Tip 2 Ağır Astım Tedavisinde 3 Temel Biyolojik Ajan, Anti Ig-E, Anti IL-5 ve AntiIL-5R

- Prof. Dr. F. Merve Tepetam
- Sağlık Bilimleri Üniversitesi
- Süreyyapaşa Göğüs Hastalıkları ve
- Göğüs Cerrahisi EAH
- İmmunoloji ve Allerji Kliniği

Küresel Yaygınlık ve Ağır Astım Yükü

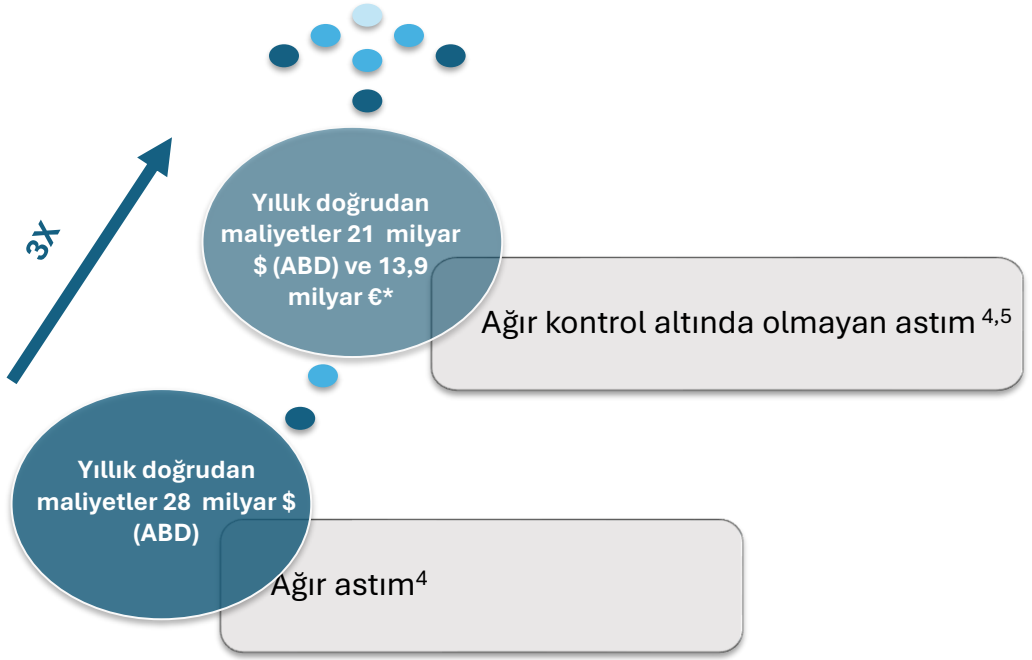
Ağır Astım Prevalansı

~%5–10 Ağır Astım prevelansı

>%50 Astımla ilgili kaynakların ağır astım tarafından kullanılması [2]

%50 Astımlı tüm yıllık sağlık maliyetleri en fazla ağır astım popülasyonundan gelmektedir [3]

Ağır Astım ile artan ekonomik yük



SA, severe asthma.

1. Wang E, et al. Chest. 2020 Apr;157(4):790-804; 2. Enilari O, et al. Ann Glob Health. 2019 Jan 22;85(1):2. 3. Nunes C, et al. Asthma Res Pract. 2017;3:1; 4. Hankin CS, et al. J Allergy Clin Immunol. 2013;131(2):AB126; 5. Accordini S, et al. Int Arch Allergy Immun. 2013;160(1):93–101.

MALİYETİNN ÇOĞUNLUĞU

İndirekt harcamalar iş günü kaybı, engellilik aylığı

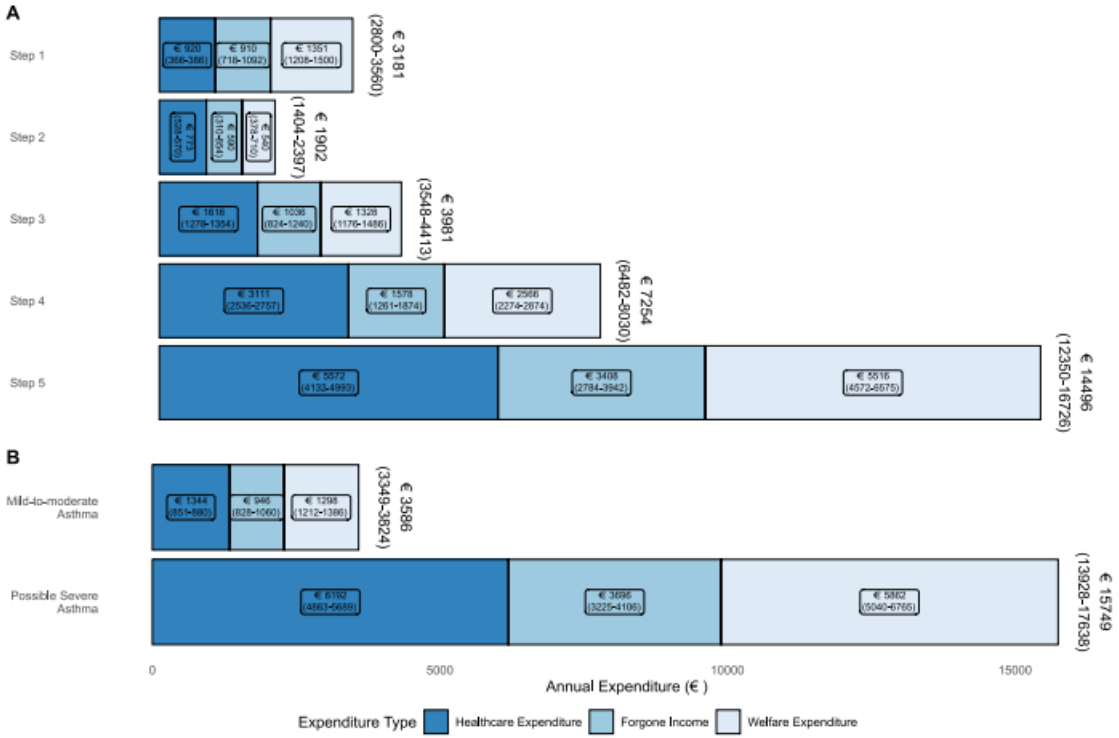


Figure 3 Total annual excess expenditure in 63 130 patients with actively treated asthma aged 18–45 years as stratified by (A) GINA 2020 Treatment Steps and (B) mild-to-moderate and possible severe asthma. Costs are calculated as increases in expenditure as compared with a matched control group. GINA, Global Initiative for Asthma.

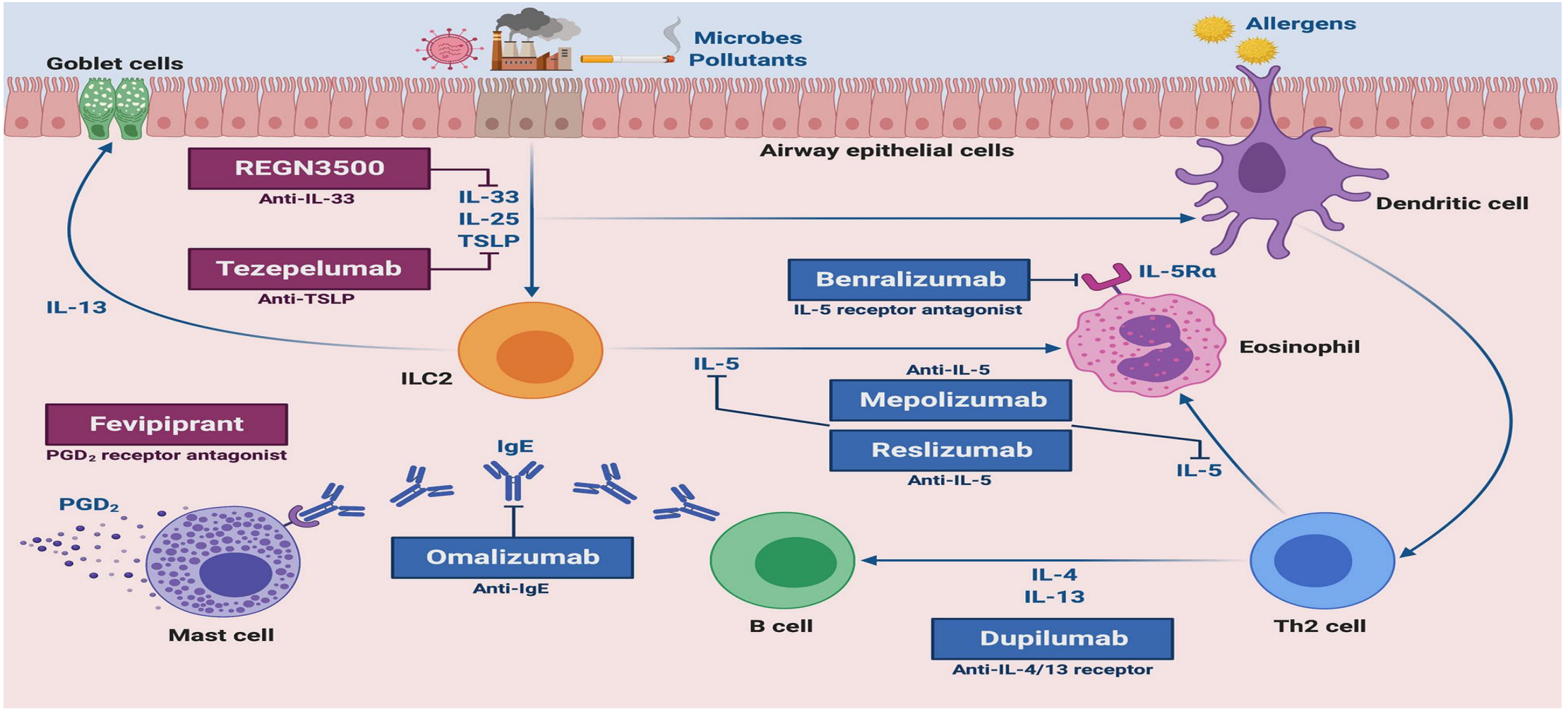
Table 4 Overview of mean, unadjusted direct, indirect and welfare expenditure in 63 130 patients aged 18–45 with actively treated asthma compared with controls

	Asthma versus controls	
	Asthma population (N=63 130)*	Controls (N=252 473)*
Direct costs	2801	1364
Indirect costs†	1613	
Welfare costs‡	5784	4664
Net costs per patient§	4170	
Total pooled annual costs for all cases¶	263 252 100	

All costs in €.
*A 1:4 age, sex, marital/cohabiting status and residence-matched control group.
†The indirect cost of asthma is defined as the difference in earned annual income between patients and controls.
‡Includes public transfer income from sick pay, student grants, social security, unemployment benefits and disability pension.
§Calculated as the difference in expenditure between cases and controls.
¶Calculated as the per-patient net cost times the number of included patients.

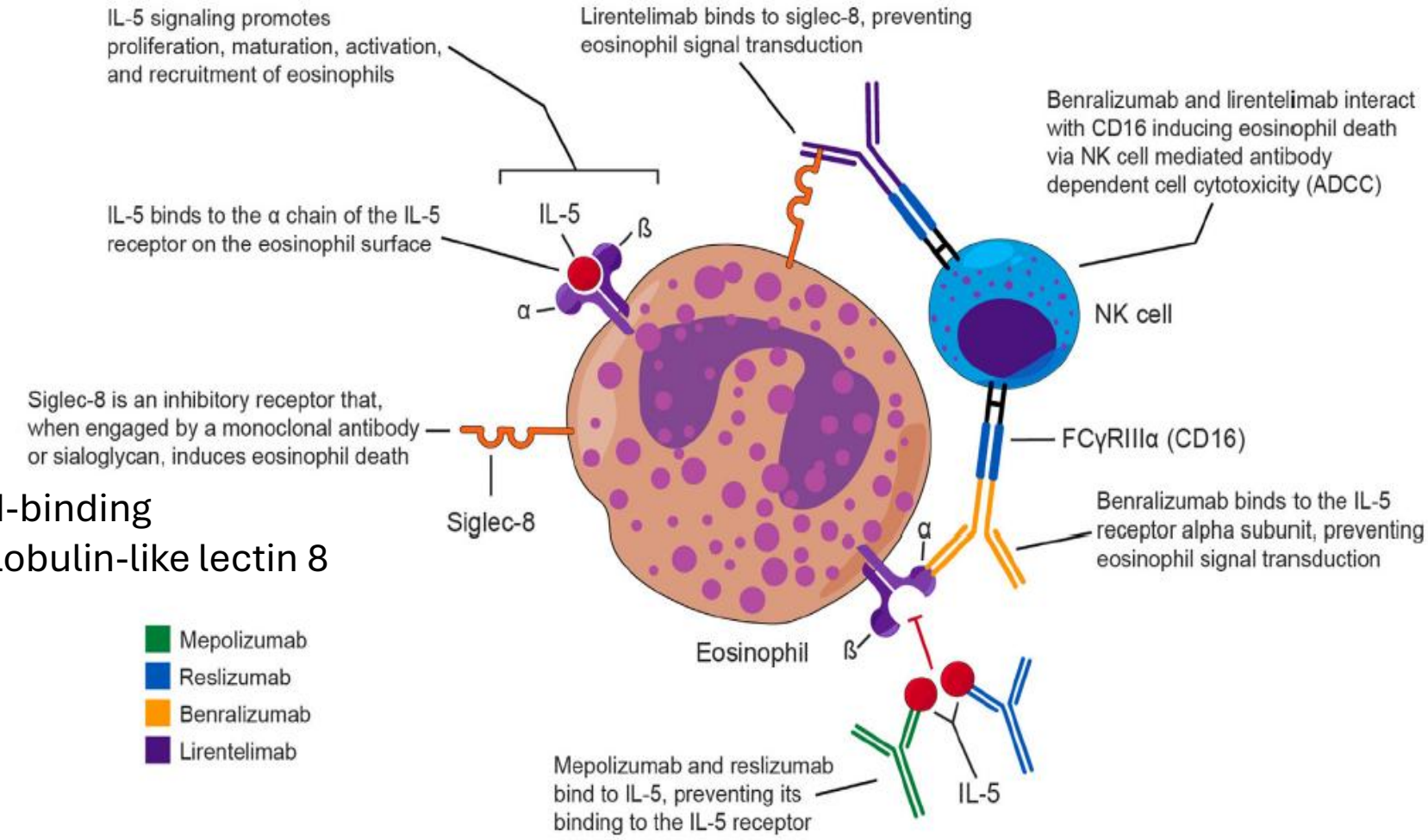
Håkansson KEJ, et al. BMJ Open Resp Res 2023;10:e001437. doi:10.1136/bmjresp-2022-001437

BiYOLOJİKLER-Moleküler HEDEFLER



Front. Immunol., 30 November 2020 https://doi.org/10.3389/fimmu.2020.603312

Anti Il 5 Tedaviler; Etki mekanizmaları



Sialic acid-binding immunoglobulin-like lectin 8

Pitlick, Li, Pongdee World Allergy Organization Journal (2022) 15:100676 http://doi.org/10.1016/j.waojou.2022.100676

MoAb ve Preparat adı	Üretici firma FDA onay tarihi	Hedef molekül	Doz/uygulama yolu	Endikasyon (5. basamak tedavi olarak)
Omalizumab **(XOLAIR)**				Perennial aeroallerjenlere duyarlılığı pozitif deri testi ve/veya spesifik IgE ile gösterilmiş, serum IgE düzeyi 30-1500 IU olan; inhale kortikosteroid ve uzun etkili beta2 agonist kullanmasına rağmen sık gündüz semptomları, gece uyanmaları ve birden fazla ağır astım alevlenmesi yaşadığı saptanmış, akciğer fonksiyonları kısıtlı olan (FEV1< %80) persistan allerjik astımlı erişkinlerin ve ergenlerin tedavisinde kullanılır.
Mepolizumab **(NUCALA)**				yüksek doz IKS ve ek olarak bir veya daha fazla kontrol ajanı kullanan (örneğin LABA vb), önceki yıl içerisinde en az iki alevlenme öyküsü olan (en az 3 gün sistemik KS tedavisi gereken) ve **kandaki eozinofil sayımı tedavi başlangıcında ≥150 hücre/µl veya önceki 12 ay içerisinde ≥300 hücre/µl** olan ağır persistan astımlı erişkin hastaların tedavisinde endikedir
Reslizumab **(CINQAIR)***	Teva Pharmaceuticals 2016	IL-5	İV infüzyon, 3 mg/kg/ 4 hf	>18 yaş, ağır eozinofilik astım
Benralizumab **(FASENRA)**				yüksek doz IKS ve ek olarak bir veya daha fazla kontrol ajanı kullanan (örneğin LABA vb.), önceki yıl içerisinde en az iki alevlenme öyküsü olan (en az 3 gün sistemik KS tedavisi gereken) ve **kandaki eozinofil sayımı ≥300 hücre/µ**l olan şiddetli eozinofilik astımı olan yetişkin hastalarda ek idame tedavisi olarak endikedir.
Dupilumab **(DUPIXENT)***	Regeneron Pharmaceuticals/ Sanofi Genzyme Astım: 2018 AD: 2017 NP: 2019	IL-4Rα (IL-4/IL-13)	SC **a**-Yükleme: 400 mg Devam: 200 mg/2 hf **b**-Yükleme:600 mg Devam: 300 mg/2 hf.	>12 yaş, **a**- Ağır eozinofilik astım **b**- Steroid bağımlı astım AD: >6 yaş** NP: >18 yaş*
Tezepelumab **(TEZSPIRE)***	2021 Astra Zeneca/Amgen	TSLP	SC 210 mg/4 hf.	>12 yaş, ağır astım

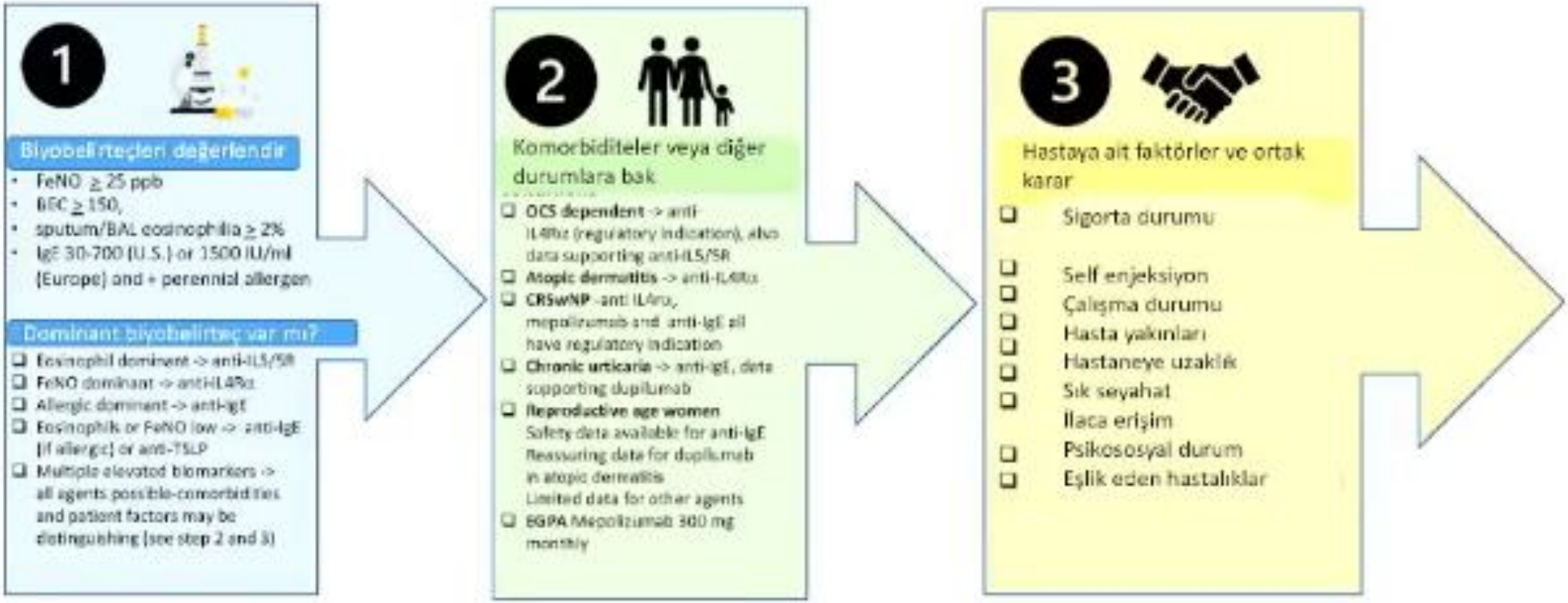
MoAb: Monoklonal antikor, **R:** Reseptör, **NP:** Nazal polip, **KSÜ:** Kronik spontan ürtiker, **AD:** Atopik dermatit, **EGPA:** Polianjitis ile birlikte olan eozinofilik granülomatosis, **HES:** Hiper eozinofilik sendrom, **hf:** Hafta, **α:** Alfa.

*Ülkemizde onayı yok, **Ülkemizde onayı >12 yaş

Ülkemizde Ruhsatlanma tarihleri

Monoklonal antikor ve preparat adı	Üretici firma	FDA onay tarihi/ Ülkemizde ruhsatlanma tarihi	Hedef Bölgesi	Doz/Uygulama Yolu	Endikasyon
Omalizumab (Xolair)	Genentech / Novartis	**Astım** 2003/2008 **KSÜ** 2014/2014 **NP*** 2020/2023	IgE	SC, 2-4 hf Kilo ve IgE düzeyine göre hesaplanır	Gebelik kategorisi: B ≥6 yaş, ağır alerjik astım (Ülkemizde ≥12 yaş) NP: ≥18 yaş KSÜ: ≥ 12 yaş
Mepolizumab (Nucala)	Glaxo Smith Kline	**Astım** 2015/2019 **EGPA*** 2017/2023 **HES*** 2017/2023 **NP*** 2021/2023	IL-5	SC 100 mg/4 hf (≥12 yaş) 40 mg/4 hf (6-11 yaş)	Gebelik kategorisi: C Ağır eozinofilik astım ≥6 yaş EGPA, HES, NP ≥18 yaş
Benralizumab (Fasenra)	Astra Zeneca	**Astım** 2017/2023	IL-5Rα	SC İlk 3 doz 30 mg/4 hf Devamı: 30 mg/8 hf	Gebelik kategorisi: B Ağır eozinofilik astım ≥18 yaş

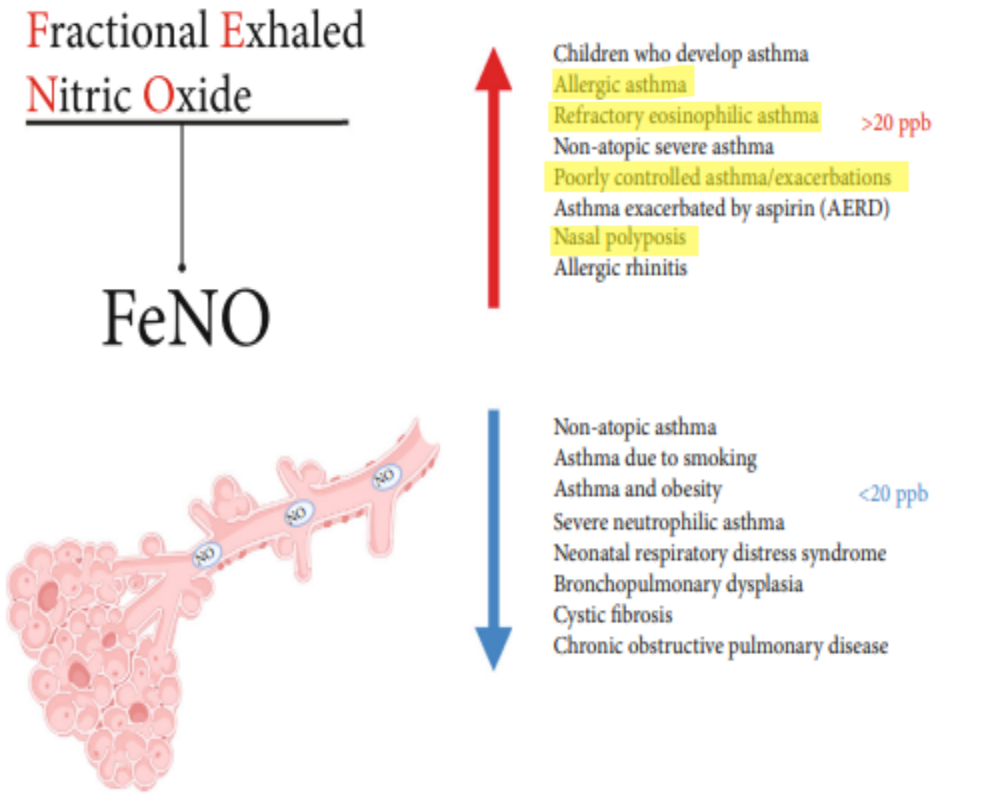
Biyolojik seçiminde yol haritası



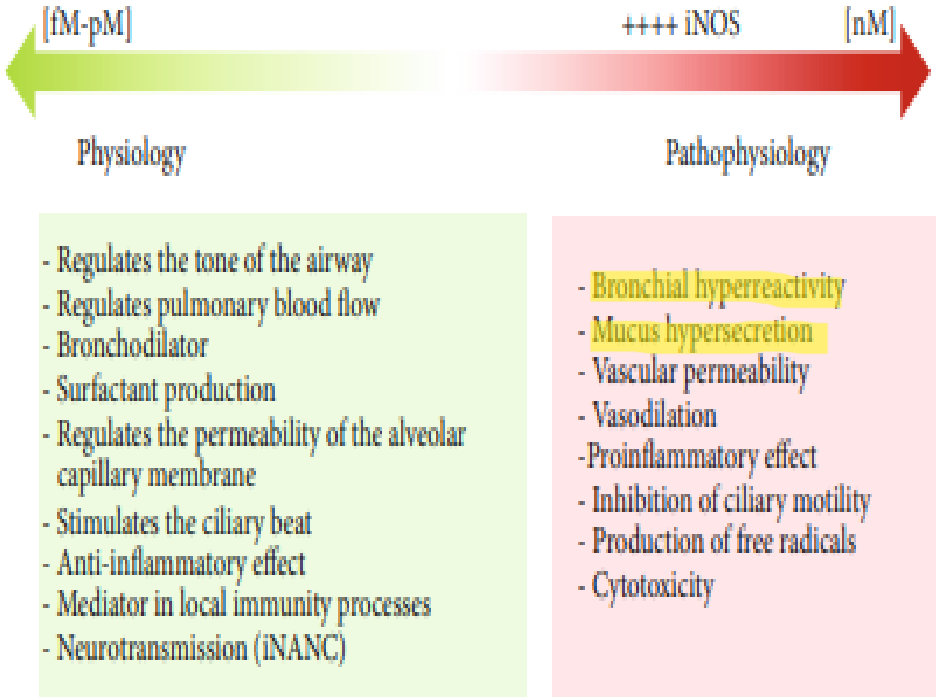
Rogers L et al. Respiratory Medicine 2023; 218: 107414

BİYOBELİRTEÇLER

FENO ARTIŞI HANGİ FENOTİPTE OLUR? NASIL PREZENTASYON GÖSTERİR?



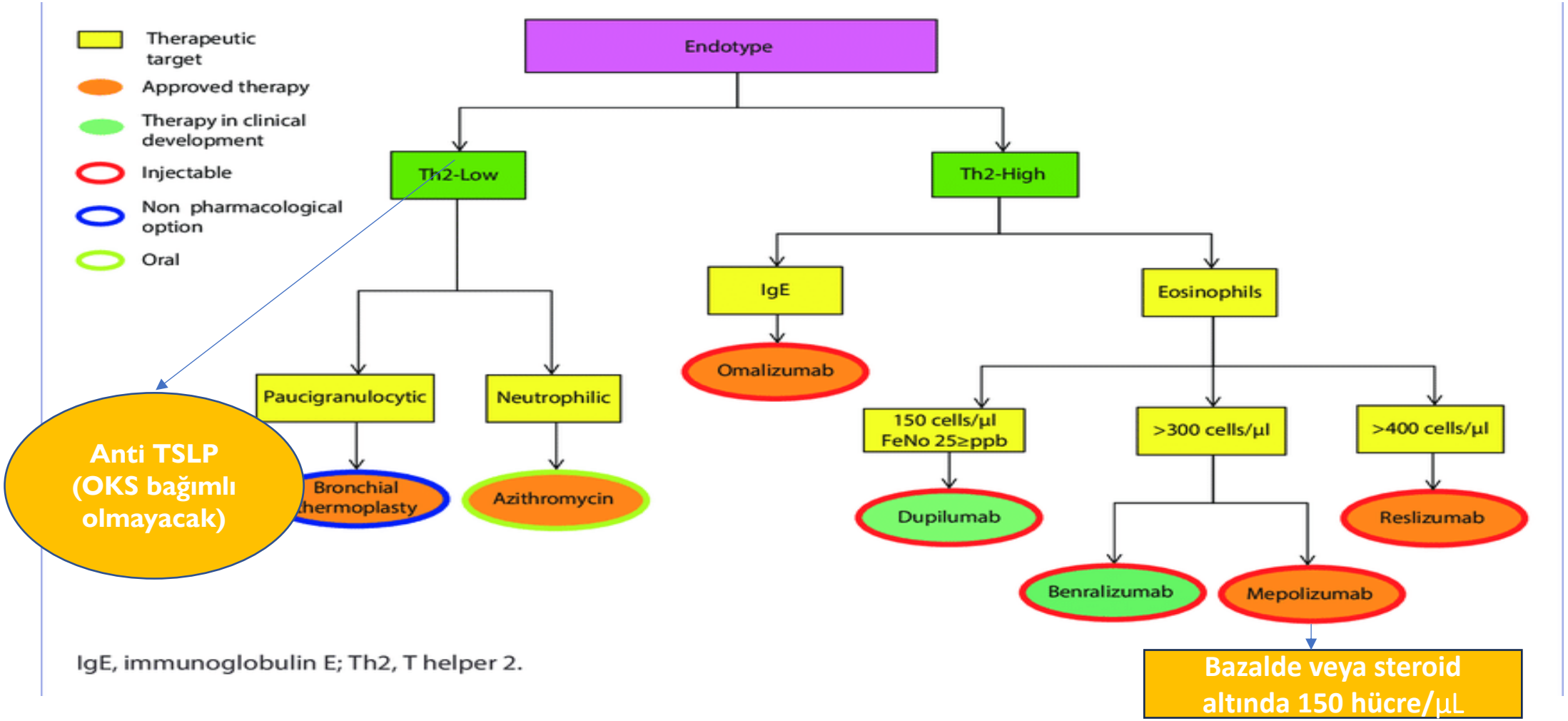
diseases that occur with high and low FeNO levels. ppb: parts per billion. AERD: aspirin-exacerbated res



of NO in the airway depending on its concentration from physiological conditions to patl
ynthase. iNANC: noncholinergic inhibitory noncholinergic.

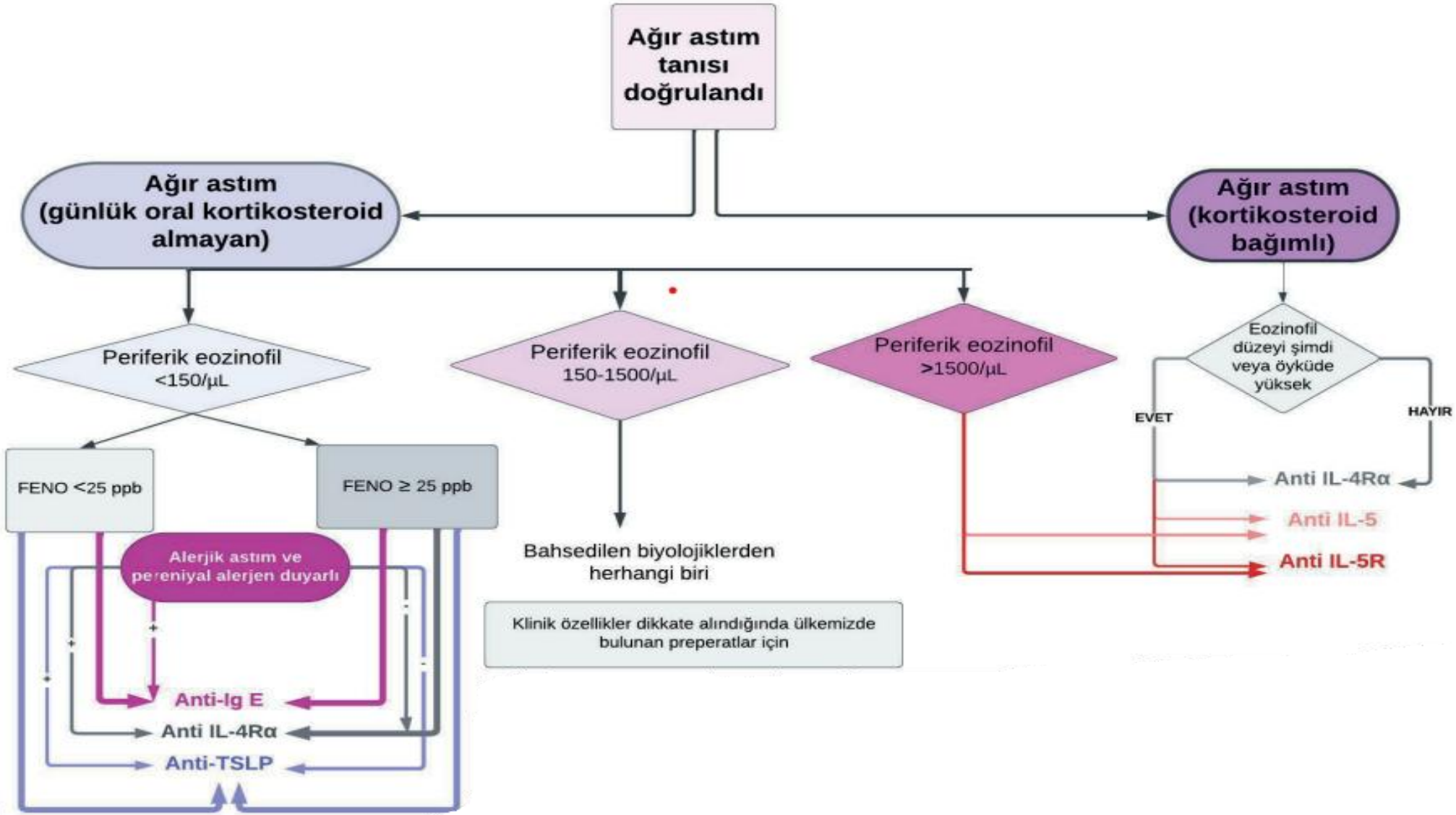
Hindawi BioMed Research International Volume 2022, Article ID 5753524, 9 pages
https://doi.org/10.1155/2022/5753524

BİYOLOJİK SEÇİMİNDE KARAR VERİRKEN İNFLAMATUAR BELİRTEÇLER



Drugs in Context 2018; 7: 212561. DOI: 10.7573/dic.212561

BİYOLOJİK TERCİHİNDE STEROİD BAĞIMLI OLMA DURUMU VE EOZİNOFİL İÇİN 150 VE 1500 CUT OF DEĞERLERİ



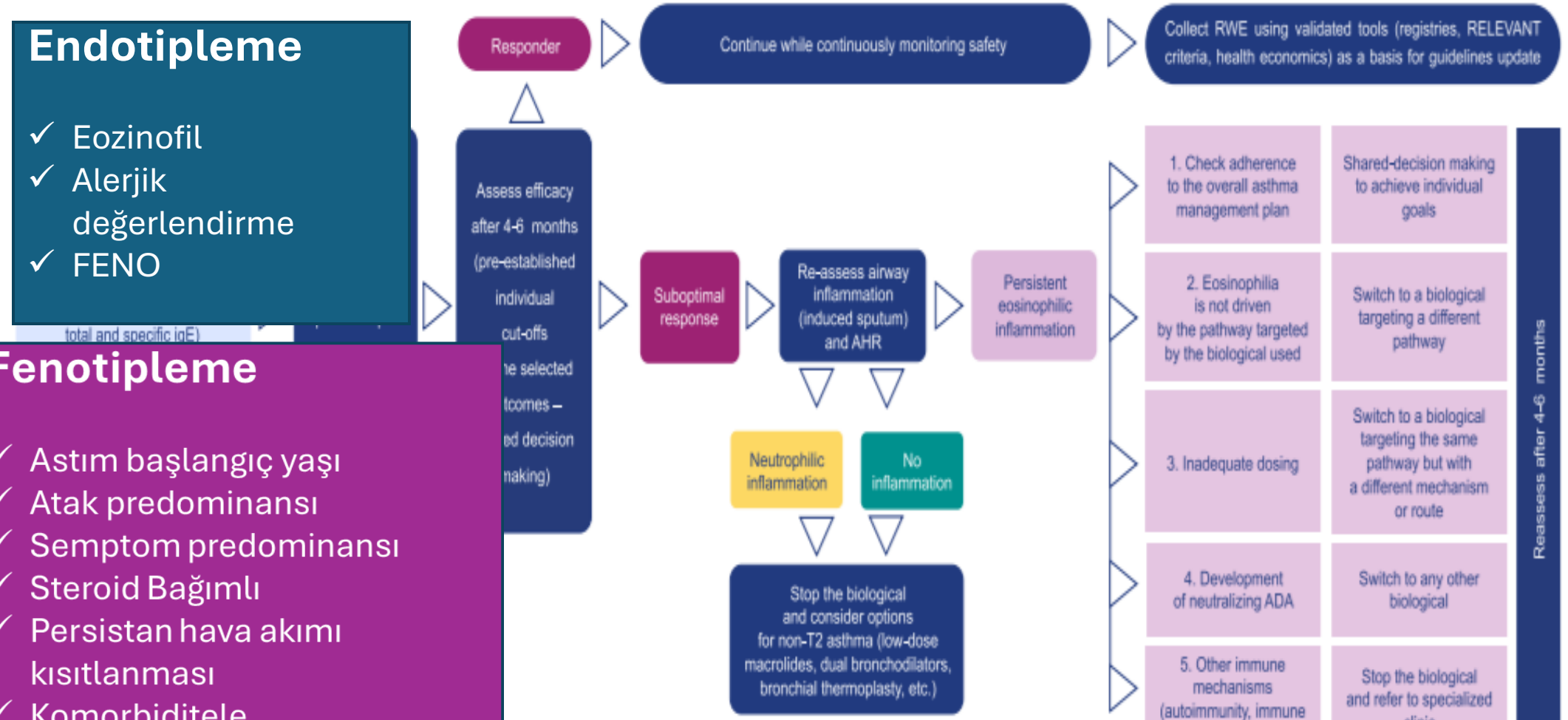
Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022 Jan 13;386(2):157-171.

Endotipleme

- ✓ Eozinofil
- ✓ Alerjik değerlendirme
- ✓ FENO

Fenotipleme

- ✓ Astım başlangıç yaşı
- ✓ Atak predominansı
- ✓ Semptom predominansı
- ✓ Steroid Bağımlı
- ✓ Persistan hava akımı kısıtlanması
- ✓ Komorbiditele
- ✓ Tasarruf: Zaman-maliyet



Ageche et al, Allergy. 2021;76:14–44

ANTİ-IGE ANTİ-IL5 ADAYI VE İYİ YANITLI ÖZELLİKLERİ

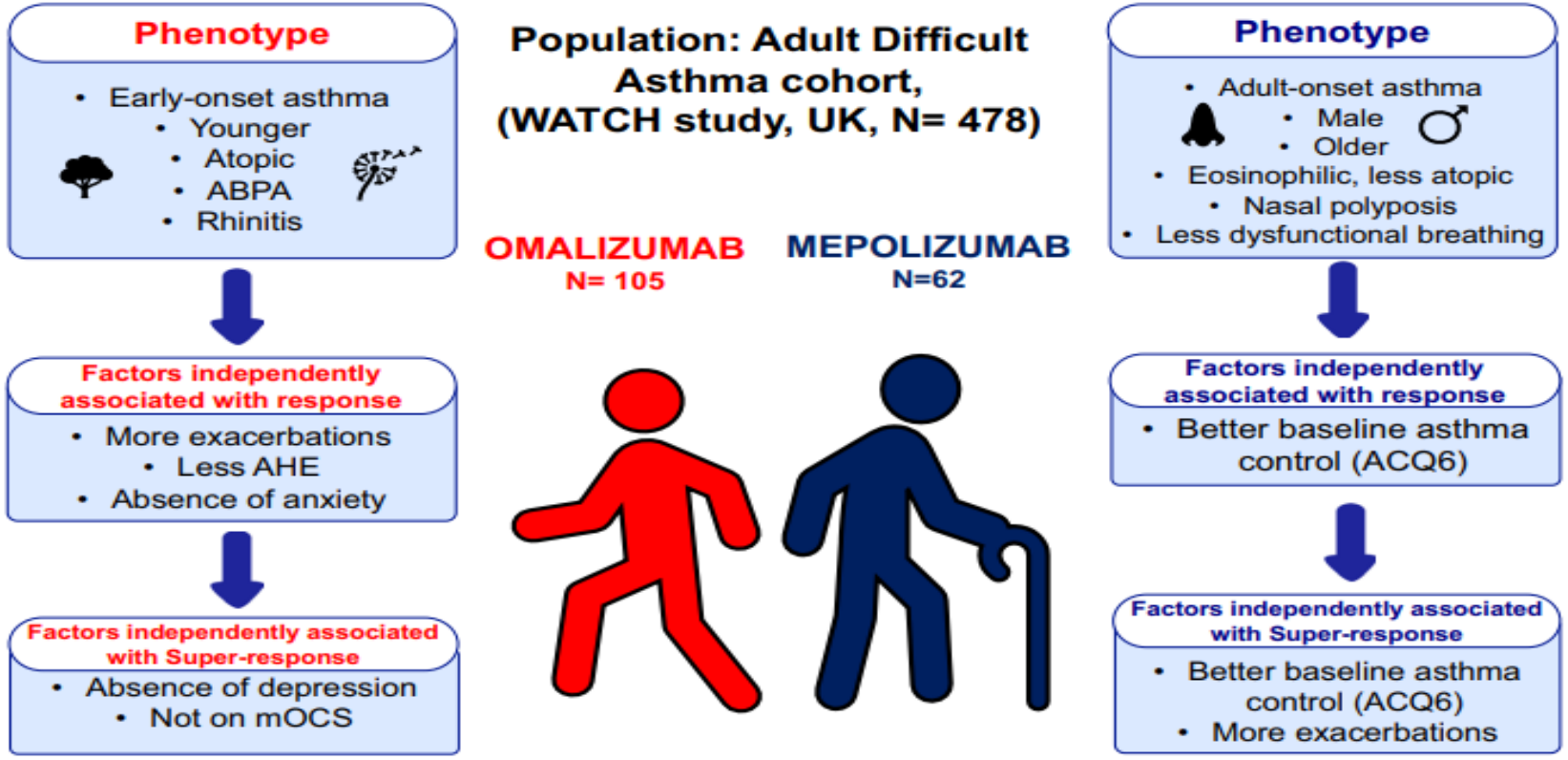
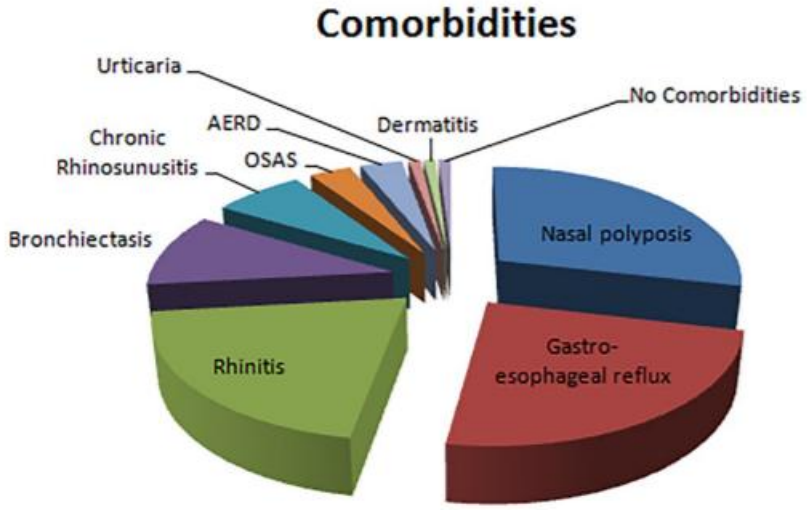


FIGURE 3 Summary of baseline phenotypic features of Omalizumab and Mepolizumab treated patients and factors independently associated with response and super-response to these drugs. ABPA: allergic bronchopulmonary aspergillosis. AHE: acute healthcare encounters, which include Emergency department/ hospital admissions. ACQ6: Asthma Control Questionnaire 6. mOCS: maintenance oral corticosteroids. WATCH: Wessex AsThma CoHort of difficult asthma

Fong et al, Clin Exp Allergy. 2021;00:1–14 WATCH STUDY.

KOMORBİDİTELER



ÜRTİKER: OMALİZUMAB
A.DERMATİT: DUPİLUMAB

NAZAL POLİP:
DUPİLUMAB (EMA)
OMALİZUMAB (EMA)
MEPOLİZUMAB (FDA)
BENRALİZUMAB (FDA)

Therapeutic Advances in Respiratory Disease 14

DÜŞÜK FEV1'DE HANGİ BİYOLOJİK

GINA 2024

Potential predictors of good asthma response to anti-IL5 or anti-IL5Rα:

- Higher blood eosinophils (strongly predictive)[685]

- Higher number of severe exacerbations in previous year (strongly predictive)[685]
- Adult-onset asthma[686]
- Nasal polyps[682]
- Maintenance OCS at baseline[682]
- Low lung function (FEV_1 <65% predicted) in one study.[687]

OLGU

56 Yaş Kadın Hasta

25 yıldır eforla artan ve irritanlar ile tetiklenen daha çok sabaha karşı bulgu veren, mevsim geçişlerinde ise pik yapan

- **Hırıltılı solunum**
- **Nefes Darlığı**
- **Öksürük**
- **Göğüste baskı hissi**

Burun tıkanıklığı, geniz akıntısı, koku alamama, yüzde basınç hissi ,ağrı

ÖZGEÇMİŞ-SOYGEÇMİŞ

31 Yaşında astım tanısı almış, ev hanımı

Sinüzit ve nazal polip (+), Polipektomi öyküsü (+) 4 kere, en son 2 yıl önce

Obezite (+) BMI: 34.5 kg/m2

TİP 2 DM: OAD alıyor

GER (-), OSA (-)

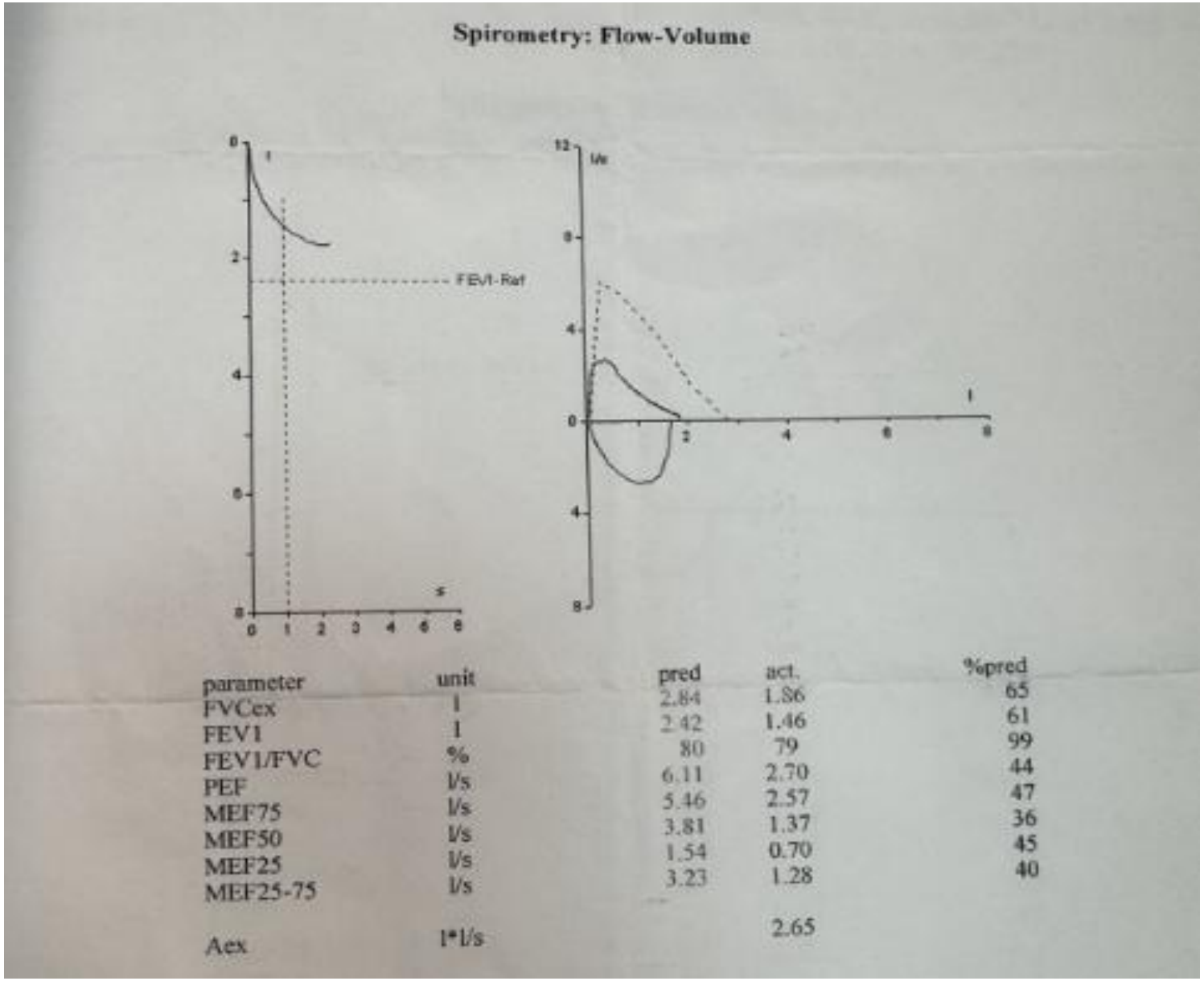
Sigara öyküsü (-)

ASA, NSAİD duyarlılığı (-)

Anne ve anneanne astım (+)

BAZAL-SFT

- FEV1:1.46 (%61)
- FVC:%1.86 (%65)
- FEV1/FVC:%79
- FEF25-75:%40
- REV: VİZİTLER ARASI FEV1 DEĞİŞKENLİĞİ=
  - 1.65-1.46=190 mL
  - 190/1460= %13



parameter	unit	pred	act.	%pred
FVCex	l	2.84	1.86	65
FEV1	l	2.42	1.46	61
FEV1/FVC	%	80	79	99
PEF	l/s	6.11	2.70	44
MEF75	l/s	5.46	2.57	47
MEF50	l/s	3.81	1.37	36
MEF25	l/s	1.54	0.70	45
MEF25-75	l/s	3.23	1.28	40
Aex	l*l/s		2.65	

ASTIMDA TANI

Astımda Tanı

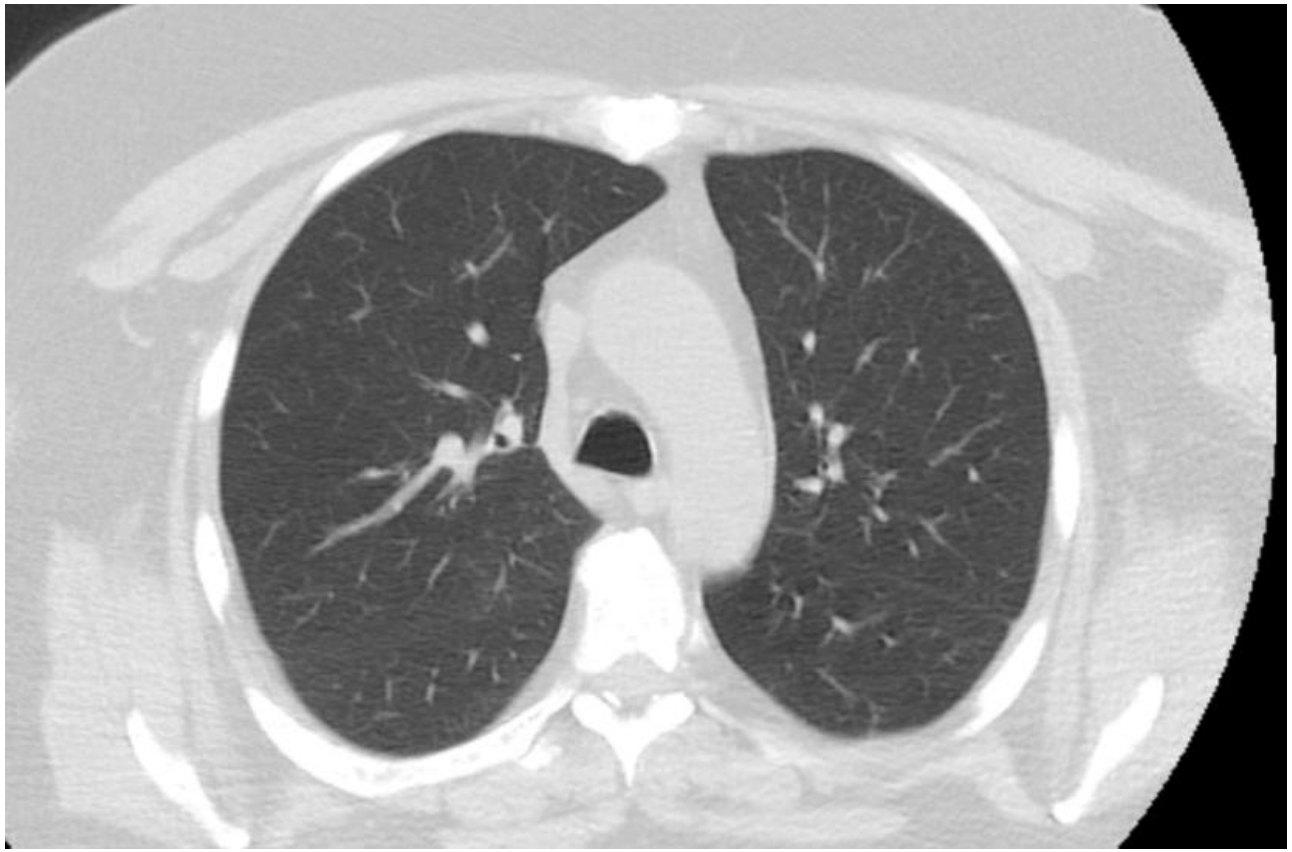
Öyküde değişken solunumsal semptomların varlığı

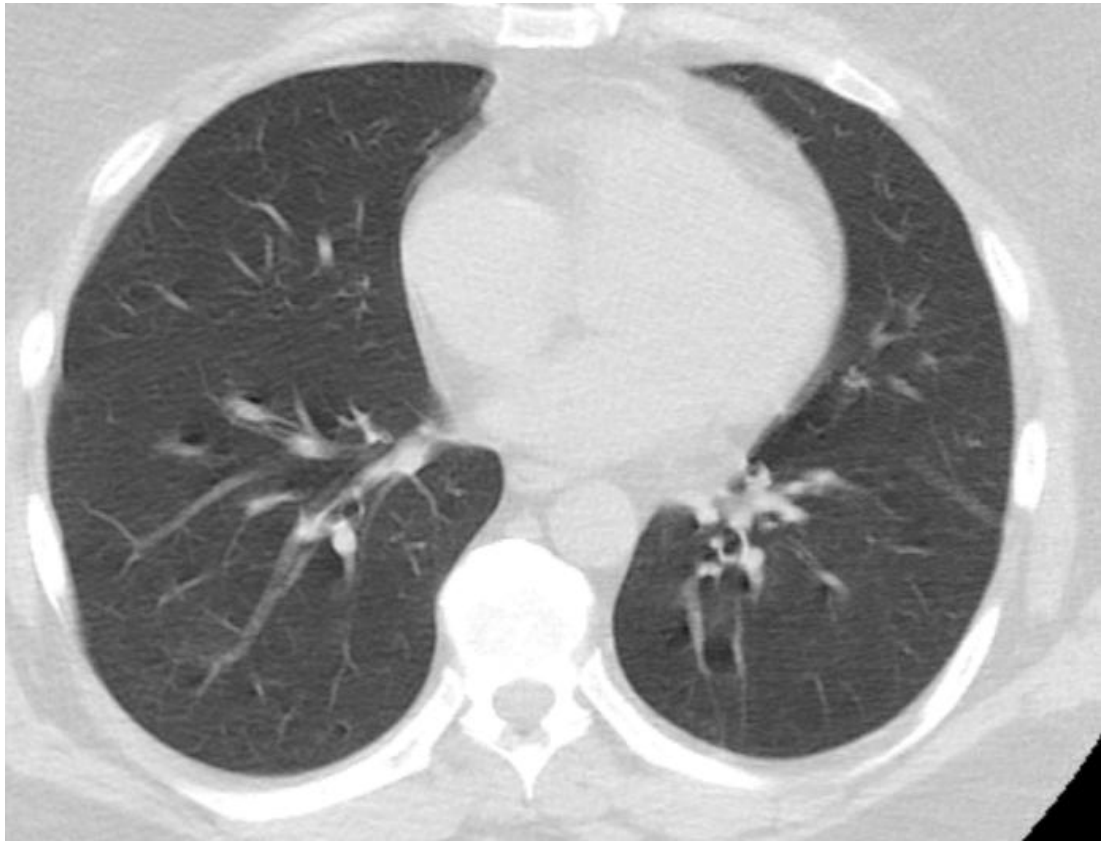
~~**Değişken hava akımı kısıtlanmasının doğrulanması**~~

GINA 2025 ASTIM TANI

- Değişken ekspiratuar hava akımı
  - Tanı sırasında havayolu obstrüksiyonu olması gerekmez
  - Semptom olduğu zaman veya sabah ölçüm yapın!

Toraks BT: Majör patoloji yok





TETKİKLER

BK:N

TİT: N

ANCA: N

ENA:N

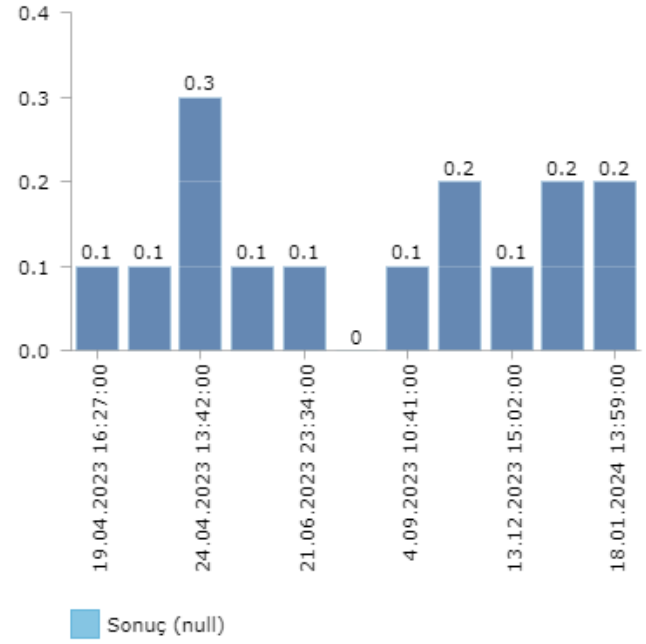
RF:N

TETKİKLER

Total IgE: 829 IU/mL

Eosinofil :0-620 hücre/µL

Eozinofil Seyri son 1 yıl 0-300 (Mepolizumab altında) Maksimum 620 hücre/µL (Şubat 2022)



22.02.2022 14:58	NEUT%				
22.02.2022 14:58	LYM %				
22.02.2022 14:58	MON%				
22.02.2022 14:58	EOS%				
22.02.2022 14:58	BASO%				
22.02.2022 14:58	NEUT				
22.02.2022 14:58	LYM				
22.02.2022 14:58	MON				
22.02.2022 14:58	EOS	0,62		0,02 - 0,50	
22.02.2022 14:58	BASO	0,02		0,00 - 0,20	

ALDIĞI TEDAVİ

1. Salmeterol + flutikazon propiyonat 500 2*1

2. Montelukast+ Desloratadin 1*1

3. Nazal Mometazon 2*2

Hemen hemen her ay acil başvurusu

Son 1 yılda 2 defa 7 gün sistemik steroid kullanımına gerek olan atak !!!!

HASTA KAÇINCI BASAMAK TEDAVİ ALIYOR?

ZOR ASTIM? AĞIR ASTIM?

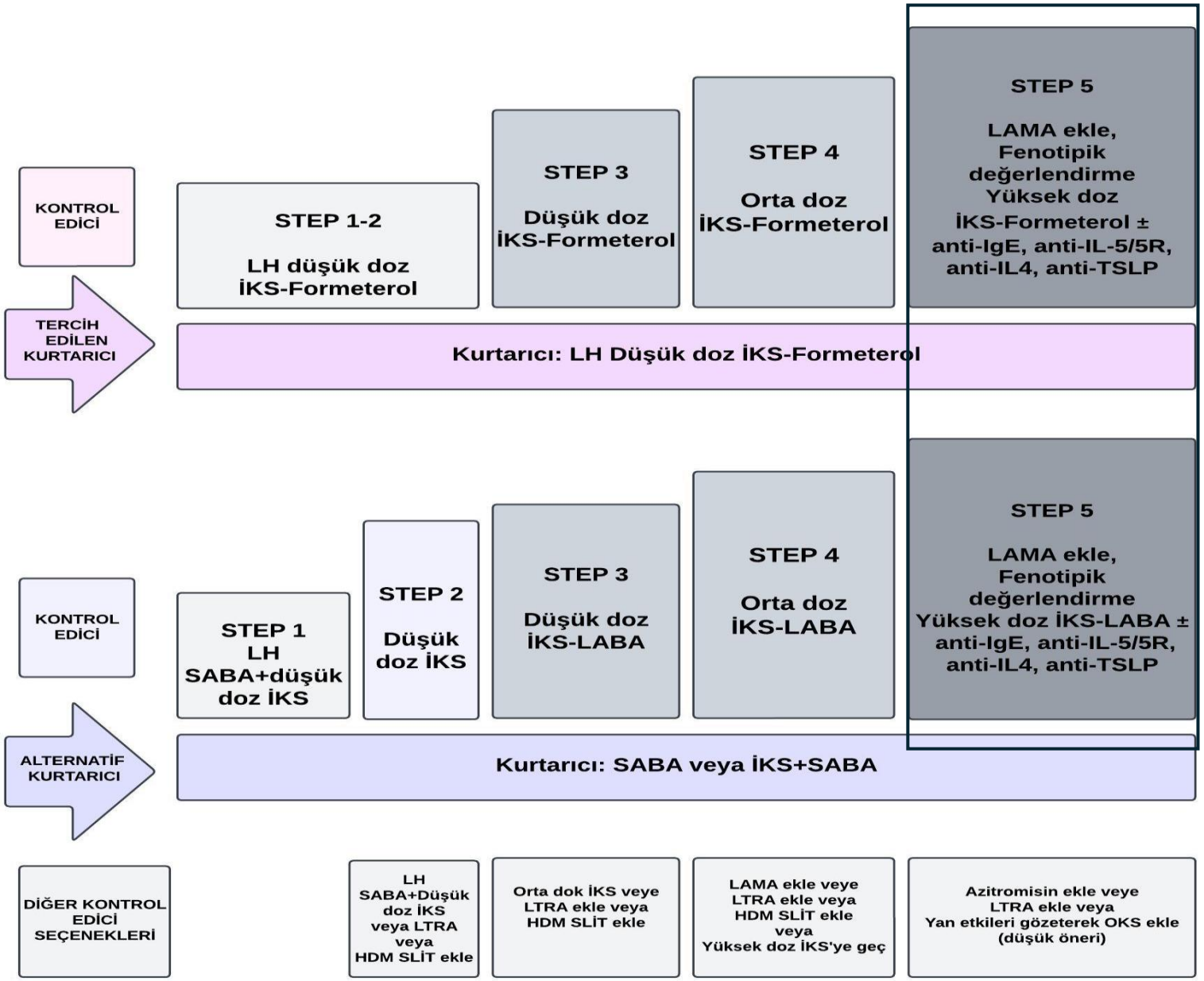
Yetişkin veya adölesan (12 yaş ve üzeri)

İnhale Kortikosteroid	Toplam günlük İKS dozu (mcg)			
	Düşük	Orta	Yüksek	Maksimum
Beklometazon dipropionat (pMDI, standart partikül, HFA)	200-500	>500-1000	>1000	2000
Beklometazon dipropionat (DPI veya pMDI, ekstra ince partikül, HFA)	100-200	>200-400	>400	800
Budesonid (DPI veya pMDI, standart partikül, HFA)	200-400	>400-800	>800	1600
Siklesonid (pMDI, ekstra ince partikül, HFA)	80-160	>160-320	>320	640
Flutikazon furoat (DPI)	100		200	
Flutikazon propiyonat (DPI)	100-250	>250-500	>500	1000
Flutikazon propiyonat (pMDI, standart partikül, HFA)	100-250	>250-500	>500	1000
Mometazon furoat (DPI)	DPI cihazına bağlı			
Mometazon furoat (pMDI, standart partikül, HFA)	200-400		>400	

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. www.ginasthma.org (2023)

BASAMAK-5 TEDAVİ YÜKSEK DOZ İKS GERİ PLANDA

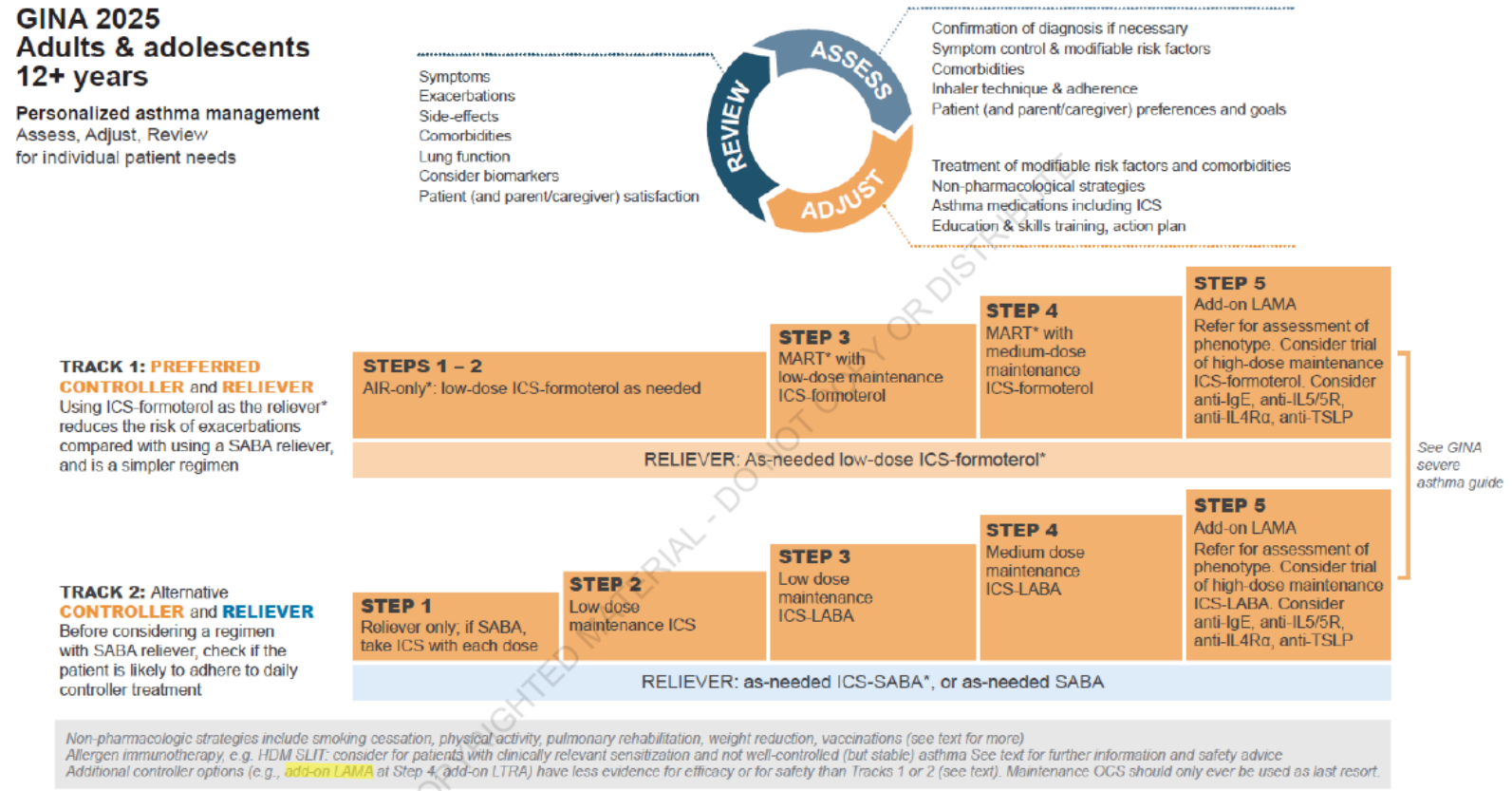
ZOR ASTIM



GINA 2025

ASTHMA TREATMENT STEPS IN ADULTS AND ADOLESCENTS

Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk



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*AIR: Anti-inflammatory reliever; Ig: immunoglobulin; ICS: inhaled corticosteroids; HDM: house dust mits; IL: interleukin; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance-and reliever therapy with ICS-formoterol; OCS: oral corticosteroid; SLIT: sublingual immunotherapy; TSLP: thymic stromal lymphopoietin. †If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.

For recommendations about initial asthma treatment in adults and adolescents, see Box 4-4 (p.75) and Box 4-5 (p.76). See Box 4-2 (p.71) for low, medium and high ICS doses for adults and adolescents. See Box 4-8 (p.84) for Track 1 medications and doses.

3 ay sonra AKT: 13 (kontrolsüz astım)

AĞIR ASTIM TANISINI DOĞRULAMAK İÇİN

- Tanıyı doğruladık
- İnhaler teknik ilaç uyumu iyi

- Tetikleyiciler gözden geçirildi.
- Komorbiditeler optimize edildi.

- Biyolojik olmayan ilaçlar (LAMA) eklendi.
- Yüksek doz IKS

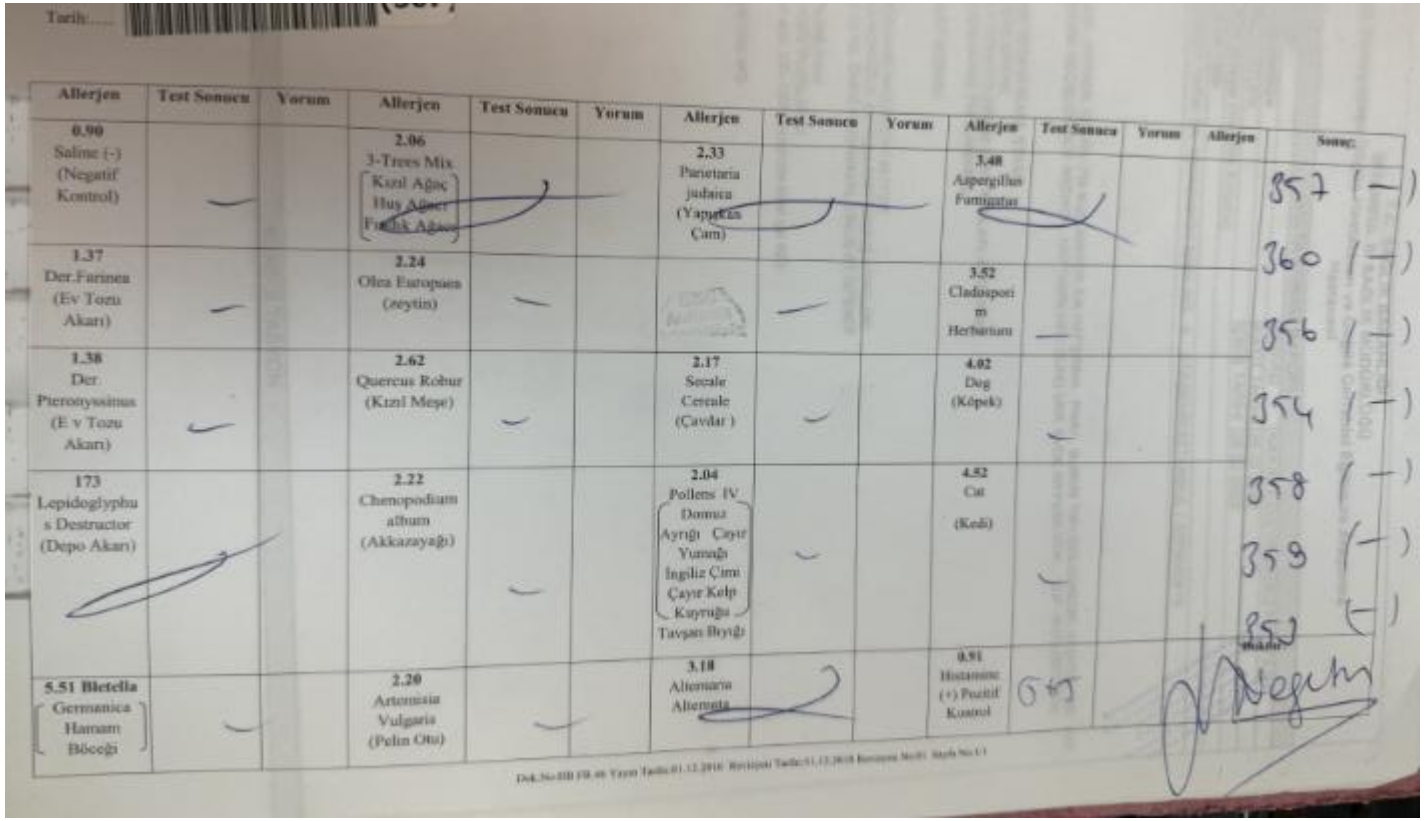
İnhaler Teknik İlaç uyumu

Kontrol edildi

iyi

Tetikleyiciler

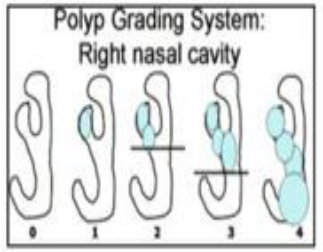
- § Sigara öyküsü yok
- § Mesleki maruziyet yok
- § Alerji deri testi (küf paneli dahil) negative
- § Spesifik Ig E negatif



Komorbiditelerin tedavisi

- ➢Obesite
- Diyet
- Egzersiz
- ➢Nazal polip
- 2 yıl önce polipektomi
- KBB konsültasyonu: nazal polip skoru:3
- Cerrahi: Hasta kabul etmedi
- Nazal flutikazon+azelastin kombinasyonuna geçildi.

Nazal polip skoru (NPS):



Nazal polip skoru (NPS)	Endoskopik polip büyüklüğü
0	Polip yok
1	Orta meatusta sınırlı küçük polipler
2	Orta meatusu tıkayan multipl polipler
3	Orta meatusu aşan büyük polipler
4	İnferior nazal kavitede total obstrüksiyon yapan büyük polipler

Endoskopik muayene bulguları için nazal polip skorlaması (NPS), radyolojik değerlendirme için Lund-Mackay skorlaması (LMS), nazal açıklığın değerlendirilmesinde nazal inspiratuar tepe akımmetri (PNIF), anterior rinomanometri ve akustik rinometri yapılabilir.

NAZAL POLİP-YAŞAM KALİTESİ SNOTT-22: 32

Turkish validation of the Sino-Nasal Outcome Test-22

Asli Cakir Cetin[1] | Ozgur Kumus[1] | Pembe Keskinoglu[2] | Semih Sutay[1] | Mustafa Cenk Ecevit[1]

SNOT 22 TÜRKÇE ANKET

Aşağıdaki şikayetleri yaşadığınızda sizin için ne kadar önemli olduğunu, bu şikayeti ne sıklıkta yaşadığınızı anımsayarak kendinizi ne kadar kötü hissettirdiğine karar veriniz ve sağ tarafta size uygun olan seçeneği işaretleyiniz.

Şikayetler	Hiç yok	Çok hafif	Hafif	Orta	Ağır	Daha kötüsü olamaz	En önemli BEŞ şikayetinizi işaretleyiniz
Burun silme ihtiyacı							
Burun tıkanıklığı							
Hapşırma							
Burun akıntısı							
Öksürük							
Geniz akıntısı							
Koyu kıvamlı burun akıntısı							
Kulak dolgunluğu							
Sersemlik							
Kulak ağrısı							
Yüzde ağrı ve veya dolgunluk- basınç hissi							
Koku veya tat duyusunda azalma							
Uykuya dalmada güçlük							
Gece uykudan uyanma							
İyi bir gece uykusu uyuyamama							
Sabah yorgun uyanma							
Yorgunluk- halsizlik							
Üretkenlik- verimlilikte azalma							
Konsantrasyon güçlüğü							
Bitkin/yılgın/dinlenememiş asabi/gergin hissetme							
Mutsuz olma							
Utanma/ mahcup olma							

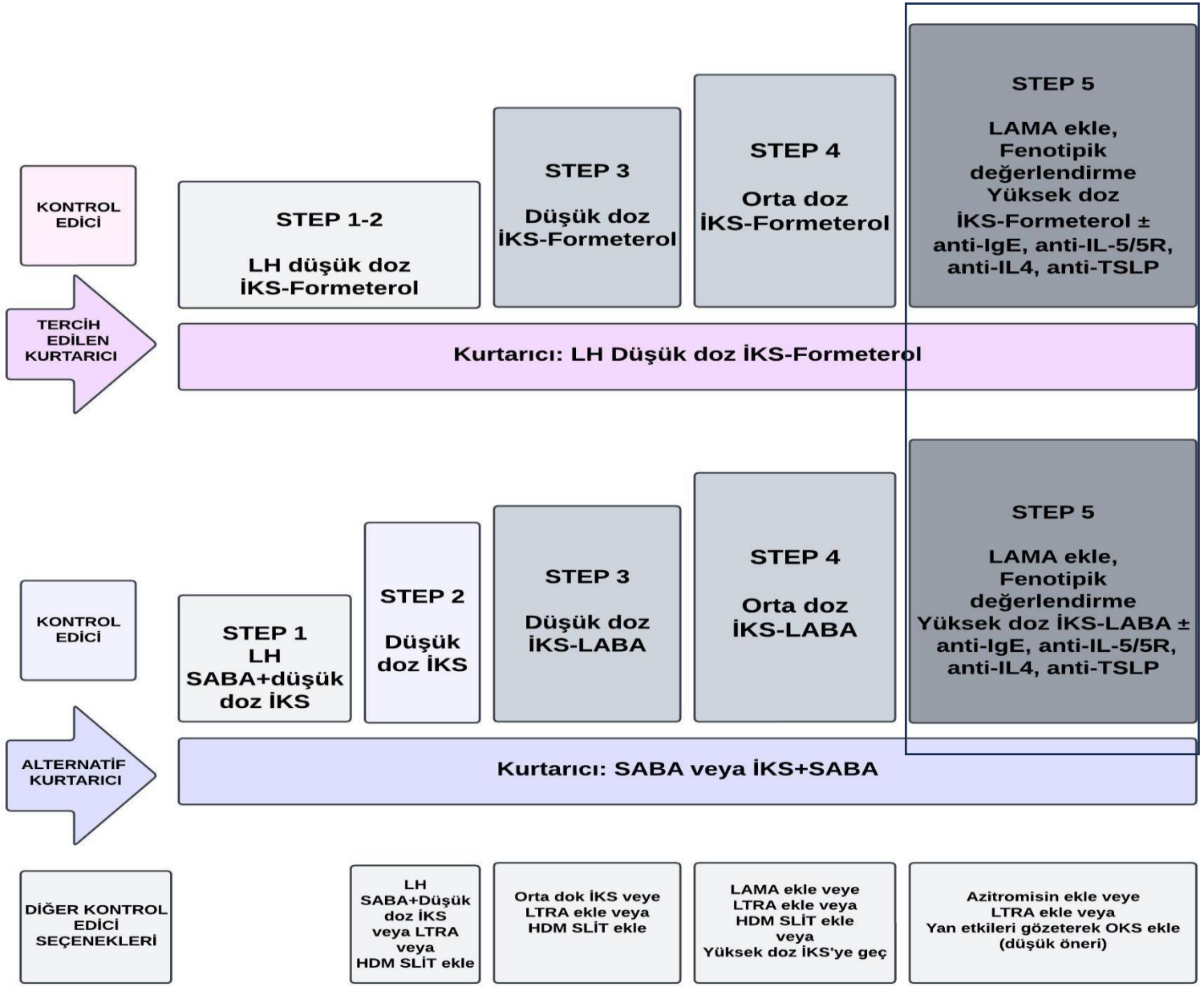
FIGURE 1 Turkish version of the SNOT-22

Clinical Otolaryngology. 2019;44:557–564.

BASAMAK ÇIKILDI

3’lü kombinasyon

Umeklidinyum 62.5 mcg+
flutkazon furoat 200 mcg+
Vilanterol 25 mcg



İKS DOZU ARTTIKÇA ETKİ/YAN ETKİ

Inhaled Corticosteroid Therapy in Adult Asthma

Time for a New Therapeutic Dose Terminology

Richard Beasley[1,2,3], James Harper[1], Grace Bird[1], Ingrid Maijers[1], Mark Weatherall[3,4], and Ian D. Pavord[5]

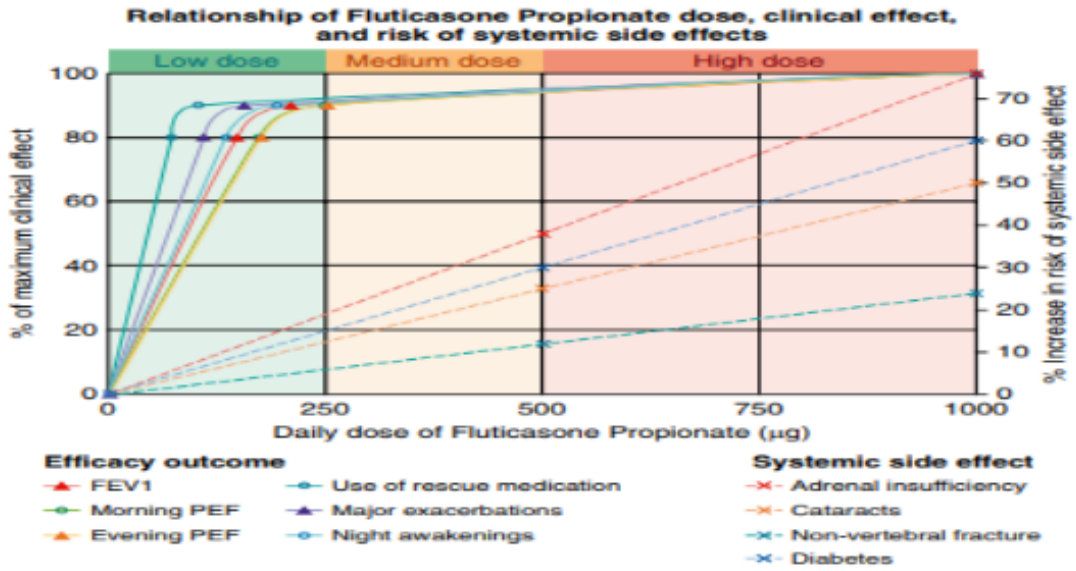


Figure 1. Schematic dose–response curves for different outcomes for efficacy and adverse effects with inhaled corticosteroids, expressed as fluticasone propionate in µg/d, derived from Tables 2 and 5. PEF = peak expiratory flow.

Am J Respir Crit Care Med Vol 199, Iss 12, pp 1471–1477, Jun 15, 2019 Copyright © 2019 by the American Thoracic Society Originally Published in Press as DOI: 10.1164/rccm.201810-1868CI on January 15, 2019
Internet address: www.atsjournals.org

GINA 2025 LAMA

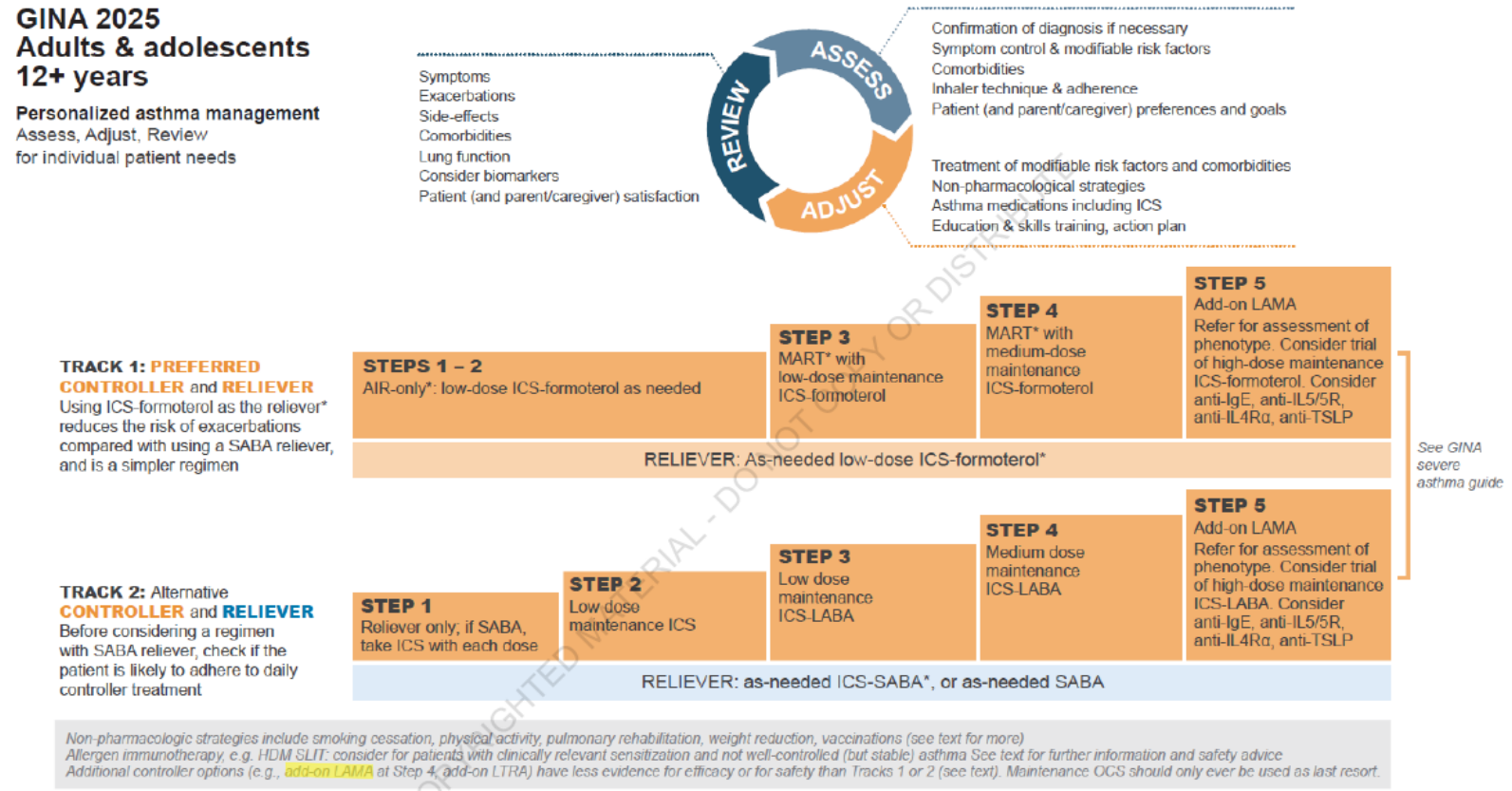
- In Track 2, Step 4 has been changed from medium-to-high dose of ICS-LABA to medium-dose ICS-LABA (p.77, p.89), reflecting the Report's longstanding emphasis on minimizing exposure to the adverse effects of high-dose ICS. If high-dose ICS-LABA is needed, its use should be limited to 3–6 months if possible.
- In Box 4-2 (p.71), daily doses of fluticasone furoate have been reclassified as low-medium (100 mcg) and medium-high (200 mcg). This change is because of the difficulty in aligning doses of this ICS with older molecules, and to avoid ambiguity about ICS-LABAs that can be used in Track 2 Step 4 of the treatment figure for adults and adolescents (p.77).
- "Other controller options" with less evidence for efficacy and/or safety than the standard treatments shown in Tracks 1 and 2 were previously shown in gray boxes underneath individual treatment steps (p.77), representing *alternatives* to the standard treatment at that step (e.g., add-on LAMA at Step 4 meant addition of LAMA to low-dose ICS-LABA). However, this was not widely understood, and it is important that referral of patients with difficult-to-treat asthma for expert advice should not be delayed by trials of multiple different add-on treatments.

Long-acting muscarinic antagonists (LAMAs): LAMAs may be considered as add-on therapy to low-dose ICS-LABA in a separate inhaler for patients aged ≥6 years (tiotropium), or in a combination ('triple') inhaler for patients aged ≥18 years (beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium) if asthma is persistently uncontrolled despite medium or high-dose ICS-LABA. Adding a LAMA to medium or high-dose ICS-LABA modestly improved lung function (Evidence A)[310,366-370] but with no difference in symptoms. In some studies, adding LAMA to ICS-LABA modestly reduced exacerbations, compared with some medium- or high-dose ICS-LABA comparators.[310,367,370] In meta-analyses, there was a 17% reduction in risk of severe exacerbations with addition of LAMA to medium- or high-dose ICS-LABA; sub-group analysis suggested that this benefit was mainly in patients with a history of exacerbations in the previous year.[371,372]

GINA 2025

ASTHMA TREATMENT STEPS IN ADULTS AND ADOLESCENTS

Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk



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*AIR: Anti-inflammatory reliever; Ig: immunoglobulin; ICS: inhaled corticosteroids; HDM: house dust mits; IL: interleukin; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; MART: maintenance-and reliever therapy with ICS-formoterol; OCS: oral corticosteroid; SLIT: sublingual immunotherapy; TSLP: thymic stromal lymphopoietin. †If prescribing LTRA, advise patient/caregiver about risk of neuropsychiatric adverse effects.

For recommendations about initial asthma treatment in adults and adolescents, see Box 4-4 (p.75) and Box 4-5 (p.76). See Box 4-2 (p.71) for low, medium and high ICS doses for adults and adolescents. See Box 4-8 (p.84) for Track 1 medications and doses.

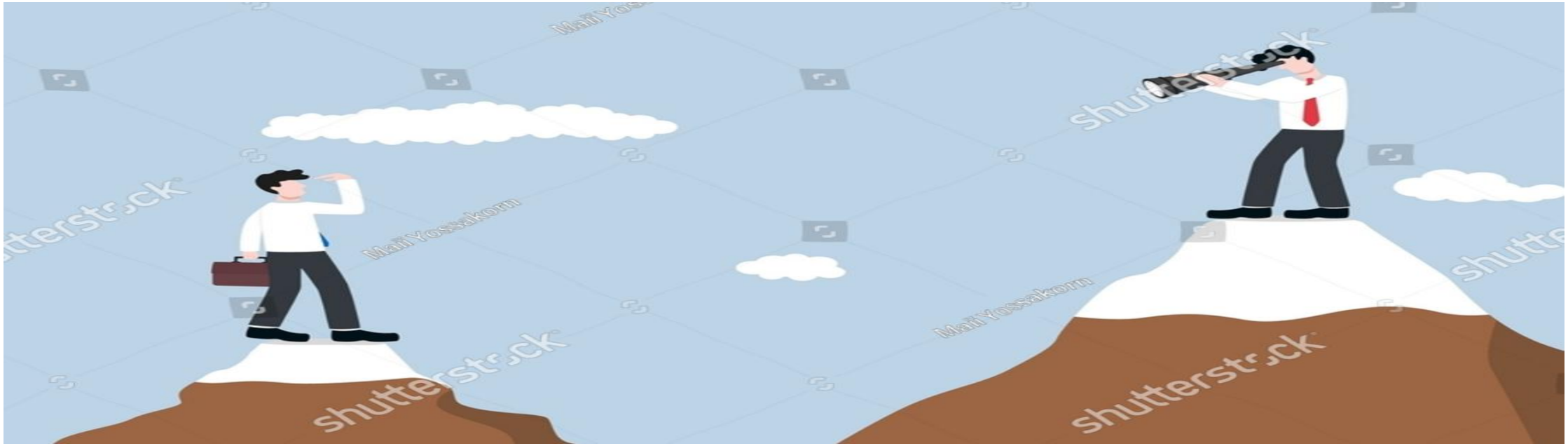
Başlangıç Dosya Özeti

Astım Başlangıç Yaşı/Hastalık süresi	**31/25 yıl**
Komorbidite	Obezite ve nazal polip
AKT GINA	Bazal: 5 **Son vizit: 13** **Kontrol dışı**
Başvurduğunda atak sayısı	**2 (Sistemik steroid 1 hafta)**
Total IgE Eozinofil	829 IU/mL 620 hücre/µL
DPT	Negatif

Zor astım/Ağır astım

SİSTEMİK STEROİDLERİN UZUN SÜRELİ KULLANIMLARININ YAN ETKİLERİNİ BİLİYORUZ

UNDERESTİMATE ETTİĞİMİZ KISA SÜRELİ KULLANIMLARI



OKS KULLANIMI-KRONİK/KISA SÜRELİ

Kronik OKS kullanımı, steroidle ilişkili komplikasyonların yanı sıra artmış mortalite ile ilişkilidir ve daha fazla steroid maruziyeti ile risk artmaktadır.[1-4]

GINA raporu, idame OKS'nin ancak diğer ek tedavi seçenekleri dışlandıktan sonra değerlendirilmesini önermektedir.[5]

OKS ile kısa süreli tedavide dahi yan etki riski artmaktadır.[6]

1.5 mlyon hasta 300.000'i oks kullanan (infeksiyon, spinal veya alerjik nedenler)

Kısa süreli OKS (<30 gün) ile tedavi edilen hastalarda değerlendirilen 3 advers olayın tümünde daha yüksek oranlar görülmüştür[6]*:

~2x

Fraktür

RR: 1.87; 95% CI: 1.69–2.07; *P*<0.001

3x

Venöz tromboemboli

RR: 3.33; 95% CI: 2.78–3.99; *P*<0.001

5x

Sepsis

RR: 5.30; 95% CI: 3.80–7.41; *P*<0.001

Eozinofilik fenotipli ağır astımı olan birçok hasta, ciddi yan etki riskinin artmasına rağmen OKS'ye güvenmektedir.[1,2]

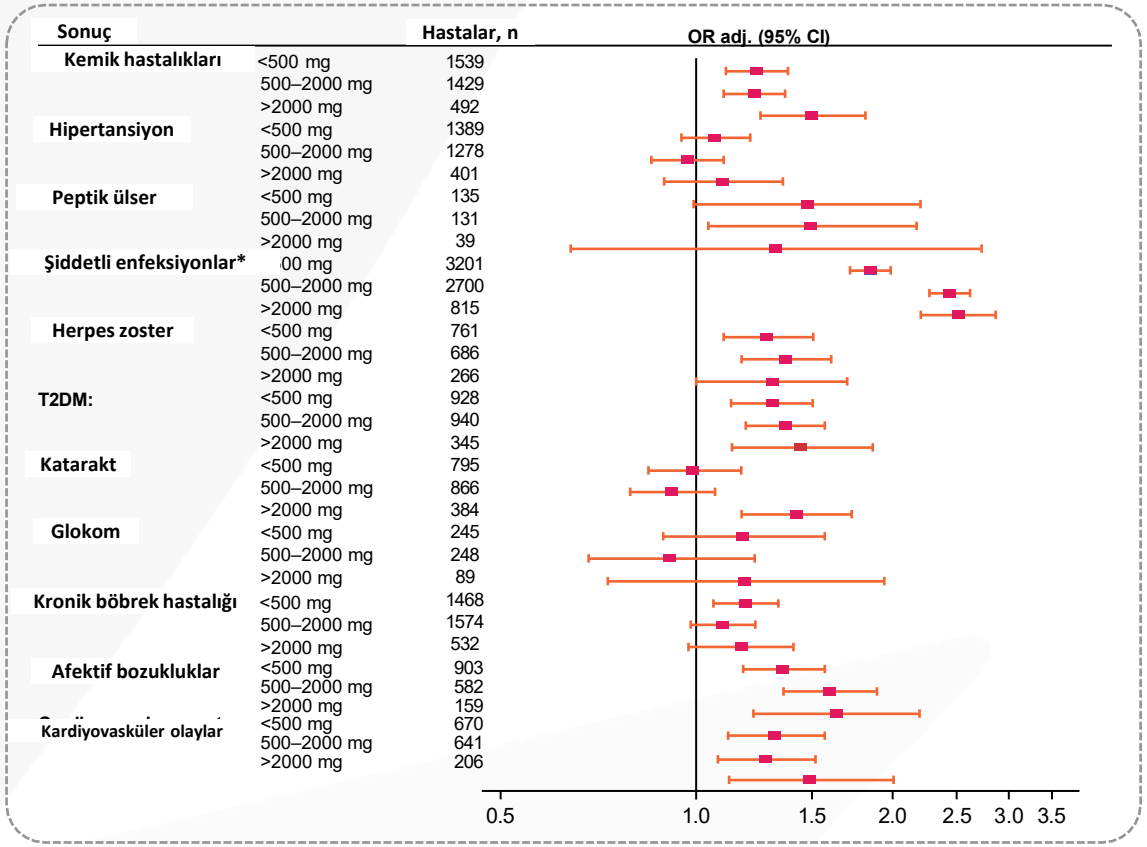
*ABD'de özel sigortalı yetişkinlerin (18-64 yaş arası) dahil edildiği retrospektif bir kohort çalışmasında (N=1.548.945), kısa süreli OKS reçetelerinin sıklığı ve ilişkili advers olaylar değerlendirildiğinde, hastaların %21'i (327.452) 3 yıllık çalışma döneminde kısa süreli OKS için ≥1 ayakta tedavi reçetesi almıştır [6] CI, güven aralığı; OKS, oral kortikosteroid; RR, hız oranı.

1. Price DB *et al. J Asthma Allergy*. 2018;11:193–204; **2.** Sullivan PW *et al. J Allergy Clin Immunol*. 2018;141:110–116; **3.** Volmer T, *et al. Eur Respir J*. 2018;52:1800703; **4.** Lee H *et al. Eur Resp J*. 2019;54:1900804; **5.** Global Initiative for Asthma. Global strategy for asthma management and prevention, 2023. Available at: https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Accessed, Sep 14, 2023.
6. Waljee AK, *et al. BMJ*. 2017;357:j1415

ATAKLARDA KULLANILAN KISA SÜRELİ OKS YAN ETKİLERİ

- **165900 case, 269000 kontrol astım**
- **Yılda ortalama bir reçete**
- **Kümülatif doz < 500 mg (iki kısa kür)**
- **Son 2 yıldaki ortalama günlük doz of ≤1 mg**

Katarakt yüksek dozda
Dozdan bağımsız Herpes Zoster ve Peptik ülser riski
O sırada (current use) kullananalarda ciddi infeksiyon, kemikle ilişkili durumlar, DM, psikiyatrik hastalıklar, KVH.
Doz ve kullanılan zamandan bağımsız olarak glokom HT ve KBY riski yok



OKS kullanımı tekrarlanan kısa süreli kürlerde dahi advers etkilere yol açmaktadır.

D, klinik uygulama araştırma veri bağlantısı; OKS, oral kortikosteroidler; OR, odds oranı; T2DM, tip 2 diabetes mellitus. Bloechliger M ve ark. Respir Res. 2018;19:75.

HANGİ FENOTİP?

Klinik-fizyolojik fenotip

- Ağır astım
- Sık atak geçiren astım
- Tedaviye dirençli astım
- Obez astım
- Fiks hava yolu obst. seyreden astım
- Başlangıç yaşına göre tanımlanmış astım; Erişkin başlangıç, erken başlangıçlı astım

Tetikleyicilere göre fenotip

- NERD
- Çevresel allerjenler
- Mesleki allerjen-irritan
- Egzersiz
- Menstrüasyon
- Hormanal
- Kirli hava

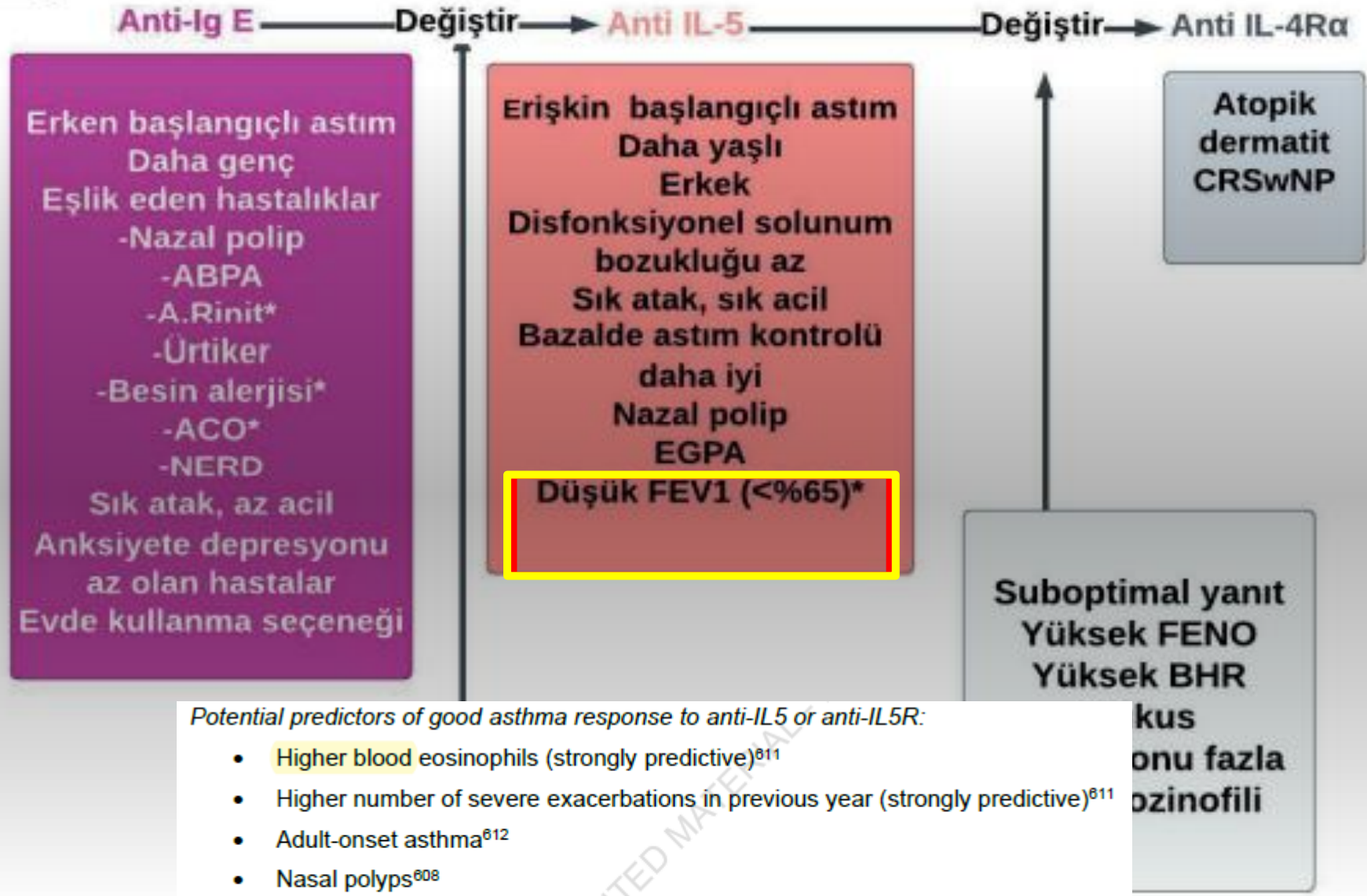
Inflamasyona göre fenotip

- Eozinofilik
- Nötrofilik
- Pauci-granulositik
- Mix Granülositik

TİP 2 ENDOTİP

NAZAL POLİPİN EŞLİK ETTİĞİ,
ERİŞKİN BAŞLANGIÇLI,
SIK ATAK GEÇİREN (Atak predominant)
OBEZ
NONATOPİK
EOZİNOFİLİK FENOTİP

OMALİZUMAB-MEPOLİZUMAB UPİLUMAB KİME?



*Kanıt düzeyi düşük
** Endikasyon dışı

Potential predictors of good asthma response to anti-IL5 or anti-IL5R:

- Higher blood eosinophils (strongly predictive)[611]
- Higher number of severe exacerbations in previous year (strongly predictive)[611]
- Adult-onset asthma[612]
- Nasal polyps[608]
- Maintenance OCS at baseline[608]
- Low lung function (FEV_1 <65% predicted in one study).[613]

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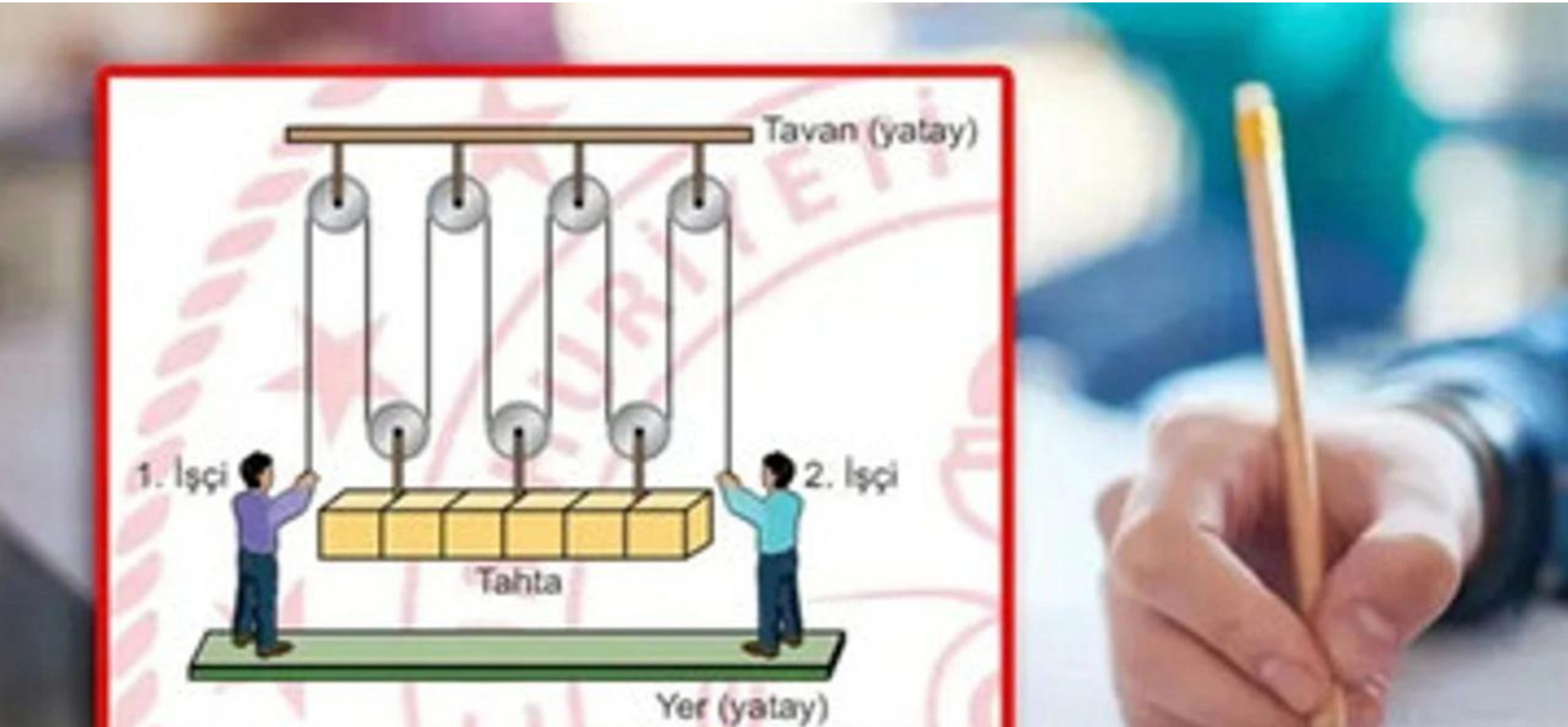
ergy 2021
Svenningsen S, Nair P. Front Med 2017;4:158
Nair P. Respirology 2020;25:1123-5.

Fong et al, Clin Exp Allergy. 2021;00:1–14 .WATCH STUDY.

TARTIŞMALI SORULAR; BİRDEN FAZLA BİYOLOJİĞE ADAY HASTADA HANGİ BİYOLOJİK



Anti-Il 5 kullanım alanları

	Mepolizumab	Reslizumab	Benralizumab	Lirentelimab
Target	IL-5	IL-5	IL-5Rα	Siglec-8
FDA approved Indications	- Asthma (age 6+) - EGPA (age 18+) - Idiopathic HES (age 12+) - CRSwNP (age 18+)	- Asthma (age 18+)	- Asthma (age 12+) -CRSwNP (2021)	- None
Dose	- Asthma age 12+ and CRSwNP: 100 mg SC every 4 weeks - Asthma age 6–11:40 mg SC every 4 weeks - EGPA and HES: 300 mg SC every 4 weeks	- 3 mg/kg IV every 4 weeks	- 30 mg SC every 4 weeks for 3 doses, then every 8 weeks	- N/A
Ongoing Clinical Trials	- EGPA - EoE - CSU - Eosinophilic fasciitis - Gleich syndrome - COPD exacerbation with eosinophilia	- CRS	- EGPA - HES - CRSwNP - EoE - EGID - CSU - AD - ABPA - Bullous pemphigoid	- EoE - EGID - CSU

Table 1. Characteristics of selected eosinophil selective biologics. *Abbreviations: IL-5, Interleukin 5; IL-5Rα, IL-5 receptor alpha subunit; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; SC, subcutaneous; IV, intravenous; CRSwNP, chronic rhinosinusitis with nasal polyposis; EoE, eosinophilic esophagitis; CSU, chronic spontaneous urticaria; COPD, chronic obstructive pulmonary disease; EGID, eosinophilic gastrointestinal disease; AD, atopic dermatitis; ABPA, allergic bronchopulmonary aspergillosis*

Pitlick, Li, Pongdee World Allergy Organization Journal (2022) 15:100676
http://doi.org/10.1016/j.waojou.2022.100676

RDBPC Çalışmalara göre sonlanım noktalarının karşılaştırılması

	ATAKLARDA AZALMA	STEROİD AZALTMA	SEMPTOM KONTROLÜ	FEV1'de İYİLEŞME
MEPOLİZUMAB	%53-58 %32 s.s kullanan	%50	ACQ **5** **0,4-0,52** ***Dahil edilme kriterleinde ACQ≥ 1,5 şartı yok; Bazal ACQ:2,2**	113-120 mL ***Bazal FEV1 :1,70-1,80; (%59-%60)***
RESLİZUMAB	%50-%59	NA **Gerçek yaşamda %50 azalma bazale göre*	ACQ **7** 0,23-0,25 ***Bazal ACQ:2,5***	160-180 mL FVC: 130 mL FEF25-75:233 mL ****Dahil edilme kriterleinde FEV1<%80 şartı yok*** ***Bazal FEV1 1,90-2,13;(%63-%70)***
BENRALİZUMAB	%28-%51 **%70 S.S kullananan**	**%75**	ACQ **6** 0,25-0,29 ***Bazal ACQ:2,8***	116-**159 mL** ***Bazal FEV1 :1,70-1,80; (%56-%58)***

ÇALIŞMAYA DAHİL EDİLME KRİTERLERİ FARKLI

TABLE I. Key differences in inclusion criteria among included studies by treatment assessed

Characteristic	Mepolizumab	Reslizumab	Benralizumab
Baseline blood eosinophil count	≥150 cells/μL at baseline or ≥300 cells/μL in past year	≥400 cells/μL	≥300 cells/μL*
Exacerbation history	≥2 Exacerbations in past year	≥1 Exacerbation in past year†	≥2 Exacerbations in past year
ICS	High	Medium-high (≥440 μg/d fluticasone)	High*
Maintenance OCS use	Allowed, any dose	Allowed but ≤10 mg/d prednisolone	Allowed, any dose
Predicted FEV_1 (%)	<80% (<90% for age <18 y) at screening	None	<80% (<90% for age <18 y) at screening and baseline
ACQ score	None	ACQ-7 score ≥1.5 at screening and baseline	ACQ-6 score ≥1.5 at screening

ICS, Inhaled corticosteroid.

*Inclusion criteria for benralizumab studies were wider for blood eosinophil count and ICS dose; however, the primary publications reported results for the 300 cells/μL or greater and high-ICS dose patient populations. Additional subgroup analyses for patients with baseline blood eosinophil counts of 150 cells/μL or greater were reported in the benralizumab pooled analysis of the phase 3 trials only and subsequently included in this study.

†Data for the end point of exacerbations requiring ED visits/hospitalizations were reported in the reslizumab pooled analysis. Patients had 2 or more exacerbations in the past year and GINA step 4/5 therapy.

Busse et al, J ALLERGY CLIN IMMUNOL JANUARY 2019

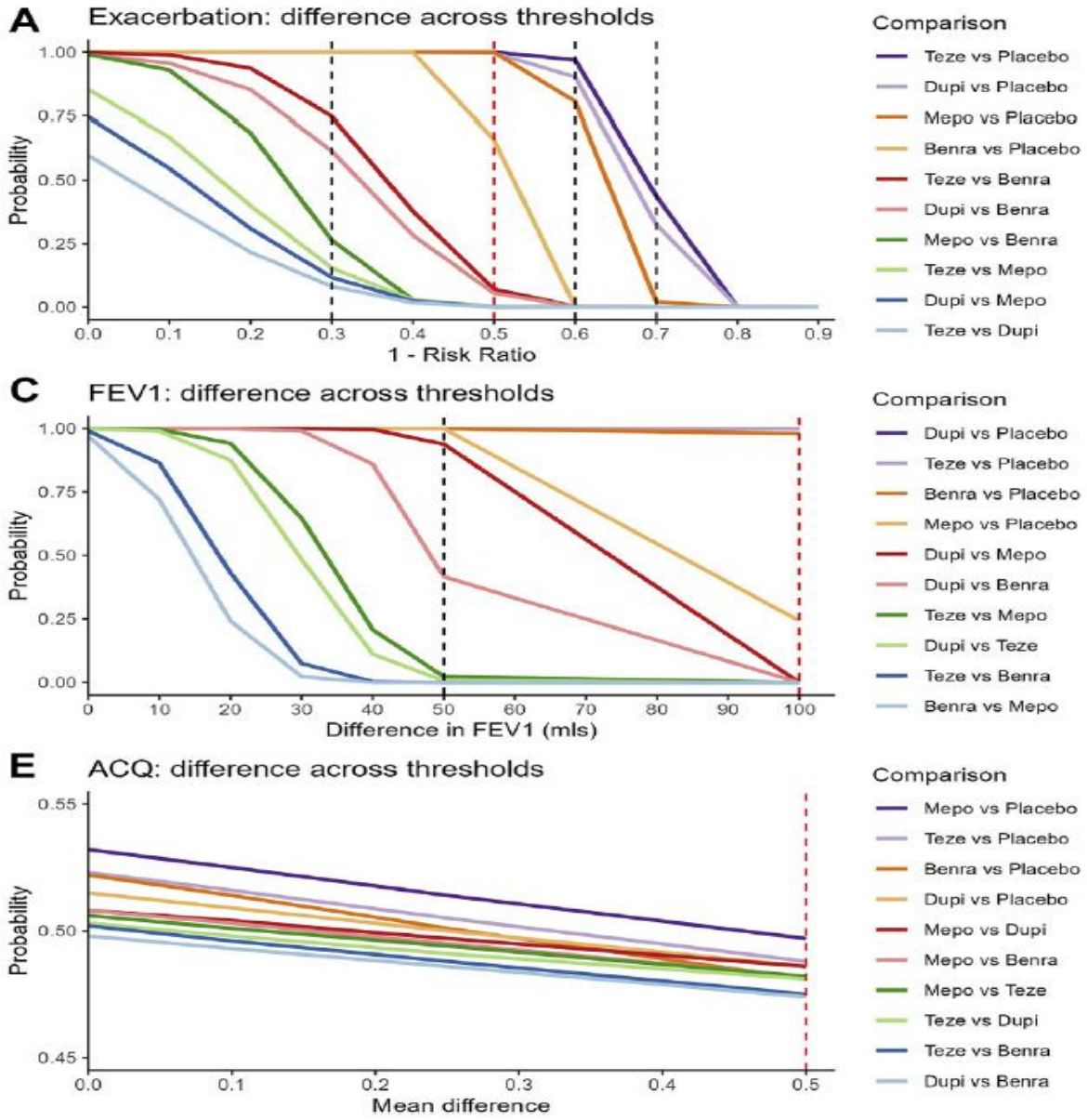
Biyolojik Karşılaştırma Metaanaliz

Biologics and immunotherapy

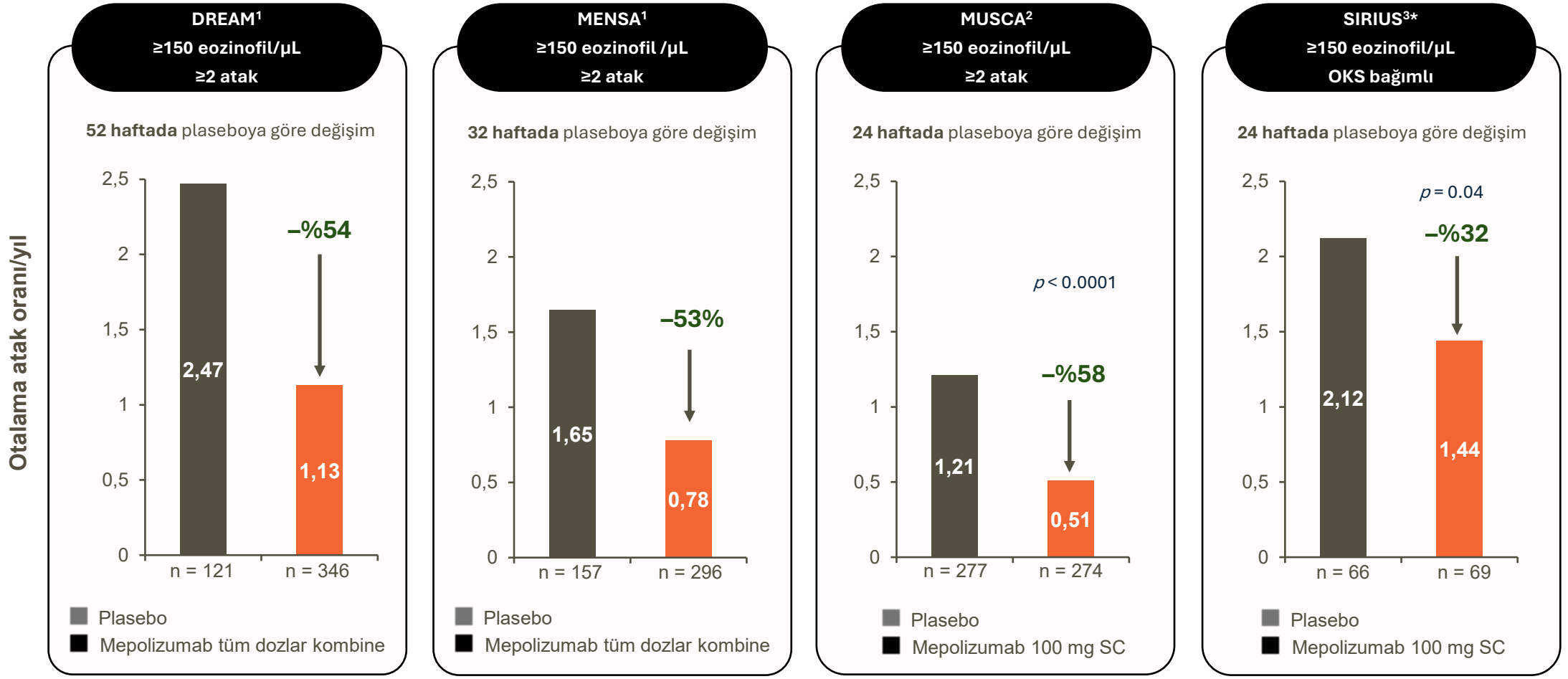
Comparative efficacy of tezepelumab to mepolizumab, benralizumab, and dupilumab in eosinophilic asthma: A Bayesian network meta-analysis

Tanawin Nopsopon, MD, MPH,[a,b,c] Grace Lassiter, MD, MPH,[d] Ming-Li Chen, MD,[b,e] G. Caleb Alexander, MD, MS,[f,g,h] Corinne Keet, MD, PhD,[i] Hwanhee Hong, PhD,[j] and Ayobami Akenroye, MBChB, MPH, PhD[a,f,k] *Boston, Mass; Bangkok, Thailand; New York, NY; Taichung, Taiwan; Baltimore, Md; and Chapel Hill and Durham, NC*

ATAKLARI azaltmada MEPOLİZUMAB
(bazalde MEPO:3,5; BENRA:2,8)
FEV1'i iyileştirme BENRALİZUMAB
ACQ iyileştirme MEPOLİZUMAB
(Dahil Edilmede Kontrolsüzlük Gerekmiyor !)



MEPOLİZUMAB-ATAKLAR



Mepolizumab ağır eozinofilik astımlı hastalarda klinik olarak anlamlı atakları devamlı olarak iyileştirir

* SIRIUS'a dahil etmek için atak öyküsü gerekmiyordu.

NOT: Klinik olarak anlamlı ataklar, sistemik kortikosteroidlerin kullanılmasını gerektiren astımın kötüleşmesi (≥3 gün [MUSCA][2] için ve en azından mevcut oral glukokortikoid idame dozunun iki katına çıkması [SIRIUS][3]) veya hastaneye yatış, veya acil servis başvurusu veya bunların bir kombinasyonu.[1–3]

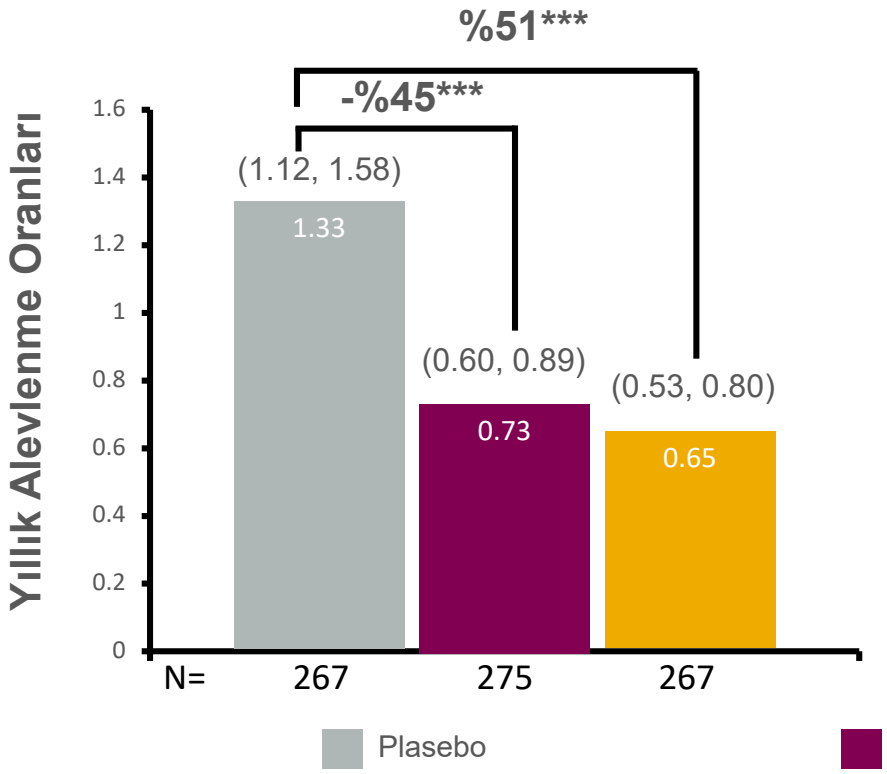
1. Ortega HG, *et al. Lancet Respir Med.* 2016;4:549–556; 2. Chupp GL, *et al. Lancet Respir Med.* 2017;5:390–400. 3. Bel EH, *et al. N Engl J Med.* 2014;371:1189–1197.

CONTENTS

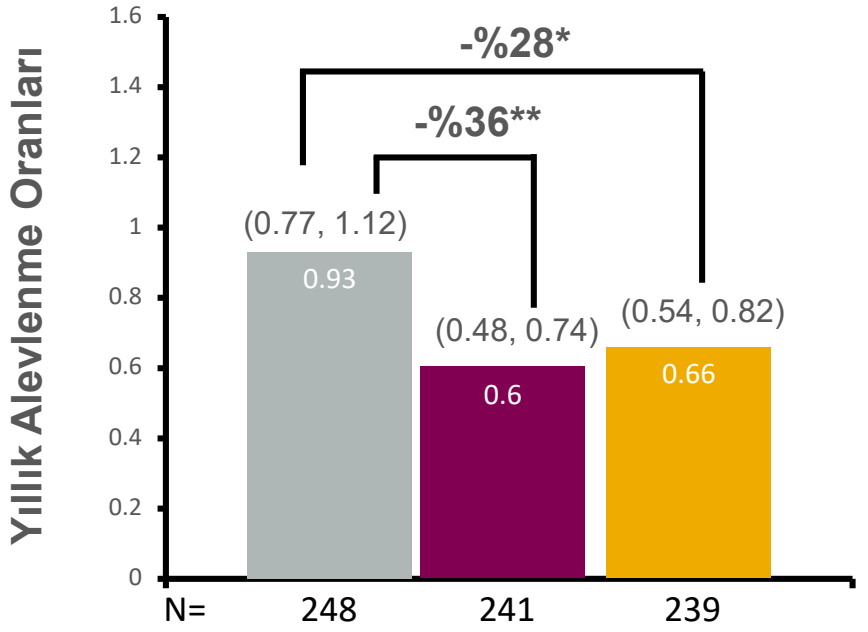
BENRALİZUMAB-ATAKLARI AZALTMA BAŞARISI

Her İki Dozlama Rejimi de AER'yi Plaseboya Kıyasla Anlamlı Ölçüde Azaltmıştır (TAK, eos ≥300 hücre/µL)

SIROCCO (48 hafta)[1]



CALIMA[a] (56 hafta)[2]



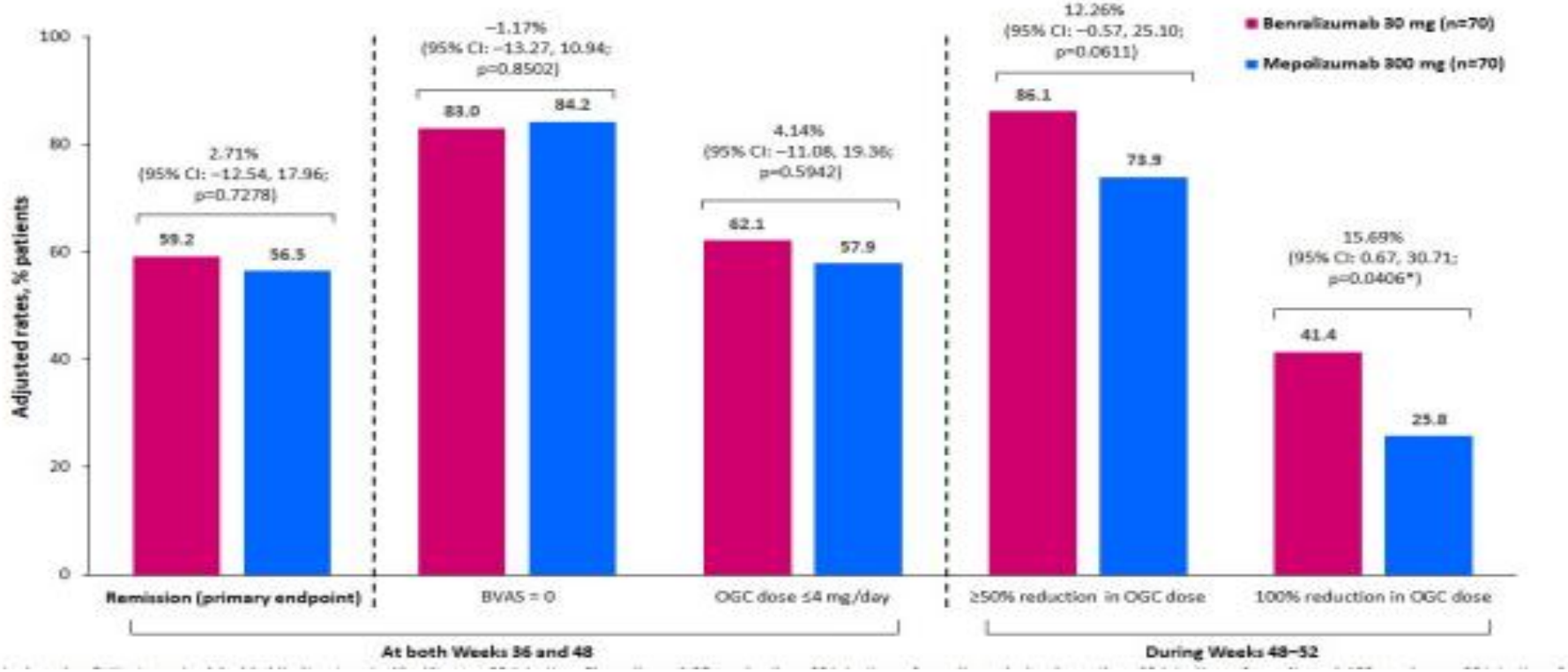
Plasebo | Benralizumab Q4W | Benralizumab Q8W

- **CALIMA çalışmasında 0.93 olarak belirlenen arka plan alevlenme oranı beklenenden düşüktür**

*P<0.05; **P<0.01; ***P<0.001. [a]CALIMA çalışmasının yüksek dozaj inhale kortikosteroid kohortundaki veriler
Eşdeğişken olarak tedavi grubu, bölge, bir önceki yıl alevlenme sayısı ve idame oral kortikosteroid kullanımını içeren negatif binomial model aracılığıyla analiz. Çubukların üzerindeki değerler %95 GA'yı gösterir.
AER = yıllık alevlenme oranı; eos = başlangıçtaki kan eozinofil sayısı; TAK = tam analiz kümesi; Q4W = 4 haftada bir; Q8W = 8 haftada bir.
Adapted from 1. Bleecker ER et al. Lancet. 2016;388;2115-27; 2. FitzGerald JM et al. Lancet. 2016; 388:2128-41

HEAD TO HEAD KAFA KAFAYA ANTI IL-5 KARŞILAŞTIRMASI VAR MI?

Benralizumab –mepolizumab
Kafa kafaya tek karşılaştırma
MANDARA ÇALIŞMASI-EGPA



Arthritis Rheumatol. 2023; 75 (suppl 9). h

Allergy

WILEY

Allergy

REVIEW OPEN ACCESS

Head-To-Head Comparison of Biologic Efficacy in Asthma: What Have We Learned?

Brian J. Lipworth[1] | Robert Greig[1] | Rory Chan[1] | Chris RuiWen Kuo[2] | Catherine Jackson[3]

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Keywords: benralizumab | dupilumab | mepolizumab | omalizumab | tezepelumab

Thus, at present, the most robust data have been gleaned from appraising indirect head-to-head comparisons of different biologics from either phase 2 or phase 3 randomised controlled trials (RCT) or from real-life health informatics data. In this regard, the numerous systematic reviews and associated meta-analyses which have been performed to indirectly compare biologics are often driven by pharmaceutical companies who may have vested interests in publishing the right result for their particular drug.

Pointedly, this article is not intended to be a systematic review or a meta-analysis of the various biologics, as this has already been done, albeit with different methodologies. For the various Forest plots, we did not factor in sample size weighting or

heterogeneity analysis, and no pooled estimate of the overall effect size was calculated, given that the H2H comparisons were made between different biologics and not versus placebo. Nonetheless, the Forest plots provide a way to assess which of the H2H comparisons are significant in terms of crude inspection of the 95% CI. A pragmatic decision was made to only include the commonly used and approved biologics comprising Omal, Mepo, Benra, Dupi, and Teze, but not reslizumab, which is rarely prescribed due to practical and fiscal issues related to its intravenous administration.

Atakları azaltmada eoz >300/µL

Tezepelumap ,

Dupilumab,

Mepolizumab,

> Benralizumab

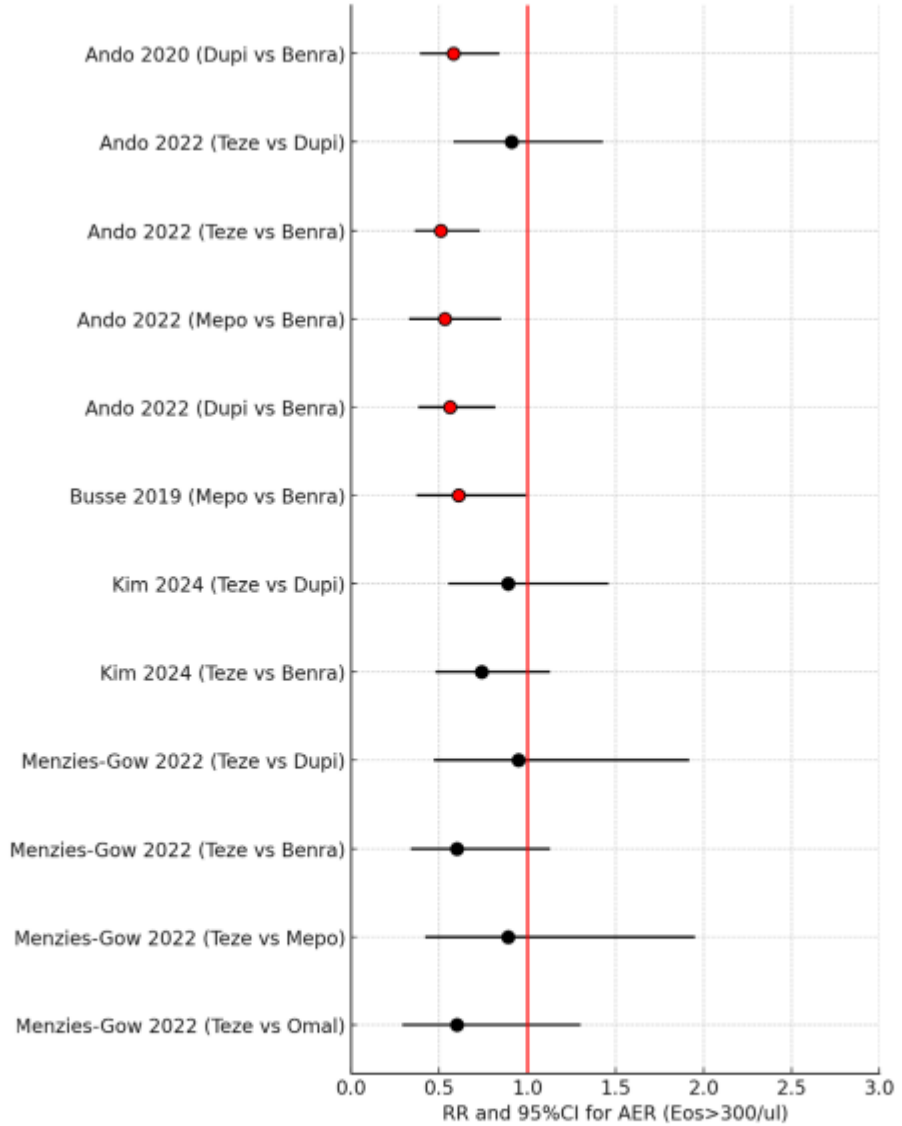


FIGURE 4 | Forest plot showing pairwise indirect comparisons of biologics in uncontrolled asthma for reductions in annualised exacerbation rates (AER) for the subgroup of patients with baseline eosinophils (Eos) ≥ 300/µL, as rate ratios (RR) and 95% confidence intervals (CI). For crude pairwise comparisons of drug A versus drug B, red circles for the RR denote a significant difference in favour of drug A where the 95% CI excludes unity. Black circles for the RR denote no significant difference between biologics where the 95% CI includes unity [45, 46, 52, 54, 55]. Benra, benralizumab; Dupi, dupilumab; Mepo, mepolizumab; Omal, omalizumab, Teze, tezepelumab.

HASTAYA AİT FAKTÖRLER

- KULLANIM KOLAYLIĞI

OTOENJEKTÖR: MEPOLİZUMAB

	Benralizumab (benralizumab)[1]	Omalizumab[2]	Mepolizumab[3]
Doz sayısı (1. Yıl)	**8**	13–26	13
Doz sayısı (2. Yıl)	**6**	13–26	13
İdame dozu	**Q8W**	Q2W–Q4W	Q4W
Kullanıma hazır enjektör (hazırlama gerekmez)	✓	✓	✓
Stabil doz (vücut ağırlığına dayalı dozaj yok)	✓	✗	✓
SC enjeksiyon	✓	✓	✓
Hastanın kendisinin uygulaması/otomatik enjektör	✓	✓	✓

Benralizumab sadece SC kullanım içindir. Önerilen Benralizumab dozu, ilk üç doz için Q4W bir kez, ardından Q8W bir kez ve sonrasında SC enjeksiyondur; dozlar üst kol, uyluk veya karın içine uygulanır.

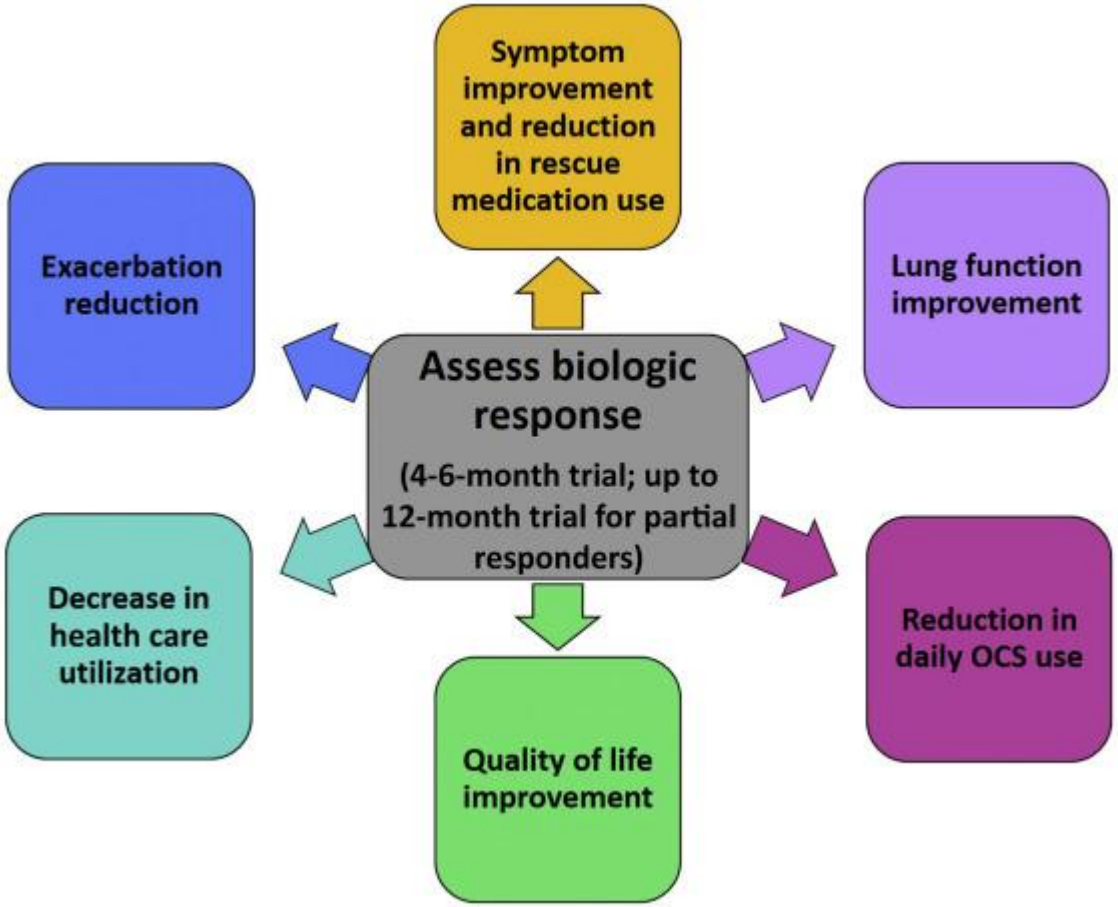
Q2W = 2 haftada bir; Q4W = 4 haftada bir; Q8W = 8 haftada bir; SC = subkutan; UK = İngiltere.

1. Fasenra [summary of product characteristics]. Luton, UK: AstraZeneca UK Limited; 2021. **2.** Xolair [summary of product characteristics]. Ireland, UK: Novartis Europharm Limited; 2020.
3. Nucala [summary of product characteristics]. Middlesex, UK: GlaxoSmithKline UK Limited; 2021. **4.** Cinqaero [summary of product characteristics]. Castleford, UK: Teva UK Limited; 2021.
5. Dupixent [summary of product characteristics]. Berkshire, UK: Aventis Pharma Limited; 2021.

Kullanıma hazır enjektör
Omalizumab ve Benralizumab

KULLANIM AVANTAJI OTOENJEKSİYON
MEPOLİZUMAB

BİYOLOJİK TEDAVİ YANITININ DEĞERLENDİRİLMESİ



Pepper et al, J Allergy Clin Immunol Pract 2021 Mar;9(3):1081-1088

TEDAVİ YANITINI ETKİLEYEN FAKTÖRLER

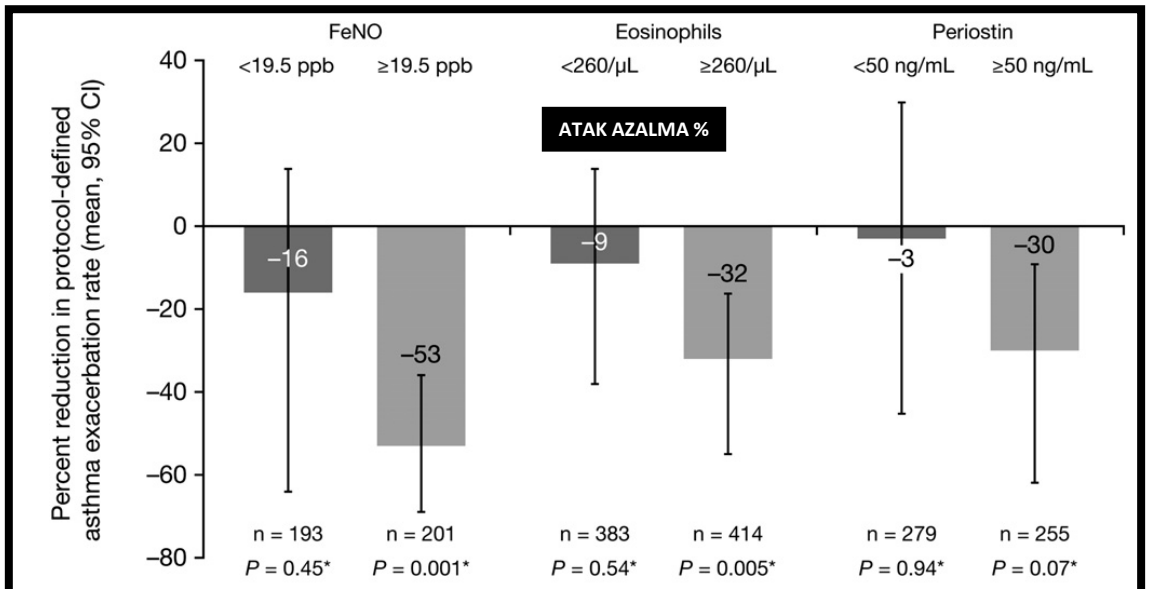
TİP2 İNFLAMASYON

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study

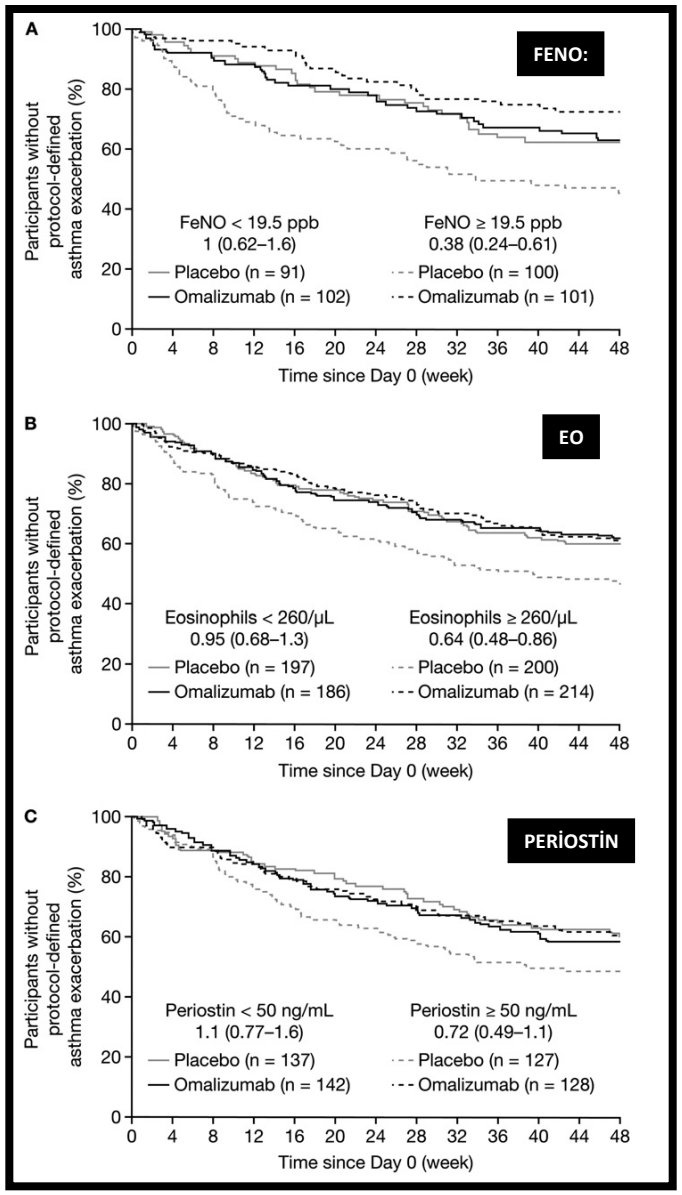
Nicola A. Hanania[1], Sally Wenzel[2], Karin Rosén[3], Hsin-Ju Hsieh[3], Sofia Mosesova[3], David F. Choy[3], Preeti Lal[3], Joseph R. Arron[3], Jeffrey M. Harris[3], and William Busse[4]

Eozinofilik grupta atakları azaltma etkisi daha mı fazla?



Exacerbation rates

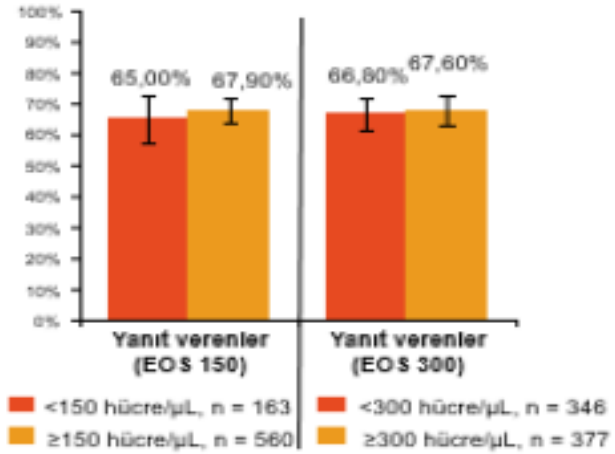
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93



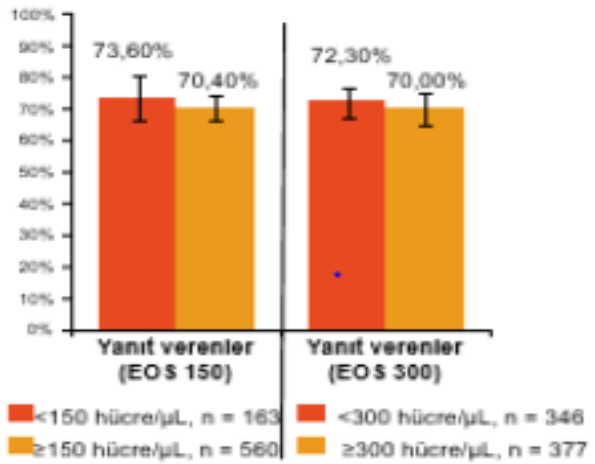
Am J Respir Crit Care Med Vol 187, Iss. 8, pp 804–811, Apr 15, 2013

GETE yanıtı, alevlenme yanıtının %40 azalması ve kombine yanıt oranları EOS sayılarına bakılmaksızın benzerdi

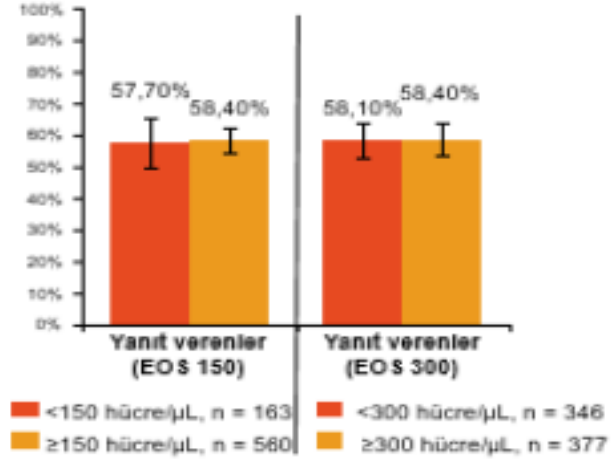
a. Hekimin küresel değerlendirmesine
b. (GETE) dayalı yanıt verenler



b. %40'lık düşüşe göre yanıt verenler
Yıllık alevlenme oranında

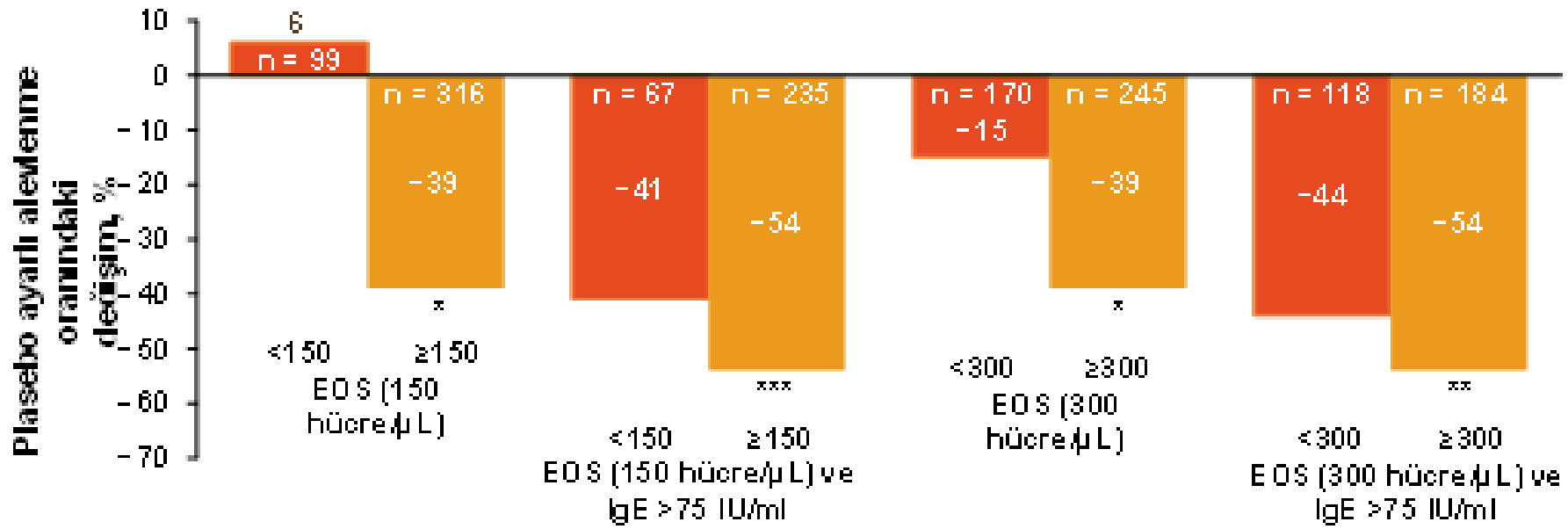


c. Kombine Yanıt verenler
(GETE + alevlenmeler)



Yetişkinlerde omalizumab tedavisine T4 -6'da (4 -6 aylık tedaviden sonra ilk etkinlik değerlendirme zamanı) 150 hücre/µL'deki kan eozinofil sayısı eşiğine göre yanıt verenler (" EOS 150 ": <150 hücre/µL, n=163; ┘ 150 hücre/µL, n=560) ve 300 hücre/µL (" EOS 300 ": <300 hücre/µL, n =346; 300 hücre/µL, n =377). a) Doktorun küresel değerlendirmesine dayanan yanıt verenler (GETE). b) Yıllık alevlenme hızında %40'lık bir düşüşe dayanan yanıt verenler. c) Kombine yanıt verenler (GETE ve alevlenme oranının kombinasyonu azalır). Hata çubukları %95 güven aralığı gösterdi.

Eozinofil –Total IgE düzeyi Omalizumab yanıtı



INNOVATE çalışma verilerinin post - hoc analizi (N = 419)

Bizim tecrübemiz?

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Tuberk Toraks 2021;69(1):39-48
Geliş Tarihi/Received: 22.02.2021 • Kabul Ediliş Tarihi/Accepted: 18.03.2021

KLİNİK ÇALIŞMA
RESEARCH ARTICLE

The significance of eosinophil and eosinophil lymphocyte ratio (ELR) in predicting response to omalizumab treatment in patients with severe allergic asthma

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İsmet BULUT[2] (ID)
Cihan ÖRÇEN[3] (ID)

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[2] *Sağlık Bilimleri Üniversitesi, Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, İmmünoloji ve Alerji Anabilim Dalı, İstanbul, Türkiye*
[3] Clinic of Chest Diseases, University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey
[3] *Sağlık Bilimleri Üniversitesi, Derince Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Kocaeli, Türkiye*

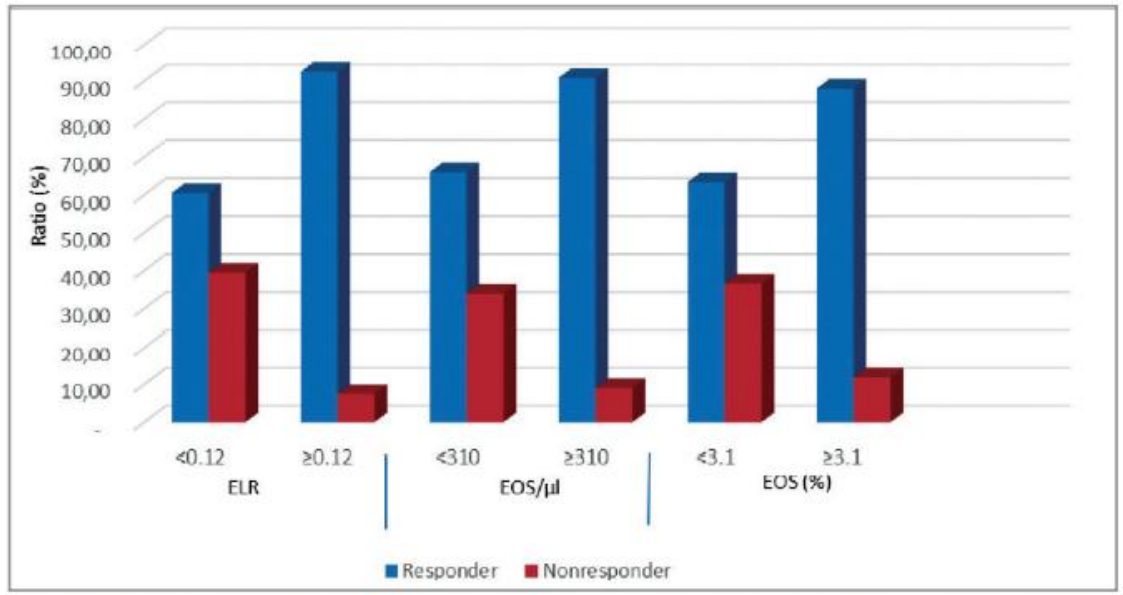
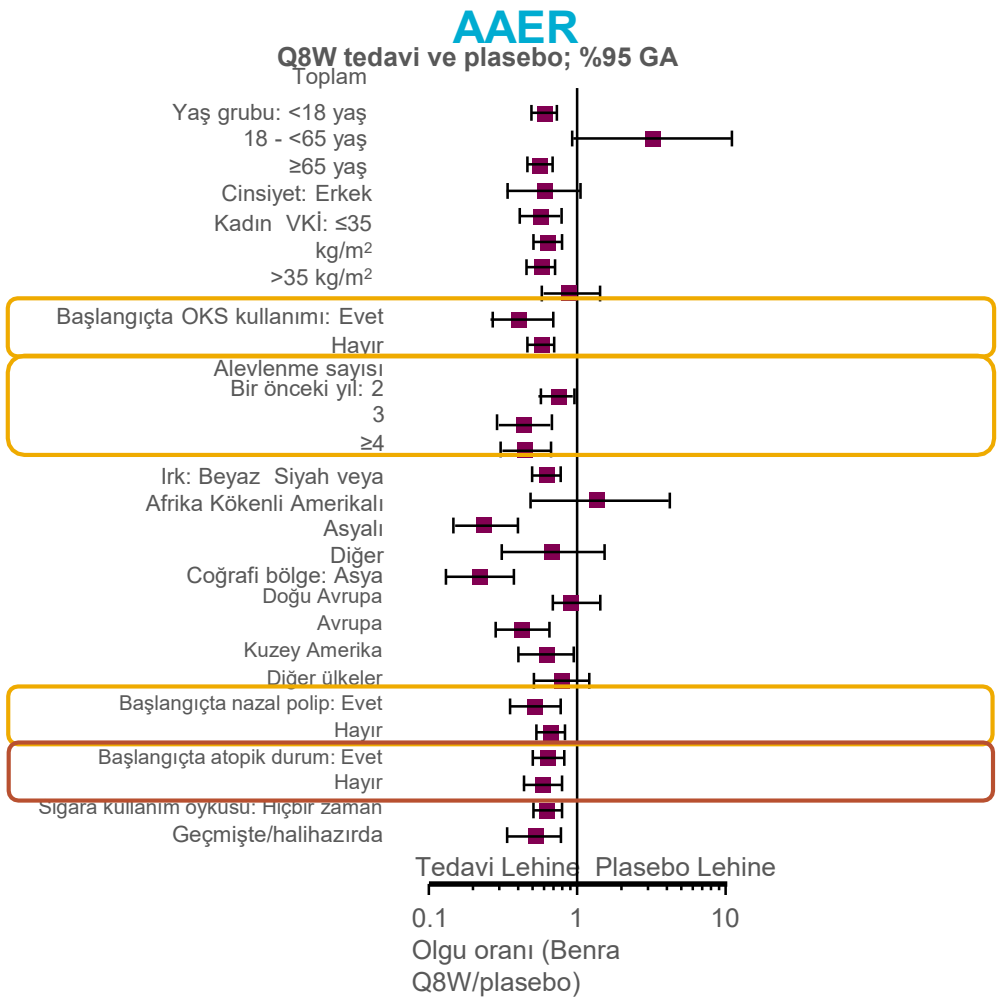
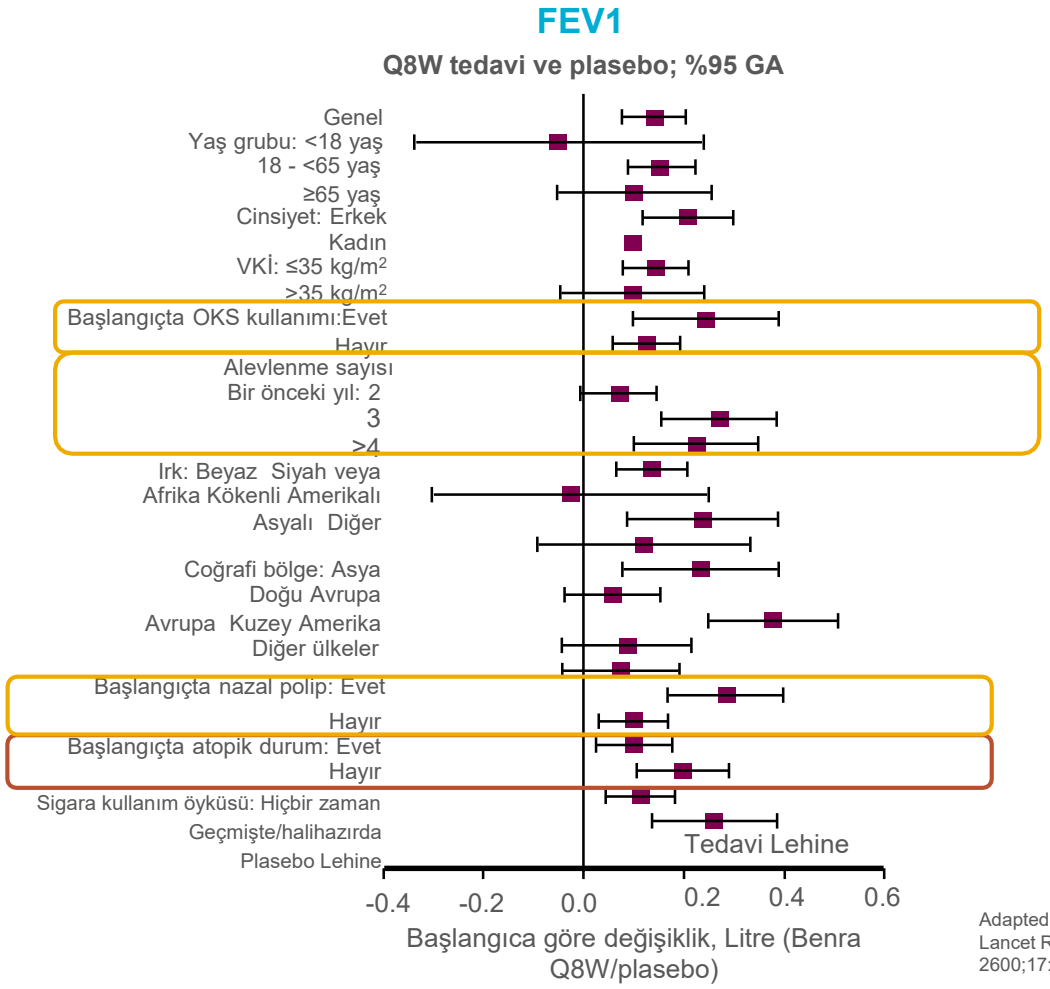


Figure 2. Relationship between the groups of responder-nonresponder and the cut off values of ELR, EOS and EOS (%)

Eozinofilik Astım Fenotipinin Spesifik Özellikleri, EOS Sayısı ≥300 hücre/µL Olan Hastalarda Benralizumabın Tedavi Etkisinde Artışla İlişkili Bulunmuştur (Tam Analiz Kümesi; Birleştirilmiş Çalışmalar, Q8W)





Adapted from: Fitzgerald JM et al. Lancet Respir Med. 2017;pii:S2213-2600;17:303442

AER analizinde tedavi, çalışma, bölge, randomizasyon sırasında OKS kullanımı ve önceki alevlenmeler açısından ayarlama yapılan negatif binomial model kullanılmıştır. FEV1 analizinde tedavi, çalışma, başlangıç değeri, bölge, randomizasyon sırasında OKS kullanımı, vizit ve vizit x tedavi açısından ayarlama yapılan karma etki tekrarlı ölçümler analiz modeli kullanılmıştır. AAER = yıllık astım alevlenme oranı; Benra = benralizumab; VKİ = vücut kütle indeksi; EOS = eozinofil; FEV1 = 1. saniyedeki zorlu ekspirasyon hacmi; FU = yıl olarak takip süresi; OKS = oral kortikosteroid; Q8W = 8 haftada bir; GA = güven aralığı.

Efficacy of Mepolizumab in Patients with Severe Eosinophilic Asthma and Concomitant Aspirin-Exacerbated Respiratory Disease: Meta-Analysis of Two Phase III Trials

	Meta-analysis (MENSA + MUSCA)
Current nasal polyps at screening	
Rate ratio (95% CI)	0.20 (0.11, 0.35)
No nasal polyps at screening	
Rate ratio (95% CI)	0.51 (0.41, 0.64)
Aspirin/NSAID intolerance at screening	
Rate ratio (95% CI)	0.66 (0.37, 1.18)
No aspirin/NSAID intolerance at screening	
Rate ratio (95% CI)	0.43 (0.35, 0.55)
AERD at screening	
Rate ratio (95% CI)	0.66 (0.24, 1.79)
No AERD at screening	
Rate ratio (95% CI)	0.45 (0.36, 0.56)

AERD, aspirin-exacerbated respiratory disease; CI, confidence interval; NSAID, non-steroidal anti-

NAZAL POLİP
MEPO:86
PL:80

AERD
MEPO:20
PL:20

	DREAM (n=616)		MENSA* (n=569)	
	Placebo	Mepolizumab	Placebo	Mepolizumab
150 cells per µL				
Exacerbation rate per year	1·65	1·16	1·65	1·00
Rate ratio *vs* placebo (95% CI)	..	0·70 (0·53–0·93)	..	0·61 (0·45–0·82)
300 cells per µL				
Exacerbation rate per year	1·98	1·03	1·74	0·85
Rate ratio *vs* placebo (95% CI)	..	0·52 (0·41–0·65)	..	0·49 (0·38–0·63)
400 cells per µL				
Exacerbation rate per year	2·13	0·98	1·78	0·79
Rate ratio *vs* placebo (95% CI)	..	0·46 (0·36–0·58)	..	0·45 (0·34–0·58)
500 cells per µL				
Exacerbation rate per year	2·26	0·94	1·81	0·75
Rate ratio *vs* placebo (95% CI)	..	0·42 (0·32–0·54)	..	0·42 (0·31–0·55)

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

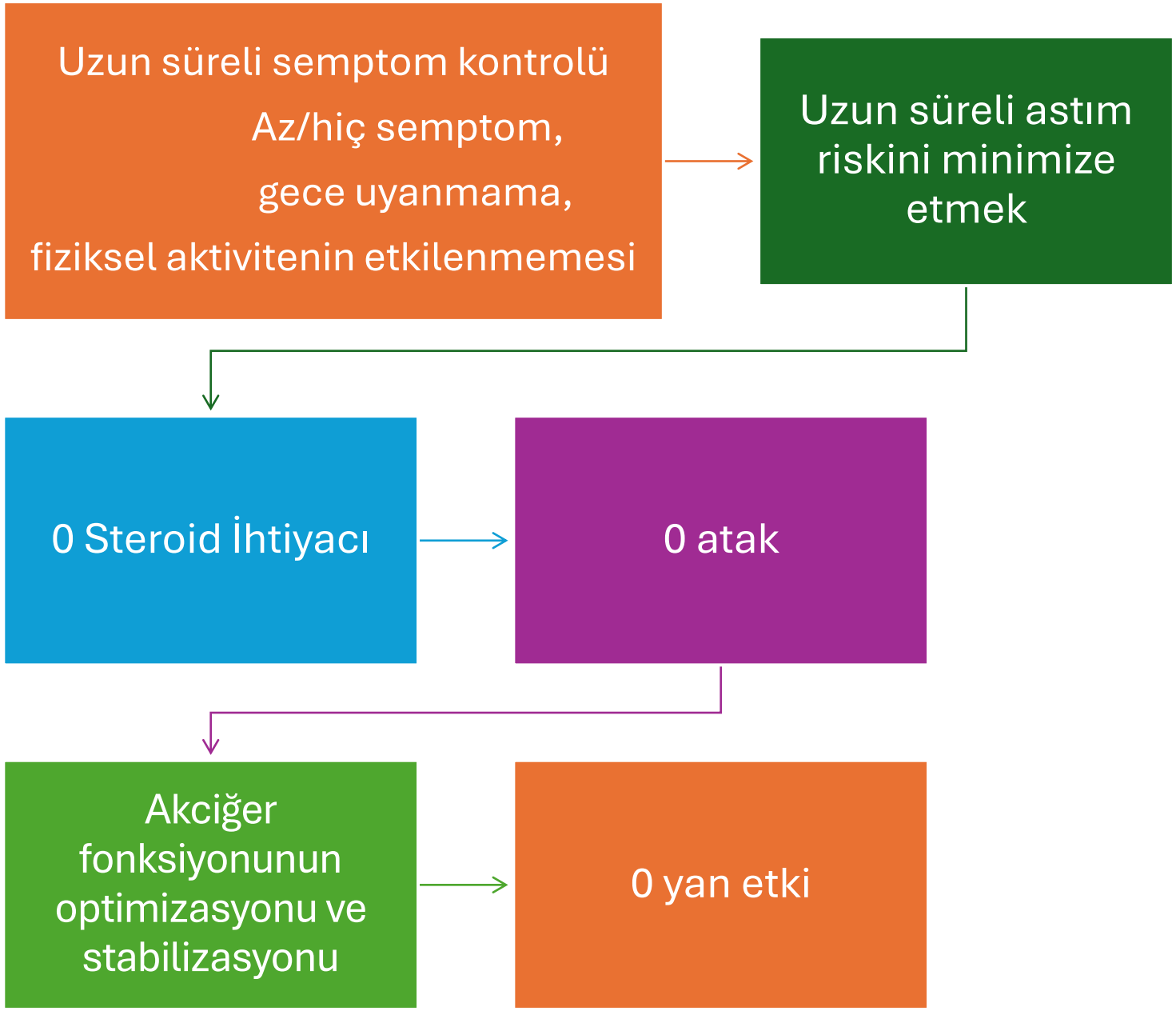
Hector G Ortega, Steven W Yancey, Bhabita Mayer, Necdet B Gunsoy, Oliver N Keene, Eugene R Bleecker, Christopher E Brightling, Ian D Pavord

	DREAM (n=616)	MENSA (n=569)	Combined* (n=1185)
Prebronchodilator FEV_1 (mL [95% CI]; n [%])			
≥150 cells per µL	2 (–93 to 97); 418 (68%)	113 (28 to 198); 423 (74%)	64 (1 to 127); 841 (71%)
≥300 cells per µL	–4 (–123 to 116); 274 (44%)	128 (25 to 232); 290 (51%)	68 (–10 to 146); 564 (48%)
≥500 cells per µL	72 (–105 to 248); 149 (24%)	113 (–24 to 250); 181 (32%)	106 (–2 to 214); 330 (28%)
Postbronchodilator FEV_1 (mL [95% CI]; n [%])			
≥150 cells per µL	22 (–71 to 114); 403 (65%)	172 (77 to 267); 386 (68%)	101 (35 to 168); 789 (67%)
≥300 cells per µL	18 (–101 to 138); 264 (43%)	202 (90 to 315); 268 (47%)	108 (26 to 191); 532 (45%)
≥500 cells per µL	83 (–90 to 255); 144 (23%)	247 (102 to 392); 166 (29%)	161 (50 to 272); 310 (26%)
SGRQ change in score (95% CI); n (%)			
≥150 cells per µL	..	–8·1 (–11·2 to –5·1); 420 (74%)	..
≥300 cells per µL	..	–10·4 (–14·2 to –6·7); 288 (51%)	..
≥500 cells per µL	..	–11·3 (–16·3 to –6·4); 179 (31%)	..
ACQ-5 change in score (95% CI); n (%)			
≥150 cells per µL	–0·14 (–0·36 to 0·08); 401 (65%)	–0·52 (–0·70 to –0·34); 402 (71%)	–0·35 (–0·49 to –0·20); 803 (68%)
≥300 cells per µL	–0·24 (–0·51 to 0·03); 262 (43%)	–0·73 (–0·95 to –0·50); 274 (48%)	–0·49 (–0·67 to –0·31); 536 (45%)
≥500 cells per µL	–0·44 (–0·83 to –0·06); 144 (23%)	–0·76 (–1·07 to –0·46); 171 (30%)	–0·61 (–0·85 to –0·37); 315 (27%)

Data are from the intention-to-treat populations from the DREAM and MENSA studies. All mepolizumab doses were combined for the analysis. n includes patients treated with either mepolizumab or placebo who provided data at week 32. *Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis. ACQ=asthma control questionnaire. ..=not available. SGRQ=St George's Respiratory Questionnaire.

Table 4: **Changes in FEV_1, SGRQ, and ACQ-5 by baseline blood eosinophil counts**

BİYOLOJİK TEDAVİ HEDEFLERİ



TAM REMİSYON
ALTTA YATAN PATOLOJİNİN İYİLEŞMESİ

EMJ Respir. 2023;11[Suppl 1]:2-10.
DOI/10.33590/emjrespir/10306104
.

Generalised framework for remission in asthma

Clinical remission on treatment

For ≥12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, and
- Optimisation and stabilisation of lung function, and
- Patient and HCP agreement regarding disease remission, and
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical remission off treatment

Same criteria maintained without asthma treatment for ≥12 months

Complete remission on treatment

Clinical remission plus the following:

- C… …f previously d… …., reduced blood or s… …r relevant n…
- In appropriate research settings: current negative bronchial hyperresponsiveness

İnceleyebildiğimiz tek biyomarker periferik eozinofil

Complete remission off treatment

Same criteria maintained without asthma treatment for ≥12 months

Reprinted from Menzies-Gow A, et al. J Allergy Clin Immunol. 2020;145(3):757-765. Copyright © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

HASTANIN MEPOLİZUMAB SONRASI İYİLEŞME DÜZEYİ

	BAZAL	MEPOLİZUMAB 4. AY	MEPOLİZUMAB 2. YIL
AKT	**13**	**18**	**21**
ACİL BAŞVURUSU	**AYDA 1**	**-**	**-**
ATAK (STEROİD GEREKTİREN)	**2**	**-**	**-**
Total IgE	**829**	**507**	**280**
Eozinofil	**620**	**190**	**200**
VAS Rinosinüzit Skoru **SNOT-22**	**9** **32**	**8**	**5** **22**

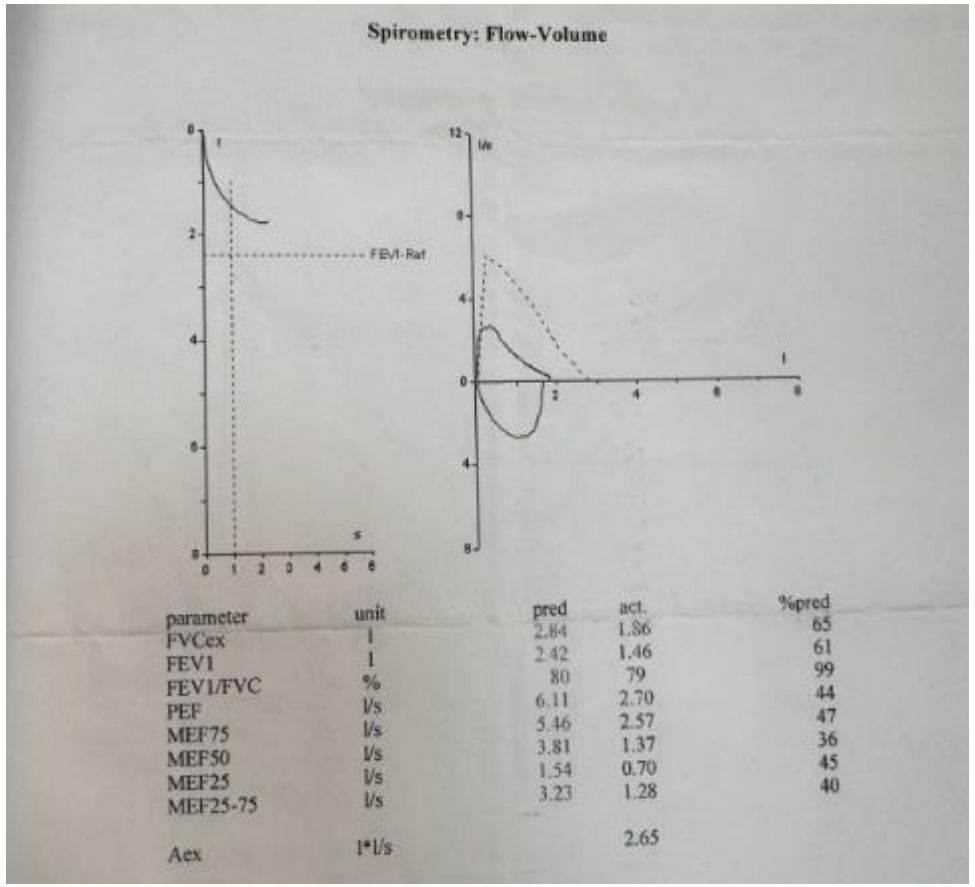
Paranazal BT

Ocak 2023

Ağustos 2023

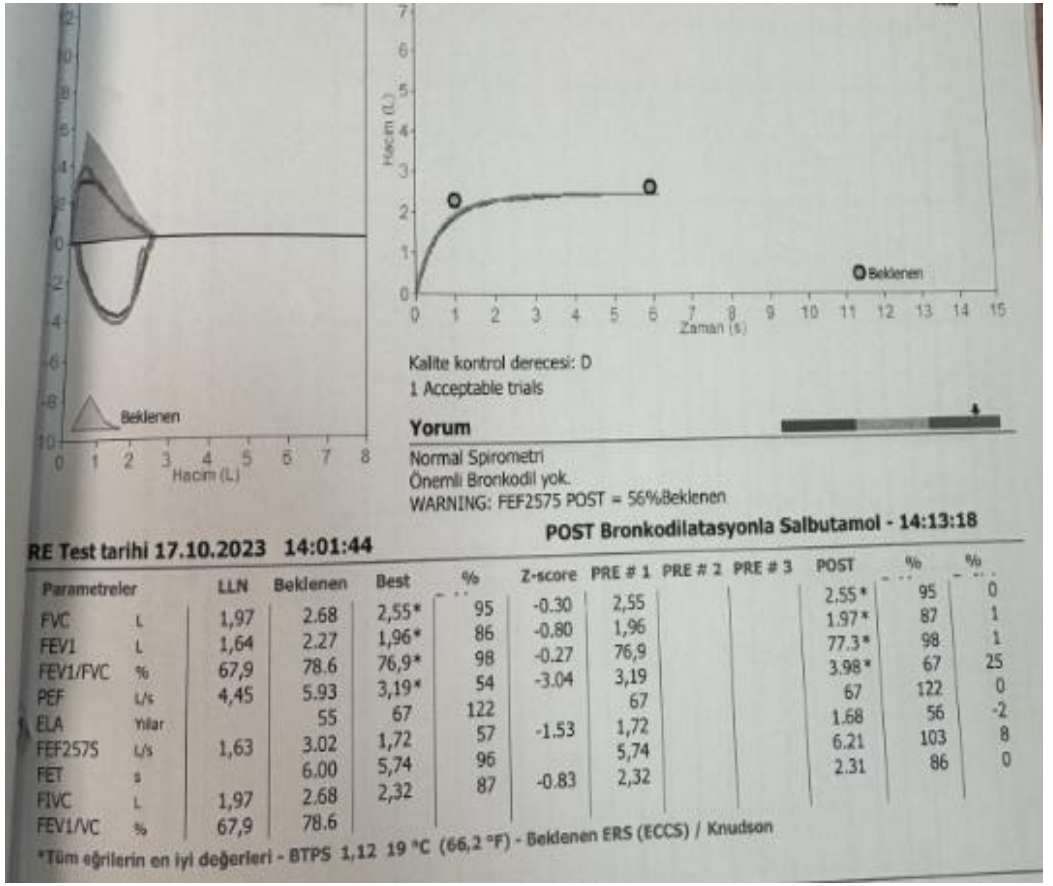
SPİROMETREDEKİ İYİLEŞME

FEV1: 1.46 (%61)



parameter	unit	pred	act.	%pred
FVCex	l	2.84	1.86	65
FEV1	l	2.42	1.46	61
FEV1/FVC	%	80	79	99
PEF	l/s	6.11	2.70	44
MEF75	l/s	5.46	2.57	47
MEF50	l/s	3.81	1.37	36
MEF25	l/s	1.54	0.70	45
MEF25-75	l/s	3.23	1.28	40
Aex	l*l/s		2.65	

FEV1:1.96 (%86)



Parametreler		LLN	Beklenen	Best	%	Z-score	PRE # 1	PRE # 2	PRE # 3	POST	%	%
FVC	L	1,97	2.68	2,55*	95	-0.30	2,55			2.55*	95	0
FEV1	L	1,64	2.27	1,96*	86	-0.80	1,96			1.97*	87	1
FEV1/FVC	%	67,9	78.6	76,9*	98	-0.27	76,9			77.3*	98	1
PEF	L/s	4,45	5.93	3,19*	54	-3.04	3,19			3.98*	67	25
ELA	Yıllar		55	67	122		67			67	122	0
FEF2575	L/s	1,63	3.02	1,72	57	-1.53	1,72			1.68	56	-2
FET	s		6.00	5,74	96		5,74			6.21	103	8
FIVC	L	1,97	2.68	2,32	87	-0.83	2,32			2.31	86	0
FEV1/VC	%	67,9	78.6									

MEPOLİZUMAB 2. YILINDA REMİSYONDA

YAN ETKİ GÖZLENMEDİ
İNFEKSİYON GELİŞMEDİ

0 ATAK

0 STEROİD

SEMPTOM KONTROLDE

%80 ÜZERİ FEV1

ORACLE RİSK ANALİZİNE GÖRE REMİSYON ORANLARI, ÇOK MERKEZLİ ÇALIŞMA (8 MERKEZ)

Tablo 1

Merkezlerin katılım oranı, n(%)	
Süreyyapaşa SUAM	135(42,3)
Ankara Bilkent şehir hastanesi	44(13,8)
Erciyes Üni. Tıp Fakültesi	42(13,2)
Karadeniz Teknik Üni Tıp Fakültesi	24(7,5)
Göztepe Medeniyet Üni Tıp Fakültesi	27(8,5)
Koç Üniversitesi Tıp Fakültesi	22(6,9)
Balıkesir Üniversitesi Tıp Fakültesi	20(6,3)
Etlik Şehir Hastanesi	5(1,6)

Biyolojiklere Suboptimal yanıt

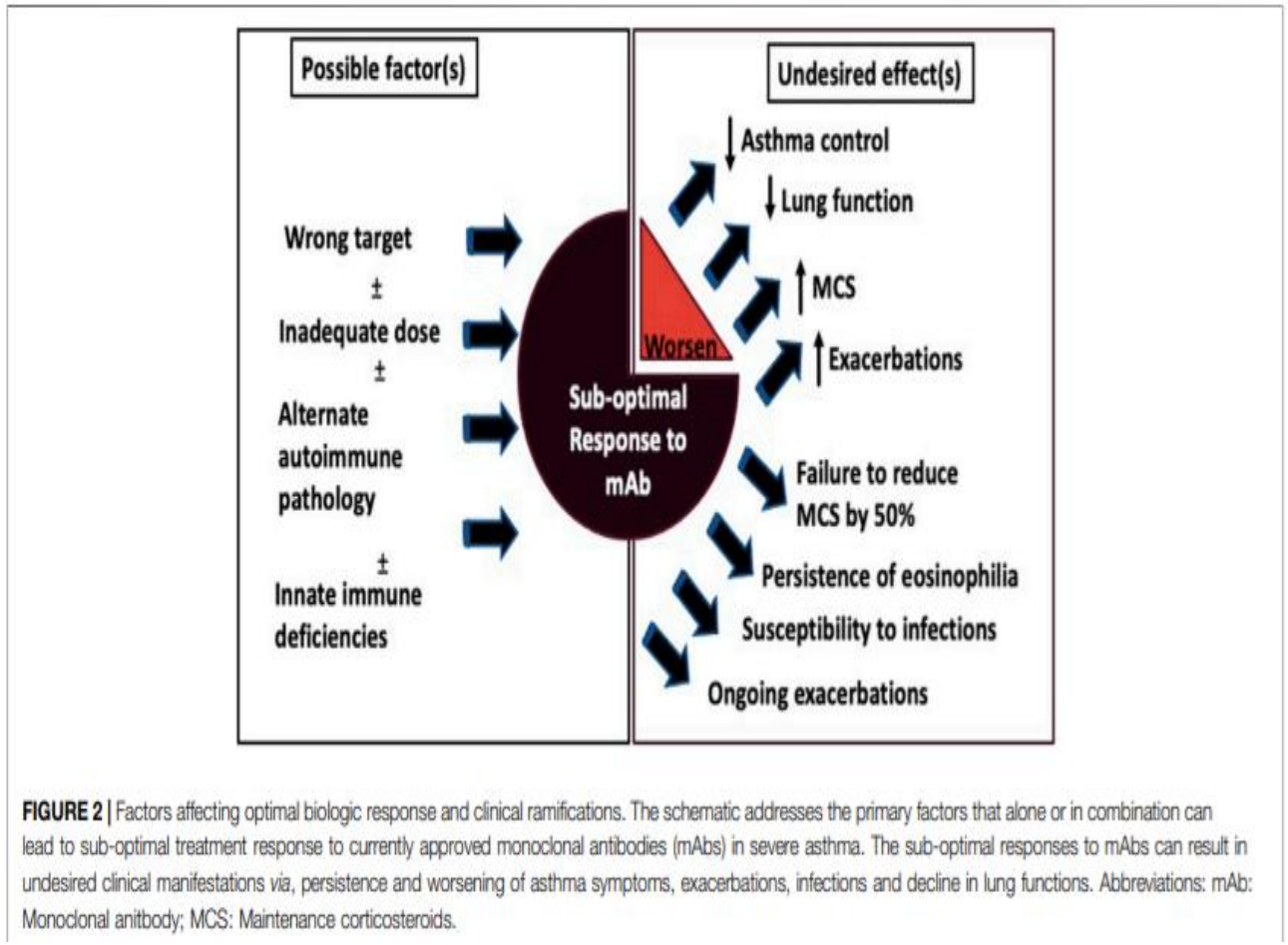


FIGURE 2 | Factors affecting optimal biologic response and clinical ramifications. The schematic addresses the primary factors that alone or in combination can lead to sub-optimal treatment response to currently approved monoclonal antibodies (mAbs) in severe asthma. The sub-optimal responses to mAbs can result in undesired clinical manifestations *via*, persistence and worsening of asthma symptoms, exacerbations, infections and decline in lung functions. Abbreviations: mAb: Monoclonal anitbody; MCS: Maintenance corticosteroids.

REVIEW at 16-24 weeks

STOP at 16-24 weeks if worsening of asthma or significant side effects from the biologic.

REASSESS by severe asthma MDT and consider stopping/switching biologic if ≥3 of following criteria are met:

- <0.5 unit improvement in ACQ-5 or -6
- Reduction in mOCS dose by <2.5mg *and* <25% of baseline prednisolone equivalence
- No reduction in exacerbations *and/or* hospital admissions for asthma
- Patient expectations of improvement are not met

Front. Pharmacol., 19 January 2022 https://doi.org/10.3389/fphar.2021.793409

Clin Exp Allergy. 2021;51:1225–1228.

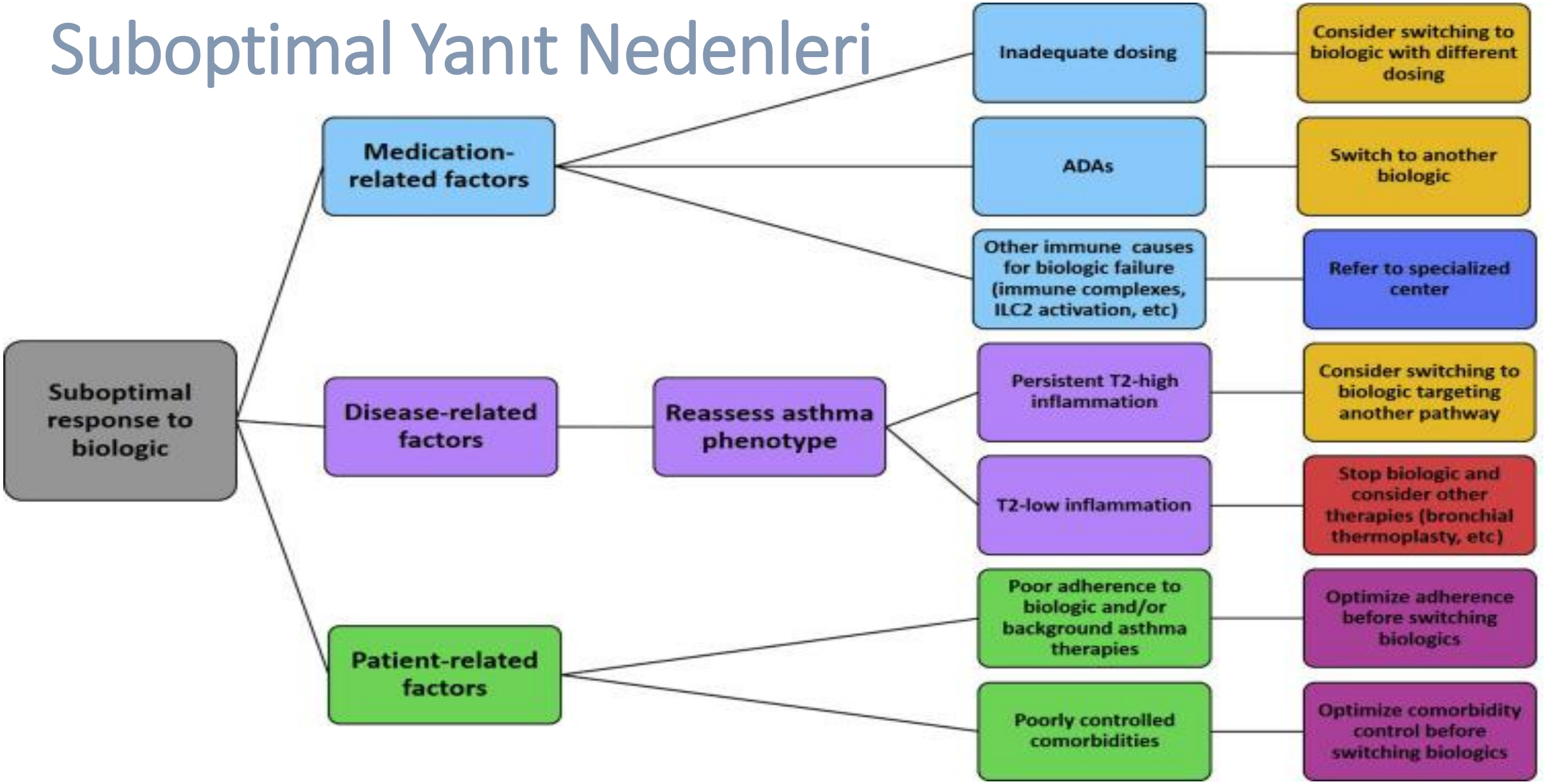
SUBOPTİMAL YANIT NEDENİ NE OLABİLİR?

HASTAYLA İLGİLİ

İLAÇLA İLGİLİ

HASTALIKLA İLGİLİ

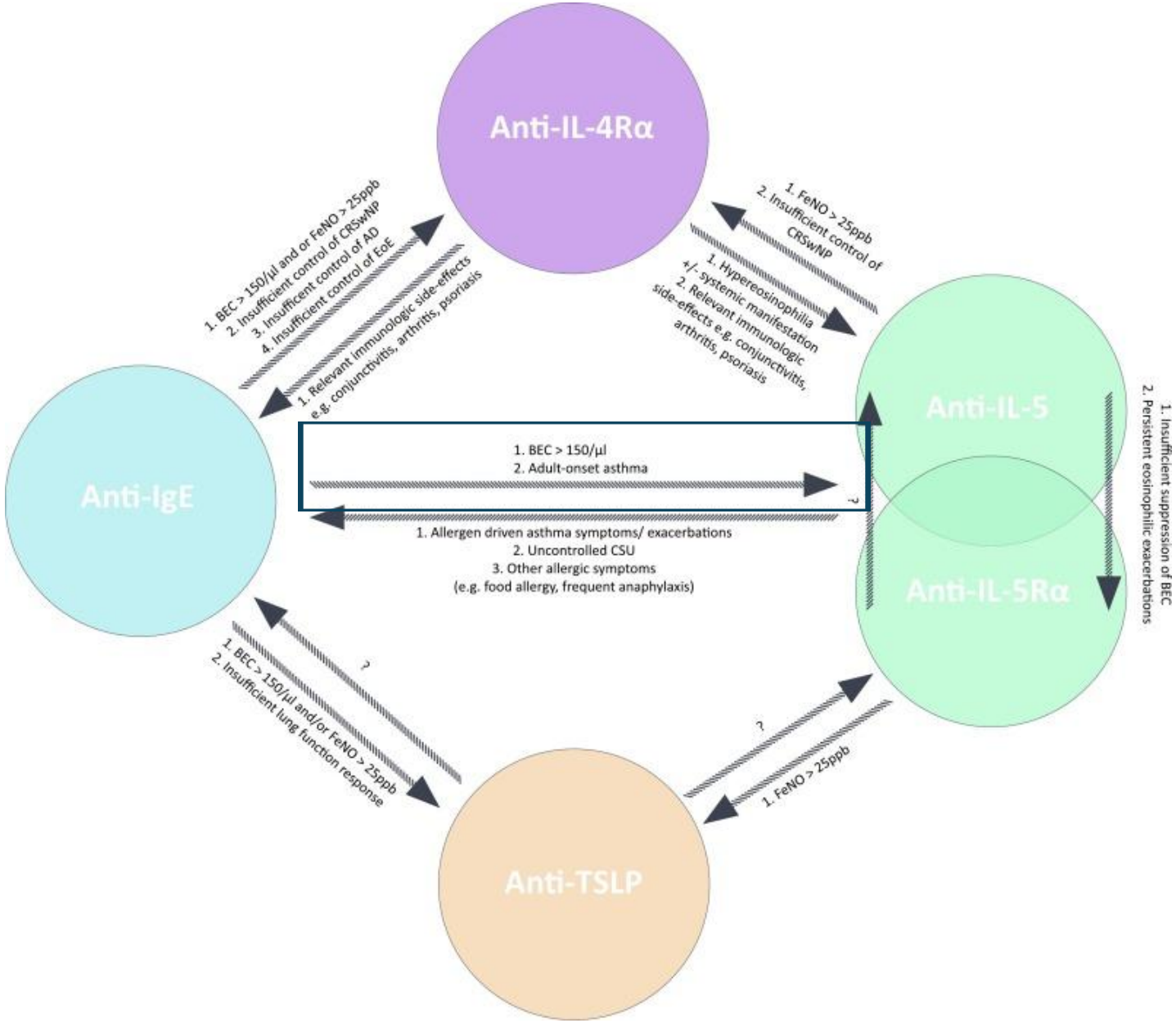
Suboptimal Yanıt Nedenleri



Pepper et al, J Allergy Clin Immunol Pract 2021 Mar;9(3):1081-1088

Biyolojik değişiminde Hamilton Stratejisi

BİYOLOJİKLER ARASI SWİTCH



Carlo Mümmler Biologics for severe asthma and beyond

AĞIR ASTIMDA BİYOLOJİK TEDAVİYİ KESME?

Omalizumab (EXPORT) kesilirse?
Atak riski artar
Astım kontrolü bozulur

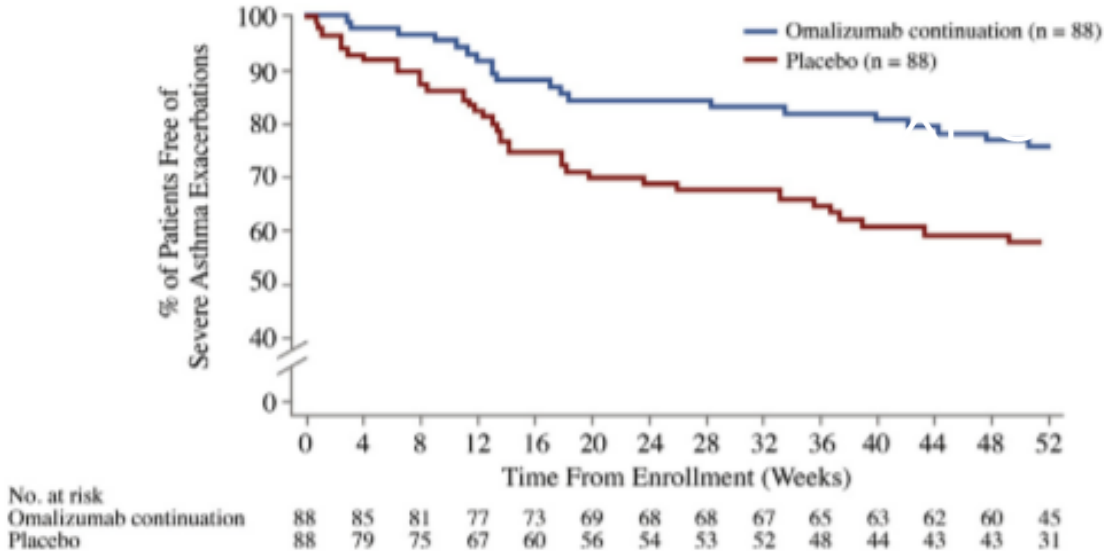


FIG 2. Time to first protocol-defined asthma exacerbation.

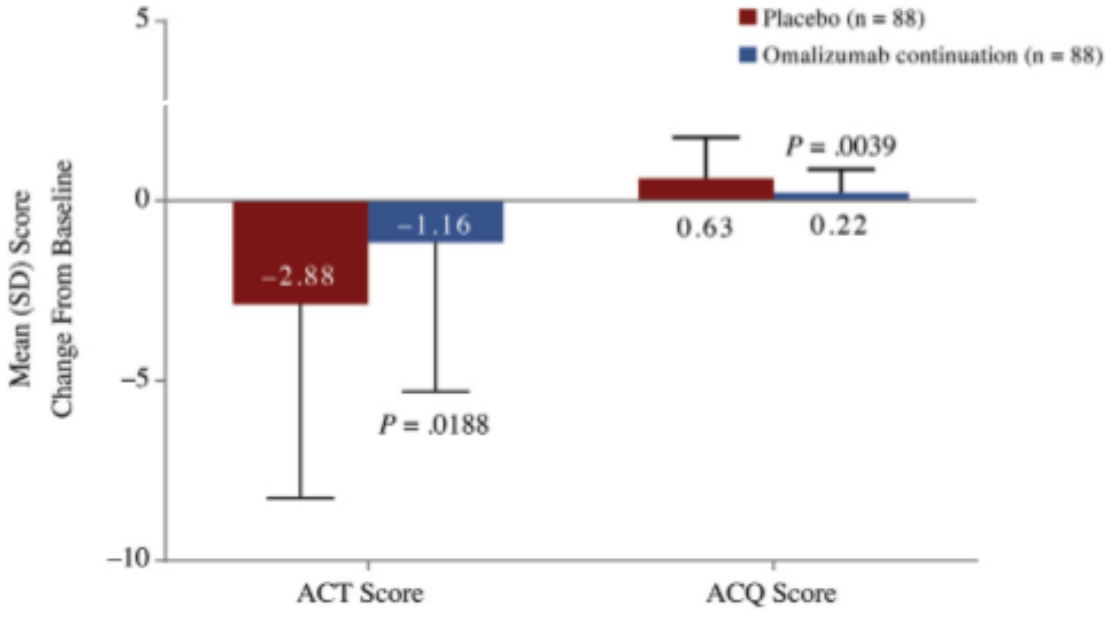


FIG 3. Mean (SD) change in ACT and ACQ scores from baseline to week 52.

Ledford D, ve ark. J Allergy Clin Immunol. 2017;140(1):162–169.e2

Omalizumab kesilen grupta ataklar eozinofil artışına bağlı

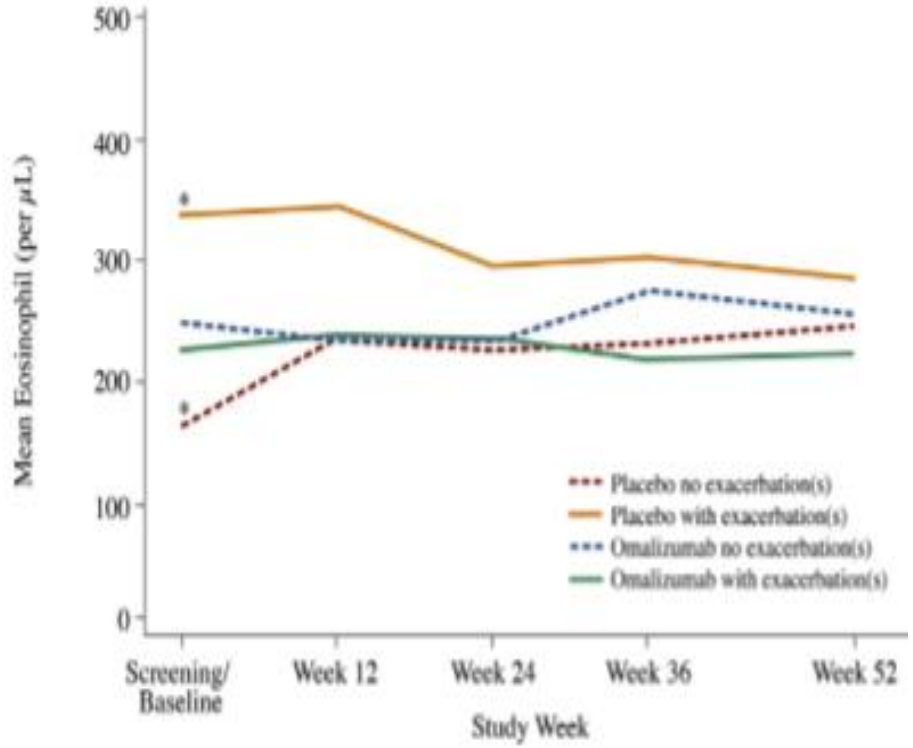


FIG 4. Eosinophils over time by treatment cohort and exacerbation statu
*At baseline, the difference in eosinophil counts was statistically significa
for the placebo groups with and without exacerbations ($P < .001$).

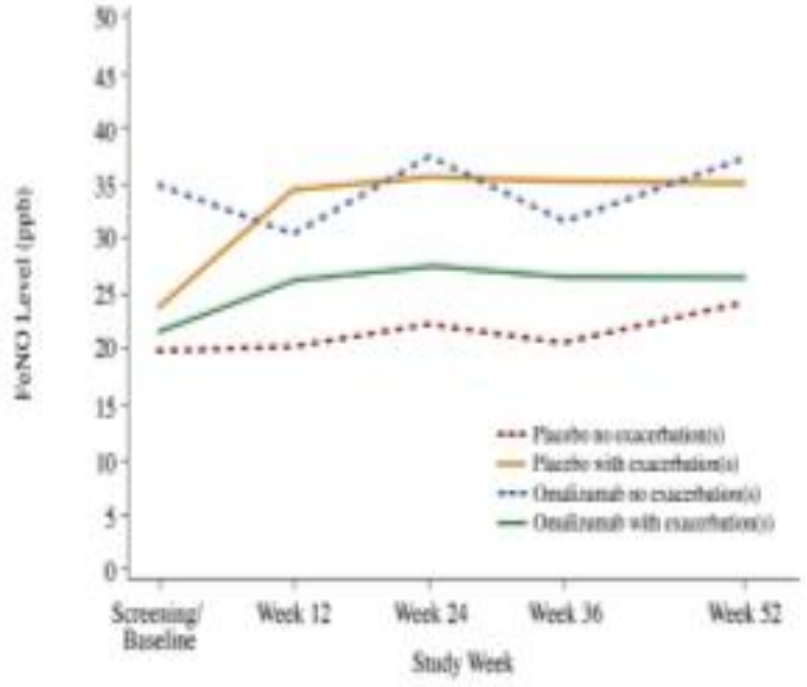


FIG 5. FeNO (in parts per billion) values over time by treatment cohort and exacerbation status.

Ledford D, ve ark. J Allergy Clin Immunol. 2017;140(1):162–169.e2

Omalizumab kesilirse gerçek yaşam verisi

Duration of the efficacy of omalizumab after treatment discontinuation in 'real life' severe asthma

49 hasta, 6 YIL omalizumab alan kendi isteğiyle bırakan hastalar 4 yıl takip

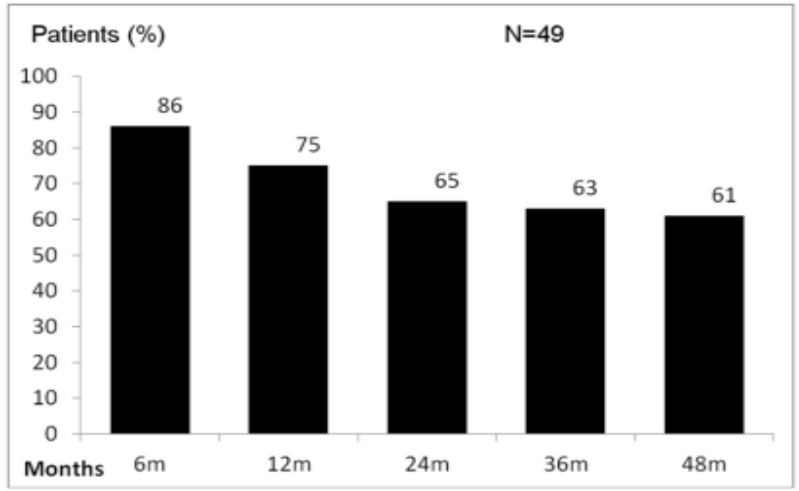


Figure 1 Number of asthmatics (%) who remained controlled over the 4-year follow-up.

There were more patients with CRS, nasal polyps and NSAIDs intolerance in the failure group than in the success group, but the difference was not statistically significant (p=0.09) (see online

http://thorax.bmj.com/ on October 29, 2017 - Published by group.bmj.com

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Tepetam et al. World Allergy Organization Journal (2023) 16:100817
http://doi.org/10.1016/j.waojou.2023.100817

Does NSAID exacerbated respiratory disease (N-ERD) accompanying severe asthma affect biological treatment response? Efficacy of omalizumab and mepolizumab in N-ERD

Fatma Merve Tepetam, MD[a]*, Şeyma Özden, MD[a], Fatma Kübra Kılıç, MD[b], Cihan Örçen, MD[c] and Tuğçe Yakut, MD[d]

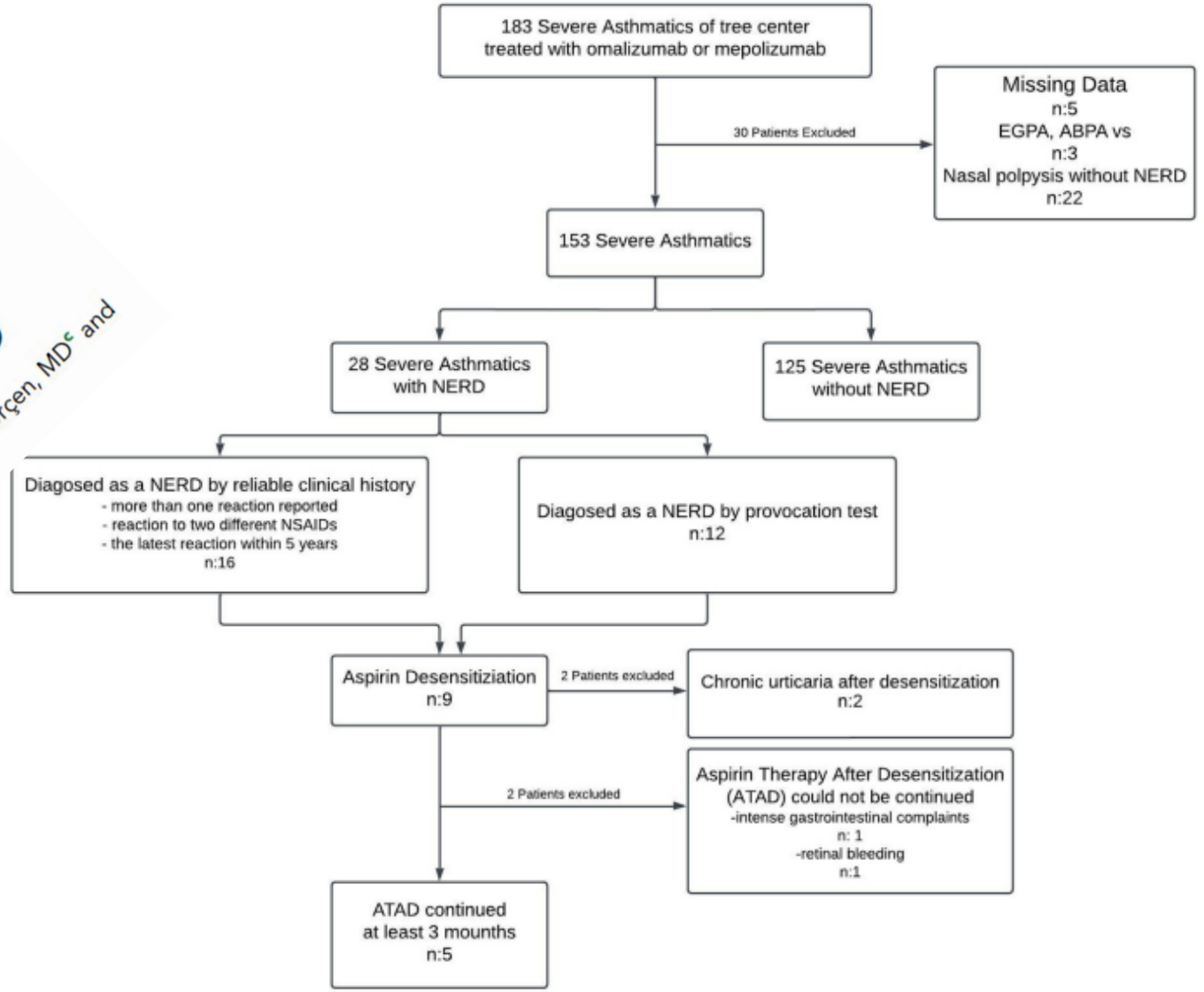


Fig. 1 Flow chart of the study design. The study population consisted of severely asthmatic patients stratifed by the presence of concomitant non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) who received omalizumab or mepolizumab treatment for at least 16 weeks. Diagnostic process of patients with NERD and aspirin desensitization treatment status before starting biologics were recorded.

	OMALIZUMAB n:19			MEPOLIZUMAB n:9		
Treatment Duration (months), Mean ± SD	37.11 ± 27.68			8.22 ± 4.66		**P value** <0.001[a]
Rhinosinusitis (VAS), range 0-10 Mean ± SD or median (25-75 percentile)	**Pre-treatment**	**Post-treatment**	**P value**	**Pre-treatment**	**Post-treatment**	**P value**
Anterior rhinitis	6.25 ± 3.65	1.81 ± 1.72	**<0.001**[c]	6.11 ± 3.37	4.11 ± 2.27	0.077[c]
Posterior rhinitis	5.50 (0.00-8.75)	1.00 (0.00-3.50)	**0.008**[b]	10.00 (7.50-10.00)	2.00 (1.00-2.50)	**0.008**[b]
Nasal obstruction	7.50 ± 2.40	2.19 ± 1.52	**<0.001**[c]	9.00 (5.50-10.00)	1.00 (0.00-2.50)	**0.023**[b]
Hyposmia	8.50 (0.75-10.00)	4.00 (0.00-9.00)	0.102[b]	6.55 ± 3.24	4.33 ± 3.43	0.206[c]
Facial pain	4.00 (3.00-4.75)	1.00 (1.00-2.00)	**0.001**[b]	3.11 ± 1.54	2.67 ± 1.32	0.466[c]

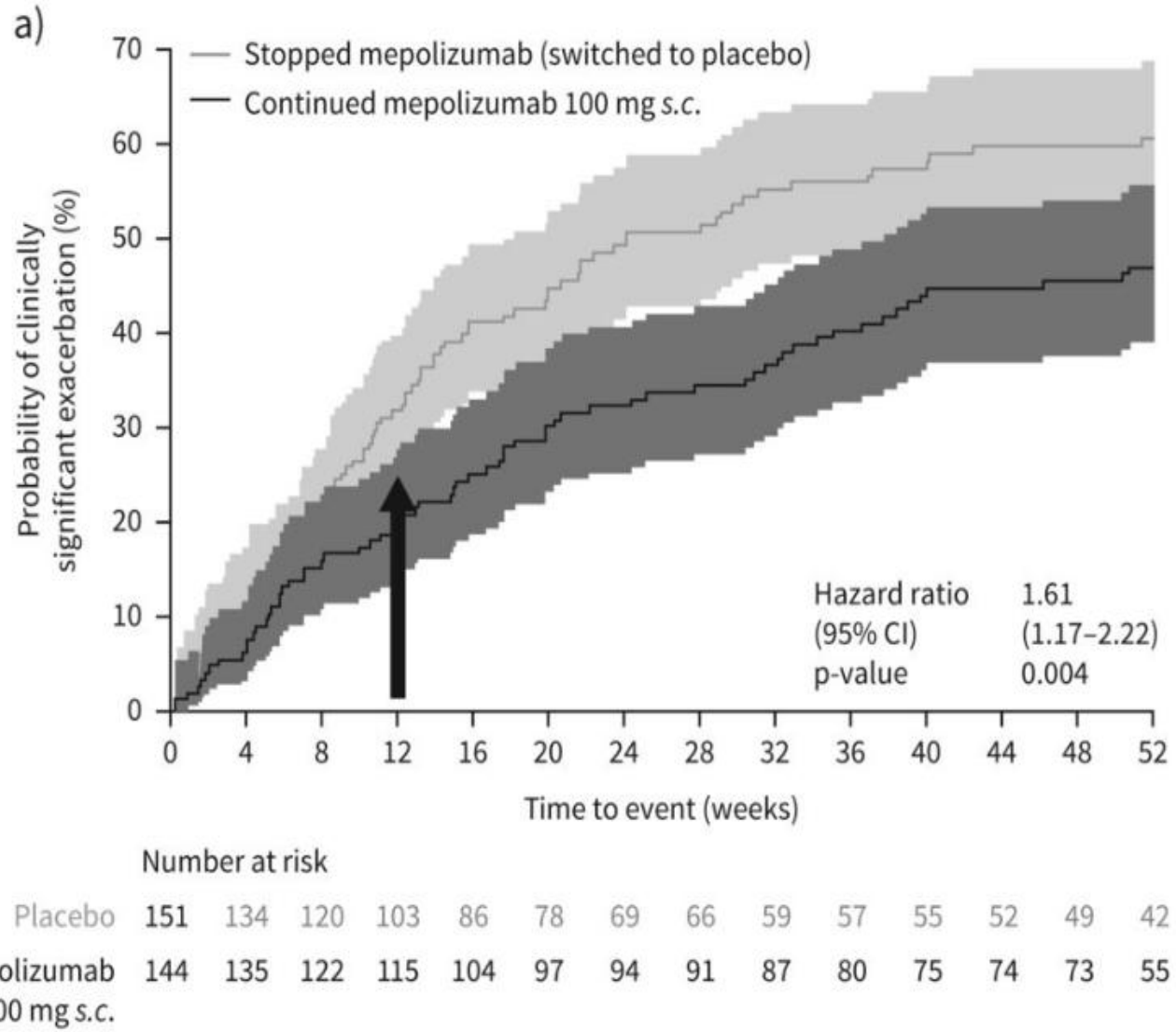
GINA -2023 BİYOLOJİK TEDAVİYİ KESME

For biologic treatments, current consensus advice is that, generally, for a patient with a good response, a trial of withdrawal of the biologic should not be considered until after at least 12 months of treatment, and only if asthma remains well controlled on medium-dose ICS therapy, and (for allergic asthma) there is no further exposure to a previous well-documented allergic trigger. There are few studies of cessation of biologic therapy,[621,622] in these studies, symptom control worsened and/or exacerbations recurred for many (but not all) patients after cessation of the biologic. For example, in a double-blind randomized controlled trial, significantly more patients who stopped mepolizumab experienced a severe exacerbation within 12 months compared with those who continued treatment. There was a small increase in ACQ-5 but no significant difference between groups.[623] Long-term safety of several biologics has been reported up to 5 or more years.[624-626]

Mepolizumab kesildikten sonra
ilk atağa kadar geçen süre anlamlı olarak azalmıştır

Primer Sonlanım Noktası:
İlk atağa kadar geçen süre

- Tedaviye devam eden hastalarda atak geçirme riski **%38 daha düşüktü.**
  - Mepolizumab kesildikten sonraki ilk atak riskinin %61 artmasına eşdeğerdir. (HR = 1.61 [%95 GA: 1.16, 2.22; *p* = 0.004])



SC, subkutan; HR, tehlike oranı; GA, güven aralığı

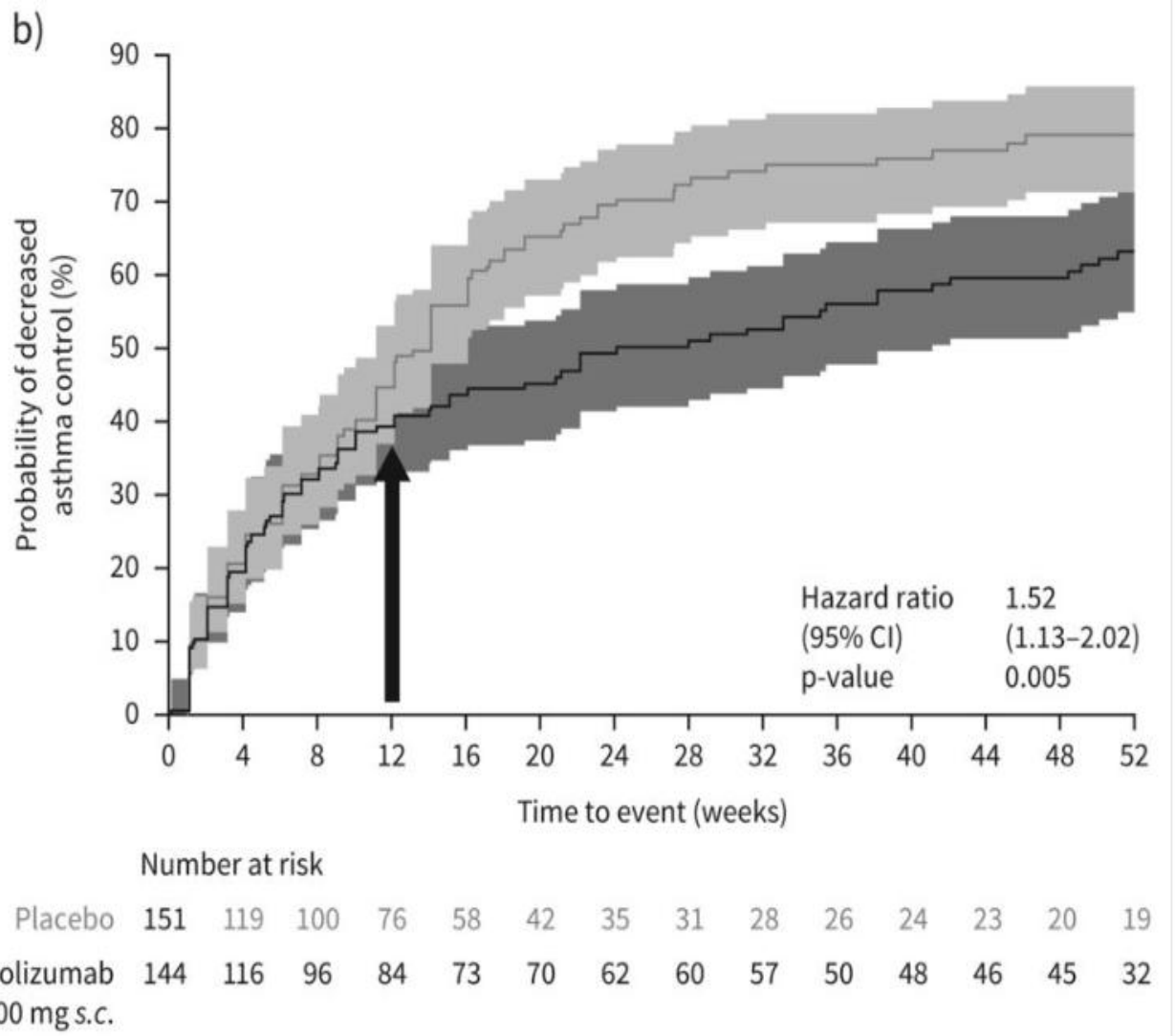
Data on File. 2020N438196_00

Mepolizumab kesildikten sonra
astım kontrolünde azalmaya kadar geçen süre kısalmıştır

Sekonder Sonlanım Noktası:

Astım kontrolünde azalmaya (başlangıca göre ACQ-5 skorunda ≥0.5 birim (MCID) artış) kadar geçen süre

- Mepolizumab tedavisi, tedaviyi kesmeye kıyasla ilk astım kontrol kaybına kadar geçen süreyi anlamlı olarak artırmıştır.
- Tedaviye devam eden hastalarda ACQ-5 skorunda ilk kez ≥0.5 birimlik artış riski %34 daha düşüktü.
- Astım kontrolünün kötüleşmesine kadar geçen süre açısından tedavi kolları arasındaki fark 12 haftadan sonra belirginleşti.



MCID, klinik açıdan önemli minimal fark; SC, subkutan; ACQ, astım kontrol anketi; HR, tehl

Data on File. 2020N438196_00

TEŞEKKÜRLER-SÜREYYA ALERJİ POWER