Biologicals in COPD Work

Debate - Pro

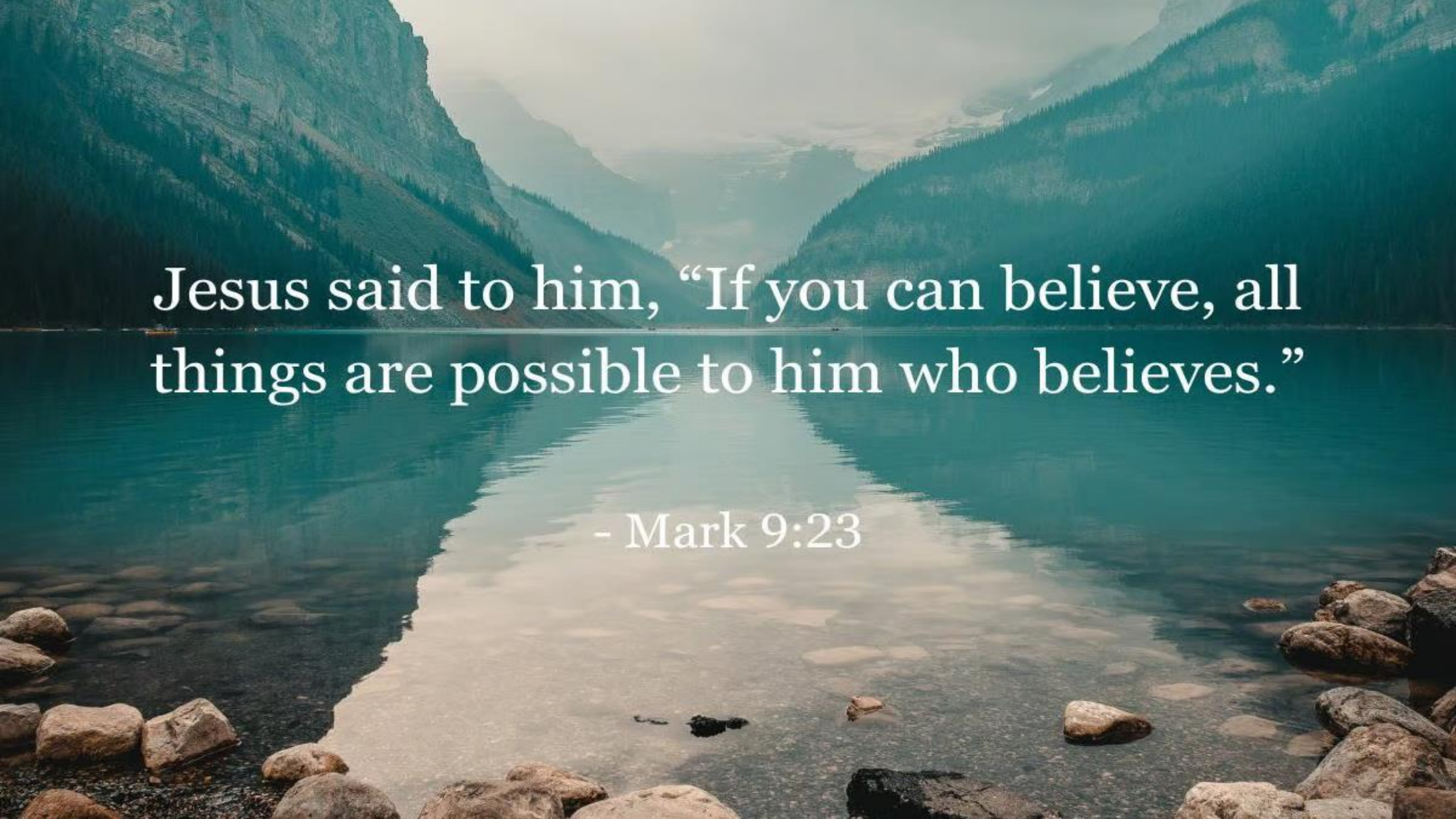
Deepak Talwar

MD, DTCD, DNB, DM (Pulmonary & Critical Medicine) FISDA, FCCP (USA), FNCCP

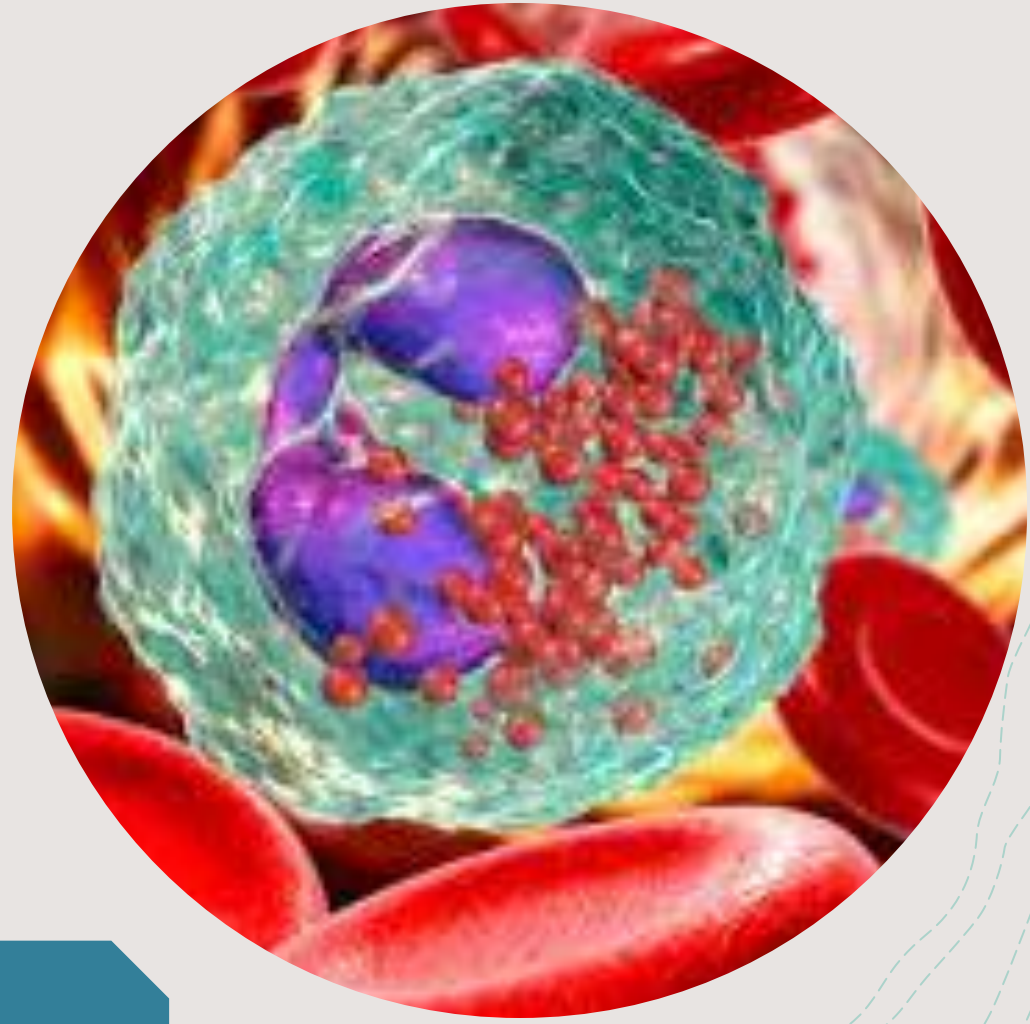
Director & Chair

Pulmonary, Sleep, Allergy & Critical Care Medicine

Metro Group of Hospitals, INDIA


Jesus said to him, “If you can believe, all things are possible to him who believes.”
- Mark 9:23

Biologicals Work in Asthma, But In COPD ..

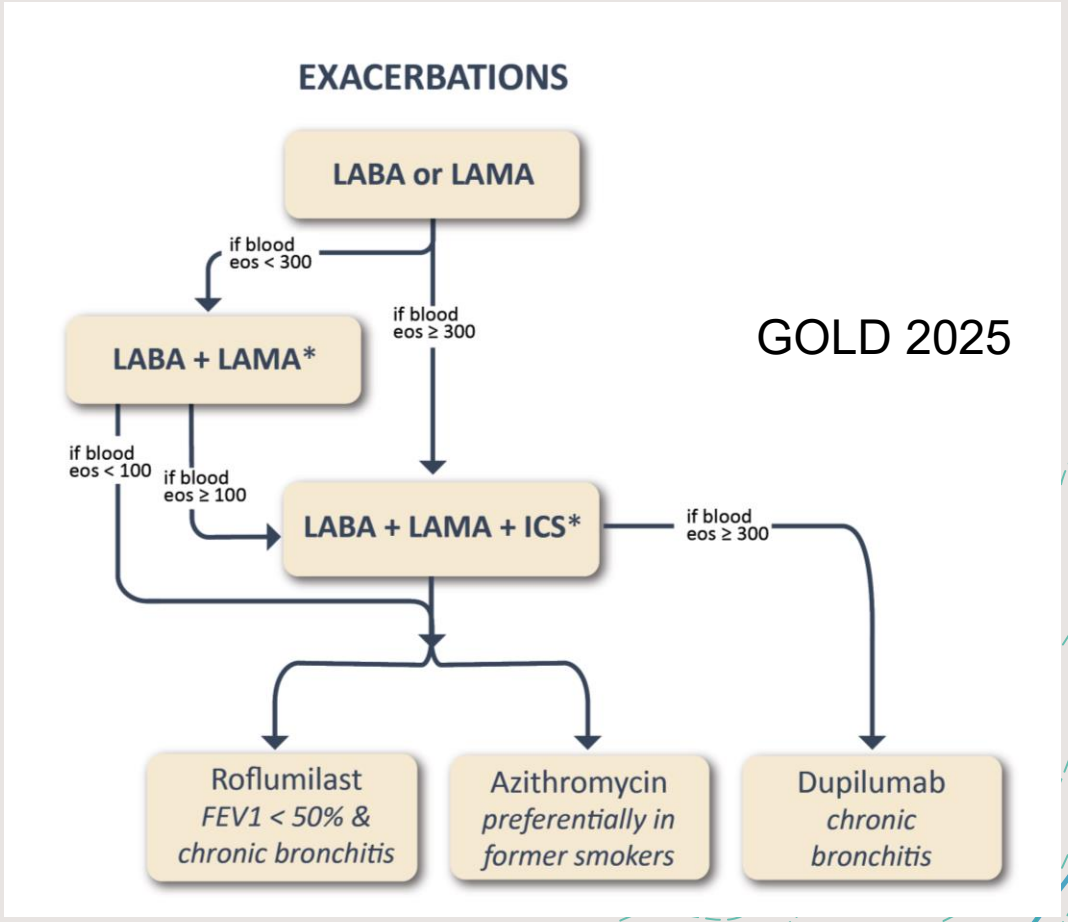


- Biologicals are targeted missiles :
  - Transformed management of severe asthma, approved @23 years
  - In COPD Anti- IL-4/13r blocker, Dupulimab approved
  - Biologicals are the future as OAD management is shifting to ‘Precision Medicine’ from Traditional Medicine

Identify Treatable Trait
Offer Treat to Target
‘ Medicine’

Biologicals in COPD : Why & When ?

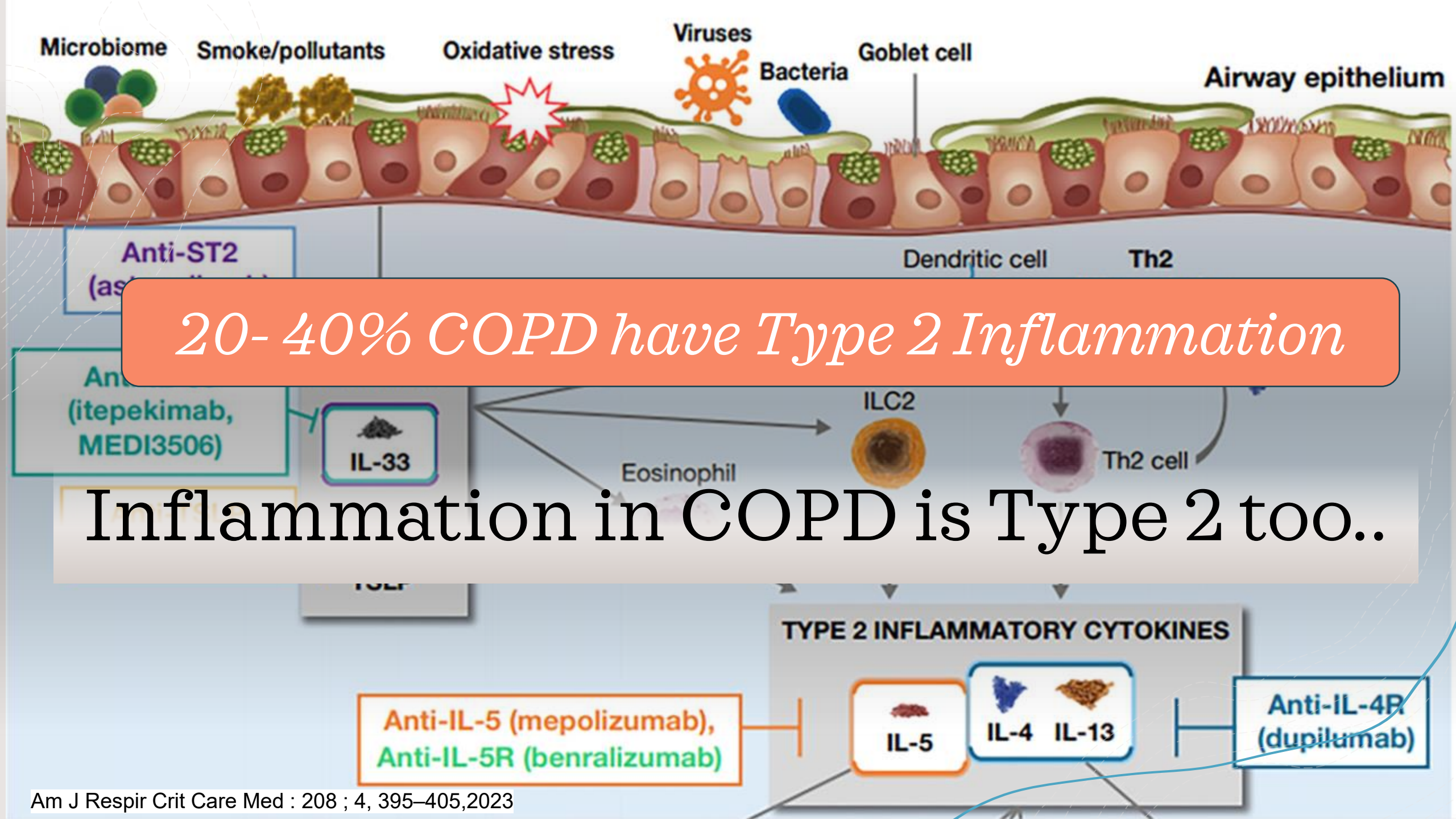
- ~ 67% exacerbate on SITT
- ~ 50% exacerbated despite add on Roflumilast/ Macrolides
- Type 2 inflammation in COPD:
  - ↑ Future risk of exacerbations in ‘f’ exacerbators
  - Some with COPD & Asthma (ACO)
- *~ 40% exacerbations in COPD are eosinophilic*



GOLD 2025

Treatable trait : Eosinophilic COPD

European Journal of Internal Medicine 2024.05.011



Am J Respir Crit Care Med : 208 ; 4, 395–405,2023

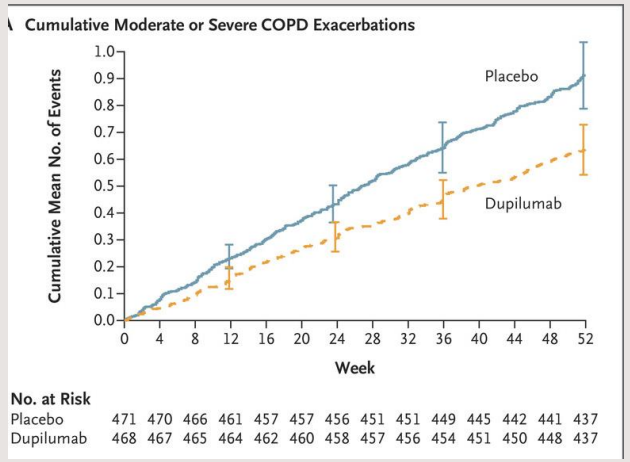
Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

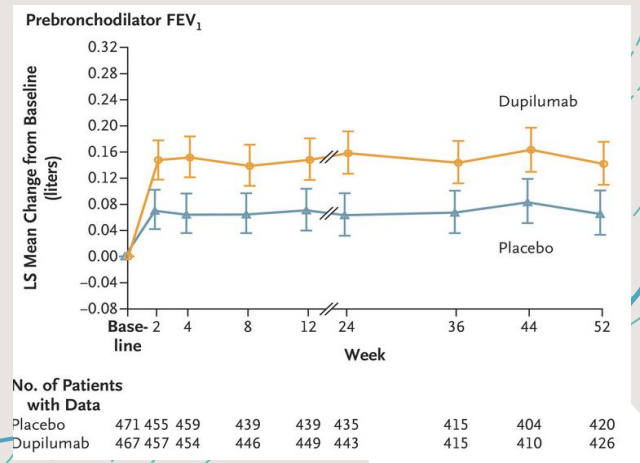
Surya P. Bhatt, M.D., M.S.P.H., Klaus F. Rabe, M.D., Ph.D., Nicola A. Hanania, M.D., Claus F. Vogelmeier, M.D., Jeremy Cole, M.D., Mona Bafadhel, M.D., Ph.D., Stephanie A. Christenson, M.D., Alberto Papi, M.D., Dave Singh, M.D., Elizabeth Laws, Ph.D., Leda P. Mannent, M.D., Naimish Patel, M.D., et al., for the BOREAS Investigators*

- Phase 3, double-blind, randomized trial
- COPD who had a blood eosinophil count of at least 300 per uml and an elevated exacerbation risk despite use of standard triple therapy
- Dupilumab (300 mg) or placebo subcutaneously once every 2 weeks

COPD with T2 inflammation (AEC ≥ 300) had fewer exacerbations, better lung function and QoL, and less severe respiratory symptoms

- 30% reduction in exacerbations
- 160 ml FEV_1

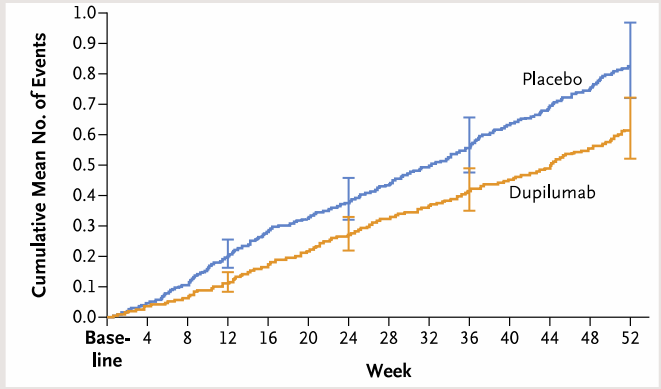


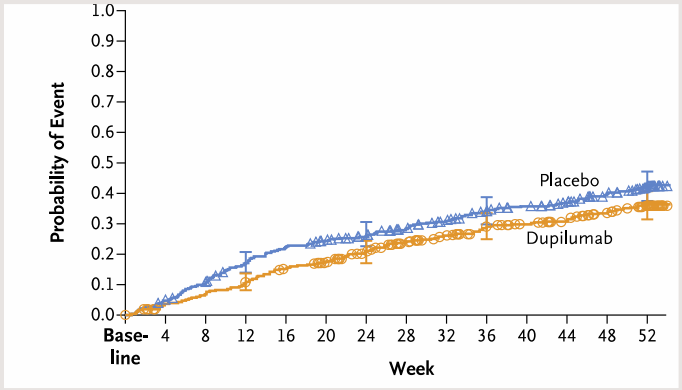


Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation

Authors: Surya P. Bhatt, M.D., M.S.P.H., Klaus F. Rabe, M.D., Ph.D., Nicola A. Hanania, M.D., Claus F. Vogelmeier, M.D., Mona Bafadhel, M.D., Ph.D., Stephanie A. Christenson, M.D., Alberto Papi, M.D. , +11 , for the NOTUS

NOTUS, Dupilumab reduced exacerbations by a magnitude never seen before with an investigational biologic in a phase 3 COPD clinical study

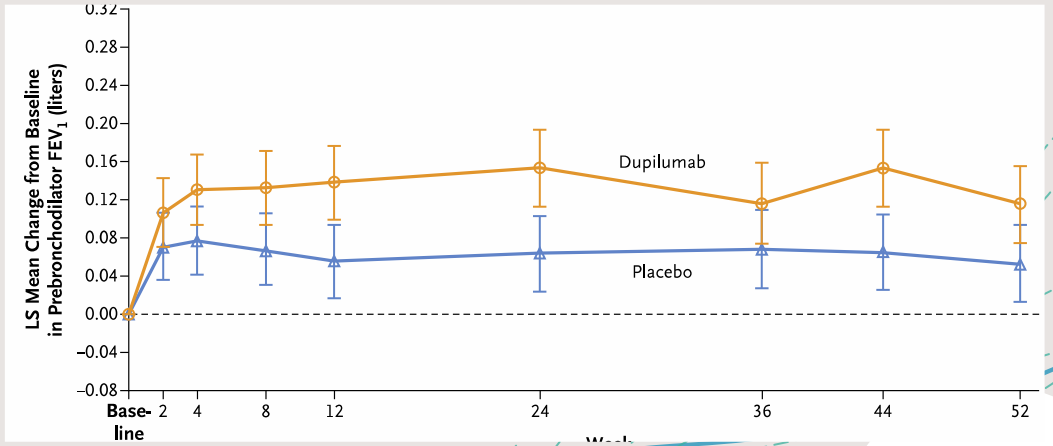




- 34% reduction in exacerbations
- 139 ml FEV_1
- ↑ Symptoms
- ↑ SGRQ

No Effect of
Age
Sex
Smoking
FEV1
Emphysema
Exacerbations

DOI: 10.1056/NEJMoa2401304



Biologicals in COPD:

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL FREE PREVIEW

Biologics for COPD — Finally Here

Alvar Agusti, M.D., Ph.D.

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Published July 19, 2023 N Engl J Med 2023;389:274-275 D

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COPD with type 2 inflammation (AEC ≥ 300) on dupilumab had fewer exacerbations, better lung function and QoL, and less severe respiratory symptoms than those who received placebo

No Signal for Safety

Biologicals in COPD: *Finally Approved*

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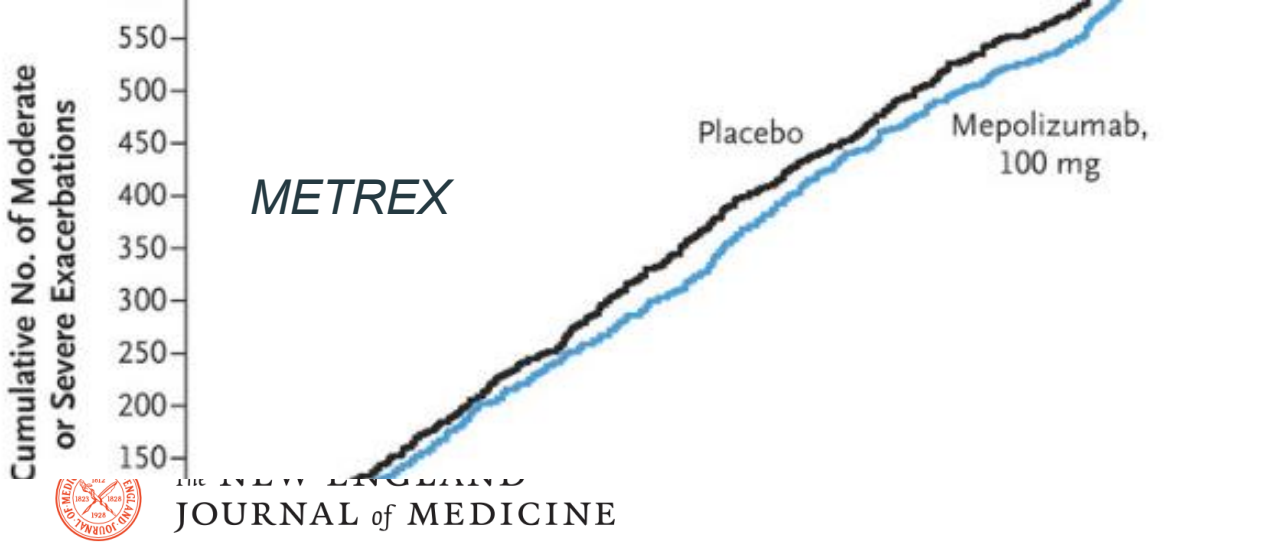
Biologicals in COPD :

Anti IL-5 -Mepolizumab

METREX & METREO

3 More Ongoing Trials

SUMMER
MATINEE
&
COPD-HELP



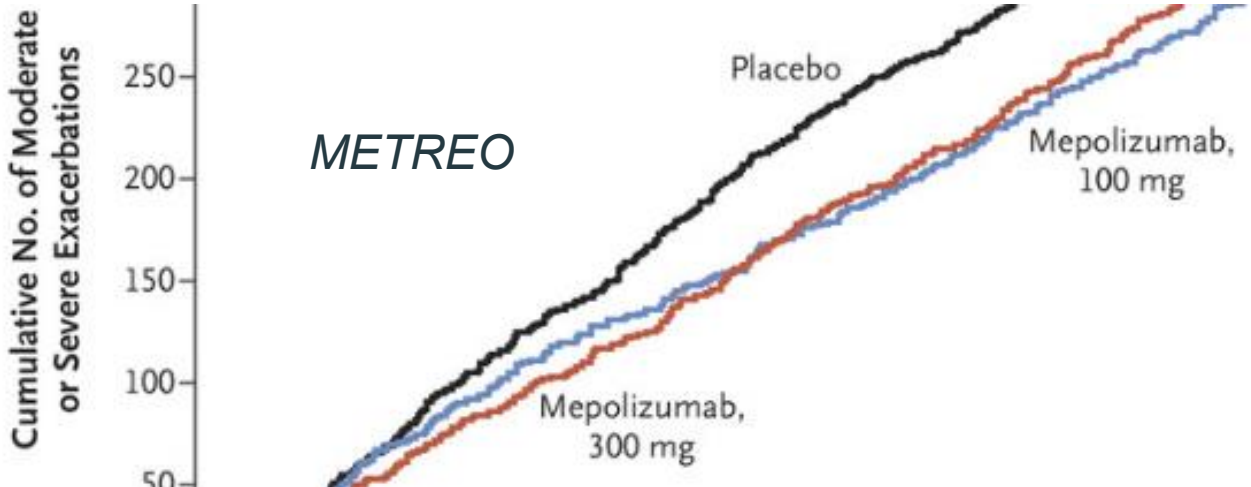
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

14-20% reduction

Authors: Ian D. Pavord, D.M., Pascal Chanez, M.D., Ph.D., Gerard J. Criner, M.D., Huib A.M. Kerstjens, M.D., Ph.D., Stephanie Korn, M.D., Ph.D., Njira Lugogo, M.D., Jean-Benoit Martinot, M.D., +7, and Frank C. Sciurba, M.D. Author Info & Affiliations



Benralizumab: *Anti IL - 5r Blocking Monoclonal antibody*

International Journal of Chronic Obstructive Pulmonary Disease

Dovepress

open access to scientific and medical research

Open Access Full Text Article

SHORT REPORT

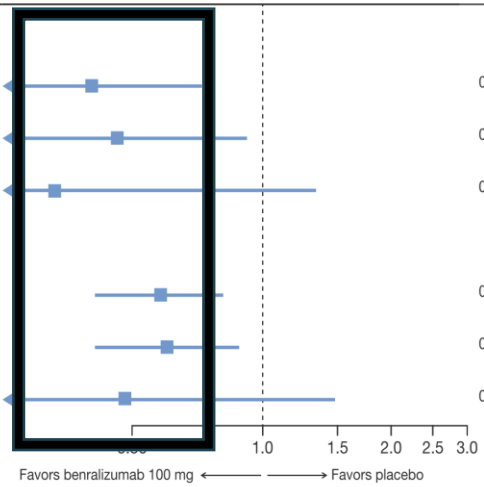
Benralizumab Prevents Recurrent Exacerbations in Patients with Chronic Obstructive Pulmonary Disease: A Post Hoc Analysis

Dave Singh[1], Gerard J Criner[2], Alvar Agusti[3], Mona Bafadhel[4], Johan Söderström[5], Gabriela Luporini Saraiva[6], Yue Song[6], Idlir Licaj[7], Maria Jison[6], Ubaldo J Martin[6], Ioannis Psallidas[8]

- Subgroup of COPD with:
  - ≥ 3 exacerbations on Triple therapy
  - Baseline AEC ≥ 300
- Benralizumab (100 mg/month) reduces risk of exacerbations @ 30- and 90-days post exacerbation (vulnerable period)

Exploratory post hoc analysis of the GALATHEA and TERRANOVA trials

	Exacerbation events		Crude rate		Rate ratio (95% CI)	*p* values
	Benralizumab	Placebo	Benralizumab	Placebo		
30 days						
Moderate/severe	14	62	1.67	4.55	0.40 (0.22, 0.72)	0.0022
Moderate	11	45	1.31	3.30	0.46 (0.24, 0.91)	0.0247
Severe	3	17	0.36	1.25	0.33 (0.08, 1.30)	0.1133
90 days						
Moderate/severe	48	127	1.93	3.74	0.58 (0.41, 0.81)	0.0017
Moderate	40	103	1.61	3.03	0.60 (0.41, 0.87)	0.0071
Severe	8	24	0.32	0.71	0.48 (0.16, 1.43)	0.1862

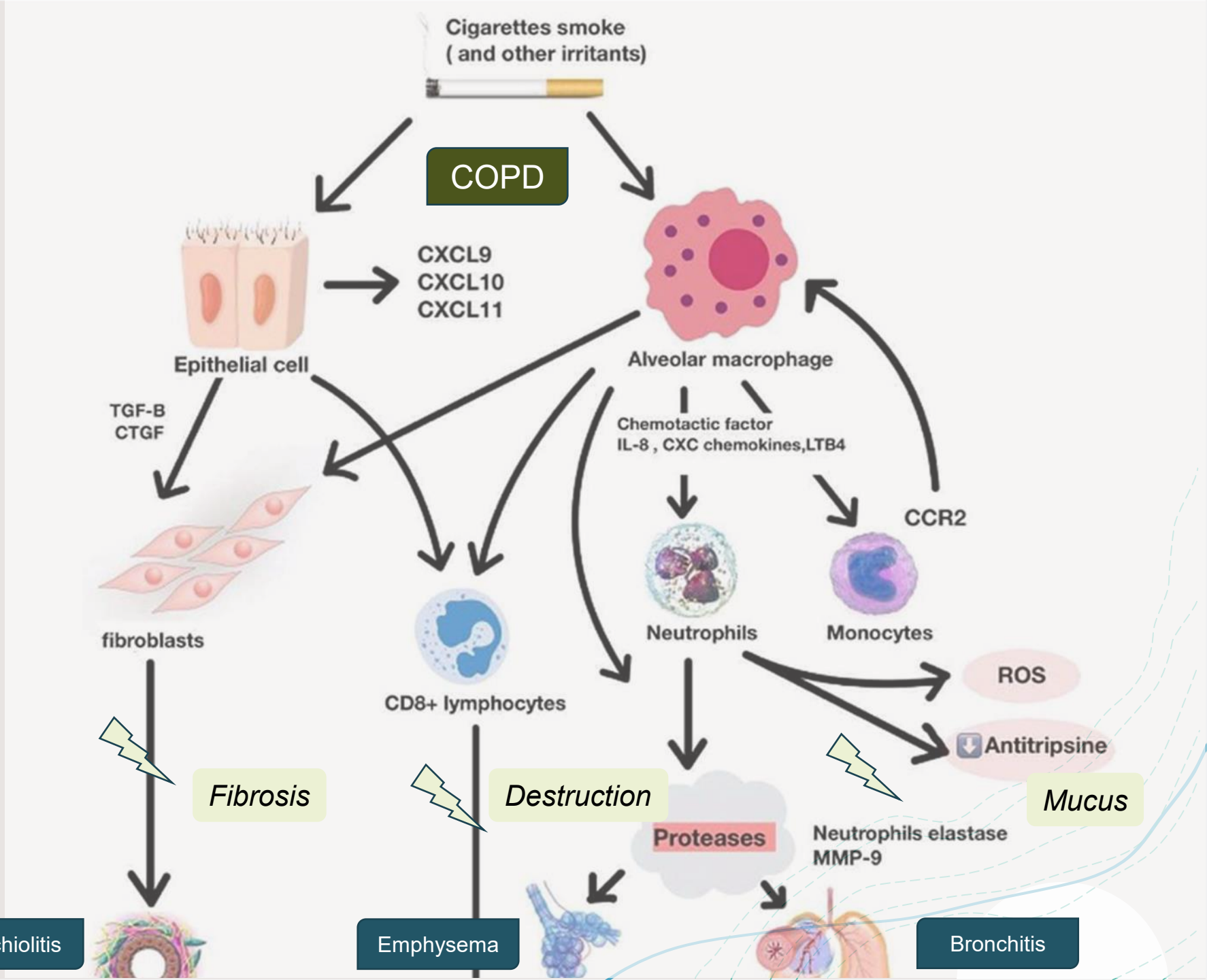


RESOLUTE - recruiting

International Journal of Chronic Obstructive Pulmonary Disease 2023:18

What More to Target In COPD ?

‘COPD is characterized by different biological pathways known as endotypes’



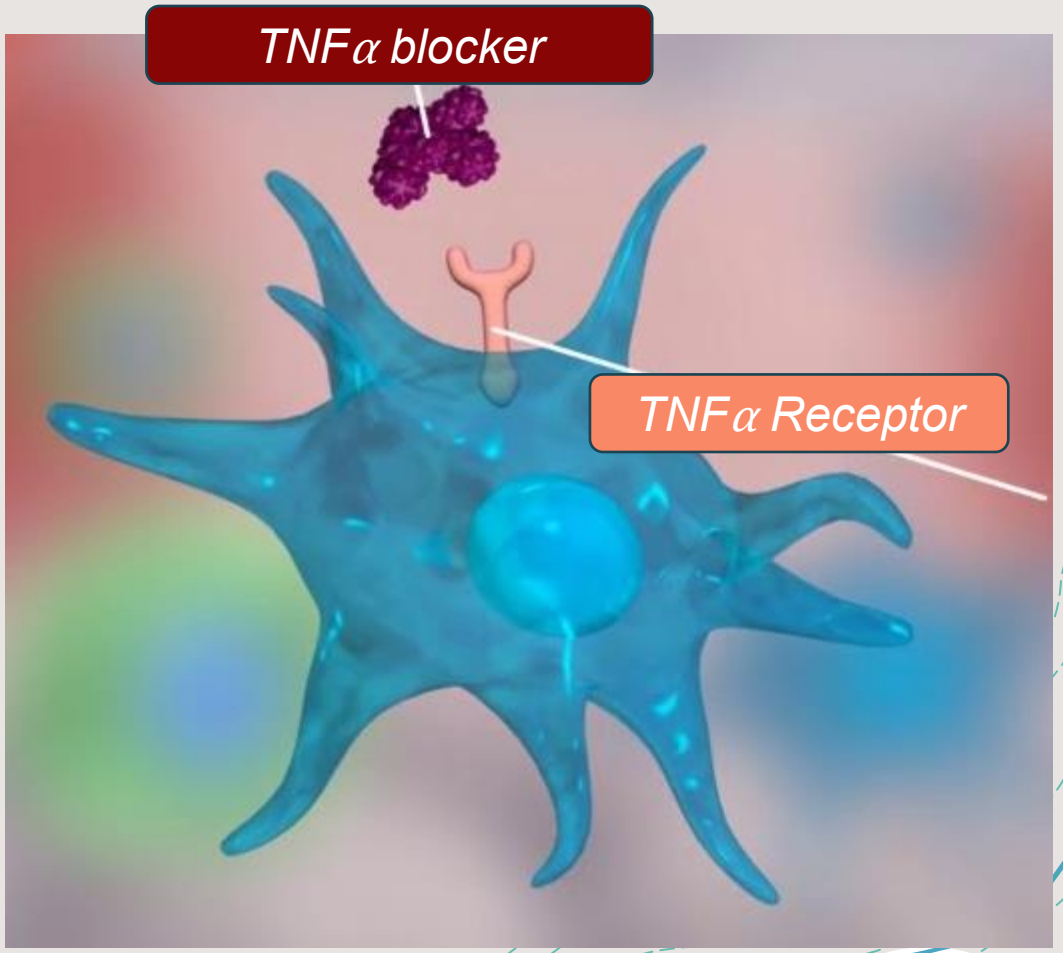
Targeting Type 1 Inflammation in COPD

+ TNF *Alpha* :

TNF *Alpha*

+ Proinflammatory cytokine
+ ~ 70% of emphysema
+ Cascade of inflammatory mediators
  + Pro-inflammatory cytokines (IL-1),
  + Chemokines (CXCL -8)
  + Proteases (MMP 9 & 12)
+ TNF alpha inhibitors :
  + Infliximab:
  + Etanercept :

No beneficial Effect
? ↑ infections



More Pneumonia's & Cancers : Signal for Non-Safety

Targeting Type 1 Inflammation in COPD

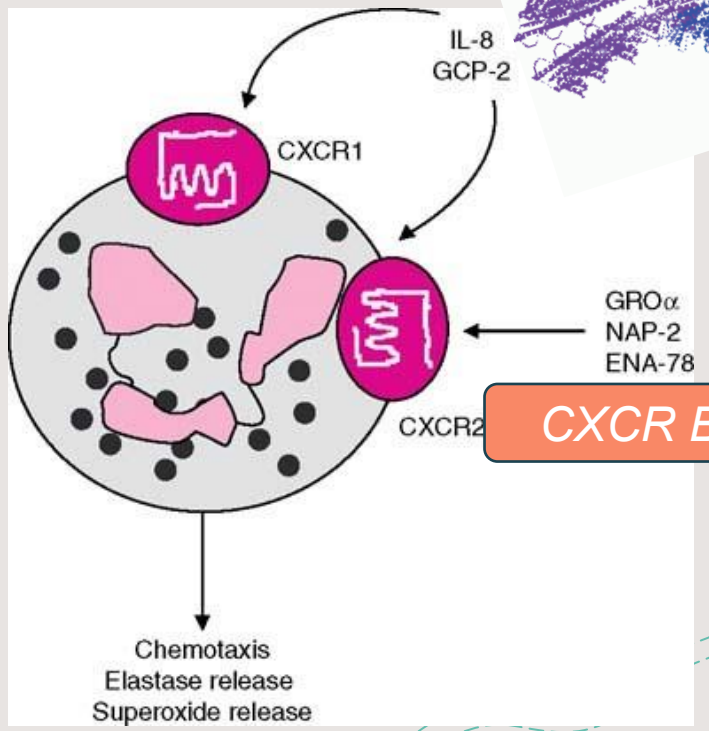
+ IL-8 & CXCR :
  + Neutrophilic Cytokine
  + Stimulates CXC Receptors 1 & 2
  + Increased Levels in BALF in COPD
  + ABX IL-8 :

Mild ↓ Dyspnea
Rest no Effect

+ CXCR2 receptor antagonist : Navarixin

↓ Dyspnea, FEV_1 ↑
Current smokers

IL-8 Blocker



CXCR Blocker

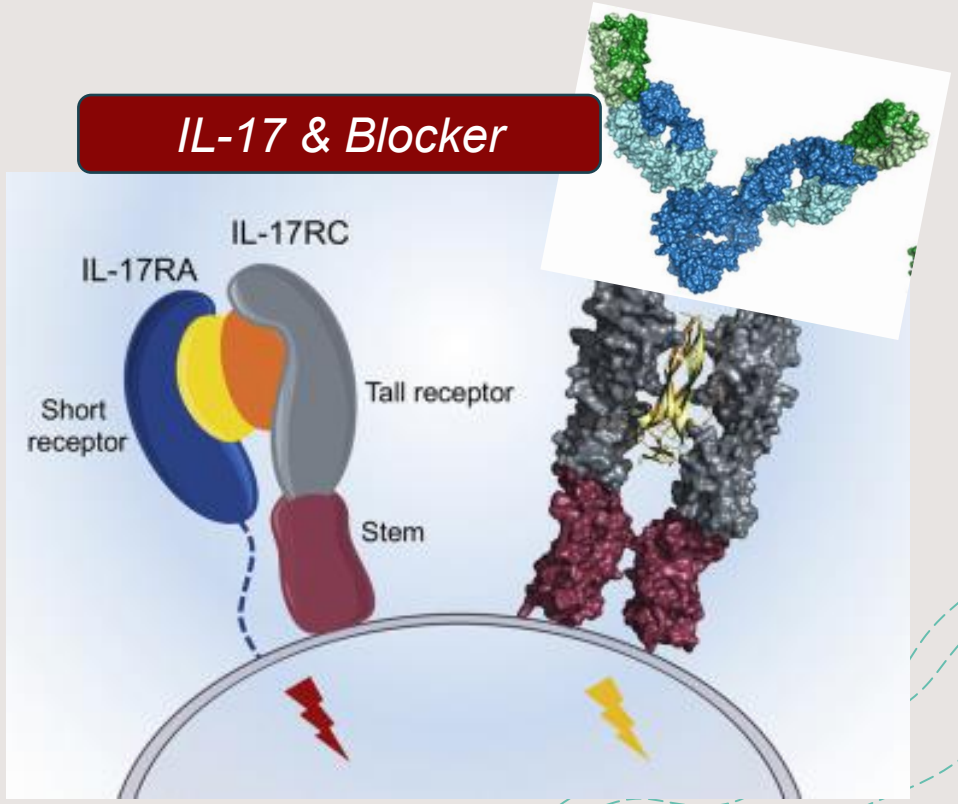
Adverse Event : ~ Neutropenia

Targeting Type 3 Inflammation in COPD

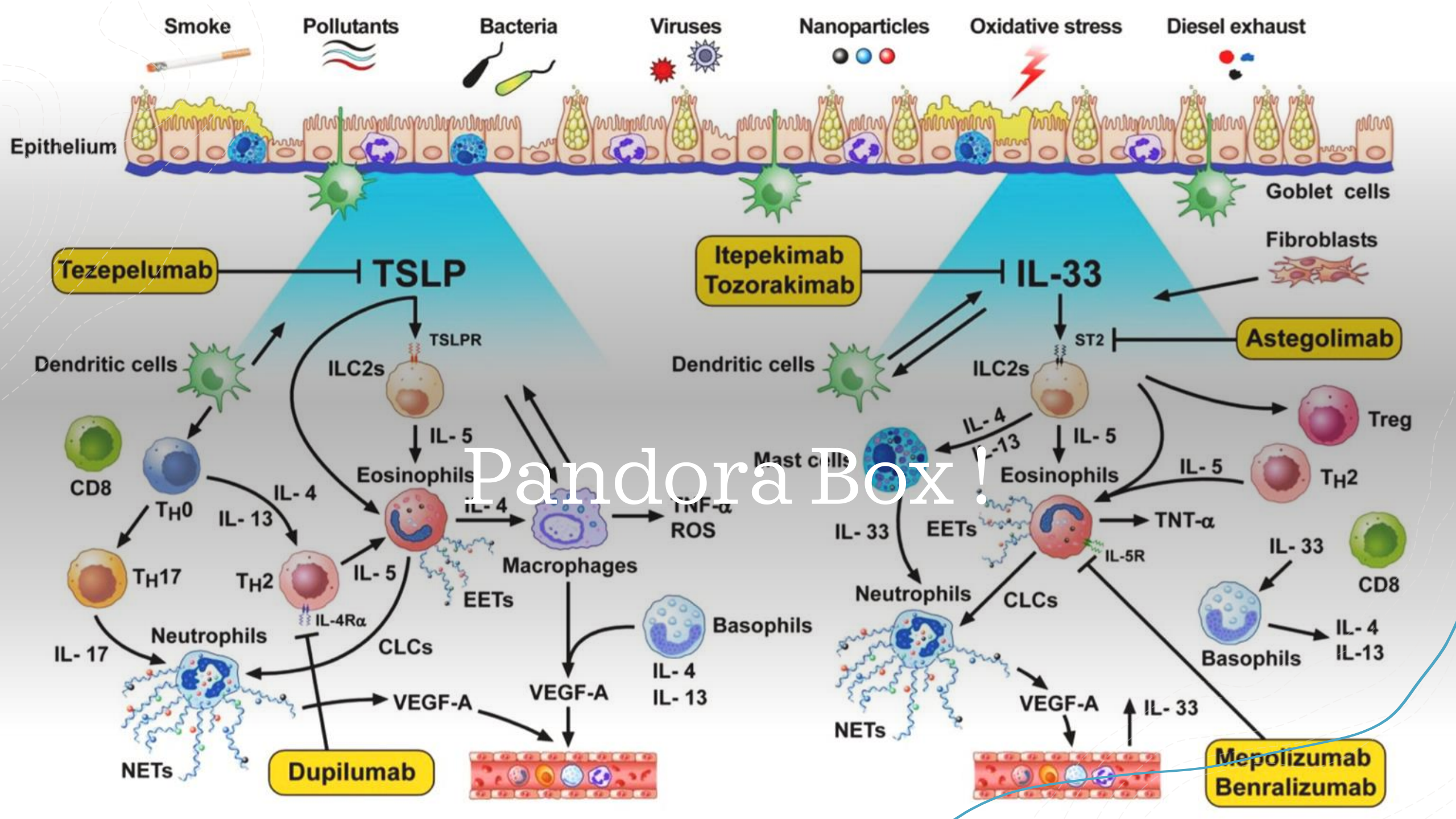
- IL- 17 :
  - 6 Chemokines & 5 Receptors
  - Crucial for host defense
  - Stimulates Inflammation & damage
- Anti IL-17
  - Studies mostly in asthma
  - Secukinumab: Neutralize IL-17A

Mild FEV_1 ↑ only

- *More infections & Exacerbations*



Adverse Event : ~ Immunosuppression

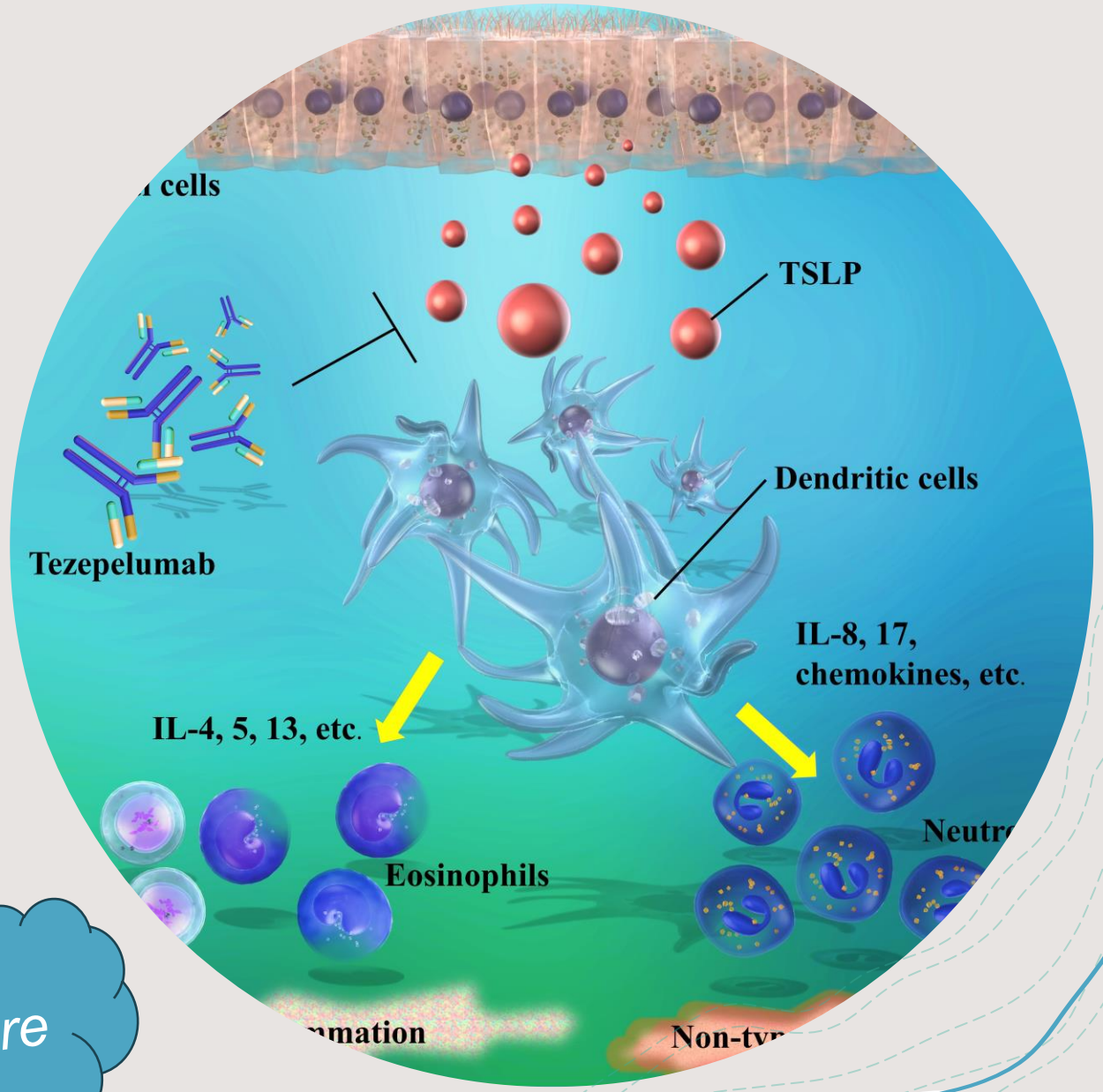

Smoke
Pollutants
Bacteria
Viruses
Nanoparticles
Oxidative stress
Diesel exhaust
Epithelium
Goblet cells
Fibroblasts
Tezepelumab
TSLP
Itepekimab
Tozorakimab
IL-33
ST2
Astegolimab
TSLPR
Dendritic cells
ILC2s
IL- 5
Eosinophils
CD8
TH0
IL- 4
IL- 13
TH17
TH2
IL-4Rα
IL- 5
EETs
IL- 4
TNF-α
ROS
Macrophages
Basophils
IL- 4
IL- 13
VEGF-A
Neutrophils
IL- 17
CLCs
NETs
Dupilumab
Mast cells
IL- 4
IL- 13
IL- 5
Treg
TH2
IL- 33
EETs
TNT-α
IL-5R
CD8
IL- 4
IL-13
NETs
VEGF-A
IL- 33
Mepolizumab
Benralizumab

Biologicals in COPD : *Anti-TSLP*

+ Epithelial cytokine (IL-7 like cytokine)
+ Increased in viral induced AE-COPD
+ Tezepelumab : Undergoing Phase 2a COURSE, clinical trial in ≥ 2 AE COPD's
  + 17% ↓ exacerbations AEC ≥ 150 cmm
  + 37% ↓ exacerbations AEC ≥ 300 cmm
  + Better lung functions & QoL
  + No safety signal

But not statistically significant

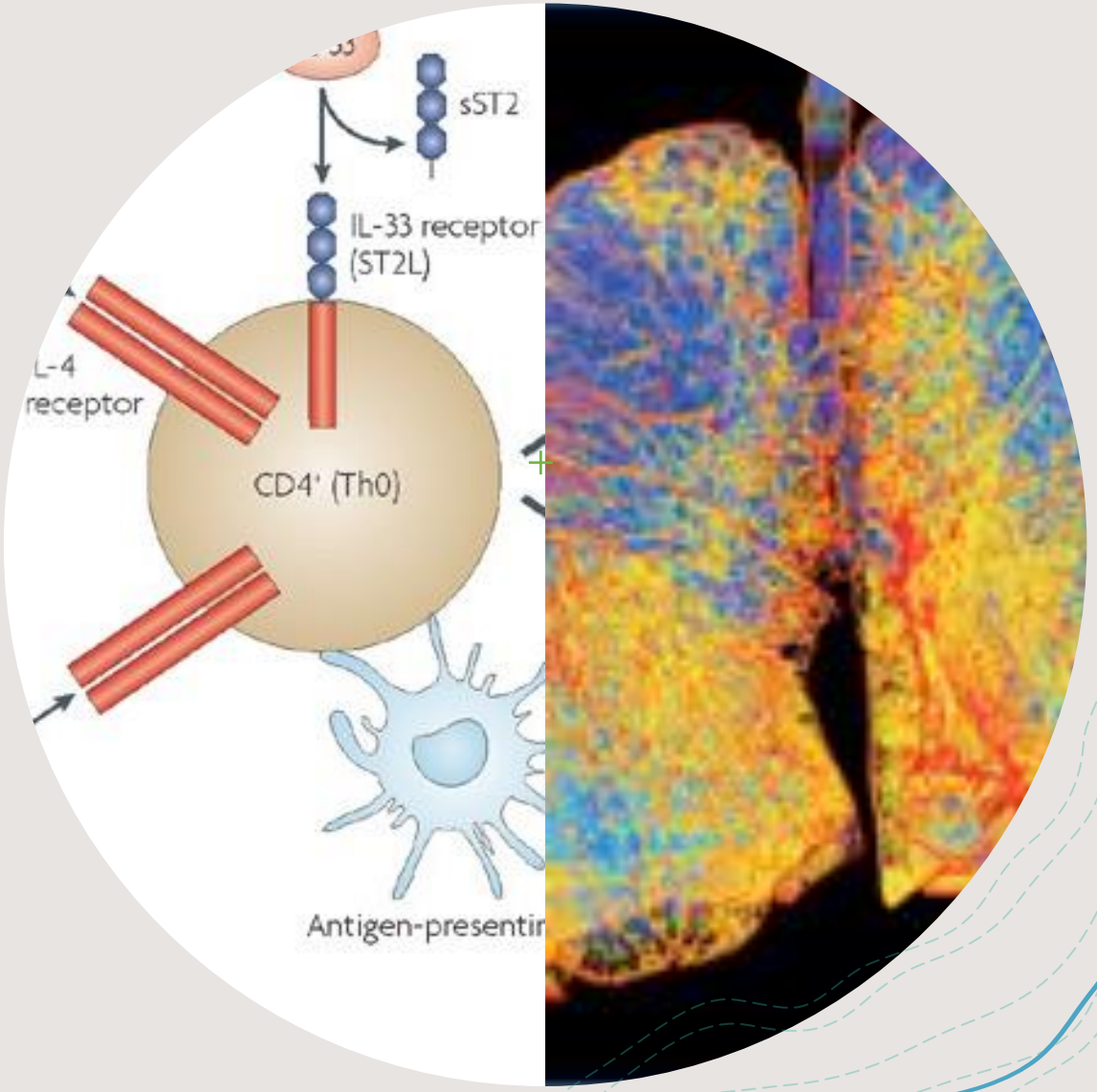
Future



Biologicals in COPD : Alarmins -*Anti-IL -33/ST2r*

- Endogenous danger signalling IL-33(sST2L)
- Crucial cytokine in viral AE-COPD
- Itepekimab : IL-33 MAB
  - Phase 2 : Reduced AE, ↑ FEV_1 (90 ml) in former smokers
  - No effect in current smokers
  - No significant AE's
  - AERIFY 1 & 2 ongoing in former smokers
- Astegolimab : Anti ST2R MAB
  - Phase 2 : *Improved QoL but no other effect*

No Signal for Safety



Lancet Respir Med. 2021;9(11):1288–1298

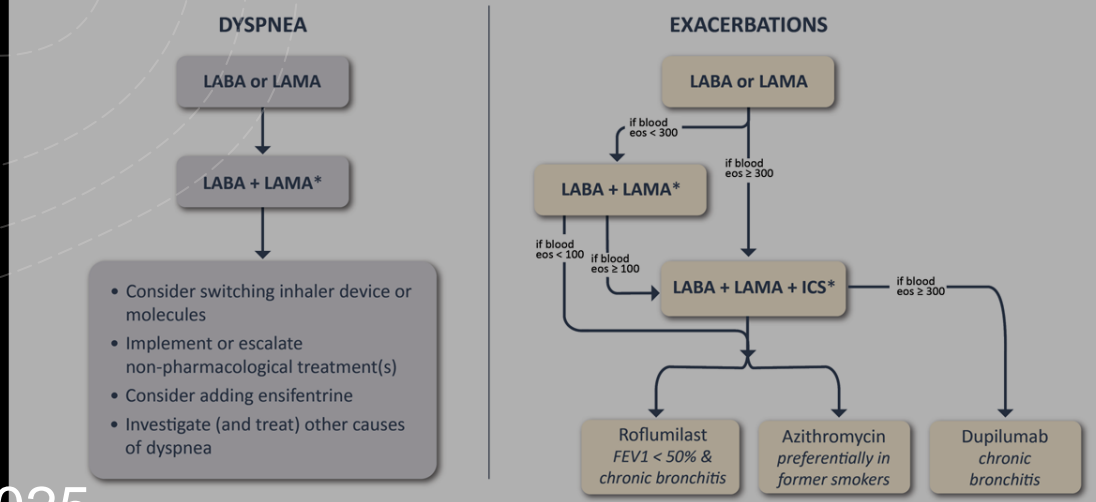
Conclusions:

- COPD is Heterogenous : Type 1 (60%), Type 2 (20-40 %) & Type 3 (?) inflammation
- Common is irreversible damage and progression despite maximized therapies
- SITT in COPD is nearly last frontier but patients suffer with Symptoms, Exacerbations, ↓ Lung functions & QoL
- Biologicals are treat to target therapies being studies extensively to fill the GAP
- COPD with Type 2 inflammation - Anti –IL-4/13 (Dupulimab) have proved benefit
- COPD with Type 1 inflammation lies with Anti TSLP and Anti IL-33 biologicals

GOLD 2025

Follow-up Pharmacological Treatment

Figure 3.9



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

Exacerbations refers to the number of exacerbations per year.

End of the Road !

Biologicals in COPD Work

Debate - Pro

Rebuttal

Deepak Talwar

MD, DTCD, DNB, DM (Pulmonary & Critical Medicine) FISDA, FCCP (USA), FNCCP

Director & Chair

Pulmonary, Sleep, Allergy & Critical Care Medicine

Metro Group of Hospitals, INDIA

OBJECTIVE:

To compare the Benralizumab, alone or in combination with prednisolone, as a treatment for Eosinophilic Endotypes of Asthma and COPD Exacerbations

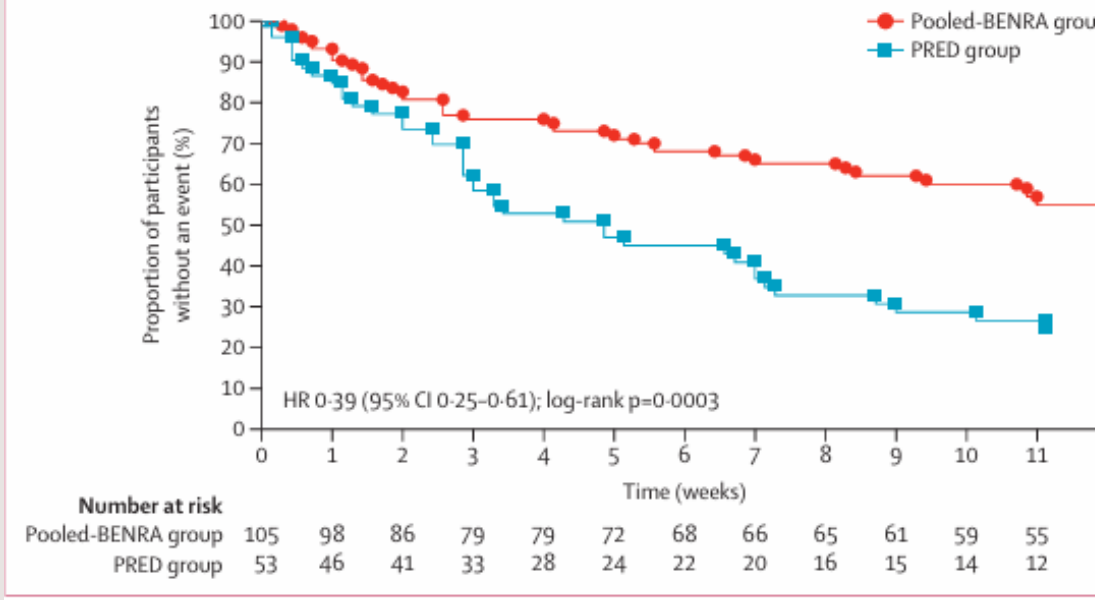
3 Groups :

1. **BENRALIZUMAB + PREDNOSOLONE**
2. **BENRALIZUMAB Only**
3. **PREDNISOLONE**

287 patients were screened for study inclusion. 158 patients who met inclusion criteria of acute eosinophilic exacerbation of asthma or COPD ,were randomly assigned to one of the 3 groups

There was a significant reduction in treatment failure risk in pooled-BENRA compared with PRED at 30 days and no difference between BENRA and BENRA plus PRED

Treatment Failures as Outcome : More In Prednisolone Group



Articles

Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial

Sanjay Ramakrishnan, Richard E K Russell, Hafiz R Mahmood, Karolina Krassowska, James Melhorn, Christine Mwasuku, Ian D Pavord, Laura Bermejo-Sanchez, Imran Howell, Mahdi Mahdi, Stefan Peterson, Thomas Bengtsson, Mona Bafadhel

JAMA.2025;333(2):143-152.doi:10.1001/jama.2024.22700

Future is Here ...

Phase III ARNASA) is investigating astegolimab with once every four weeks and once every fortnight, versus placebo.

Trials to watch: Four biologics concluding pivotal COPD trials

As the first biologic for COPD could soon be approved by the FDA, other candidates are coming to the end of pivotal studies.

Abigail Beaney | July 25, 2024

The AERIFY-1 and AERIFY-2 Phase III trials Itepekimab in former and current smokers