IL13 and IL4 in Asthma

Joo Hun Park, M.D.
Dept. of Pulmonary and Critical Care Medicine
Ajou University School of Medicine

Outline

- Overview

→ Definition of Severe asthma

→ Pathophysiology of Severe asthma

- Monoclonal antibody

→ IL-13 antibody

→ IL-4 antibody

- Summary

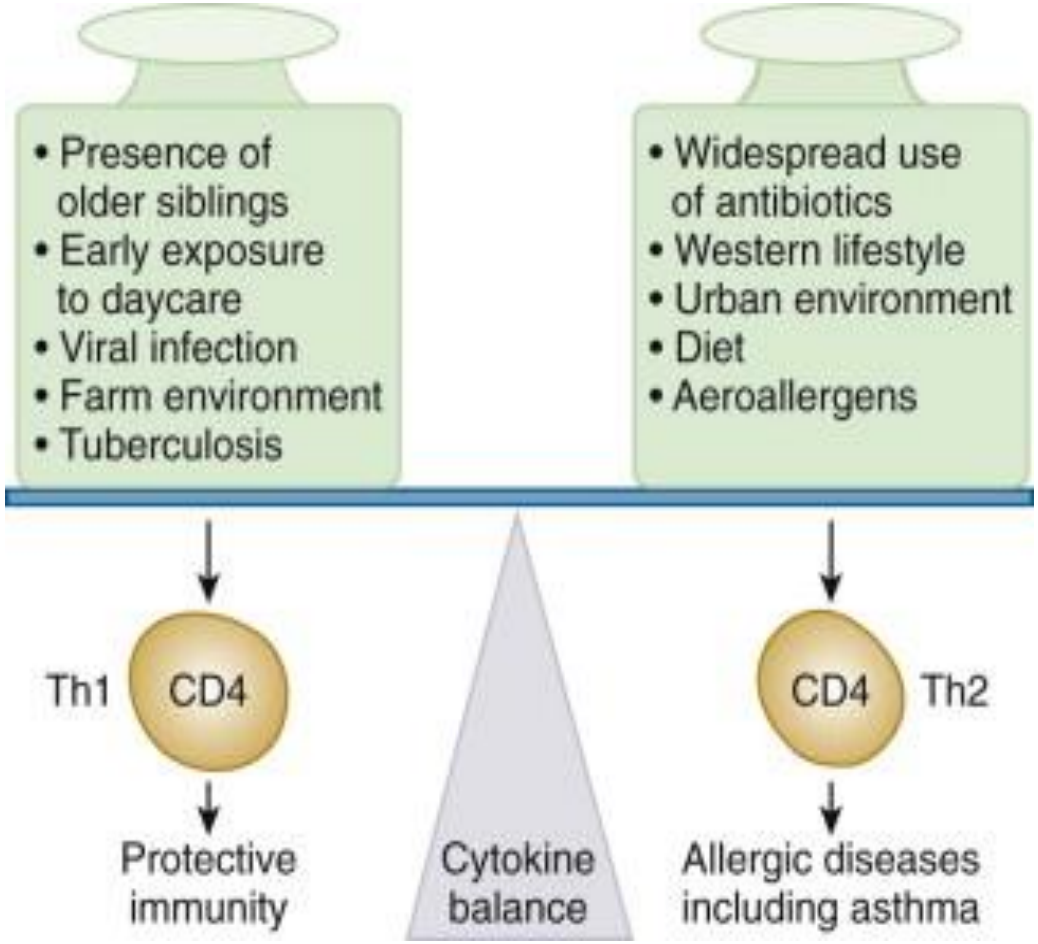
- Overview

→ Definition of Severe asthma

→ Pathophysiology of Severe asthma

→ Biomarkers

Determinants of Asthma



Murray & Nadel 5th edition, p 887

Severe Asthma

- Difficult asthma : uncontrolled symptoms due to
  → Alternative diagnosis
  → Poor compliance
  → Ongoing allergen exposure
  → Co-morbidities
- Refractory asthma
  → Causes of difficult asthma addressed
  → Still poor asthma control
  despite high-intensity treatment

Hambly et al, Curr Opin Pulm Med 2014 ; 20 : 87-94
Bel et al, Thorax 2011 ; 66: 910 - 917

Features of Refractory Asthma

- Varying peak flows
- Chronic airflow limitation
- Rapidly progressive loss of lung function
- Mucus production
- Varying responses to high-dose ICS)

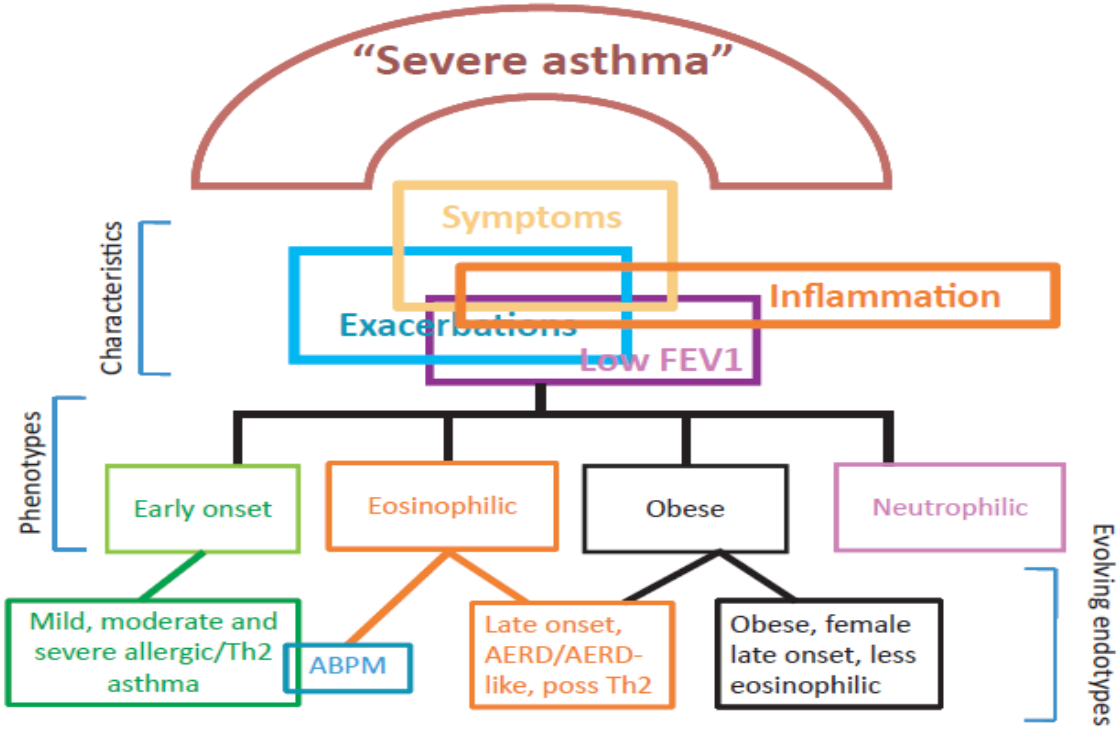
Proceedings of the ATS workshop AJRCCM 2000 ; 162: 2341 - 2351

Severe Asthma

- 10-20 % of asthmatics : refractory to current gold standards of treatment
- From phenotype to endotype

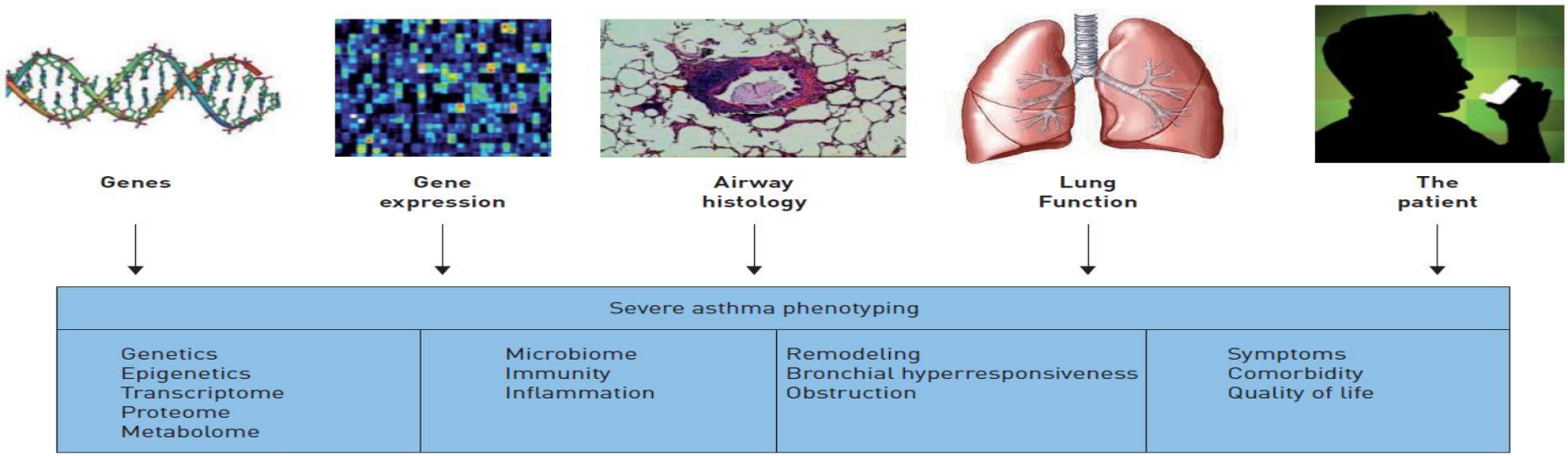
→ Endotype : a subtype of a condition defined by functional or pathophysiological mechanism

Wenzel S Clin Exp Allergy 2012; 42: 65-658

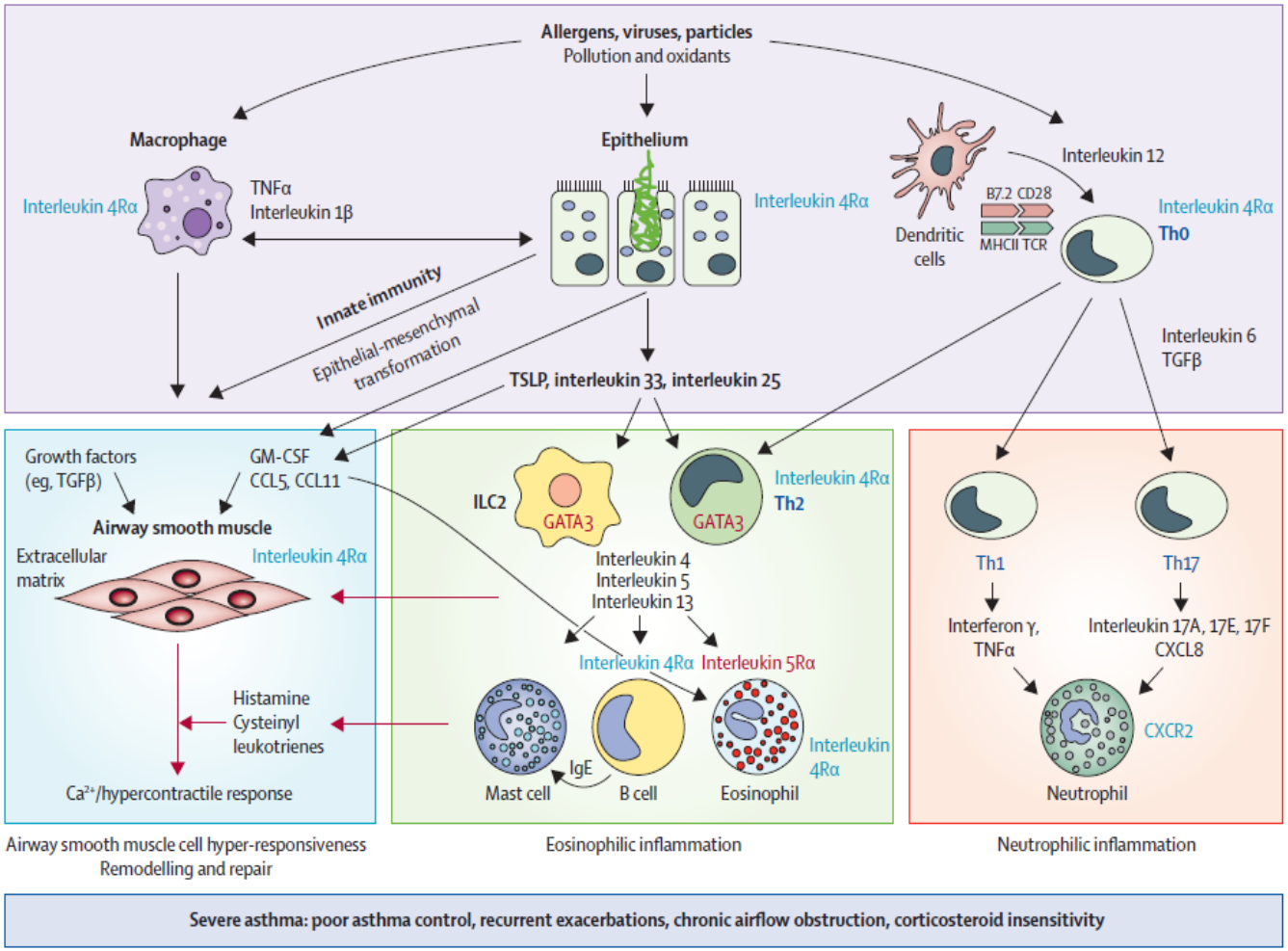


Wenzel S Clin Exp Allergy 2012; 42: 65-658

Cung KF et al ERJ 2014; 43: 343-373



Pathophysiologic Mechanism Underlying Severe Asthma



ILC2 : type 2 innate lymphoid cells
TSLP : thymic stromal lymphoprotein

Chung KF Lancet 2015; 386: 1086-1096

Role of IL4 and IL 13 in Asthma

- IL4

→ Th2 cell differentiation

→ Eosinophil recruitment

& Mast cell development

→ Switching of B cells to IgE production

→ Airway remodelling

& mucus hypersecretion

Barnes PJ et al. J Clin Invest 2008; 118: 3546-3556

- IL13

→ Pathophyisologically similar to IL-4

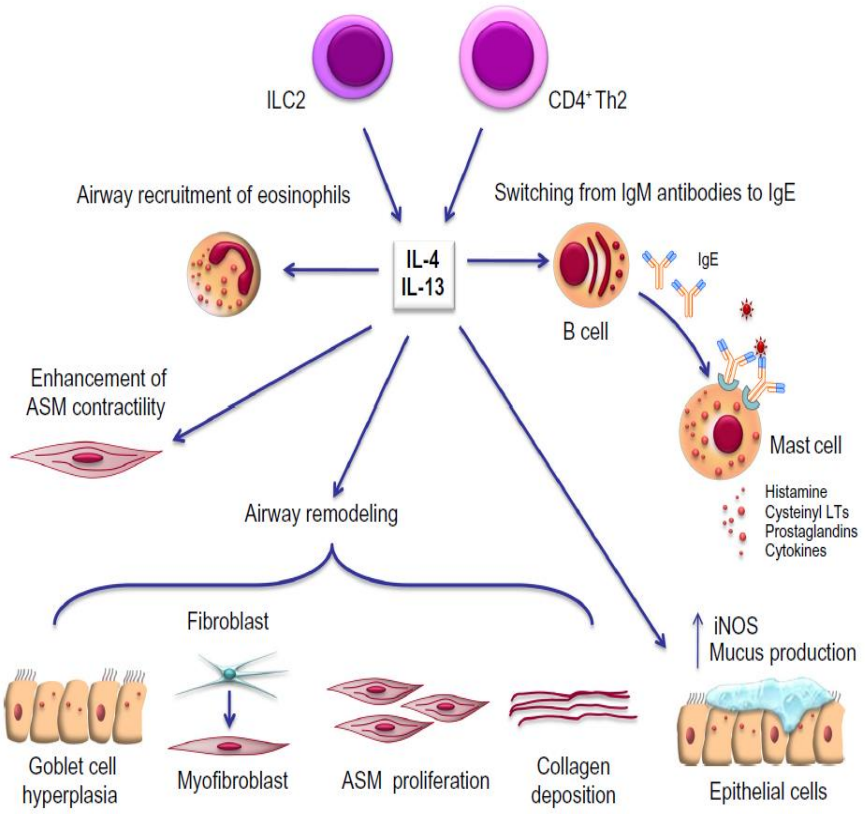
→ Airway hyperresponsiveness

→ Bronchial fibroblast proliferation

& basophil recruitment

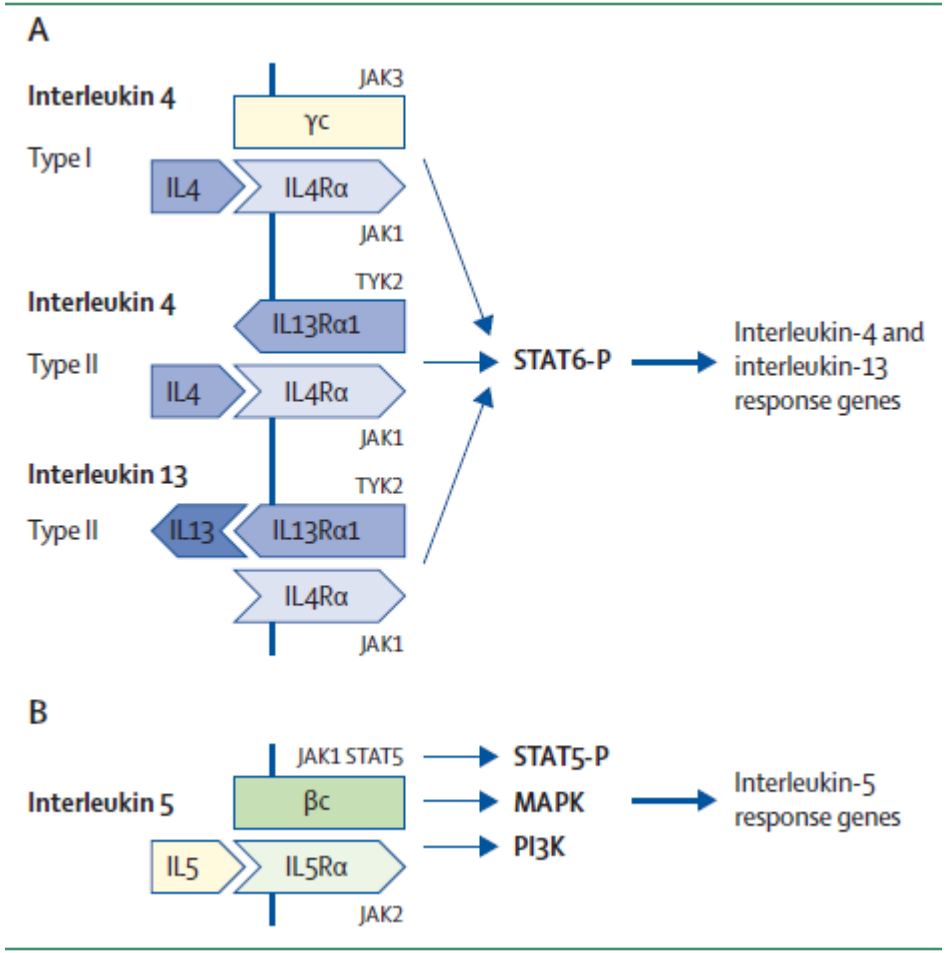
Wills Karp M et al Immunol Rev 2004; 202: 175-190

Yang G et al. Cytokine 2004; 28: 224-232



Vatrella et al J Asthma Allergy 2014; 7:123-13

Signalling Pathways of IL-4 and IL-13



Chung KF Lancet 2015; 386: 1086-1096

Monoclonal Antibody

- IL-13 antibody
- IL-4 Rα antibody

Debate in ATS May 19, 2015 Monoclonal Antibodies Are Important Therapies for Severe Asthma

Con; Barnes PJ

Pro; M Kraft

Monoclonal Antibodies on Trial

- IL-13

→ Lebrikizumab

→ Tralokinumab

→ GSK679586

- IL-4 Rα : blocks IL 4 and IL 13

→ Dupilumab

→ AMG 317

→ Pitrakinra

Biomarkers for Therapy Based on Th2 cells

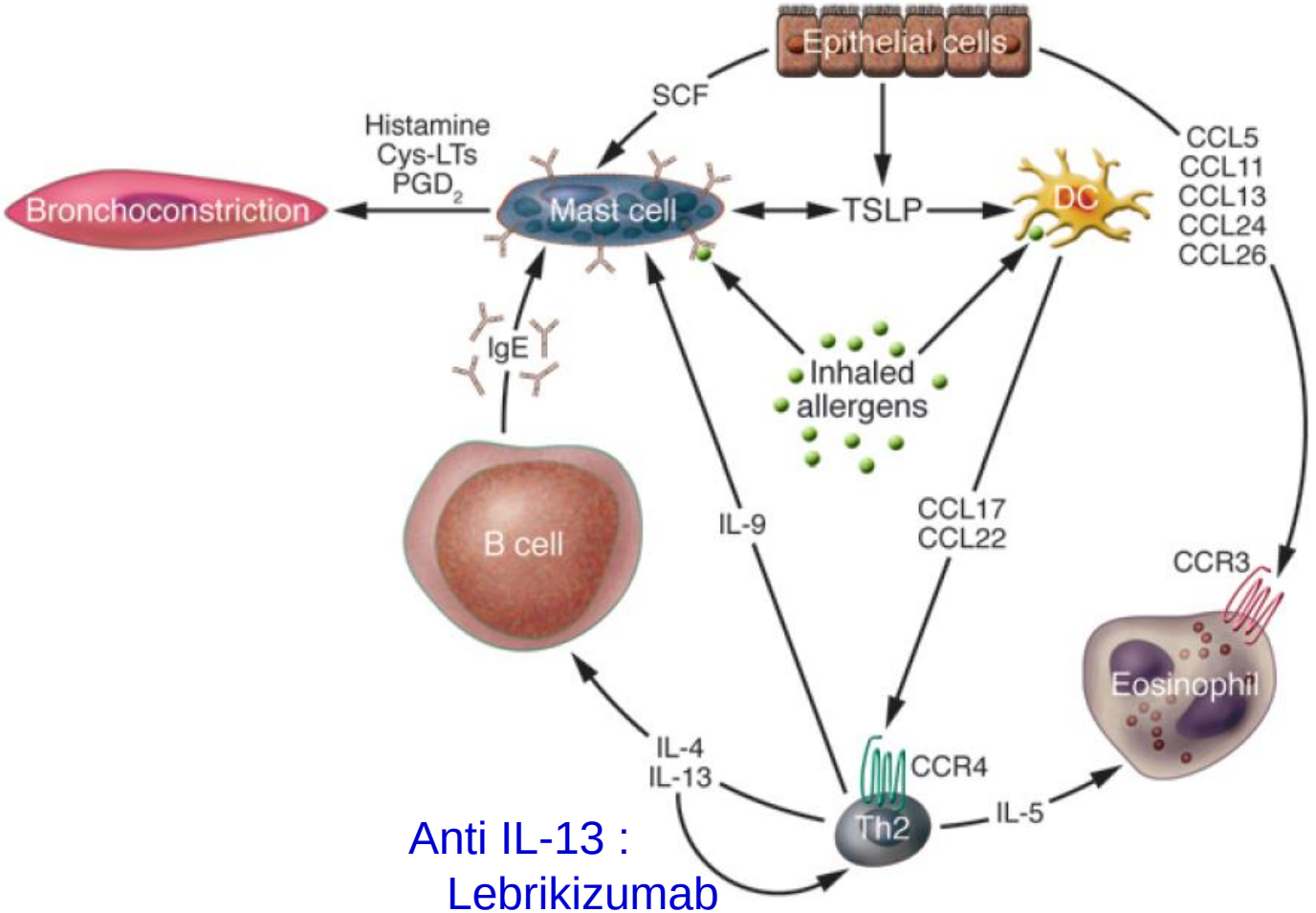
- Blood and sputum eosinophil
- Eosinophilic airway inflammation

→Periostin

→FeNO

- IgE

Therapy Based on Cytokines in Asthma



Anti IL-13 :

Lebrikizumab

Tralokinumab

RCT with Lebrikizumab

Study	No.	Population	Main Findings
Corren et al 2011,NEJM	219	Uncontrolled asthma despite ICS	• FEV_1 ↑in high periostin group • Exacerbation rate↓ in pts with Th2 inflammation profile
Noonan et al 2013, JACI	212	Mild asthmatics not using ICS	• No difference in FEV_1 • Reduction in treatment failure
Scheerens et al 2014, Clin Exp All	29	Mild asthmatics	• Late allergic response ↓
Hanania et al 2014, JACI	463	Uncontrolled asthma despite ICS	• FEV_1 ↑ & exacerbation rate↓ in high periostin group.

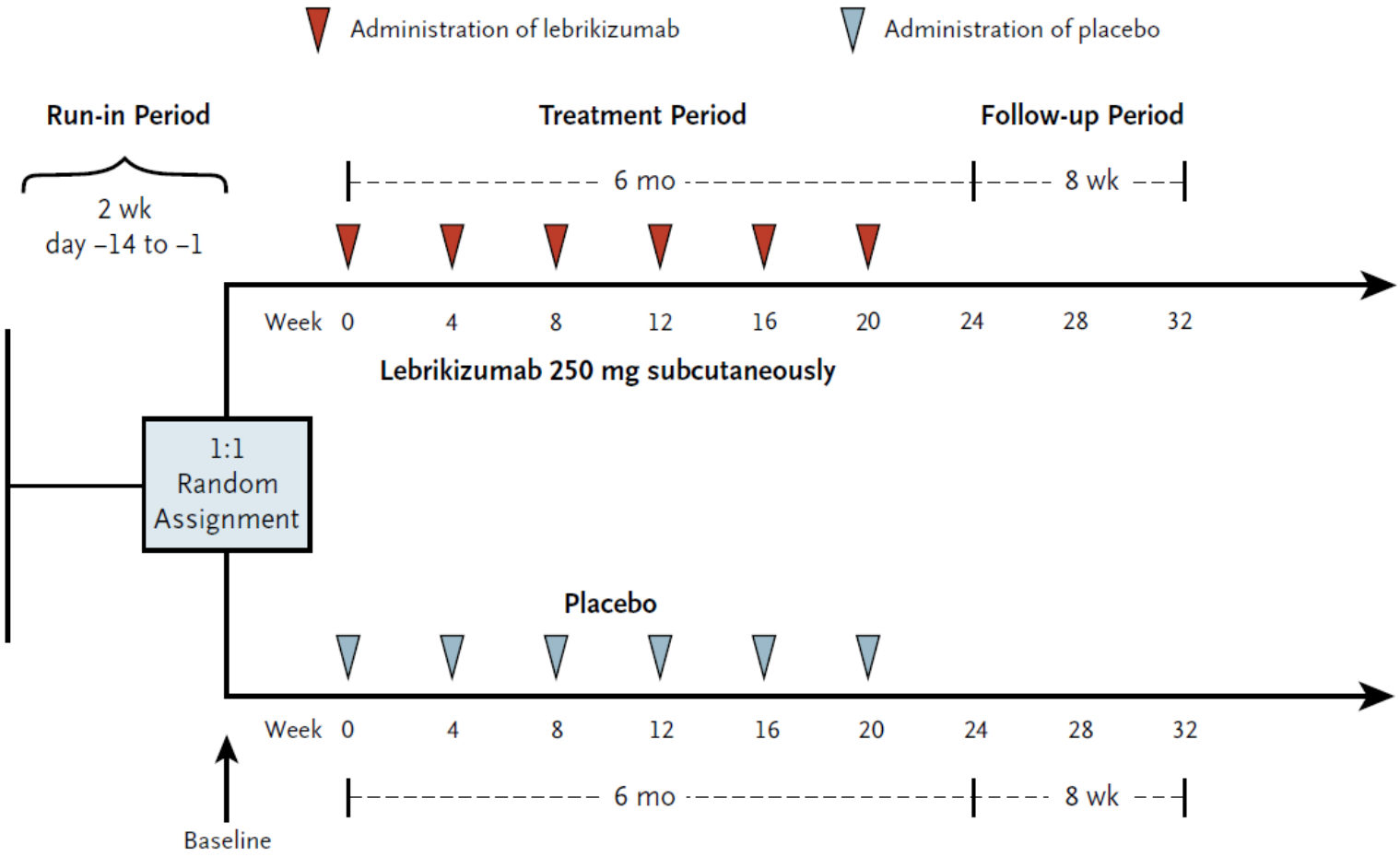
Lebrikizumab in Adult Asthmatics

- Subjects : 219 Asthmatics
- **Uncontrolled asthma**
- Pre Bronchodilator FEV_1 : 40-80 %
- FEV_1 improvement ≥ 12%

- **ICS or LABA :**
- **Not altered during treatment period**

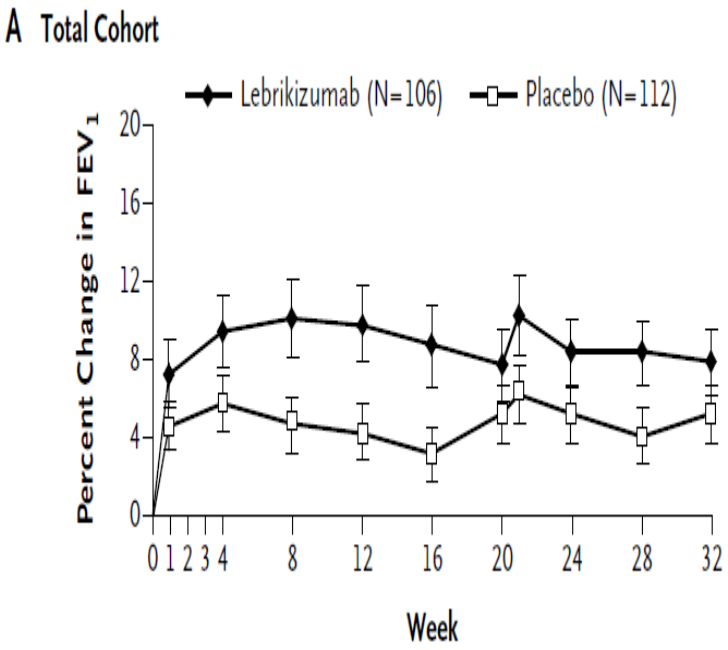
Corren J, NEJM 2011; 365 : 1088-1098

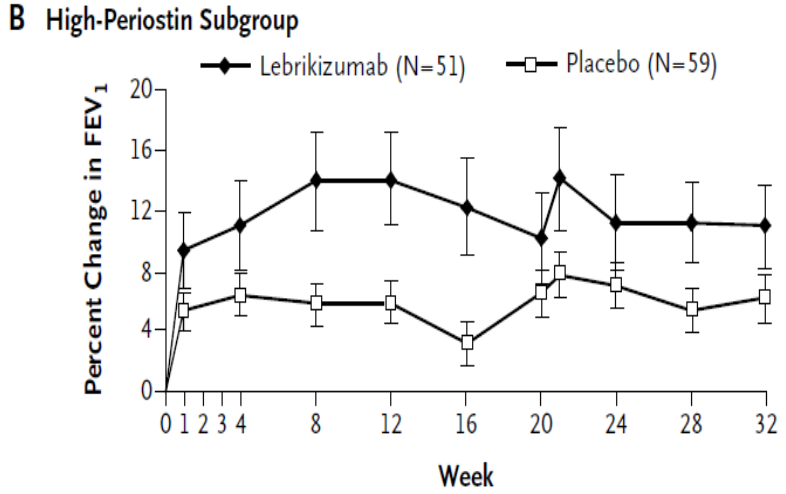
Lebrikizumab in Adult Asthmatics

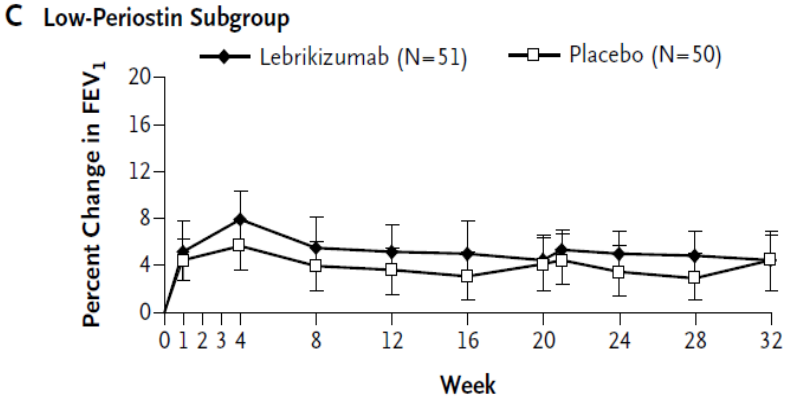


Corren J, NEJM 2011; 365 : 1088-1098

Lebrikizumab in Adult Asthmatics







Corren J, NEJM 2011; 365 : 1088-1098

Between Lebrikizumab and Placebo

- ACQ, asthma symptoms, rescue medication

→ No difference

- **Severe exacerbation rate throughout week 24**

→ **p=0.08 in high periostin group**

→ p =0.44 in low periostin group

- Musculoskeletal side effects

→ 13.2% in lebrikizumab vs. 5.4% in placebo

p=0.045

Corren J, NEJM 2011; 365 : 1088-1098

Lebrikizumab in Adult Asthmatics

- Lebrikizumab

→ **Greater improvement of lung function and reduction of severe exacerbation rate in high periostin group**

Corren J, NEJM 2011; 365 : 1088-1098

The effects of Lebrikizumab in Mild Asthma

- Objective : to evaluate lebrikizumab in mild asthmatics by bronchial allergen challenge.

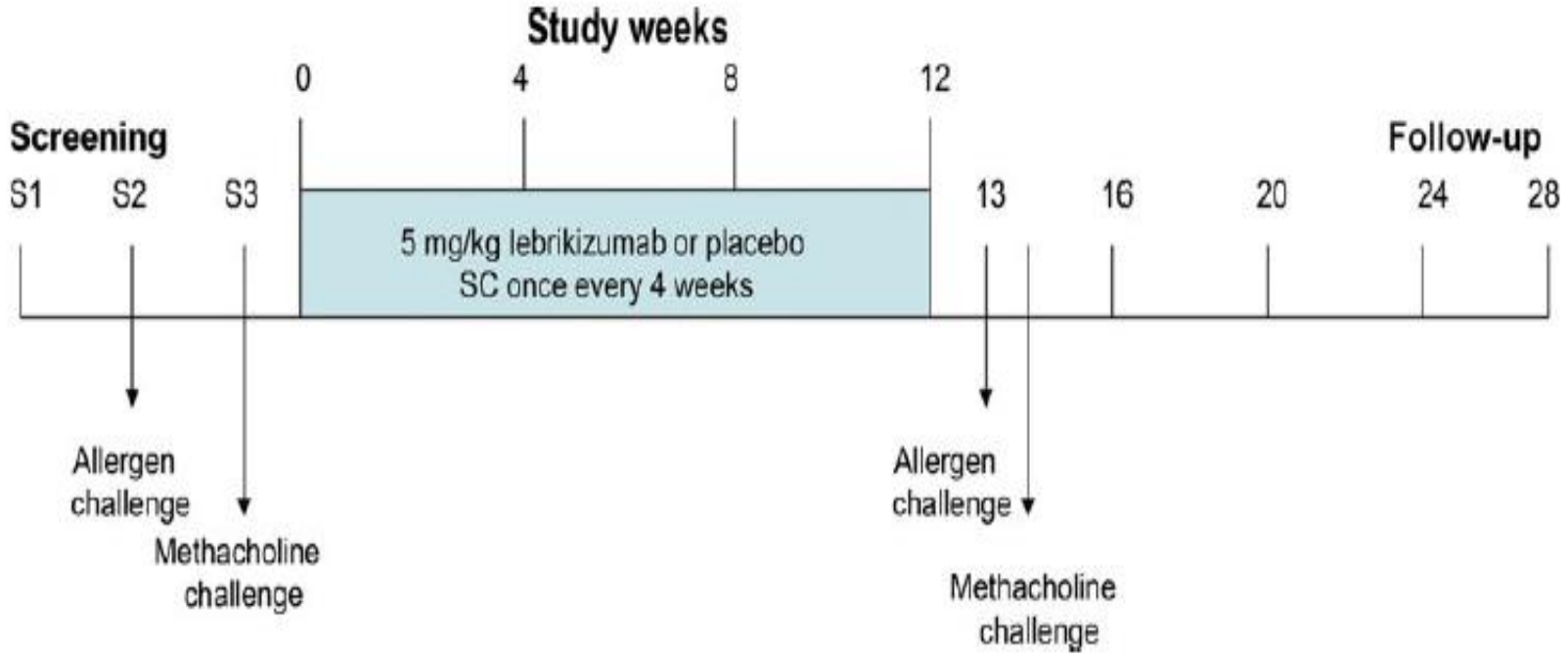
- 29 subjects treated only with intermittent SABA

→ Lebrikizumab (n = 13) or placebo (n = 16)

→ SQ every 4 weeks over 12 weeks

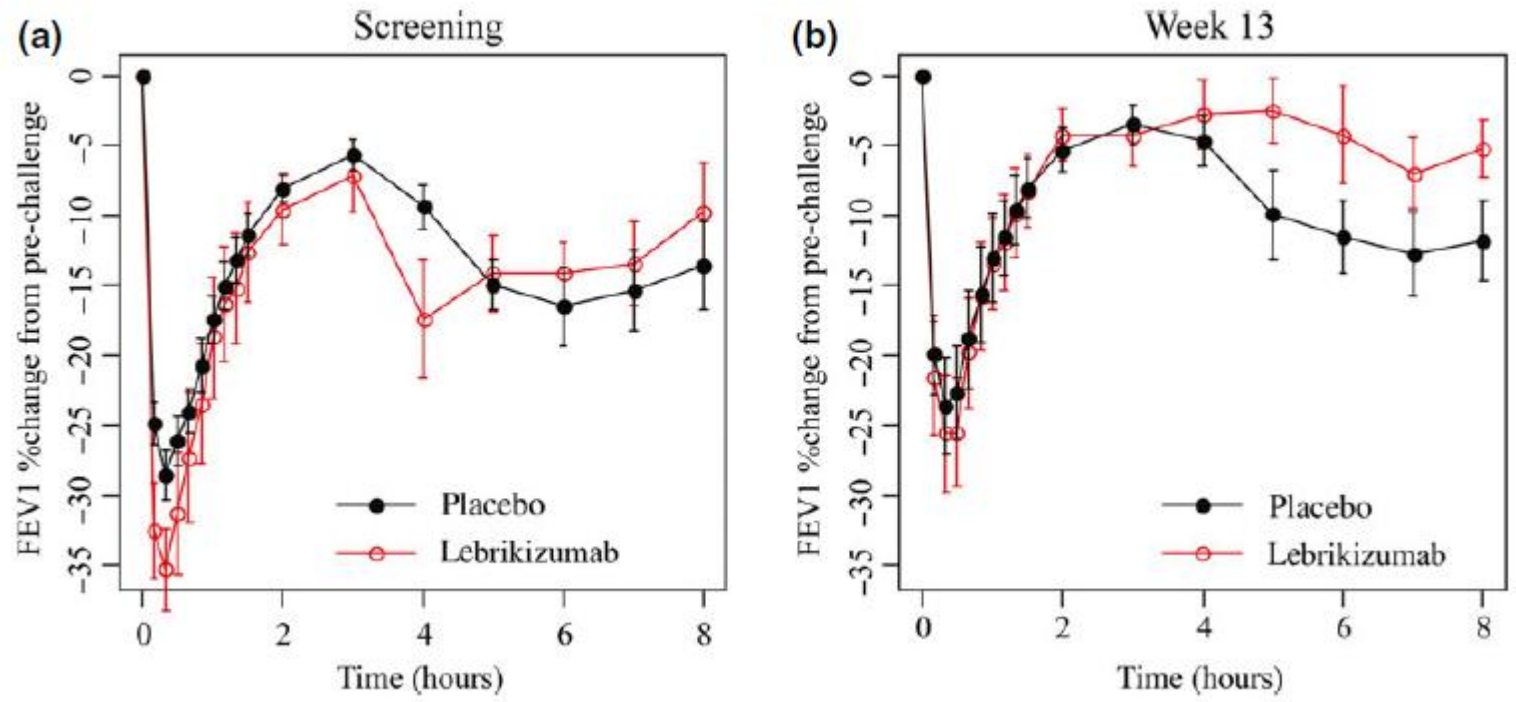
Scheerens H et al, Clin Exp Allergy 2014; 44 : 38 - 46

The effects of Lebrikizumab in Mild Asthma



Scheerens H et al, Clin Exp Allergy 2014; 44 : 38 - 46

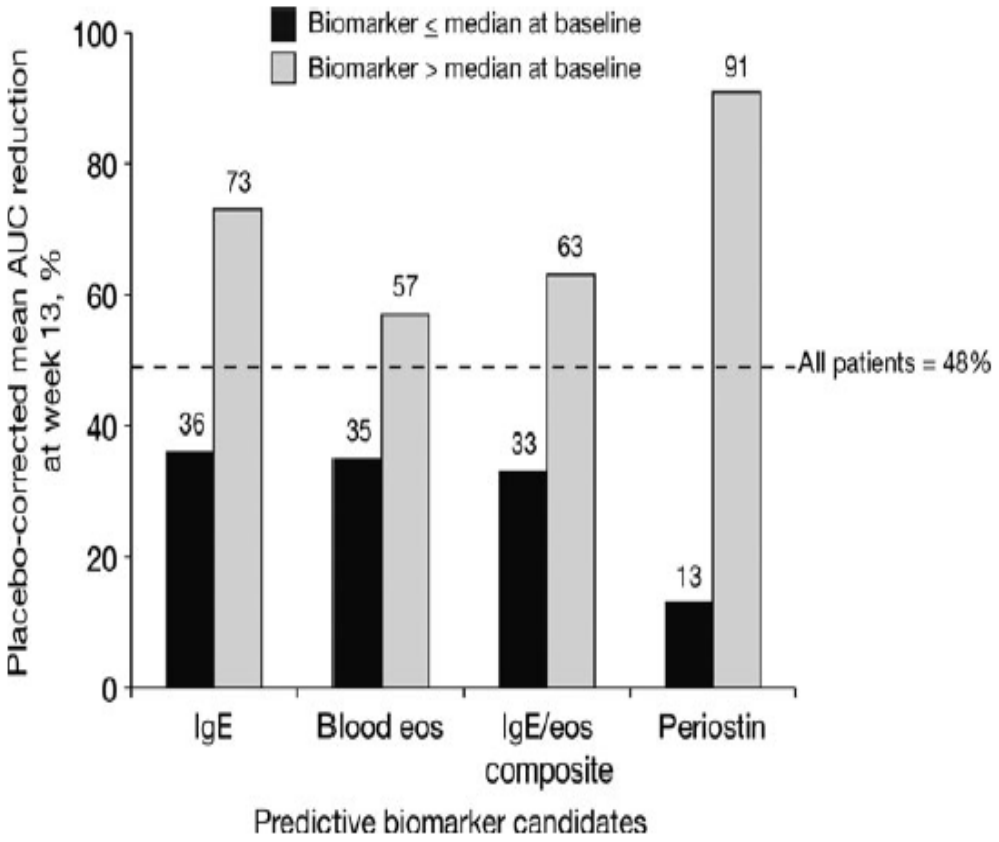
The effects of Lebrikizumab in Mild Asthma



Scheerens H et al, Clin Exp Allergy 2014; 44 : 38 - 46

Lebrikizumab : Greater but not Statistically Significant Effect on Late Asthmatic Response

Late Asthma Response Reduction



Scheerens H et al, Clin Exp Allergy 2014; 44 : 38 - 46

The effects of Lebrikizumab in Mild Asthma

- Lebrikizumab reduced the late asthmatic response in subjects with mild asthma.

Scheerens H et al, Clin Exp Allergy 2014; 44 : 38 - 46

RCT with Tralokinumab

Study	No.	Population	Main Findings
Piper et al 2013, ERJ	194	Uncontrolled asthma	• FEV_1 ↑ • No difference in symptom score
Brightling CE 2015, Lancet Resp med	452	Severe Uncontrolled asthma	• FEV_1 ↑ • No reduction of exacerbation rate

Tralokinumab in Moderate to Severe Asthma

- 194 moderate to severe uncontrolled asthmatics

→ Tralokinumab 150, 300, 600 mg or placebo

→ Every 2 weeks for 12 week treatment

→ Continued pre-study asthma controller therapy

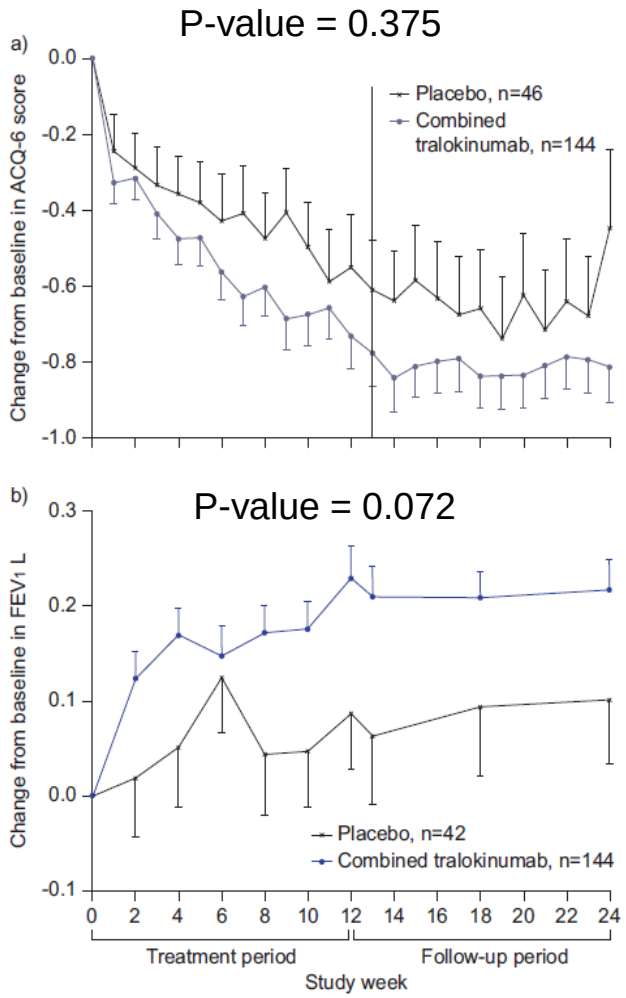
- At week 13

→ Primary : Asthma control questionnaire score (ACQ6)

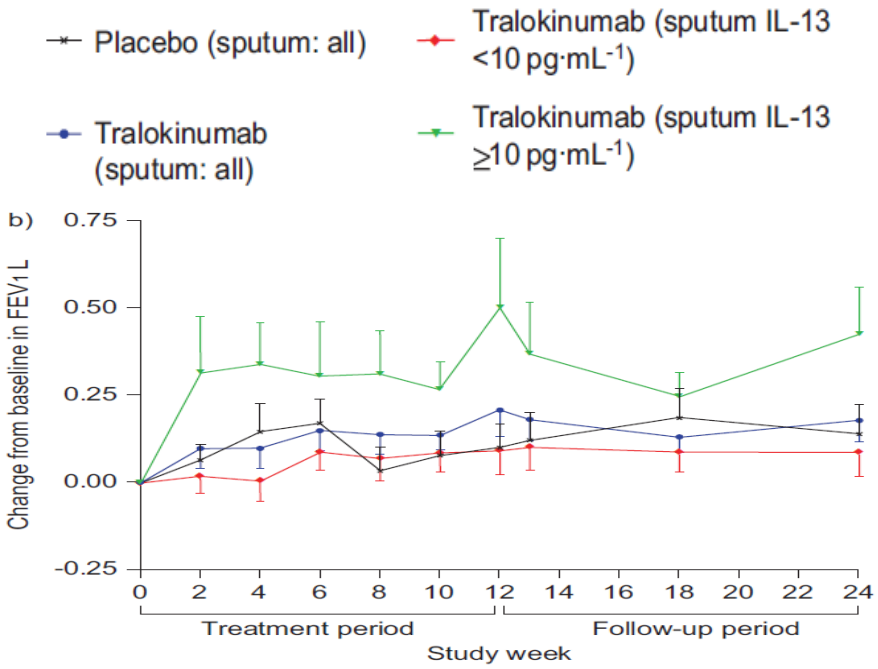
→ Secondary : pre BD FEV_1, rescue β_2-agonist use, safety

Piper et al ERJ 2013; 41: 330 – 338

Tralokinumab in Moderate to Severe Asthma



Rescue β_2-agonist use Decreased for Tralokinumab P=0.02



Piper et al ERJ 2013; 41: 330 – 338

Tralokinumab in Moderate to Severe Asthma

- Tralokinumab

→ Improved lung function

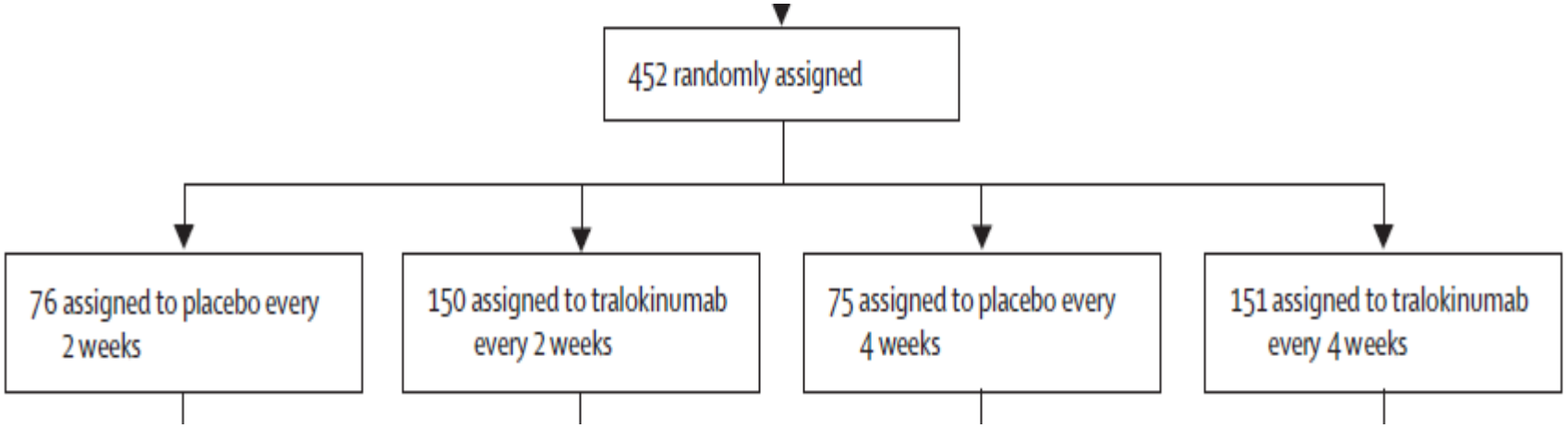
→ Maintained 12 weeks after the final dose

→ No improvement of ACQ 6 score

Piper et al ERJ 2013; 41: 330 – 338

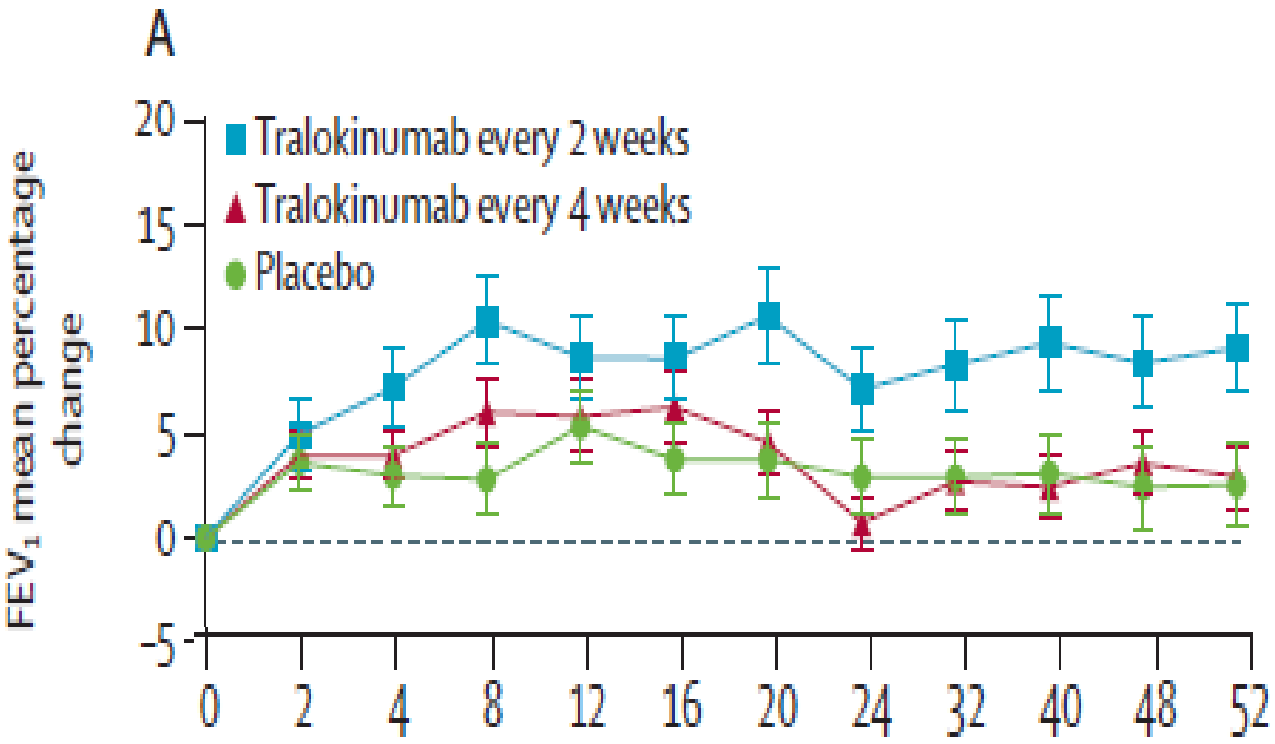
Efficacy and Safety of Tralokinumab in Patients with Severe Uncontrolled Asthma

Severe uncontrolled asthma
Continued pre-study controller (ICS + LABA)



Brightling CE Lancet Respir Med 2015;3(9):692-701

Efficacy and Safety of Tralokinumab in Patients with Severe Uncontrolled Asthma



Brightling CE Lancet Respir Med 2015;3(9):692-701

Efficacy and Safety of Tralokinumab in Patients with Severe Uncontrolled Asthma

	All (n=33)	Periostin-high group (n=18)	Periostin-low group (n=15)
Primary endpoint			
Asthma exacerbation rate			
Percent reduction versus placebo (95% CI; p value)	44% (-22 to 74; 0·147)	67% (2 to 89; 0·046)	-32% (-273 to 53; 0·597)

Brightling CE Lancet Respir Med 2015;3(9):692-701

Efficacy and Safety of Tralokinumab in Patients with Severe Uncontrolled Asthma

- Tralokinumab in severe uncontrolled asthma

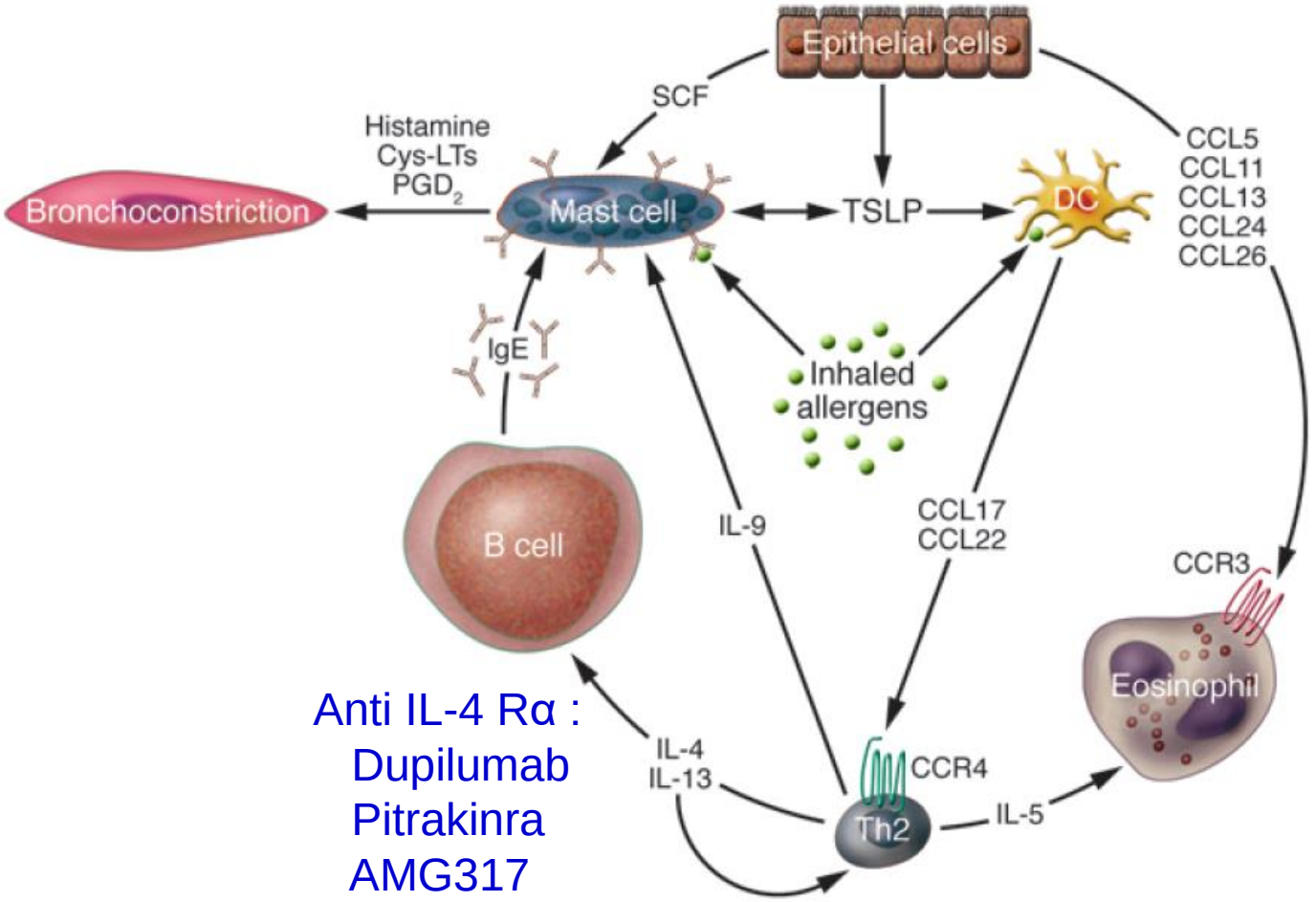
→ Acceptable safety and tolerability profile

→ No reduction of exacerbation rates in severe uncontrolled asthma.

→ Improvement in FEV_1

Brightling CE Lancet Respir Med 2015;3(9):692-701

Therapy Based on Cytokines in Asthma



Anti IL-4 Rα :
- Dupilumab
- Pitrakinra
- AMG317

RCT with Dupilumab

Study	No.	Population	Main Findings
Wenzel S et al 2013, NEJM	104	Persistent Mod to Severe asthmatics & elevated eosionphil	• FEV_1 ↑ • Exacerbation rates ↓
Wenzel S et al 2016, Lancet	452	Uncontrolled asthma Regardless of eosinophil count	• FEV_1 ↑ • Exacerbation rates ↓

Dupilumab in Persistant Asthma

- Goal : to evaluate duplimab in persistent, moderate to severe asthmatics with elevated eosinophil level

- Patients

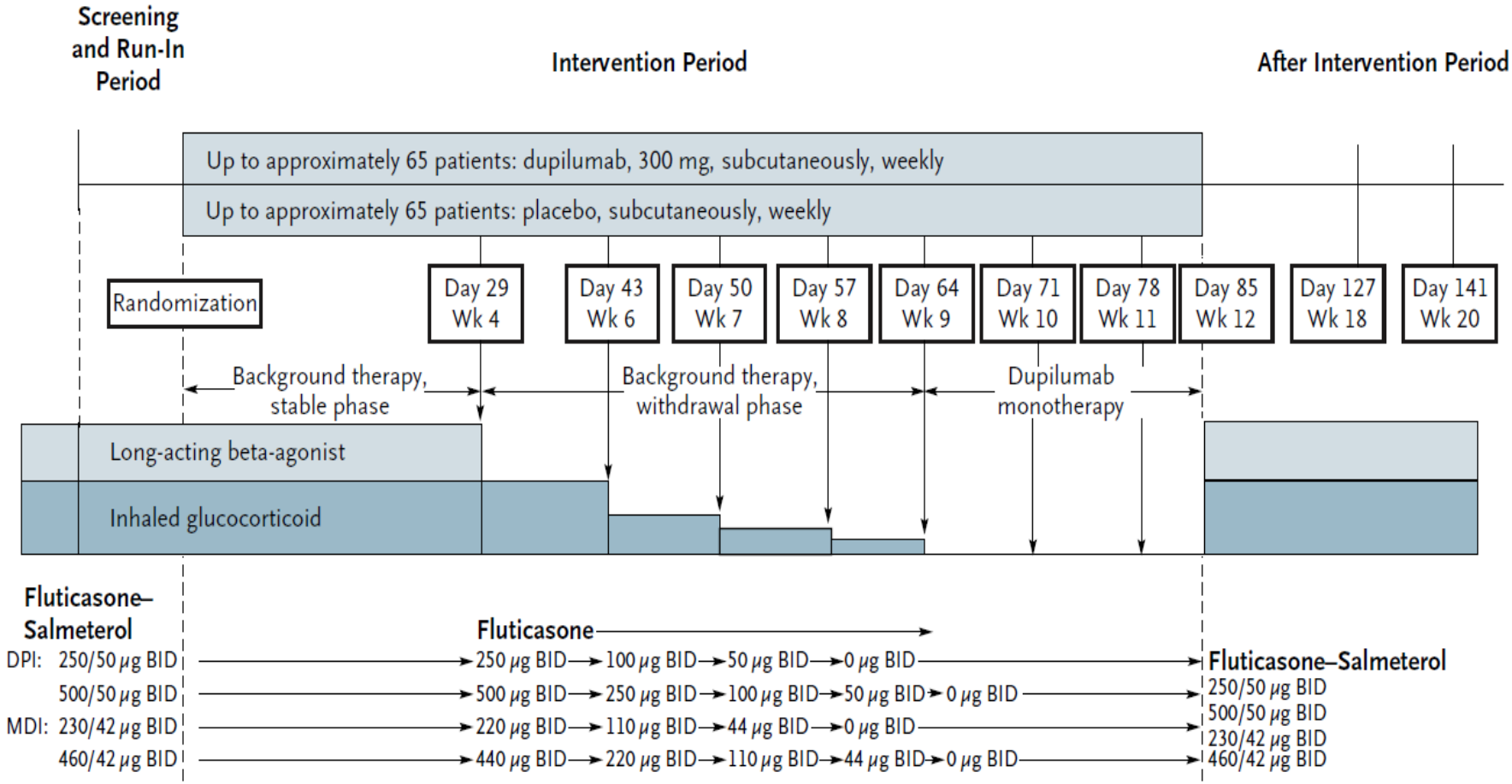
→ 18- 65 years old asthmatics

→ Eosinophil : blood $\geq$ 300 cells/μL or sputum $\geq$ 3%

→ Not-well controlled with high dose ICS plus LABA

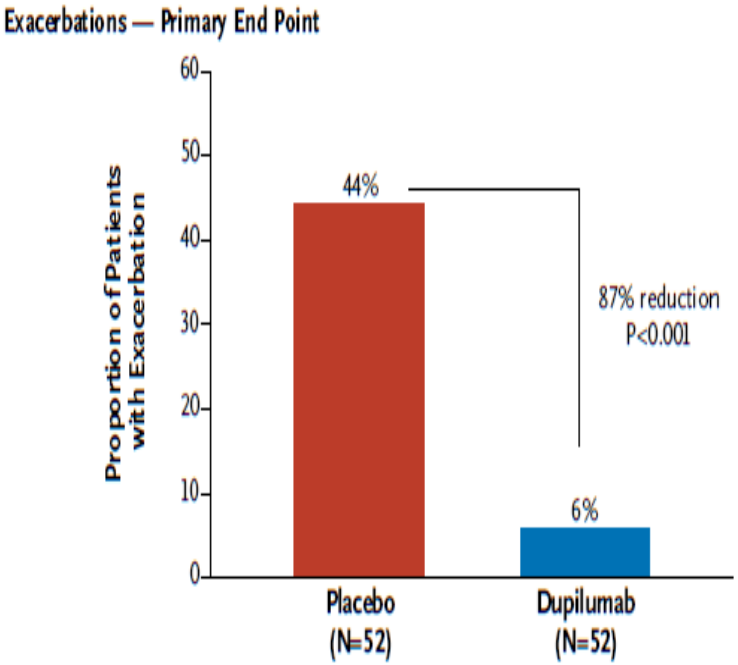
Wenzel S NEJM 2013; 386: 2455 – 2466

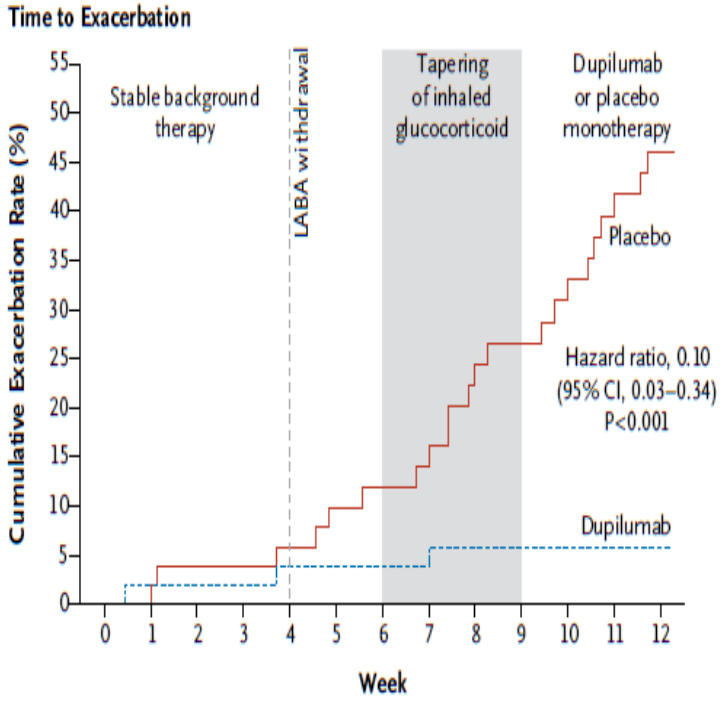
Dupilumab in Persistant Asthma



Wenzel S NEJM 2013; 386: 2455 – 2466

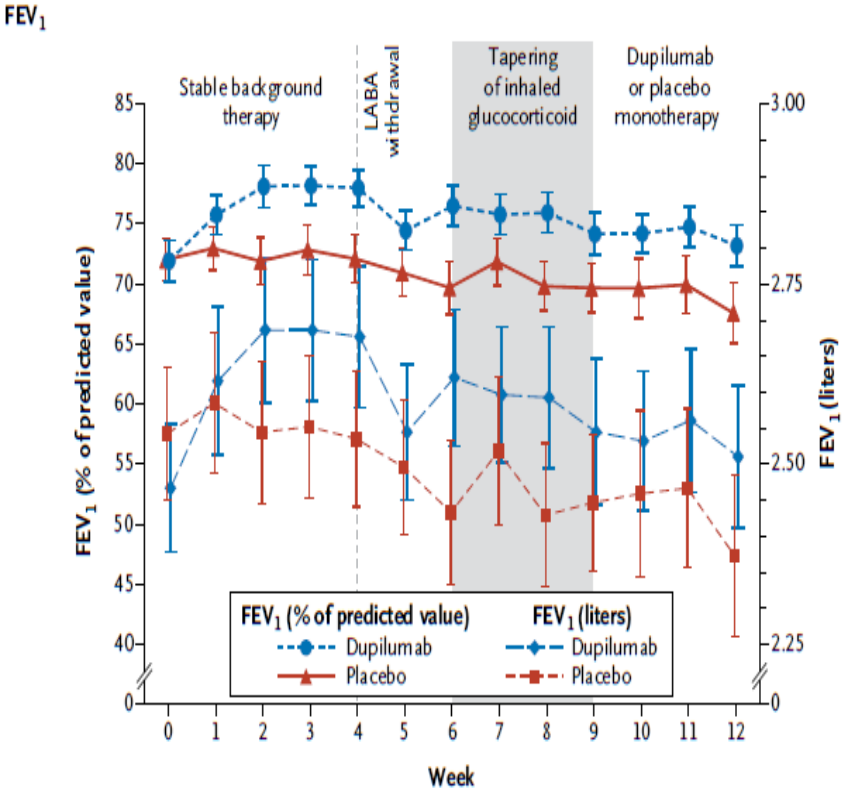
Dupilumab in Persistant Asthma

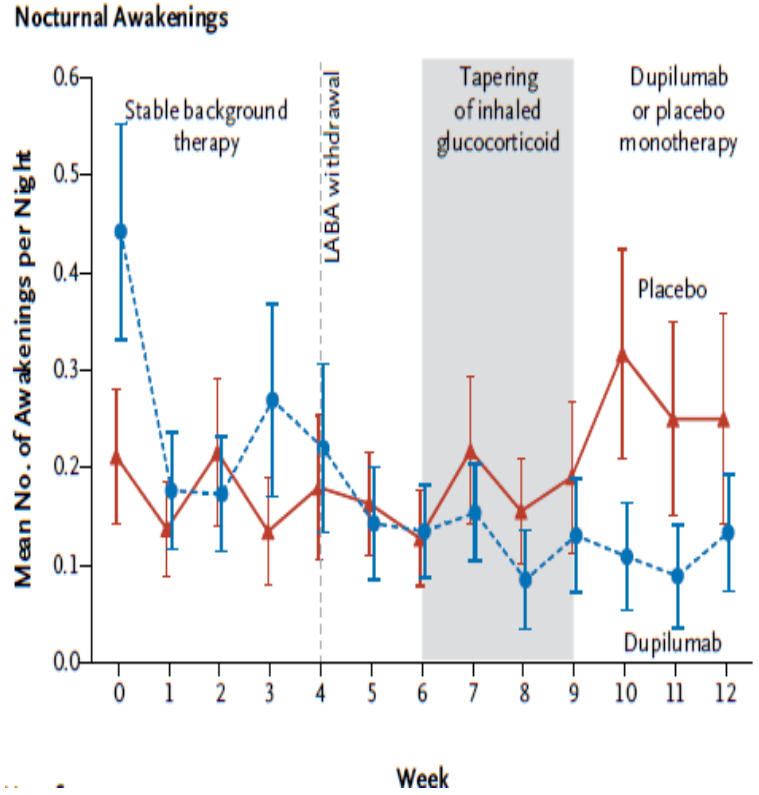




Wenzel S NEJM 2013; 386: 2455 – 2466

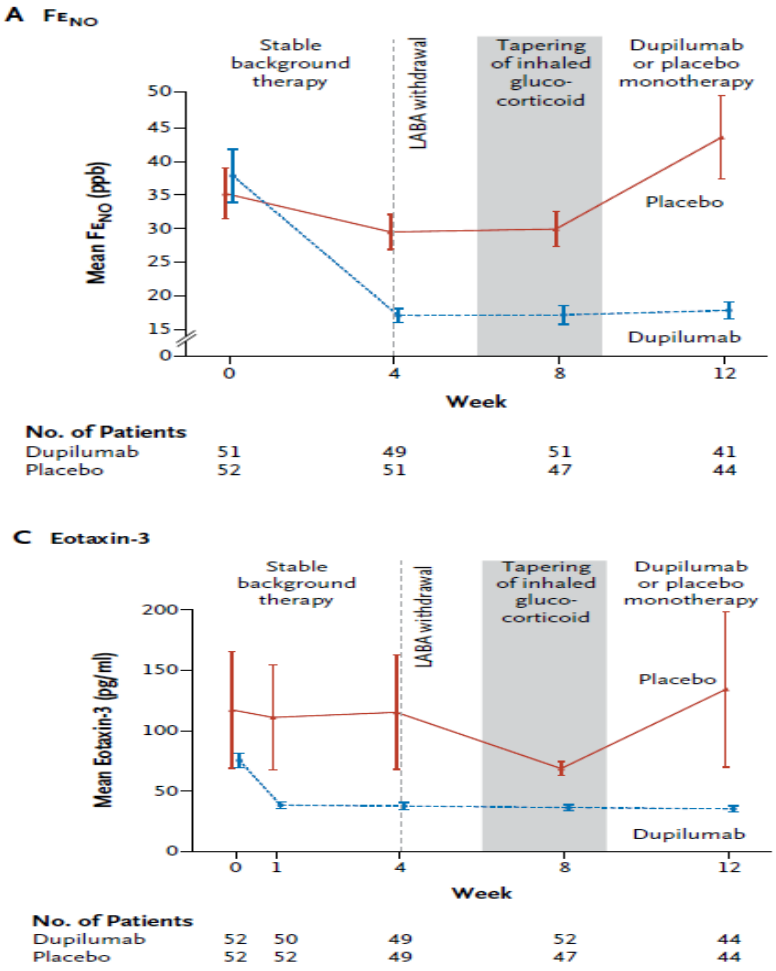
Dupilumab in Persistant Asthma





Wenzel S NEJM 2013; 386: 2455 – 2466

Dupilumab in Persistant Asthma



Wenzel S NEJM 2013; 386: 2455 – 2466

Dupilumab in Persistant Asthma

- Dupilumab in persistent, moderate to severe asthmatics with elevated eosinophil level

→ Fewer asthma exacerbations

→ Improved lung function and asthma control

→ Reduced Th2 associated inflammatory markers

Wenzel S NEJM 2013; 386: 2455 – 2466

Dupilumab Efficacy and Safety in Persistant Asthma

- Dupilumab in uncontrolled persistent asthma irrespective of eosinophil level

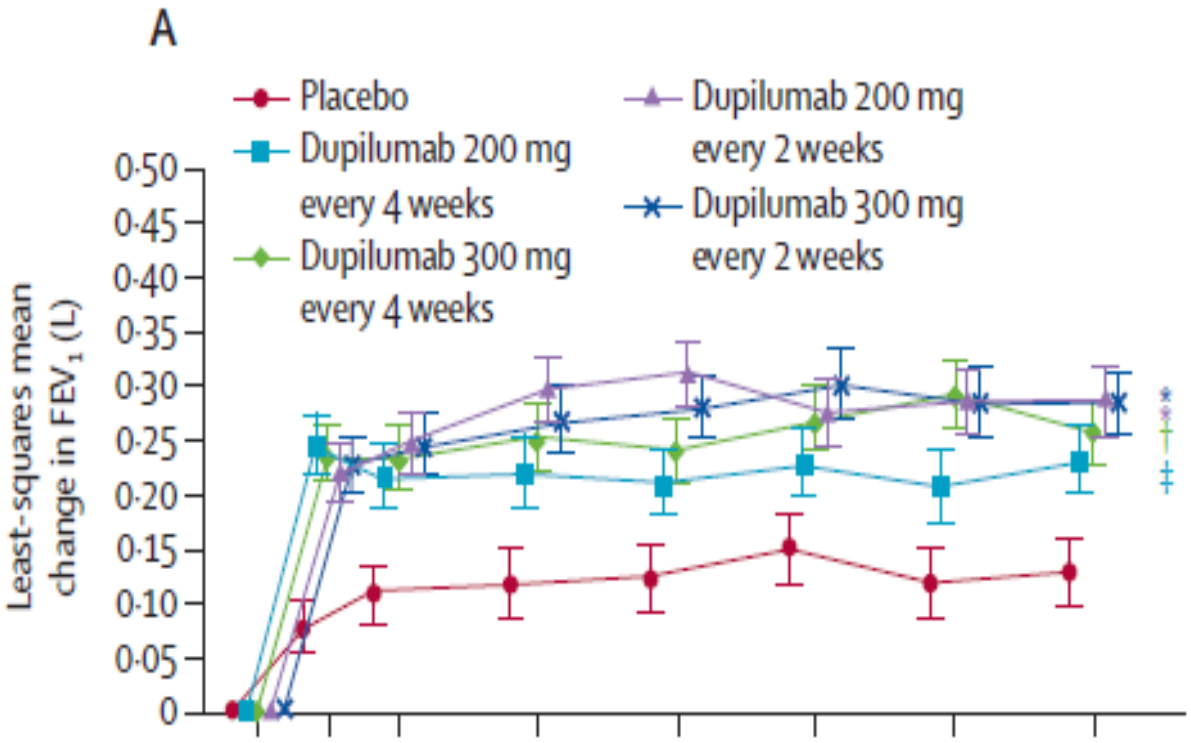
→ 158 in Placebo group, 611 in dupilumab

→ 200 mg or 300 mg SC every 2 weeks or every 4 weeks

→ over 24 weeks

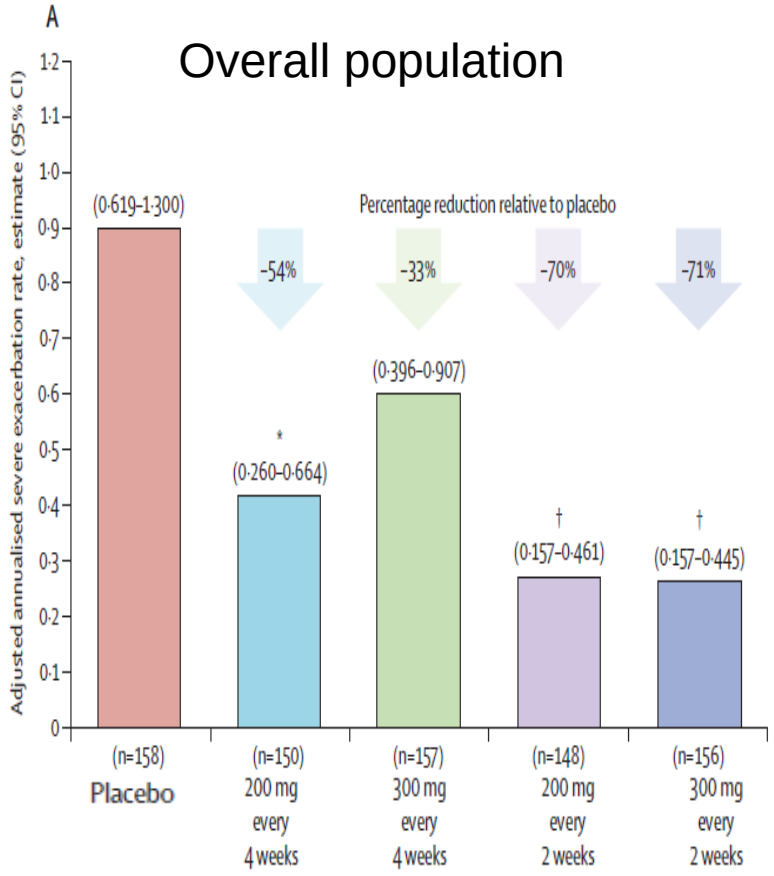
Wenzel S Lancet 2016; 388: 31 – 44

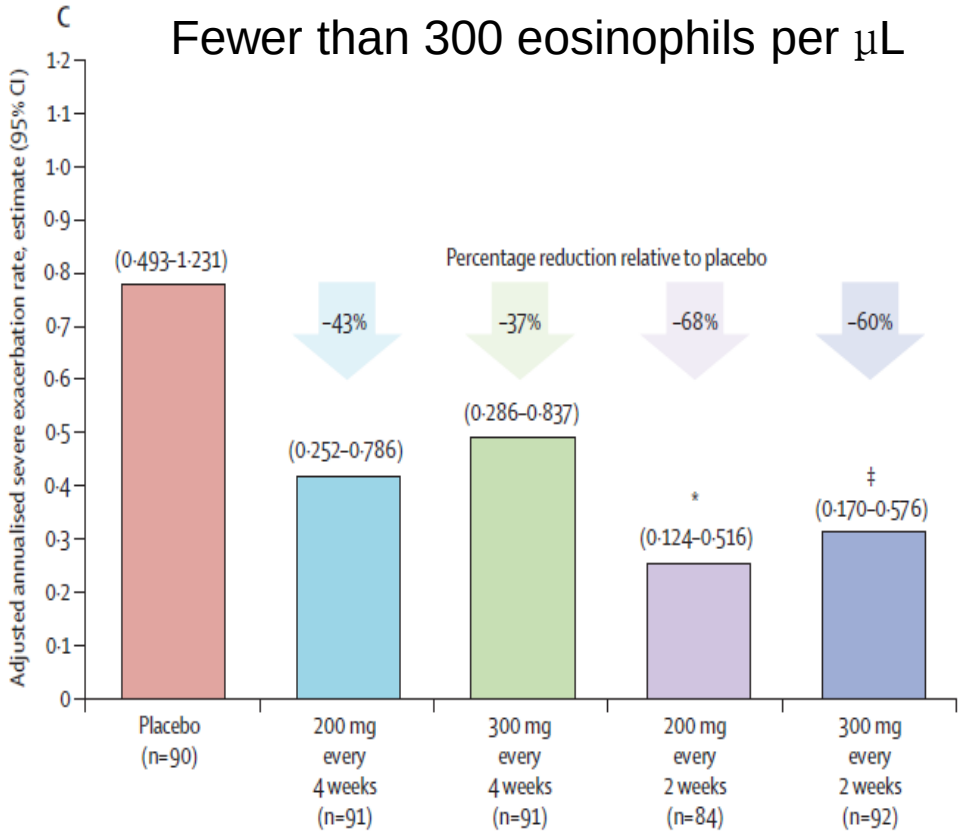
Dupilumab Efficacy and Safety in Persistant Asthma



Wenzel S Lancet 2016; 388: 31 – 44

Dupilumab Efficacy and Safety in Persistant Asthma





Wenzel S Lancet 2016; 388: 31 – 44

Dupilumab Efficacy and Safety in Persistant Asthma

- Dupilumab in uncontrolled persistent asthma irrespective of eosinophil level

→ Fewer asthma exacerbations

→ Improved lung function and asthma control

→ Favorable safety profiles

Wenzel S Lancet 2016; 388: 31 – 44

AMG 317 in Asthma

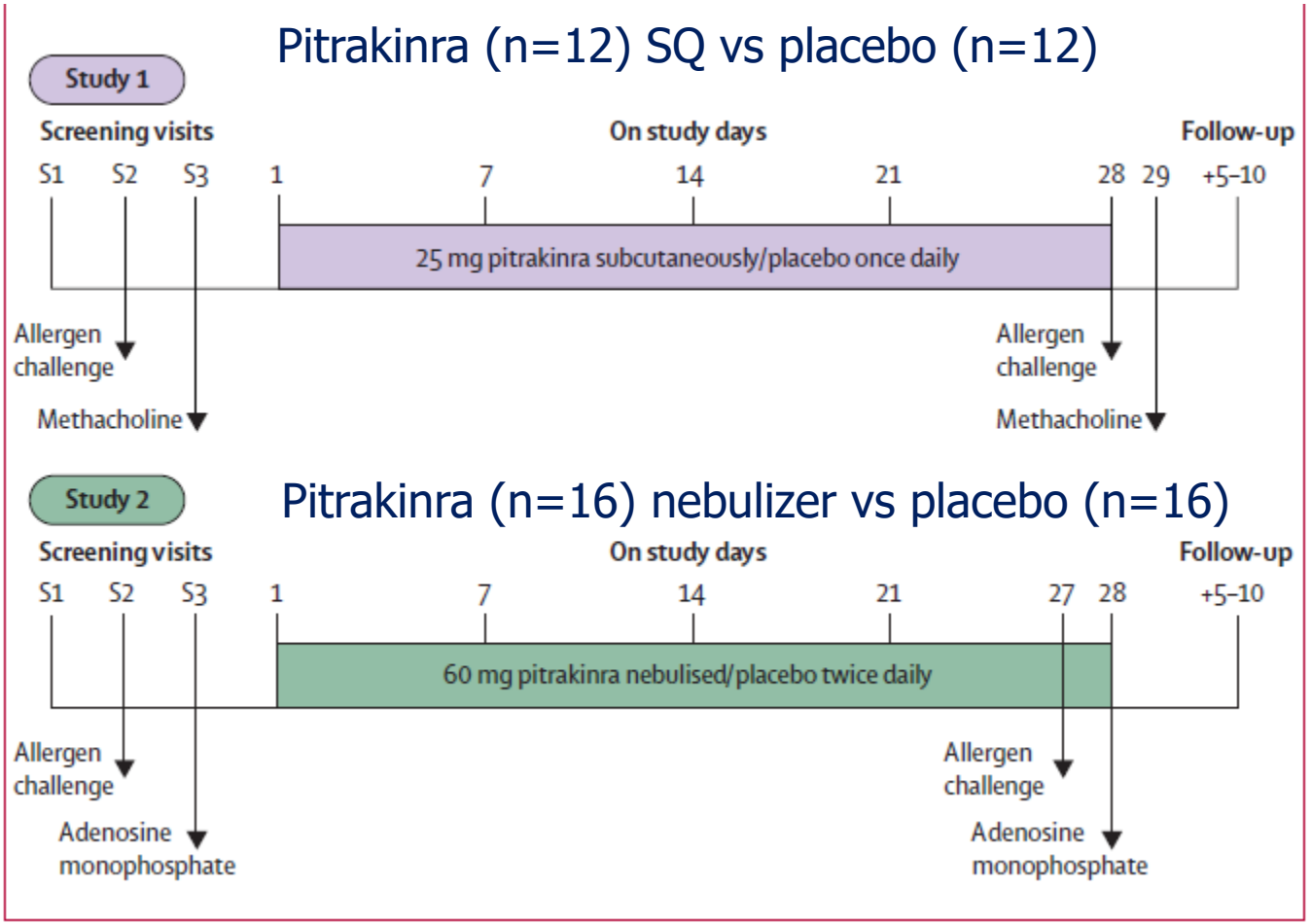
- AMG 317 in moderate to severe asthma

→ fewer exacerbation rate in highest dose AMG 317

→ Clinically significant improvements in asthmatics with higher ACQ scores.

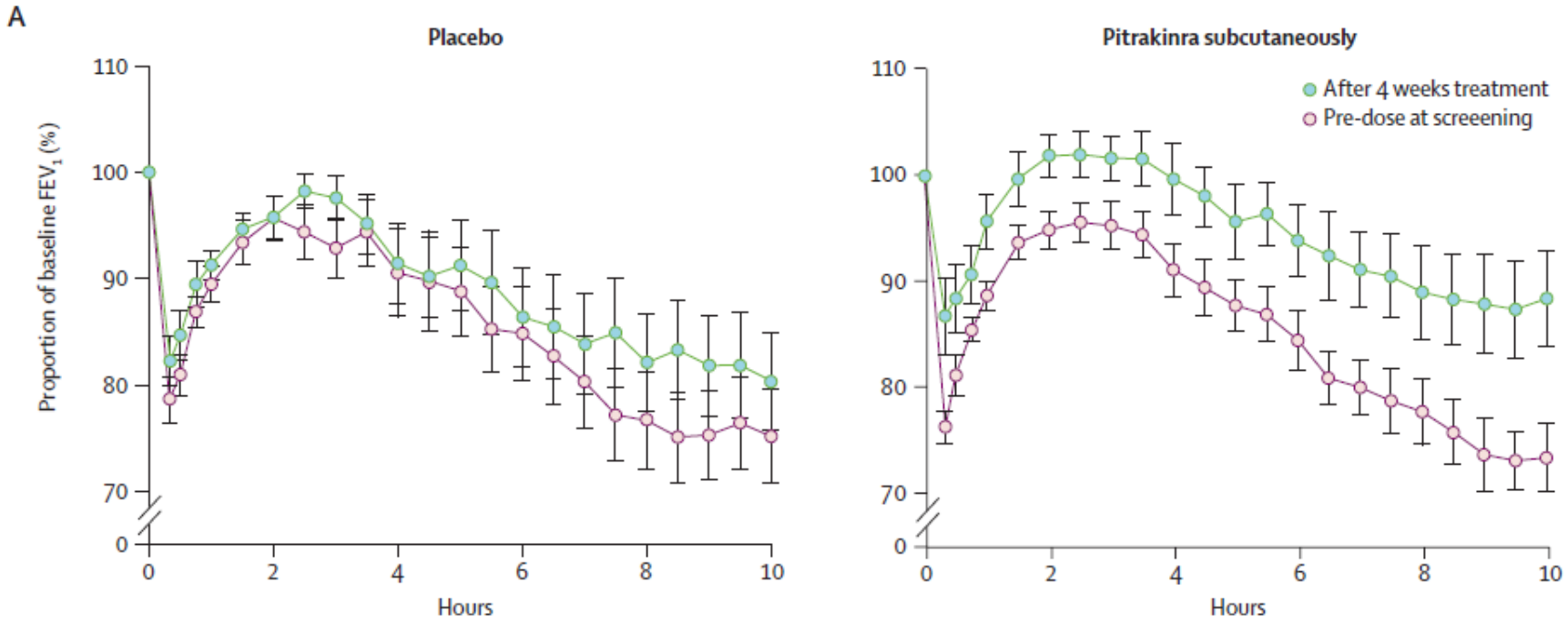
Corren J AJRCCM 2000; 161: 309 – 329

Pitrakinra (IL-4 Rα antibody) in Asthmatics



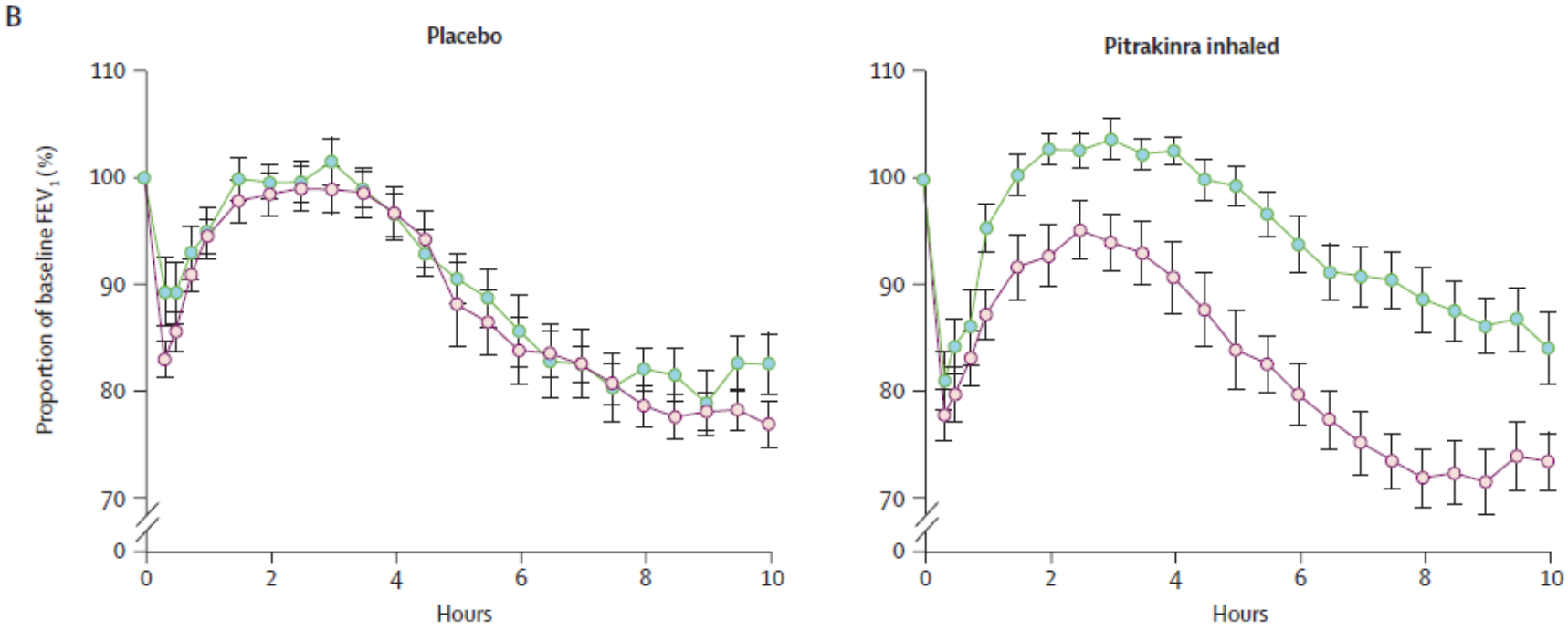
Wenzel S Lancet 2007; 370:1422-1431

Pitrakinra in Asthmatics



Wenzel S Lancet 2007; 370:1422-1431

Pitrakinra in Asthmatics



Wenzel S Lancet 2007; 370:1422-1431

Allergen induced FEV_1 Response

	Placebo	Pitrakinra	Comparison	Difference or ratio (95% CI)	p value
Study 1 (pitrakinra group n=12, placebo group n=12)					
Average percentage fall in FEV_1	9·4%	3·1%	Placebo/pitrakinra	3·0 (0·91 to 10·12)	0·068
AUC (L·h)	17·6	19·2	Placebo–pitrakinra	-1·6 (-3·25 to 0·03)	0·054
Maximum percentage fall in FEV_1	23·1%	17·1%	Placebo–pitrakinra	6·0% (-4·37 to 16·32)	0·243
Study 2 (pitrakinra group n=15, placebo group n=14)					
Average percentage fall in FEV_1	15·9%	4·4%	Placebo/pitrakinra	3·7 (2·08 to 6·25)	0·0001
AUC (L·h)	18·4	21·6	Placebo–pitrakinra	-3·1 (-4·63 to -1·65)	0·0002
Maximum percentage fall in FEV_1	27·6%	16·1%	Placebo–pitrakinra	11·5% (5·21 to 17·85)	0·0009

Wenzel S Lancet 2007; 370:1422-1431

Summary

Summary

- Difficult asthma : uncontrolled symptoms due to
  → Alternative diagnosis
  → Poor compliance
  → Ongoing allergen exposure
  → Co-morbidities
- Therapeutic intervention against IL4 and IL13 can be a good option in refractory asthma.
- Biomarkers for therapy based on Th2 cells

→ Blood & sputum eosinophil, periostin, FeNO, IgE

Summary : anti IL-13

- Lebrikizumab

→ FEV_1 improvement & lower exacerbation rates in asthmatics with high periostin level

→ Reduces late asthma response in mild asthma

- Tralokinumab

→ No change of ACQ-6

→ FEV_1 : improved & maintained 12 weeks after final dose

→ Better response in those with higher 13 conc. in sputum

Summary : anti IL-4 Rα

- Anti IL-4 Rα blocks IL-4 and IL-13
- Duplimab

→ FEV_1 improvement in blood eosinophil ≥ 300 cells per µL

→ Reduced severe exacerbation rate irrespective of baseline eosinophil count

→ FEV_1 improvement irrespective of baseline eosinophil count at follow up research.

- Pitrakinra in asthmatics (inhibiting IL-4 and IL-13)

→ Reduced decrease in FEV_1 with allergen challenge

→ Fewer asthma related events

Thank you for your attention.