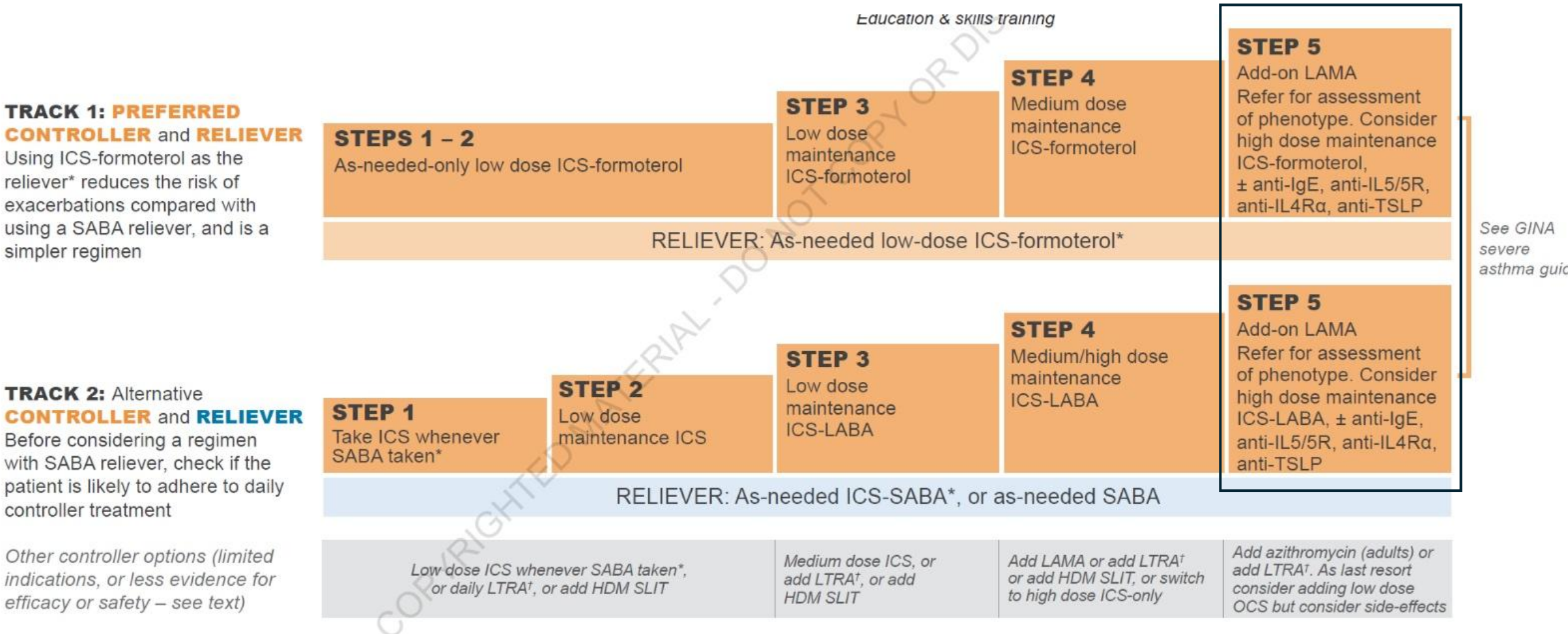
Atopik-Eozinofilik Overlap Hastada Hangi Biyolojiği Tercih Edelim?

- Uzm. Dr. Şeyma ÖZDEN
- Sağlık Bilimleri Üniv. Süreyyapaşa EAH İmmunoloji ve Allerji Kliniği



FENOTİP-ENDOTİP KAVRAMLARI

American College of Allergy, Asthma & Immunology

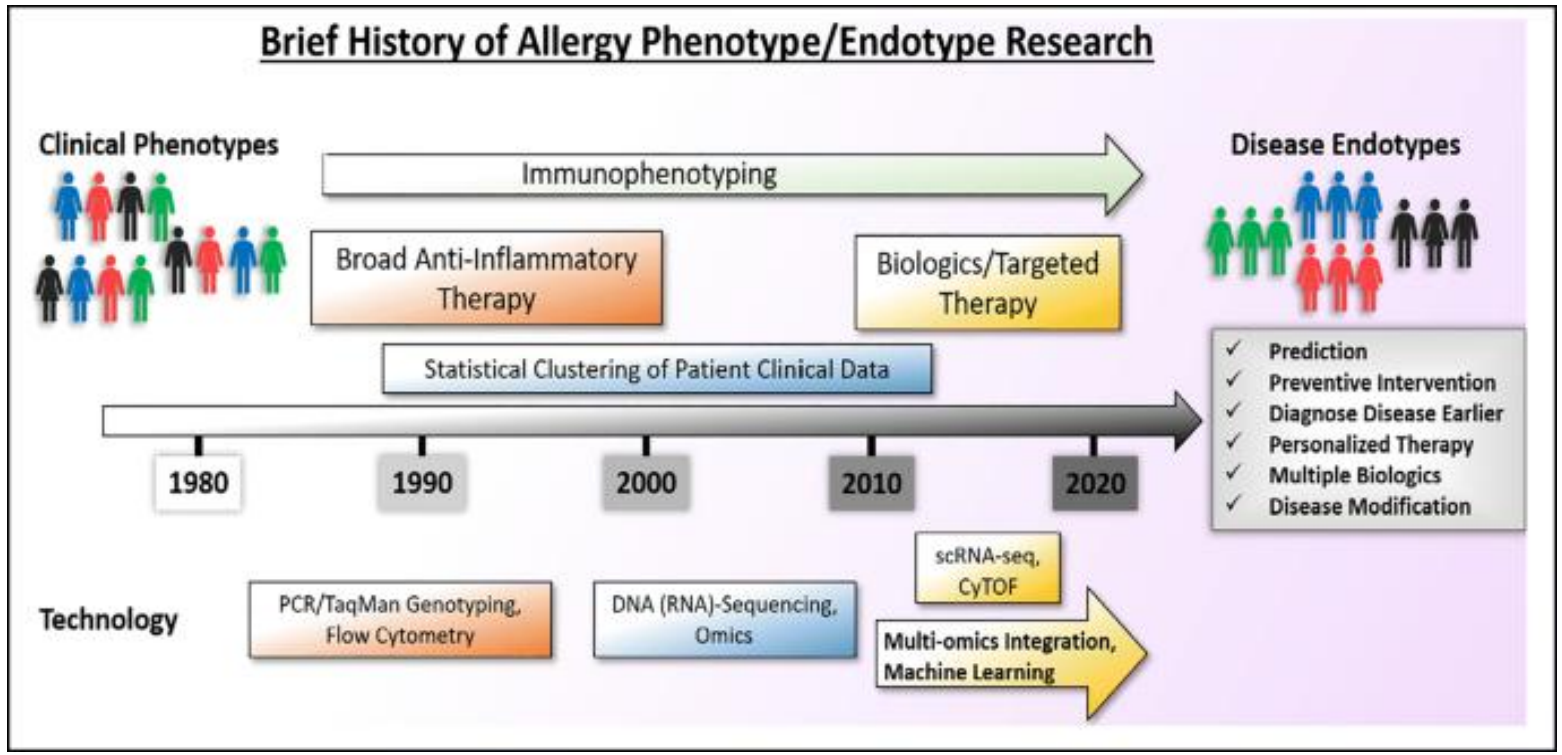
Fenotip

- Genotipinin çevre ile etkileşiminden kaynaklanan bir bireyin gözlemlenebilir özellikleri kümesi

Endotip

- Bir organizmanın gözlemlenebilir özelliklerini açıklayan spesifik bir patobiyolojik mekanizma

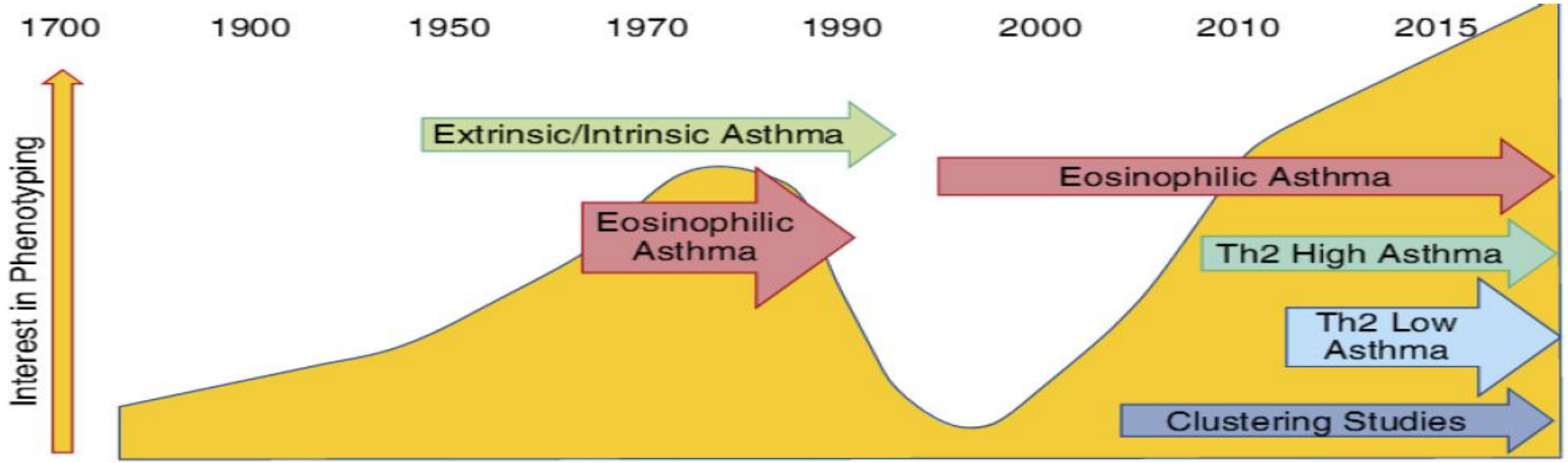
ENDOTİPLEME –KİŞİSELLEŞTİRİLMİŞ TEDAVİ



Öngörü
Önleyici girişim
Erken teşhis
Kişiselleştirilmiş tedavi
Biyolojikler arasında tercih
Hastalığın modifikasyonu
(REMİSYON)

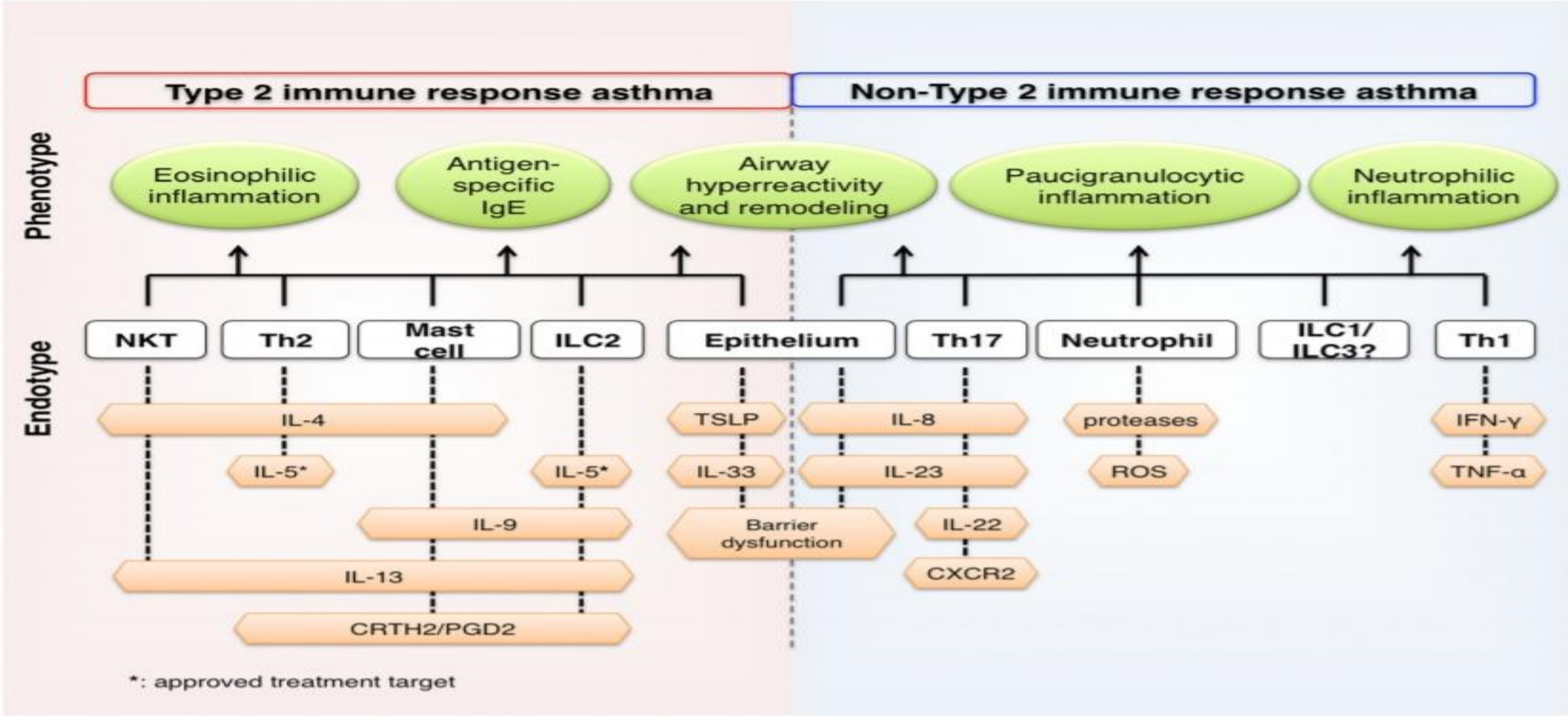
Clinical Reviews in Allergy & Immunology volume 60, pages200–219 (2021)

FENOTİP VE KÜMELEME ANALİZLERİ



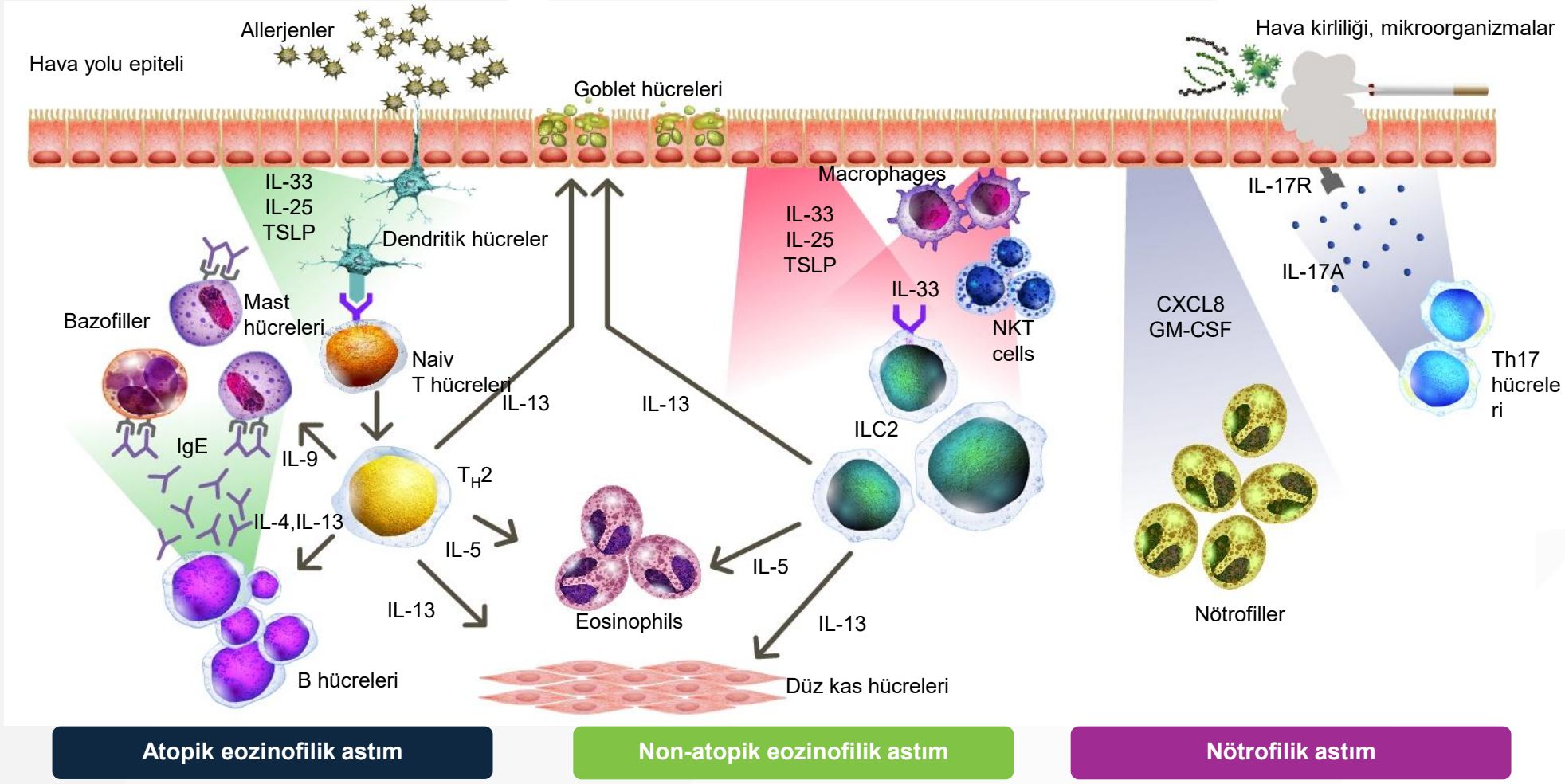
GauthierM, et al. ARJCCM 2015; 192: 660-8

FENOTİP/ENDOTİP KAVRAMLARI



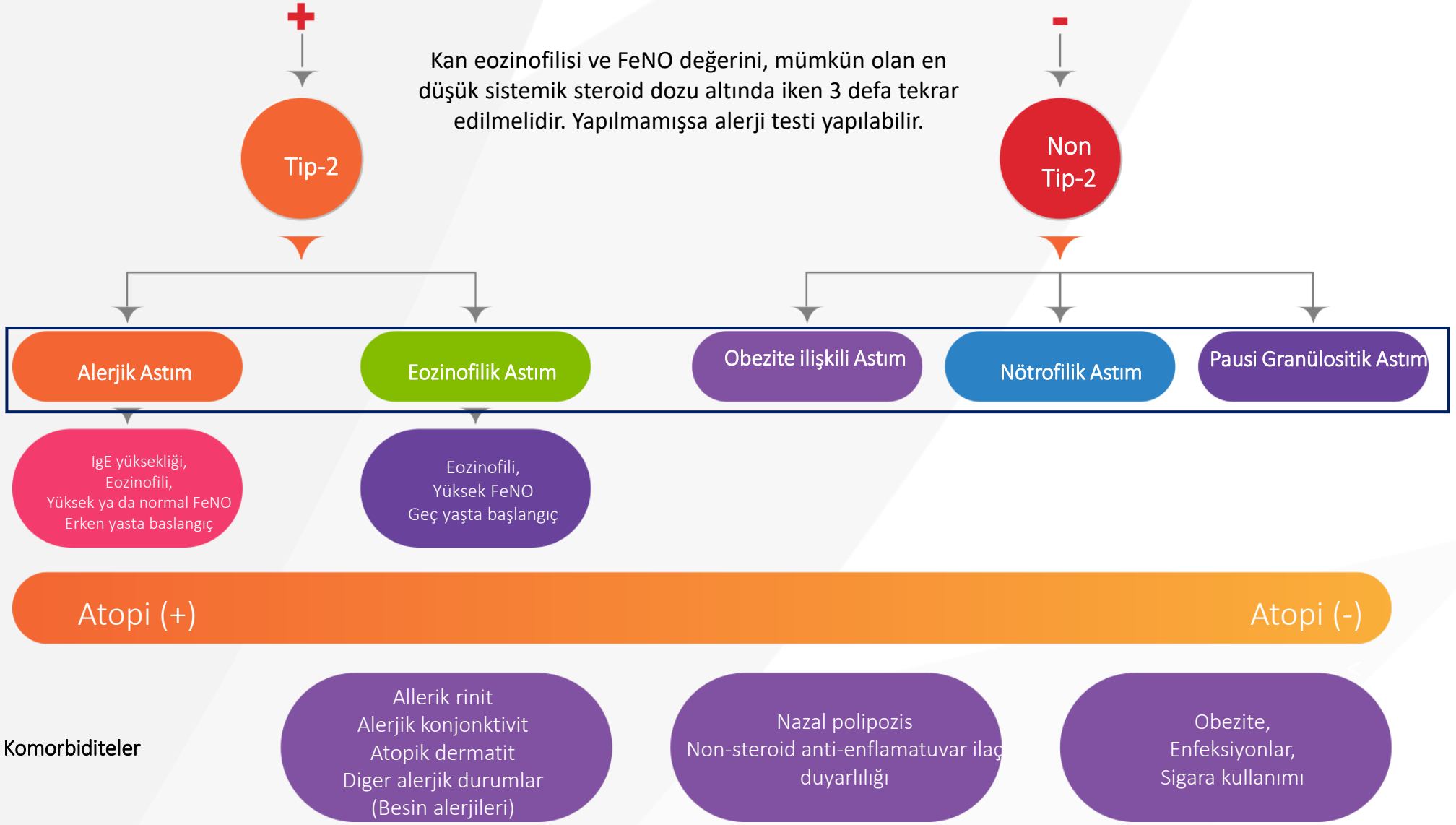
Akdis C et. Curr Allergy Asthma Rep 2016:16:70

Ağır astım gelişim mekanizmaları



....

Ağır astımda Tip 2 ve Tip 2 olmayan endotipler[1]



1. AİD-TTD Erişkin ve Çocuklarda Ağır Astım Tanı ve Tedavisi El Kitapçığı 2020 https://www.toraks.org.tr/site/sf/books/2021/03/6b337f96a09c47ce696cfdc81bb413c890177ea9c3681f7f555460f30e55707c.pdf *Son erişim tarihi:04.09.2023*

OLGU

61 yaşında erkek hasta.

Sağlık personeli, emekli.

Sigara kullanımı yok.

47 yıldır (14 yaşından beri) eforla irritanlarla artan daha çok sabaha karşı olan

- hırıltılı solunum,
- nefes darlığı,
- öksürük ve
- göğüste baskı hissi

47 yıldır pereniyal

- hapşurma
- göz ve burunda akıntı,
- burunda tıkanıklık

OLGU

Başvurduğunda hemen hemen her ay en az 1 hafta steroid kullanmayı gerektiricek 3-4 acil başvurusu, hastane yatışı yok.

Aspirin, novalgin, dıkloron, majezık gibi NSAİ ilaçlar kullandıktan 15 dk sonra

- ürtiker ,
- nefes darlığı ve
- burunda tıkanıklık , akıntı oluyor.

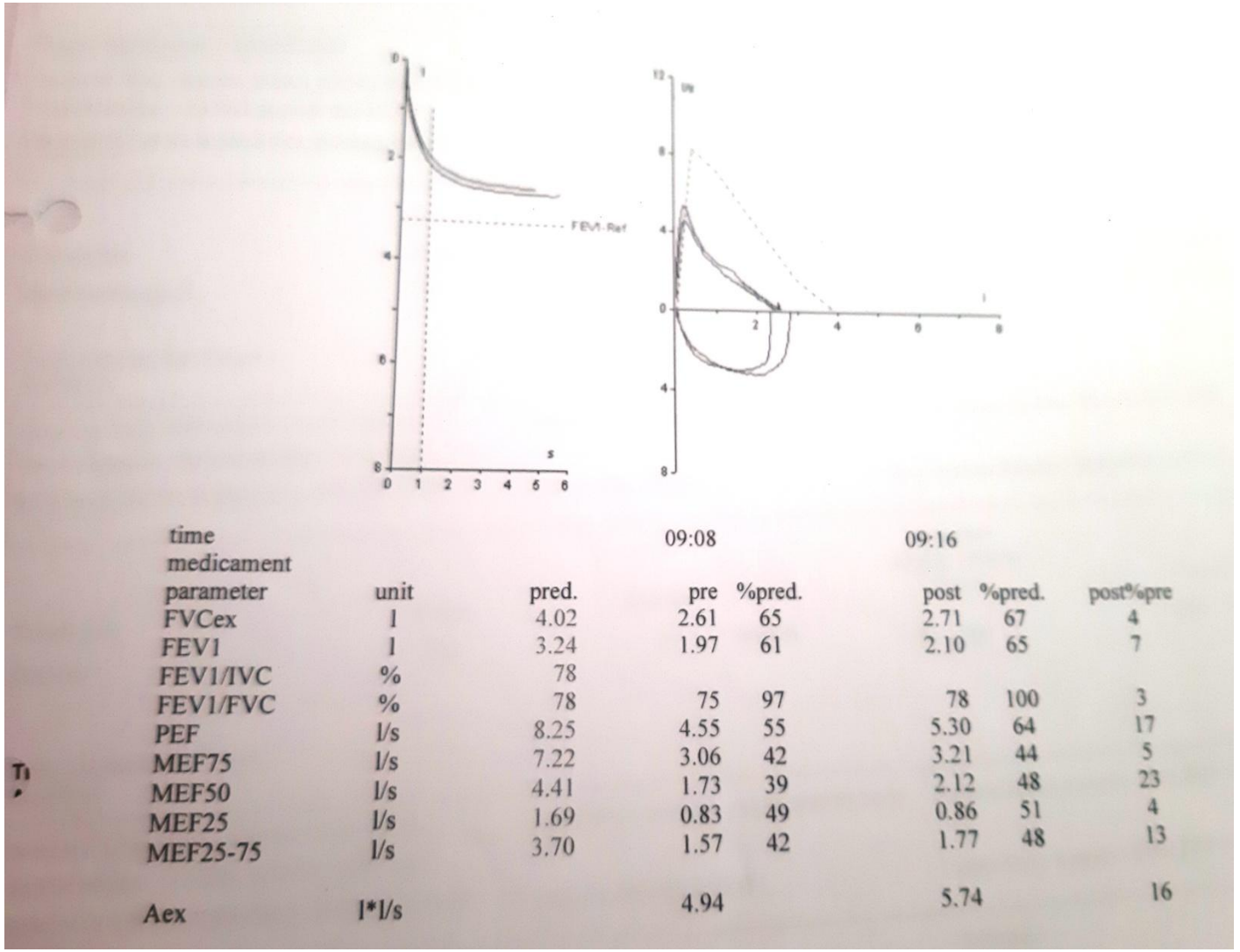
Glokom (%60 görme kaybı var)

Lumbal disk herni dışında ek hastalık yok

Ailede atopik hastalık yok

SFT

- FEV1:1,97 (%61)
- FVC:2,61 (%65)
- FEV1/FVC: %75
- FEF25-75:%42
- FET:5 sn
- Rev:+%7 130 mL
- PEF:+%17
- Vizitler arası değişkenlik 2200-1970=230 mL (+)



time			09:08		09:16		
medicament							
parameter	unit	pred.	pre	%pred.	post	%pred.	post%pre
FVCex	l	4.02	2.61	65	2.71	67	4
FEV1	l	3.24	1.97	61	2.10	65	7
FEV1/IVC	%	78					
FEV1/FVC	%	78	75	97	78	100	3
PEF	l/s	8.25	4.55	55	5.30	64	17
MEF75	l/s	7.22	3.06	42	3.21	44	5
MEF50	l/s	4.41	1.73	39	2.12	48	23
MEF25	l/s	1.69	0.83	49	0.86	51	4
MEF25-75	l/s	3.70	1.57	42	1.77	48	13
Aex	l*l/s		4.94		5.74		16

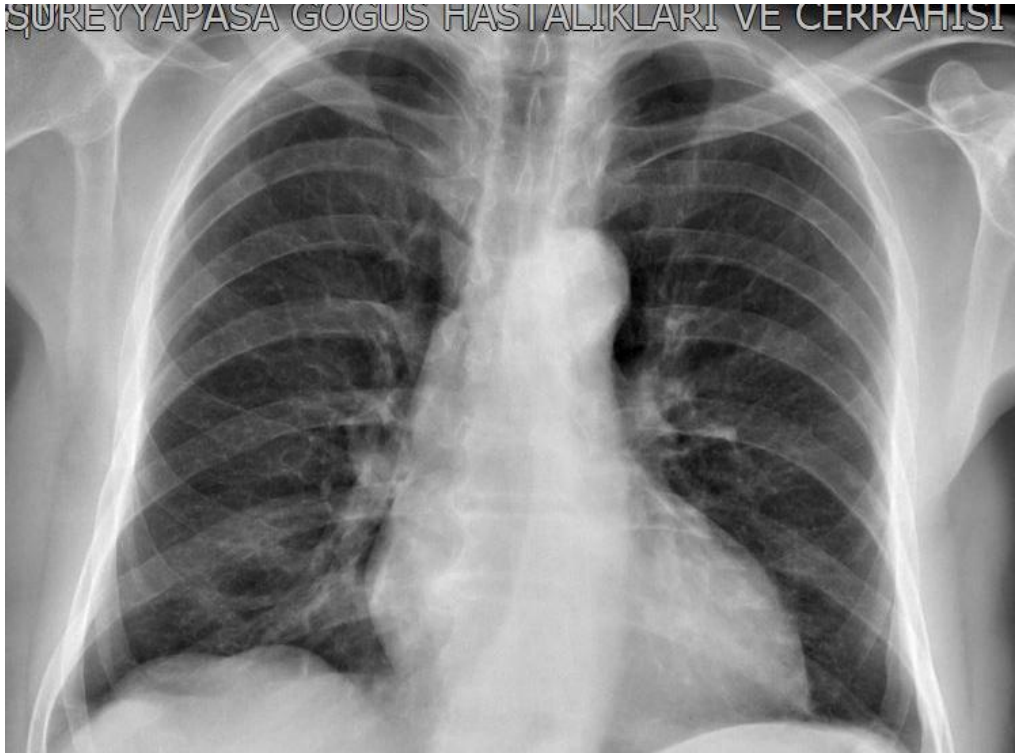
Dosya Özet

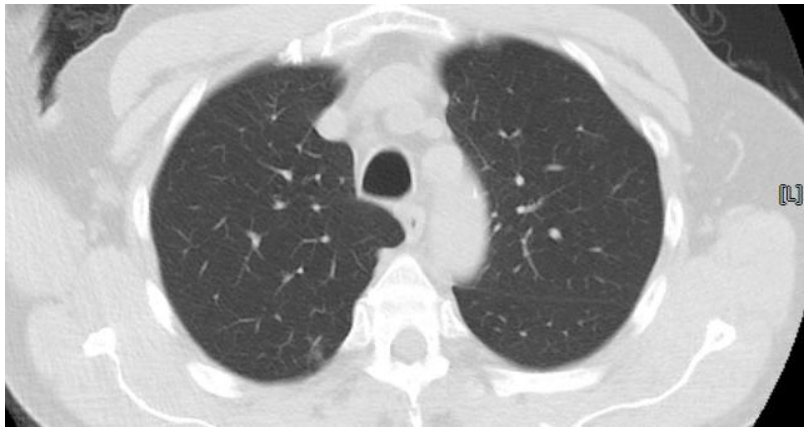
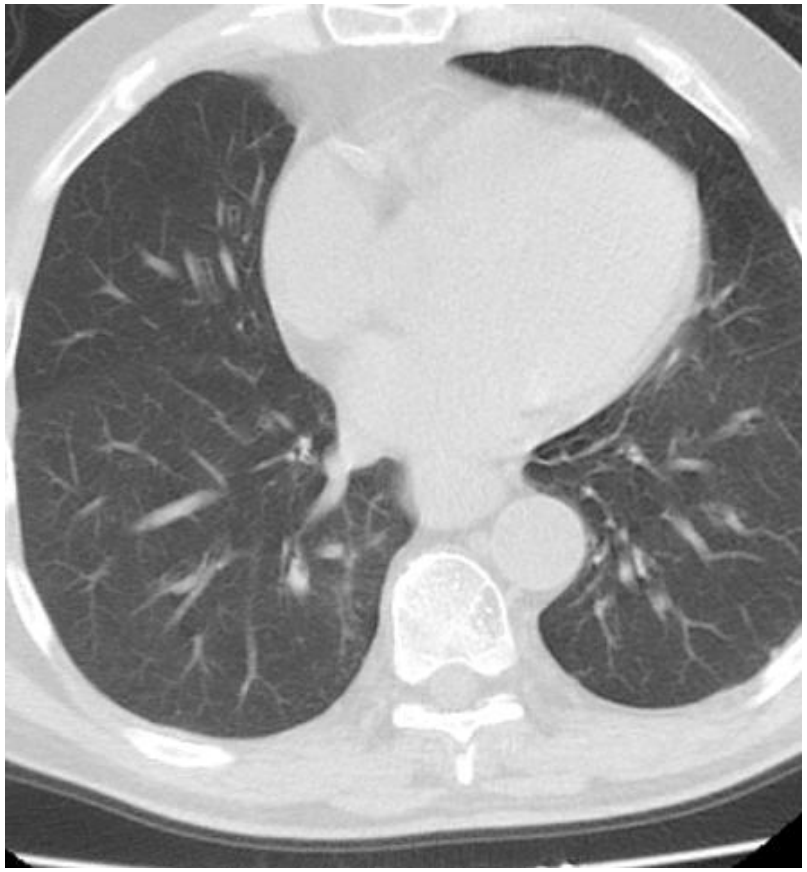
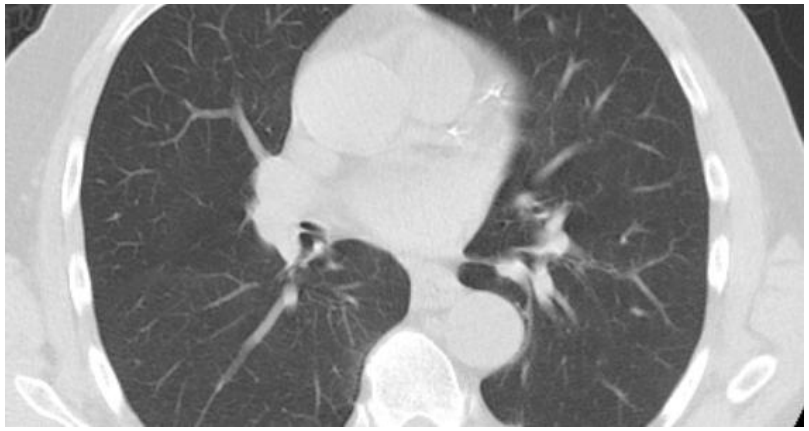
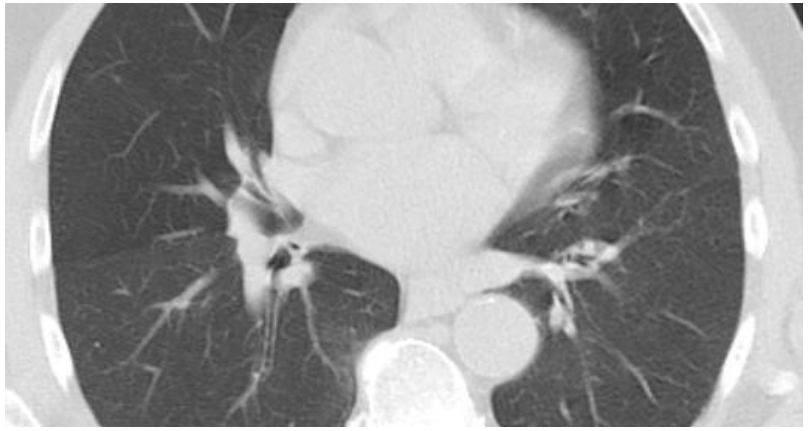
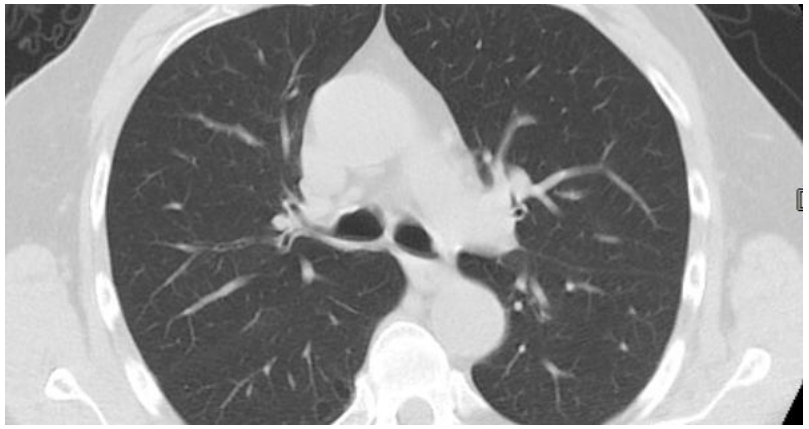
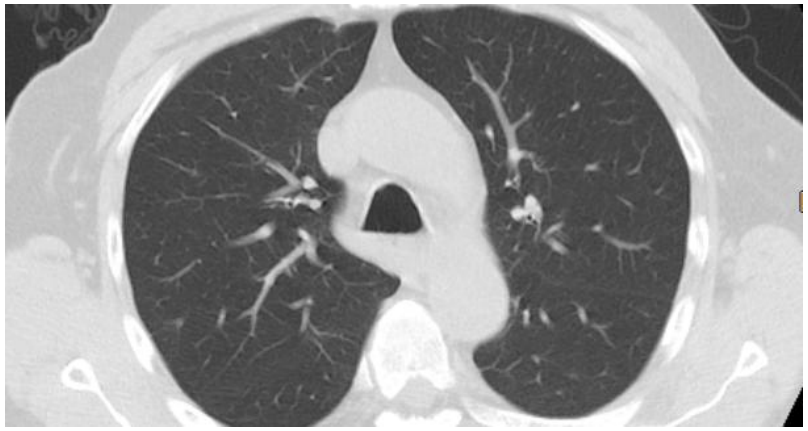
Semptomlar astım için tipik mi **Değişken hava akımı kısıtlaması var mı**	**Evet** **Evet**
A.rinit, Astım, başlangıç yaşı NSAİ ilaç duyarlılığı Semptomlarda kötüleşme yaşı	15 49 51
VKİ:	60 kg /1.65^2 =22
Atak Yatış	Son 1 yılda 3 kere sistemik steroid 7 gün almış Yok
Astım Kontrol Testi puan GINA 'ya göre	5 Kontrol dışı
Komorbiditeler GER,psikiyatrik hst Pereniyal rinit. Sinüzit, Nazal Polip OSA semptomu	 Yok Var Horlama var, tanıklı apne yok
Fizik Muayene	Bilateral ekspratuar ronkus

Tetkikler

Serum Total IgE	310-443 IU/ml
Eozinofil	400-780/uL
Alerji deri testi	(skin prick testi)
Dermatophagoides p	9*3
Dermatophagoides f	3*10

PA GRAFİ



Toraks BT

Kullandığı İlaçlar

Salmeterol+flutikazon 500 2*1 ve gerektiğinde (SALBUTAMOL)

Montelukast + Desloratidin 1*1

Mometozan nazal steroid 2*2

- **3 kere 7 gün boyunca 48 mg**

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)

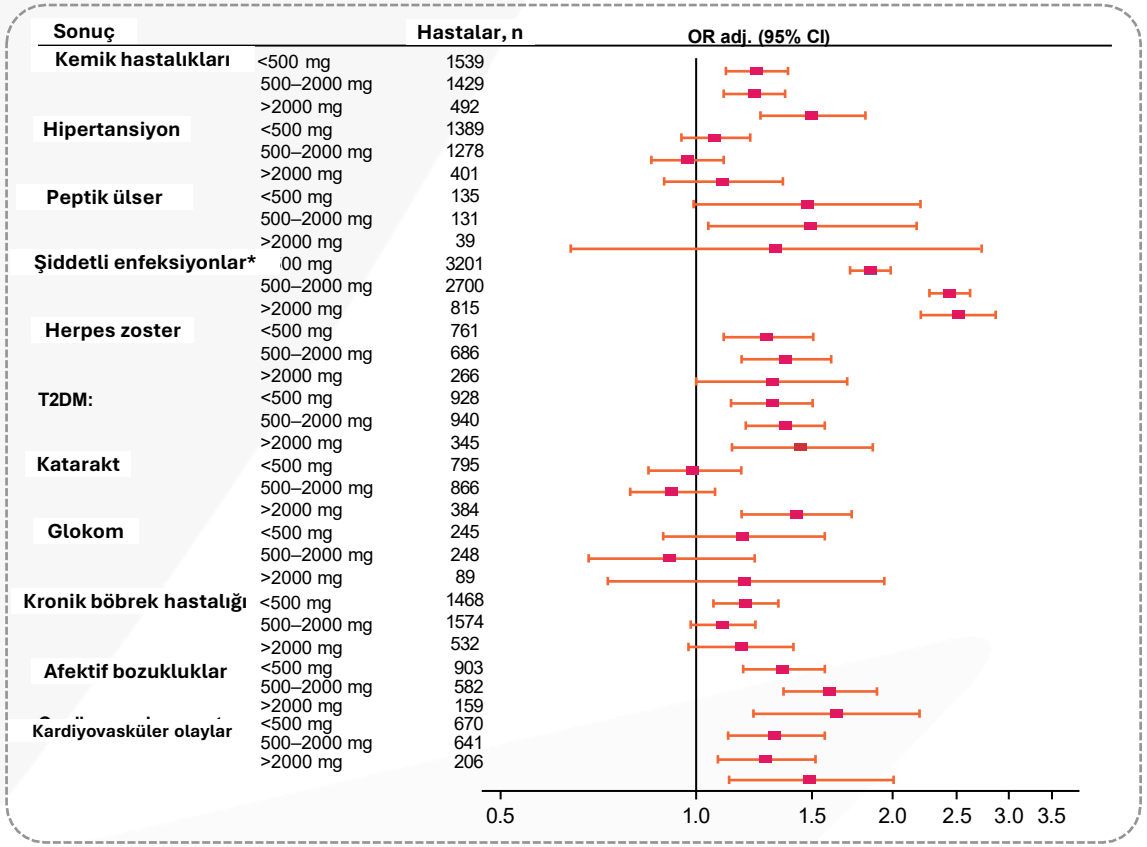
Değerlendirme

- Astım **T**anısının doğrulanması (ayırıcı tanı)
- İnhaler **T**eknik
- **T**etikleyiciler
- KomorbidiTeler
- Nonfarmakolojik **T**edavi
- Biyolojik dışı **T**edaviler

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.

-BİYOLOJIK OLMAYAN İLAÇLAR
-MART

Montelukast alıyor

LAMA? GLOKOM açısından riskli

Formeterol+budesonid (yüksek doz)

- **160/4.5 3*2 ve gerektiğinde (MART)**

ENDOTİPLEMEDE BELİRTEÇLER NELER?

Type 2 İnflamasyon

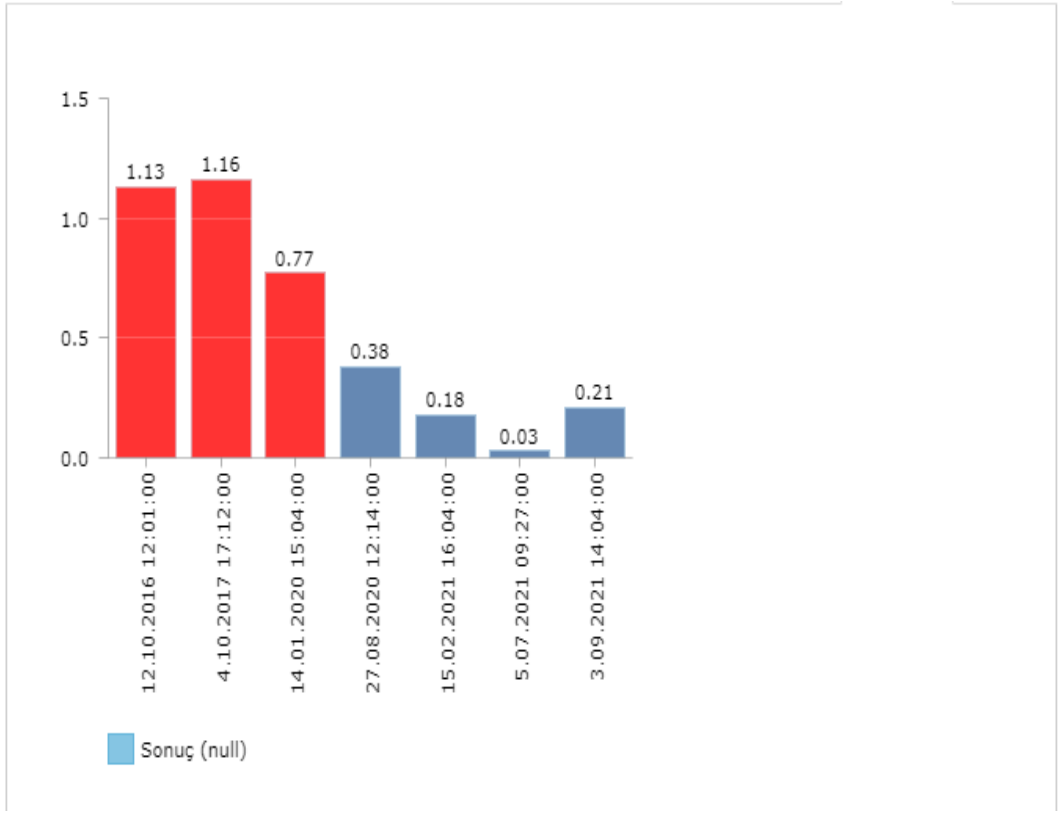
- Periferik eozinofil ≥ 150/µL
  - ve/veya
- FENO ≥ 20 ppb
  - ve/veya
- İndükte balgamda eozinofil ≥ %2
  - ve/veya
- Astımın klinik olarak alerjen kaynaklı olması
  - ve/veya
- İdame tedavide OCS ihtiyacı

(En düşük OCS dozunda periferik eozinofil ve FENO ‘nun en az 3 kere tekrarı)

S.Steroid kullanan hasta Eozinofil seyri-enabız

Orta-yüksek doz IKS-LABA Kullanan hastaların %65’inin eozinofil kategorisi yer değiştiriyor

30.09.2021	MONO%	9	%	0 - 12	
30.09.2021 14:25	NEU%	67.1	%	37.0 - 80.0	
30.09.2021	NLR	3.44			



HASTANIN KLİNİK-İNFLAMATUAR FENOTİPİ?

Hangi Astım fenotipi?

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, Çoculuk çağında başlangıç

Tetikleyicilere göre fenotip

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

Inflamasyona göre fenotip

- Eozinofilik
- Nötrofilik
- Pauci-granulositik
- Mix Granülositik

Wenzel S. Lancet 2006;368 (26):804-11

Table 1

Features of the currently FDA approved biologics

Biologic	Target	FDA approved (yr)	Patient population with clinical benefit in phase 3 studies	Route of administration	Dosing	Interval of administration	Main effect on asthma	Effect on biomarkers
Omalizumab (Xolair)	IgE	2003	Uncontrolled moderate-to-severe allergic asthma with total IgE serum level ≥30 IU/mL and specific IgE or positive skin prick test to a perennial allergen and FEV ≤ 80% [5,69,70]	Subcutaneous	75–600 mg, depending on weight and baseline total IgE level	2–4 weeks, depending on weight and baseline total IgE level	Reduction exacerbation rate [5,69]	-Minimal reduction in FeNO [70] -Reduction in free circulating IgE [5]
Mepolizumab (Nucala)	IL-5	2015	Severe eosinophilic asthma with blood eosinophils ≥150–300 cell/μL, and ≥2 exacerbations previous year or dependent on oral glucocorticoids [7–9]	Subcutaneous	100 mg	4 weeks	-Reduction exacerbation rate [7–9] -Glucocorticoid-sparing effect [8]	Reduction blood and sputum eosinophils [7,9,41]
Reslizumab (Cinqaero)	IL-5	2016	Uncontrolled (ACQ ≥ 1,5) severe eosinophilic asthma with blood eosinophils ≥400 cell/μL [10–12]	Intravenous	3 mg/kg	4 weeks	Reduction exacerbation rate [10–12]	Reduction blood and sputum eosinophils [10–12,71]
Benralizumab (Fasenra)	IL-5R α	2017	Severe eosinophilic asthma with blood eosinophils ≥300 cell/μL, and ≥2 exacerbations previous year or dependent on oral glucocorticoids [13,14,15**]	Subcutaneous	30 mg	First three doses interval of 4 weeks, thereafter 8 weeks	-Reduction exacerbation rate [13,14,15**] -Glucocorticoid-sparing effect [15**]	Reduction blood and sputum eosinophils [13,14,72]
Dupilumab (Dupixent)	IL-4Rα	2018	Severe eosinophilic asthma, FEV1 ≤ 80%, and with either blood eosinophils >150 cell/μL and episode of worsening asthma previous year, or glucocorticoid dependent asthma [16**,17**]	Subcutaneous	300 mg	2 weeks	-Reduction exacerbation rate [16**,17**] -Increase FEV [16**] -Glucocorticoid-sparing effect [17**]	-Reduction FeNO and total IgE level [16**,17**] -Transient increase blood eosinophils [16**,17**]

2008

2019

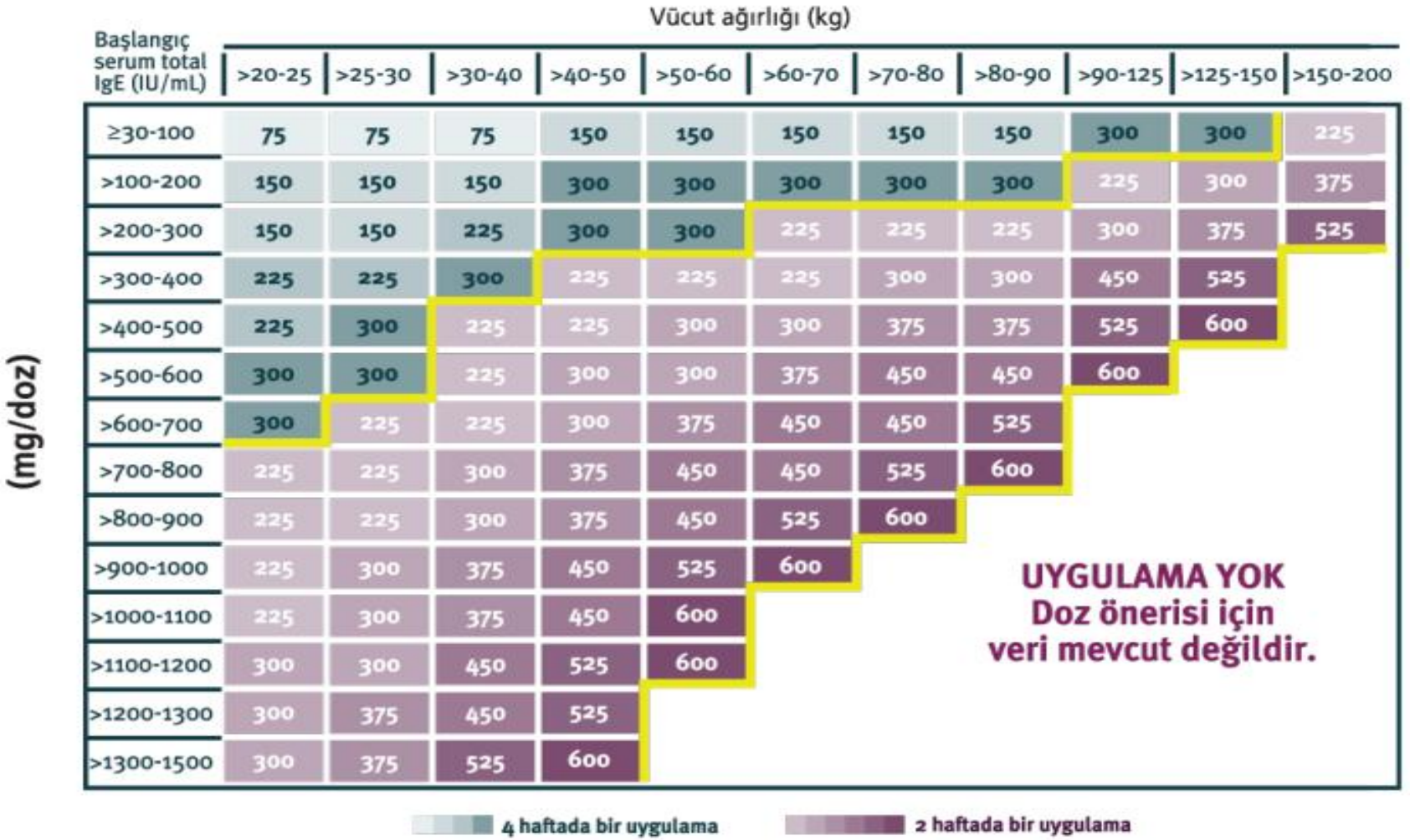
2023

New biologics for severe asthma Eger and Bel 1

BİYOLOJİK

- 2013 yılında
- Omalizumab tedavisine eklendi
- 28 Günde bir 600 mg

OMALİZUMAB DOZ TABLOSU



OMALİZUMAB İLE NELER DEĞİŞTİ?

	Bazal (2013)	Omalizumab (1.yıl)	Omalizumab (7. yıl)	Omalizumab (10.yıl)
AKT	5	22	23	24
Atak	3-4/ayda	-	-	-
Rinit Skoru	21	14	6	5
Koku Skoru	2	4	8	8
Hastane yatış	-	-	-	-
FEV_1	1.78(54)	2.32(72)	2.80(92)	2.92(96)
FEF_{25-75}	1.15(31)	2.05(56)	1.95(57)	2.06(63)
Total IgE	443	958	721	213
Eosinofil	780	400	340	120

Received: 14 May 2020 | Accepted: 19 May 2020

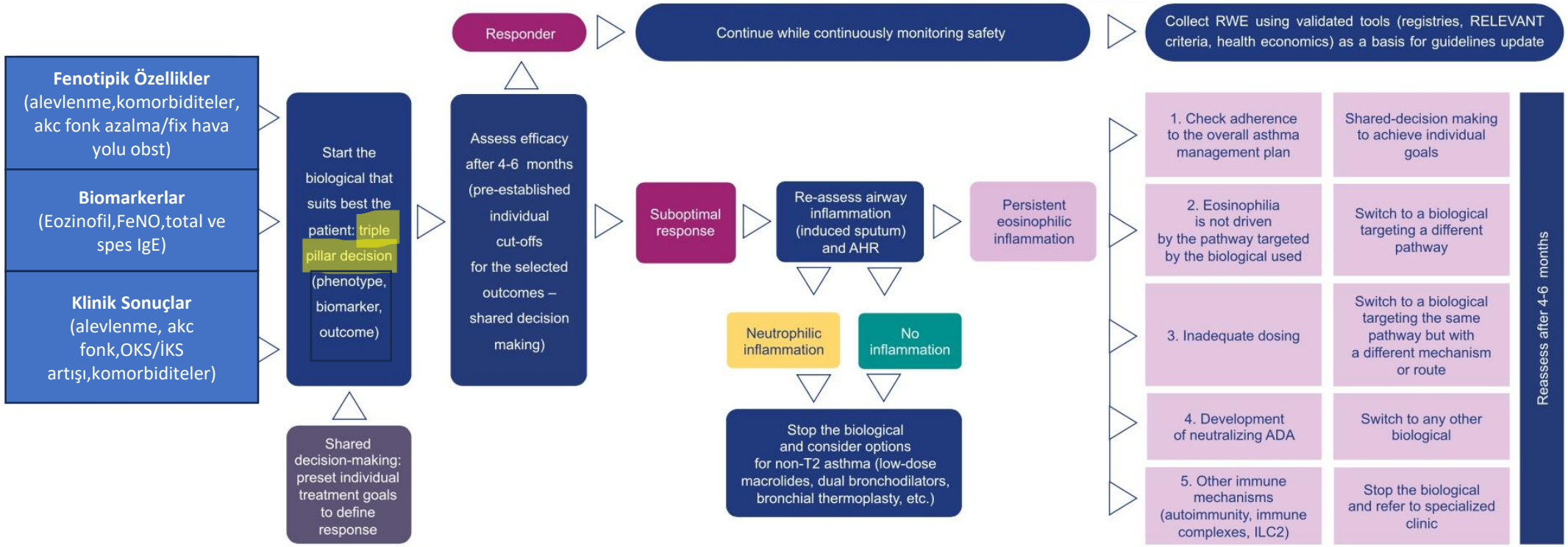
DOI: 10.1111/all.14425

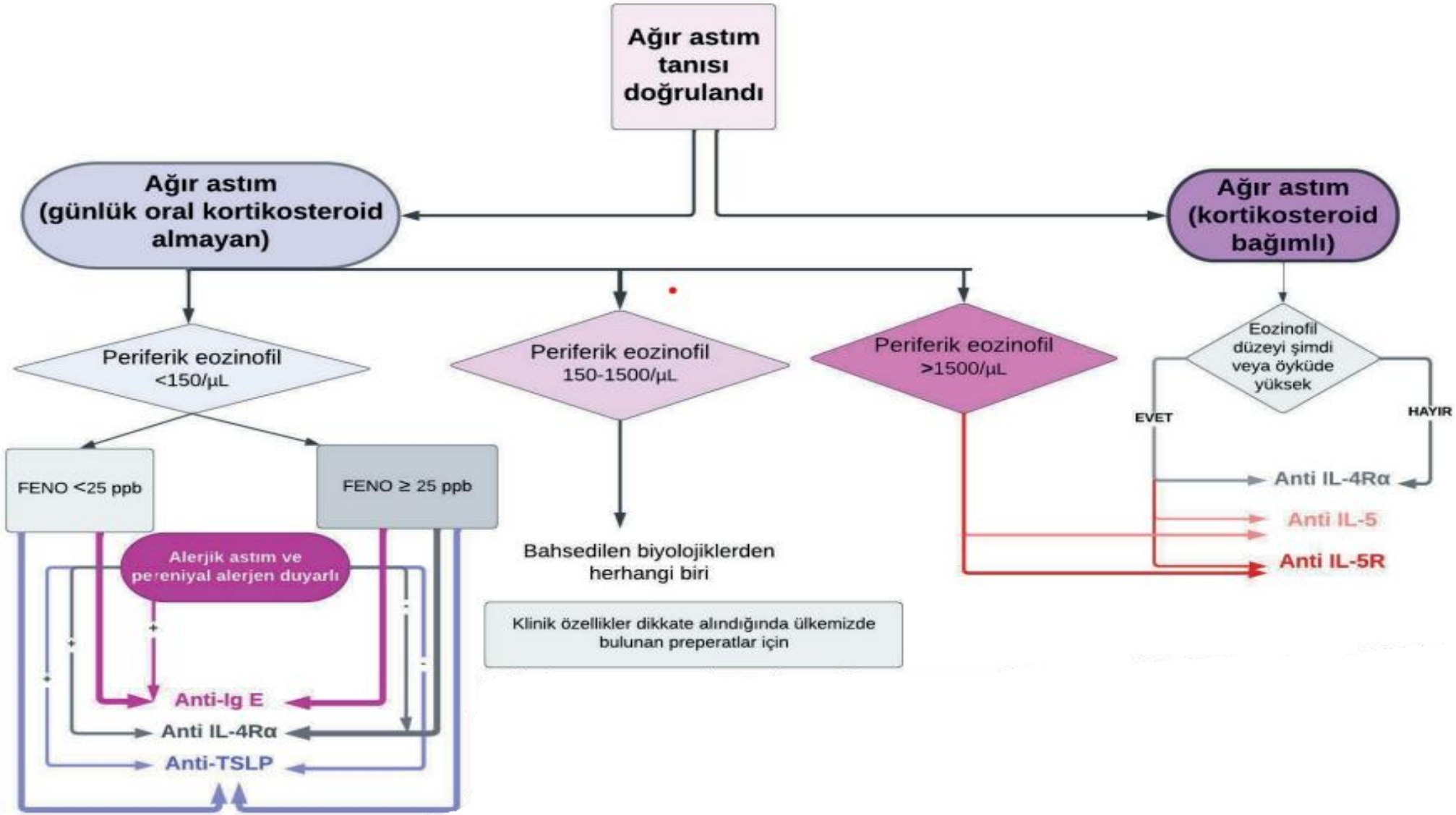
Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

GUIDELINES

EAACI Biologicals Guidelines—Recommendations for severe asthma

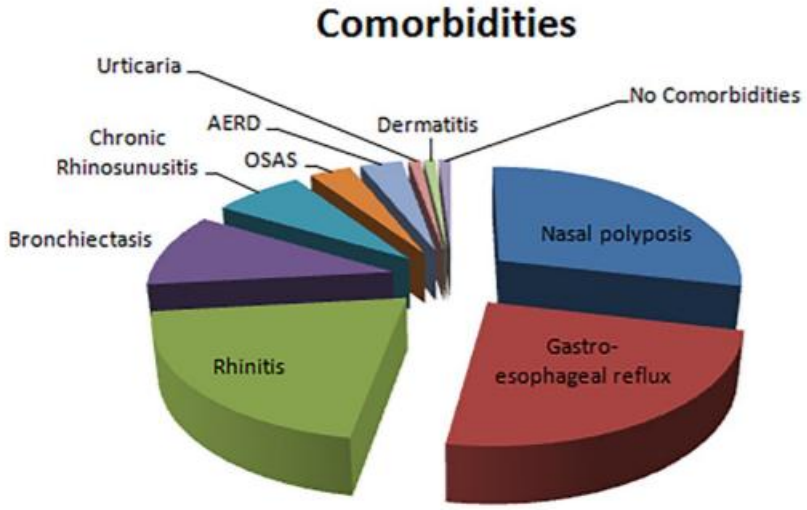
Ioana Agache[1] | Cezmi A. Akdis[2,3] | Mubeccel Akdis[2] | Giorgio Walter Canonica[4] | Thomas Casale[5] | Tomas Chivato[6] | Jonathan Corren[7] | Derek K. Chu[8] | Stefano Del Giacco[9] | Thomas Eiwegger[10,11,12] | Breda Flood[13] | Davide Firinu[9] | James E. Gern[14] | Eckard Hamelmann[15] | Nicola Hanania[16] | Irene Hernández-Martín[17] | Rebeca Knibb[18] | Mika Mäkelä[19] | Parameswaran Nair[20,21] | Liam O'Mahony[22] | Nikolaos G. Papadopoulos[23,24] | Alberto Papi[25] | Hae-Sim Park[26] | Luis Pérez de Llano[27] | Oliver Pfaar[28] | Santiago Quirce[29] | Joaquin Sastre[30] | Mohamed Shamji[31,32] | Jurgen Schwarze[33] | Oscar Palomares[34] | Marek Jutel[35,36]


Fenotipik Özellikler (alevlenme,komorbiditeler, akc fonk azalma/fix hava yolu obst)
Biomarkerlar (Eozinofil,FeNO,total ve spes IgE)
Klinik Sonuçlar (alevlenme, akc fonk,OKS/İKS artışı,komorbiditeler)
Start the biological that suits best the patient: triple pillar decision (phenotype, biomarker, outcome)
Shared decision-making: preset individual treatment goals to define response
Assess efficacy after 4-6 months (pre-established individual cut-offs for the selected outcomes – shared decision making)
Responder
Continue while continuously monitoring safety
Collect RWE using validated tools (registries, RELEVANT criteria, health economics) as a basis for guidelines update
Suboptimal response
Re-assess airway inflammation (induced sputum) and AHR
Persistent eosinophilic inflammation
Neutrophilic inflammation
No inflammation
Stop the biological and consider options for non-T2 asthma (low-dose macrolides, dual bronchodilators, bronchial thermoplasty, etc.)
1. Check adherence to the overall asthma management plan
Shared-decision making to achieve individual goals
2. Eosinophilia is not driven by the pathway targeted by the biological used
Switch to a biological targeting a different pathway
3. Inadequate dosing
Switch to a biological targeting the same pathway but with a different mechanism or route
4. Development of neutralizing ADA
Switch to any other biological
5. Other immune mechanisms (autoimmunity, immune complexes, ILC2)
Stop the biological and refer to specialized clinic
Reassess after 4-6 months



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

KOMORBİDİTELER



<u>ÜRTİKER:</u> OMALİZUMAB
<u>A.DERMATİT:</u> DUPİLUMAB

<u>NAZAL POLİP:</u>
DUPİLUMAB
OMALİZUMAB
MEPOLİZUMAB)

Therapeutic Advances in Respiratory Disease 14

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ORIGINAL ARTICLE

WILEY

Real-world Omalizumab and Mepolizumab treated difficult asthma phenotypes and their clinical outcomes

Wei Chern Gavin Fong[1,2] | Adnan Azim[2,3] | Deborah Knight[3] | Heena Mistry[1,2,3] | Anna Freeman[2,3] | Mae Felongco[2,3] | Aref Kyyaly[1,2,3] | Matthew Harvey[3] | Patrick Dennison[3] | Hongmei Zhang[4] | Peter Howarth[2,3] | Syed Hasan Arshad[1,2,3] | Ramesh J. Kurukulaaratchy[1,2,3]

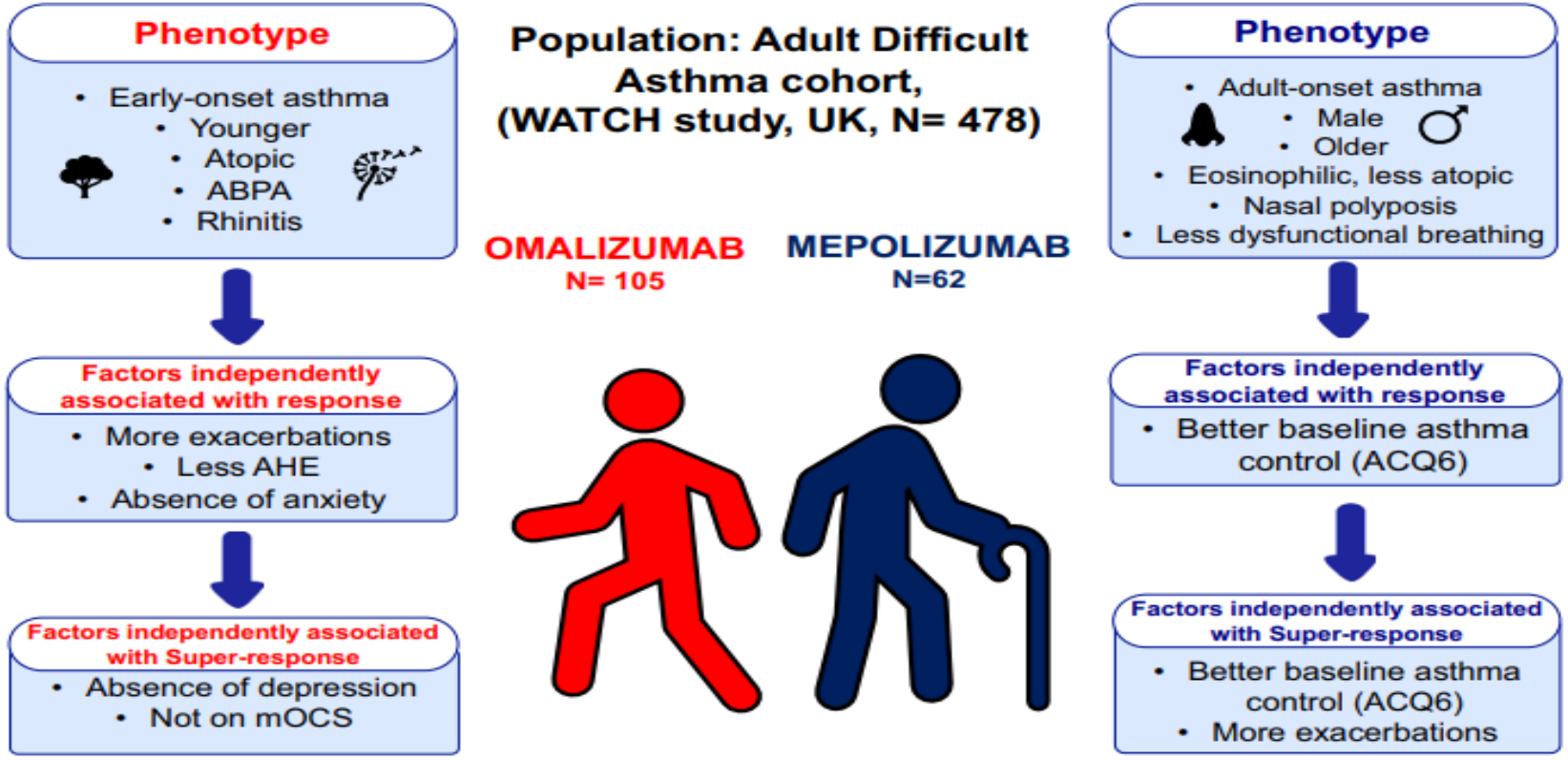


FIGURE 3 Summary of baseline phenotypic features of Omalizumab and Mepolizumab treated patients and factors independently associated with response and super-response to these drugs. ABPA: allergic bronchopulmonary aspergillosis. AHE: acute healthcare encounters, which include Emergency department/ hospital 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.

OMALİZUMAB-MEPOLİZUMAB UPİLUMAB KİME?

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

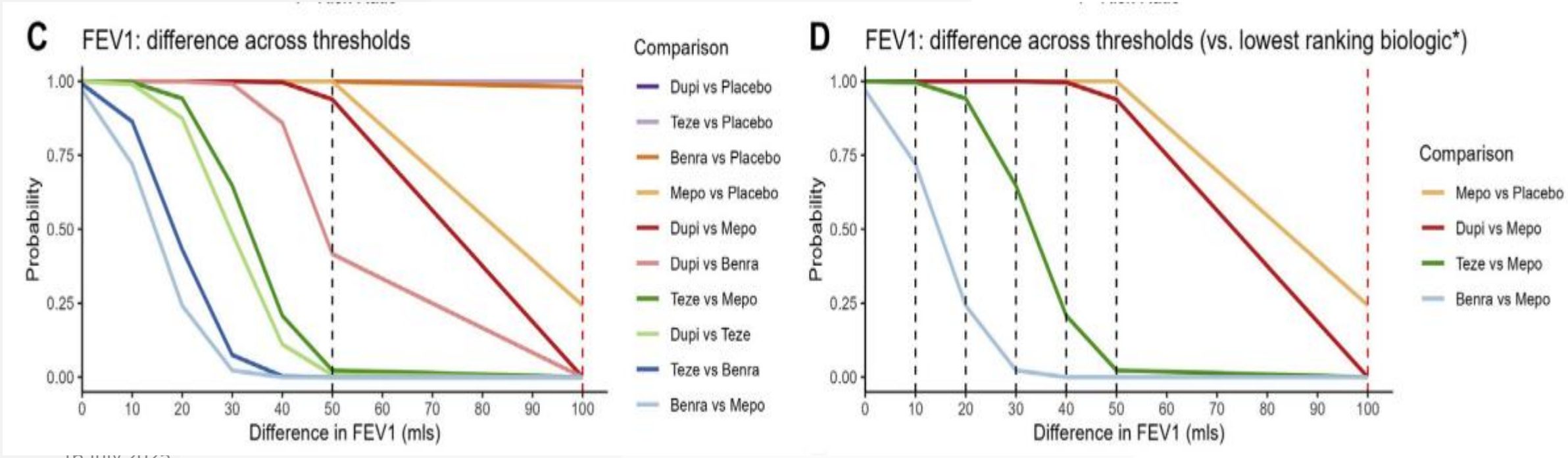
Nair P, et al. Allergy 2021
Svenningsen S, Nair P. Front Med 2017;4:158
Nair P. Respirology 2020;25:1123-5.

BİYOLOJIKLERDE FEV1 DEĞİŞİMİ 100 mL üzeri

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



- PEKİ YA BİZİM TECRÜBEMİZ?

Comparison of omalizumab and mepolizumab treatment efficacy in patients with atopic and eosinophilic “Overlap” severe asthma

Biological agent preference in atopic-eosinophilic severe asthma

Fatma Merve Tepetam, MD[a,*], Ali Burkan Akyıldız, MD[a], Şeyma Özden, MD[a], Cihan Örcen, MD[b], Tuğçe Yakut, MD[c], Özge Atik, MD[a]

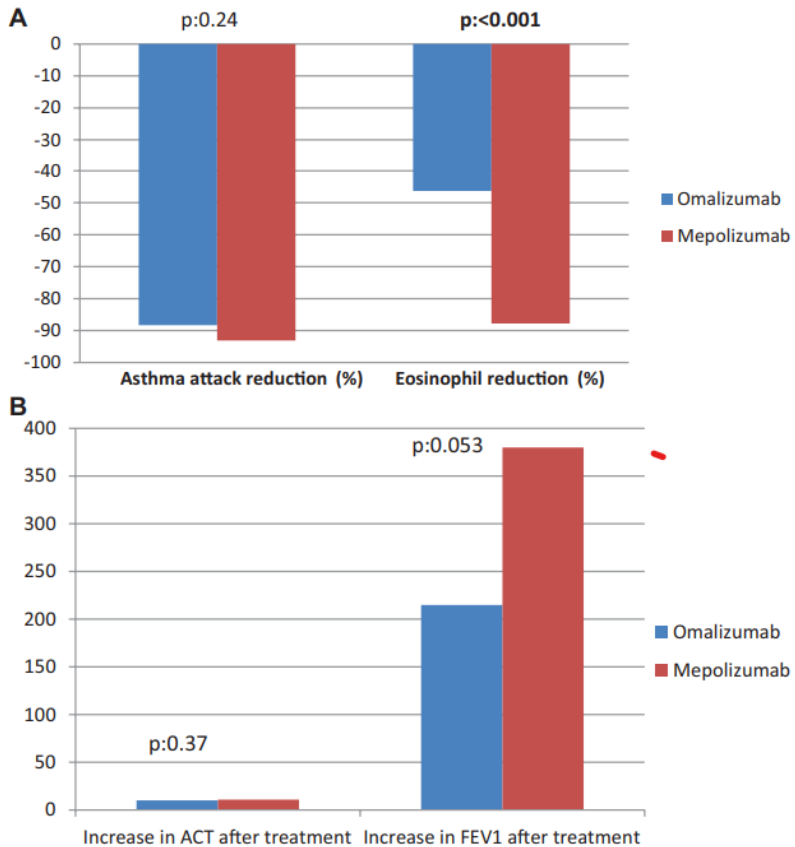
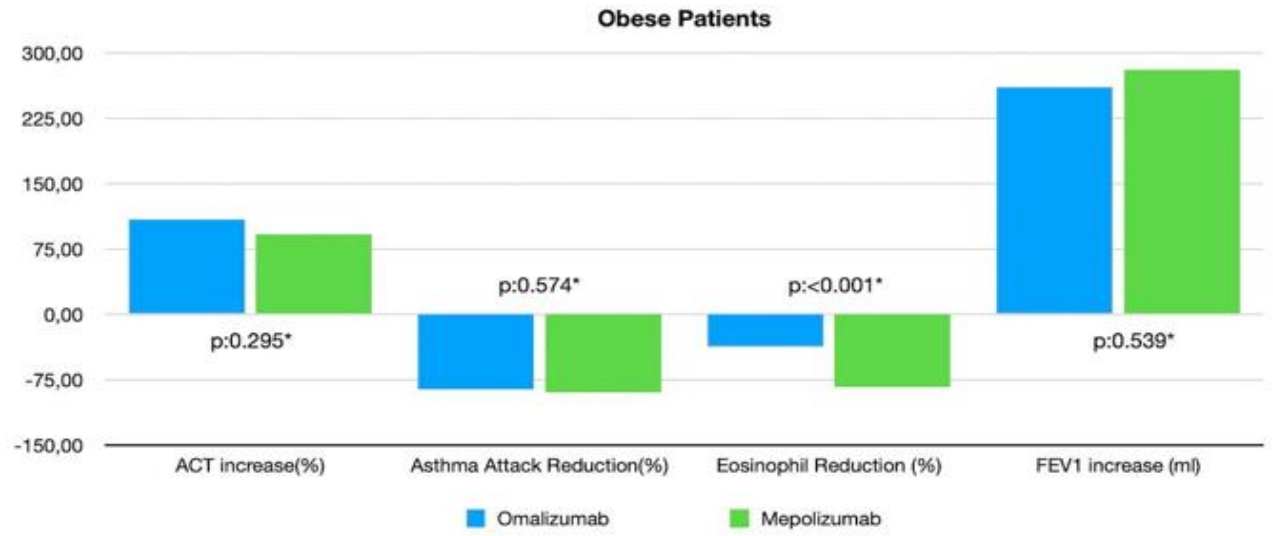


Figure 1 (A) Comparison of the reduction of asthma attacks and eosinophil levels after omalizumab and mepolizumab treatment. (B) Comparison of improvements in ACT and FEV1 after omalizumab and mepolizumab treatment. ACT = asthma control test, FEV1 = forced expiratory volume in 1 second.

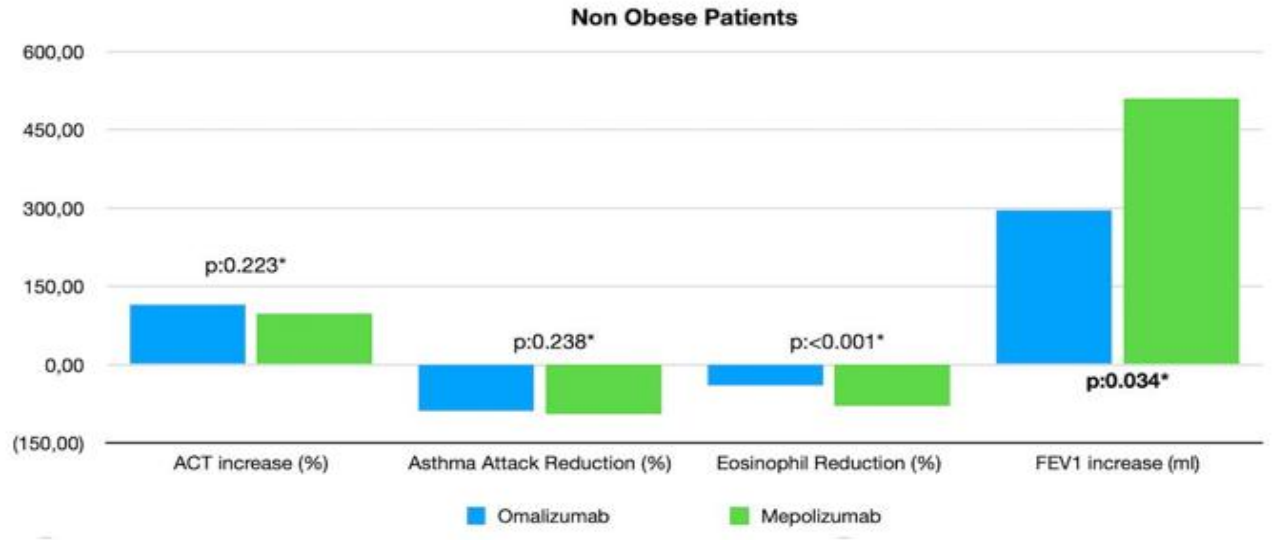
Bizim Tecrübemiz
121 Hasta
Omalizumab: 88
Mepolizumab: 33
Obez: 44
Nonobez: 77

Şekil 1-a,b



The phenotypic heterogeneity of obese and nonobese patients with severe asthma and comparison of omalizumab–mepolizumab treatment efficiency in these patients

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



SONUÇ

BİYOLOJİKLER ARASI KAFA KAFAYA ÇALIŞMA YOK

OVERLAP HASTADA HANGİ BİYOLOJİK?

Teşekkürler...