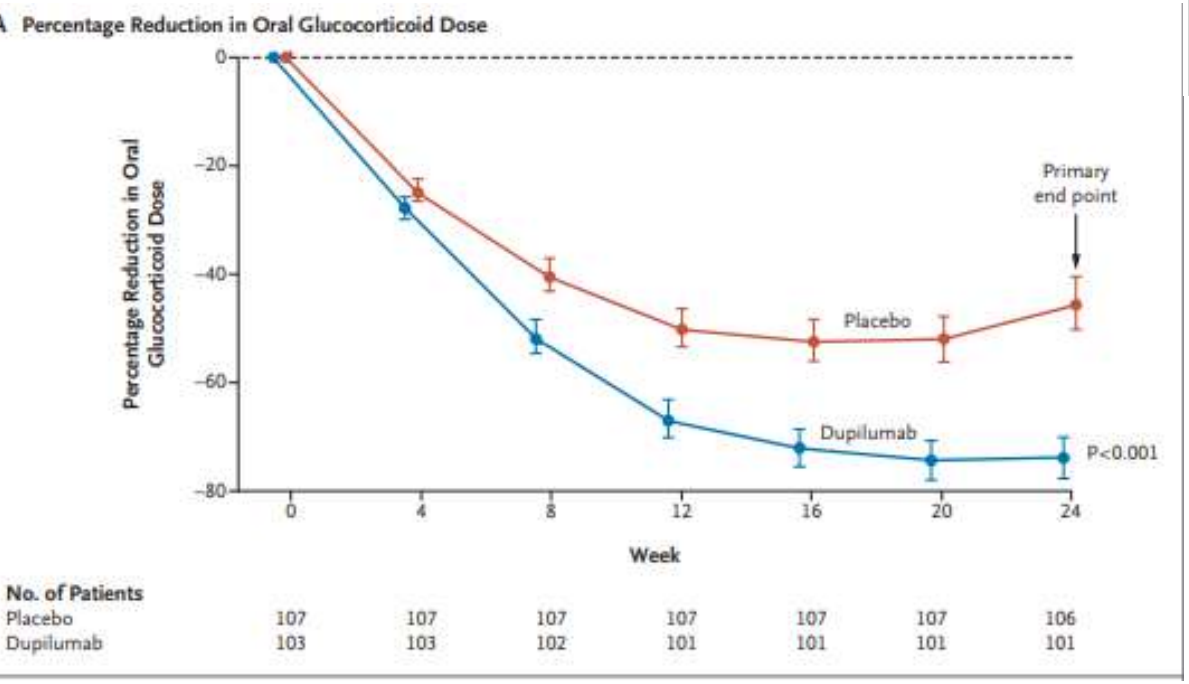
Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

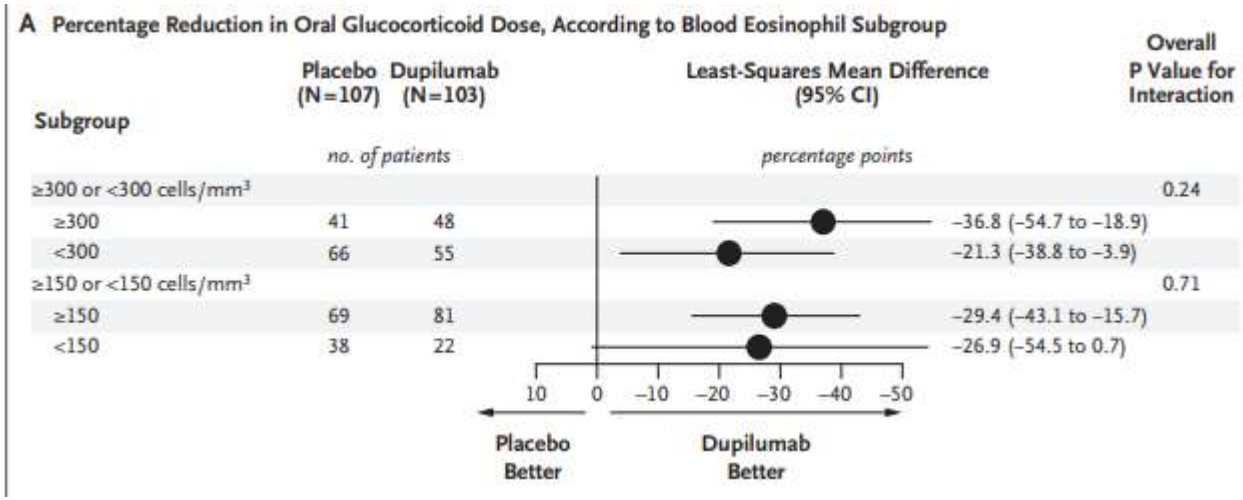
Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D.,

Rabe et al	**≥**12 yrs poorly controlled asthma on oral corticosteroids for last 6 months (5-35 mg prednisolone equivalent) and high ICS-LABA**(≥500µg FP)** Pre BD FEV1 - <80% No eosinophil cut off	Dupilumab 300mg Vs placebo every 2 wks(1:1) (103 vs 107) Duration- 24 weeks Age – 51.9 vs 50.7 **OCS dose – 11.79 vs 11.83** FEV1 – 51.64% vs 52.69% AEC(cells/µL) - 370 vs 325 FeNO (ppb) – 35.5 vs 39.6	**% reduction in OCS at 24 weeks**

Liberty asthma venture trial

OGC dose change – 70.1% vs 41.1%



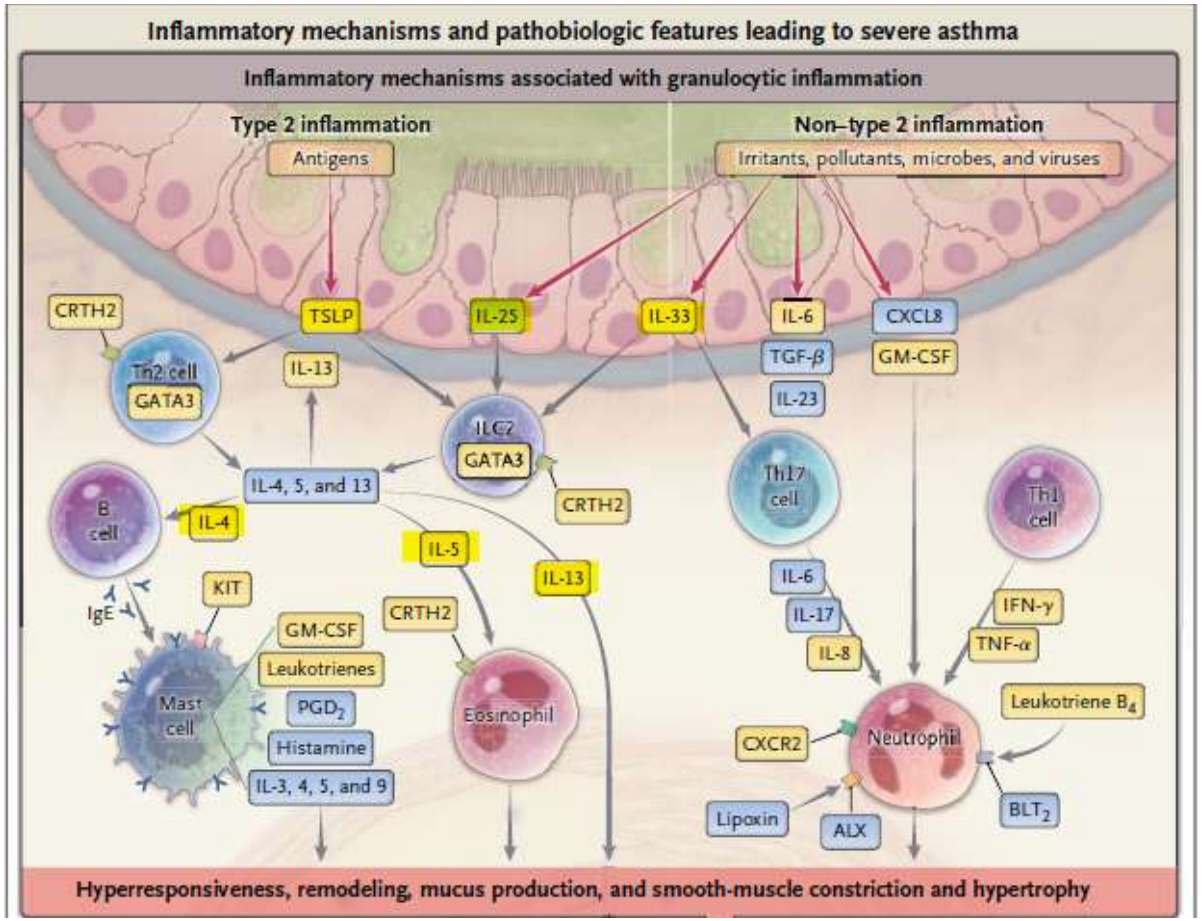


52% vs 29% had no exacerbations even on stopping OCS
59% lesser exacerbation risk when compared to placebo

Therapy	Asthma Exacerbation	Lung Function	Corticosteroid Weaning	Special Considerations
Omalizumab	Reduces by 25%	Minimal or equivocal improvement	Decreases use of ICS, but no data that it helps with OCS weaning	Only s.c. biologic approved for children 6–11 yr old
Mepolizumab	Reduces by ~50%	Inconsistent effect	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (14%)	Standard s.c. dosing has not been shown to decrease sputum eosinophilia; approved at higher dosing for EGPA
Reslizumab	Reduces by ~50–60%	Improved	Has not been specifically evaluated for this indication	Only weight-based dosing i.v. biologic approved for asthma
Benralizumab	Reduces by ~25–60%	Improved	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (50%)	Only s.c. biologic that offers every-8-wk dosing
Dupilumab	Reduces by ~50–70%	Improved	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (50%)	Only biologic that can be self-administered s.c.; showed benefit with $Fe_{NO} \geq 25$ ppb regardless of eosinophil count

Anti-epithelial cytokine antibodies

Tezepelumab	Itepekimab	Astegolimab
Anti-TSLP	Anti-IL 33	Anti- IL 33 receptor inhibitor
Human IgG2	Fully human IgG4	Human IgG2
210mg sc every 4 weeks	300mg sc every 2 weeks	70mg/ 490mg every 4 weeks
NAVIGATOR Study **DESTINATION Study**	**Phase 2 RCT**	**ZENYATTA Study(phase IIb)**


Inflammatory mechanisms and pathobiologic features leading to severe asthma
Inflammatory mechanisms associated with granulocytic inflammation
Type 2 inflammation
Non–type 2 inflammation
Antigens
Irritants, pollutants, microbes, and viruses
CRTH2
TSLP
IL-25
IL-33
IL-6
CXCL8
TGF-β
GM-CSF
IL-23
Th2 cell
GATA3
IL-13
ILC2
GATA3
CRTH2
Th17 cell
Th1 cell
IL-4, 5, and 13
B cell
IL-4
IL-5
IL-13
IL-6
IL-17
IL-8
IFN-γ
TNF-α
KIT
IgE
GM-CSF
Leukotrienes
PGD2
Histamine
IL-3, 4, 5, and 9
CRTH2
Mast cell
Eosinophil
Neutrophil
CXCR2
Leukotriene B4
BLT2
Lipoxin
ALX
Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy

TEZEPELUMAB

- US-FDA approved - 2021
- Labelled indications:
- **Add-on maintenance** treatment of patients with **Severe asthma aged 12 years and older**

- Dose: 210 mg sc q4 weeks

pathway trial

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

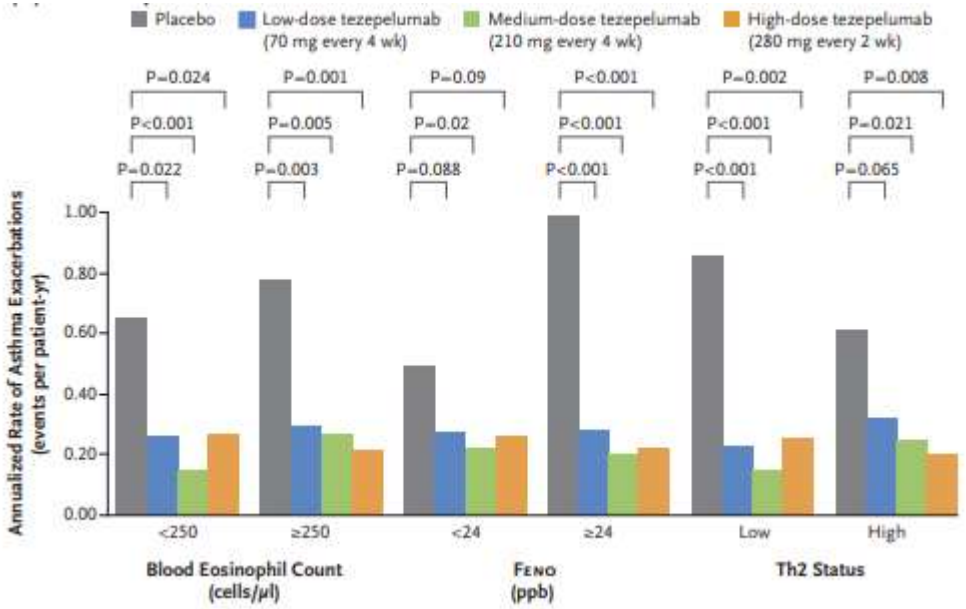
September 7, 2017
N Engl J Med 2017; 377:936-946
DOI: 10.1056/NEJMoa1704064

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

The NEW ENGLAND JOURNAL of MEDICINE

- Phase 2, multicenter, randomized, double-blind, placebo-controlled trial.
- 18-75 yrs uncontrolled asthma on >500 µg FP at least 6 months before enrollment & ≥2 exacerbations Duration: 52 wks
- Tezepelumab dose- 70mg q4W (n=138), 210mg q4W (n=137), 280mg q2W (n=137)

- Outcomes: Asthma exacerbation rates & FEV1 change at 52 weeks
- Results:
  - Exacerbation rates lower in all groups- 62%, 71% and 66%.
  - FEV1 higher in all groups- 120ml, 130ml, 150ml.
- Tezepelumab had lower rates of exacerbations and better lung function independent of blood eosinophil counts.



The NEW ENGLAND JOURNAL of MEDICINE

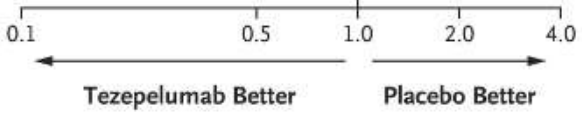
ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

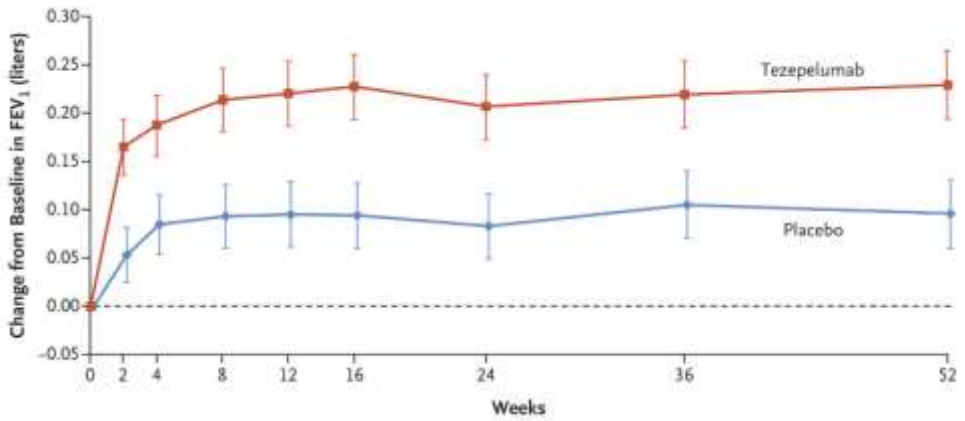
Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D.,

NAVIGATOR (2016)	12-80 yr, poorly controlled asthma on med- high ICS-LABA (≥500µg of FP) for >12 m History of ≥ 2 exacerbations requiring systemic steroids FEV1 <80%	**Placebo, Tezepelumab 210 mg s.c. every 4 wks for 52 wks** Age – 49 vs 49.9 **AEC – 353 vs 327** **FeNO – 46.3 vs 41.4** **Total IgE – 614.1 vs 515.7**	**Annual exacerbation rate, FEV1 change**

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)



- Rate ratio – 0.44
- Significant effect irrespective of baseline eosinophils, FeNO at baseline and allergic status
- FEV1 change is 230 ml vs 90 ml



Non type 2 cytokine antibodies

Risankizumab	Brodalumab	Golimumab
Anti-IL 23	Anti-IL 17A receptor	Anti-TNF alpha
90mg sc every 4 weeks	210mg sc every 2 weeks	100mg sc every 4 weeks
Phase 2 RCT	**Phase 2 RCT**	**Phase 2 RCT**
Not beneficial	**Not beneficial**	**Not effective**

Anti IL-13 Biologics

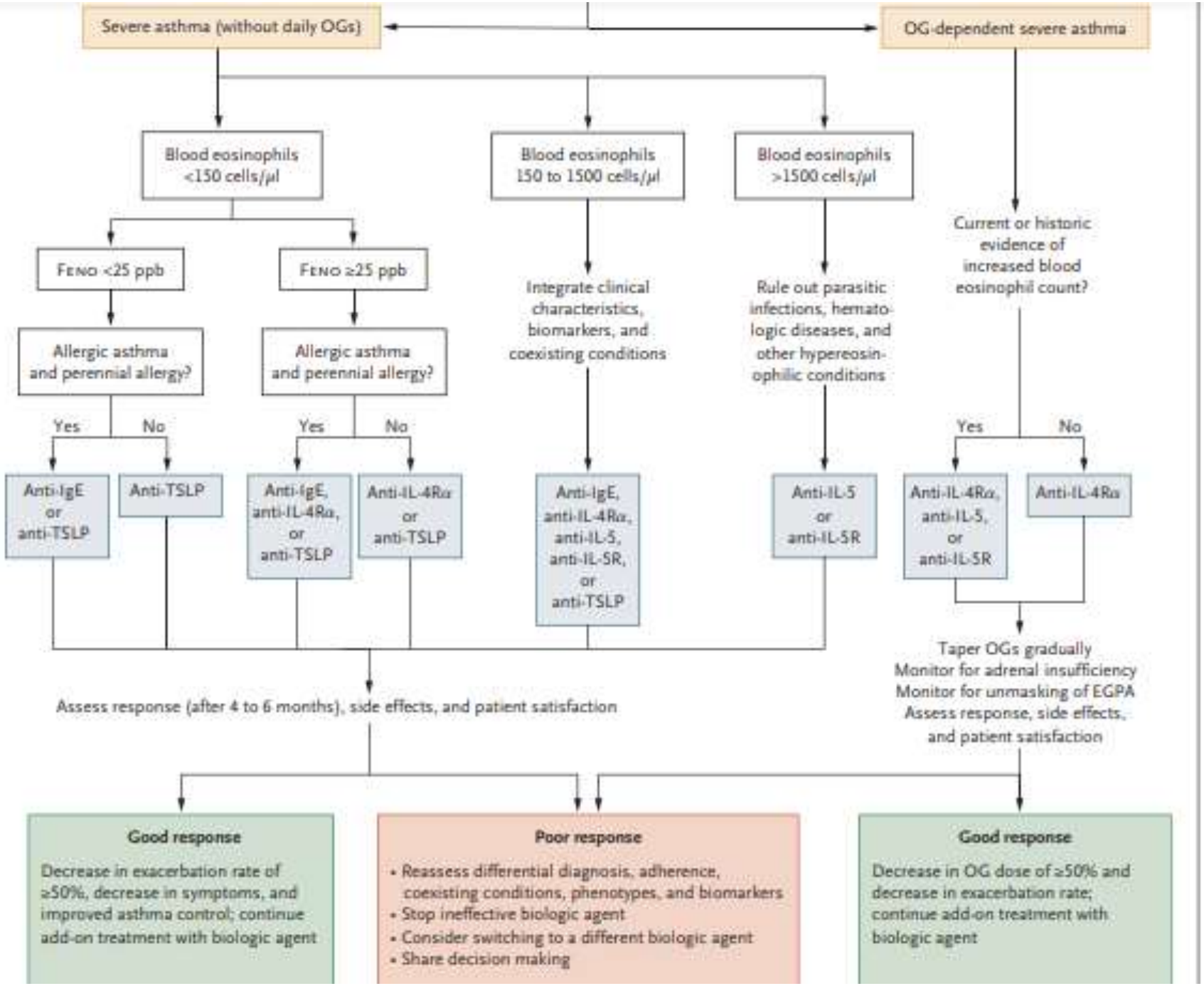
The following therapeutic antibodies targeting IL-13 have been studied

Lebrikizumab	Tralokinumab
Anti-IL-13 mAb	Anti-IL-13 mAb
Humanised IgG4	Fully human IgG4
37.5mg or 125mg sc every 4 weeks	300mg sc every 2 weeks
LAVOLTA 1 & 2 study	**STRATOS 1 & 2**

1. Thomson NC, et al. Biologics: Targets and Therapy 2012;6:329–335;
2. Piper E, et al. Eur Respir J 2013;41:330–338.

CHOOSING A BIOLOGICAL

	Anti IgE antibody	**Anti IL-4R antibody**	**Anti IL-5 /IL-5R antibody**
Indication	Severe allergic asthma	Severe type 2 asthma	Severe eosinophilic asthma
Age	Children, adolescents, young adults	Children, adolescents, young adults	ADULTS
Allergy	Prerequisite – sensitization to perennial allergen	Irrespective to allergy	Irrespective to allergy
DOMINANT BIOMARKER	**Total IgE (for dosing)**	**INCREASED FeNO**	**INCREASED EOSINOPHIL**
AEC	Slightly better response with increased count	Increased counts	Increased counts
FeNO	Slightly better response with increased FeNO	BETTER RESPONSE if FeNO >25 ppb	Irrespective of FeNO
Coexisting conditions	Allergic rhinitis, CRS with nasal polyposis, chronic urticaria	Atopic dermatitis, CRS with nasal polyposis	CRS with nasal polyposis



Brucelle et al , biologicals in asthma

FOLLOWING UP ON A BIOLOGICAL

- Limited data regarding time to follow up, frequency of visits, type of monitoring and deciding treatment failure
- Few measures like FEV1 starts to improve in 2-3 wks of dupilumab, but may take several months to assess efficacy (exacerbations, glucocorticoid)
- GINA suggests – initial evaluation at 4 months for efficacy –

1. If good response – follow up 3-6 monthly
2. If no response – alternative biological
3. Unclear – extend till 6-12 months

J.Darveaux/Ann Allergy Asthma Immunol 125 (2020) 122-123

FOLLOWING UP ON A BIOLOGICAL

- No consensus on monitoring AEC/FeNO/IgE during therapy
- EXCEPT IF NEW SYMPTOMS OCCUR ON DUPILUMAB ASSOCIATED WITH EOSPINOPHILIA
- No guidelines on how to step down if controlled
- No current evidence on immune modulating effect – hence stopping leads to loss of asthma control
- Not curative, after discontinuing of drug – disease re-occurs (Mollard, Respir Med 201;108:571-6)

J.Darveaux/Ann Allergy Asthma Immunol 125 (2020) 122-123

Summary of biological therapies

Therapy	Mechanism of action	Endotype	Predictors of response	Comments
Omalizumab	Humanized mAb Inhibits activity of IgE	Moderate–severe allergic asthma IgE ≥30 IU/ml, Positive Skin prick test or Specific IgE to perennial allergen	Blood eosinophils ≥ 260 FeNO ≥ 20ppb Allergen driven symptoms Childhood onset asthma	75 to 375 mg SC every 2 or 4 weeks

Doruduchi et al Annals of Allergy, Asthma and Immunology 2019

Adverse effects
Headache (6%-12%) ,Arthralgias (3%-8%), serum sickness like reaction Anaphylaxis (0.3%) – **blackbox warning** Cardiovascular events, including transient ischemic attack and ischemic stroke Eosinophilic granulomatosis and polyangiitis Not associated with increased parasitic infections or malignancy – although IgE is important but not essential for host defnces against parasites or malignancy

(Cassale, JACI in Practice 2019;7:1437.0 Long JACI 2014 ; 134:560.7) Schoettler et al CHEST March 2020

Summary of biological therapies

Therapy	Mechanism of action	Endotype	Predictors of response	Comments
Mepolizumab	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/blood eosinophils ≥150 or 300 cells/μl	Higher blood eosinophils+ More exacerbations in previous year + Adult onset Asthma + Nasal polyposis +	100 mg SC every 4 weeks (bodyweight > 40 kg); 40 mg SC every 4 weeks (bodyweight < 40 kg)
Reslizumab	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/blood eosinophils ≥400/μl		3 mg/kg IV every 4 weeks
Benralizumab	Humanized mAb inhibits actions of IL-5 receptor	Severe eosinophilic asthma/blood eosinophils 300 cells/μl		30 mg SC every 4 weeks X 3 doses, then every 8weeks

Doruduchi et al Annals of Allergy, Asthma and Immunology 2019

Adverse effects of Anti-IL5

Mepolizumab	Benralizumab	Reslizumab
Headache (19%)	Antibody response with neutralizing activity (12%)	Antibody to medication (5%)
Injection site reaction (8%-15%)	Headache (8%)	Transient increased CK (20%)
Tiredness (5%)	Pharyngitis (5%)	Oropharyngeal pain (3%)
2/1327 developed zoster , vaccination recommended for adults >50 yrs 4 wks prior to treatment		Increased malignancies observed at 6 mo (diverse types)
		Anaphylaxis (0.3%) – black box warning

Schoettler et al CHEST March 2020

Summary of biological therapies

	Mechanism of action	Endotype	Predictors of response	Comments
Dupilumab	Human mAb inhibits actions of IL-4 and IL-13	Blood eosinophils ≥150/µl FENO >25 ppb	Higher eosinophils Higher FeNO Mod/Sev Atopic dermatitis Nasal Polyposis	400 or 600 mg (two injections) SC followed by 200 or 300mg every other week

Doruduchi et al Annals of Allergy, Asthma and Immunology 2019

Adverse effects of Dupilumab

Injection site reaction (10%-18%), Oral herpes simplex infection(4%)

Antibody response with neutralizing activity (2%-4%) Conjunctivitis (10%)

Eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia

Hypersensitivity reaction

Schoettler et al CHEST March 2020

CHANGING FROM ONE TO OTHER BIOLOGIC

- No head to head comparison exist between biologics in asthma
- Changing from one to other –

OSMO (Efficacy and safety of mepolizumab in uncontrolled patients with severe eosinophilic asthma following a switch from omalizumab) – (n=145)

clinically significant exacerbations and exacerbation requiring ED are less frequent (1.18 & 0.19 /yr vs 3.26 & 0.63 /yr 12 months before screening) – 64% reduction and FEV1 improved by 120 ml

- Small study improved asthma control and elimination of sputum eosinophilia when OCS dependent patients on mepolizumab who continued to have sputum eosinophilia associated with asthma exacerbations when changed to iv reslizumab (n=10)

(Mukerjee, Am J Respir Cric Care Med 208;197:38-46)

THANK YOU