IL TRATTAMENTO DELL'ASMA SEVERO: NUOVE PROSPETTIVE TERAPEUTICHE

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Bronchial Asthma heterogeneity in clinical presentation

- **Large difference in clinical manifestations, related to:**
  - **Severity of the disease**
  - **Heterogeneity of inducers and/or triggers**
  - **Level of adherence to therapeutic plan**
- **Existance of different phenotypes**
  - **Clinical and functional**
  - **Biological**
- **Difference in:**
  - **Strategy of asthma treatment**
  - **Strategy in asthma management**

A new definition of asthma (GINA 2014): a heterogeneous disease

DEFINITION OF ASTHMA

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma and that distinguish it from other respiratory conditions.

- *Allergic asthma*: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroid (ICS) treatment.
- *Non-allergic asthma*: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often respond less well to ICS.
- *Late-onset asthma*: some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS or are refractory to corticosteroid treatment.
- *Asthma with fixed airflow limitation*: some patients with long-standing asthma develop fixed airflow limitation that is thought to be due to airway wall remodeling.
- *Asthma with obesity*: some obese patients with asthma have prominent symptoms and little eosinophilic airway inflammation.

Bronchial Asthma heterogeneity in clinical presentation

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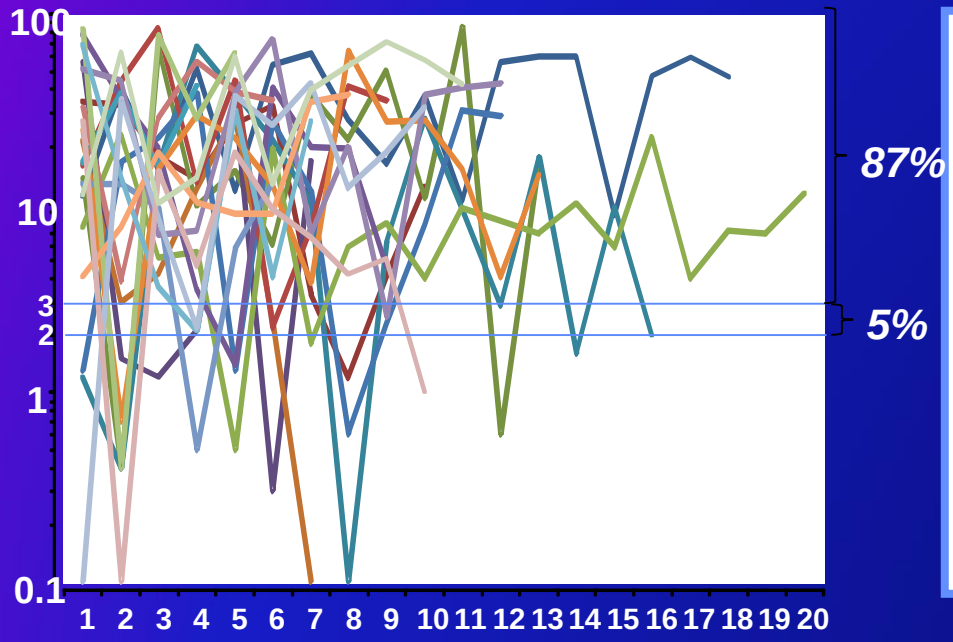
Asthma phenotypes
Eosinophilic vs non-eosinophilic asthma

- **Eosinophilic phenotype**
  - Allergen-induced asthma, children asthma
  - Severe asthma with frequent exacerbations (CS-dependent asthma)
- **Non eosinophilic phenotype**
  - Specific “triggers” (pollutants, endotoxins, chemicals, viruses)
  - In all asthma severity levels
  - Stable over time ?
  - Lower response to ICS

    → different therapeutic strategies ?

Both eosinophilic and non-eosinophilic inflammatory patterns in asthma seem fairly stable over time

Sputum Eosinophils



Dente et al, IAAI 2015

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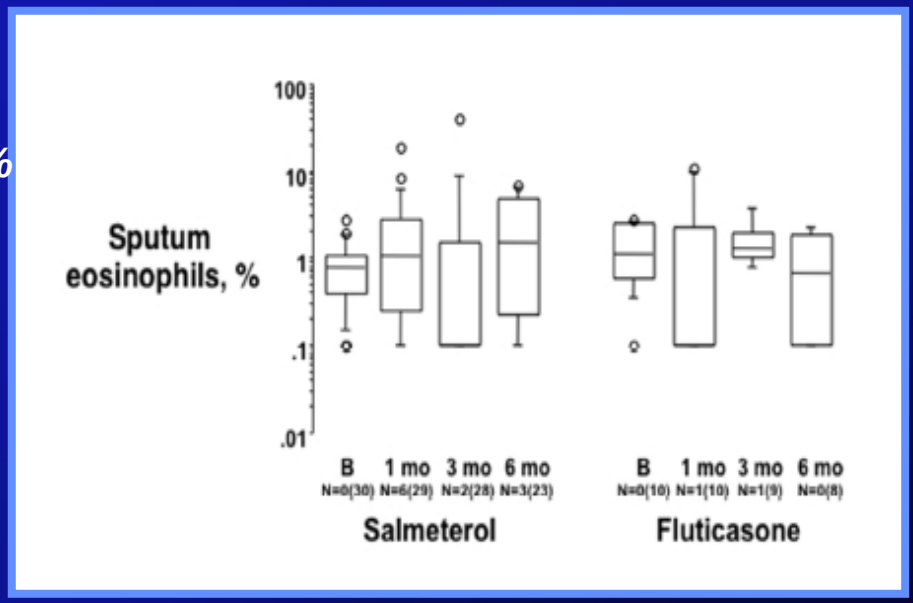
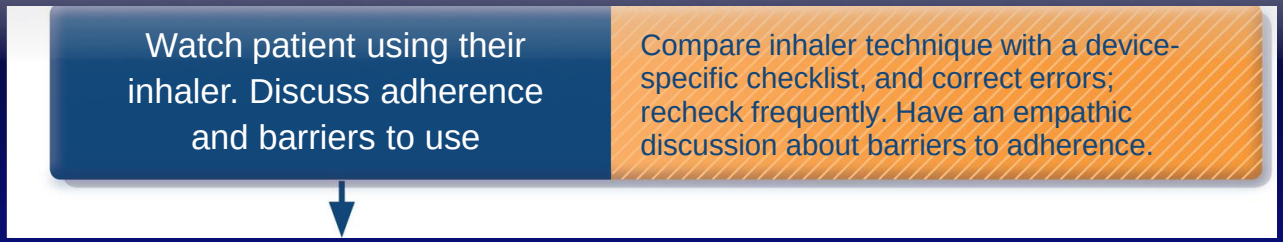


Bacci et al, Respirology 2012

How to distinguish between uncontrolled and severe asthma



Adherence to asthma maintenance therapy in real life

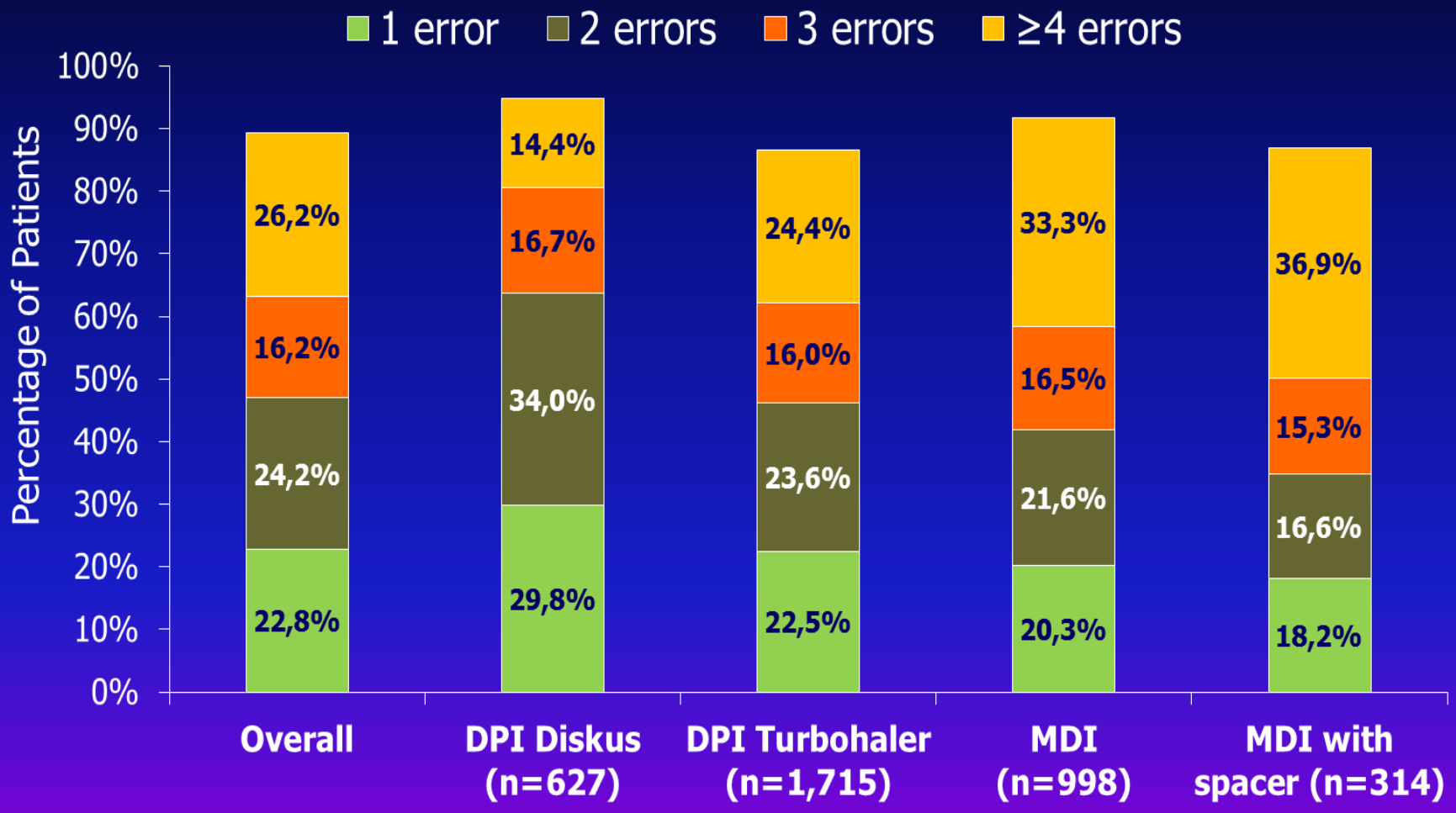
Reference	Title	Adherence
Partridge *Pulm Med* 2006	Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study	45% used maintenance medication as prescribed
De Marco *et al. Int Arch Allergy Immunol* 2005	Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma	34% had used maintenance medication as prescribed
Janson *et al. Eur Respir J* 2001	The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II	Adherence ranged from 17% in Italy to 49% in the UK
Breekveldt-Postma *et al. Pharmaco-epidemiol Drug Saf* 2008	Treatment with inhaled corticosteroids in asthma is too often discontinued	14.1% of the patients with fixed combined and 8.3% of patients with single ICS treatment still continued treatment at 1 year
Stallberg *et al. Resp Med* 2003	Living with asthma in Sweden. The ALMA study	34% regularly followed the prescriptions
Adam *et al. J Allergy Clin Immunol* 2002	Inadequate use of asthma medication in the USA: results of the asthma in national population survey	21% had used maintenance medication as prescribed
Currigan *et al. Prim Care Resp J* 2011	Asthma therapy: there are guidelines, and then there is real life	Even compliant patients take only 30–50% of prescribed medication at the correct time

Check adherence with asthma medications

- **Poor adherence:**
  - **Is very common: it is estimated that 50% of adults and children do not take controller medications as prescribed**
  - **Contributes to uncontrolled asthma symptoms and risk of exacerbations and asthma-related death**
- **Contributory factors**
  - **Unintentional (e.g. forgetfulness, cost, confusion) and/or**
  - **Intentional (e.g. no perceived need, fear of side-effects, cultural issues, cost)**
- **How to identify patients with low adherence:**
  - **Ask an empathic question, e.g. "*Do you find it easier to remember your medication in the morning or the evening?*", or "*Would you say you are taking it 3 days a week, or less, or more?*"**
  - **Check prescription date, label date and dose counter**
  - **Ask patient about their beliefs and concerns about the medication**

GINA 2016, Box 3-12

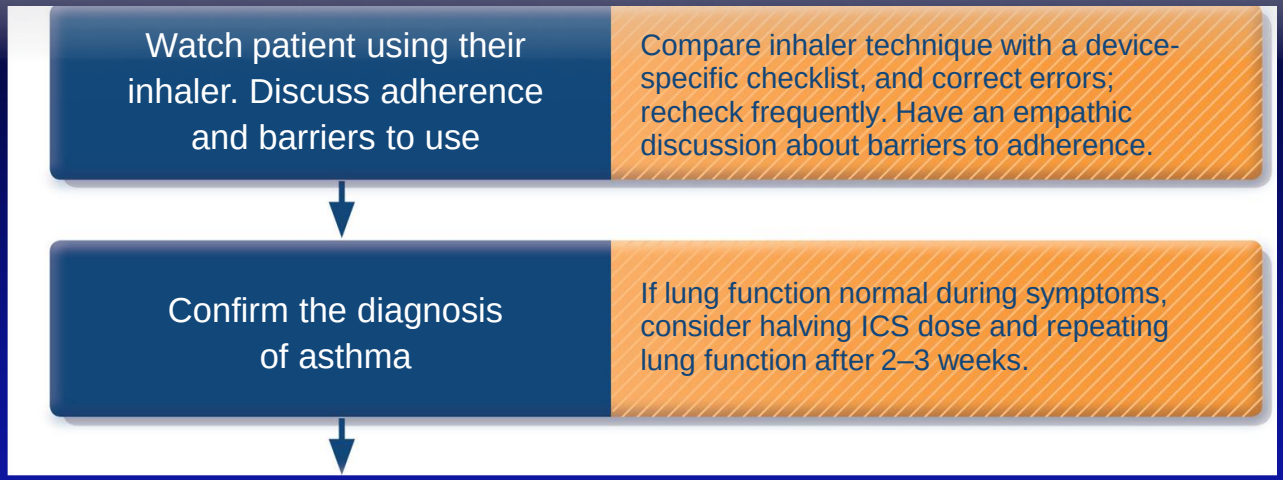
Inhaler-specific serious error



n=3.654 asthma patients

Price D, Roche N, Lavorini F et al IPCRG meeting 2014

How to distinguish between uncontrolled and severe asthma



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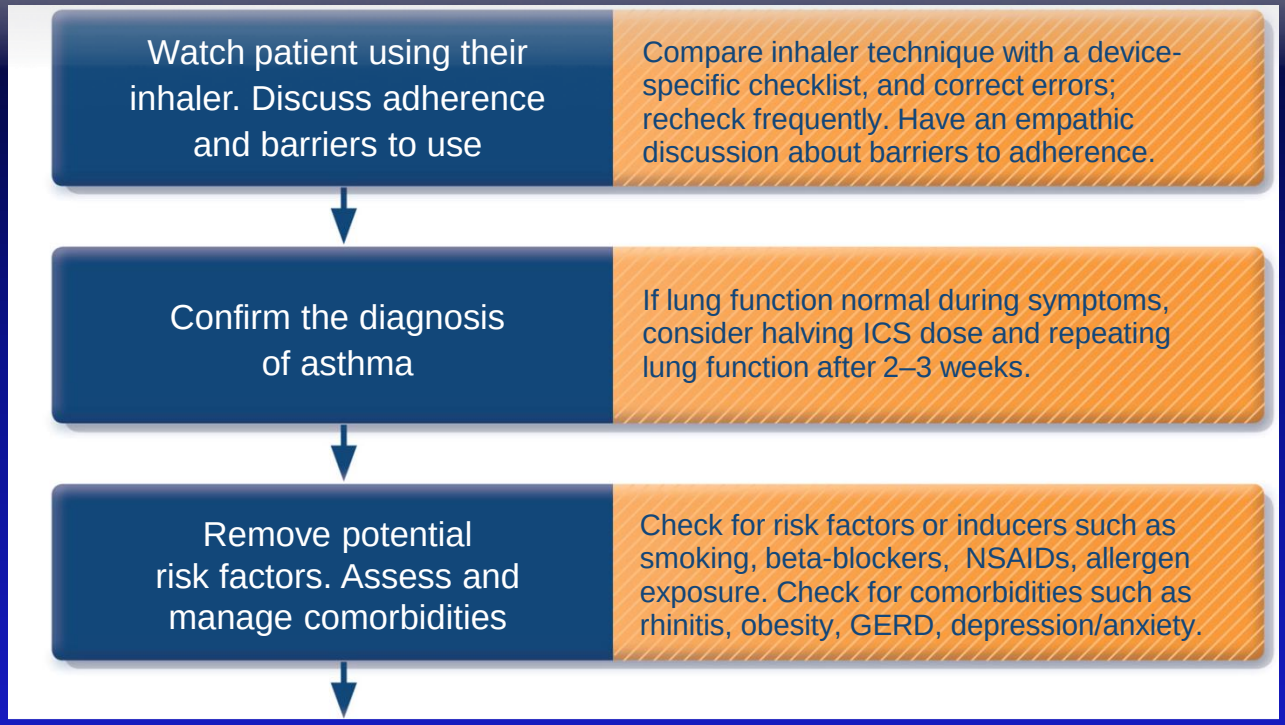


International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

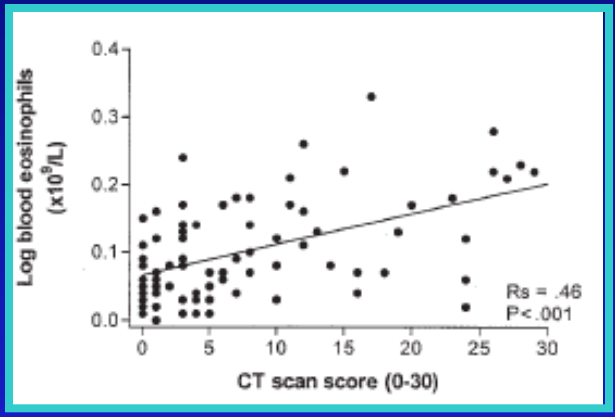
Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

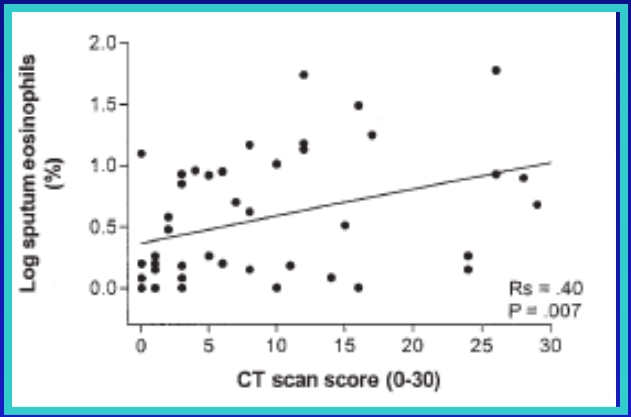
Eur Respir J 2014; 43: 343–373

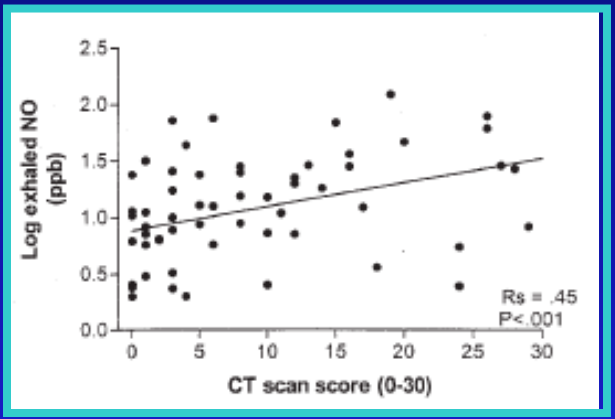
TABLE 7 Comorbidities and contributory factors

1) Rhinosinusitis/(adults) nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety, depression
3) Vocal cord dysfunction
4) Obesity
5) Smoking/smoking related disease
6) Obstructive sleep apnoea
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
9) Gastro-oesophageal reflux disease (symptomatic)
10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors

Chronic sinusitis in severe asthma is related to sputum eosinophilia







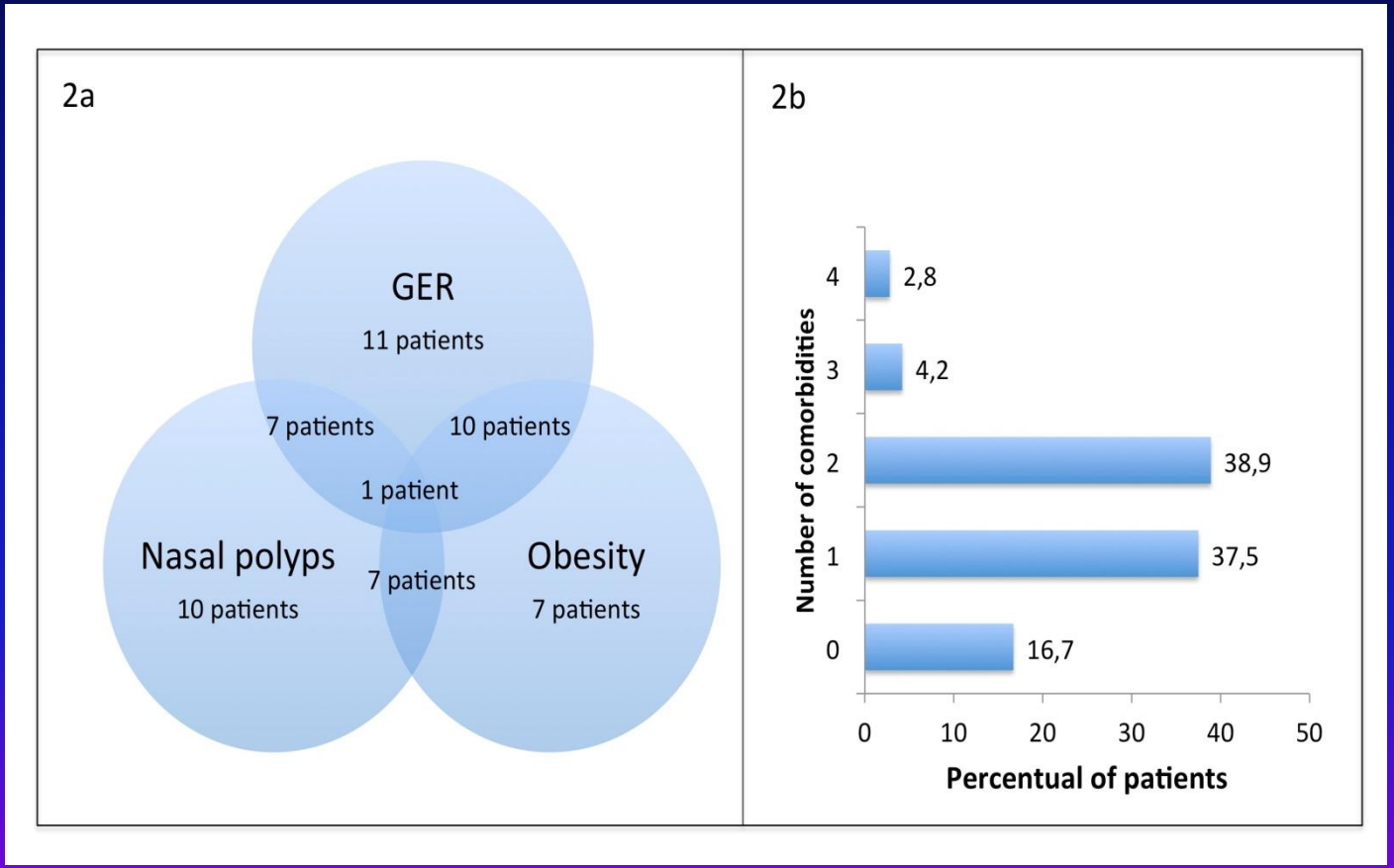
ten Brinke A et al J Allergy Clin Immunol 2002

Severe difficult-to-treat asthmatics with UAD require more frequently OS, and have a different sputum pattern

	SCUAD	No SCUAD
Number	35	29
Age, yrs	58.6 (10.3)	55.6 (13.8)
Asthma duration, yrs	19.1 (9.8)	23.8 (9.8)
PEF variability	40.8 (15.3)	42.2 (19.8)
Exac, last yr	4.6 (2.5)	4.8 (4.1)
OCS treat, last yr	4.4 (2.4)	3.0 (1.5) **
FEV1, %pred	74.8 (16.7)	69.3 (14.0)
Sputum Neut, %	47.2 (8.5-85.0)	60.9 (1.2-94.4) **
Sputum Eos, %	12.0 (0.0-79.8)	5.5 (0.0-98.0) **

Dente et al (unpublished data)

Prevalence of comorbidities in a large group of severe asthmatics (ERS/ATS 2014)



Novelli et al, Respirology 2017

Multivariate analysis of predictors of poor control, lower lung function and sputum eosinophilia

Indipendent variables	Dependent variables OR (95% CI)		
	Poor control	Lower lung function	Sputum eos ≥3%
Age (> vs < median value)	0.7 (0.2-1.9)	0.8 (0.3-2.5)	0.2 (0.0-1.3)
Gender (F vs M)	0.87 (0.3-2.8)	**0.3 (0.1-0.9)***	1.6 (0.2-12.1)
Smoke (Yes vs No-Ex)	0.4 (0-4.9)	0.3 (0.0-4.0)	0.5 (0.0-18.7)
Duration of asthma (> vs < median value)	1.9 (0.6-6.1)	**5.1 (1.4-18.8)***	**0.1 (0.01-0.5)***
Obesity (Y vs N)	**4.9 (1.6-15.4)***	1.6 (0.5-4.9)	0.6 (0.1-2.8)
CRSwNP (Yes vs N)	0.9 (0.3-2.7)	**2.9 (1-9.1)** §	**16.2 (1.7-151.7)***
GER (Yes vs N)	1.4 (0.5-4.2)	0.5 (0.2-1.8)	0.6 (0.1-2.9)

*p<0.05, § p=0.06

Novelli et al, Respirology 2017

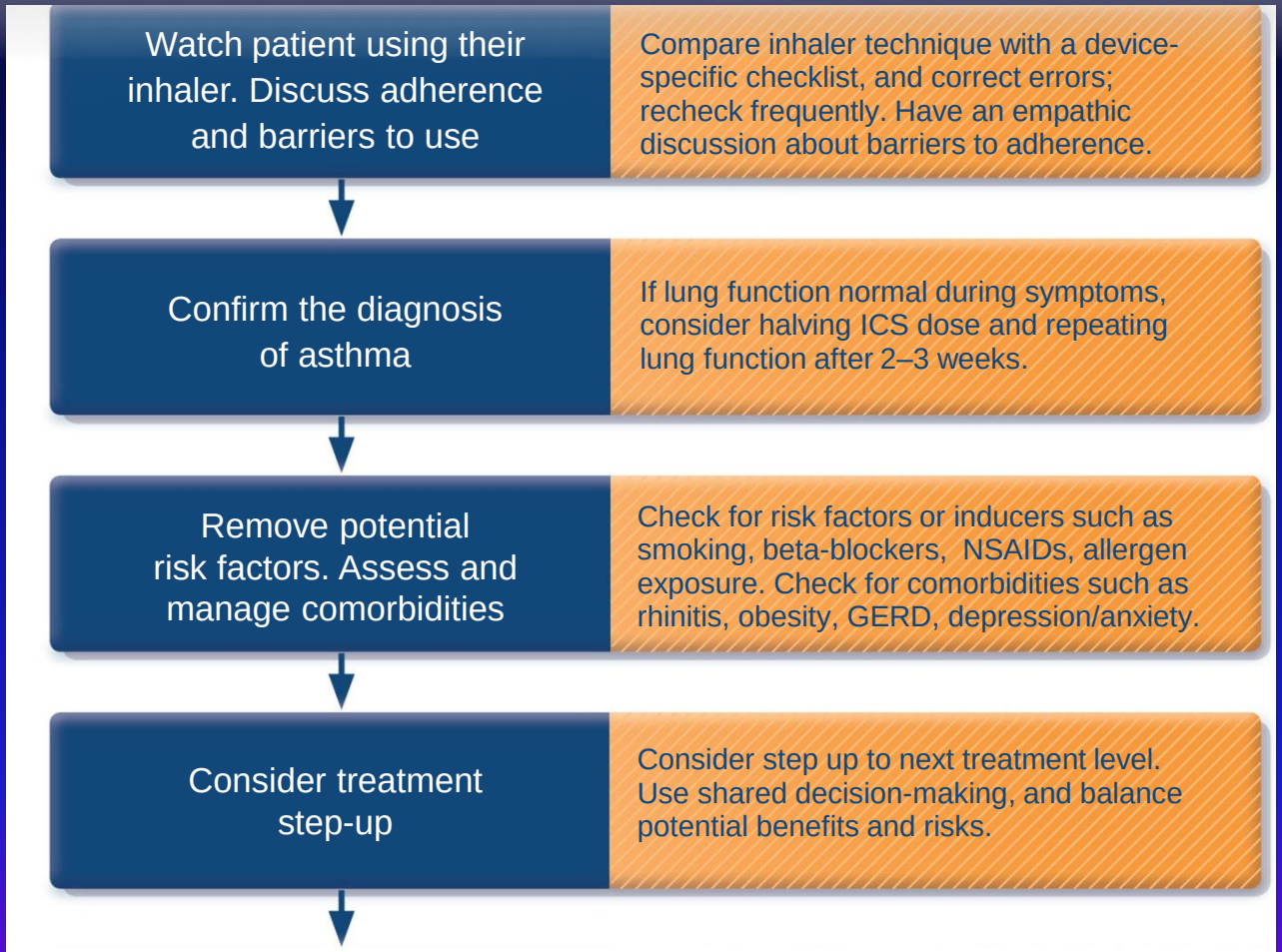
Asthma and Obesity

Table 1 Implications of obesity and the relationship with asthma. Obese asthmatics have multiple consequences related to excess adipose tissue, including mechanical or physiologic effects on lung function and the airways as well as changes in the immune response and metabolic effects. The combination of these alterations contributes to the phenotypic characteristics of the obese asthmatic

Mechanical or physiologic effects	Lung function	• Restriction or reduced total lung capacity and decreased expiratory reserve volume • Ventilation and perfusion mismatch
	Airways Changes	• Bronchial hyperresponsiveness • Loss of deep breath induced bronchodilation • Reduced exhaled NO (certain phenotypes)
Immune and metabolic effects	Immune function	• Decreased airway eosinophils (lumen, sputum) • Increased airway neutrophils • Predominately Th-1 related inflammation versus Th-2 • Potential IL-17 related inflammation • Enhanced inflammatory/oxidative response to elevated leptin levels
	Metabolic function	• Higher plasma and airway leptin levels with reduced airway leptin receptors • Leptin receptors in visceral fat and relationship with bronchial hyperresponsiveness • Leptin may increase oxidative stress levels • Effect of adiponectin remains unclear • Lower L-arginine/ADMA ratio and increase in oxidative stress resulting in an impaired bronchial dilatory response

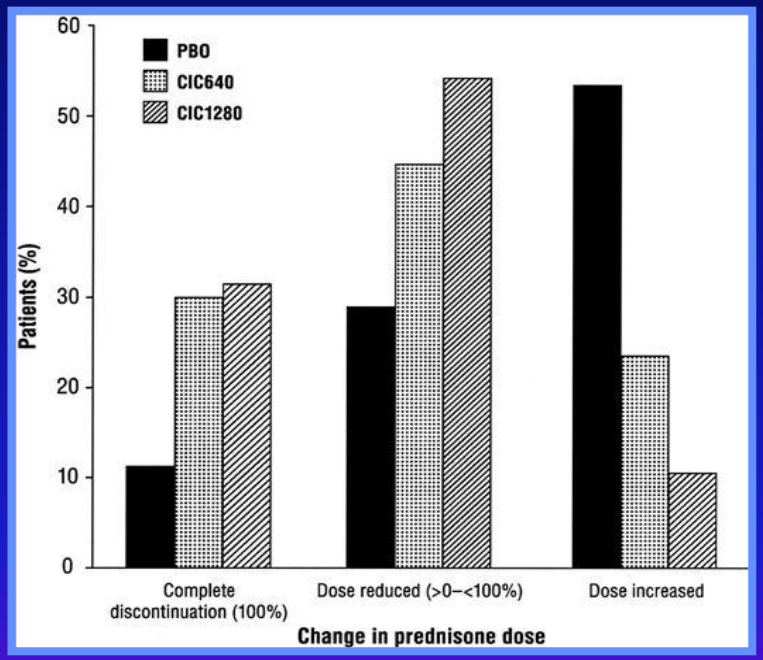
Baffi et al, Asthma Res Pract 2015

How to distinguish between uncontrolled and severe asthma



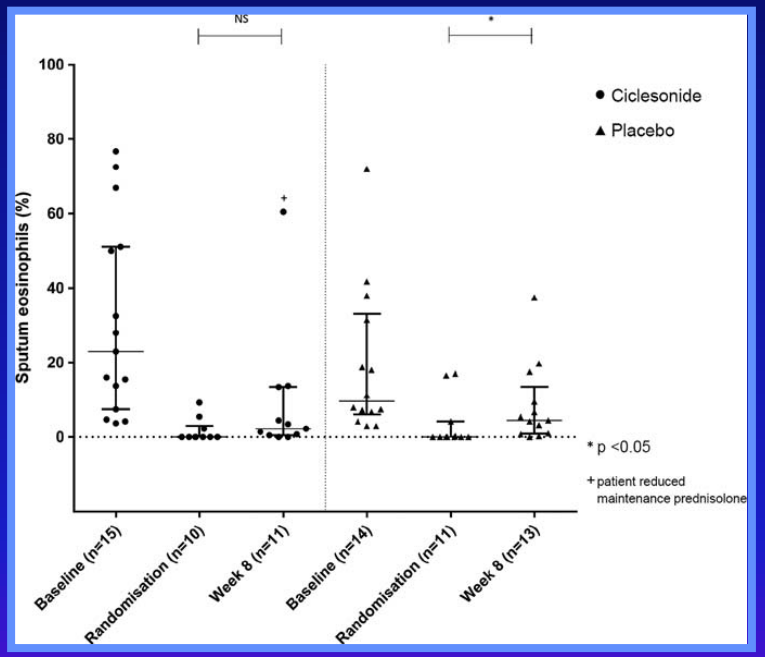
Higher dose of ICS in patients with poorly controlled severe asthma

Ciclesonide significantly reduces the need for OCS in patients with severe, persistent asthma



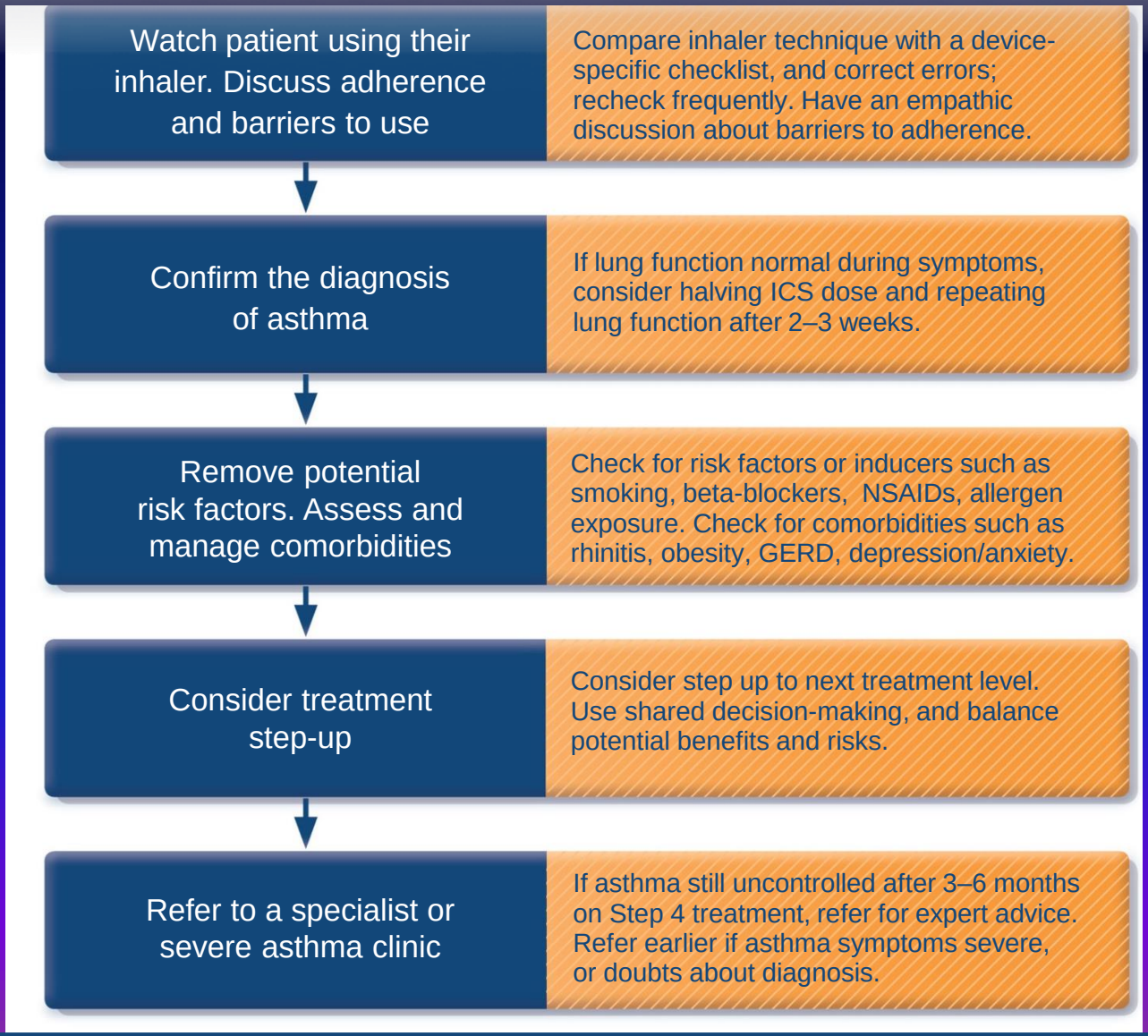
Bateman E., et al. Chest 2006

Median (IQR) sputum eosinophil count before and after 8 weeks of ciclesonide or placebo in addition to usual treatment

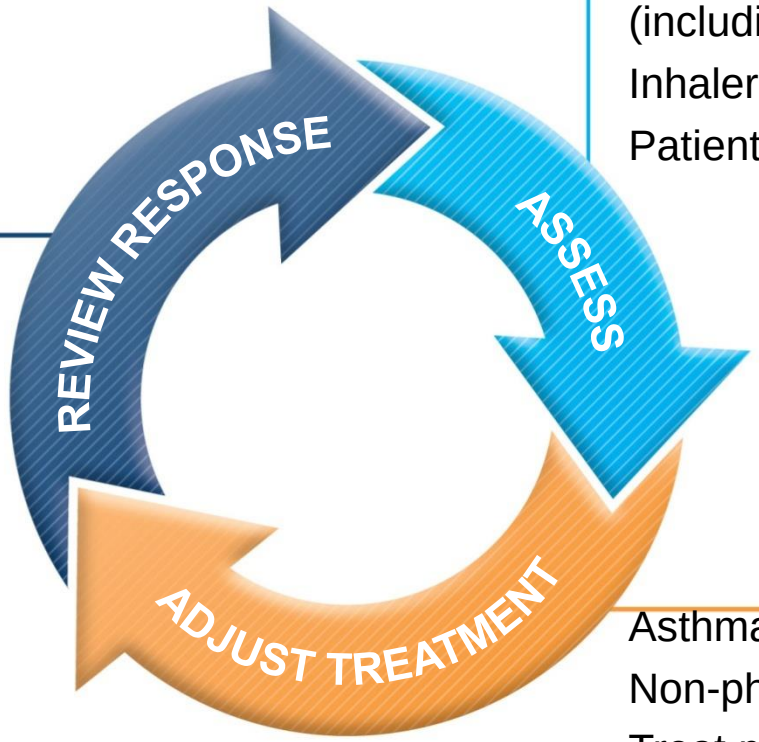


Hodgson D, et al. Thorax 2015

How to distinguish between uncontrolled and severe asthma



The control-based asthma management cycle



Diagnosis

Symptom control & risk factors (including lung function)

Inhaler technique & adherence

Patient preference

Symptoms

Exacerbations

Side-effects

Patient satisfaction

Lung function

Asthma medications

Non-pharmacological strategies

Treat modifiable risk factors

GINA 2016, Box 3-2

Assessment of asthma severity

Assessing asthma severity in clinical practice

The severity of *initial* symptoms is only a weak predictor of the response to treatment, as patients with frequent initial symptoms may rapidly become well controlled with initiation of low-dose ICS. Asthma severity can be more reliably assessed once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years.

Different asthma phenotypes may respond differently to specific medications. Once patients have been on controller treatment for several months, asthma severity can be defined as follows.

- *Mild asthma* is asthma that can be well controlled (according to the criteria set out in Box 2.2) with low-intensity treatment such as low-dose ICS, leukotriene receptor antagonists or chromones, or with reliever medication alone.
- *Moderate asthma* is asthma that can be well controlled with treatment such as low-dose ICS/LABA.
- *Severe asthma* is asthma that requires treatment with high-dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite these medications. This is the definition recommended by the recent European Respiratory Society/American Thoracic Society Task Force on Severe Asthma.[93] While many patients may have uncontrolled asthma that may be difficult to treat due to persistent problems with adherence, or comorbidities such as severe sinus disease or obesity, the Task Force definition of severe asthma only includes patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.[93]

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TABLE 3 Definition of severe asthma for patients aged ⩾6 years

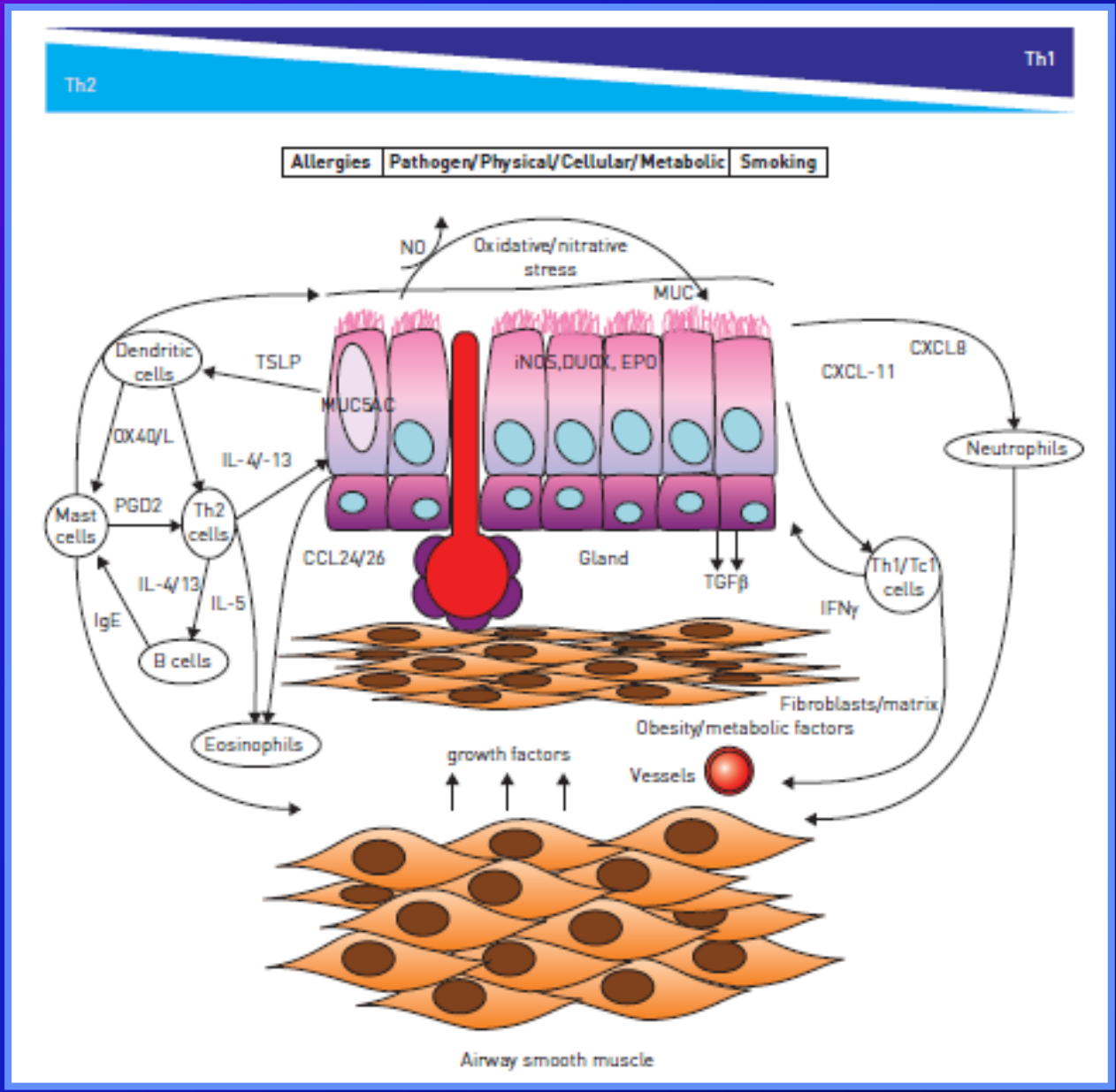
Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

Severe asthma: heterogeneity of mechanisms



Chung et al, ERJ 2014

Asthma treatment: open points

- **Mild asthma:**
  - Regular low-dose ICS vs «as-needed» therapy
  - Low-dose ICS vs LRTA
- **Moderate asthma:**
  - Regular low-medium dose ICS/LABA vs SMART therapy
- **Severe asthma:**
  - Anticholinergics drugs
  - Omalizumab: efficacy and safety
  - New biologics
  - Bronchial Thermoplasty

Management of severe asthma

Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

- **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[289] (Evidence B). However, this carries the risk of systemic side-effects;[284] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p49) (Evidence D).
- **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[284] (Evidence D), but the potential long-term side-effects should be taken into account. Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[177]
- **Add-on treatments without phenotyping**: other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting anti-cholinergic bronchodilator, tiotropium*, showed improved lung function and decreased reliever use.[290]
- **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[130] (Evidence A).
- **Phenotype-guided add-on treatment**: patients with severe asthma may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[5,6,126,284] Patients with severe allergic asthma with elevated IgE levels may benefit from anti-IgE therapy[291] (Evidence A), and LTRAs may be helpful for patients found to be aspirin sensitive[281] (Evidence B).
- **Non-pharmacological interventions**: bronchial thermoplasty may be helpful in selected patients with severe asthma (Evidence B),[90] but more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations (see Appendix Chapter 6).[132] Carefully controlled trials are important as a large placebo effect has been seen in studies to date.[90] High-altitude treatment[284] (Evidence C) or psychological interventions[292] (Evidence C) may be helpful in patients with severe asthma. The place of these therapies and strategies in severe asthma has not been established.[132]

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Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

N Engl J Med 2012.

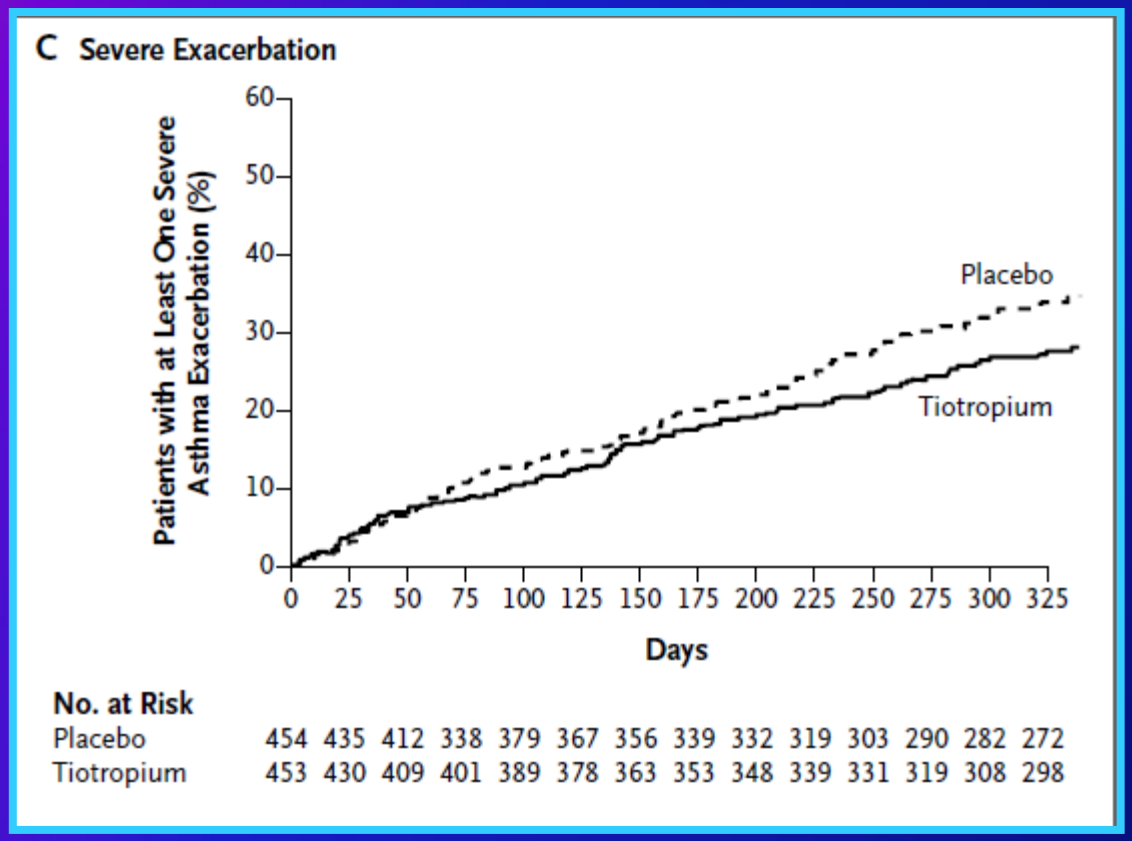
BACKGROUND

Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs).

METHODS

In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 μg) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year.

Third coprimary endopoint (severe exacerbations)



Severe exacerbation rate

- **- 21%**
- **Time to first ex: + 56 days**
- **NNT: 15**

Minor changes in symptoms

- ACQ7

- **-0.09 in trial 1 (n.s.)**
- **-0.13 in trial 2 (p=0.06)**

- AQLQ

- **-0.04 in trial 1 (n.s.)**
- **-0.18 in trial 2 (p=0.02)**

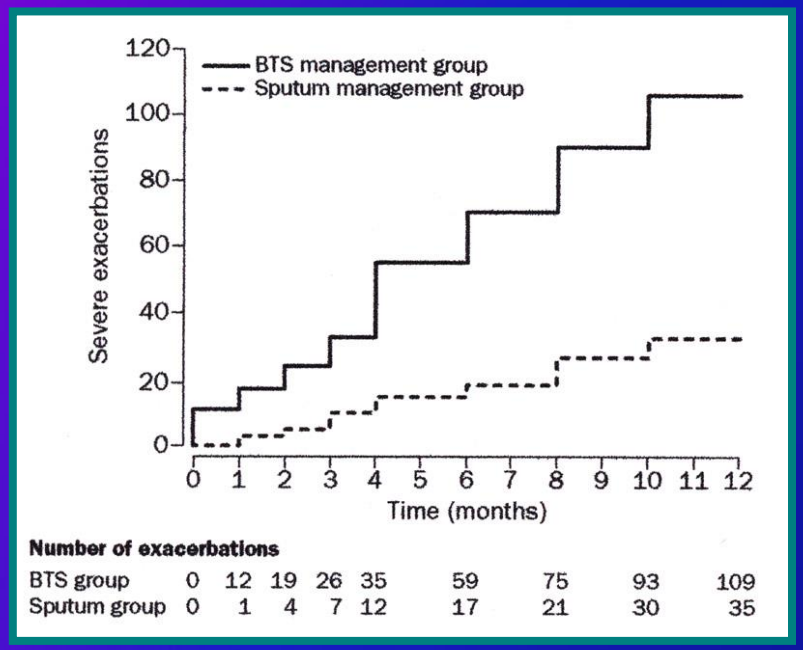
Kerstjens et al, NEJM 2012

Management of severe asthma

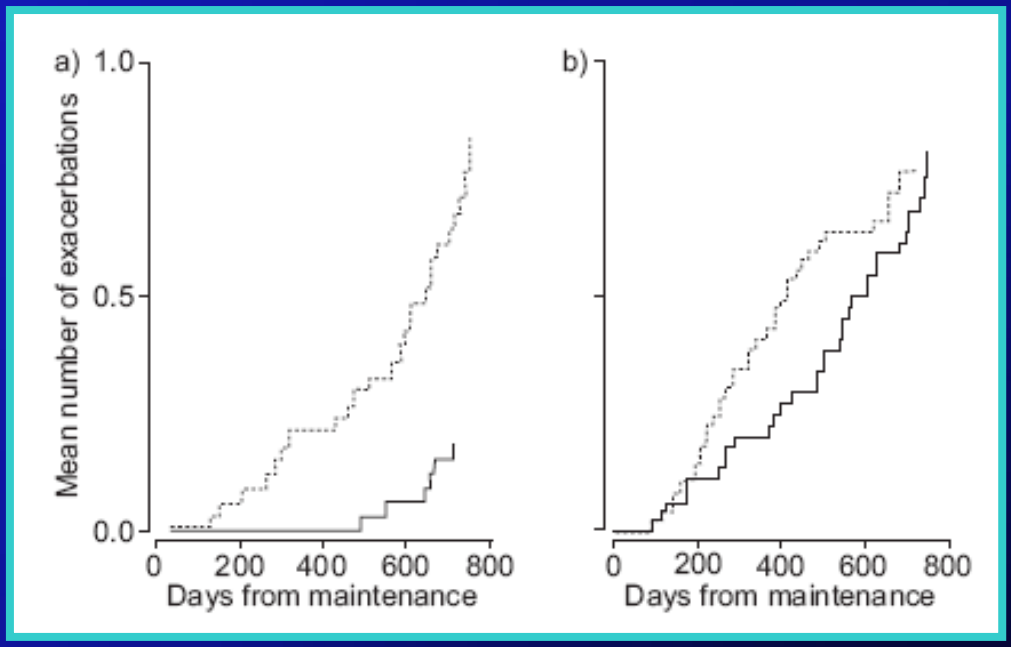
Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

- **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[289] (Evidence B). However, this carries the risk of systemic side-effects;[284] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p49) (Evidence D).
- **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[284] (Evidence D), but the potential long-term side-effects should be taken into account. Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[177]
- **Add-on treatments without phenotyping**: other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting anti-cholinergic bronchodilator, tiotropium*, showed improved lung function and decreased reliever use.[290]
- **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[130] (Evidence A).
- **Phenotype-guided add-on treatment**: patients with severe asthma may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[5,6,126,284] Patients with severe allergic asthma with elevated IgE levels may benefit from anti-IgE therapy[291] (Evidence A), and LTRAs may be helpful for patients found to be aspirin sensitive[281] (Evidence B).
- **Non-pharmacological interventions**: bronchial thermoplasty may be helpful in selected patients with severe asthma (Evidence B),[90] but more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations (see Appendix Chapter 6).[132] Carefully controlled trials are important as a large placebo effect has been seen in studies to date.[90] High-altitude treatment[284] (Evidence C) or psychological interventions[292] (Evidence C) may be helpful in patients with severe asthma. The place of these therapies and strategies in severe asthma has not been established.[132]

The control of sputum eosinophilia is associated with a reduction in asthma exacerbations, but only for eosinophilic exacerbations



Green et al, Lancet 2002



Jayaram et al, ERJ 2006

Management of severe asthma

Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

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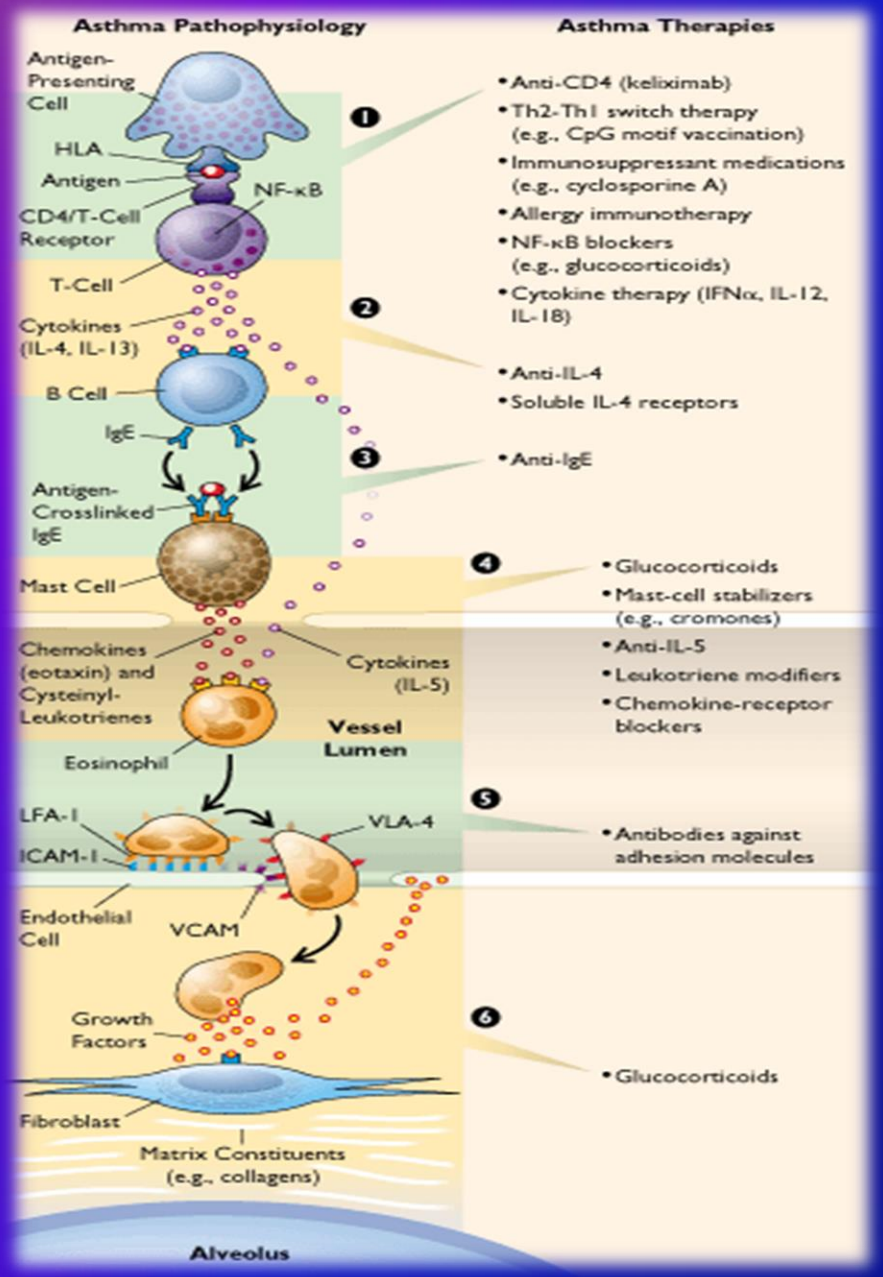
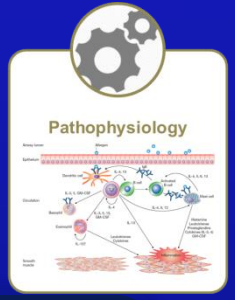
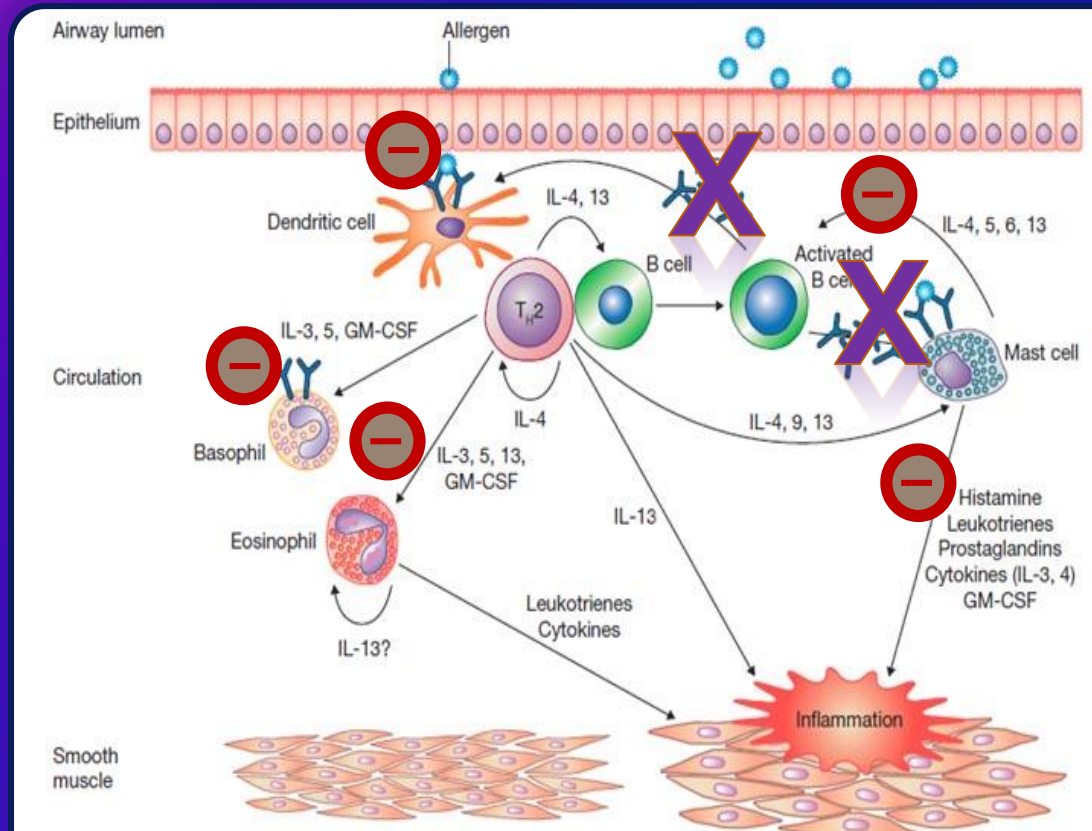
Multiple Levels to Target Novel Therapies



1. Antigen presentation
2. Th-2 cell stimulation and release of Th-2 cytokines
3. Mast cell activation (IgE)
4. Eosinophil recruitment and activation.
5. Upregulation of adhesion molecule expression in blood vessels and epithelium.
6. Activation of resident cells such as fibroblasts.

Effects of blocking IgE on allergic inflammatory cascade





Modificato da Humbert et al JACI Pract 2014*;2:525*

NON è un singolo effetto!

Bloccare le IgE induce ad effetti diretti e indiretti agendo su molte componenti cellulari legate alla risposta immune Th2 mediata

Le IgE sono un attore chiave nell'induzione e nel mantenimento della risposta allergica (infiammazione): rappresentano IL target primario della terapia farmacologica

Impact on T-lymphocytes and B-lymphocytes[5]

Binds free IgE and down-regulates IgE receptors (FcεRI) on mast cells, basophils and DCs

↓ IL-2, IL-4, **IL-5**, IL-13 and GM-CSF[1–4]

↓ Peripheral, sputum and sub-mucosal **eosinophilia**[1]

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

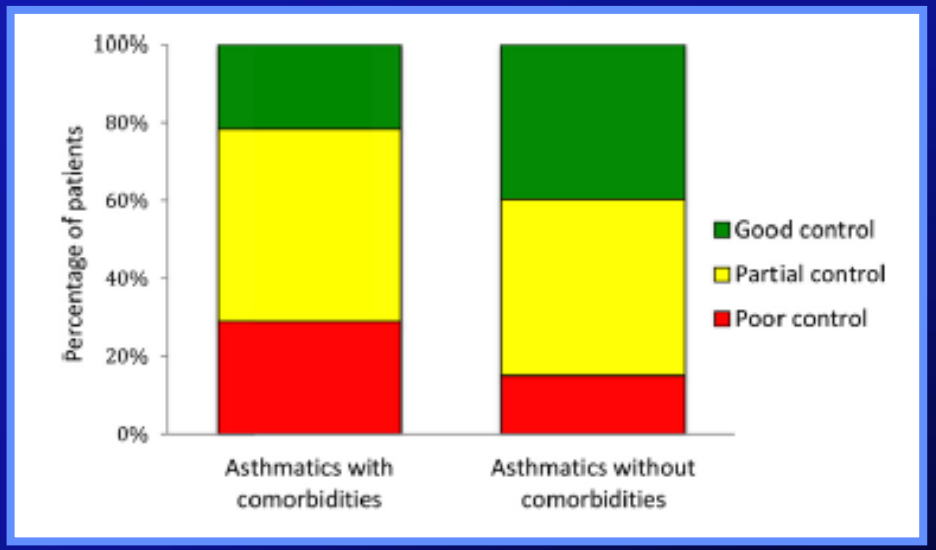
Asthma control in severe asthmatics under treatment with omalizumab: A cross-sectional observational study in Italy

Federica Novelli [a], Manuela Latorre [a], Letizia Vergura [a], Maria Filomena Caiaffa [b], Gianna Camiciottoli [c], Gabriella Guarnieri [d], Andrea Matucci [e], Luigi Macchia [f], Andrea Vianello [g], Alessandra Vultaggio [e], Alessandro Celi [a], Mario Cazzola [h], Pierluigi Paggiaro [a,*], on behalf of the Xolair Italian Study Group[1]

[a] Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Italy
[b] Chair and School of Allergology and Clinical Immunology, University of Foggia, Italy
[c] Department of Experimental and Clinical Medicine, University of Firenze, Italy
[d] Department of Cardiologic, Thoracic and Vascular Sciences, University of Padova, Italy
[e] Department of Biomedicine, Immunoallergology Unit, AOU Careggi, Florence, Italy
[f] Chair and School of Allergology and Clinical Immunology, University of Bari – Aldo Moro, Bari, Italy
[g] Respiratory Pathophysiology Division, University-City Hospital of Padova, Italy
[h] Unit of Respiratory Clinical Pharmacology, Department of Systems Medicine, University of Torvergata, Roma, Italy

Asthma control in severe asthmatics under treatment with omalizumab: A cross-sectional observational study in Italy

	No exacerbations ($N = 167$)	Exacerbations≥1 ($N = 125$)
General characteristics		
Age, yrs	51.6 ± 13.2	52.5 ± 14.4
Gender, M/F %	39.5/60.5	34.4/65.6
Smoke, Y/Ex/N %	3.6/28.1/67.1	3.2/25.6/71.2
PY (ex + current smokers)	12.5 (0.5–57)	10 (1.2–67.5)
BMI	26.0 (16.7–40.6)	27 (17.4–46.8)§
Familiarity for asthma, *n*(%)	72 (45.3)	52 (42.3)
Onset of asthma, yrs	24.5 (0–71)	29 (0–75)
Total serum IgE, UI/ml	363 (26–2353)	303 (31–2000)
Comorbidities		
Rhinitis, *n* (%)	108 (65.9)	80 (64.5)
Sinusitis, *n* (%)	43 (27)	52 (43.3)*
Nasal polyps, *n* (%)	30 (18.5)	43 (35.2)*
Aspirin intolerance, *n* (%)	25 (15)	35(29.4)*
Obesity, *n* (%)	28 (16.9)	38 (30.4)*
GORD, *n* (%)	47 (29.4)	55(45.1)*
Mental disorders, *n* (%)	10 (6.3)	11 (9.2)
Lung function		
Pre-BD FEV1, L	2.19 ± 0.83	1.93 ± 0.74*
Pre-BD FEV1, % of pred.	77.8 ± 18.6	70.6 ± 22.4*
Post-BD FEV1, % of pred.	81.6 ± 16.3	73.0 ± 23.6*
Inflammatory markers		
FeNO, ppb	22 (3.70–246.6)	27 (0–239.1)§
Blood eosinophils, n/mm3	260 (10–1266)	316.9 (0–1570)
Blood eosinophils, %	3.9 (0–17)	4.3 (0–22.5)
ACT score	22 (10–25)	20 (6–25)#
Therapy		
High dose of ICS, %	37.1	53.6*
LABA, %	89.7	91.1
OCS, %	3.3	12.5*
Tiotropium, %	7.0	21.4#
Antileukotrienes, %	57.9	59.8
Theophylline, %	9.1	11.7
Months of Omalizumab therapy	32 (5–79)	36 (4–120)



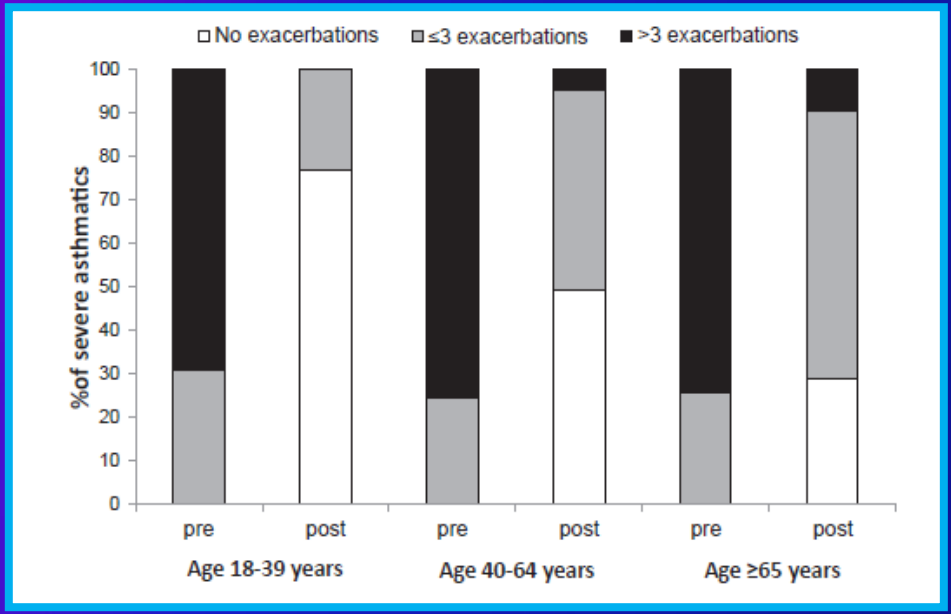
Novelli et al, Pulm Pharm Ther 2014

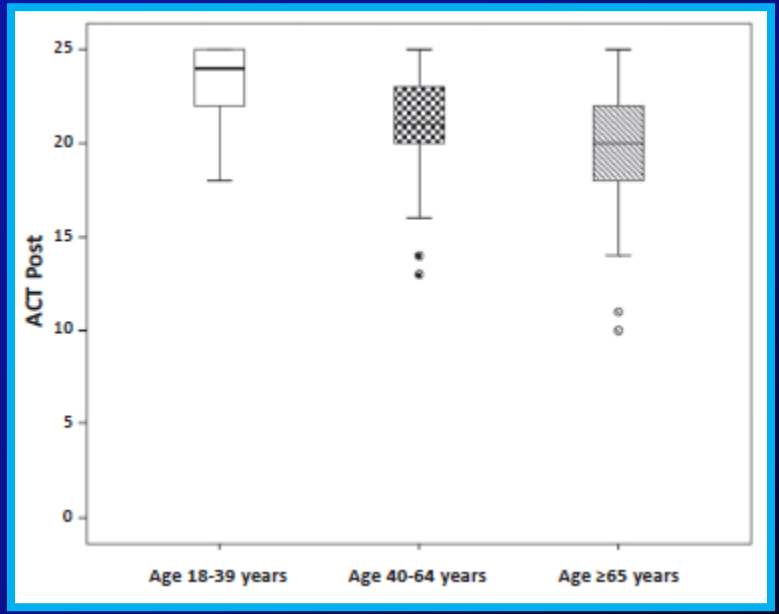
Effects of omalizumab in severe asthmatics across ages: A real life Italian experience

B. Sposato [a, *], M. Scalese [b], M. Latorre [c], N. Scichilone [d], A. Matucci [e], M. Milanese [f], S. Masieri [g], G. Rolla [h], G. Steinhilber [i], Y. Rosati [j], A. Vultaggio [e], I. Folletti [k], S. Baglioni [l], E. Bargagli [m], M. Di Tomassi [a], R. Pio [n], A. Pio [n], U. Maccari [o], C. Maggiorelli [o], M.G. Migliorini [a], L. Vignale [p], N. Pulerà [q], G.E. Carpagnano [r], M.P. Foschino Barbaro [r], A. Perrella [a], P.L. Paggiaro [c]

[a] *Pneumologia, Ospedale Misericordia, Grosseto, Italy*

Respir Med 2016

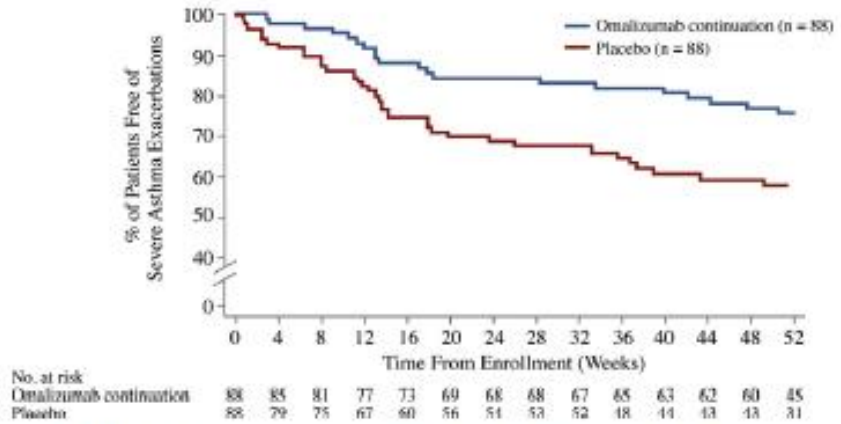




A randomized multicenter study evaluating Xolair persistence of response after long-term therapy

Dennis Ledford, MD,[a] William Busse, MD,[b] Benjamin Trzaskoma, MS,[c] Theodore A. Omachi, MD, MBA,[c] Karin Rosén, MD,[c] Bradley E. Chipps, MD,[d] Allan T. Luskin, MD,[e] and Paul G. Solari, MD[c] *Tampa, Fla, Madison, Wis, and South San Francisco and Sacramento, Calif*

J Allergy Clin Immunol 2017



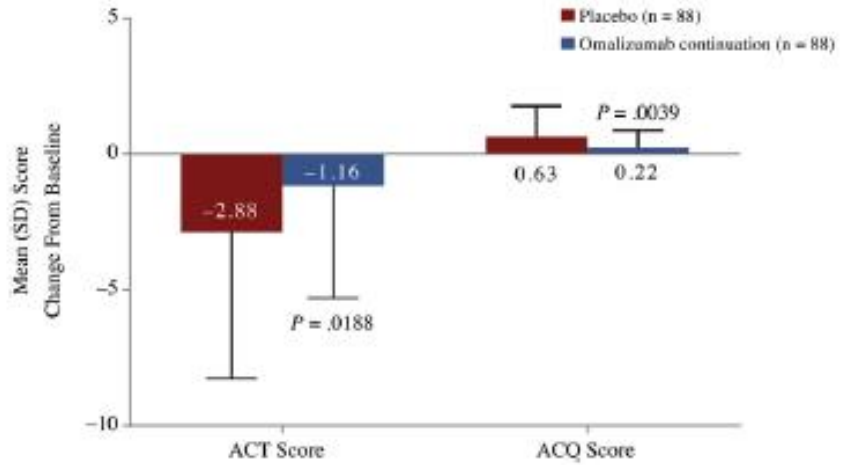
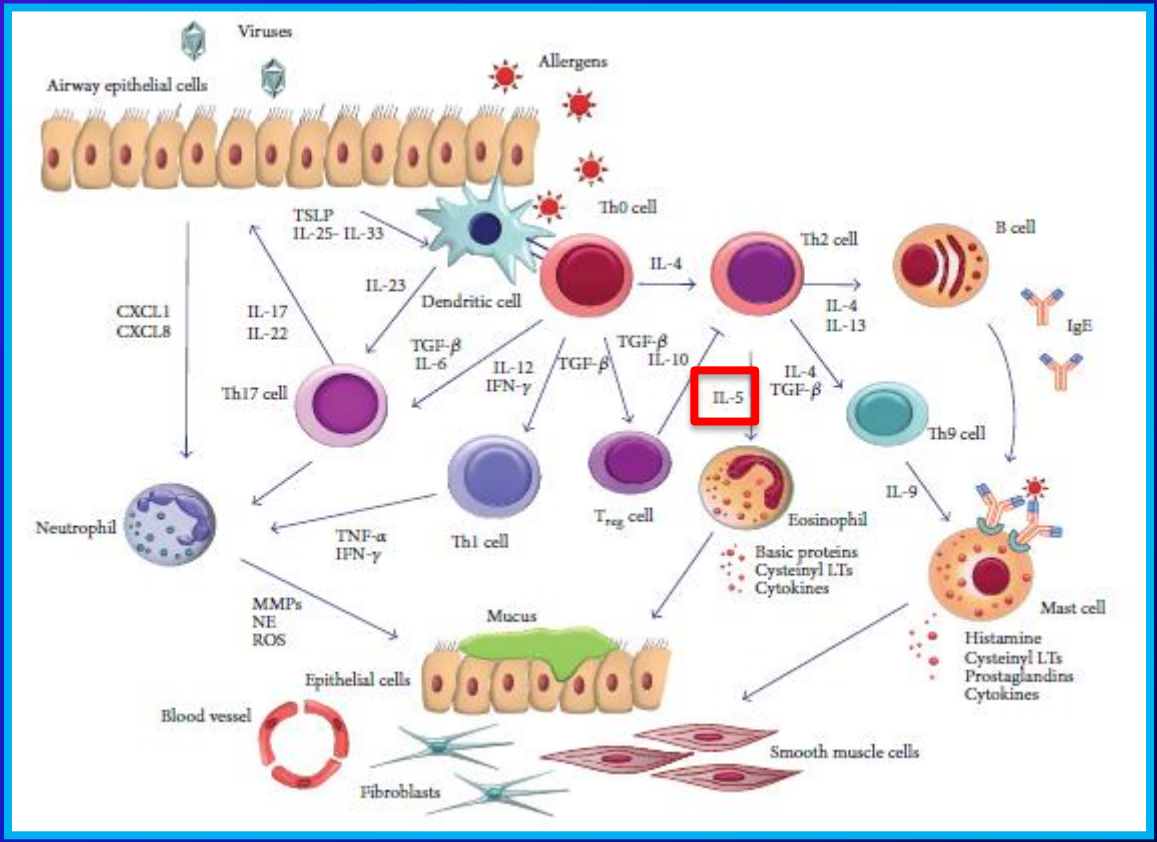


FIG 2. Time to first protocol-defined asthma exacerbation.

New biologic drugs in asthma

Name	Target	Phase	Biomarkers
Mepolizumab	IL-5	On the market	**Blood eos**
Benralizumab	IL-5 R	Phase III	**Blood eos**
Reslizumab	IL-5	Phae III	**Blood eos**
Lebrikizumab	IL-13	Phase III → stop	**Periostin**
Tralokinumab	IL-13	Phase II-III	**DPP-4, periostin**
Dupilumab	IL-4	Phase III	**FeNO ?**
Brodalumab	IL-17	Phase II → stop	**??**
??			

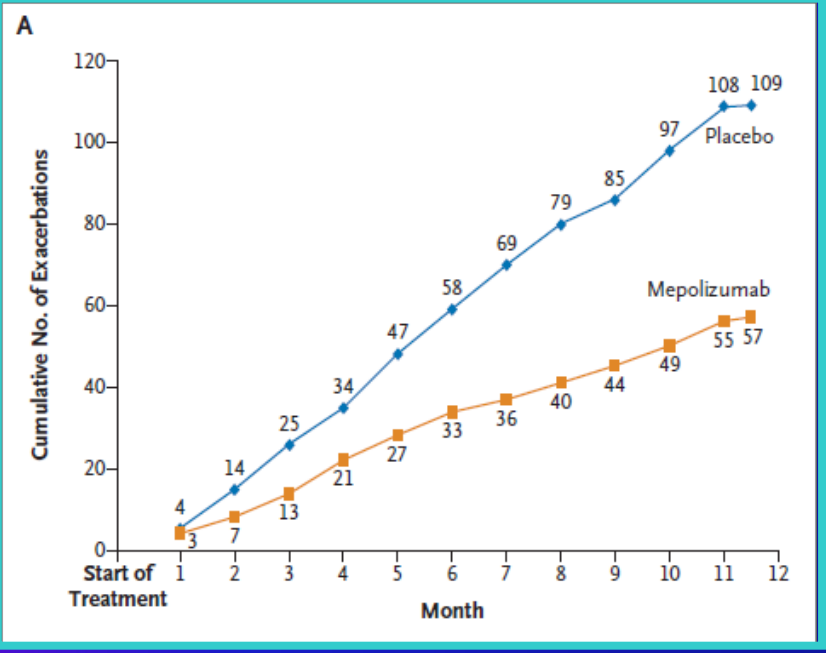
Different targets for intervention on the «inflammatory cascade»

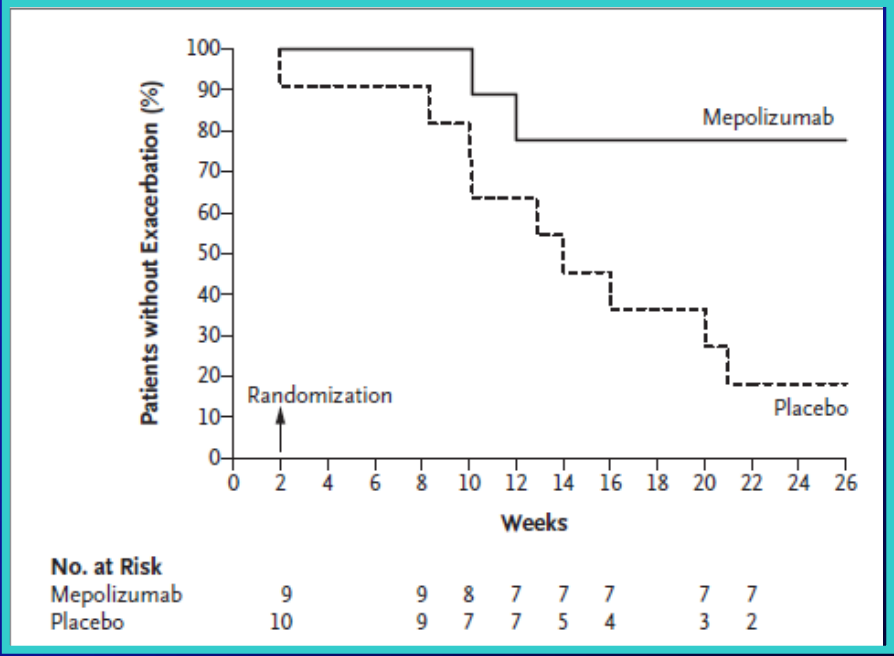


Pelaia et al, Med Inflamm 2015

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P., Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc., Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.





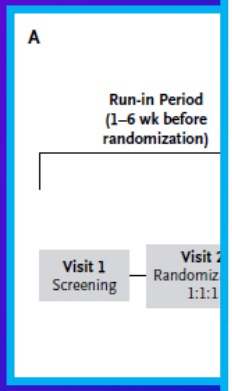
N ENGL J MED 360;10 NEJM.ORG MARCH 5, 2009

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D., Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D., Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

Mep… wit…

Hector G. …
Guy G. Bru…
Marc Humber…
Stev…

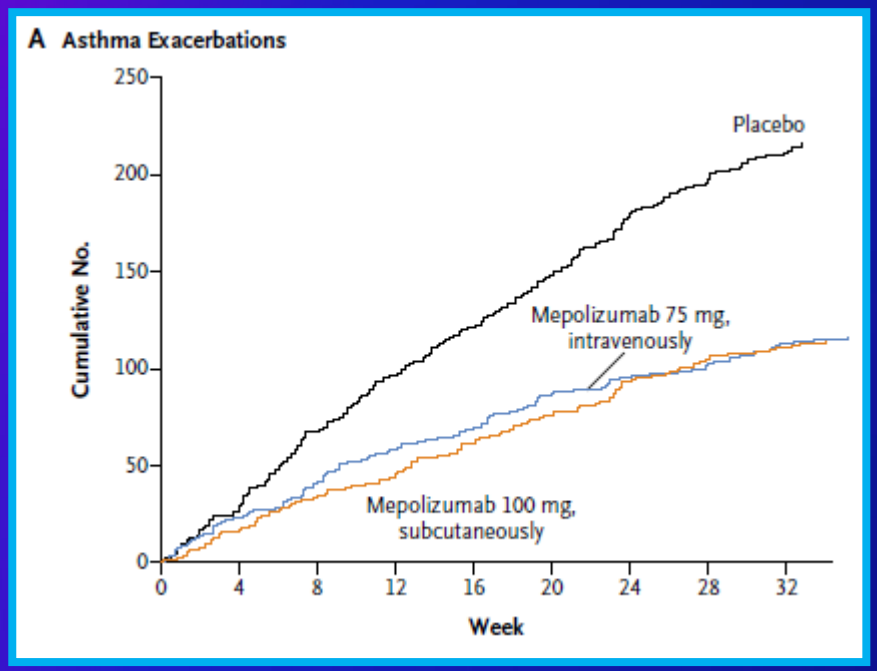


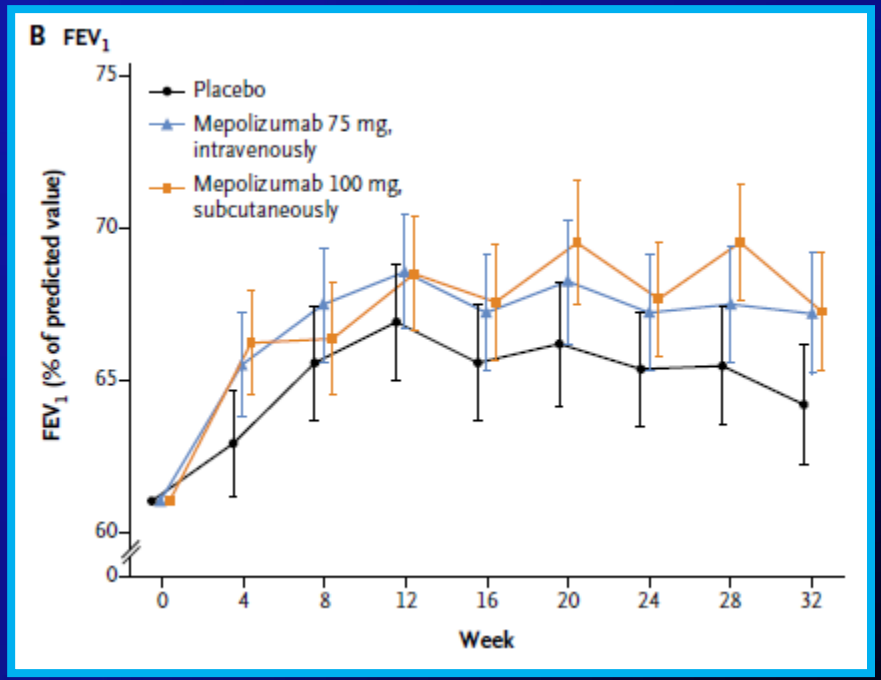
Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

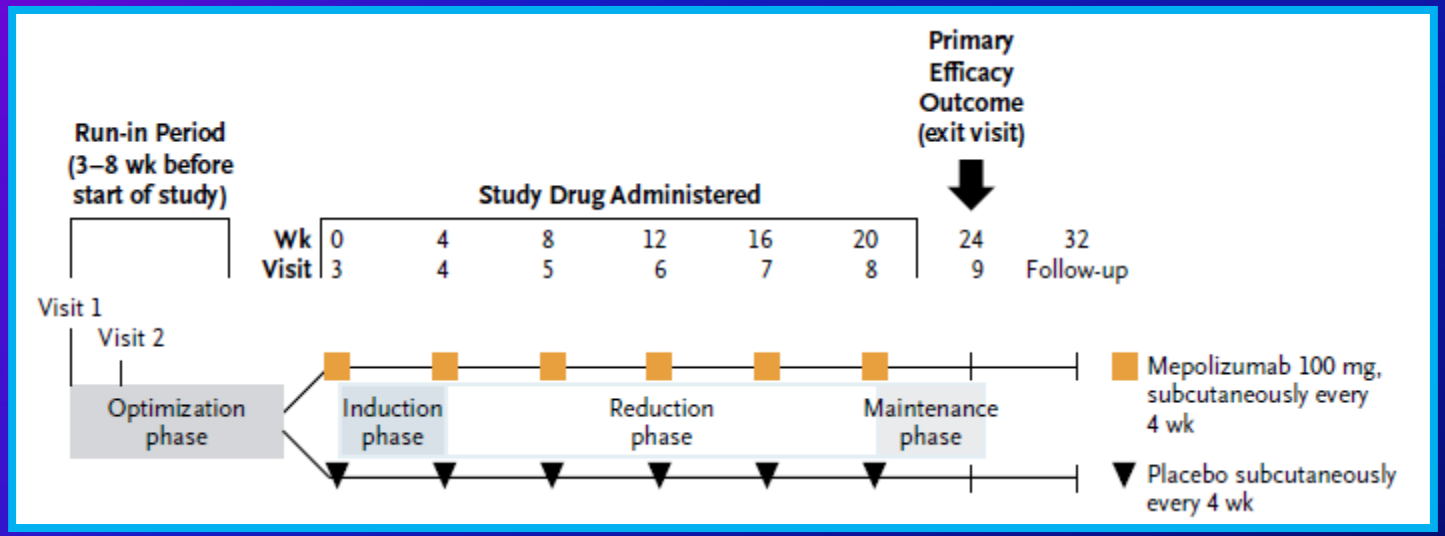
This article was published on September 8, 2014, at NEJM.org.

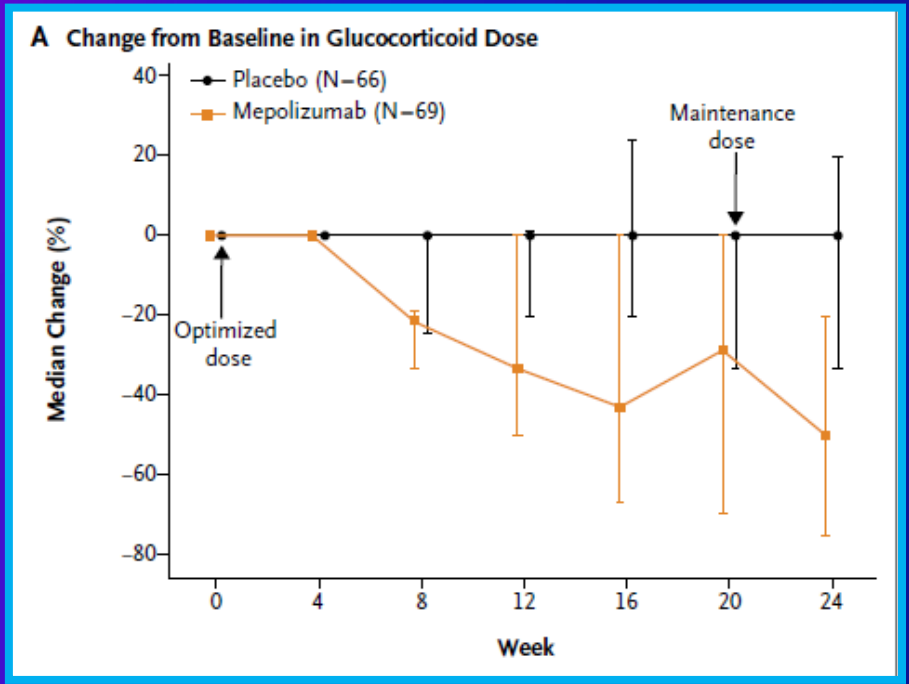


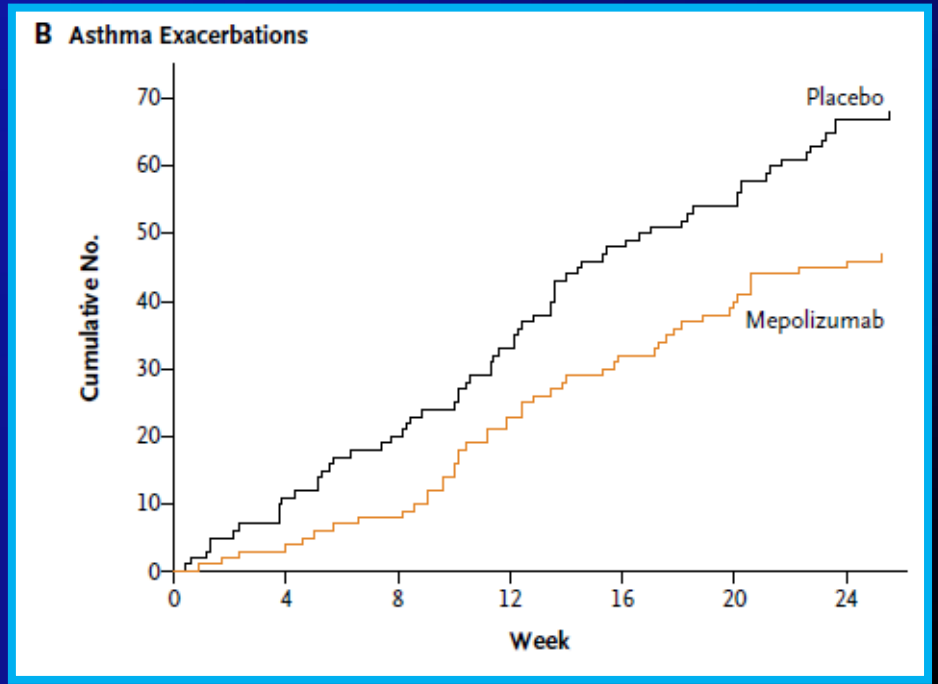


Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Bel et al, NEJM 2014



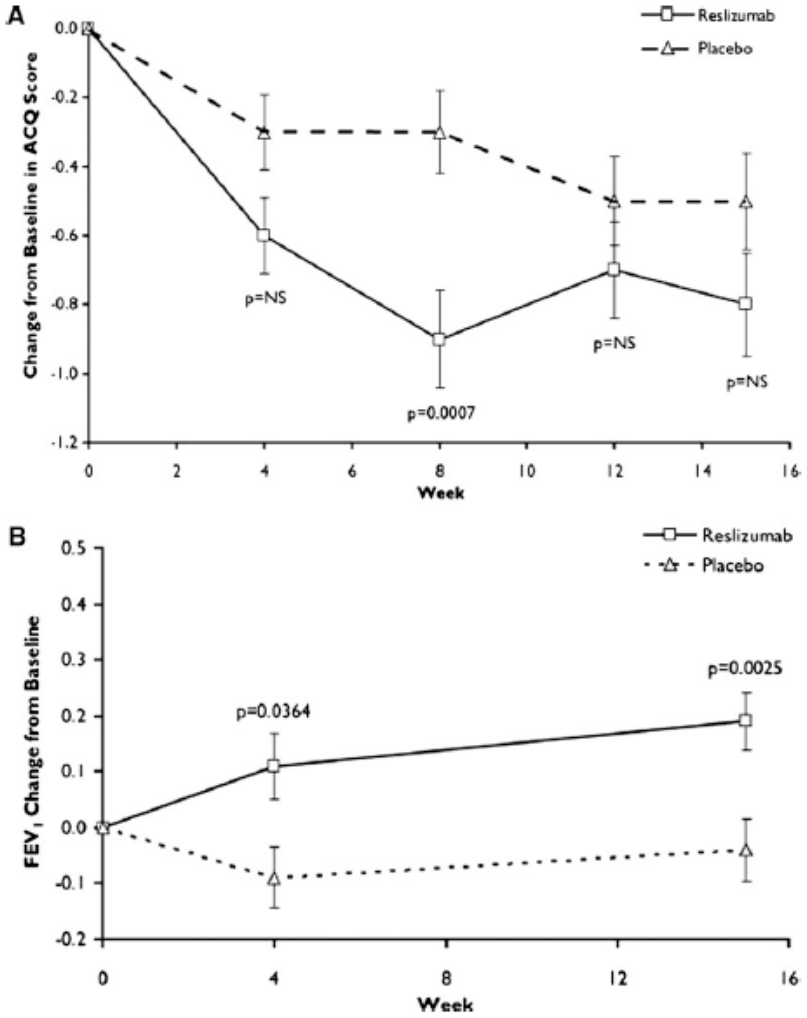


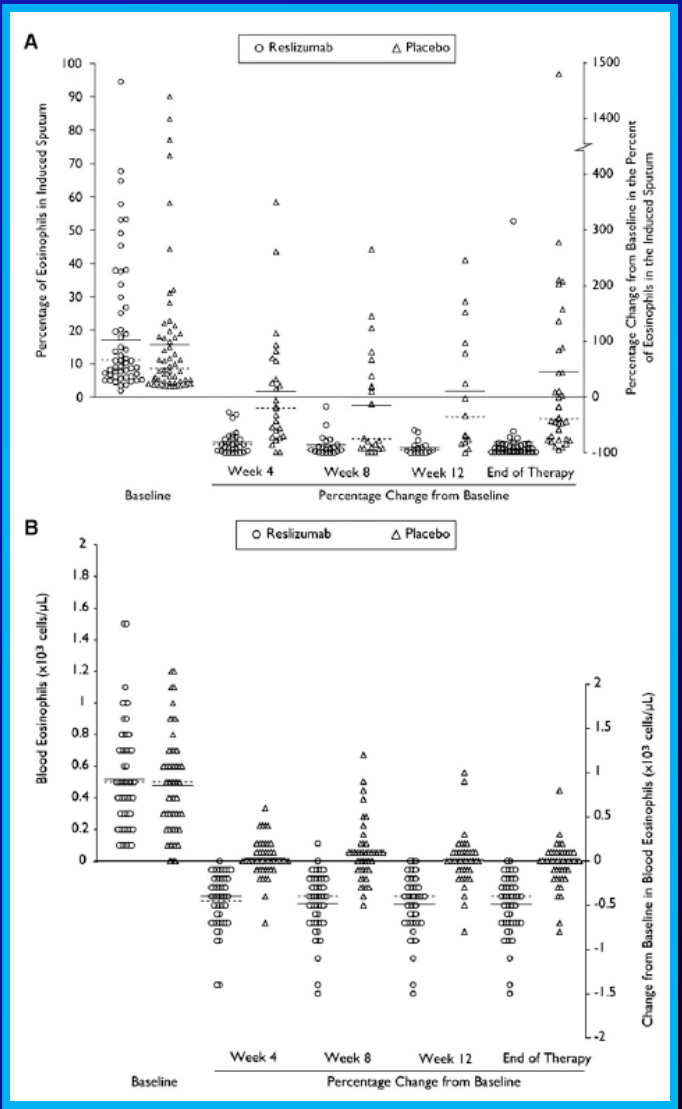


Reslizumab for Poorly Controlled, Eosinophilic Asthma

A Randomized, Placebo-controlled Study

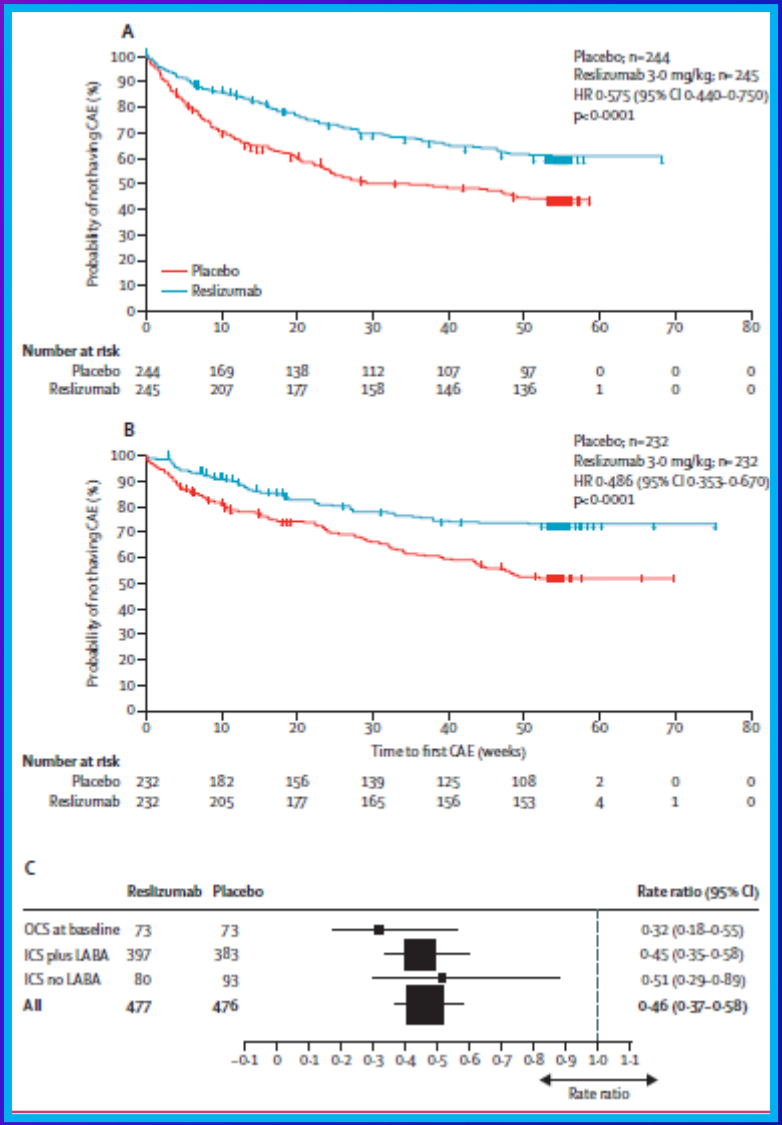
Mario Castro[1], Sameer Mathur[2], Frederick Hargreave[3†], Louis-Philippe Boulet[4], Fang Xie[5], James Young[6], H. Jeffrey Wilkins[5], Timothy Henkel[5], and Parameswaran Nair[3]; for the Res-5-0010 Study Group

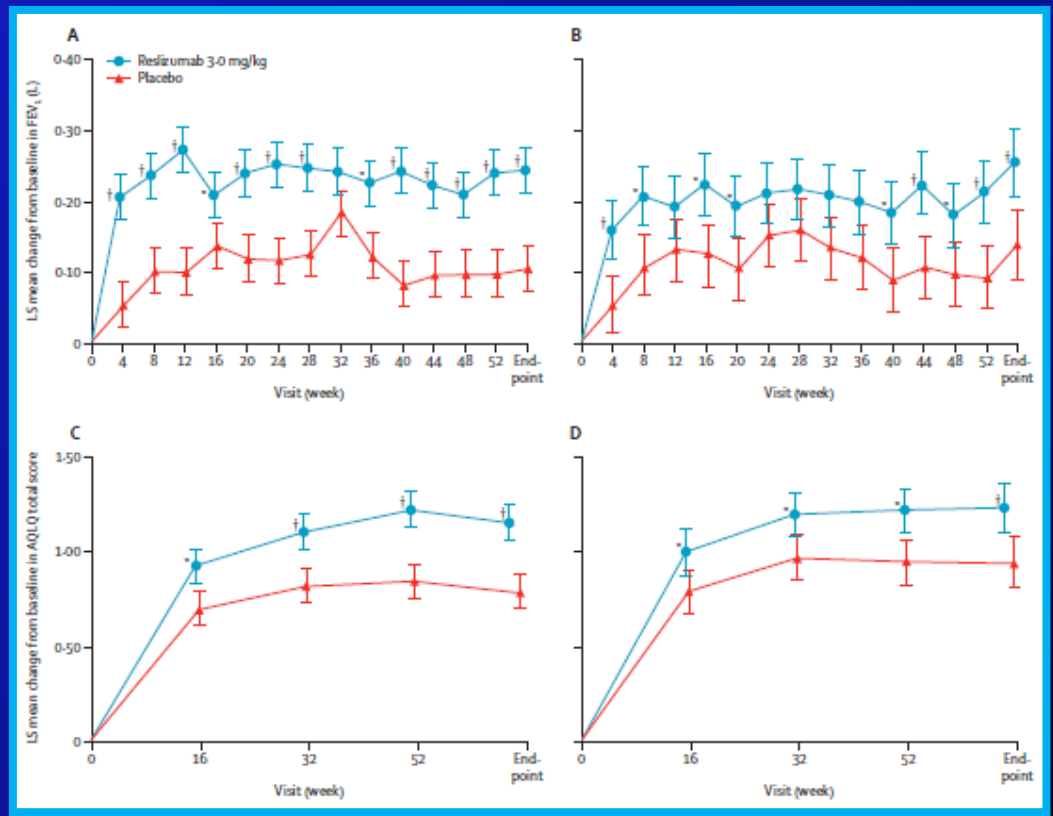




Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

Castro et al, Lancet RespirMed 2015

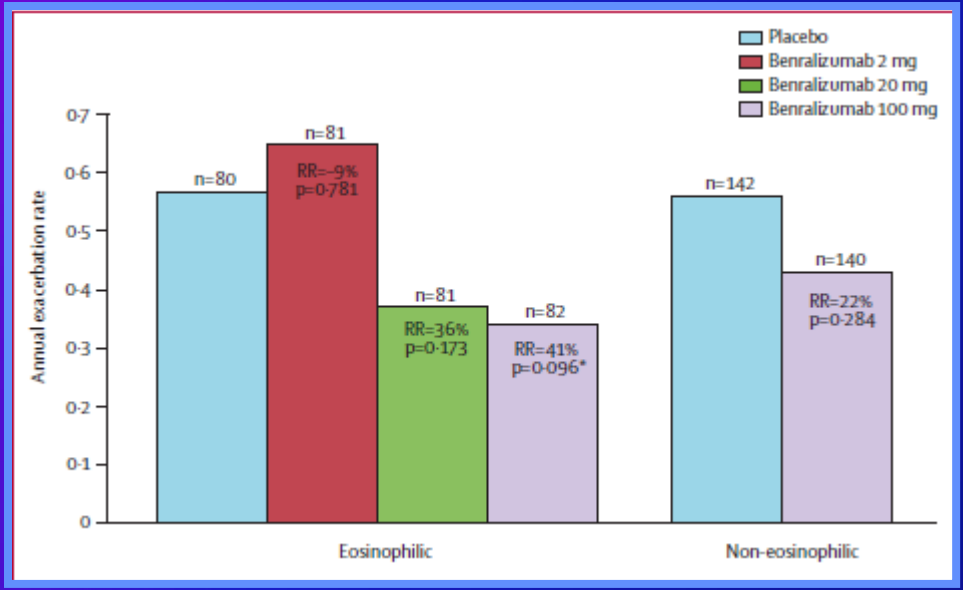


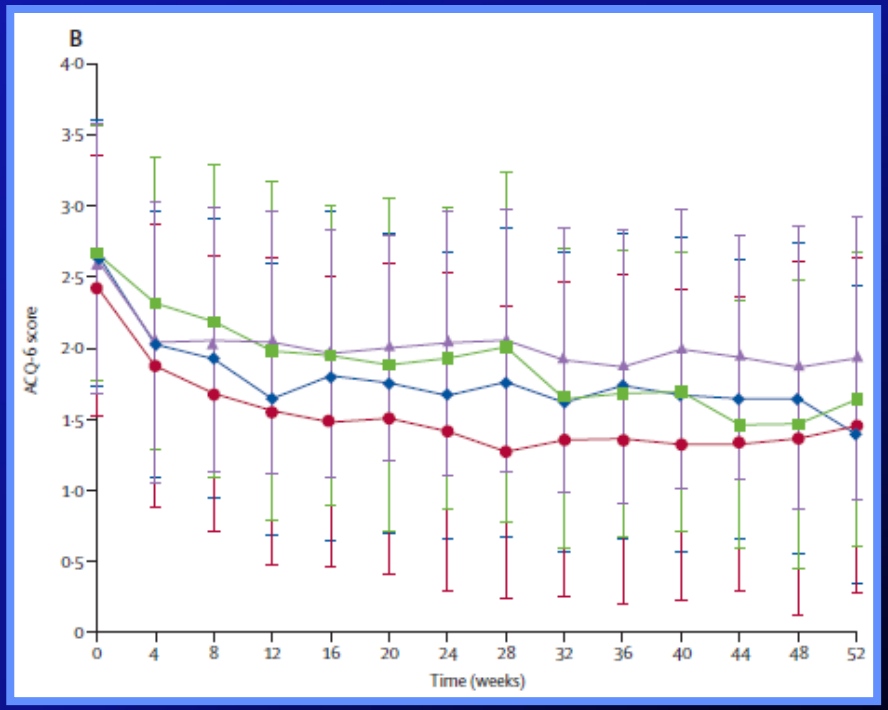


Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study

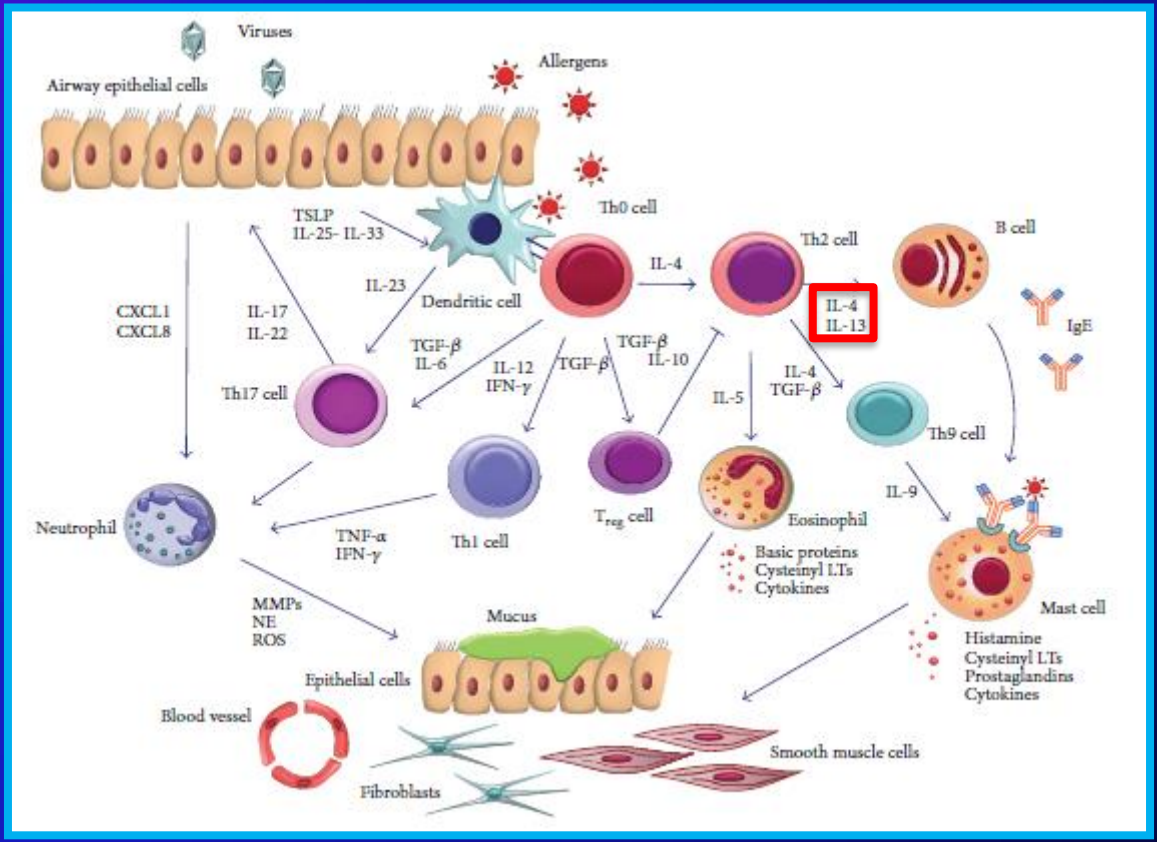
Mario Castro, Sally E Wenzel, Eugene R Bleecker, Emilio Pizzichini, Piotr Kuna, William W Busse, David L Gossage, Christine K Ward, Yanping Wu, Bing Wang, Deepak B Khatry, René van der Merwe, Roland Kolbeck, Nestor A Molfino, Donald G Raible

Lancet Respir Med 2014; 2: 878–90





Different targets for intervention on the «inflammatory cascade»



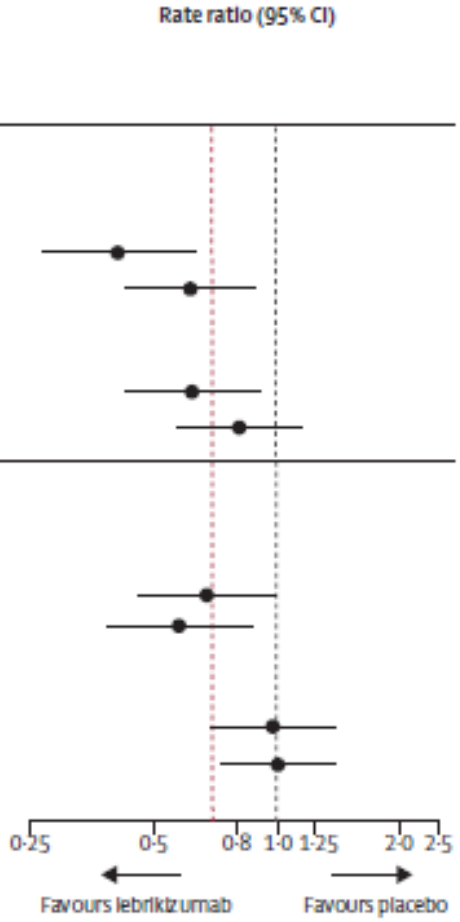
Pelaia et al, Med Inflamm 2015

Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials

Nicola A Hanania, Phillip Korenblat, Kenneth R Chapman, Eric D Bateman, Petr Kopecky, Pierluigi Paggiaro, Akihito Yokoyama, Julie Olsson, Sarah Gray, Cecile T J Holweg, Mark Eisner, Charles Asare, Saloumeh K Fischer, Kun Peng, Wendy S Putnam, John G Matthews

Lancet Respir Med 2016; 4: 781–96

	n	Adjusted exacerbation rate (per patient per year)	Rate difference (lebrikizumab–placebo)	Rate reduction (%)	Rate ratio (lebrikizumab vs placebo, 95% CI)	p value
LAVOLTA I						
Eosinophil high						
Placebo	141	1·23				
Lebrikizumab 37·5 mg	144	0·50	−0·73	60%	0·40 (0·26–0·62)	<0·0001
Lebrikizumab 125 mg	136	0·75	−0·49	39%	0·61 (0·42–0·88)	0·0090
Eosinophil low						
Placebo	221	0·60				
Lebrikizumab 37·5 mg	216	0·37	−0·23	39%	0·61 (0·42–0·90)	0·0132
Lebrikizumab 125 mg	223	0·48	−0·12	20%	0·80 (0·56–1·14)	0·2110
LAVOLTA II						
Eosinophil high						
Placebo	140	0·83				
Lebrikizumab 37·5 mg	144	0·57	−0·26	32%	0·68 (0·46–1·01)	0·0566
Lebrikizumab 125 mg	134	0·48	−0·35	43%	0·57 (0·38–0·88)	0·0100
Eosinophil low						
Placebo	214	0·48				
Lebrikizumab 37·5 mg	212	0·48	0·00	1%	0·99 (0·70–1·40)	0·9649
Lebrikizumab 125 mg	223	0·50	0·02	−3%	1·03 (0·74–1·45)	0·8534



Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial

Christopher E Brightling, Pascal Chanez, Richard Leigh, Paul M O'Byrne, Stephanie Korn, Dewei She, Richard D May, Katie Streicher, Koustubh Ranade, Edward Piper

Lancet Respir Med 2015; 3: 692–701

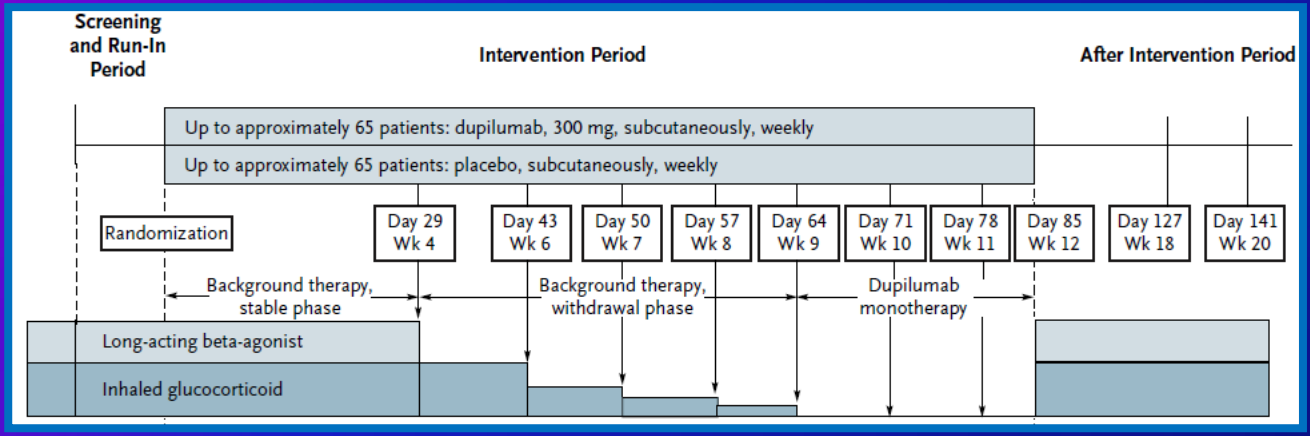
	All (n=33)	DPP-4-high group (n=24)	DPP-4-low group (n=8)	Periostin-high group (n=18)	Periostin-low group (n=15)
Primary endpoint					
Asthma exacerbation rate					
Percent reduction versus placebo (95% CI; p value)	44% (–22 to 74; 0·147)	57% (–30 to 86; 0·134)	–7% (–886 to 88; 0·950)	67% (2 to 89; 0·046)	–32% (–273 to 53; 0·597)
Secondary endpoints (difference from placebo)					
Prebronchodilator FEV_1					
Percent change from baseline (95% CI; p value)	12·21% (1·74 to 22·67; 0·022)	20·41% (1·30 to 39·52; 0·037)	–0·94% (–15·35 to 13·47; 0·897)	15·14% (0·35 to 29·92; 0·045)	8·00% (–7·04 to 23·04; 0·294)
ACQ-6					
Mean change from baseline (95% CI; p value)	–0·55 (–1·07 to –0·04; 0·036)	–0·89 (–1·63 to –0·14; 0·020)	–0·43 (–1·41 to 0·56; 0·390)	–0·68 (–1·31 to –0·06; 0·033)	–0·23 (–1·10 to 0·64; 0·596)
AQLQ(S)					
Mean change from baseline (95% CI; p value)	0·70 (0·12 to 1·28; 0·019)	1·26 (0·48 to 2·04; 0·002)	0·24 (–0·87 to 1·35; 0·663)	0·64 (–0·11 to 1·39; 0·095)	0·71 (–0·23 to 1·65; 0·138)

DPP-4=dipeptidyl peptidase-4. FEV_1=forced expiratory volume in 1 s. ACQ-6=Asthma Control Questionnaire-6. AQLQ(S)=Asthma Quality of Life Questionnaire-Standardised Version.

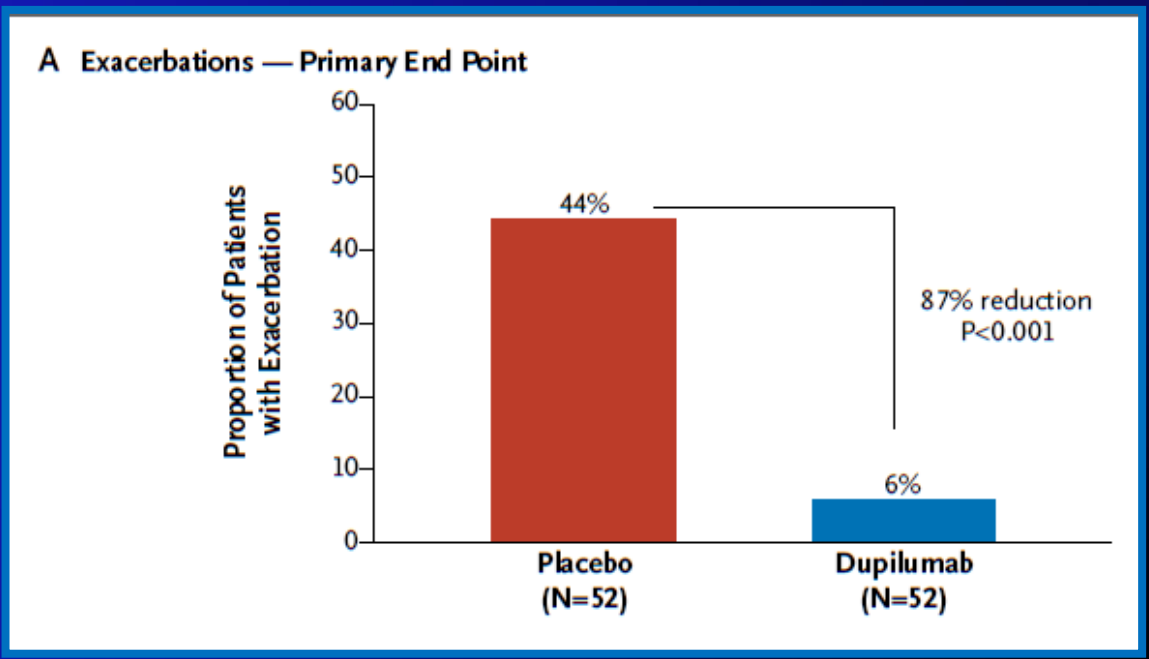
Table 3: **Asthma exacerbation rate, FEV_1, ACQ-6, and AQLQ(S) for tralokinumab every 2 weeks versus placebo in patients who were reversible at baseline and not receiving long-term oral corticosteroids**

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

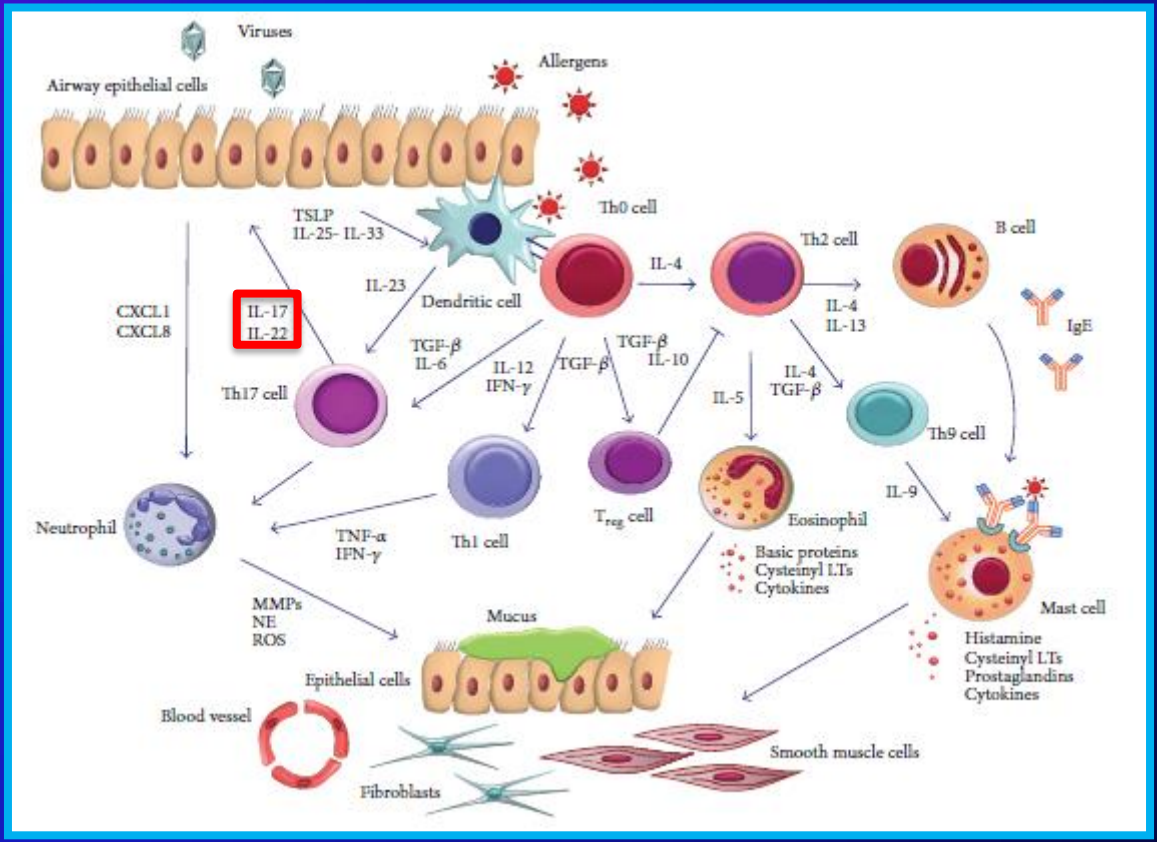
Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.



N Engl J Med 2013;368:2455-66.



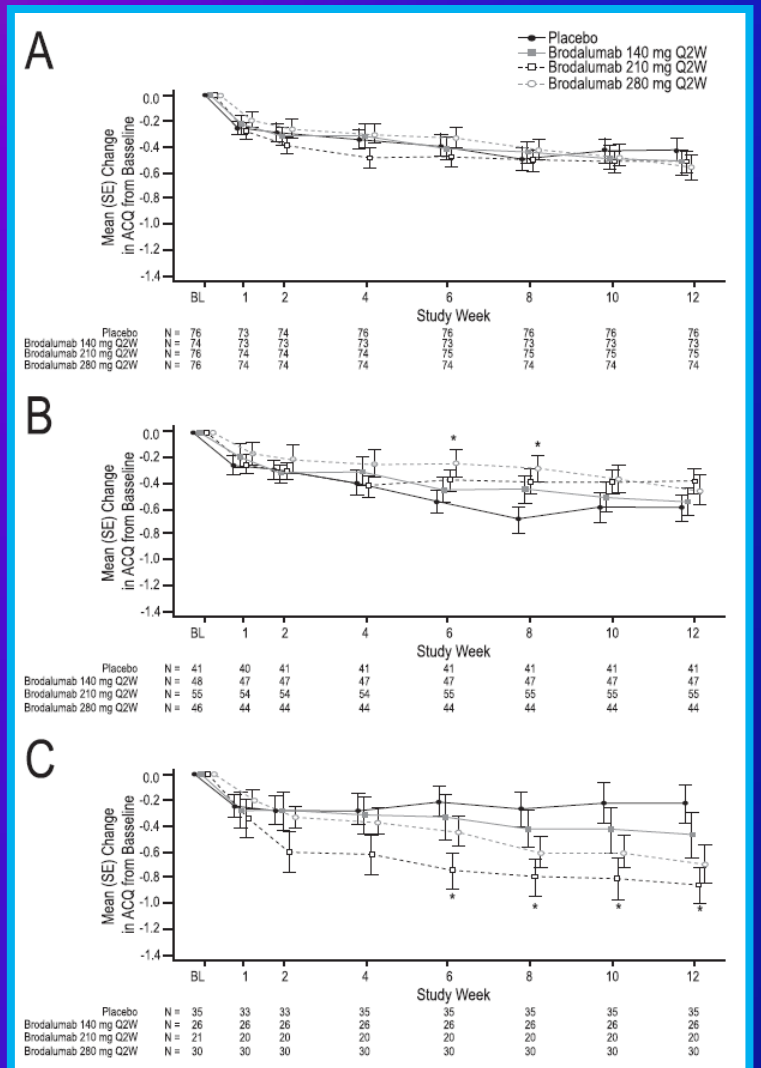
Different targets for intervention on the «inflammatory cascade»

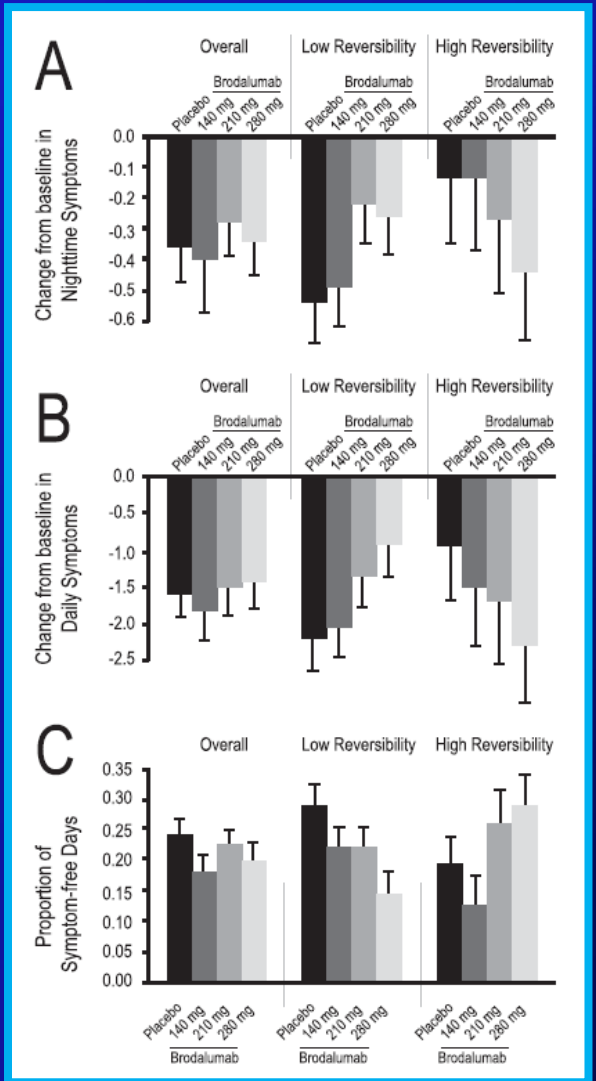


Pelaia et al, Med Inflamm 2015

Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma

Busse et al, AJRCCM 2013





In a subgroup with high reversibility

Management of severe asthma

Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

- **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[289] (Evidence B). However, this carries the risk of systemic side-effects;[284] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p49) (Evidence D).
- **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[284] (Evidence D), but the potential long-term side-effects should be taken into account. Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[177]
- **Add-on treatments without phenotyping**: other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit. In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting anti-cholinergic bronchodilator, tiotropium*, showed improved lung function and decreased reliever use.[290]
- **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[130] (Evidence A).
- **Phenotype-guided add-on treatment**: patients with severe asthma may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[5,6,126,284] Patients with severe allergic asthma with elevated IgE levels may benefit from anti-IgE therapy[291] (Evidence A), and LTRAs may be helpful for patients found to be aspirin sensitive[281] (Evidence B).
- **Non-pharmacological interventions**: bronchial thermoplasty may be helpful in selected patients with severe asthma (Evidence B),[90] but more studies are needed to identify its efficacy and long-term safety in broader severe asthma populations (see Appendix Chapter 6).[132] Carefully controlled trials are important as a large placebo effect has been seen in studies to date.[90] High-altitude treatment[284] (Evidence C) or psychological interventions[292] (Evidence C) may be helpful in patients with severe asthma. The place of these therapies and strategies in severe asthma has not been established.[132]

What we need to know about the mechanisms of BT

- More pathologic data
  - Bronchial biopsies before and after intervention
  - Thickness of airway wall by CT
- More physiologic data
  - Airway variability over time
  - Small airways measurements
- More data on inflammatory changes
  - Non invasive biomarkers (eNO, induced sputum)

Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: Clinical and histopathologic correlations.

Pretolani M[1], Bergqvist A[2], Thabut G[3], Dombret MC[4], Knapp D[5], Hamidi F[1], Alavoine L[6], Taillé C[4], Chanez P[7], Erjefält JS[2], Aubier M[8].
J Allergy Clin Immunol. 2016 Sep 5 epub

BACKGROUND: The effectiveness of bronchial thermoplasty (BT) has been reported in patients with severe asthma, yet its effect on different bronchial structures remains unknown.

OBJECTIVE: We sought to examine the effect of BT on bronchial structures and to explore the association with clinical outcome in patients with severe refractory asthma.

METHODS: Bronchial biopsy specimens (n = 300) were collected from 15 patients with severe uncontrolled asthma before and 3 months after BT. Immunostained sections were assessed for airway smooth muscle (ASM) area, subepithelial basement membrane thickness, nerve fibers, and epithelial neuroendocrine cells. Histopathologic findings were correlated with clinical parameters.

RESULTS: BT significantly improved asthma control and quality of life at both 3 and 12 months and decreased the numbers of severe exacerbations and the dose of oral corticosteroids. At 3 months, this clinical benefit was accompanied by a reduction in ASM area (median values before and after BT, respectively: 19.7% [25th-75th interquartile range (IQR), 15.9% to 22.4%] and 5.3% [25th-75th IQR], 3.5% to 10.1%, $P < .001$), subepithelial basement membrane thickening (4.4 μm [25th-75th IQR, 4.0-4.7 μm] and 3.9 μm [25th-75th IQR, 3.7-4.6 μm], $P = 0.02$), submucosal nerves (1.0 ‰ [25th-75th IQR, 0.7-1.3 ‰] immunoreactivity and 0.3 ‰ [25th-75th IQR, 0.1-0.5 ‰] immunoreactivity, $P < .001$), ASM-associated nerves (452.6 [25th-75th IQR, 196.0-811.2] immunoreactive pixels per mm^2 and 62.7 [25th-75th IQR, 0.0-230.3] immunoreactive pixels per mm^2, $P = .02$), and epithelial neuroendocrine cells (4.9/mm^2 [25th-75th IQR, 0-16.4/mm^2] and 0.0/mm^2 [25th-75th IQR, 0-0/mm^2], $P = .02$). Histopathologic parameters were associated based on Asthma Control Test scores, numbers of exacerbations, and visits to the emergency department (all $P \leq .02$) 3 and 12 months after BT.

CONCLUSION: BT is a treatment option in patients with severe therapy-refractory asthma that downregulates selectively structural abnormalities involved in airway narrowing and bronchial reactivity, particularly ASM, neuroendocrine epithelial cells, and bronchial nerve endings.

Main evolution in asthma guideline: «Asthma as a heterogeneous disease»

- **Identification of different phenotypes**
  - **According to etiology**
  - **According to pathogenesis**
  - **According to severity**
- **Implication for treatment («target therapy»)**
  - **With current drugs**
  - **With biologic drugs**
  - **With allergen-immunotherapy**
  - **With thermoplasty**
- **«tailoring» asthma approach**