AĞIR ASTIMDA DEĞERLENDİRME VE DOĞRU BİYOLOJİK TEDAVİ SEÇİMİ

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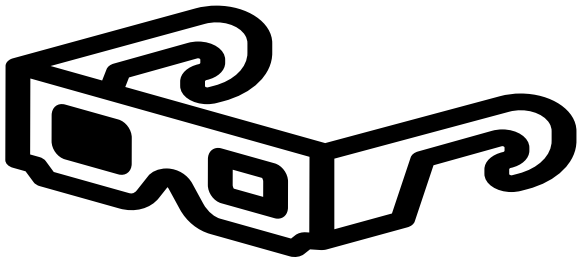
- Süreyyapaşa Göğüs Hastalıkları ve
- Göğüs Cerrahisi EAH
- İmmunoloji ve Allerji Kliniği

GSK ‘nın Koşulsuz Eğitim Desteği ile

NP-TR-CAU-PPTX-260001

ASTIMDA PATOGENİK SÜREÇ-TEDAVİ HEDEFLERİ



Hava yolu inflamasyonu

Bronş hiperreaktivitesi

Bronkokonstruksiyon

Remodeling

- Bronş düz kas kalınlaşması
- Goblet hücre metaplazisi
- Epitelyal hasar
- Subepitelyal fibrozis
- Anjiyogenezis
- Ekstraselüler matriks artışı

ASTIM TEDAVİ HEDEFLERİ-TARİHÇE

1900-1940
1951
- ADRENALİN
- SİSTEMİK STEROİD

1960
1970
- SABA
- IKS-KROMOLIN

1980
1990
- LABA
- MONTELUKAST

2000s
- OMALİZUMAB

Semptom giderme
Bronkonstruksiyon

İnflamasyon (1995)

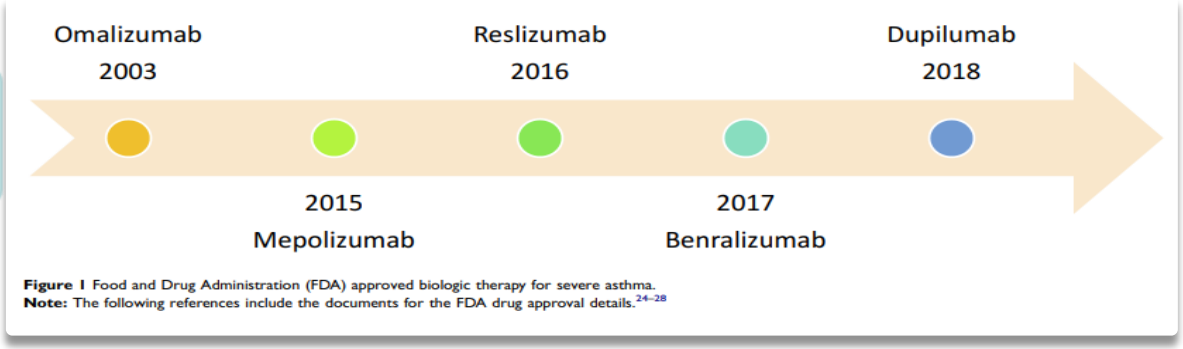
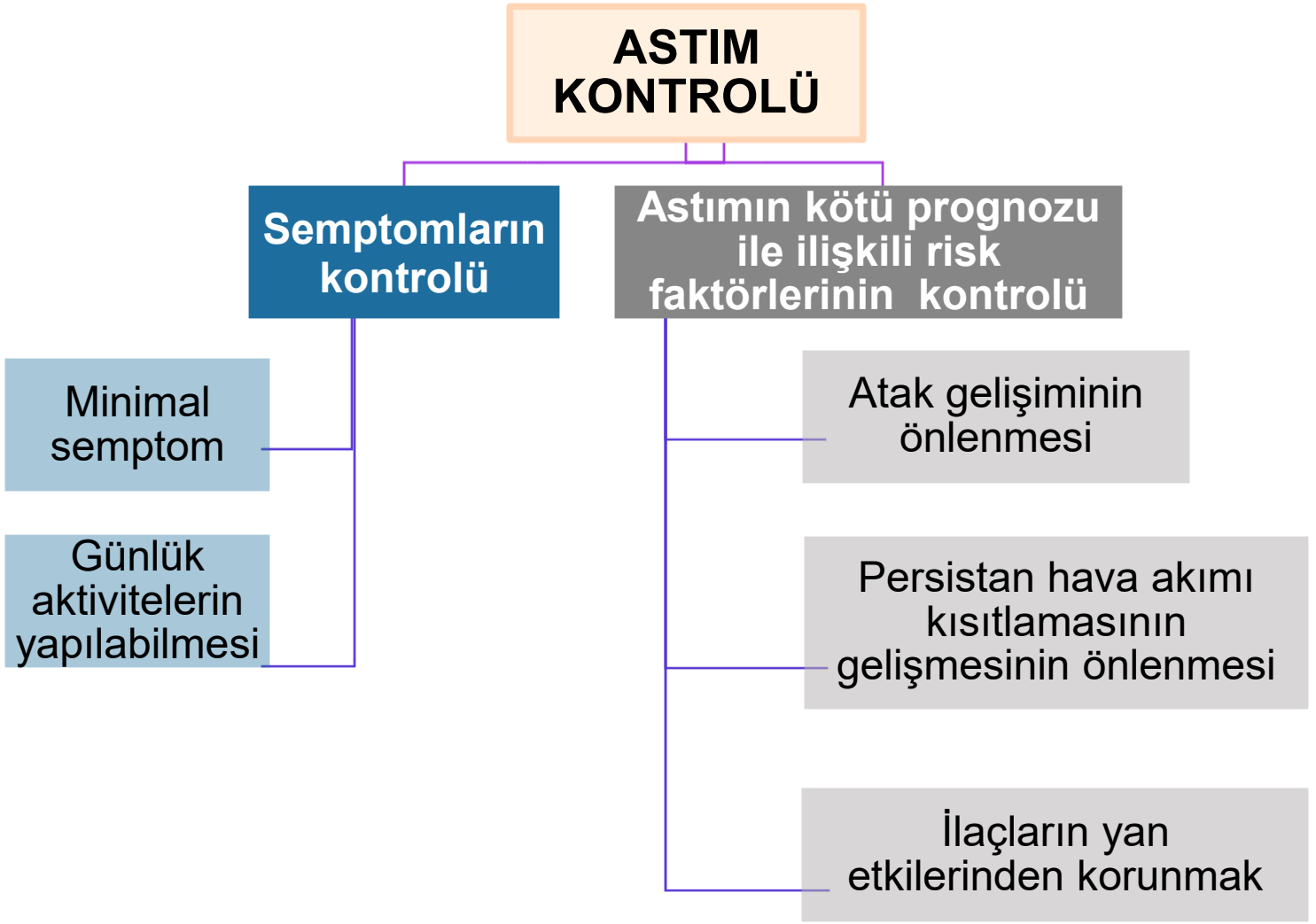


Figure 1 Food and Drug Administration (FDA) approved biologic therapy for severe asthma.
Note: The following references include the documents for the FDA drug approval details.[24–28]

Semptom, inflamasyon azaltılması
Atakların azaltılması (2014)
Progresyonun azaltılması

TEDAVİ SEÇİMİNDE AMAÇ



Astım kontrolü

Semptom kontrolü

- Gece ve gündüz semptom sıklığı
- Gece uyanma
- Aktivite kısıtlaması
- Kurtarıcı ilaç gereksinimi

Son 4 hafta içinde

1. Haftada 2'den fazla astım semptom varlığı
2. Astım nedeni ile herhangi bir gece uyanma
3. Haftada 2'den fazla kurtarıcı ilaç kullanma ihtiyacı
4. Astım nedeni ile herhangi bir aktivitenin kısıtlanması

Hiçbiri yok	1-2'si varsa	3-4'ü varsa
İYİ KONTROL	KISMİ KONTROL	KONTROLSÜZ

Astım Kontrol Testi, Astım Kontrol Anketi

Gelecekte gelişebilecek istenmeyen sonuçlar için risk faktörlerinin kontrolü

Semptom kontrolü iyi olsa da değerlendir!!

Alevlenme risk faktörleri

- Kontrolsüz astım
- Son bir yılda ≥1 ağır alevlenme
- Daha önce entübasyon/YBÜ öyküsü
- Aşırı SABA kullanımı
- Yetersiz IKS kullanımı
- Hatalı inhaler teknik
- İKS uyumsuzluğu
- Komorbiditeler
- Sosyoekonomik, psikolojik problemler
- Düşük FEV1, yüksek reversibilite
- Eozinofili, FeNO yüksekliği
- Maruziyetler: sigara, allerjen

Kalıcı hava yolu obst. risk faktörleri

- Erken doğum, düşük doğum ağırlığı ve infant dönemde aşırı kilo alımı
- Ağır alevlenme öyküsü olan hastanın İKS kullanmaması
- Maruziyetler
- Düşük FEV1, balgam yada kan eozinofili

İlaç yan etki gelişimi için risk faktörleri

- Sık SKS kullanımı
- Uzun süre, yüksek doz IKS kullanımı
- P450 inhibitör kullanımı
- İnhaler tekniğin kötü olması

- Zayıf semptom kontrolü

(sık gündüz semptomu, kurtarıcı ihtiyacı, aktivite kısıtlaması, gece astım sebepli uyanma, AKT<20)

- En az 3 gün OKS kullanımı gerektiren sık atak (≥2/yıl)
- Hastaneye yatışla sonlanan ağır atak

Kontrolsüz astım

- 4-5. basamak tedaviye (orta veya yüksek doz İKS+LABA/KEİ veya idame OKS) rağmen kontrol altına alınamayan veya semptom kontrolünü sağlamak ve atak riskini azaltmak için bu basamakta tedavi gereken astım

Tedavisi zor astım

FENO SÜPRESYON TESTİ (İKS UYUMU)

- Başlangıç FeNO ölçülür
- 5–14 gün yüksek doz İKS ± kısa süreli oral steroid verilir
- FeNO yeniden ölçülür
- **≥% 20 YÜKSELME → negatif supresyon**
- **mutlak değerin >40 ppb olması**
- ***İnhaler teknik ve uyumu gözden geçir!!!**

- Tanı doğru
- Yüksek doz tedavi
- Tedavi uyumu tam, inhaler teknik doğru
- Komorbiditeler kontrol altına alınmış
- Maruziyetler önlenmiş

Ya da

- Bu koşullarda tedavi dozu azaltıldığında kontrolsüz olan astım

Ağır astım

Ağır astım merkezine yönlendir

ENDOTİPLEMEDE BELİRTEÇLER NELER?

Type 2 İnflamasyon

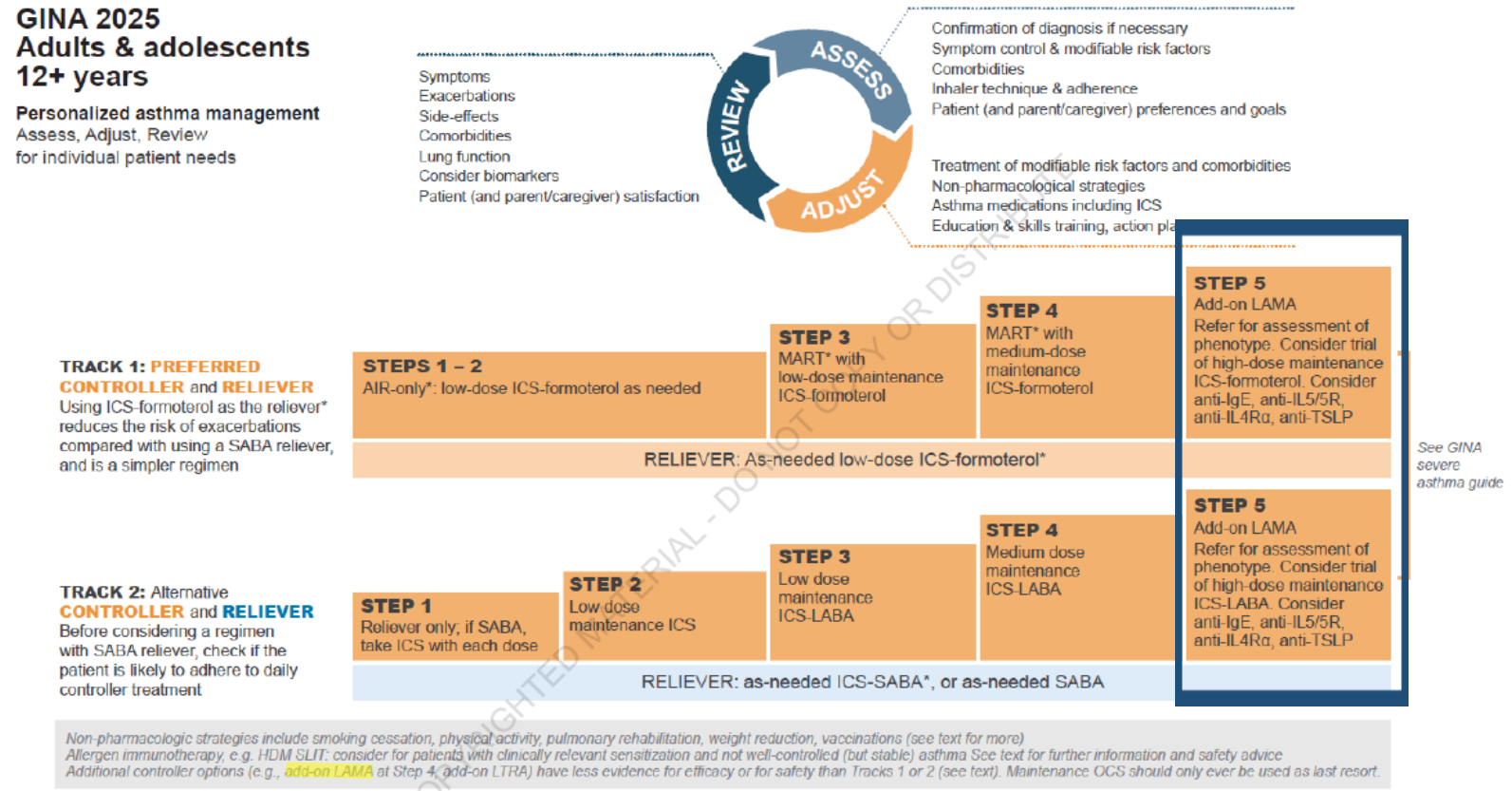
- Periferik eozinofil ≥ 150/µL
  - ve/veya
- FENO ≥ 20 ppb
  - ve/veya
- İndükte balgamda eozinofil ≥ %2
  - ve/veya
- Astımın klinik olarak alerjen kaynaklı olması
  - ve/veya
- İdame tedavide OCS ihtiyacı

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

GINA 2025

ASTHMA TREATMENT STEPS IN ADULTS AND ADOLESCENTS

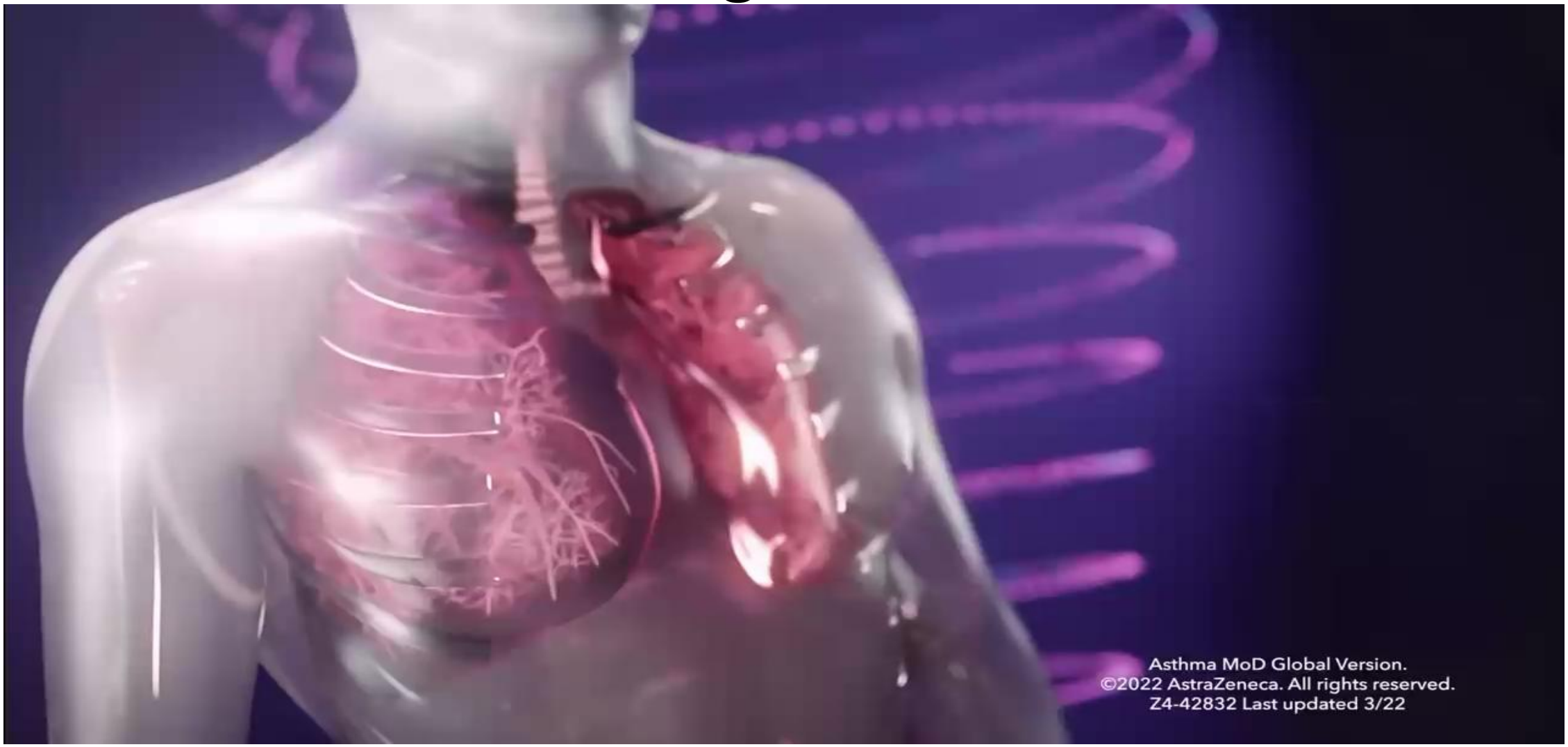
Box 4-6. Personalized management for adults and adolescents to control symptoms and minimize future risk



*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.

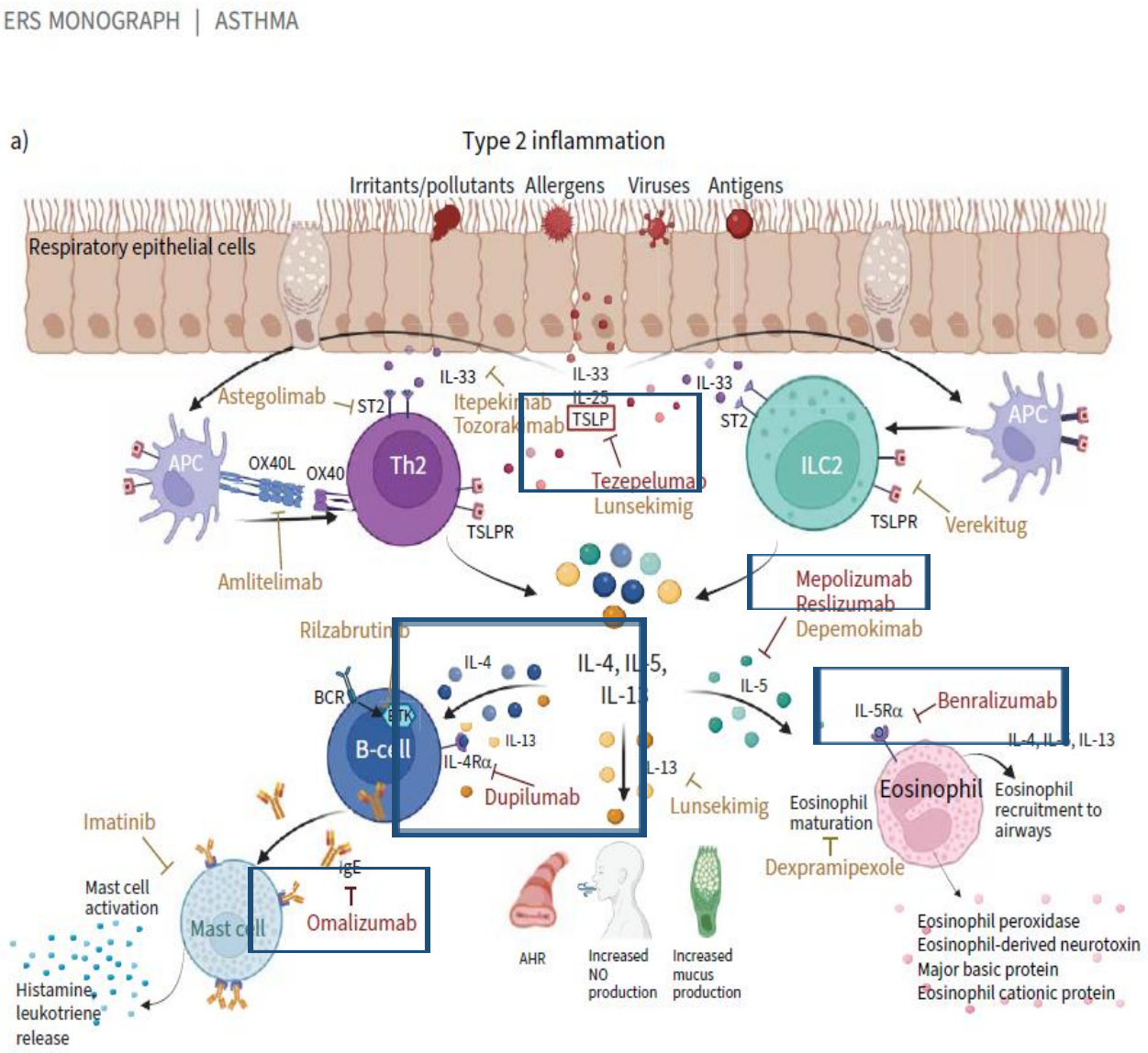
Astım İmmuno-Patogenezi



EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

GÜNCEL BİYOLOJİKLER TEDAVİ HEDEFLERİ

ERS MONOGRAPH | ASTHMA



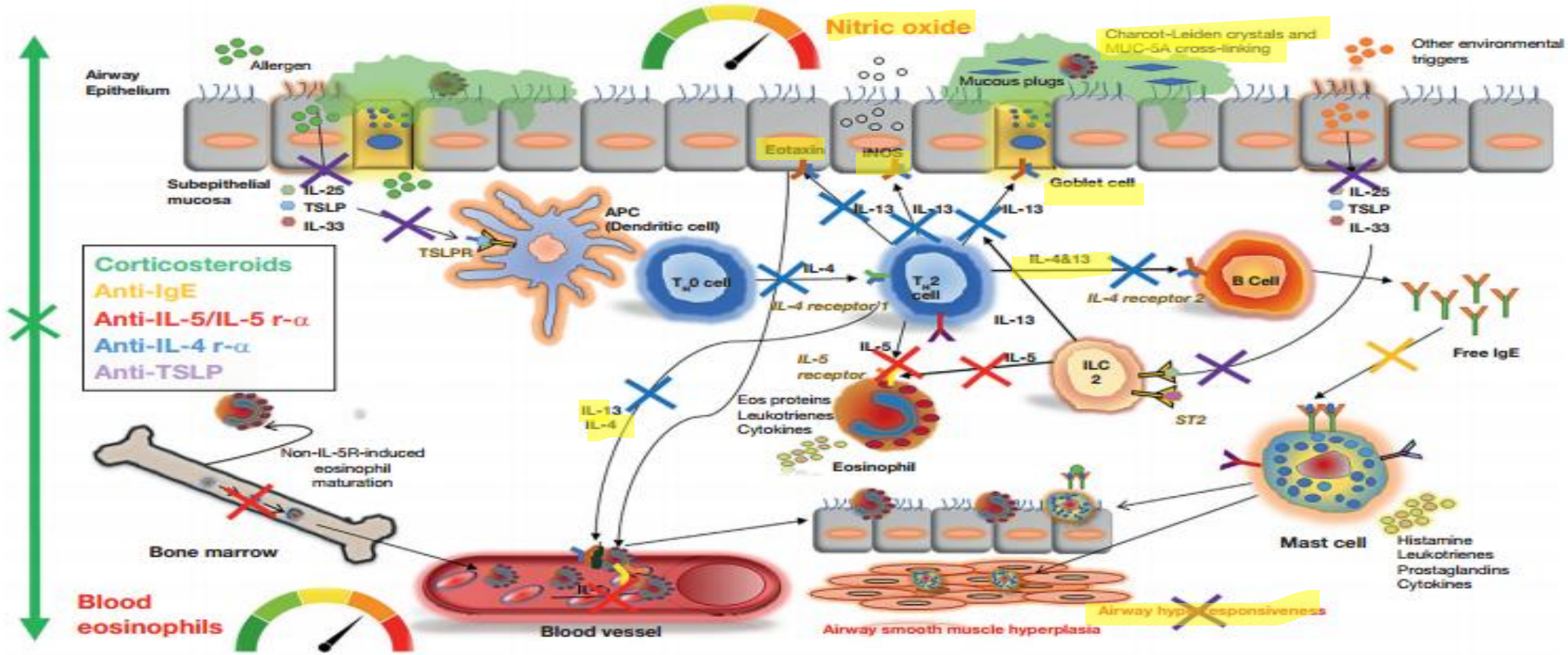
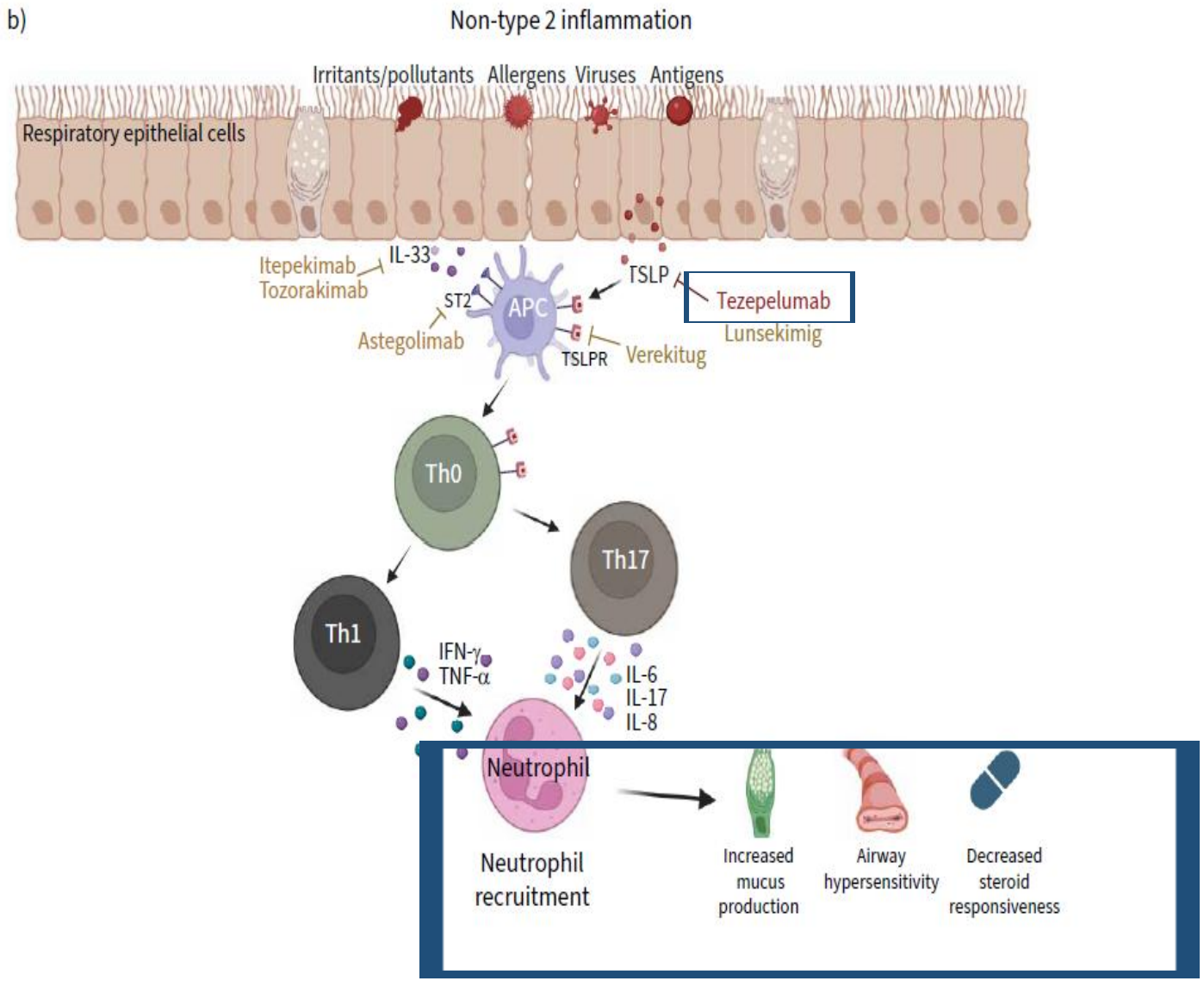


Figure 2 – *Diagram showing type 2 inflammatory cascade in severe asthma and the effects of antiinflammatory therapies. The type 2 immune response may be set off by a trigger (eg, allergen, smoke or pollution, infection) in the airways, leading to epithelial alarmin signalling with downstream type 2 cytokine (IL-5, IL-4, and IL-13) activity and migration of circulating eosinophils to the airways in most patients, and non-type 2 mechanisms in others (eg, mastocyte activation). In type 2 inflammatory severe asthma, blood eosinophils reflect circulating IL-5 and the systemic pool of available effector cells, whereas fractional exhaled nitric oxide reflects IL-13 activity in the airway compartment (mucus hypersecretion, bronchial motor tone, and chemotaxis of eosinophils).*[5,24,34,64] *Corticosteroids have broad biologic and clinical effects at the cost of associated toxicity. Targeting the end products of the type 2 pathway, such as IgE, has had modest success in asthma. In the past decade, a strategy based on blocking progressively more proximal drivers of inflammation such as IL-5, IL-4, IL-13, and TSLP has proven successful. APC = antigen presenting cell; Eos = eosinophils; MUC-5A = mucin 5-A; iNOS = inducible nitric oxide synthase; TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor.*

NON TİP 2 BİYOLOJİKLER

ERS MONOGRAPH | ASTHMA



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/µl** 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

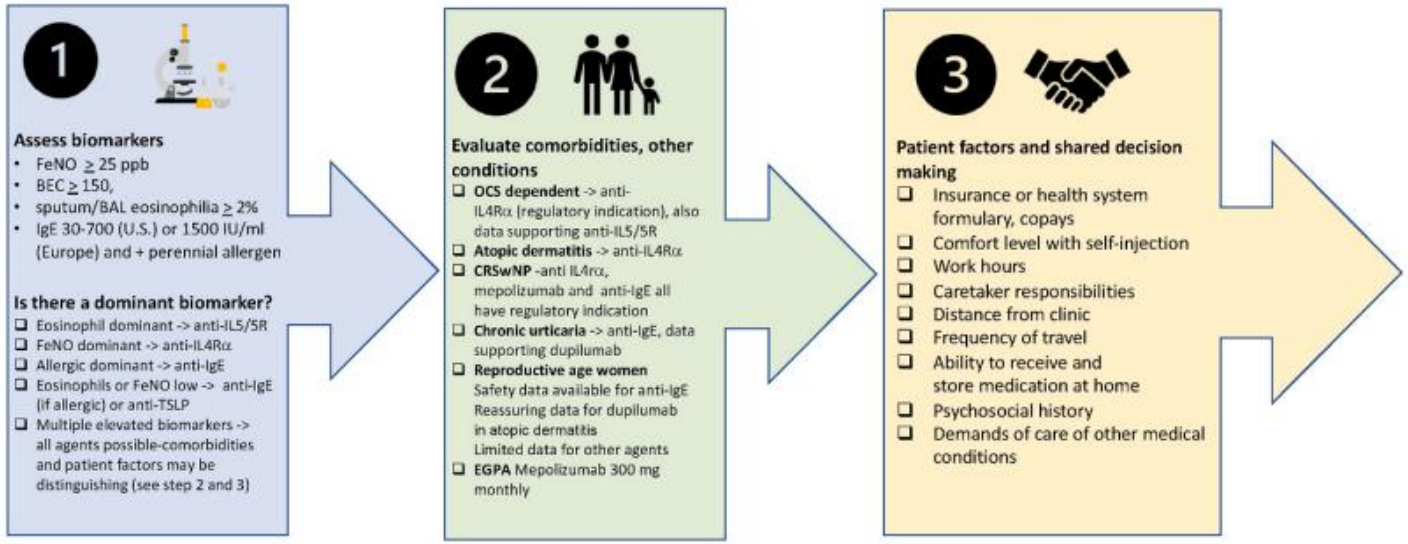


Fig. 2. A pragmatic approach to choosing an asthma Biologic.

BİYOBELİRTEÇLER

FENO ARTIŞI HANGİ FENOTİPTE OLUR? NAS

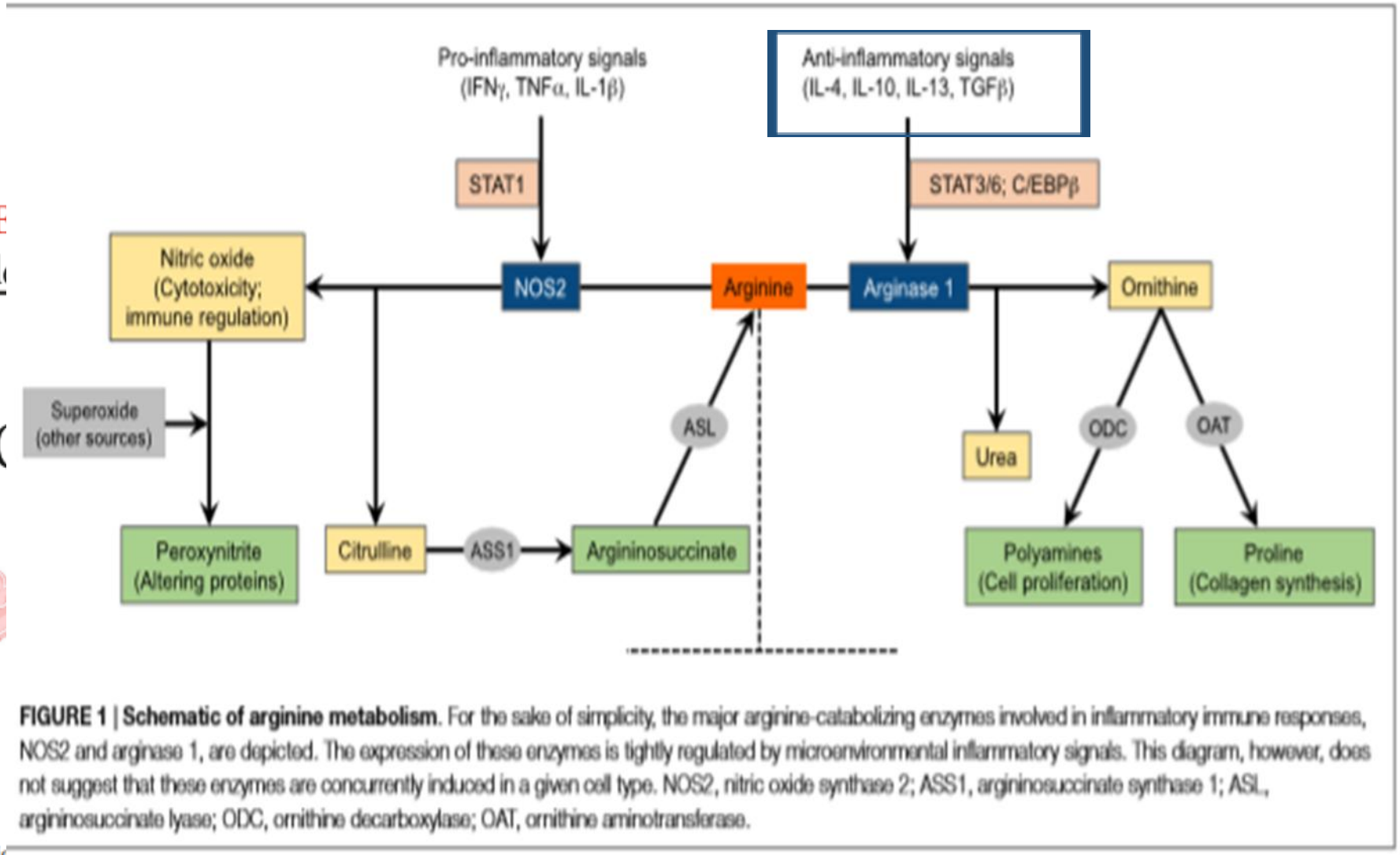


FIGURE 1 | Schematic of arginine metabolism. For the sake of simplicity, the major arginine-catabolizing enzymes involved in inflammatory immune responses, NOS2 and arginase 1, are depicted. The expression of these enzymes is tightly regulated by microenvironmental inflammatory signals. This diagram, however, does not suggest that these enzymes are concurrently induced in a given cell type. NOS2, nitric oxide synthase 2; ASS1, argininosuccinate synthase 1; ASL, argininosuccinate lyase; ODC, ornithine decarboxylase; OAT, ornithine aminotransferase.

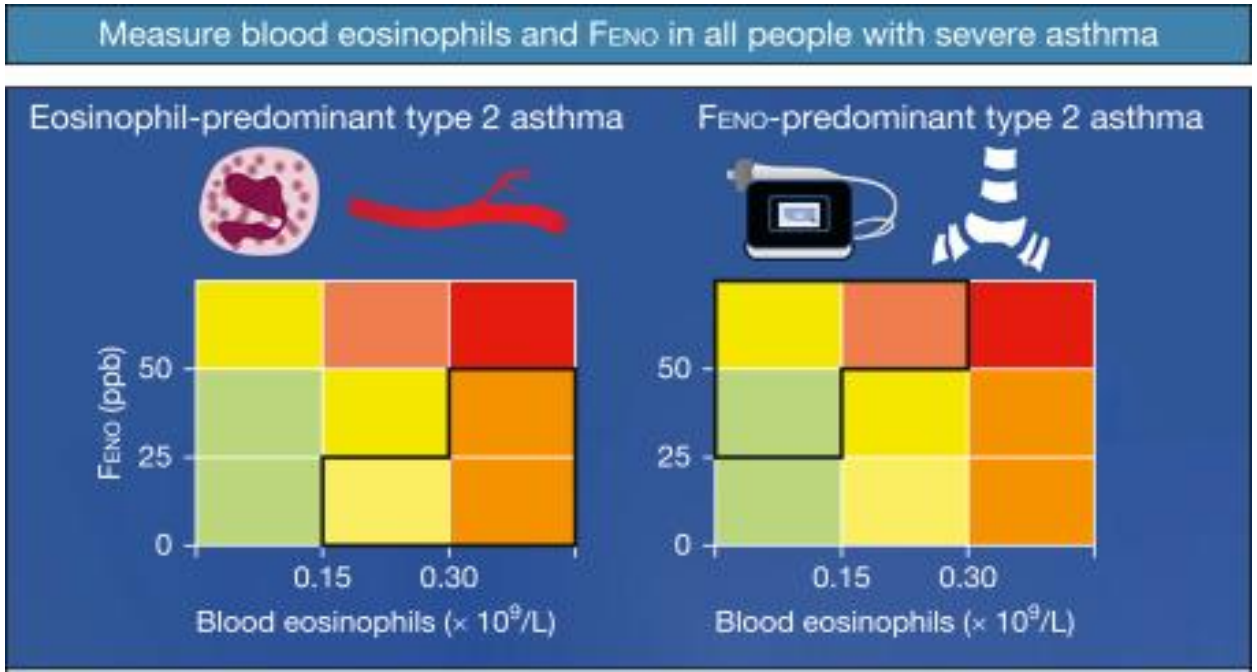
Hindawi BioMed Research International Volume 2022, Article ID 5753524, 9 pages
https://doi.org/10.1155/2022/5753524

TABLE 2 Responsiveness of biomarkers to anti-inflammatory treatments commonly used in obstructive airway disease

Biomarker	ICS	OCS	Omalizumab	Mepolizumab	Benralizumab	Dupilumab	Tezepelumab
***Fe*NO**	+++	++	+	0	0	+++	++
Blood eosinophils	+	+++	+	+++	++++	0[#]	++
IgE	0	0	+++[##]	0	0	+++	++

0: no effect; +: small effect (10–30% reduction); ++: moderate effect (30–60% reduction); +++: large effect (60–90% reduction); ++++: complete effect (90–100% reduction). [#]: dupilumab treatment may lead to a transient increase in blood eosinophil count; [##]: free IgE.

EOZİNOFİL BASKIN-FENO BASKIN FENOTİP



Greater % of late-onset asthma	Greater % of early onset
Less allergy	Allergy
Less AHR	AHR ++
Less atopic. More CRSwNP, EGPA	Eczema, atopic rhinitis > CRSwNP
Blood eos signal > FENO signal	FENO signal > blood eos signal
OCS > ICS sensitivity	ICS > OCS sensitivity
Anti-IL-5/-5R ~ Anti-IL-4R ~ Anti-TSLP response	Anti-IL-4R/Anti-TSLP > Anti-IL-5/-5R response
← Many patients have features of both →	
↑Eosinophils and/or ↑FENO = ↑risk of attacks, ↑response to biologics	

167#2 CHEST FEBRUARY 2025]

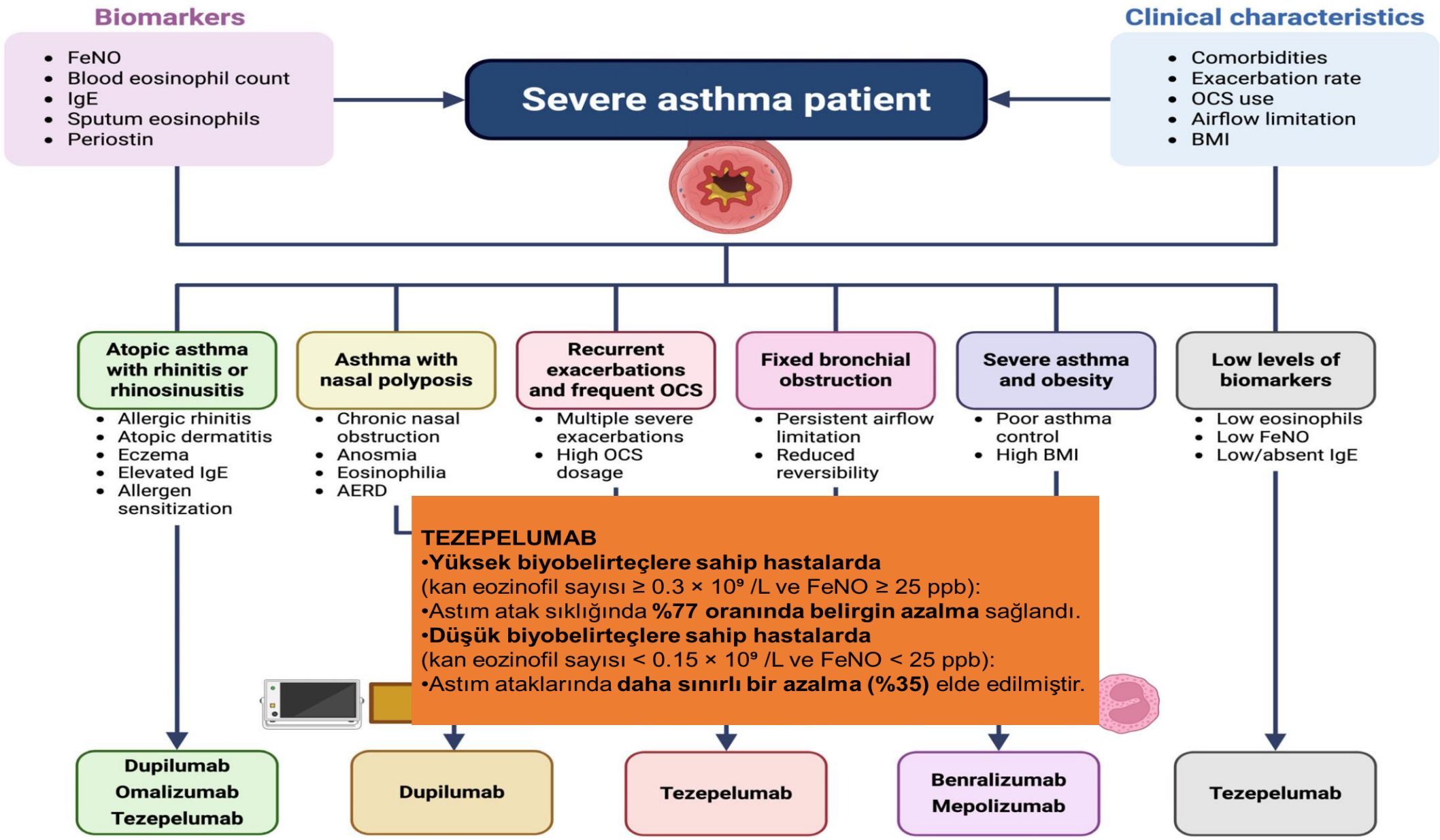
FENO-EOZİNOFİLİK-NONEOZİNOFİLİK ATAK İLİŞKİSİ

FeNO < 20 ppb olması durumunda:

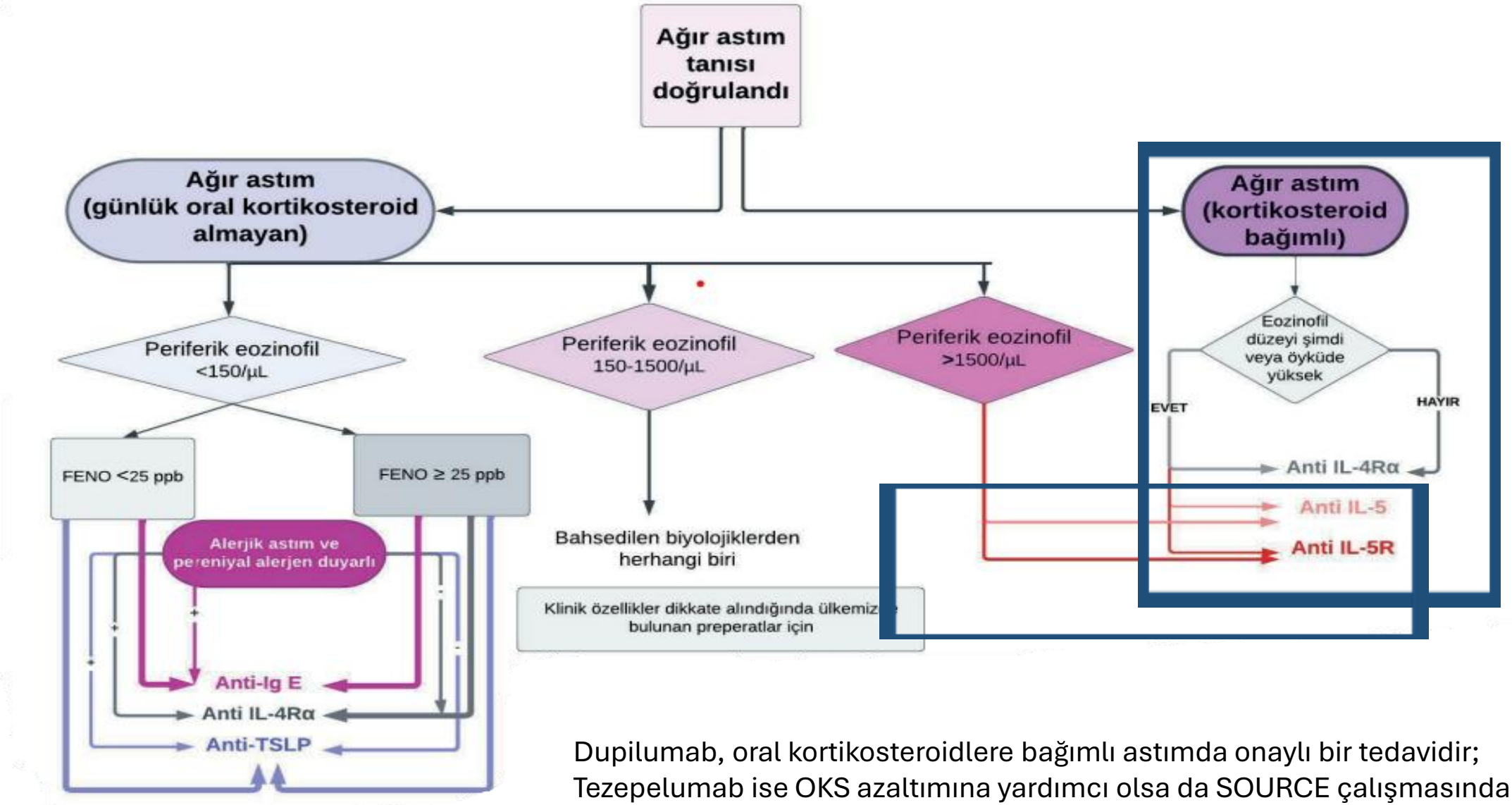
Non-eozinofilik, enfeksiyöz atakları öngörmede %100 pozitif prediktif değer saptanmıştır.

Yüksek FeNO düzeyleri (> 50 ppb) durumunda:

Alevlenme sırasında balgam eozinofilisini öngörmede %77 pozitif prediktif değer göstermiştir.


Biomarkers
FeNO
Blood eosinophil count
IgE
Sputum eosinophils
Periostin
Clinical characteristics
Comorbidities
Exacerbation rate
OCS use
Airflow limitation
BMI
Severe asthma patient
Atopic asthma with rhinitis or rhinosinusitis
Allergic rhinitis
Atopic dermatitis
Eczema
Elevated IgE
Allergen sensitization
Asthma with nasal polyposis
Chronic nasal obstruction
Anosmia
Eosinophilia
AERD
Recurrent exacerbations and frequent OCS
Multiple severe exacerbations
High OCS dosage
Fixed bronchial obstruction
Persistent airflow limitation
Reduced reversibility
Severe asthma and obesity
Poor asthma control
High BMI
Low levels of biomarkers
Low eosinophils
Low FeNO
Low/absent IgE
TEZEPELUMAB
•Yüksek biyobelirteçlere sahip hastalarda
(kan eozinofil sayısı ≥ 0.3 × 10⁹ /L ve FeNO ≥ 25 ppb):
•Astım atak sıklığında %77 oranında belirgin azalma sağlandı.
•Düşük biyobelirteçlere sahip hastalarda
(kan eozinofil sayısı < 0.15 × 10⁹ /L ve FeNO < 25 ppb):
•Astım ataklarında daha sınırlı bir azalma (%35) elde edilmiştir.
Dupilumab
Omalizumab
Tezepelumab
Dupilumab
Tezepelumab
Benralizumab
Mepolizumab
Tezepelumab

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



Dupilumab, oral kortikosteroidlere bağımlı astımda onaylı bir tedavidir; Tezepelumab ise OKS azaltımına yardımcı olsa da SOURCE çalışmasında ana hedefe ulaşamamıştır.

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

STEROİD BAĞIMLI ASTIMDA BİYOLOJİK SEÇENEKLERİ

- ➡️ Benralizumab, Dupilumab ve Mepolizumab → Steroid yükünü azaltmada etkili
- ➡️ **Dupilumab → OCS-bağımlı astımda onaylı**
- ➡️ Tezepelumab → Destekleyici ama SOURCE'da başarısız

GÜNCEL BİYOLOJİKLER ENDİKASYONLAR VE SONUÇLAR

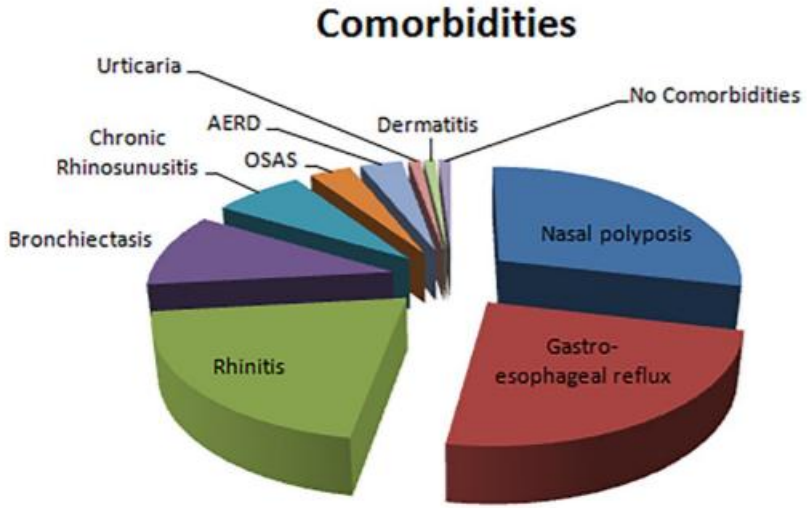
TABLE 1 Summary of currently available biologic therapies, detailing their targets, indications and outcomes

	Omalizumab (*s.c.*)	Dupilumab (*s.c.*)	Mepolizumab (*s.c.*)	Reslizumab (*i.v.*)	Benralizumab (*s.c.*)	Tezepelumab (*s.c.*)
Target	IgE	IL-4/IL-13	IL-5	IL-5	IL-5 receptor	TSLP
Patient age, years	⩾6	⩾6	⩾6	⩾18	⩾6	⩾12
Frequency	Once every 2 weeks or once every 4 weeks	Once every 2 weeks	Once every 4 weeks	Once every 4 weeks	Once every 4 weeks for first 3 doses then once every 8 weeks	Once every 4 weeks
Eligibility requirements, biomarkers	Allergic asthma: Sensitivity to ⩾1 aeroallergen, total IgE 30–700 IU·mL^{-1}	Moderate–severe asthma with type 2 inflammation: Blood eosinophils⩾150 cells·µL^{-1} or systemic corticosteroid dependent	Eosinophilic asthma: Blood eosinophils ⩾150 cells·µL^{-1}	Eosinophilic asthma: Blood eosinophils ⩾400 cells·µL^{-1}	Blood eosinophils ⩾ 150 cells·µL^{-1}	No specific biomarker threshold
Other approved indications	Chronic spontaneous urticaria, CRSwNP, food allergies	Atopic dermatitis, CRSwNP eosinophilic oesophagitis, prurigo nodularis, COPD[#]	EGPA, hypereosinophilic syndrome, CRSwNP	N/A	EGPA	N/A
Outcomes						
Exacerbation rate reduction	25–50%	50–70%	~50%	~50%	~50%	50–70%
Maintenance OCS reduction		++	++		++	–
Quality of life improvement		+	+	+	+	++
FEV_1 improvement	+/–	++	+/–	+	+/–	++

CRSwNP: chronic rhinosinusitis with nasal polyps; EGPA: eosinophilic granulomatosis with polyangiitis; N/A: not applicable; ++: significant effect; +: moderate effect; +/–: variable effect; –: no effect. [#]: current indication requires blood eosinophils ⩾300 cells·µL^{-1}.

ERS MONOGRAPH | ASTHMA

KOMORBİDİTELER



Therapeutic Advances in Respiratory Disease 14

ÜRTİKER, ÇOKLU BESİN ALERJİSİ:

OMALİZUMAB

A.DERMATİT, KOAH, EOZİNOFİLİİK ÖZOFAJT

DUPİLUMAB

EGPA:

BENRALİZUMAP

MEPOLİZUMAB

HES MEPOLİZUMAB

NAZAL POLİP:

DUPİLUMAB (EMA)

OMALİZUMAB (EMA)

MEPOLİZUMAB (FDA)

BENRALİZUMAB (FDA)

💊 Gebelikte ve Emzirme Döneminde Biyolojik Tedaviler

Biyolojik ajanlar hedefe yönelik olup düşük yan etki riski taşır.

- Plasentayı geçebilir ve anne sütünde tespit edilebilir.

- Randomize çalışma yok, ancak klinik deneyimler güvenli olduğunu göstermektedir.

- **Omalizumab: RCC:EXPECT doğumsal anomali riskini artırmaz**.

- Mepolizumab, Benralizumab, Reslizumab, Dupilumab, Tezepelumab: Hayvan çalışmaları ve vaka raporları fetal veya neonatal olumsuz etki bildirilmemiştir.

ANNE SÜTÜNE GEÇİŞ

- 3️⃣ **Anne Sütüne Geçiş**
- **İV RESLİZUMAB!!!**

İlaç	Anne Sütüne Geçiş Oranı
Mepolizumab	≤ %0,5
Tezepelumab	≤ %0,5
Reslizumab	%5–7
Benralizumab	Veri yok
Dupilumab	Veri yok

GEBELİKTE BİYOLOJİK ÖNERİLERİ

- Astım kontrolünü sürdürmek, olası ilaç risklerinden daha önemlidir.
- Kontrolsüz astım erken doğum ve düşük doğum ağırlığı ile ilişkilidir.
- Biyolojik tedaviler gebelik öncesi, süresince ve emzirmede kullanılabilir.
- Steroid yan etkileri veya hastane yatışı olan hastalarda devam ettirilebilir.
- Hasta-hekim ortak kararı (shared decision-making) esastır.

DÜŞÜK FEV1'DE HANGİ BİYOLOJİK

GINA 2025

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]

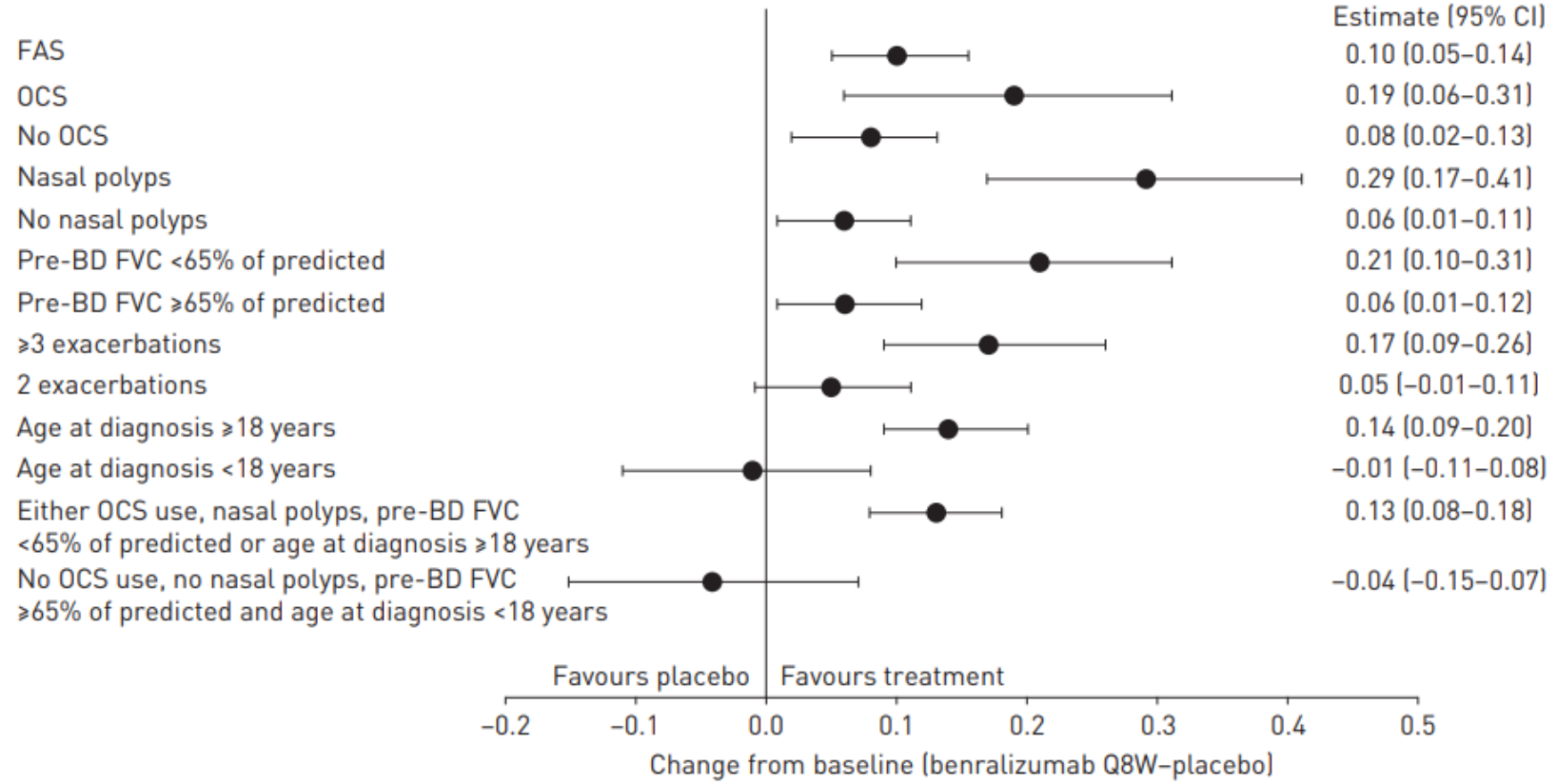
Clinical Trial > Eur Respir J. 2018 Oct 18;52(4):1800936. doi: 10.1183/13993003.00936-2018. Print 2018 Oct.

Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma

Eugene R Bleecker [1], Michael E Wechsler [2], J Mark FitzGerald [3], Andrew Menzies-Gow [4], Yanping Wu [5], Ian

Affiliations + expa

PMID: 30139780



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)***

CHEST

Choosing the Right Biologic for the Right Patient With Severe A

Simon Couillard, MD, FRCPC; David J. Jackson,

TABLE 1] Therapeutic Strategies of Biologics Approved in Asthma

Therapeutic Strategy (Biologic)	Selection Criteria	Asthma Attacks	S					
Anti-IgE (omalizumab)	Serum IgE 30-700 with perennial aeroallergen sensitization	+	U					
Anti-IL-5 and anti-IL-5R (mepolizumab, reslizumab, benralizumab)	Blood eosinophils ≥ 0.15 $\times 10^9$ cells/L at screening or ≥ 0.3 $\times$ 10^9/L in past year	++	++	+	+	0/+	EGPA[a] ++ HES[a] ++ CRSwNP +	Major clinical effects proportional to eosinophilia
Anti-IL-4 and anti-IL-13 (dupilumab)	Blood eosinophils ≥ 0.15 $\times$ 10^9/L, FENO ≥ 25 ppb, or both	++	++	+	++	Unclear[b]	AD ++ CRsNP ++ EoE ++ PN ++	Induces transient eosinophilia independent of efficacy
Anti-TSLP (tezepelumab)	None[c]	++	0	+	++	+	?	Major efficacy when blood eosinophils, FENO, or both are raised; lesser yet significant efficacy when biomarkers low

TABLE 2] Summary of Corticosteroid-Sparing Effects of Biologics Based on Randomized Controlled Trials

Biologic	Trial	Median Reduction in OCS Dose With Active and Placebo, %	Change in FEV_1 Before Bronchodilator Administration Active Minus Placebo, mL	Reduction in Asthma Attack Rates, %
Omalizumab	NA	NA	NA	NA
Mepolizumab[23]	SIRIUS	50 vs 0	114	32
Benralizumab[22]	ZONDA	75 vs 25	113	55
Dupilumab[1]	VENTURE	100 vs 50	220	59
Tezepelumab[56]	SOURCE	Not significant (100 vs 75)	260	Not significant (31)

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

Workup

Woman, 35 y of age

- Asthma diagnosis confirmed ✓
- Asthma is uncontrolled ✓
- Environmental triggers optimized ✓
- Adherence and inhaler technique ?
- Comorbidities reviewed ✓
- Phenotyped ✓
  - Allergic/childhood onset
  - Corticosteroid dependence: 0
- Biomarkers measured ✓
  - IgE 350 kU/L (↑)
  - F_{ENO} 45 ppb (↑)
  - Blood Eos 0.35×10^9/L (↑)
- Physiologic features/Imaging reviewed ✓
  - FEV_1 65%, FEV_1 to FVC ratio 0.57
  - Normal findings on chest radiograph

2. Considering which biologic

- All options below are reasonable choices - status quo is not.
- The following features should be discussed and weighed with the patient
- Payer reimbursement criteria may need to be considered

Options	Features	Comments
Omalizumab	• Young woman of child-bearing age • Fits prescription criteria • Allergic / childhood onset	• Most data in pregnancy • IgE↑, sensitised • Modest effect on attacks
Dupilumab or tezepelumab	• Eos and F_{ENO} raised • Spirometry results obstuctive • History of severe asthma attacks • Childhood onset	• Only mAbs to ↓↓ F_{ENO} and ↑↑ FEV_1 • Large effect on attacks • First choice here if no plans for children
Mepolizumab or benralizumab	• Eos raised • History of severe asthma attacks	• Large effect on attacks
Reslizumab	• Eos raised	• Intravenous therapy, no • subcutaneous option

3. Making a choice

- Shared decision-making is essential.
- If no short-term plans for pregnancy, dupilumab or tezepelumab are preferred for their broad clinical impacts (Attacks, FEV_1)
- Failure to achieve optimal response within 6 mo should prompt reevaluation

BULMACA OLGU

:

* 46 yaşında erkek
* Erişkin başlangıçlı astım
* **Mevcut tedavi:**
* Son **2 yıldır günlük 10 mg prednizolon** (idame tedavisi)
* **Biyobelirteç profili:**
* Kan eozinofil sayısı: **0.16 × 10^9/L**
* FeNO: **125 ppb (belirgin yüksek)**
* Serum IgE: **180 kU/L**
* Yaygın aeroalerjenler için **deri testleri negatif**
* **Geçmiş laboratuvar bulguları:**
* Prednizolon öncesi kan eozinofilleri: **0.4 – 0.6 × 10^9/L
* FeNO: **sürekli yüksek (120–150 ppb)**
* **Eşlik eden hastalık:**
* **Nazal polipli kronik rinosinüzit (CRSwNP)**
* **ANCA negatif**

)

OMALİZUMAB DEĞİL

TEZEPELUMAB DEĞİL

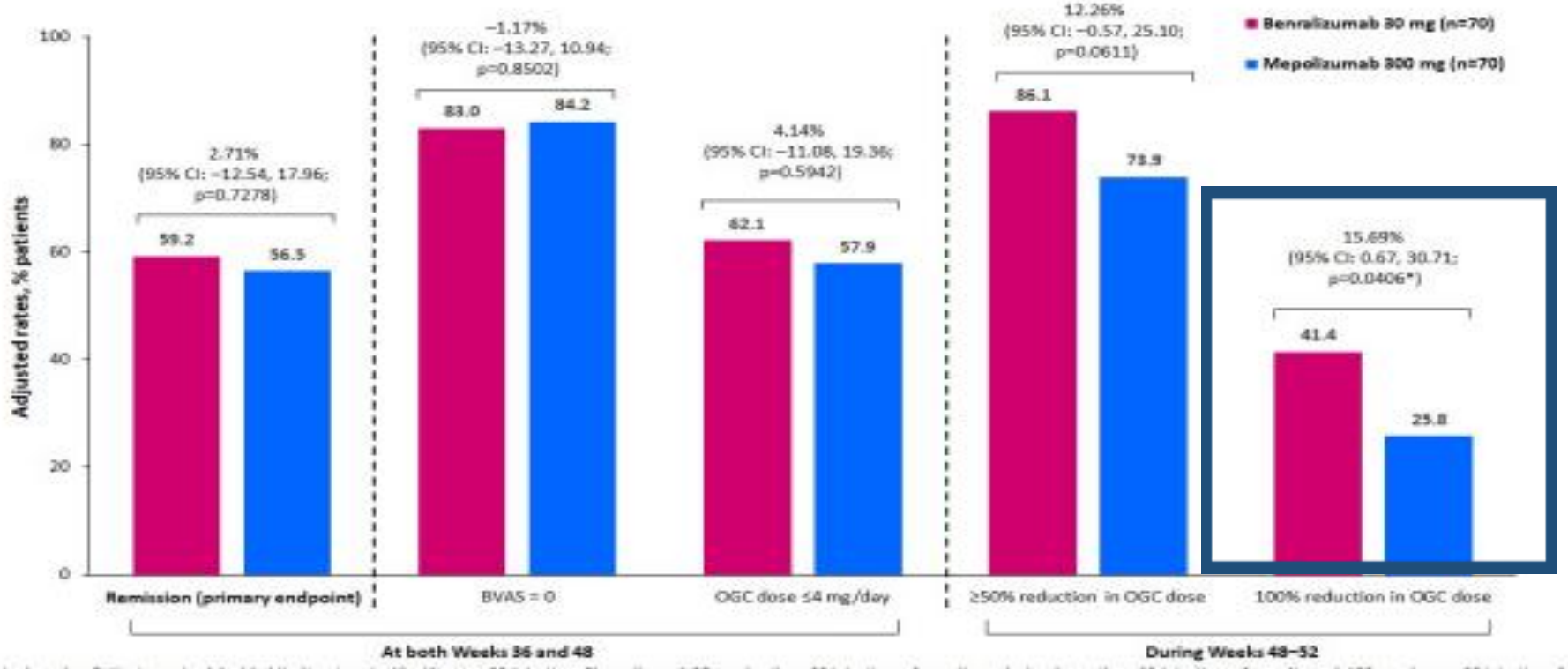
NEDEN BENRALİZUMAB
NEDEN DEĞİL

NEDEN MEPOLİZUMAB
NEDEN DEĞİL

NEDEN DUPİLUMAB DEĞİL
NEDEN DUPİLUMAB

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 EAACI

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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Received: 15 January 2025 | **Revised:** 11 March 2025 | **Accepted:** 19 March 2025

Funding: The authors received no specific funding for this work.

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

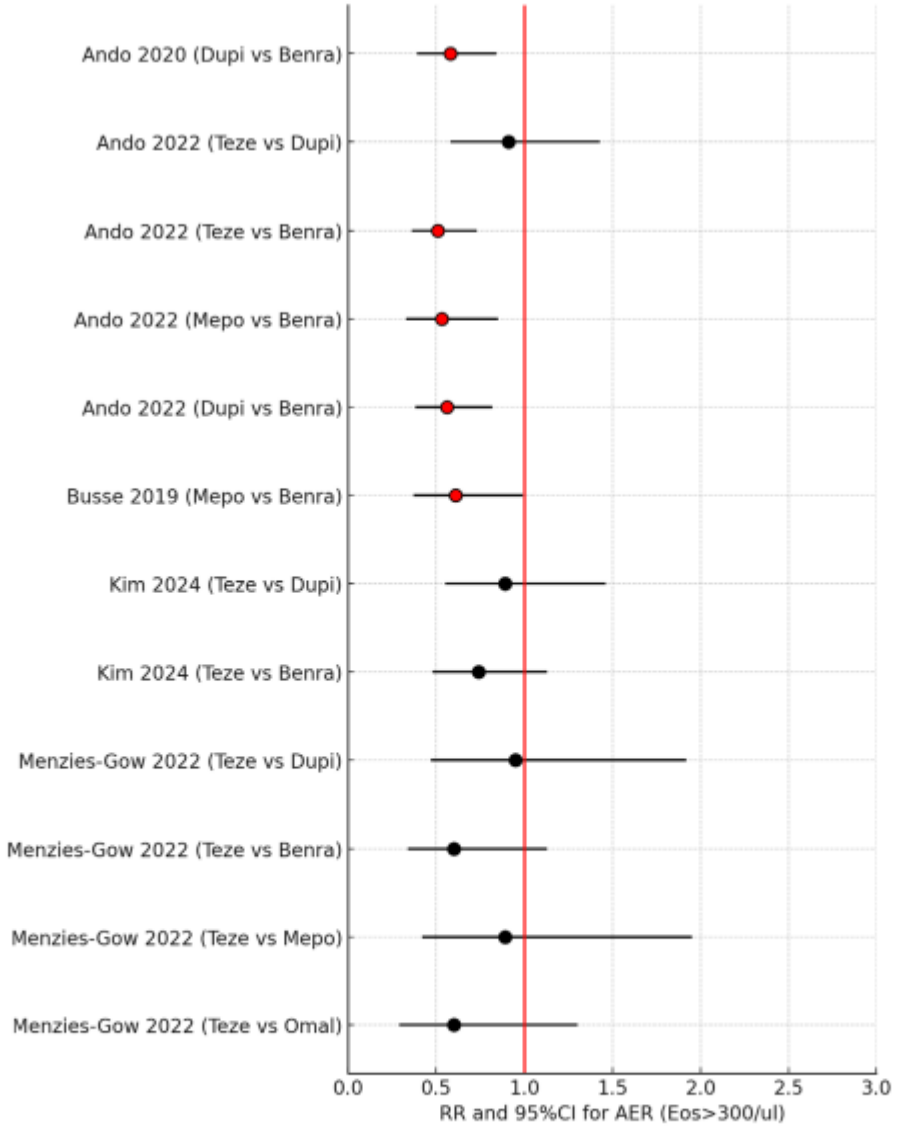


FIGURE 4 | Forest plot showing pairwise indirect comparisons of biologics in uncontrolled asthma for reductions in annualised exacerbation rates (AER) for the subgroup of patients with baseline eosinophils (Eos) ≥ 300/µL, as rate ratios (RR) and 95% confidence intervals (CI). For crude pairwise comparisons 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

TEDAVİ HEDEFİ

REMİSYON

MEPOLİZUMAB KLİNİK REMİSYON

1 year post-mepolizumab initiation

Only complete outcome data set†

Exacerbation-free	OCS-free	ACT score ≥20	FEV_1 ≥80%
Exacerbation-free	OCS-free	ACT score ≥20	
Exacerbation-free	OCS-free		

OCS sparing →

REDES
Proportion of patients (n=144/318) achieving all criteria, n (%)
43 (30%)
55 (38%)
65 (45%)

30% of patients with SA-EP achieved 4-component clinical remission at 1 year post-mepolizumab initiation

In a real-world study, mepolizumab enabled patients with SA-EP to meet a clinical remission comprising of composite endpoints.

†Percentages for those subjects with all data, excluding those with missing FEV_1 or ACT data (n=174).
ACT, asthma control test; BD, bronchodilator; FEV_1, forced expiratory volume in the first second; OCS, oral corticosteroid; SA-EP, severe asthma with eosinophilic phenotype.
Pavord I, *et al. Front Immunol.* 2023 Apr 12;14:1150162.

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:

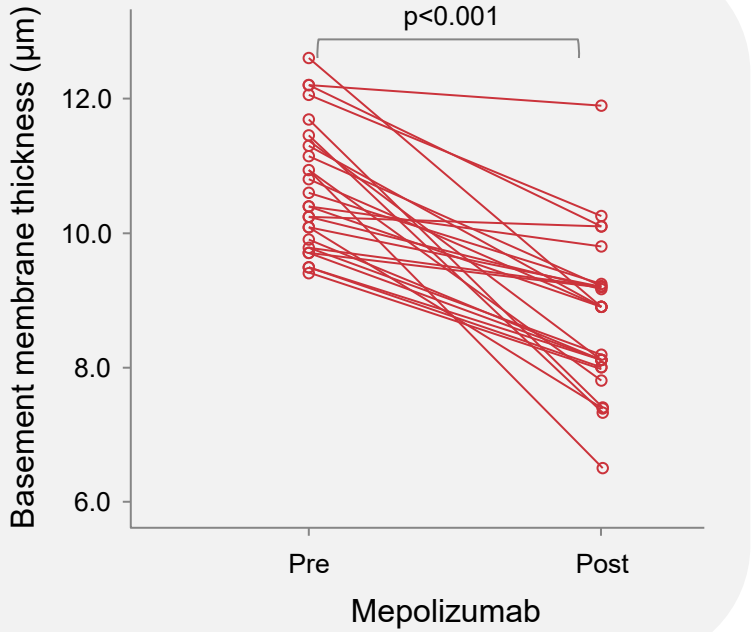
- C... ...f previously d... ..., reduced blood or sp... ... relevant m...
- In... ...tive bronchial hyperresponsiveness

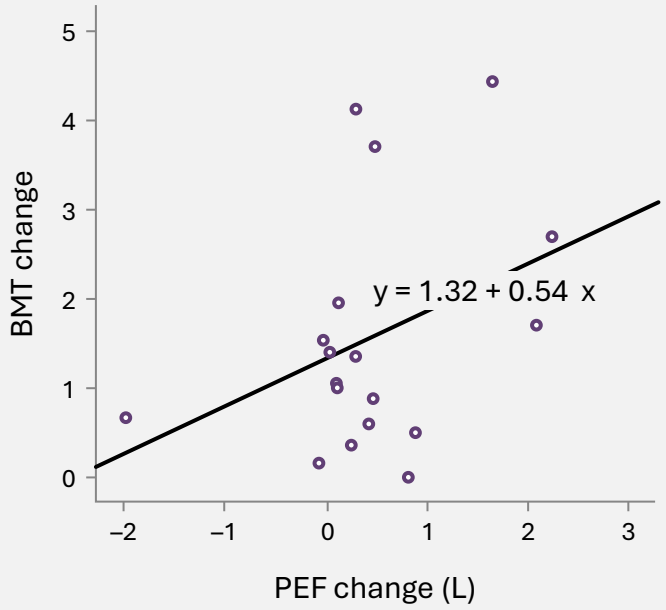
İnceleyebildiğimiz tek biyomarker periferik eozinofil

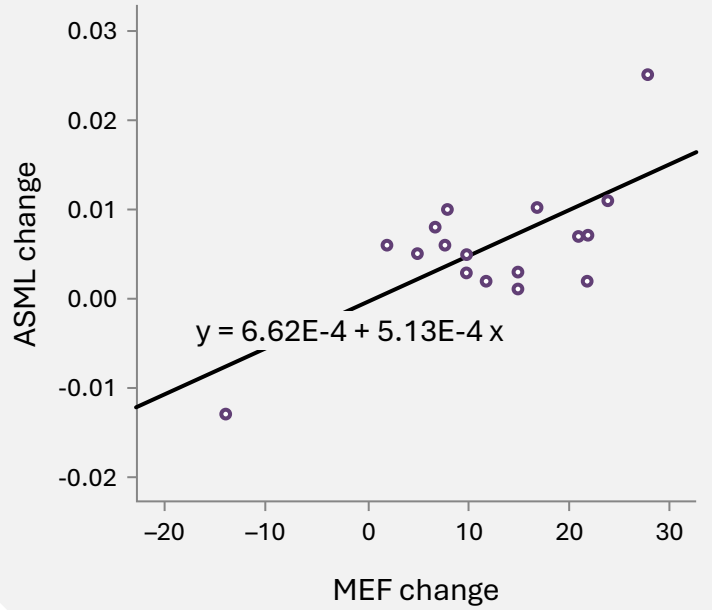
Complete remission off treatment

Same criteria maintained without asthma treatment for ≥12 months

MESILICO:MEPOLİZUMAB SONRASI BAZAL MEMBRAN KALINLIĞI







1 Mepolizumab was associated with reduced reticular basement membrane collagen thickness **(p<0.001)** and improved FEV_1 and FVC **(both p<0.001).**

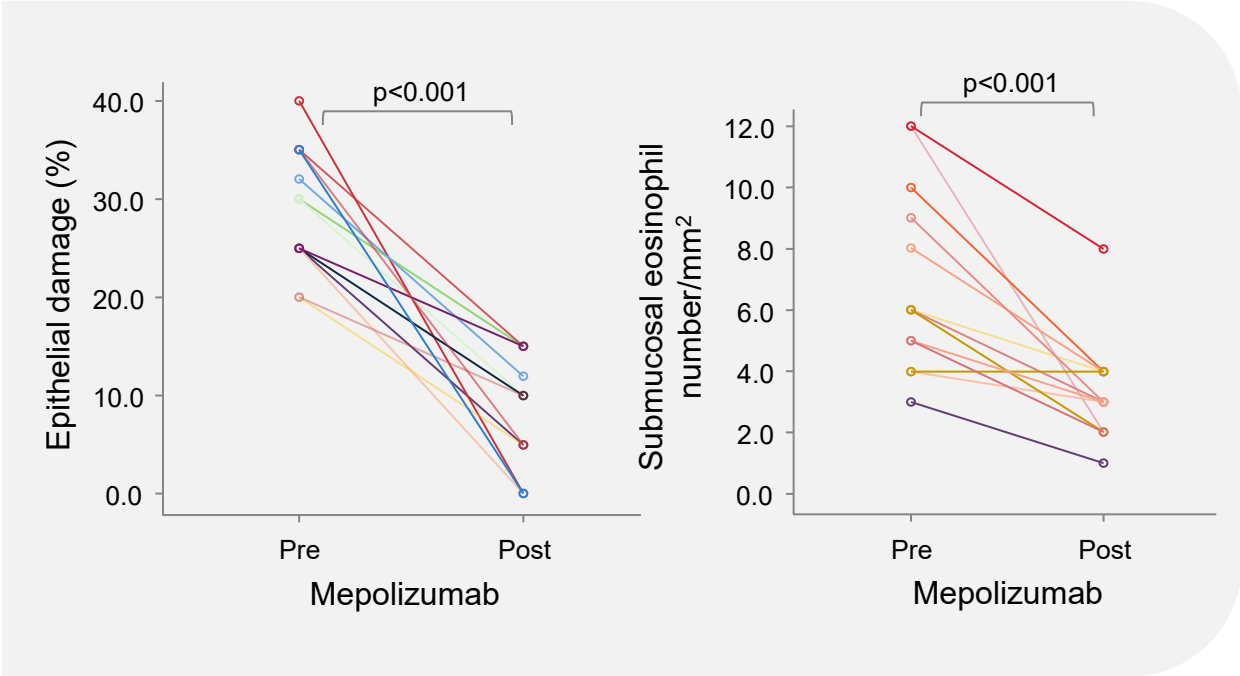
2 Change in PEF was positively correlated with change in reticular basement membrane collagen layer thickness **(p=0.013, r=0.559).**

3 Change in MEF was positively correlated with change in ASML in biopsy (**p<0.001, r=0.779**).

Graphics adapted from Domvri K, *et al. ERS 2023.* Poster #3152 by GSK

No equivalent data with reslizumab or benralizumab.
ASML, airway smooth muscle area; BMT, basement membrane thickness; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MEF, maximum expiratory flow; PEF, peak expiratory flow.
Domvri K, *et al.* ERS 2023. Poster #3152.

MESILICO: MEPOLİZUMAB SONRASI EPİTEL HASARINDA AZALMA



Improvement in epithelial integrity with mepolizumab was associated with a decrease in submucosal eosinophils.

Graphics adapted from Domvri K, et al. ERS 2023. Poster #3152 by GSK

No equivalent data with reslizumab or benralizumab. H&E, haematoxylin and eosin; IL, interleukin; SD, standard deviation.
Domvri K, et al. ERS 2023. Poster #3152.

AĞIR ASTIMDA BİYOLOJİK TEDAVİYİ KESME?

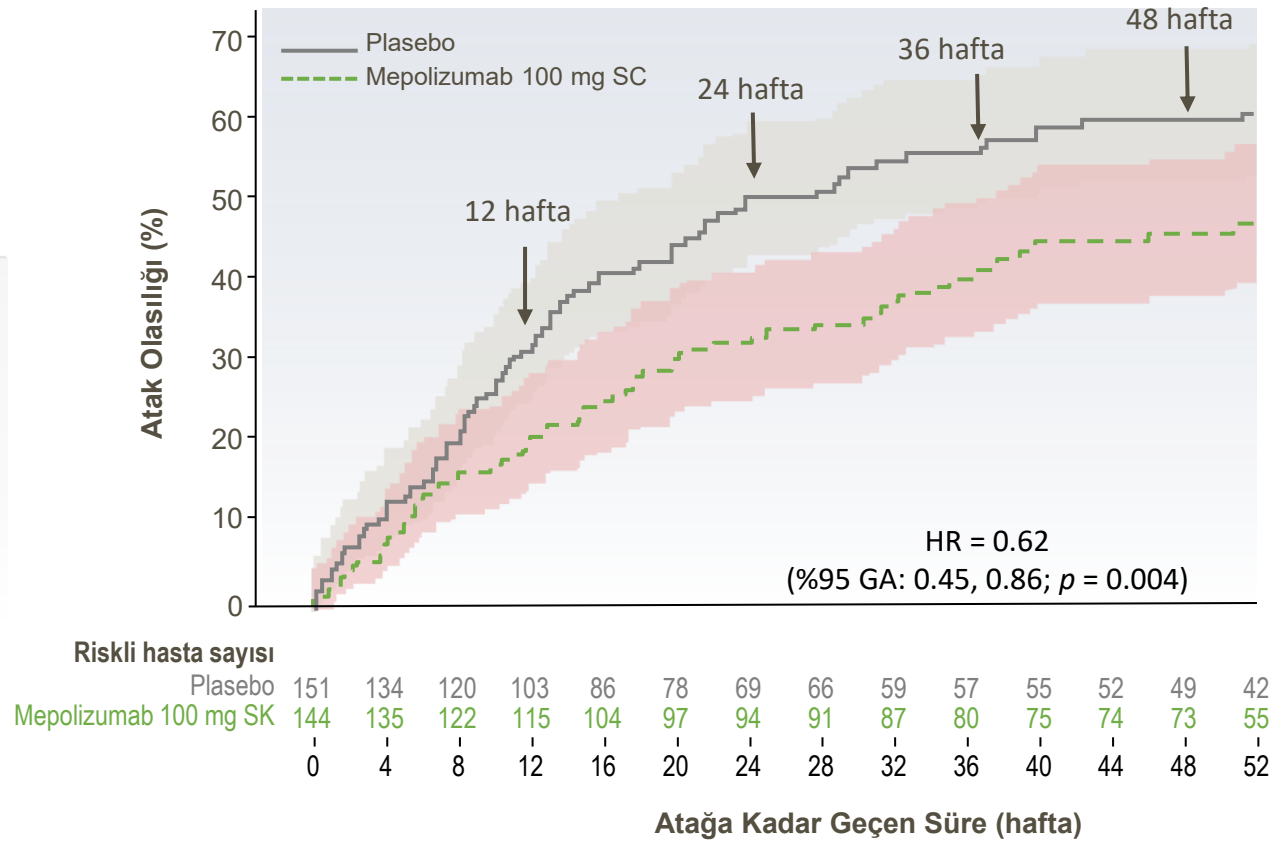
GINA -2025 BİYOLOJİK TEDAVİYİ KESME

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 İlk 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

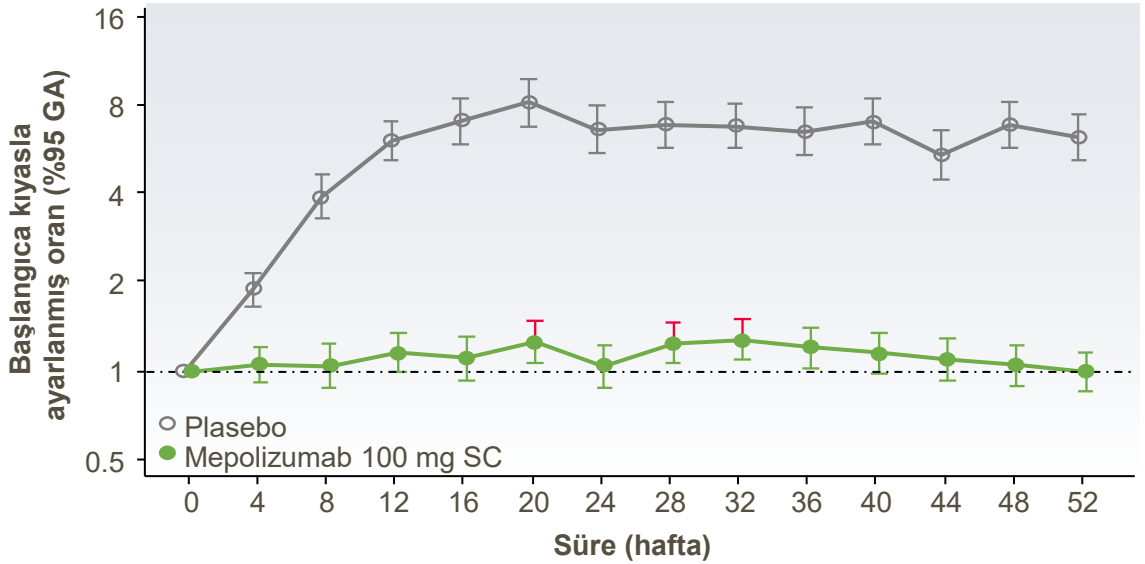
Data on File. 2020N438196_00

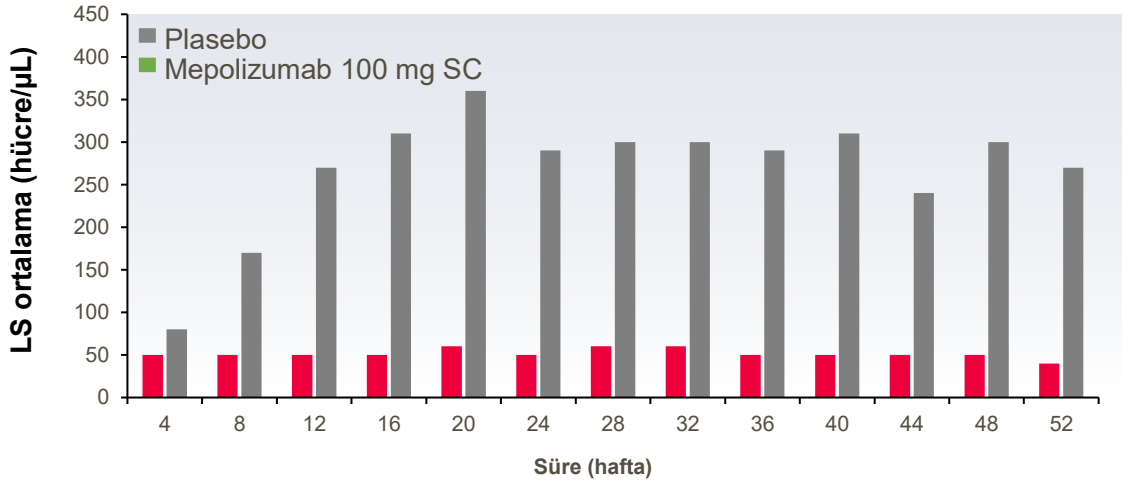
Mepolizumab Kesildikten Sonra Kan Eozinofil Sayısı Yükselmiştir

Sekonder Sonlanım Noktası:

Başlangıca göre 12., 24., 36. ve 52. haftalarda kan eozinofil sayısı oranı

- Mepolizumab tedavisine devam eden hastaların başlangıç kan eozinofil sayısında çok az değişiklik oldu.[1]
  - LS ortalaması 40 ve 60 hücre/µL[1]
- Mepolizumab tedavisi kesilen (plasebo) hastaların kan eozinofil sayısı 4 haftada yükseldi.[1]
  - 52. haftada LS ortalaması: 270 hücre/µL[1]
  - Önceki Faz III çalışmaların başlangıç değerleri ile benzerdi (230–320 hücre/µL)[2-4]





LS, en küçük kareler; SC, subkutan

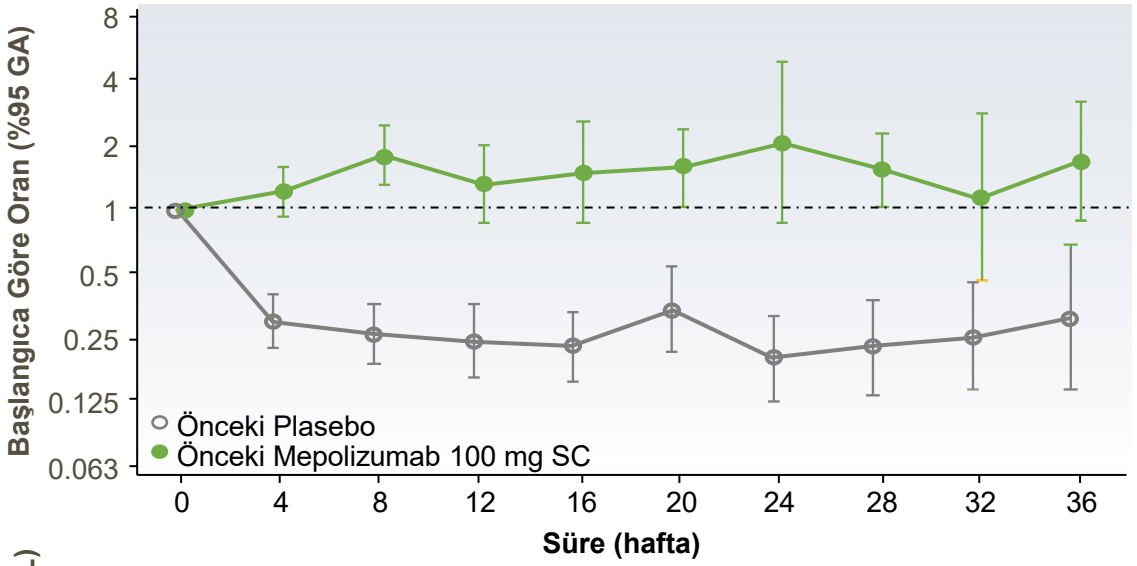
1. Data on File. 2020N438196_00. 2. Pavord ID, et al. *Lancet*. 2012;380:651–659. 3. Bel EH, et al. *N Engl J Med.* 2014;371:1189–1197. 4. Ortega HG, et al. *N Engl J Med*. 2014;371:1198–1207.

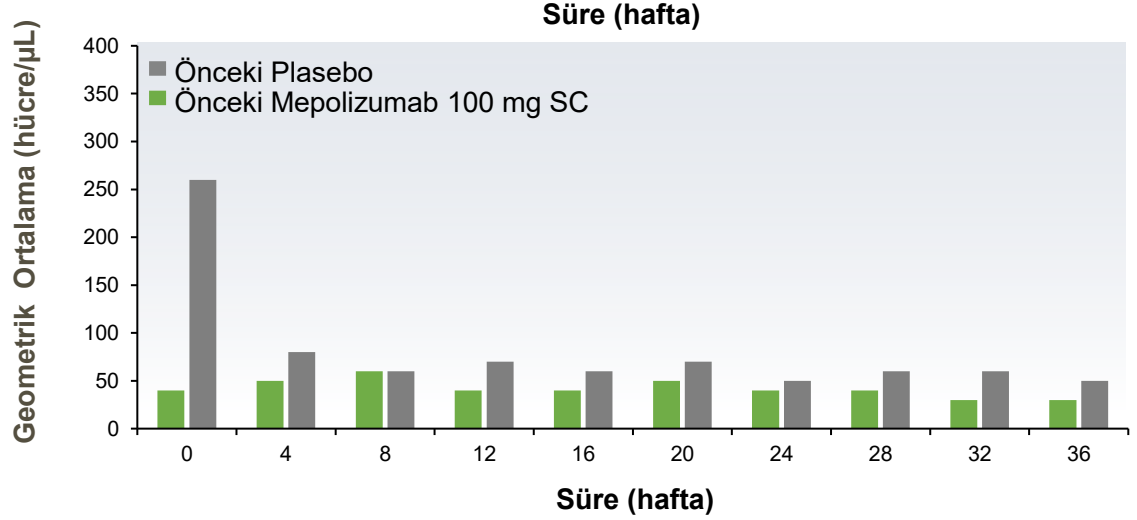
Yeniden mepolizumab tedavisi başlanmasıyla kan eozinofil sayısı tedaviye devam eden hastalarla uyumlu seviyelere kadar azalmıştır

Etkililik Sonlanım Noktası (D Bölümü)

Başlangıca göre kan eozinofil sayısı oranı

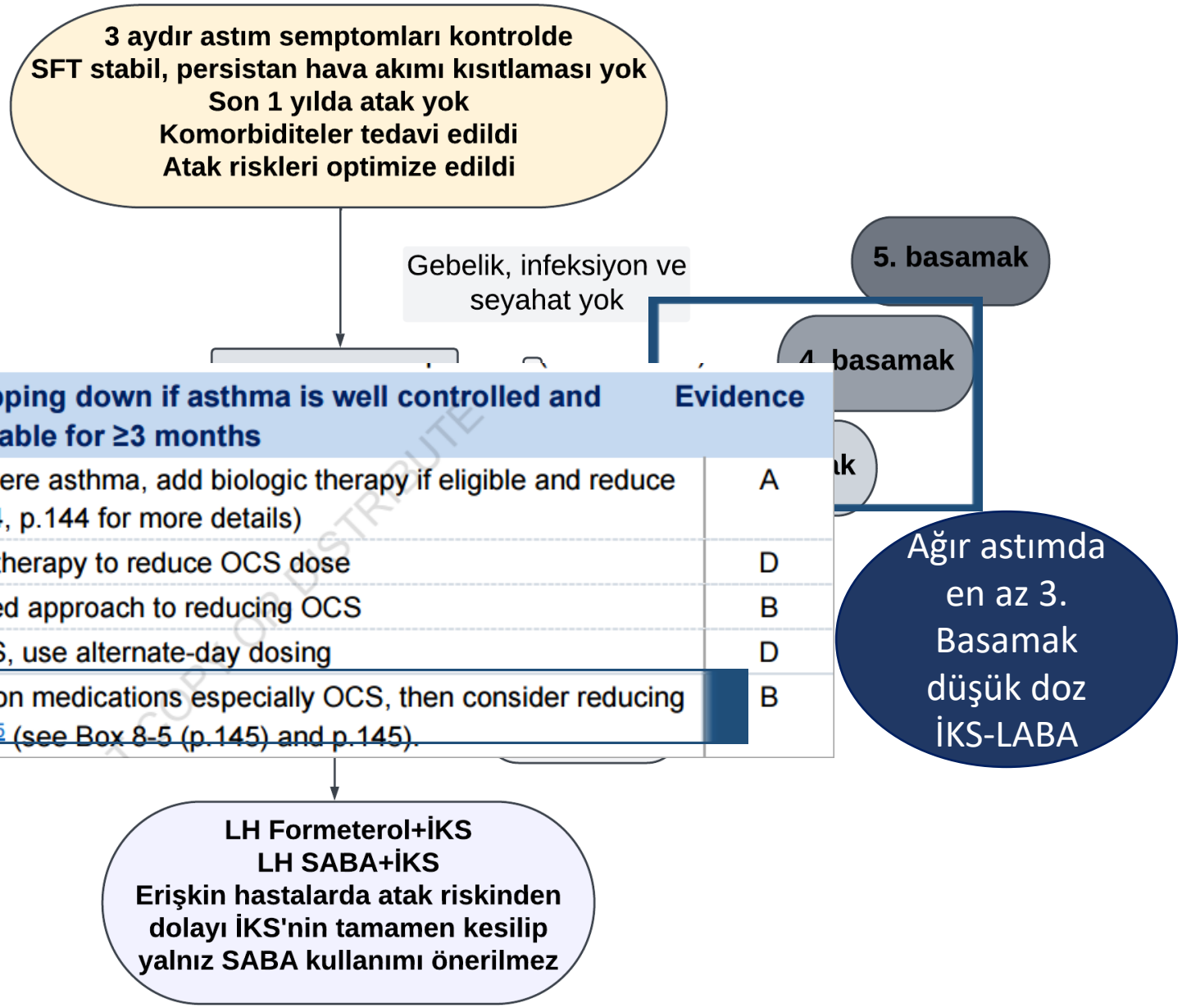
- Mepolizumab tedavisine devam eden hastalarda başlangıç kan eozinofil sayısı korundu.
  - Geometrik ortalama 30 – 60 hücre/µL
- Mepolizumab kesildikten (önceki plasebo) sonra yeniden verilmesiyle kan eozinofil sayısı 4 haftada mepolizumaba devam eden hastalar ile benzer seviyelere geldi.
  - 36. haftada geometrik ortalama: 50 hücre/µL





Data on File. 2020N438196_00

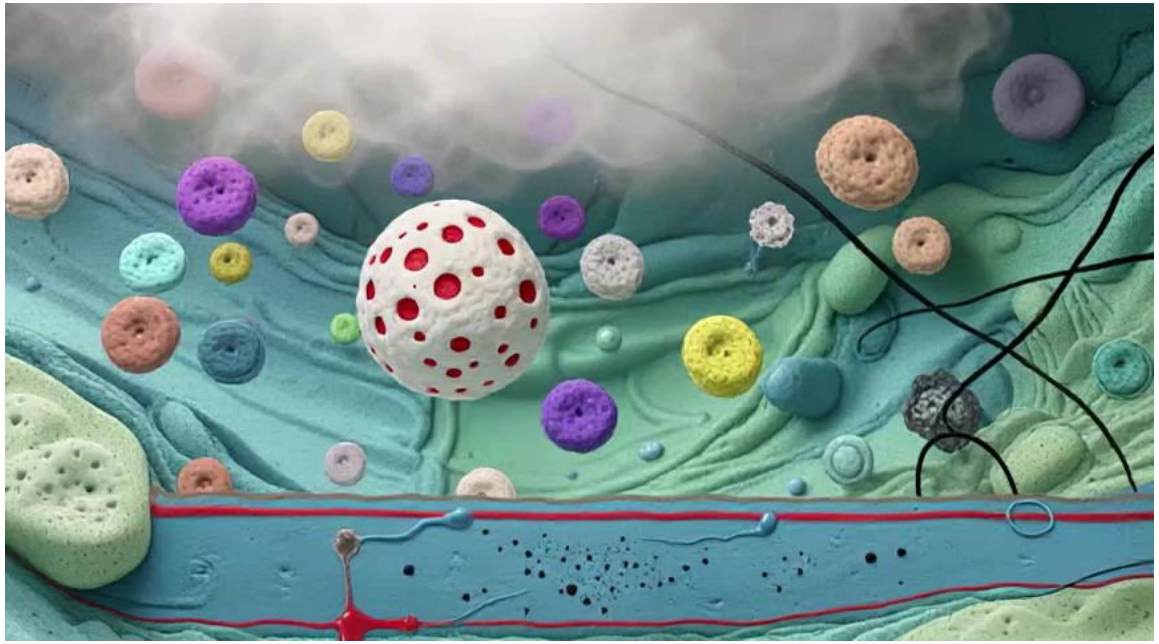
ASTIMDA-AĞIR ASTIMDA BASAMAK



Current step	Current medication and dose	Options for stepping down if asthma is well controlled and lung function stable for ≥3 months	Evidence
Step 5	High-dose ICS-LABA plus oral corticosteroids (OCS)	If Type 2-high severe asthma, add biologic therapy if eligible and reduce OCS (see Box 8-4, p.144 for more details)	A
		Optimize inhaled therapy to reduce OCS dose	D
		Use sputum-guided approach to reducing OCS	B
		For low-dose OCS, use alternate-day dosing	D
	Biologic therapy plus high-dose ICS-LABA	Cease other add-on medications especially OCS, then consider reducing ICS-LABA dose[385] (see Box 8-5 (p.145) and p.145).	B

Önce Add on tedavileri kesme

DOĞRU HASTAYA
DOĞRU BİYOLOJİĞİ
DOĞRU ZAMANDA
BAŞLAMAK…



Astımda İnflamasyona Nokta Atışı Tedavi ile Remisyon