Erişkin Ağır Astımda Bireysel Tedavi
Fenotipik yaklaşım

Dr. Sevim Bavbek

Ankara Üniversitesi Tıp Fakültesi
Göğüs Hastalıkları ABD
İmmünoloji ve Allerji BD

Akış

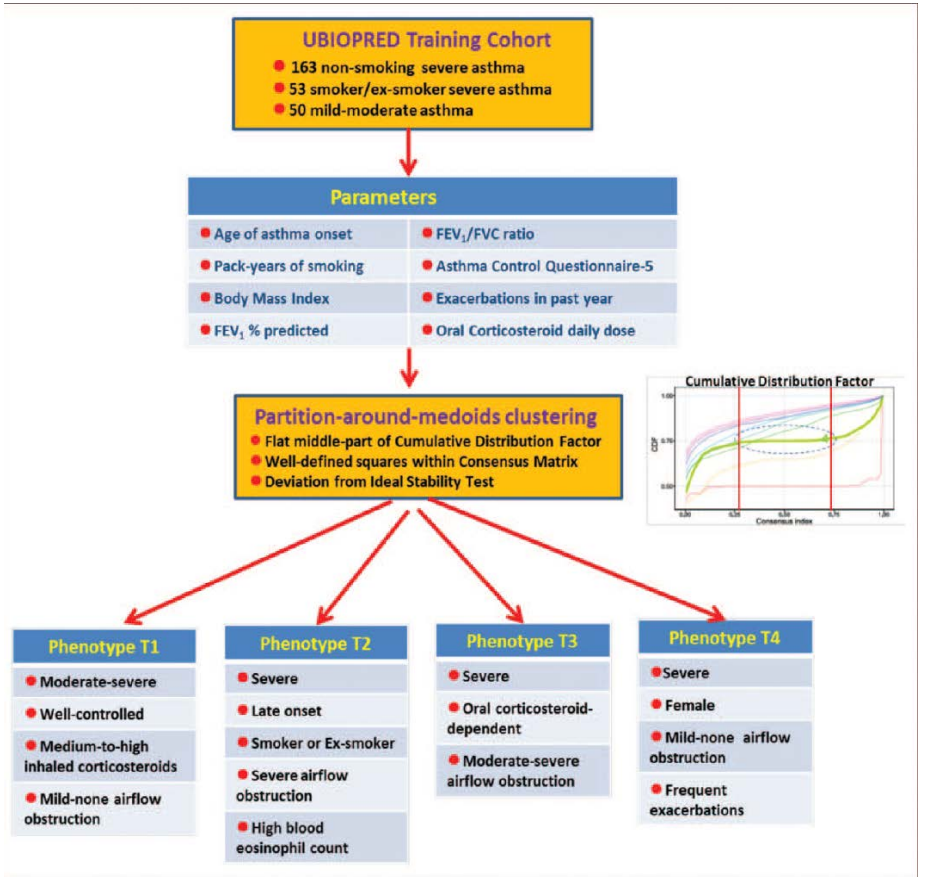
- **Fenotipler**
- **Endotipler**
  - **Anti-T2 yaklaşımlar**
    - **Anti-IgE**
    - **Anti-IL-5 MoAbs**
      - **Mepolizumab**
      - **Reslizumab**
      - **Benralizumab**
    - **Dupilumab**
  - **Anti-Non T2 yaklaşımlar**

Astım fenotipleri

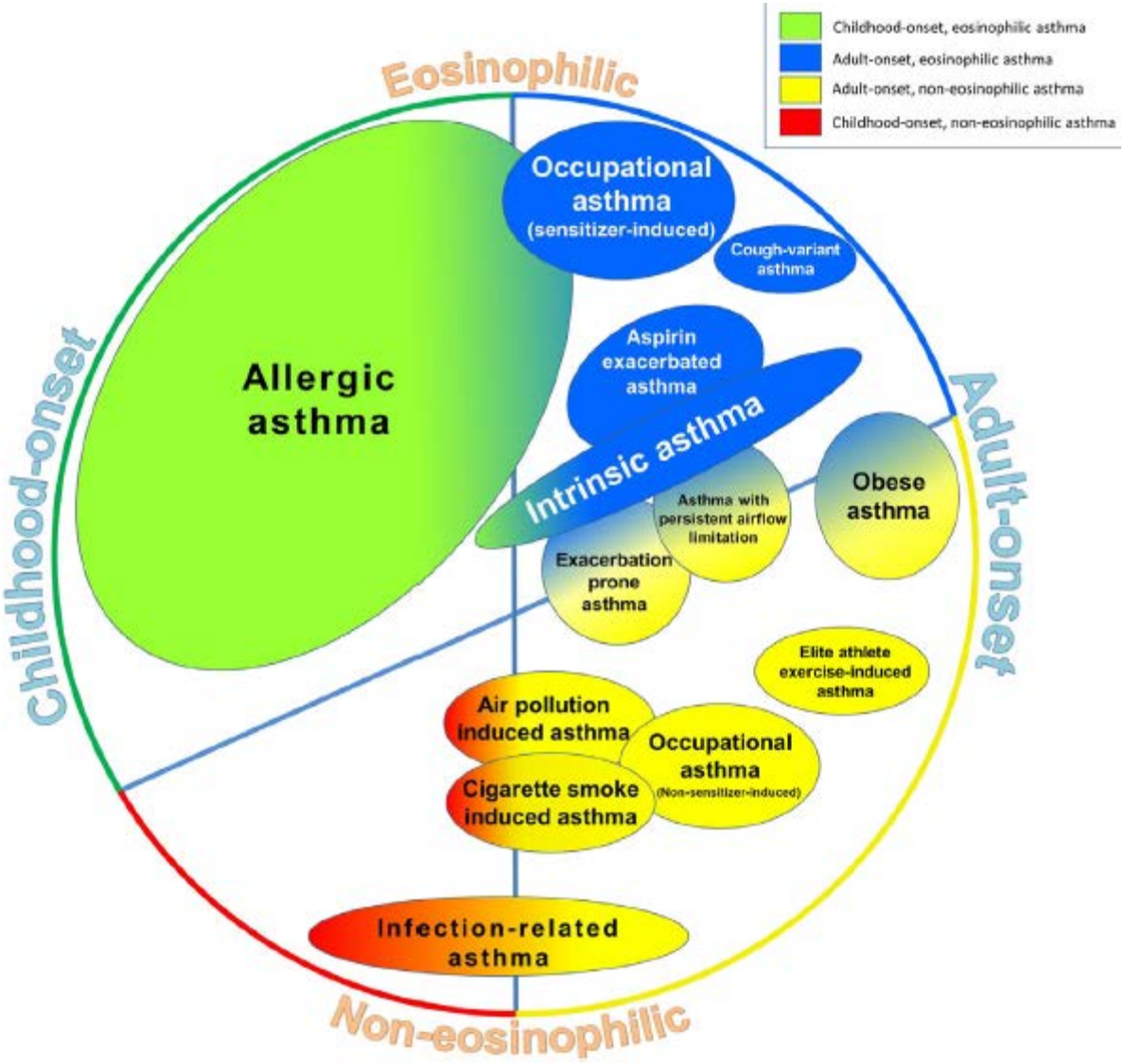
- **SARP**

Cluster 1 **Mild Allergic Asthma**	Early onset; atopic; normal lung function ≤ 2 controller medications; minimal health care utilization minimal sputum eosinophilia
Cluster 2 **Mild-Moderate Allergic Asthma**	Most common cluster; early onset; atopic; borderline FEV1 but reverse to normal; ≤ 2 controller medications; low health care utilization, infrequent need for oral corticosteroids minimal sputum eosinophilia
Cluster 3 **More Severe Older Onset Asthma**	Older; very late onset; higher BMI (obese); less atopic; slightly decreased FEV1 with some reversibility; frequent need for oral corticosteroids despite ≥ 3 controller medications including high doses of inhaled corticosteroids sputum eosinophilia
Cluster 4 **Severe Variable Allergic Asthma**	Early onset; atopic; severely decreased FEV1, but very reversible to near normal; high frequency of symptoms and albuterol use; "variable" with need for frequent oral corticosteroids; high health care utilization sputum eosinophilia
Cluster 5 **Severe Fixed Airflow Asthma**	Older; longest duration; less atopic; severely decreased FEV1 with less reversibility (COPD similarities); high frequency of symptoms and albuterol use despite oral corticosteroids; high health care utilization; co-morbidities Both sputum eosinophilia and neutrophilia

- **GINA 2014**
  - **Allerjik astım**
  - **Non-allerjik astım**
  - **Geç başlayan astım**
  - **Fiks hava yolu obstrüksiyonu ile seyreden astım**
  - **Obezite ile birlikte olan astım**



- **Jarjour NN et al. AJRCCM 2012; 185: 356-62**
- **Curr Opin Pulm Med 2017, 23:**



Hekking PP. Et al. Allergy Clin Immunol Pract 2014;2:671-80

Severe Asthma Phenotypes — How Should They Guide Evaluation and Treatment?

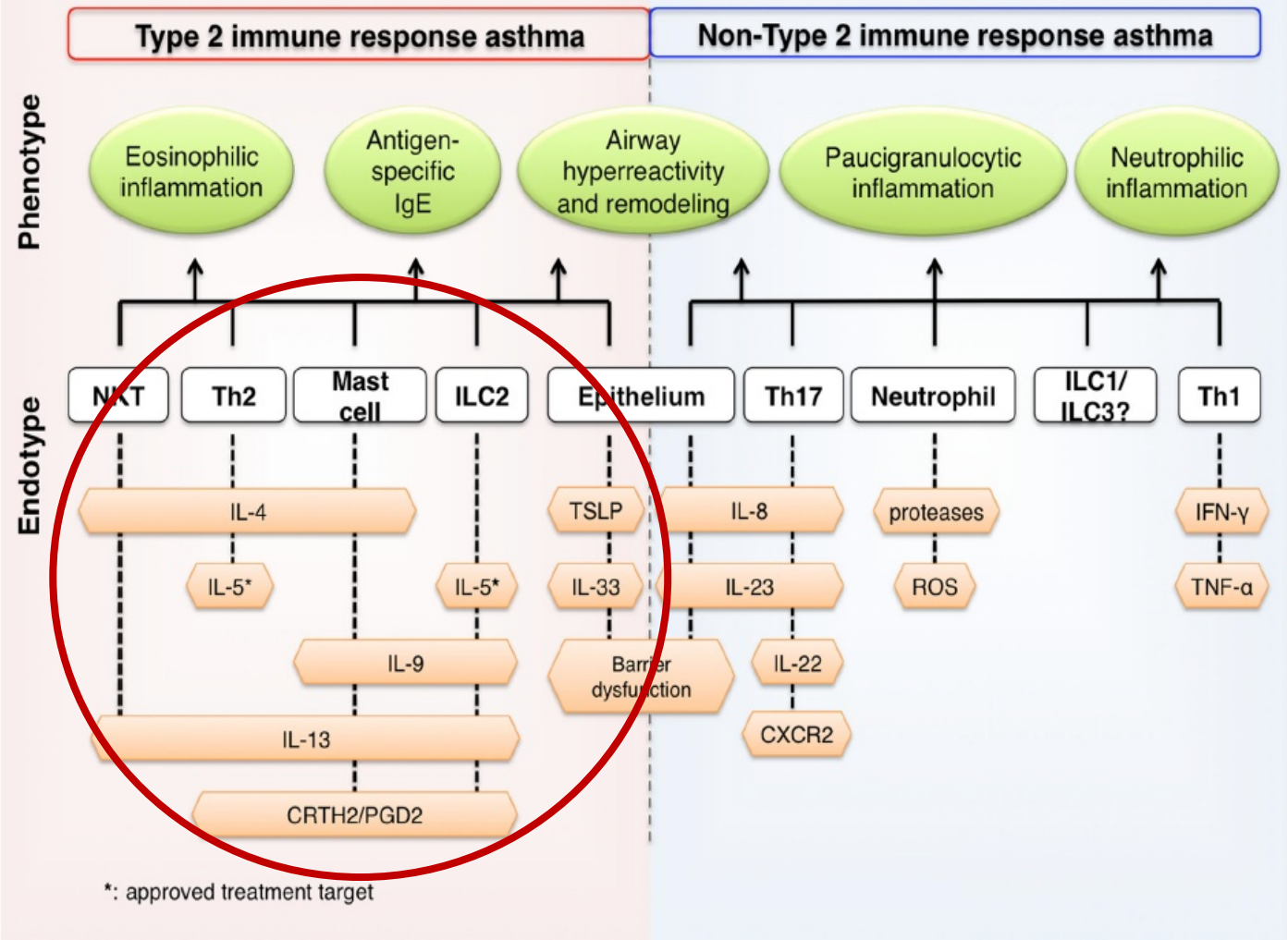
Anne M. Fitzpatrick, PhD[a], and Wendy C. Moore, MD[b] *Atlanta, Ga; and Winston-Salem, NC*

TABLE II. "Severe" asthma clusters identified by other investigators outside of the Severe Asthma Research Program (SARP)

Reference	Population	Age group	N	No. of clusters identified	No. of "severe" clusters	Description of "severe" clusters
2008 Haldar et al[24]	Secondary care, refractory asthma	Adults	187	4	4	(1) Early onset, atopic (2) Later onset, obese, noneosinophilic (3) Early onset, atopic with high symptom expression (4) Late onset, few symptoms but active eosinophilic inflammation
Kim et al[25]	Secondary care, asthma	Adults	2567	4	1	(1) Adult onset obstructive asthma
Amelink et al[26]	Secondary care, adult-onset asthma	Adults	200	3	2	(1) Severe eosinophilic inflammation (2) Frequent symptoms, high health care utilization and low sputum eosinophils
Schatz et al[27]	Severe or difficult-to-treat asthma	Children	518	5	5	(1) White males, no tobacco exposure (2) Females, no tobacco exposure (3) Predominantly nonatopic with airflow obstruction (4) Passive smoke exposure with airflow obstruction and elevated IgE (5) Non-white race with airflow obstruction and elevated IgE
2014 Schatz et al[27]	Severe or difficult-to-treat asthma	Adolescents and adults	3612	5	5	(1) White female, adult-onset asthma with low IgE (2) Early onset, atopic with elevated IgE (3) White male with airflow obstruction (4) Non-white asthma with elevated IgE (5) Adult onset with aspirin sensitivity
Newby et al[28]	Severe, refractory asthma	Adults	349	5	5	(1) Early onset, atopic (2) Late onset, obese with frequent exacerbations (3) Least severe asthma, nonatopic with normal lung function (4) Late onset, eosinophilic asthma (5) Severe but reversible airflow obstruction
Zaihra et al[29]	Secondary care, difficult-to-treat asthma	Adults	125	4	3	(1) Late onset with airflow obstruction (2) Obese females (3) Early onset with airflow obstruction
2017 Lefaudeux et al[30]	Mild-to-severe asthma	Adults	418	4	4	(1) Well controlled (2) Late onset with airflow obstruction, obesity, and smoking (3) Airflow obstruction but no smoking (4) Obese females with no smoking or airflow obstruction

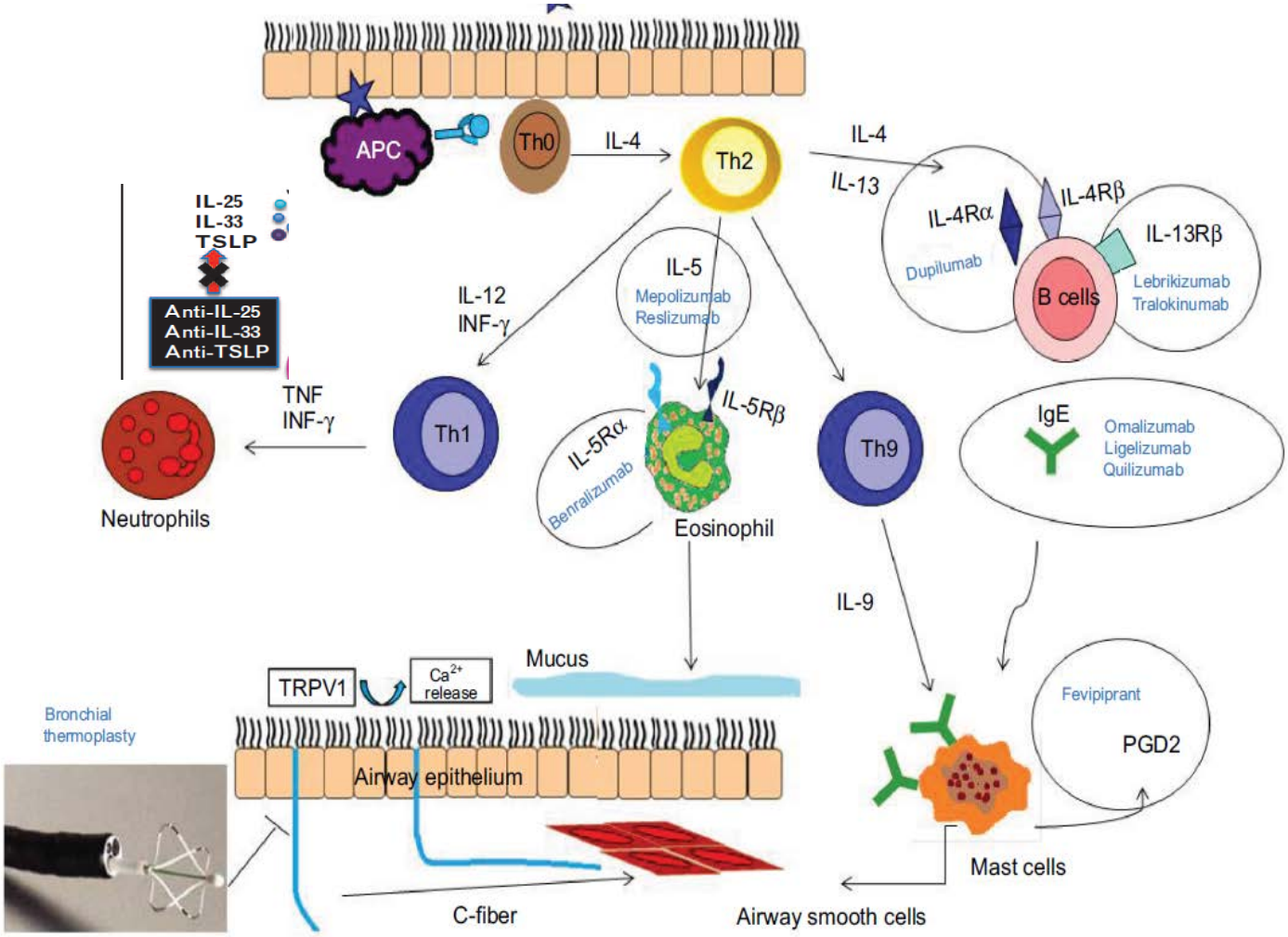
J Allergy Clin Immunol Pract 2017;5:901-8)

Fenotip ve endotipler



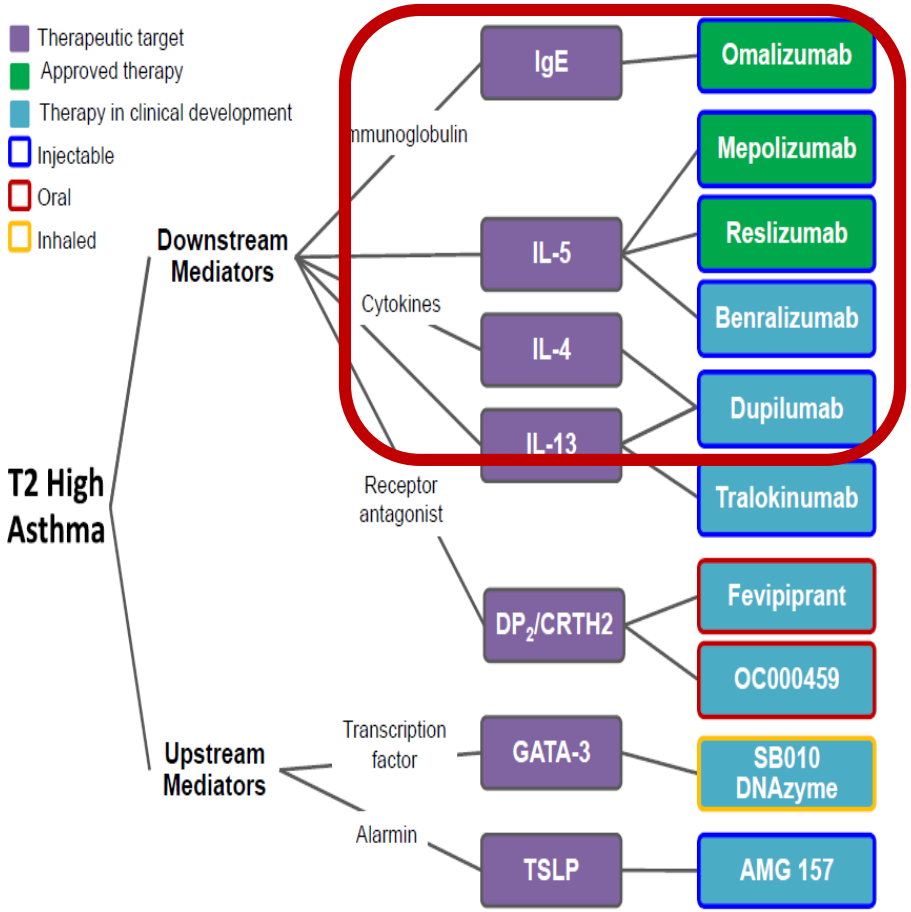
Akdis C et. Curr Allergy Asthma Rep 2016: 16:70

Astımda biyolojikler



Menzella F et al. J of Asthma Allergy 2017:10: 237-47

Astım endotiplerine yönelik biyolojikler



- **Non-Tip 2 yaklaşımlar**
  - **Anti- TNF-a**
  - **Anti-TH-17A/ Anti-TH-17R (Secukinumab/Brodalumab)**
  - **Anti GM-CSF**
  - **Anti-CXC R2**
  - **Makrolid antibiyotikler**

Peppere AN et al. J Allergy Clin Immunol Pract 2017;5:909-16

Anti-IgE (omalizumab)

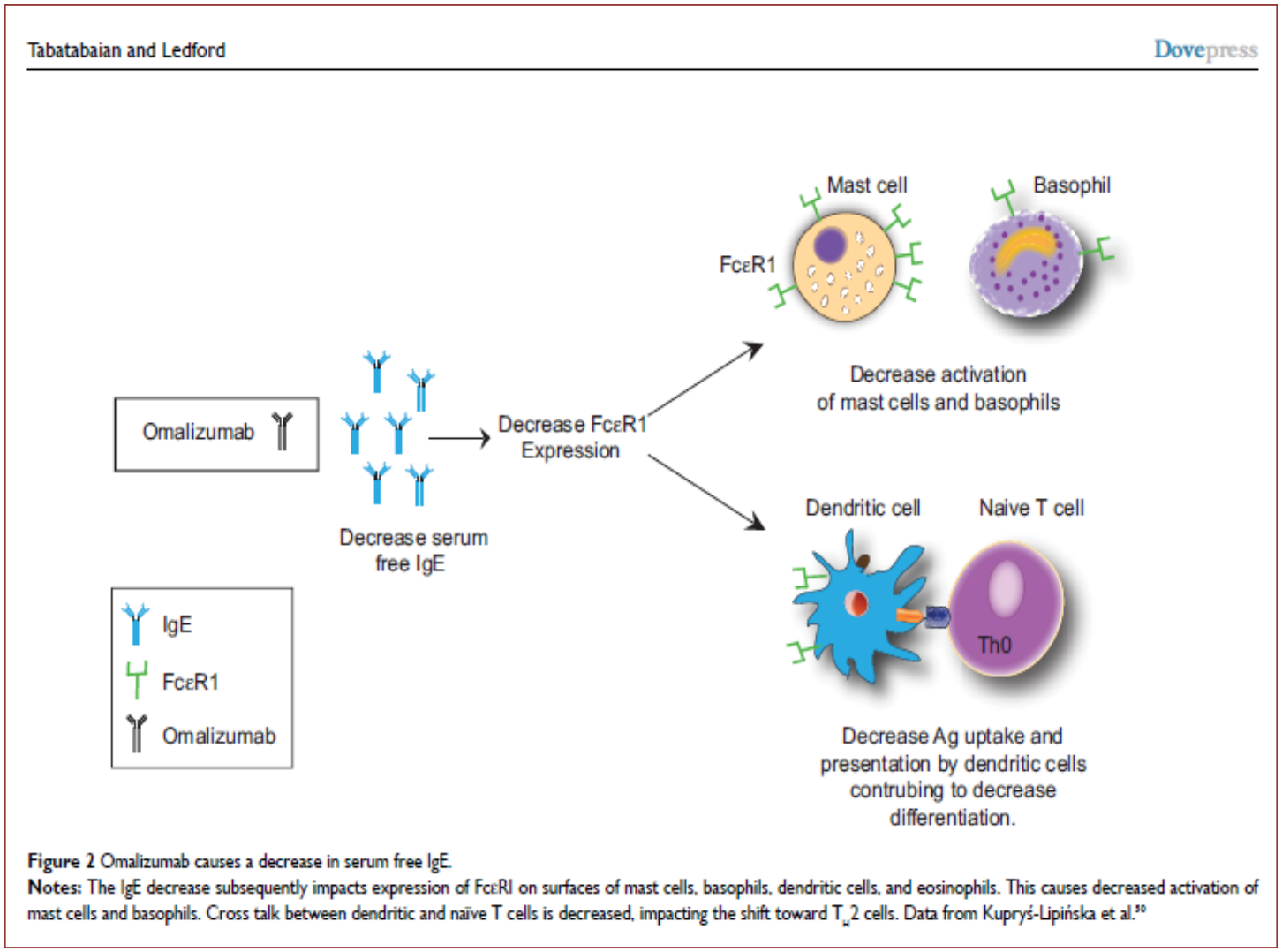
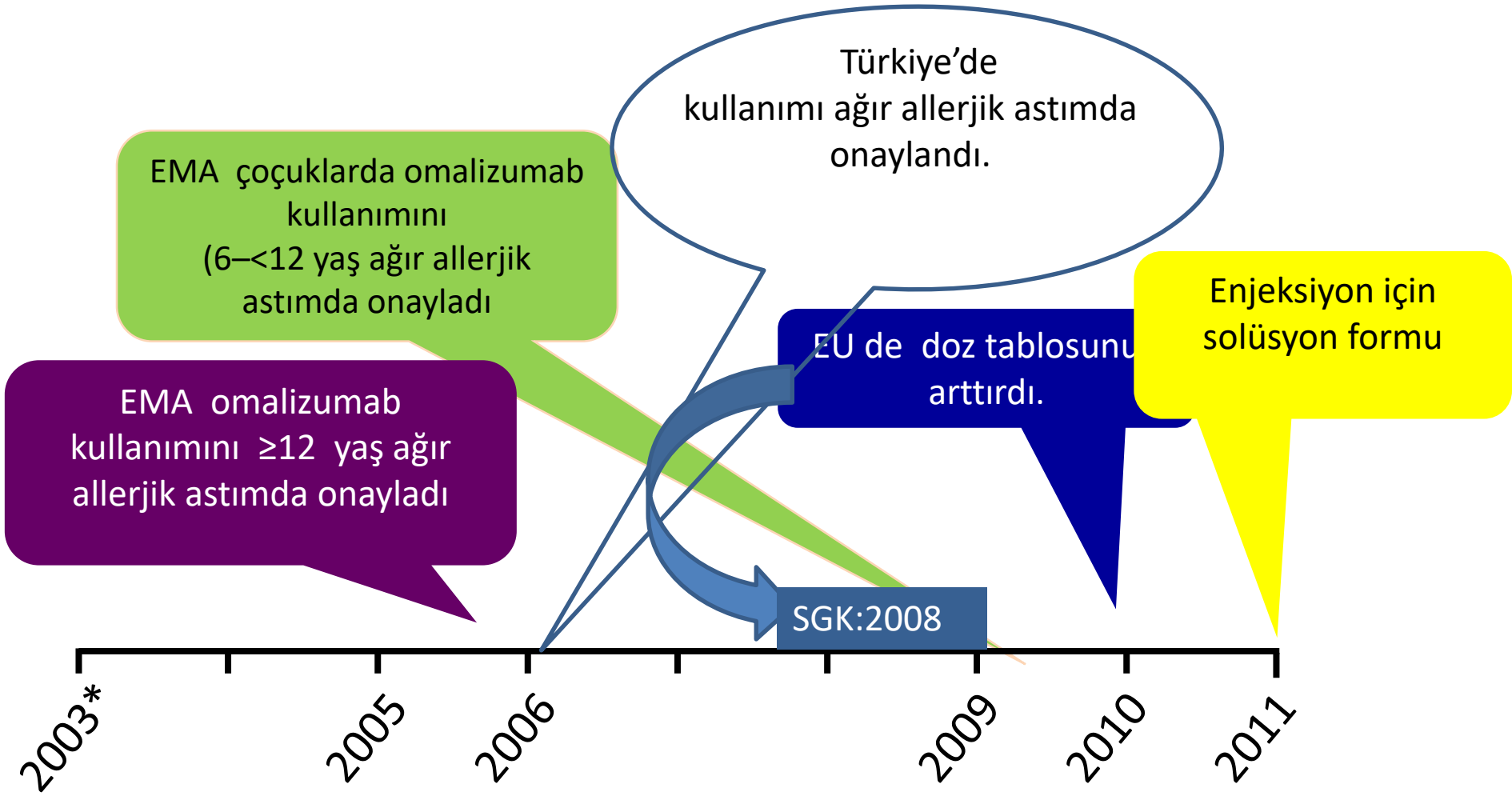


Figure 2 Omalizumab causes a decrease in serum free IgE.
Notes: The IgE decrease subsequently impacts expression of FcεRI on surfaces of mast cells, basophils, dendritic cells, and eosinophils. This causes decreased activation of mast cells and basophils. Cross talk between dendritic and naïve T cells is decreased, impacting the shift toward T_H2 cells. Data from Kupryś-Lipińska et al.[30]

Astımda Omalizumab

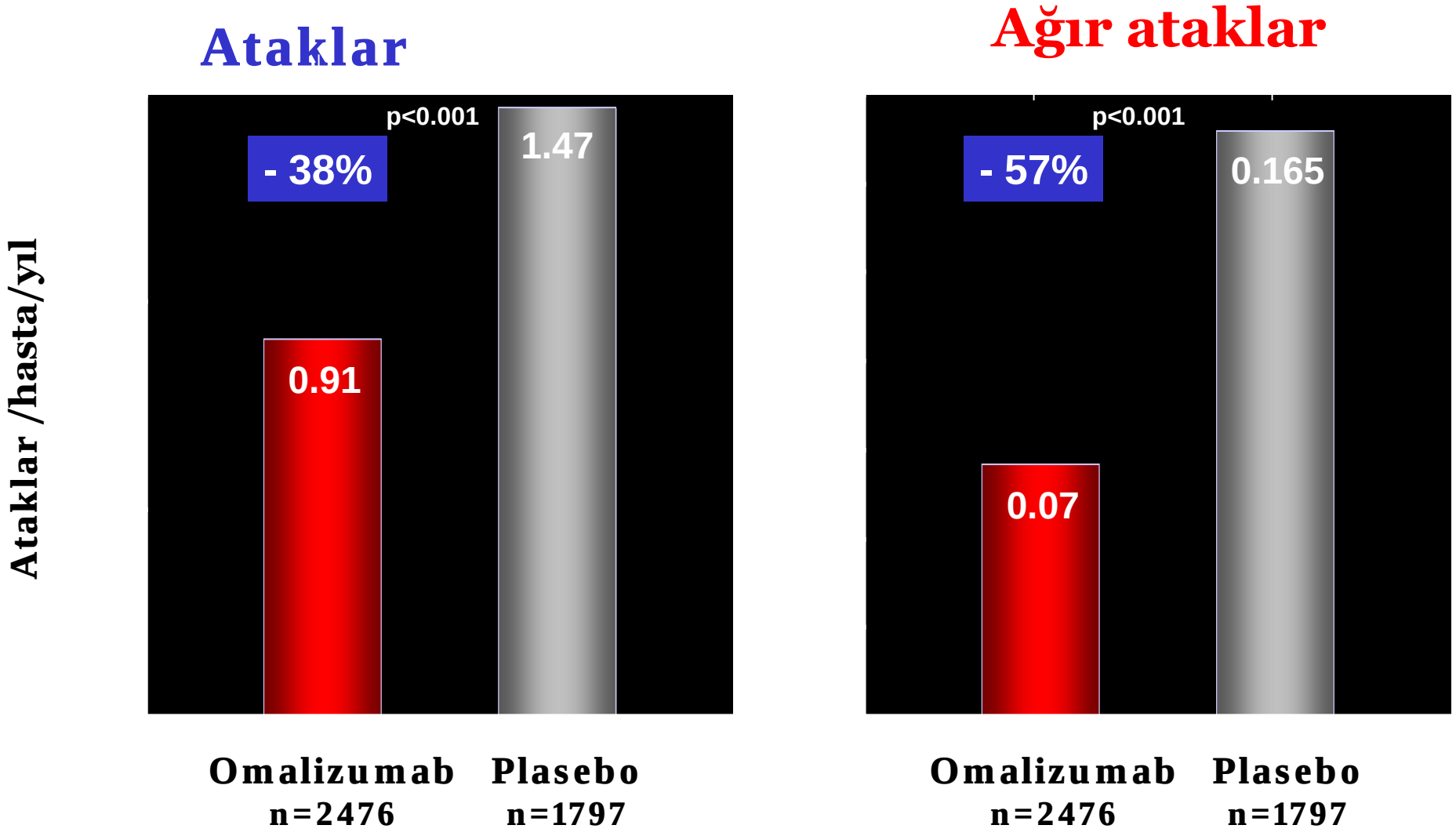


*FDA ≥12 yaş orta/ağır astımda onayladı.
†Avrupada sadece allerjik ağır astımda onaylı

Omalizumab: Faz III 7 RKÇ, ortak sonuç

yaş, cins, bazal IgE düzeyinden bağımsız

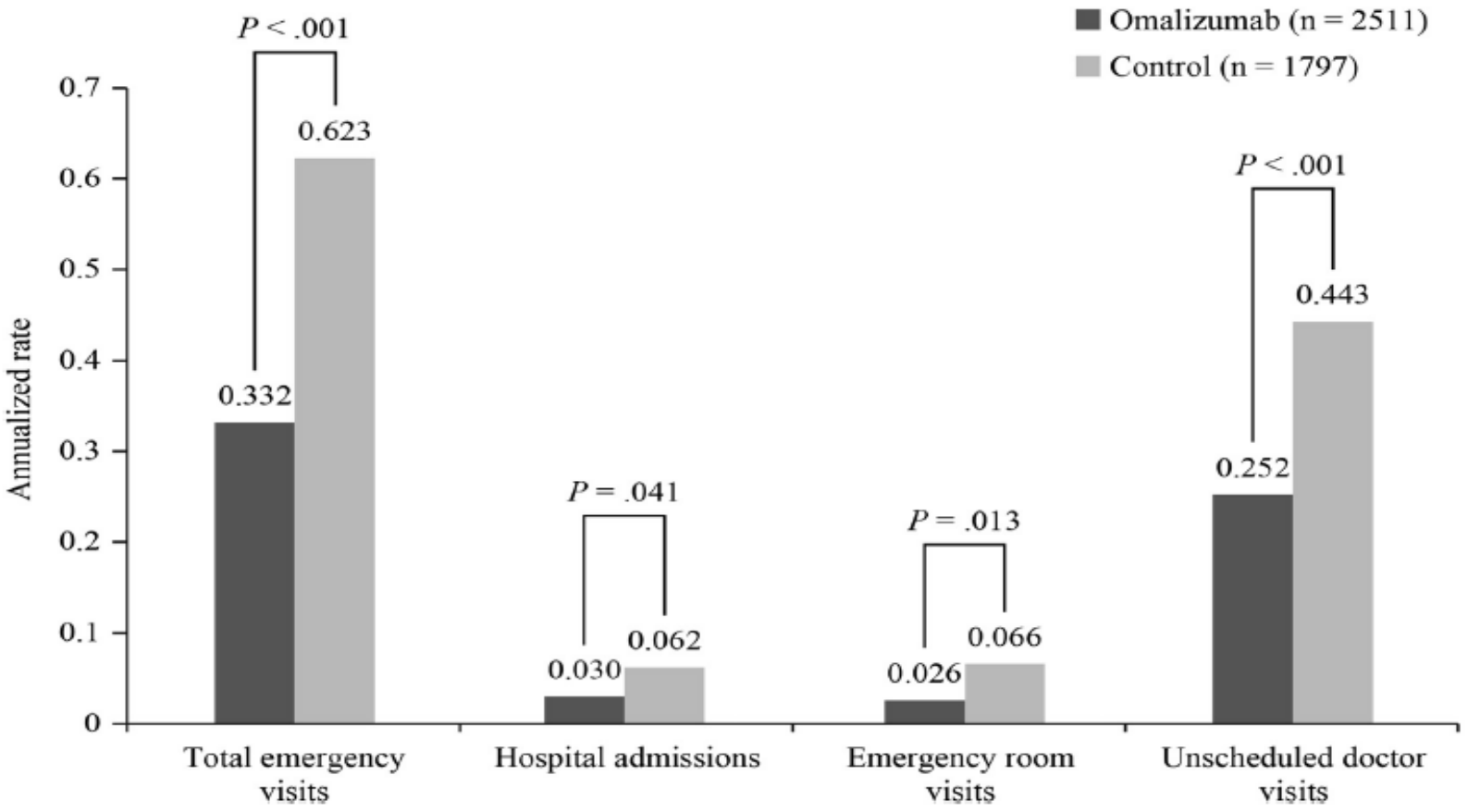
4308 hasta sonucu



Bousquet J, et al. Allergy 2005: 60: 302-8

Omalizumab

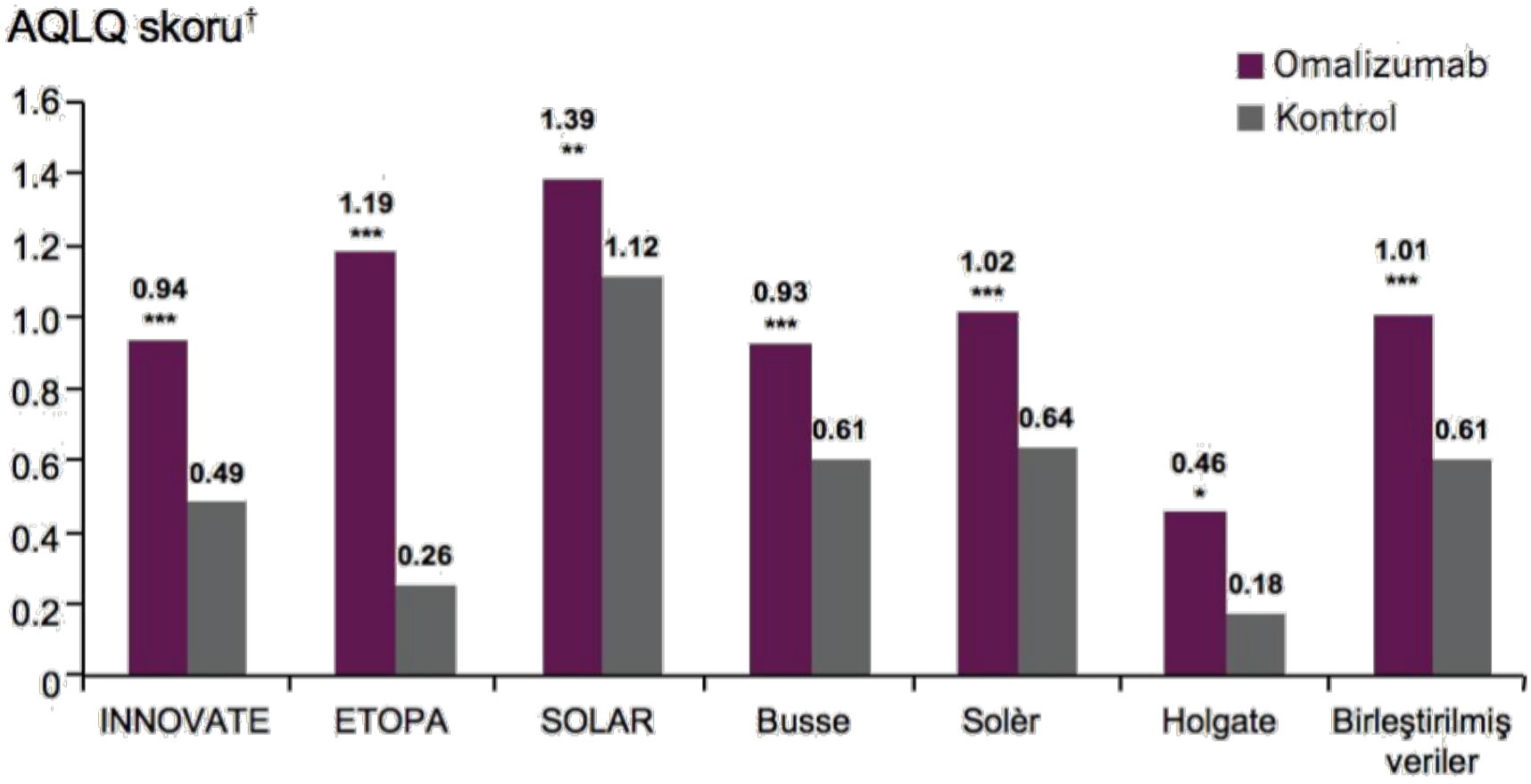
toplam acil başvuru (%47),
hastaneye yatış (%52),
acil başvuru(%61)
planlanmamış doktor ziyareti (%47) azalmış



Bousquet J, et al. Allergy 2005

Omalizumab: Yaşam kalitesi

Faz III RKÇ



Kontrol grubuyla karşılaştırıldığında *p<0.05; **p<0.01; ***p<0.001
†Başlangıca göre değişiklik (en küçük kareler ortalaması)

Chipps B, et al. Curr Med Res Opin 2006

Omalizumab: Faz III çalışma verileri
ek sonuçlar

- %62.9 yanıt vermiş
- IKS dozunda anlamlı azalma
- Astım semptomlarında anlamlı azalma
- Astım kontrolünde düzelme
- Kurtarıcı ilaç kullanımında azalma
- FEV1 düzelme (3 çalışma), PEF değişmemiş

Omalizumab endikasyonu

1. Ağır persistan allerjik astımlı,
   Yüksek doz IKS+ LABA kullanımı
   1. Sık atak
   2. Sık gece/gündüz semptomu
2. Yıl boyu inhalan allerjen duyarlı (deri testi/sIgE)
3. Max: 150 kg
4. Serum IgE: 30-1500 IU/ml
6. ≥6 yaş

‘Real-life’ effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review

I. Abraham[1,2,3], A. Alhossan[1,4], C. S. Lee[5], H. Kutbi[1,6] & K. MacDonald[3]

24 çalışma, 4117 kişi

Table 1 Summary of designs, time points of assessments, and effectiveness outcomes reported

Study	Design	Retrospective data pre-omalizumab therapy	Country	Evaluable N at baseline (omalizumab-treated)	Physicians/ centers	Time points of assessments reported: 16 weeks	6 months	1 year	Other
Molimard et al. (2008) (27)	Prospective	1 year	France	146					≥5 months
Brusselle et al. (2009) (28)	Prospective	1 year	Belgium	158	35	✓		✓	
Korn et al. (2009) (29)	Prospective	1 year	Germany	280	134	✓	✓		
Cazzola et al. (2010) (31)	Prospective	1 year	Italy	142	13			✓	
Korn et al. (2010) (41)	Retrospective	16 weeks	Germany	471	220	✓			
Molimard et al. (2010) (30)*	Prospective	1 year	France, Germany	166					≥16 weeks
Bousquet et al. (2011) (42)	Prospective	1 year	Various‡	272	106	✓			32 weeks
Costello et al. (2011) (32)	Retrospective	6 months	Ireland	63	6		✓		
Rottem et al. (2012) (33)	Retrospective	1 year	Israel	33				✓	
Rubin et al. (2012) (43)	Prospective	Not specified	Brazil	78					Week 12 and Week 20
Schumann et al. (2012) (37)	Prospective	16 weeks	Germany	195	85	✓	✓		
Sweeney et al. (2012) (36)	Retrospective	Not specified	UK	59		Not specified			
Tzortzaki et al. (2012) (34)	Retrospective	1 year	Greece, Cyprus	60	4	✓		✓	4 years
Vennera et al. (2012) (35)	Prospective	1 year	Spain	266	30	✓		✓	2 years
Barnes et al. (2013) (39)	Retrospective	1 year	UK	136	10	✓		✓	
Braunstahl et al. (2013) (40)	Prospective	1 year	Various†	925		✓		✓	8 months, 18 months, 2 years
Grimaldi-Bensouda et al. (2013) (38)	Prospective	1 year	France	374	129				M = 1.67 years
Kelmenson et al. (2013) (46)	Prospective	0	USA	4					5 months
Subramaniam et al. (2013) (47)	Retrospective	6 months	Ireland	30			✓		
Alfarroba et al. (2014) (45)	Retrospective	1 year	Portugal	26			✓	✓	2 years
Tajiri et al. (2014) (50)	Prospective	1 year	Japan	31		✓		✓	
Vieira et al. (2014) (44)	Prospective	1 year	Portugal	15		✓		✓	2 years
Novelli et al. (2015) (49)	Prospective	1 year	Italy	306	26				32 months
Tiro et al. (2015) (48)	Prospective	1 year	Mexico	47					3 years

Allergy 71 (2016) 593–610;

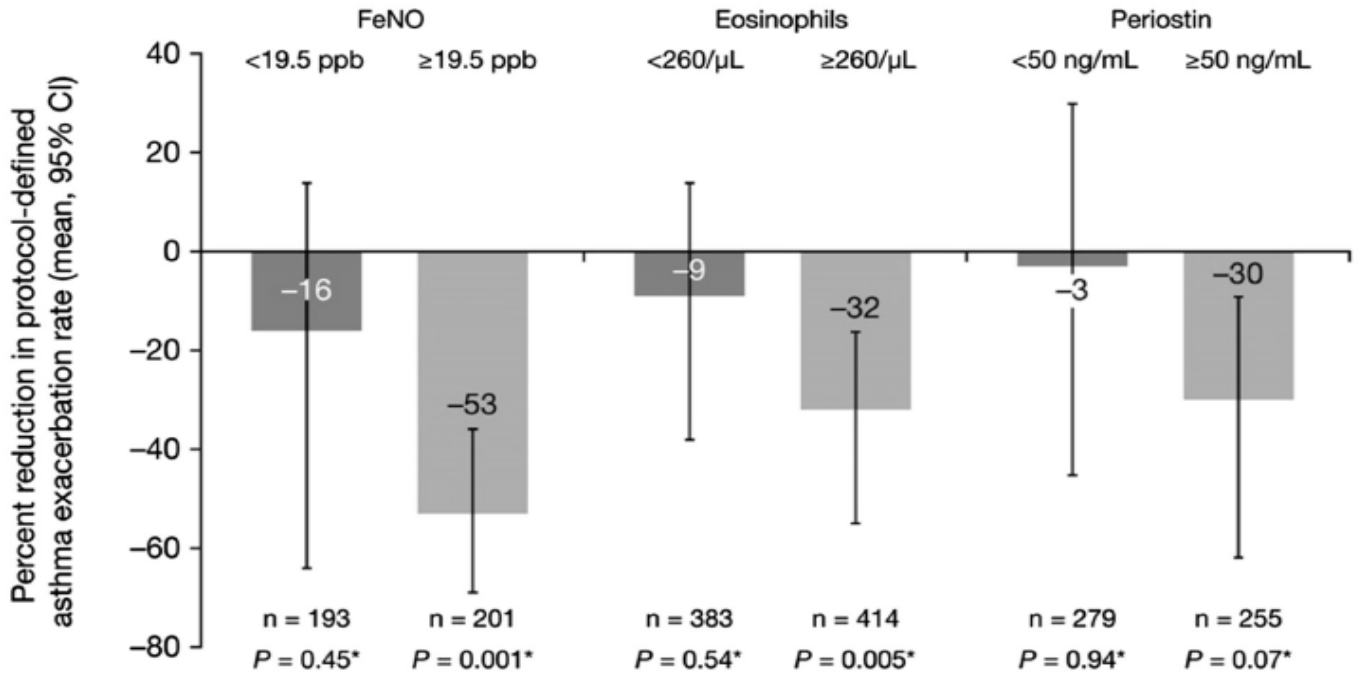
Omalizumab: Gerçek yaşam verileri

%69-%72,%82,%88 yanıtlılık

RKÇ verilerini destekliyor

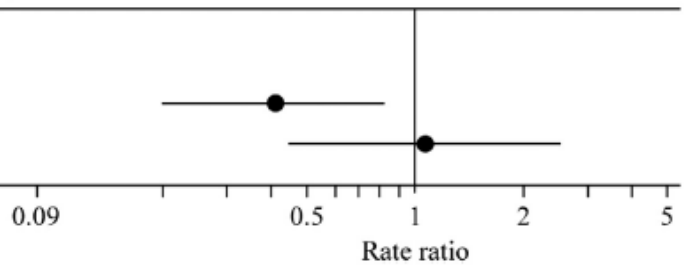
* Astım ataklarında ↓
* Hastane başvuruları/yatışlarda/yatış süresinde ↓
* Astım semptomlarında ↓, astım kontrolünde ↑
* Yaşam kalitesinde düzelme
* Oral steroidlerin dozunda azalma/ kesilme
* FEV1/PEF düzelme
* Benzer güvenlik ve tolerabilite

Omalizumab yanıtında biyobelirteçler



%27 vs. ⬇ %59

Subgroups	Total n	Rate ratio (95% CI) (Omalizumab/placebo)
Eosinophil counts		
High	91	0.41 (0.20-0.82)
Low	126	1.07 (0.45-2.53)



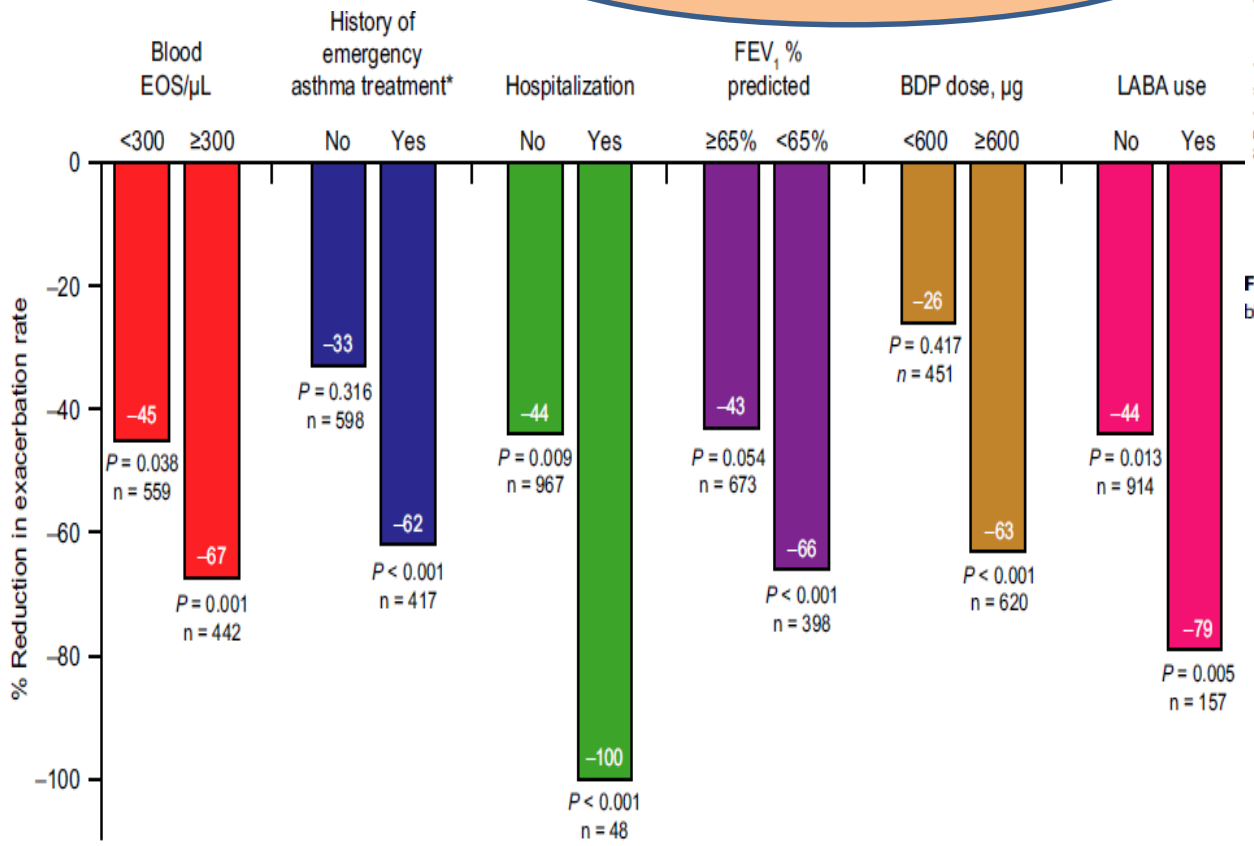
Hanania NA et al. Am J Respir Crit Care Med 2013;187: 804-11
Busse W. Et al. JACI 2013; 485-6

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]

Atak: %55↓

Tüm parametreler atak : %86↓



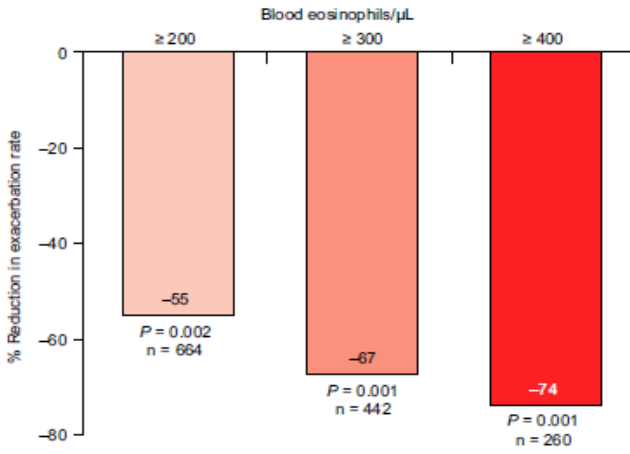
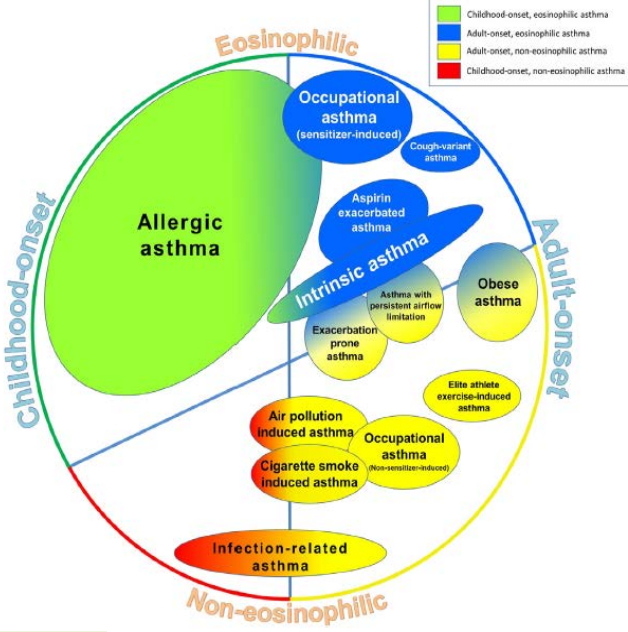


FIGURE 2 Relative percentage change in exacerbation rate by blood eosinophil levels

Casale T et al. Allergy. 2017;1–8.

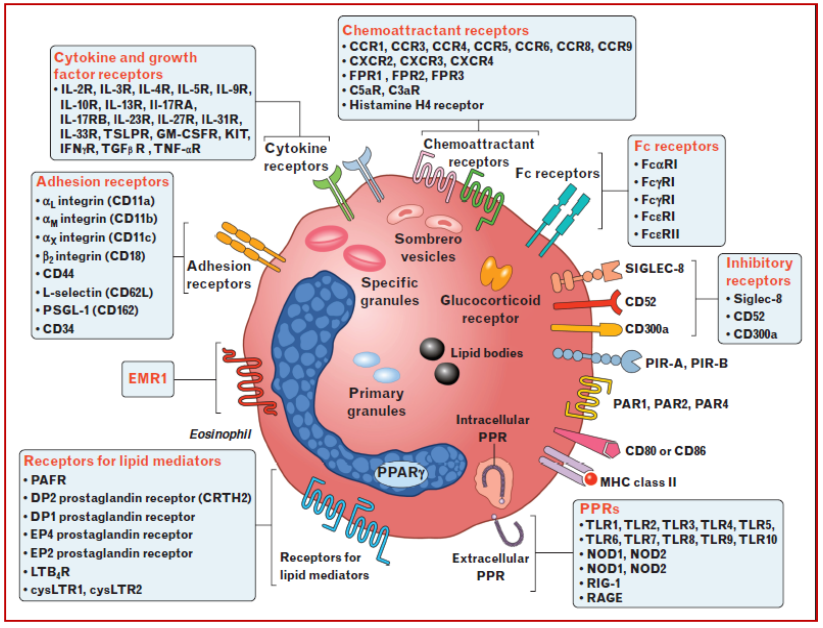
Eozinofilik ağır astım

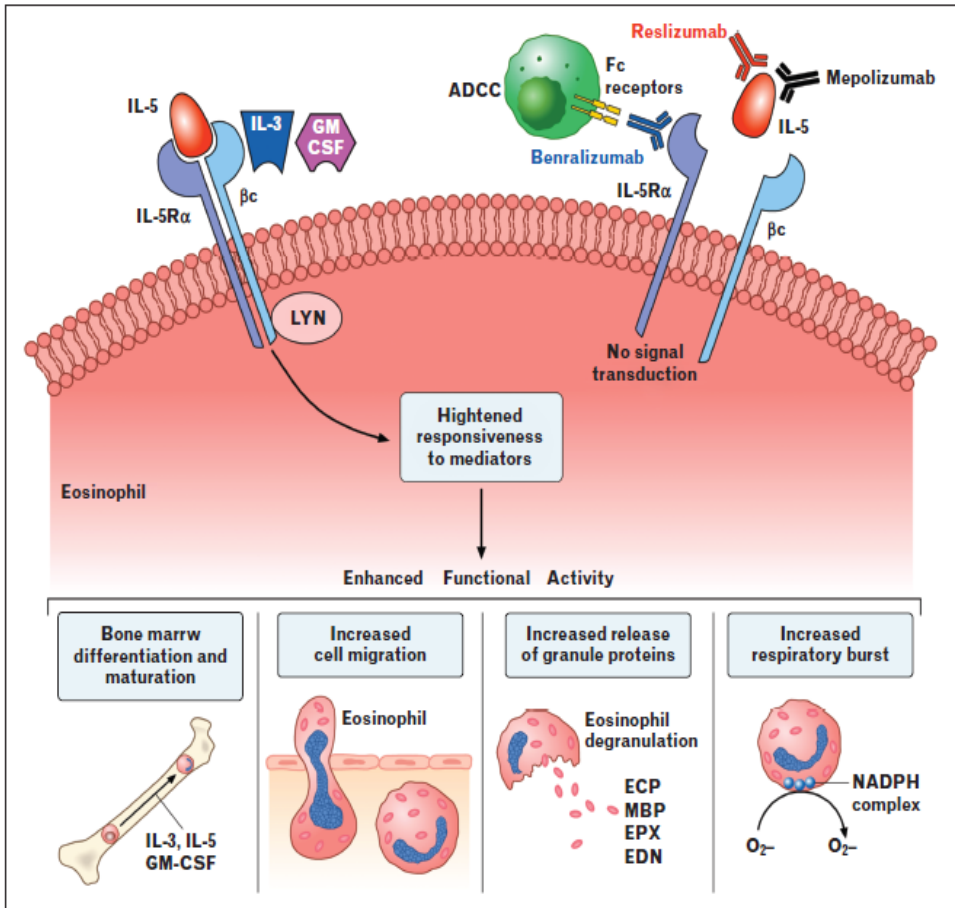
- **Prevalans**
  - **IKS kullanmayan: %36-80**
  - **IKS kullanan: %17-39-50**
  - **Ağır astım: %45-%90**
- **Balgamda eozinofil:**
  - **>%2 (KS kullanmayan)**
  - **%2-4 (yüksek doz IKS)**
- **Perifer kanda eozinofil:**
  - **%2.7/ 260 hücre/uL (IKS altında astımı kontrol altında olmayan hastalar)**



IL-5: Th2, Tip 2ILC, mast h, bazofil, NK, eozinofil

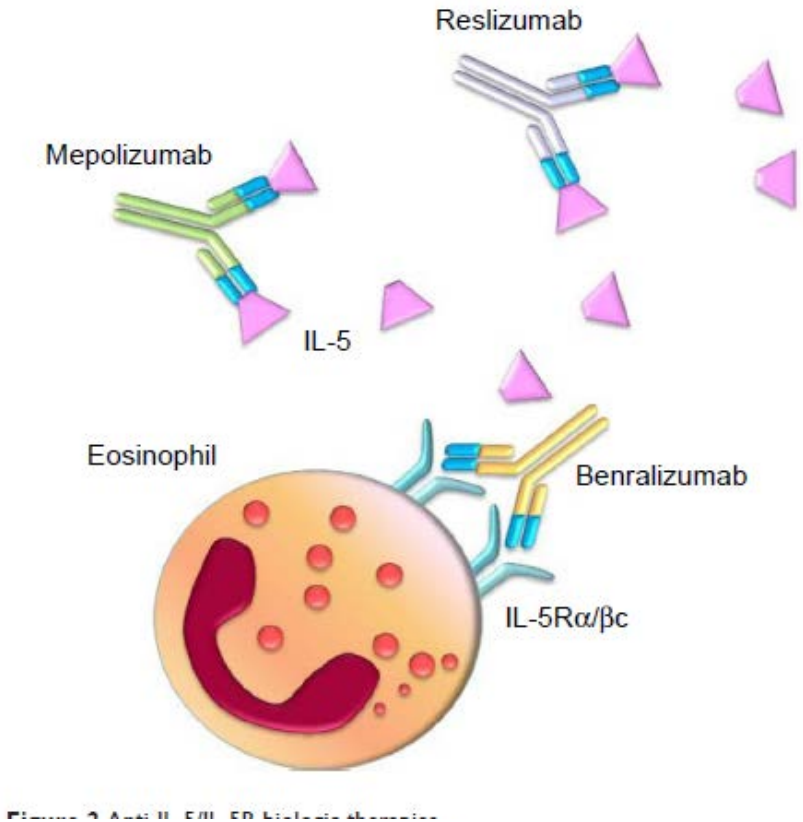
IL-5Rα: Eozinofil, bazofil, mast hücre, B lenfosit





Curr Opin Allergy Clin Immunol 2016, 16:186–200

Anti-IL-5s

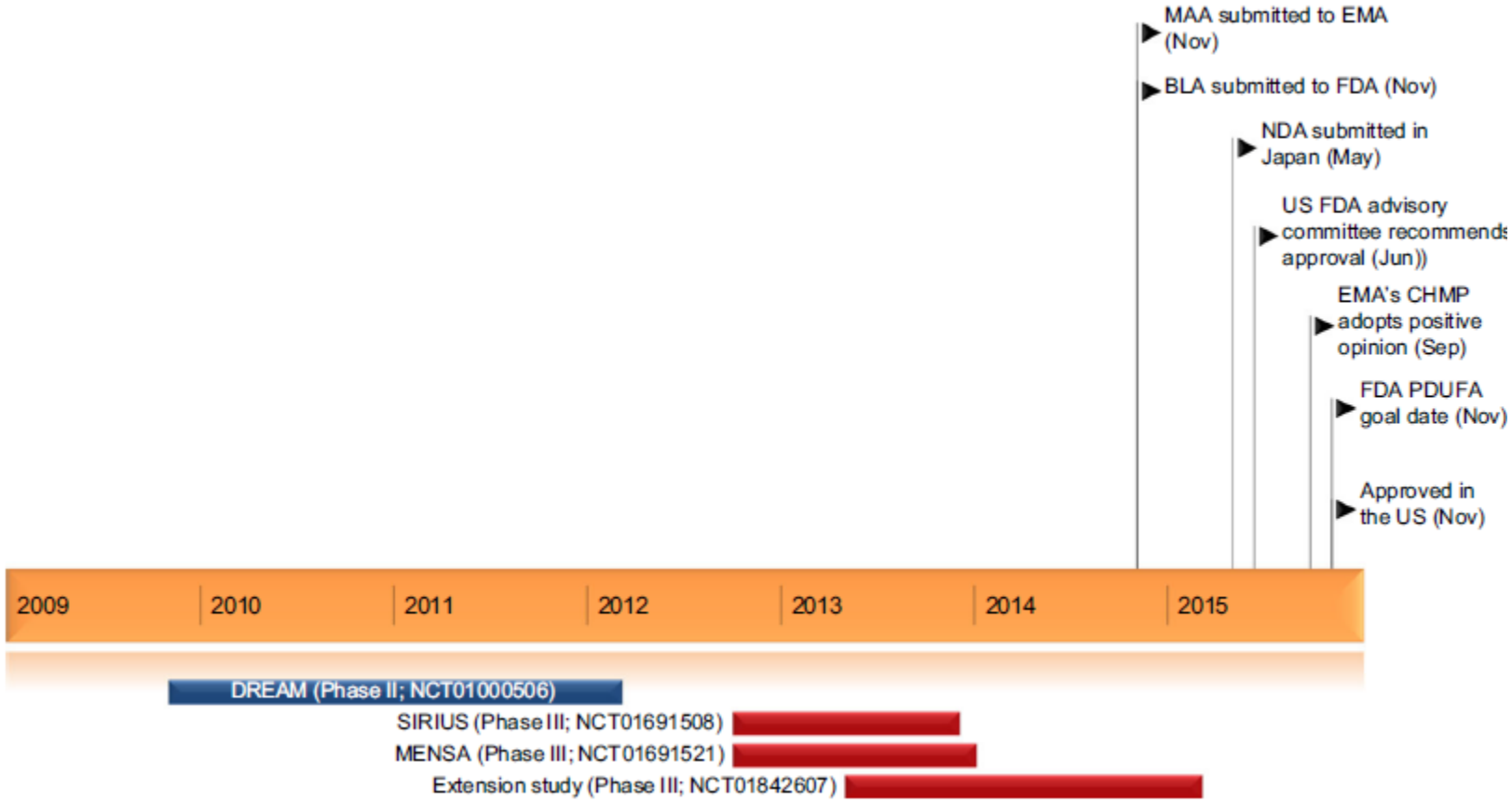


- **Anti IL-5: FDA, EMA**
  - **Mepolizumab, Reslizumab**
- **Anti-IL-5Rα: FDA, EMA**
  - **Benralizumab**

Pelaila G. et al. Therapeuticks and Clin Risk Management 2016, 12: 1075- 82

Mepolizumab

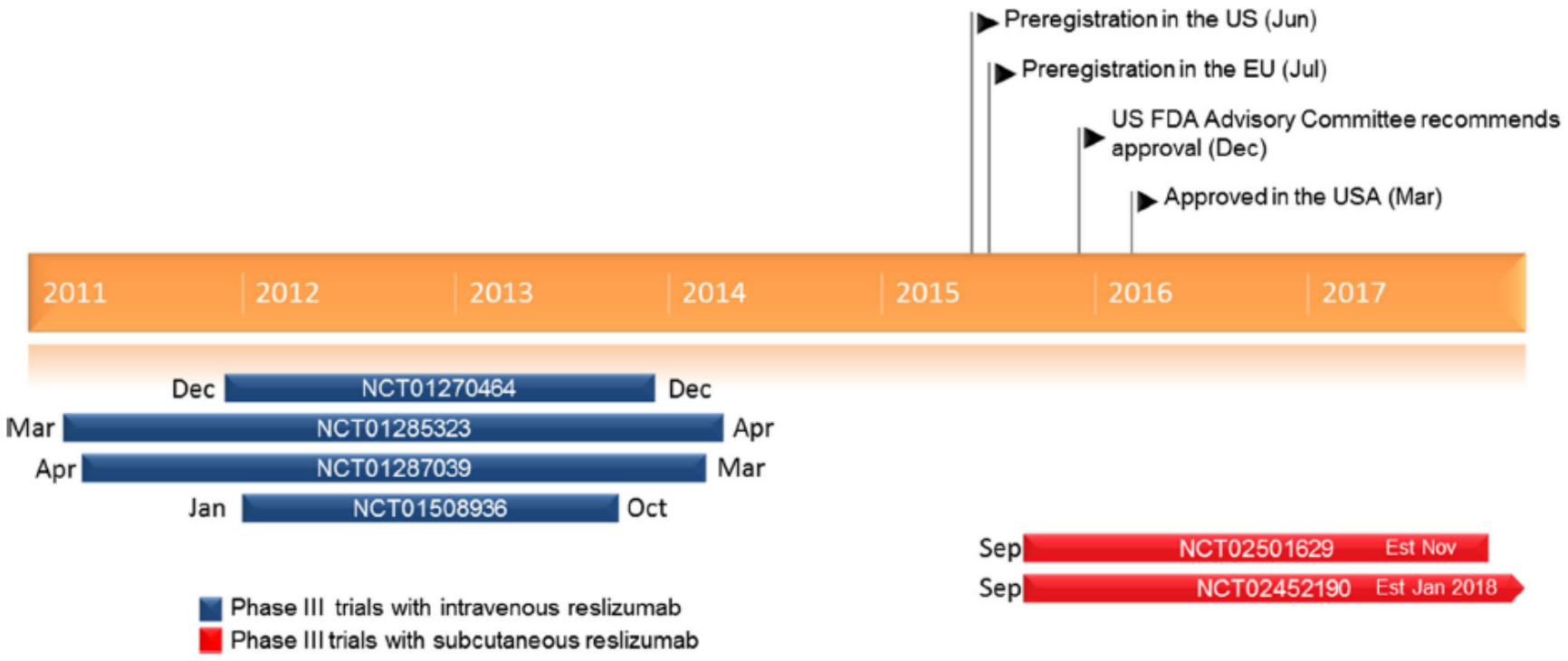
100 mg, sc,/4 hafta, >12 yaş, ağır eozinofilik fenotip, 150 eozinofil/uL, atak öyküsü



Drugs (2015) 75:2163–2169
DOI 10.1007/s40265-015-0513-8

Reslizumab: Anti-IL-5

3 mg/kg IV, 20–50 dk. infüzyon (50 ml SF, 2ml/dk)/4 hf.
yaş: ≥18, ağır eozinofilik astımlı, FDA: anafilaksi uyarısı



Mepolizumab: klinik çalışmaları

ilk çalışma: endobronşial biyopsi (%55) , BAL (%80),KI (%52), kan (%100) azalma

***: balgam ve >2 atak/yıl kriteri ilk kez kullanılmış**

Table 1. Clinical trials of mepolizumab in asthma (anti-interleukin-5, IgG_1 – Bosatria – GSK)

First author/ref/year	Disease severity	No. of patients treated	Dosage/delivery	Outcome summary
Flood-Page *et al.* [58], 2003	Mild asthma	11	750 mg i.v. every 4 weeks for 3 months	↓Blood Eos; ↓Airway Eos only by 50% = PEF, FEV_1, bronchial hyperresponsiveness
Haldar *et al.* [53], 2009	Eosinophilic asthma Sputum eoz>%3	61	750 mg i.v. every 4 weeks for 1 year	↓Blood + Sputum Eos; ↓Severe exacerbations; ↑QoL = FEVj, bronchial hyperreactivity
Nair *et al.* [55], 2009	Prednisone-dependent Sputum eoz>%3	9	750 mg i.v. every 4 weeks for 5 months	↓Blood + Sputum Eos; ↓Exacerbations; Prednisone sparing effect
Pavord *et al.* [57], 2012 DREAM	Severe eosinophilic asthma Sputum eoz>%3, NO, blood eos. >300	462	75–250–750 mg i.v. every 4 weeks for 13 infusions	↓Blood + Sputum Eos; ↓Exacerbations = FEV_1, AQLQ, and ACQ scores
Bel *et al.* [51▪▪], 2014 SIRIUS	Severe eosinophilic asthma kan eozinofili>150	135	100 mg s.c. every week for 20 weeks	Glucocorticoid sparing effect; ↓Exacerbations; Improvement ACQ-5 score
Ortega *et al.* [56▪▪], 2014 MENSA	Severe eosinophilic asthma kan eozinofili>150	385	75 mg i.v. or 100 mg s.c. every 4 weeks for 32 weeks	↓Blood + Sputum Eos; ↓Exacerbations; ↑FEV_1; ↑ACQ-5 score
Basu *et al.* [60], 2015	Severe eosinophilic asthma			Healthcare resources and costs of mepolizumab versus placebo in a clinical trial (MENSA Study)

Curr Opin Allergy Clin Immunol 2016, 16:186–200

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

Hector G Ortega, Steven W Yancey, Bhabita Mayer, Necdet B Gunsoy, Oliver N Keene, Eugene R Bleecker, Christopher E Brightling, Ian D Pavord

- **1192 hasta(846 mepo. 346 pl)**
- **Ortak sonuç: atak/yıl sayısında %47 ⇓**
- **Kanda:**
- **≥150 eozinofil/uL : %52 azalma**
- **≥500 eozinofil/uL: %70 azalma**
- **2 eşik değer:**
  - **≥300 eozinofil**
  - **≥150 eozinofil: OKS almakta ise**

Ortega HG et al. Lancet Respir Med. 2016,

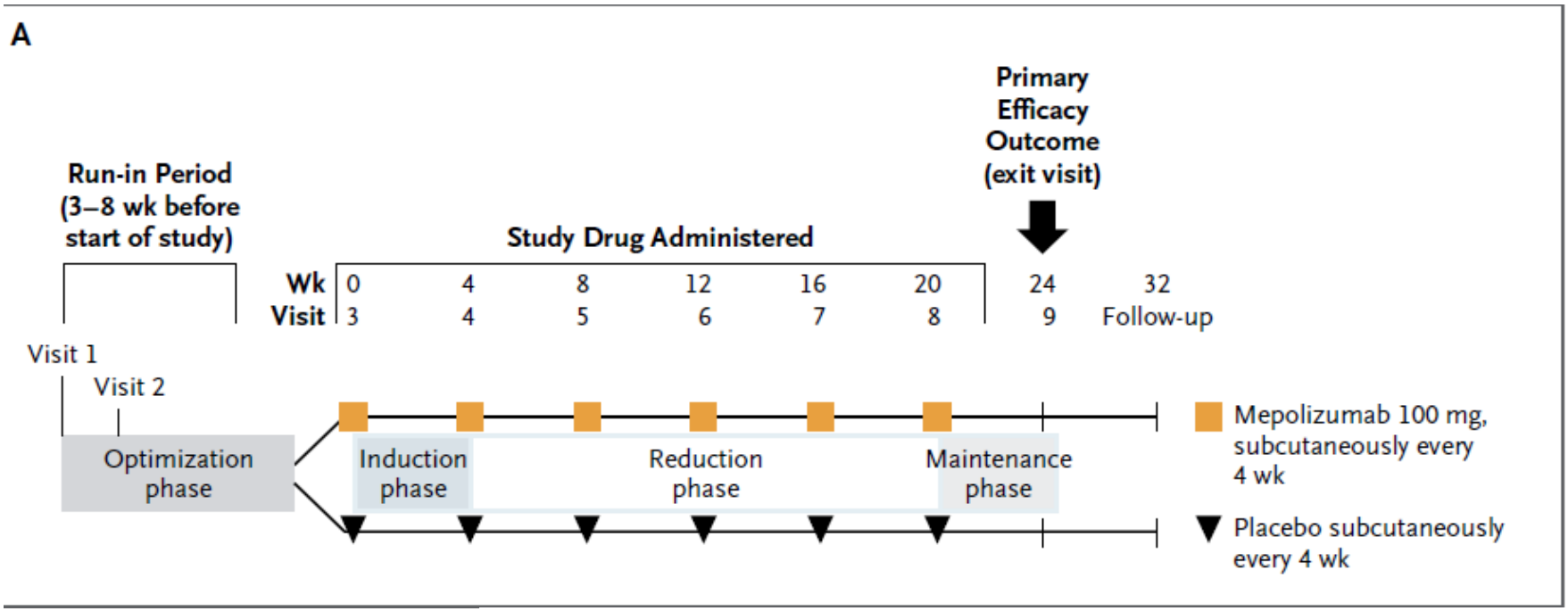
Düzenli oral KS: 30-40% ağır astımlı
Steroid sparing ilaç ihtiyacı var

Mep. vs. Placebo: 4 hf, 20hf, RDBPC

ORIGINAL ARTICLE

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*



N Engl J Med 2014,. DOI: 10.1056/NEJMoa1403291, DOI: 10.1056/NEJMoa1403290

Tüm hastalar OKS+yüksek doz IKS+ ek kontrol edici

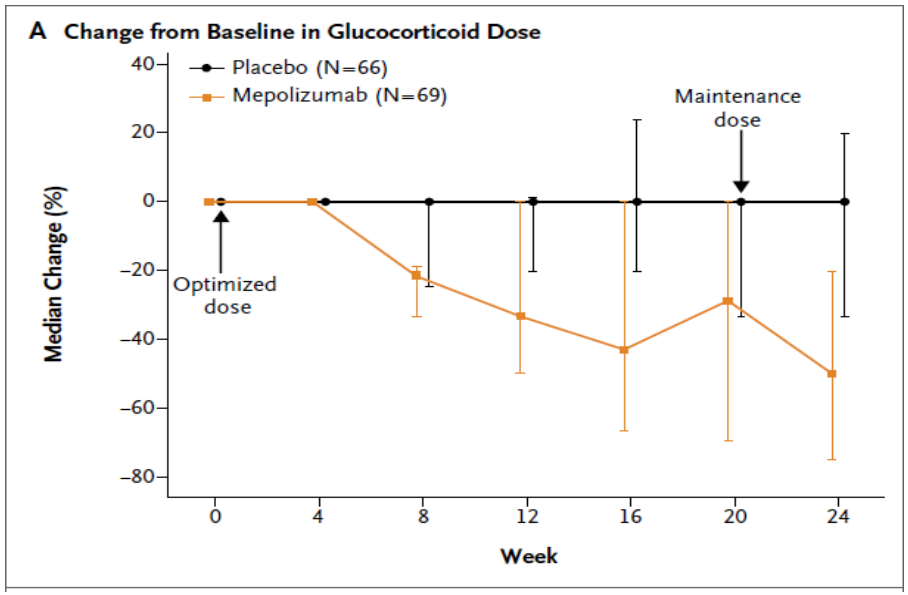
kan eosinophil : ≥ 300 /µlt /bir önceki yıl, 150 /µlt optimizasyonda, ≥2 atak/yıl

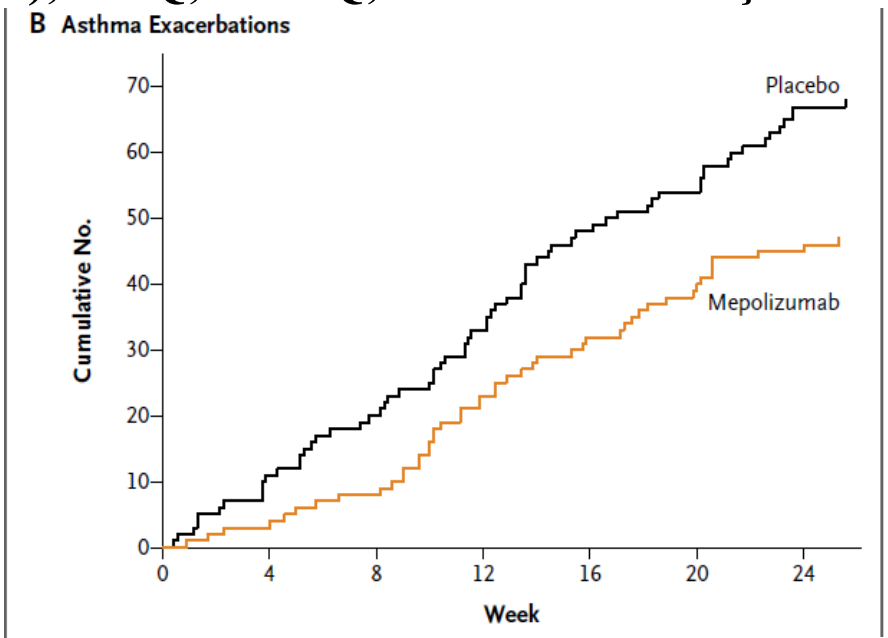
Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=66)	Mepolizumab (N=69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1:FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/µl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)

N Engl J Med 2014,. DOI: 10.1056/NEJMoa1403291, DO

OKS dozu: 50% azalma (Mep), Pl. (değ.yok), (p:0.007)
OKS azalmayanlar: Mepo: 36% vs. Placebo: 56%
Mepo: 3.2 mg/day vs. Pl: 10 mg/gün prednisolone (çalışma sonu)
Ataklar: 32% in Mep. vs. placebo (p:0.04), ACQ, SGRQ, FEV1: düzelmiş





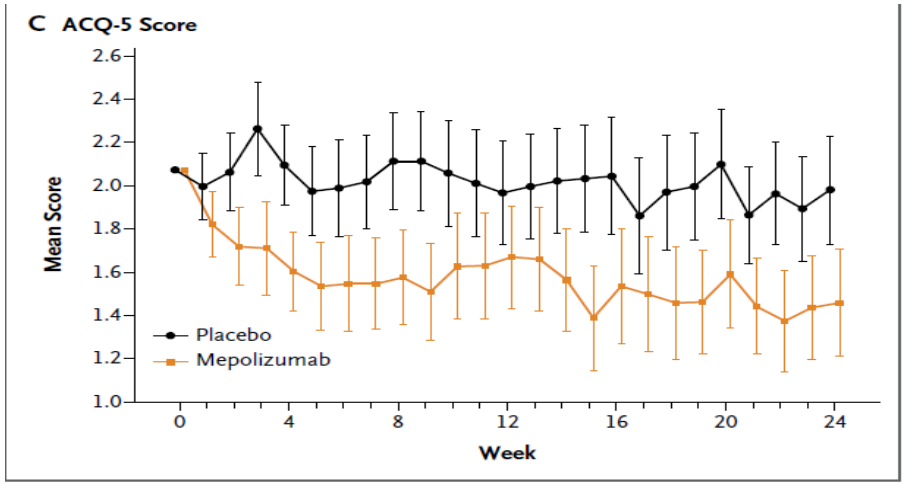


Table 3. Summary of Adverse Events.

Event	Placebo (N=66)	Mepolizumab (N=69)
	no. of patients (%)	
Adverse event		
Any	61 (92)	57 (83)
Nonasthma	60 (91)	57 (83)
Worsening of asthma	8 (12)	2 (3)
Related to study drug*	12 (18)	21 (30)
Leading to discontinuation of study drug or withdrawal from the study	3 (5)	3 (4)
Serious adverse event		
During treatment	12 (18)	1 (1)
Fatal	1 (2)	0

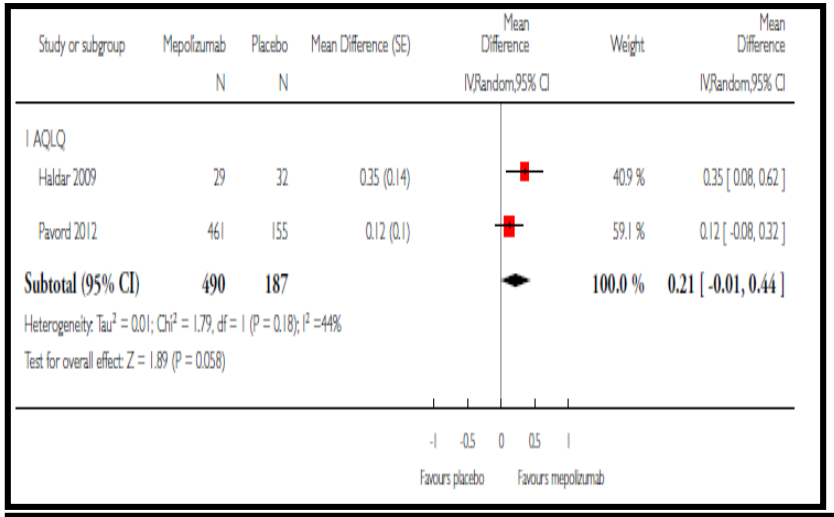
Mepolizumab
8 çalışma, 1701 hasta
2015

Cochrane Library

Cochrane Database of Systematic Reviews

Mepolizumab versus placebo for asthma (Review)

Powell C, Milan SJ, Dwan K, Bax L, Walters N



Analysis 1.3. Comparison 1 IV Mepolizumab versus placebo, Outcome 3 Rate of clinically significant exacerbations.

Review: Mepolizumab versus placebo for asthma

Comparison: 1 IV Mepolizumab versus placebo

Outcome: 3 Rate of clinically significant exacerbations

Study or subgroup	Mepolizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 75 mg mepolizumab versus placebo						
Pavord 2012	153	155	-0.6539 (0.1443)		51.7 %	0.52 [0.39, 0.69]
Ortega 2014	191	191	-0.6349 (0.1492)		48.3 %	0.53 [0.40, 0.71]
Subtotal (95% CI)	**344**	**346**			**100.0 %**	**0.52 [0.43, 0.64]**
Heterogeneity: Tau² = 0.0; Chi² = 0.01, df = 1 (P = 0.93); I² =0.0%						
Test for overall effect: Z = 6.22 (P < 0.00001)						
2 250 mg mepolizumab versus placebo						
Pavord 2012	152	155	-0.4943 (0.1447)		100.0 %	0.61 [0.46, 0.81]
Subtotal (95% CI)	**152**	**155**			**100.0 %**	**0.61 [0.46, 0.81]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.42 (P = 0.00064)						
3 750 mg mepolizumab versus placebo						
Pavord 2012	156	155	-0.734 (0.1468)		100.0 %	0.48 [0.36, 0.64]
Subtotal (95% CI)	**156**	**155**			**100.0 %**	**0.48 [0.36, 0.64]**
Heterogeneity: not applicable						
Test for overall effect: Z = 5.00 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.40, df = 2 (P = 0.50), I² =0.0%						

0.5 0.7 1 1.5 2

Favours mepolizumab Favours placebo

- **Heterojen (7IV, 1 sc)**
- **Astım atakları ↓**
- **Yaşam kalitesi**
- **Astım kontrolü düzeliyor (bazı çalışmalarda)**
- **FEV1 (bir çalışma)**
- **İdeal hasta grubu, ideal doz rejimi ve tedavi süresi?**
- **(SIRIUS) yok**

Cochrane Library

Cochrane Database of Systematic Reviews

Mepolizumab versus placebo for asthma (Review)

Powell C, Milan SJ, Dwan K, Bax L, Walters N

Reslizumab (Anti-IL-5)

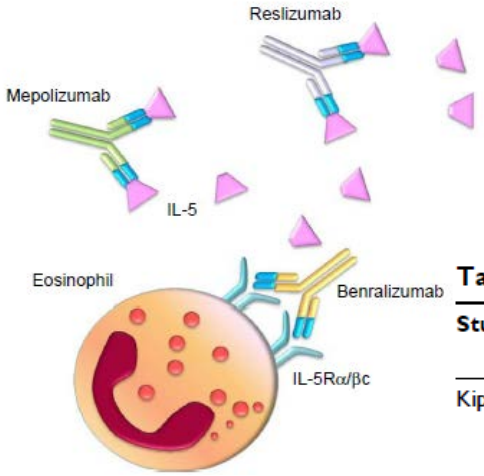


Table 1 Studies of reslizumab in asthma

Study	Study design	Number of patients	Population	Regimen	Main findings
Kips et al[21]	Randomized, double blind	32	Symptomatic severe persistent asthmatics despite using high-dose inhaled or oral corticosteroids	Single dose of reslizumab IV at doses ranging from 0.03 to 1.0 mg/kg or placebo	No biological activity seen at doses below 0.03 mg/kg. Dose of 1.0 mg/kg produced a significant reduction in eosinophil counts. No improvement in pulmonary function or symptom scores
Castro et al[22]	Multicenter, randomized, double blind, placebo controlled	106	Poorly controlled asthmatics with airway reactivity, on high-dose ICS+ to a second controller, and sputum eosinophils ≥3%	Reslizumab 3.0 mg/kg IV or placebo at baseline and at weeks 4, 8, and 12	A trend toward improved ACQ scores, with patients with nasal polyps with a more substantial response. A trend toward improvement in exacerbation rates (8% vs 19%). Eosinophils significantly decreased in sputum
Castro et al[26]	Two replicate trials, multicenter, randomized, double blind, placebo controlled	953	Poorly controlled asthmatics despite using at least medium-dose ICS with or without a controller and a blood eosinophil count of ≥400 cells per μL	Reslizumab 3 mg/kg IV or placebo every 4 weeks × 13 doses	Reduction in rates of asthma exacerbations and improvement in FEV_1 and asthma control
Corren et al[27]	Multicenter, randomized, double blind, placebo controlled	496	Poorly controlled asthmatics despite using at least medium-dose ICS with or without a controller without preselection eosinophil count criteria	Reslizumab 3.0 mg/kg IV or placebo every 4 weeks × 4 doses	No difference in FEV_1 in both study groups. Subgroup analysis in subjects with blood eosinophil count of ≥400 cells per μL had improvements in FEV_1, ACQ scores, and rescue inhaler use
Bjermer et al[28]	Multicenter, randomized, double blind, placebo controlled	315	Poorly controlled asthmatics despite using at least medium-dose ICS with or without a controller and a blood eosinophil count of ≥400 cells per μL	Reslizumab 0.3 or 3.0 mg/kg IV or placebo every 4 weeks × 4 doses	The 3.0 mg/kg dose had improvement in pulmonary function and self-reported asthma control and quality of life

Kan eozinofil sayısının azaldığı ilk çalışma

Faz 2

FEV

Breath

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

Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O'Brien, Stephanie Korn

- **2 paralel, 953 hasta, çok merkezli (232 merkez), uluslararası**
  - **2-4 hf. tarama,**
  - **52 hf. tedavi**
  - **90 gün izlem (52 hf sonra)**
- **IV Reslizumab (3 mg/kg) vs. Pl/ 4 hafta**
  - **Eozinofil ≥ 400/µL**
  - **Kontrolsüz astım (orta/yüksek doz ICS: FP: ≥440 µg/gün+ 2. kontrol edici),**
  - **≥1 atak/bir önceki yıl**

Lancet Respir Med. 2015 ;23.

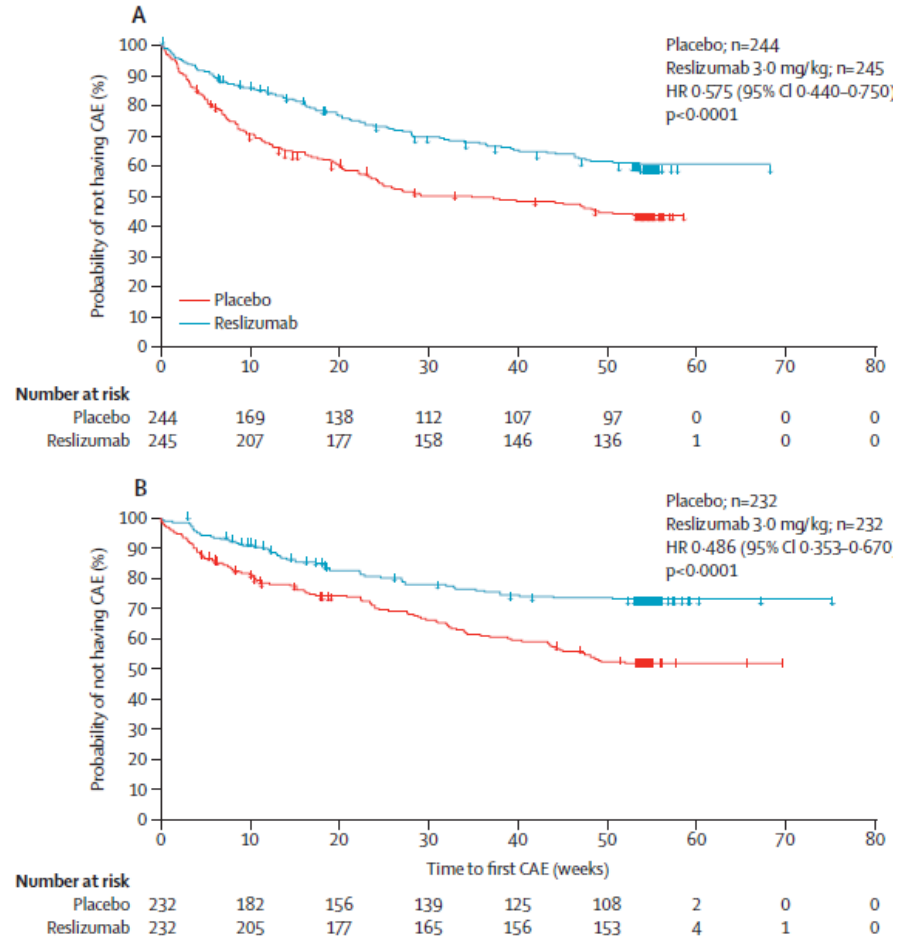
Yılık astım atak sayısı : 50-59% azalmış

İlk atak zamanı: uzamış

ACQ-7: düzelmiş, FEV1: düzelmiş, AQLQ: düzelmiş (4.hf. dan itibaren)

Kan eozinofil sayısı: azalmış (4.hf. dan itibaren)

Çalışma 1 **Çalışma 2**



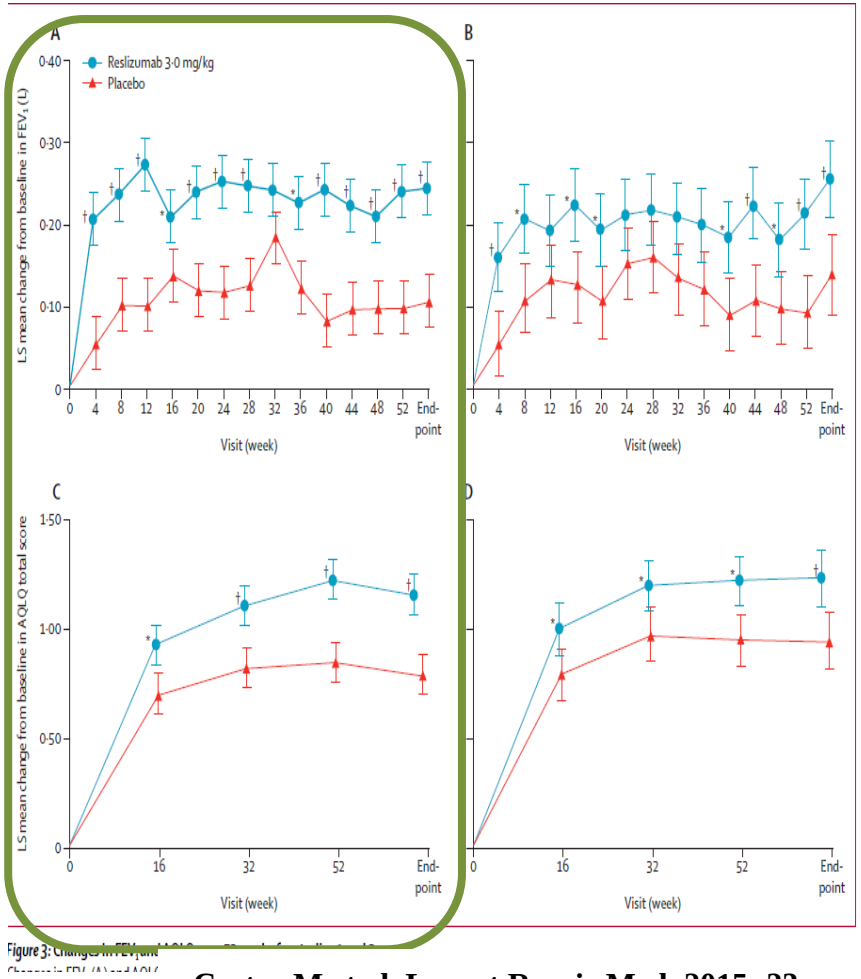
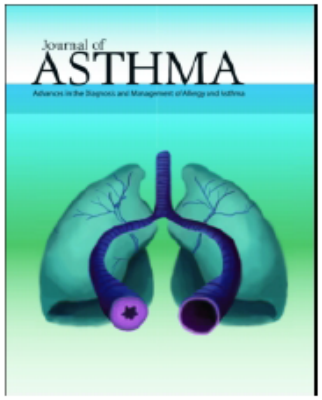


Figure 3: Change in FEV1 and Change in FEV1 (A) and AQLQ

Castro M et al. Lancet Respir Med. 2015 ;23.



Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

The efficacy and safety of Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis

Çalışma sayısı az (5 RCTs)
Uzun dönem güvenlik ve etkinlik çalışılmamış
Basılmamış çalışmalar alınmamış

J Asthma. 2017 Apr;54(3):300-307

Reslizumab: 3 mg/kg, IV, en az 16 hf. ted.
4 çalışma, 1,366 hasta
Astım atakları, kan eozinofil düzeyi: anlamlı azalma
ACQ ve FEV1: anlamlı düzelme

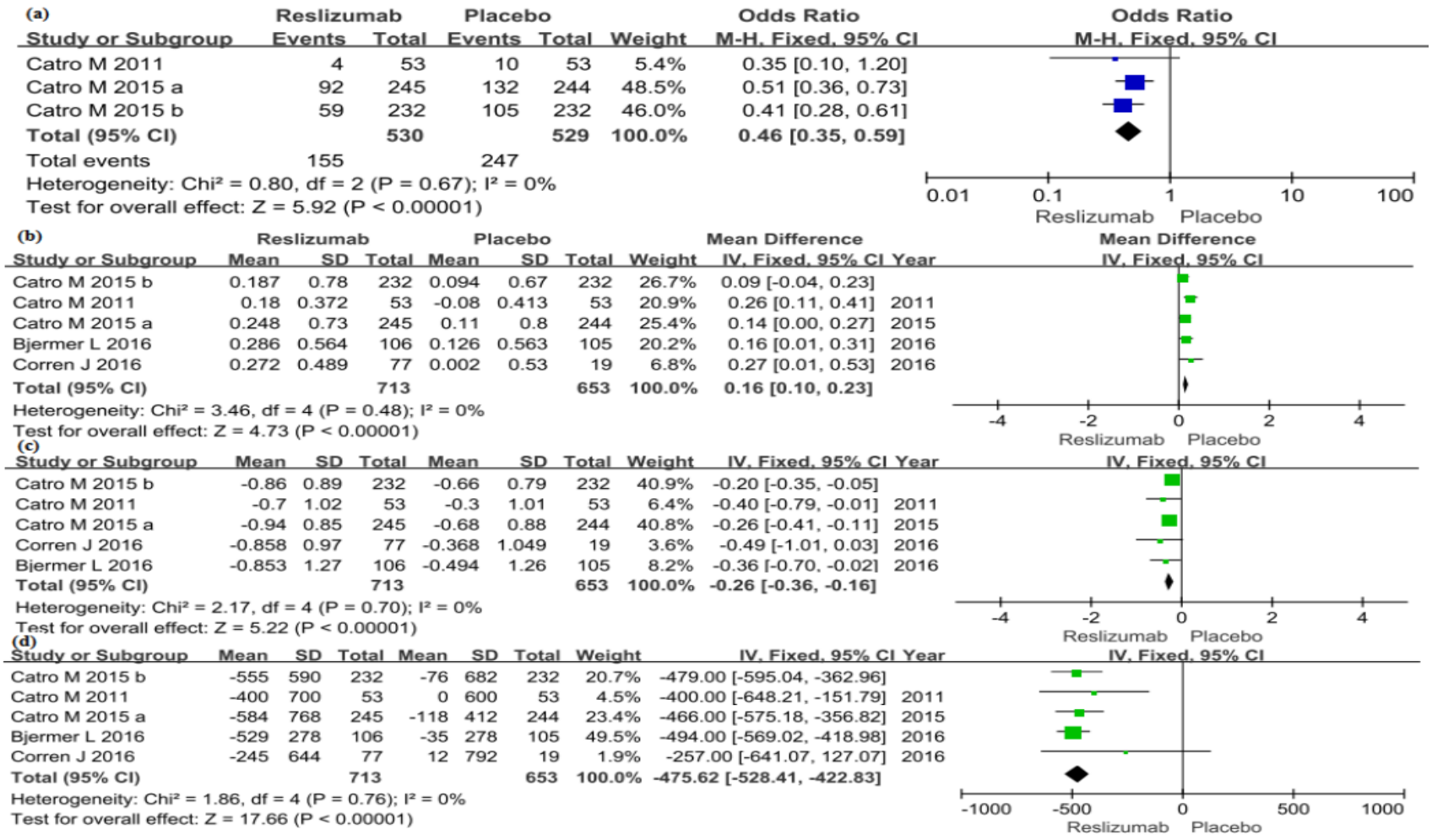
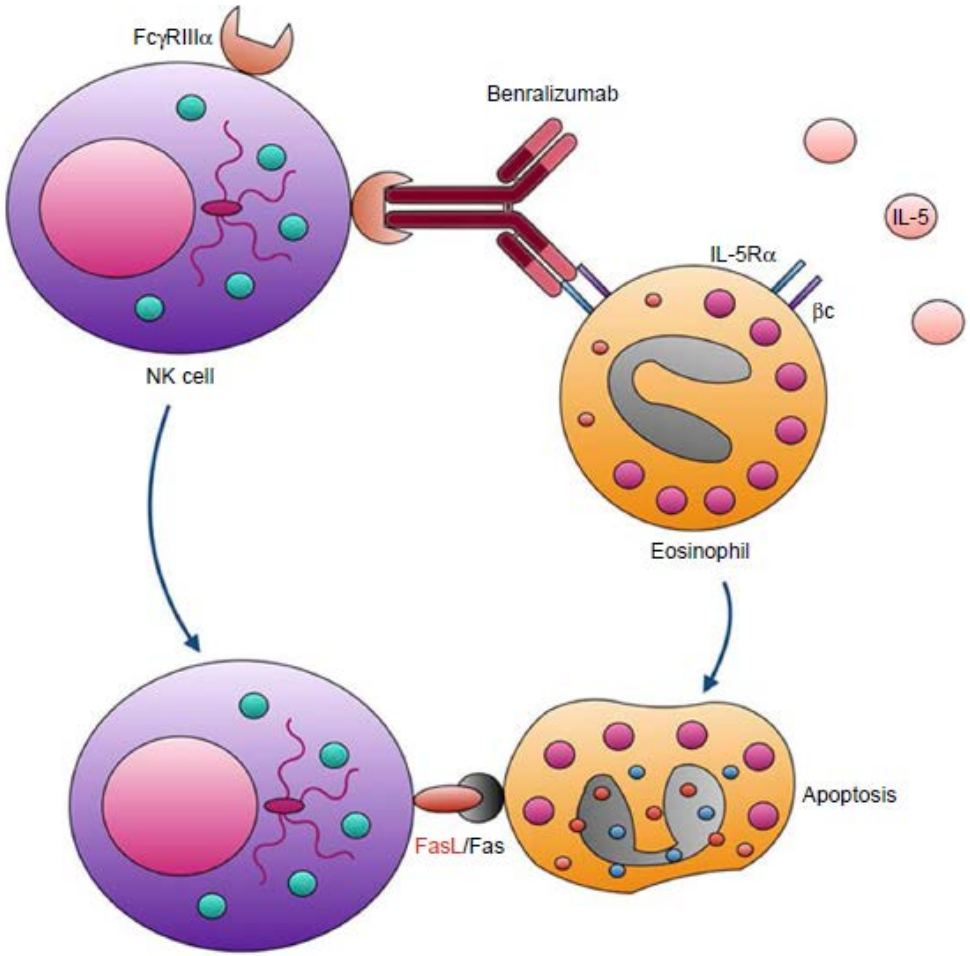


Figure 3 Forest plots showing changes in (a) asthma exacerbation , (b) FEV1, (c) ACQ score and (d) blood eosinophil counts in the treatment studies. FEV1: a forced expiratory volume in 1 s, ACQ: Asthma Control Questionnaire,

Benralizumab



Pelaia C et al. Drug Design, Development and Therapy 2018:12 619–628

Benralizumab

Table 1 Benralizumab: summary of the main pre-marketing clinical trials

Authors	Duration	Dosage	Main results
Laviolette et al 2013[55]	12 weeks	100 and 200 mg	Lower numbers of blood eosinophils
Castro et al 2014[58]	52 weeks	2, 20, and 100 mg	Fewer asthma exacerbations, lower numbers of blood eosinophils
Nowak et al 2015[59]	12 weeks	0.3 and 1 mg/kg	Fewer asthma exacerbations, lower serum levels of ECP and EDN
Park et al 2016[57]	52 weeks	2, 20, and 100 mg	Fewer asthma exacerbations, higher FEV_1
Bleecker et al 2016[61] SIROCCO	48 weeks	30 mg	Fewer asthma exacerbations, higher FEV_1
FitzGerald et al 2016[62] CALIMA	56 weeks	30 mg	Fewer asthma exacerbations, higher FEV_1
Nair et al 2017[63] ZONDA	28 weeks	30 mg	Lower intake of oral corticosteroids, fewer asthma exacerbations
Ferguson et al 2017[64] BISE	12 weeks	30 mg	Lower numbers of blood eosinophils

Pelaia C et al. Drug Design, Development and Therapy 2018:12 619–628

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

Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators*

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

J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators*

- **İlk Faz 3 çalışmalar**
- **1205/1306 ağır, ağır, kontrolsüz astımlı, (28 ülke)**
- **Yüksek doz IKS+LABA rağmen**
  - **(≥2 astım atağı/bir önceki yıl), 12-75 yaş**
- **Eozinofil: ≥300/µL veya ≤ 300 µL (2:1).**
- **Benralizumab 30 mg, sc, 48 hf**

İlk 3 DOZ: 30 mg/4 hf,
30 mg/4 hf (Q4W)
30 mg/8 hf (Q8W)
placebo (1:1:1)

Lancet. 2016: 5. pii: S0140-6736(16)31322-8.

CALIMA ve SIROCCO karşılaştırma

Yüksek doz IKS+LABA +≥300 eozinofil

	CALIMA		SIROCCO[28]	
	Benralizumab Q4W	Benralizumab Q8W	Benralizumab Q4W	Benralizumab Q8W
Annual rate of exacerbations	↓ 36%	↓ 28%	↓ 45%	↓ 51%
Prebronchodilator FEV_1 (L)	↑ 0·125	↑ 0·116	↑ 0·106	↑ 0·159
Total asthma symptom score (score 0–6)‡	↓ 0·12§	↓ 0·23	↓ 0·08§	↓ 0·25

FEV_1=forced expiratory volume in 1 s. Q4W=once every 4 weeks. Q8W=once every 8 weeks (first three doses Q4W). *See Bleecker and colleagues.[28] †All results are differences from placebo; week 56 results presented for CALIMA and week 48 results presented for SIROCCO. ‡Reduced score indicates improvement. §Non-significant.

Table 5: Efficacy results for patients receiving high-dosage ICS plus LABA with baseline blood eosinophils ≥300 cells per µL in the CALIMA and SIROCCO studies*†

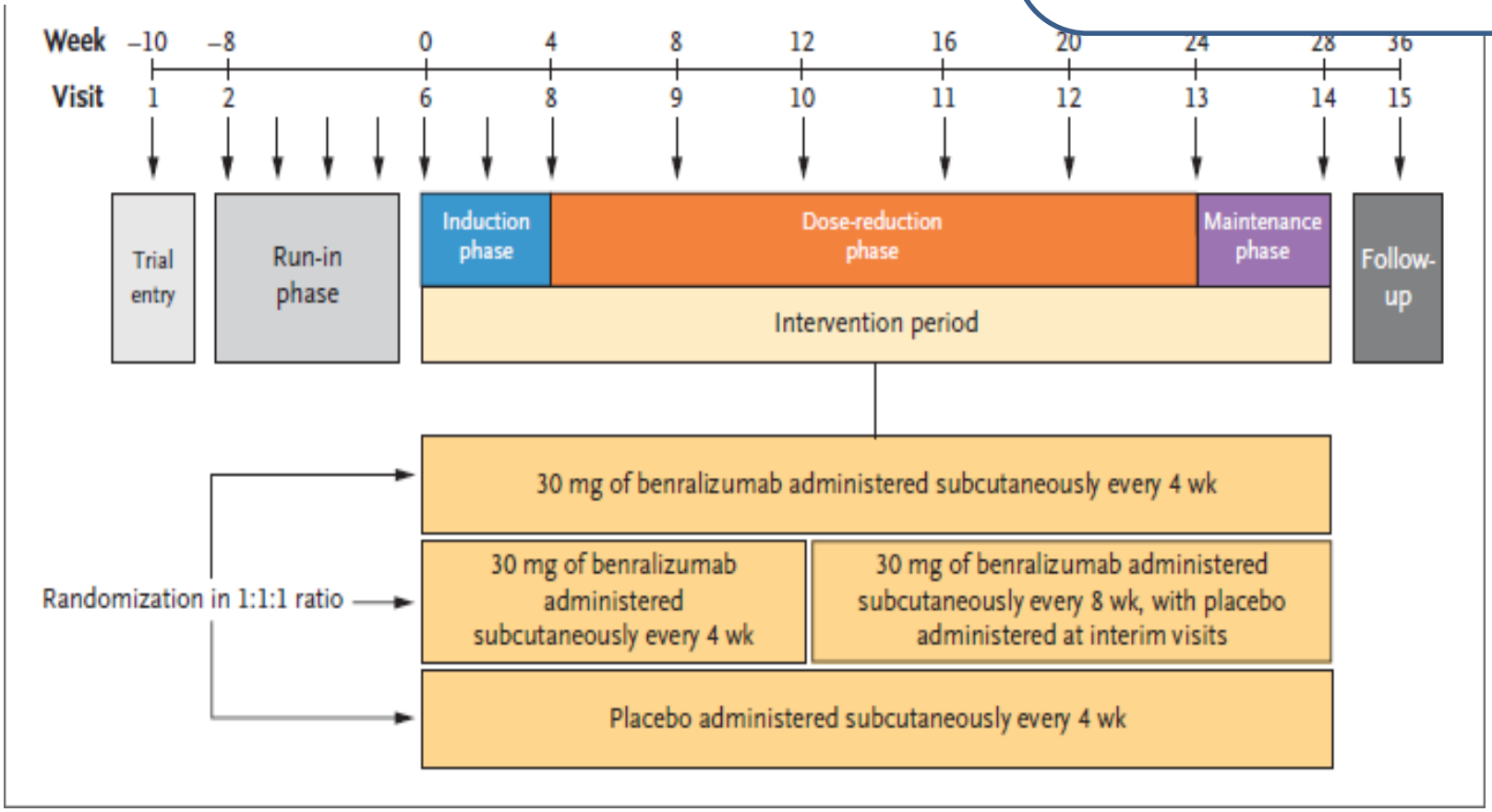
Lancet. 2016; 5. pii: S0140-6736(16)31322-8

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

Eozinofil: ≥150/µL, %15
Eozinofil: ≥300/µL, %85
Orta-Yük.doz IKS+LABA
OKS:7.5 to 40.0 mg/gün, en az 6 aydır



NEJM. 2017; DOI: 10.1056/NEJMoa1703501

ORIGINAL ARTICLE

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (–5.4 to 93.4)	18.2 (–3.0 to 126.0)	22.6 (–3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

NEJM. 2017; DOI: 10.1056/NEJMoa1703501

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

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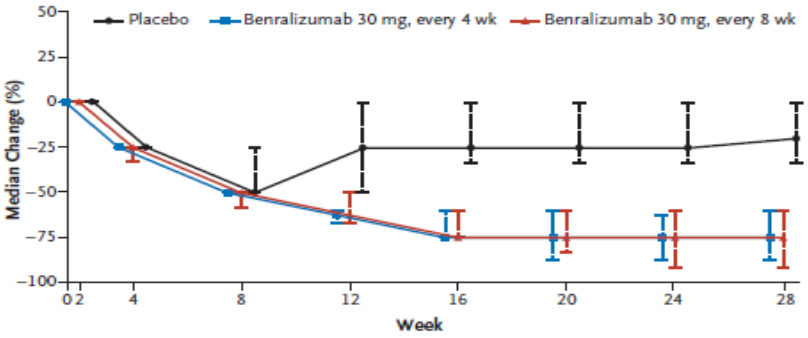
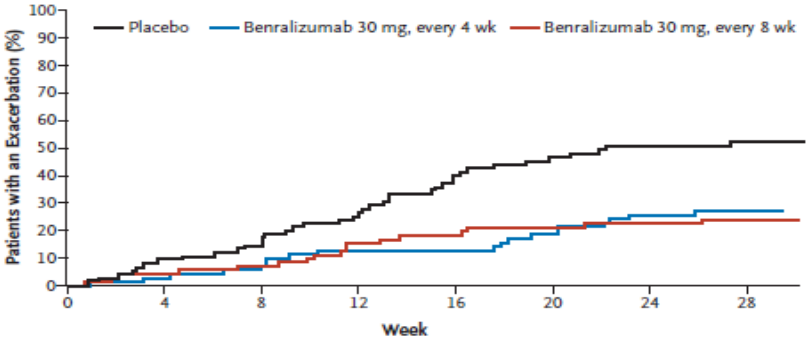
A Change from Baseline in Oral Glucocorticoid Dose



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

B Time to First Asthma Exacerbation



No. at Risk								
Benralizumab 30 mg, every 4 wk	72	69	67	62	61	56	51	45
Benralizumab 30 mg, every 8 wk	73	68	66	60	58	56	55	51
Placebo	75	68	64	56	45	40	37	31

OKS

Benra: OKS final doz: %75 azalmış

%56-%52 OKS tümüyle kesilmiş

Pl: OKS final doz: %25 azalmış

%15 OKS tümüyle kesilmiş

ATAKLAR

4 hf ara ile: %55 azalmış (vs. pl, P = 0.003)

8 hf ara ile: %70 azalmış (vs. pl, P <0.001)

NEJM. 2017; DOI: 10.1056/NEJMoa1703501

Front. Med. 2018, 12(3): 340–349
https://doi.org/10.1007/s11684-017-0565-0

Efficacy and safety of benralizumab in patients with eosinophilic asthma: a meta-analysis of randomized placebo-controlled trials

Table 1 Characteristics of the randomized controlled trials included in the meta-analysis

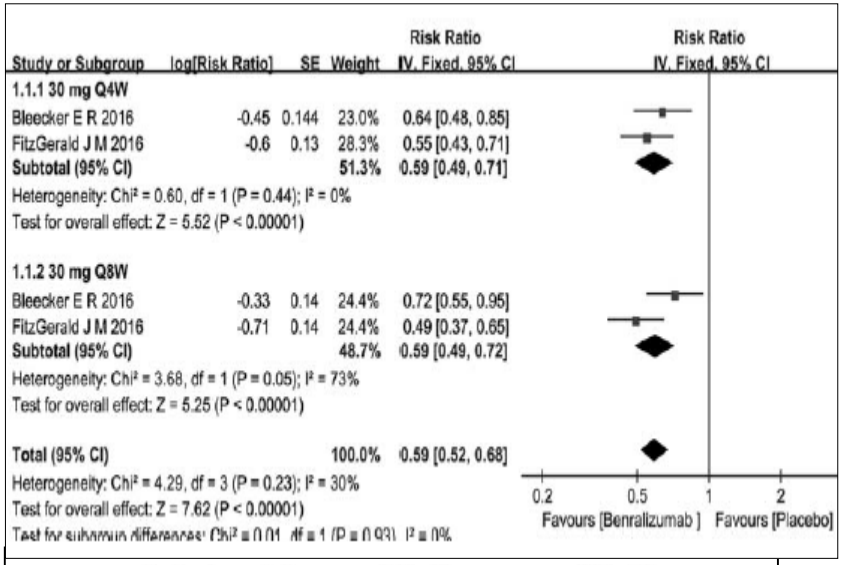
Reference	Study design	No. of subjects (treatment /placebo)	Age (year)	Doses of benralizumab used	Routine	Treatment duration	Outcomes	Follow-up
Laviolette *et al.*, 2013 [21] [a]	mRCT	4/5	18–65	100 mg Q4W	SC	8 weeks	Blood, sputum eosinophils; adverse events	20 weeks
Castro *et al.*, 2014 [22] [b]	mRCT	244/80	18–75	2, 20, 100 mg Q8W	SC	52 weeks	Blood eosinophils; asthma exacerbations; FEV1	52 weeks
Park *et al.*, 2016 [23] [b]	mRCT	60/21	20–75	2, 20, 100 mg Q8W	SC	40 weeks	Blood eosinophils; asthma exacerbations; FEV1; PEF; ACQ-6	52 weeks
FitzGerald *et al.*, 2016 [24] [b]	mRCT	480/248	12–75	30 mg Q4W or 30 mg Q8W	SC	56 weeks	Asthma exacerbations; FEV1; ACQ-6; AQLQ	56 weeks
Bleecker *et al.*, 2016 [14] [a]	mRCT	542/267	12–75	30 mg Q4W or 30 mg Q8W	SC	48 weeks	Asthma exacerbations; FEV1; ACQ-6; AQLQ	48 weeks

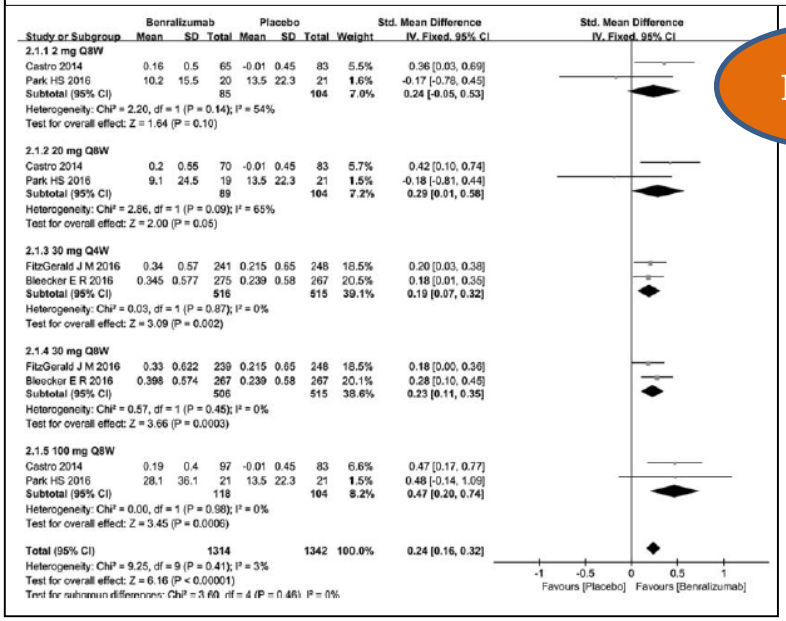
1951 hasta
>300 eozinofil
ZONDA alınmamış

Front. Med. 2018, 12(3): 340–349
https://doi.org/10.1007/s11684-017-0565-0

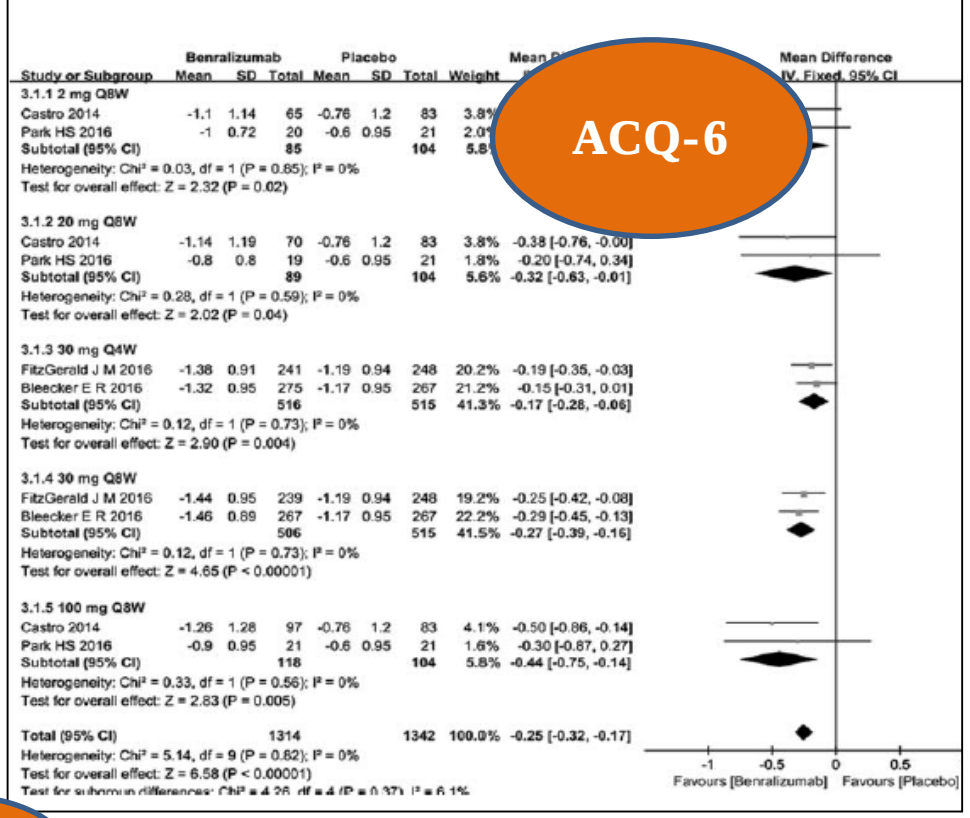
Atak

Efficacy and safety of benralizumab in patients with eosinophilic asthma: a meta-analysis of randomized placebo-controlled trials

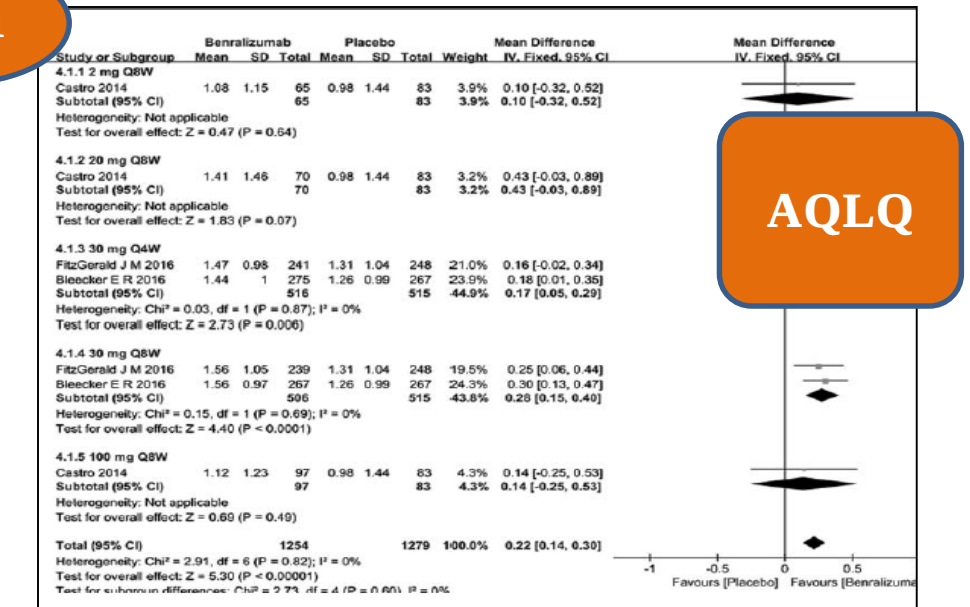




FEV1

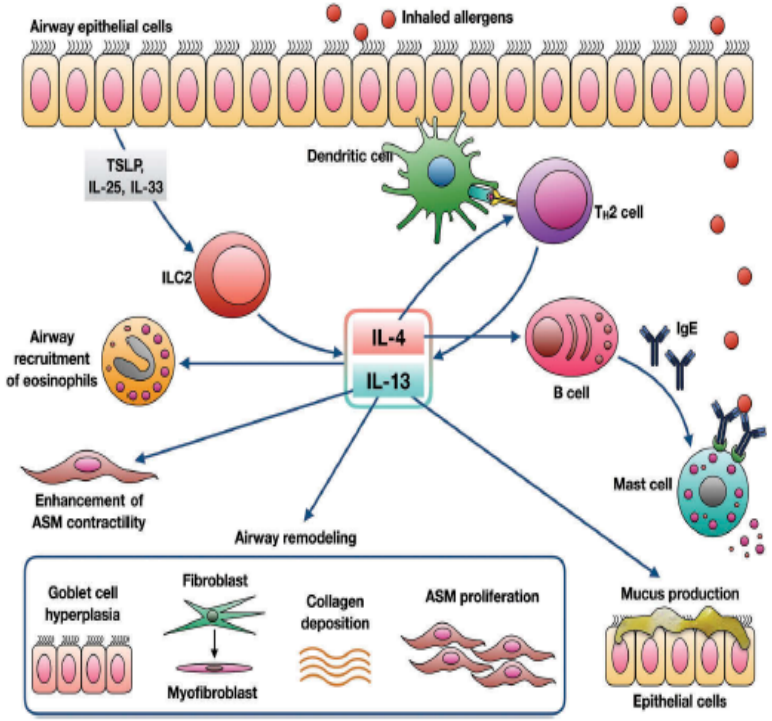


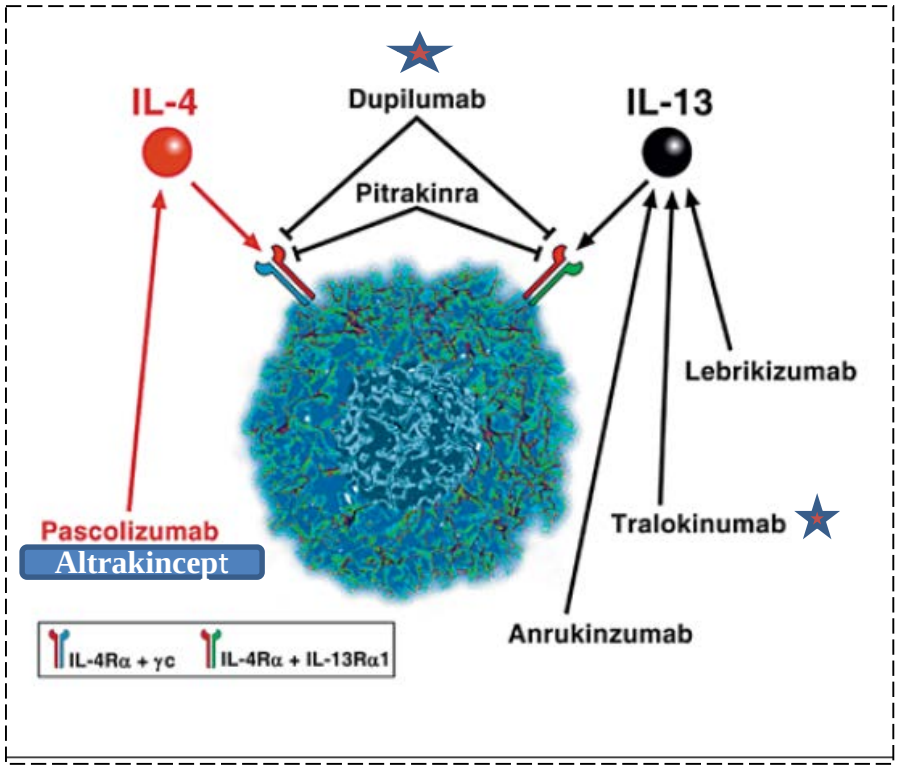
ACQ-6



AQLQ

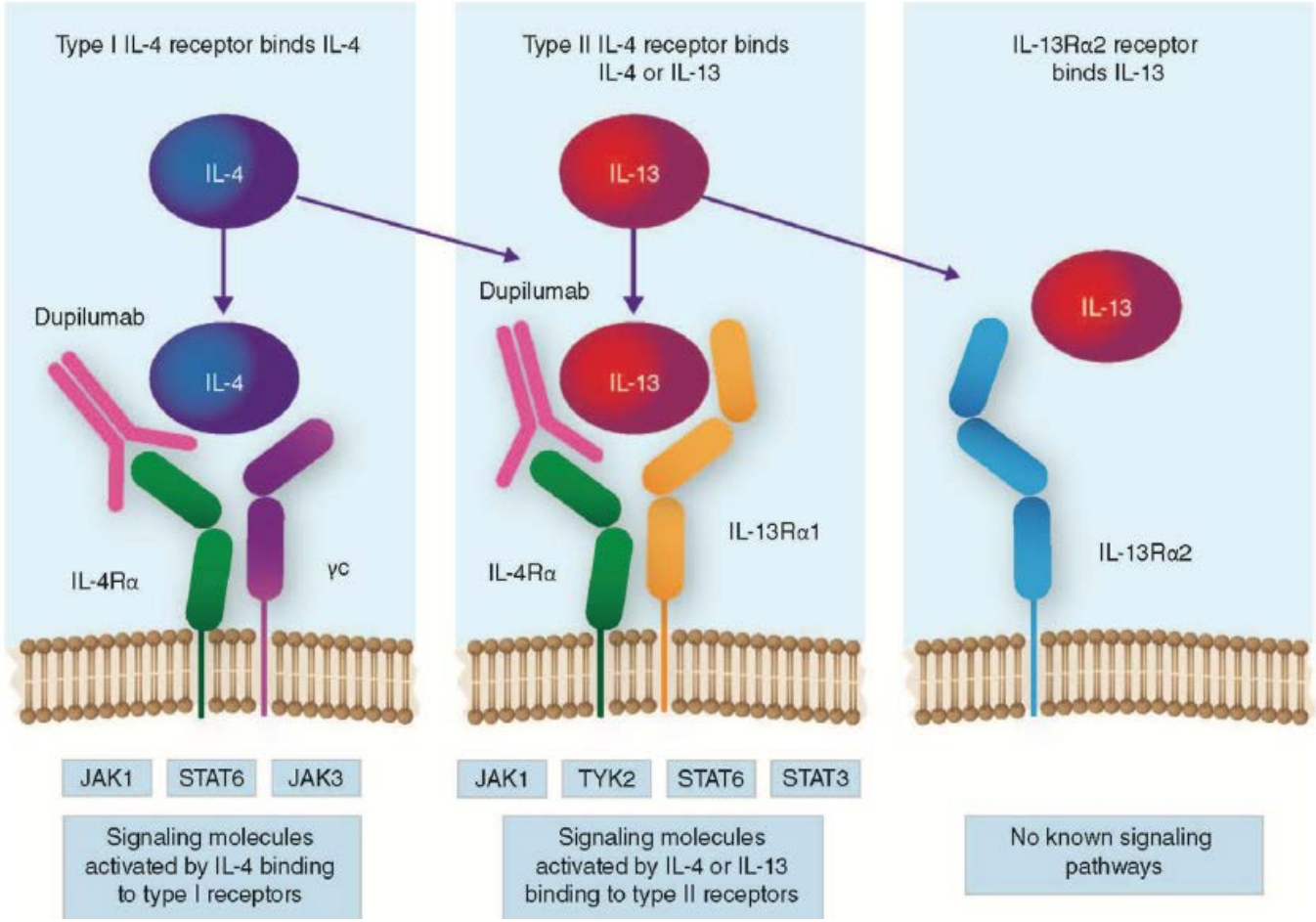
IL-4 ve IL-13
Anti IL-4/Anti IL-13





Pelaiaa C, et al. EXPERT OPINION ON BIOLOGICAL THERAPY, 2017

Dupilumab (Anti IL-4R MoAb)



J ;2016;75: 506-15

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

200 mg/2 hf,
İlk gün: 400 mg yükleme dozu
300 mg/2 hf,
İlk gün: 600 mg yükleme dozu
sc, 52 hf

Table 1. Selected Baseline Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
FE_{NO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	43?±747

DOI: 10.1056/NEJMoa180409215

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

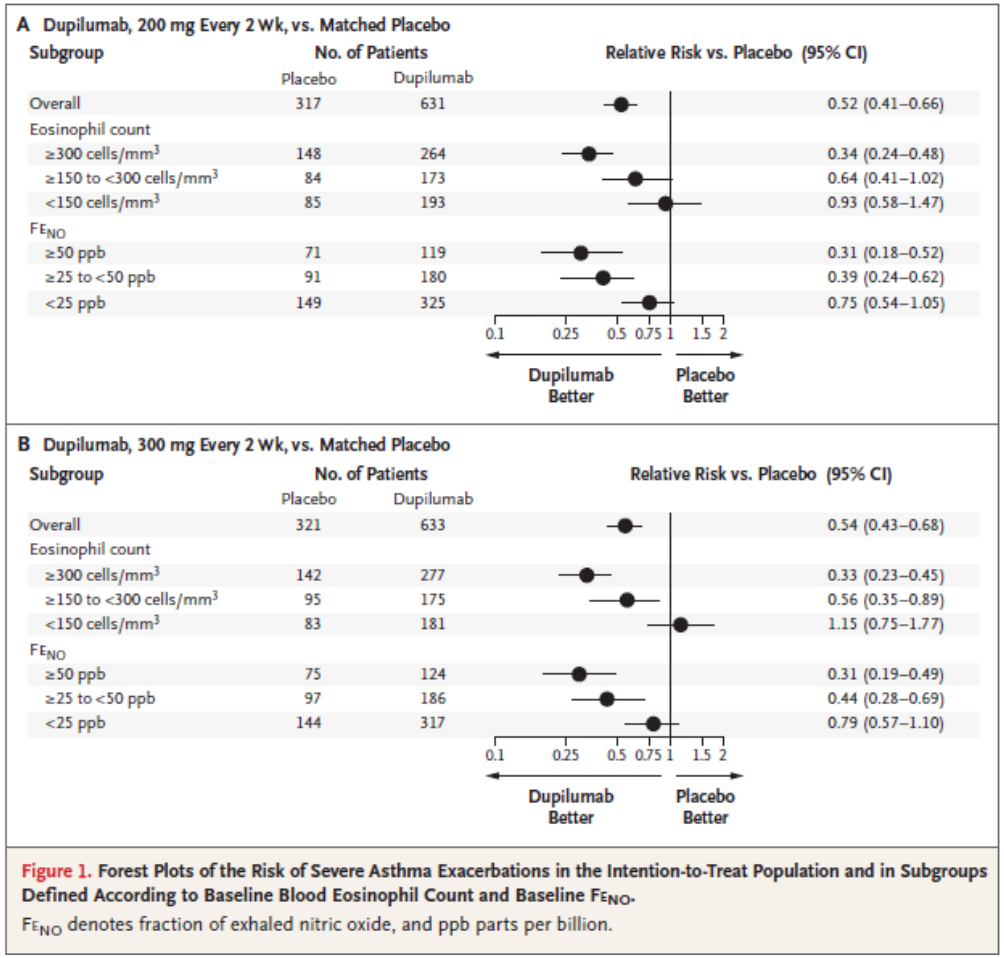


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FE_{NO}.

FE_{NO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

200 mg/2 hf,
300 mg/2 hf,
sc,
52 hf

Ataklar

***200 mg/2 hf:**
%47 azalma (vs. pl)
>300 eoz: %65
150-300: %35.6
<150 eoz: pl benzer

***300 mg/2 hf:**
%52 azalma (vs. pl)
>300 eoz: %67
150-300 eoz: %44.3
<150 eoz: pl benzer

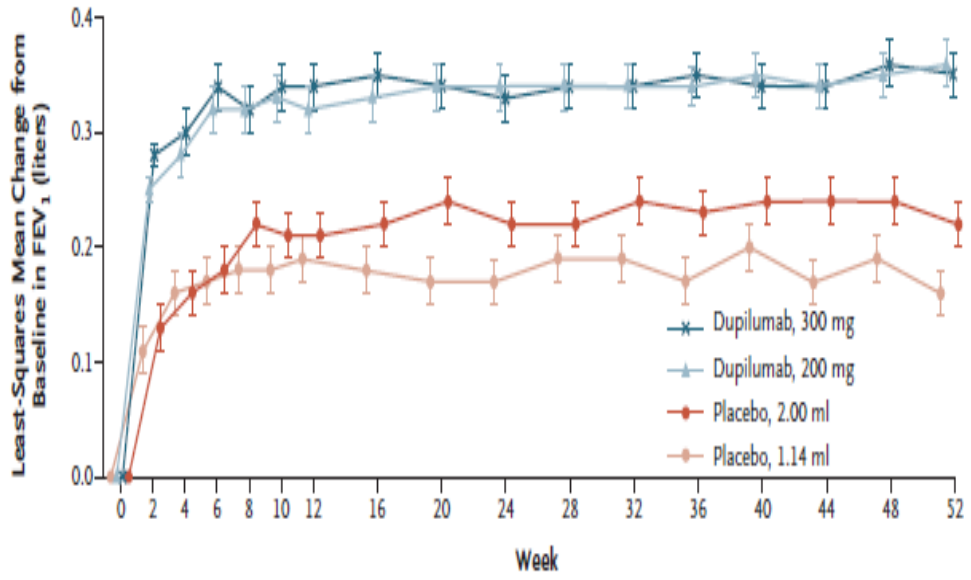
DOI: 10.1056/NEJMoa1804092

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper



No. at Risk

Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

FEV1

2.hf da etkili

12. hf da

***200 mg/2hf:**

0.32 litre artmış (Pl: 0.18 litre)

***300 mg/2hf**

0.34 litre

(Pl: 0.13 litre)

(Tüm parametreler için)

En etkin olduğu hastalar

>150 eoz+

FeNO of ≥25 ppb

DOI: 10.1056/NEJMoa1804092

ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D.,

Faz III,
İlk gün: 600 mg yükleme dozu
300 mg/2 hf,
sc,
24 hf

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo Group (N = 107)	Dupilumab Group (N = 103)	Total (N = 210)
Age — yr	50.7±12.8	51.9±12.5	51.3±12.6
Male sex — no. (%)	42 (39)	41 (40)	83 (40)
No. of severe asthma exacerbations in previous year	2.17±2.24	2.01±2.08	2.09±2.16
Time since first oral glucocorticoid prescription — yr	1.64±3.54	1.77±3.52	1.70±3.52
Daily oral glucocorticoid dose — mg/day			
Dose before adjustment phase	11.83±6.02	11.79±6.40	11.81±6.20
Adjusted dose	11.75±6.31	10.75±5.90	11.26±6.12
Prebronchodilator FEV_1 — liters	1.63±0.61	1.53±0.53	1.58±0.57
Prebronchodilator FEV_1 — % of predicted value	52.69±15.14	51.64±15.28	52.18±15.18
FEV_1 reversibility — liters†	0.28±0.32	0.29±0.31	0.28±0.31
Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
FE_{NO} — ppb	39.62±34.12	35.55±28.34	37.61±31.38

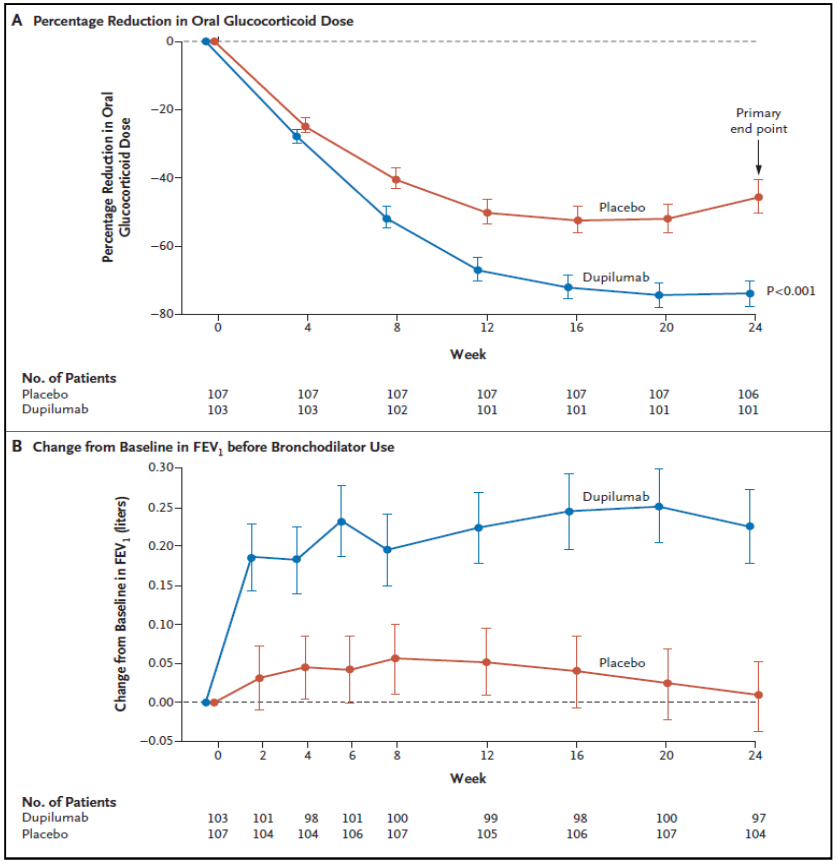
DOI: 10.1056/NEJMoa1804093

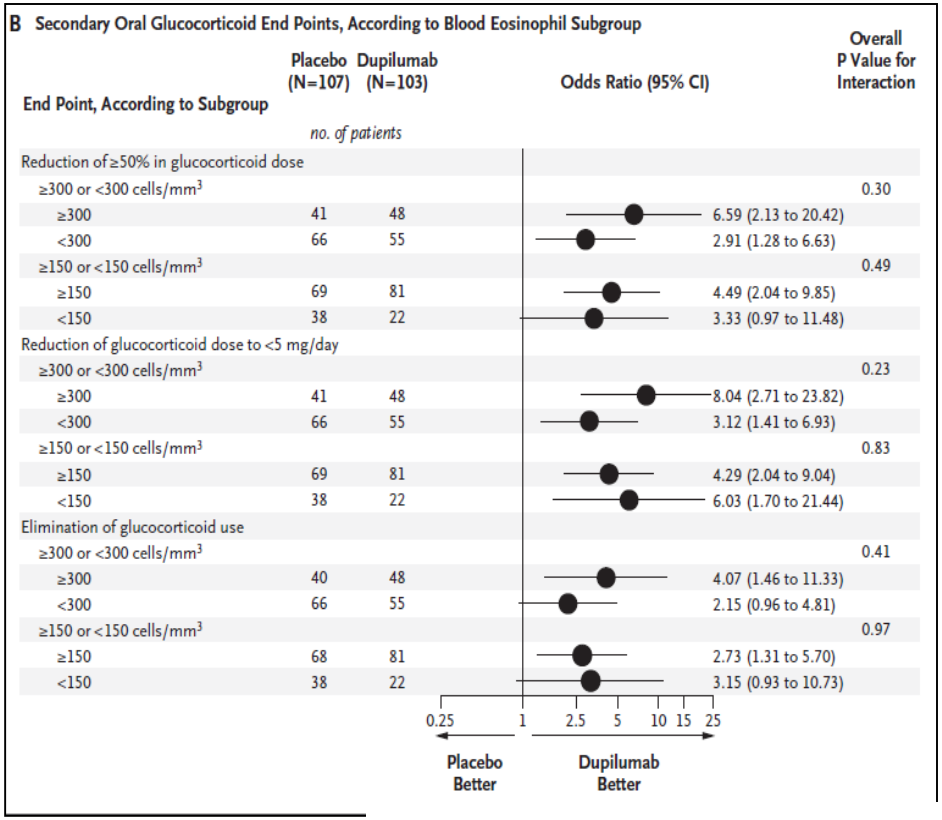
ORIGINAL ARTICLE

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D.,

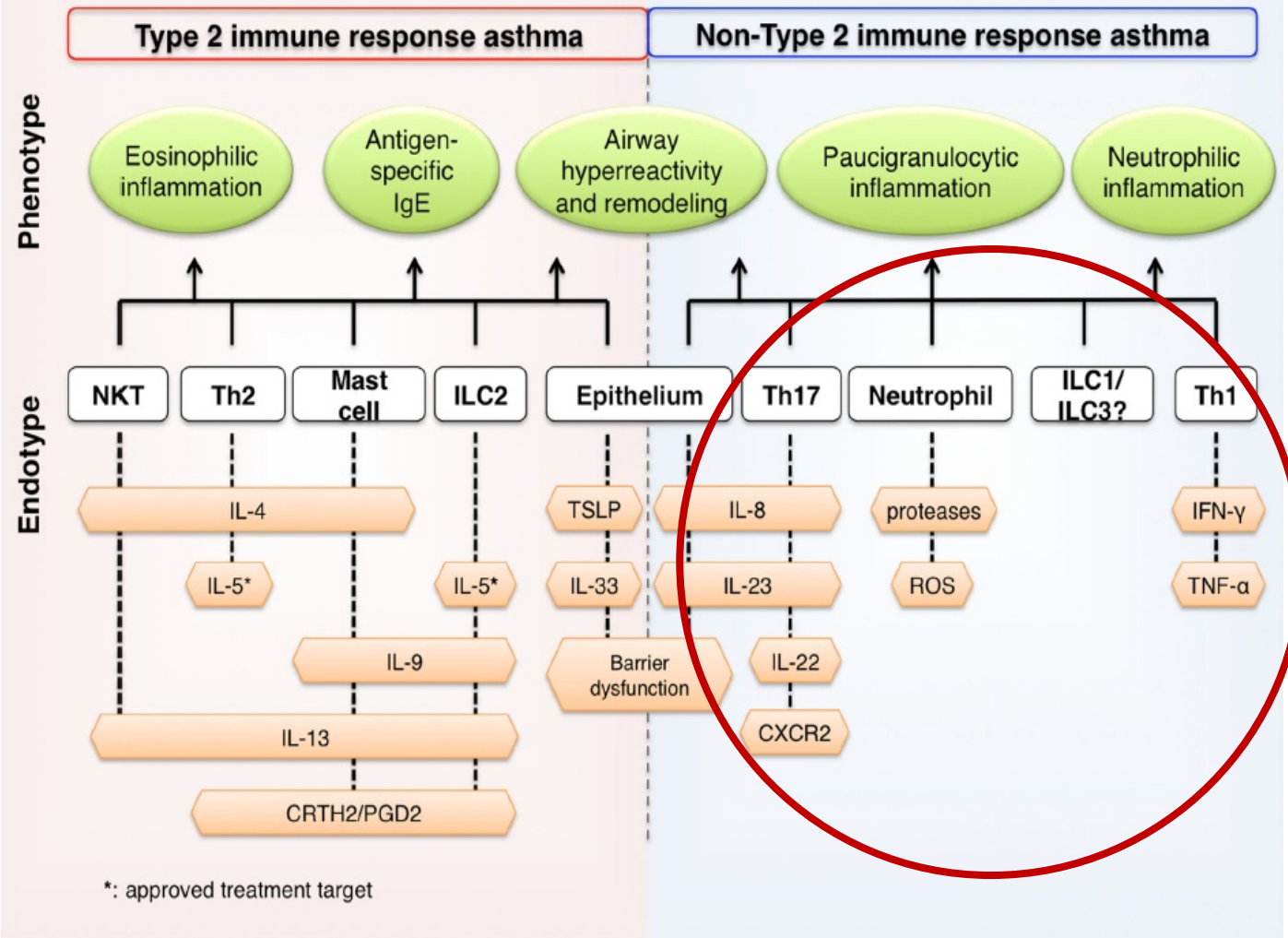
OKS dozu
Dup. %70, Pl %41 azalma..
Ataklar: %59
FEV1 artışı: 220 ml
Eozinofiliden bağımsız ancak >300 eozinofili
FeNO>25 ppb daha etkin
ACQ-5 düzelmiş, FeNO ↓





DOI: 10.1056/NEJMoa1804093

Fenotip ve endotipler



Akdis C et. Curr Allergy Asthma Rep (2016) 16:70

Non T2 astım

- **Anti- TNF-a**
- **Anti-TH-17A/ Anti-TH-17R (Secukinumab/Brodalumab)**
- **Anti GM-CSF**
- **Anti-CXC R2**
- **Makrolid antibiyotikler**
- **Az sayıda çalışma var**

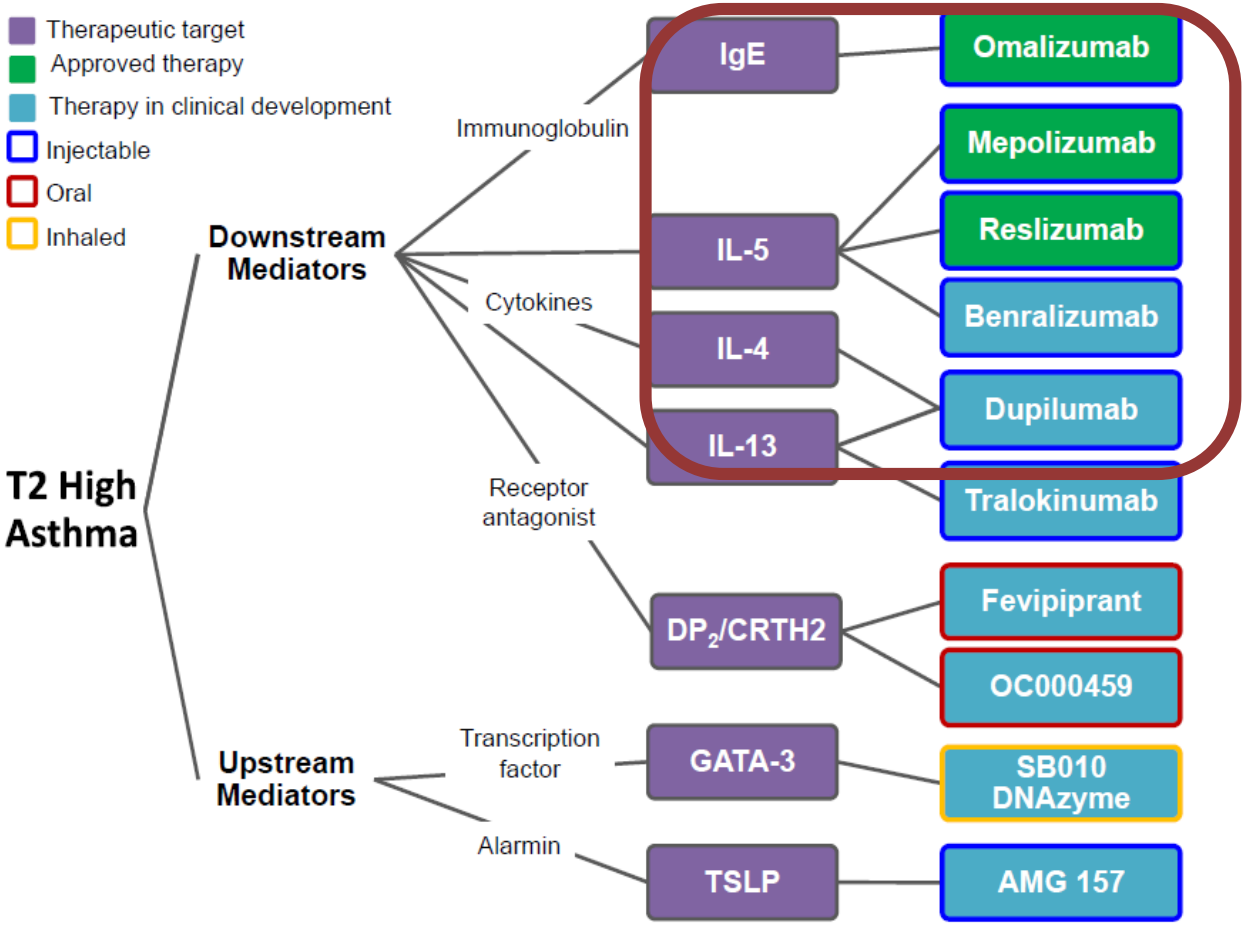
Non T2 astım

- T2 inflamasyonun azlığı bir endotip değil mi?
- Hedef alınan moleküller patofizyolojide önemli değildir !
- Uygun hasta grubu seçilmemiştir!
- Patofizyoloji daha iyi anlaşılmalı

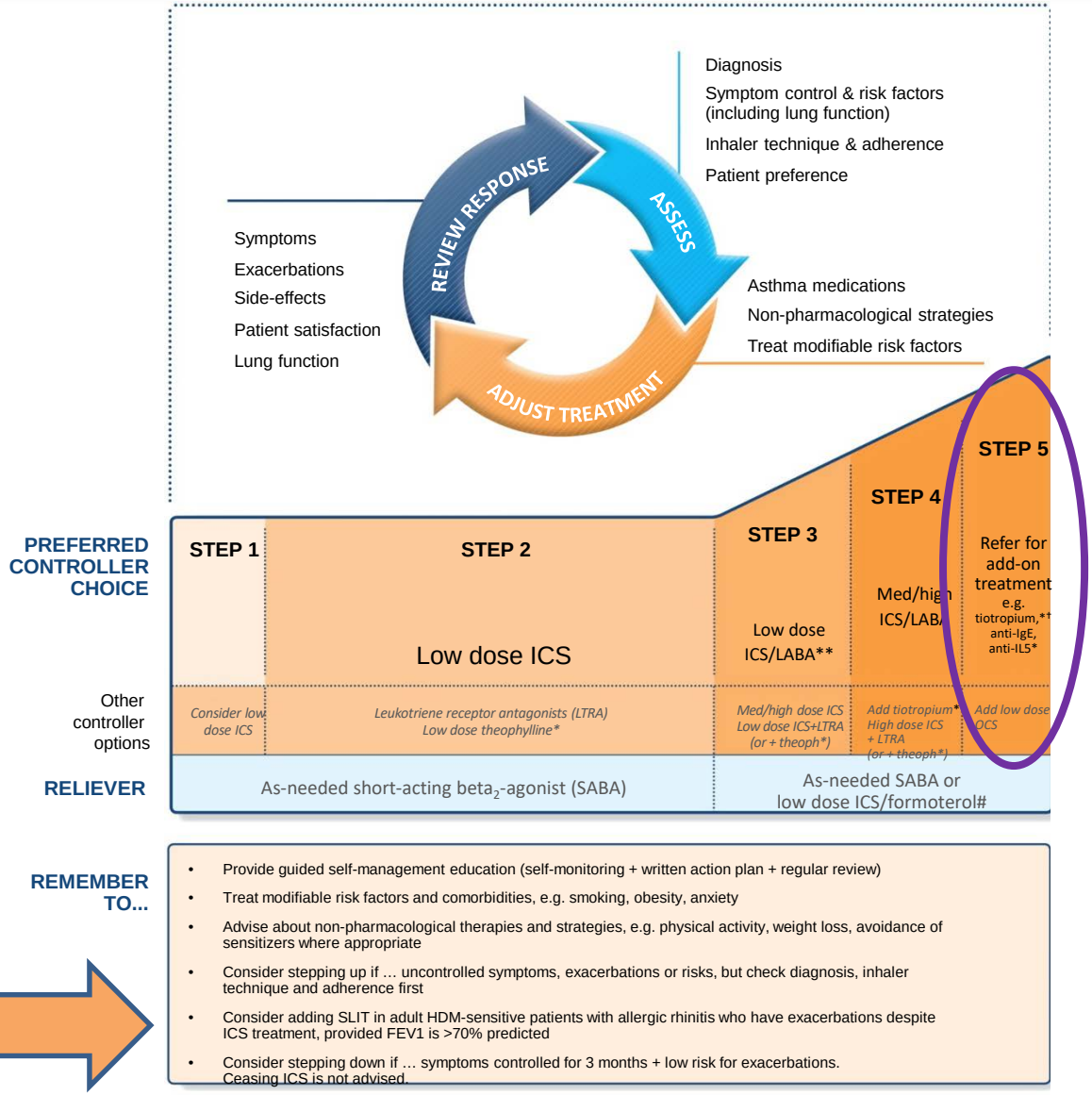
Clinical Commentary Review

Biologic Therapy and Novel Molecular Targets of Severe Asthma

Amber N. Pepper, MD[a], Harald Renz, MD[b], Thomas B. Casale, MD[a], and Holger Garn, PhD[b] *Tampa, Fla; and Marb*
Germany



J Allergy Clin Immunol Pract 2017;5:909-16



SLIT added as an option

Astımda fenotipe göre tedavi seçimi

U-BIOPRED

Table 1 Asthma phenotypes in relation to characteristics

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Genetics	Response to therapy
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases	Specific IgE; T_H2 cytokines; thick SBM	17q12; T_H2-related genes	Corticosteroid-responsive; T_H2-targeted
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic	Corticosteroid-refractory eosinophilia; IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Exercise-induced		Mild; intermittent with exercise	Mast-cell activation; T_H2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear	Lack of T_H2 biomarkers; oxidative stress		Responsive to weight loss, antioxidants and possibly to hormonal therapy
Neutrophilic		Low FEV1; more air trapping	Sputum neutrophilia; T_H17 pathways; IL-8		Possibly responsive to macrolide antibiotics

RESEARCH ARTICLE

Efficacy and Safety of Anti-Interleukin-5 Therapy in Patients with Asthma: A Systematic Review and Meta-Analysis

Fa-Ping Wang[1☯‡], Ting Liu[1☯‡], Zhu Lan[2], Su-Yun Li[3], Hui Mao[1]*

1 Department of Respiratory Medicine, West China Hospital, Sichuan University, Chengdu, 610041, China, **2** Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, 610041, China, **3** Department of Respiratory Medicine, First Affiliated Hospital of Henan College of Traditional Chinese Medicine, Zhengzhou, 450000, China

10 Mepolizumab

5 Reslizumab

5 Benralizumab

Conclusions

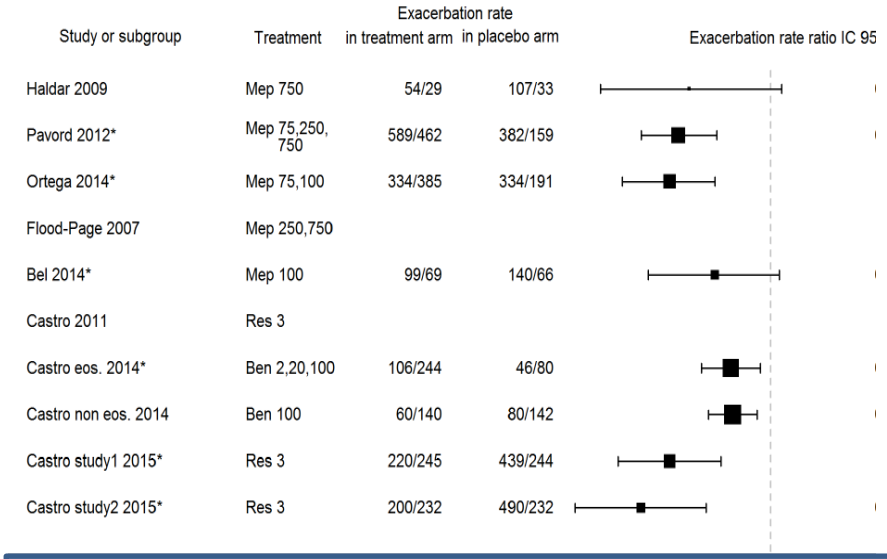
Anti-interleukin 5 monoclonal therapies for asthma could be safe for slightly improving FEV_1 (or FEV_1% of predicted value), quality of life, and reducing exacerbations risk and blood and sputum eosinophils, but have no significant effect on PEF, histamine PC20, and SABA rescue use. Further trials required to establish to clarify the optimal antibody for different patients.

doi: 10.1111/cea.12853
Clinical & Experimental Allergy, **47**, 129–138

SYSTEMATIC REVIEWS AND META-ANALYSIS

Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials

Y. Cabon[1], N. Molinari[1,2], G. Marin[1], I. Vachier[3], A. S. Gamez[3], P. Chanez[4] and A. Bourdin[2,3]



No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available

5 Mepo, 3 Res, 2 Benra

IL- 5s vs. plasebo

ACQ: düzelmiş

Ataklar: azalmış (40%)

FEV1:artmış

Cabon Y. et al. Clin Exp Allergy 2016

Cochrane Library

Cochrane Database of Systematic Reviews

Anti-IL5 therapies for asthma (Review)

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

Cochrane Database Syst Rev. 2017 Sep 21;9:CD010834.

13 çalışma, 6000 hasta, 4 Mepolizumab, 4 Reslizumab, 5 Benralizumab

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.

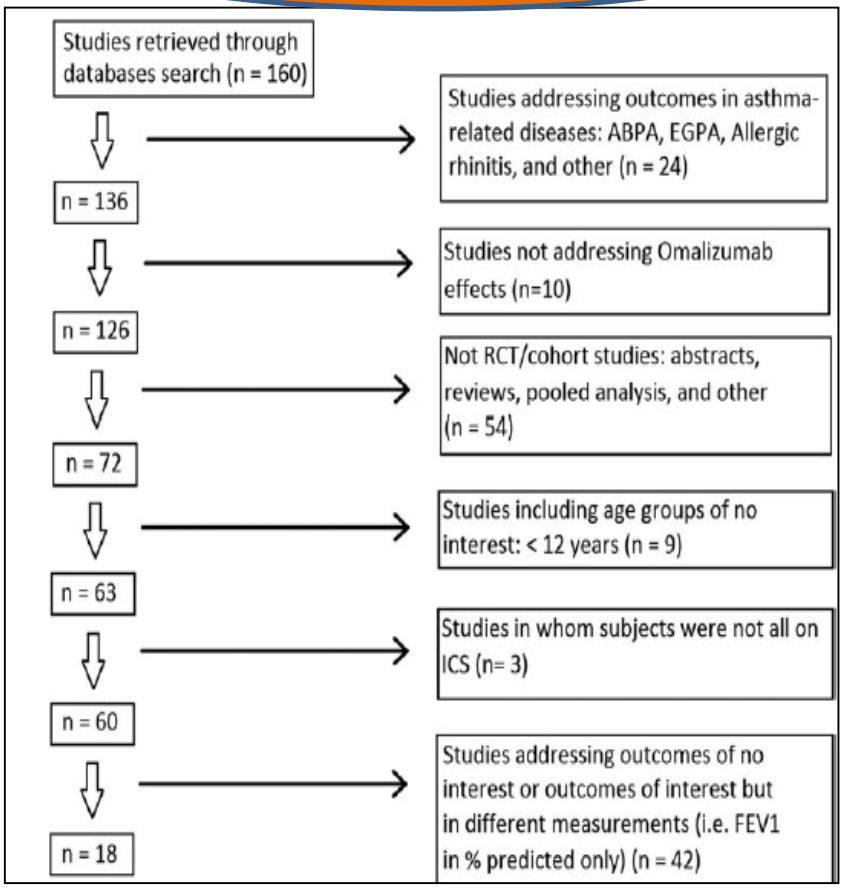
JOURNAL OF ASTHMA
2018, VOL. 55, NO. 1, 89–100
http://dx.doi.org/10.1080/02770903.2017.1306548

Taylor & Francis
Taylor & Francis Group

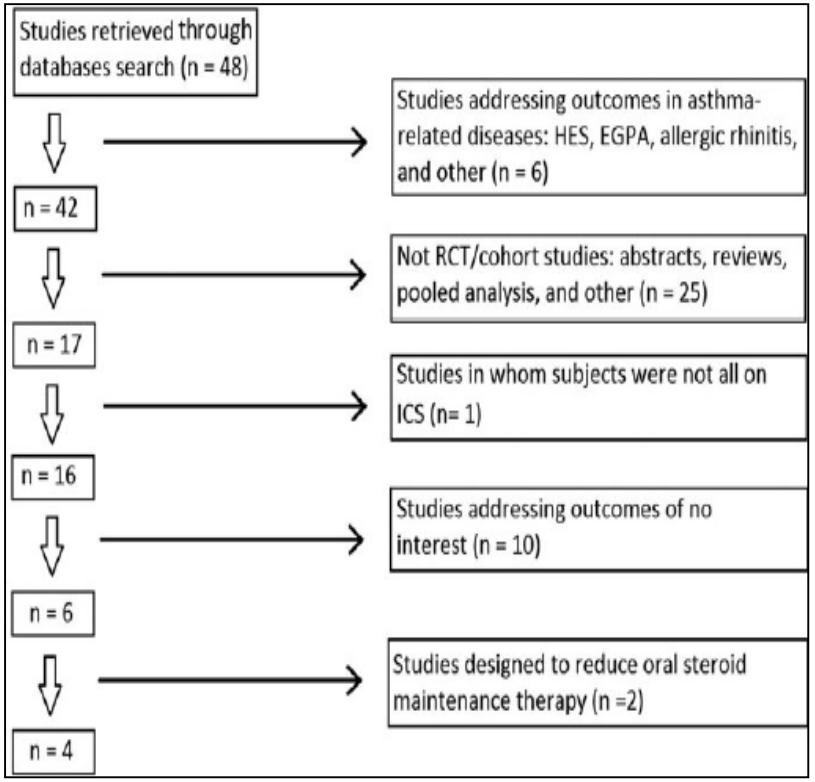
Omalizumab versus Mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: A network meta-analysis

Zahi Nachef, MD[a], Amita Krishnan, MD[b], Terry Mashtare, PhD[c], Tingting Zhuang[c], and M. Jeffery Mador, MD[a]

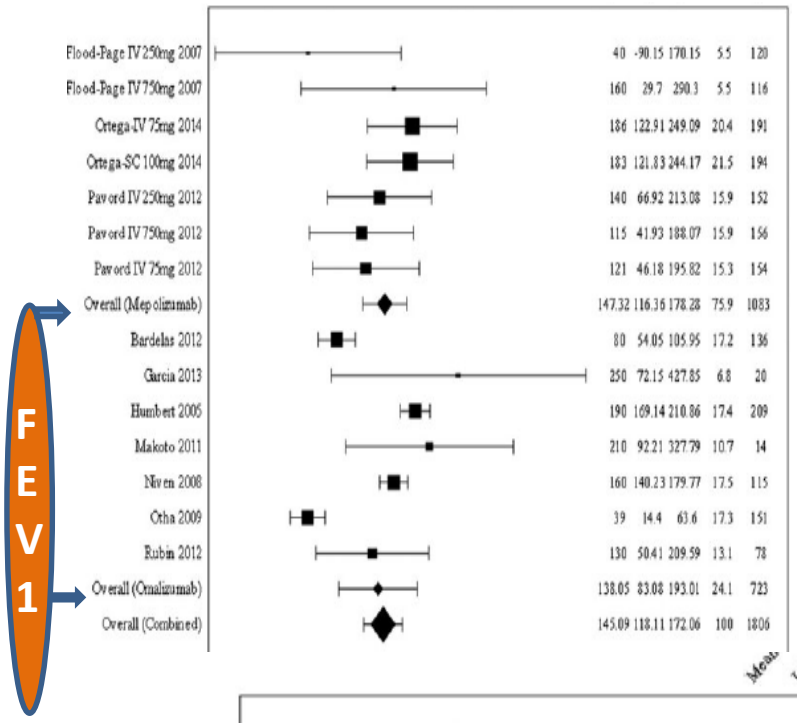
Omalizumab: 18

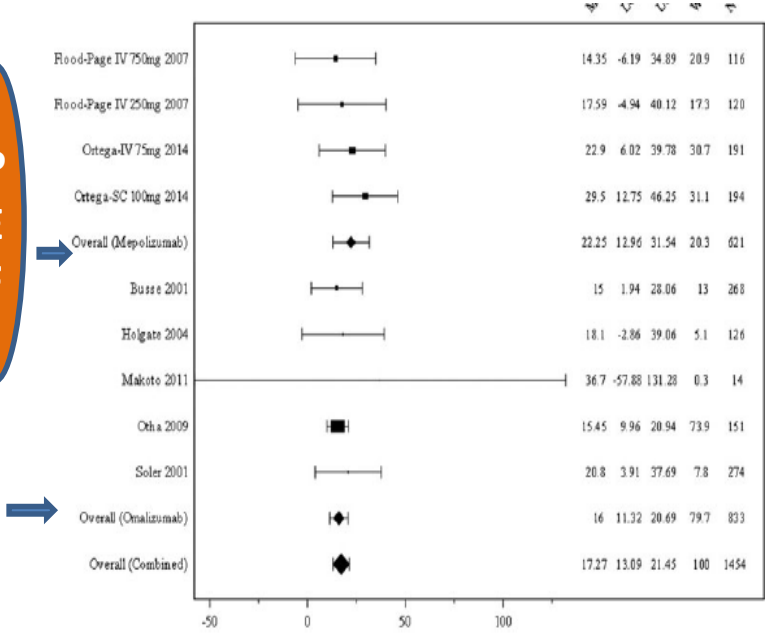


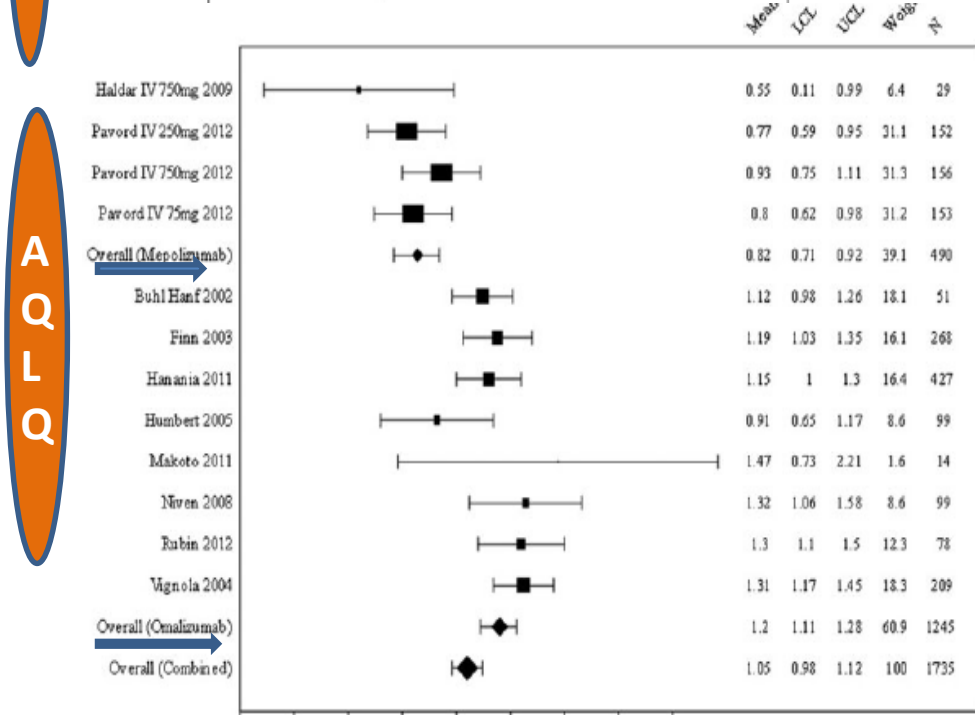
Mepolizumab: 4

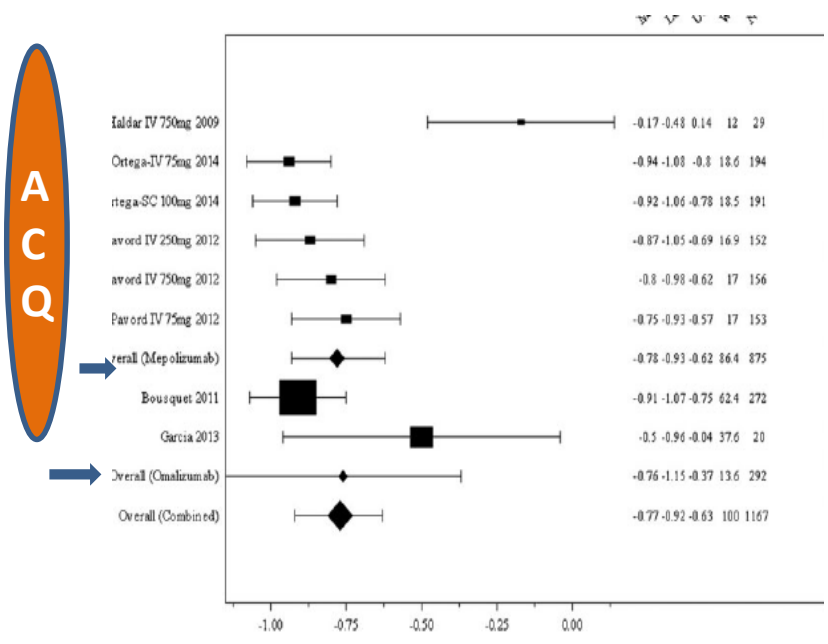


Nachef Z et al. J of Asthma, 2018; 55(1): 89-100



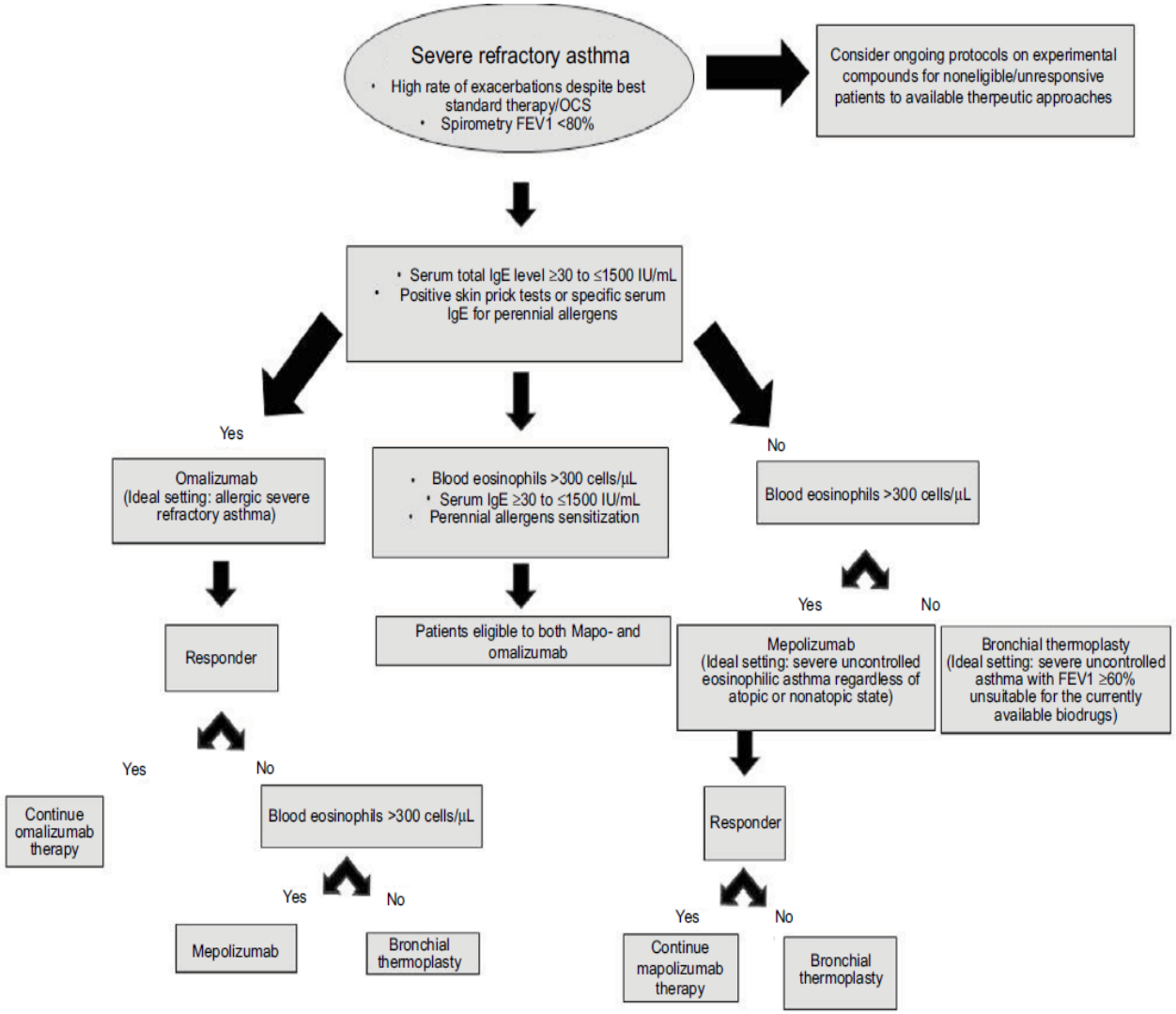






Nachef Z et al. J of Asthma, 2018; 55(1): 89-100

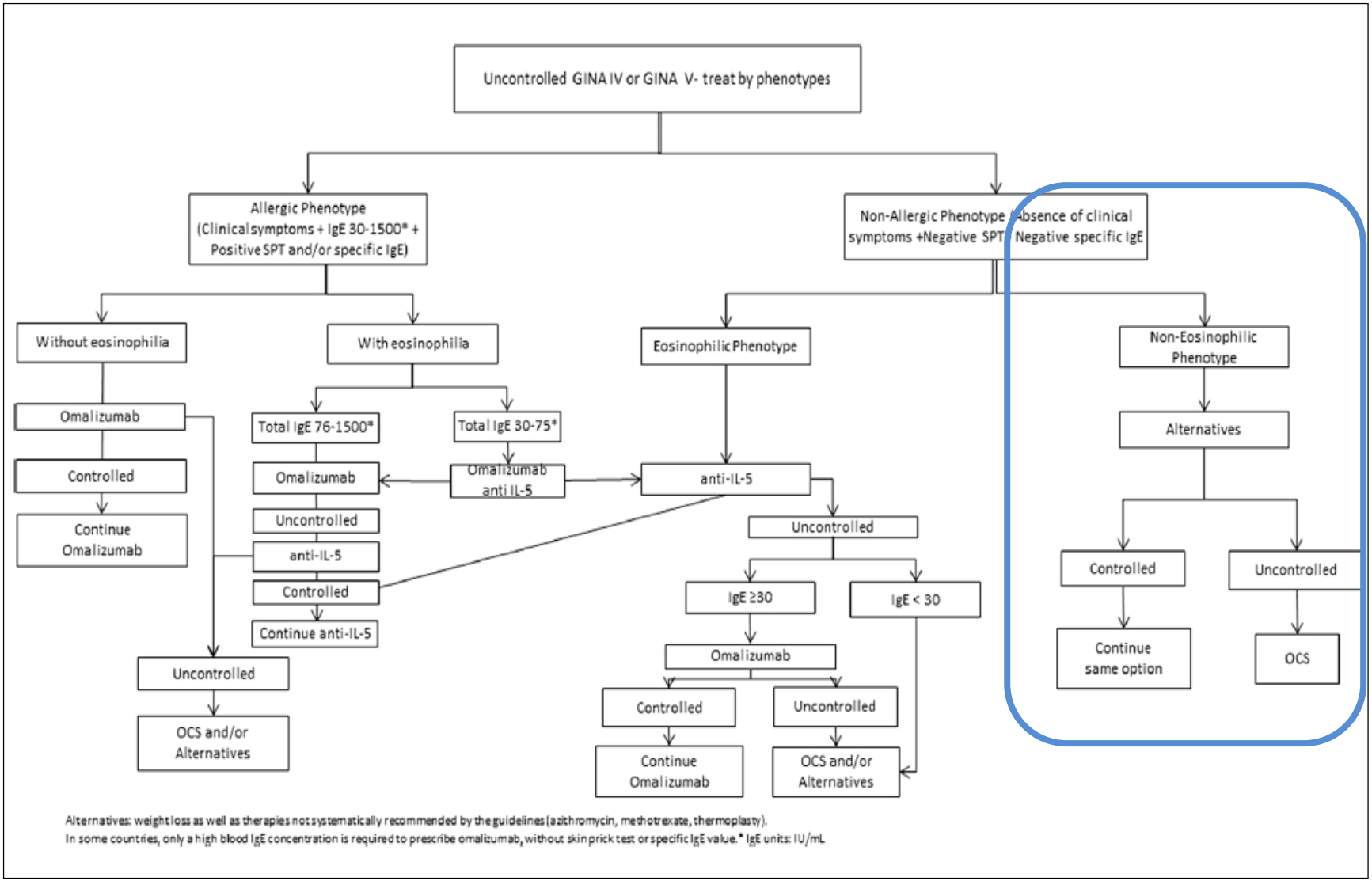
Innovative treatments for severe refractory asthma: how to choose the right option for the right patient?



Menzella F et al. J of Asthma and Allergy 2017:10 237–247

Overlapping Effects of New Monoclonal Antibodies for Severe Asthma

Christian Domingo[1,2]



Drugs, 2017;DOI 10.1007/s40265-017-0810-5

Asthma Endotypes and an Overview of Targeted Therapy for Asthma

*Sarah Svenningsen[1] and Parameswaran Nair[1,2]**

[1] Department of Medicine, McMaster University, Hamilton, ON, Canada, [2] St Joseph's Healthcare, Hamilton, ON, Canada

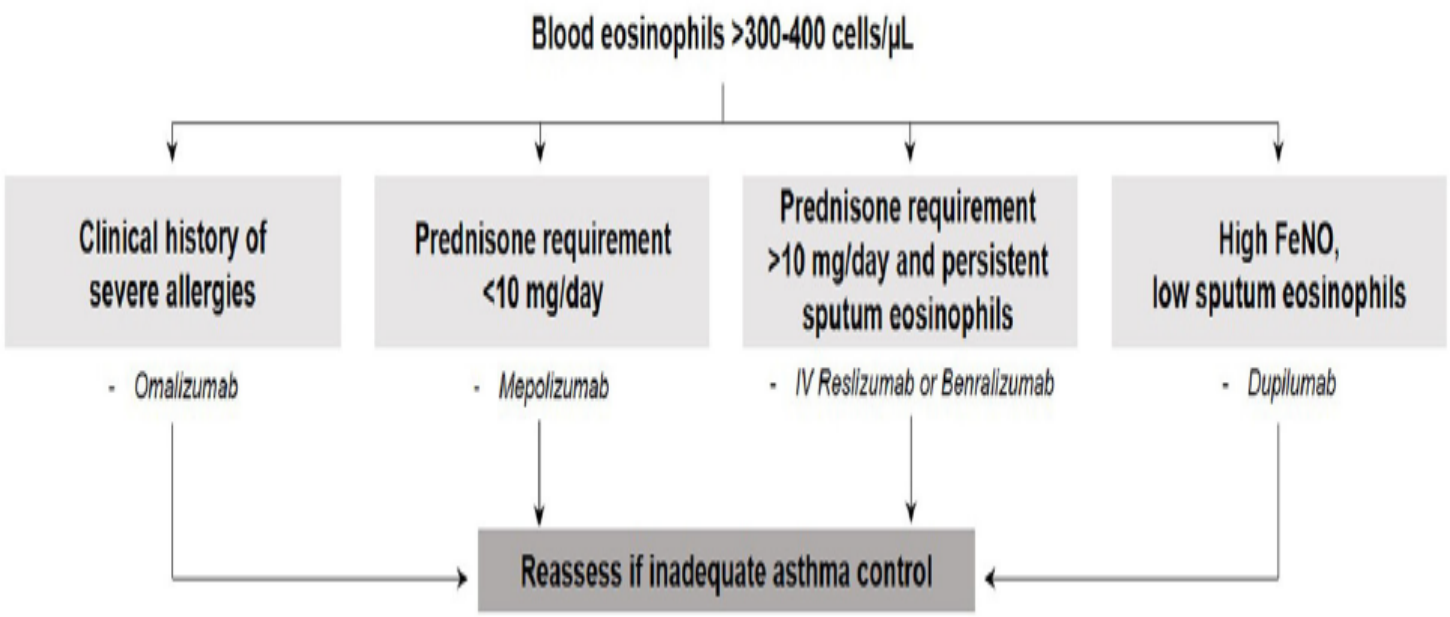
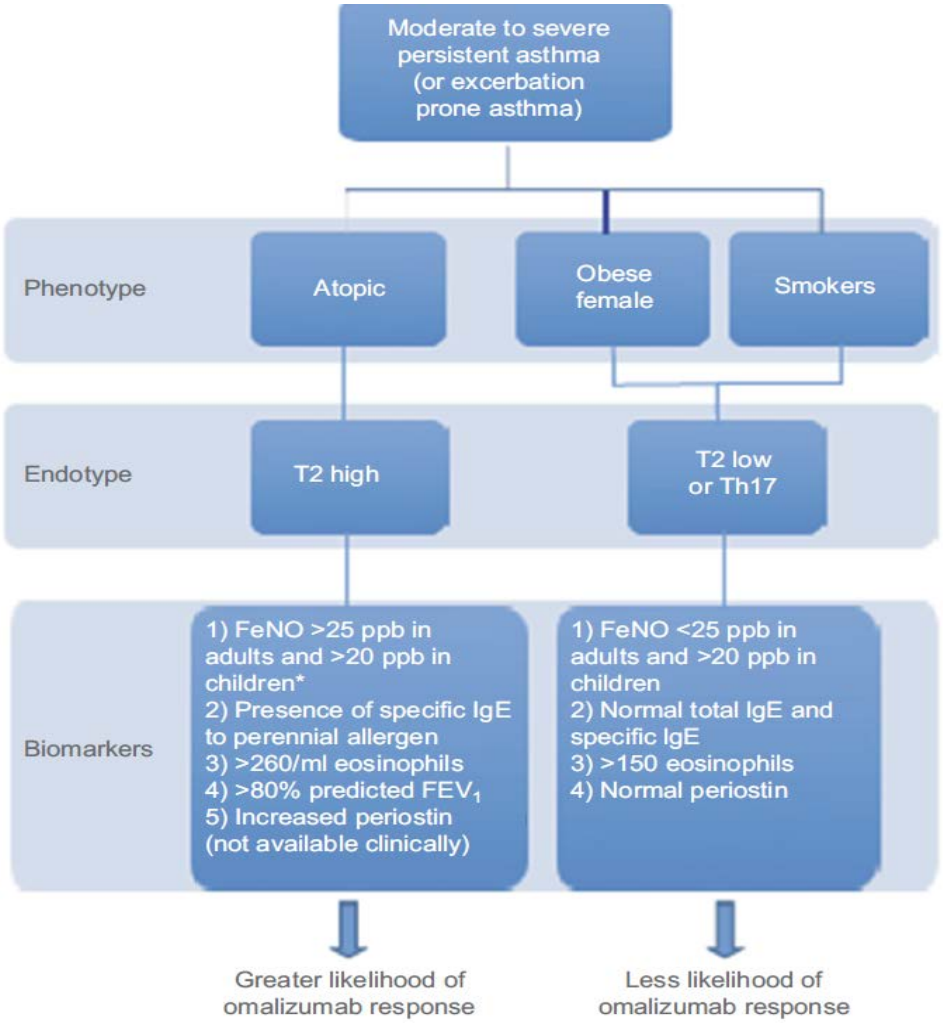


FIGURE 2 | General scheme to choose the appropriate monoclonal antibody based on simple clinical features.

Front. Med. 4:158. doi:10.3389/fmed.2017.00158

Astımda fenotipe göre tedavi seçimi



Dennis K Ledford et al. J Asthma and Allergy 2018:11 53–61

Sonuç-1

- Fenotipik/endotipik heterojenite
- Farklı hedefler aynı fenotipte
- Farklı fenotipte de aynı hedefler olabilir
- Uygun biyomarkerlar

Sonuç-2

- **Biyolojiklerin seçiminde**
  - **Etkinlik**
  - **Maliyet**
  - **Ülkede bulunurluk**
  - **Güvenlik verileri**
  - **Uygulama kolaylığı**

Sonuç-3

- **Biyolojiklerin seçiminde:**
  - **Endüstri etkisi??**
  - **Head-to head çalışmalar**