ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ
Ποια και σε ποιους?

ΚΩΝΣΤΑΝΤΙΝΟΣ ΣΑΜΙΤΑΣ
ΠΝΕΥΜΟΝΟΛΟΓΟΣ - ΕΠΙΜΕΛΗΤΗΣ Β'
7Η ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ»

Conflict of interest (Δήλωση σύγκρουσης συμφερόντων)

Honorarium (τιμητικές αμοιβές) ως προσκεκλημένος ομιλητής από τις φαρμακευτικές εταιρείες Novartis, Elpen, Bristol, Medi-Globe/Rontis, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK

Συμμετοχή σε advisory board (συμβουλευτική επιτροπή) των φαρμακευτικών εταιρειών GSK

Ερευνητικές επιχορηγήσεις (unrestricted research grants) από τις φαρμακευτικές εταιρείες GSK, Novartis

Κάλυψη εξόδων συμμετοχής (εγγραφής, ταξιδιού και διαμονής) σε ελληνικά και διεθνή συνέδρια από τις φαρμακευτικές εταιρείες MSD, Menarini, Novartis, Elpen, GSK, Demo, Pharmathen, AstraZeneca, Galenica

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

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TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

Ορισμός σοβαρού άσθματος

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

Όταν η διάγνωση του άσθματος έχει επιβεβαιωθεί και οι συννοσηρότητες έχουν ελεγχθεί, **σοβαρό άσθμα** ορίζεται ως το άσθμα

- που απαιτεί θεραπεία με υψηλές δόσεις ICS + ένα 2ο ρυθμιστικό φάρμακο (και/ή OCS), ώστε να είναι ελεγχόμενο **ή**
- που παραμένει "μη ελεγχόμενο" παρά την ως άνω θεραπεία
- το ελεγχόμενο άσθμα που απορυθμίζεται με την μείωση των υψηλών δόσεων ICS ή των OCS (ή άλλων βιολογικών παραγόντων)

Τι σημαίνει "uncontrolled" – μη ελεγχόμενο άσθμα? Οποιοδήποτε από τα παρακάτω 4 κριτήρια:

- Κακός έλεγχος συμπτωμάτων: σταθερά τιμές ACQ >1.5 ή ACT <20
- Συχνές παροξύνσεις: 2 ή περισσότερες ώσεις OCS το προηγούμενο έτος
- Σοβαρές παροξύνσεις: ≥ 1 νοσηλεία για παρόξυνση το προηγούμενο έτος
- Μόνιμη απόφραξη των αεραγωγών: FEV_1<80% προβλεπόμενης.

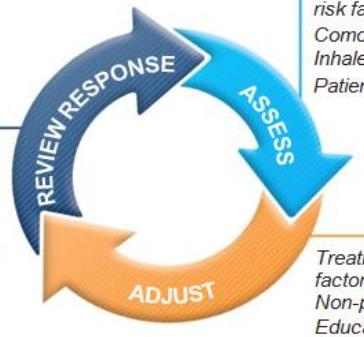
ERS/ATS Guidelines Severe Asthma Eur Respir J. 2014

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol ‡		
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*				

* Off-label; data only with budesonide-formoterol (bud-form)
† Off-label; separate or combination ICS and SABA inhalers
‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

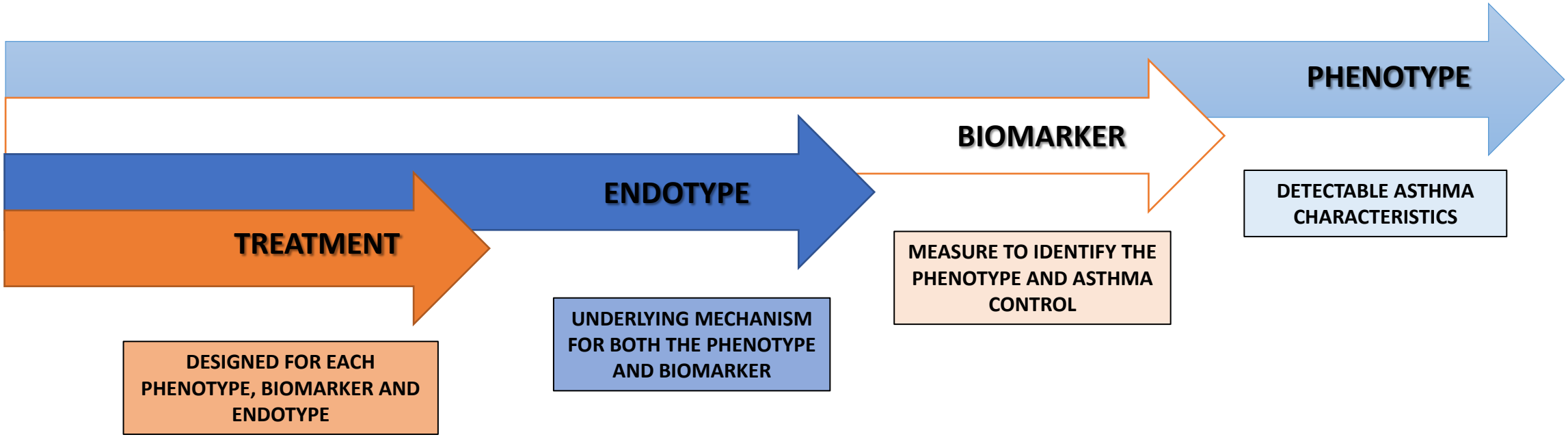
STEP 5

High dose ICS-LABA

Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

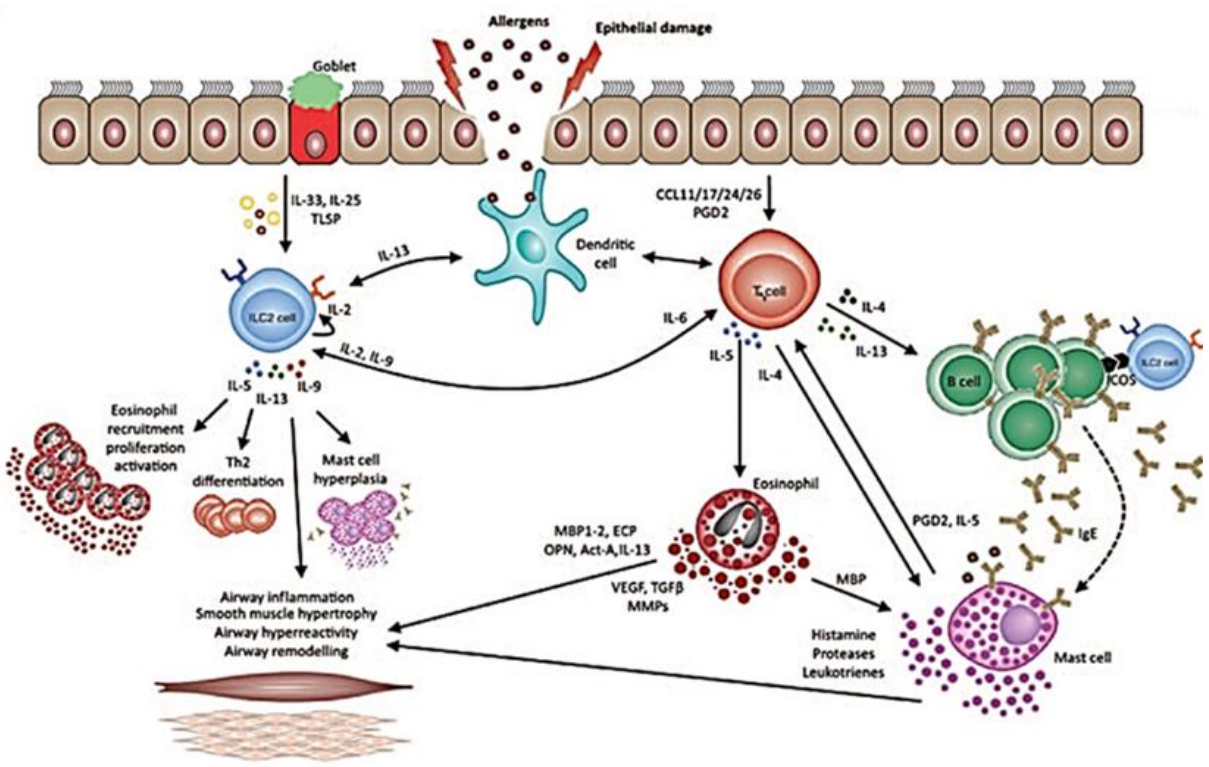
Add low dose OCS, but consider side-effects

Από τον φαινότυπο και τον βιοδείκτη στον ενδότυπο & τη στοχευμενη θεραπεία

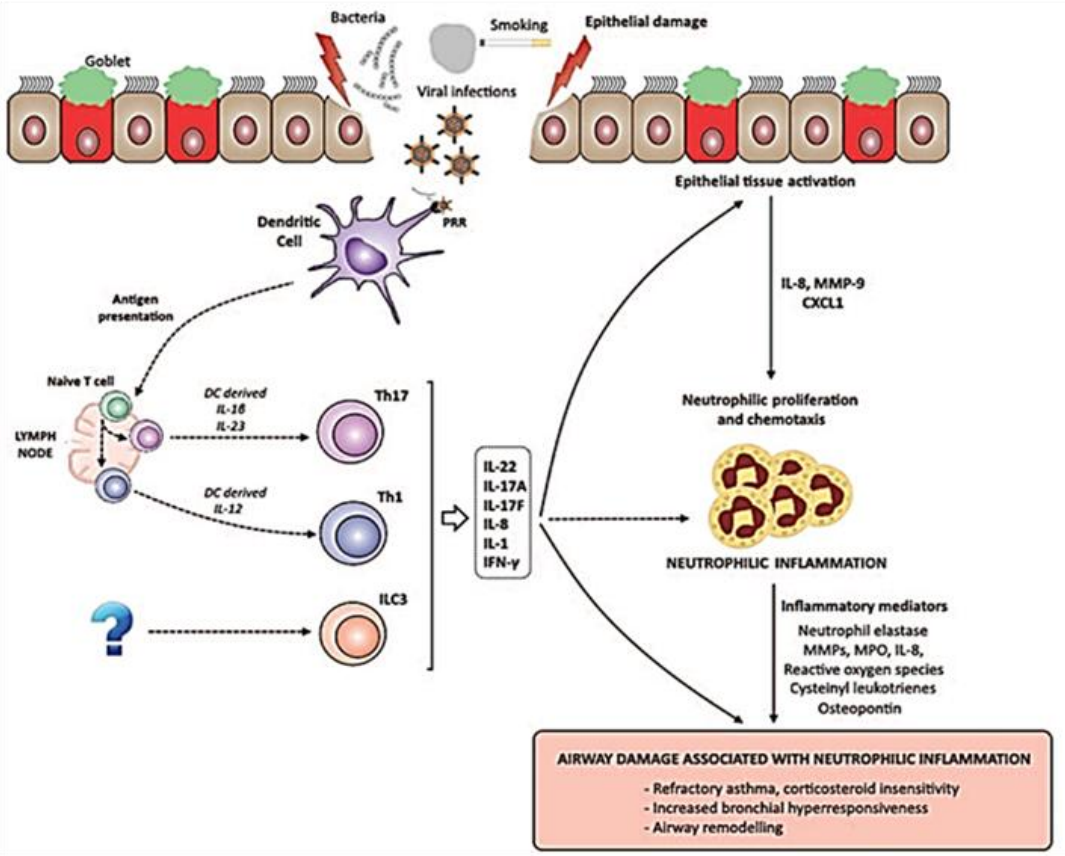


ΣΟΒΑΡΟ ΑΣΘΜΑ: Διαλέγοντας τον κατάλληλο φαινότυπο/ενδότυπο

T2-HIGH ASTHMA

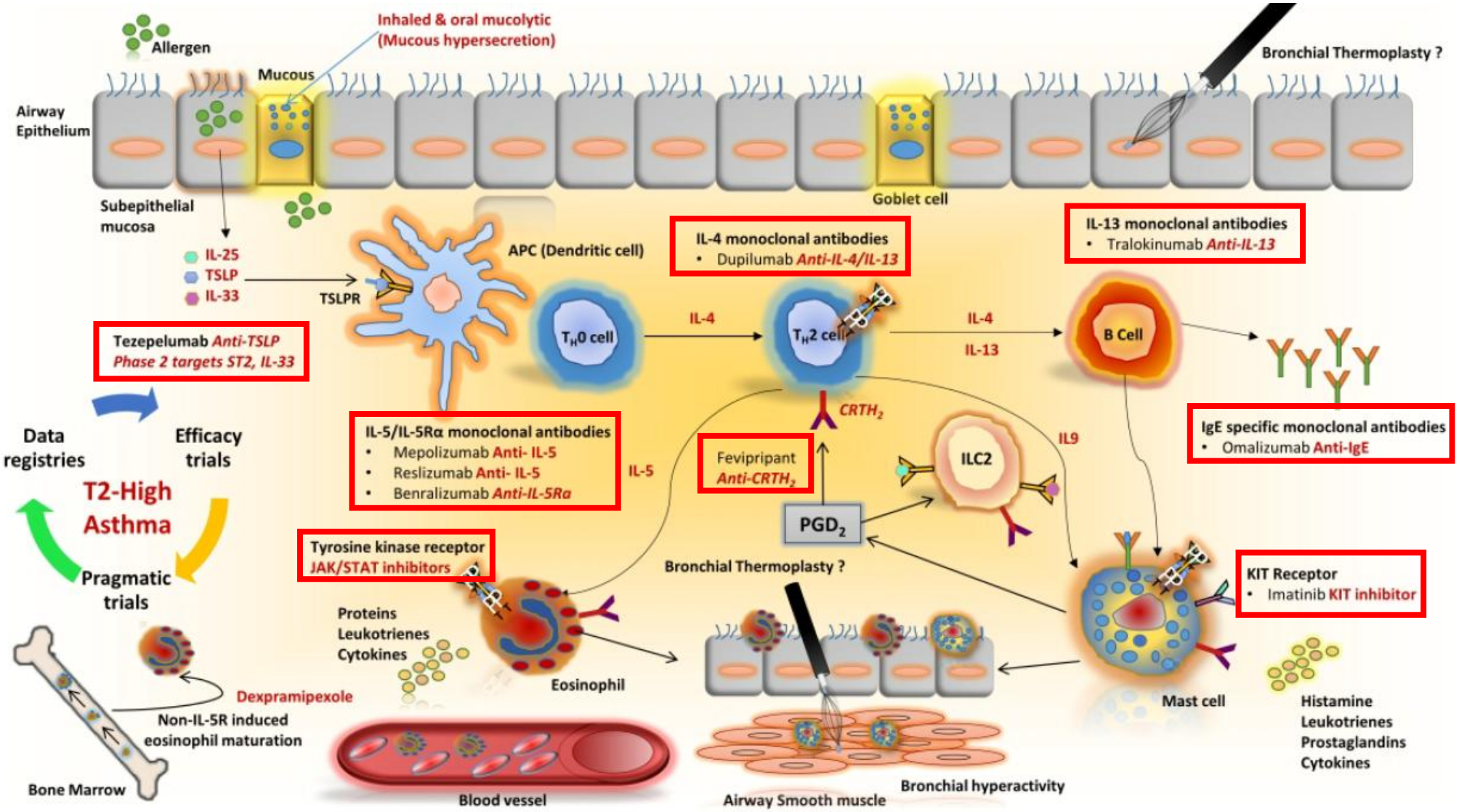


T2-LOW ASTHMA



Samitas K, Zervas E, Gaga M. Curr Opin Pulm Med 2017

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ



Siddiqui et al. 2019 AJRCCM in press

Πώς μπορώ να διαλέξω ανάμεσα σε τόσες επιλογές?

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

ΤΙ ΥΠΑΡΧΕΙ...

- Omalizumab
- Mepolizumab
- Reslizumab
- Benralizumab

ΤΙ ΕΡΧΕΤΑΙ...

- Dupilumab
- Fevipiprant
- Tezepelumab

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

ΤΙ ΥΠΑΡΧΕΙ...
στην δική μας καθημερινή πράξη

- Omalizumab
- Mepolizumab
- Reslizumab
- Benralizumab

ΤΙ ΕΡΧΕΤΑΙ...

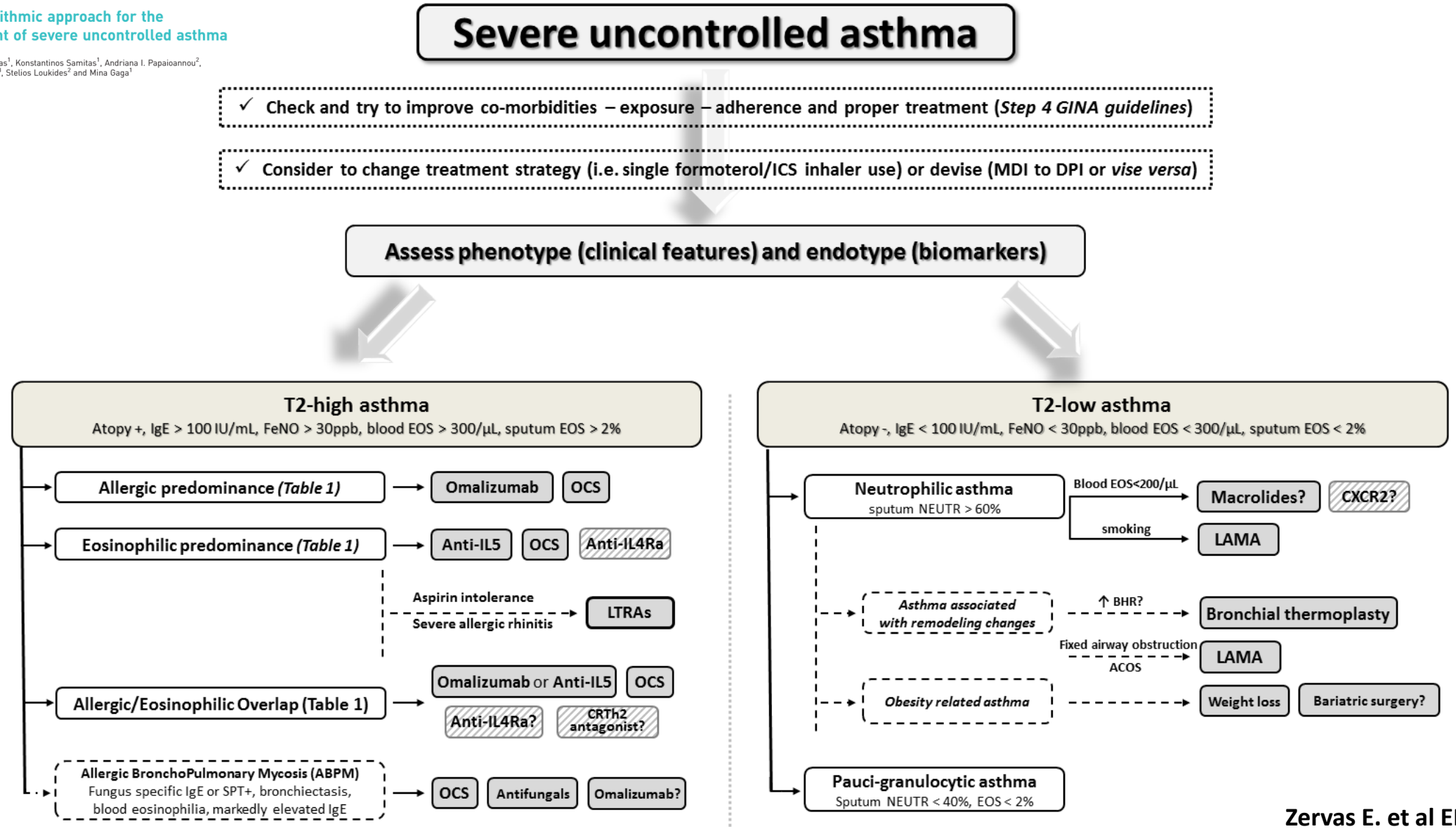
- Dupilumab
- Fevipiprant
- Tezepelumab

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

ERJ open research

An algorithmic approach for the treatment of severe uncontrolled asthma

Eleftherios Zervas[1], Konstantinos Samitas[1], Andriana I. Papaioannou[2], Petros Bakakos[3], Stelios Loukides[2] and Mina Gaga[1]



Zervas E. et al ERJ OR 2017

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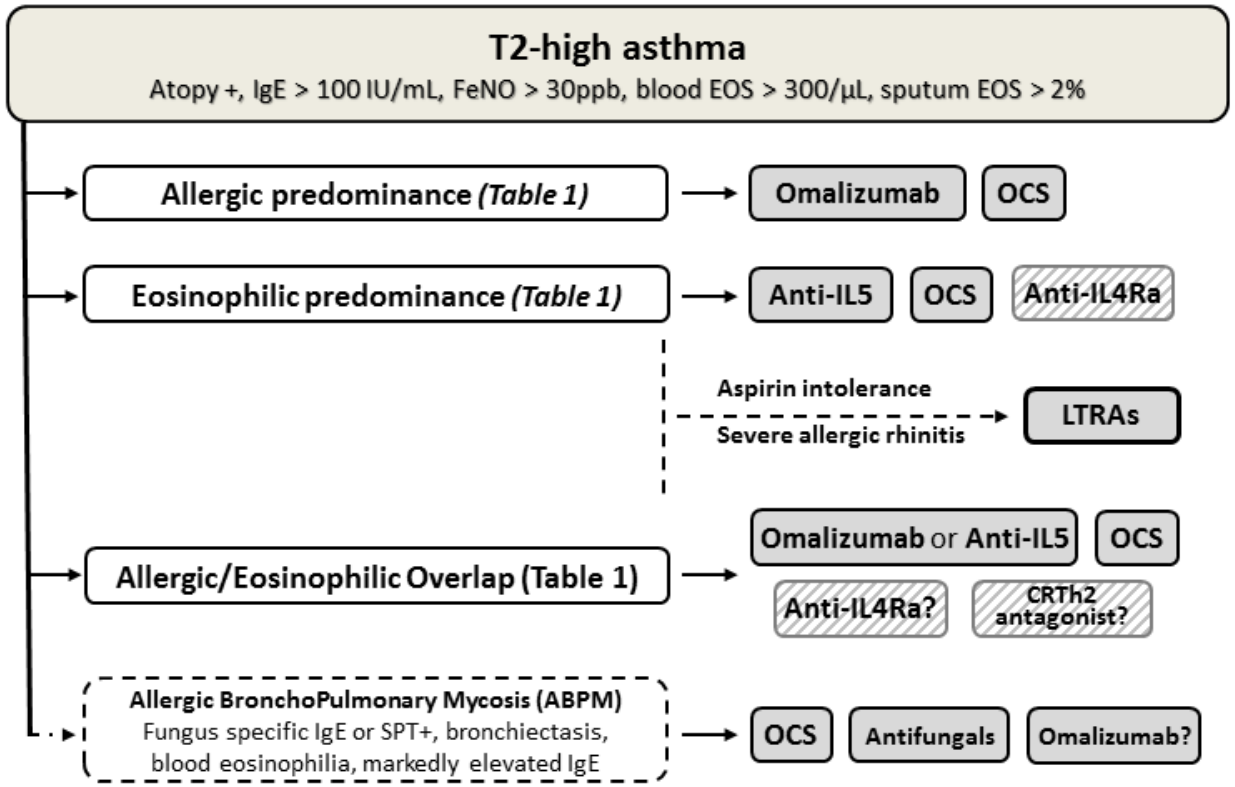

Zervas E. et al ERJ OR 2017

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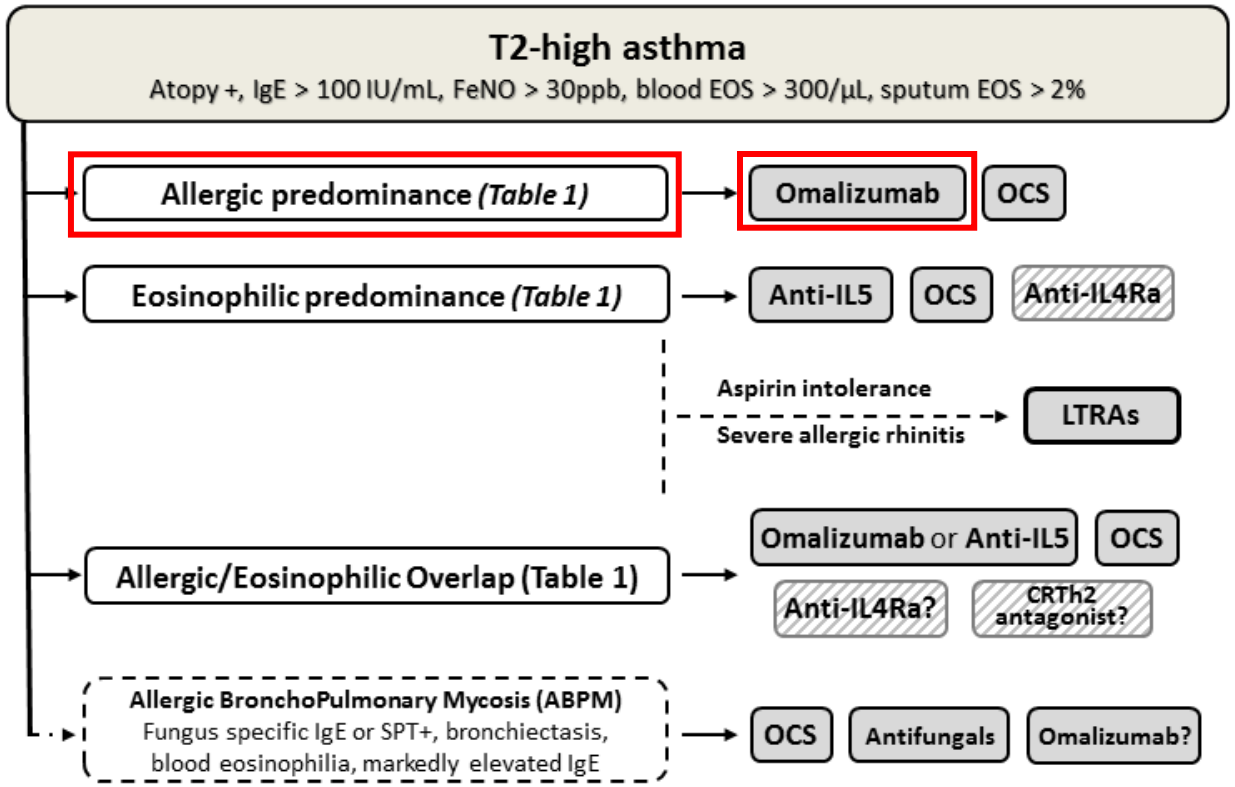
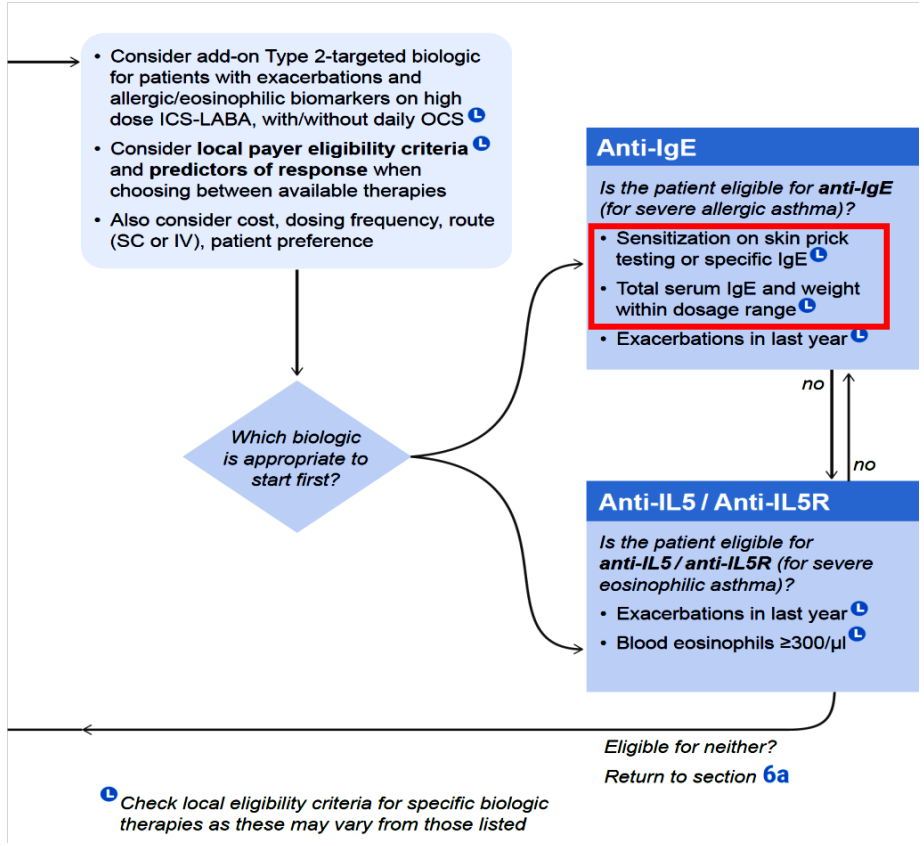
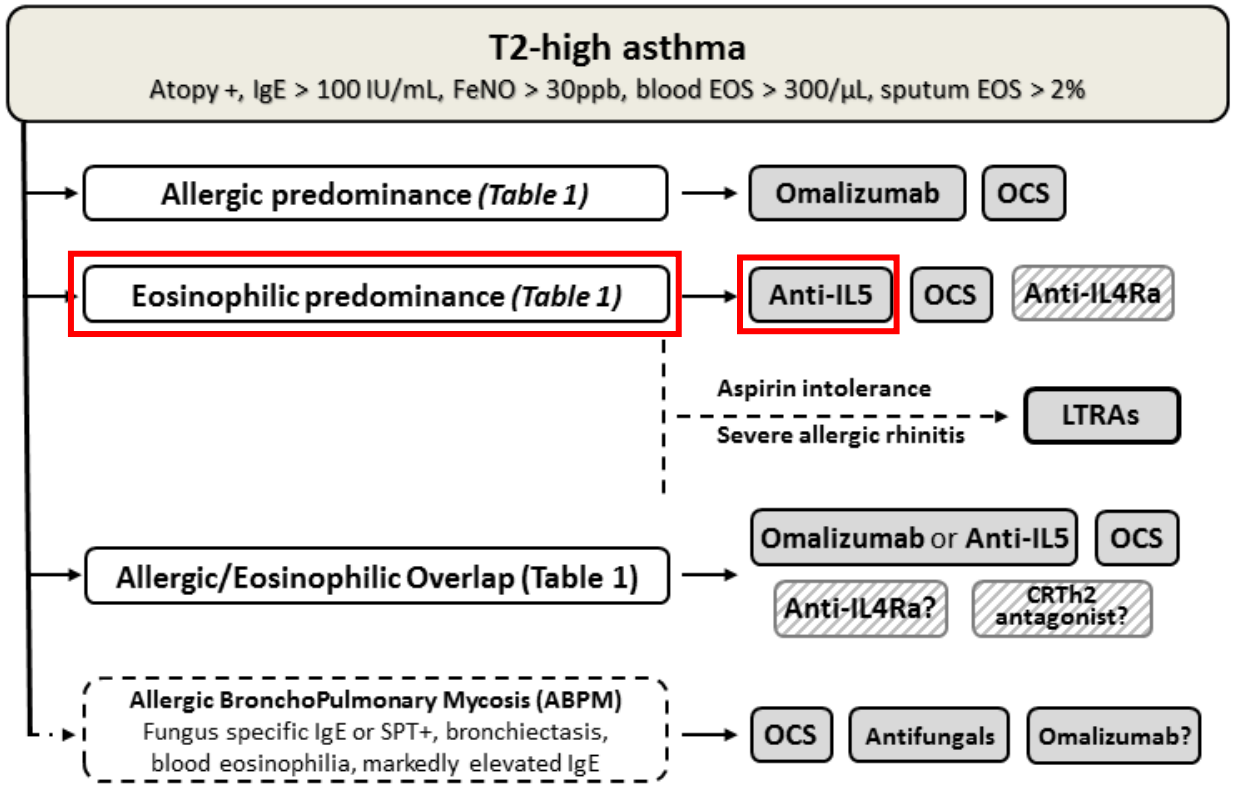


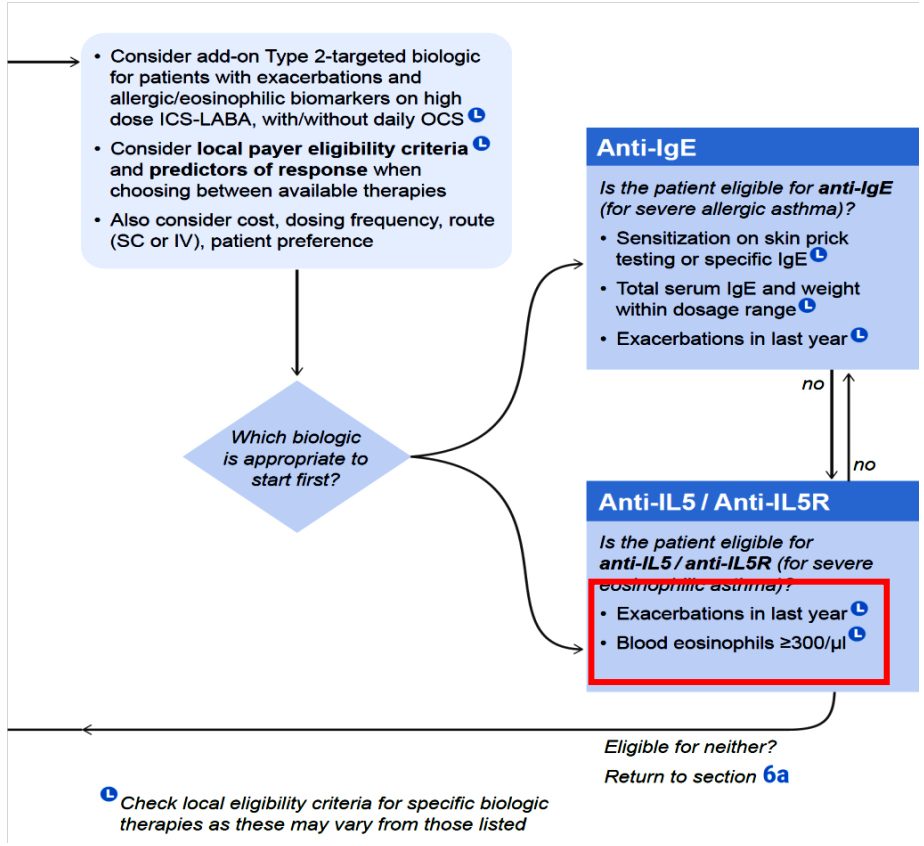


Zervas E. et al ERJ OR 2017

Difficult to treat and Severe Asthma- GINA 2018

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ





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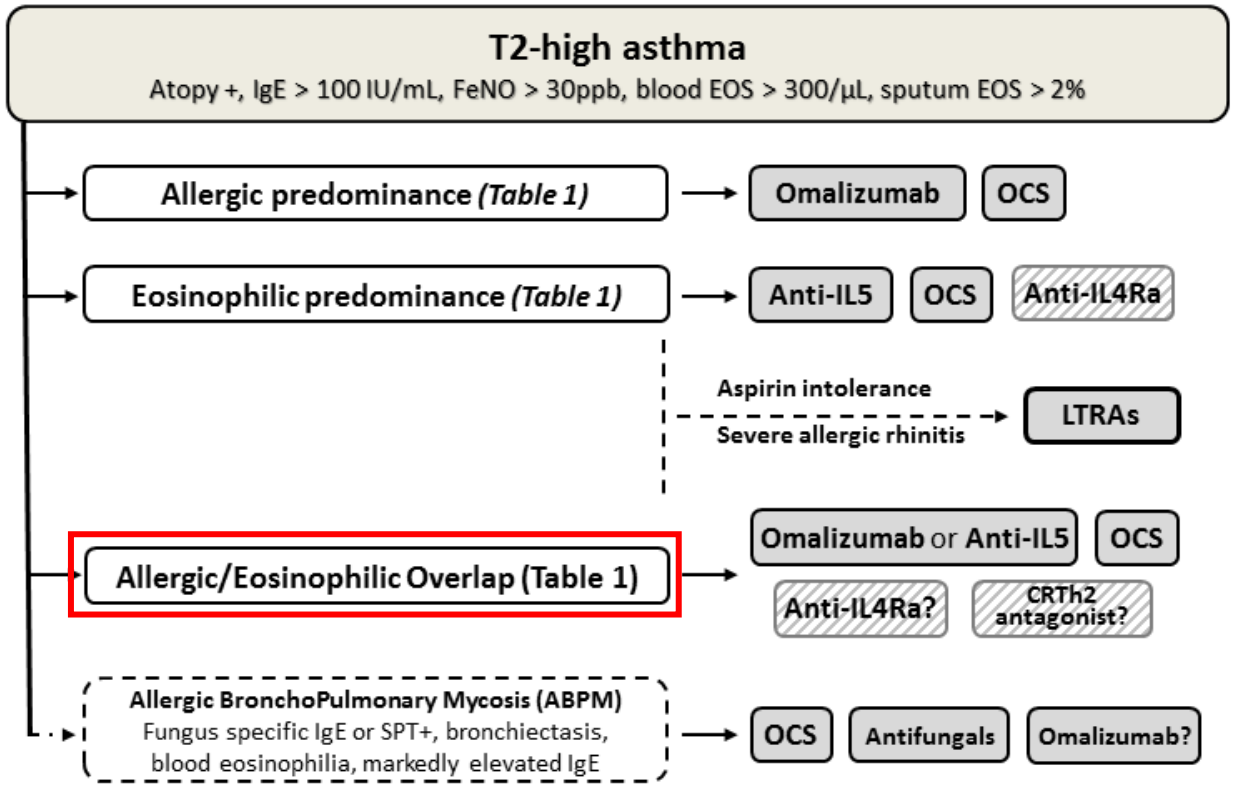
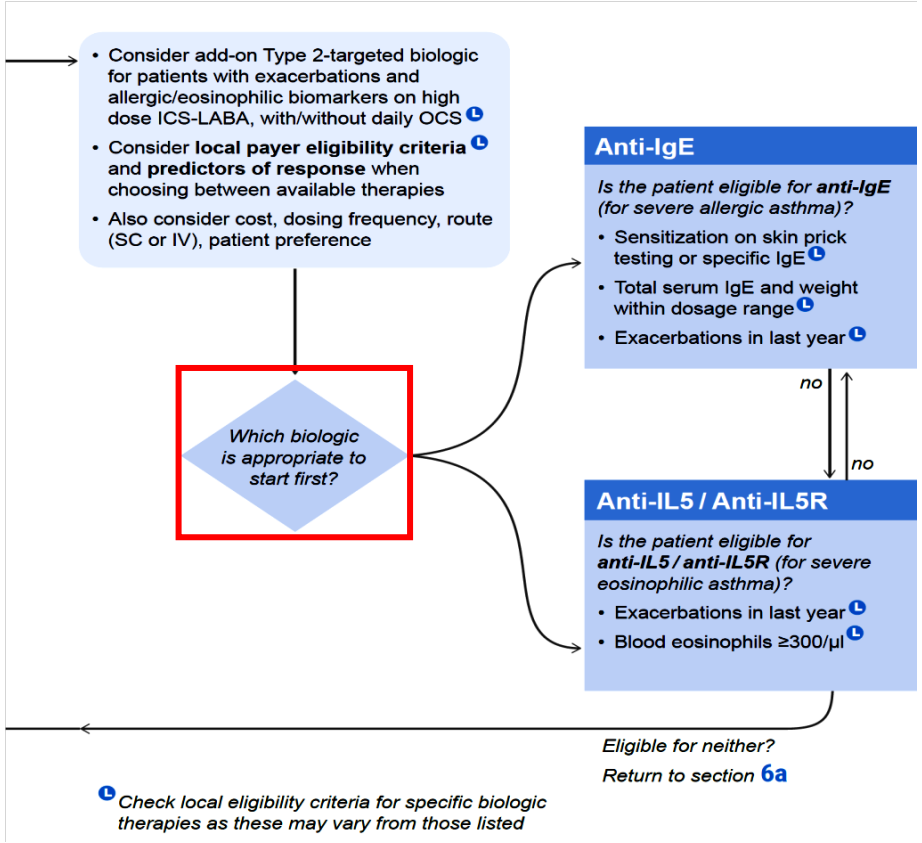




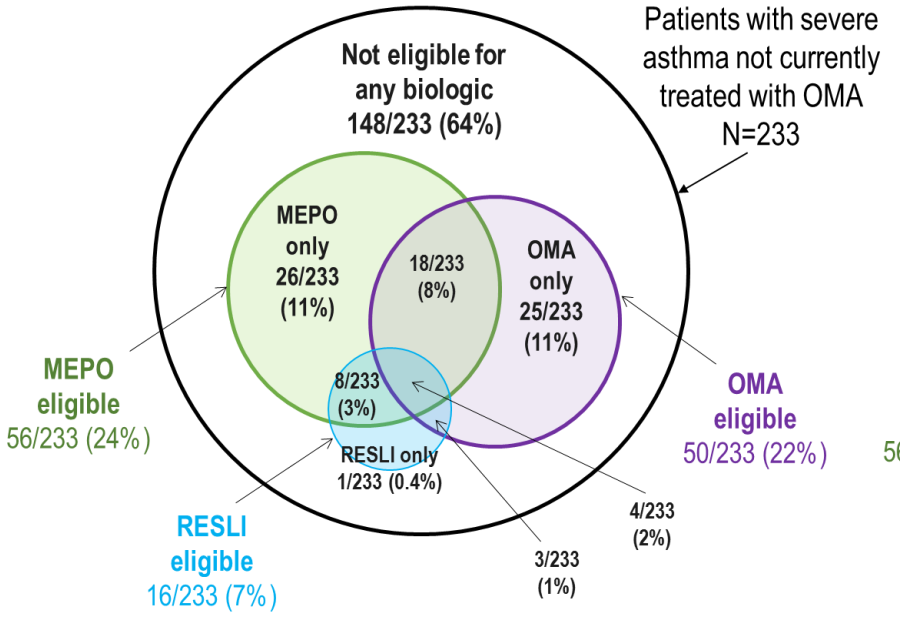
Zervas E. et al ERJ OR 2017

Difficult to treat and Severe Asthma- GINA 2018

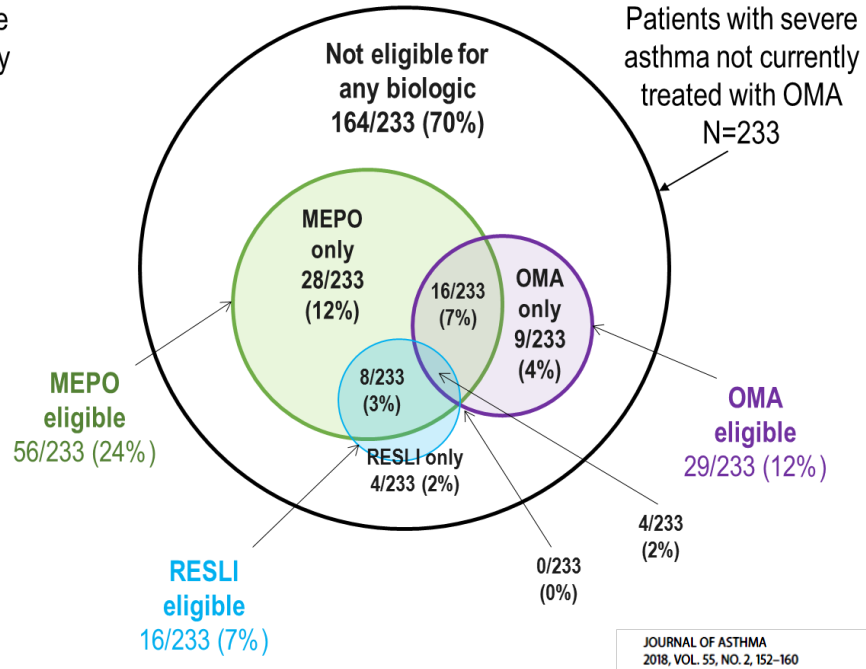
ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

- **Ήωσινοφιλικό και αλλεργικό άσθμα:** συχνότητα εμφάνισης αλληλοεπικάλυψης

A. EU1 omalizumab eligibility criteria



B. EU2 omalizumab eligibility criteria



Το **35-71%** των ασθενών με την ένδειξη θεραπείας για το omalizumab είχε την ένδειξη για mepolizumab, ανάλογα με τα κριτήρια επιλογής (AUS/CAN/USA: 35%; EU1: 42%, EU2: 73%)

JOURNAL OF ASTHMA
2018, VOL. 55, NO. 2, 152–160
https://doi.org/10.1080/02770903.2017.1322611
Taylor & Francis
Taylor & Francis Group
OPEN ACCESS Check for updates

Biologic treatment eligibility for real-world patients with severe asthma: The IDEAL study

Frank C. Albers, MD, PhD[a], Hana Müllerová, PhD[b], Necdet B. Gunsoy, PhD[c], Ji-Yeon Shin, BSc[d], Linda M. Nelsen, MHS[e], Eric S. Bradford, MD[a], Sarah M. Cockle, PhD[f], and Robert Y. Suruki, ScD[g,h]

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

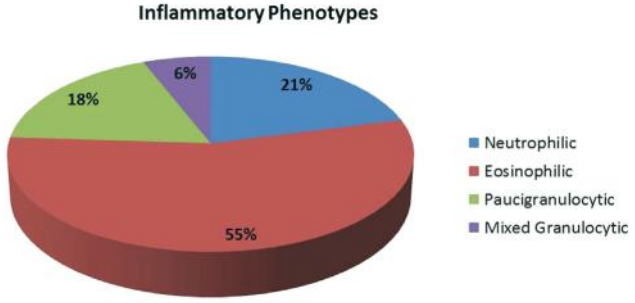
- **Ήωσινοφιλικό και αλλεργικό άσθμα:** συχνότητα εμφάνισης αλληλοεπικάλυψης

Table 1 Demographic, functional, clinical and inflammatory characteristics of severe asthmatics in Belgium.

Patient characteristics	
N.	350
Female (%)	57%
Age	55 ± 0.8
Age at onset	
<12 years	32%
12–40 years	36%
>40 years	31%
Height, m	167 ± 0.5
Weight, kg	75 ± 0.9
BMI	26 (16–43)
Smoking status	
Never	200 (57%)
Ex-smoker	108 (31%)
(pack-years median IQR)	(15 (11–24))
Current smokers	40 (12%)
(pack-years median IQR)	(11 (10–15))
Atopy, %	70
Current house environment (%)	
Country side	39
Suburban area	29
City	31
Unknown	1
FEV_1, % pred	68 ± 1.2
FVC, % pred	89 ± 1.1
FEV_1/FVC, %	63 ± 0.7
FEV_1 reversibility (% from baseline)	11 ± 0.8
FRC (%) (n = 271)	120 ± 2
RV (%) (n = 311)	140 ± 2.8
TLC (%) (n = 305)	102 ± 1.1
DLCO (%) (n = 273)	78 ± 1.2
KCO (%) (n = 273)	97 ± 1.3
Airway inflammatory indices	
$FENO_{50}$ (ppb) (n = 271)	26 (4–250)
Sputum eosinophil count (%) (n = 86)	7 (0–92)
Sputum neutrophil count (%) (n = 86)	51 (0–99)
Sputum inflammatory subphenotype (n = 86)	
Paucigranulocytic	17%
Eosinophilic (≥3%)	55%
Neutrophilic (≥76%)	22%
Mixed granulocytic	6%
Serum IgE (kU/l) (n = 295)	207 (2–10,000)
Blood eosinophils (%) (n = 272)	3 (0–50)
Blood eosinophils (/mm^3) (n = 272)	240 (0–3144)

Table 1 (*continued*)

Patient characteristics	
Specific immunotherapy, %	0.6
Comorbidities (%)	
Rhinosinusitis % (Y/N/Ukn)	49% (167/151/32)
Gastrooesophageal reflux (Y/N/Ukn)	36% (124/205/21)
Nasal polyps (Y/N/Ukn)	19% (167/151/32)
Overweight (Y/N/Ukn)	47% (162/173/15)
Psychopathology (Y/N/Ukn)	19% (65/266/19)
Catamenial asthma (Y/N/Ukn)	0.9% (3/340/7)
Aspirin sensitive asthma (Y/N/Ukn)	8% (28/315/7)
Occupational asthma (Y/N/Ukn)	4% (15/328/7)
Churg Strauss syndrom (Y/N/Ukn)	3% (10/333/7)
ABPA (Y/N/Ukn)	3% (11/332/7)
Bronchiectasis (Y/N/Ukn)	16% (54/289/7)
Emphysema (Y/N/Ukn)	7% (24/319/7)
Treatment of comorbidities	
Proton pump inhibitors	39%
Anti-depressive/anxiolytics	17%/14%
Intranasal steroids	39%
Oral steroids courses during previous yr	2.03 (0–7)
Number of hospitalisations during previous yr	0.95 (0–7) (n = 113)
Number of hospitalization during the last three years	1.7 (0–8) (n = 103)



Στο Βελγικό SA registry περίπου **50%** των ασθενών με σοβαρό άσθμα είχαν ένδειξη για θεραπεία τόσο με omalizumab όσο και με mepolizumab

Respiratory Medicine (2014) **108**, 1723–1732

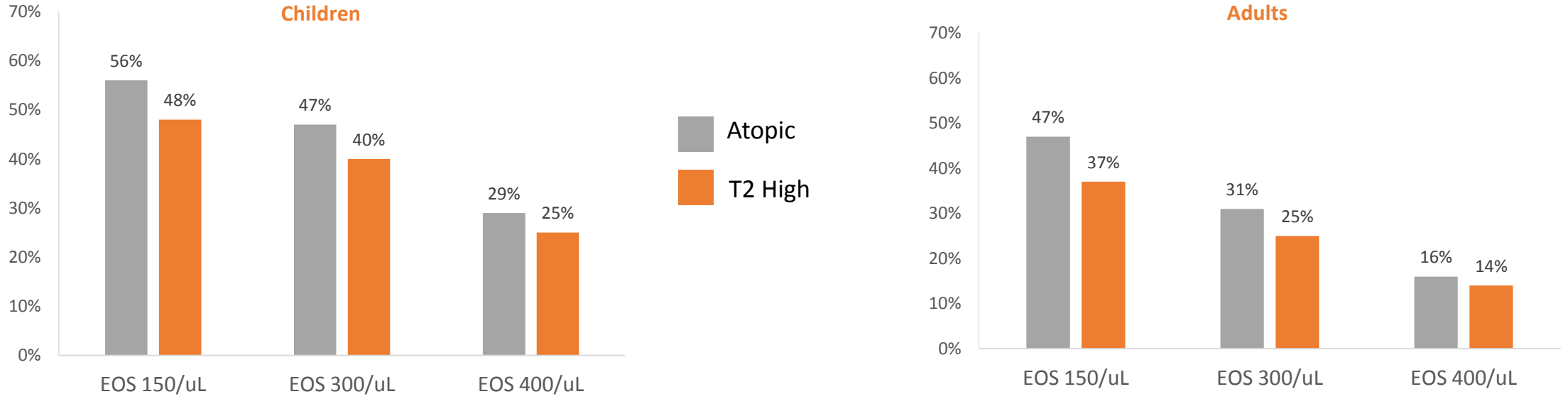
Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR)

F. Schleich [a,*], G. Brusselle [b], R. Louis [a], O. Vandenplas [c], A. Michils [d], C. Pilette [e], R. Peche [f], M. Manise [a], G. Joos [b]

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

- **Ήωσινοφιλικό και αλλεργικό άσθμα:** συχνότητα εμφάνισης αλληλοεπικάλυψης

NHANES survey: Overlap between Eosinophilic and atopic or T2 high phenotypes

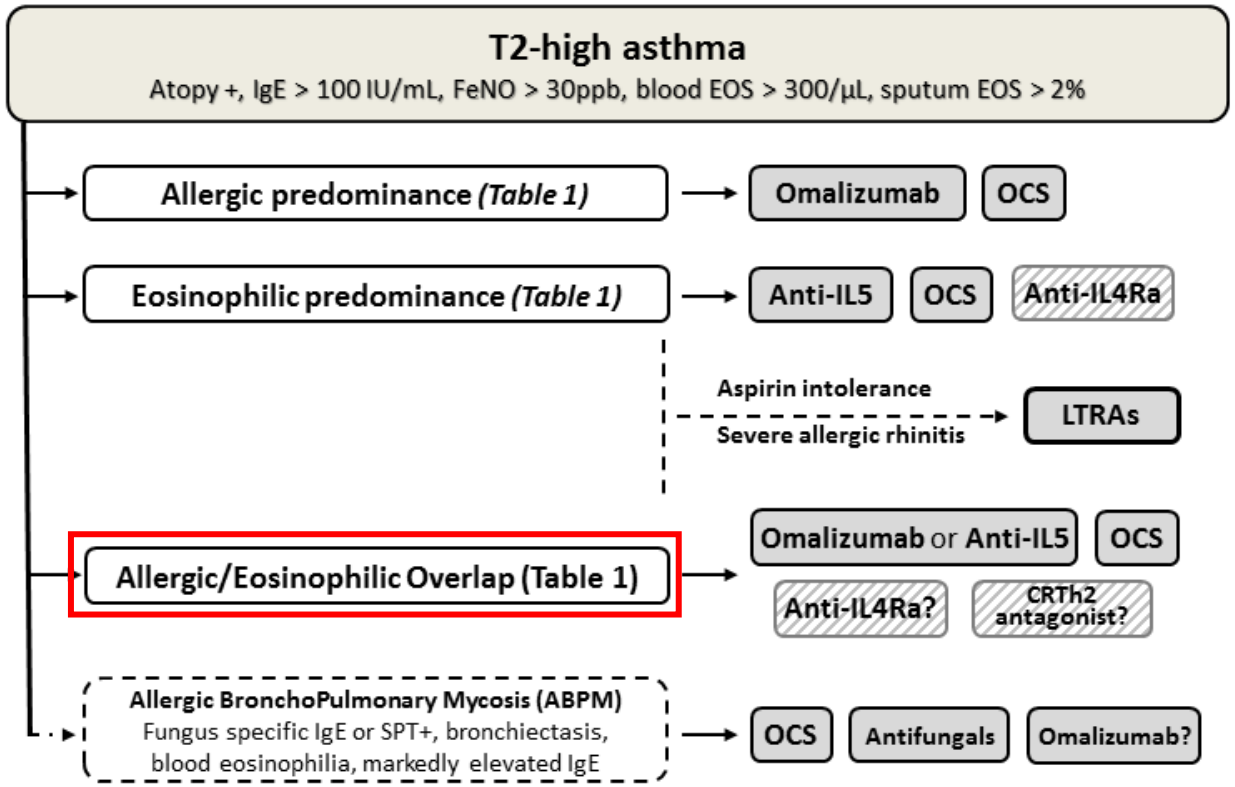


~45% of children and one-third of adults can be classified with all three phenotypes simultaneously[1]

EOS + Atopic + T2 High

Adapted from Tran TN *et al.* 2016.

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ



A. Allergic predominant asthma	B. Eosinophilic predominant asthma
1. Early onset	1. Late onset
2. ***SPT/RAST (+) with clinically significant allergies****	2. SPT/RAST (-) or (+) with no clinically significant allergies
3. IgE > 100 IU/ml	3. IgE < 100 IU/ml
4. Allergic rhinitis	4. Nasal Polyps
5. High FeNO (30-50 ppb)	5. Very high FeNO > 50 ppb
6. Blood eosinophils < 300 cells/µl	6. ***Blood eosinophils > 300 cells/µl ****

TABLE 2. Clinical features and biomarkers that can be used to differentiate between allergic and eosinophilic severe asthma. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic or eosinophilic predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma.

Zervas E. et al ERJ OR 2017

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

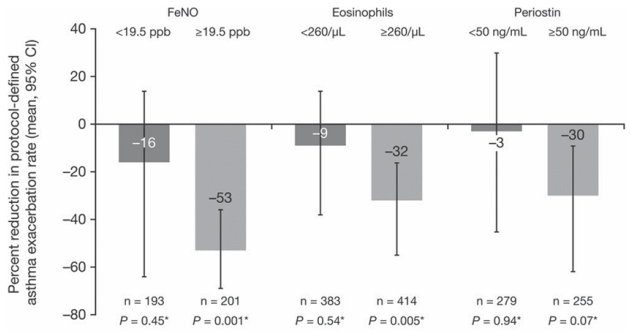
- **Θεραπευτικοί αλγόριθμοι… δεν είναι όλα μαύρα - άσπρα**

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

➢ **Θεραπευτικοί αλγόριθμοι… δεν είναι όλα μαύρα - άσπρα**

OMALIZUMAB (ANTI-IGE) MAY HAVE AN ENHANCED AFFECT IN T2-HIGH ASTHMA SUBGROUPS

Mean % reduction in exacerbation rate in low- and high-biomarker subgroups[1]

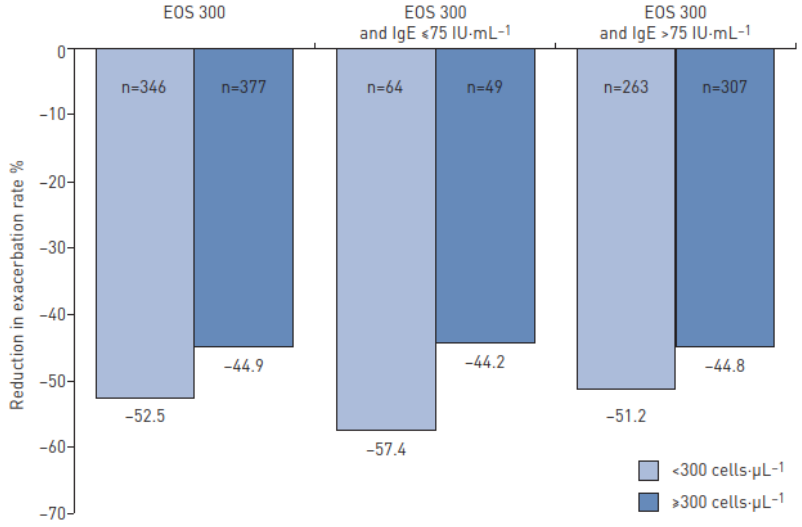


Adapted from Hanania NA *et al.* 2013

Post-hoc analysis of a double-blind RCT of 850 patients receiving omalizumab or placebo for 48 weeks:[1]

After 48 weeks, reductions in exacerbations were greater in high vs. low subgroups for all three biomarkers:[1]

- FENO (53% vs. 16%)
- Eosinophils (32% vs. 9%)
- Periostin (30% vs. 3%, p=NS for both)



Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study

Marc Humbert[1,2,3], Camille Taillé[4], Laurence Mala[5], Vincent Le Gros[5], Jocelyne Just[6] and Mathieu Molimard[7] on behalf of the STELLAIR investigators[8]

TABLE 4 Primary end-points at T_{4-6} (time of first effectiveness assessment after 4–6 months of treatment) by blood eosinophil count measured in the year prior to omalizumab initiation (T_{-12}) in minors (6–17 years) and adults (≥18 years)

	<300 cells·μL⁻¹		≥300 cells·μL⁻¹		Total	
	Minors	Adults	Minors	Adults	Minors	Adults
Subjects	39	346	110	377	149	723
GETE score#						
Responder	25 (64.1) (47.2–78.8)	231 (66.8) (61.5–71.7)	90 (81.8) (73.3–88.5)	255 (67.6) (62.7–72.3)	115 (77.2) (69.6–83.7)	486 (67.2) (63.7–70.6)
Reduction in annual exacerbation rate¶						
Exacerbations between T_0 and T_{4-6} n	1.6±1.3	1.7±1.1	2.1±1.6	1.8±1.3	1.9±1.5	1.8±1.2
Annual rate change %	−64.7±67.5	−52.5±89.6	−58.6±95.4	−44.9±97	−60.2±88.8	−48.5±93.5
Responder with a ≥40% reduction in the annual exacerbation rate	31 (79.5) (63.5–90.7)	250 (72.3) (67.2–76.9)	86 (78.2) (69.3–85.5)	264 (70.0) (65.1–74.6)	117 (78.5) (71.1–84.8)	514 (71.1) (67.6–74.4)
Combination+						
Combined responder	23 (59.0) (42.1–74.4)	201 (58.1) (52.7–63.4)	78 (70.9) (61.5–79.2)	220 (58.4) (53.2–63.4)	101 (67.8) (59.7–75.2)	421 (58.2) (54.5–61.8)

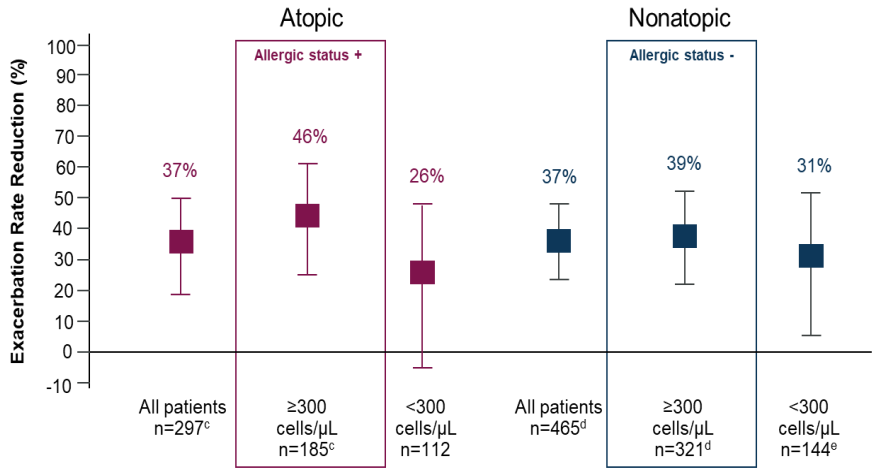
ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

➢ **Θεραπευτικοί αλγόριθμοι… δεν είναι όλα μαύρα - άσπρα**

BENRALIZUMAB

Μείωση παροξύνσεων και βελτίωση πνευμονικής λειτουργίας
ανεξάρτητα
αλλεργικού προφίλ των ασθενών

Ρυθμός μείωσης Παροξύνσεων



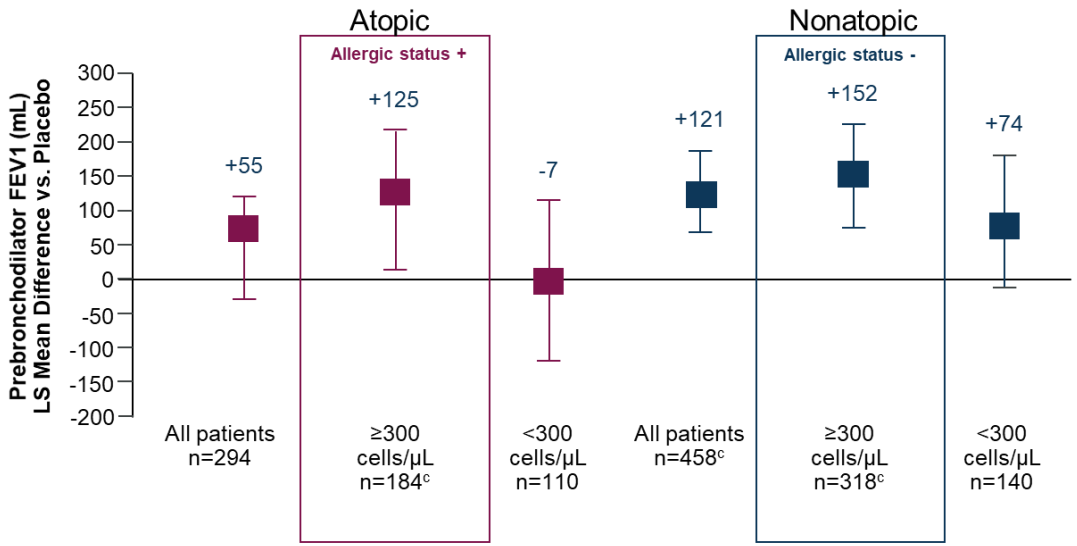
Κριτήρια Αλλεργικού προφίλ[a]: Ατοπία[b] and συγκέντρωση IgE ορού 30-700 kU/L

[a]Adapted from criteria for omalizumab treatment. [b]By Phadiatop test. Nominal [c]p=0.0002. [d]p<0.0001. [e]p=0.0257.

Data are from the pooled adult intention-to-treat population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies. Estimates were calculated by using a negative binomial model, with adjustment for study code, treatment, region, oral corticosteroid use at time of randomization, and prior exacerbations. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients' having different exposure times during which the events occurred. Error bars are 95% confidence interval.

EOS = eosinophil; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting β2-agonists; Q8W = first 3 doses every 4 weeks, then every 8 weeks.

Chipps BE et al. Article and supplementary data. *Ann Allergy Asthma Immunol*. 2018;120:504-511.



Κριτήρια Αλλεργικού προφίλ[a]: Ατοπία[b] and συγκέντρωση IgE ορού 30-700 kU/L

[a]Adapted from criteria for omalizumab treatment. [b]by Phadiatop test. [c]Nominal p≤0.05.

Data are from the pooled adult intention-to-treat population from the high-dosage ICS/LABA treatment cohorts of the SIROCCO and CALIMA studies. Prebronchodilator FEV1 change is from baseline to EOT (SIROCCO: Week 48; CALIMA: Week 56). Estimates were calculated by using a mixed-effects model for repeated measures analysis with adjustment for study code, treatment, baseline value, region, oral corticosteroid use at time of randomization, visit, and visit × treatment. Error bars are 95% CI.

EOS = eosinophils; EOT = end of treatment; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting β_2-agonists; LS = least squares; Q8W = first 3 doses every 4 weeks, then every 8 weeks.

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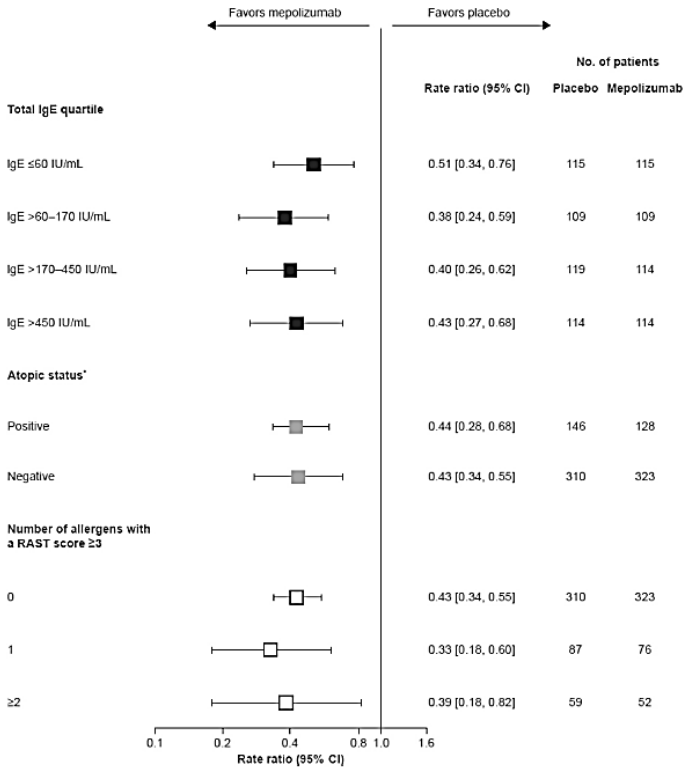
MEPOLIZUMAB

Respiratory Medicine 154 (2019) 69–75

Effect of mepolizumab in severe eosinophilic asthma according to omalizumab eligibility

Marc Humbert[a], Frank C. Albers[b], Daniel J. Bratton[c], Steven W. Yancey[d], Mark C. Liu[e], Soichiro Hozawa[f], Jean-Pierre Llanos[g], Namhee Kwon[h,*]



Data from two Phase 3 studies (MENSA [MEA115588/NCT01691521]; MUSCA [200862/ NCT02281318])

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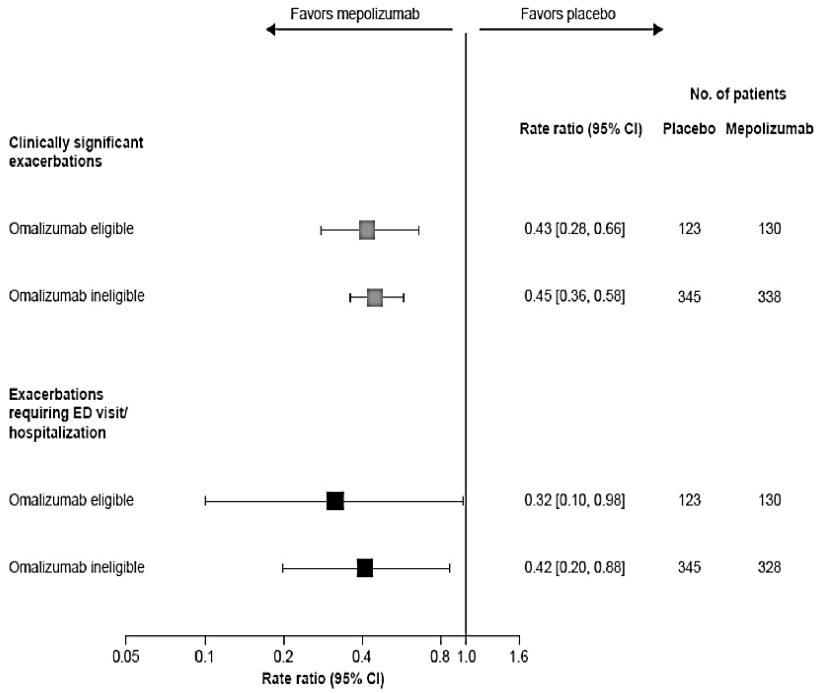

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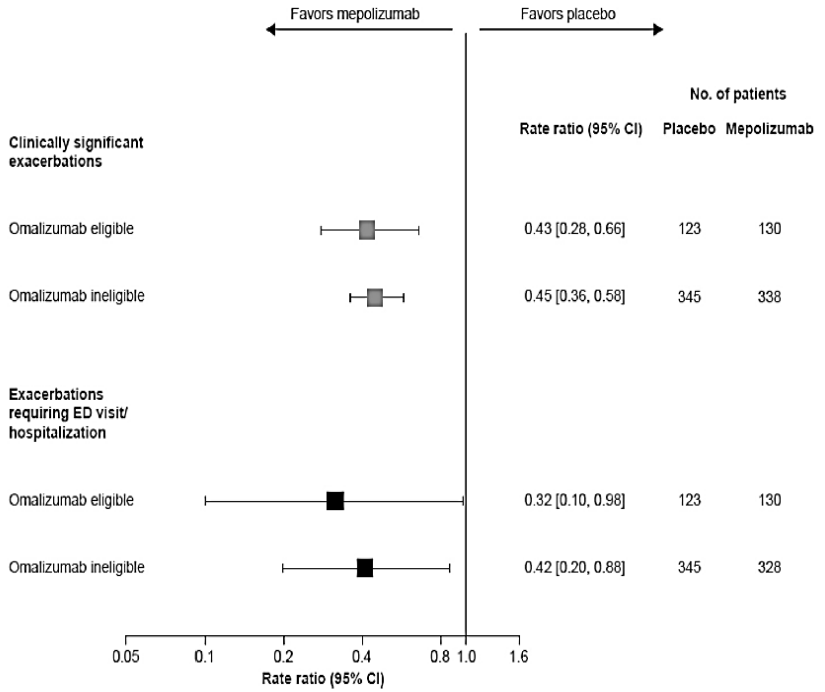
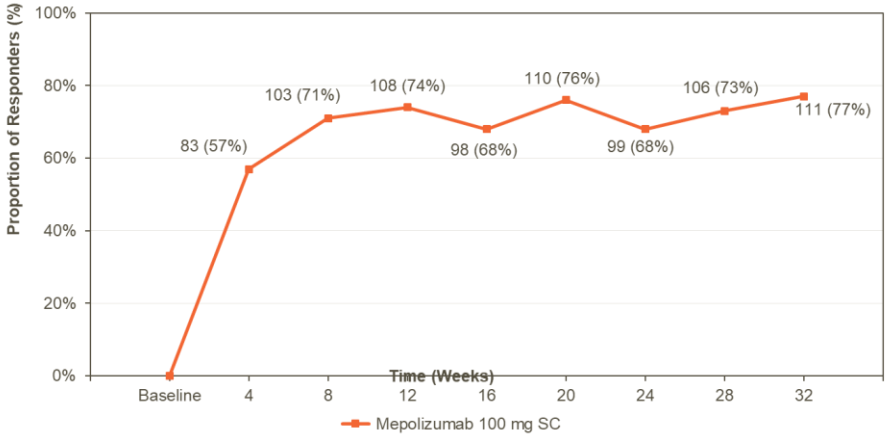
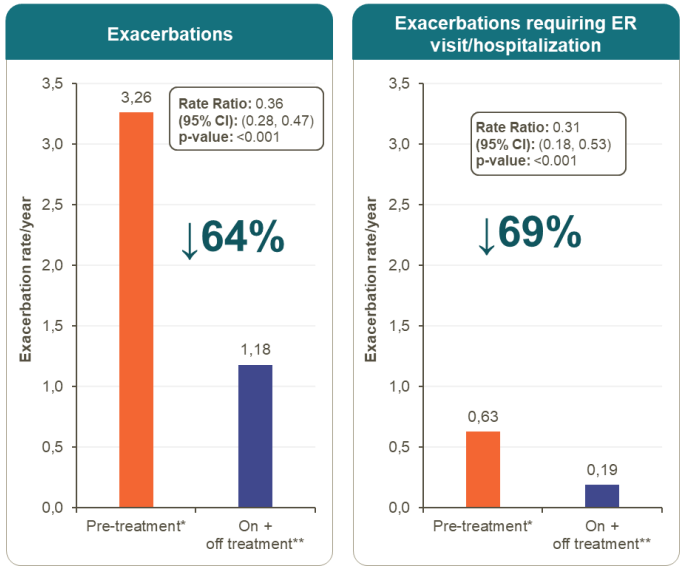


A multi-centre, open-label, single arm, 32-week treatment study in subjects with severe eosinophilic asthma not optimally controlled with current Omalizumab treatment who are Switched from omalizumab to MepOlizumab 100 mg subcutaneous (study number 204471-the OSMO study)



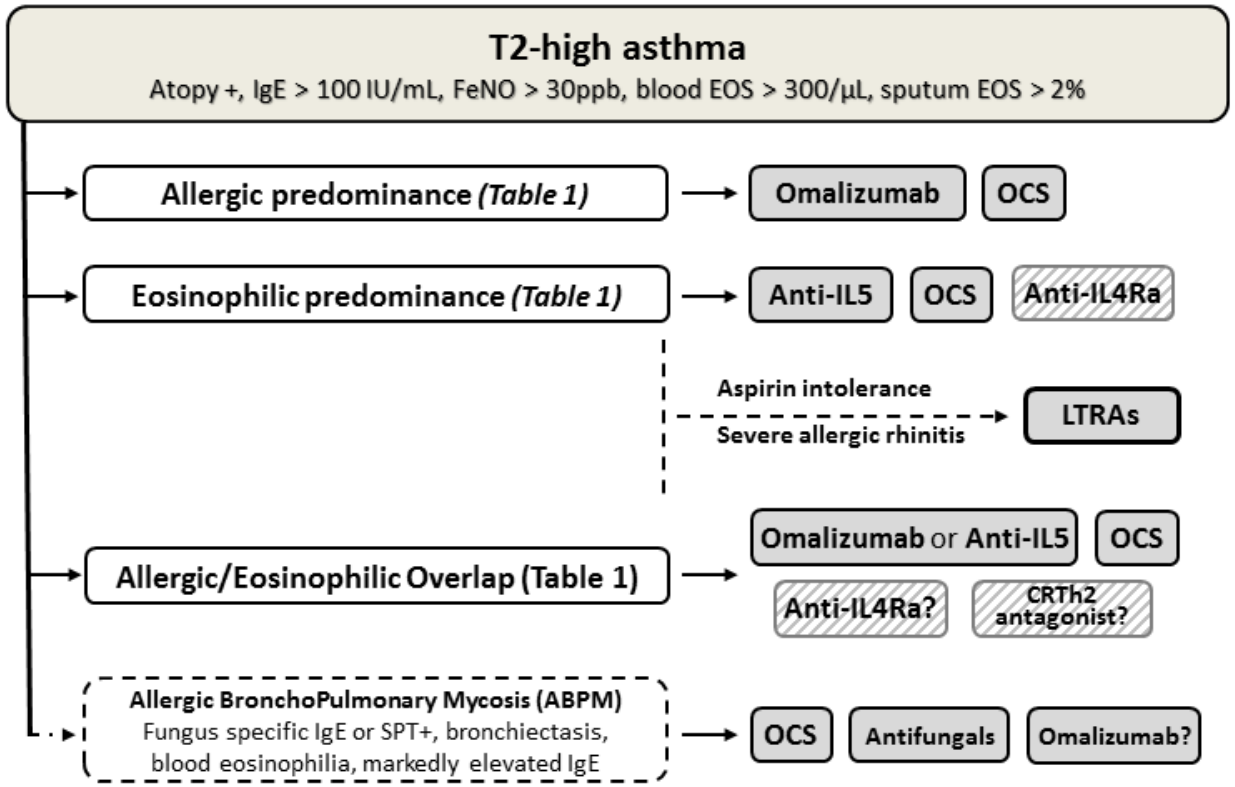
OSMO study: Exacerbations (ITT population)



Data from two Phase 3 studies (MENSA [MEA115588/NCT01691521]; MUSCA [200862/ NCT02281318])

Chapman et al, Allergy 2019, Doi: 10.1111/all.13850

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ



Zervas E. et al ERJ OR 2017

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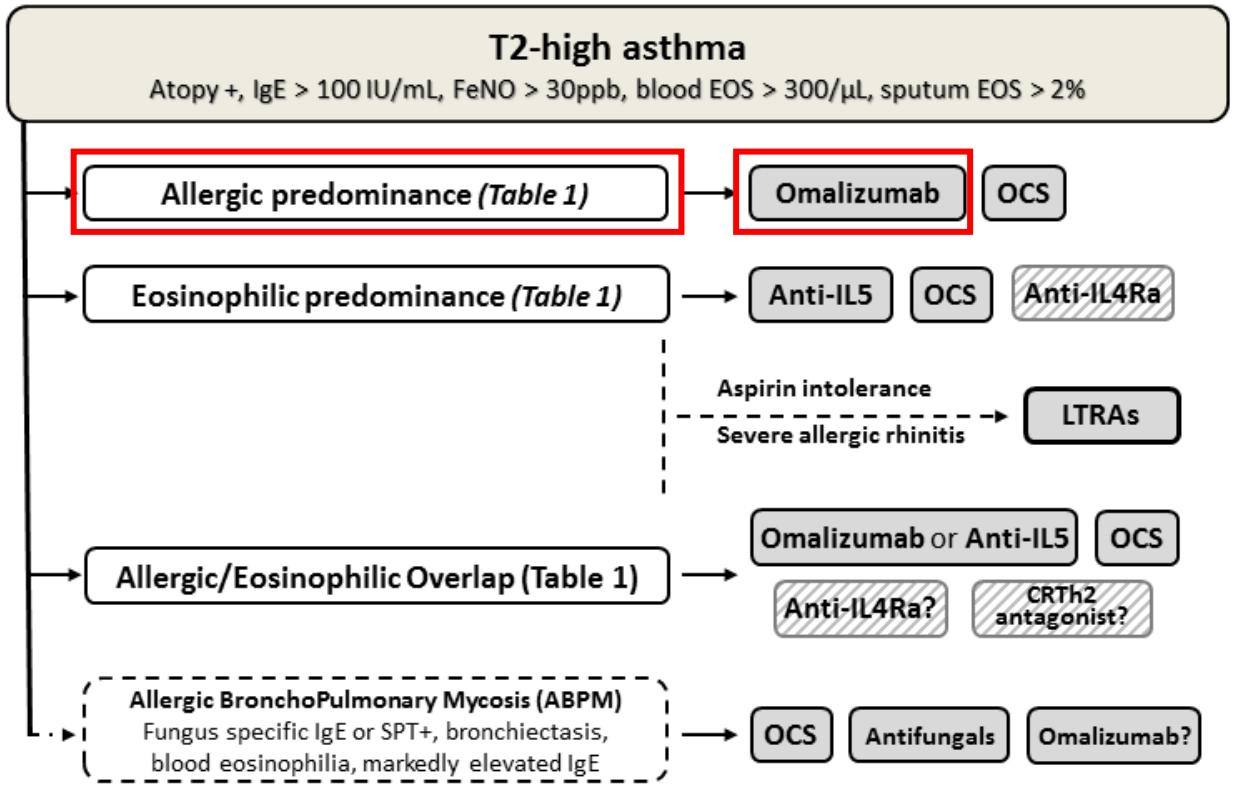

Zervas E. et al ERJ OR 2017

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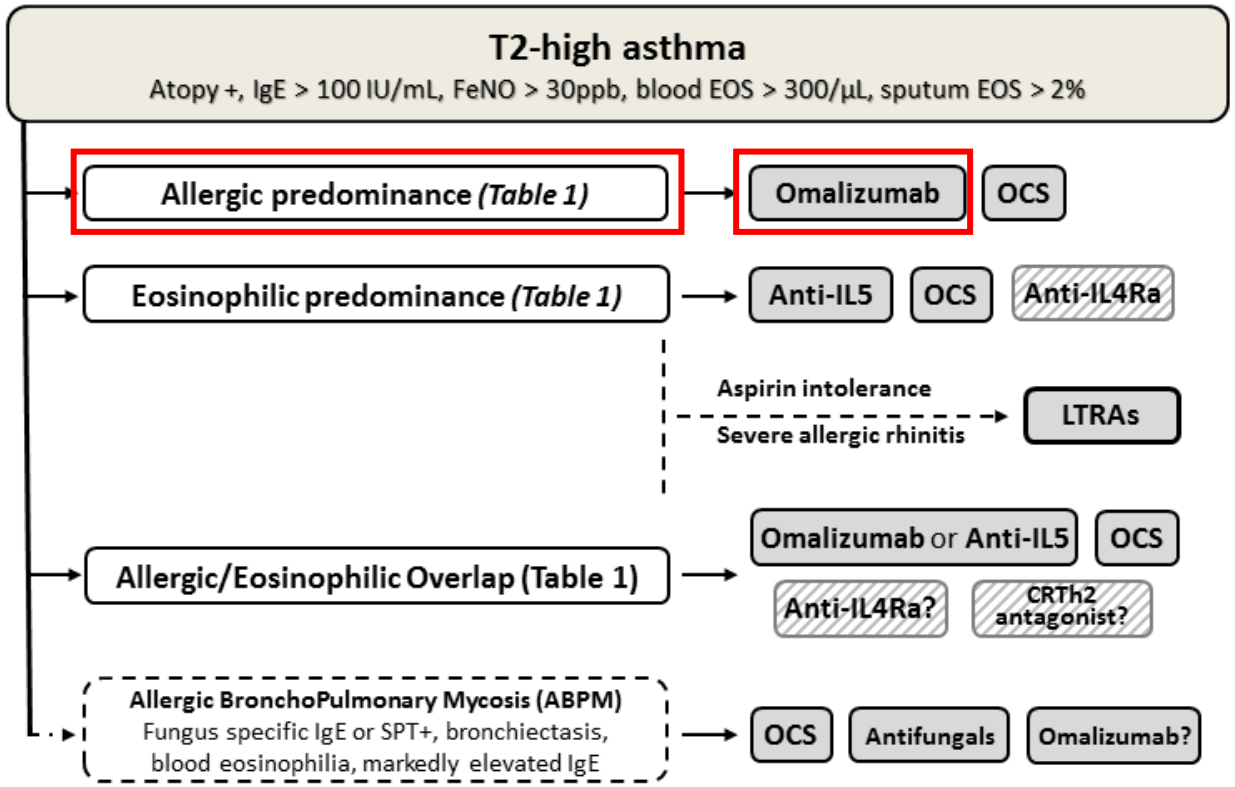
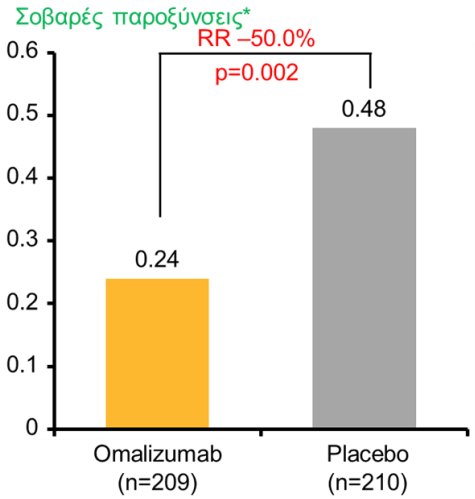
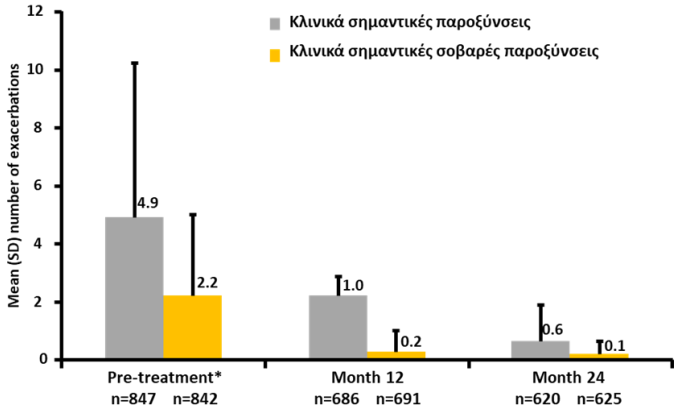


Μείωση παροξυσμών και επειγουσών επισκέψεων

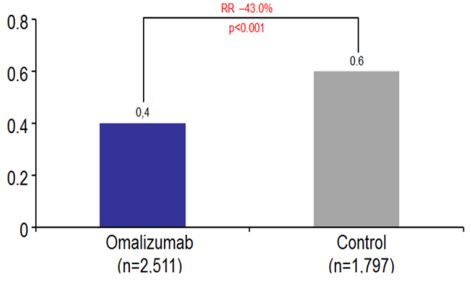
Clinical Evidence (INNOVATE) | *Real-World Evidence (eXpeRience Registry)*





Μείωση χρήσης OCS – "steroid sparing effect"

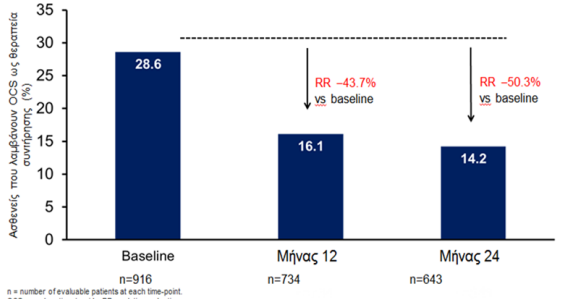
Clinical Evidence[1] | *Real-World Evidence*[2]



Μέσος όρος χρήσης στεροειδών 24–52 weeks

RR = relative reduction.

1. Maykut R, et al. J Allergy Clin Immunol 2006;117:S10,39 (abstract).

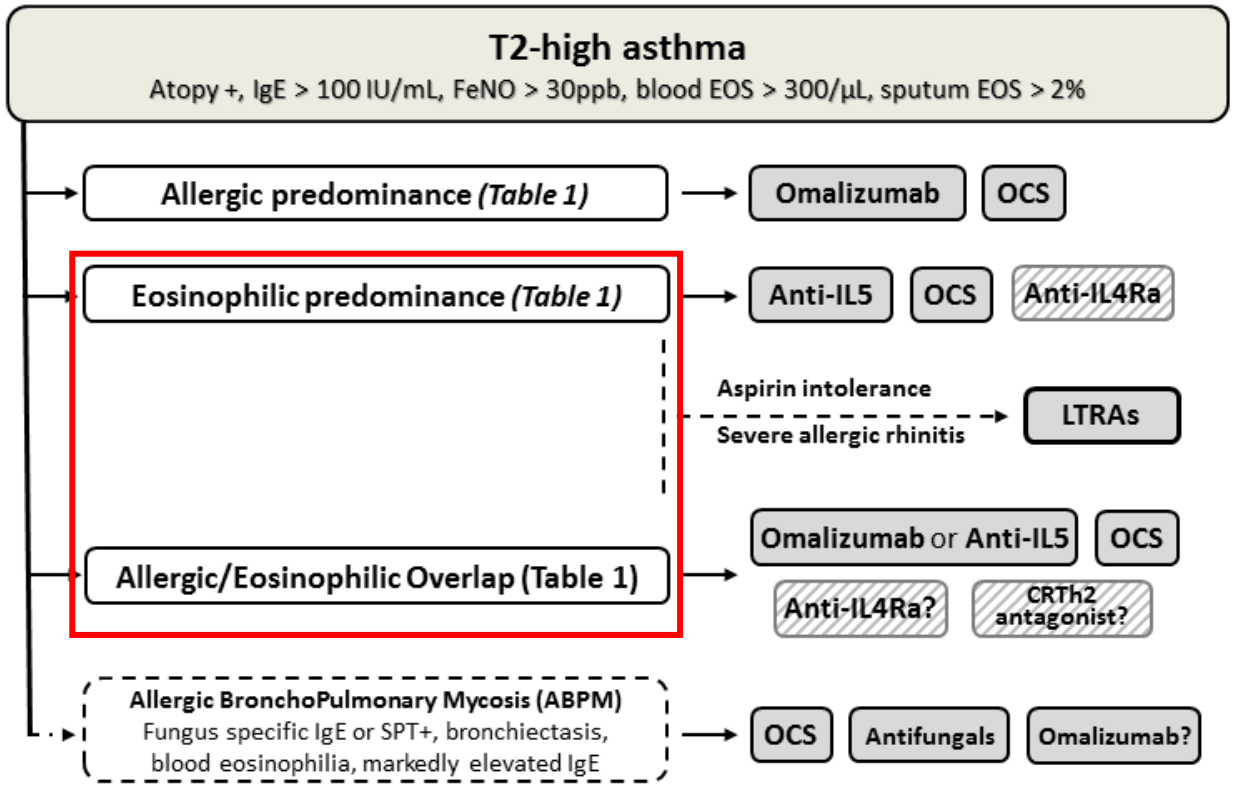


n = number of evaluable patients at each time-point. OCS = oral corticosteroids; RR = relative reduction.

2. Braunstahl GJ, *et al.* Respir Med 2013;107:1141–51.

Zervas E. et al ERJ OR 2017

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ



Zervas E. et al ERJ OR 2017

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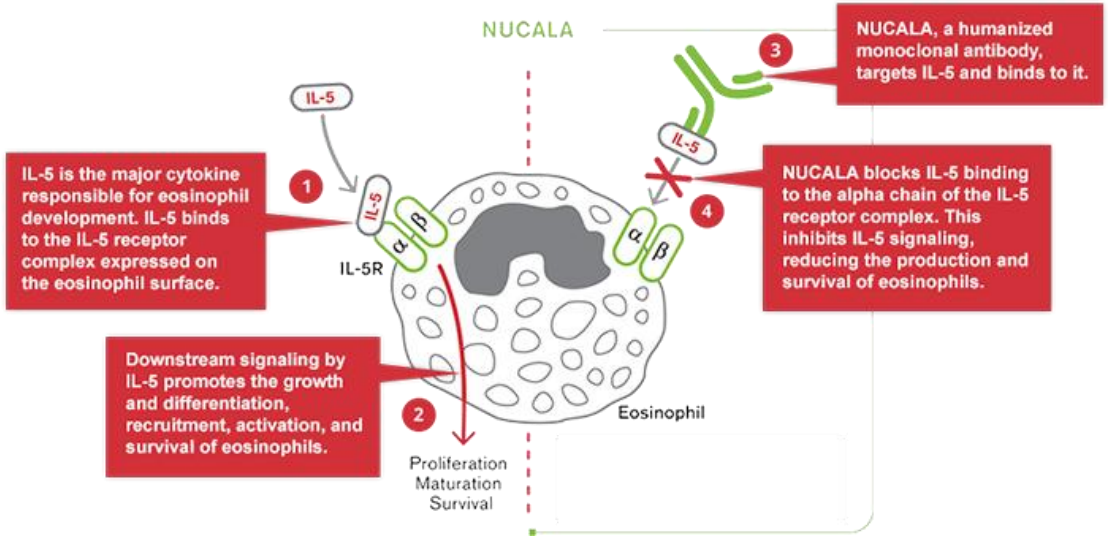
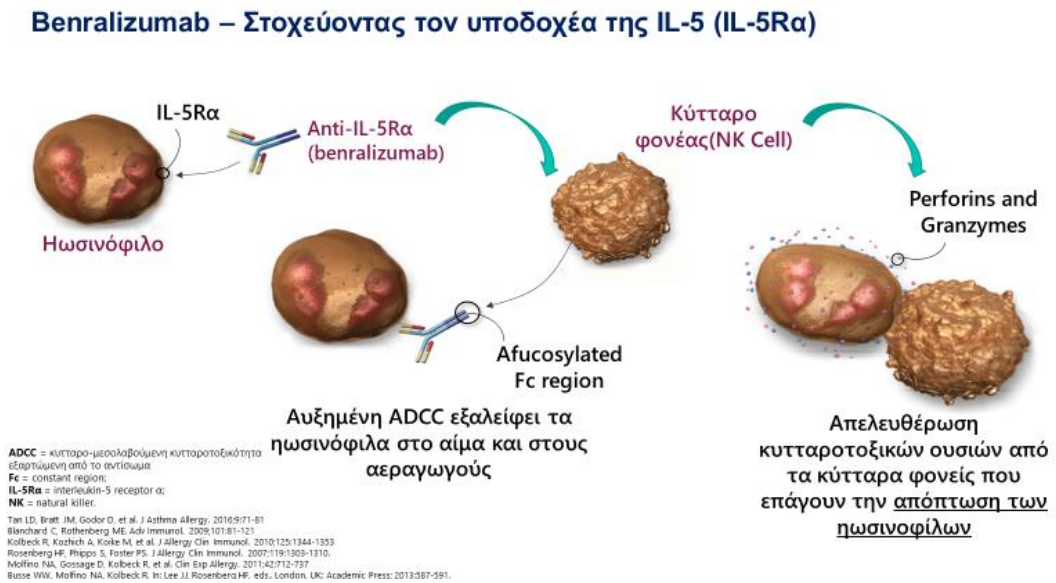
MEPOLIZUMAB



BENRALIZUMAB



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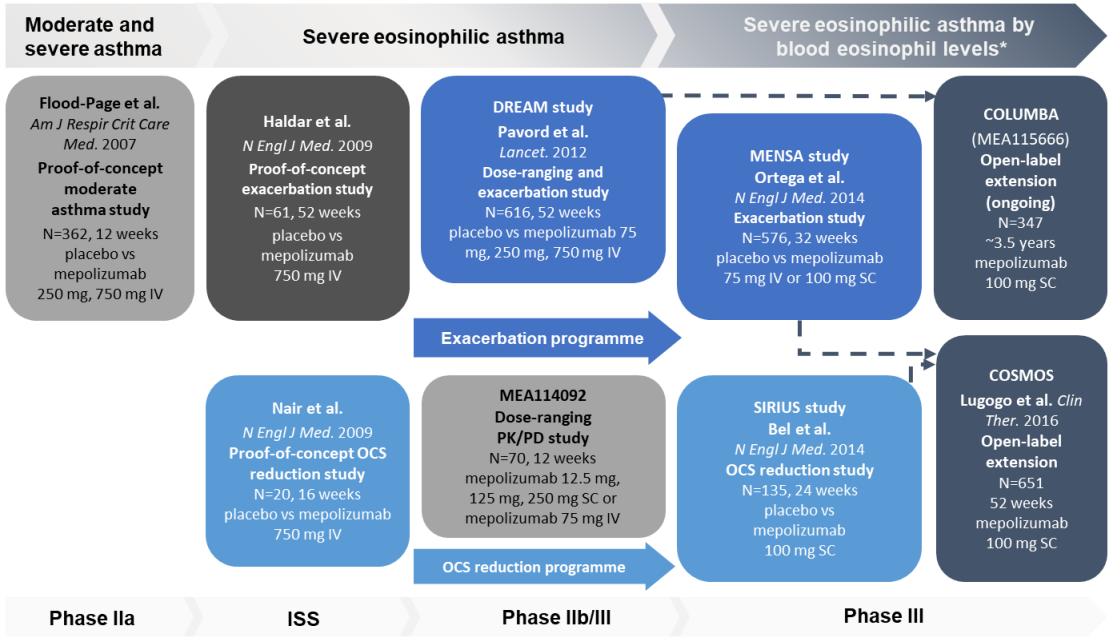
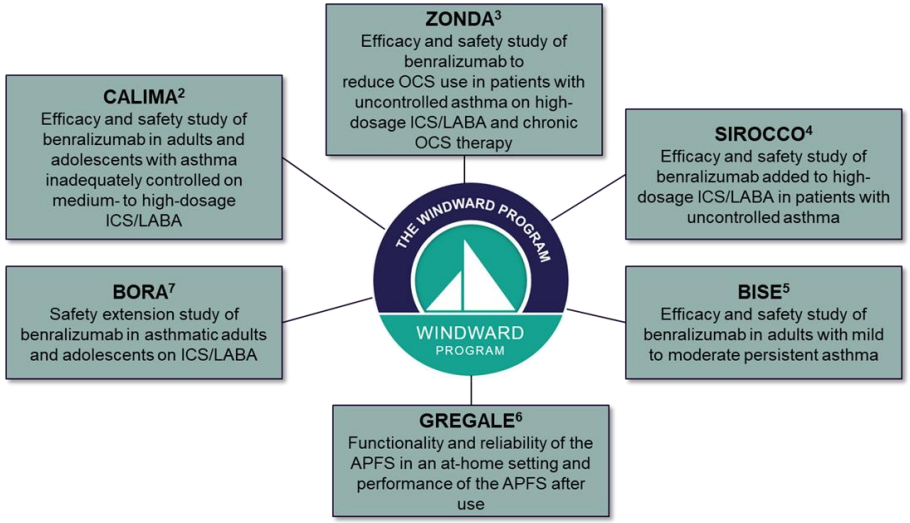


BENRALIZUMAB

- **Six Phase 3 trials in ~3068 patients** and at 798 sites across 26 countries[1]
- **The largest Phase 3** development program for a biologic in respiratory disease[1]



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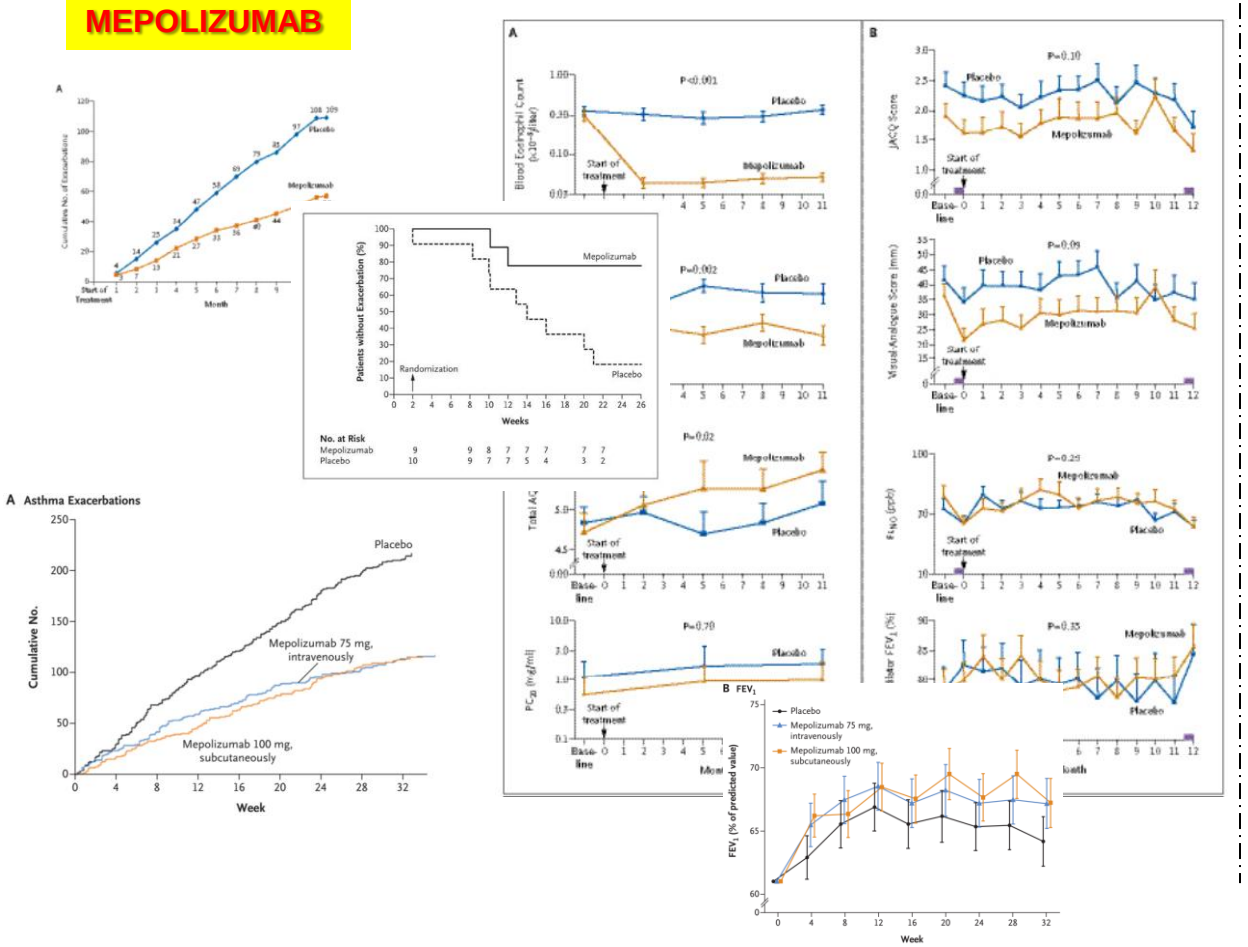

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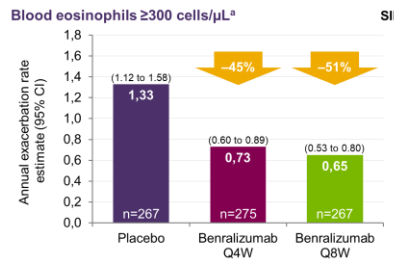
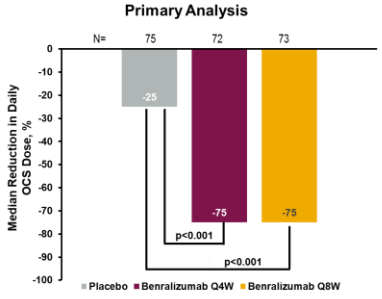


Annual exacerbation rate ratio vs. placebo[b]

Q4W
0.55 (0.42 to 0.71)
p<0.0001

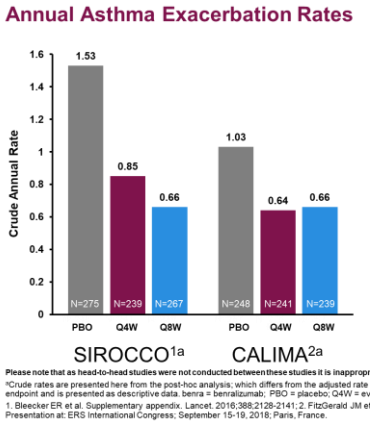
Q8W
0.49 (0.37 to 0.64)
p<0.0001

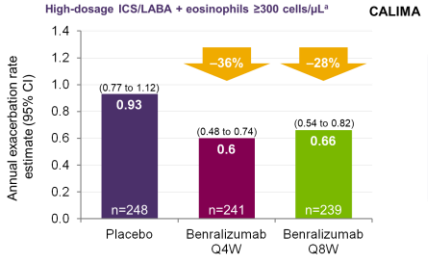


Categorical Analysis

Reduction in Final OCS Dose, n (%)	Placebo N=75	Benra 30 mg Q4W, N=72	Benra 30 mg Q8W, N=73
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
No change or any increase in OCS dose	35 (47)	17 (24)	15 (21)
OR (95 %CI)	–	4.09 (2.22 – 7.57)	4.12 (2.22 – 7.63)
p-vakue	–	<0.001	<0.001

- **Reduction in final OCS daily dose was 4X greater with benra vs. placebo (median baseline OCS dose was 10 mg/d in all groups)**





Annual exacerbation rate ratio vs. placebo[b]

Q4W
0.64 (0.49 to 0.85)
p=0.0018

Q8W
0.72 (0.54 to 0.95)
p=0.0188

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

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1. Matching-Adjusted Indirect Comparison of **Benralizumab** *versus* Interleukin-5 Inhibitors: Systematic Review.
   Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui MK, Lindner L, Xu X.
   Eur Respir J. 2018 Oct 11. pii: 1801393. doi: 10.1183/13993003.01393-2018. [Epub ahead of print]
   PMID: 30309978
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2. Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis.
   Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D.
   Lung. 2018 Oct;196(5):517-530. doi: 10.1007/s00408-018-0151-5. Epub 2018 Aug 23.
   PMID: 30167841
   Similar articles

3. Reslizumab Compared with **Benralizumab** in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis.
   Casale TB, Pacou M, Mesana L, Farge G, Sun SX, Castro M.
   J Allergy Clin Immunol Pract. 2018 Sep 11. pii: S2213-2198(18)30576-2. doi: 10.1016/j.jaip.2018.08.036. [Epub ahead of print]
   PMID: 30217529
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4. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison.
   Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, Bratton DJ, Gunsoy NB.
   J Allergy Clin Immunol. 2018 Sep 8. pii: S0091-6749(18)31278-8. doi: 10.1016/j.jaci.2018.08.031. [Epub ahead of print]
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Lung. 2018 Oct;196(5):517-530. doi: 10.1007/s00408-018-0151-5. Epub 2018 Aug 23.

Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis.

Iftikhar IH[1], Schimmel M[2], Bender W[2], Swenson C[2], Amrol D[3].

⊕ Author information

Abstract

BACKGROUND: Several new biologics have been studied in patients with eosinophilic asthma with varying degrees of response on clinical outcomes. No head-to-head trial has directly compared the efficacy of these drugs.

OBJECTIVE: To synthesize data on the relative efficacy of benralizumab, dupilumab, lebrikizumab, mepolizumab, reslizumab, and tralokinumab using network meta-analysis.

DATA SOURCES: We searched PubMed from inception to December 15th, 2017.

DATA EXTRACTION AND SYNTHESIS: We used the 'frequentist' methodology with random effect models using primarily 'netmeta' function in R to generate network meta-analysis results. Outcomes assessed included changes in forced expiratory volume-in 1 s (FEV_1), asthma control questionnaire (ACQ), and asthma quality of life questionnaire (AQLQ). We also separately analyzed the annualized rate ratios for asthma exacerbations for each drug and compared to placebo. For all outcomes assessed, all drugs were superior to placebo except tralokinumab. In terms of magnitude of effect, dupilumab, followed by reslizumab and benralizumab showed the greatest increase in FEV_1, 0.16L (95% CIs: 0.08-0.24), 0.13L (0.10-0.17), and 0.12L (0.08-0.17), compared to placebo. While mepolizumab, followed by dupliumab, benralizumab, and reslizumab showed reductions in ACQ scores, in order of magnitude of effect, dupilumab, followed by mepolizumab, benralizumab, and reslizumab showed the greatest increase in AQLQ scores. All drugs decreased asthma exacerbations but the results were only significant for reslizumab and dupilumab.

CONCLUSIONS: All drugs except for tralokinumab showed improvements in FEV_1, ACQ, and AQLQ. Only reslizumab and dupilumab were associated with statistically significant reductions in asthma exacerbation rates.

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Reslizumab Compared with Benralizumab in Patients with Eosinophilic Asthma: A Systematic Literature Review and Network Meta-Analysis.

Casale TB[1], Pacou M[2], Mesana L[3], Farge G[2], Sun SX[4], Castro M[5].
Author information

Abstract
BACKGROUND: The interaction of IL-5 with its receptor on eosinophils increases the activation and maintenance of eosinophils; blocking this interaction reduces asthma symptoms in patients with the eosinophilic phenotype. Reslizumab, which binds to IL-5, and benralizumab, which targets the IL-5 receptor α subunit, have not been compared in head-to-head trials.

OBJECTIVE: To indirectly compare reslizumab with benralizumab in similar patient populations using a network meta-analysis.

METHODS: A systematic literature review was conducted and a network meta-analysis was performed on eligible studies using the Markov Chain Monte-Carlo simulation method and a Bayesian statistical framework.

RESULTS: Eleven studies were identified, 4 of which evaluated clinically relevant doses and had outcomes at similar time points. To control for population differences, subgroups were selected for the base-case efficacy analysis: a benralizumab subgroup with blood eosinophil levels of greater than or equal to 300 cells/μL (n = 1537) and a reslizumab subgroup in Global Initiative for Asthma step 4/5 with 2 or more previous exacerbations and greater than or equal to 400 eosinophils/μL (n = 318). Safety was analyzed in the full population (N = 3462). Reslizumab significantly improved Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores compared with benralizumab once every 4 weeks and there were reasonably high posterior probabilities that reslizumab is superior to benralizumab once every 4 weeks and once every 8 weeks for ACQ score, AQLQ score, FEV_1, and clinical asthma exacerbations.

CONCLUSIONS: This indirect comparison suggests that reslizumab may be more efficacious than benralizumab in patients with eosinophilic asthma in Global Initiative for Asthma step 4/5 with elevated blood eosinophil levels (benralizumab, ≥300/μL; reslizumab, ≥400/μL) and 2 or more exacerbations in the previous year.

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

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J Allergy Clin Immunol. 2018 Sep 8. pii: S0091-6749(18)31278-8. doi: 10.1016/j.jaci.2018.08.031. [Epub ahead of print]

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

Busse W[1], Chupp G[2], Nagase H[3], Albers FC[4], Doyle S[5], Shen Q[6], Bratton DJ[7], Gunsoy NB[5].

Author information

Abstract

BACKGROUND: Three anti-IL-5 pathway-directed therapies are approved for use in patients with severe eosinophilic asthma (SEA); however, no head-to-head comparison data are available.

OBJECTIVE: We sought to compare the efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with SEA, according to baseline blood eosinophil counts.

METHODS: This indirect treatment comparison (ITC) used data from a Cochrane review and independent searches. Eligible studies were randomized controlled trials in patients aged 12 years or greater with SEA. End points included annualized rate of clinically significant exacerbations and change from baseline in Asthma Control Questionnaire score and FEV_1. An ITC was performed in patients with Asthma Control Questionnaire scores of 1.5 or greater and stratified by baseline blood eosinophil count.

RESULTS: Eleven studies were included. All treatments significantly reduced the rate of clinically significant exacerbations and improved asthma control versus placebo in all blood eosinophil count subgroups. Mepolizumab reduced clinically significant exacerbations by 34% to 45% versus benralizumab across subgroups (rate ratio ≥400 cells/μL: 0.55 [95% CI, 0.35-0.87]; ≥300 cells/μL: 0.61 [95% CI, 0.37-0.99]; and ≥150 cells/μL: 0.66 [95% CI, 0.49-0.89]; all P < .05) and by 45% versus reslizumab in the 400 cells/μL or greater subgroup (rate ratio, 0.55 [95% CI, 0.36-0.85]; P = .007). Asthma control was significantly improved with mepolizumab versus benralizumab (all subgroups: P < .05) and versus reslizumab in the 400 cells/μL or greater subgroup (P = .004). Benralizumab significantly improved lung function versus reslizumab in the 400 cells/μL or greater subgroup (P = .025).

CONCLUSIONS: This ITC of the licensed doses suggests that mepolizumab was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared with reslizumab or benralizumab in patients with similar blood eosinophil counts.

J Allergy Clin Immunol Pract. 2018 Sep 11. pii: S2213-2198(18

Reslizumab Compared with Benra
Literature Review and Network Me

Casale TB[1], Pacou M[2], Mesana L[3], Farge G[2], Sun SX

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Eur Respir J. 2018 Oct 11. pii: 1801393. doi: 10.1183/13993003.01393-2018. [Epub ahead of print]

Matching-Adjusted Indirect Comparison of Benralizumab *versus* Interleukin-5 Inhibitors: Systematic Review.

Bourdin A[1,2], Husereau D[3,4], Molinari N[5], Golam S[6], Siddiqui MK[7], Lindner L[8], Xu X[9].

Author information

Abstract

The relative efficacy of benralizumab, an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that directly depletes eosinophils *versus* other IL-5-targeted treatments for patients with severe, uncontrolled asthma, is not yet fully characterised.We performed a matching-adjusted indirect comparison (MAIC) of benralizumab *versus* mepolizumab and reslizumab. Trials were selected through systematic review and evaluation of trial methods. Benralizumab patient-level data were weighted to match treatment effect-modifying patient characteristics of comparator trials before indirect efficacy comparisons.After matching adjustment, benralizumab and mepolizumab reduced exacerbations *versus* placebo by 52% and 49%, respectively (rate ratio [RR]: 0.94; 95% confidence interval [CI]: 0.78-1.13; N=1524) and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR: 1.00; 95% CI: 0.57-1.75; N=1524). Benralizumab and mepolizumab similarly improved prebronchodilator forced expiratory volume in 1 second at 32 weeks (difference=0.03 L; 95% CI: -0.06-0.12; N=1443). Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC.MAIC is a robust way to indirectly compare efficacies of treatments from trials with heterogeneous patient populations. When baseline patient characteristics were matched across asthma trials, benralizumab and mepolizumab yielded similar efficacy.

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

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Trial record **1 of 1** for: predictumab

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Study of Magnitude and Prediction of Response to Omalizumab and Mepolizumab in Adult Severe Asthma. (PREDICTUMAB)

ClinicalTrials.gov Identifier: NCT03476109

PREDICTUMAB STUDY

Belgian severe asthma network

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	100 participants
Allocation:	Randomized
Intervention Model:	Factorial Assignment
Intervention Model Description:	Severe asthma patients who are eligible to both anti-IgE (omalizumab) and anti-IL-5 (mepolizumab) therapies, will be randomized to decide the first treatment to start. Patients will then be prolonged or switched to the other according to the clinical response. There will be 5 possibilities: oma(lizumab) group, mepo(lizumab) group, oma-mepo switch, mepo-oma switch, and oma/mepo failure.
Masking:	Single (Outcomes Assessor)
Masking Description:	The analysis of the response rate and magnitude, as well as of biomakers predicting the response, will be performed by an independent assessor and a biostatistician.
Primary Purpose:	Treatment
Official Title:	Predictive Factors and Magnitude of Response to Omalizumab and Mepolizumab in Allergic and Eosinophilic Severe Asthma: a Pragmatic Multicenter Trial in Belgium.
Actual Study Start Date :	May 10, 2019
Estimated Primary Completion Date :	December 31, 2020
Estimated Study Completion Date :	December 31, 2020

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

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PrecISE (Precision Interventions for Severe and/or Exacerbation-Prone Asthma) Network Study

PrecISE STUDY

Detailed Description:

PrecISE is a clinical study sponsored by the U.S. National Heart, Lung, and Blood Institute (NHLBI) to investigate several treatments for severe asthma. PrecISE will enroll 800 adults and teenagers (ages 12 years and older) with severe asthma who have symptoms that are not well-controlled on high dose of inhaled corticosteroids including those who have frequent asthma attacks. Each person who agrees to enroll in the PrecISE study will receive several treatments for research purposes based on their type of severe asthma.

The goal of PrecISE is to understand how to treat different types of severe asthma, by using precision medicine. Precision medicine is an approach that targets treatments to defined subgroups of patients who share similar characteristics, for example, patients with a certain genetic variation or patients with high number of blood eosinophils.

Researchers from over 30 locations across the US, as well as sites in Canada and the United Kingdom, are involved in PrecISE.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	800 participants
Allocation:	Randomized
Intervention Model:	Crossover Assignment
Intervention Model Description:	Treatment sequence will be randomly assigned as either test treatment followed by matching placebo or vice-versa.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	PrecISE (Precision Interventions for Severe and/or Exacerbation-Prone Asthma) Network Study
Estimated Study Start Date :	November 2019
Estimated Primary Completion Date :	June 2023
Estimated Study Completion Date :	June 2023

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΟ ΣΟΒΑΡΟ ΑΣΘΜΑ

ΣΥΜΠΕΡΑΣΜΑΤΑ

1. Η στοχευμένη θεραπεία με μονοκλωνικά αντισώματα αποτελεί το μέλλον της θεραπείας του σοβαρού άσθματος – ειδικότερα του T2-high ενδότυπου

2. Οι κλινικές μελέτες των αντι-ηωσινοφιλικών θεραπειών παρουσιάζουν ομοιότητες αλλά και σημαντικές διαφορές (κλινικά χαρακτηριστικά των ασθενών, ορισμός του «ηωσινοφιλικού φαινοτύπου» κ.τ.λ.) δεν επιτρέπουν άμεσες συγκρίσεις

3. Η έμμεση σύγκριση των αντι-ηωσινοφιλικών θεραπειών είναι δύσκολη και με αντικρουόμενα αποτελέσματα. Τυχόν διαφορές που υπάρχουν μένουν να αποδειχθούν στην κλινική πράξη…

4. Αναπάντητα ερωτήματα παραμένουν…
   a) Βιοδείκτες για την επιλογή καταλληλότερης θεραπείας και εκτίμησης της ανταπόκρισης
   b) Διάρκεια θεραπείας?
   c) Ρίσκο υποτροπής σε διακοπή? Βιοδείκτες?
   d) Συγκριτικές μελέτες μεταξύ βιολογικών θεραπείων – Real World Registries

28ο ΠΑΝΕΛΛΗΝΙΟ Πνευμονολογικό ΣΥΝΕΔΡΙΟ
ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC THORACIC SOCIETY
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ΚΩΝΣΤΑΝΤΙΝΟΣ ΣΑΜΙΤΑΣ
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ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ»

‘ Η ΣΩΤΗΡΙΑ ’