Treatable traits in asthma
Precision medicine

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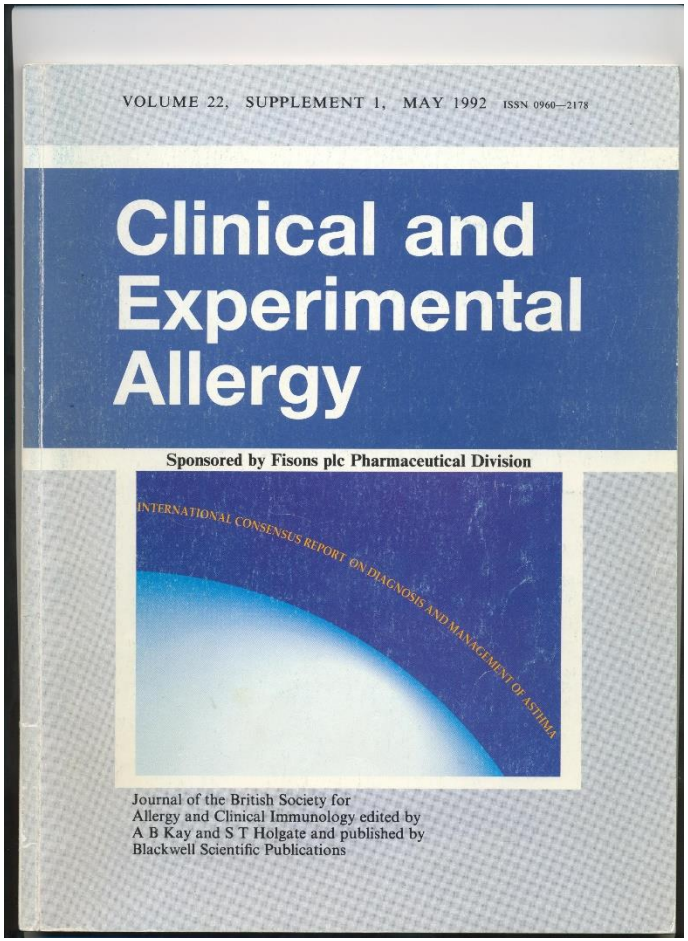
Presentation outline

- The time of the blockbusters
- Anti-IgE as the first example of precision medicine in asthma treatment
- The paradigmatic history of anti-IL-5 as a case for precision medicine in asthma
- Reassessment of ICS efficacy and effectiveness according to the eosinophilic trait
- The treatable traits in asthma beyond airway inflammation
- Will the future mark the return of the blockbusters?

What is asthma?

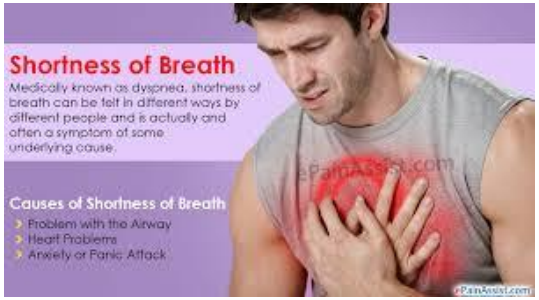


1992

- Chronic inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils. In suscpetible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli

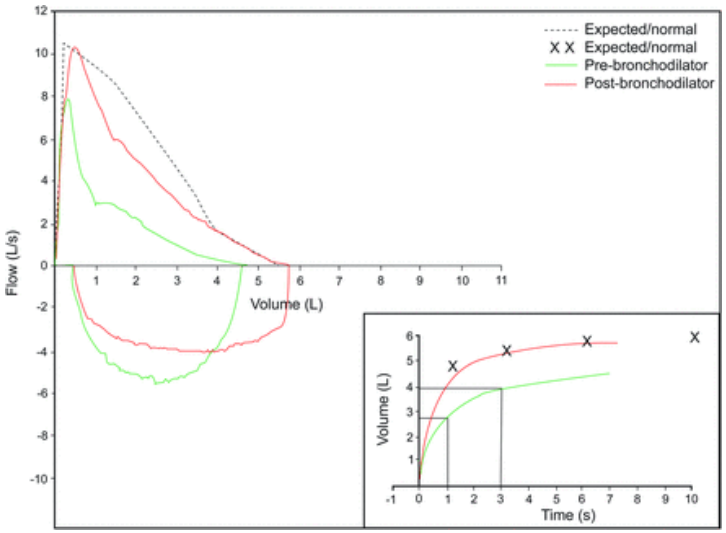
Common way to diagnose and assess asthma in clinical practice and in RCT

- History taking



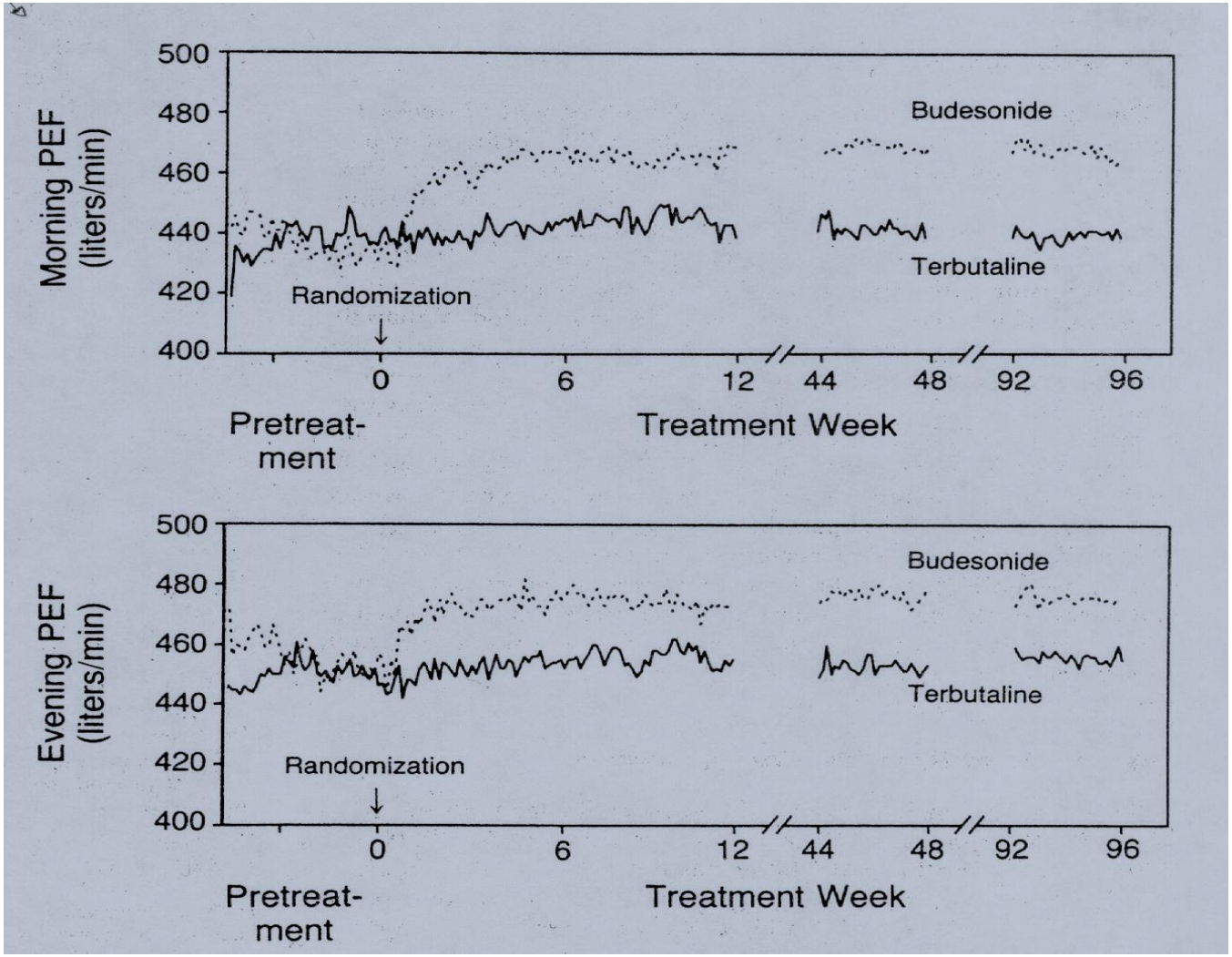
- Spirometry- Reversibility

12% from baseline and 200 ml



Time of blockbusters

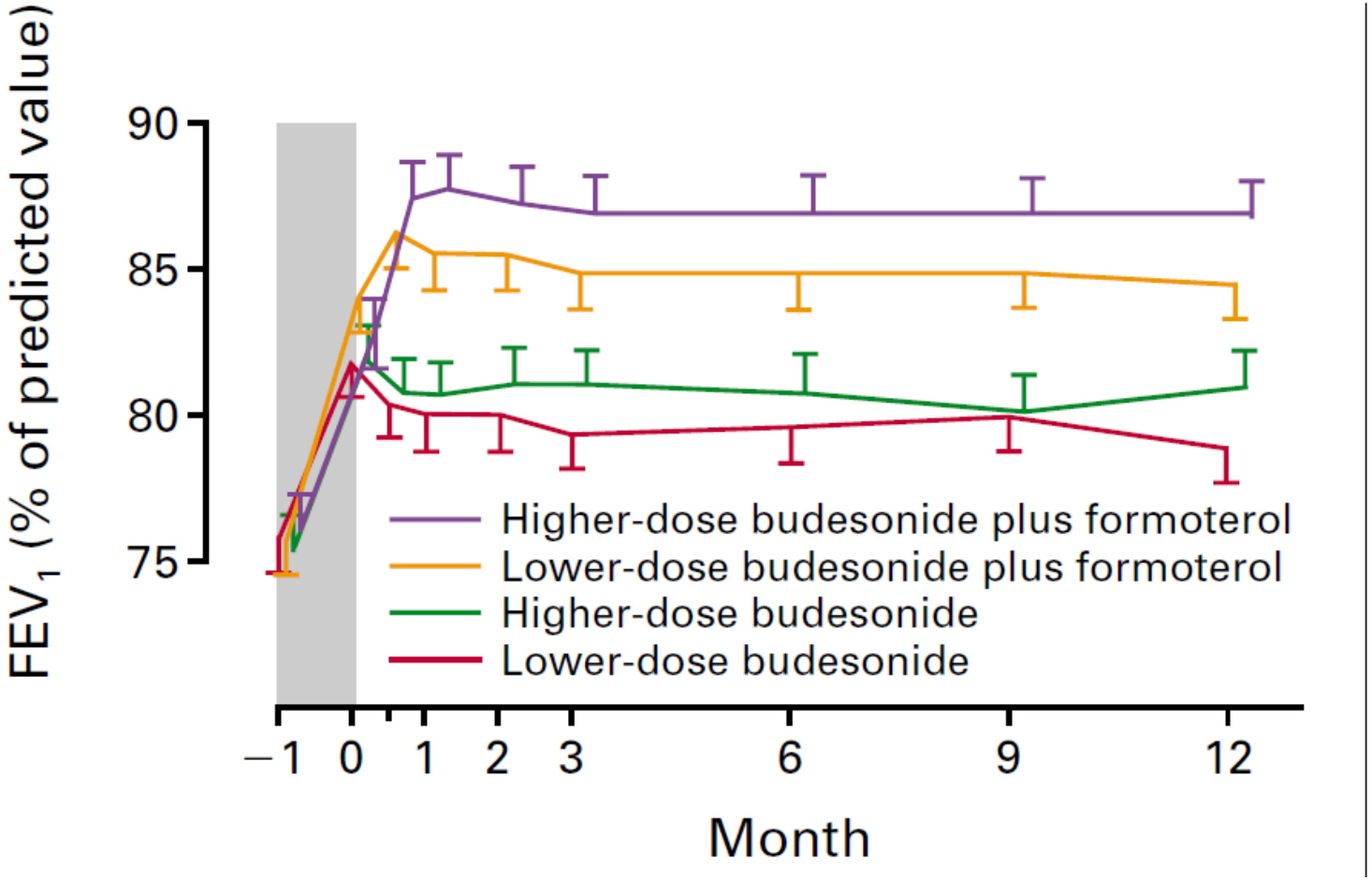
Effect of inhaled budesonide vs terbutaline on Peak Expiratory Flow Rates in asthmatics



Haathela et al N Engl J Med 1991

Effect of inhaled ICS and ICS/LABA on airway calibre

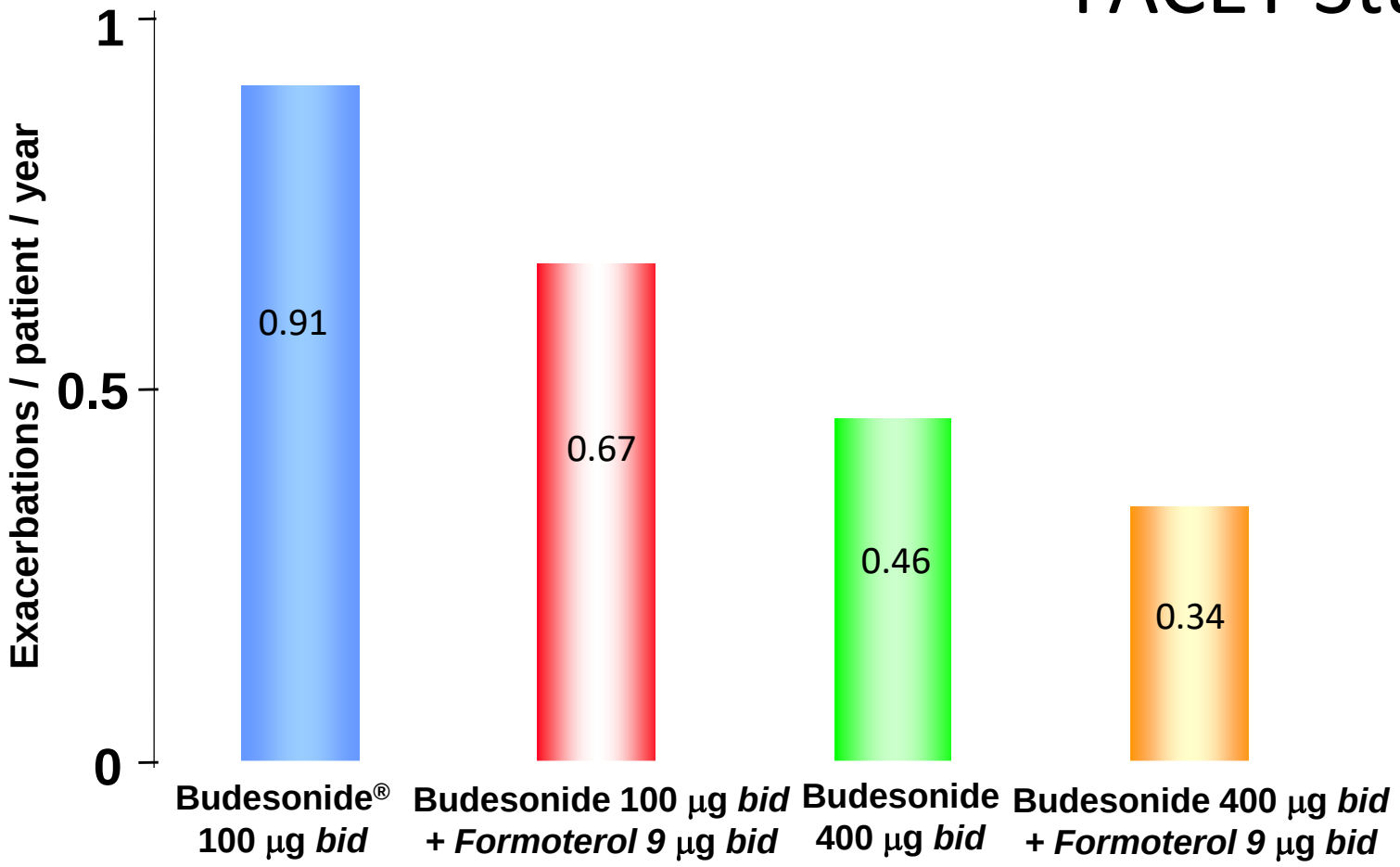
FACET Study



Pauwels et al N Engl J Med 1997

Effect of inhaled ICS and ICS/LABA on severe exacerbations

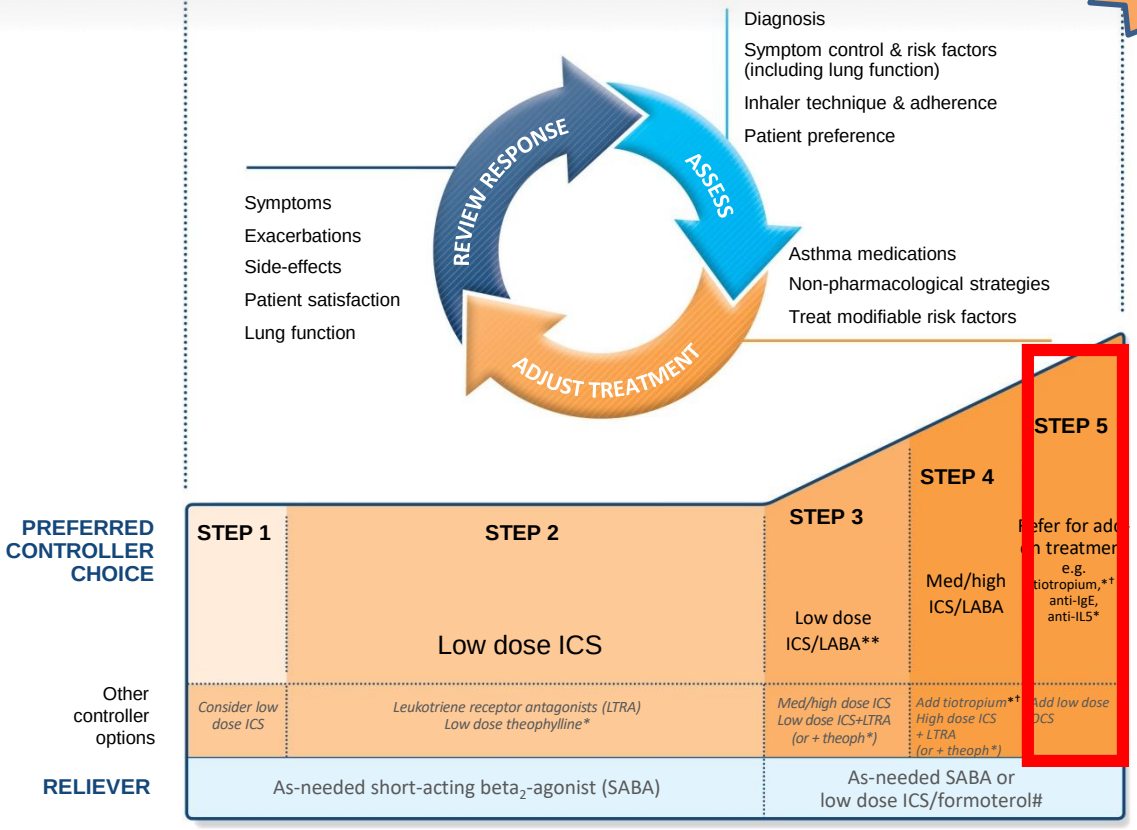
FACET Study



Pauwels et al N Engl J Med 1997

Stepwise approach to control asthma symptoms and reduce risk

UPDATED 2017

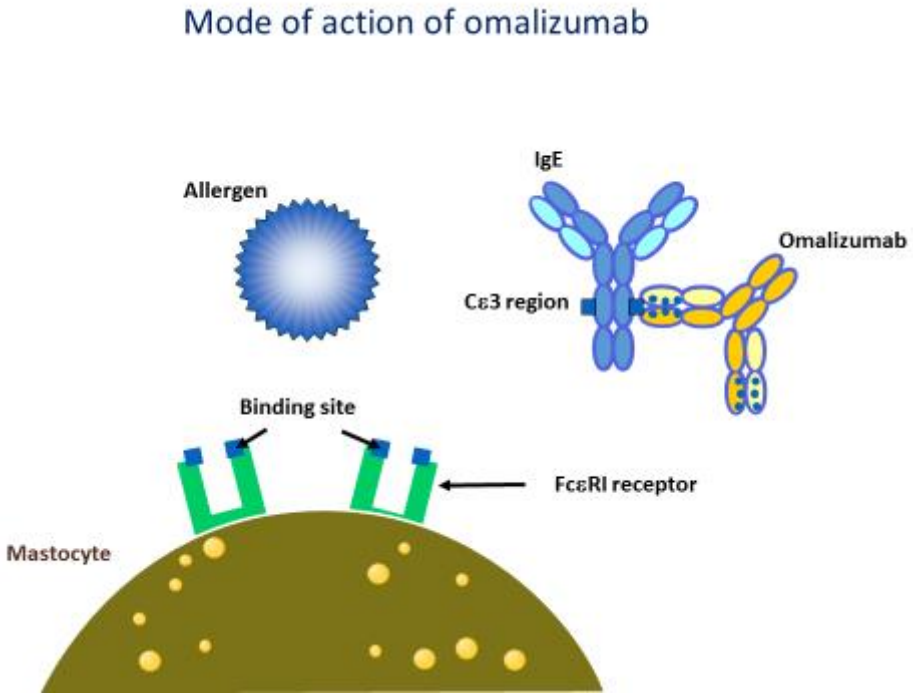


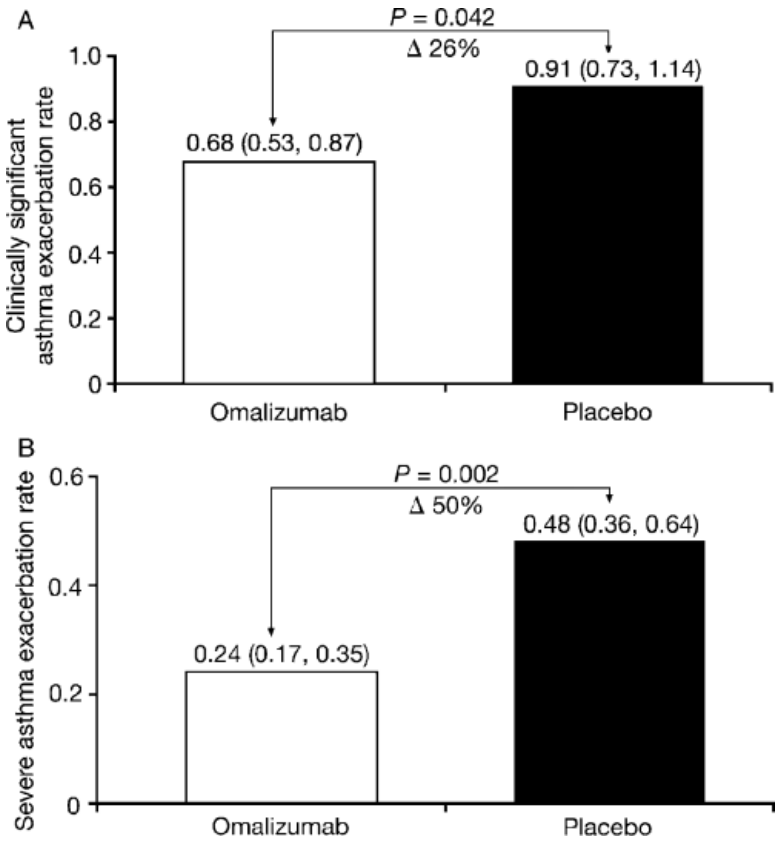
REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

Anti-IgE as first example of precision medicine in asthma

Efficacy of Anti-IgE omalizumab in reducing exacerbation in severe asthma





Sensitized to perennial aeroallergen
Serum IgE 30-700 Ku/l
Effect particularly clear when selecting patients with IgE > 76Ku/L

Humbert M et al N Allergy 2004

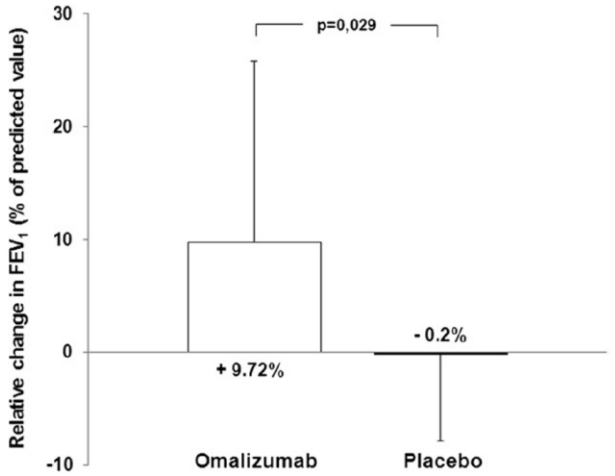
Bousquet J et al Resp Med 2007

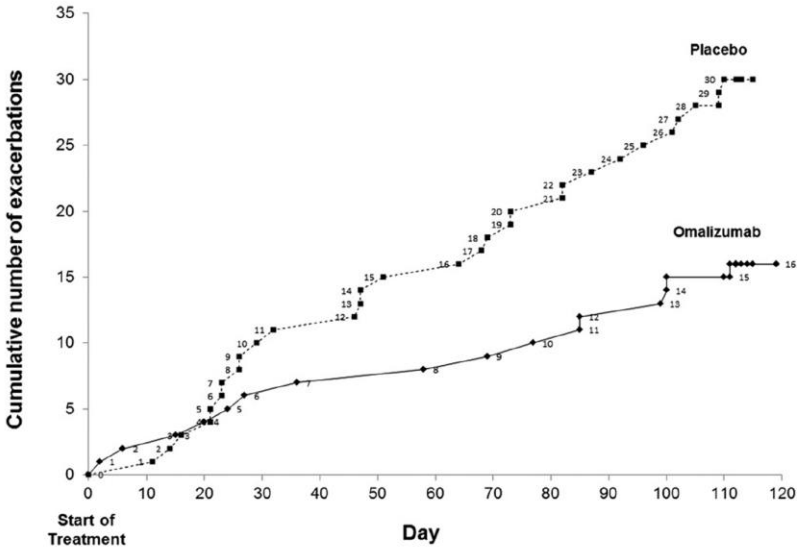
A Proof-of-Concept, Randomized, Controlled Trial of Omalizumab in Patients With Severe, Difficult-to-Control, Nonatopic Asthma

Gilles Garcia, MD, PhD; Antoine Magnan, MD, PhD; Raphaël Chiron, MD; Cécile Contin-Bordes, MD, PhD; Patrick Berger, MD, PhD; Camille Taillé, MD, PhD; Gilles Devouassoux, MD, PhD; Frédéric de Blay, MD, PhD; Louis-Jean Couderc, MD, PhD; Alain Didier, MD, PhD; Dermot S. O'Callaghan, MD; Pierre-Olivier Girodet, MD, PhD; Isabelle Bourdeix, PhD; Vincent Le Gros, MD; and Marc Humbert, MD, PhD

Characteristics	Placebo (n = 21)	Omalizumab (n = 20)
Age, y	54.6 ± 12.8	55.0 ± 9.7
Female patients	13 (61.9)	13 (65.0)
Male patients	8 (38.1)	7 (35.0)
Weight, kg	70.8 ± 11.8	78.5 ± 15.1
BMI	25.7 ± 3.4	29.7 ± 5.8
IgE, IU/mL	160 ± 142	153 ± 96
IgE level < 100 IU/mL	10 (47.6)	8 (40)
FEV_1 absolute value, L	2.07 ± 0.90	1.67 ± 0.80
FEV_1 % predicted	71.3 ± 21.3%	61.2 ± 17.1%
Inhaled corticosteroids, μg/d	2,667 ± 1,111	2,710 ± 1,230
Long-acting β_2-agonists	21 (100)	20 (100)
Oral steroids	7 (33.3)	8 (40.0)
Daily oral steroids dose, mg/d	23.0 ± 13.0	35.9 ± 53.4
Patients using leukotriene modifiers	11 (52.4)	8 (40.0)
Patients using theophylline	1 (4.8)	3 (15.0)
ACQ score	2.2 ± 1.2	2.2 ± 0.98
FENO, ppb	58.8 ± 35.4	32.5 ± 19.2
Asthma exacerbations during the previous year	5.48 ± 4.60	5.05 ± 3.10
Never smokers	15 (71.4)	15 (75.0)
Patients with aspirin- or other NSAID-related asthma	5 (23.8)	4 (20.0)

Data given as mean ± SD or No. (%). ACQ = Asthma Control Questionnaire; FENO = fraction of exhaled nitric oxide; NSAID = nonsteroidal antiinflammatory drug; ppb = parts per billion.

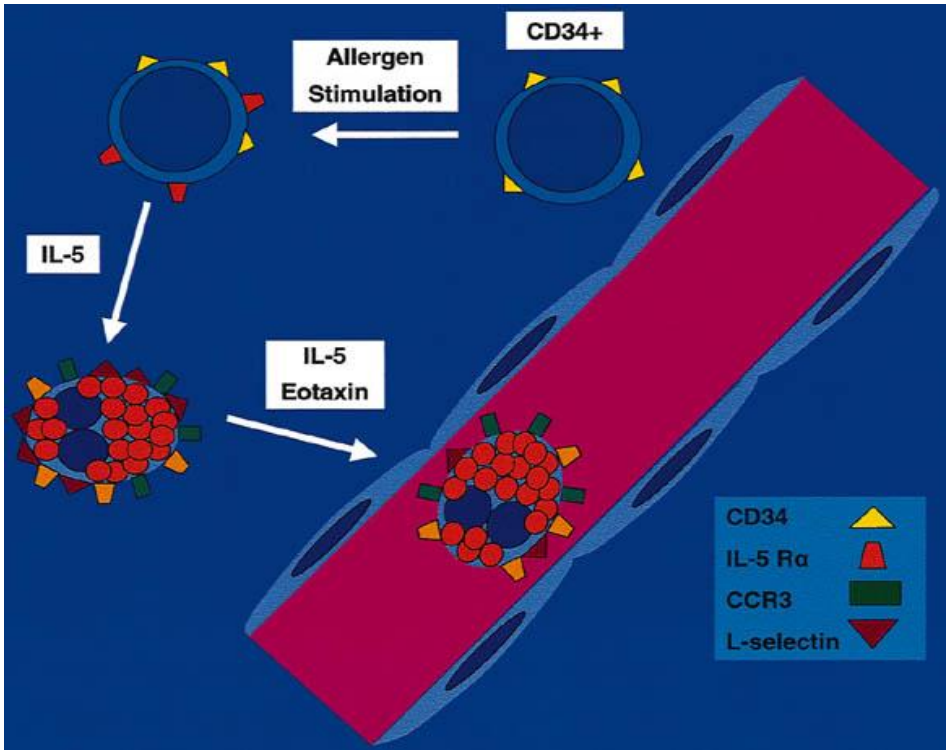


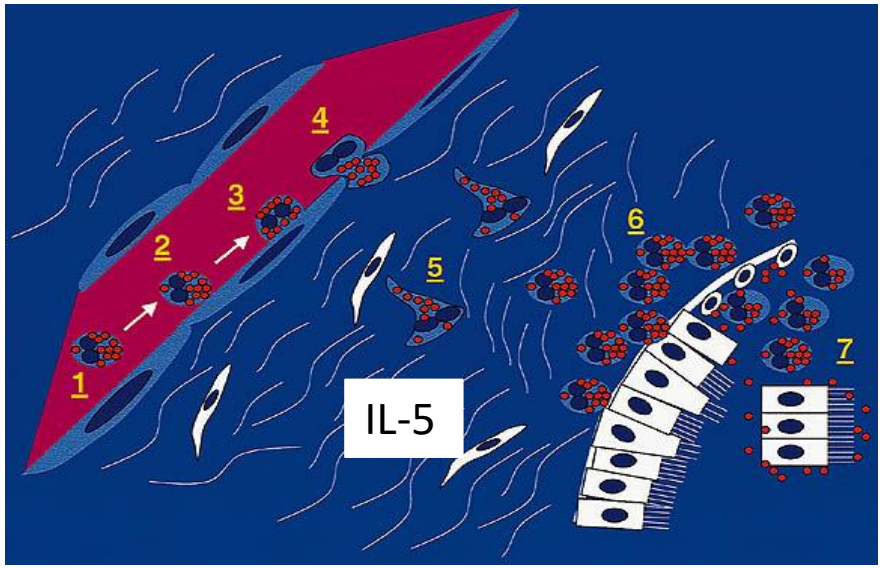


Garcia et al Chest 2013

The paradigmatic history of anti-IL5 as a strong case for the utility of precision medicine in asthma

Cytokine network governing eosinophilia



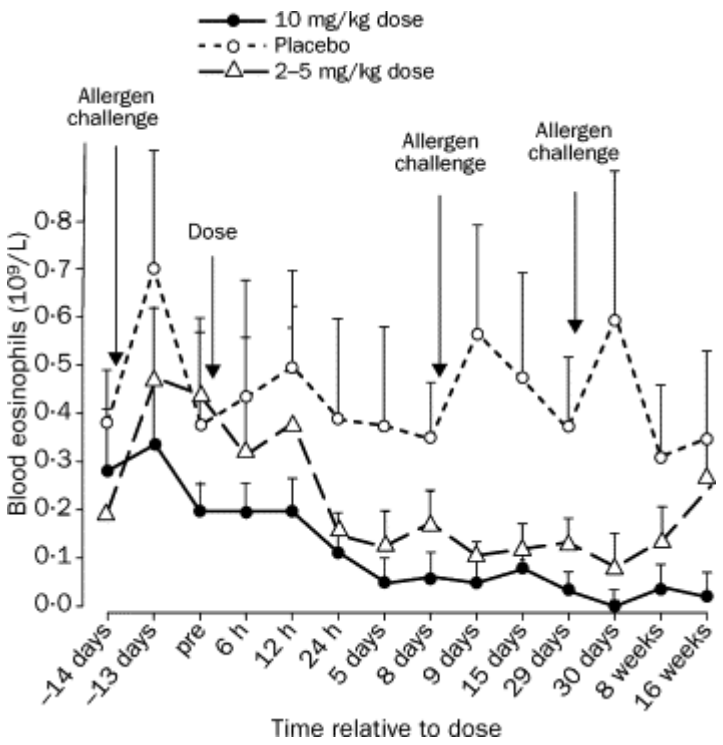


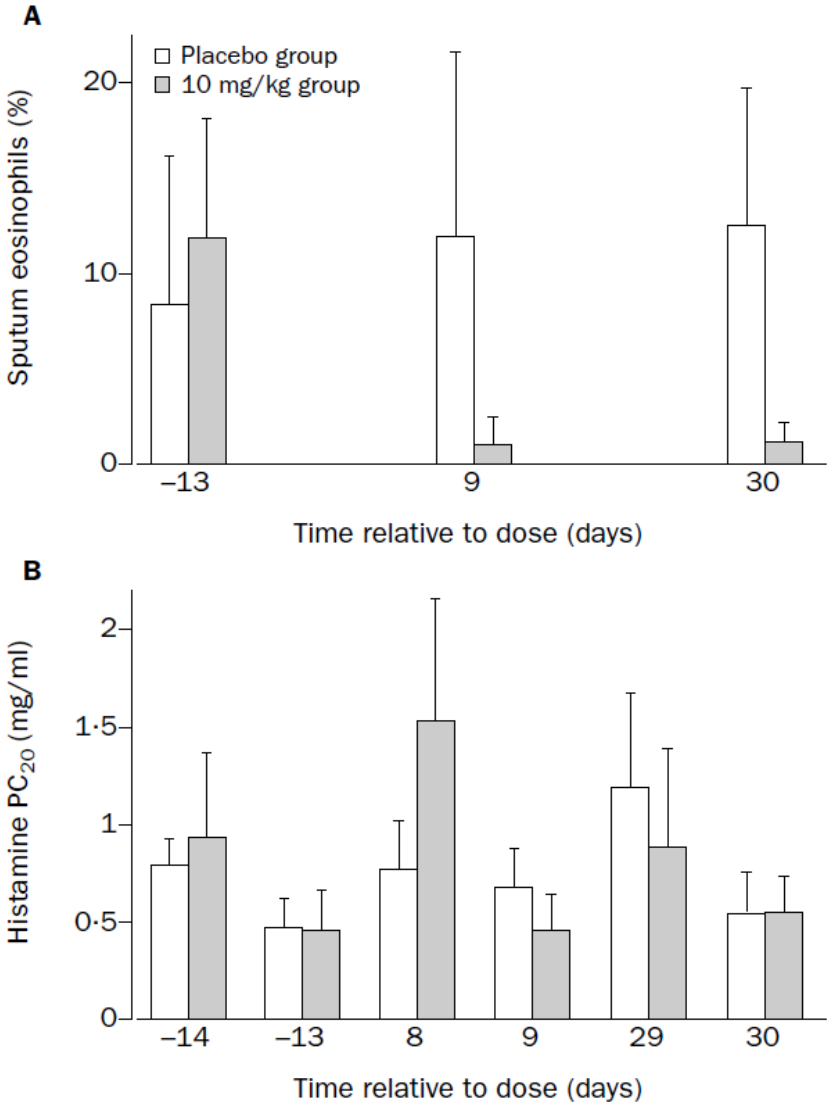
Bone marrow differentiation

Tissue survival

Gleich J et al JACI 2000

Failure of anti-IL-5 to prevent acute and late phase reaction after bronchial allergenic challenge

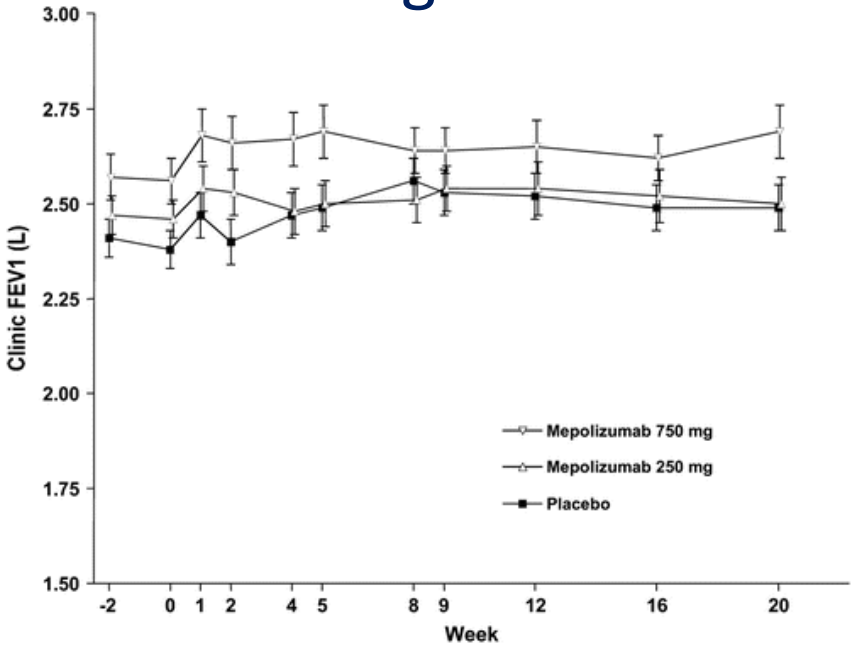


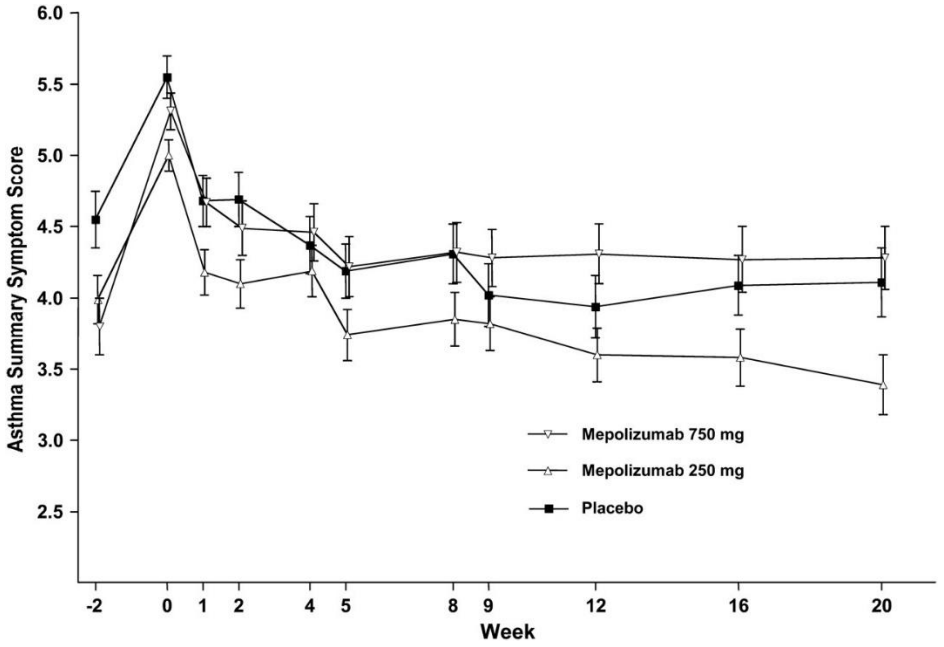


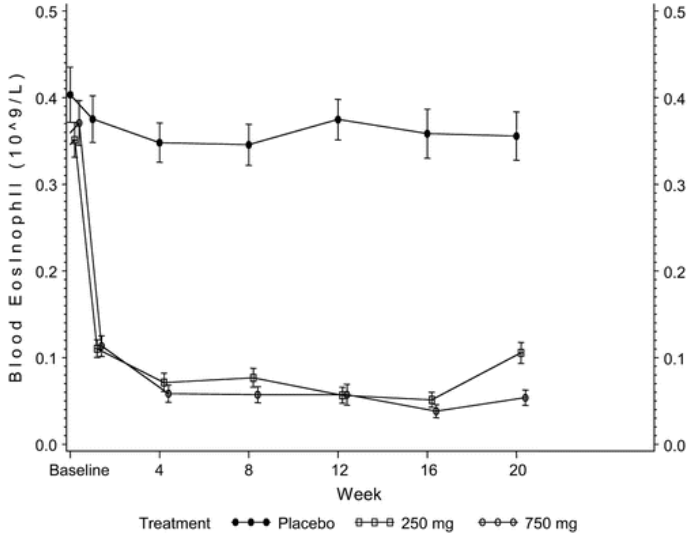
No effect on acute and late phase reaction!

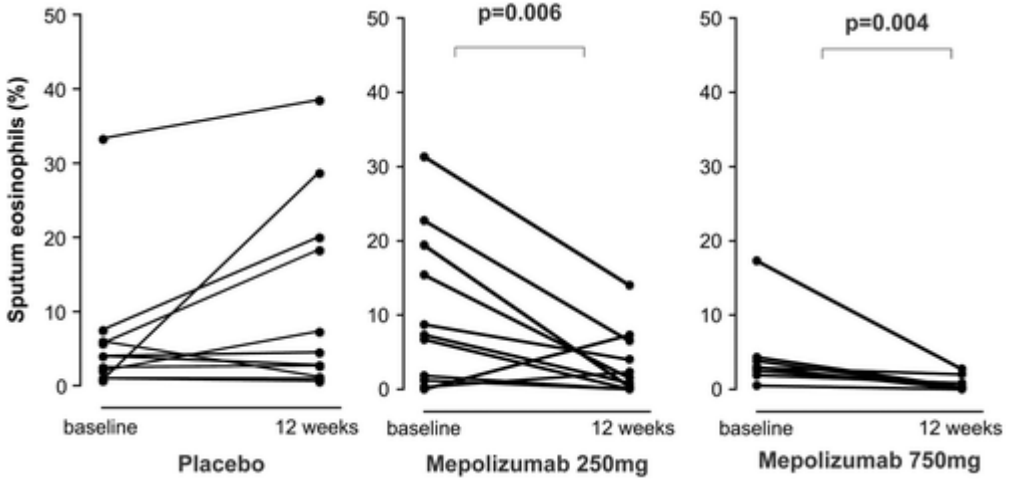
Leckie M et al Lancet 2000

Failure of anti-IL-5 mepolizumab to improve symptoms and lung function in severe non selected asthmatics









Flood Page P et al Am J Resp Crit Care Med 2007

Anti-IL-5-Mepolizumab reduces exacerbation in eosinophilic refractory asthma

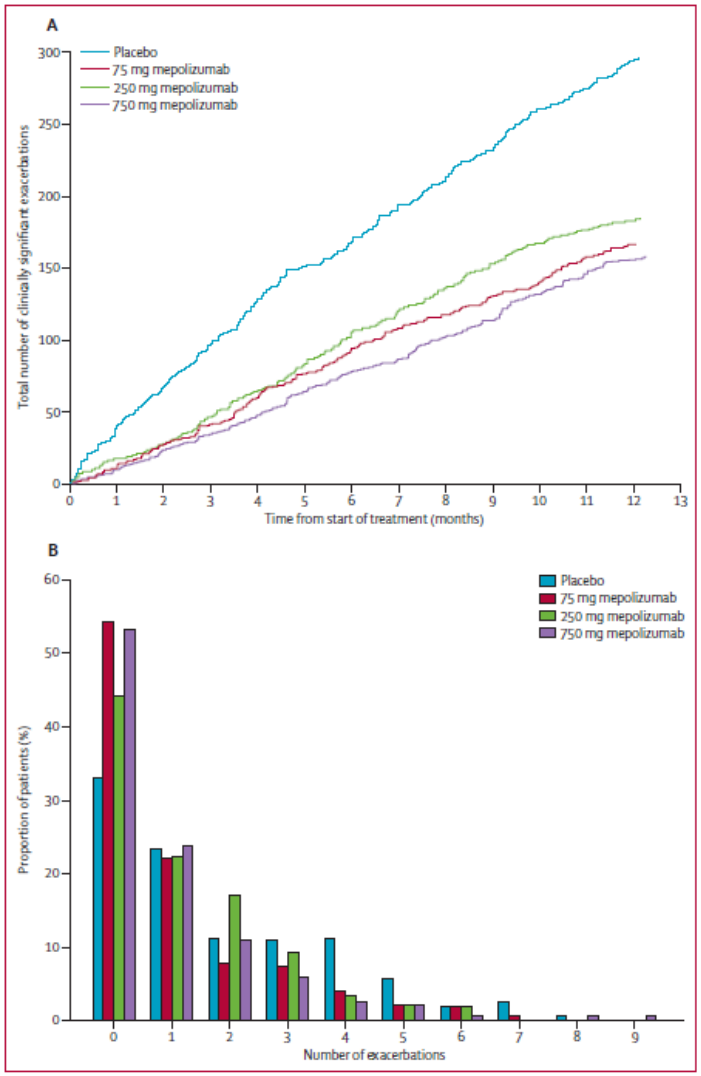
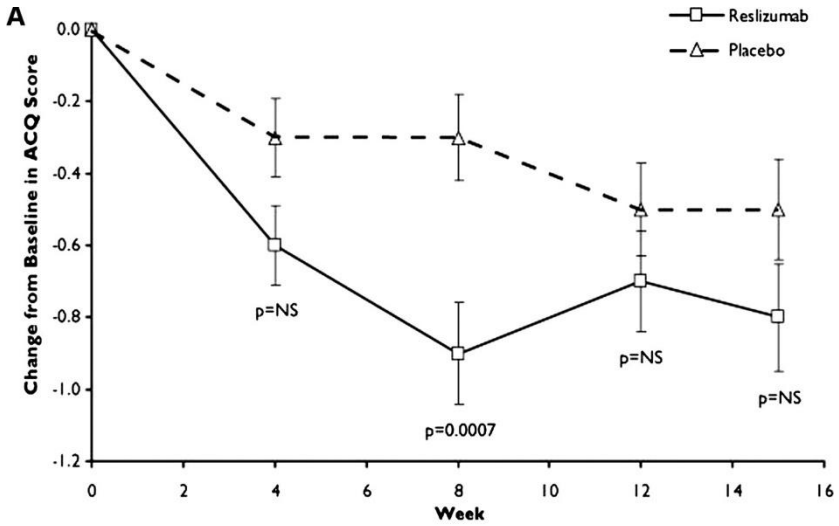


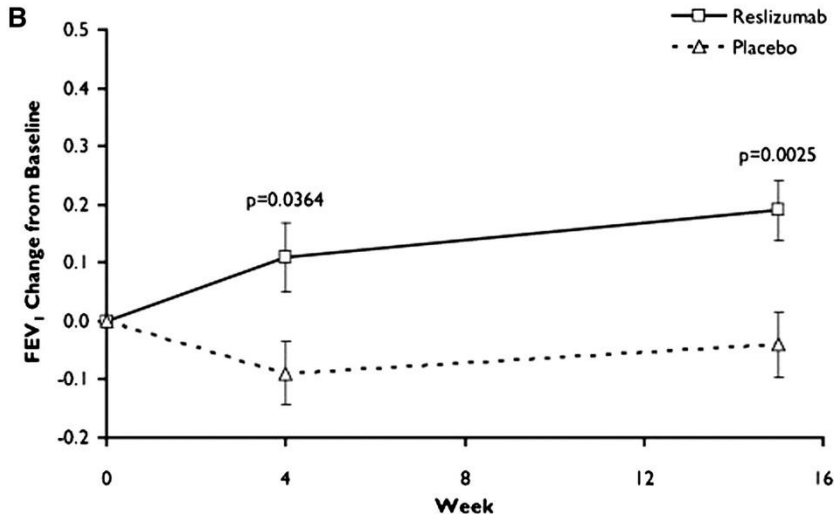
Figure 2: Number of exacerbations in each treatment group
(A) Cumulative number of exacerbations with time and (B) distribution of number of exacerbations.

- Severe/refractory asthma
- Two exacerbations in the previous year requiring systemic corticoids
- Eosinophilic inflammation
  - FENO > 50 ppb
  - Sputum eos > 3%
  - Blood eos > 300/µl

Pavord I et al Lancet 2012

Anti-IL-5 Reslizumab improves asthma control and lung function in severe eosinophilic asthma



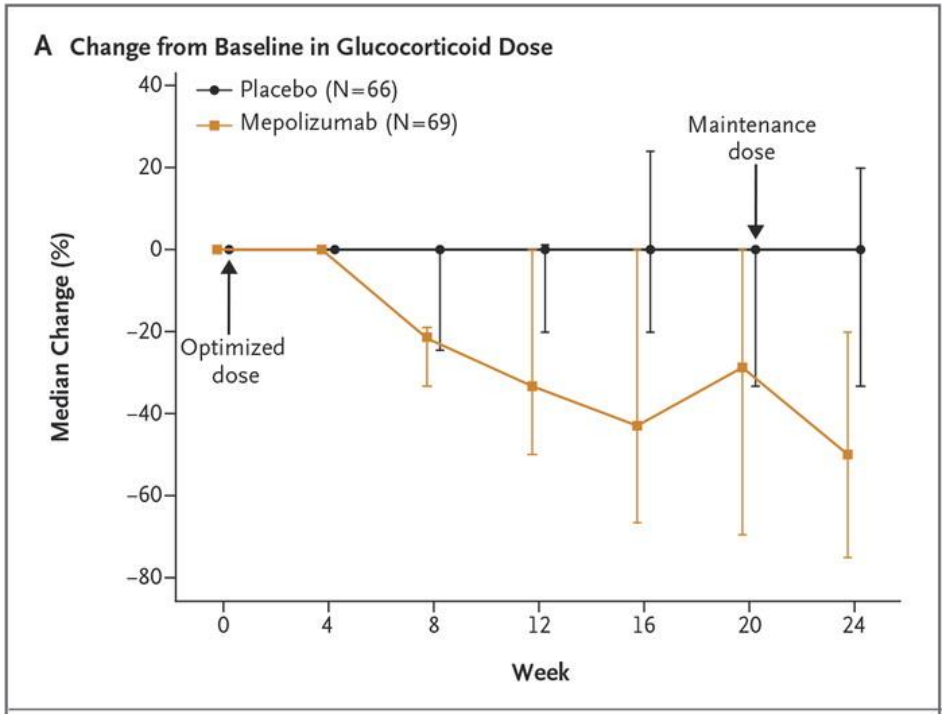


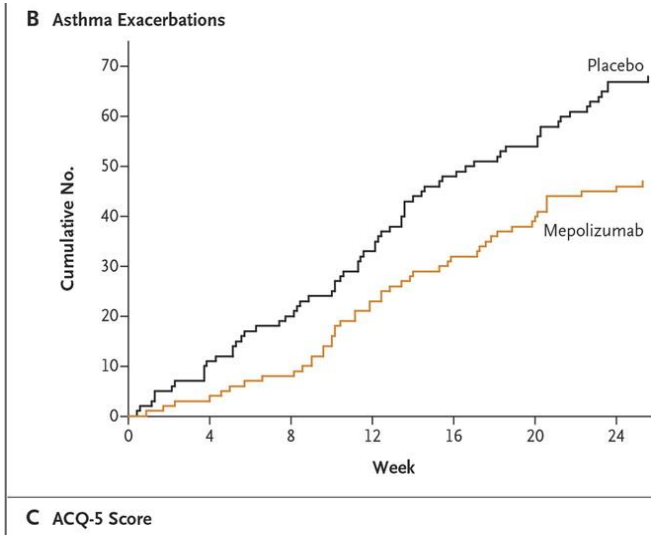
- Severe/refractory asthma
- ACQ >1.5
- Eosinophilic inflammation
  Sputum eos > 3%

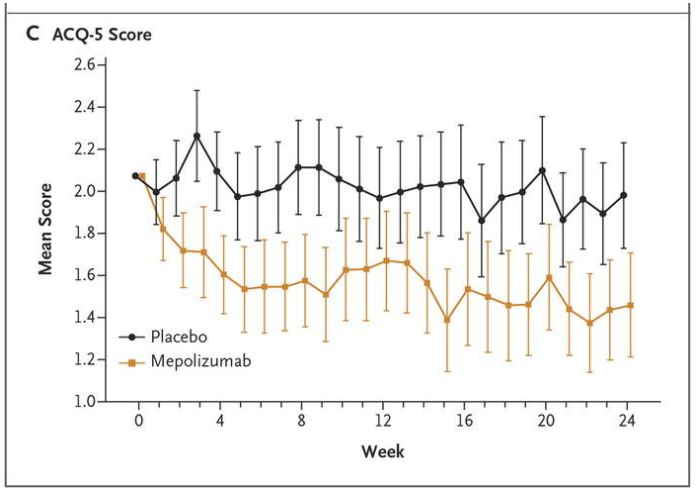
Change in asthma control was particularly clear in those with nasal polyposis and ACQ > 2

Castro M et al Am J Respir Crit Care Med 2011

Anti-IL-5-Mepolizumab improves asthma control in steroid dependent eosinophilic refractory asthma







Bel E et al N Engl J Med 2014

Impact of blood eosinophil counts on mepolizumab effect on exacerbation

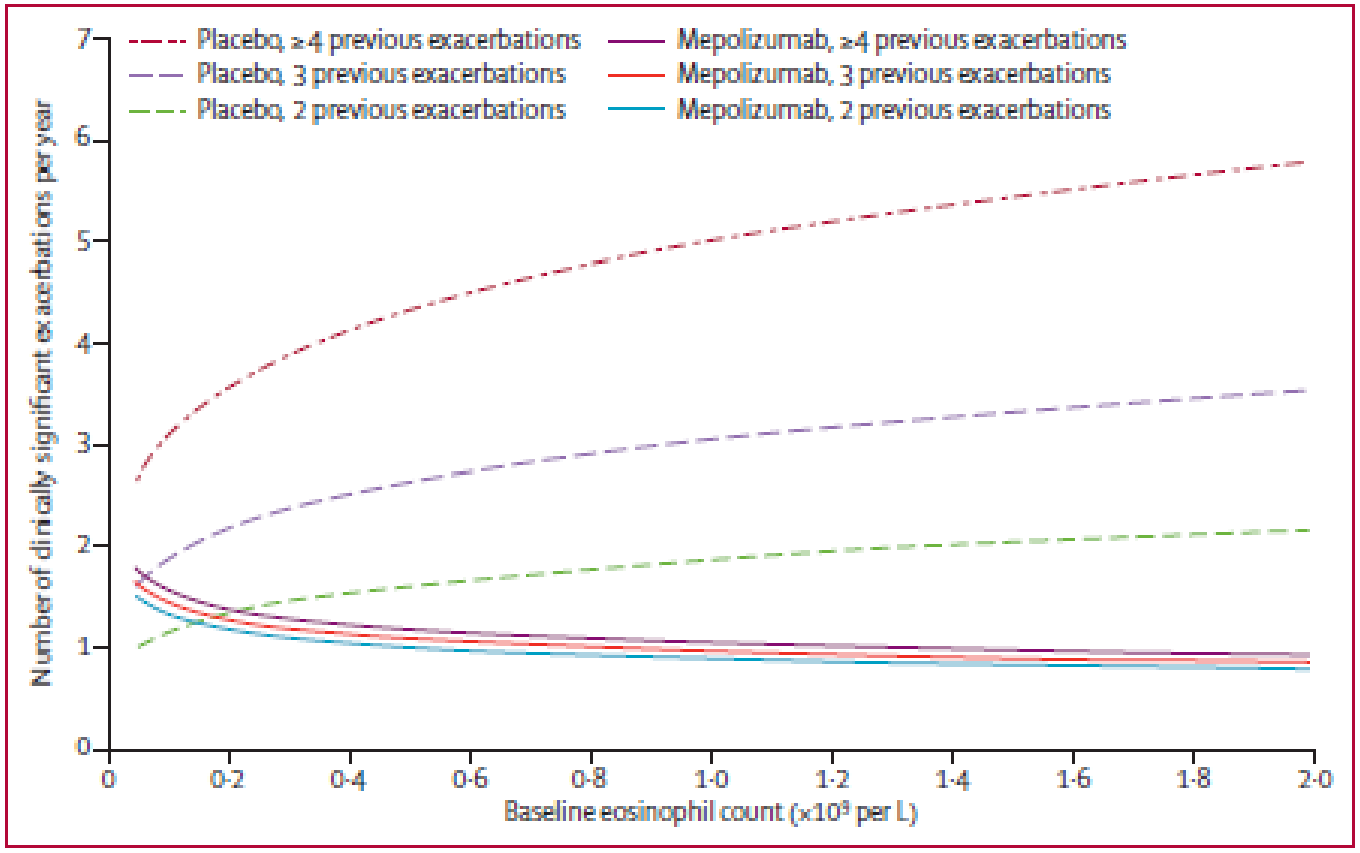
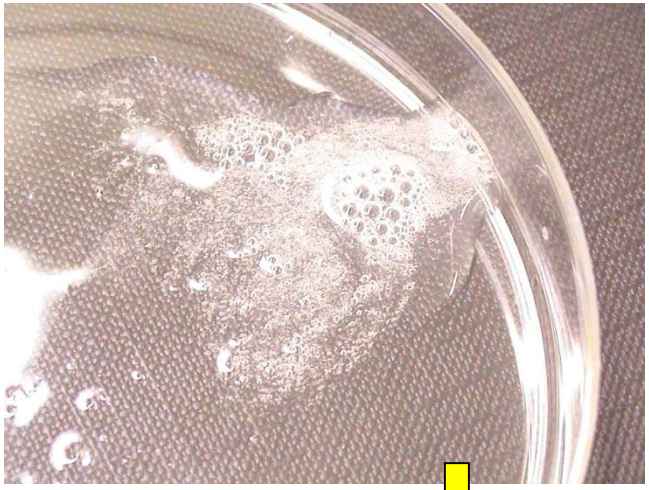


Figure 4: **Predictive modelling of rate of exacerbations**
Done on the basis of blood eosinophil count at baseline, history of exacerbations, and treatment with mepolizumab or placebo.

Pavord I et al Lancet 2012

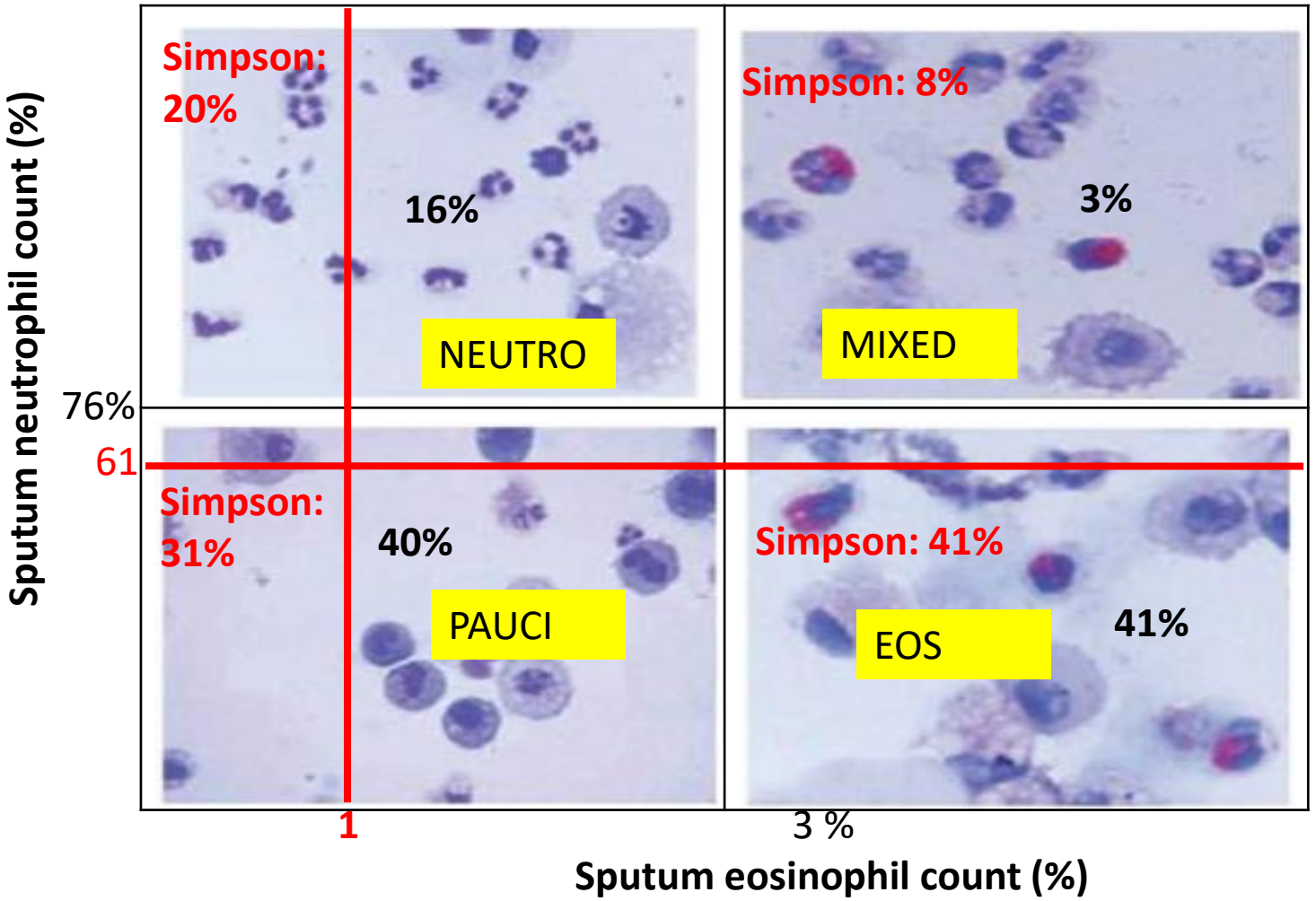
Reassessment of ICS effect based on airway inflammatory phenotype

Induced sputum: from bench to bedside



Bakakos P et al Cur Med Chemestry 2011

Classification of asthma according to inflammatory phenotypes



Simpson J et al Respirol 2006

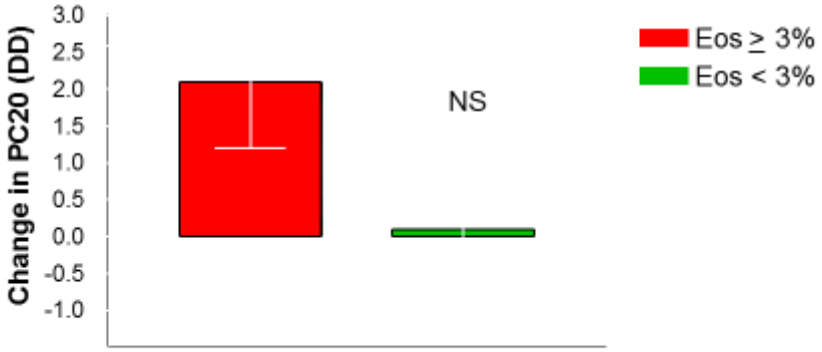
Schleich BMC Pulm Med 2013

Improvement in lung function and quality of life in asthmatics after ICS is related to sputum eosinophilia

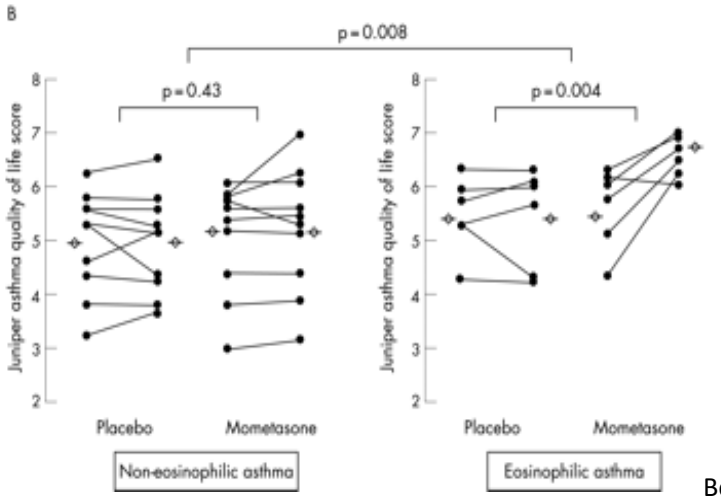
Sputum eosinophilia as a predictive factor for response to inhaled corticoids in asthma

(coourse of inhaled budesonide 800 µg/d for 6 weeks)

p<0.05

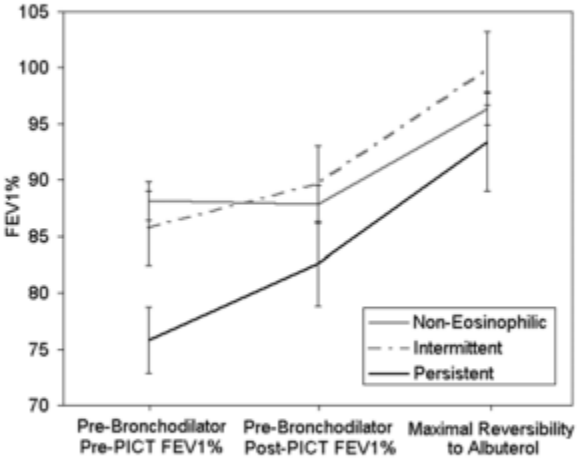


Pavord I et al Lancet 1999



Berry et al Thorax 2007

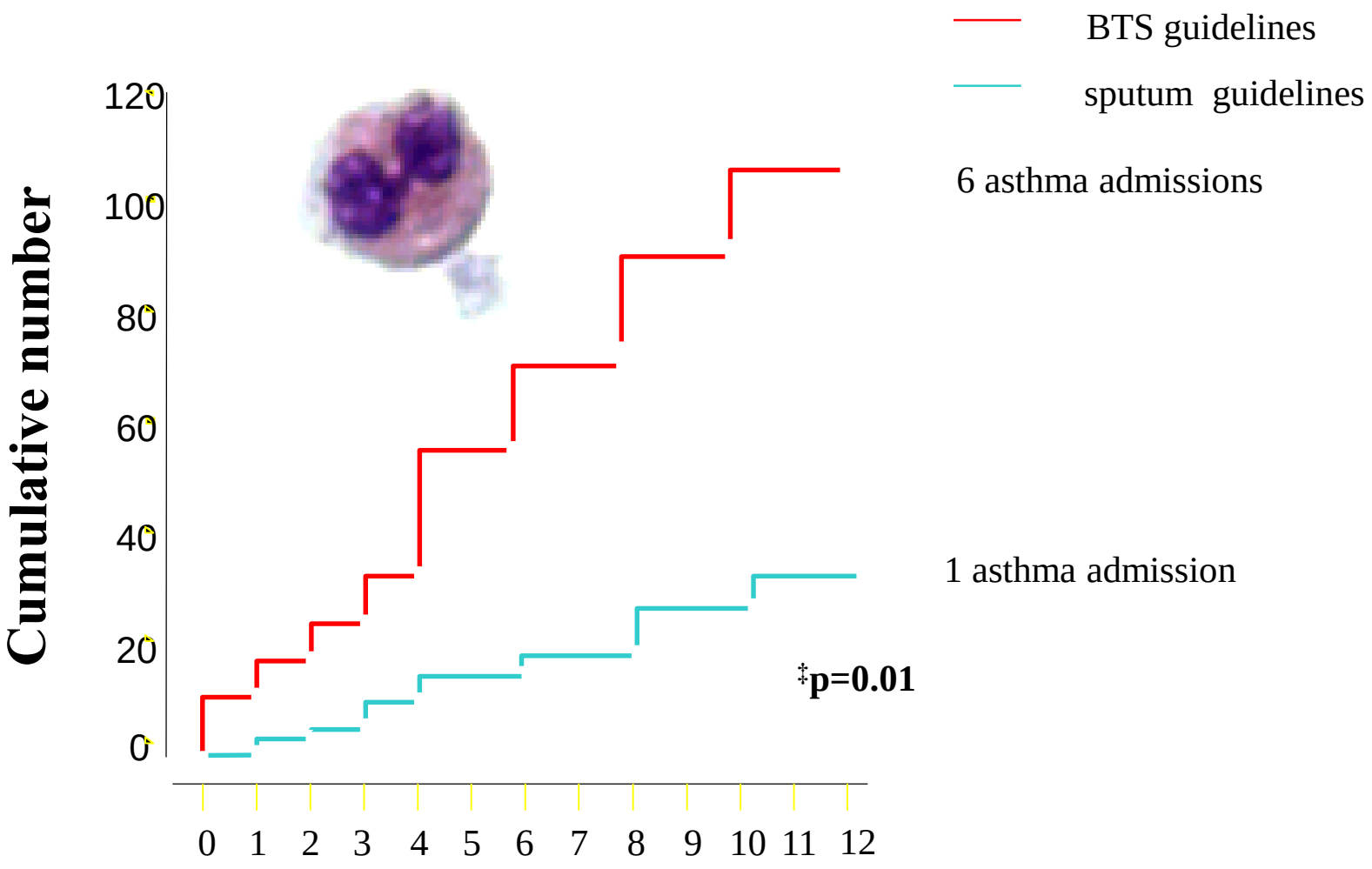
Non eosinophilic asthma (< 2% sputum eosinophils) fails to improve lung function after inhaled corticoids



%Δ in FEV_1 (L)	Non-Eosinophilic	Intermittent	Persistent	p
Pre- to Post-PICT	-0.2%	4.7%	8.6%	0.001
Post-PICT to Max Rev	10.1%	12.1%	13.5%	0.32

K Wong Mc Grath et al AJRCCM 2012

Adjusting ICS to curb sputum eosinophils results in a reduction of exacerbation in moderate to severe asthma



Green R et al Lancet 2002

Effectiveness of ICS in asthmatics in real life

- Retrospective study
- Asthmatic patients:
  - Asthma Clinic of Liege
  - Available sputum and blood cell counts
  - Exclusion criteria:
    - OCS at the time of the visit or during the previous 6 weeks
    - Treatment with omalizumab
    - Treatment with mepolizumab

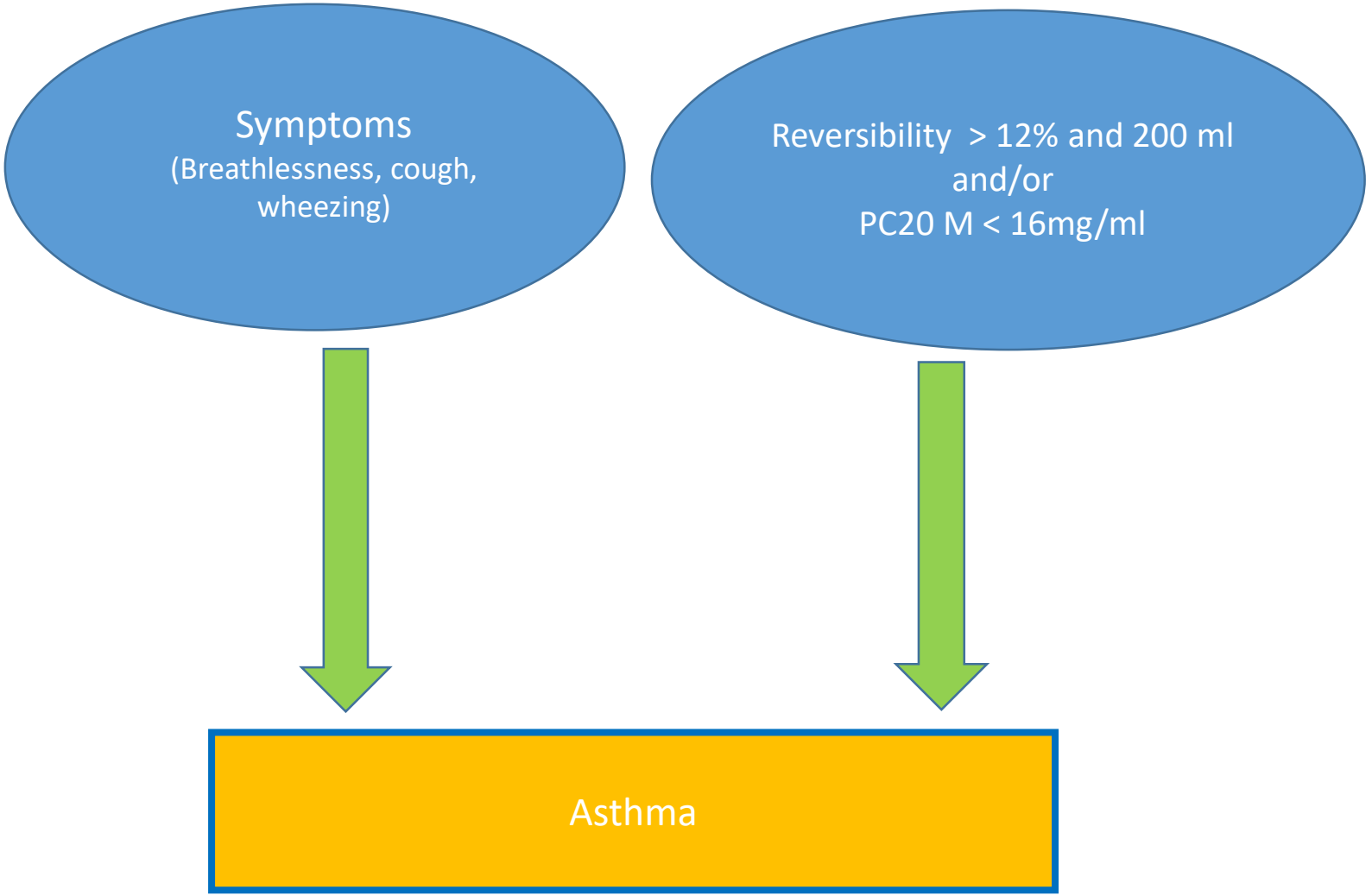
→ 101 patients with an initiation/increased dose of ICS between 2 visits
- 79 eosinophilic asthmatics
- 22 non-eosinophilic asthmatics

→ 60 patients with a cessation/decreased dose of ICS between 2 visits
- 22 eosinophilic asthmatics
- 38 non-eosinophilic asthmatics

- Outcomes:
  - Clinical outcomes
  - Sputum analysis
  - Blood analysis

Demarche S BMJ Open 2017

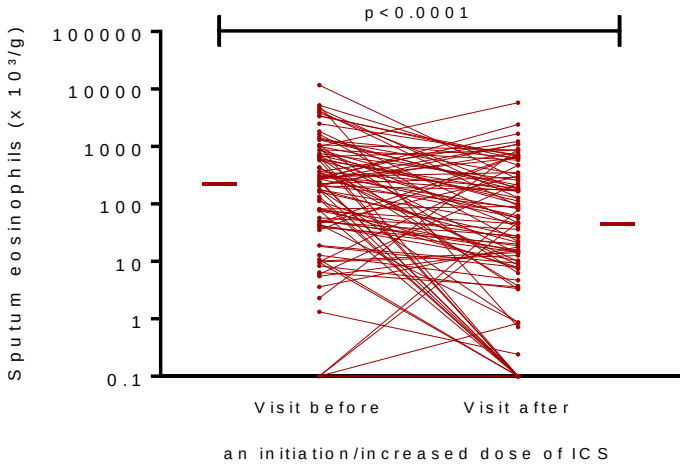
Operational definition of asthma



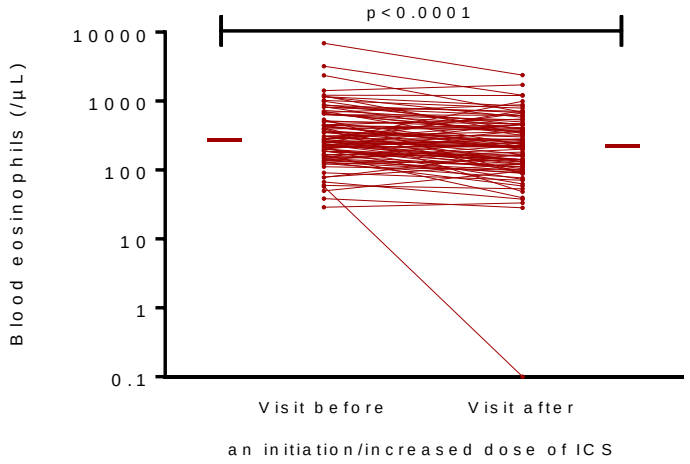
Retrospective study in real life N=224	Patients with an initiation/increasedd ose of ICS between 2 visits N= 101	Patients with a cessation/decreased dose of ICS between 2 visits N=60	Patients with non ICS or stable dose of ICS between 2 visits N=63
Time between 2 visits (years)	1 (0.5-2.6)	1.5 (0.9-2.6)	2 (0.7-3.8)
Women, N (%)	56 (55)	33 (55)	41 (65)
Age (years)	53 (40-63)	51 (37-62)	53 (44-66)
BMI (Kg/m2)	26±5.1	26.4±4.7	26.8±49
Atopy, N (%)	52 (51)	35 (58)	32 (51)
Age of asthma onset (years)	41 (16-57)	31 (8-53)	46 (27-55)
Smoking status NS CS Ex S	 53 (52) 11 (11) 37 (37)	 31 (52) 11 (18 18 (30)	 32 (51) 15 (24) 16 (25)
Variation in ICS dose	800 (400-1200)	900 (500-1200)	0

Effectiveness of increasing the dose of ICS on eosinophilic inflammation in asthmatics in real life

Median fall by 80%



Median fall by 20%



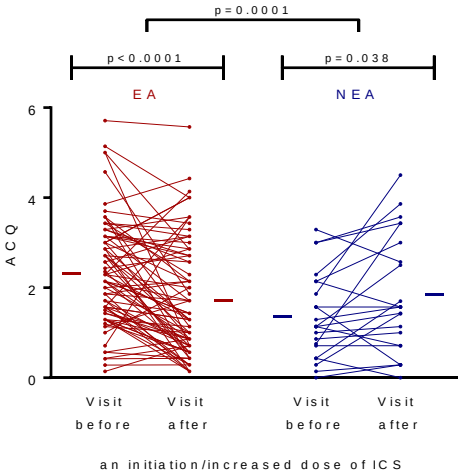
Median

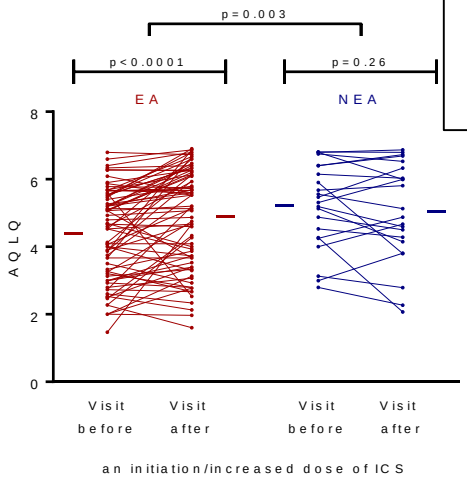
Demarche S et al BMJ open 2017

Sputum eosinophilia as a predictive factor for response to inhaled corticoids in asthma in real life

Median increase in beclomethasone 800µg/d from 400 to 1000µg/d

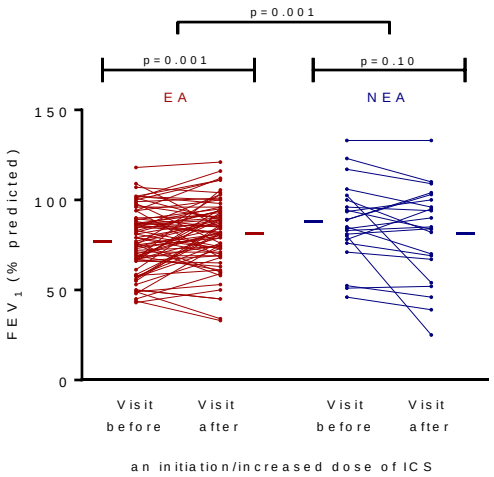
EA: ≥3%
n=79

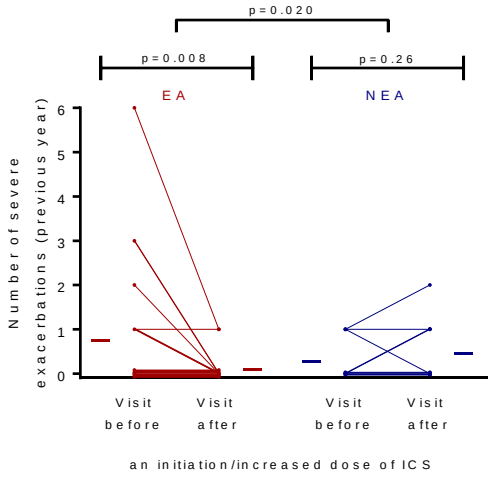




Mean

NEA: < 3%
n=22





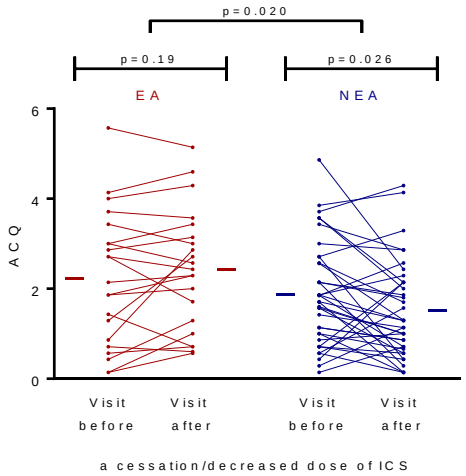
Demarche S et al BMJ open 2017

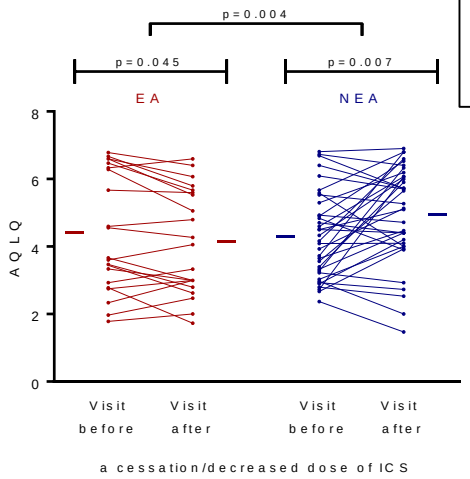
Stepping down inhaled corticoids in asthmatics in real life

Median decrease in beclomethasone 900 µg/d

from 1600 µg/d to 450 µg/d

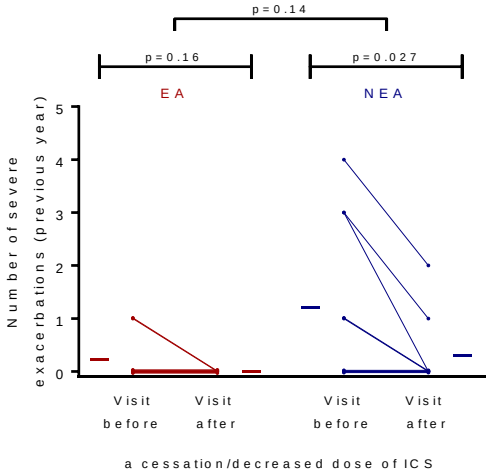
EA: ≥3%
n=22

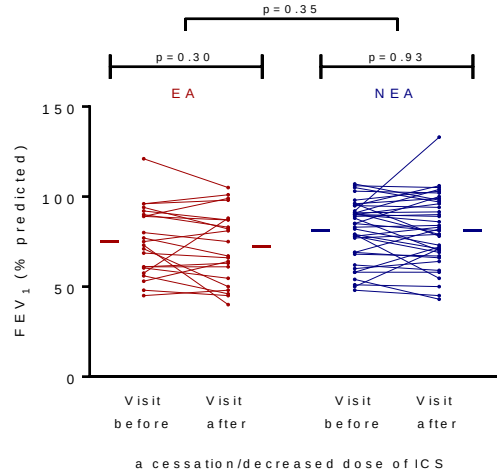




Mean

NEA: < 3%
n=38





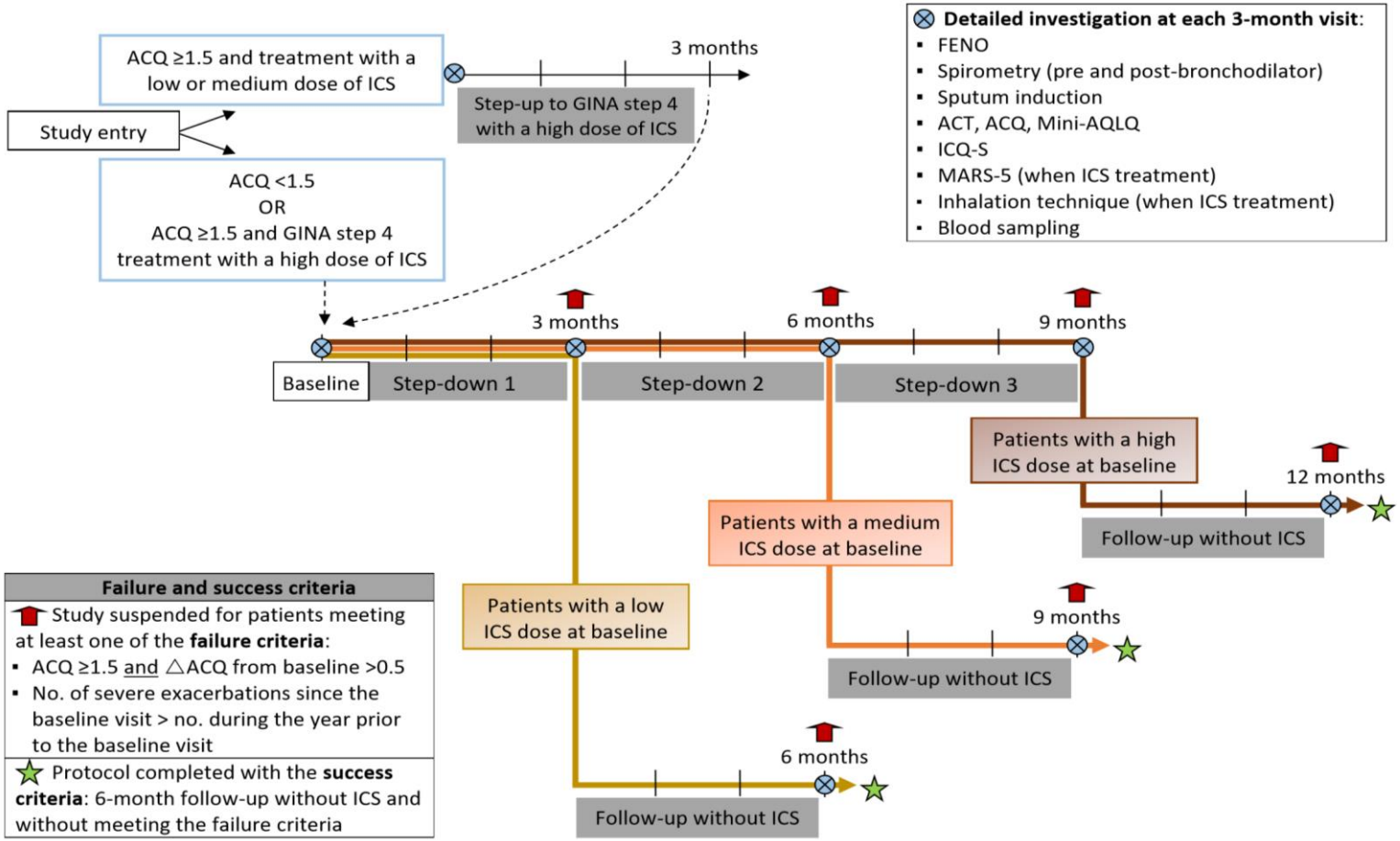
Demarche S et al BMJ open 2017

Stepping down of ICS in non eosinophilic asthma

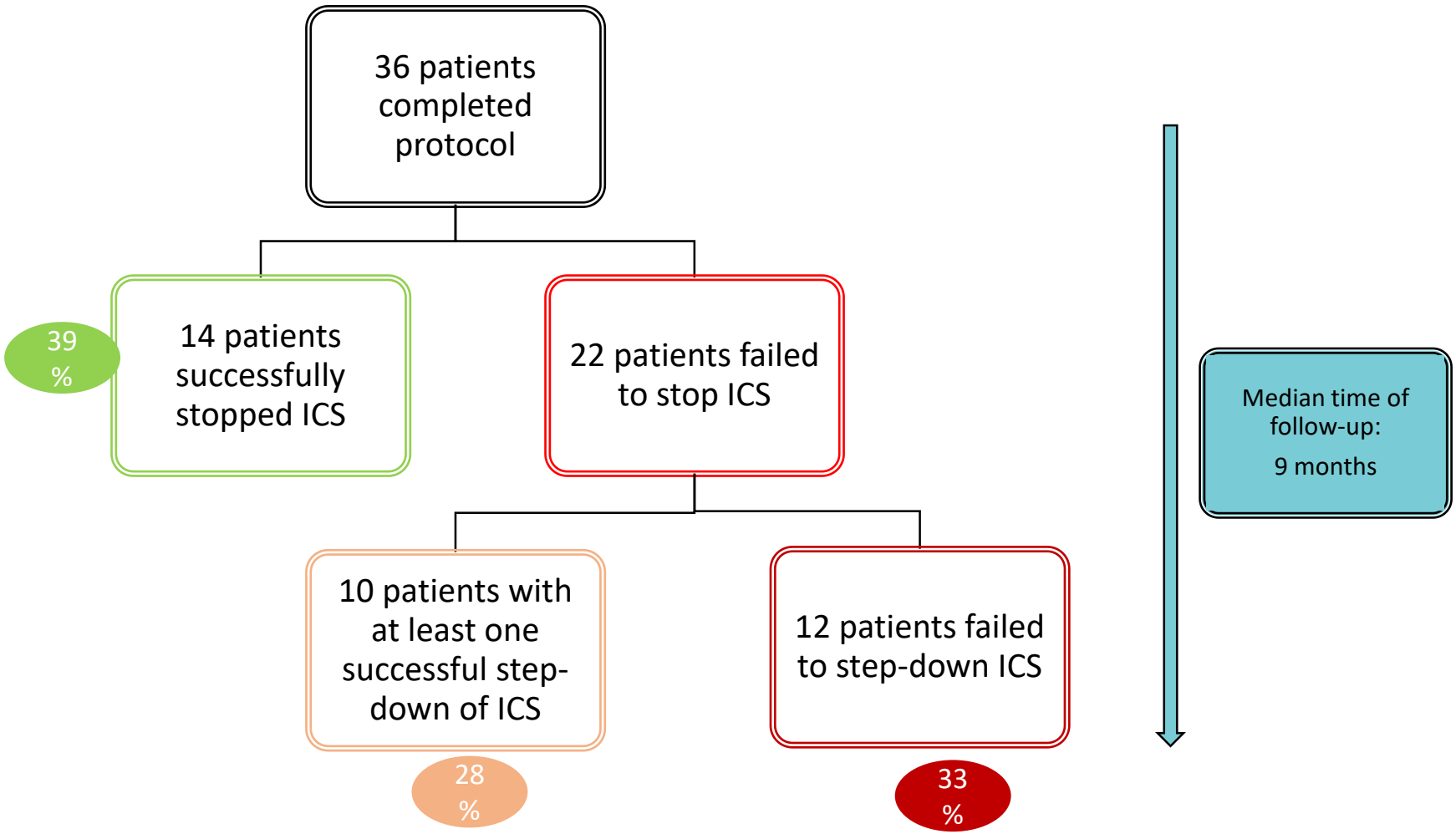
- Prospective longitudinal study
- Aim:
  - To assess the proportion of non-eosinophilic asthmatics in whom ICS may be withdrawn without any clinical degradation.
  - To determine the predictive markers of a failure to stop treatment with ICS.
- Asthmatic patients:
  - Inclusion criteria
    - Asthma Clinic of Liege
    - ≥18 years old
    - Sputum eosinophils <3%
    - Blood eosinophils <400/µL
    - Treated with ICS at the same dose since the previous 3 months
  - Exclusion criteria
    - history of near-fatal asthma requiring a stay in intensive care unit
    - treated with oral corticosteroids (OCS) at screening visit or in the previous 4 weeks
    - treated with omalizumab
    - pregnant women

Demarche S, submitted to Clin Exp Allergy 2017

Study Flow Chart



Reducing ICS is feasible in non eosinophilic asthma

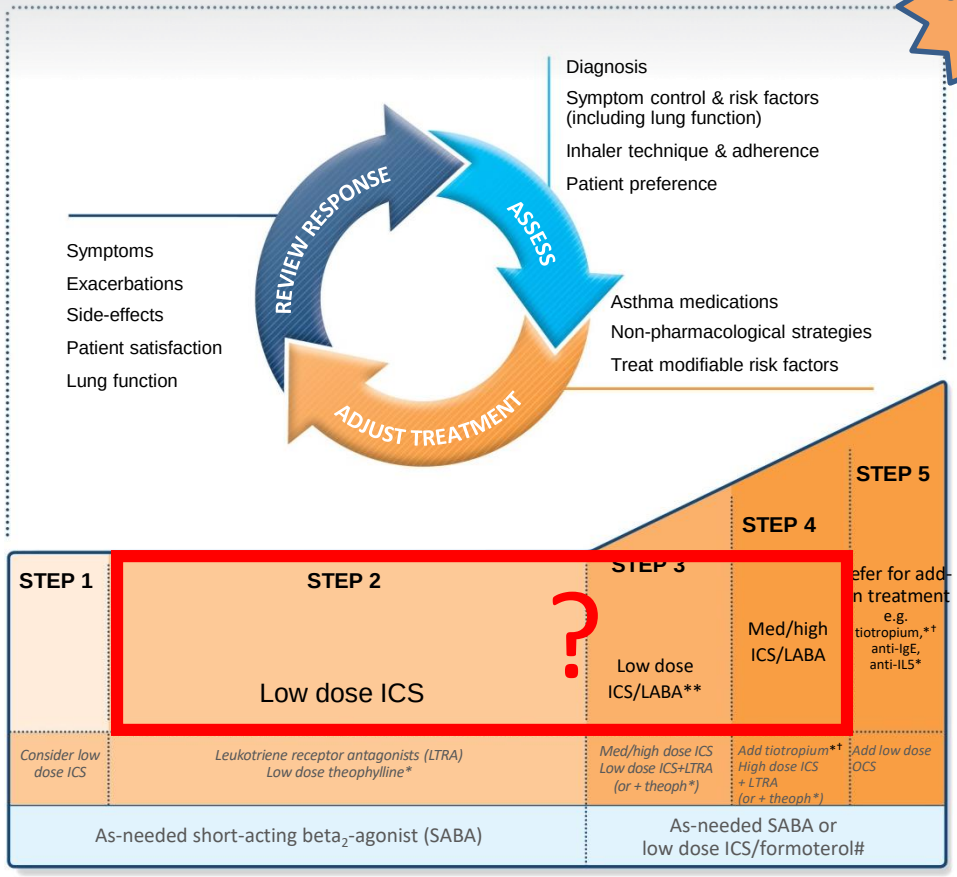


Predicting factor of failure to step down ICS in non eosinophilic asthma

	N	AUC	95% CI	Best threshold	Sensitivity	Specificity	PPV	NPV
Predictors at baseline								
Age, years	36	0.77	0.62-0.93	**>59**	59%	93%	93%	59%
Blood eosinophils, /µL	36	0.77	0.61-0.93	**>110**	68%	86%	88%	63%
Predictors after the first step-down								
ACQ	35	0.79	0.61-0.96	>1.5	86%	71%	82%	77%
ACT	35	0.73	0.54-0.92	<20.5	86%	64%	78%	75%
Mini-AQLQ	35	0.70	0.51-0.89	<4.8	71%	64%	75%	60%
Sputum eosinophils, %	34	0.73	0.56-0.90	>0.9%	65%	86%	87%	63%
Blood eosinophils, /µL	35	0.85	0.72-0.99	>141	81%	86%	89%	75%

Stepwise approach to control asthma symptoms and reduce risk

UPDATED 2017



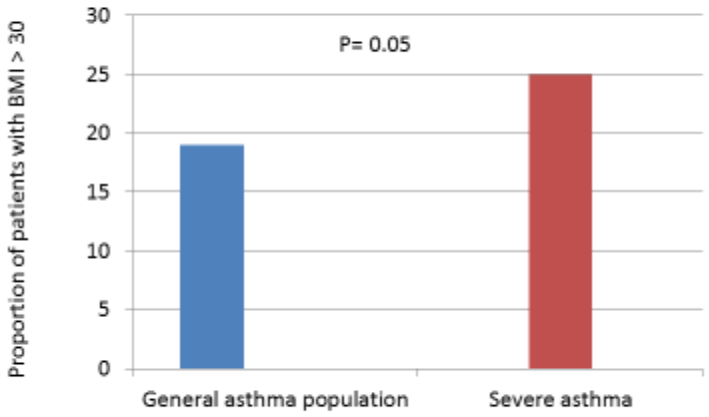
REMEMBER TO...

- Provide guided self-management education (self-monitoring + written action plan + regular review)
- Treat modifiable risk factors and comorbidities, e.g. smoking, obesity, anxiety
- Advise about non-pharmacological therapies and strategies, e.g. physical activity, weight loss, avoidance of sensitizers where appropriate
- Consider stepping up if … uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first
- Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is >70% predicted
- Consider stepping down if … symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised.

Other treatable traits beyond immuno/inflammatory features

Obesity is highly prevalent in severe asthma

Obesity increases the risk of severe asthma

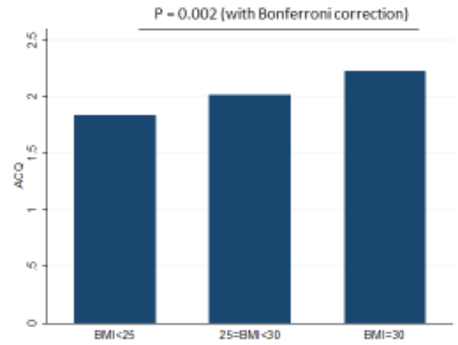


N=833; CHU Liege asthma clinic

N=350; Belgian severe asthma registry (F Schleich, Respir Med 2014)

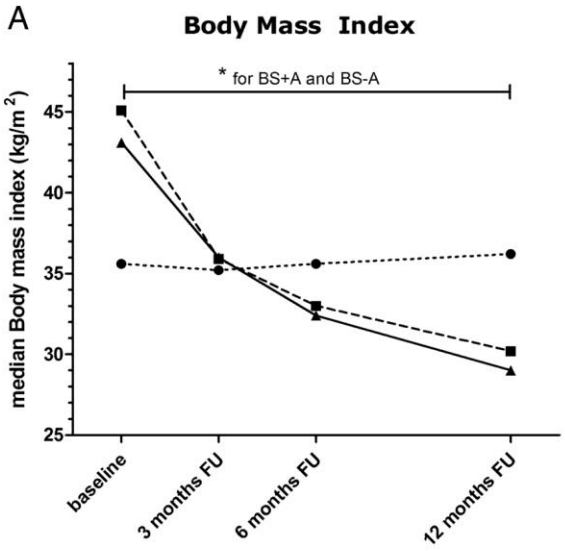
Obesity is associated with poor asthma control

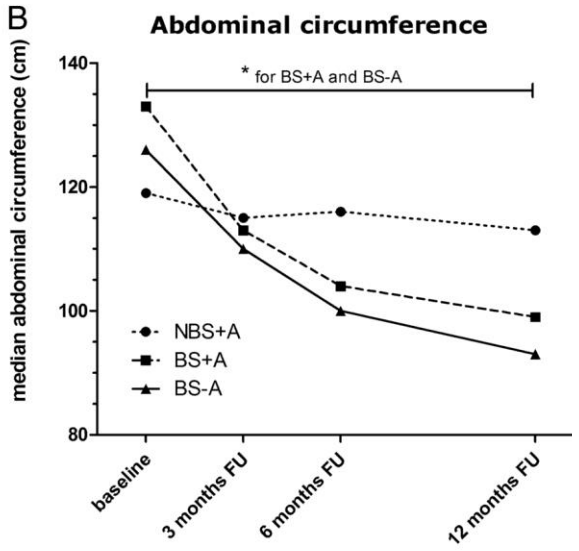
	BMI<25	25≤BMI<30	BMI≥30	ANOVA
N = 854	358	293	173	-
ACQ	1.8 ± 1.2	2.0 ± 1.2	2.2 ± 1.2	0.002

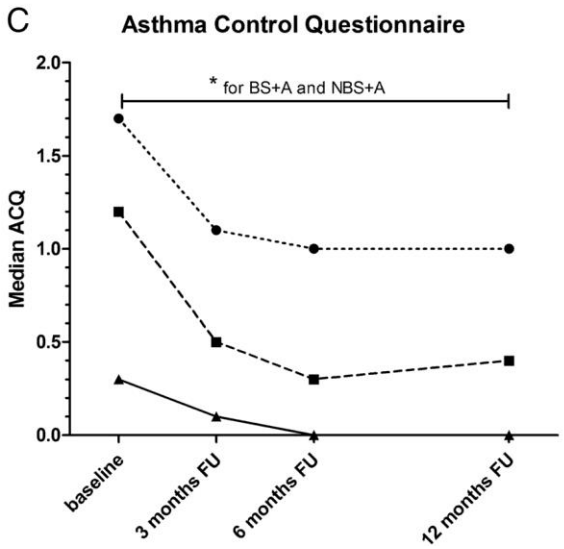


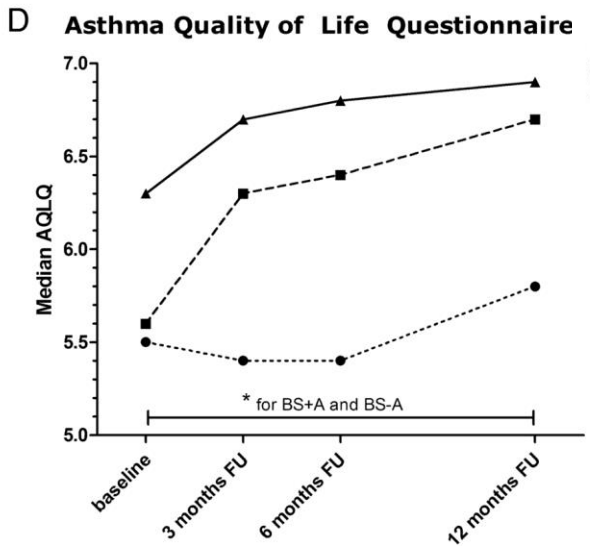
Data CHU Liege Asthma Clinic

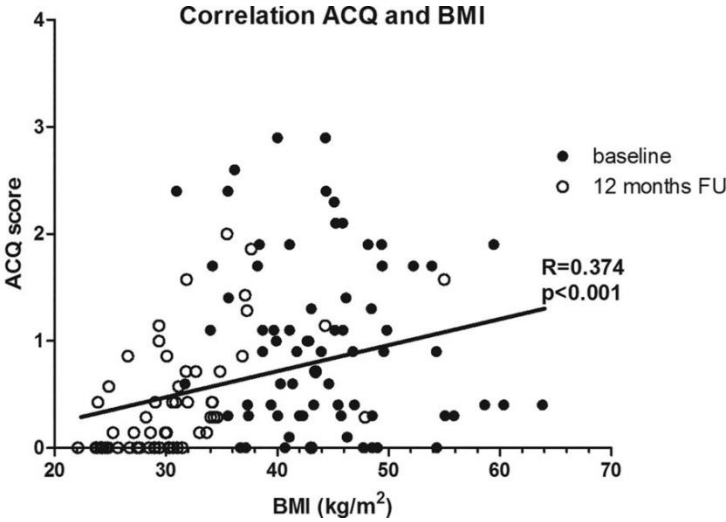
Effect of bariatric surgery on asthma control











Van Huisstede A et al Thorax 2015

OSA in asthma is related to poor asthma control

- Population drawn from asthma clinic (n=472)
  - High risk OSA by validated questionnaire (SA-SDQ)
  - Lack of Asthma control by ACQ > 1.5
- After correcting for obesity, presence of GERD, nasal disease OSA was still significant
  - Uncontrolled asthma OR = 3.01 for having OSA
- Patients difficult to control asthma should be screened for OSA

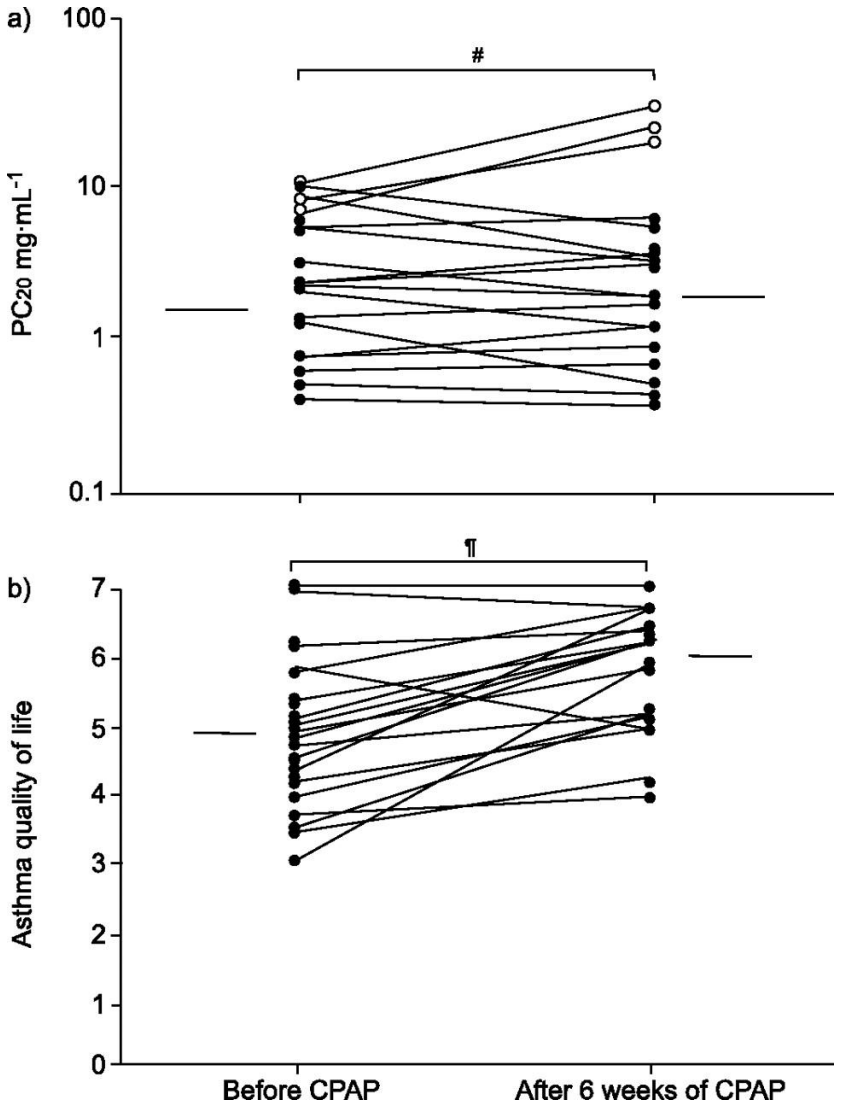
Teodorescu M et al Chest 2010

Impact of CPAP on asthmatic patients with OSA
demonstrated by PSG AHI > 15

TABLE 2 Functional and clinical characteristics of the subjects at baseline (pre-) and after 6 weeks of treatment (post-) with continuous positive airway pressure (CPAP)

	Pre-CPAP	Post-CPAP
FEV_1 % pred	82.2±13.6	80.4±13.6
FEV_1/FVC %	77.3±8.3	76.3±10.1
PC_{20} mg·mL^{-1}	2.2 (1.3–3.5)	2.5 (1.4–4.5)
AHI	48.1±23.6	2.6±2.5***
QOLAs	5.0±1.2	5.8±0.9***
QOLAp	4.1±1.4	6.0±1.0***

Data are presented as mean±SD or geometric means (95% confidence interval), *i.e.* average of three individual geometric means before and after CPAP. FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; PC_{20}: provocative methacholine concentration causing a 20% fall in FEV_1; AHI: apnoea/hypopnoea index; QOLAs: quality of life specific to asthma; QOLAp: quality of life specific to obstructive sleep apnoea. ***: $p \leq 0.001$.



Lafond C et al Eur Respir J 2007

Take home messages

- Targeting moderately high IgE and high blood eosinophils with anti-IgE and anti-IL5 respectively proves to be efficient in reducing asthma exacerbation and improving asthma control

- The magnitude of the clinical response to anti-IL-5 is proportional to blood eosinophil counts

- Assessing airway eosinophilia may allow to better target the asthmatics responsive to and in need of ICS. Precision medicine is not only for stepping up treatment but also for stepping down when appropriate.

- Comorbid condition such as obesity or SAS are also treatable traits worth being considered in severe asthma

Current Medicinal Chemistry, 2011, *18*, 1415-1422

Induced Sputum in Asthma: From Bench to Bedside

P. Bakakos*[,1], F. Schleich[2], M. Alchanatis[1] and R. Louis[2]

[1]*1st Respiratory Medicine Department, University of Athens, Medical School, Athens, Greece*

[2]*Department of Pneumology CHU Liege, GIGA I³ research group, University of Liege, Belgium*

Abstract: During recent years there has been a growing interest in using non-invasive biomarkers to understand and monitor the airway inflammation in subjects with respiratory tract disorders and mainly asthma and chronic obstructive pulmonary disease (COPD). Sputum induction is generally a well-tolerated and safe procedure and a European Respiratory Society Task Force has published a comprehensive review on sputum methodology. Induced sputum cell count and, to a lesser extent, mediator measurements have been particularly well validated. In asthma, the sputum and the cell culture supernatant can be used for the measurement of a variety of soluble mediators, including eosinophil-derived proteins, nitric oxide (NO) derivatives, cytokines and remodelling-associated proteins. Sputum eosinophilia (> 3%) is a classic feature of asthma although half of the patients seems to be non eosinophilic. Measuring the percentage of sputum eosinophils has proved to be useful in the clinical arena in helping to predict short term response to inhaled corticosteroids (ICS) and tailor the dose of ICS in the severe patients but there is scope for the application of other induced sputum markers potentially useful in clinical practice. The widespread application of induced sputum in asthma across the spectrum of disease severity has given insight into the relationship between airway function and airway inflammation, proposed new disease phenotypes and defined which of these phenotypes respond to current therapy, and perhaps most importantly provided an additional tool to guide the clinical management of asthmatic patients. To date sputum induction is the only non-invasive measure of airway inflammation that has a clearly proven role in asthma management.

Keywords: Induced sputum, asthma, biomarkers, clinical applications.

INTRODUCTION

During recent years there has been a growing interest in using non-invasive biomarkers to understand and monitor the airway inflammation in subjects with respiratory tract disorders. Currently available data seem to underline the robustness of induced sputum as a method for assessing airway inflammation in diseases such as asthma and chronic obstructive pulmonary disease (COPD).

Induced sputum samples the central airways and its cellular components (e.g. eosinophils and neutrophils), protein components (e.g. mucins and cytokines) and microbiological components (e.g. viruses and bacteria) can be used as markers of disease severity, exacerbation or progression [1].

Induced sputum cell count and, to a lesser extent, mediator measurements have been particularly well validated [2]. Normal ranges for sputum cell counts from a relatively large adult population have been published [3-5].

Sputum induction is generally a well-tolerated and safe procedure even in patients with severe obstructive airway diseases assessed either in stable condition or during an exacerbation. However, some differences in methodology still exist between various research groups. An important question, therefore, is whether those differences in methodology influence the validity and reliability of induced sputum in the assessment of airway inflammation.

The widespread application of induced sputum in asthma, and across the spectrum of disease severity has given an insight into the relationship between airway function and airway inflammation, proposed new disease phenotypes and defined which of these phenotypes respond to current therapy, and perhaps most importantly provided an additional tool to guide the clinical management of asthmatic patients [6].

The aim is to identify through non-invasive or minimally invasive methods of assessment of airway inflammation the future risk of poor asthma control or exacerbations. Although induced sputum eosinophils and exhaled nitric oxide are the most widely investigated candidates for use in the clinical arena, there is scope for a great deal of improvement in their application and other biomarkers may prove to be useful or even better [7].

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0929-8673/11 $58.00+.00

METHODOLOGY

Since the first description of a standardised method to induce and process sputum in asthma in 1992 by Pin *et al.* [8], there has been an impressive increase in the number of papers in which researchers have used induced sputum to study various aspects of airways inflammation. Thus, in response to the interest in sputum analysis, a European Respiratory Society Task Force has published a comprehensive review on sputum methodology [9-12].

Sputum Induction and Collection

Induced sputum is usually collected in the morning. Induction is performed using an ultrasonic nebuliser. Two different approaches for induction have been used:

a) inhalation of the same (3–4.5%) or increasing (3, 4 and 5%) concentrations of aerosolized hypertonic saline over fixed time periods [8, 13]

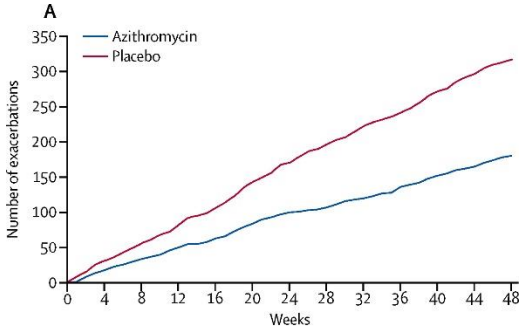
b) inhalation of the same concentration of hypertonic saline (4.5%) over increasing time periods [14].

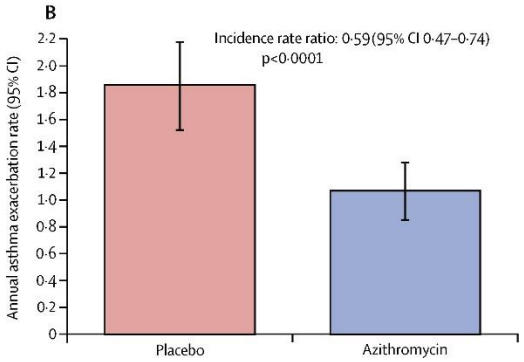
The choice of technique does not seem to influence the differential sputum cell count. The duration of sputum induction has to be kept standard as it may influence the sputum cell composition. It generally ranges from 10-20 min. A sputum cell count resulting from an induction of 5 min can definitely not be compared with that of an induction of 20 min. The early sample contains more granulocytes while the proportion of mononuclear cells increases with the duration of the induction [15].

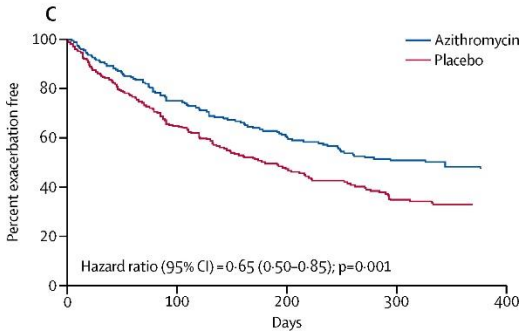
Irrespective of the induction technique used, the challenge procedure should be performed in a standardized way that includes the necessary safety procedures, as hypertonic saline can cause severe airway constriction in asthmatic subjects. Subjects should be pretreated with inhaled short-acting β_2-agonists. It has been shown that obtaining sputum from the same asthmatic subjects with or without pretreatment with salbutamol, does not influence the cellular composition [16]. It is also recommended to use isotonic instead of hypertonic saline when post bronchodilator FEV1 is < 65% predicted [17]. Using either hypertonic or isotonic saline does not change the cellular or the biochemical readouts [18,19]. The ERS Task Force conclusions regarding the safety of sputum induction could serve as guidelines, particularly for those who are inexperienced in performing sputum induction procedures [9]. Adding sal-

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

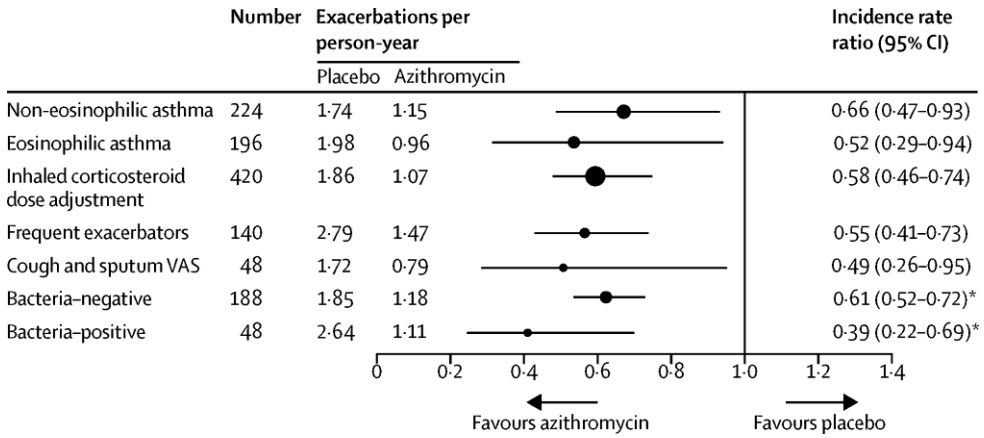
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson







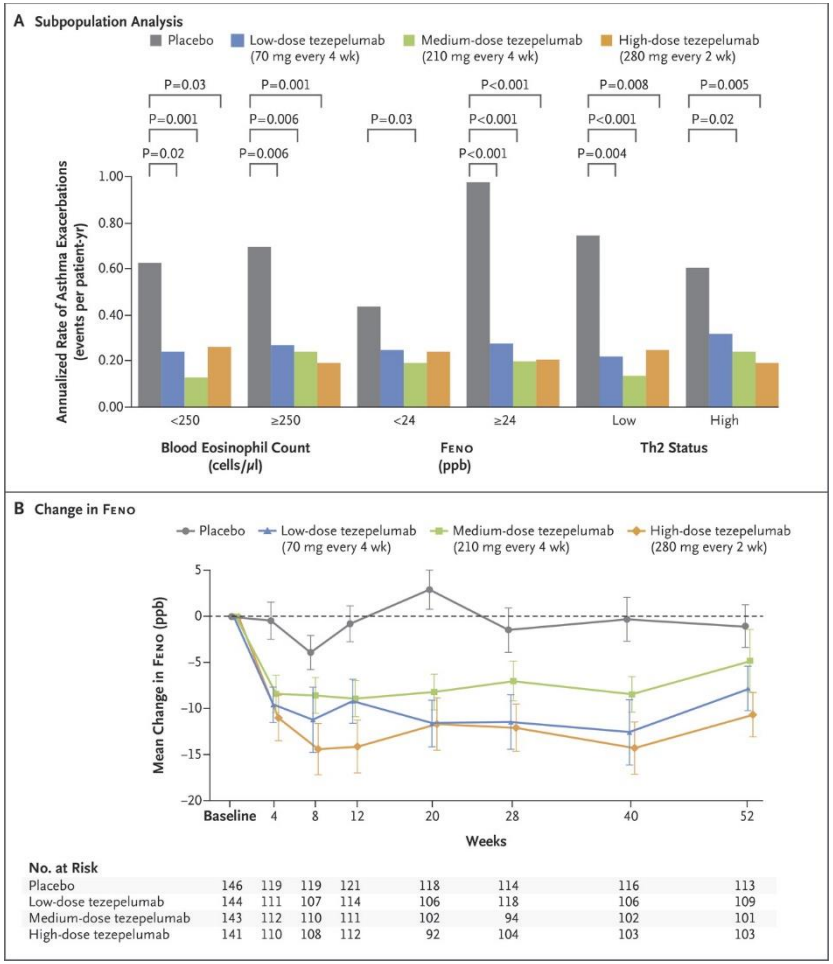
500 mg 3X/week



ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

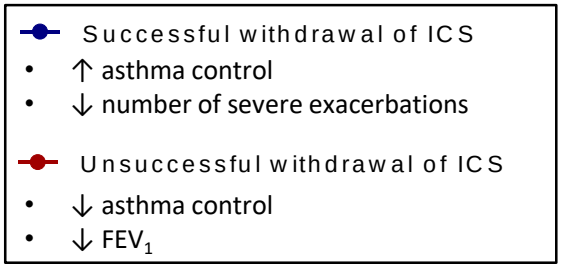
Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

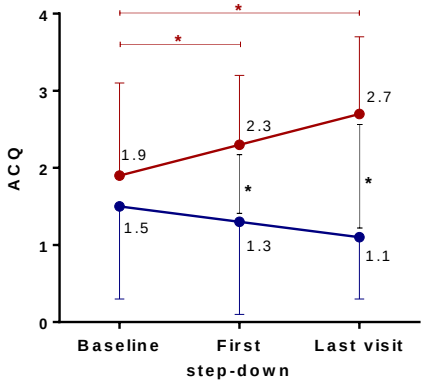


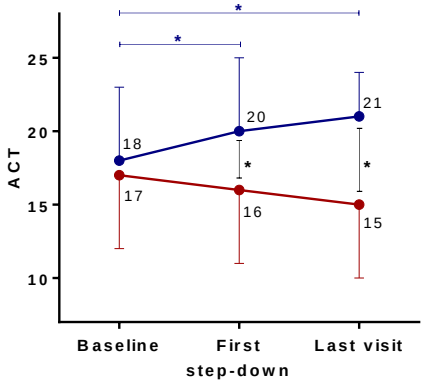
No. at Risk

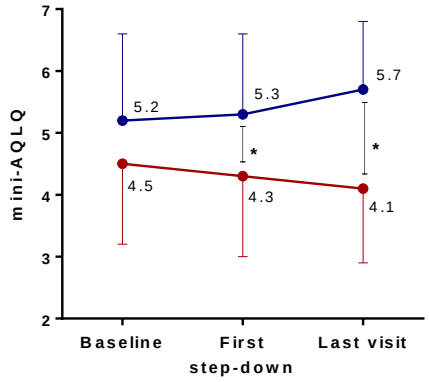
Placebo	146	119	119	121	118	114	116	113
Low-dose tezepelumab	144	111	107	114	106	118	106	109
Medium-dose tezepelumab	143	112	110	111	102	94	102	101
High-dose tezepelumab	141	110	108	112	92	104	103	103

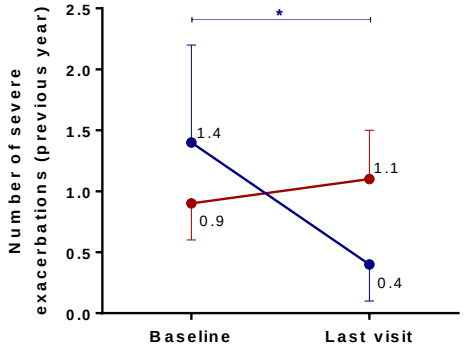
Reducing ICS is feasible in non eosinophilic asthma

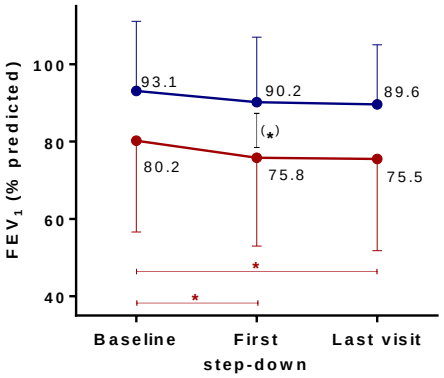










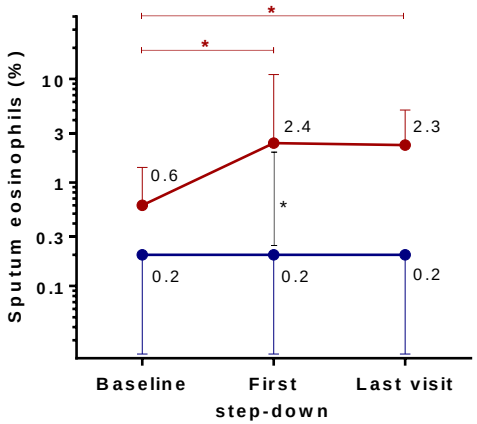


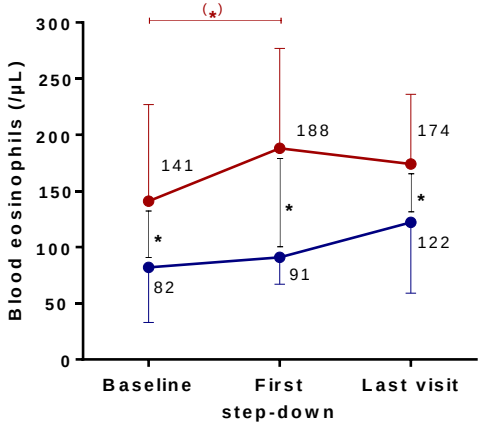
Data presented as mean and SD; * p <0.05; (*) p =0.05

Change in eosinophilic inflammation after reducing ICS in non eosinophilic asthma

Successful withdrawal of ICS
- /

Unsuccessful withdrawal of ICS
- ↑ sputum eosinophils
- ↑ blood eosinophils





Data presented as median and IQR; * p <0.05; (*) p =0.05

University of Liege
Faculty of Medicine
Departments of Clinical Pharmacy and Respiratory Medicine
CIRM and GIGA I³ – Research Units

LIÈGE université

Asthma control and corticosteroid responsiveness according to asthma inflammatory phenotypes

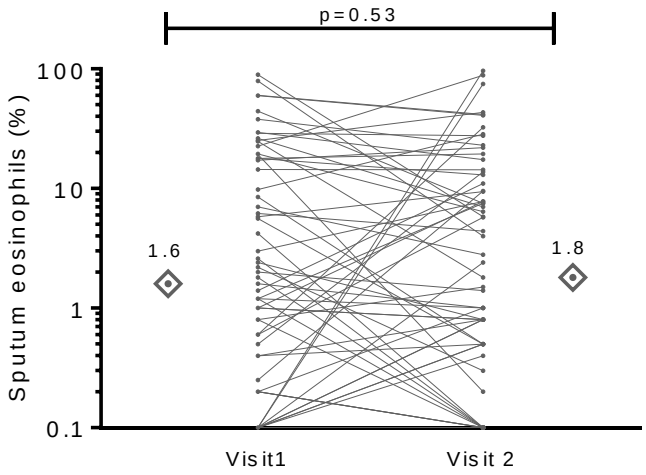
Sophie Demarche

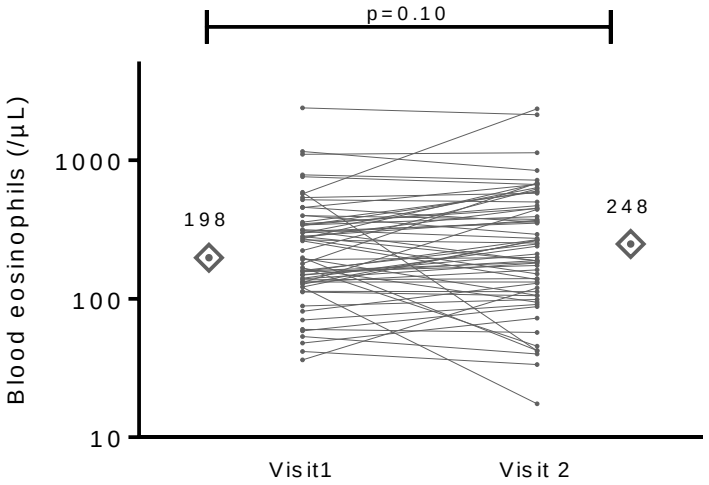
Promoters: Prof. T. Van Hees and Prof. R. Louis

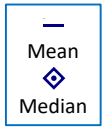
Thesis submitted to fulfill the requirements for the degree of doctor in biomedical and pharmaceutical sciences 2017

Stable dose of ICS and eosinophilic inflammation in asthmatics in real life

ICS:
800(0-2000) BDP equ.





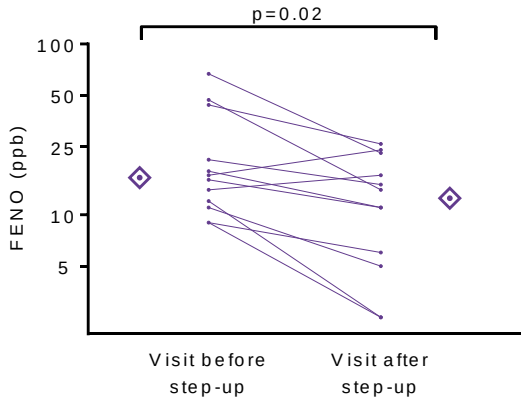


Demarche S et al BMJ open 2017

2. Step-down of ICS in non-eosinophilic asthma

- Intermediate phase of step-up

	Non-eosinophilic asthmatics with an ACQ ≥1.5 and treated with a low or medium dose of ICS at study entry (N=13)		
Age, years	54 (50-65)		
Women, N (%)	7 (54)		
Atopy, N (%)	4 (31)		
Smoking status, N (%) Non-smokers Current smokers Ex-smokers	 4 (31) 3 (23) 6 (46)		
	Visit before step-up	Visit after step-up	p value
FEV_1, % predicted	81.5 ± 15.7	82.7 ± 15.3	0.70
FVC, % predicted	86.4 ± 16.0	90.9 ± 20.6	0.28
ACT	15 ± 3	17 ± 4	0.31
ACQ	2.4 ± 0.7	2.2 ± 0.8	0.17
Mini-AQLQ	4.0 ± 0.8	4.3 ± 0.9	0.40
FENO, ppb	17 (12-33)	13 (6-20)	**0.02**
Sputum eosinophils, %	0.6 (0.2-1.0)	0.6 (0.2-2.0)	0.68
Sputum neutrophils, %	77 (65-90)	73 (47-79)	0.13
Blood eosinophils, /µL	109 (77-178)	124 (78-172)	0.31
Blood neutrophils, /µL	3911 (2611-4838)	4403 (3038-5159)	0.13
ICS dose (BDP CFC equ.)	800 (500-800)	2000 (2000-2000)	-
LABA, N (%)	11 (85)	13 (100)	0.50
LTRA, N (%)	3 (23)	3 (23)	1.0
Theophylline, N (%)	1 (8)	1 (8)	1.0



Demarche S, submitted to Clin Exp Allergy 2017

Asthma Clinic at CHU Liege
A two visit investigation plan

Visit 1 – 45-60 min

- Patients under usual treatment
- Detailed history taking with including questions on age at onset, environemental exposures, triggers of attack, exacerbation rate
- Measurement of exhaled nitric oxide (FeN0)
- Spirometry + reversibility test using 400 µg Ventolin
- Auto-administred questionnaire ACQ and ACT
- Sputum induction by inhalation of saline using an ultrasonic nebulizer (4.5% NaCl when post bronchodilation FEV1 is $\geq$ 65% predicted, isotonic saline 0.9% when FEV1 is < 65% predicted

Visit 2 – 45 min

- Withdrawal of bronchodilating agents
- Bronchial provocative challenge (PC20 methacholine)
- Consultation with the physician to initiate or adjust treatment

Definition of Asthma (GINA 2017)

- 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.

Demarche *et al. BMC Pulmonary Medicine* (2016) 16:46
DOI 10.1186/s12890-016-0208-2

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

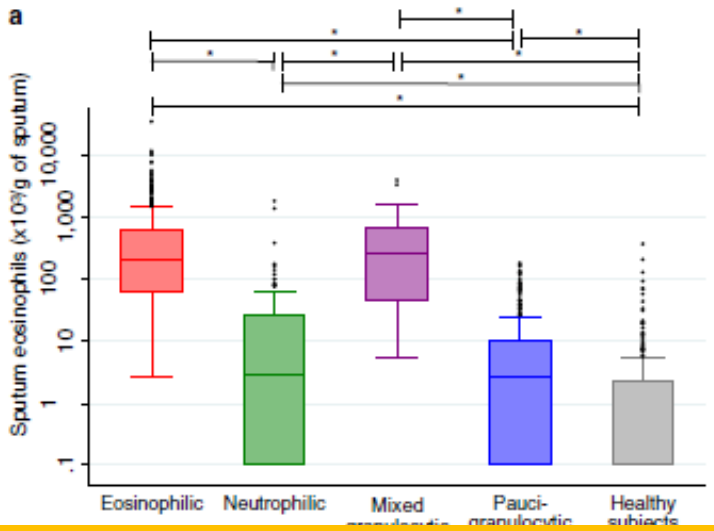
Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory?

Sophie Demarche[1,2,3*], Florence Schleich[1,2], Monique Henket[1,2], Virginie Paulus[1,2], Thierry Van Hees[3] and Renaud Louis[1,2]

Table 1 Demographic, functional and treatment characteristics of asthmatics classified by phenotypes and healthy subjects

	Eosinophilic asthma	Neutrophilic asthma	Mixed granulocytic asthma	Paucigranulocytic asthma	Healthy subjects	*p* value
N (% of asthmatics)	350 (42)	134 (16)	31 (4)	318 (38)	194	-

N=833



Pauci granulocytic asthma may be low grade eosinophilic inflammation

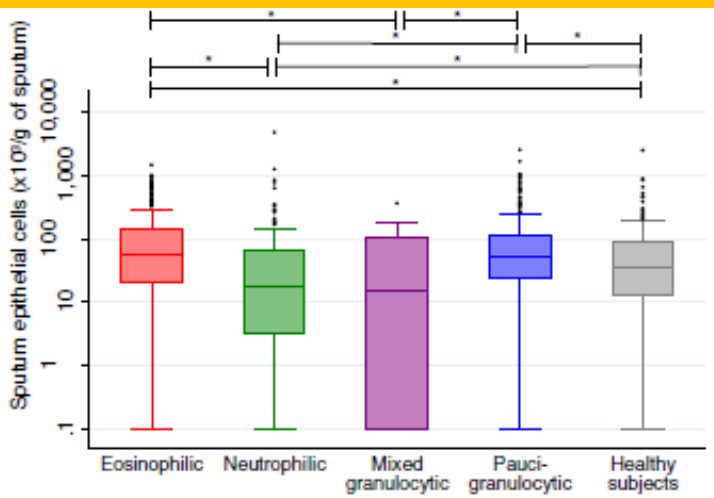


Fig. 1 Absolute sputum eosinophils (**a**) and absolute sputum epithelial cells (**b**) in asthma phenotypes and healthy subjects. * $p < 0.005$. Values of 0 were assigned to 0.1 because of the use of a logarithmic scale

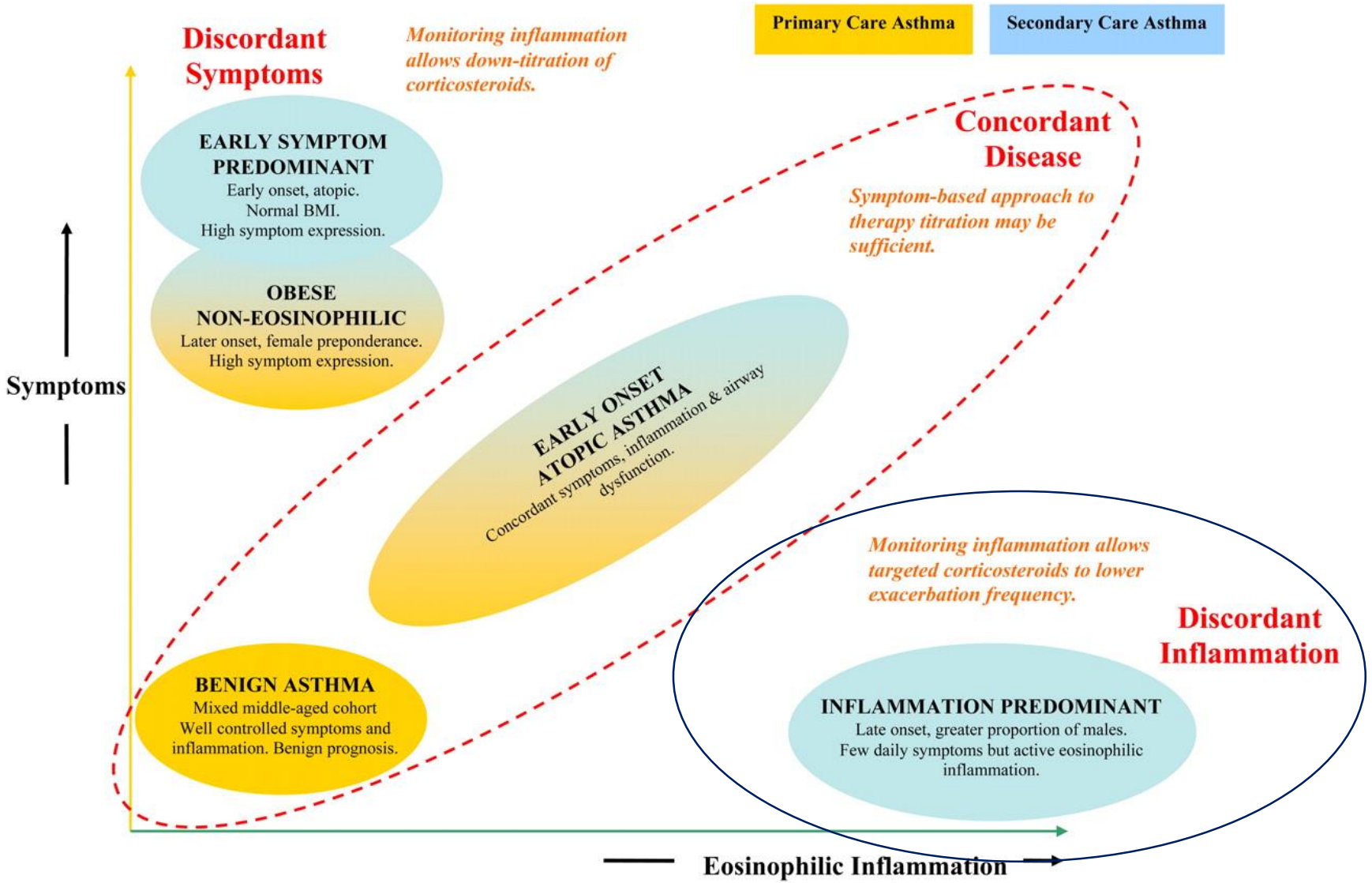
Definition of Asthma (GINA 2006)

- A chronic inflammatory disorder of the airways
- Many cells and cellular elements play a role
- Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
- Widespread, variable, and often reversible airflow limitation

What is the goal of asthma treatment?

- To achieve symptom control
- To maintain normal lung function
- To prevent exacerbation

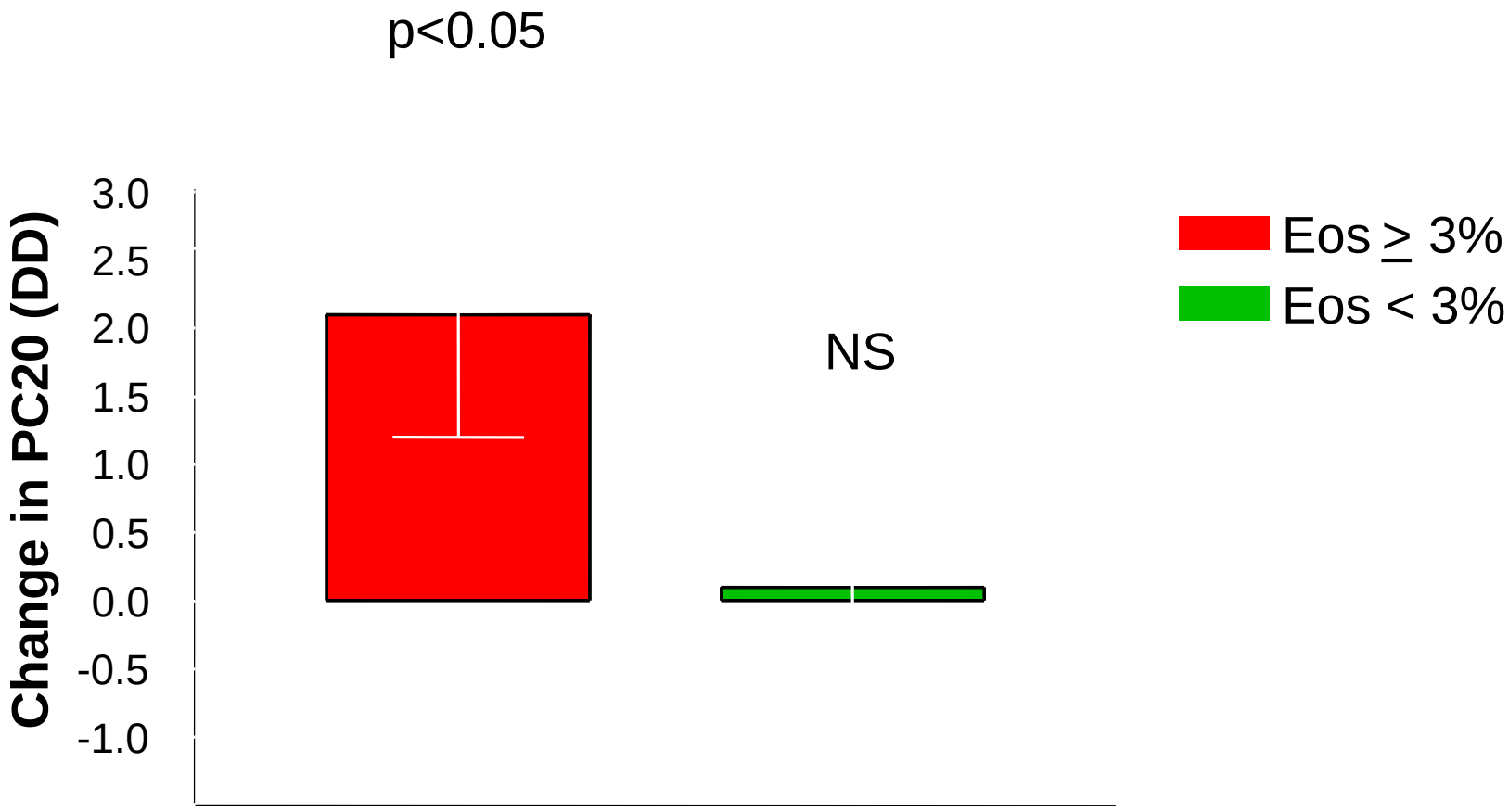
Cluster analysis of clinical asthma phenotypes



Haldar P Am J Respir Crit Care Med 2008

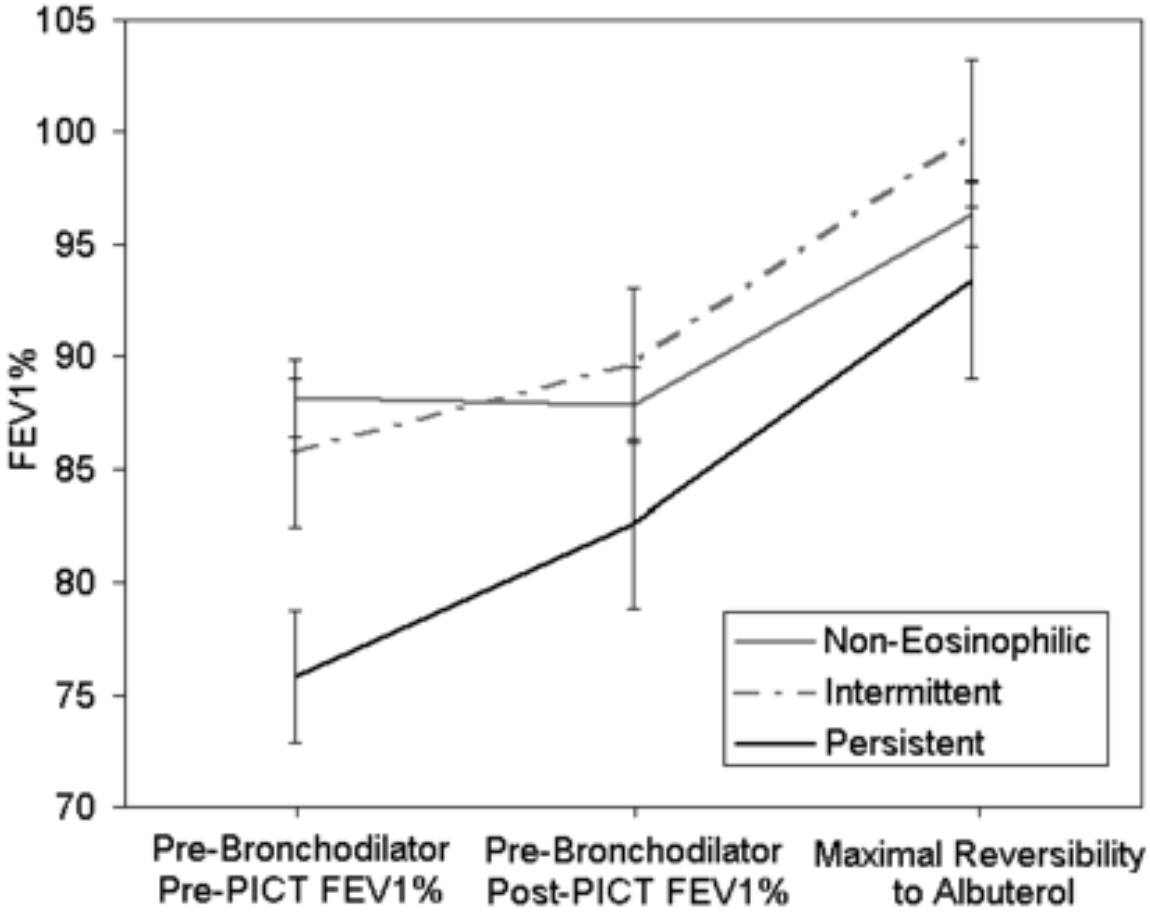
Sputum eosinophilia as a predictive factor for response to inhaled corticoids in asthma

(coourse of inhaled budesonide 800 µg/d for 6 weeks)



Pavord I et al Lancet 1999

Non eosinophilic asthma (< 2% sputum eosinophils) fails to improve lung function after inhaled corticoids



%Δ in FEV_1 (L)	Non-Eosinophilic	Intermittent	Persistent	p
Pre- to Post-PICT	-0.2%	4.7%	8.6%	0.001
Post-PICT to Max Rev	10.1%	12.1%	13.5%	0.32

K Wong Mc Grath et al AJRCCM 2012