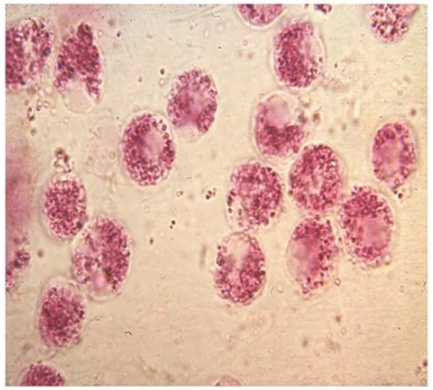
ΚΛΙΝΙΚΑ ΣΕΜΙΝΑΡΙΑ ΣΤΗΝ ΠΝΕΥΜΟΝΟΛΟΓΙΑ 2019
ΕΤΑΙΡΕΙΑ ΜΕΛΕΤΗΣ ΠΝΕΥΜΟΝΟΠΑΘΕΙΩΝ
ΚΑΙ ΕΠΑΓΓΕΛΜΑΤΙΚΩΝ ΠΑΘΗΣΕΩΝ ΘΩΡΑΚΑ

Αποφρακτικές παθήσεις του αναπνευστικού

Σοβαρό εωσινοφιλικό άσθμα
Διάγνωση - Θεραπεία



Εύα Φούκα, MD, PhD

Επιμελήτρια Α΄ΕΣΥ, Πνευμονολογική Κλινική ΑΠΘ

22-23 Φεβρουαρίου 2019
Θεσσαλονίκη

Conflicts of Interest

I have received travel Grants from ASTRA ZENECA, NOVARTIS, GSK, BOEHRINGER INGELHEIM, ELPEN, BAYER, MENARINI and PHARMATEN.
I have also received honorarium lecture fees from ASTRA ZENECA, ELPEN, CHIESI, BOEHRINGER INGELHEIM, NOVARTIS and GSK

Θεραπευτική αντιμετώπιση του άσθματος – ανεκπλήρωτοι στόχοι

- Ορισμένοι ασθενείς με άσθμα

  δεν εμφανίζουν το βέλτιστο έλεγχο

  με τα τρέχοντα πρότυπα θεραπείας,

  ακόμα και όταν ακολουθούνται οι εθνικές

  και διεθνείς κατευθυντήριες οδηγίες

- Το μη ελεγχόμενο άσθμα συνδέεται με

  σημαντική νοσηρότητα, μεγάλο αριθμό

  νοσηλειών, υψηλή θνητότητα και με

  σοβαρή οικονομική επιβάρυνση

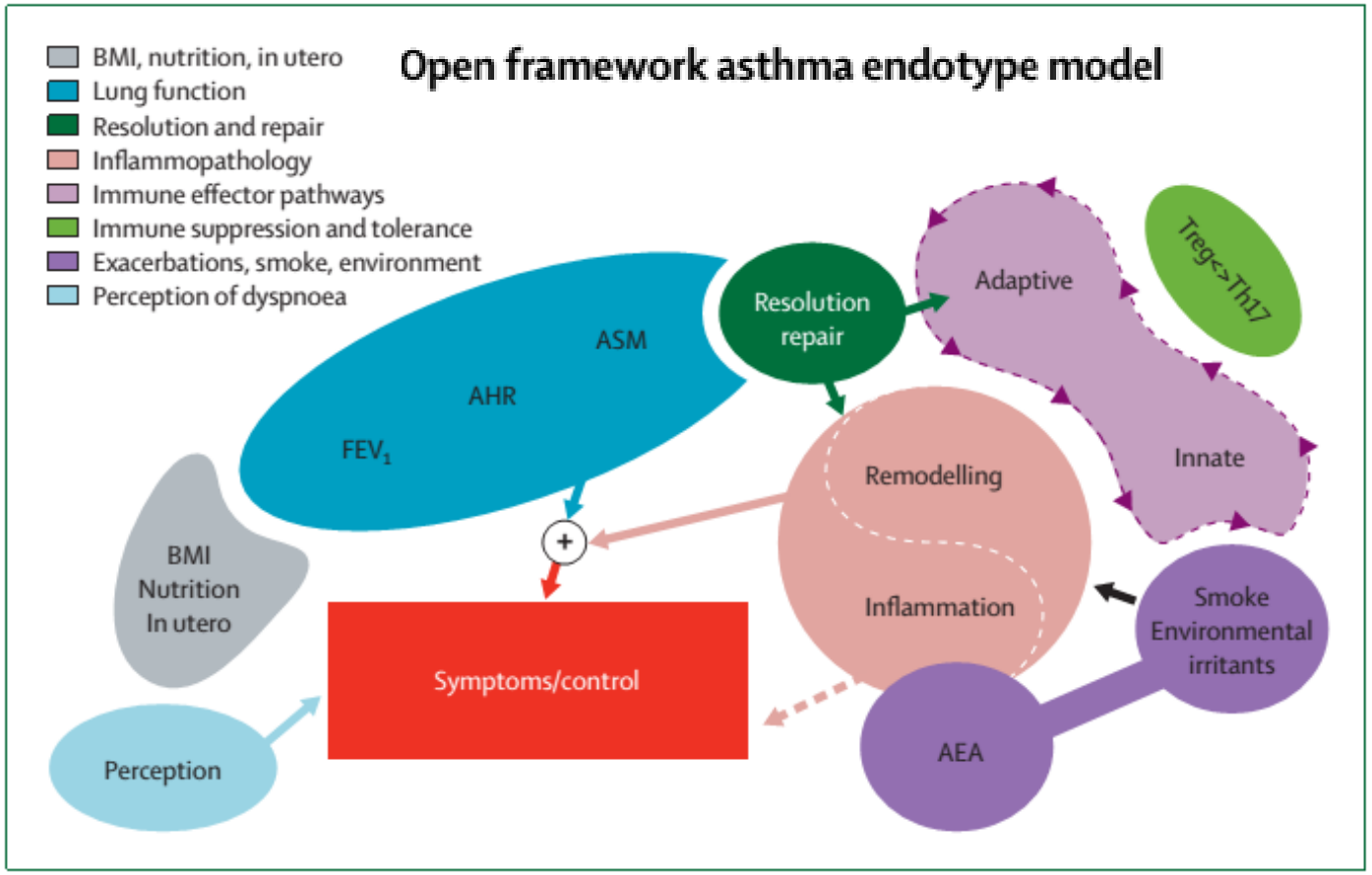
Το 5-10% των ασθενών έχουν σοβαρό άσθμα που δεν ανταποκρίνεται στις συμβατικές θεραπείες

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018

Το σοβαρό άσθμα χαρακτηρίζεται από μεγάλη ετερογένεια

Wenzel SE, Nat Med. 2012; 18: 716-25

Ενδότυπος: υπότυπος της νόσου που ορίζεται λειτουργικά και παθολογικά από έναν υποκείμενο μοριακό μηχανισμό



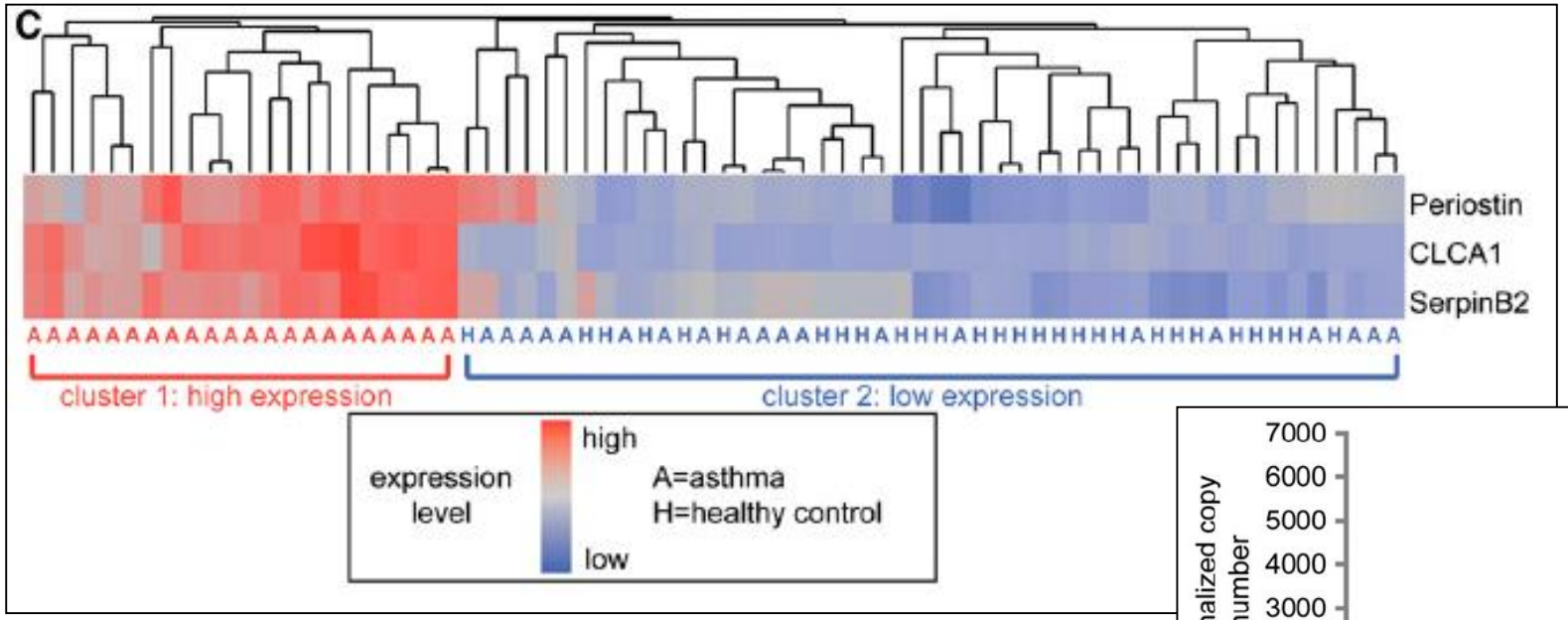
Σχετίζονται με διακριτά κλινικά χαρακτηριστικά και διαφορετική ανταπόκριση στη θεραπεία

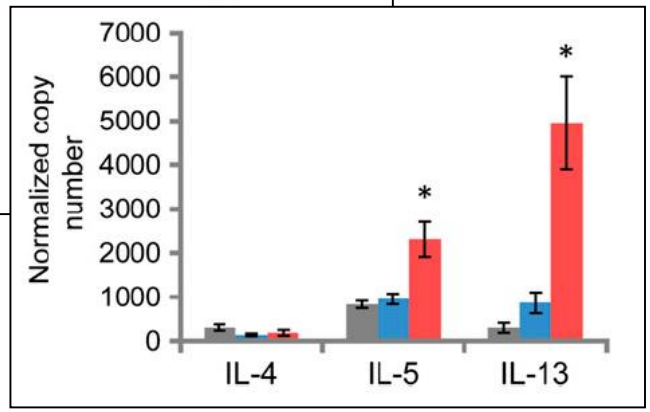
Anderson G. LANCET 2008

T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma

Prescott G. Woodruff[1,2], Barmak Modrek[3], David F. Choy[4], Guiquan Jia[4], Alexander R. Abbas[3], Almut Ellwanger[1], Joseph R. Arron[4*], Laura L. Koth[1,5], and John V. Fahy[1,2*]

"Th2 high – Th2 low" άσθμα



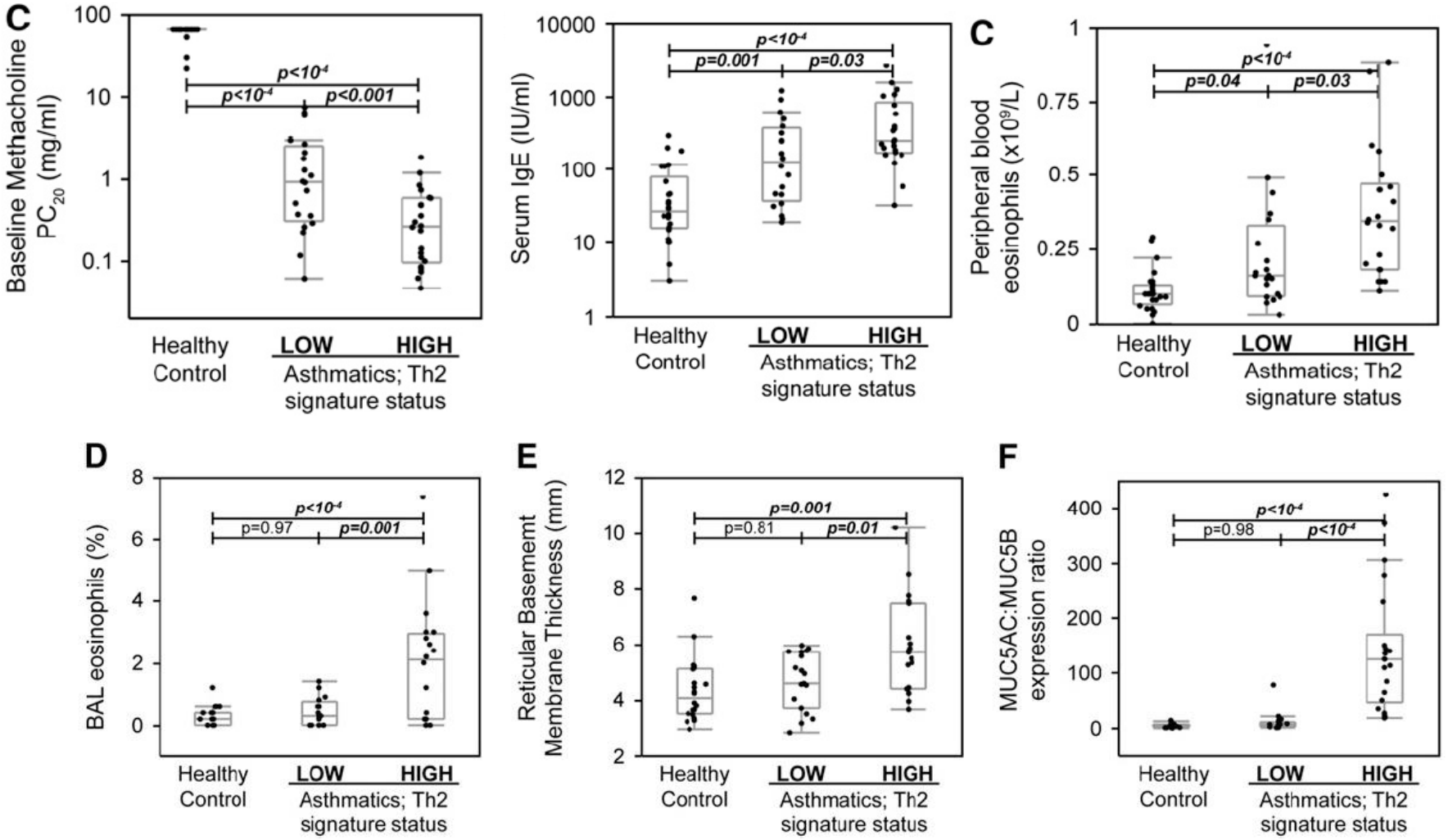


Methods:

* Investigating the gene expression in epithelial brushings from 42 patients with mild-moderate asthma and 28 non-asthmatics controls

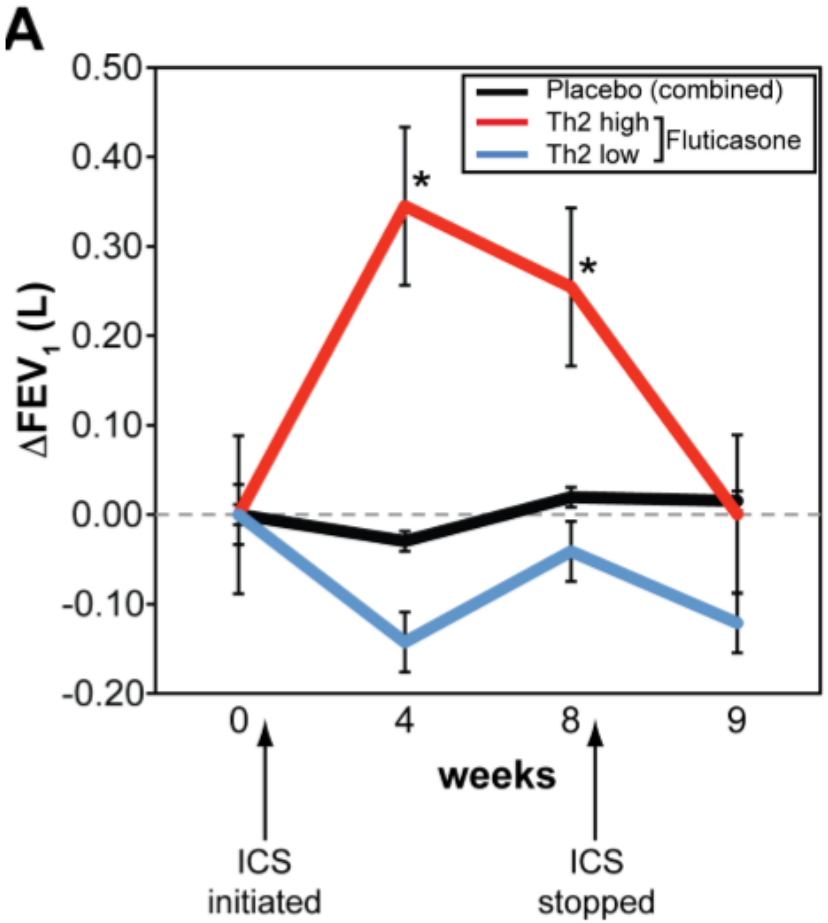
Woodruff, AJRCCM 2009; 180: 388-395

Th2-high asthma: increased markers of allergy, eosinophilic inflammation and airway remodelling



Woodruff, AJRCCM 2009; 180: 388-395

Only asthmatics with “Th2 high” profile responded to anti-inflammatory therapy with ICS

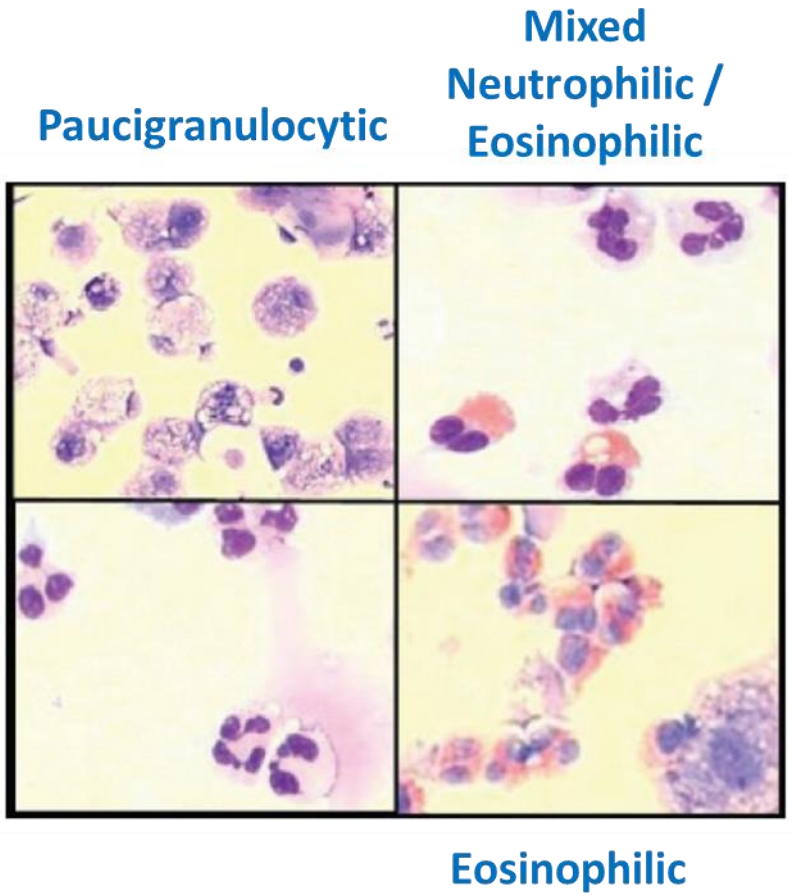


After 8 weeks of FP 2x 500 mcg BID, increased FEV1 was found only in TH2-high asthmatics

Woodruff, AJRCCM 2009; 180: 388-395

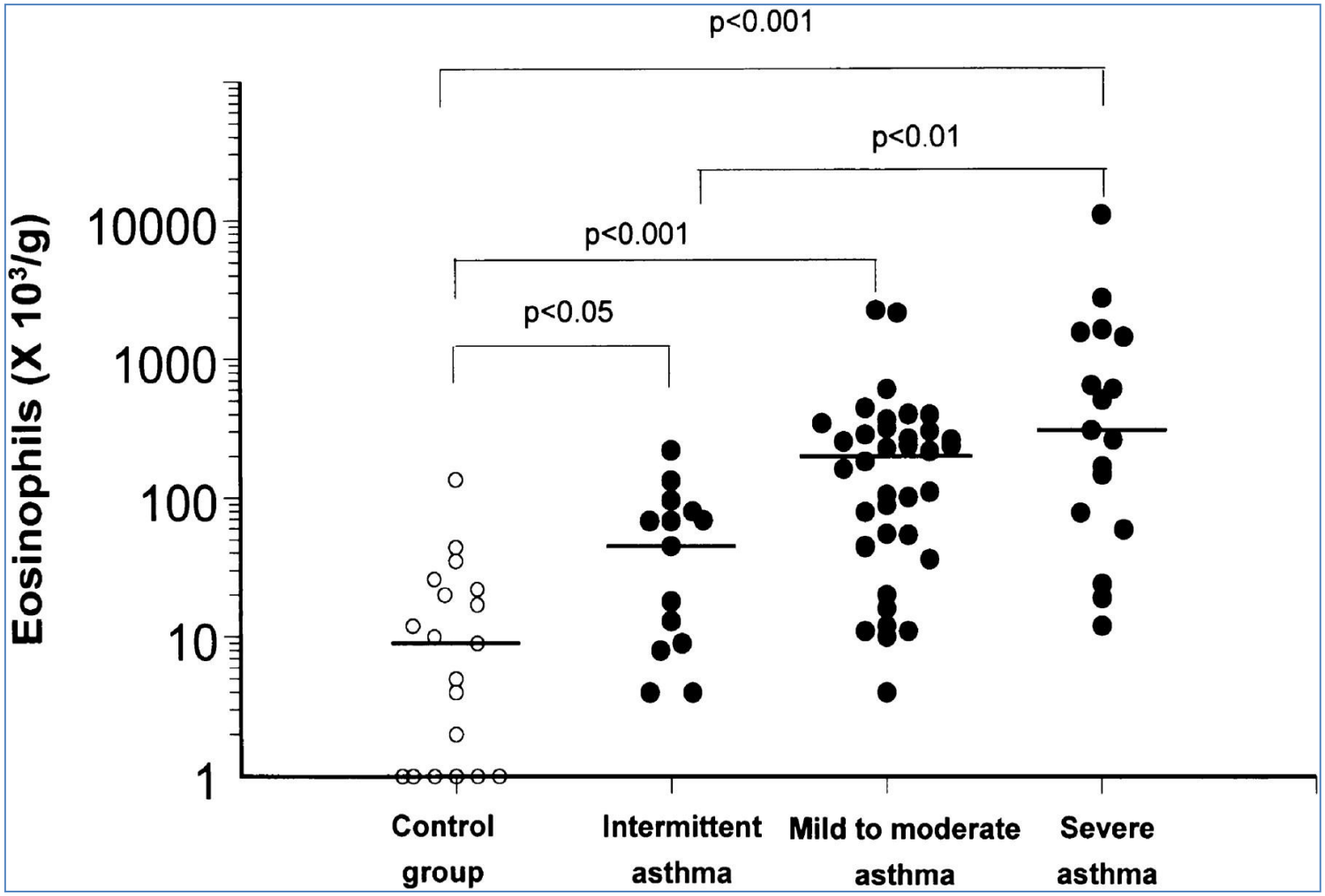
Ο ηωσινοφιλικός φαινότυπος του άσθματος

- Αναφέρεται στην **ηωσινοφιλία στους αεραγωγούς**
- Δεν υπάρχει ομοφωνία ως προς τον ορισμό **-> 2 ή 3%** **Ηωσινόφιλα** στα προκλητά πτύελα?



Haldar, JACI 2007 Haldar, AJRCCM 2008, Berry, Thorax 2007, de Groot, *ERJ Open Res*. 2015, Nixon J, *Pharmacol Ther* 2016

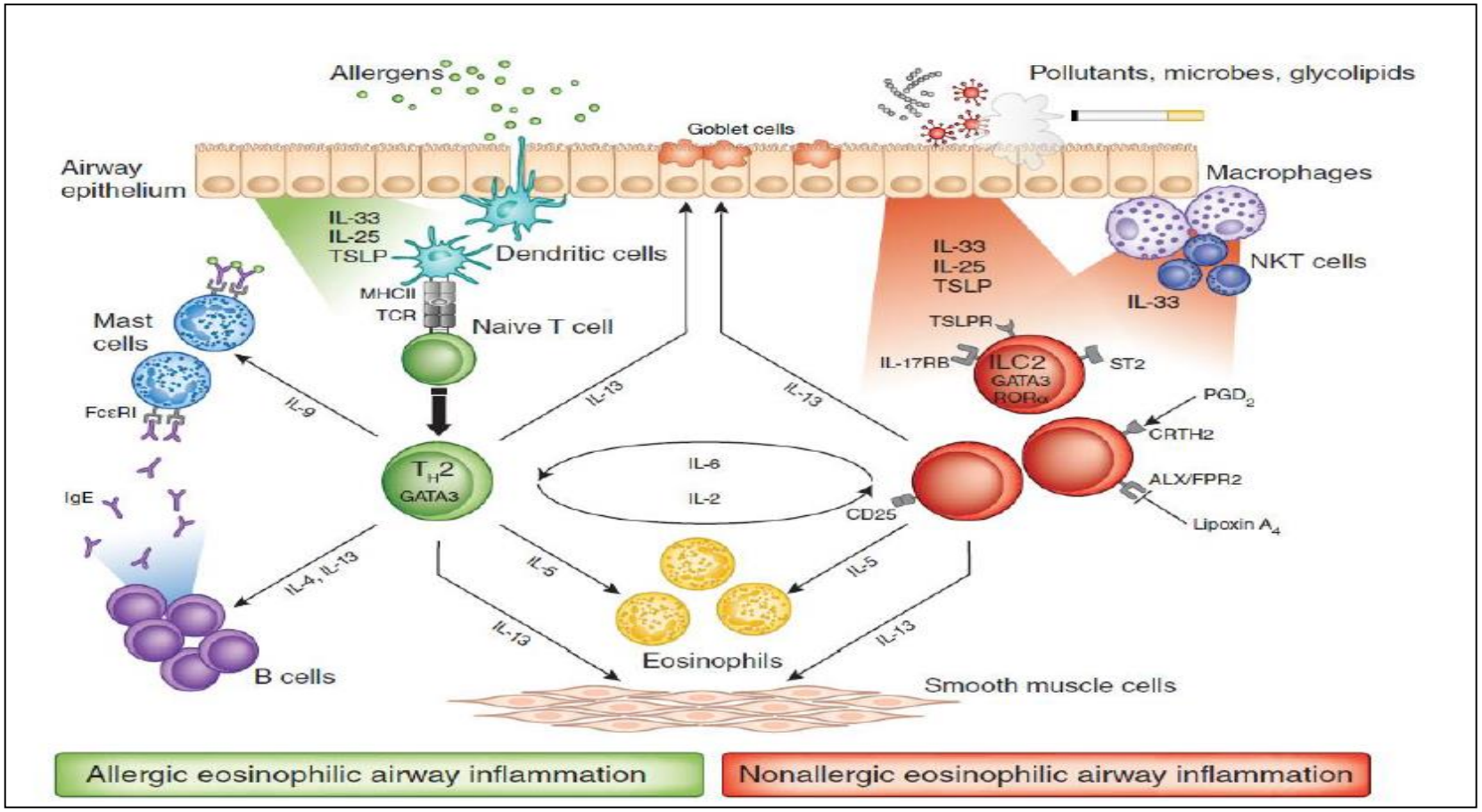
Sputum eosinophil levels in asthma according to the severity



Louis R. AJRCCM. 2000; 161: 9-16

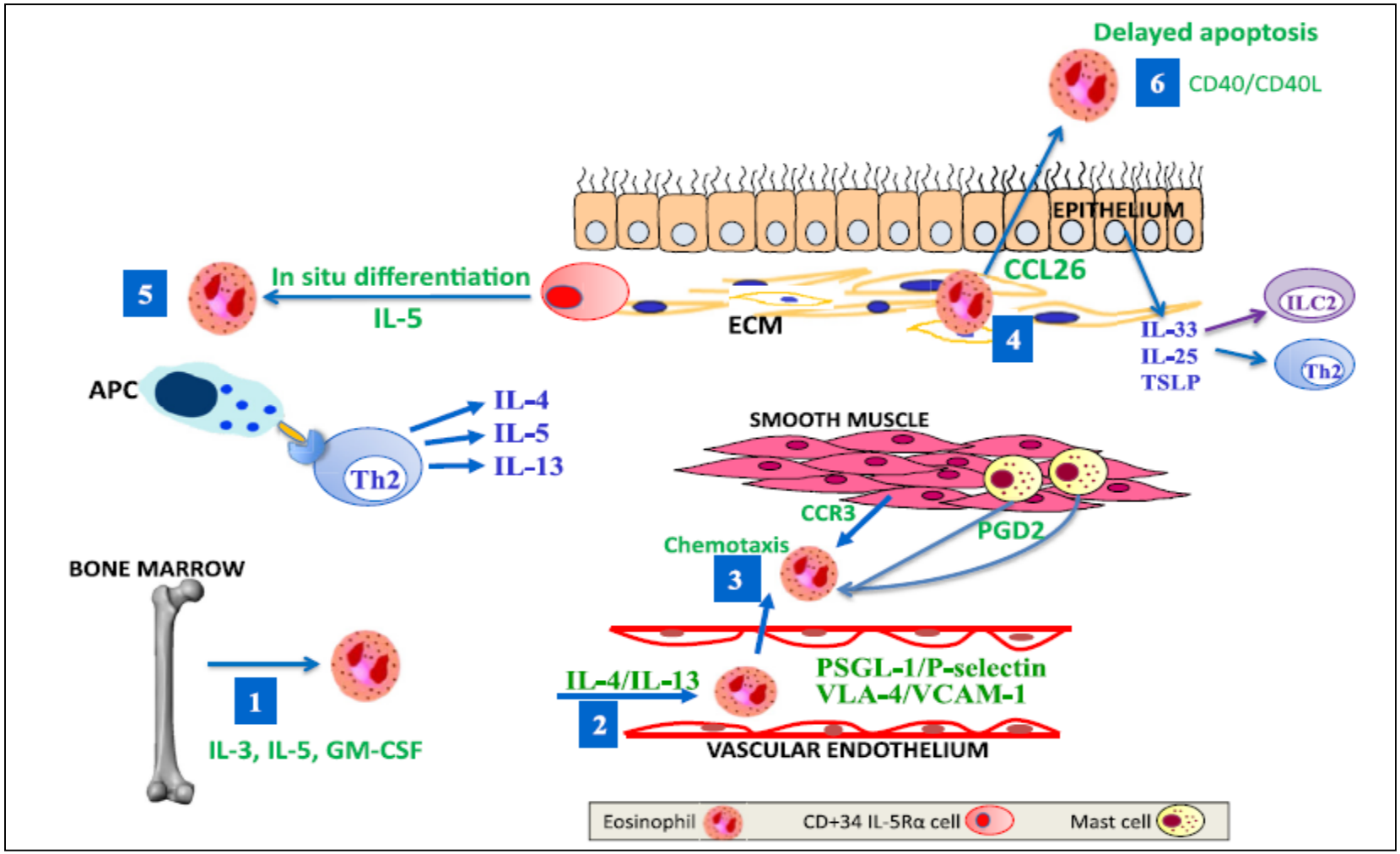
T2 high – T2 low asthma:

Two different pathways (TH2 and ILC2) produce Type-2 cytokines and result in eosinophilia



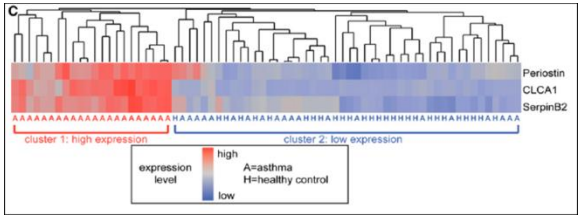
Brusselle GG, Nat Med 2013; 19: 977-9

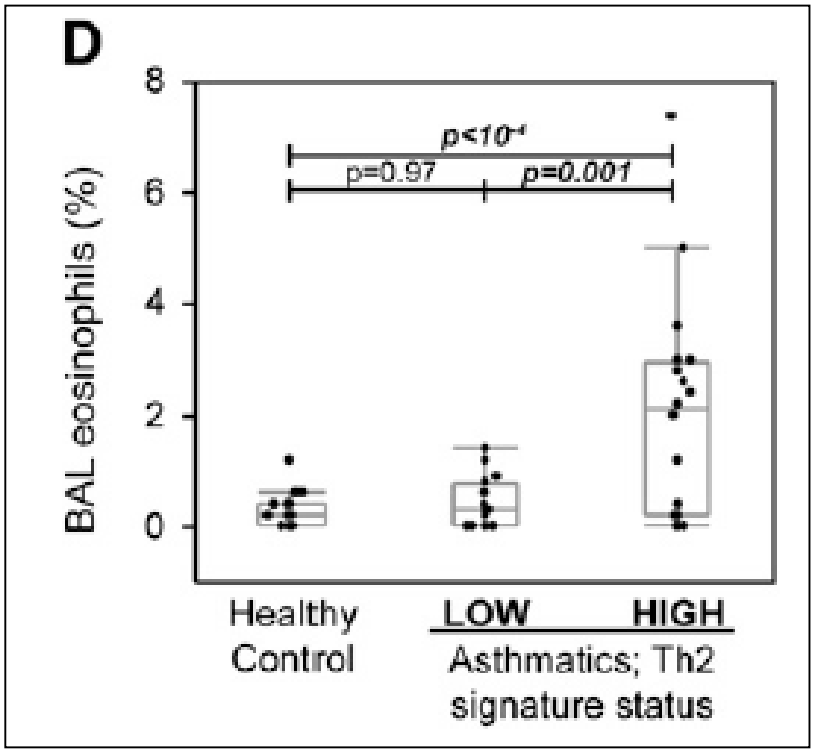
Mechanisms of eosinophil migration into the lungs

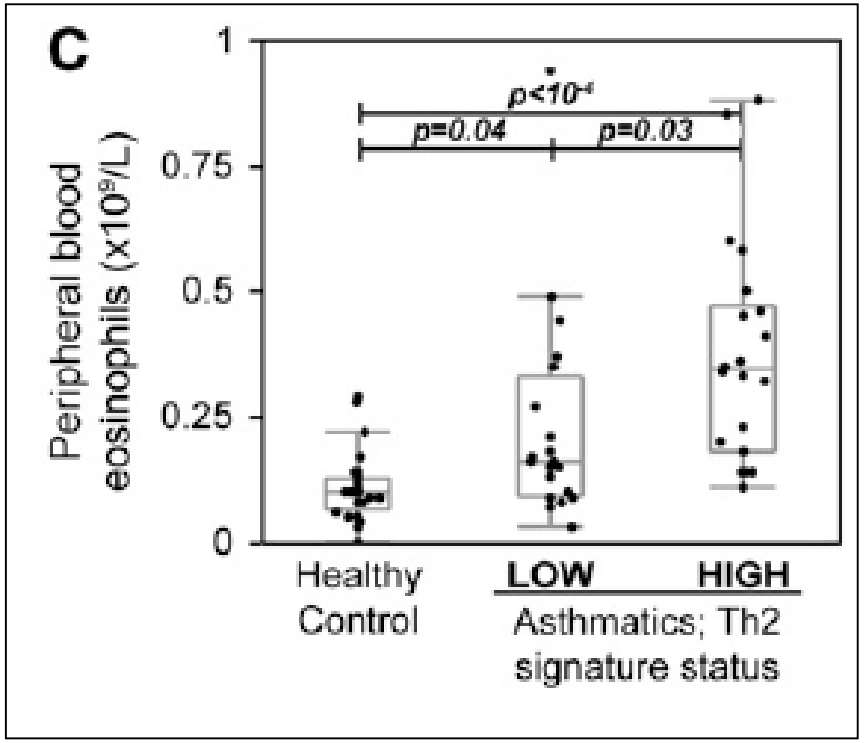


Woolnough K, Immunol Allergy Clin North Am. 2015;35:477-92

Sputum and blood eosinophils are both associated with the T2-high asthma endotype







Woodruff, AJRCCM 2009; 180: 388-395

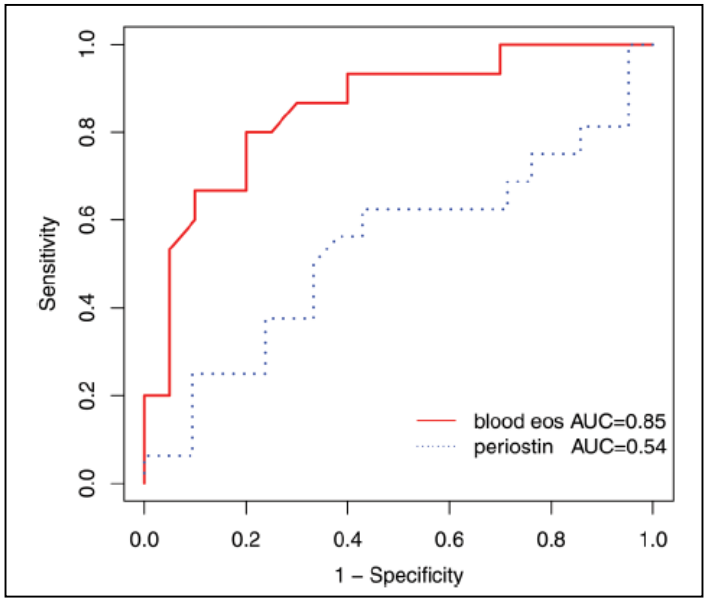
Blood eosinophils as surrogates for sputum eosinophils in severe asthma

Table 2 Sensitivity, specificity, PPV and NPV of different surrogate markers using alternative cut-points to diagnose eosinophilic airway inflammation (less than, more than or equal to 3% sputum eosinophils)

	Threshold	Sensitivity	Specificity	PPV	NPV
Blood eosinophils	>0.22×10^9/L	86	79	60	93
Blood eosinophils	≥0.25×10^9/L	79	84	64	91
Blood eosinophils	≥0.27×10^9/L	78	91	79	91
FE_{NO} level	>20 ppb	74	57	40	87
FE_{NO} level	≥24 ppb	74	63	42	87
FE_{NO} level	≥42 ppb	63	92	74	89
FE_{NO} level	>50 ppb	56	92	67	84
Serum periostin (in-house)	>26 ng/mL	54	57	29	77

NPV, negative predictive value; PPV, positive predictive value.

Severe asthma cohort

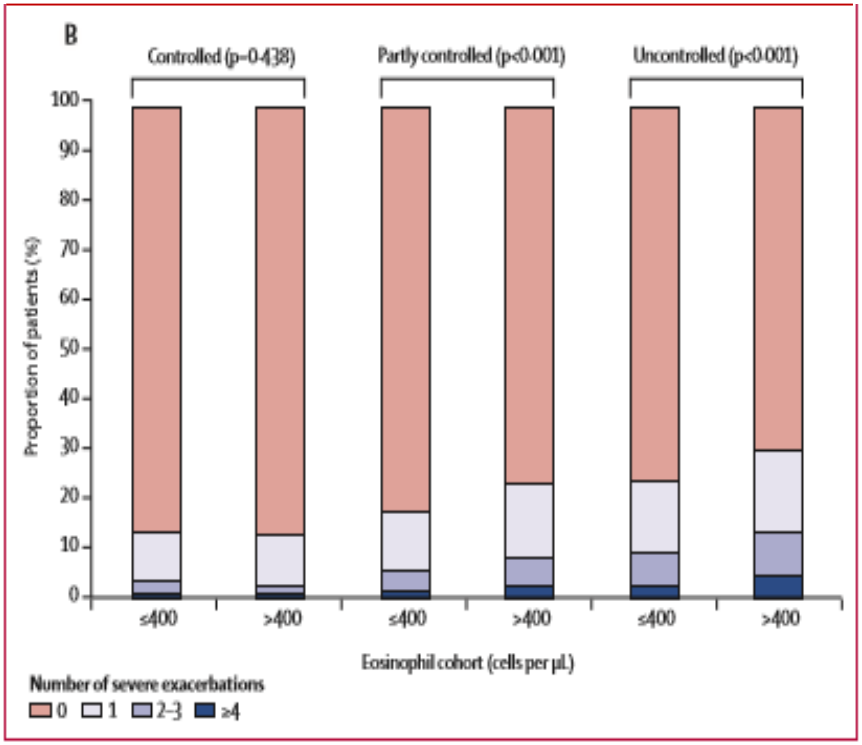


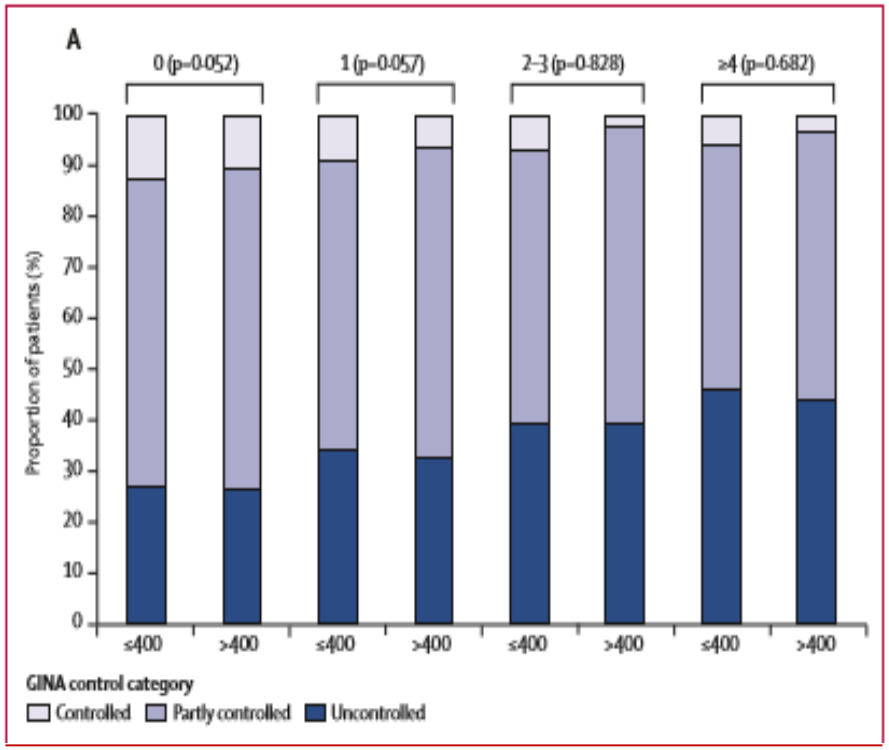
The diagnostic accuracy described as ROC AUC was 85% (p<0.001, 95% CI 0.81-0.96)

Wagener, Thorax 2015; 70: 115-120

Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study

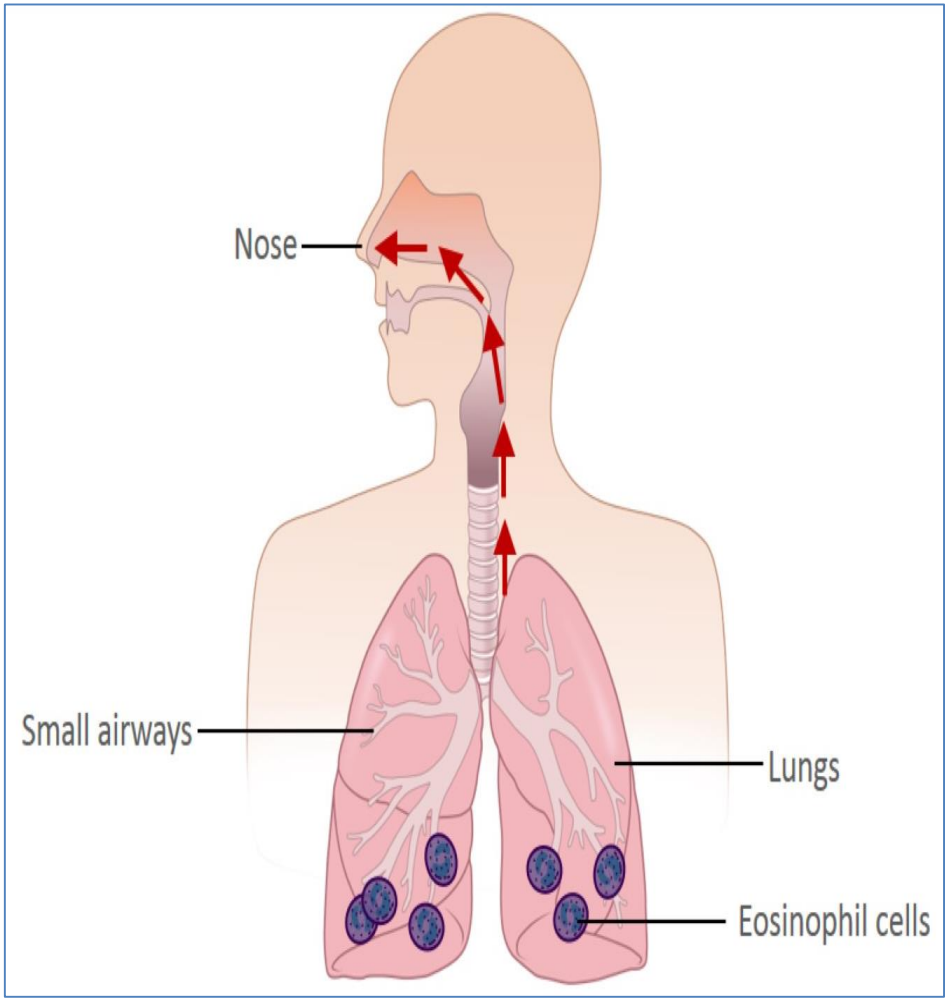
Bl-eos >400 cells/µL are associated with **severe asthma exacerbations** and **poor asthma control**





Price DB, Lancet Respir Med. 2015; 3: 849-58

The severe asthma eosinophilic phenotype



- **Sputum and peripheral blood eosinophilia**
- Adult onset and equal distribution between sexes
- Lack of atopy
- Chronis sinusitis with nasal polyposis
- Aspirin sensitivity
- Low FEV1 and persistent airflow limitation
- Distal inflammation with air trapping and dynamic hyperinflation
- Frequent, severe exacerbations
- Severe impact on quality of life

De Groot JC. ERJ Open Res. 2015 Sep 23;1(1)

Severe eosinophilic asthma: a roadmap to consensus

Roland Buhl[1], Marc Humbert[2], Leif Bjermer[3], Pascal Chanez[4], Liam G. Heaney[5], Ian Pavord[6], Santiago Quirce[7], Johann C. Virchow[8], Stephen Holgate[9] and the expert group of the European Consensus Meeting for Severe Eosinophilic Asthma[10]

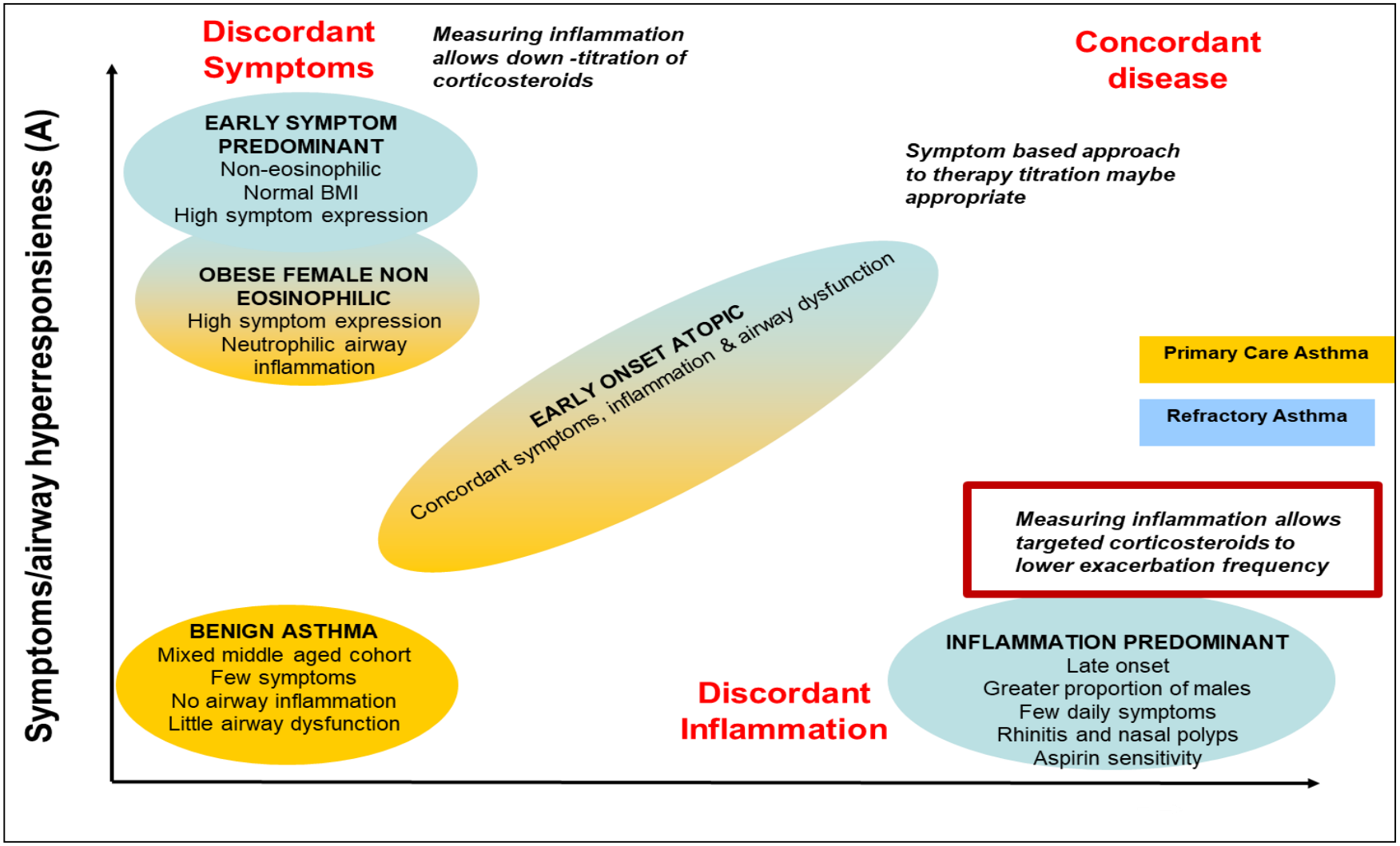
TABLE 1 Possible diagnostic scheme for severe eosinophilic asthma (SEA)

Major criteria	Minor criteria
Diagnosis of severe asthma	Late onset of disease
Evidence of high-load eosinophilic disease (persistent blood or sputum eosinophilia detected on ⩾2 occasions)	Upper airway disease (*i.e.* chronic rhinosinusitis, often with nasal polyposis)
Frequent exacerbations (⩾2 per year)	Role of other biomarkers (*e.g.* F_{ENO}, periostin and DPP-4)
Dependence (continuous or intermittent) on oral corticosteroids to achieve asthma control	Fixed airflow obstruction
	Air trapping/presence of mucus plugs

DPP-4: dipeptidyl peptidase-4; F_{ENO}: exhaled nitric oxide fraction.

Buhl R, Eur Respir J 2017; 49: 1700634

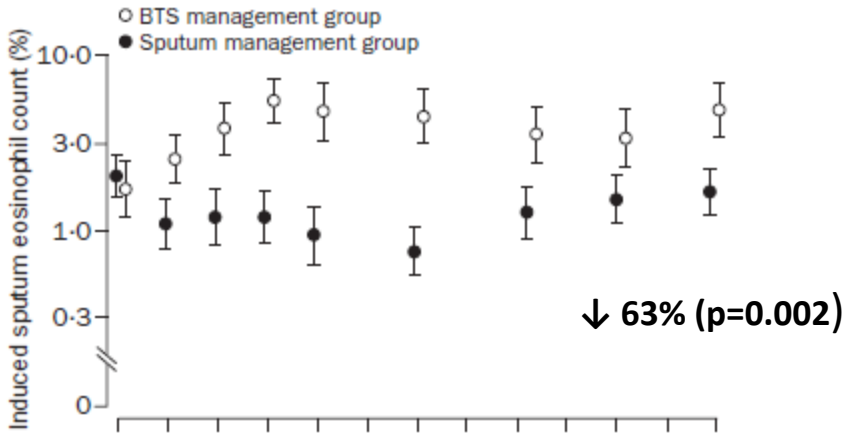
Ο τυπικός ασθενής με ΣΕΑ έχει λίγα σχετικά συμπτώματα παρά την ενεργό φλεγμονή των αεραγωγών

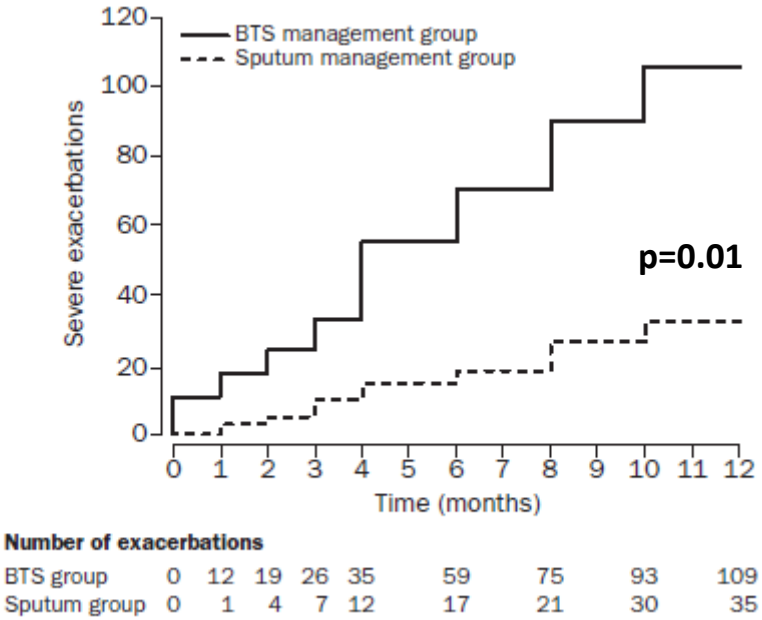


Haldar , AJRCCM 2008;178:218-24

Treatment directed at normalization of sputum Eos reduces asthma exacerbations and admissions

Sputum Eos<1%: ↓ **anti-inflammatory therapy**
Sputum Eos 1-3%: **no changes in anti-inflammatory therapy**
Sputum Eos>3%: ↑**anti-inflammatory therapy**

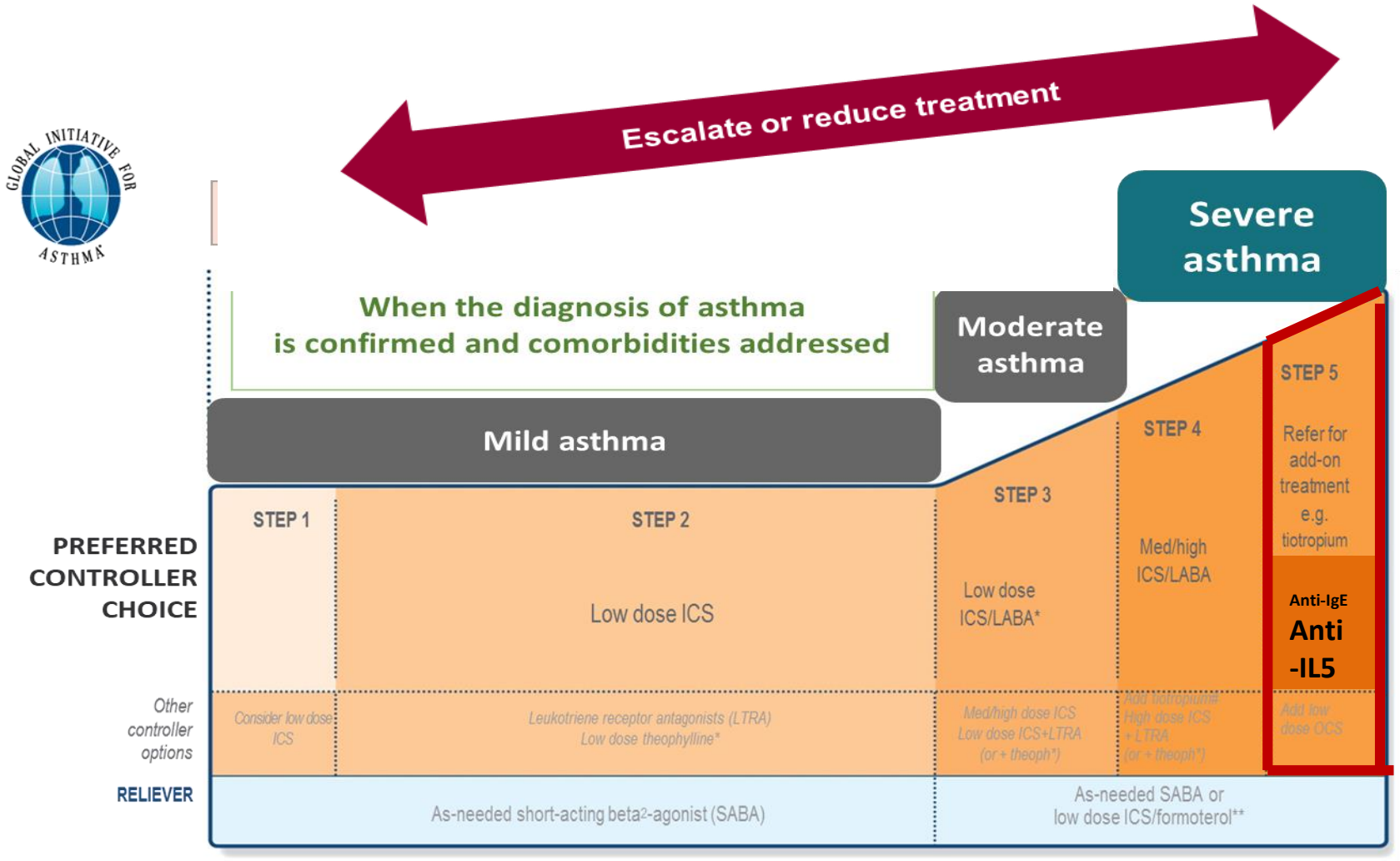




- 63% reduction in the sputum eosinophil count (p=0.002)
- Fewer severe asthma exacerbations (35 vs 109; p=0·01)
- Reduced ED admissions (1 vs 6, p=0.047)

Green, Lancet 2002; 360:1715-21

GINA Guidelines
Anti-IL5 therapies for severe eosinophilic asthma



Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018

Τα συστηματικά κορτικοστεροειδή μπορούν να αμβλύνουν την εωσινοφιλική φλεγμονώδη διαδικασία

"Refractory" Eosinophilic Airway Inflammation in Severe Asthma

Effect of Parenteral Corticosteroids

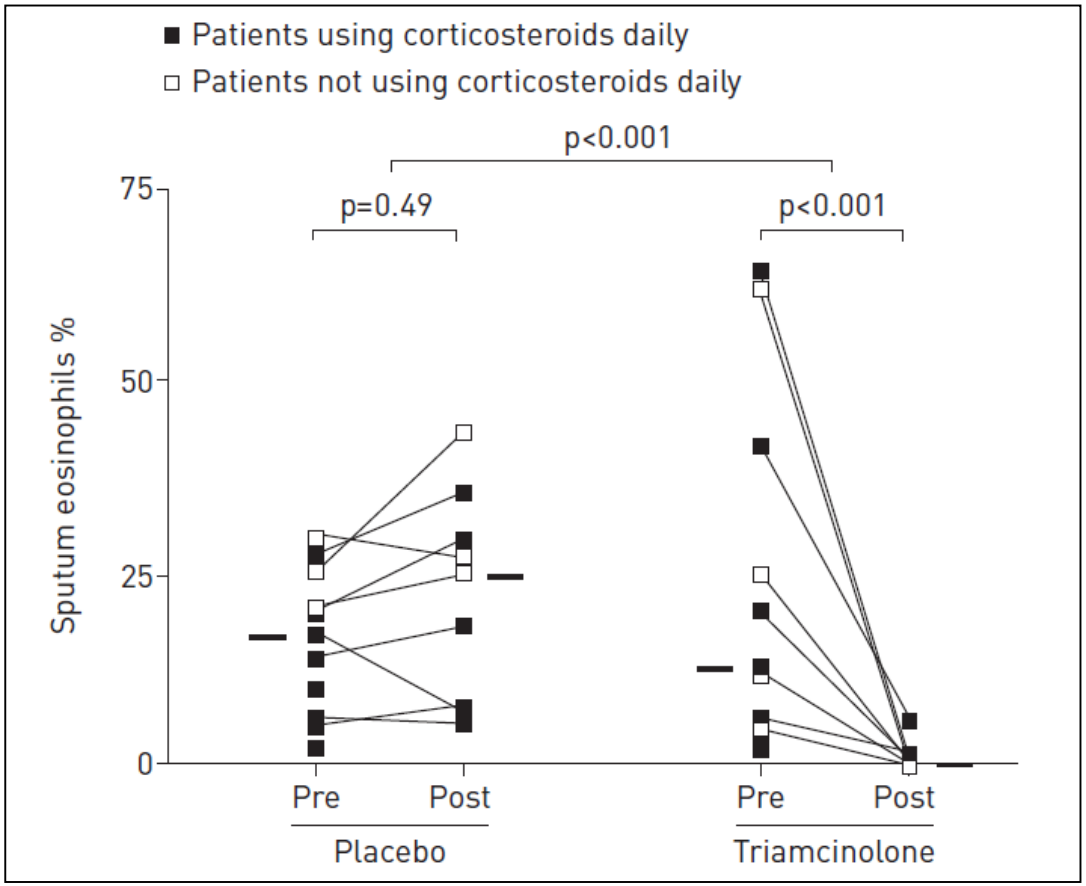


Figure 1. Effect of treatment with intramuscular triamcinolone (*circles*) or placebo (*squares*) on sputum eosinophil percentages in 22 patients with severe asthma. (*Open symbols*) Patients using oral corticosteroids on a daily basis. (*Closed symbols*) Patients not using oral corticosteroids on a daily basis. *Lines* represent median values.

Ten Brinke A, AJRCCM 2004; 170: 601–605

Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature

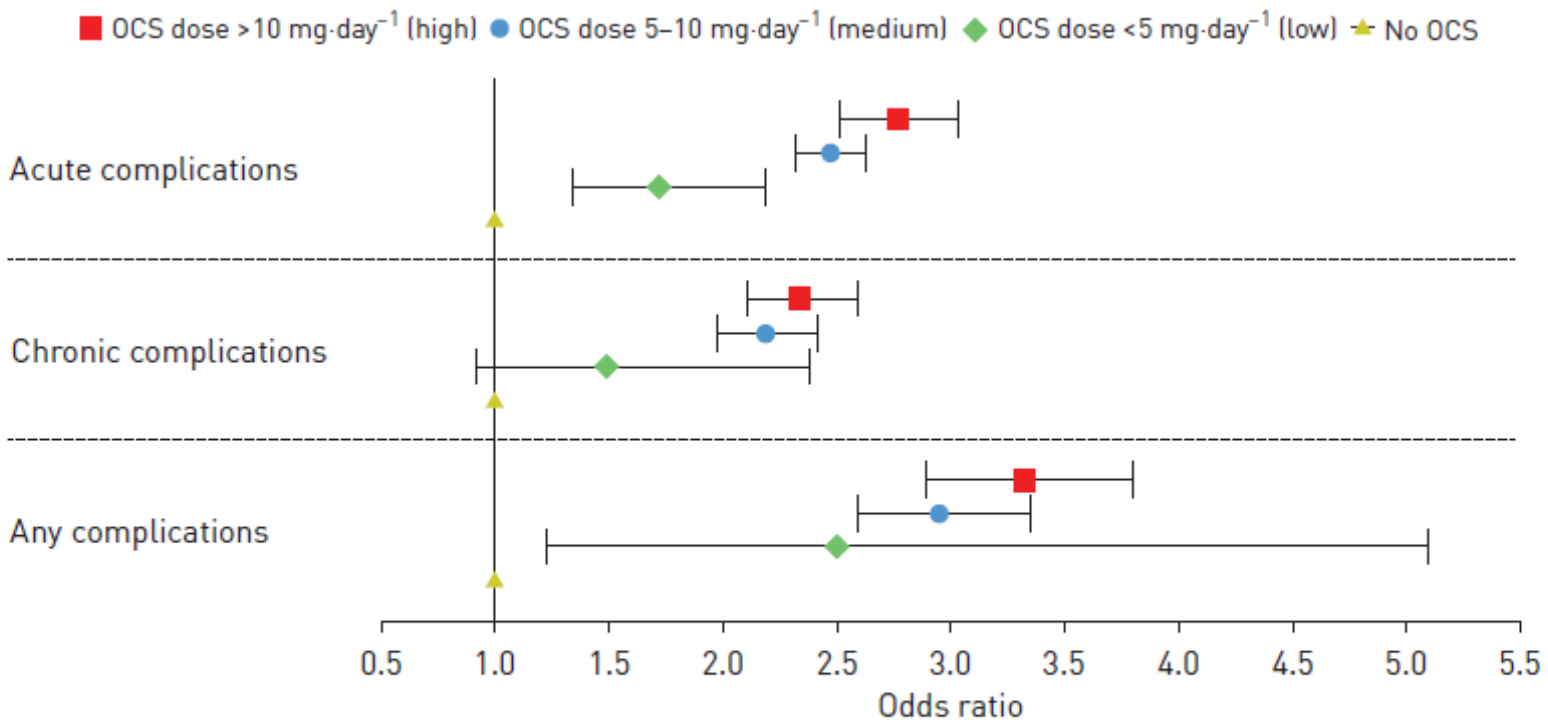
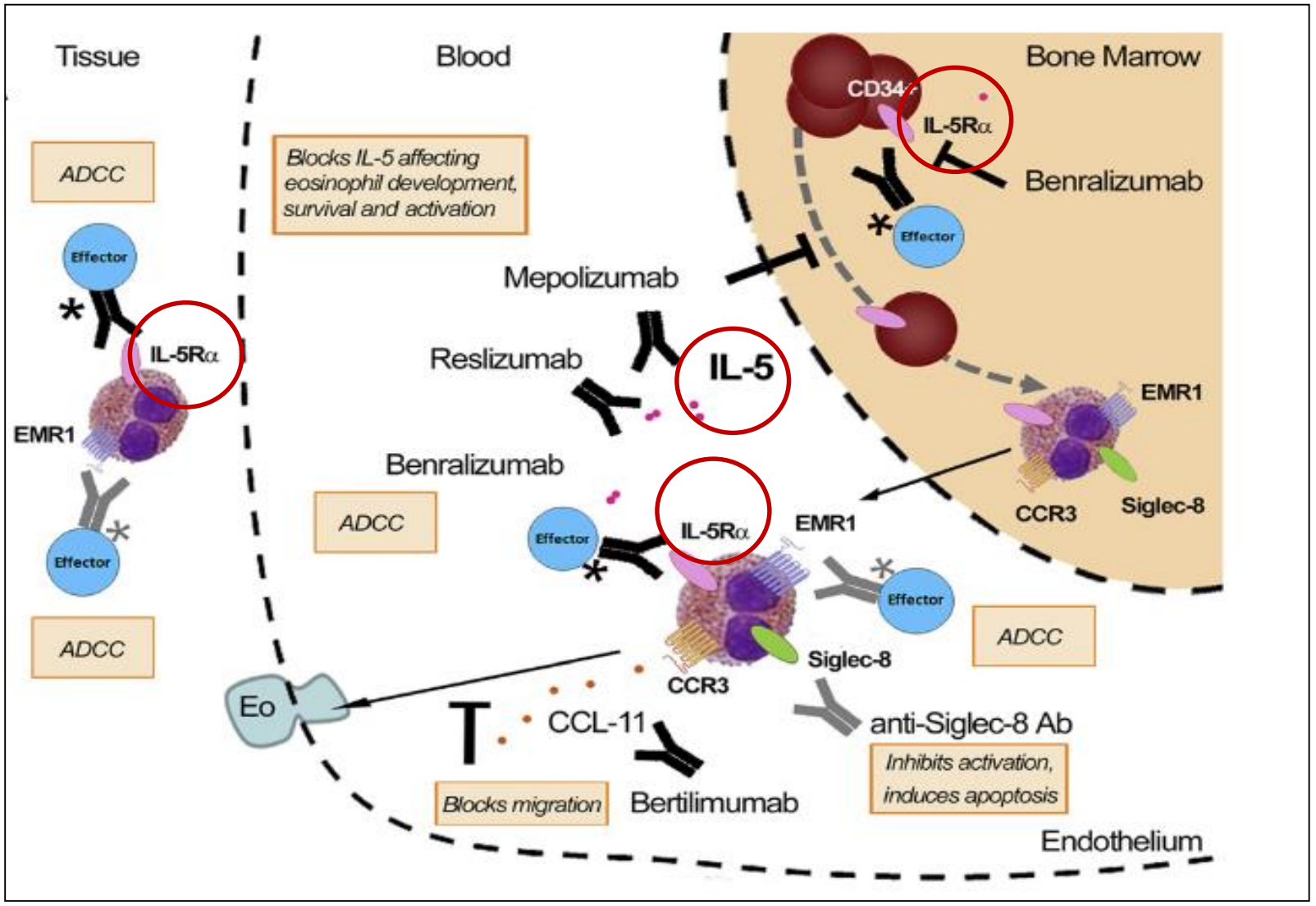


FIGURE 1 Risk of developing oral corticosteroid (OCS)-related complications by OCS dose exposures. OCS doses <5 mg·day^{-1} are considered low, 5–10 mg·day^{-1} medium and >10 mg·day^{-1} high. OR >1 describes a higher risk for developing OCS-related side-effects. Reproduced and modified from [23] with permission.

Volmer T, Eur Respir J 2018; 52: 1800703

Η IL-5 αποτελεί έναν ελκυστικό θεραπευτικό στόχο στο σοβαρό εωσινοφιλικό άσθμα



Legrand, J Allergy Clin Immunol Pract 2015

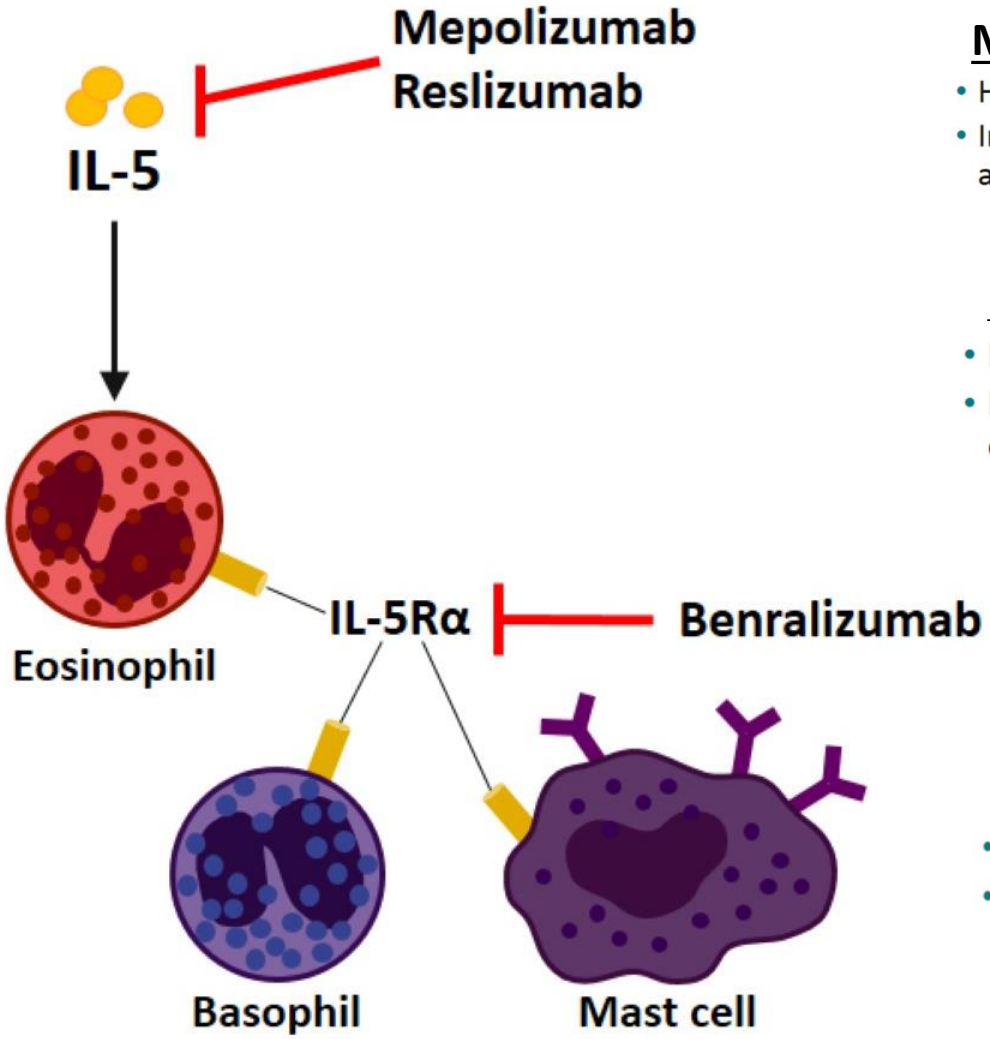
Διαφορές μεταξύ των εγκεκριμένων για το ΣΕΑ anti-IL5 θεραπειών

	Mepolizumab	Reslizumab	Benralizumab
Date of approval	04 November 2015 (FDA)[1] 03 December 2015 (EMA)[2]	23 March 2016 (FDA)[3] 16 August 2016 (EMA)[4]	14 November 2017 (FDA)[5] 08 January 2018 (EMA)[6]
Mechanism of action	Anti-IL-5 mAb[1,2]	Anti-IL-5 mAb[3,4]	Anti-IL-5R mAb[5,6]
Δοσολογικό σχήμα	100 mg Q4W	3 mg/kg	30mg Q4W (x3) & μετά 30mg Q8W
Οδός χορήγησης	SC	IV	SC
Φαρμακολογική μορφή	Σκόνη για διάλυμα προς έγχυση	Διάλυμα προς έγχυση	Προγεμισμένη σύριγγα
Ηωσινόφιλα αίματος	≥150 cells/μl	≥400 cells/μl	≥300 cells/μl

EMA 2018

1. FDA. Drugs@FDA: FDA Approved Drug Products. Mepolizumab. Available from: www.accessdata.fda.gov/scripts/cder/daf/ [accessed September 2018]; 2. EMA. Human medicines. Mepolizumab. Available from: www.ema.europa.eu/ema/ [accessed September 2018]; 3. FDA. Drugs@FDA: FDA Approved Drug Products. Reslizumab. Available from: www.accessdata.fda.gov/scripts/cder/daf/ [accessed September 2018];
4. EMA. Human medicines. Reslizumab. Available from: www.ema.europa.eu/ema/ [accessed September 2018]; 5. FDA. Drugs@FDA: FDA Approved Drug Products. Benralizumab. Available from: www.accessdata.fda.gov/scripts/cder/daf/ [accessed September 2018]; 2. EMA. Human medicines. Benralizumab. Available from: www.ema.europa.eu/ema/ [accessed September 2018].

Anti-IL5/IL5-R θεραπείες στο ΣΕΑ: Mepolizumab, Reslizumab, Benralizumab (IL5-R)



Mepolizumab

- Humanized Mab against IL-5
- Indicated for add-on maintenance in severe eosinophilic asthma in pts ≥ 12 years of age
  - Subcutaneous administration

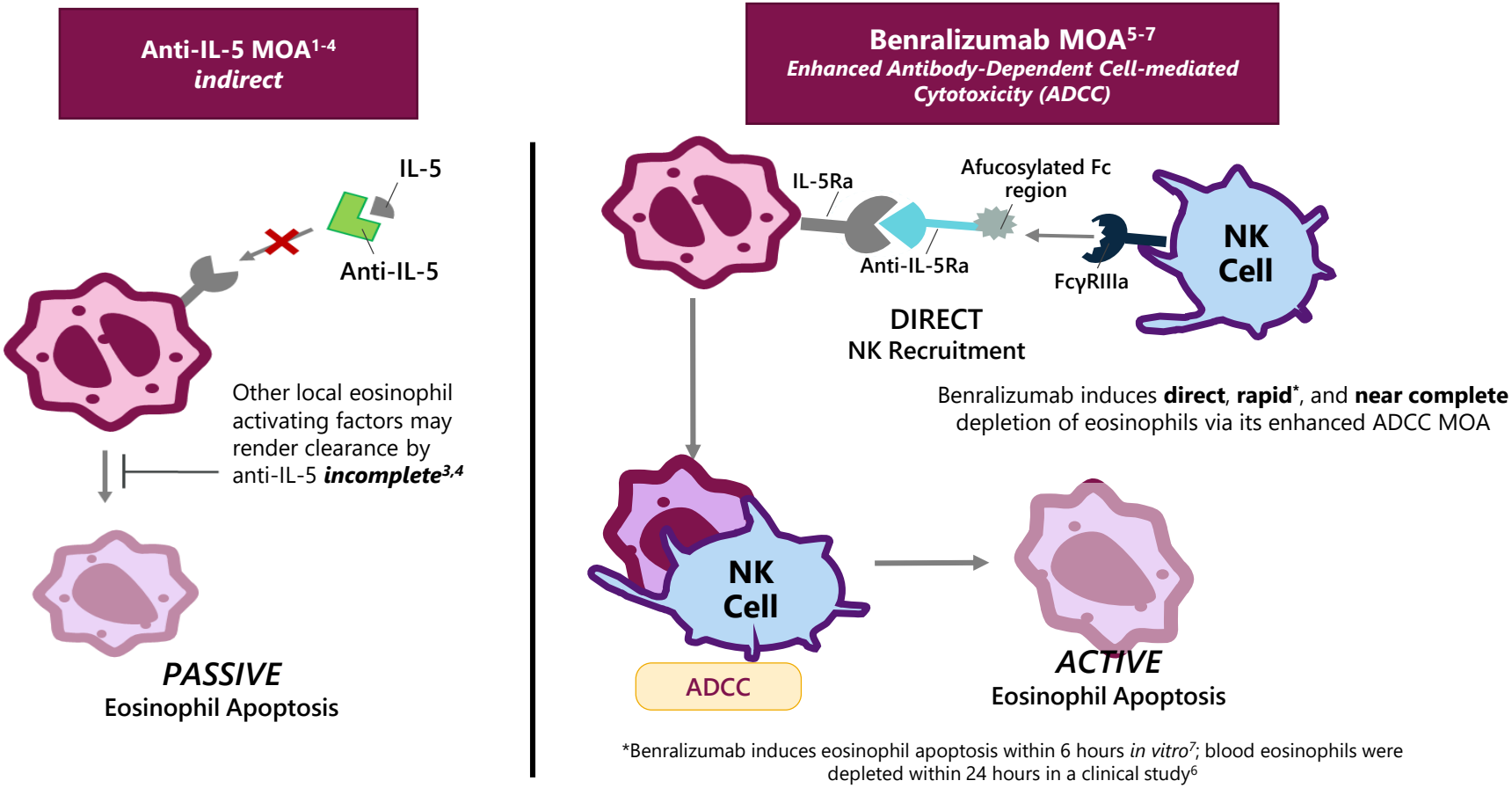
Reslizumab

- Humanized Mab against IL-5
- Indicated for maintenance add-on for severe eosinophilic asthma, ≥ 18 years of age
  - Administered via IV infusion

Benralizumab

- Humanized Mab against the IL-5 receptor-α
- Indicated for maintenance add-on for severe eosinophilic asthma in patients ≥ 12 years of age[a]
  - Subcutaneous injection

Benralizumab induces direct, rapid and near complete depletion of eosinophils via antibody-dependent cell-mediated cytotoxicity

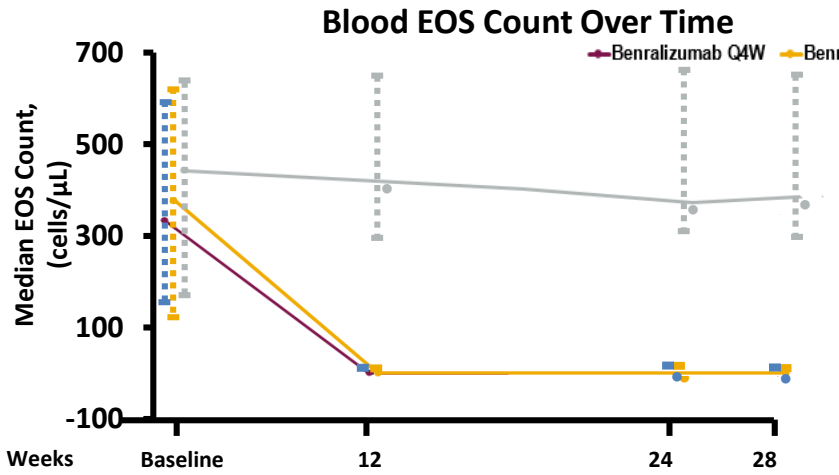


*Benralizumab induces eosinophil apoptosis within 6 hours *in vitro*[7]; blood eosinophils were depleted within 24 hours in a clinical study[6]

1. Patterson MF, et al. J Asthma Allergy. 2015;8:125-134; 3. Flood-Page P, et al. Am J Respir Crit Care Med. 2003.167:199-204; 4. Sehmi R et al. Clin Exper Allergy. 2016;793-802; 5. Kolbeck R et al. JACI 2010;125:1344-1353; 6. Laviolette M et al. J Allergy Clin Immunol. 2013;132:1086-1096;

Anti-IL5 θεραπείες:Επίδραση στον αριθμό των Bl-Eos

Benralizumab: σχεδόν πλήρης εξαφάνιση



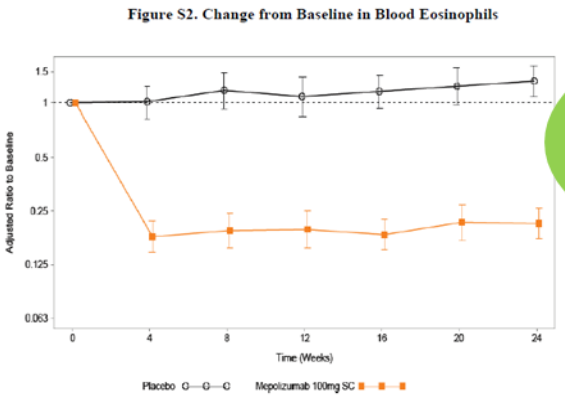
Nair P et al. Supplementary appendix. *N Engl J Med*. 2017

↓~100%

Median blood percent changes in EOS counts were reduced from baseline by 100% in patients treated with benralizumab Q4W and Q8W compared to 6% for patients in the placebo group

EOS = eosinophil; Q4W = every 4 weeks; Q8W = every 8 weeks. Error bars represent upper and lower quartiles.

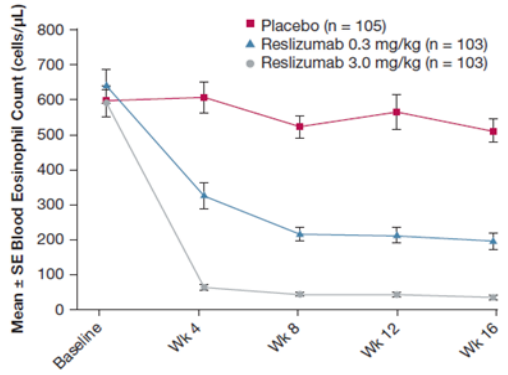
Mepolizumab: μείωση, αλλά όχι εξαφάνιση



↓84%

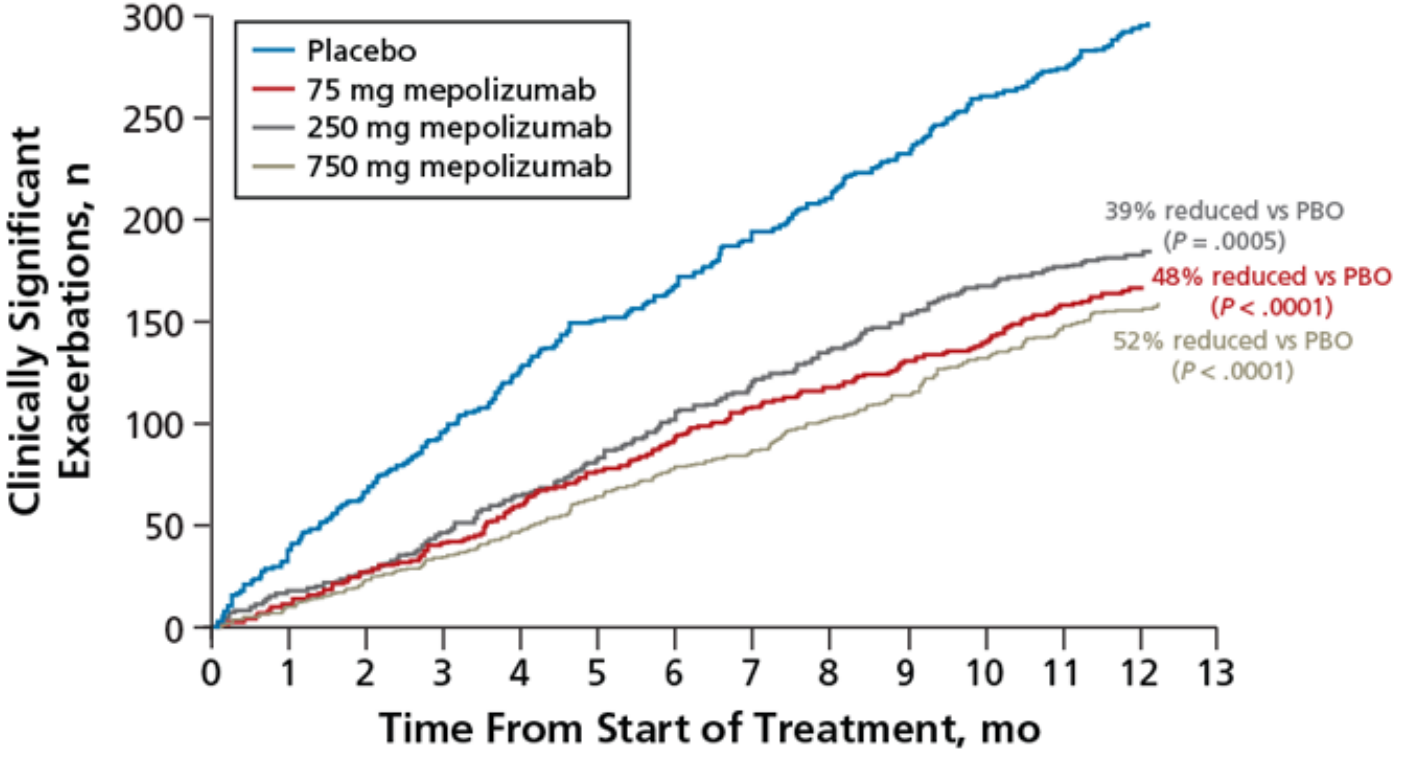
Bel E et al Supplement NEJM 2016

Reslizumab: Ομοίως



Bjermer L et al Chest 2016

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial



621 patients with ≥2 exacerbations in previous year, sputum eosinophils > 3%, FeNO > 50 ppb, and blood eosinophils >300/cc were randomised to mepolizumab 75 mg, 250 mg, 750 mg or placebo.

Pavord Lancet 2012;380:651-59

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

MENSA STUDY

- **576 patients with recurrent (≥2) asthma exacerbations and >150 cells/µL at baseline or >300 cells/µL during the 12-month period before screening, despite high doses of ICS**

Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.75	0.93	47 (29 to 61)†	<0.001	0.81	53 (37 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (–41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (–66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	–0.50±0.07	–0.92±0.07	–0.42 (–0.61 to –0.23)	<0.001	–0.94±0.07	–0.44 (–0.63 to –0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	–9.0±1.2	–15.4±1.2	–6.4 (–9.7 to –3.2)	<0.001	–16.0±1.1	–7.0 (–10.2 to –3.8)	<0.001

Ortega, N Engl J Med 2014;371:1198-207

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma (SIRUS investigation)

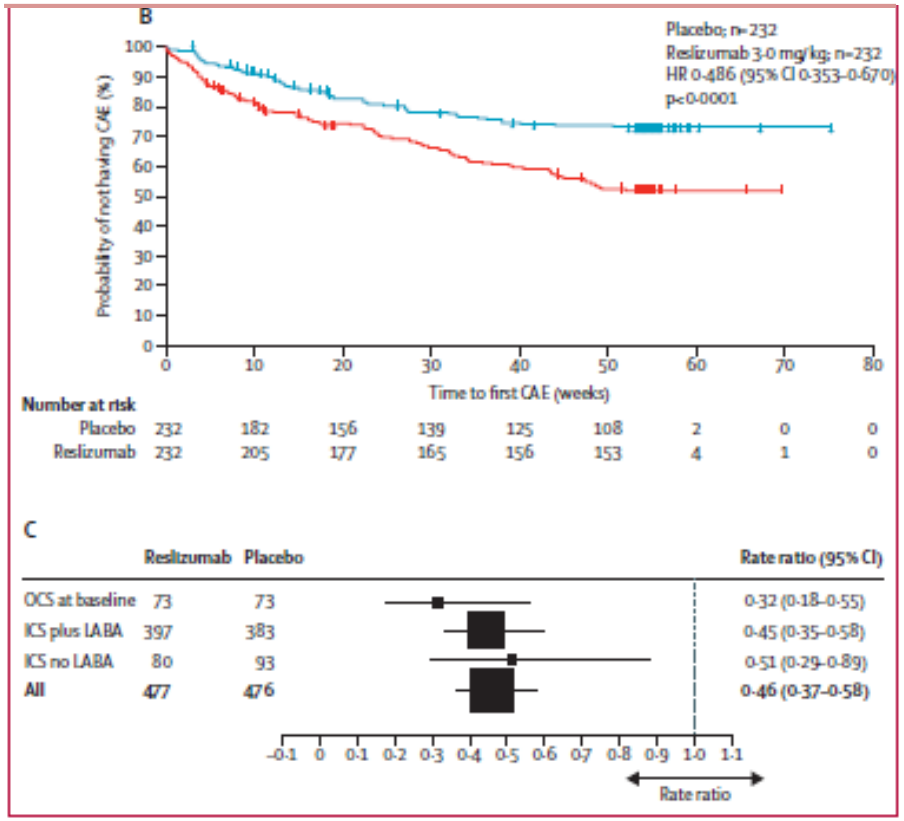
- **Blood eosinophil level of ≥300 cells/µL during the 12-month period before screening or ≥150 cells/µL during the optimization phase**

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

Bel, N Engl J Med 2014.371:1189-97

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

- **953 Patients with ≥1 asthma exacerbations during the previous year and >400/µLB-Eos at baseline**



- **Significant reduction in the frequency of asthma exacerbations compared with PBO**

Study 1: RR 0.50 [95% CI 0.37–0.67];
Study 2: 0.41 [0.28–0.59];
both p<0.0001

- Grater benefit **in the OCS-treated subset of patients**

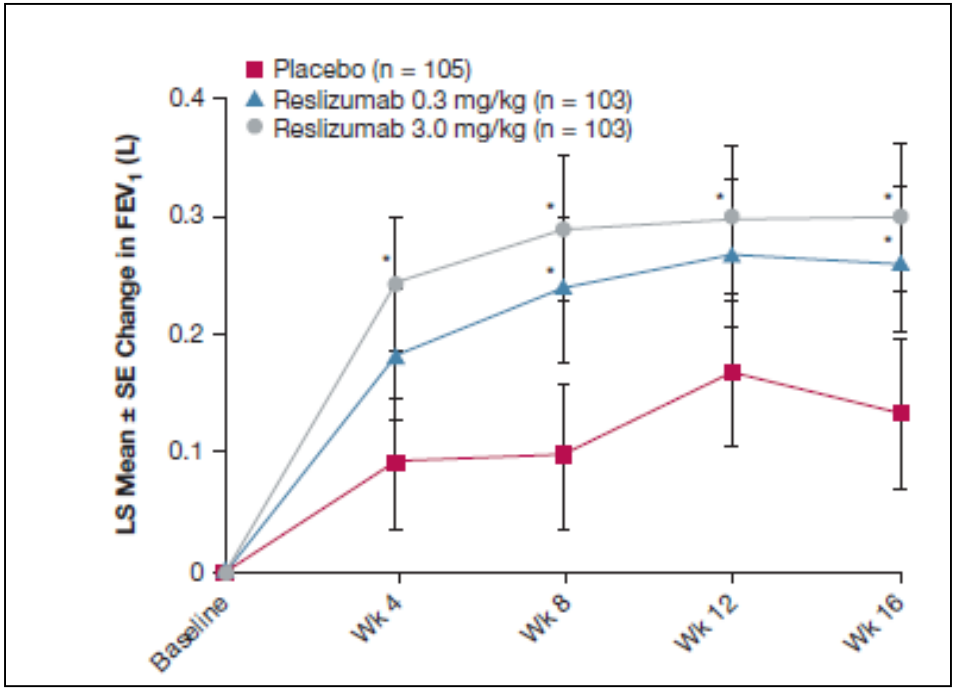
Castro, Lancet Respir Med. 2015; 3:355-66

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

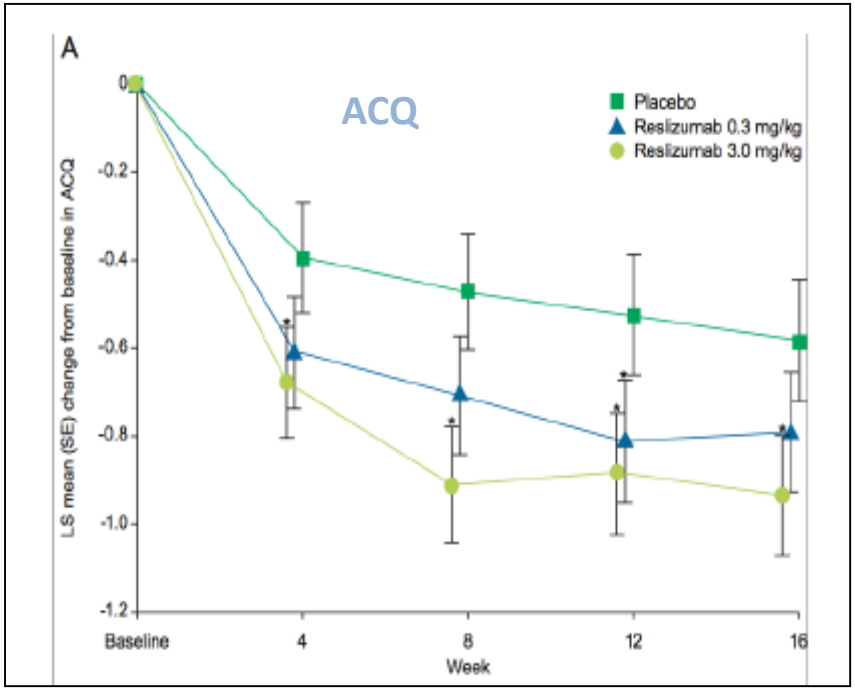
A Randomized Phase 3 Study

- 315 patients, inadequately controlled (ACQ≥1.5) by at least a medium dose of ICS and at least one Bl-Eos count of ≥400 cells/µL during the screening period
- Reslizumab 0.3 mg/Kg i.v., 3.0mg/Kg i.v. or PBO, once every 4 wks for 16 wks

Change in baseline FEV_1



Change in baseline symptoms



*P≤ 0.05

Bjermer L, CHEST. 2016; 150: 789-798

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

Bleecker ER, Lancet. 2016; doi: 10.1016/S0140-6736(16)31324-1

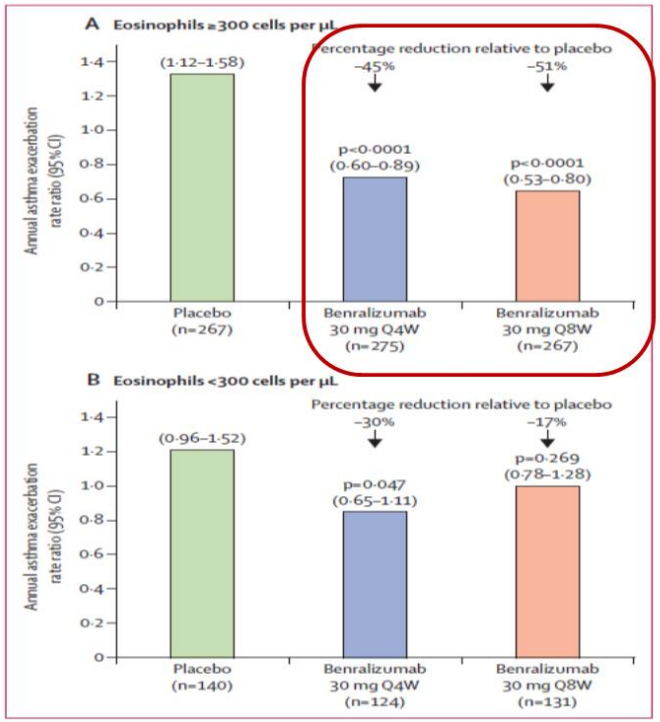
- 1205 patients **with ≥2 exacerbations** during the previous year, **while on high doses ICS + LABA** were randomized to receive Benralizumab 30mg s.c. Q4W, Benralizumab Q8W or placebo (1:1:1) for 48 wks as add on to their standard Tx

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

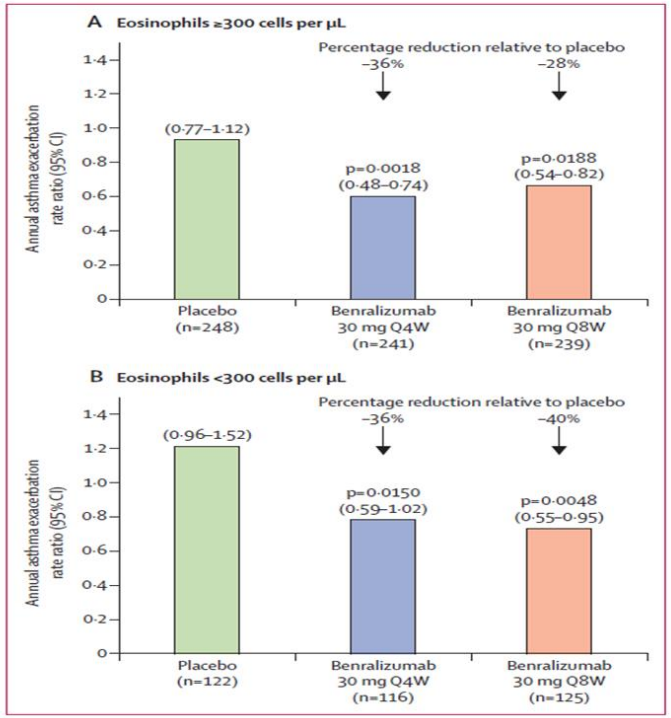
FitzGerald JM, Lancet. 2016; doi: 10.1016/S0140-6736(16)31322-8

- 1306 patients **with ≥2 exacerbations** during the previous year, **while on both high and medium doses ICS + LABA** were randomized to receive Benralizumab 30mg s.c. Q4W, Benralizumab Q8W or placebo (1:1:1) for 56 wks as add on to their standard Tx

SIROCCO



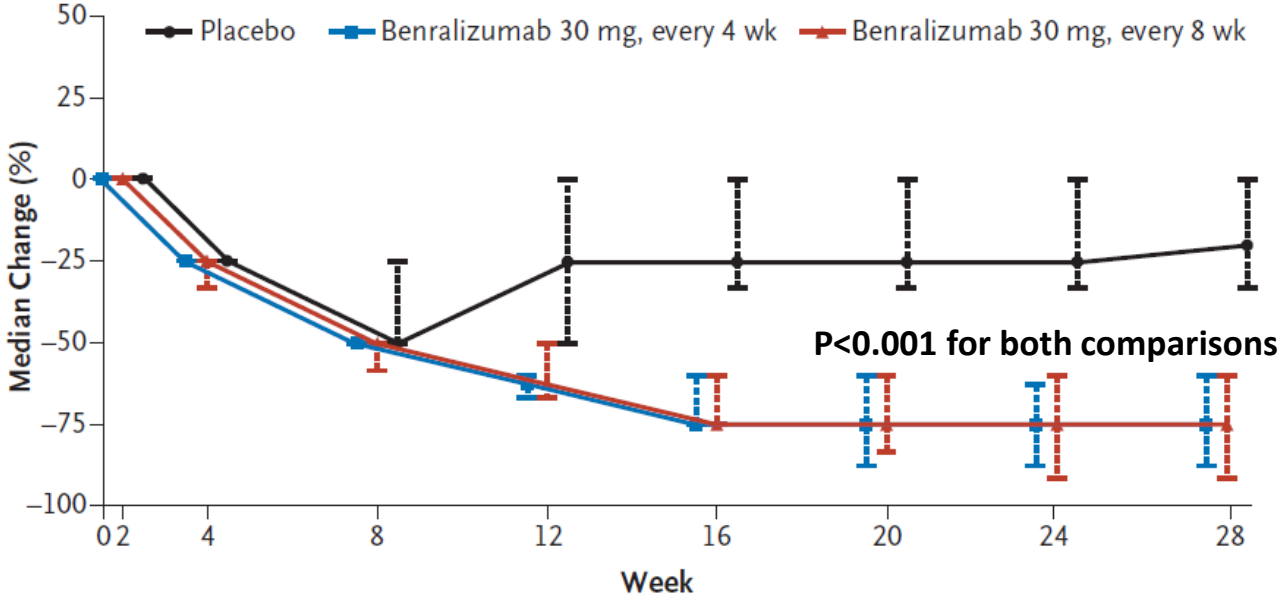
CALIMA



Annual asthma exacerbation rates according to baseline Bl-Eos concentrations

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

A Change from Baseline in Oral Glucocorticoid Dose



No. at Risk

Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

Nair P, N Engl J Med 2017;376:2448-58

Anti-IL5 therapies for asthma (Review)

Farne HA, Wilson A, Powell C, Bax L, Milan SJ

Cochrane Library

Cochrane Database of Systematic Reviews

Authors' conclusions

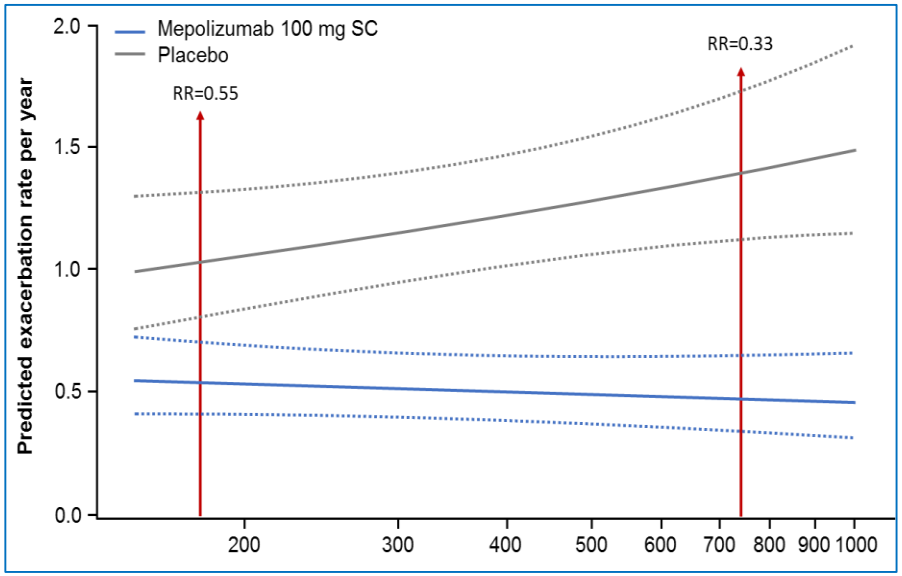
Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control. These treatments roughly halve the rate of asthma exacerbations in this population. There is limited evidence for improved HRQoL scores and lung function, which may not meet clinically detectable levels. There were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although there remains a question over adverse events significant enough to prompt discontinuation.

Further research is needed on biomarkers for assessing treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-eosinophilic patients, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-immunoglobulin E. For benralizumab, future studies should closely monitor rates of adverse events prompting discontinuation.

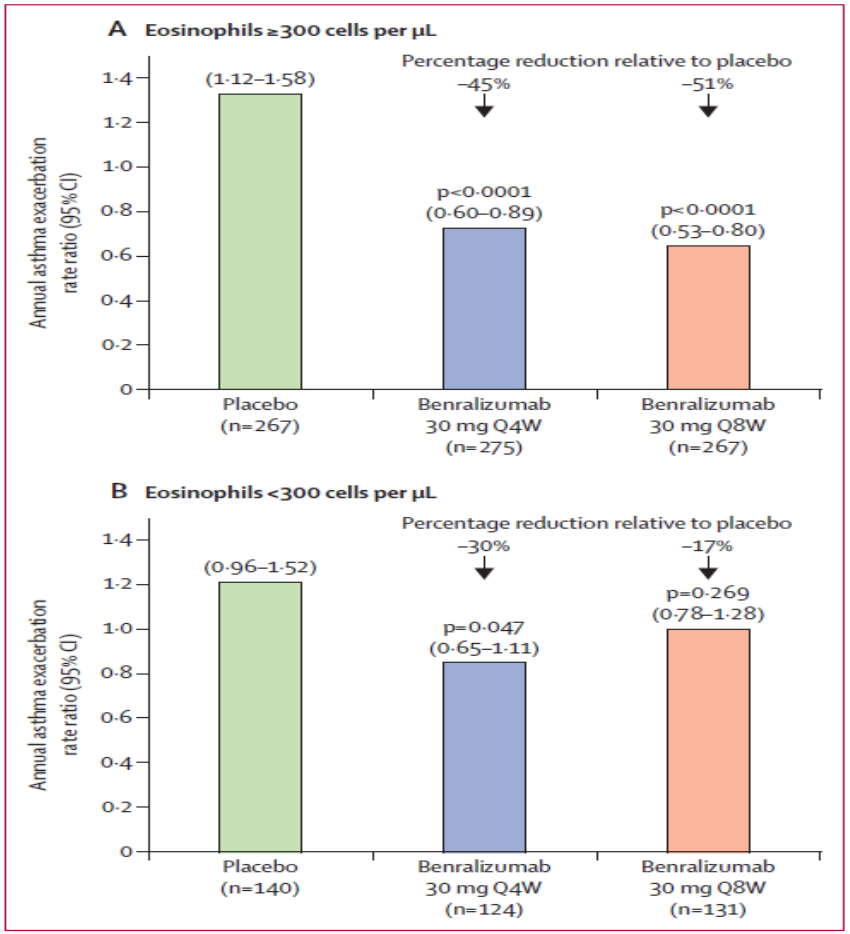
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD010834.
DOI: 10.1002/14651858.CD010834.pub3.

Baseline eosinophil counts are predictive of anti-IL5 treatment benefit

MUSCA[1]



SIROCCO[2]

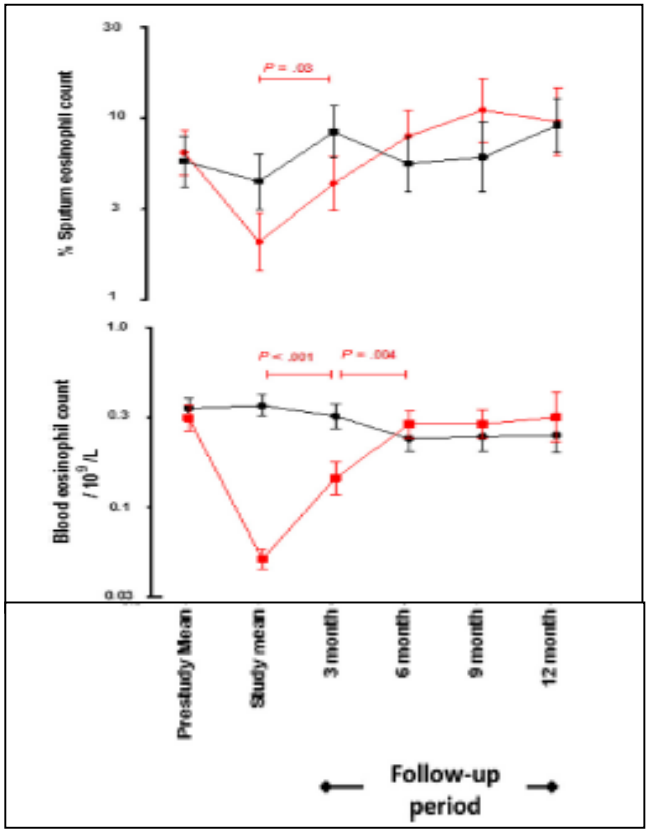


1. Chupp et al Lancet Respir Med 2017, 2. FitzGerald JM, Lancet. 2016

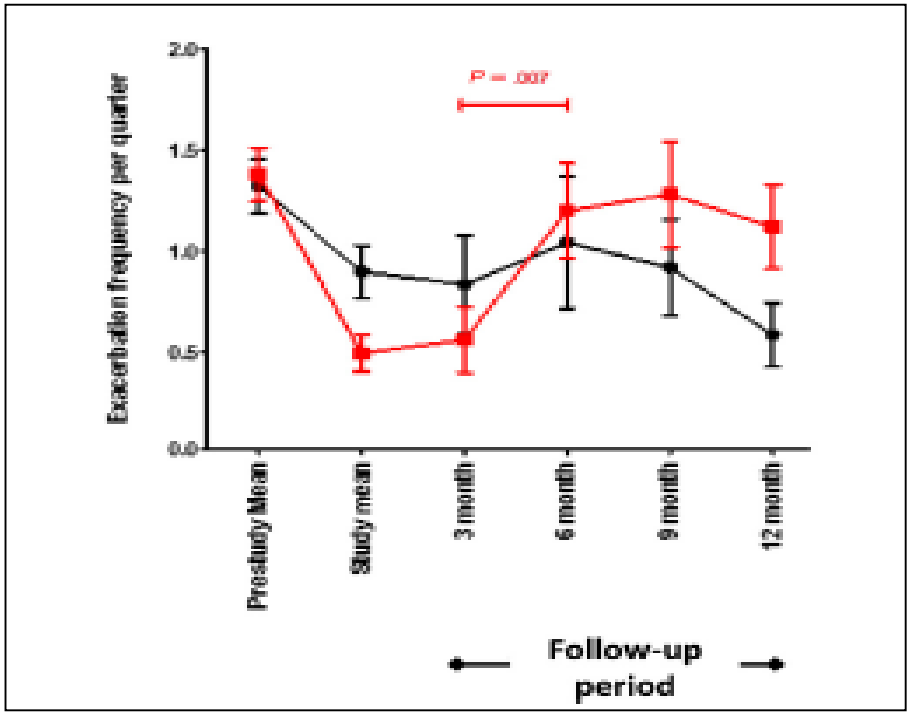
A sustained therapeutic benefit of anti-IL5 therapy requires continued dosing

Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: A 12-month follow-up analysis

Sp-Eos and Bl-Eos



Exacerbation frequency



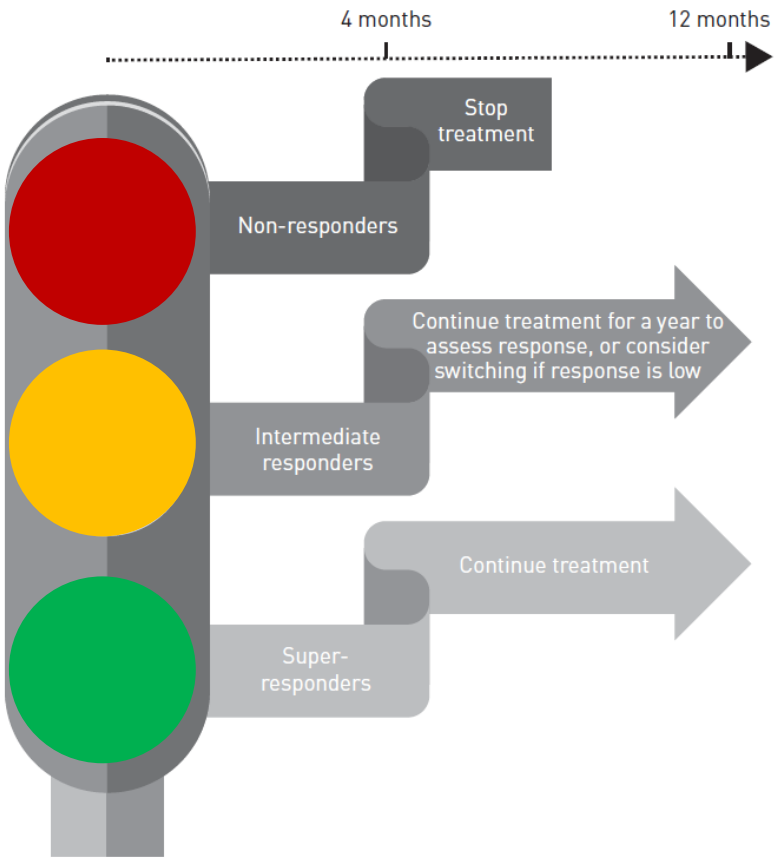
Haldar, JACI 2014; 133:921-923

Παρακολούθηση ασθενών που λαμβάνουν anti-IL5 θεραπείες

- Πώς γίνεται η παρακολούθηση των ασθενών που λαμβάνουν anti-IL5 θεραπείες;
- Πώς μπορούμε να προσδιορίσουμε ποιοι ασθενείς ανταποκρίθηκαν στη θεραπεία;
- Υπό ποιες κλινικές συνθήκες πρέπει οι ασθενείς να σταματήσουν ή να αλλάξουν θεραπεία;

Παράγοντες που αξιολογούμε

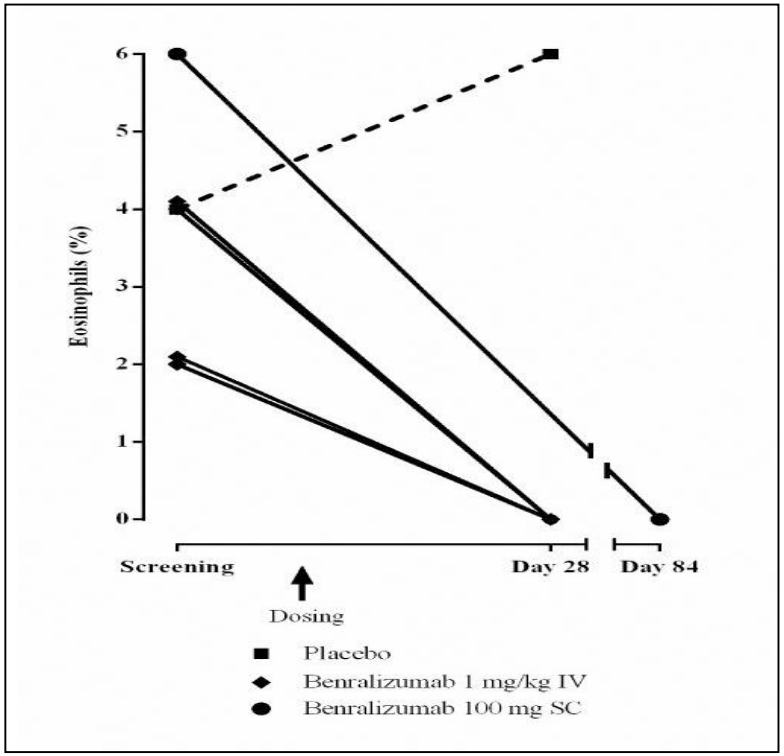
- Μείωση των παροξύνσεων
- Βελτίωση στα συμπτώματα (ACT, ACQ, αποκατάσταση της όσφρησης, ποιότητα ύπνου κ.α.)
- Συνολική βελτίωση της κατάστασης της υγείας (AQLQ, SGRQ)
- Εκτίμηση των συννοσηροτήτων



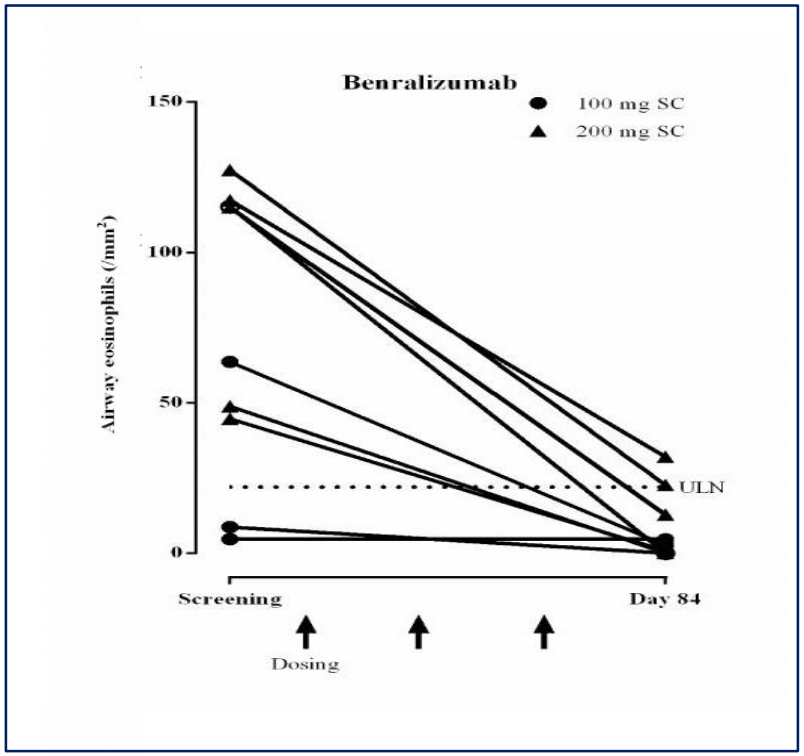
Buhl R, Eur Respir J 2017; 49: 1700634

Σε ορισμένους ασθενείς δεν παρατηρείται πλήρης εξαφάνιση των Eos στους ιστούς με τις anti-IL5 θεραπείες

Bone marrow

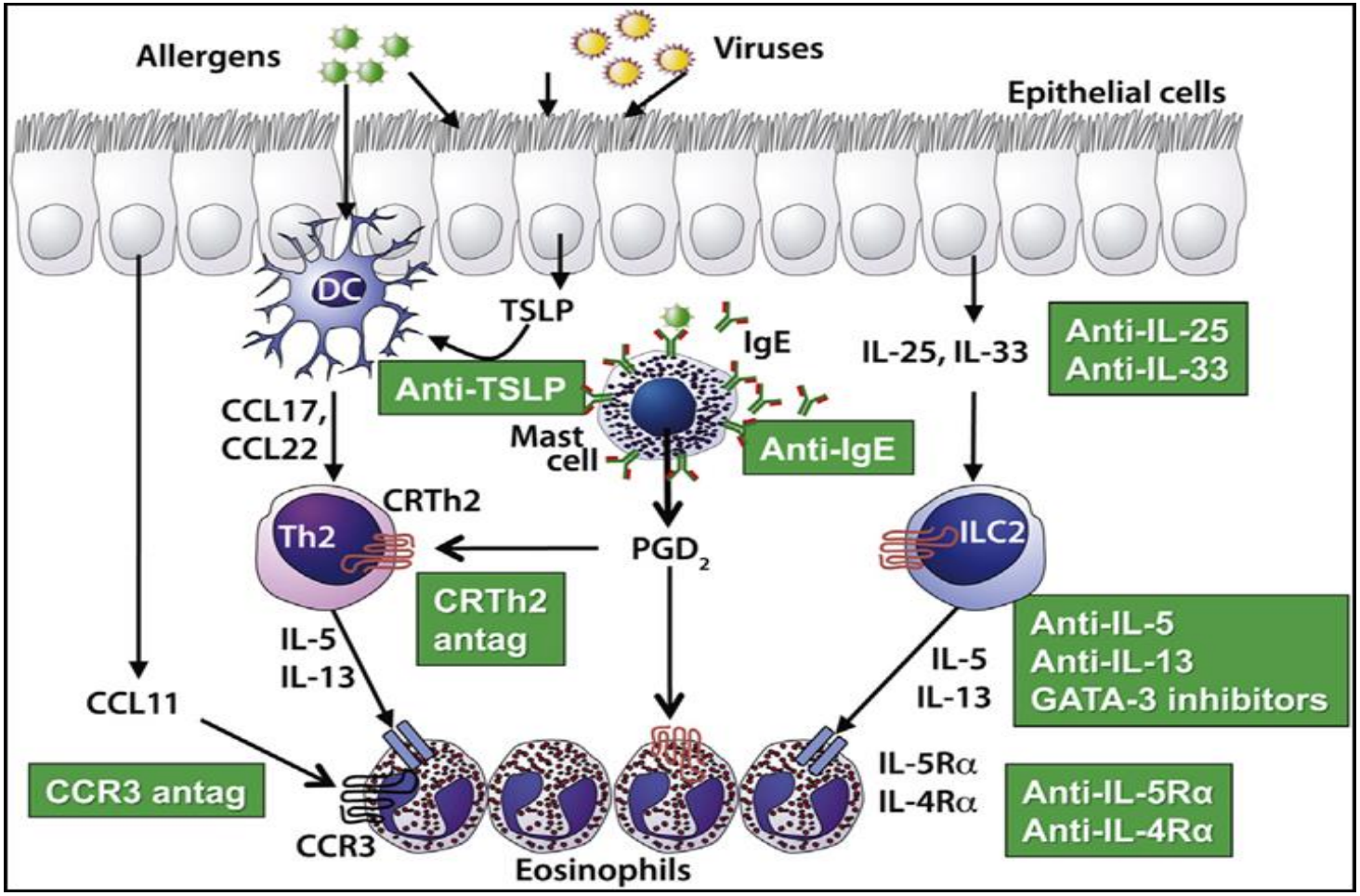


Airway mucosa/submucosa



Laviolette M, Allergy Clin Immunol. 2013; 132: 1086–1096.e5

Potential targets for severe eosinophilic asthma



Barnes PJ, J Allergy Clin Immunol. 2015; 136: 531-545

Αποτελεσματικότητα του Omalizumab στη μείωση των παροξύνσεων σε σχέση τα επίπεδα των εωσινοφίλων στο περιφερικό αίμα

Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma

T. B. Casale[1] | B. E. Chipps[2] | K. Rosén[3] | B. Trzaskoma[3] | T. Haselkorn[4] | T. A. Omachi[3] | S. Greenberg[5,6] | N. A. Hanania[7]

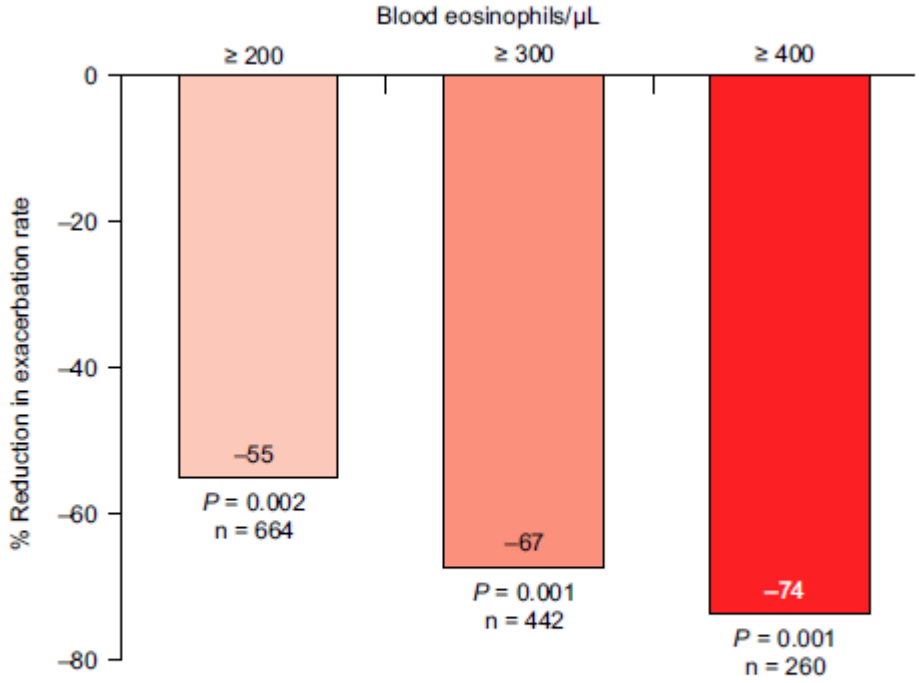
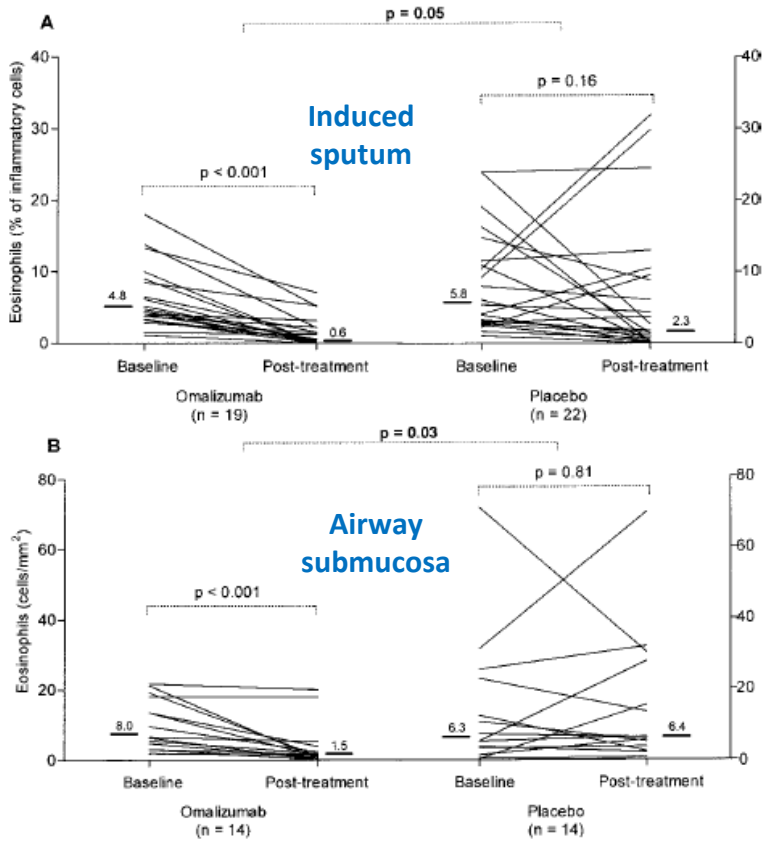


FIGURE 2 Relative percentage change in exacerbation rate by blood eosinophil levels

Casale TB. Allergy. 2018;73:490–497.

Omalizumab attenuates airways and systemic eosinophilia

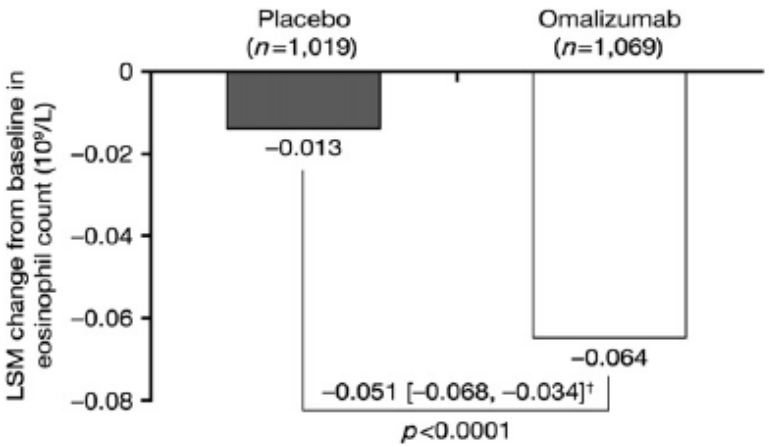
Effects of Treatment with Anti-immunoglobulin E Antibody Omalizumab on Airway Inflammation in Allergic Asthma



Djukanovic, AJRCCM 2004;170:583-593

Effect of omalizumab on peripheral blood eosinophilia in allergic asthma

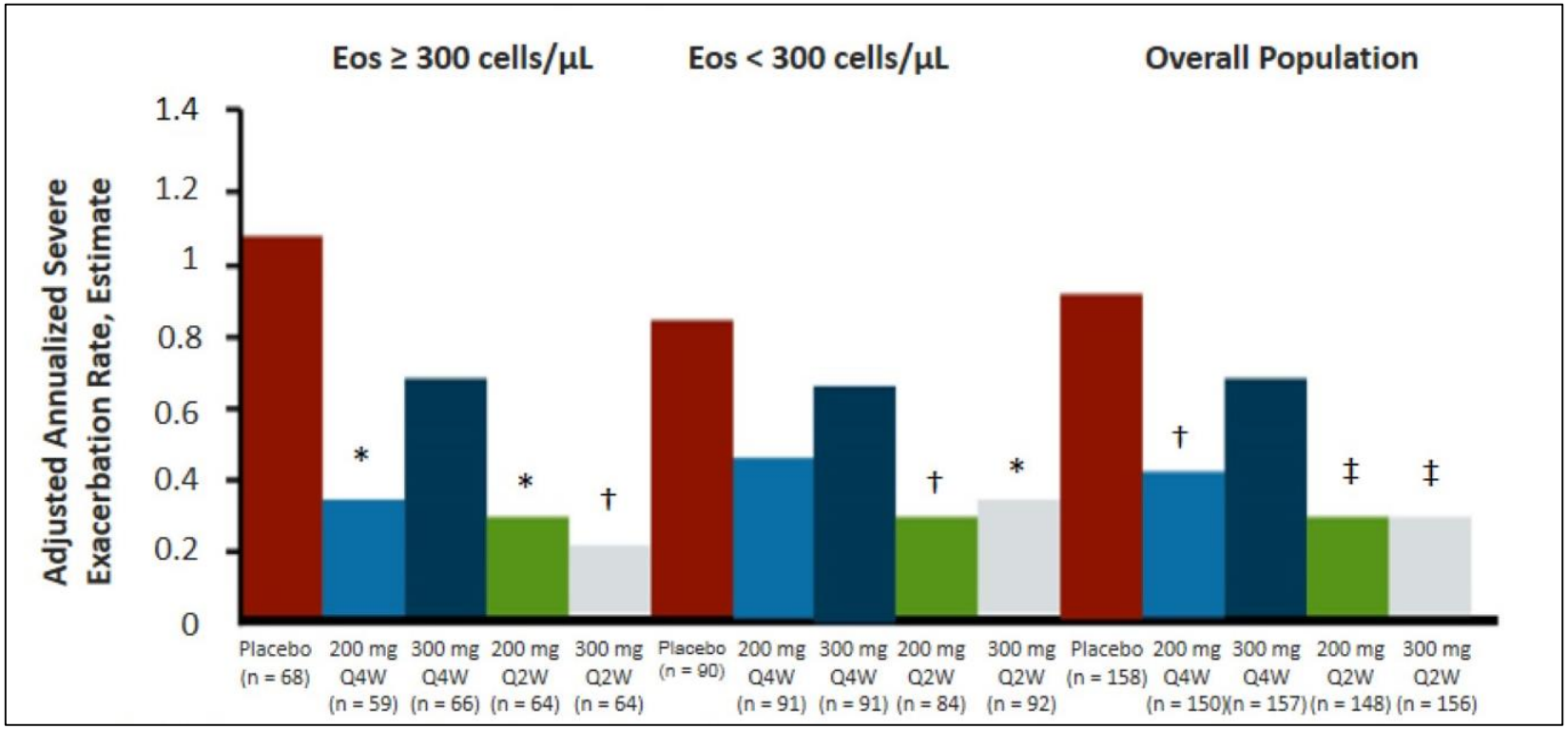
Eosinophils in peripheral blood



Massanari, Respir Med 2010; 104: 188-96

Dupilumab (anti-IL13/IL4-Rα) significantly reduced exacerbations irrespective of baseline eosinophil count

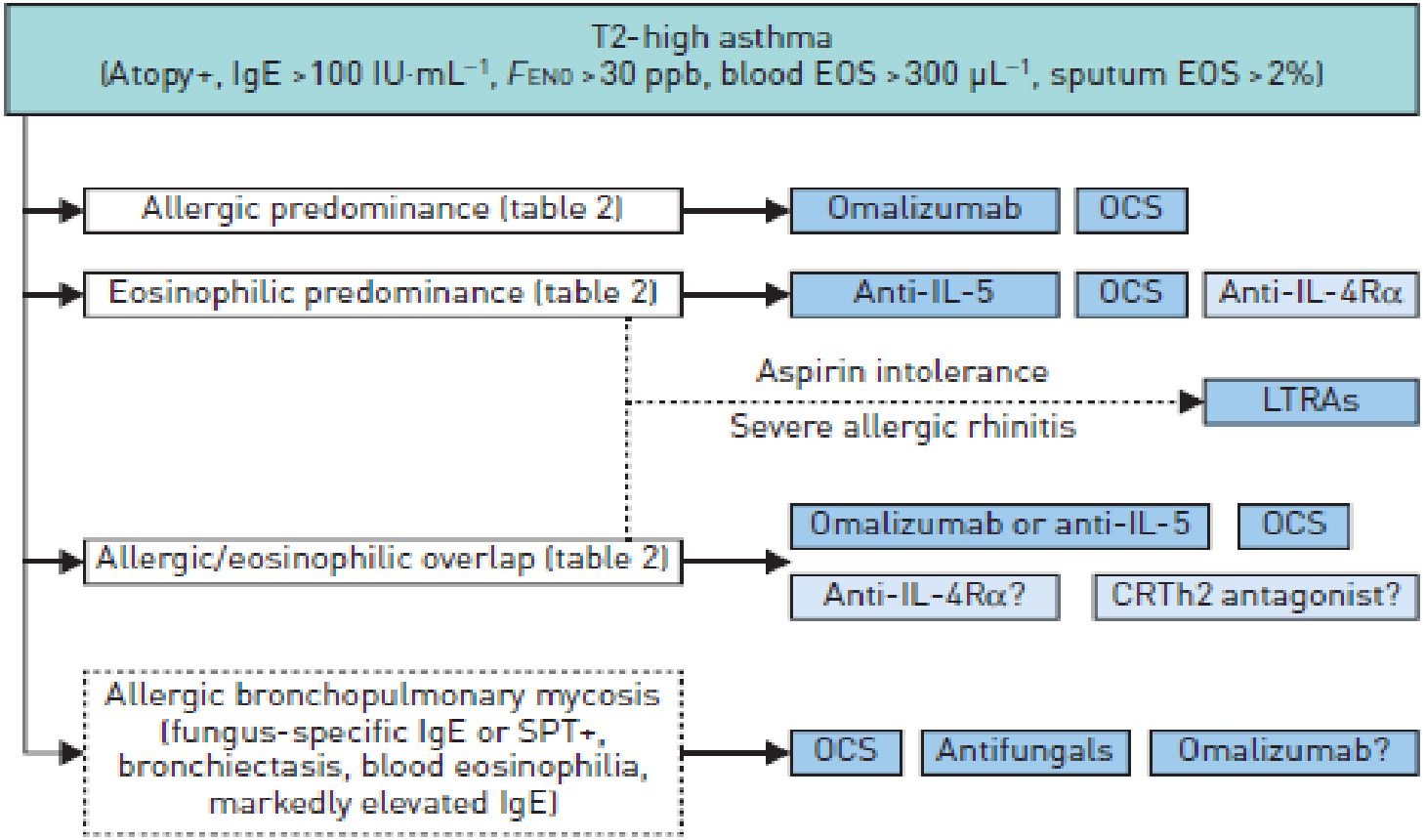
- **769 patients were randomly assigned (1:1:1:1:1) to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, over a 24-week period**



The effects may be greater in patients with peripheral blood eosinophilia, particularly at the 300mg dosing every 2 weeks

Wenzel S, Lancet. 2016;388:31-44

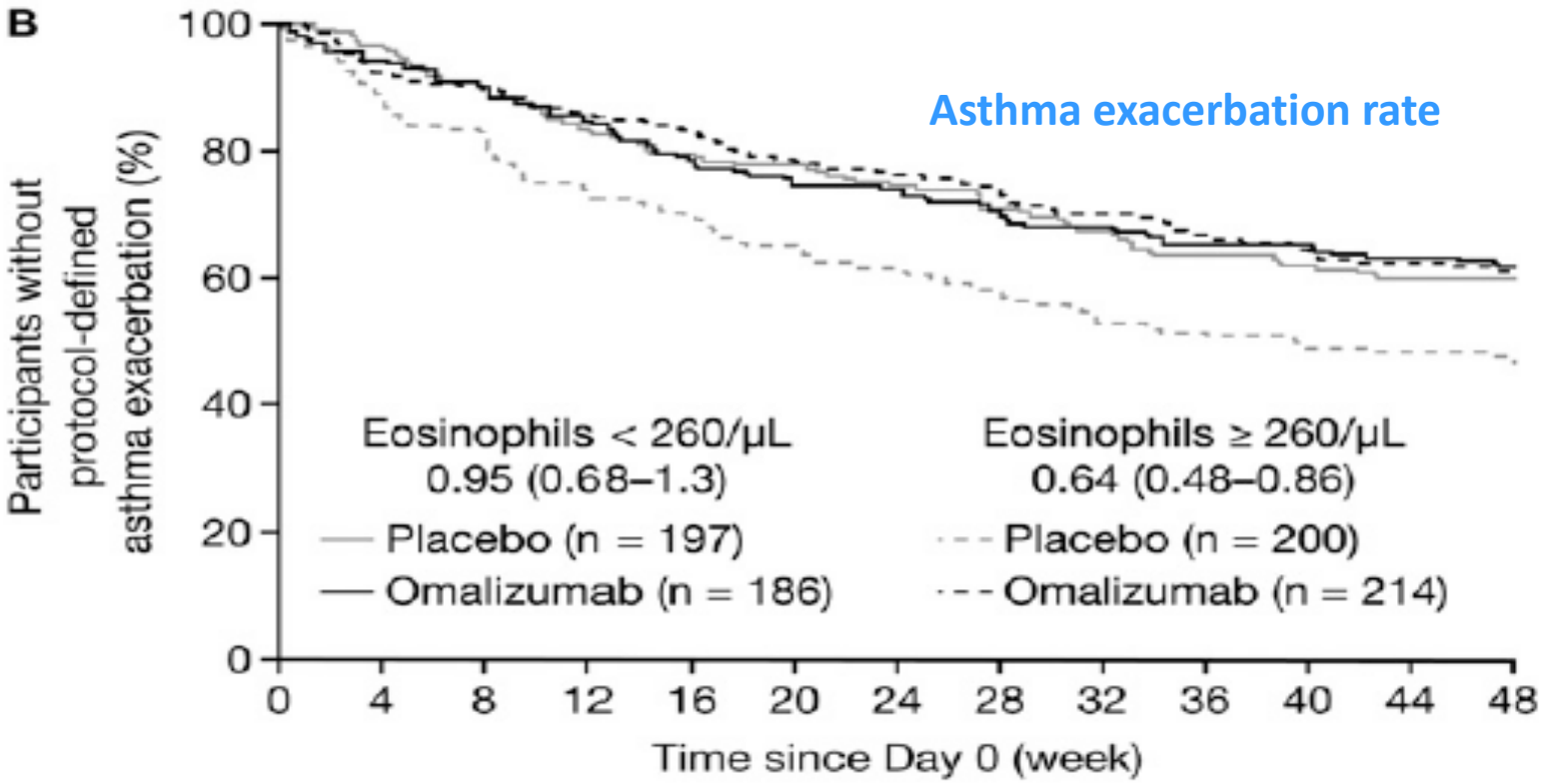
An algorithmic approach for the treatment of severe uncontrolled asthma



Zervas E, ERJ Open Res 2018; 4: 00125-2017

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study



Bl-Eos
> 260 cells/µL

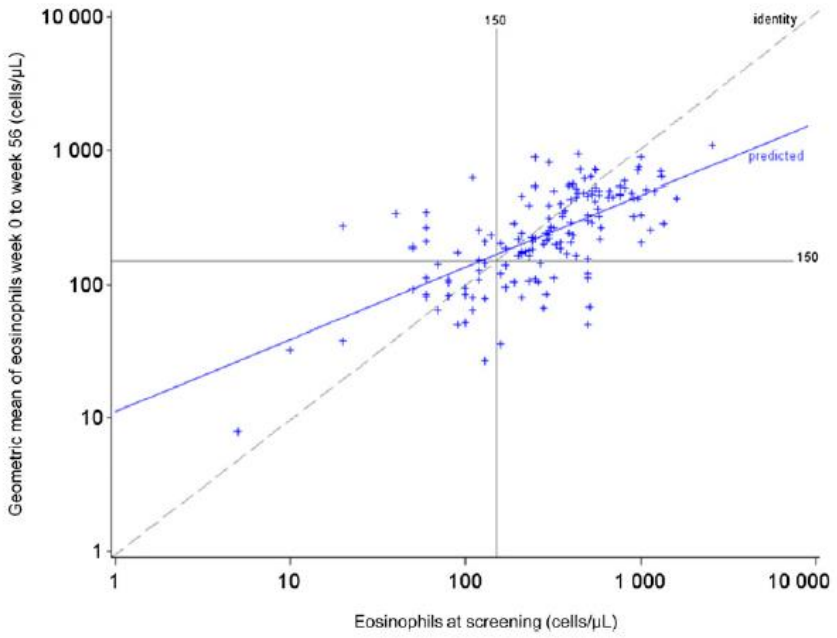
Higher exacerbation rates in the placebo group:
predictive of exacerbations

Greater benefit from omalizumab:
predictive of treatment response

Hanania. AJRCCM 2013;187:804–811.

Blood Eosinophil Count Is a Useful Biomarker to Identify Patients with Severe Eosinophilic Asthma

Screening Bl-Eos versus the geometric mean after screening



- **85%** of the subjects with **a screening Bl-Eos count of >150 cells/ml remained at 150 cells/ml or greater** in the following year

- **67%** of the subjects with **a screening Bl-Eos count of <150 cells/ml remained below the proposed cut-off of 150 cells/ml or greater** in the following year.

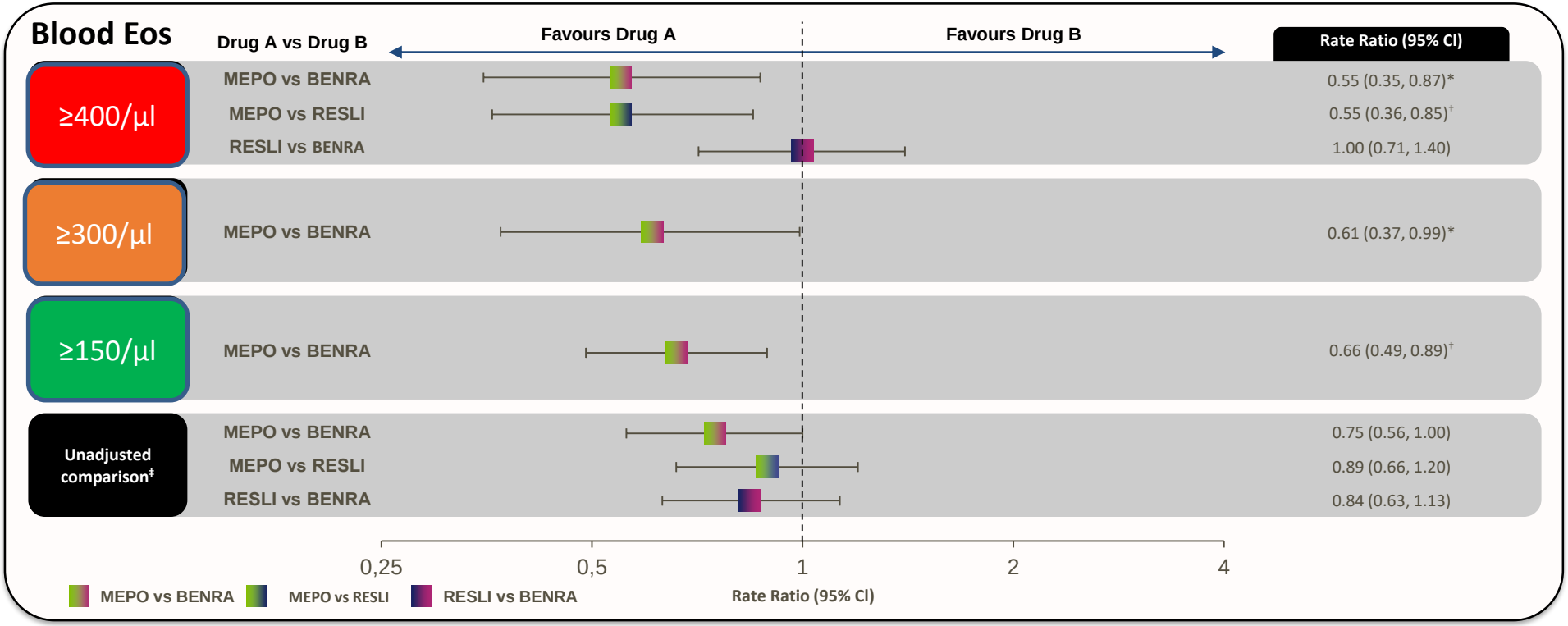
Katz, Ann Am Thorac Soc. 2014; 11: 531-536

Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison

William Busse, MD,[a] Geoffrey Chupp, MD,[b] Hiroyuki Nagase, PhD,[c] Frank C. Albers, PhD,[d] Scott Doyle, DPhil (Cand),[e] Qin Shen, PhD,[f] Daniel J. Bratton, PhD,[g] and Necdet B. Gunsoy, PhD[e] *Madison, Wis, New Haven, Conn, Tokyo, Japan, Research Triangle Park, NC, Brentford and Uxbridge, United Kingdom, and Upper Providence, Pa*

Κλινικά σημαντικές παροξύνσεις άσθματος

Έμμεση σύγκριση των θεραπειών ανάλογα με τη βασική τιμή ηωσινοφίλων

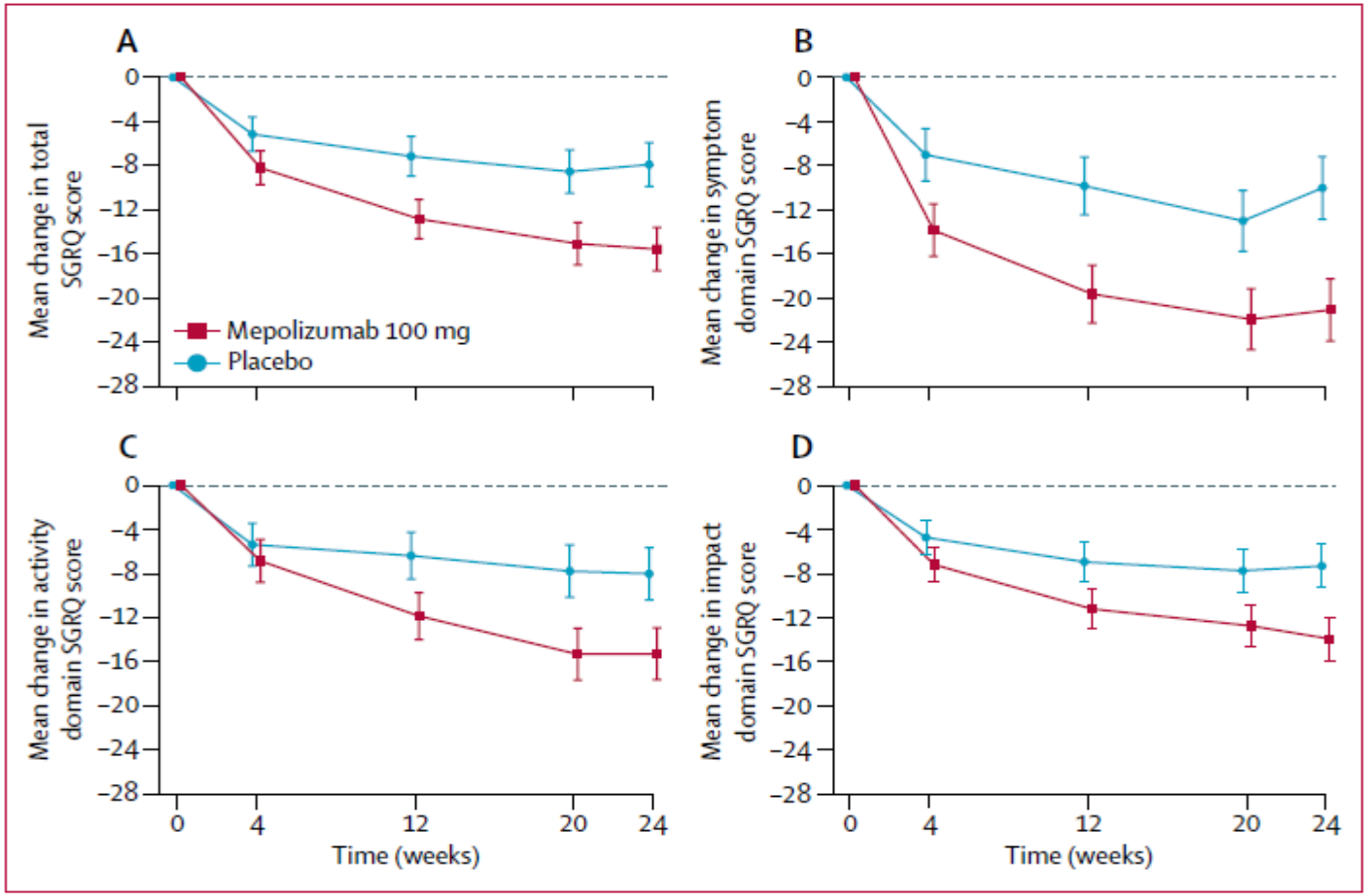


* $p < 0.05$, † $p < 0.01$; ‡ Raw data have not been adjusted for ACQ, exacerbations or blood eosinophil threshold. Note: No comparisons with RESLI were possible below 400 cells/µL due to the inclusion criteria. Only data from patients with ≥450 cells/µL were available from BENRA studies and used in the ≥400 cells/µL comparison.
BENRA, benralizumab; MEPO, mepolizumab; RESLI, reslizumab.

Busse W, et al. *J Allergy Clin Immunol.* 2018. doi: https://doi.org/10.1016/j.jaci.2018.08.031.

Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial

- 576 patients with recurrent (≥2) asthma exacerbations and >150 cells/µL at baseline or >300 cells/µL during the 12-month period before screening, despite high doses of ICS plus additional controller medication(s)



QoL

Chupp GL, Lancet Respir Med. 2017;5:390-400

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

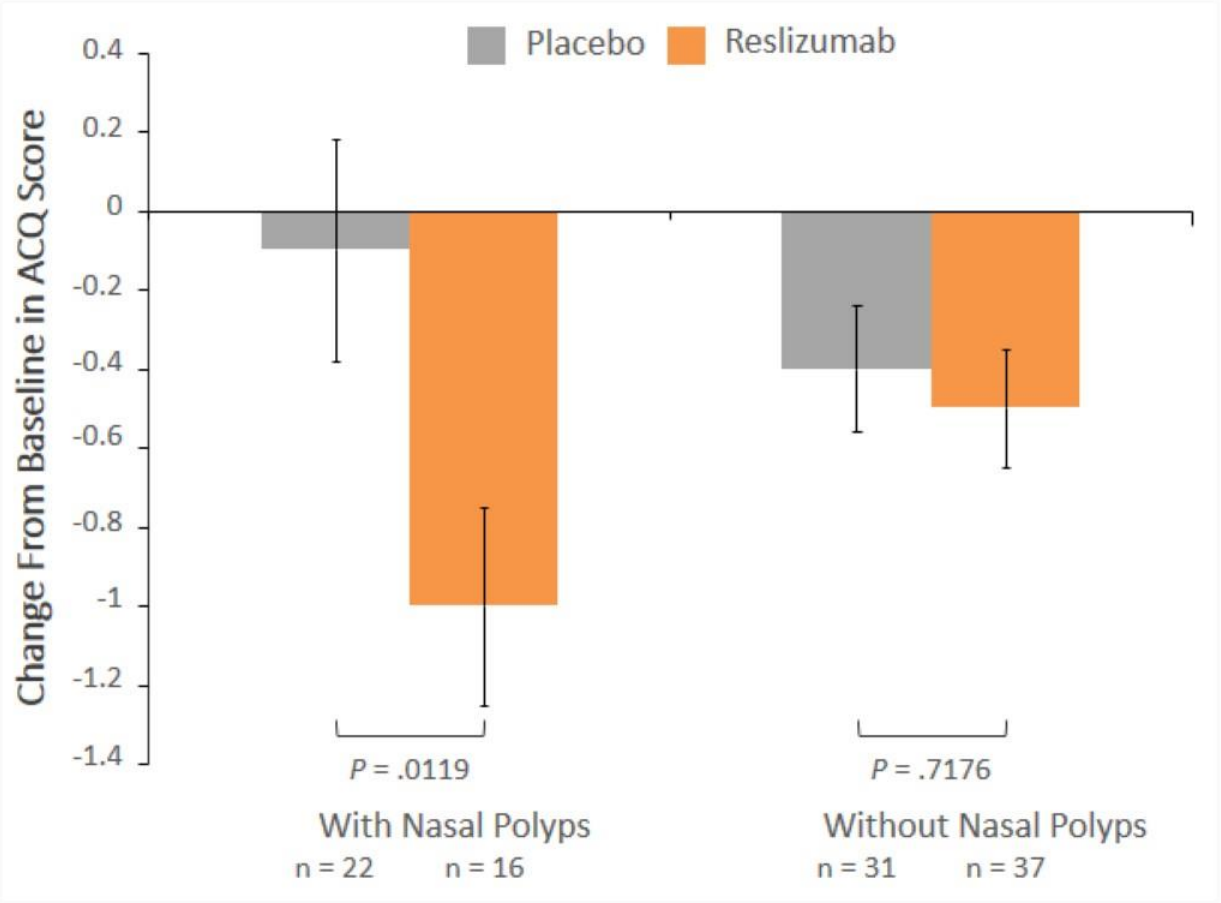
	DREAM (n=616)		MENSA (n=569)		Combined* (n=1185)	
	Placebo (n=155)	Mepolizumab (n=461)	Placebo (n=189)	Mepolizumab (n=380)	Placebo (n=344)	Mepolizumab (n=841)
≥150 cells per µL						
n (%)	121 (78%)	346 (75%)	157 (83%)	296 (78%)	278 (81%)	642 (76%)
Exacerbation rate per year	2·47	1·13	1·65	0·78	1·94	0·92
Rate ratio vs placebo (95% CI)	..	0·46 (0·35–0·60)	..	0·47 (0·35–0·63)	..	0·48 (0·39–0·58)
≥300 cells per µL						
n (%)	86 (55%)	216 (47%)	106 (56%)	202 (53%)	192 (56%)	418 (50%)
Exacerbation rate per year	2·66	1·11	1·98	0·78	2·19	0·89
Rate ratio vs placebo (95% CI)	..	0·42 (0·31–0·56)	..	0·39 (0·28–0·55)	..	0·41 (0·33–0·51)
≥400 cells per µL						
n (%)	64 (41%)	149 (32%)	87 (46%)	161 (42%)	151 (44%)	310 (37%)
Exacerbation rate per year	3·12	1·03	2·06	0·66	2·36	0·81
Rate ratio vs placebo (95% CI)	..	0·32 (0·23–0·46)	..	0·32 (0·22–0·46)	..	0·34 (0·27–0·44)
≥500 cells per µL						
n (%)	50 (32%)	114 (25%)	66 (35%)	124 (33%)	116 (34%)	238 (28%)
Exacerbation rate per year	3·34	0·92	2·11	0·58	2·49	0·75
Rate ratio vs placebo (95% CI)	..	0·27 (0·19–0·39)	..	0·27 (0·18–0·41)	..	0·30 (0·23–0·40)

Data are from the intention-to-treat populations from the DREAM and MENSA studies. All mepolizumab doses were combined for the analysis. *Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis.

Table 2: Reduction in exacerbation rate stratified by baseline blood eosinophil count

Ortega HG, Lancet Respir Med. 2016;4:549-556

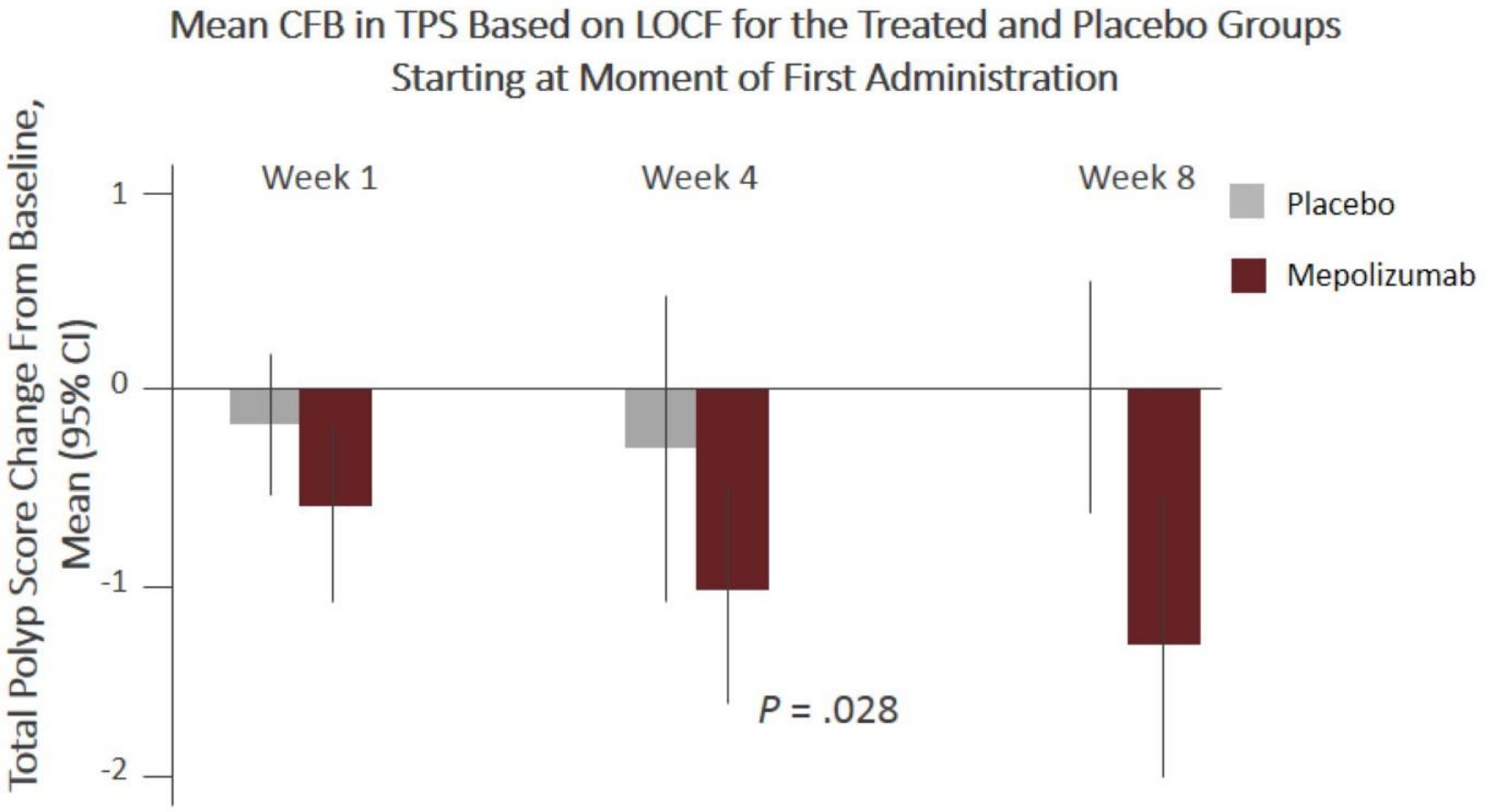
The Nasal Polyp Endotype



Reslizumab IV 3.0 mg/kg is licensed in the United States and in the European Union for the treatment of severe eosinophilic asthma in adults 18 years and older

Castro M, et al. *Am J Respir Crit Care Med*. 2011;184:1125-1132.

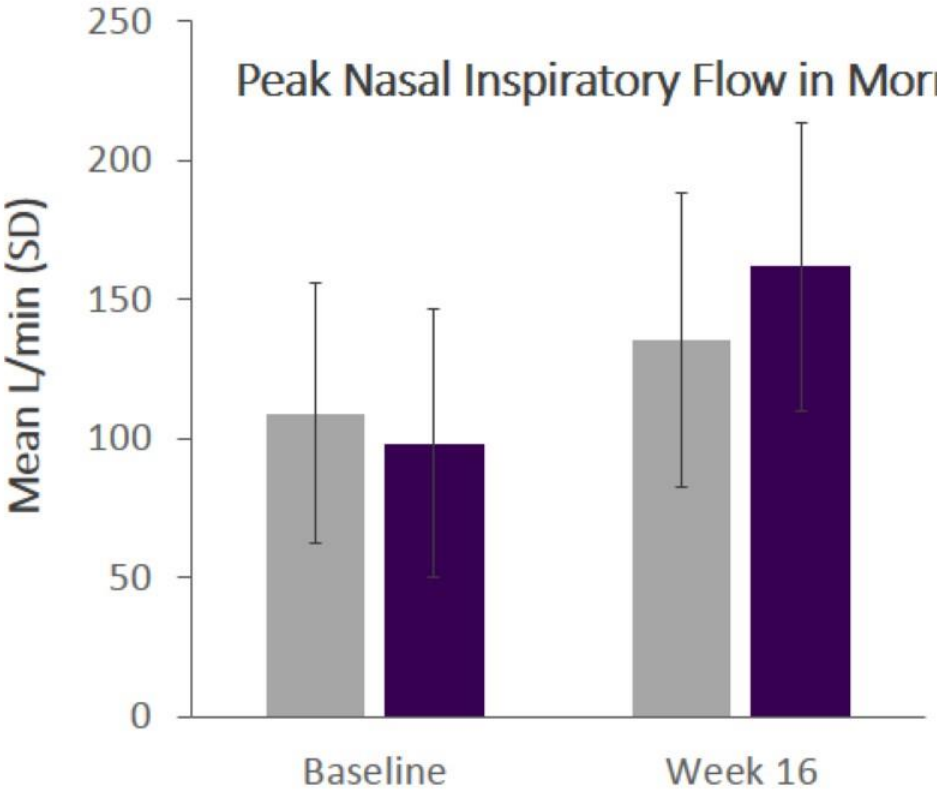
Effect of Mepolizumab on Total Polyps Score

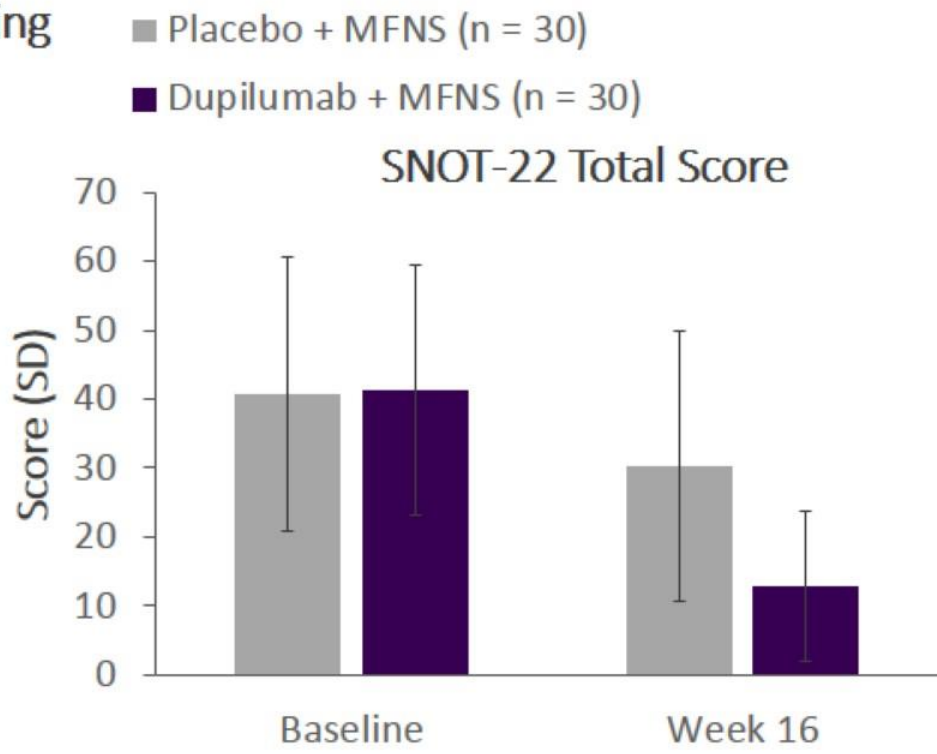


The primary endpoint was the difference in TPS at week 8 (visit 5) vs baseline (visit 2). By using LOCF, the CFB with mepolizumab was -1.30 (SD 1.72), and with placebo was 0.00 (SD 0.94), resulting in a treatment difference of 1.20 (SD 1.51; *P* = .28, Mann-Whitney U Test)

Gevaert P, et al. *J Allergy Clinical Immunol*. 2011;128:989-995.

Effect of SC Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis

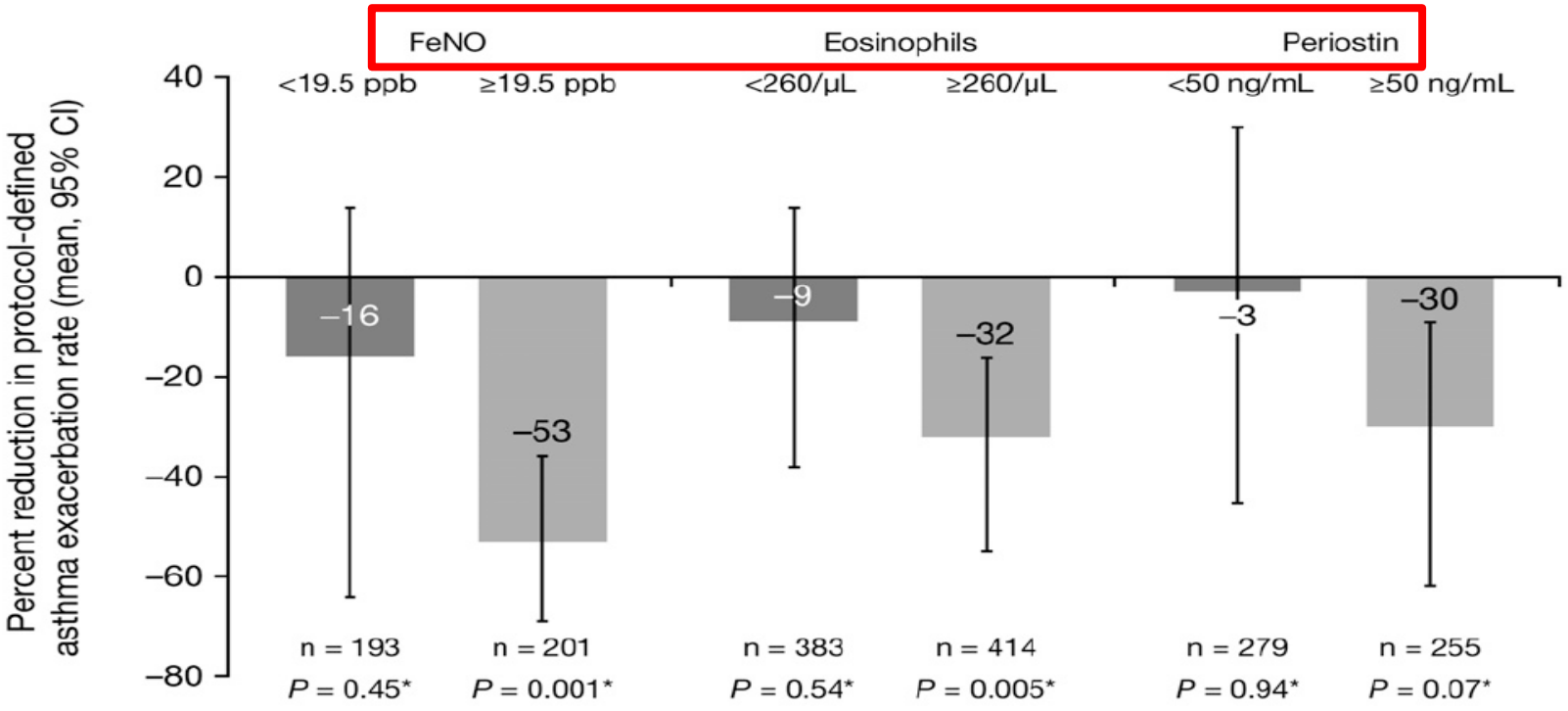




Bachert C, et al. *JAMA.* 2016;315:469-479.

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania. AJRCCM 2013;187:804–811.

ERJ Express. Published on June 25, 2015 as doi: 10.1183/09031936.00012415

Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes

Guus A. Westerhof[1], Daniël A. Korevaar[2], Marijke Amelink[1], Selma B. de Nijs[1], Jantina C. de Groot[3], Junfeng Wang[2], Els J. Weersink[1], Anneke ten Brinke[3], Patrick M. Bossuyt[2] and Elisabeth H. Bel[1]

TABLE 4 Distribution of marker thresholds at 95% sensitivity and specificity in different asthma phenotypes

	Lower threshold sensitivity ⩾95%	Upper threshold specificity ⩾95%
F_{ENO} ppb	8.6–15.1	48.5–69.5
Blood eosinophils $\times 10^9$ cells·L^{-1}	0.06–0.095	0.34–0.73
Total IgE kU·L^{-1}	8.5–25.5	389–2181
F_{ENO} + blood eosinophils	0.086–0.138#	0.656–0.75#

Data are presented as ranges. F_{ENO}: exhaled nitric oxide fraction; Ig: immunoglobulin. #: All test combinations were log transformed; these values correspond to an individual's probability of sputum eosinophilia, as determined by the formula provided in online supplementary figure E3.

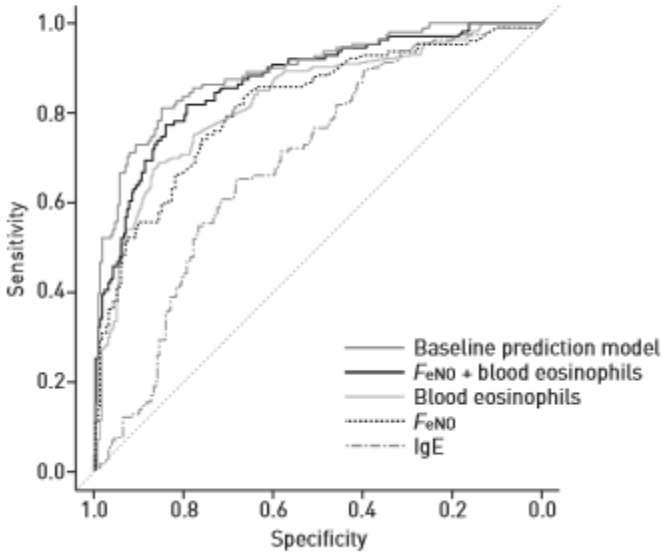
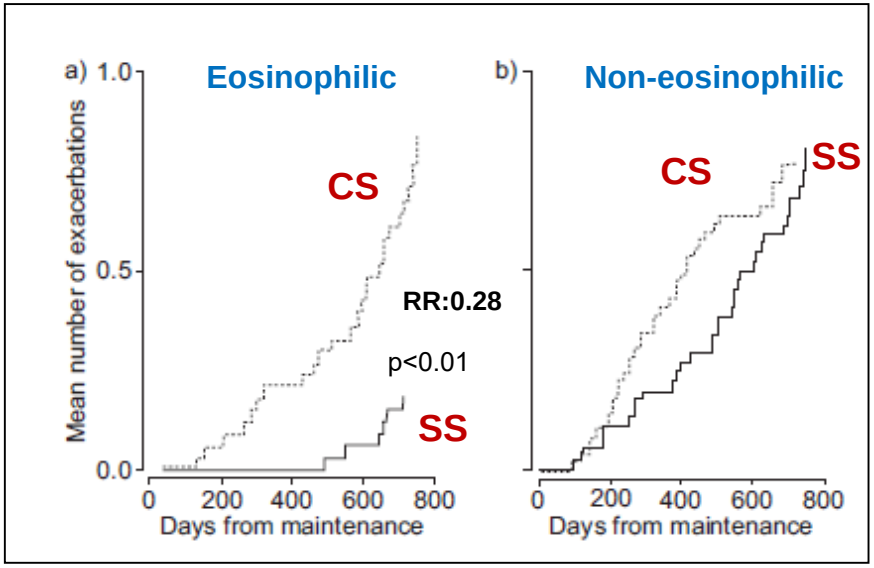
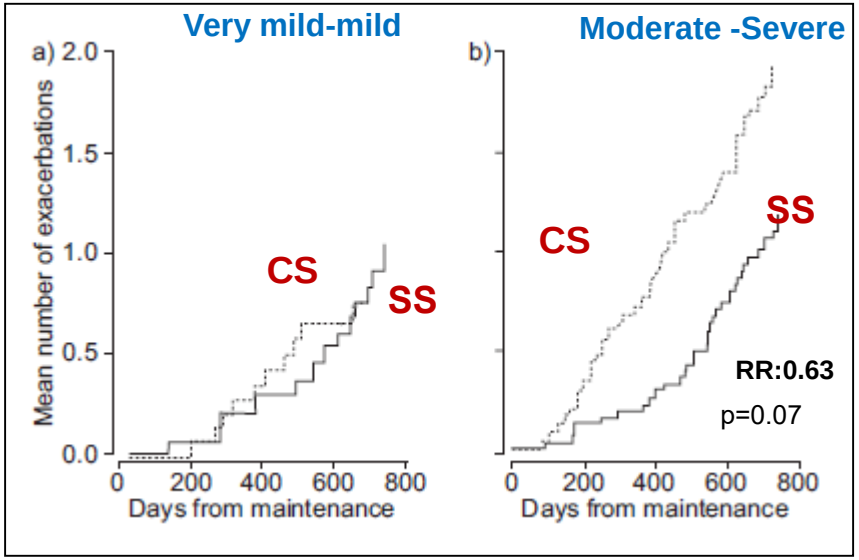


FIGURE 1 Receiver operating characteristic curves for exhaled nitric oxide fraction (F_{ENO}), blood eosinophils, total immunoglobulin (Ig)E and a combined model. n=336.

Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations

CS: clinical strategy, based on symptoms and spirometry
SS: sputum strategy, sputum cell counts guiding CS to keep Eos≤2%





Jayaram, Eur Respir J 2006; 27: 483-494