Severe Asthma
What's New

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What is severe asthma?

Review of the Terminology – GINA

Uncontrolled Asthma

- Frequent asthma symptoms and/or flare-ups (exacerbations)
- Many of these patients may potentially have mild asthma, i.e. their asthma could be well-controlled with low dose ICS, if taken regularly

Difficult-to-treat Asthma

- Asthma uncontrolled despite prescribing high dose preventer treatment (not “difficult patients”!)
- Contributory factors may include incorrect diagnosis, incorrect inhaler technique, poor adherence, comorbidities

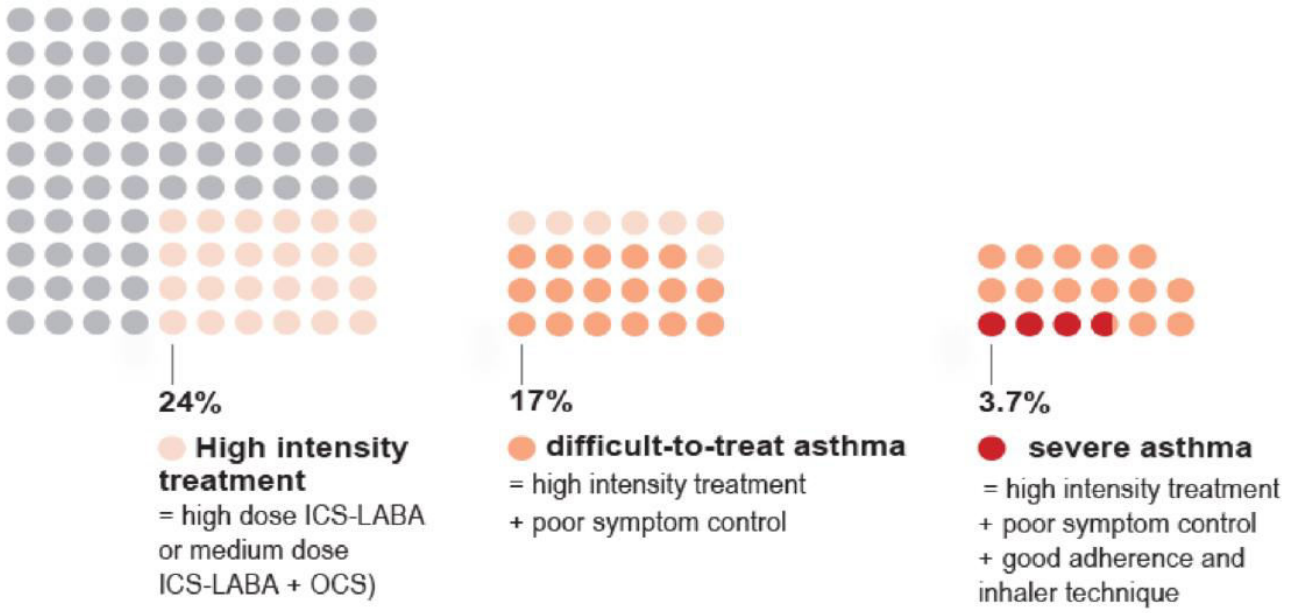
Severe Asthma

- Asthma that is uncontrolled despite **adherence** to **maximal optimised** therapy and **treatment of contributory factors**, or that worsens when high dose treatment is decreased

Introduction – severe asthma

- Severe asthma is a retrospective label
- Severe asthma is uncontrolled despite adherence to optimized high dose ICS-LABA with treatment of contributory factors
- Patients with severe asthma experience a heavy burden of symptoms, exacerbations and medication side effects
- Patients with severe asthma have high healthcare utilization costs related to medication, physician visits and hospitalizations

What proportion of adult asthma is severe asthma?



Data from Hekking et al, JACI 2015

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Nonadherence in the era of severe asthma biologics and thermoplasty

Joy Lee, Tunn Ren Tay, Naghmeh Radhakrishna, Fiona Hore-Lacy, Anna Mackay, Ryan Hoy, Eli Dabscheck, Robyn O'Hehir, Mark Hew

European Respiratory Journal 2018 51: 1701836; **DOI:** 10.1183/13993003.01836-2017

- Consecutive patients with difficult asthma were assessed for eligibility for novel therapies
- Medication adherence, defined as taking >75% of prescribed doses, was assessed by Electronic Monitoring Devices (EMD) over an 8-week period
- Nonadherence was confirmed in 20 out of 45 (44.4%) patients
- **Among those eligible for novel therapies, with confirmed nonadherence in 16 out of 32 (50%) patients with EMD data**

Addressing suboptimal adherence

Am J Respir Crit Care Med. 2009 Nov 1;180(9):817-22. doi: 10.1164/rccm.200902-0166OC. Epub 2009 Jul 30.

The prevalence of nonadherence in difficult asthma.

Gamble J[1], Stevenson M, McClean E, Heaney LG.

- **88% patients admitted to nonadherence after initial denial**
  - 35% patients filled fewer than 50% of their ICS prescriptions
  - 21% patients filled more than 100% of their ICS prescriptions

J Allergy Clin Immunol. 2011 Dec;128(6):1185-1191.e2. doi: 10.1016/j.jaci.2011.09.011. Epub 2011 Oct 21.

Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence.

Williams LK[1], Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, Chowdhry VK, Favro D, Lanfear DE, Pladevall M.

- **24% of asthma exacerbations are attributable to nonadherence to ICS**
- Adherence > 75% is associated with reduced risk of exacerbations compared to adherence < 25% (HR = 0.61; 95% CI = 0.41 – 0.90)

Ask about adherence at each visit, be empathetic

Incorrect inhaler technique

Respir Care. 2005 Oct;50(10):1360-74; discussion 1374-5.

Problems with inhaler use: a call for improved clinician and patient education.

Fink JB[1], Rubin BK.

- **28 – 68% of patients do not use their MDI's or DPI's correctly**
- 39 – 67% of nurses, doctors, and respiratory therapists are unable to perform or demonstrate inhaler technique
- 5 to 7 billion dollars are wasted every year due to improper inhaler use
- Improper technique leads to poor control and increases risk of exacerbation and adverse effects

NPJ Prim Care Respir Med. 2017 Apr 13;27(1):24. doi: 10.1038/s41533-017-0022-1.

Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review.

Klijn SL[1], Hiligsmann M[2], Evers SMAA[2], Román-Rodríguez M[3], van der Molen T[4], van Boven JFM[4].

- Checking and correcting inhaler technique takes 2 – 3 minutes
- Trained pharmacists and nurses can provide highly effective inhaler technique training
- Effectiveness of intervention wanes with time elapsed since intervention

Assess inhaler technique at each visit

A General Approach

1. Does the patient truly have severe asthma?

2. Is the patient a candidate for biologic therapy?

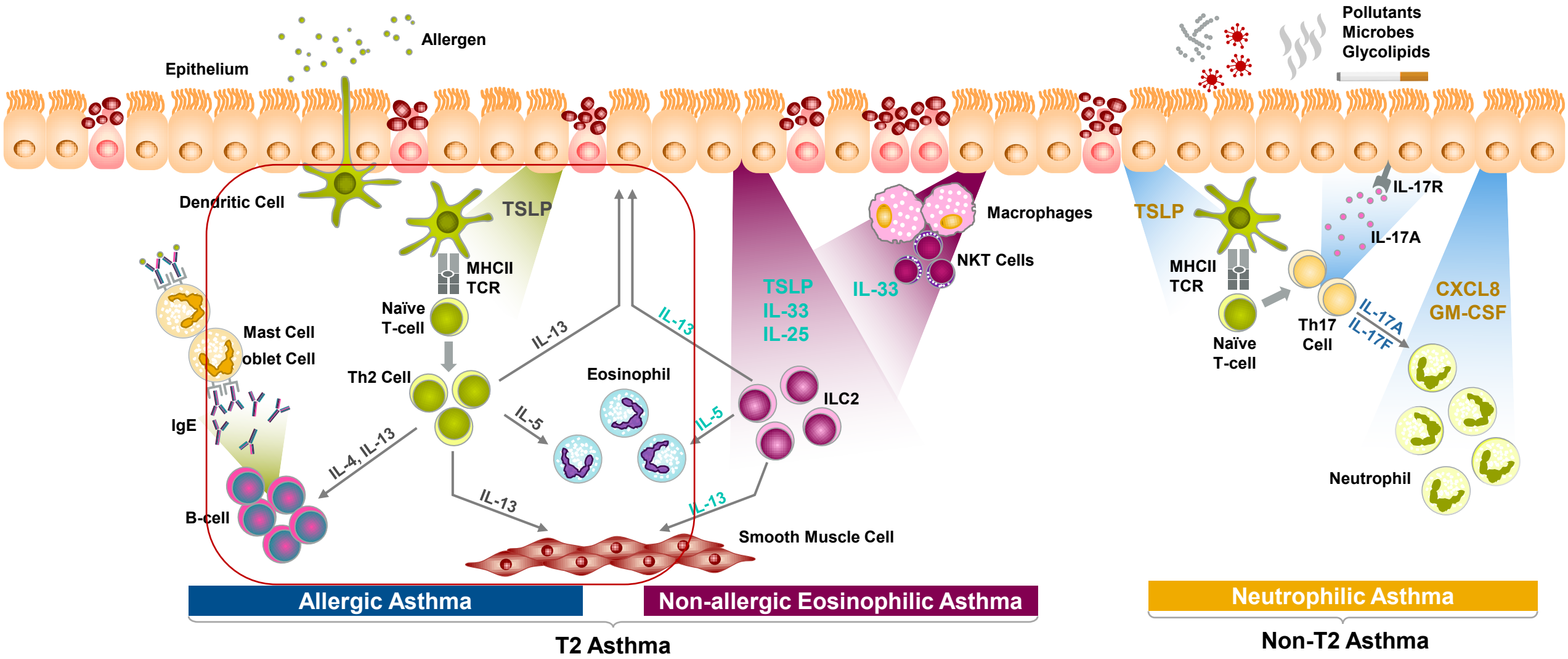
3. Which is the most appropriate biologic therapy?

4. How to follow-up a patient on biologic therapy?

Newer Therapeutic Modalities for Severe Asthma:

- Biologics
- Bronchial Thermoplasty

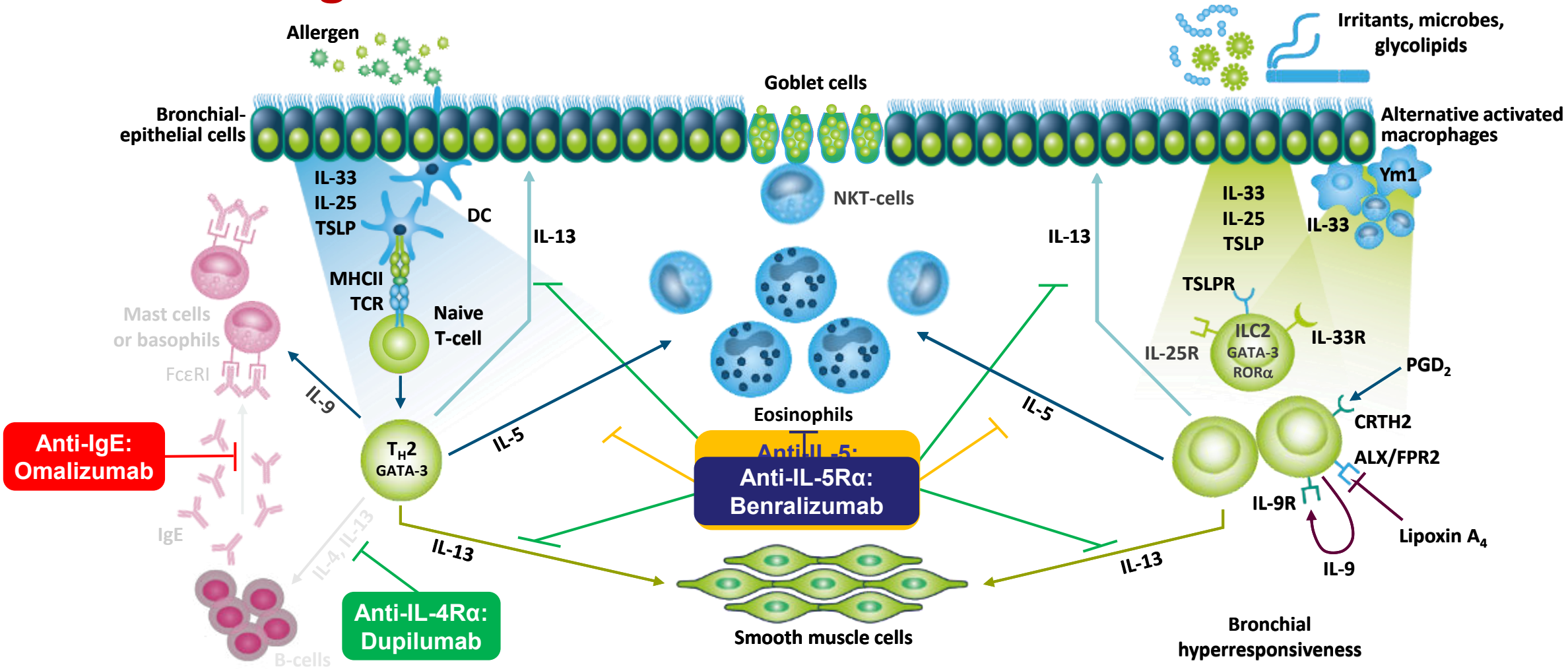
Inflammatory pathways of Asthma (T2 and Non T2)



CXCL8=C-X-C Motif Chemokine Ligand 8; GM-CSF=granulocyte-macrophage colony-stimulating factor; IgE=immunoglobulin E; IL=interleukin; ILC2=innate lymphoid cell 2; MHC=major histocompatibility complex; NKT=natural killer T cell; R=receptor; TCR=T-cell receptor; T2=type 2; Th=T helper; TSLP=thymic stromal lymphopoietin.

Adapted from Brusselle G et al. *Ann Am Thorac Soc*. 2014;11(Suppl 5):S322-S328 and Pelaia G et al. *Nature Rev Drug Dis*. 2012;11:958-972.

Biologic therapies target key pathways in the pathogenesis of allergic and non-allergic asthma



Omalizumab binds to IgE reducing the amount of free IgE that is available to trigger the allergic cascade

1. Brusselle GG et al. *Nat Med*. 2013;19:977-979. 2. Lambrecht BN, Hammad H. *Nat Immunol*. 2015;16:45-56. 3. Omalizumab [summary of product characteristics]. Novartis. 2015. 4. Dupilumab [summary of product characteristics]. Sanofi-Aventis. 2018. 5. Tan L et al. *J Asthma Allergy*. 2016;9:71-81. 6. Kolbeck R et al. *J Allergy Clin Immunol*. 2010;125:1344-1353. 7. Molfino NA et al. *Clin Exp Allergy*. 2011;42:712-737.

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

- Objective: To assess the effects of omalizumab versus placebo or conventional therapy for asthma in adults and children.

- 25 randomised, placebo-controlled clinical trials involving 6382 people with mainly moderate to severe Asthma were studied. Treatment duration ranged between 8 and 60 weeks

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

Analysis 1.2. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid),

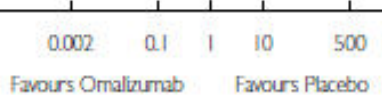
Analysis 1.4. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 4 Mortality.

Review: Omalizumab for asthma in adults and children

Comparison: 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid)

Outcome: 4 Mortality

Study or subgroup	Experimental n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate to severe asthma					
Busse 2001	0/268	1/257		30.3 %	0.32 [0.01, 7.85]
Busse 2011	0/208	0/211			Not estimable
Lanier 2009	0/421	0/206			Not estimable
Massanari 2010	0/139	0/136			Not estimable
Ohta 2009	0/158	0/169			Not estimable
SOLAR	0/209	0/196			Not estimable
Sol r 2001	0/274	0/272			Not estimable
Subtotal (95% CI)	**1677**	**1447**		**30.3 %**	**0.32 [0.01, 7.85]**
Total events: 0 (Experimental), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
2 Severe asthma					



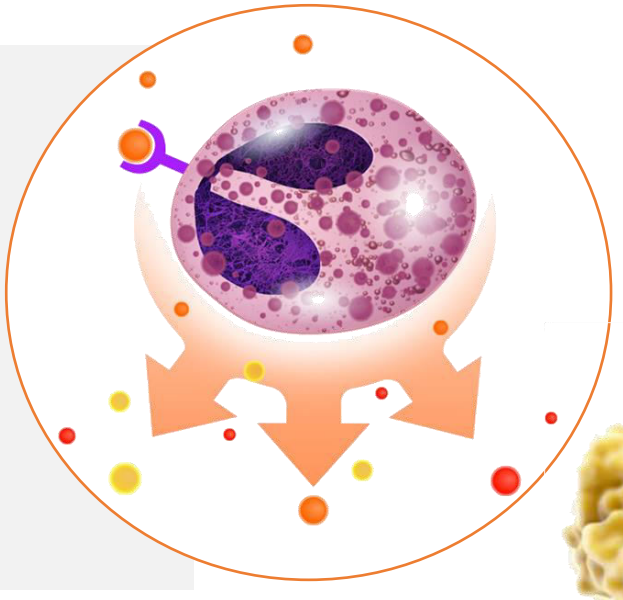
(Continued . . .)

Mepolizumab targets IL-5

IL-5[1]

Major cytokine responsible for eosinophil:

- ✓ **Recruitment**
- ✓ **Maturation**
- ✓ **Activation**
- ✓ **Survival**



Mepolizumab[2]

- ✓ **First humanised mAb that targets IL-5**

1. Garcia G, Taille C et al. Anti-interleukin-5 therapy in severe asthma *Eur Resp Rev* 2013

2. Nucala – Swiss Prescribing Information www.swissmedicinfo.ch,

MEPOLIZUMAB : PHASE IIB/III CLINICAL STUDIES

DREAM
(Pavord ID *et al* 2012)

Dose-**R**anging **E**fficacy **A**nd safety with **M**epolizumab

MENSA
(Ortega HG *et al* 2014)

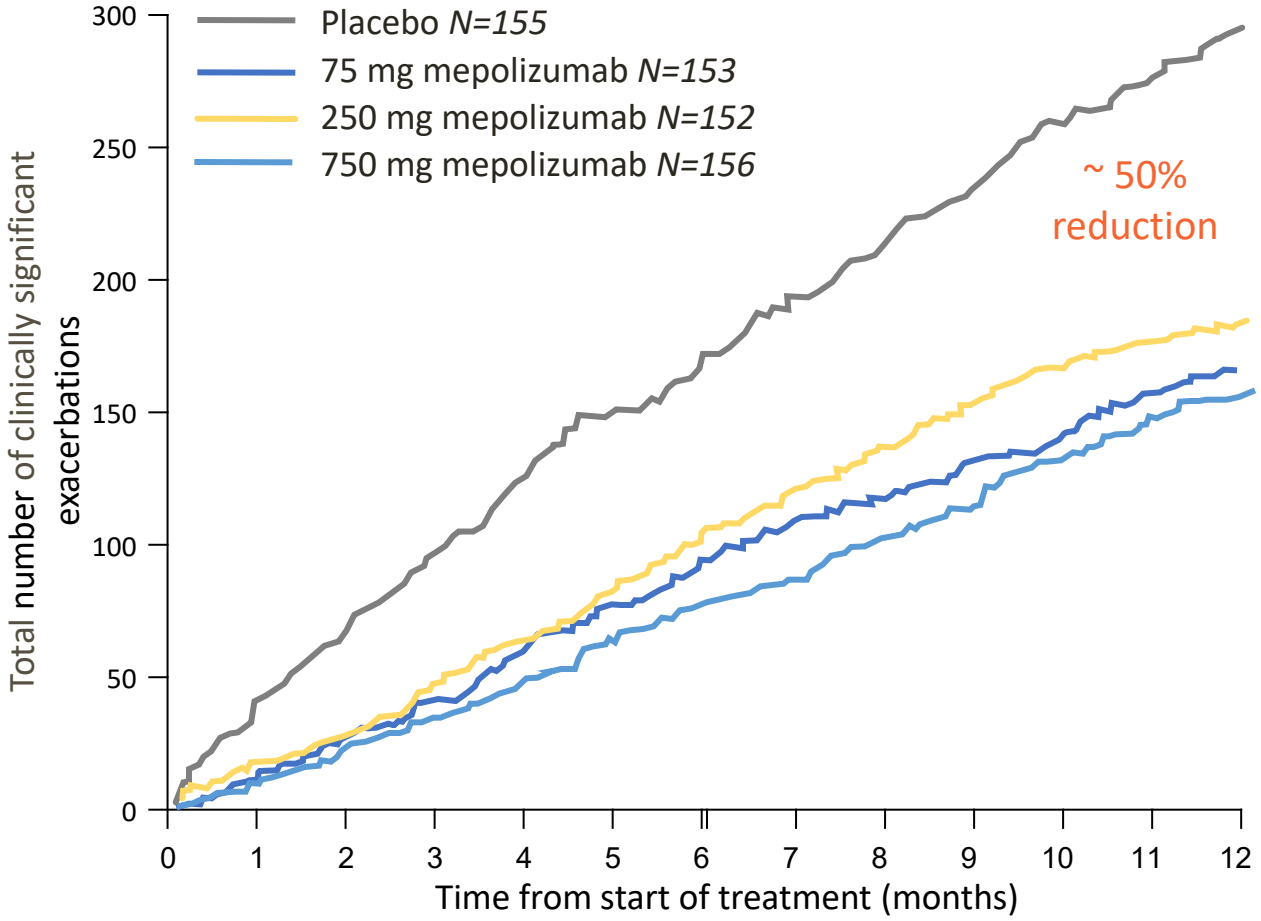
MEpolizumab as adjunctive therapy i**N** Patients with **S**evere **A**sthma

SIRIUS
(Bel EH *et al* 2014)

The **S**tero**I**d **R**educt**I**on with mepoliz**U**mab **S**tudy

FREQUENCY OF CLINICALLY SIGNIFICANT EXACERBATIONS

DREAM: primary efficacy endpoint



Primary endpoint

Rate of clinically significant exacerbations per year

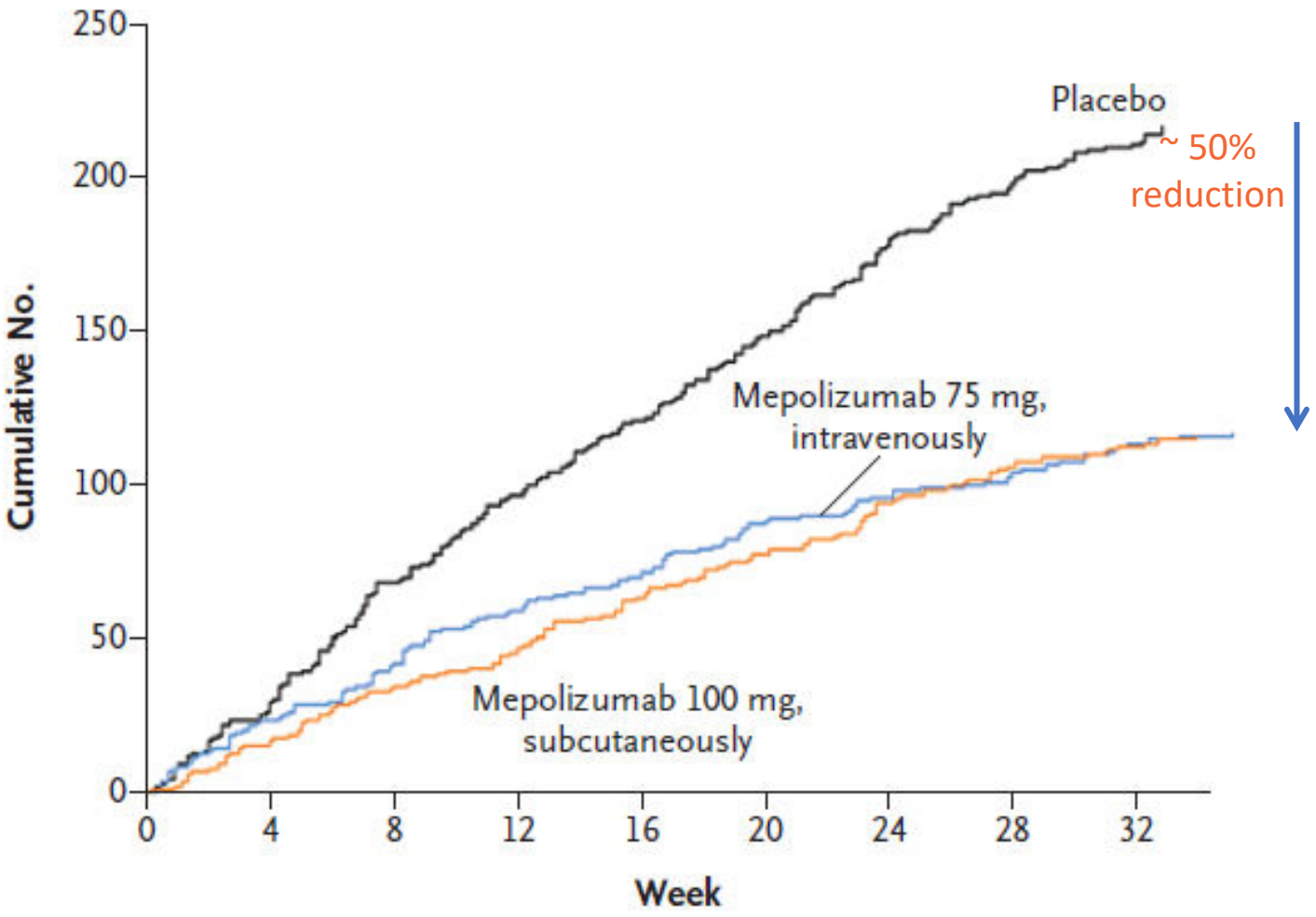
- Placebo: 2.40
- 250mg: 1.46 (39% reduction, p<0.001)
- 75 mg: 1.24 (48% reduction, p<0.001)
- 750 mg: 1.15 (52% reduction, p<0.001)

Pavord ID et al. *Lancet*. 2012;380:651–659.

Mepolizumab is approved for subcutaneous administration only

RATE OF CLINICALLY SIGNIFICANT EXACERBATIONS

MENSA: PRIMARY EFFICACY ENDPOINT



Primary endpoint
Rate of clinically significant exacerbations per year

- Placebo: 1.74
- 75 mg IV: 0.93 (47% reduction, p<0.001)
- **100 mg SC: 0.83 (53% reduction, p<0.001**)

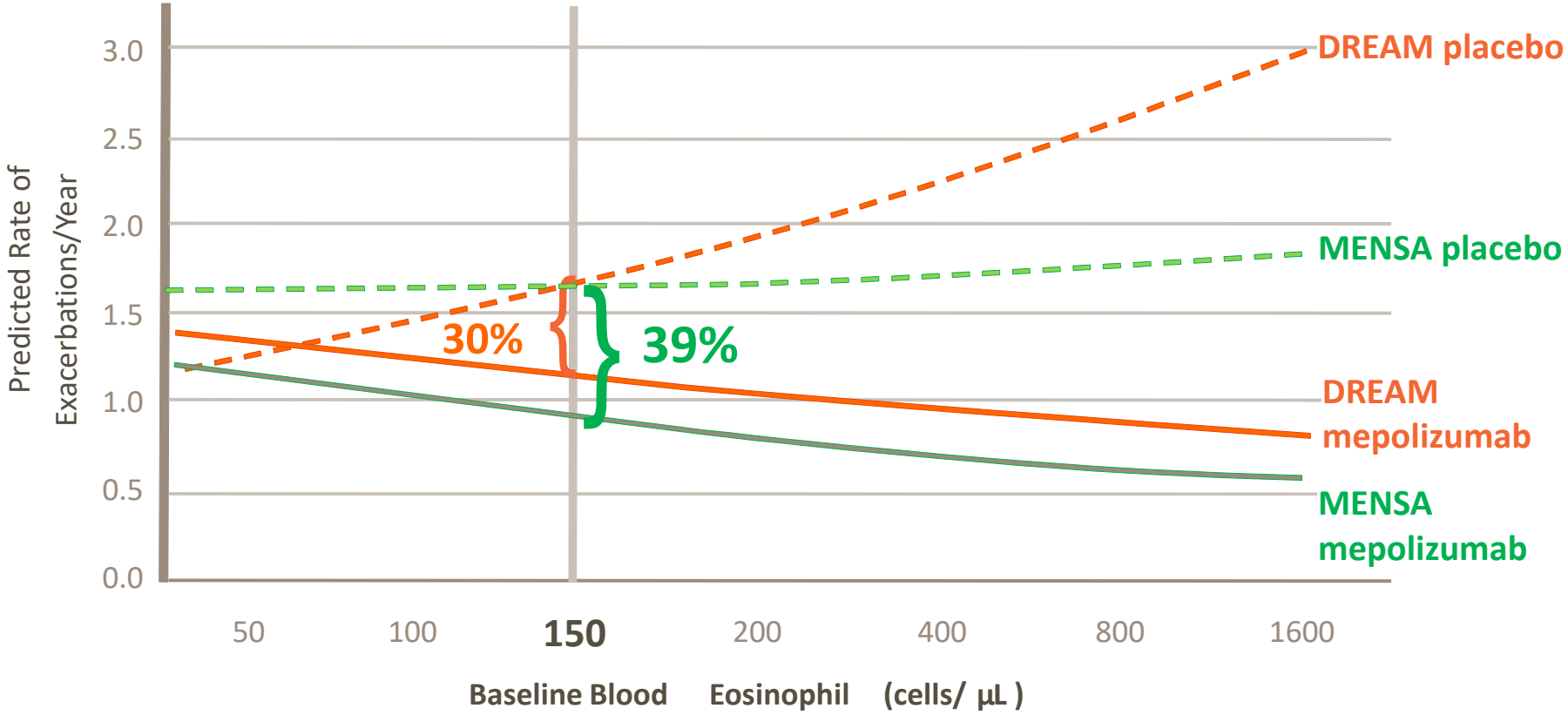
Mepolizumab is approved for subcutaneous administration only

Ortega HG, et al. *N Engl J Med*. 2014;371:1198-1207

The DREAM and MENSA Studies

DREAM and MENSA Modelling Analysis

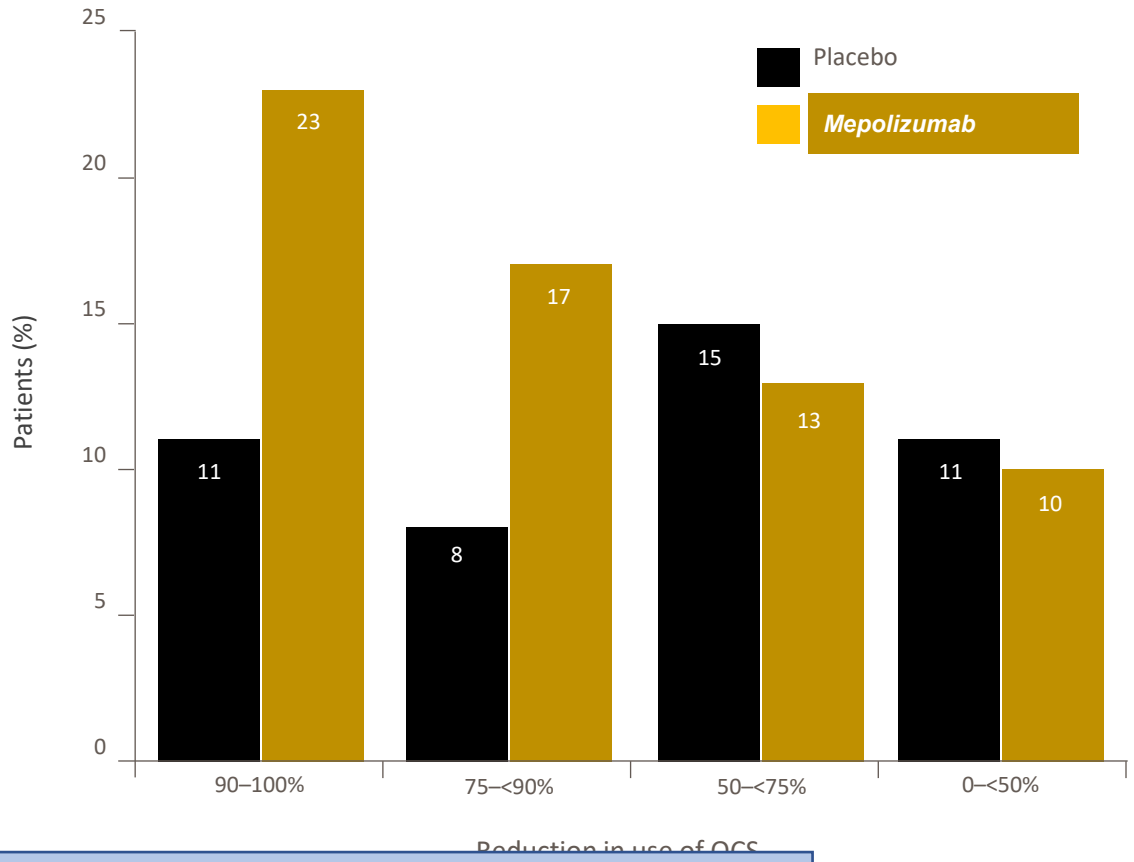
Meaningful reduction in exacerbation was achieved at a baseline **blood eosinophil count of 150 cells/µL** in MENSA analysis



Ortega et al. Lancet Respir Med 2016

THE SIRIUS STUDY

- Double-blind, multicentre placebo controlled study (n-135)
  - Atleast 6 month history of OCS- 0-35mg/day
  - Duration- 20 weeks
  - History of ≥ 2 exacerbations requiring systemic steroids
  - Eosinophilic inflammation- Blood eosinophil ≥ 150/µL,
- Mepolizumab dose- 100mg sc
- Outcome- Reduction in GC dose, rate of exacerbations, safety



Conclusion: 2.39 times higher odds of achieving a reduction in OCS dose in patients receiving Mepolizumab versus placebo

Reslizumab

- US FDA approval in 2016

- Labelled indications:
- **Add-on maintenance** treatment of patients with **severe asthma aged 18 years** and older, and with an **Eosinophilic phenotype**

- **Intravenous infusion- 3mg/kg once every 4 weeks** given over 20-50 minutes

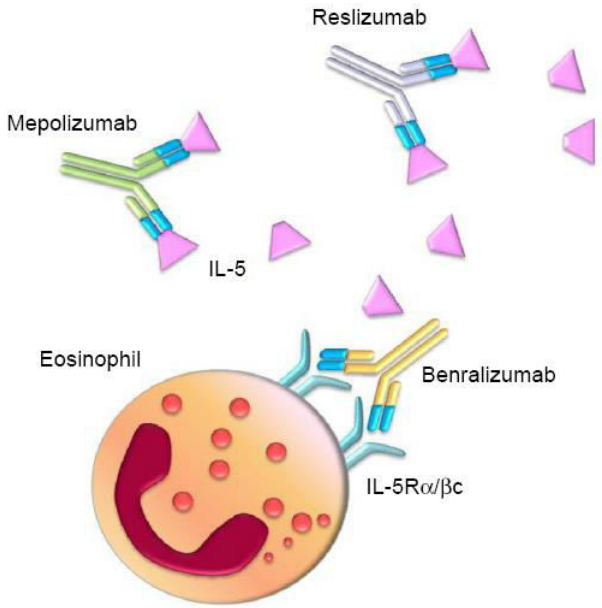


Figure 2 Anti-IL-5/IL-5R biologic therapies.

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

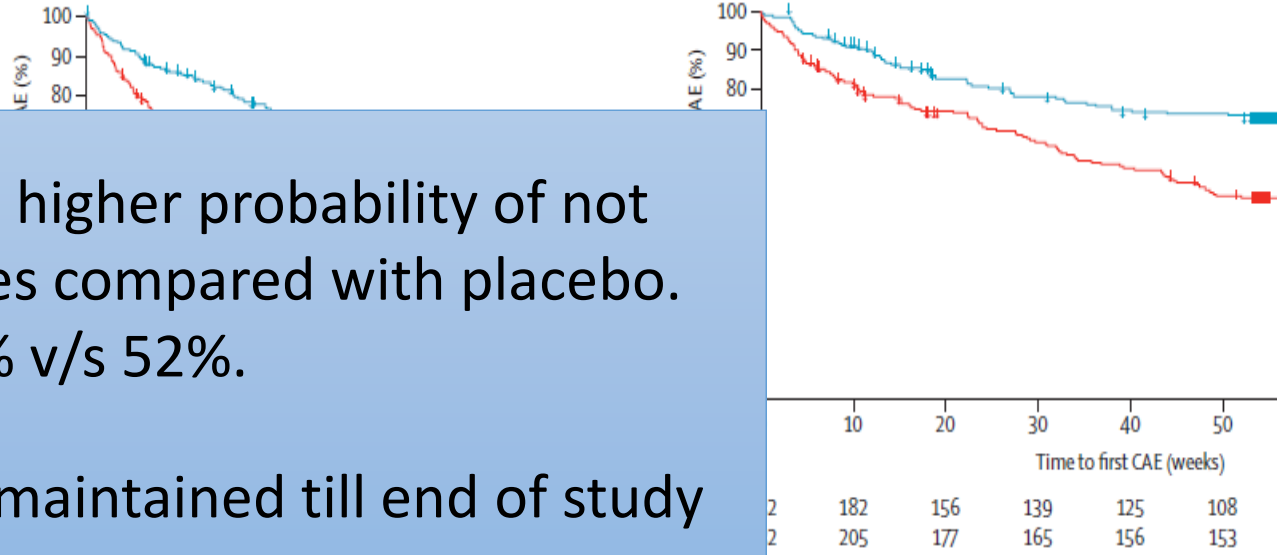
Lancet Respir Med 2015
Published Online
February 23, 2015
http://dx.doi.org/10.1016/S2213-2600(15)00042-9

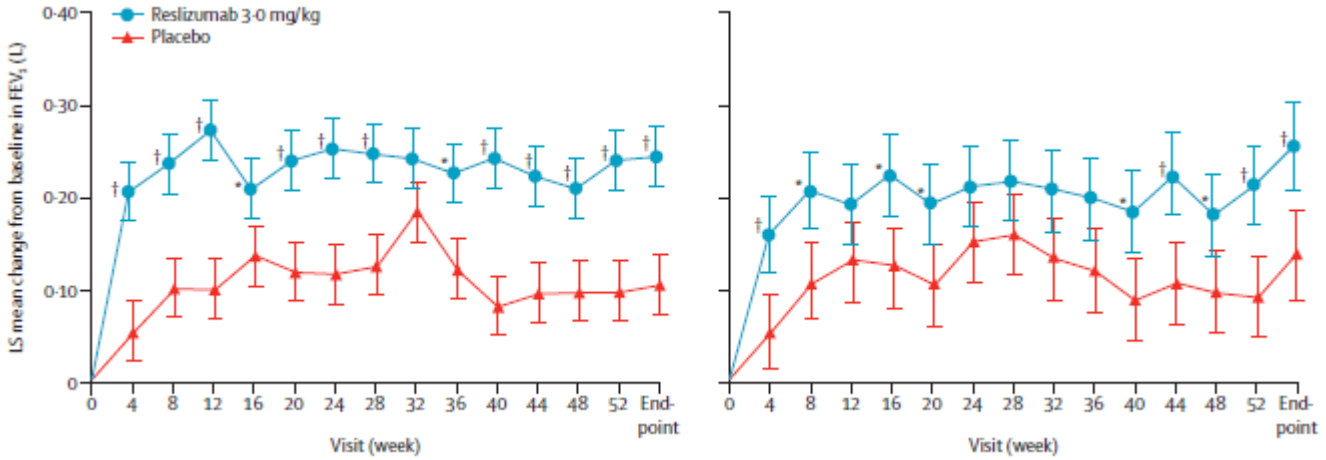
Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O'Brien, Stephanie Korn

- 2 Double-blind, multicentre, parallel group placebo controlled study (n 953)
  - 12-75 yr, ICS
  - Duration
  - History c steroids
  - Eosinophilic inflammation- Blood eosinophil ≥ 400/µL,
- IV Reslizumab (3mg/kg) every 4 weeks
- Outcome- Annual frequency of clinical asthma exacerbations

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%.

FEV1 improvement by week 4 and maintained till end of study





Benralizumab

- FDA approved - 2017
- Labelled indications:
- **Add-on maintenance** treatment of patients with **severe asthma aged 12 years and older**, and with an eosinophilic phenotype

- Dose: **30 mg every 4 weeks** for the first 3 doses followed by 30 mg **every 8 weeks**

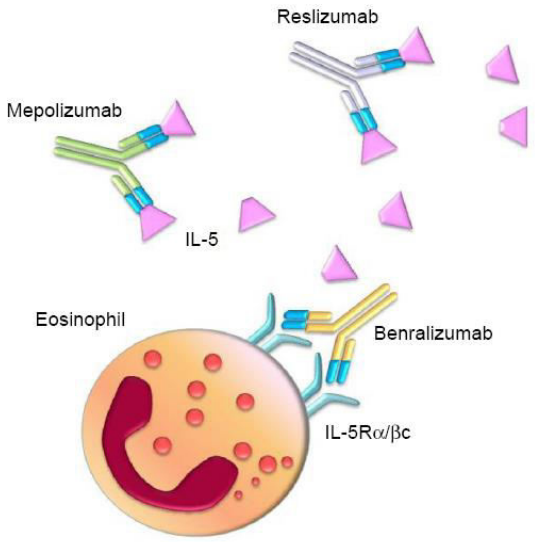


Figure 2 Anti-IL-5/IL-5R biologic therapies.

Important studies

- SIROCCO study- RCT 2016
- CALIMA study- RCT 2016
- BORA study- RCT 2018
- ANDHI Study- RCT 2021

SIROCCO

- Double-blind, multicentre, RCT (n-1205)
  - 12-75 yr, poorly controlled asthma on high ICS-LABA
  - Duration- 48 weeks
  - History of ≥ 2 exacerbations requiring systemic steroids
  - Eosinophilic inflammation- Blood eosinophil ≥ 300/µL,
- Benralizumab 3omg every 4 wks, 8 wks (1st 3 doses 4 weekly)
- Outcome- Annual exacerbation rate, FEV1 change
- Results:
  - Both groups reduced AER- 0.55 & 0.49 for 4 wkly a
  - Both g for 4 w

CALIMA

- Double-blind, multicentre, RCT (n-1306)
  - 12-75 yr, poorly controlled asthma on med- high ICS-LABA
  - Duration- 56 weeks
  - History of ≥ 2 exacerbations requiring systemic steroids
  - 2 groups: Blood eosinophil ≥ 300/µL, <300/µL
- Benralizumab 3omg every 4 wks, 8 wks (1st 3 doses 4 weekly)
- Outcome- Annual exacerbation rate, FEV1 change in both groups
- Results:
  - Both groups reduced AER- 0.60 & 0.66 for 4

nd 8 wkly

Conclusion: Benralizumab leads to an improvement in lung function and reduce asthma exacerbations in people with severe eosinophilic asthma.

Randomized Controlled Trial > N Engl J

doi: 10.1056/NEJMoa1703501. Epub 2017 Ma

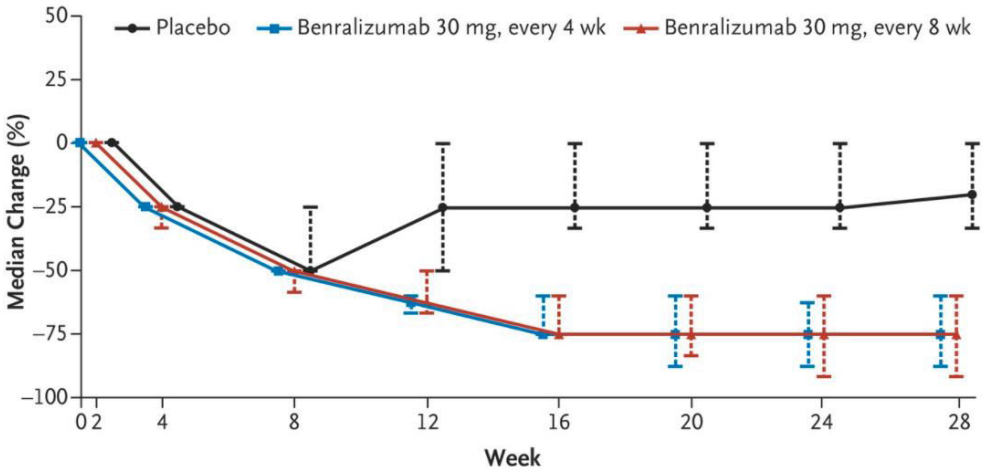
Oral Glucocorticoid-Spa in Severe Asthma

Parameswaran Nair [1], Sally Wenzel [1], Klaus

- RCT (n= 220)
- Duration: 28 weeks
- Benralizumab- 30 mg sc q4 wk or q8 wk (1st 3 doses q4 week) v/s placebo
- Outcome: Percentage change in the oral glucocorticoid dose from baseline to week 28

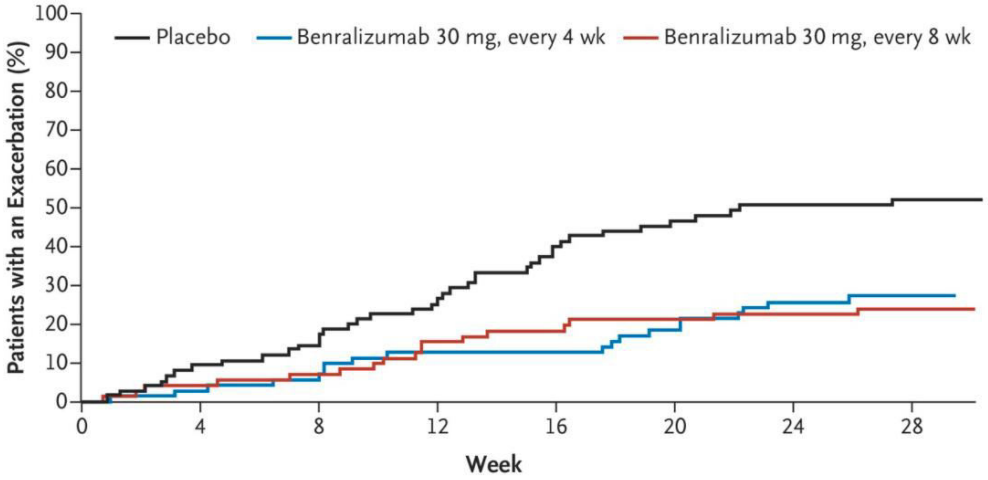
Conclusion: Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates

A Change from Baseline in Oral Glucocorticoid Dose



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
Placebo	74	75	73	74	74	73	73	72

B Time to First Asthma Exacerbation

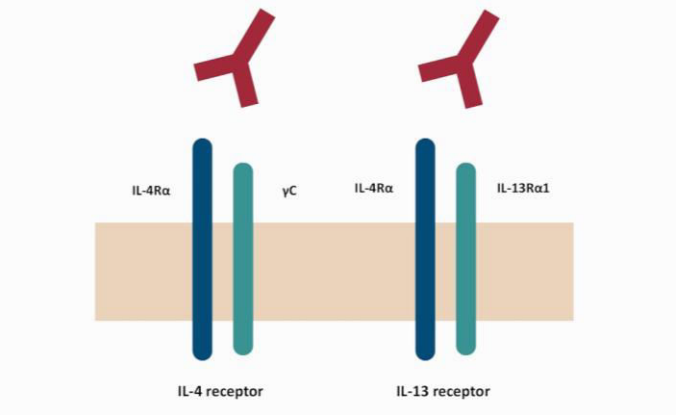


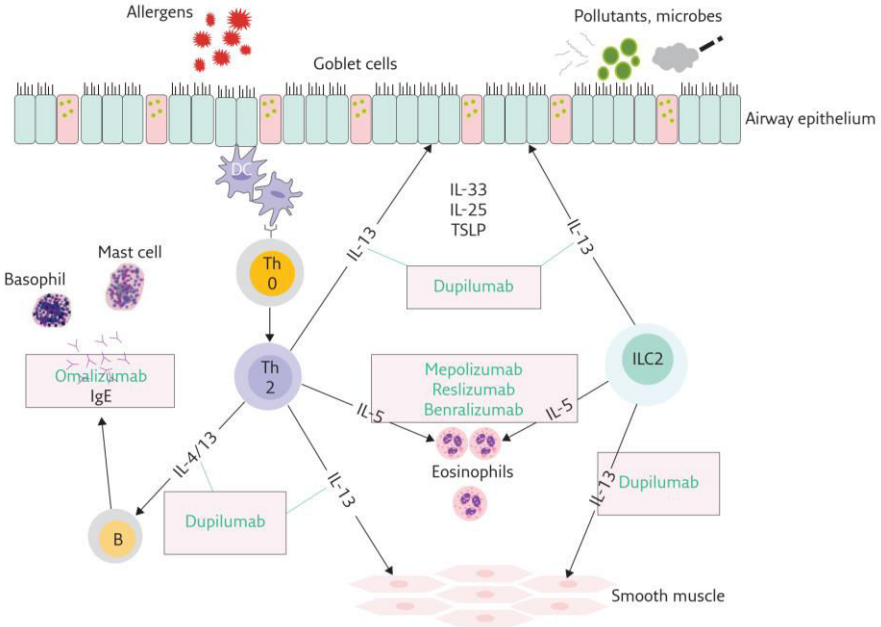
No. at Risk								
Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

Dupilumab

- US FDA approval 2017
- Interleukin-4 receptor alpha antagonist- inhibits action of IL-4 & IL-3
- 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

- Initial dose of 600 mg (two 300 mg sc) followed by 300 mg given every 2 weekly (Q2W)





Liberty Asthma Quest Trial

ORIGINAL ARTICLE

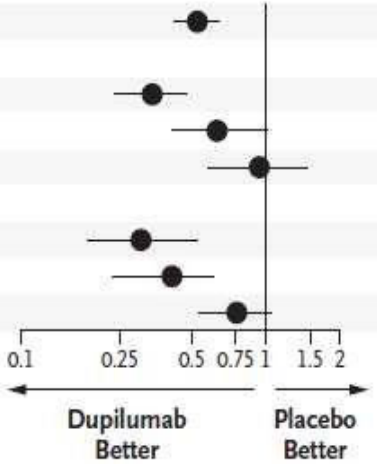
N Engl J Med 2018;378:2486-96.

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

- Double-blind, multicentre, RCT (n-1264)
  - 12-75 yr, poorly controlled asthma on high ICS-LABA
  - Duration- 52 weeks
  - History of ≥ 1 exacerbations requiring systemic steroids
- Dupilumab: 200mg v/s 300mg every 2 wks
- Outcome- Annual exacerbation rate, FEV1 change
- Results:

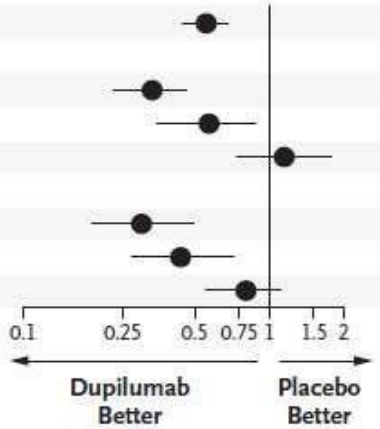
Conclusion: Dupilumab is associated with better lung function and asthma control. Greater benefits in patients with higher baseline levels of eosinophils.

Subgroup	No. of Patients: Placebo	No. of Patients: Dupilumab	Relative Risk vs. Placebo (95% CI)
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: Placebo	No. of Patients: Dupilumab	Relative Risk vs. Placebo (95% CI)
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)
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)



upilumab, 300 mg every2wk

Anti IL-13 Biologics

The following therapeutic antibodies targeting IL-13 have been studied

Lebrikizumab	Tralokinumab
Roche/Genentech	AZ/MedImmune
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.

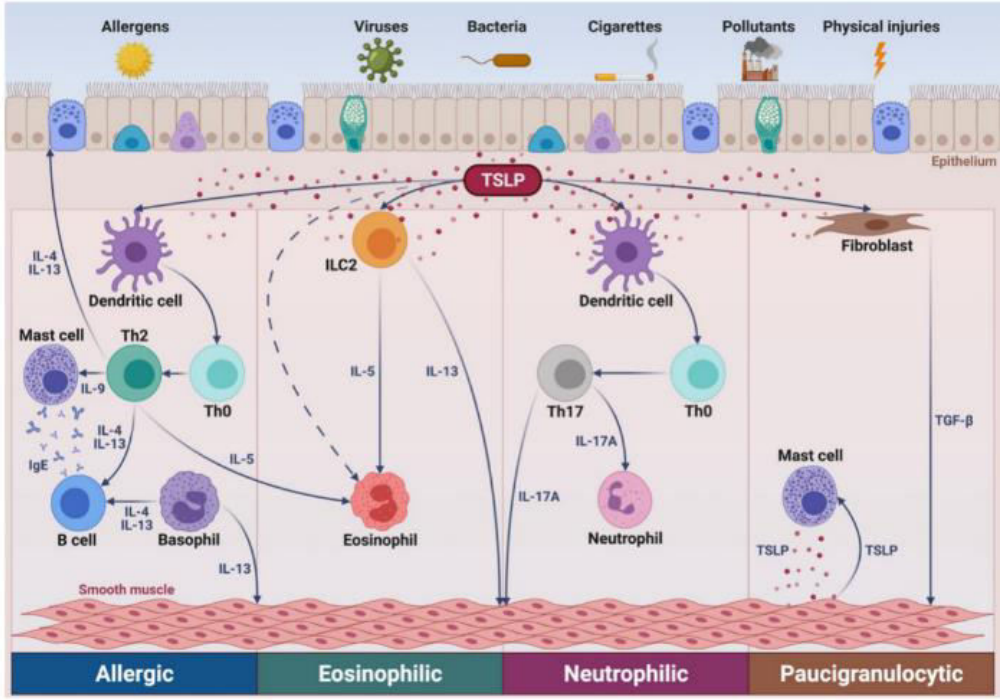
Anti-epithelial cytokine antibodies

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

Tezepelumab

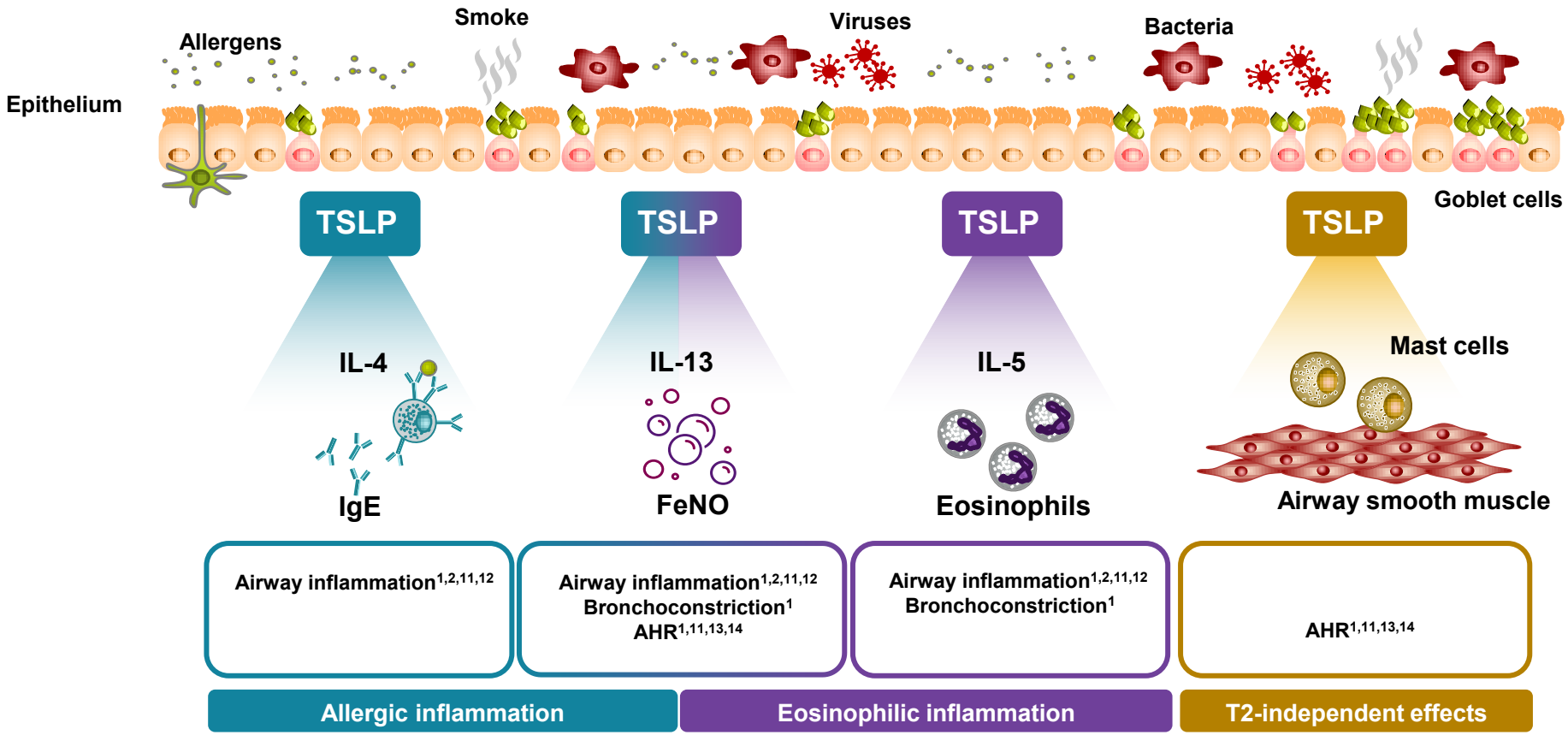
- US-FDA approved - 2021
- Labelled indications:
- **Add-on maintenance** treatment of patients with **Severe asthma aged 12 years and older**

- Dose: 210 mg sc q4 weeks



TSLP Drives Allergic and Eosinophilic Inflammation and T2-independent Effects from the Top of the Cascade

- **Epithelial cells are the primary source** of TSLP[4]
- TSLP initiates multiple **downstream innate and adaptive immune responses** involved in asthma inflammation and pathology[1–3,5–10]



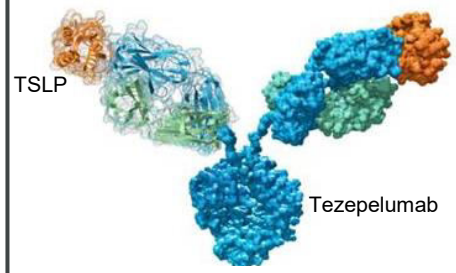
AHR = airway hyperresponsiveness; FeNO = Fractional Exhaled Nitric Oxide; IgE = Immunoglobulin E; IL = Interleukin; T2 = Type 2; TSLP = Thymic Stromal Lymphopoietin

Figure adapted from Porsbjerg CM et al. *Eur Respir J.* 2020;56:2000260, Ishmael FT. *J Am Osteopath Assoc.* 2011;111(suppl 7):S11–S17, and Gauvreau GM et al. *Expert Opin Ther Targets* 2020;24:777–792, which was based on Brusselle G, Bracke K. *Ann Am Thorac Soc.* 2014;11(suppl 5):S322–S328, Brusselle G et al. *Nat Med*. 2013;19:977–979, and Lambrecht BN, Hammad H. *Nat Immunol.* 2015;16:45–56

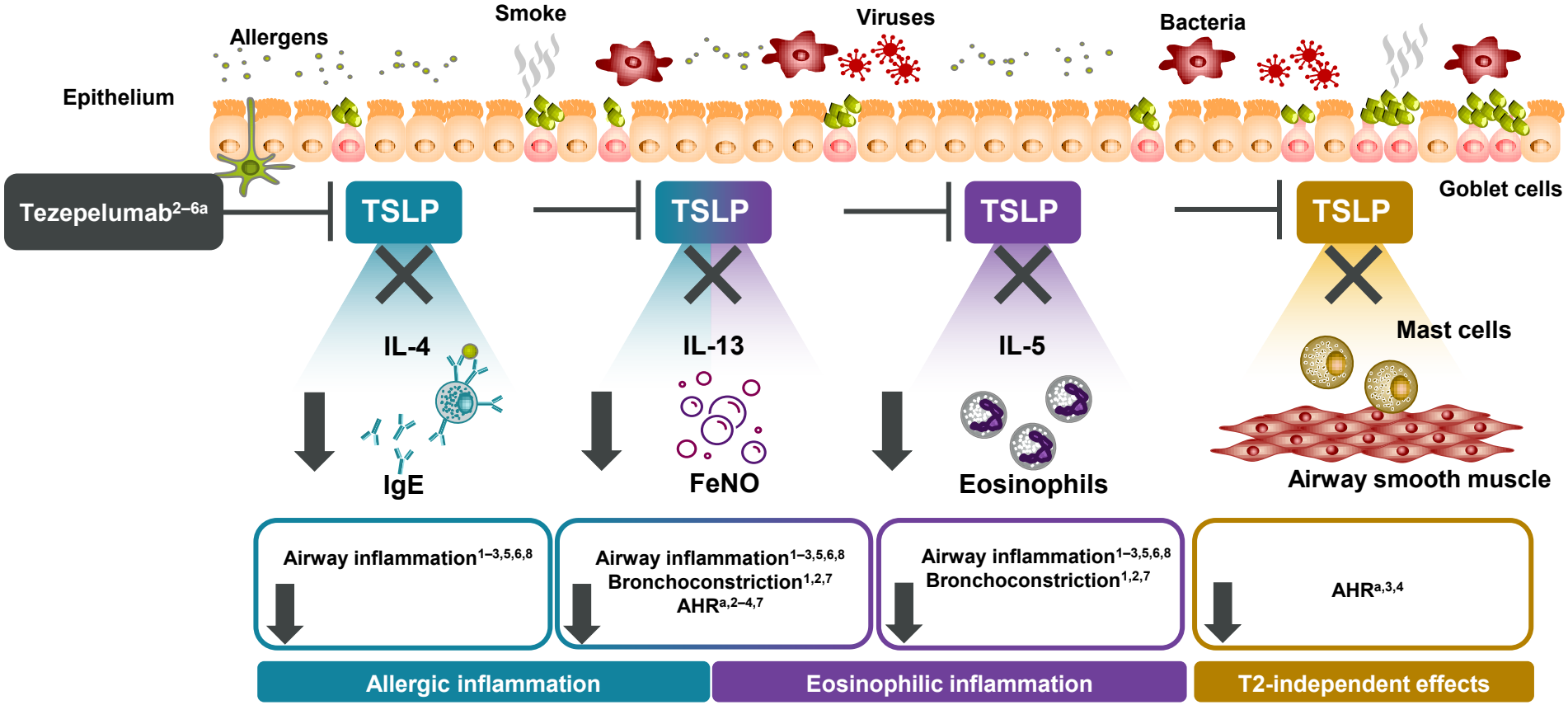
1. Gauvreau GM et al. *Expert Opin Ther Targets.* 2020;24:777–792; 2. Porsbjerg CM et al. *Eur Respir J.* 2020;56:2000260; 3. Roan F et al. *J Clin Invest*. 2019;129:1441–1451; 4. Bartemes KR, Kita H. *Clin Immunol*. 2012;143:222–235; 5. Soumelis V et al. *Nat Immunol.* 2002;3:673–680; 6. West EE et al. *Drug Discov Today Dis Mech*. 2012;9:10.1016/j.ddmec.2012.09.003; 7. Kaur D et al. *Chest*. 2012;142:76–85; 8. Allakhverdi Z et al. *J Exp Med*. 2007;204:253–258; 9. Watanabe N et al. *Nat Immunol.* 2004;5:426–434; 10. Ito T et al. *J Exp Med.* 2005;202:1213–1223; 11. Ishmael FT. *J Am Osteopath Assoc.* 2011;111(suppl 7):S11–S17; 12. Comeau MR, Zeigler SF. *Mucosal Immunol.* 2010;3:138–147; 13. Allakhverdi Z et al. *J Allergy Clin Immunol.* 2009;123:958–960; 14. Robinson DS. J *Allergy Clin Immunol.* 2004;114:58–65

Tezepelumab Represents a New Class of Biologic, Targeting TSLP and Blocking Inflammation from the Top of the Cascade

Tezepelumab is a human monoclonal antibody (IgG2λ) that binds to TSLP, specifically blocking it from interacting with its receptor[1]



Tezepelumab bound to TSLP



[a]The UPSTREAM study used a tezepelumab dose of 700 mg every 4 weeks for 3 months[4]

AHR = airway hyperresponsiveness; FeNO = Fractional Exhaled Nitric Oxide; IgE = Immunoglobulin E; IgG = Immunoglobulin G; IL = Interleukin; T2 = Type 2; TSLP = Thymic Stromal Lymphopoietin

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1. Menzies-Gow A et al. *Respir Res.* 2020;21:268; 2. Gauvreau GM et al. *N Engl J Med.* 2014;370:2102–2110; 3. Diver S et al. *Lancet Respir Med.* 2021;doi 10.1016/S2213-2600(21)00226-5: Jul 9 [Epub ahead of print]; 4. Sverrild A et al. *Eur Respir J.* 2021;doi 10.1183/13993003.01296-2021: May 28 [Epub ahead of print]; 5. Menzies-Gow A et al. *N Engl J Med.* 2021;384:1800–1809; 6. Corren J et al. *N Engl J Med.* 2017;377:936–946; 7. Porsbjerg CM et al. *Eur Respir J.* 2020;56:2000260; 8. Gauvreau GM et al. *Expert Opin Ther Targets* 2020;24:777–792

Evidence from the PATHFINDER Clinical Program Supports the Efficacy, Safety, and Mechanism of Tezepelumab

PATHWAY[1]

Phase IIb

Efficacy and safety of tezepelumab in **adults with severe, uncontrolled** asthma

N=550[a]

Age range = 18–75

Tezepelumab dose:
70 mg Q4W;
210 mg Q4W;
280 mg Q2W

NAVIGATOR[2]

Phase III

Efficacy and safety of tezepelumab in **adults and adolescents with severe, uncontrolled** asthma

N=1061[a]

Age range = 12–80

Tezepelumab dose:
210 mg Q4W

SOURCE[3,4]

Phase III

Efficacy and safety of tezepelumab in reducing **oral corticosteroid use** in **adults** with OCS-dependent asthma

N=150[a]

Age range = 18–80

Tezepelumab dose:
210 mg Q4W

CASCADE[5]

Phase II

Effect of tezepelumab on **airway inflammatory cells, remodelling,** and **hyperresponsiveness** in patients with moderate-to-severe uncontrolled asthma

N=116[a]

Age range = 18–75

Tezepelumab dose:
210 mg Q4W

[a]Intention-to-treat population[1–5]
OCS = Oral Corticosteroids; Q2W = Every 2 Weeks; Q4W = Every 4 Weeks

1. Corren J et al. *N Engl J Med.* 2017;377:936–946; 2. Menzies-Gow A et al. *N Engl J Med.* 2021;384:1800–1809; 3. Wechsler M et al. Presented at: ATS International Conference; May 14–19, 2021; 4. Wechsler ME et al. Presented at: ATS International Conference; May 14–19, 2021;
5. Diver S et al. *Lancet Respir Med*. 2021;doi 10.1016/S2213-2600(21)00226-5: Jul 9 [Epub ahead of print]

Pathway trial

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

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

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

- Phase 2, multicenter, randomized, double-blind, placebo-controlled trial.
- Severe uncontrolled asthma patients, Duration: 52 wks
- Tezepelumab dose- 70mg (n=138), 210mg (n=137), 280 (n=137) sc q4 weekly
- Outcomes: Asthma exacerbation rates & FEV1 change at 52 weeks
- Results:
  - Exacerbation rates lower in all groups- 62%, 71% and 66%.

Conclusion: Patients with severe, uncontrolled asthma who received Tezepelumab had lower rates of exacerbations and better lung function independent of blood eosinophil counts.

Navigator trial

ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

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

The NEW ENGLAND JOURNAL of MEDICINE

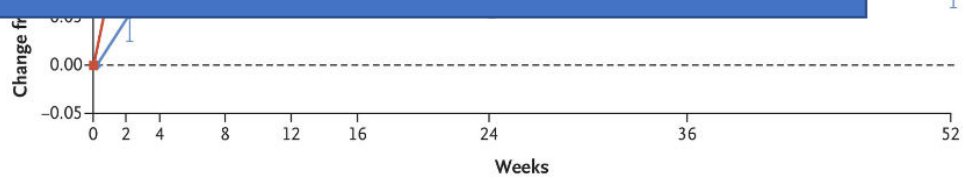
Metrics

May 13, 2021
N Engl J Med 2021; 384:1800-1809
DOI: 10.1056/NEJMoa2034975

- Phase 3, multicenter, randomized, double blind, placebo-controlled trial.
- 12 to 80 years sever uncontrolled asthma patients, Duration: 52 wks
- Tezepelumab 210mg sc q4 weekly
- Out
  -
  -

on the Asthma Control Questionnaire=6

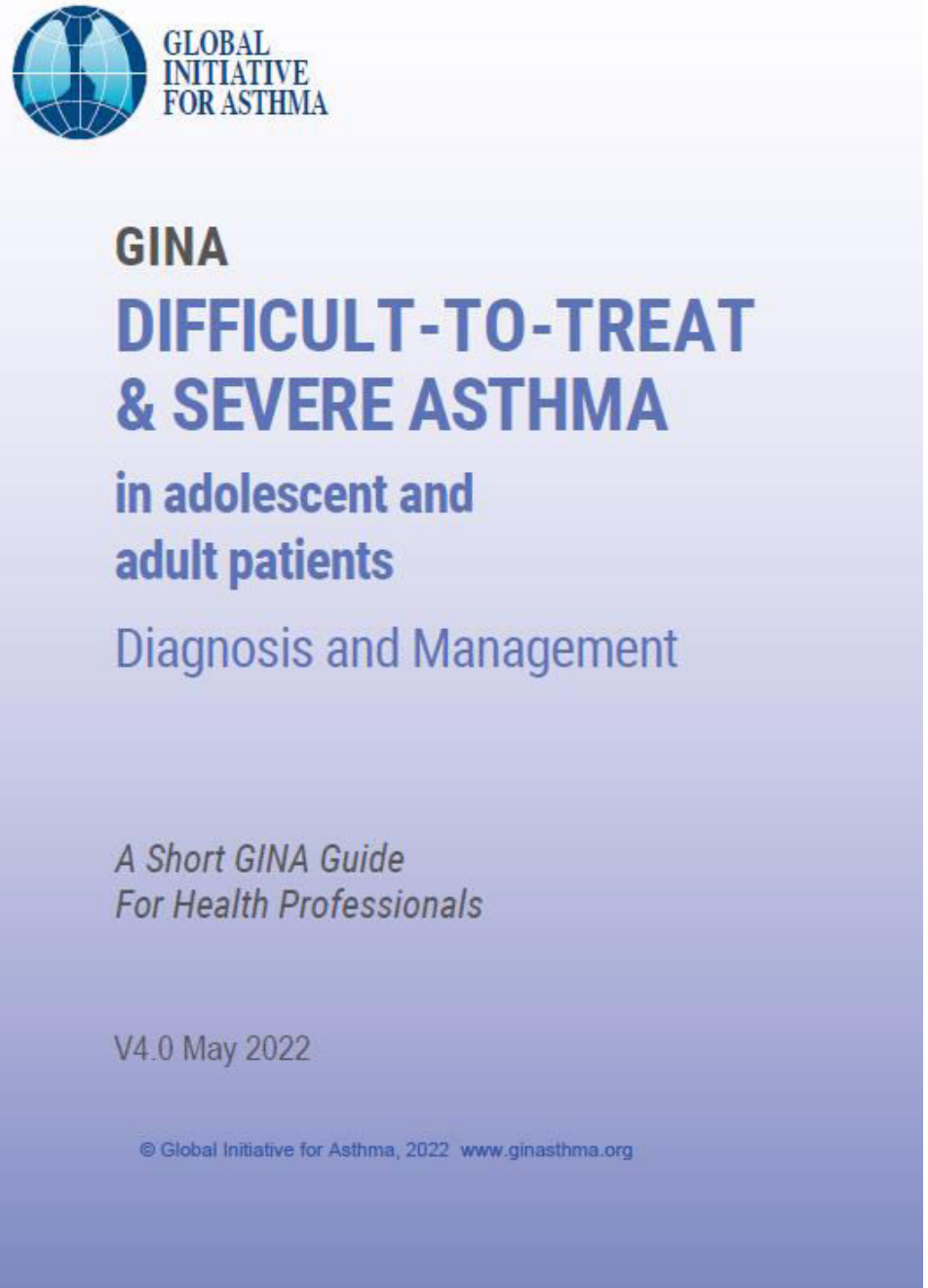
Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (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)
			0.39 (0.32–0.49)
			0.68 (0.51–0.92)
			0.32 (0.25–0.42)
			0.68 (0.51–0.92)
			0.40 (0.28–0.56)
			0.27 (0.19–0.38)
			0.42 (0.33–0.53)
			0.49 (0.36–0.67)



Conclusion: Patients with severe, uncontrolled asthma who received Tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life than those who received placebo.

Available biologics for Severe Asthma

Drug	Indication	Dose	Frequency
Omalizumab	Moderate–severe persistent asthma uncontrolled by ICS in age ≥12 years; positive for perennial aeroallergens	75-375 mg, SC, (dose is weight and S Ig E dependent)	2/ 4 weekly
Mepolizumab	Add-on maintenance for severe asthma (SA) in ages ≥18 years with eosinophilic phenotype	100mg, SC	4 weekly
Benralizumab	Add-on maintenance for SA in ≥18 years with eosinophilic phenotype	30mg, SC	First 3 dose 4 weekly, then 8 weekly
Dupilumab	Add-on maintenance for SA > 12 years with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO	Not yet approved in India	
Tezepelumab	TSLP blocker, for add-on maintenance of adult and pediatric patients aged 12 years and older with severe asthma	Not yet approved in India	



The GINA Approach to Severe Asthma

GP OR SPECIALIST CARE

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 Confirm the diagnosis (asthma/differential diagnoses)

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

- *yes* → DIAGNOSIS: *"Severe asthma"* → If not done by now, refer to a specialist, if possible
- *no* → Consider stepping down treatment, OCS first (if used)

Does asthma become uncontrolled when treatment is stepped down?

- *yes* → Restore previous dose → DIAGNOSIS: *"Severe asthma"*
- *no* → Continue optimizing management

Key

- decision, filters
- intervention, treatment
- diagnosis, confirmation

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Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

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

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

yes

no

7 Consider *other* treatments

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

Not currently eligible for T2-targeted biologic therapy

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

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Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider **local payer eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Eligibility | *Predictors of asthma response*

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no ↕ *no*

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no ↕ *no*

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

no ↕ *no*

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?

- Higher blood eosinophils +++
- Higher FeNO +++

Eligible for none? Return to section **7**

Choose one if eligible*; trial for at least 4 months and assess response

*Good asthma response?**

- *unclear* → Extend trial to 6-12 months* → *Good asthma response?**
- *yes* → **Good response to T2-targeted therapy**
- *no* → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible*

no → **Little/no response to T2-targeted therapy**

No evidence of Type 2 airway inflammation

No evidence of Type 2 airway inflammation. Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

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Monitor / Manage severe asthma treatment

Continue to optimize management

9 Review **response**

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

yes

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months*
- For **oral treatments:** consider decreasing/stopping OCS first (and check for adrenal insufficiency), then stopping other add-on medication
- For **inhaled treatments:** consider decreasing after 3-6 months; continue at least moderate dose ICS-LABA
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

no

If no good response to Type 2-targeted therapy

- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on low dose azithromycin
  - Consider bronchoscopy for alternative/additional diagnoses
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS

No evidence of Type 2 airway inflammation. Go to section **10**

10 Continue to **optimize management** as in section **3**, including:

- Inhaler technique
- Adherence
- Comorbidity management
- Non-pharmacologic strategies
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Notes:

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

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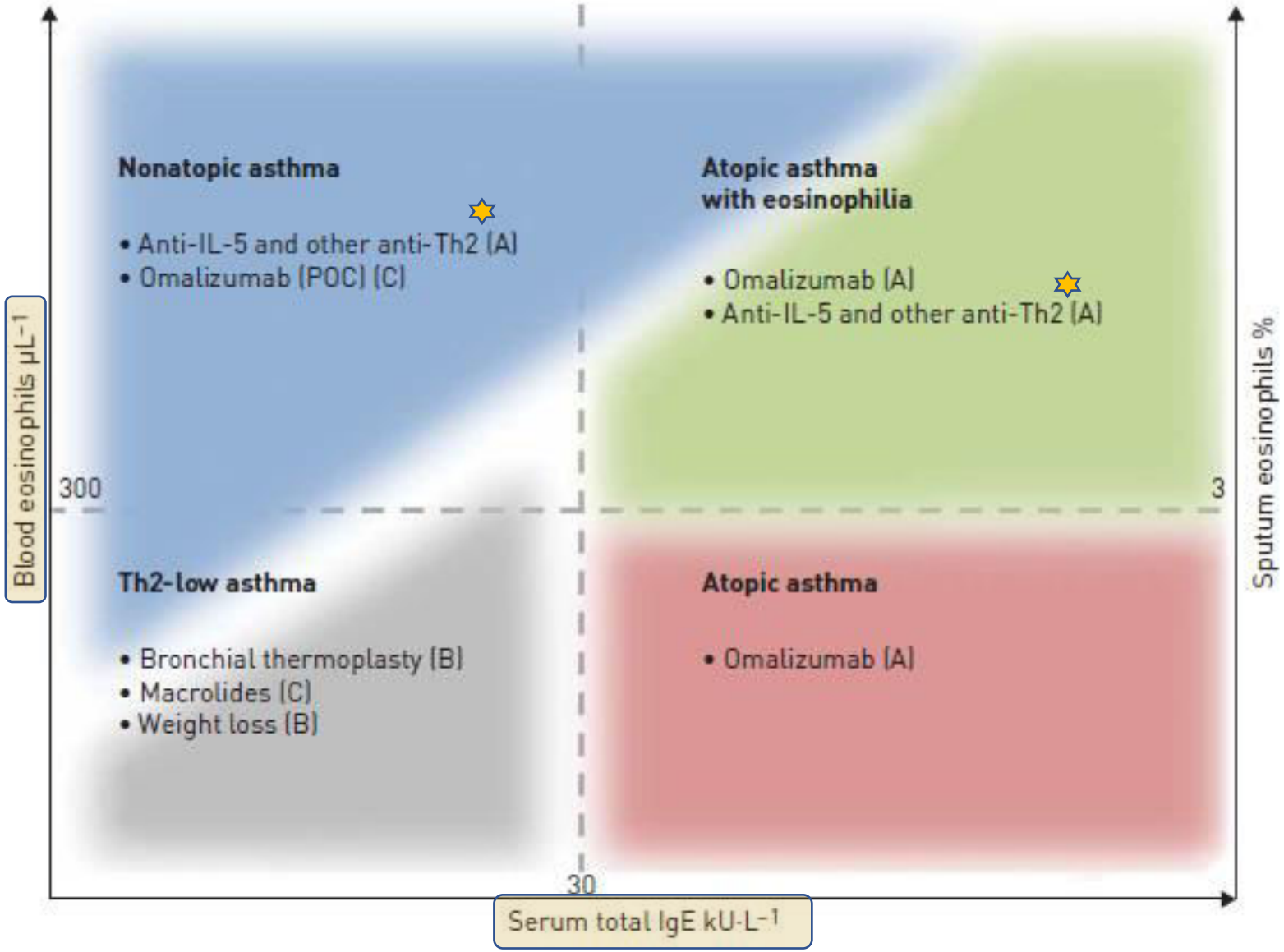
Which is the most appropriate biologic therapy?

Consider Age, Eosinophil count and IgE levels

No head-to-head trials for biologic agents



Other anti-Th2:
- Anti IL5 receptor alpha
- Anti IL4 receptor alpha

Conclusions

- The newer biologics open an avenue for the treatment of severe asthma
- Ensuring accurate diagnosis of severe asthma, adherence to standard therapy, and optimization of comorbid conditions is a pre-requisite before considering biologic therapy
- Phenotypic evaluation helps guide selection of appropriate biologic agent
- Dupilumab and Tezepelumab are newer additions to the arsenal of biologic therapies. They can be also used in selected patients without Th2 inflammation.
- Close monitoring of patients on therapy is essential