Omalizumab - Νεότερα δεδομένα

Πορπόδης Κωνσταντίνος
Πνευμονολόγος
Επ. Καθηγητής ΑΠΘ

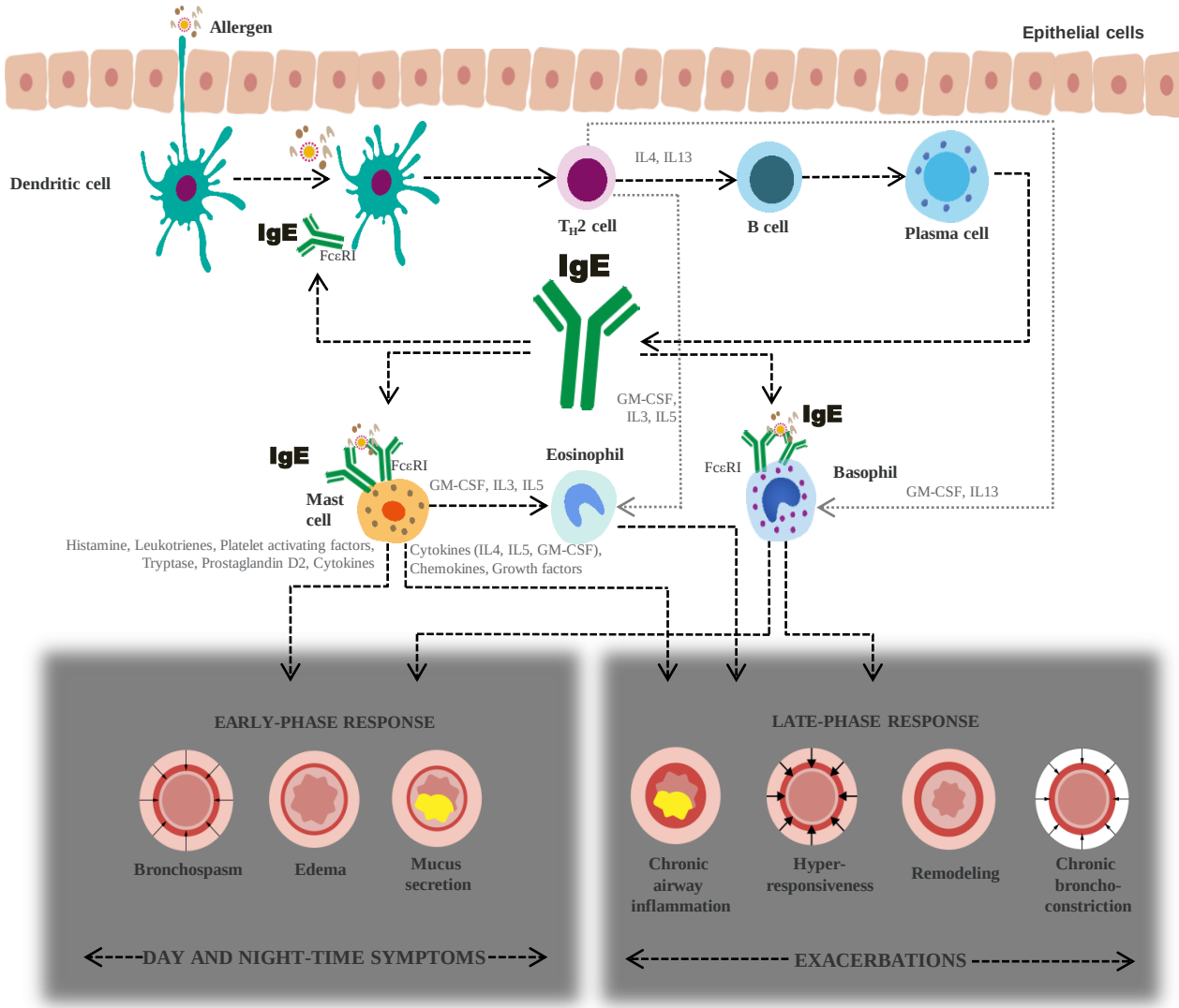
Conflict of interest (Δήλωση σύγκρουσης συμφερόντων)

- Συμμετοχή σε advisory board (συμβουλευτική επιτροπή) των φαρμακευτικών εταιρειών Novartis, Chiessi, Menarini

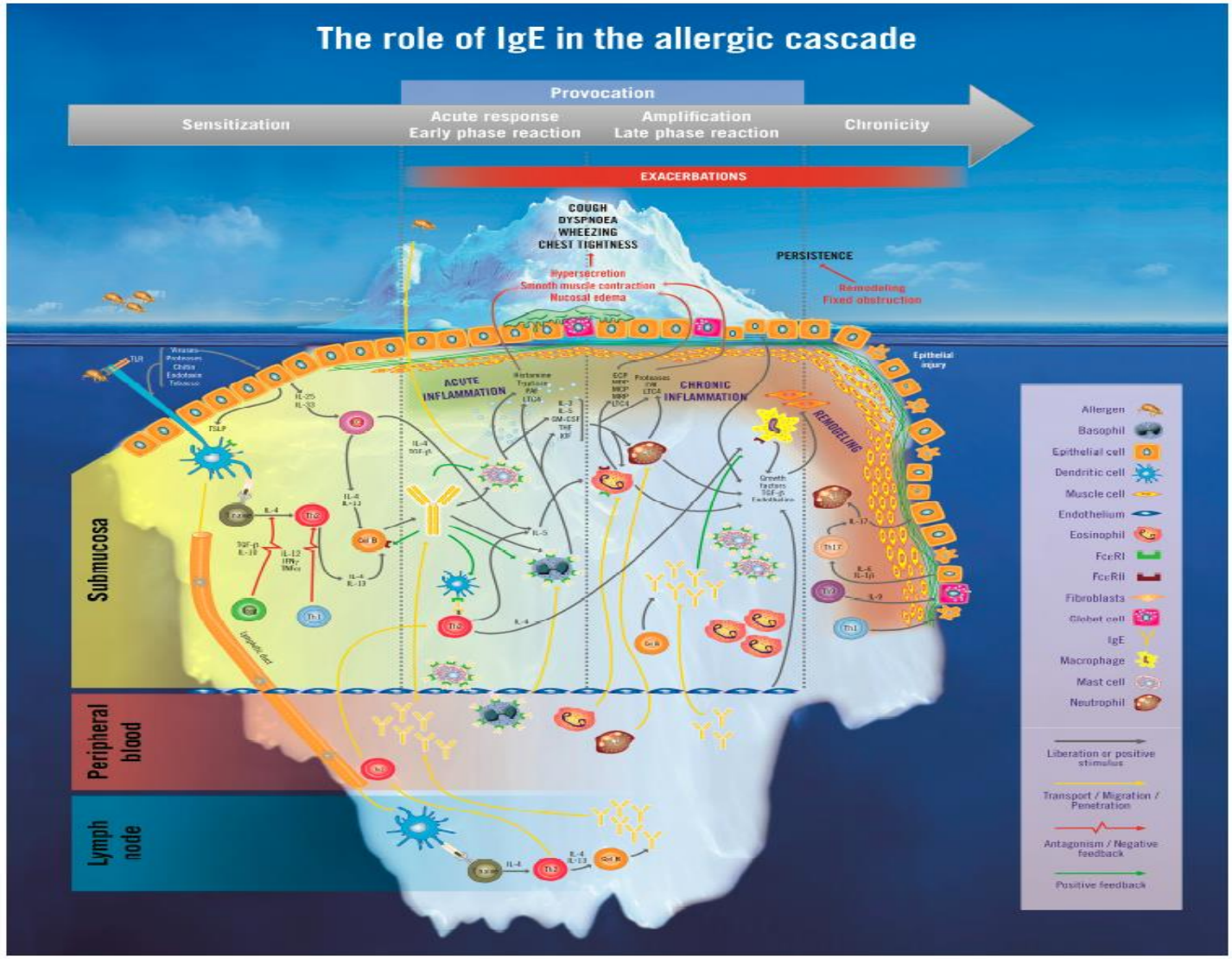
- Honorarium (τιμητικές αμοιβές) ως προσκεκλημένος ομιλητής από τις φαρμακευτικές εταιρείες Astra, Novartis, UCB, Chiessi, Menarini, Glaxo, MSD

- Κάλυψη εξόδων συμμετοχής (εγγραφής, ταξιδίου και διαμονής) σε ελληνικά και διεθνή συνέδρια από τις φαρμακευτικές εταιρείες Astra, Novartis, Elpen, Chiessi, UCB, GSK, Roche, Takeda

Ο κεντρικός ρόλος της IgE στην παθοφυσιολογία του σοβαρού αλλεργικού άσθματος



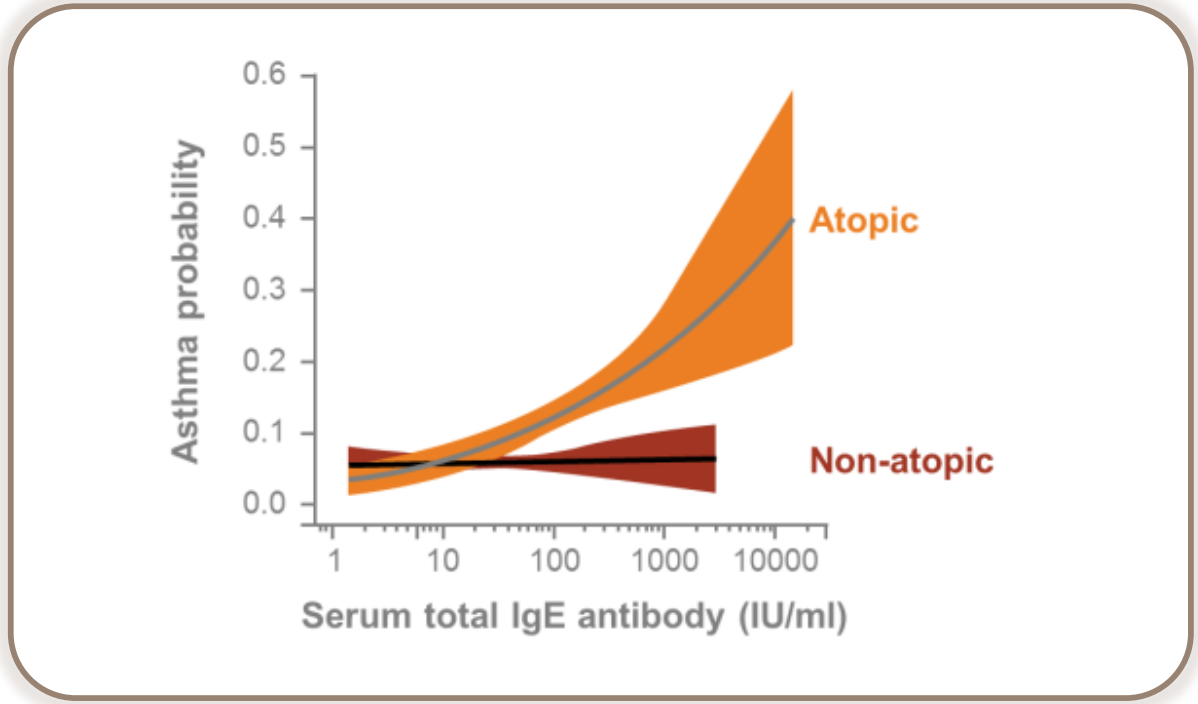
Olin JT & Wechsler ME. *BMJ* 2014



Palomares et. al., Int J Mol Sci. 2017 Jun 21;18(6).

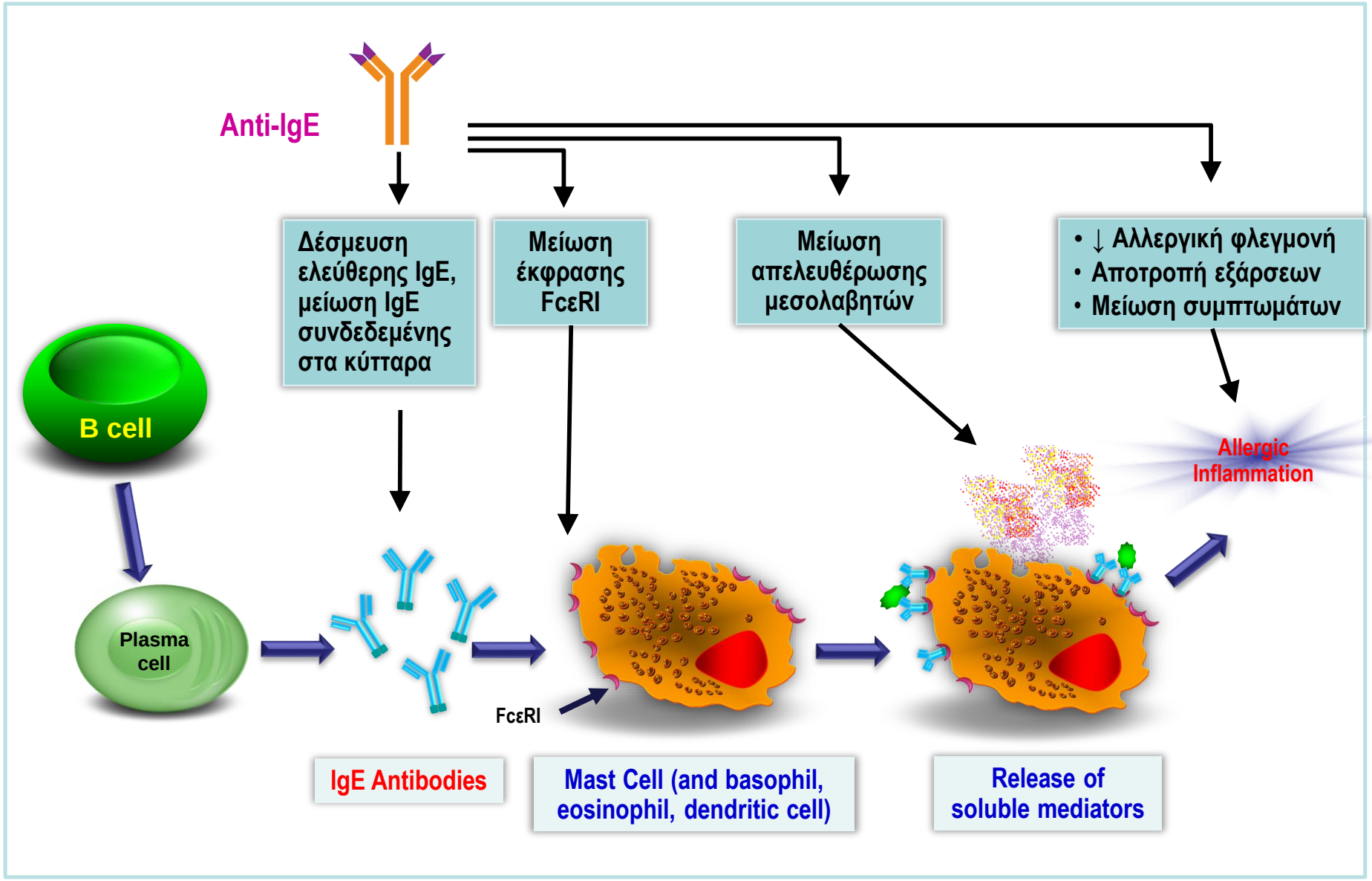
Η υπέρμετρη παραγωγή IgE αποτελεί παράγοντα κινδύνου για την ανάπτυξη άσθματος

- Έχει αναφερθεί συσχέτιση μεταξύ των επιπέδων της IgE και του κινδύνου εμφάνισης άσθματος σε ενήλικο πληθυσμό[1,2]



1. Burrows B, et al. *N Engl J Med* 1989;320:271-7.
2. Gergen P, et al. J Allergy Clin Immunol. 2009;124(3):447–453

Μηχανισμός δράσης omalizumab



Holgate ST, et al. *Nat Rev Immunol.* 2008;8:218-230.

Ερωτήματα 1

Μείωση των παροξύνσεων ?

Μείωση επισκέψεων σε ΤΕΠ/Νοσηλειών ?

Βελτίωση των συμπτωμάτων ?

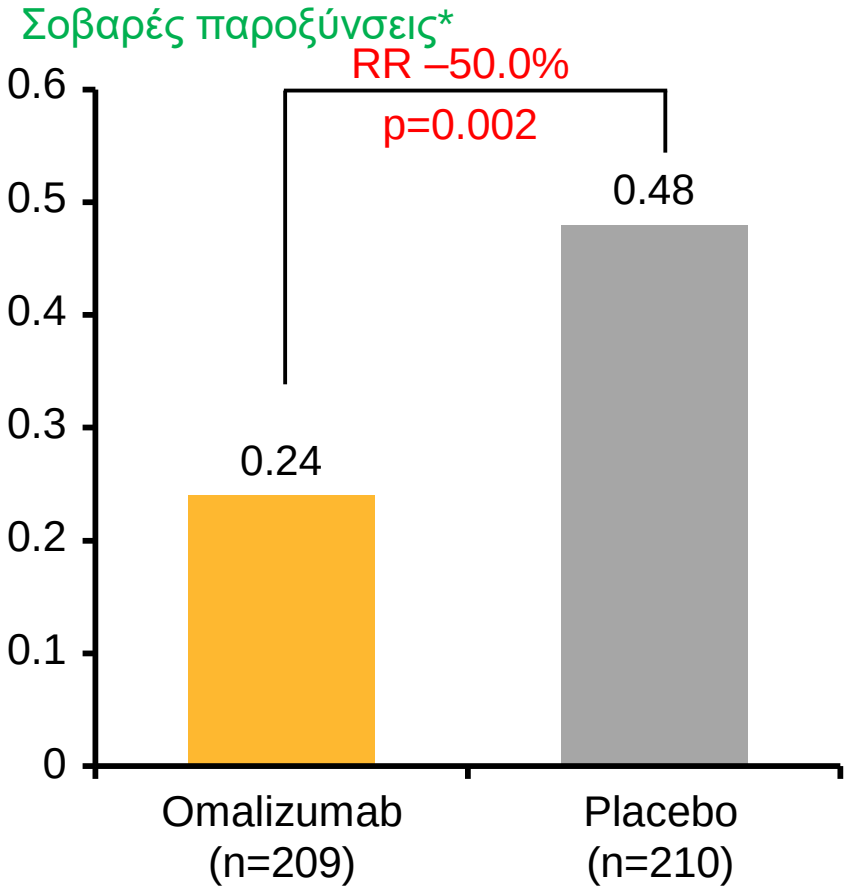
Μείωση των κορτικοειδών (OS) ?

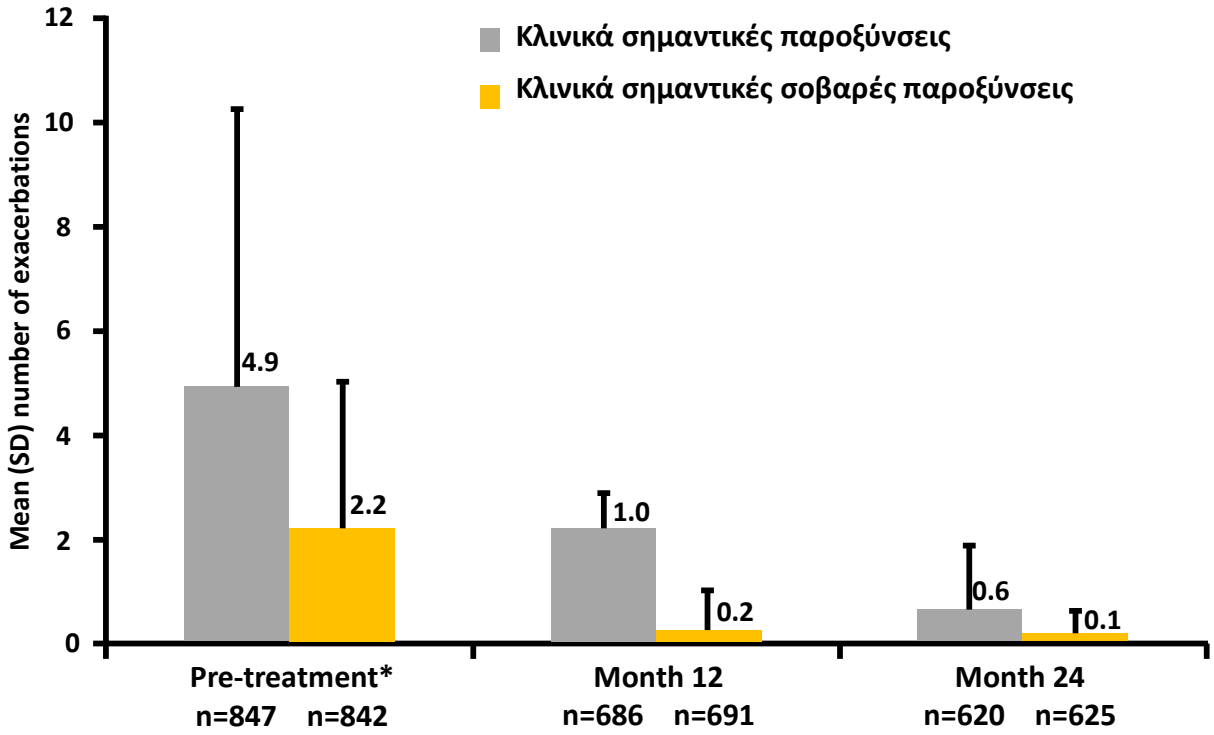
Ασφάλεια?

Το Omalizumab μειώνει σημαντικά τις παροξύνσεις

Clinical Evidence (INNOVATE)

Real-World Evidence (eXpeRience Registry)



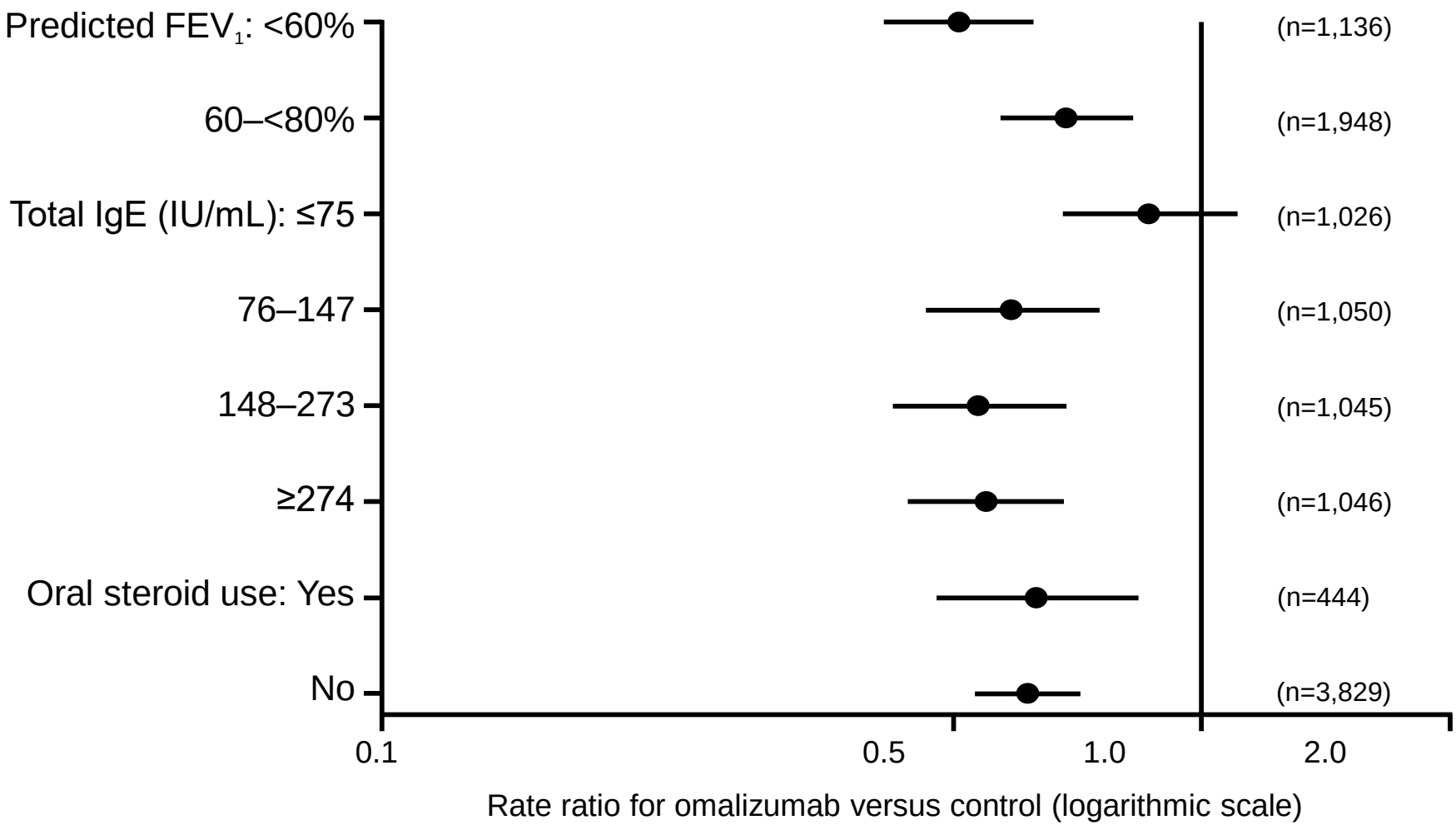


*Severe exacerbation defined as reduction in PEF or FEV_1 to <60% of personal best and requiring treatment with systemic corticosteroids.
FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; RR = relative reduction.

Humbert M, et al. Allergy 2005;60:309–16.

Braunstahl, G.J., et al., Respiratory Medicine (2013) 107, 1141-1151

Σταθερή αποτελεσματικότητα στη μείωση παροξύνσεων ανεξαρτήτως πνευμονικής λειτουργίας, IgE και χρήσης OCS



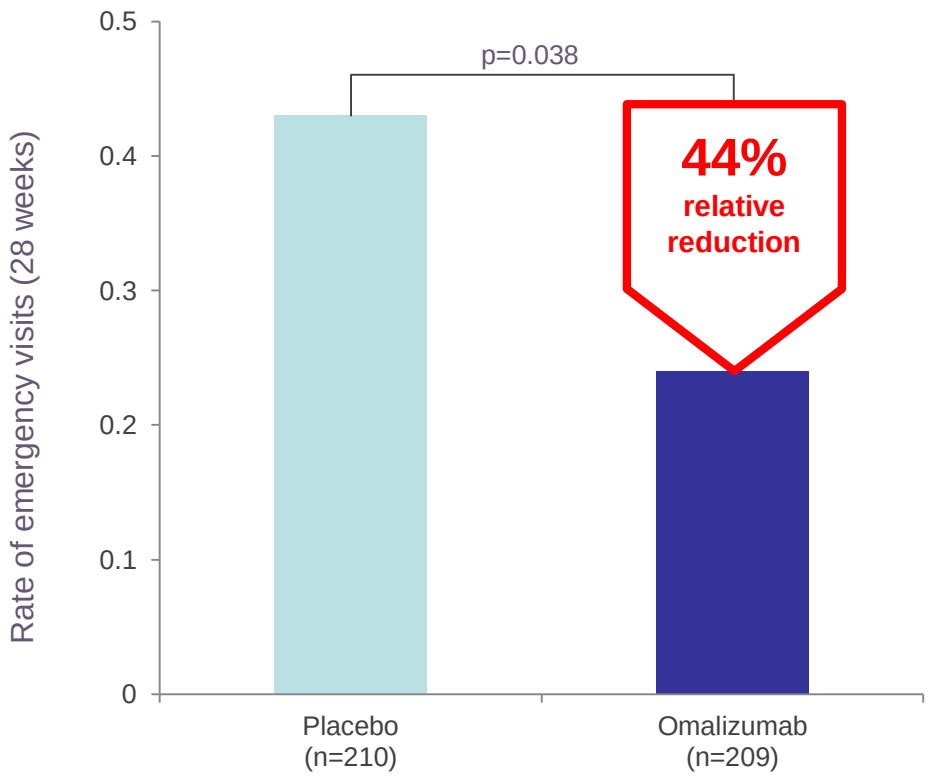
FEV1 = forced expiratory volume in 1 second;
IgE = immunoglobulin E.
Novartis, data on file.

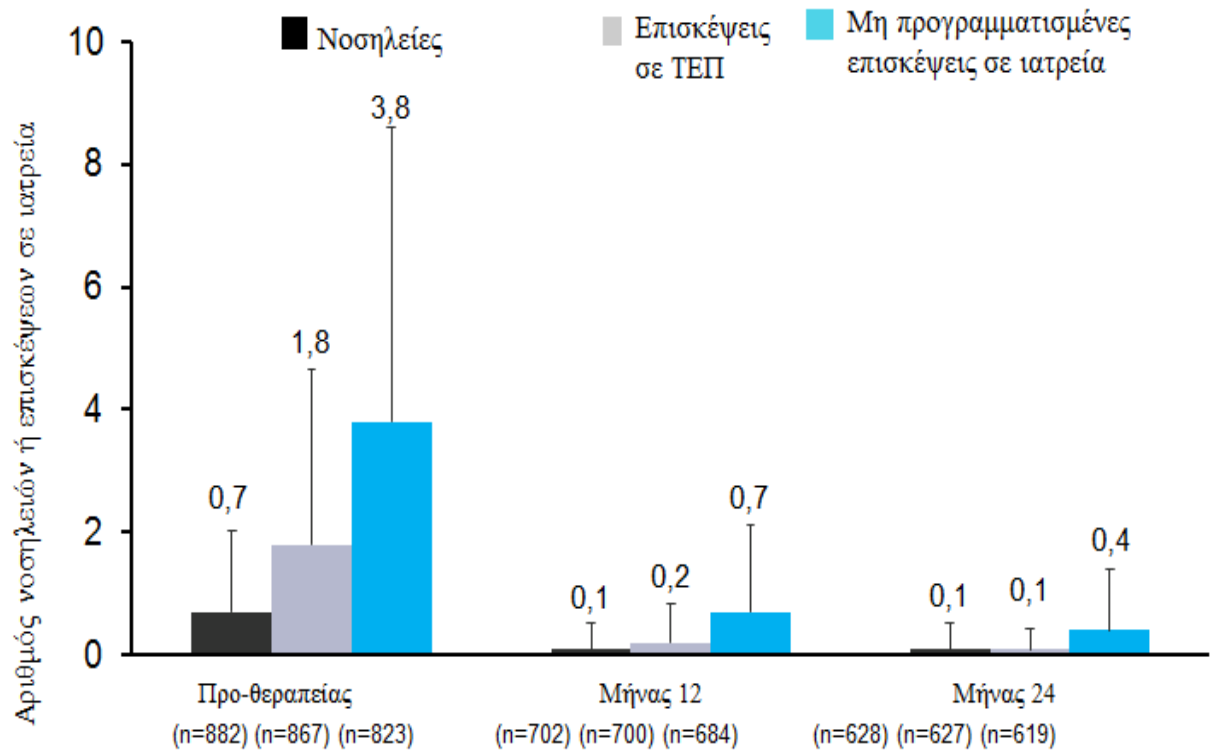
Το Omalizumab μειώνει σημαντικά τη χρήση πόρων υγείας

Clinical Evidence (INNOVATE)

Real-World Evidence (eXpeRience Registry)

Επισκέψεις σε επείγοντα

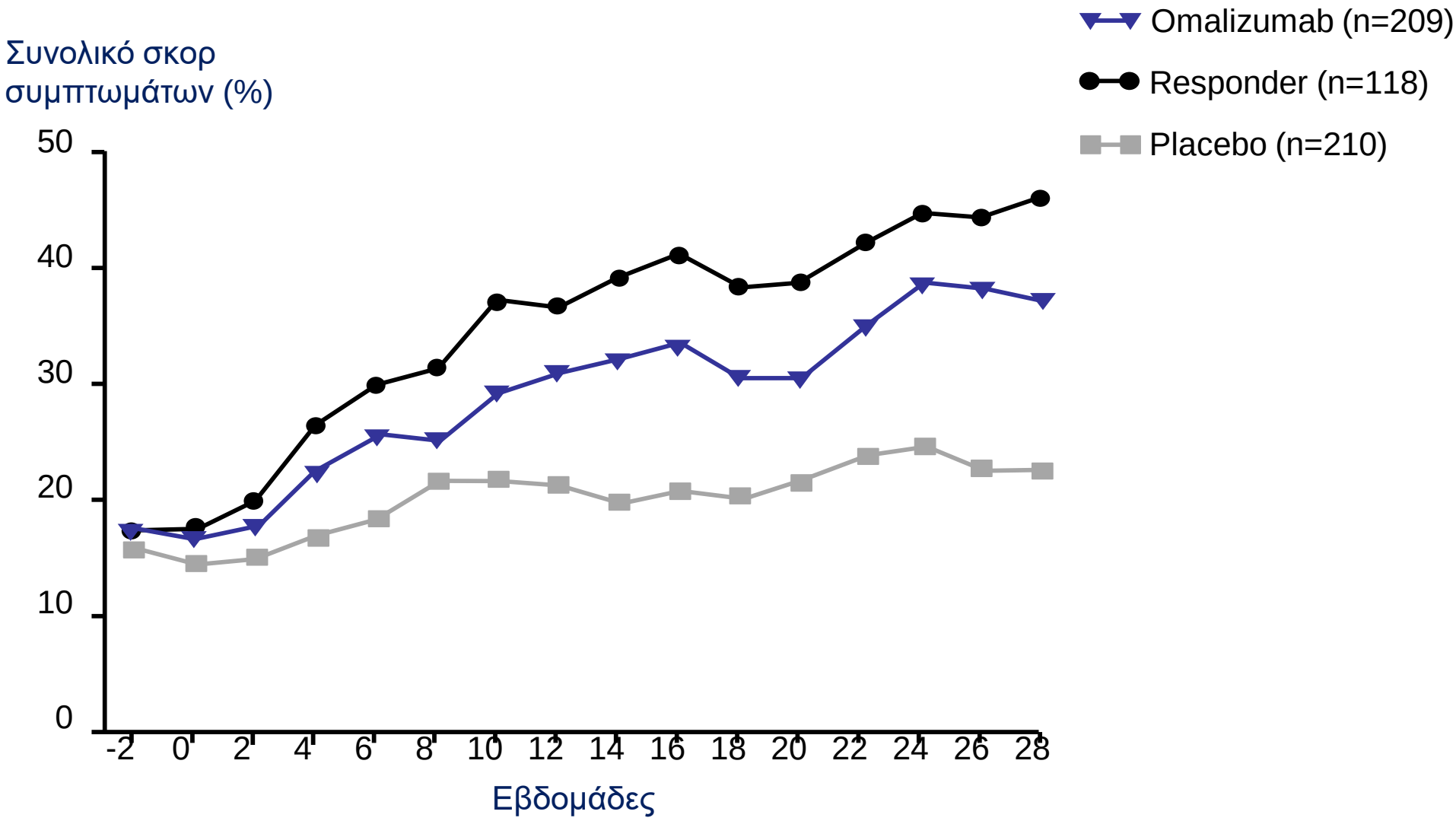




Humbert M, et al. Allergy 2005;60:309–16,

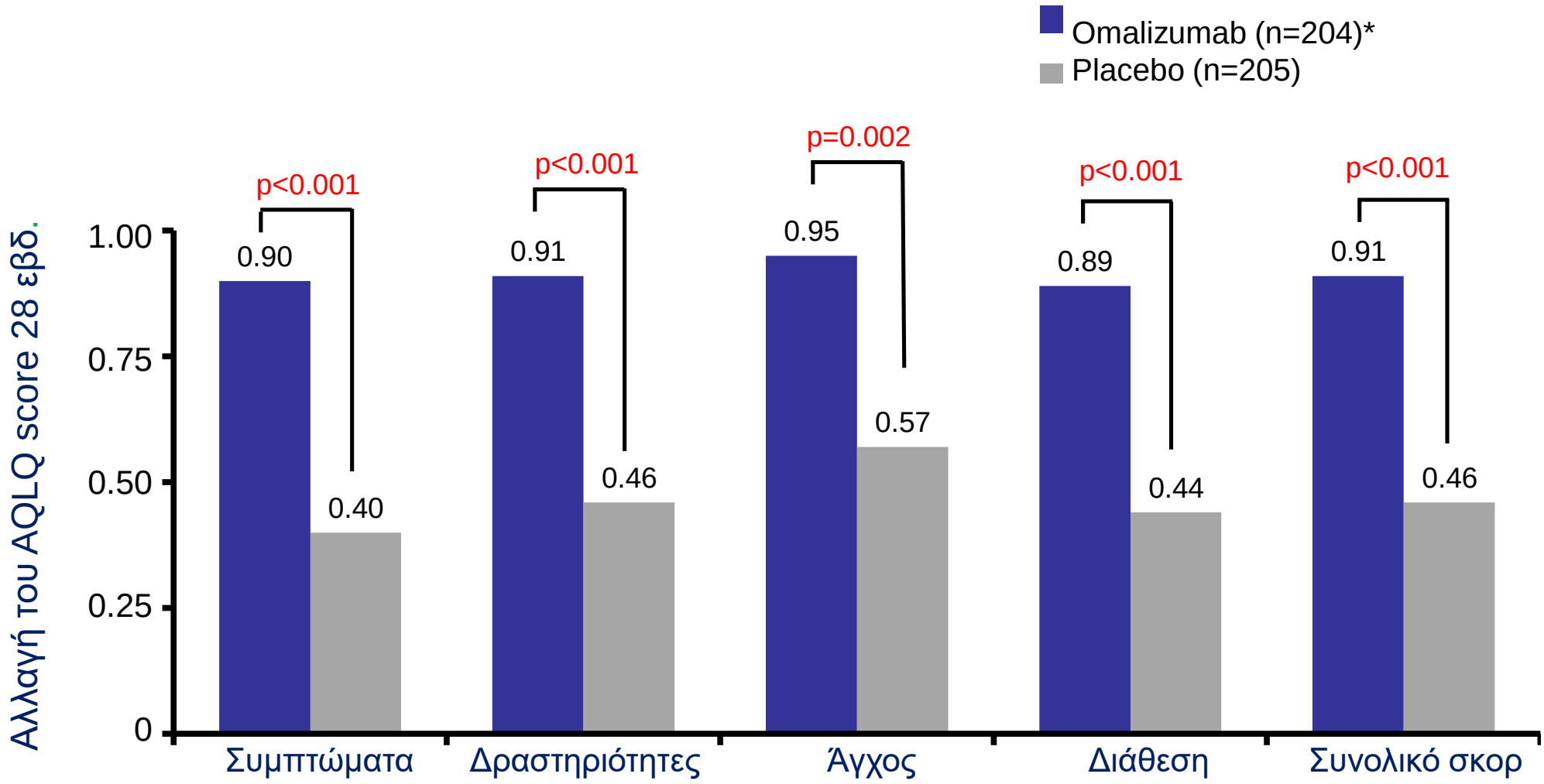
Braunstahl GJ, *et al.* Respir Med 2013;107:1141–51

Βελτίωση των συμπτωμάτων μέρα με τη μέρα



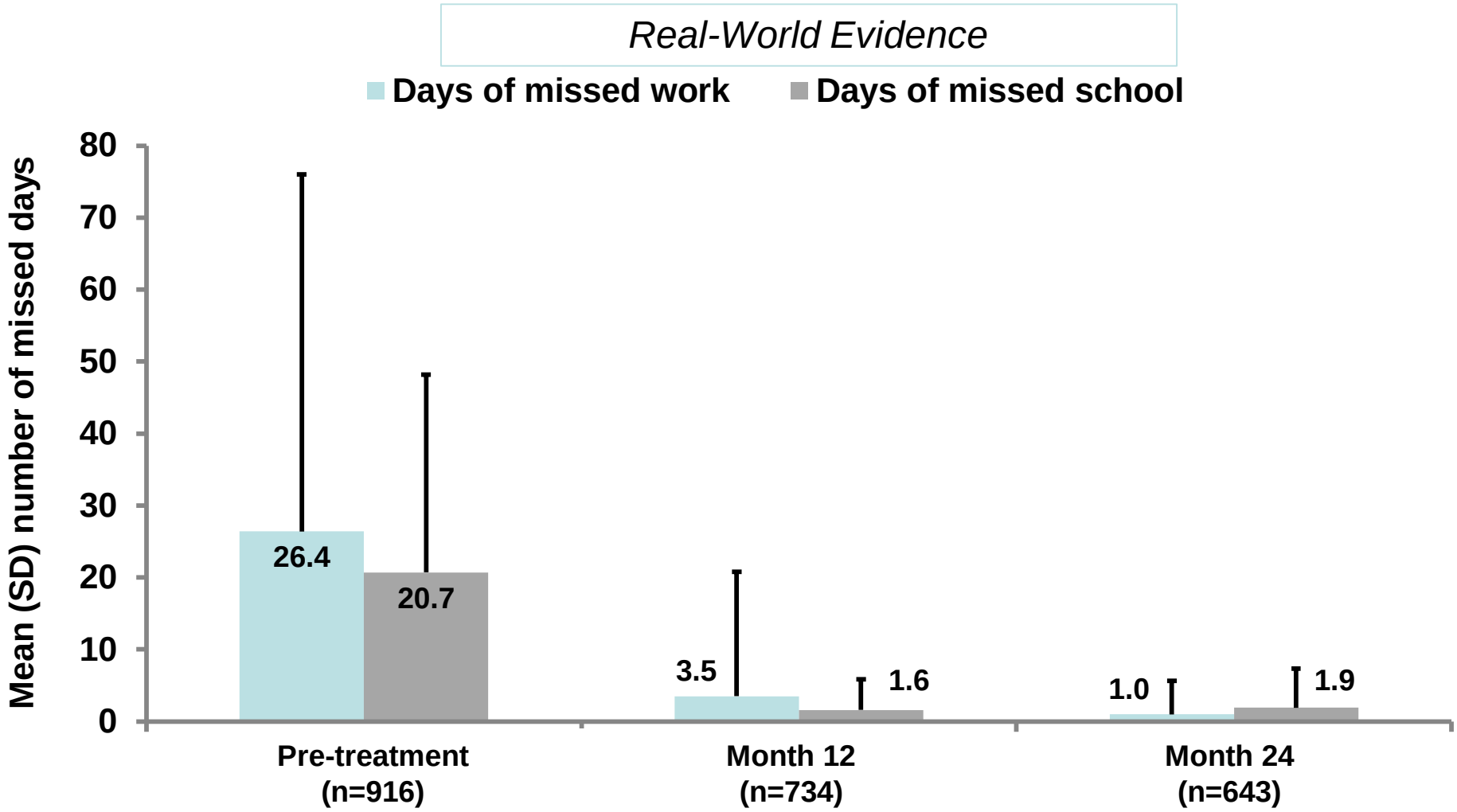
Post-hoc analysis of data from the INNOVATE study at Weeks 26–28.
Humbert M, et al. Allergy 2008;63:592–6.

Σημαντική βελτίωση στην ποιότητα ζωής



*n=203 for the exposure domain.
AQLQ = Asthma Quality-of-Life Questionnaire.
Humbert M, et al. Allergy 2005;60:309–16.

The eXpeRience Registry: Ημέρες που χάθηκαν από την εργασία/το σχολείο ανά ασθενή



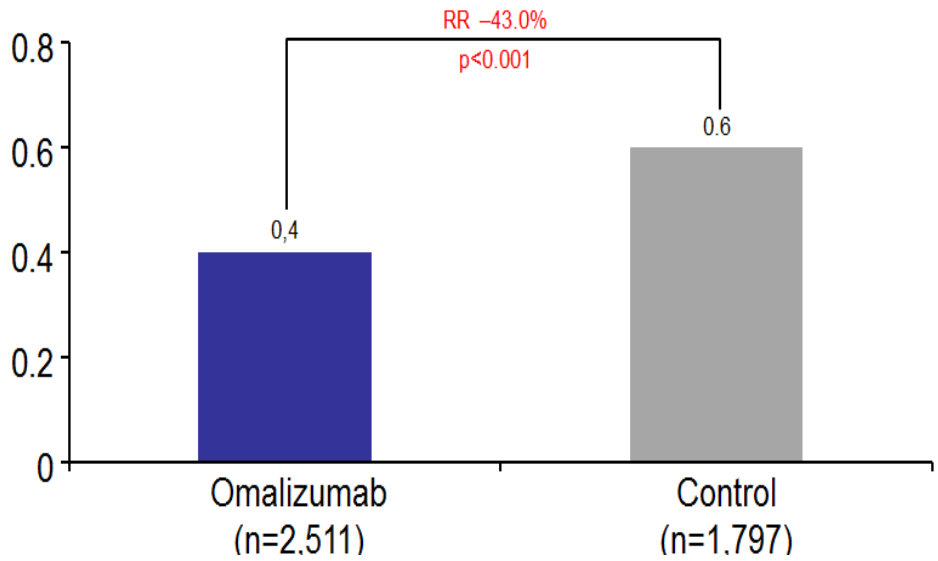
'Pre-treatment' is for 12 months prior to baseline. Annualized data are presented for 'Month 12' (combining 16 weeks, 8 and 12 months) and 'Month 24' (combining 18 and 24 months data). Error bars represent standard deviation (SD).

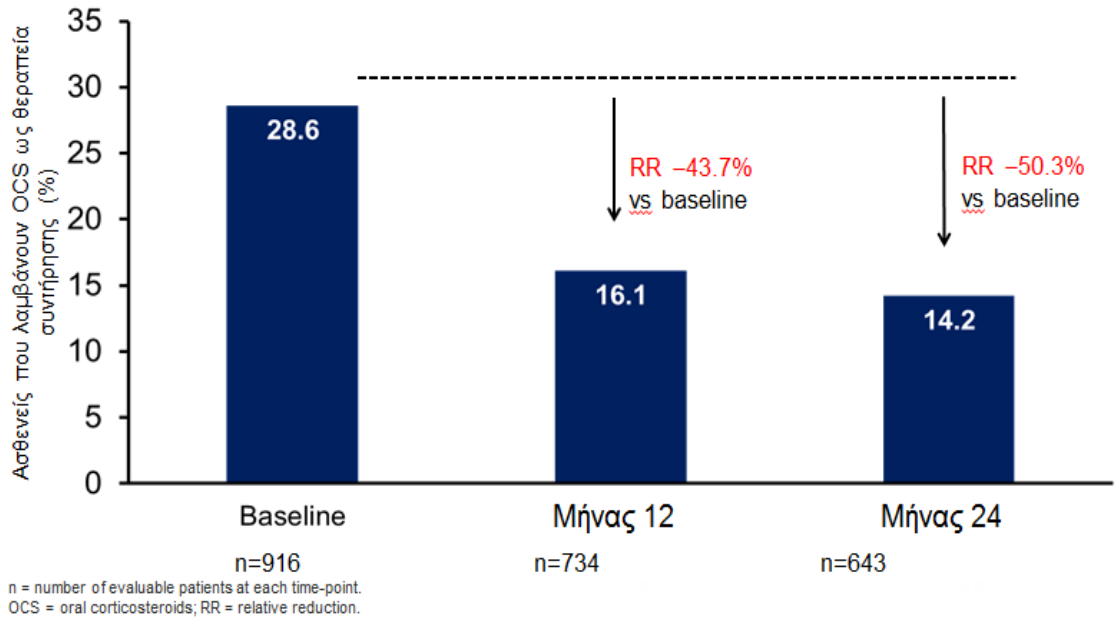
Braunstahl G-J, et al. Respir Med 2013;107:1141−51.

Σημαντική μείωση της ανάγκης χρήσης συστηματικών κορτικοειδών

Clinical Evidence[1]

Real-World Evidence[2]





Μέσος όρος χρήσης στεροειδών
24–52 weeks

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

RR = relative reduction.

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

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

Προφίλ ασφαλείας με το Omalizumab

Πιο συχνές ανεπιθύμητες ενέργειες (≥5% ασθενών)

Ανεπιθύμητες ενέργειες	Omalizumab (%) (n=3,678)	Control (%) (n=2,452)
Οποιαδήποτε ενέργεια	74.8	75.2
Λοίμωξη ανώτερου αναπνευστικού	15.7	15.7
Κεφαλαλγια	15.5	15.6
Ρινοφαρυγγίτιδα	14.4	15.9
Ιγμορίτιδα	10.1	12.0
Κυνάγχη	6.4	6.0
Βήχας	5.9	7.1
Βρογχίτιδα	5.2	5.6
Γρίπη	5.0	6.6

Πάνω από 7,500 αλλεργικούς ασθενείς (>5,000 υπό omalizumab)[1]

- Οι αντιδράσεις ήταν ήπιες ως μέτριες στην βαρύτητα τους και μικρής διάρκειας
- **Σοβαρές αλλεργικές αντιδράσεις σε ποσοστό 0,1 %**
- Οι αντιδράσεις εμφανίστηκαν με την ίδια συχνότητα στις ομάδες του Omalizumab και του εικονικού φαρμάκου

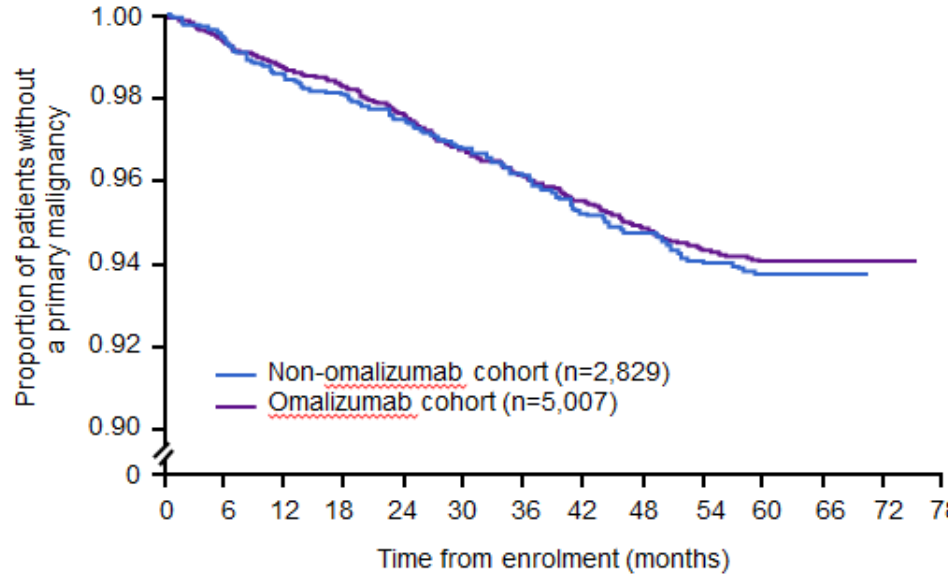
Corren J, et al. Clin Exp Allergy 2009

Ασφάλεια

Short-term safety

Long-term safety (EXCELs)

- 124 περιπτώσεις αναφυλαξίας αναφέρθηκαν σε ~57.300 ασθενείς που έλαβαν omalizumab (ποσοστό 0.2%)[1]
- Το 2007 προτάθηκε από το *Omalizumab Joint Task Force (OJTF)* χαμηλότερη συχνότητα αναφυλακτικών αντιδράσεων στο **0,09%**[2]



Clinical implications: This study reports prospective clinical practice data indicating that omalizumab therapy is not associated with an increased risk of malignancy.

1. Limb et al. J Allergy Clin Immunol 2007

2.American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology

Long A, et al. ATS 2013

Ερωτήματα 2

Χρόνος εκτίμησης αποτελεσματικότητας ?

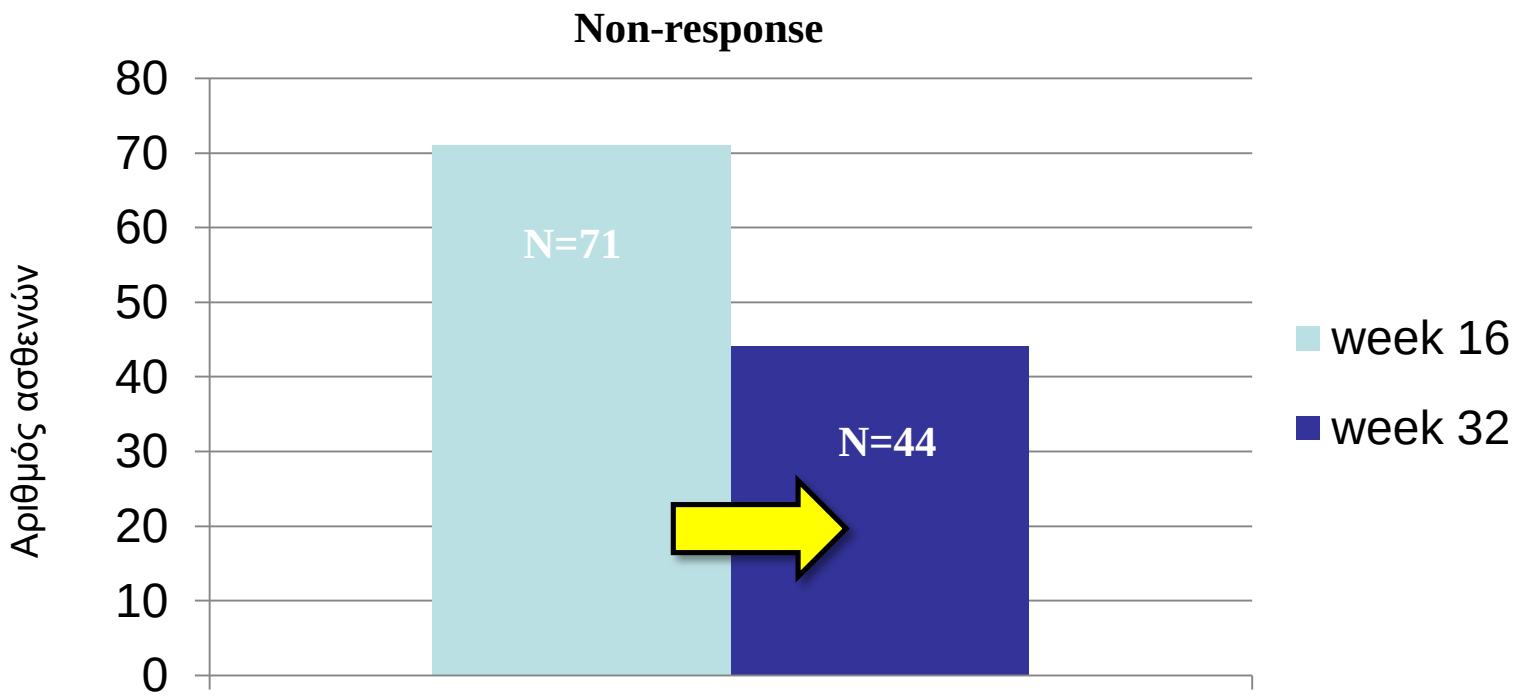
Διάρκεια χορήγησης - διακοπή ?

Βιοδείκτες, εωσινόφιλα ?

Παροξύνσεις από ιογενείς λοιμώξεις ?

Ανταπόκριση στο Omalizumab στους 4 και στους 8 μήνες

- **72,8% των ασθενών αποκρίθηκαν στη θεραπεία στους 4 μήνες** *(190/261)*
- **38% των ασθενών που δεν αποκρίθηκαν στους 4 μήνες αποκρίθηκαν στους 8 μήνες** *(27/71)*



*Response = excellent or good rating by physician's GETE; non-response = moderate, poor or worsening asthma
272 patients were randomized to receive omalizumab.
GETE = Global Assessment of Treatment Effectiveness.
Bousquet J, et al. Allergy 2011;66:671–8.

Bousquet J et al. Allergy 2011

Ερωτήματα 2

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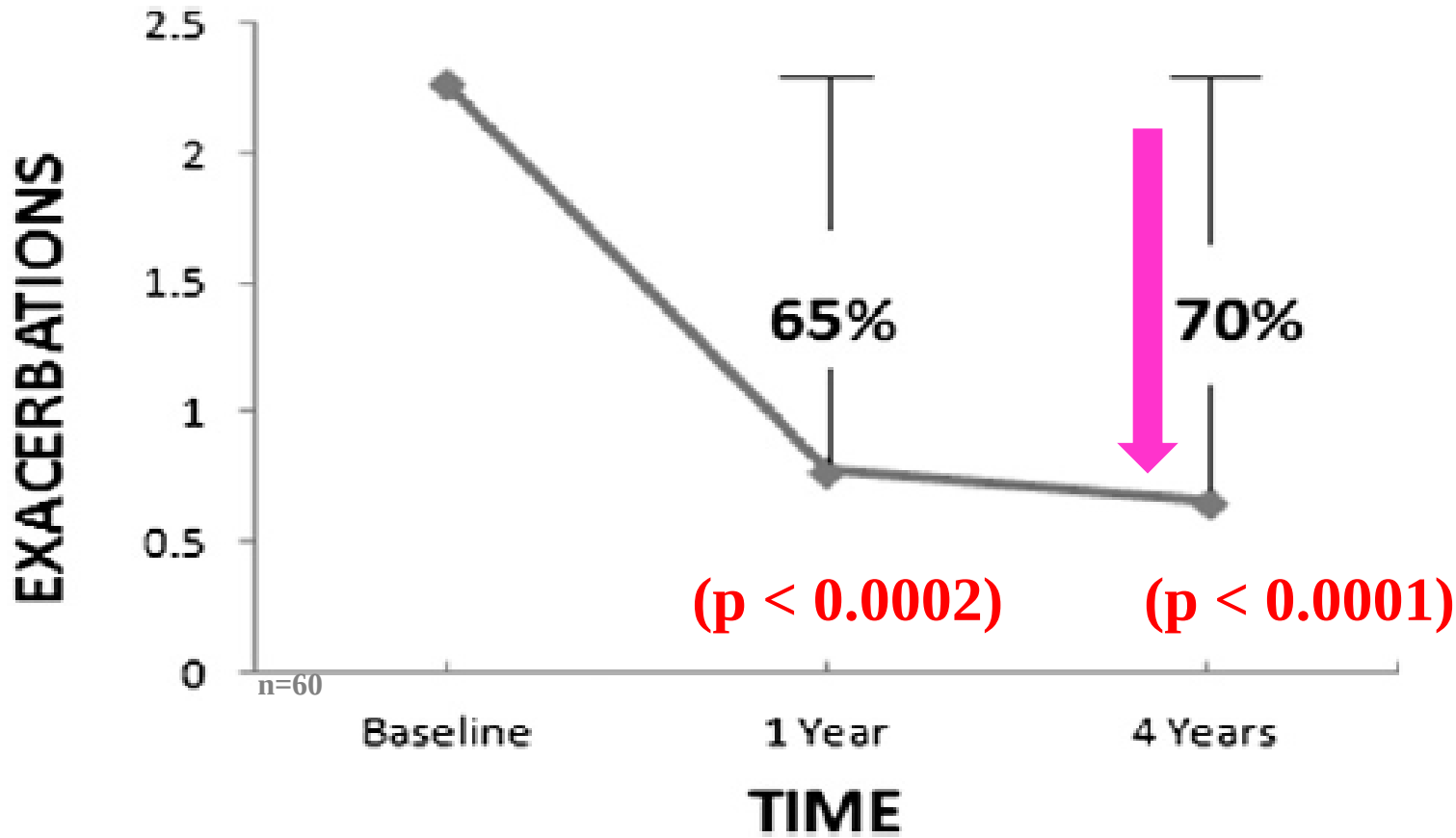
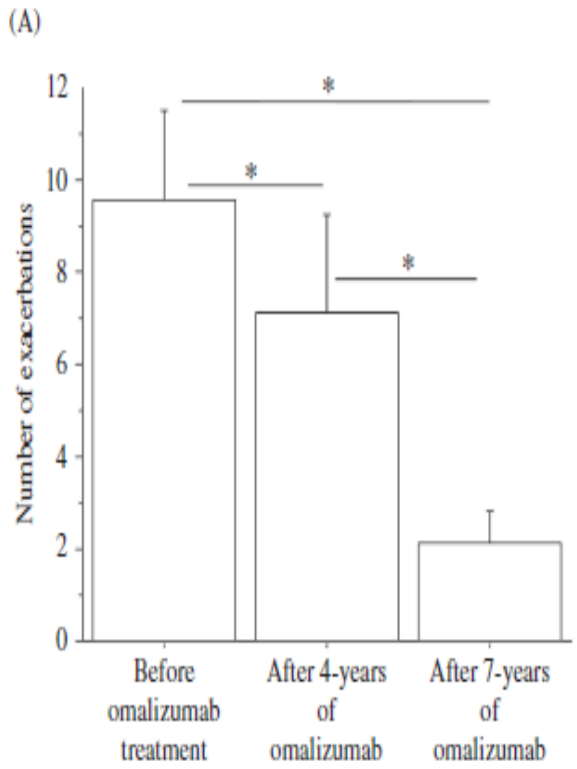
Αποτελεσματικότητα μετά από 4 χρόνια συνεχούς θεραπείας



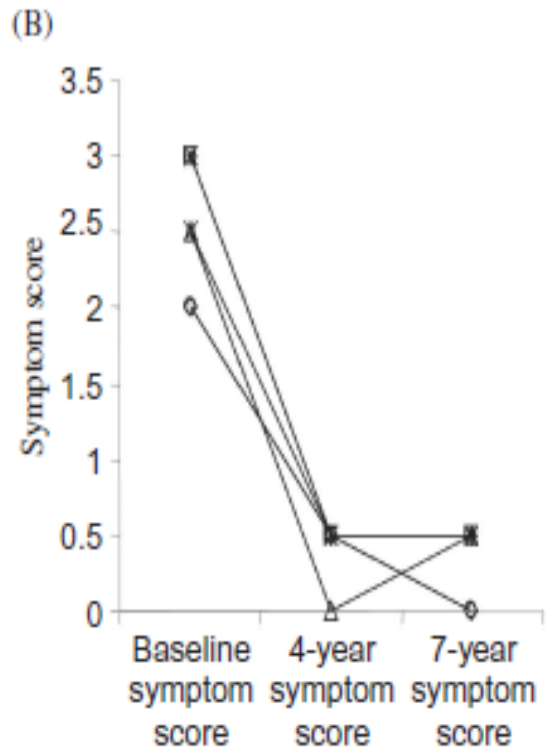
Tzortzaki, E.G., et al., Pulm Phar Ther, 2012

Αποτελεσματικότητα μετά από 7 χρόνια συνεχούς θεραπείας

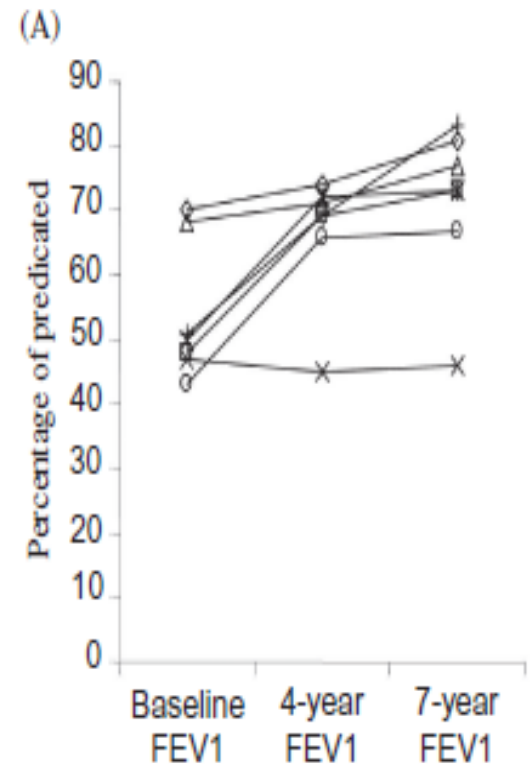
Exacerbations



Symptom score



The FEV1 (% of predicted)

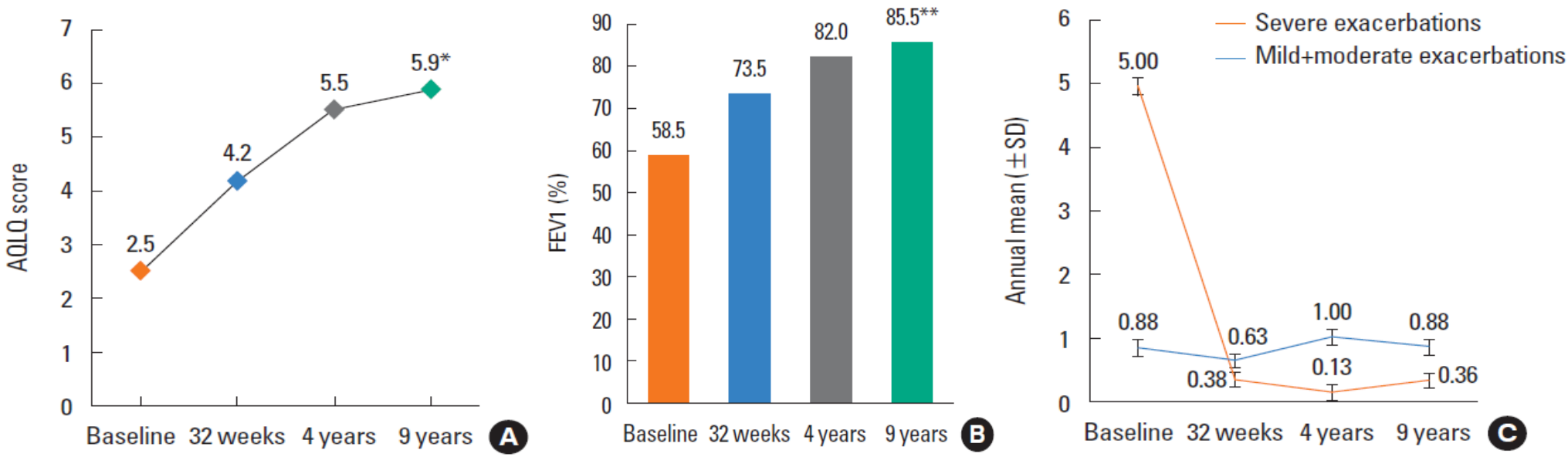


Pace E, et al. Journal of Asthma 2011

Real-life Efficacy of Omalizumab After 9 Years of Follow-up

Francesco Menzella,[1*] Carla Galeone,[1] Debora Formisano,[2] Claudia Castagnetti,[1] Patrizia Ruggiero,[1] Anna Simonazzi,[1] Luigi Zucchi[1]

[1]*Department of Cardio-Thoracic-Vascular and Intensive Care Medicine, Pneumology Unit, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*
[2]*Scientific Directorate, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*



Menzella F., et. al., Allergy Asthma Immunol Res. 2017

Real-life Efficacy of Omalizumab After 9 Years of Follow-up

Francesco Menzella,[1*] Carla Galeone,[1] Debora Formisano,[2] Claudia Castagnetti,[1] Patrizia Ruggiero,[1] Anna Simonazzi,[1] Luigi Zucchi[1]

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[2] *Scientific Directorate, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy*

Table. Changes in ICS doses, LABAs, and other medications at baseline, 32 weeks, and 4 and 9 years

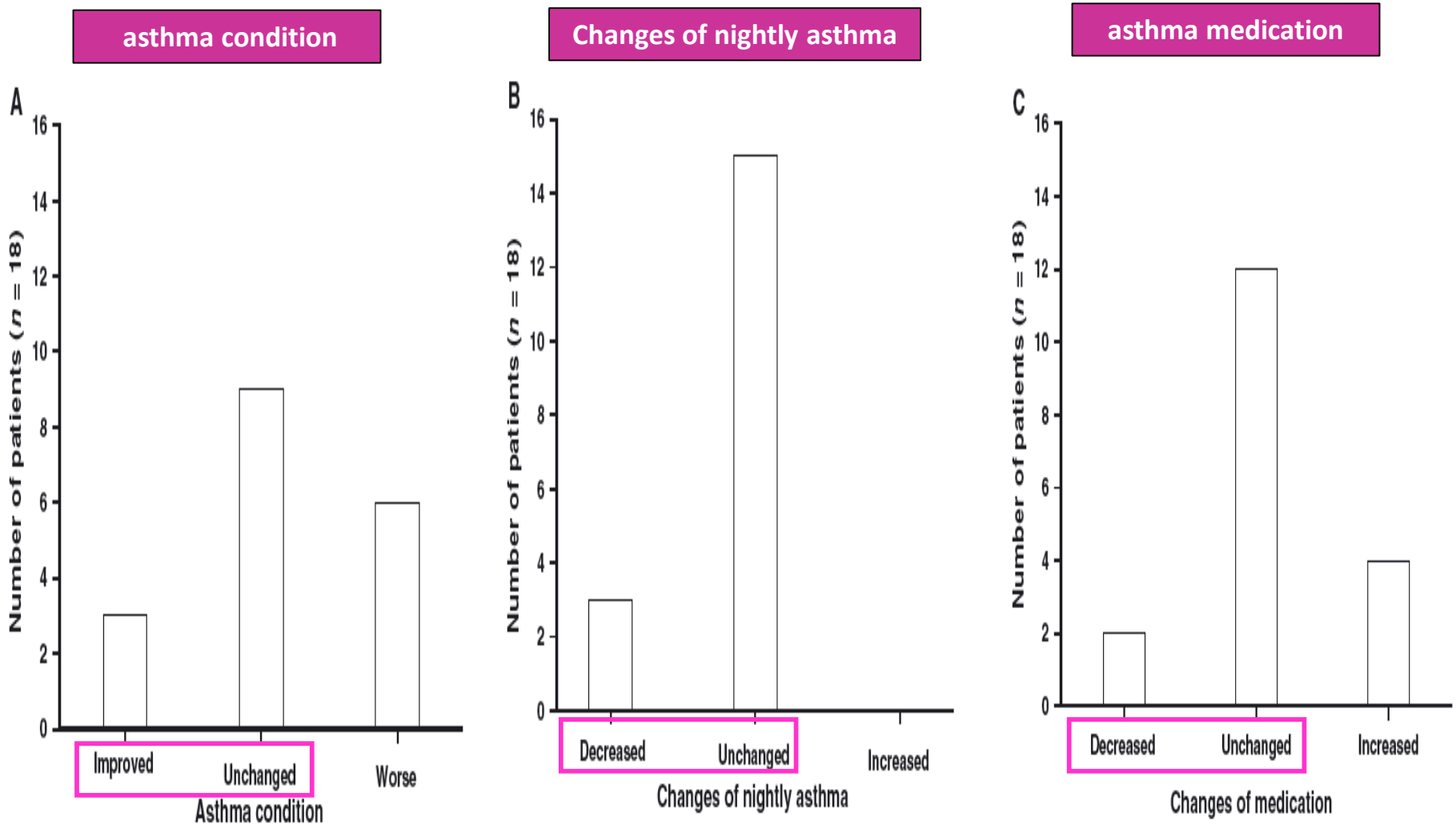
Asthma therapy	Bas			
ICS dose				
High dose*				
Medium dose†				
Low dose‡				
LABAs				
Oral corticosteroids				
Anti-leukotrienes				
LAMAs				
Theophylline				
SABAs	8	7	3	2

After 9 years, there were no safety concerns for continued use of omalizumab. There were no changes in blood count, creatinine, or liver function parameters. No patient showed any systemic or local side effects related to omalizumab treatment over the entire follow-up period. In addition, no asthma-related hospitalizations or emergency department visits were documented over the last 5 years.

At last follow-up, 7 patients continued to use LABAs and all were given ICS (1 high dose, 2 medium doses, and 5 low doses). At 32 weeks, there were 2 and 6 patients on high and medium l 5 patients at 4 years. the use of lower dose also reflected in the l medications, and in ukotrienes at 9 years

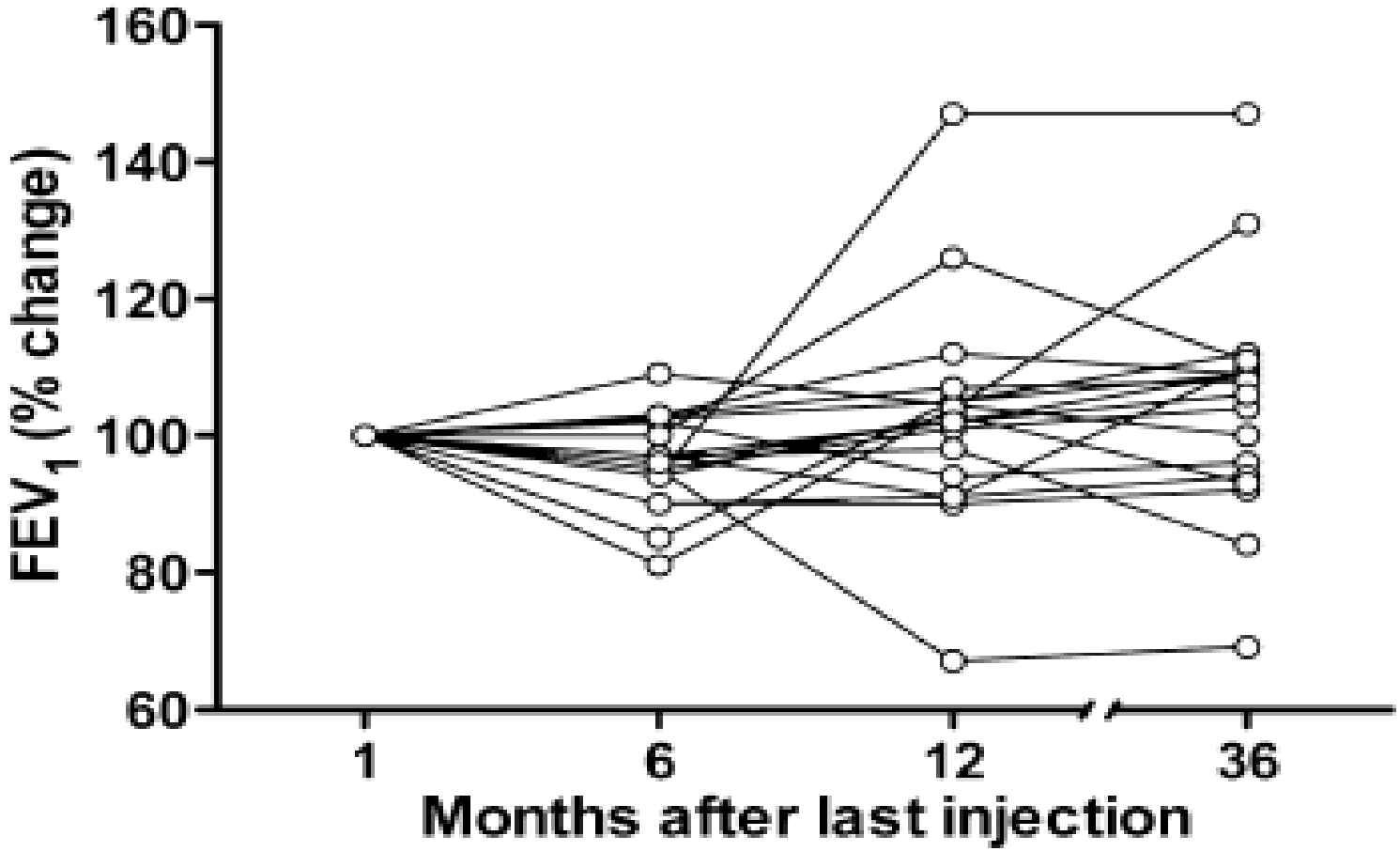
Menzella F., et. al., Allergy Asthma Immunol Res. 2017 Jul;9(4):368-372

6 χρόνια συνεχούς θεραπείας
1 χρόνο μετά τη διακοπή



Nopp et al, Allergy 2007:

6 χρόνια συνεχούς θεραπείας
1 χρόνο μετά τη διακοπή
3 χρόνια μετά τη διακοπή



Nopp et al, Allergy 2010:

Ερωτήματα 2

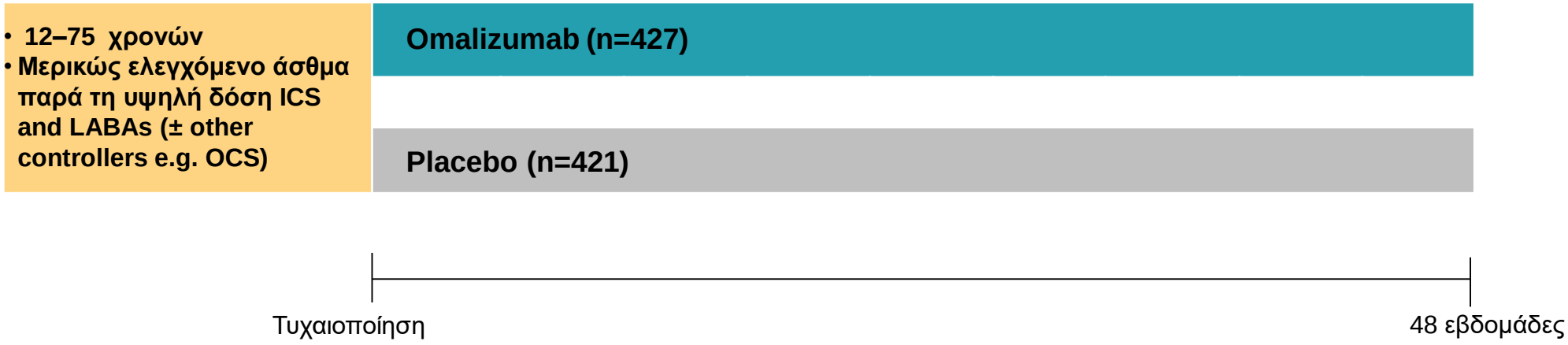
Χρόνος εκτίμησης αποτελεσματικότητας ?

Διάρκεια χορήγησης - διακοπή ?

Βιοδείκτες, εωσινόφιλα ?

Παροξύνσεις από ιογενείς λοιμώξεις ?

EXTRA βιοδείκτες : Σχεδιασμός μελέτης

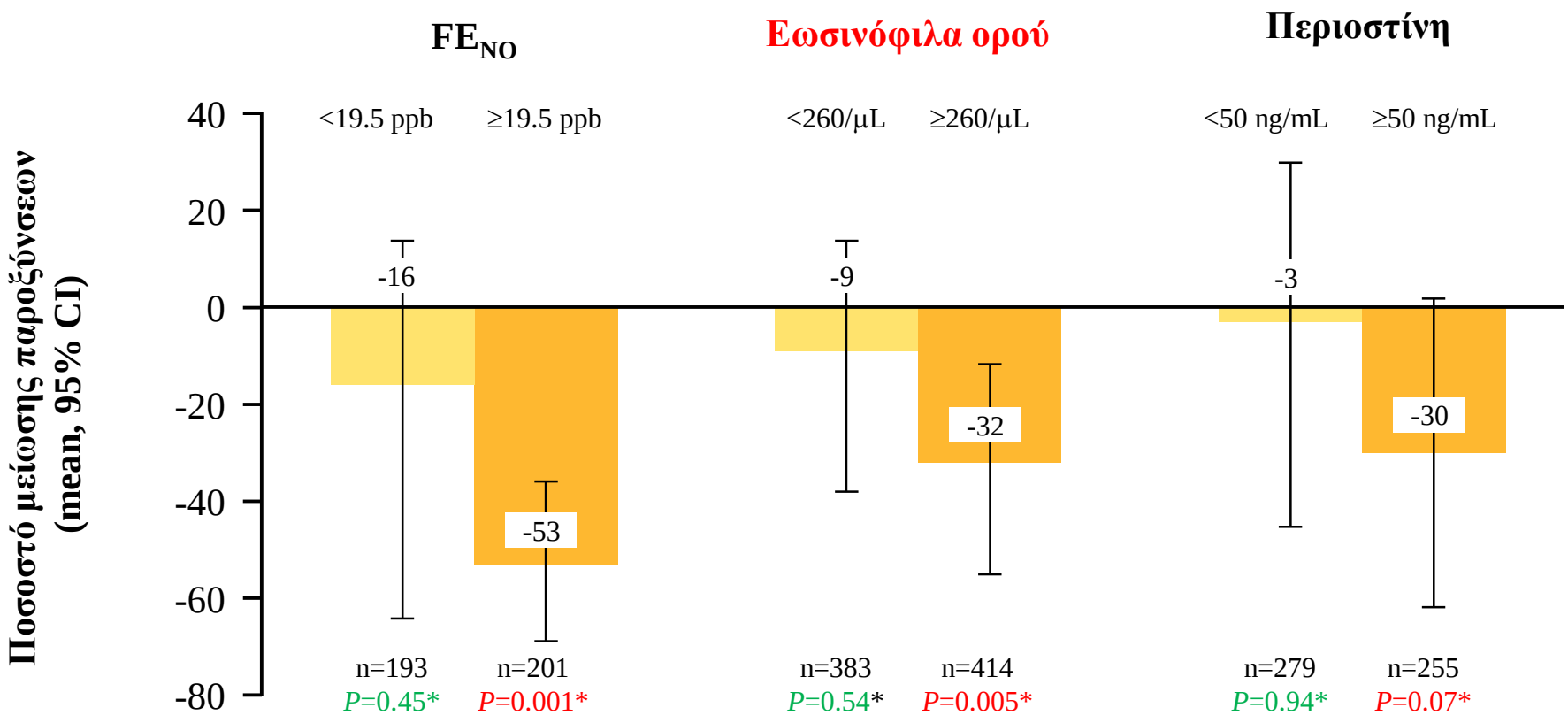


- **Αξιολόγηση βιοδεικτών:**
  - FENO
  - Εωσινόφιλα περιφερικού αίματος
  - Περιοστίνη ορού

  ως προγνωστικών δεικτών της ανταπόκρισης σε θεραπεία με omalizumab

FE_{NO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroids;
LABA = long-acting β_2-agonist
(i.e. high-dose ICS plus LABA ± controller); OCS = oral corticosteroids.
Hanania NA, et al. Am J Respir Crit Care Med, 2013; 187:804-11.

Μείωση των παροξύνσεων σε ασθενείς με αυξημένους βιοδείκτες σε 48 εβδ. (EXTRA)



*Exacerbation reduction P values; omalizumab versus placebo in each biomarker subgroup.
CI = confidence interval; FE_{NO} = fractional exhaled nitric oxide.
Hanania NA, et al. Am J Respir Crit Care Med, 2013; 187:804-11.

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

Study design and participants

This multi-center, non-interventional, retrospective, observational study was performed in France from December 21st 2015 to September 30th 2016 using data from medical records of patients with SAA treated with omalizumab. Hospital-based pulmonologists and pediatric pulmonologists with experience in treating severe asthma were asked to provide data of all their consecutive patients meeting the STELLAIR inclusion criteria. Physicians could include consecutive patients

Inclusion criteria were any patient: ≥6 years of age; who had been treated with omalizumab for poorly controlled SAA; with a documented blood EOS measurement taken within 12 months prior to omalizumab treatment initiation; with the number of exacerbations recorded during the 12 months prior to omalizumab initiation; and who had a documented physician evaluation of response to omalizumab after 4 to 6 months of treatment and number of exacerbations recorded. Patients that refused collection of their medical data for research purposes were excluded in accordance with the ethics committee requirements.

Eur Respir J 2018; 51: 1702523

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

The aim of the STELLAIR [Next Steps Toward personalized care: EvaLuating responders to XoLAIR® treatment in patients with severe allergic asthma] study was to determine the importance of pre-treatment blood EOS as a predictive measure for response to omalizumab.

- A decrease in the annual exacerbation rate with a 'responder' defined as having a reduction in the annual exacerbation rate of at least 40%. An asthma exacerbation was defined as a significant worsening of asthma requiring a short burst of oral corticosteroids (OCS) or, for patients treated with an OCS, an increase in the OCS dose regimen. The annual exacerbation rate was calculated by adjusting the number of exacerbations according to the duration of exposure to omalizumab treatment; treatment duration was 4–6 months for all patients and 12 months for 706 patients (81%).

The median blood EOS_{T-12} was more than twice as high in minors compared with adults (619 cells/µL vs 308 cells/µL) (Table 3). The distribution of EOS_{T-12} ranged from 0 to ≥1000 cells/µL and was on average higher in minors than adults. A total of 52.1 % (n=377) of adult SAA patients had a blood EOS ≥300 cells/µL.

Eur Respir J 2018; 51: 1702523

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]

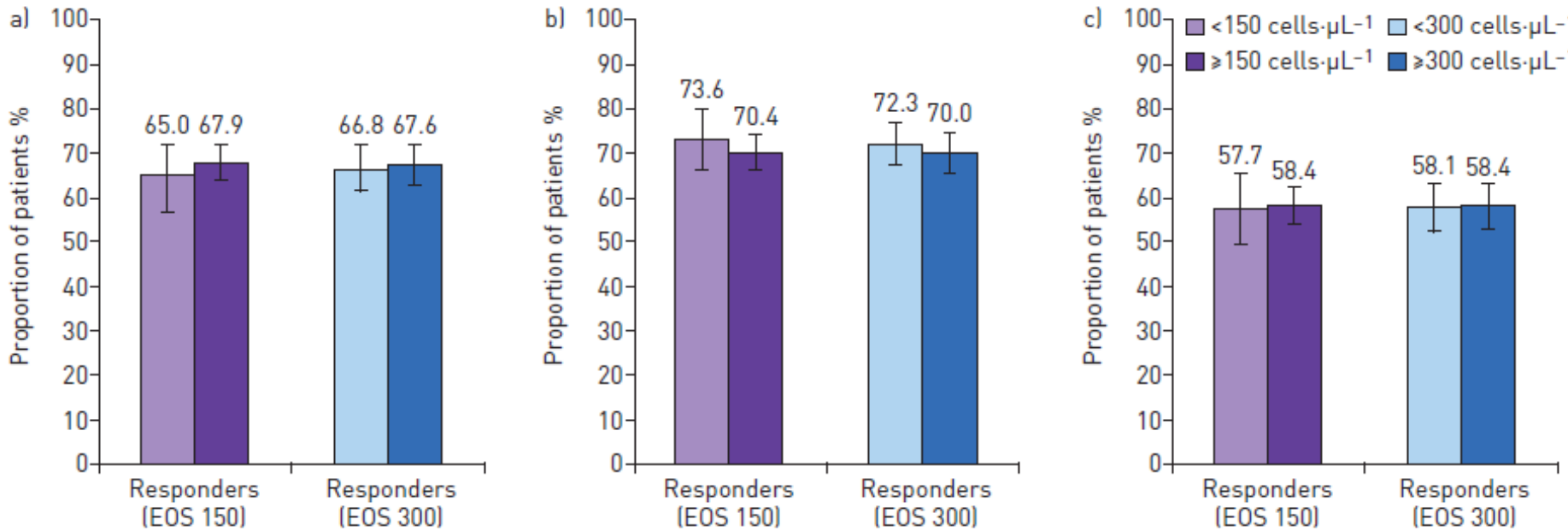


FIGURE 3 Responders to omalizumab treatment in adults (≥18 years) at T_{4-6} (time of first effectiveness assessment after 4–6 months of treatment) according to blood eosinophil count cut-off at 150 cells·μL^{-1} ("EOS 150": <150 cells·μL^{-1}, n=163; ≥150 cells·μL^{-1}, n=560) and 300 cells·μL^{-1} ("EOS 300": <300 cells·μL^{-1}, n=346; ≥300 cells·μL^{-1}, n=377). GETE: Global Evaluation of Treatment Effectiveness. a) Responders based on physician's global evaluation (GETE). b) Responders based on a ≥40% decrease in the annual exacerbation rate. c) Combined responders (combination of GETE and exacerbation rate decrease). Error bars indicate 95% confidence intervals.

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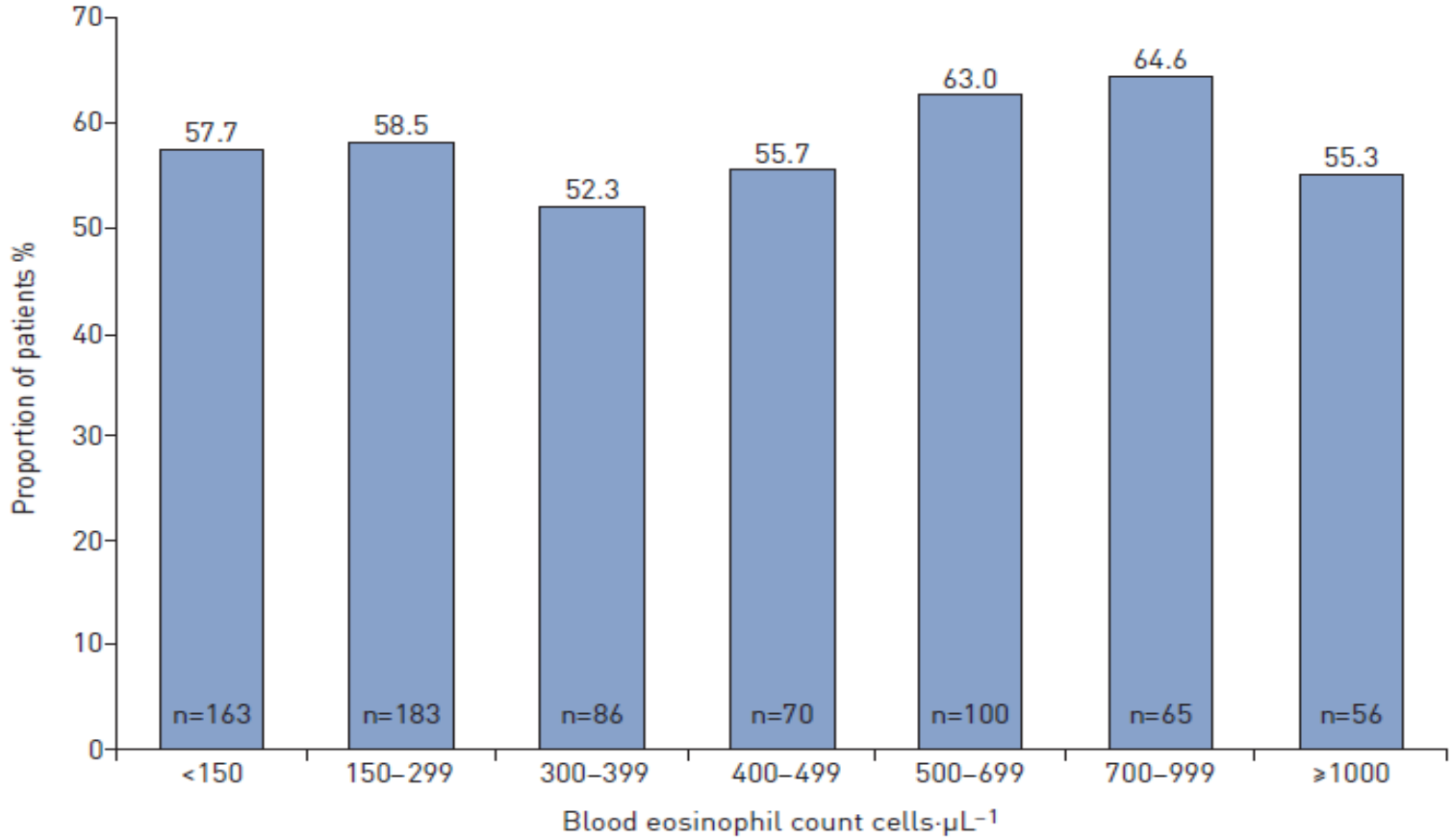

FIGURE 4 Combined responders to omalizumab treatment in adults (≥18 years) according to the distribution of blood eosinophil count in the whole population.

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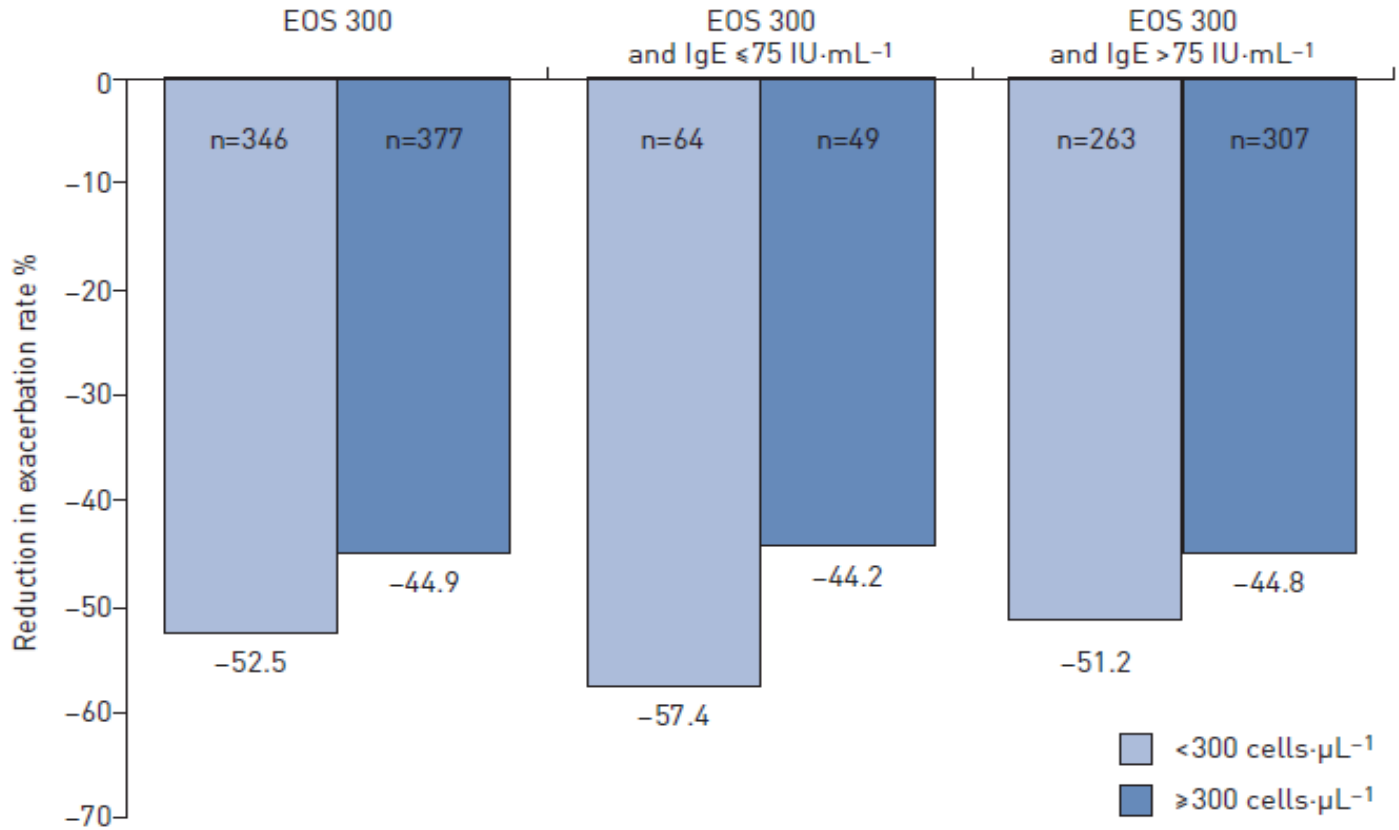

FIGURE 5 Reduction in asthma exacerbation rate according to blood eosinophil count (cut-off 300 cells·μL^{-1} ("EOS 300")) and serum IgE (cut-off 75 IU·μL^{-1}) in adults (≥18 years) with severe allergic asthma.

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Ερωτήματα 2

Χρόνος εκτίμησης αποτελεσματικότητας ?

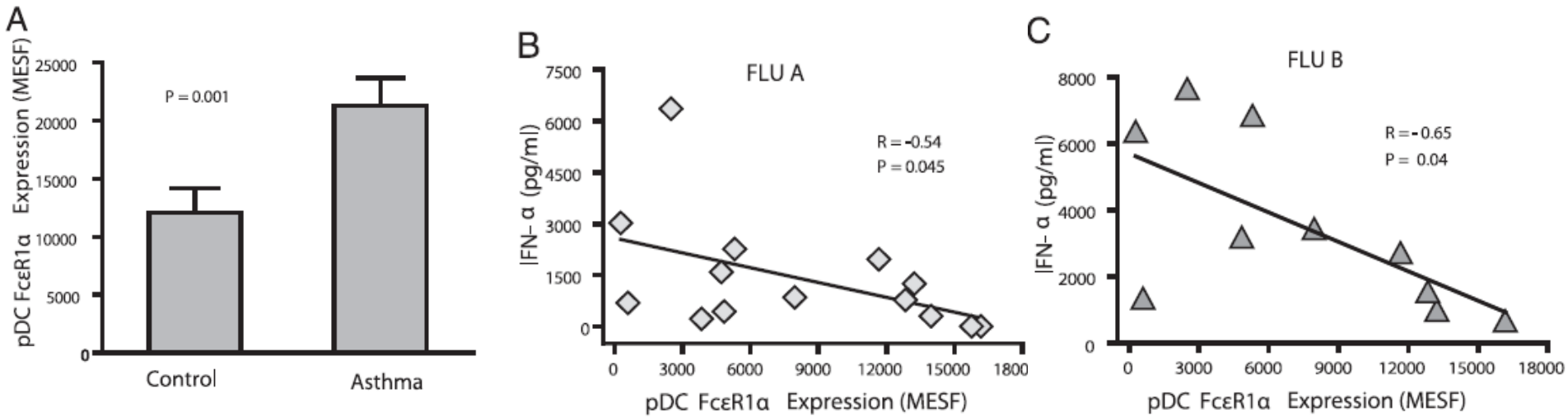
Διάρκεια χορήγησης - διακοπή ?

Βιοδείκτες, εωσινόφιλα ?

Παροξύνσεις από ιογενείς λοιμώξεις ?

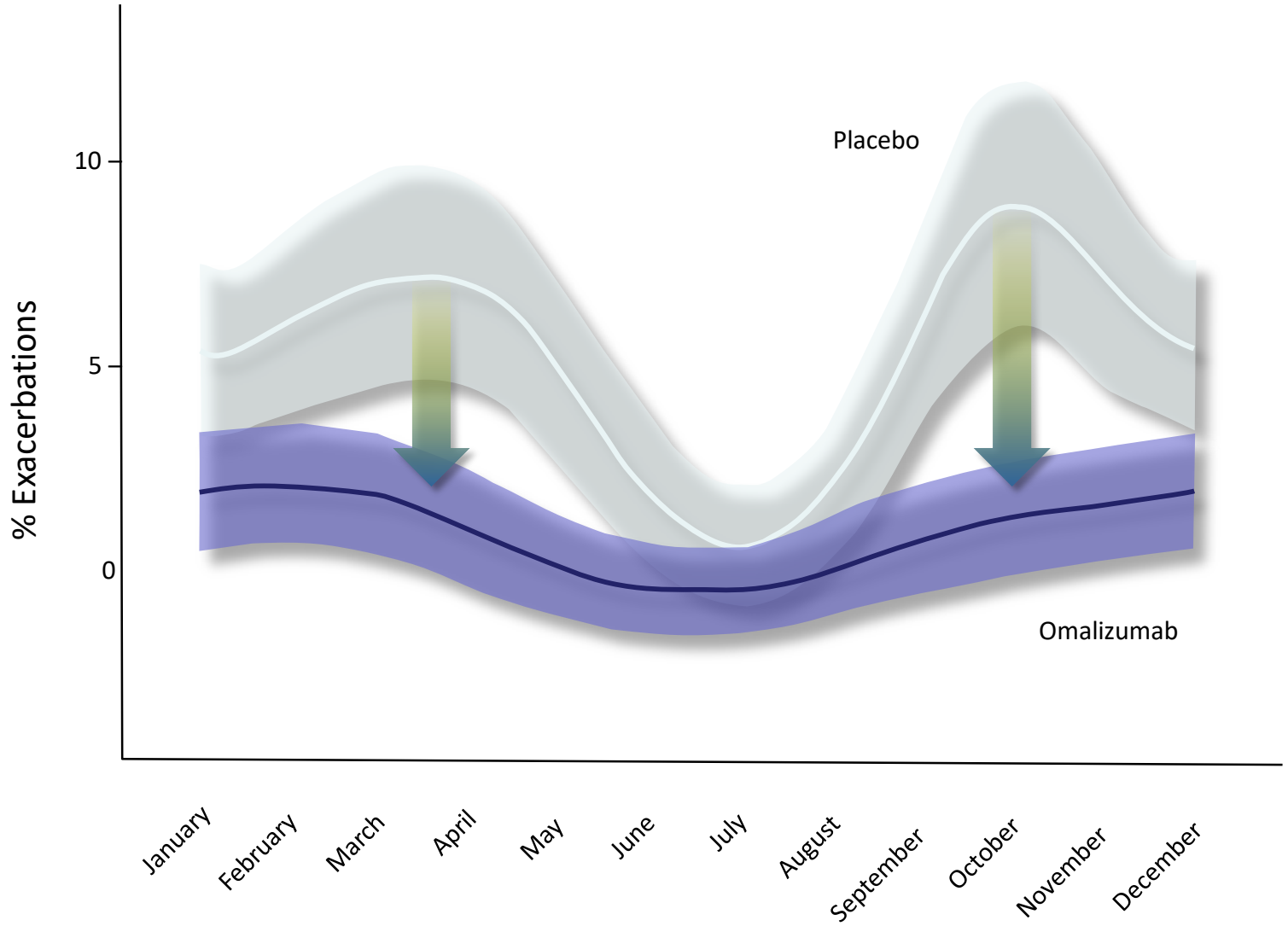
Αυξημένη παραγωγή FcεR1α στα pDCs ασθενών με αλλεργικό άσθμα

Η παραγωγή της IFN-α κατά την έκθεση σε στους ιούς της γρίπης τύπου A και B είναι **αντιστρόφως ανάλογη** της έκφρασης των FcεR1α υποδοχέων στα pDCs



Gill MA et al. J Immunology 2010;184:5999-6006

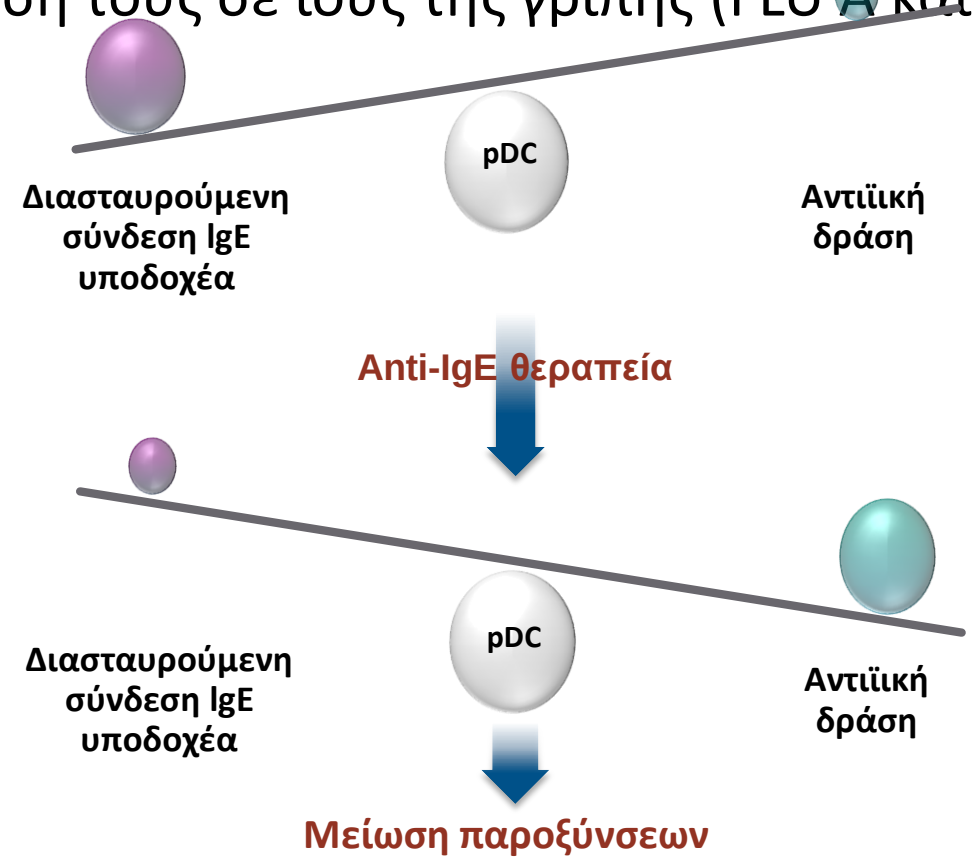
Τυχαιοποιημένη μελέτη της χρήσης του omalizumab σε παιδιά που ζουν σε αστικές περιοχές με χαμηλή ποιότητα ζωής (inner-city children) – Μελέτη ICATA



Busse W, et al. N Engl J Med 2011;364:1005–15.

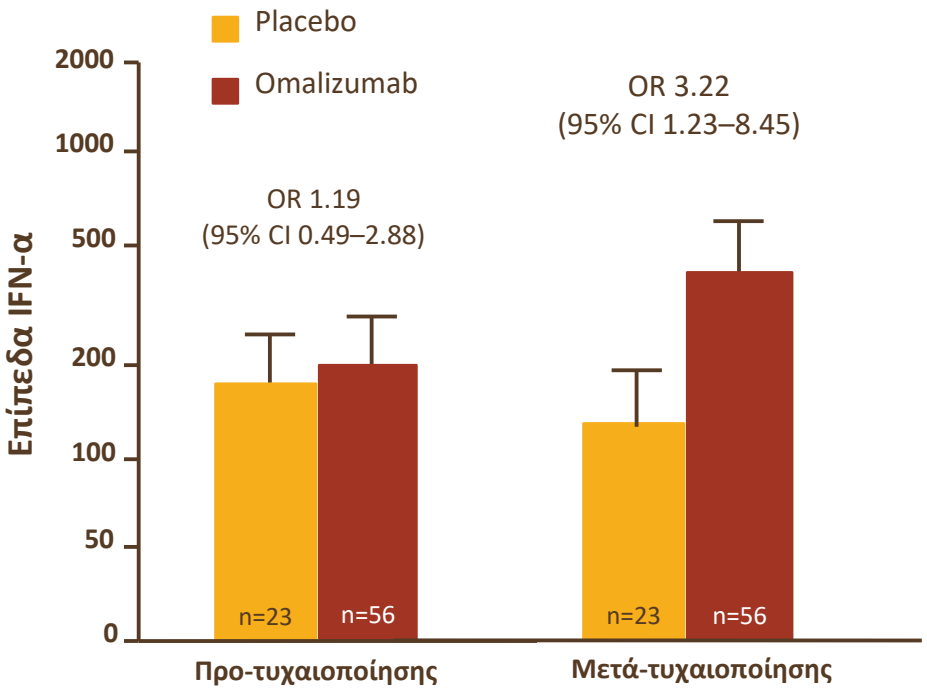
Μειωμένη παραγωγή IFN-α σε ασθενείς με αλλεργικό άσθμα

Η διασταυρούμενη σύνδεση της IgE στους FcεR1 υποδοχείς των pDCs διαφοροποιεί την παραγωγή IFN-α από τα pDCs κατά την έκθεσή τους σε ιούς της γρίπης (FLU A και FLU B)

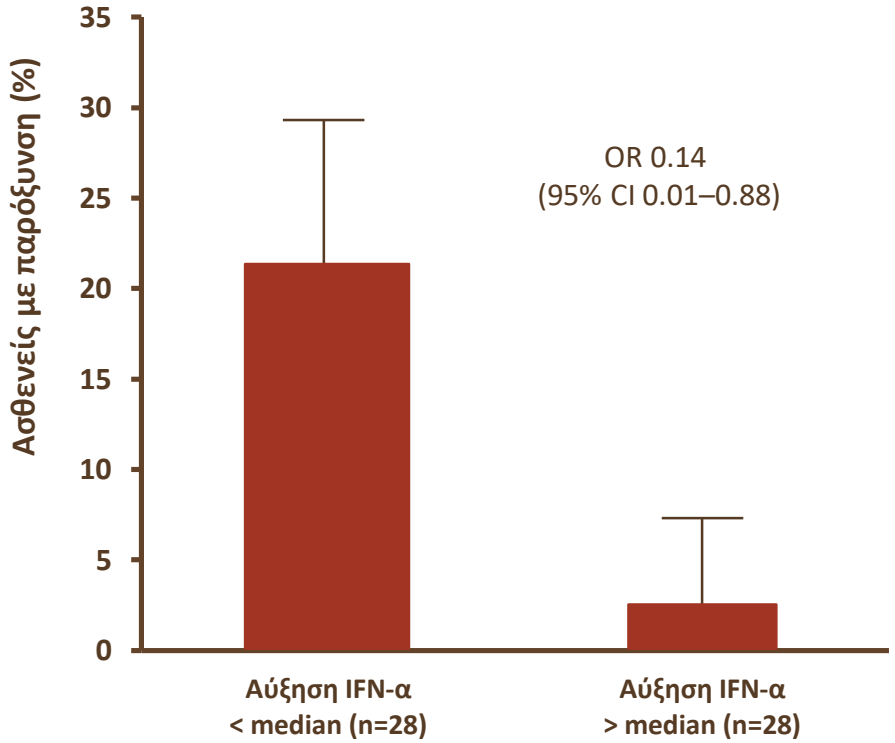


Αποτελέσματα

Το omalizumab αποκαθιστά την παραγωγή IFN-α μετά από την έκθεση σε RV



Οι ασθενείς που λάμβαναν omalizumab και είχαν μεγαλύτερη αποκατάσταση της παραγωγής IFN-α μετά από την έκθεση σε RV είχαν λιγότερες παροξύνσεις



Teach SJ et al. J Allergy Clin Immunol. 2015

Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma

Ann Esquivel[1], William W. Busse[1], Agustin Calatroni[2], Alkis G. Togias[3], Kristine G. Grindle[1], Yury A. Bochkov[1], Rebecca S. Gruchalla[4], Meyer Kattan[5], Carolyn M. Kercsmar[6], G. Khurana Hershey[6], Haejin Kim[7], Petra Lebeau[2], Andrew H. Liu[8,9], Stanley J. Szefler[9], Stephen J. Teach[10], Joseph B. West[11], Jeremy Wildfire[2], Jaqueline A. Pongracic[12], and James E. Gern[1]

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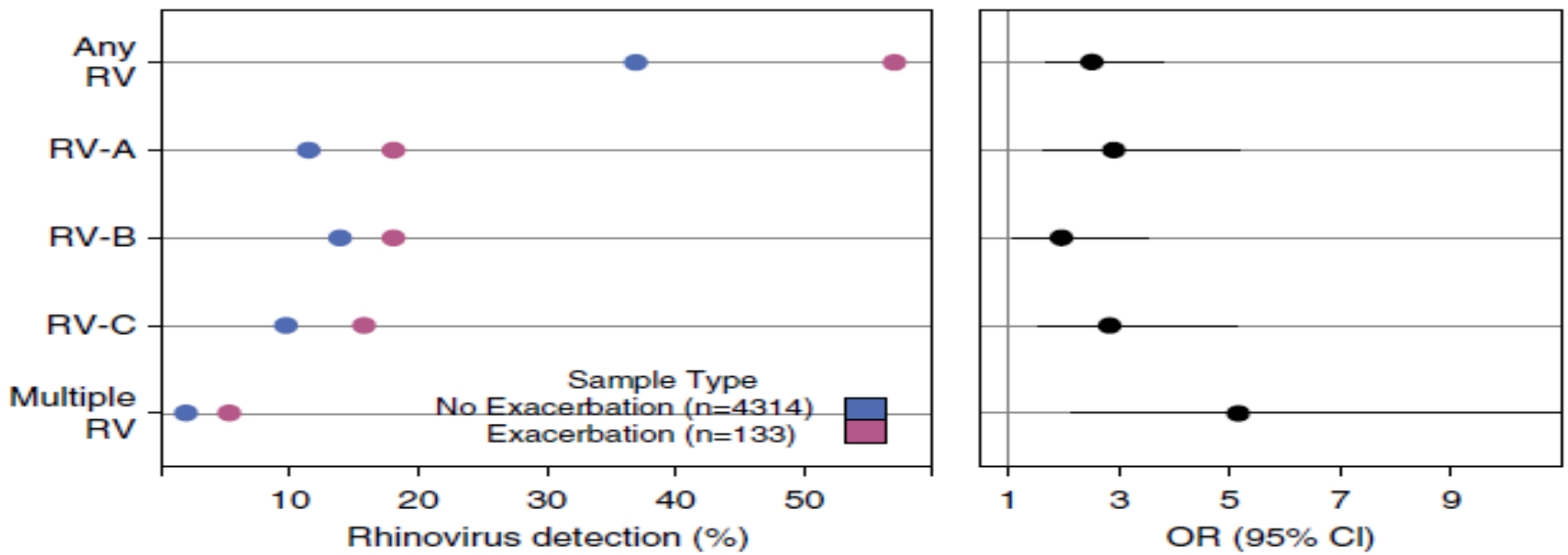

Figure 2. Comparison of rhinovirus (RV) detection in exacerbation versus nonexacerbation samples. The graphs depict (*A*) the prevalence of RV detection in exacerbation versus nonexacerbation samples and (*B*) the odds ratio (OR) (95% confidence interval [CI]) between exacerbation samples with RV detection versus no RV detected.

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Table 2. Rhinovirus Species and Frequency and Duration of Infection

	Frequency (*per 16-wk Monitoring Period*)				Duration (*d*)			
	Placebo [*Mean (SE); n*]	Omalizumab [*Mean (SE); n*]	OR (95% CI)	*P* Value	Placebo [*Mean (SE)*]	Omalizumab [*Mean (SE)*]	OR (95% CI)	*P* Value
Any RV	3.4 (0.19); n = 84	3.3 (0.11); n = 243	0.95 (0.84–1.08)	0.47	12.4 (0.49)	11.2 (0.29)	0.90 (0.82–0.99)	0.03
RV-A	1.8 (0.12); n = 50	1.5 (0.07); n = 156	0.86 (0.73–1.01)	0.06	10.6 (0.68)	10.6 (0.39)	1.01 (0.87–1.16)	0.94
RV-B	1.7 (0.10); n = 59	1.4 (0.05); n = 154	0.87 (0.76–1.01)	0.06	12.3 (0.88)	11.9 (0.57)	0.97 (0.82–1.15)	0.70
RV-C	1.4 (0.09); n = 49	1.4 (0.05); n = 149	1.03 (0.88–1.20)	0.72	11.6 (0.94)	9.5 (0.33)	0.82 (0.68–0.98)	0.03
Multiple	2.0 (0.27); n = 16	1.9 (0.14); n = 61	0.94 (0.68–1.30)	0.70	16.1 (1.75)	13.7 (0.88)	0.85 (0.66–1.09)	0.20

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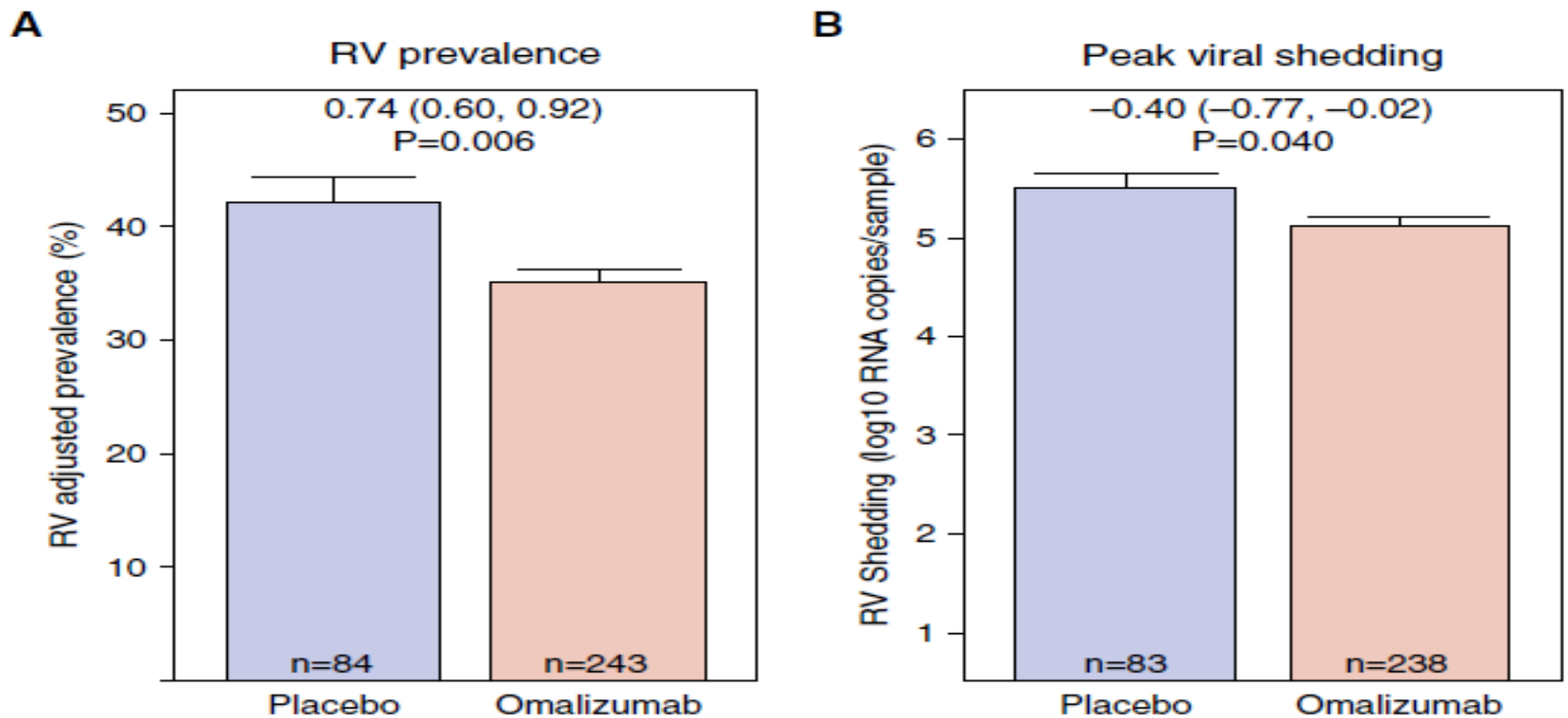

Figure 3. Omalizumab effects on viral detection. *Bars* represent omalizumab versus placebo effects on (*A*) rhinovirus (RV) prevalence (odds ratio and 95% confidence interval) and (*B*) peak viral shedding ($\log_{10}$ difference and 95% confidence interval). The counts represent the number of participants with at least one virus sample detected.

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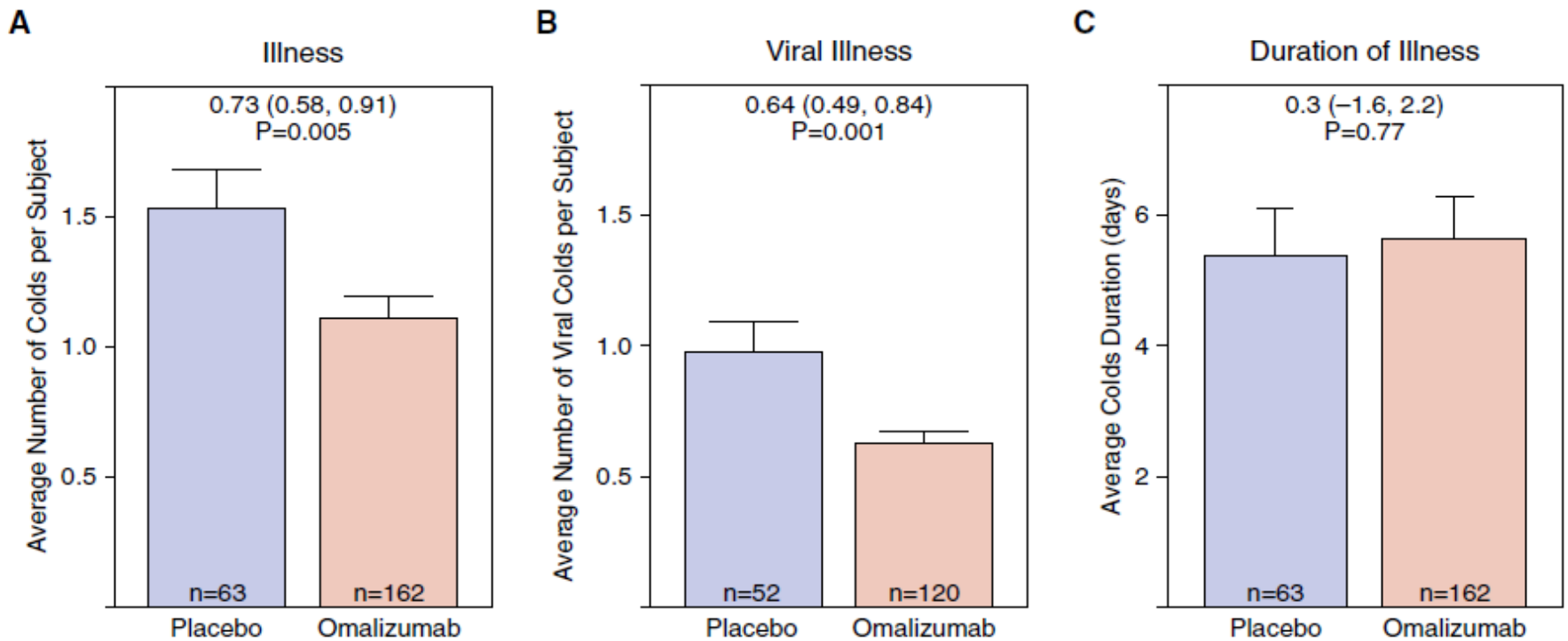

Figure 4. Omalizumab's effects on illnesses. (*A*) Mean numbers of illnesses per subject were calculated for the groups treated with omalizumab versus standard therapy. Data shown are the risk ratio (95% confidence interval). (*B*) Mean numbers of viral illnesses per subject were calculated for the group treated with omalizumab versus standard therapy. Data shown are the risk ratio (95% confidence interval). (*C*) Symptom duration of respiratory illnesses is depicted for children in the omalizumab and standard therapy groups. The numbers represent the number of participants with at least one (*A* and *C*) illness or (*B*) viral illness from randomization to the end of the 90 days.

Συμπεράσματα

Ερωτήσεις