Phenotypic Management Of Asthma

Dr Sanjay Singh Rawal

DM seminar

22 Oct 2021

Introduction

- Asthma :
  - ✓ Vague term describing
  - ✓ Group of clinical symptom
  - ✓ With reversible expiratory airflow limitation or bronchial hyper responsiveness
  - ✓ Presence of airway inflammation
  - ✓ Intrinsic v/s Extrinsic ; atopic v/s non atopic

Sally E Wenzel .Nat Med .2012

Introduction

- Lancet editorial 2006 –

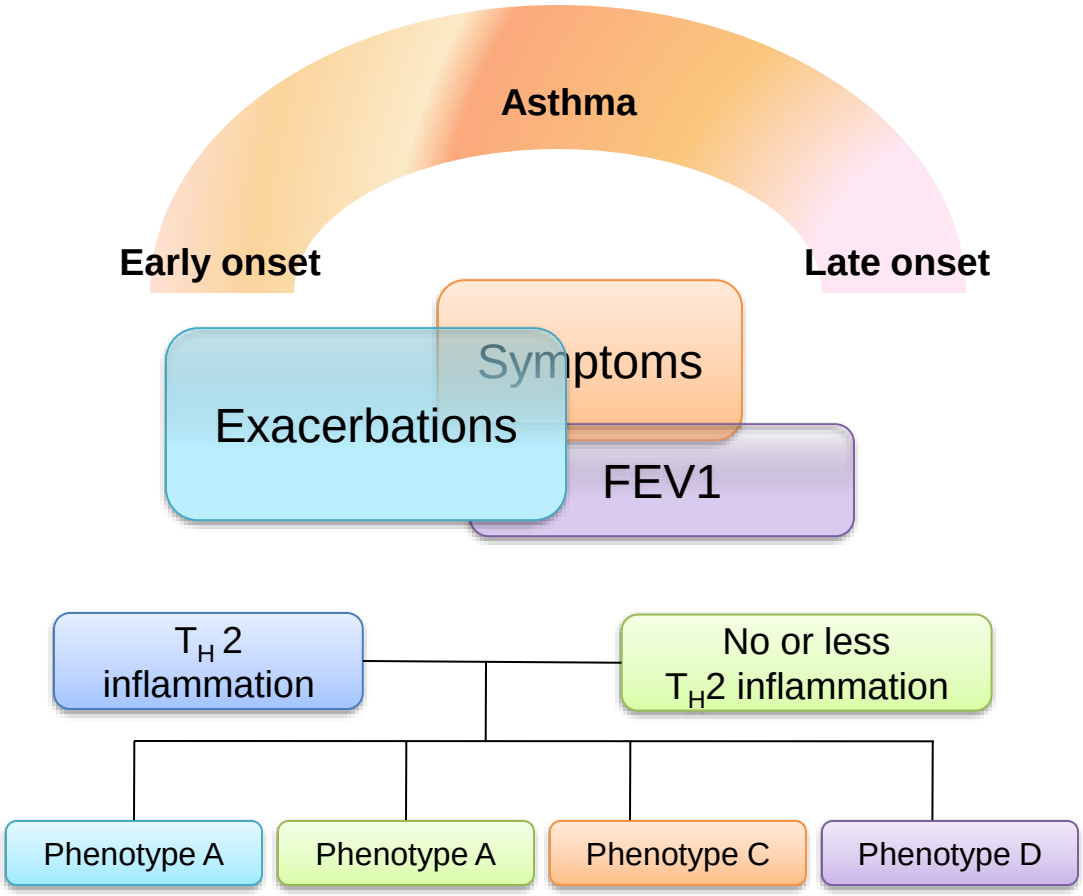
"A plea to abandon asthma as a disease concept"

Single disease entity → heterogenous , encompassing multiple subgroups

Sally E Wenzel .Nat Med .2012

Asthma – Current view

Schematic representation of umbrella term – “asthma”



Sally E Wenzel .Nat Med .2012

Need for stratifying asthma

- Uninformative from the point of view of the etiology of the disease
- "One fits all"  Individualized precision medicine
- Availability of biomarkers and biologicals

Sally E Wenzel .Nat Med .2012

Phenotypes and endotypes

The Asthma Syndrome

Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics

Observable characteristics with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

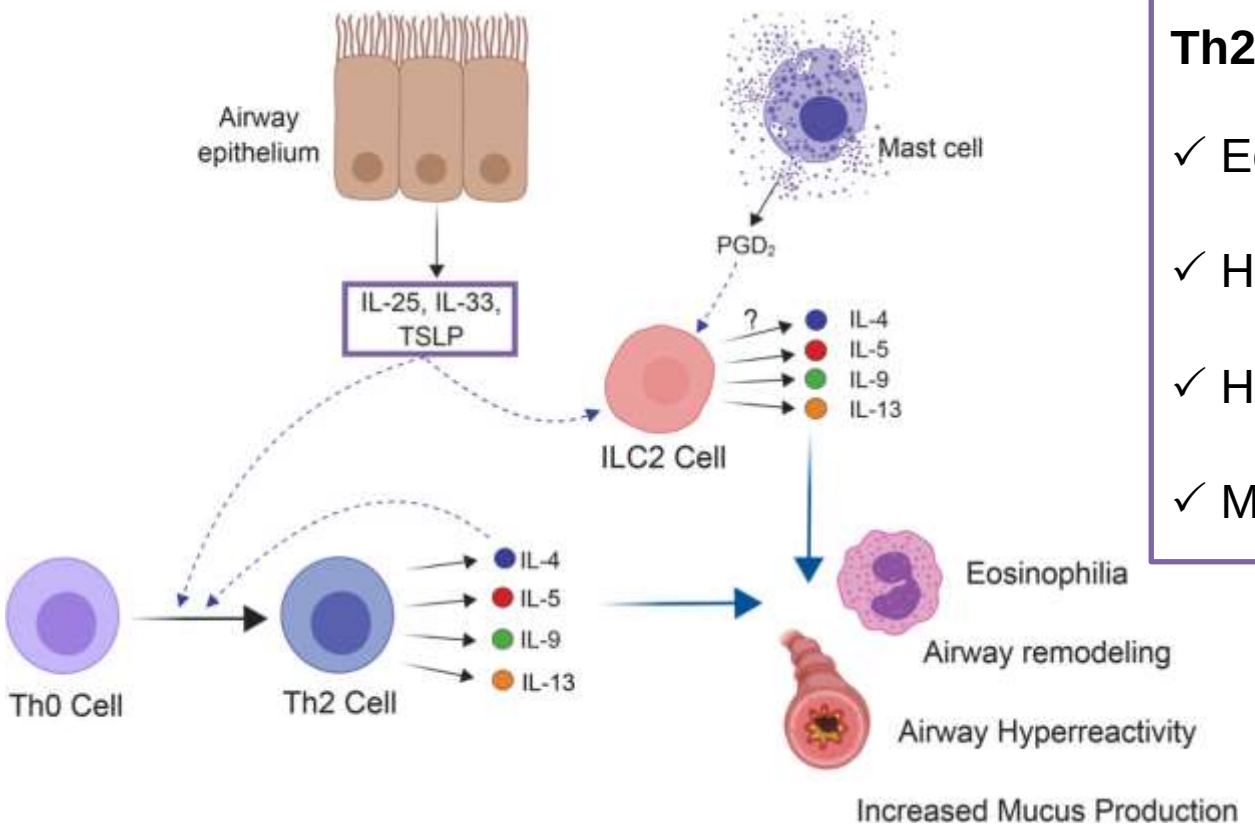
Asthma Endotypes

Distinct disease entities which may be present in clusters of phenotypes but each defined by a specific biological mechanism

Endotype 1 | Endotype 2 | Endotype 3 | Endotype 4 | Endotype 5

Jan Lotvall et al .J Allergy clin Immunol.2011

Th2 mediated asthma

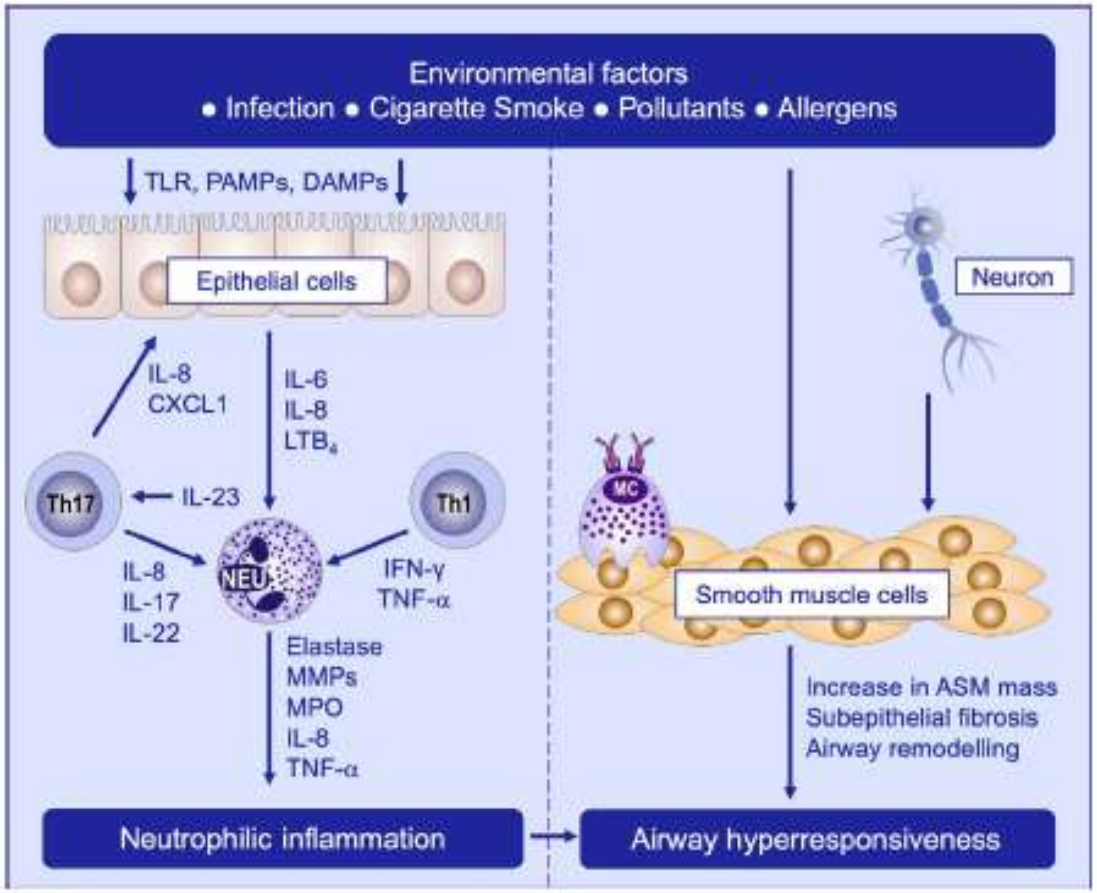


Th2 mediated asthma

- ✓ Eosinophilic
- ✓ High FeNO
- ✓ High IgE
- ✓ Mediated by IL-4,5,13

Daniel Hamilton et al.Clin Rev allergy Immunol.2020 Oct.

Non Th2 mediated asthma



Non Th2 mediated asthma

✓ Neutrophilic

✓ Mediated by Il-1,6,17 &

TNF

Sze E et al Allergy. 2020 Feb

Predominant features and characteristics of endotypes and phenotypes in asthma

Characteristic	Type 2 High Endotype	Type 2 Low Endotype
Phenotype and clinical profile		
Atopic	Early onset, glucocorticoid sensitive	—
Late onset	Often accompanied by chronic sinus disease	—
AERD	Polypoid rhinosinusitis with respiratory reaction after exposure to aspirin or other NSAID	—
Nonatopic	—	Adult onset
Obesity	—	Female preponderance
Older age	—	Late onset; often steroid insensitive
Cytokines	Interleukin-4, -5, and -13; GM-CSF	TGF-β, interferon-γ, interleukin-6, -17, -1β, and -8, TNF-α
Cellular	Eosinophilic	Neutrophilic or paucigranulocytic
Onset	Frequently younger age but severe asthma may develop in older age	Usually present in older age
Atopy	High	Low
Glucocorticoid responsiveness	Usually responsive, particularly in mild and moderate asthma	Often relatively refractory
Severity	Variable, can be severe	Often severe

Sandra C et al N Engl J Med Sep 2019

Eosinophilic asthma

- **Eosinophil :**

  ✓ BAL eosniophil > 2%

  ✓ Sputum eosinophil >3%- gold standard type 2 inflammation marker

- **Serum periostin :**

  ✓ Extracellular matrix protein

  ✓ IL-4, 13 mediated

  ✓ Eosinophil degranulation, production of TGF-beta, cys-LTs

  ✓ Biomarker of persistent eosinophilic airway inflammation despite corticosteroid use

  ✓ Assessment of greater response to anti T2 based therapies

Kuruvilla et al clinic Rev Allergy Immunol 2019 April

Eosinophilic asthma

- **DPP4- IL 13 pathway :**
  - ✓ Increased DPP-4 mRNA expression following IL-13 stimulation in asthma patients
  - ✓ Can predict response to anti IL-13 therapies
- **FeNO :**
  - ✓ Signifies IL-4, 13 activity
  - ✓ Concentration : >50ppb , airway inflammation and steroid responsiveness
- **Urinary LT4 :**
  - ✓ Highly sensitive discriminator of AERD from aspirin-tolerant asthma
  - ✓ Cutoff value of 166 pg/ mg Cr for prediction of aspirin sensitivity with 89% specificity
  - ✓ High negative predictive value, it could potentially be used as a clinical test to assess the risk of AERD in asthma patients with concomitant nasal polyps

Kuruvilla et al clinic Rev Allergy Immunol 2019 April

Non eosinophilic asthma

- Late onset eosinophilic asthma
- Dual positive - Th17/Th2 in some patients
- Cytokines – IL-1b,6,23
- Neutrophilic asthma :
  - ✓ Increased p38 kinase/mitogen activated protein kinase
  - ✓ Corticosteroids inhibit neutrophil apoptosis
  - ✓ Impaired alveolar macrophage phagocytosis of apoptotic cells - efforocytosis
- Neutrophilia may be absent as type 2 cytokine inhibits IL-8

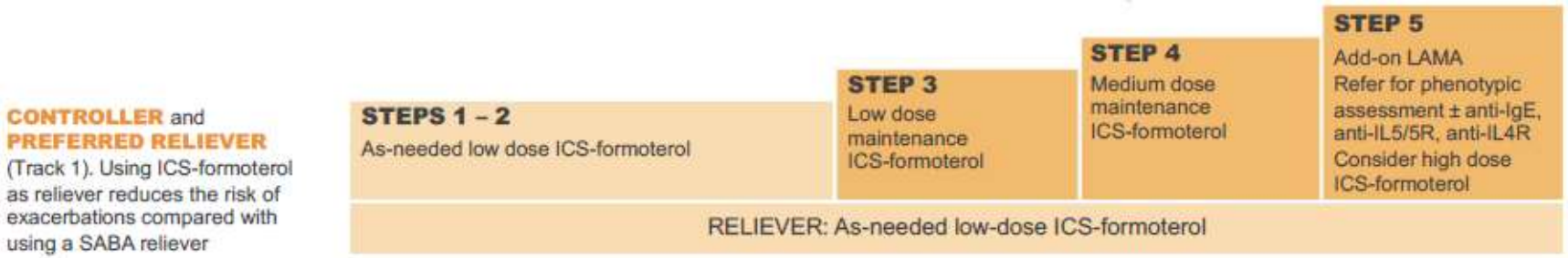
Kuruvilla et al clinic Rev Allergy Immunol 2019 April

Non eosinophilic asthma

- **Clinical features :**
  - ✓ Patients develop asthma at an older age
  - ✓ Demonstrate impaired lung function
  - ✓ Less bronchodilator reversibility
  - ✓ Less atopy
  - ✓ Corticosteroid insensitive

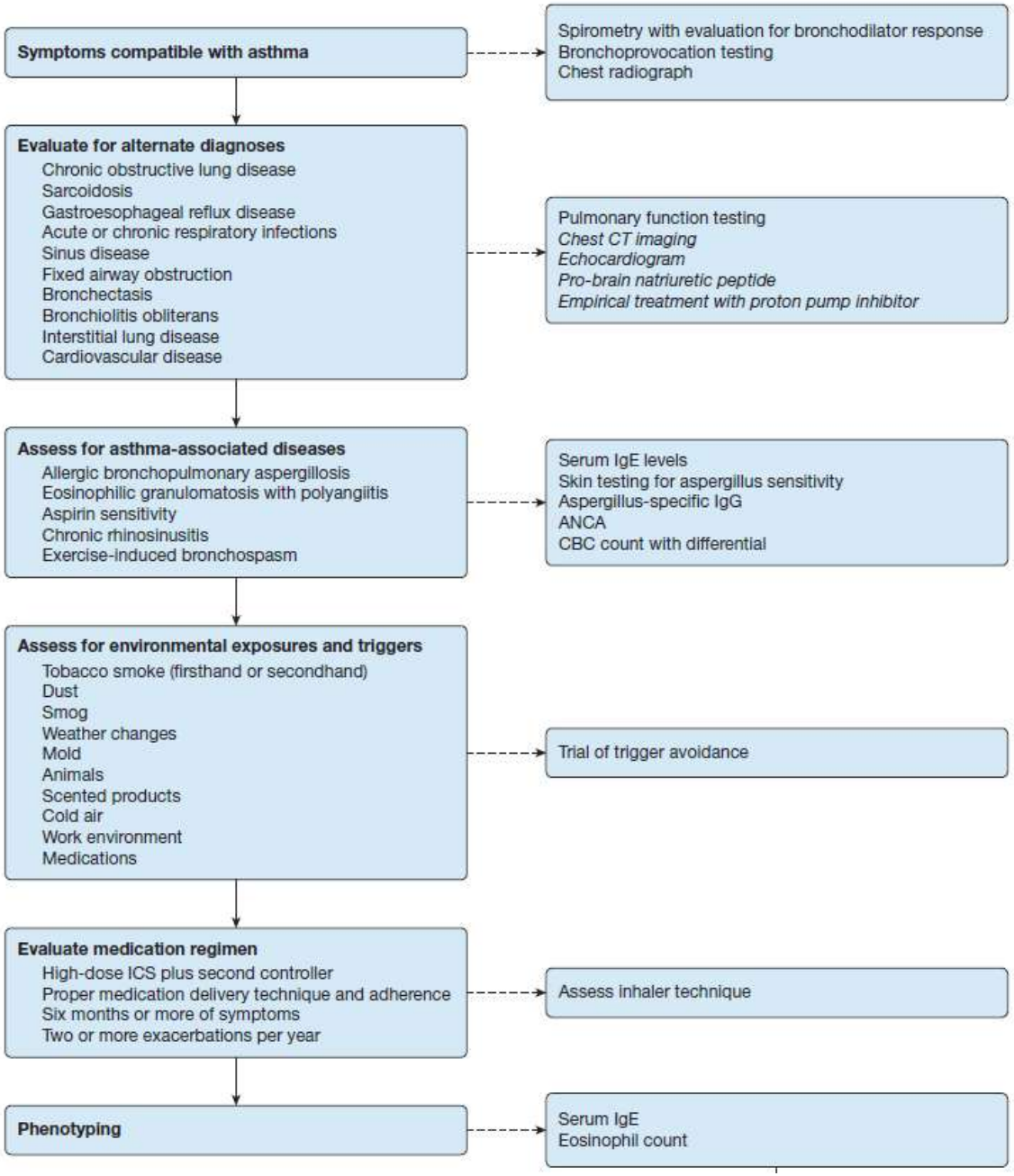
Kuruvilla et al clinic Rev Allergy Immunol 2019 April

Where does phenotype assessment come in asthma management and evaluation?



GINA 2021

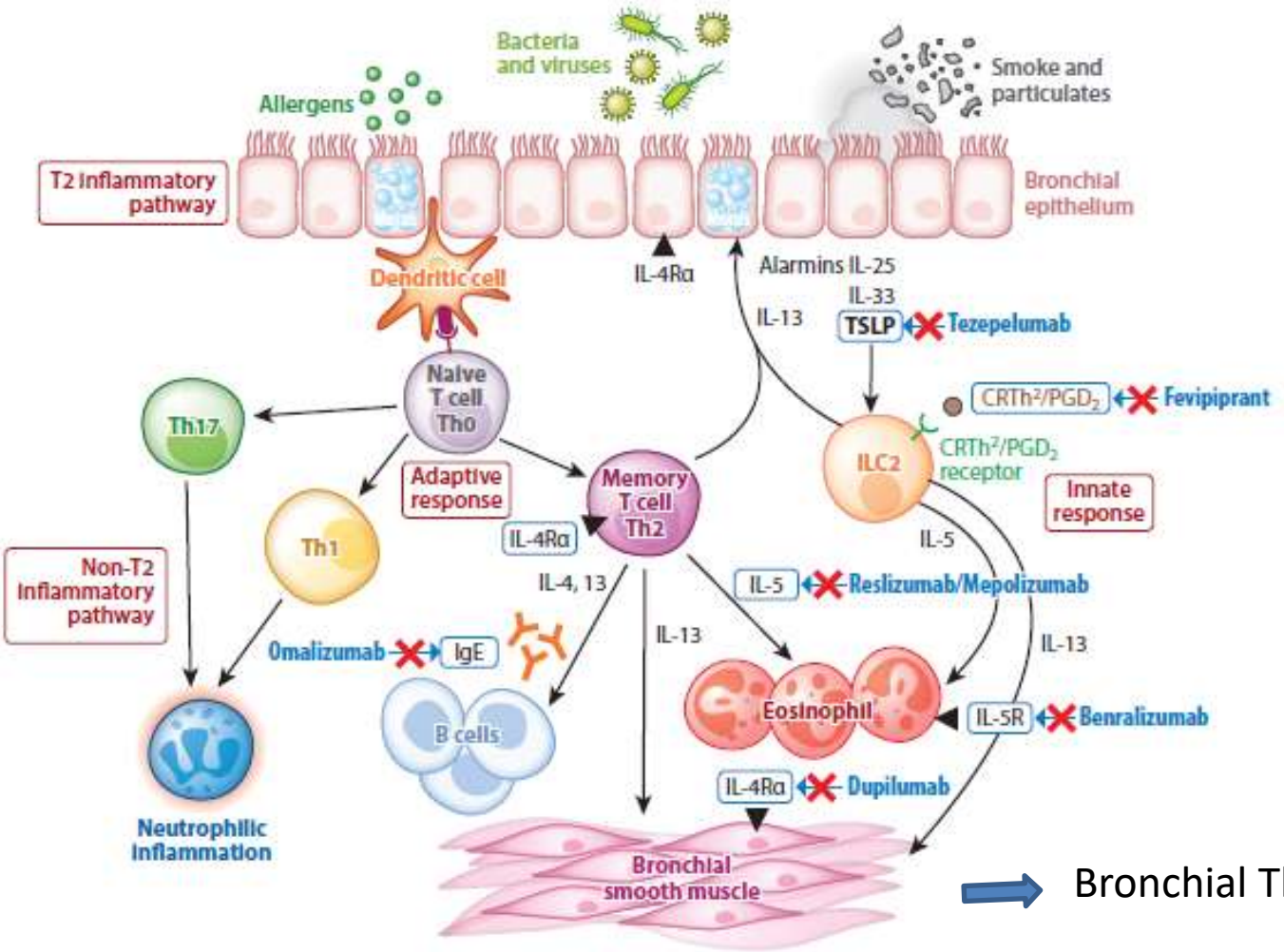
Evaluation of patient with severe asthma



Targeted asthma therapy

Schoettler et al CHEST March 2020

Mechanisms of currently available targeted asthma therapy



Chupp et al The Annual Review of Medicine 2020

Omalizumab

BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
OMALIZUMAB	Severe, allergic asthma Size: 525 Age, mean: 39.0- 39.3; Range 12-74 Pre –treatment FEV1: 67.7-68.2% Time :28 weeks	Exacerbation per patient (during trial) SSP: -48.1% SRP: -40.9%	Pre-BDR FEV1 (% predicted) +2.93%

Omalizumab v/s Placebo

Asthma exacerbation:

Stable steroid period- 14.6 v/s 23.3 , p- 0.009

Steroid reduction period- 21.3 v/s 32.3 , p- 0.004

Steroid dose reduction : Beclomethasone reduction (75% v/s 50%) -, p <0.001

Beclomethasone discontinuation -39.6 % v/s 19.1 % , p<0.001

Busse et al J Allergy clinImmunol.2001 Aug

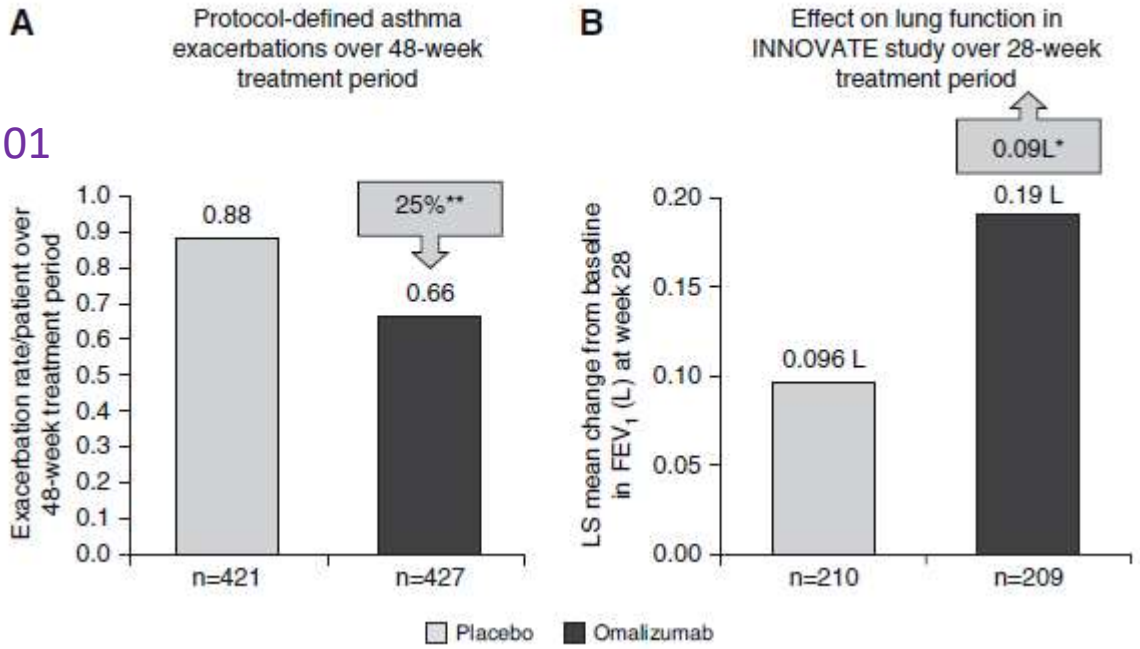
Omalizumab

BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
OMALIZUMAB **INNOVATE TRAIL**	Severe, poorly controlled asthma Size: 419 Age, mean: 43.3- 43.4; Range 12-75 Pre –treatment FEV1: 61.0-61.6% Time :28 weeks	Rate of exacerbation (during trial) -26% Rate of severe exacerbation (during trial) -50%	Pre-BDR FEV1 (% predicted) +0.094% FEV1% predicted +2.8%
OMALIZUMAB **EXTRA TRAIL**	Severe, poorly controlled allergic asthma Size: 850 Age, mean: 43.7- 45.3; Range 12-75 Pre –treatment FEV1: 64.4-65.4% Time :48 weeks	Rate of exacerbation (during trial) -25%	N/A

Doruduchi et al Annals of Allergy, Asthma and Immunology 2019

Omalizumab

p Value- < 0.01



p Value- < 0.05

EXTRA Trial :

reduced the rate of asthma exacerbations by 25% ,

INNOVATE Trial:

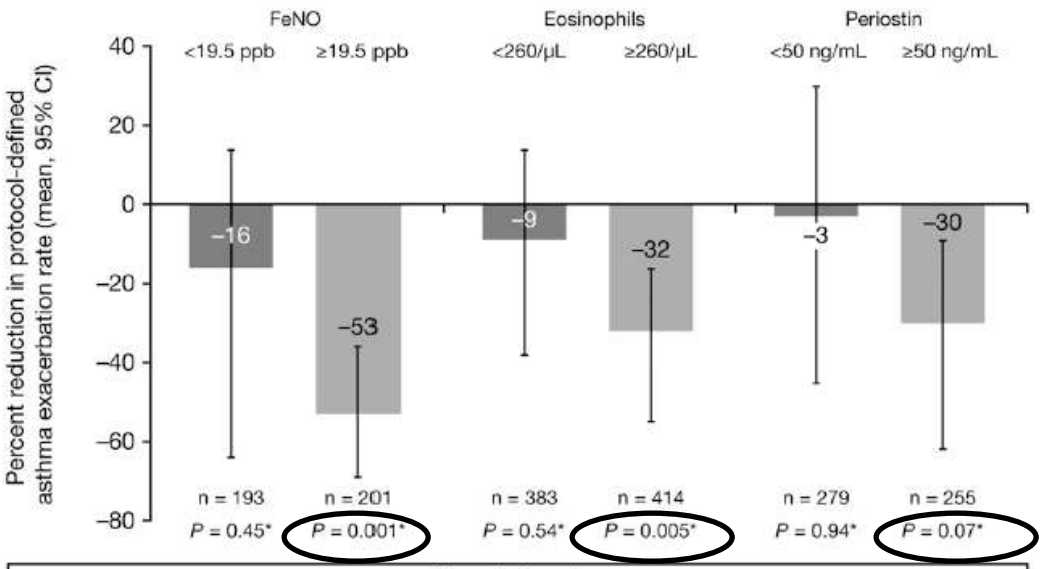
Reduced the rate of asthma exacerbations by 25% ,

Severe exacerbations by 50%

Hanania et al .Am J Respir Crit Care Med. 2013

Humbert et al Allergy 2005

Omalizumab



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

✓ Mean percent reduction in protocol defined exacerbation rates in high v/s low biomarker subgroups (EXTRA study)

Hanania et al .Am J Respir Crit Care Med. 2013

Omalizumab

Cochrane Library

Cochrane Database of Systematic Reviews

Omalizumab for asthma in adults and children (Review)

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

Omalizumab v/s placebo

25 RCT

19 studies as an adjunct to treatment with steroids

Exacerbation- 16 % v/s 26% over 16-60 wks

Hospitalisation- 0.5 % v/s 3% over 28-60 wks

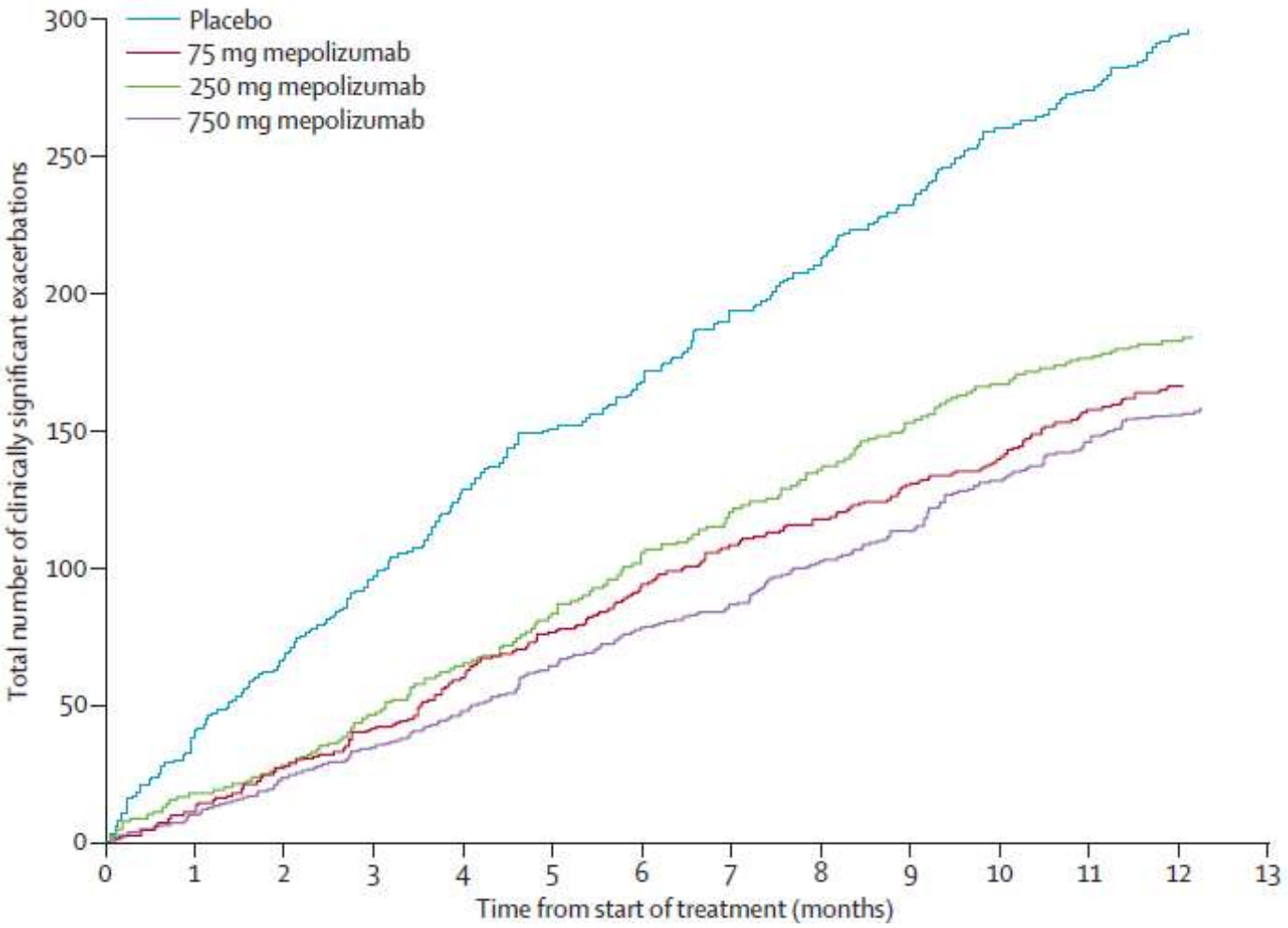
Reduction in ICS dosage – 118 mcg BDP eqivalent/day

Normansell et al Cochrane database of systemic reviews 2014

Mepolizumab

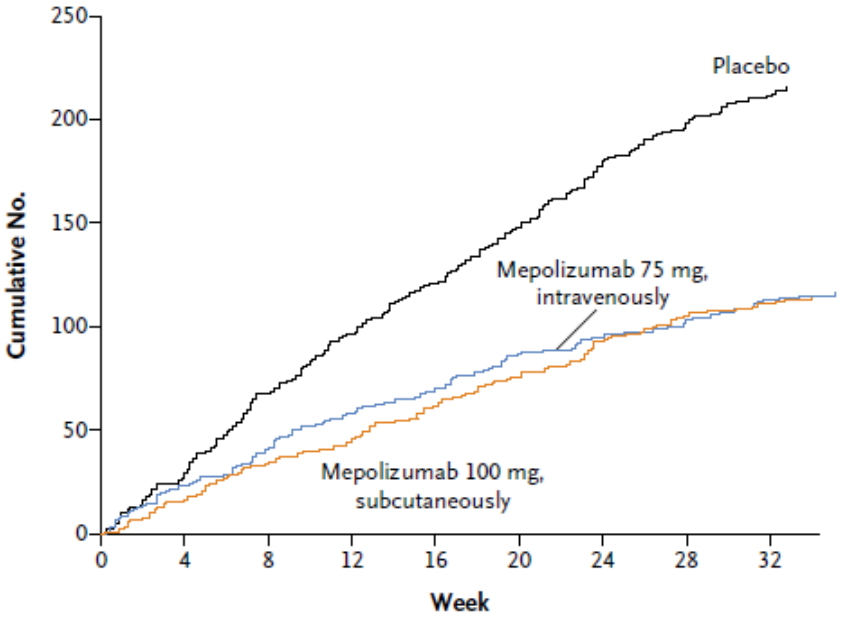
BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
MEPOLIZUMAB DREAM TRIAL Pavord et al Lancet Aug 18 2012	Severe, uncontrolled , eosinophilic asthma Size: 616 Age, mean: 46.4- 50.2; Range 12-74 Initial FEV1: 59-61% Time :52 weeks	Exacerbation (per patient per year) 75mg :-**48%** 250mg:**-39%** 750mg**:-52%**	Pre-BDR FEV1 75mg: +0.061L 250mg: +0.081L 750mg:+0.056L
MEPOLIZUMAB MENSA TRIAL Ortega et al N Eng J Med Sep 2014	Severe, uncontrolled , eosinophilic asthma Size: 576 Age, mean: 49-51; Range 12-82 Initial FEV1: 59-62% Time :32 weeks	Exacerbation (per patient per year) **IV :-47%** **SC: -53%**	Pre-BDR FEV1 IV :**+0.100L** SC: **+0.098L** Post-BDR FEV1 IV **:+0.146L** SC**:+0.138L**

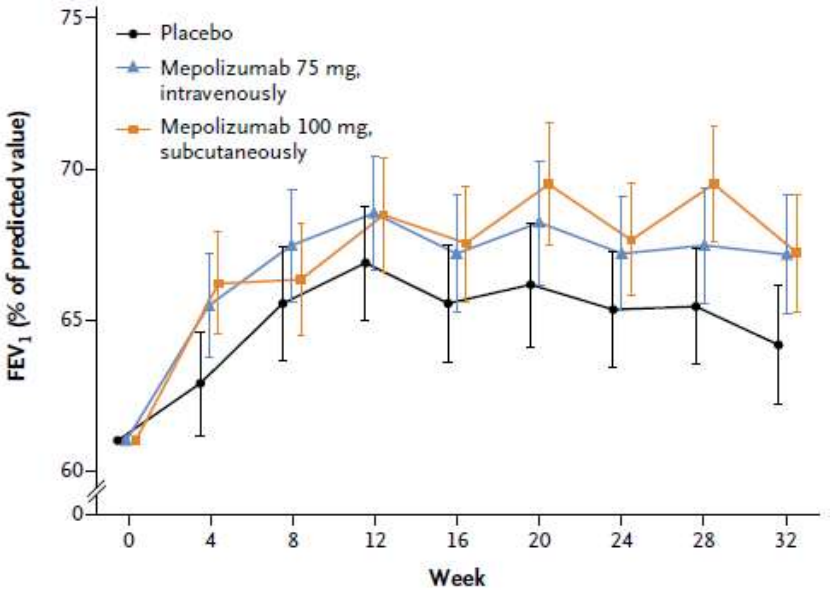
DREAM trial



Pavord et al Lancet Aug 18 2012

MENSA trial





Rate of exacerbation reduced by

47% (Intravenous group)

53%(subcutaneous group)

P value - <0.001

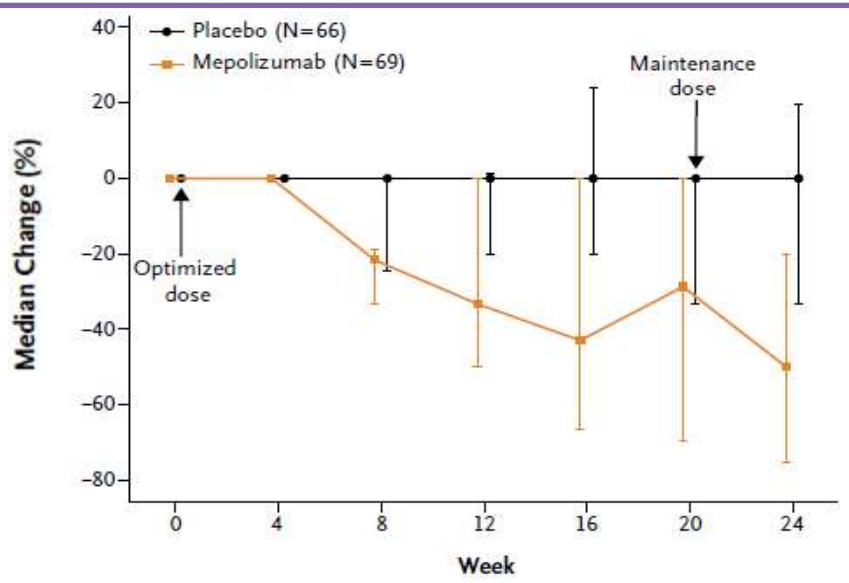
Increase in FEV1 from baseline at 32 weeks

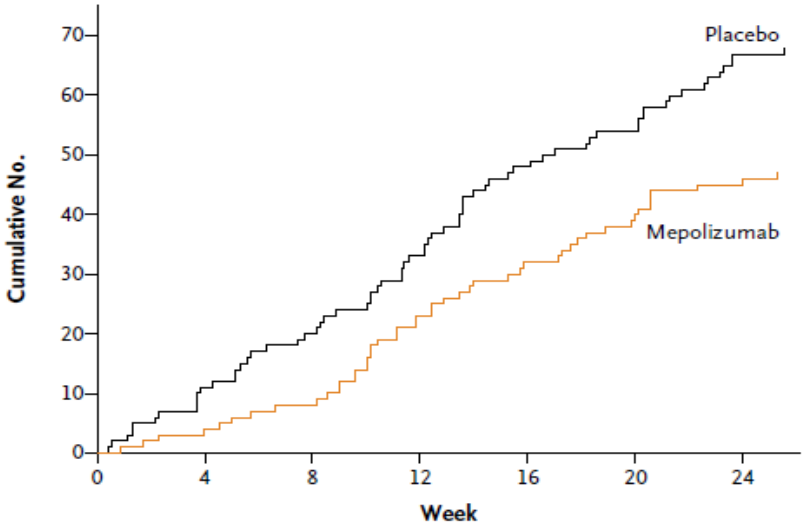
100 ml (intravenous group) p value -0.02

98 ml (subcutaneous group) p value-0.02

Ortega et al N Engl J Med Sep 2014

Oral glucocorticoid sparing effect of mepolizumab in eosinophilic asthma





Median percentage reduction from baseline in daily glucocorticoid dose was **50%** in mepolizumab group v/s no reduction in placebo group at 24 weeks

p value – 0.007

Cummulative rate of significant asthma exacerbations:

Relative reduction of **32%** in mepolizumab group v/s placebo group at 24 weeks. **p value – 0.04**

Bel et al N Engl J Med Sep 25 2014

Cochrane database of systemic review

- Mepolizumab versus placebo for asthma
- n = 8 trials , participants = 1707
- Severity of asthma – mild atopy to severe asthma
- 2 studies (eosinophilic asthma) , n=690
  - ✓ Significant reduction in exacerbation rate
  - ✓ Risk ratio =0.52
- 4 studies with eosinophilic asthma, n=468
  - ✓ No statistical significance in exacerbation

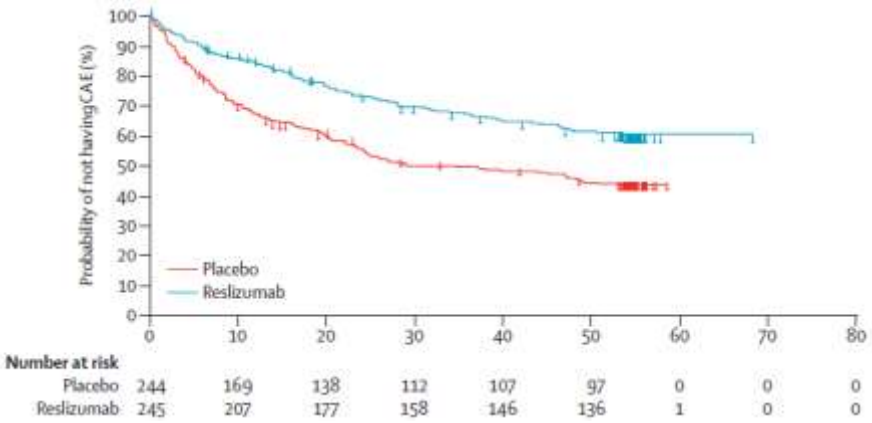
Powell et al Cochrane database of systemic reviews 2015

Reslizumab

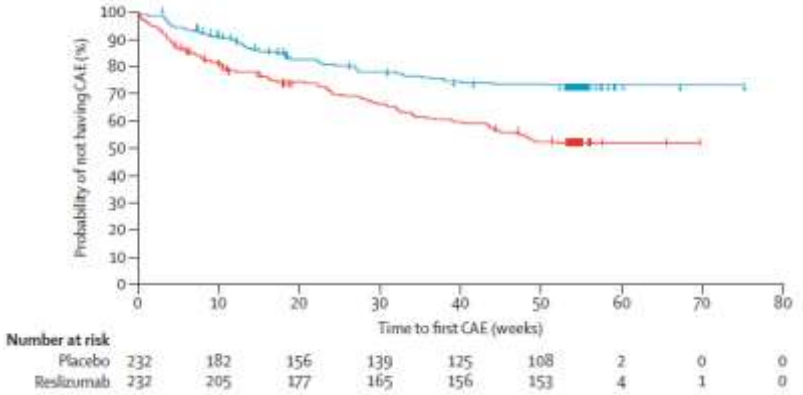
BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
RESLIZUMAB	Moderate-severe, uncontrolled, eosinophilic asthma Size: 953 Age: median: 48-49; Range 12-75 Pre –treatment FEV1: 63.6-70.4% Time :52 weeks	Exacerbation (per patient per year) Study1: -50% Study2: -59%	Pre-BDR FEV1 Study1: +0.126L Study2: +0.090L

Castro et al Lancet Respir Med Feb 23 2015

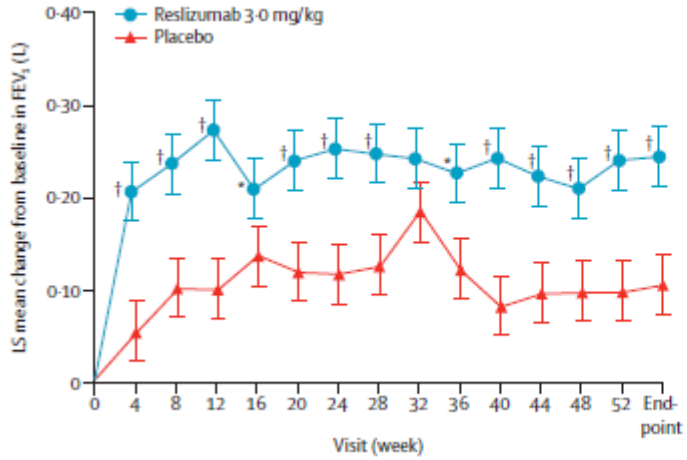
Reslizumab

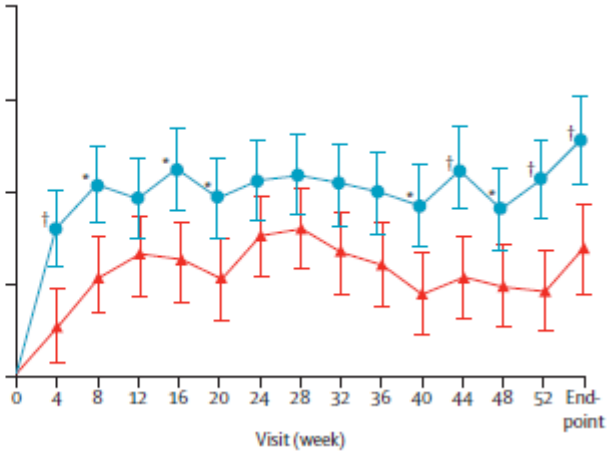


Placebo, n=244, Reslizumab 3.0mg/kg, n=245
HR 0.575(95% CI 0.440 -0.750)
p <0.0001



Placebo, n=232, Reslizumab 3.0mg/kg, n=232
HR 0.486(95% CI 0.353 -0.670)
p <0.0001





FEV1 improvement by week 4 and maintained till end of study

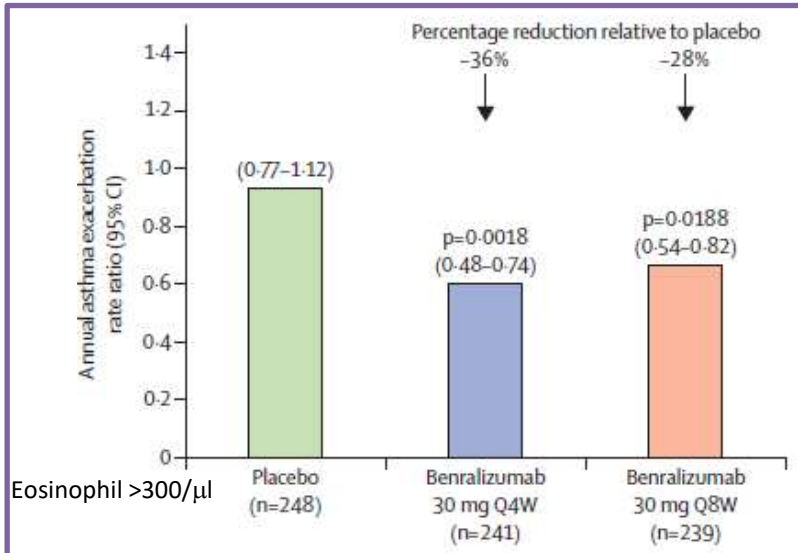
Castro et al Lancet Respir Med Feb 23 2015

Benralizumab

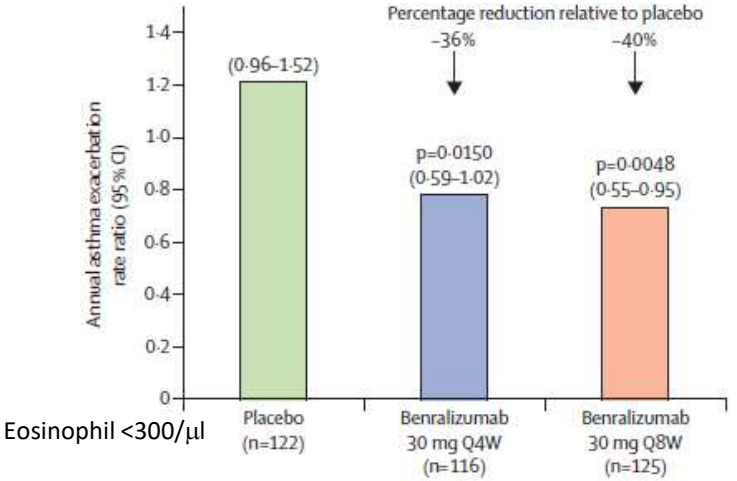
BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
BENRALIZUMAB	Severe, uncontrolled , eosinophilic asthma Size: 1306 Age, mean: 48.8- 50.0; Range 12-75 Pre-treatment FEV1: 57.7-58.9% Time :56 weeks	<u>Annual rate ratio</u> Q4w :-36% Q8w:-28%	<u>Pre-BDR FEV1</u> Q4w :+0.125L Q8w:+0.116L
			CALIMA,Fitzgerald et al. Lancet Sep 2016
BENRALIZUMAB	Severe, uncontrolled , eosinophilic asthma Size: 1205 Age, mean: 47.6-50.1; Range 12-75 Pre-treatment FEV1: 56.1-57.4% Time :48 weeks	<u>Annual rate ratio</u> Q4w :-45% Q8w:-51%	<u>Pre-BDR FEV1</u> Q4w :+0.106L Q8w:+0.159L

SIROCCO.Bleecker E et al. Lancet Sep2016

Benralizumab

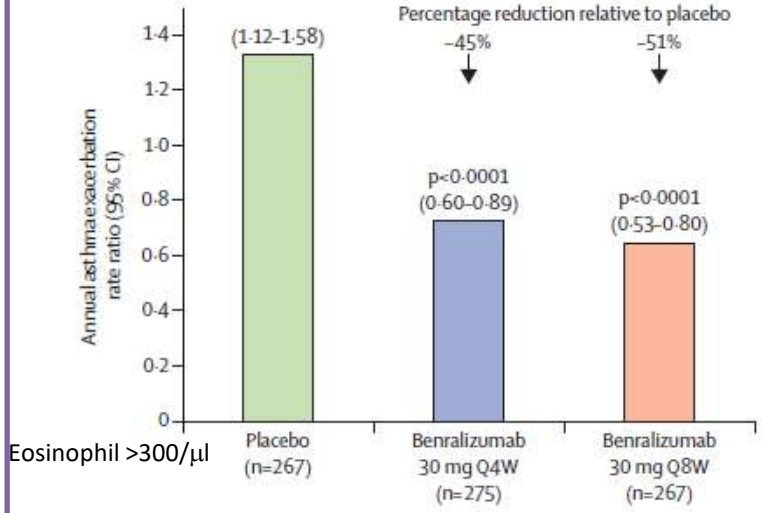


Eosinophil >300/µl

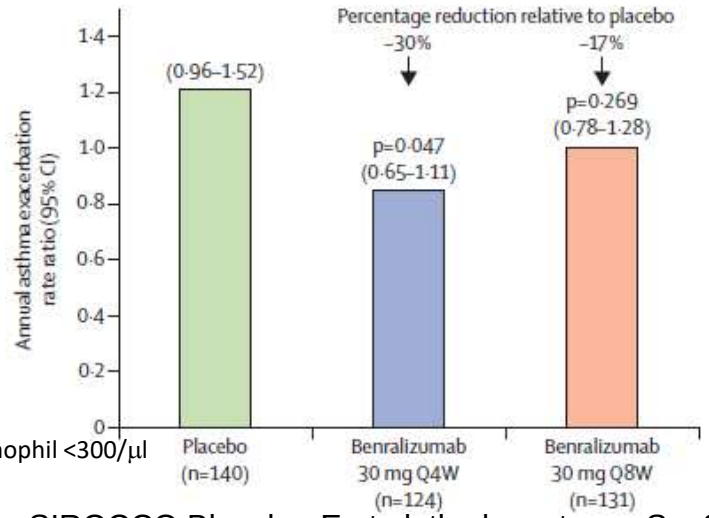


Eosinophil <300/µl

CALIMA,Fitzgerald et al. the lancet.com. Sep 2016



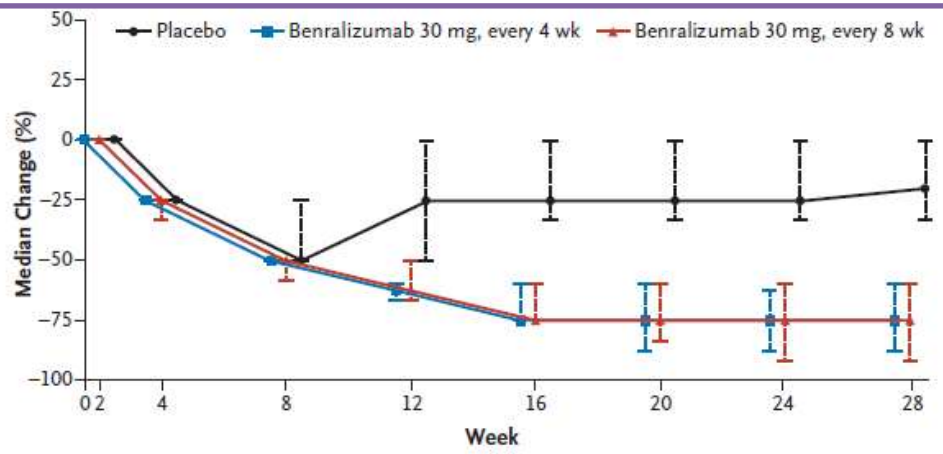
Eosinophil >300/µl



Eosinophil <300/µl

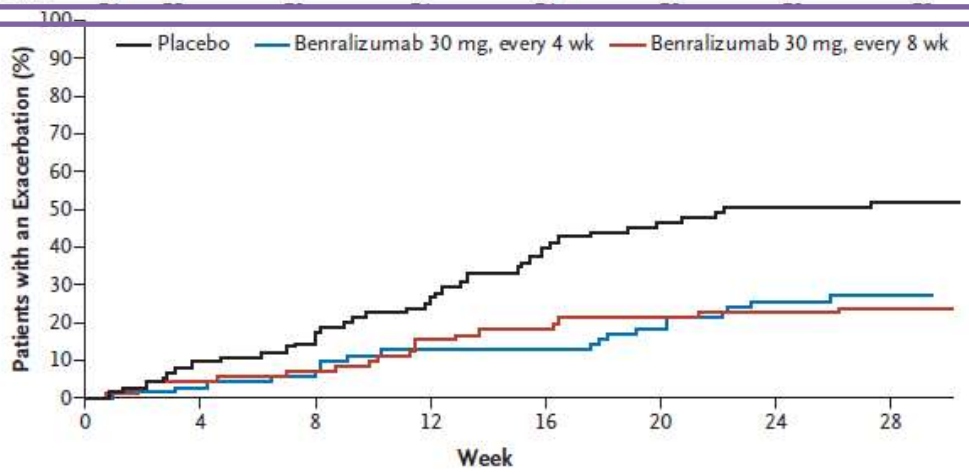
SIROCCO.Bleecker E et al. the lancet.com.Sep2016

Benralizumab



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68

Change from baseline in oral glucocorticoid dose:
75% in either regimen v/s
25 % in placebo group
P value =< 0.001



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

Exacerbation rate -
4wk regimen : 55 % lower rate than placebo
8 wk regimen : 70% lower rate than placebo

Nair et al.NEJM May 2017

Anti IL-5 therapies for asthma -review

Cochrane Library

Cochrane Database of Systematic Reviews

13 RCTs/ 6000

Age- > 12 yrs with diagnosis of asthma

Intervention – Anti IL-5 therapy v/s placebo in addition to current standard of care for asthma

Outcome – clinically significant asthma exacerbation(>3 day course of systemic steroid) with or without hospital admission

Treatments targeting IL-5 or the IL-5 receptor reduce **'clinically significant'** asthma exacerbation rates by **approximately half** in participants with severe eosinophilic asthma already on standard of care therapy with a history of poor control.

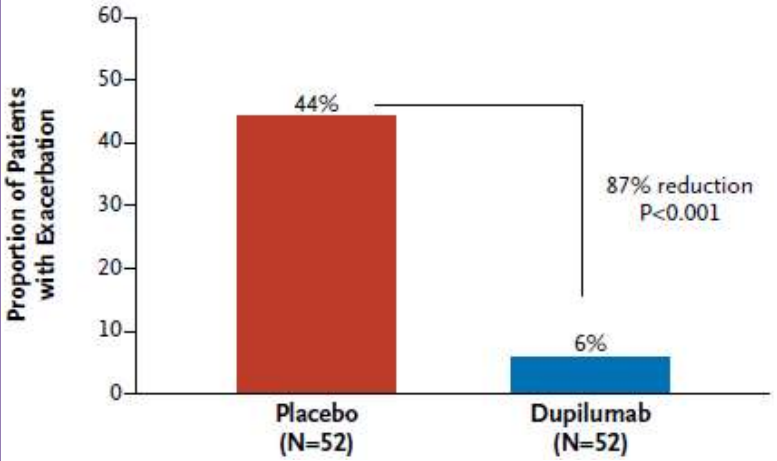
Dupilumab

BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
DUPILUMAB	Persistent,moderate-severe, eosinophilic asthma Size: 104 Age: mean: 37.8-41.6, Range 18-65 Pre –treatment FEV1: 72.0% Time :12 weeks	Occurrence of asthma exacerbation (during trial) -87%	Pre-BDR FEV1 +0.270L

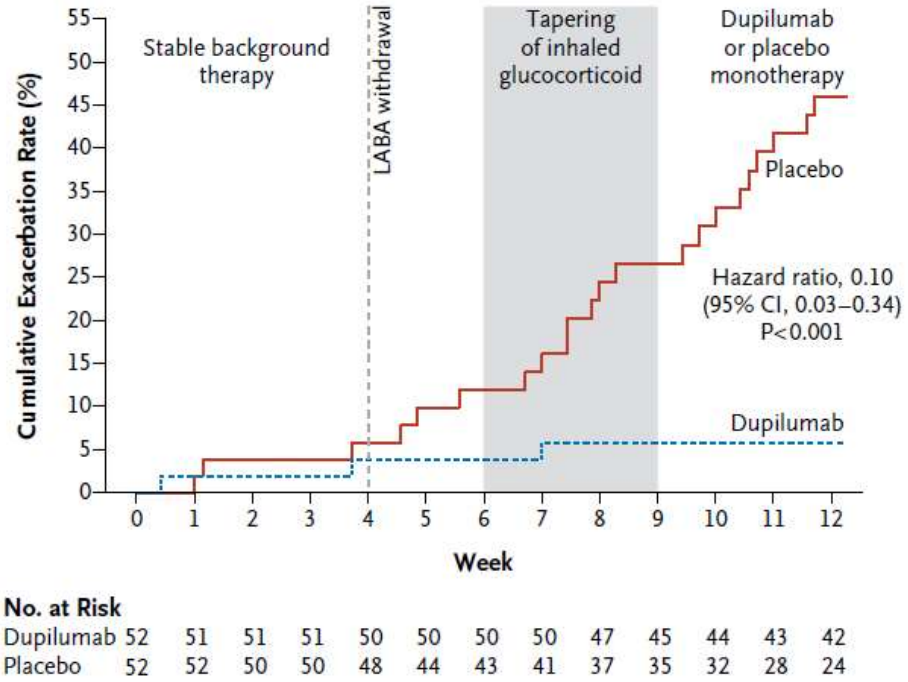
Wenzel et al N Engl J Med June 27 2013

Dupilumab

Exacerbations



Time to exacerbation



Reduced proportion of patients with asthma exacerbation events – **87% relative to placebo**

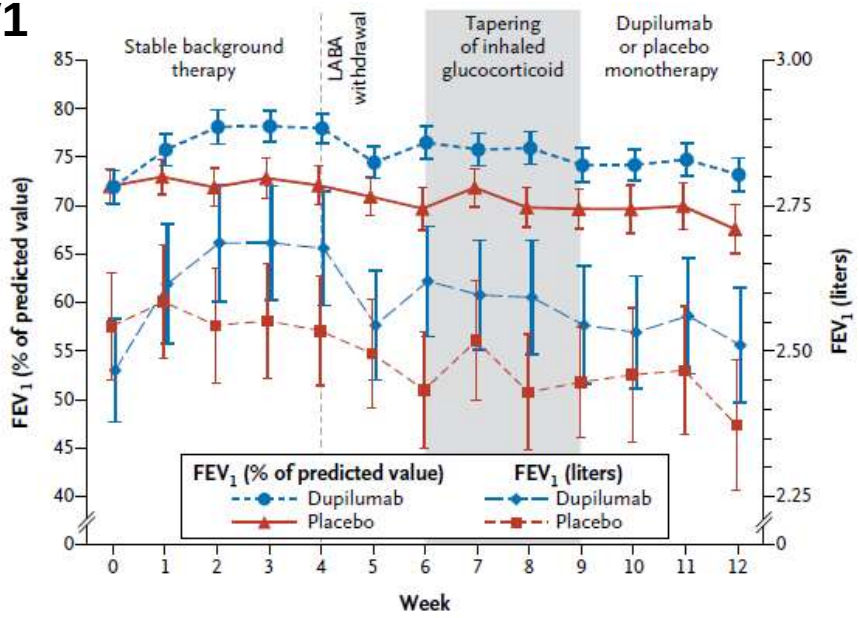
Over and above ICS+LABA substantial effect on objective and patient related end points

Efficacy maintained despite discontinuation of background therapy

Wenzel et al N Engl J Med June 27 2013

Dupilumab

FEV1



No. of Patients													
FEV_1 (% of predicted value)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36
FEV_1 (liters)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36

Increased in FEV1 > 200ml v/s placebo

Effect sustained during tapering and discontinuation

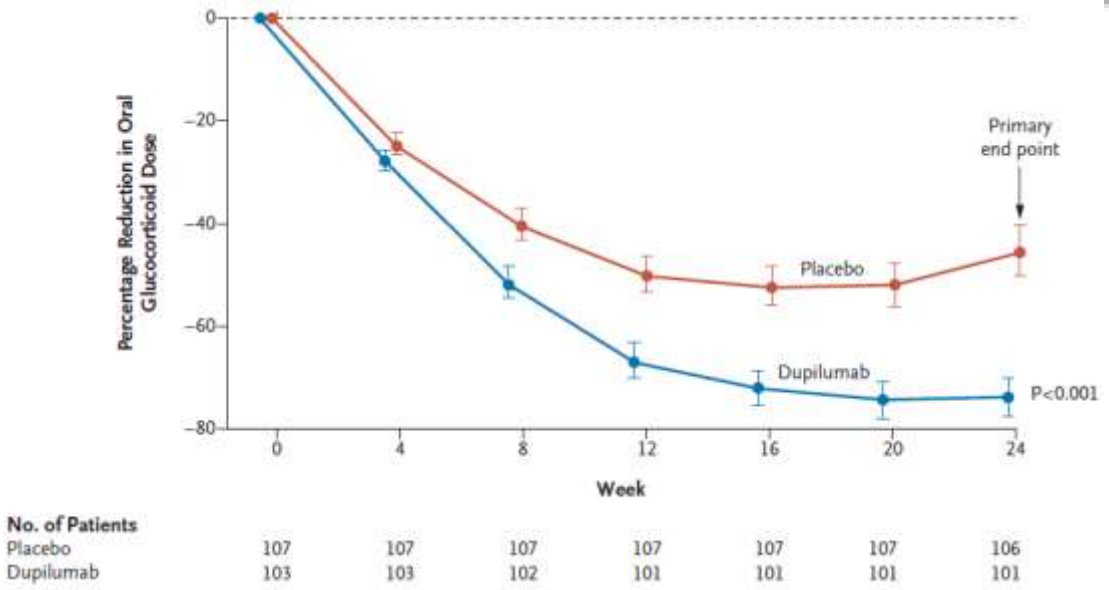
Wenzel et al N Engl J Med June 27 2013

Dupilumab

BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
DUPILUMAB	Severe,oral glucocorticold dependent asthma Size: 210 Age: median: 50.7-51.9; Range >=12 Pre –treatment FEV1: 51.64-52.69% Time :24 weeks	Annualized rate of severe exacerbation events Overall:-59% Eos-high:-71% Eos-low:-60%	Pre-BDR FEV1 Overall:+0.22L Eos-high:+0.32L Eos-low:+0.24L

Rabe et al N Engl J Med June28 2018

Liberty asthma venture



Percentage reduction in oral glucocorticoid dose
-70.1% in v/s -41.9%

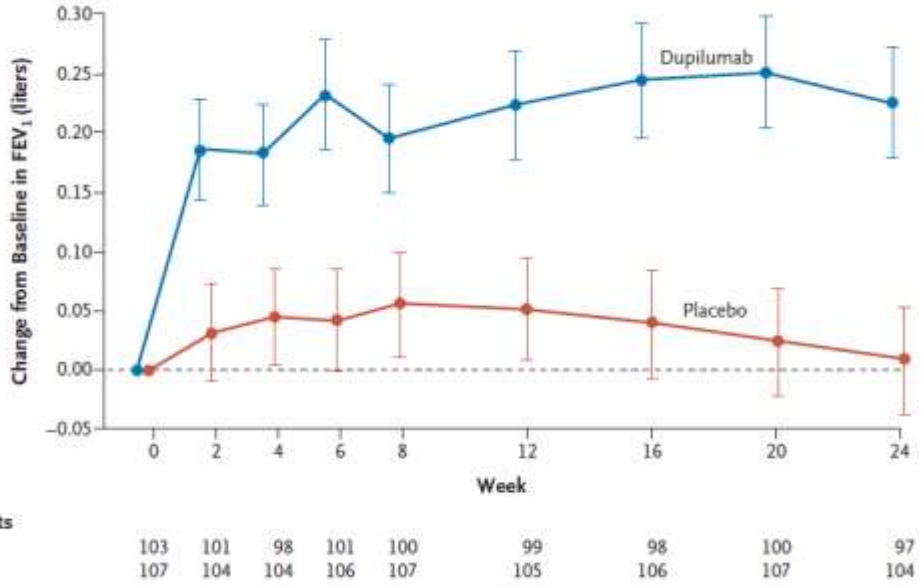
50% dose reduction : 80% v/s 50%

33% dose reduction to <5mg/d

discontinued oral glucocorticoid – 48% v/s 25%

Change from baseline in FEV1 before bronchodilator use

increase in FEV1- 220ml



Rabe et al N Engl J Med June28 2018

Dupilumab

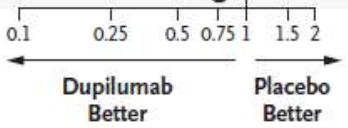
BIOLOGICAL AGENT	POPULATION	EXACERBATION RATE	LUNG FUNCTION
DUPILUMAB	Uncontrolled, moderate-to-severe asthma Size: 1902 Age: mean 47.9; Range 12+ Pre –treatment FEV1: 58.43% Time :52 weeks	Adjusted annualized rate of severe exacerbation Overall: 200mg:-47.7% 300mg:-46.0% Eos high: 200mg:-65.8% 300mg:-67.4%	Pre-BDR FEV1 Overall: 200mg:+0.14L 300mg:+0.13L Eos high: 200mg:+0.21L 300mg:+0.24L

Castro et al N Engl J Med May 21 2018

Liberty asthma quest

Dupilumab,200 mg every2wk, v/s matched placebo

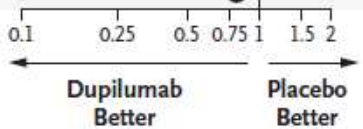
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm^3	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm^3	84	173	0.64 (0.41–1.02)
<150 cells/mm^3	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



Adjusted annualised rate of asthma exacerbation : 200mg/2wk v/s placebo- 0.46 % v/s 0.87 % (47.7% lower rate, p-<0.001)

Dupilumab,300 mg every2wk, v/s matched placebo

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/mm^3	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm^3	95	175	0.56 (0.35–0.89)
<150 cells/mm^3	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)

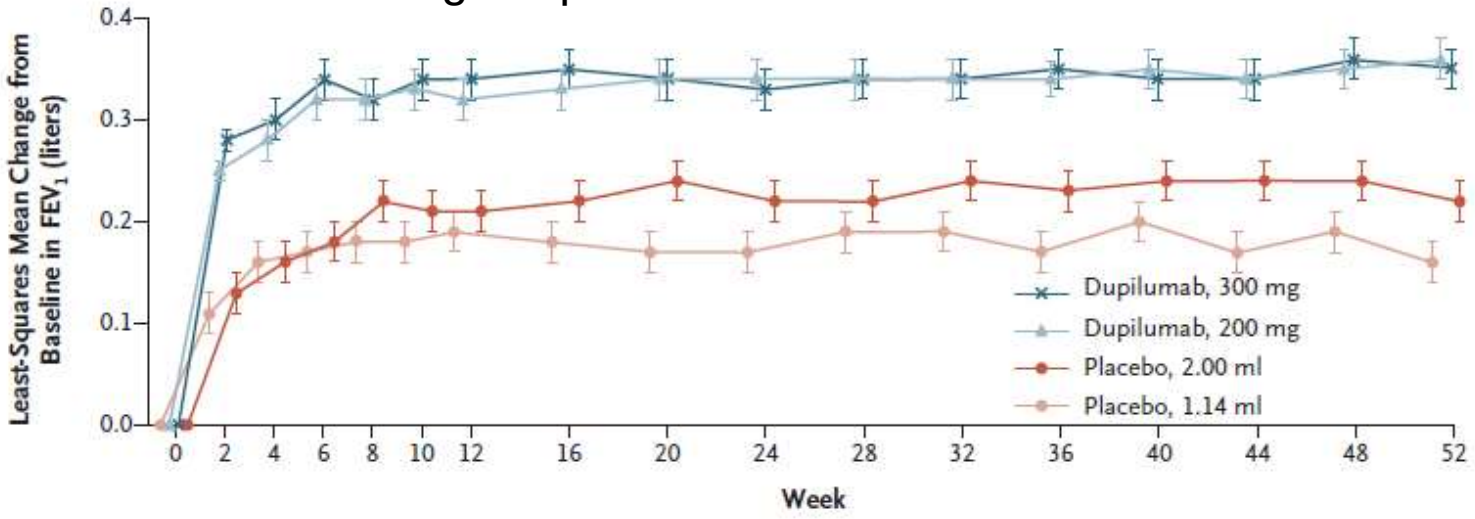


Adjusted annualised rate of asthma exacerbation : 300mg/2wk v/s placebo- 0.52 % v/s 0.97 % (46 % lower rate, p-<0.001)

Castro et al N Engl J Med May 21 2018

Liberty asthma quest

Change in prebronchodilator FEV1 from baseline



No. at Risk																
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

- ✓ Change in prebronchodilator FEV1 from baseline
- ✓ Low dose dupilumab v/s placebo : 0.32 v/s 0.18 ltrs(diff ,0.14 ltrs , p < 0.001)
- ✓ High dose dupilumab v/s placebo: 0.34 v/s 0.21ltrs (diff, 0.13 ltrs , p <0.001)

Castro et al N Engl J Med May 21 2018

PGD2 receptor antagonist

Study	Study population	Study design
To assess safety and efficacy of fevipiprant ,an oral antagonist of prostaglandin receptor, DP2, compared with placebo when added to standard of care of asthma therapy in patients with uncontrolled asthma ZEAL 1(n= 662) & ZEAL 2(n=685)	Patients >12 yrs with uncontrolled asthma	Phase 3, randomised , multicentre, parallel group,placebo controlled and double blinded Duration – 12 wks Fevipiprant -150mg OD

Results :
No statistical significance in primary end point (mean change from base line in pre dose FEV1

Mario castro et al,Eclinicalmedicine, 2021 Apr

PGD2 receptor antagonist

Study	Study population	Study design
To investigate whether fevipiprant reduces asthma exacerbations in patients with severe asthma LUSTER 1 & LUSTER 2	Patients >12 yrs with uncontrolled asthma	Phase 3, randomised , multicentre, parallel group,placebo controlled and double blinded Duration – 52 wks Randomised (1:1:1) into fevipiptrant (150 , 450 mg) and placebo

Results :
Consistent and moderate reduction in asthma exacerbation rates in both studies with 450 mg of fevipiprant → statistically not significant

Brightling CE et al,lancet respir med. 2021 Jan

Tezepelumab

Study	Study population	Study design
To investigate efficacy and safety of tezepelumab in patients with uncontrolled asthma PATHWAY	Patients >12 yrs with uncontrolled asthma	Phase 2, randomised ,placebo controlled and double blinded Duration – 52 wks Randomised (1:1:1 :1) into Tezepelumab 70mg/4wk,n=145 (low) 210mg/4k, n=145(med) 280mg/2wks , n=146 (high) placebo, n=148

Results :

Treatment with tezepelumab resulted in reduced rate of asthma exacerbation at week 52 in all 3 groups as compared to placebo, p=<0.001, independent of baseline blood eosinophil level

Corren et al .N Engl J Med. Sep 7 2017

Tezepelumab

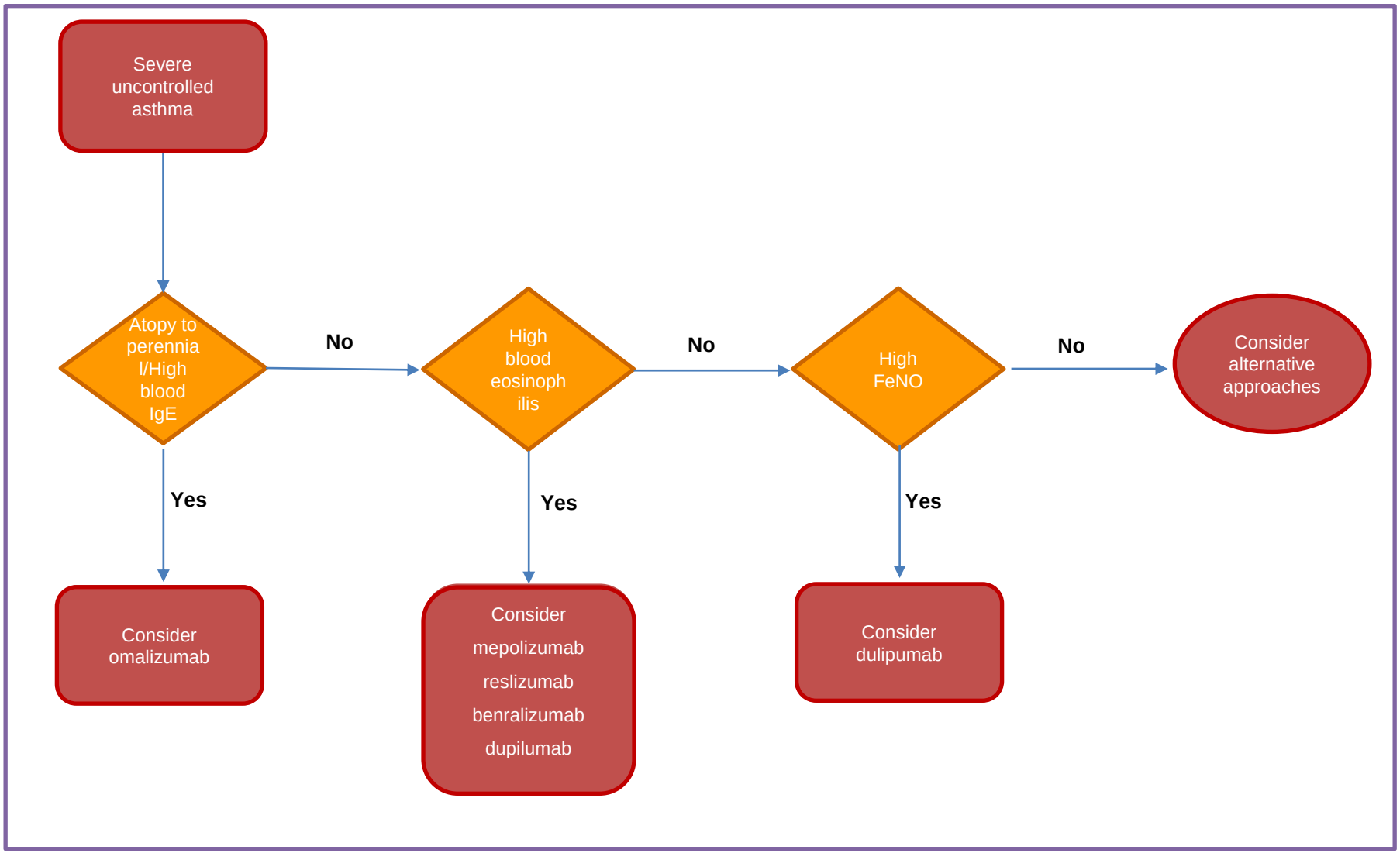
Study	Study population	Study design
To investigate efficacy and safety of tezepelumab in patients with uncontrolled asthma NAVIGATOR	Patients >12 yrs with uncontrolled asthma	Phase 3, randomised ,placebo controlled and double blinded Duration – 52 wks Randomised (1:1) into Tezepelumab 210mg/2wk,n=529 placebo, n=532

Results :

Annualised rate of asthma exacerbation rate: Tezepelumab (0.93) v/s placebo (2.10)
Rate ratio- 0.44 , p <0.001
Pre bronchodilator FEV1 (week 52)- 0.23 v/s 0.09 ltrs , diff- 0.13 ltrs , p- <0.001

Andrew Menzies et al N Engl J Med.May 13 2021

Algorithm for selecting ideal biological treatment for severe uncontrolled asthma



Dragonieri et al . Asthma Research and Practice 2021

Treatment with biologicals based on endotyping

Therapy	Mechanism of action	Endotype	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	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%)
Anaphylaxis (0.3%) – **blackbox warning**
Serum sickness-like reaction ,
Cardiovascular events, including transient ischemic attack and ischemic stroke
Eosinophilic granulomatosis and polyangiitis

Schoettler et al CHEST March 2020

Treatment with biologicals based on endotyping

Therapy	Mechanism of action	Endotype	Comments
Mepolizumab	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/blood eosinophils ≥150 or 300 cells/μl	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%) Injection site reaction (8%-15%)	Antibody response with neutralizing activity (12%) Headache (8%) Pharyngitis (5%)	Antibody to medication (5%) Transient increased Creatinephosphokinase (20%) Oropharyngeal pain (3%) Increased malignancies observed at 6 mo (diverse types) Anaphylaxis (0.3%) – black box warning

Schoettler et al CHEST March 2020

Treatment with biologicals based on endotyping

Therapy	Mechanism of action	Endotype	Comments
Dupilumab	Humanized mAb inhibits actions of IL-4 and IL-13	Blood eosinophils ≥150/µl FENO >25 ppb	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 reactionsood eosinophils ≥150/µl

Schoettler et al CHEST March 2020

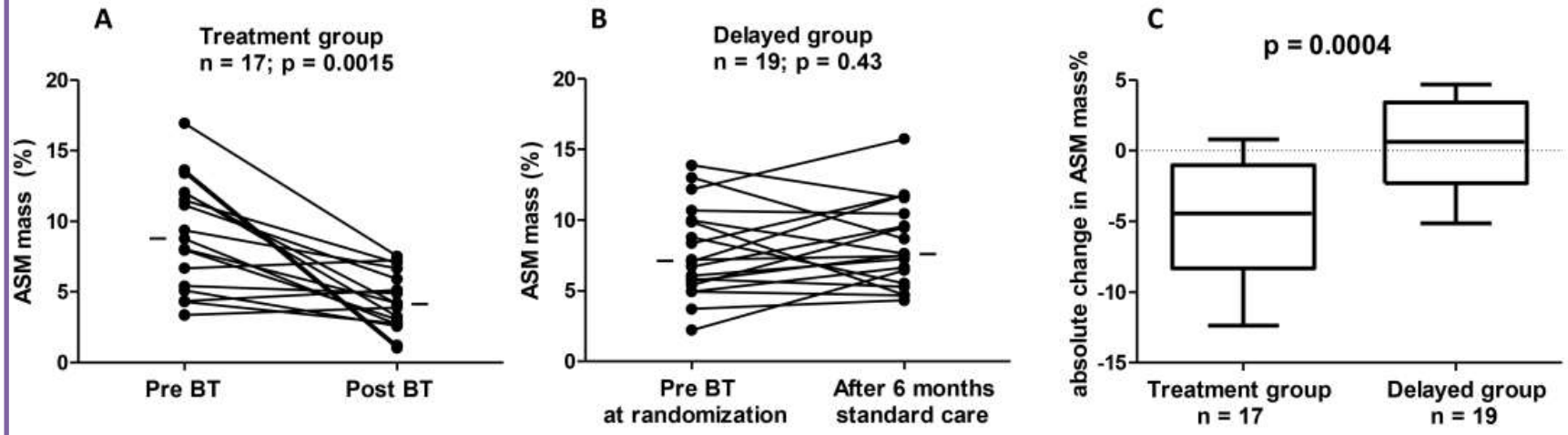
Bronchial thermoplasty – TASMA trial

Population	Intervention	Comparison	Outcome
N=40, Severe asthma patients between 18 and 65 years old Design: RCT in two centers (UK/ Netherlands each	Bronchial thermoplasty	Patients were randomized into A= immediate BT treatment and B= 6 months delayed BT treatment control group (1:1 ratio, n=20 per group).	1.To assess the effect of BT on ASM mass 2. To identify patient characteristics that correlate with BT response

Goorsenberg et al Am J Respir Crit Care Med 2021 Jan

TAMSA trial - results

Airway smooth muscle decrease after bronchial thermoplasty as compared with the randomized control group



Improvement in asthma control questionnaires (ACQ) and asthma quality of life Questionnaires AQLQ

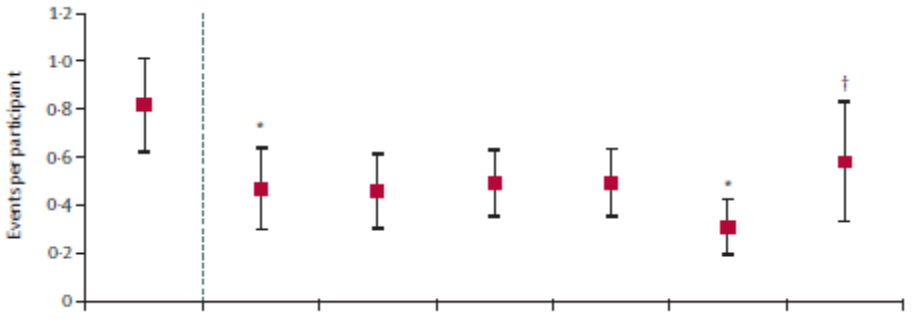
Goorsenberg et al Am J Respir Crit Care Med 2021 Jan

Safety and effectiveness of bronchial thermoplasty in patients with persistent asthma (BT 10 +)

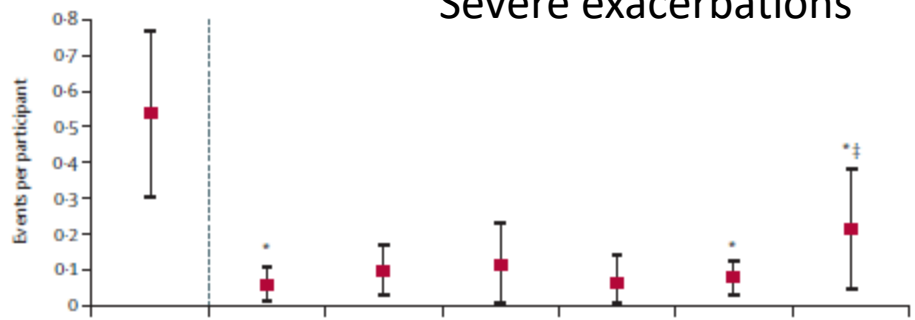
Population	intervention	Comparisons	Outcome
N=192.	BT	A. Treated: Subjects that received BT in a prior study (AIR, RISA, or AIR2) B. Control: Subjects that participated in prior study (AIR) or (RISA) but did not receive BT. C. Sham: Subjects that participated in the AIR2 study, were blinded and did not receive the treatment	A. **Primary Safety Endpoint**: Absence of clinically significant post-treatment respiratory changes defined as bronchiectasis and bronchostenosis from Baseline (pre-BT) CT. B. **Primary Effectiveness:** Endpoints at 10 or more years following the subjects' last BT procedure; Asthma Exacerbations, ER Visits,Hospitalizations,

Chaudhuri et al Europ Resp Journal 2017

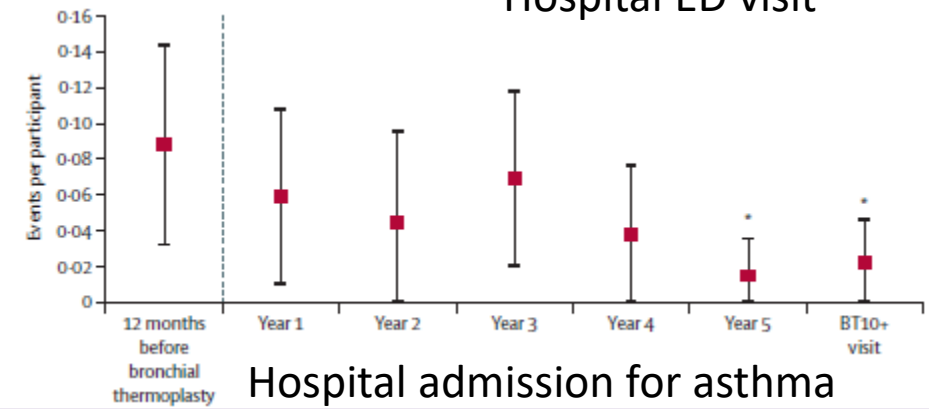
Safety and effectiveness of bronchial thermoplasty in patients with persistent asthma (BT 10 +)



Severe exacerbations



Hospital ED visit



Hospital admission for asthma

Severe exacerbation/participant
12 months prior to BT - 0.82
During 1 st year after BT - 0.47
During 5 th year after BT - 0.31
12 months prior to BT10 + visit – 0.58

Hospital emergency department visits per participant was lower at year 1 after BT, year 5 after BT, and during the 12 months before the BT10+ visit

Lower rates of admissions to hospital for asthma at year 5 and during the 12 months before the BT10+ visit

Chaudhuri et al Europ Resp Journal 2017

Conclusion

- Heterogenous disorder with variable response to available therapies.
- Novel biological therapies available to treat patients with severe asthma.
- Possible to provide personalised medicine based on available biomarkers
- Combination of biologicals and head to head studies for biologicals still awaited