Airway Remodeling in Asthma

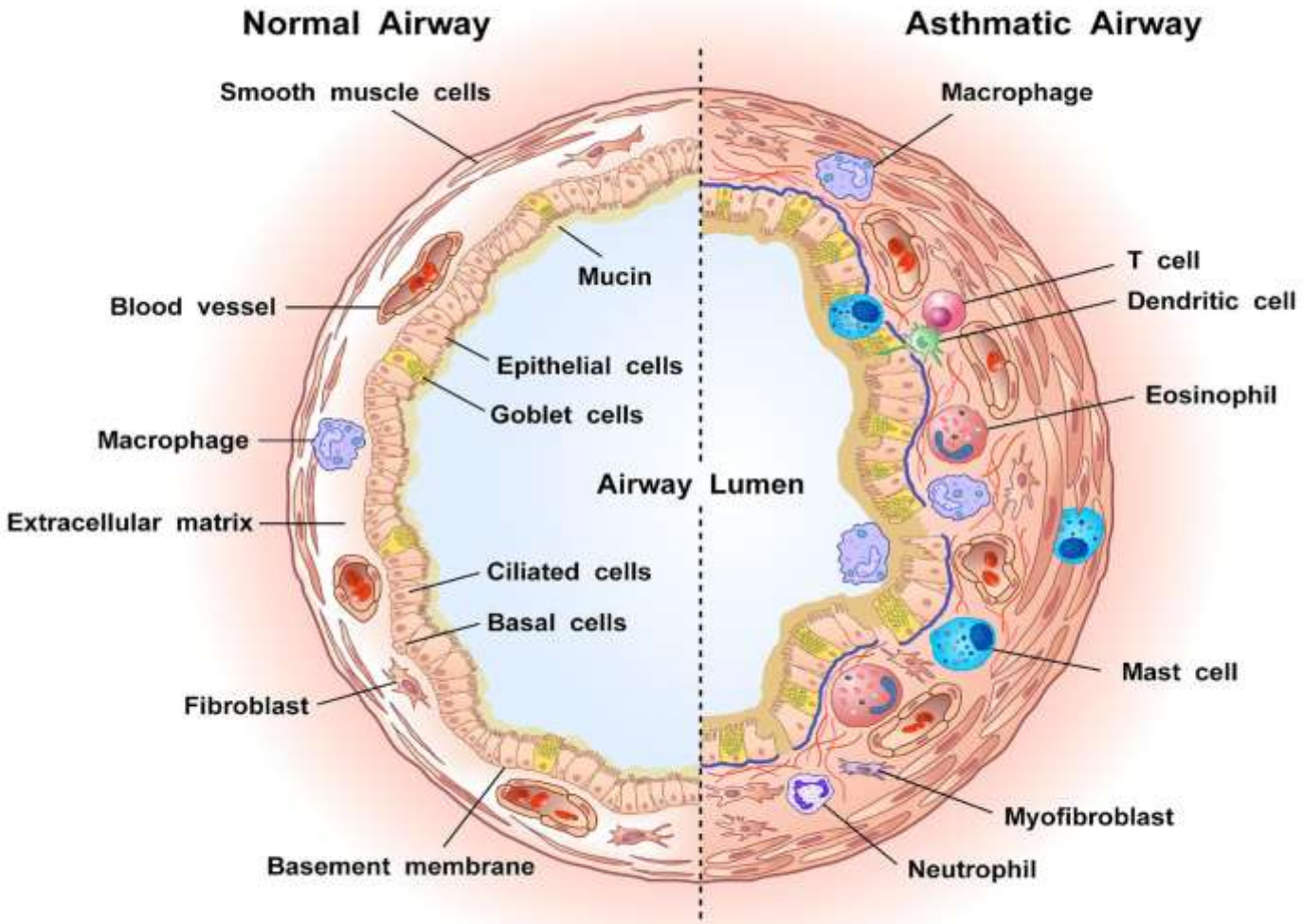
- **GINA Meeting – December 2025**
- **Cecilia Calabrese, Gabriella Guarnieri, Sara Maio, Gilda Varricchi**

1.mechanisms and relationship to inflammation

2. effect of ICS therapy on remodeling

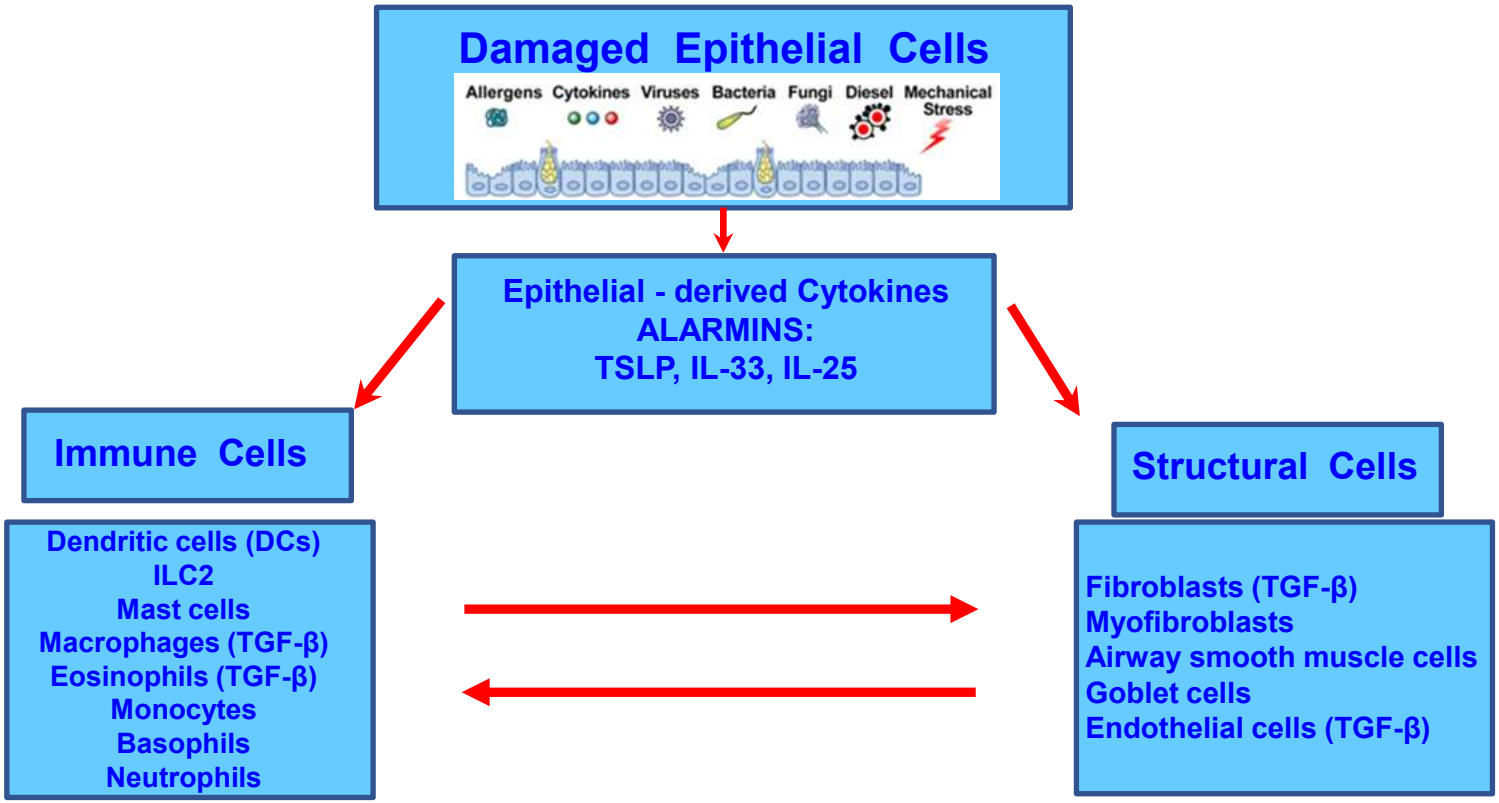
3. long-term longitudinal studies on FEV1 decline in asthmatics with and without ICS therapy

Structural Changes of AiRem in Asthma



Varricchi *et al., Allergy 2025:* Front. Med. (Lausanne) 2020

Pathogenesis of AiRem in Severe Asthma



Heterogeneity of AiRem

- **AiRem in most patients may occur early in the disease process**
- **Importantly, onset of airway remodeling has been identified in pre-school children as young as 1-year-old and in school-age children, persisting through adulthood**
- **AiRem proceeds from a potentially reversible inflammatory phase to a less modifiable fibrotic structural phase**

Respir Res 2017; Front. Med. (Lausanne) 2021

Biologics Can Influence Certain Aspects of AiRem in Severe Asthma

TABLE 1 Effects of biologics on specific features of airway remodeling

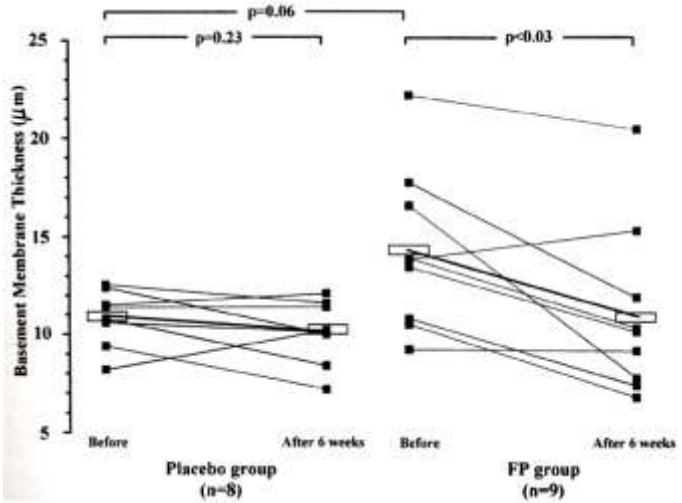
Varricchi et al. Allergy 2022

Biologics	Form	Target	Biological effects	Effects on airway remodeling
Omalizumab	Humanized IgG1-κ mAb	IgE	• ↓ circulating total IgE • Downregulation of FcεRI receptors on basophils, mast cells, and DCs	• ↑ FEV_1 • ↓ RBM thickness • ↓ airway wall thickness in CT • ↓ fibronectin deposition • Prevents IgE-mediated ECM deposition in vitro
Reslizumab	Humanized IgG4-κ mAb	IL-5	Blockage of IL-5/IL-5R binding	• ↑ FEV_1
Mepolizumab	Humanized IgG1-κ mAb	IL-5	Blockage of IL-5/IL-5R binding	• ↑ FEV_1 • ↓ airway eosinophils and TGF-β1$^+$ eosinophils • ↓ tenascin expression
Benralizumab	Humanized IgG1-κ mAb	IL-5 receptor (IL-5Rα)	↓ eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity (ADCC)	• ↑ FEV_1 • ↓ airway eosinophils • ↓ ASM mass
Dupilumab	Human IgG4 mAb	IL-4 receptor α chain (IL-4Rα)	• Blockage of IL-4/IL-4Rα binding • Blockage of IL-13/IL-4Rα binding	• ↑ FEV_1 • prevents eosinophil infiltration into lung tissue in a mouse model of asthma
Tezepelumab	Human IgG2-λ mAb	TSLP	Blockage of TSLP/TSLPR binding	• ↑ FEV_1 • ↓ airway eosinophils • ↓ AHR to mannitol • ↓ airway inflammation • ↓ TGF-β1 • ↑ CT scan-determined lumen area

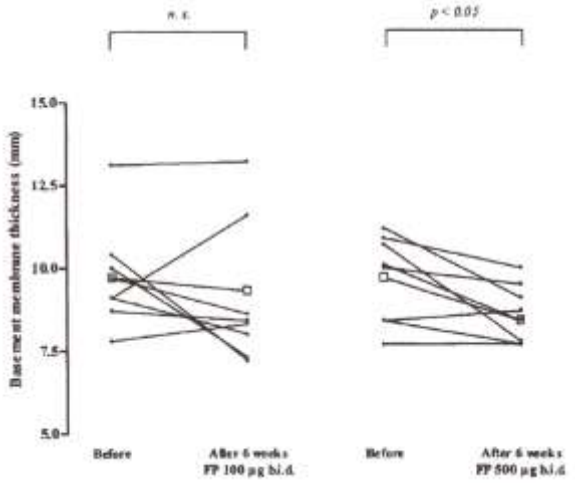
The early efficacy of Biologics suggests: primarily target inflammatory component of remodeling

ICS effects on Airway Remodeling (AiRem) - 1

-Several data suggested that ICS administered for at least 6 weeks helps in recovery of epithelial damage, decreases RBM thicknesses and collagen deposition, reduces goblet cell hyperplasia, restored the integrity of epithelial cell monolayers through the redistribution of tight junction proteins.
-The association of LABA to ICS decreased goblet cell metaplasia and vessels density



Olivieri et al, AJRCCM 1997



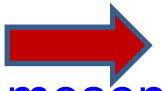
Chetta et al, AJRCCM 2003

- Effects are modest, dose-dependent, and highly variable between subjects

Tiotiu A,* Open Respiratory Archives 7 (2025). *Bergeron C, Chest 2006

ICS effects on modulation of lung fibroblast

- In young fibroblasts, fluticasone is able to almost completely prevent the induction of α-SMA by TGF-β, thus blocking myofibroblast differentiation.
- In intermediate fibroblasts, the effect is partial, while in senescent fibroblasts, the response to the steroid is almost completely lost.



Remodeling is age-dependent, with less plasticity of the mesenchymal compartment in "older" tissues.

The efficacy of ICS have a minimal impact on structural remodeling in the advanced stage of SA

Cazes et al., Journal of Immunology 2001

Inhaled corticosteroids and decline of lung function in community residents with asthma

P Lange, H Scharling, C S Ulrik, J Vestbo *Thorax* 2006;61:100–104.

234 asmatici adulti; studio longitudinale di popolazione generale (Copenhagen) (1991-2003).
2 gruppi: 44 trattati con ICS, 190 non trattati (sia al basale che al fw-up).
Outcome: declino annuale del FEV1 misurato dopo circa 10 anni.

Table 2 Multiple linear regression of ΔFEV_1 in ml/year in 234 subjects with asthma based on a mean observation period of 10 years

Variable	Estimate (ml/year)	SE	p value
Intercept*	49.5	5.7	<0.001
Sex			
Women	0		
Men	5.6	5.6	0.319
Smoking			
Non-smokers	0		
Starters	16.6	17.1	0.333
Quitters	8.6	7.6	0.259
Light smokers	2.1	8.7	0.805
Heavy smokers	22.5	7.3	0.002
Wheezing			
No	0		
Yes	−13.1	6.0	0.030
ICS			
No	0		
Yes	−17.8	7.1	0.013

SE, standard error of the estimate; ICS, inhaled corticosteroids.
The intercept represents the mean annual decline in a non-smoking asthmatic woman without wheezing who is not treated with ICS. The estimate for different variables represents the difference in the annual decline in FEV_1 between

FEV_1 of 22.5 ml/year whereas those treated with ICS have a 17.8 ml/year lower decline in FEV_1).

Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE

Roberto de Marco, PhD,[a] Alessandro Marcon, MSc,[a] Deborah Jarvis, FFPHM,[b] Simone

(J Allergy Clin Immunol 2007;119:611-7.)

667 asmatici adulti; studio di popolazione generale (European Community Respiratory Health Survey) (1991-2002).
Durata uso di ICS
Outcome: declino annuale del FEV1 misurato dopo circa 10 anni.

TABLE III. Multiple regression coefficients* with 95% CIs and related *P* values for the association between the mean decline in FEV_1 and sex, age, and BMI at baseline and smoking habits and ICS use during the follow-up

Covariate	Coefficient (mL/y)	95% CI	*P* value
Sex† (female)	−9.5	−20.4; 1.4	.09
Age‡ (y)	0.8	0.2; 1.4	.005
BMI‡ (kg/m^2)	−0.4	−1.3; 0.5	.40
Smoking habits‡ (lifetime pack-years)	0.04	−0.2; 0.3	.76
Use of ICSs†			
<8.7 months	−3.9	−14.4; 6.5	.46
8.7 months to 4 years	−4.8	−15.5; 6.0	.38
>4 years	−10.7	−21.3; −0.1	.048

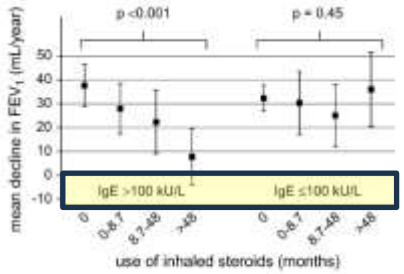


FIG 2. Unadjusted mean annual decline in FEV_1 (with 95% CIs and *P* value for trend), according to the level of total IgE and to the time of ICS use during the follow-up (nonusers, 1st, 2nd, and 3rd tertile). Elevated (>100 kU/L) total IgE levels were present in 47% of the subjects included in the analysis.

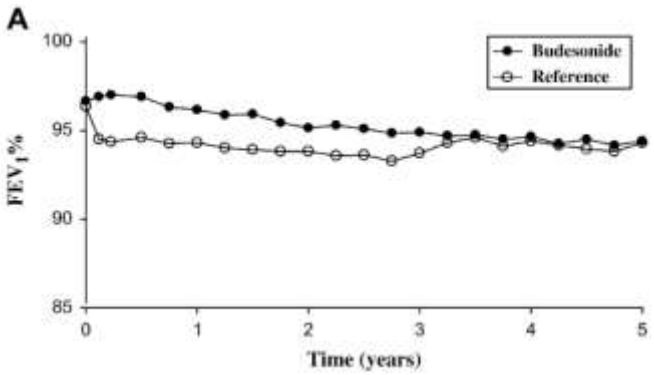
double-blind treatment

7241 pazienti (5-66 a) con recente insorgenza di asma lieve-persistente
Trattati: nuova assunzione di budesonide per 3 anni; controlli: no budesonide per 3 anni; + 2 anni tutti trattati con budesonide.
Outcome: decremento del FEV1 in percento predetto.

TABLE IV. Change in postbronchodilator percent predicted FEV_1 over the study

	Budesonide	Reference	Difference
Overall	−2.17 (0.21)	−2.27 (0.21)	0.10 (0.30), $P = .74$
Age-by-sex stratum			
5–10 y, female	−0.84 (0.57)	0.26 (0.56)	−1.10 (0.80), $P = .17$
Male	−2.28 (0.46)	−1.96 (0.48)	−0.32 (0.66), $P = .63$
11–17 y, female	−1.46 (0.64)	−0.50 (0.63)	−0.95 (0.89), $P = .29$
Male	−0.42 (0.70)	0.51 (0.74)	−0.93 (1.01), $P = .36$
18-66 y, female	−1.89 (0.38)	−3.04 (0.39)	1.15 (0.54), $P = .034$
Male	−4.73 (0.49)	−4.91 (0.47)	0.18 (0.67), $P = .79$
Both sexes	−2.96 (0.30)	−3.81 (0.30)	0.85 (0.42), $P = .044$

Only patients entered into the open-label phase are shown. Data are presented as means (SEs) of the 5-year change estimated by means of mixed model analysis.



The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: Effectiveness of early intervention with budesonide in mild persistent asthma

William W. Busse, MD,[a] Søren Pedersen, MD,[b] Romain A. Pauwels, MD,[c,†] Wan C. Tan, MD,[d] Yu-Zhi Chen, MD,[e] Carl Johan Lamm, PhD,[f] and Paul M. O'Byrne, MD,[g] on behalf of the START Investigators Group Madison, Wis, Kolding,

J ALLERGY CLIN IMMUNOL
VOLUME 121, NUMBER 5
2008

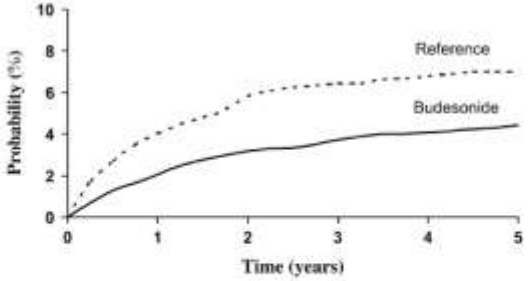


FIG 4. Cumulative probability of having a first SARE. The curves are based on life-table estimates (interval width, 0.25 years) by using all patients entered into the study. The number of patients at risk in the budesonide *(Reference)* group is 3597 (3568) at time 0, 2613 (2486) at time 2.50 years, and 2337 (2195) at time 4.50 years.

SARE: un evento che richiede ospedalizzazione o accsesso al PS per riacutizzazzione/morte per asma.

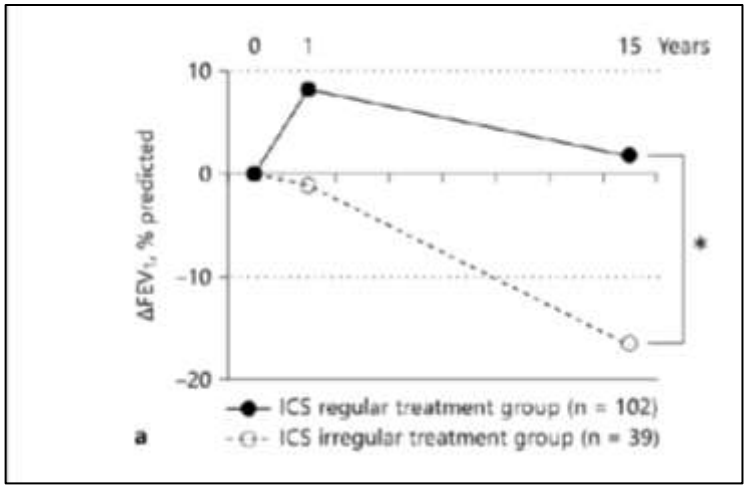
Clinical implications: Although early intervention with ICSs did not affect lung function, this approach can lead to improved asthma control and result in the need for less additional medication.

Impact of Inhaled Corticosteroid Treatment on 15-Year Longitudinal Respiratory Function Changes in Adult Patients with Bronchial Asthma

Terufumi Shimoda[a] Yasushi Obase[b] Reiko Kishikawa[a] Tomoaki Iwanaga[a]

Int Arch Allergy Immunol 2013;162:323–329

167 adulti asmatici con visita basale nel 1995 e fw-up 1996 e 2010. Inizio assunzione beclometasone nel 1995.
2 gruppi: trattamento regolare con ICS (visite regolari ogni 4 mesi e aderenza >= 80%) e trattamento irregolare con ICS.
Outcome: decremento del FEV1 in percento predetto.



ICS regular treatment

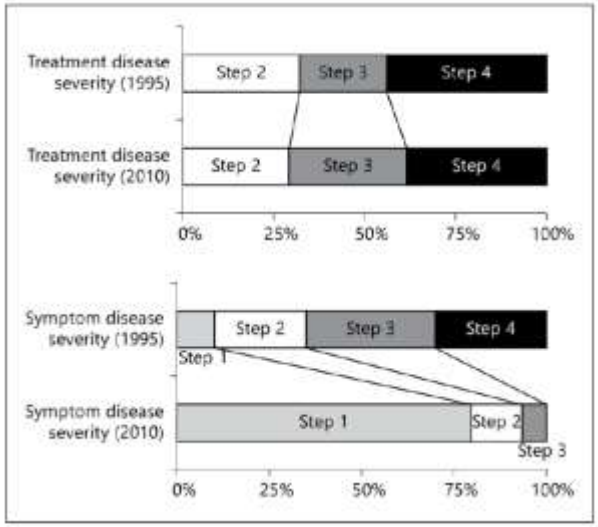


Fig. 3. Changes in treatment and symptom steps. Treatment steps in the regular treatment group (steps 2/3/4) changed from 32/24/44 to 29/33/38%, respectively, over 15 years, showing a proportional reduction at step 4. The symptom steps (steps 1/2/3/4) changed over 15 years, from 10/25/35/30 to 77/17/6/0, respectively, in the regular treatment group, showing that ICS had improved the overall severity significantly ($p < 0.01$).

Airway Remodeling in Asthma: questions?

-ICS and correlation with lung function decline is still debated: early treatment with ICS may prevent worsening of lung function?

-ICS have effects on remodeling, however these effects are modest, dose-dependent, and highly variable between subjects.

-The early efficacy of some biologics in remodeling suggests that they primarily target inflammatory component of remodeling: but early and sustained modulation can prevent the progression to fixed small airway obstruction?