KOAH’da Yeni Tedavi Yaklaşımları: Çağımızda İnflamasyonun Hedeflenmesi Nasıl ve Ne zaman?

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GSK ‘nın Koşulsuz Eğitim Desteği ile

NP-TR-CAU-PPTX-260001

Sunum Planı

- Neden İnflamasyon Hedeflenmeli
- İnflamasyonu Hedefleyen Güncel Tedaviler
- Kime? / Ne Zaman?
- Hangi Tedavi? / Nasıl?
- İnflamasyonu Hedefleyen Gelecek Tedaviler

Neden İnflamasyon Hedeflenmeli?

KOAH Tanım

- Kalıcı, **sıklıkla progressif** hava akımı obstrüksiyonuna neden olan

havayolları (bronşit, bronşiolit) ve alveollerde (amfizem) anormalliklerin neden olduğu

kronik solunumsal semptomlar (nefes darlığı, öksürük, balgam ve/veya **alevlenmeler**) ile karakterize

heterojen bir akciğer durumudur

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Hastalık Aktivitesi

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● Hastalık aktivitesi; 1) hastalığın patolojik sonuçlarına neden olan 2) tedavi ile kontrol edilebilir(geri döndürülebilir) biyolojik yollar

● Farmakolojik tedaviler, sigara bırakma, aşılar, pulmoner rehabilitasyon, volüm azaltıcı işlemler => hastalık aktivitesini azaltabilir

● Hastalık aktivitesi ile ilgili biyobelirteçler; tip 2 inflamasyon için kan eozinofilleri, ancak diğer biyobelirteçler?

● Düşük hastalık aktivitesi => Hem kısa hem de uzun vadede herhangi bir alevlenmeyi önlemek amacıyla KOAH'ta bir tedavi hedefi (alevlenme Ø, semptomlarda kötüleşme Ø, akc fonksiyonlarında düşüş Ø, ..) Amaç erken dönemde düşük hastalık aktivitesi ile yapısal hasar ve progresyonu en aza indirmek)

● **Hastalık Stabilitesi=** alevlenme Ø, semptomlarda kötüleşme Ø, akc fonksiyonlarında düşüşün olmadığı düşük hastalık aktivitesi

Hastalık Kontrolü: alevlenme Ø, semptomlarda kötüleşme olmayan düşük hastalık aktivitesi + (semptomlar eşik değer altında)

!!! KONTROL STABİLİTEDEN DAHA İDDİALI

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İnflamasyonu Hedefleyen Güncel Tedaviler Neler?

Anti-Inflammatory Maintenance Therapy

Figure A3.3

Inhaled Corticosteroids	• Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggesta beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • If patients with COPD have features of asthma, treatment should always contain an ICS • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Combinations can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ Roflumilast improves lung function and reduces moderate and severe exacerbations **(Evidence A)** • Ensifentrine improves lung function **(Evidence A)** but an effect on exacerbations has not been evaluated in patients at increased exacerbation risk
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered (**Evidence B**) • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators & Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and N-acetylcysteine reduces the risk of exacerbations in select populations **(Evidence B)** • Antioxidant mucolytics are recommended only in selected patients **(Evidence A)**

Biologics	• In patients with COPD with blood eosinophils ≥ 300 cells/µL (**see Figure 3.11**) who are uncontrolled on triple therapy:
	  ▪ Dupilumab reduces exacerbations, improves lung function and quality of life, in patients with chronic bronchitis, over 52 weeks **(Evidence A)**
	  ▪ Mepolizumab reduces exacerbations, in patients with and without chronic bronchitis, over 52 to 104 weeks **(Evidence A)**

Other Anti-Inflammatory Agents	• Statin therapy is not recommended for prevention of exacerbations (**Evidence A**) • Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

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Stabil KOAH’ta Anti-inflamatuar Tedaviler

İnhaler Kortiko-steroidler (IKS)	• IKS ile düzenli tedavi, özellikle ağır hastalarda pnömoni riskini artırır(**Kanıt A**). • LABA/IKS kombinasyonu, orta-çok ağır alevlenmeleri olan KOAH hastalarında, alevlenmeleri azaltmada, yaşam kalitesi ve akciğer fonksiyonunu iyileştirmede mono komponentlerinden daha etkilidir (**Kanıt A**). • KOAH’ta LABA/IKS kullanımını teşvik etmiyoruz. **IKS için bir endikasyon var ise, LABA/LAMA/IKS** kombinasyonunun LABA/IKS’ye üstün olduğu gösterilmiş, bu nedenle tercih edilen seçimdir. • LABA/LAMA/IKS üçlü inhaler tedavi; LABA/IKS, LABA/LAMA ve LAMA tedavileri ile karşılaştırıldığında, akciğer fonksiyonları, semptomlar ve yaşam kalitesini iyileştirir ve alevlenmeleri azaltır (**Kanıt A**).Son veriler LABA/LAMA fix doz kombinasyon tedavisine karşı üçlü inhaler tedavilerin; semptomatik, sık ve/veya ağır alevlenmeleri olan KOAH hastalarında mortalite üzerine faydalı etkilerini desteklemektedir. • KOAH’lı hastalarda astım özellikleri varsa, tedavi her zaman bir IKS içermelidir. • IKS kullanımından bağımsız, kan Eoz sayısı <%2 olanlarda pnömoni riskinin arttığının kanıtları mevcuttur (**Kanıt C**). • Kombinasyon tek veya multipl inh tedavi ile verilebilir. Tek inh tedavi, multipl inh tedaviden daha uygun ve etkili olabilir.
Oral Glukokortikoidler	• Uzun süreli oral kortikosteroid kullanımı; faydalarının kanıtı olmamakla(Kanıt C) birlikte, çok sayıda yan etkilere(Kanıt A) sahiptir.
PDE İnhibitörleri	• Kronik Bronşitli, ağır-çok ağır, alevlenmel öyküsü olan KOAH hastalarında; **Roflumilast** akciğer fonksiyonlsrını iyileştirir, orta ve ağır alevlenmeleri azaltır **(Kanıt A).** • **Ensifentirin** akciğer fonksiyonlarını iyileştirir **(Kanıt A)** fakat alevlenmeler üzerine etkisi değerlendirilmemiştir.

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Stabil KOAH'ta Anti-inflamatuar Tedaviler

Antibiyotikler	• Uzun dönem Azitromisin ve Eritromisin alevlenme sıklığını azaltır **(Kanıt A).** • Uygun tedaviye rağmen alevlenmeleri olan tercihen (ancak yalnızca değil) eski sigara içenlerde Azitromisin düşünülebilir (**Kanıt B**). • Azitromisin ile tedavi; bakteriyel direnç artışı **(Kanıt A)** ve işitme kaybı **(Kanıt B)** ile ilişkilidir.
Mukoregülatuar & Antioksidanlar	• Seçilmiş popülasyonda düzenli Erdostein, Karbosistein ve NAC gibi mukolitikler, alevlenme riskini azaltır **(Kanıt B).** •Antioksidan mukolitikler seçilmiş hastalarda tavsiye edilir **(Kanıt A).**
Biyolojikler	• Triple tedavi ile kontrol altına alınamayan ve kan Eozinofil sayısı ≥300/uL; **Dupilumab** kr bronşiti olan hastalarda alevlenmeleri azaltır, akciğer fonksiyonu ve yaşam kalitesini iyileştirir (**Kanıt A)** **Mepolizumab** (kr bronşit olsun olmasın) alevlenmeleri azaltır (**Kanıt A)**
Diğer Anti-İnflamatuar Ajanlar	• Sitatin tedavisi alevlenmeleri önlemek için önerilmez **(Kanıt A).** • Simvastatin, statin endikasyonu olmayan artmış alevlenmeleri olan KOAH hastalarında alevlenmeleri önlemez**(Kanıt A).** Fakat gözlemsel çalışmalar kardiyovasküler ve metabolik endikasyonlar için statin kullanan KOAH hastalarında bazı pozitif etkilere sahip olabildiğini destekler **(Kanıt C).** • Lökotren modifiye ediciler, KOAH hastalarında yeterince test edilmemiştir.

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Kime?
Ne zaman?

Takip Farmakolojik Tedavi

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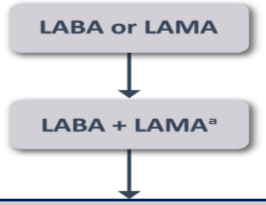
2 Adjust Treatment

FOLLOW-UP treatment - for patients with COPD who are already receiving maintenance pharmacological treatment

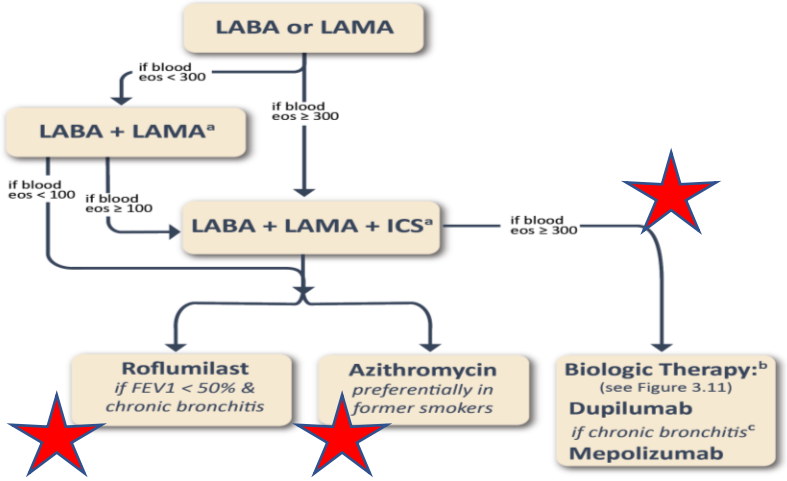
- **CONTINUE CURRENT TREATMENT** unless dyspnea or exacerbation management require optimization

- **Persistan DİSPNE varsa**



- İnhaler cihazını veya molekülü değiştirmeyi düşün
- Non-farmakolojik tedavileri uygula
- Ensifentrin eklemeyi düşün
- Dispnenin diğer nedenlerini araştır (ve tedavi et)

- **Bir veya daha fazla orta veya ağır Alevlenme varsa**



[a]Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

[b]Listed in order of approval in the US.

[c]Patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes. Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eosinophils ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

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Kime? / Ne zaman?

- **Alevlenme öyküsü** ve/veya **Semptomatik!**
- Kan eozinofil düzeyi?
- Kronik bronşit var mı?
- Enfeksiyon öyküsü?
- Ex-smoker?

HHS Public Access
Author manuscript
Lancet. Author manuscript; available in PMC 2016 May 17.

Published in final edited form as:
Lancet. 2015 May 2; 385(9979): 1789–1798. doi:10.1016/S0140-6736(15)60693-6.

Current concepts in targeting COPD pharmacotherapy: making progress towards personalized management

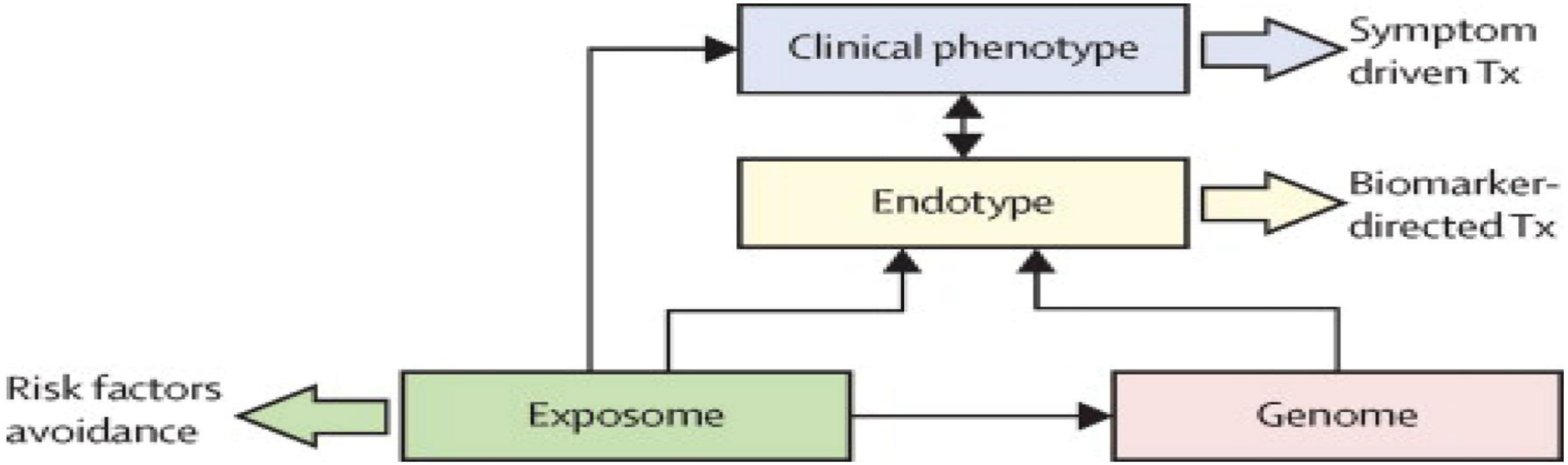

Figure 2.
Diagram depicting the inter-relationships (small arrows) between the 'exposome' (a term that describes the "totality of human environmental exposures, from conception onwards" (102)), the genetic background of the individual (Genome), the Endotype (biological networks that enable and restrict reactions) and the final clinical expression of the disease (Clinical Phenotype). Large arrows indicate different therapeutic strategies. For further explanation, see text.

Lancet. 2015 May 2; 385(9979): 1789–1798. doi:10.1016/S0140-6736(15)60693-6.

Farklı Endotipler

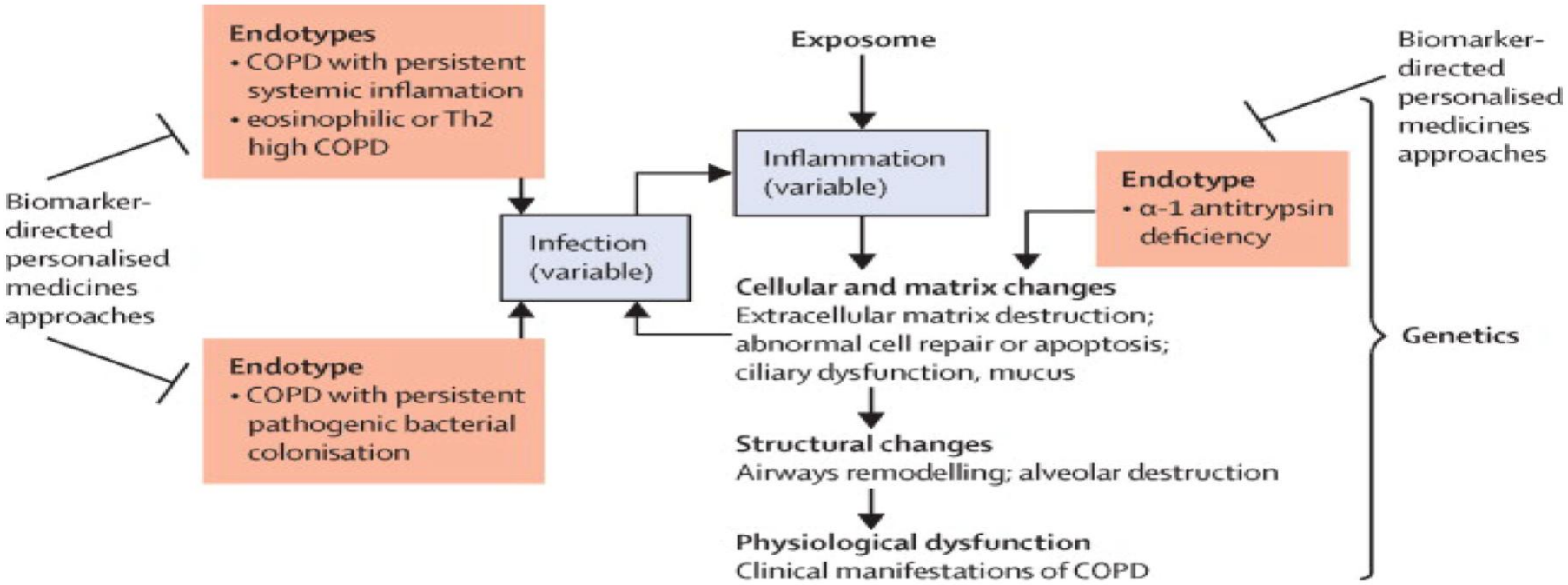

Figure 3.
Our current understanding of potential endotypes of COPD. Depicted are the relationships between inflammation, cellular changes, structural changes and physiological dysfunction in COPD, and the role that chronic infection can play in perpetuating inflammation. Superimposed are potential endotypes of COPD (in red text) that relate to subtypes of inflammation, the presence of colonization with pathogenic bacteria and the absence of a mechanism protective against extracellular matrix destruction (alpha-1 antitrypsin deficiency).

Lancet. 2015 May 2; 385(9979): 1789–1798. doi:10.1016/S0140-6736(15)60693-6.

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Review

Personalized COPD Care: The Future of Precision-Based Therapies

Leslie K. Appleton, Nicola A. Hanania and Muhammad Adrish *

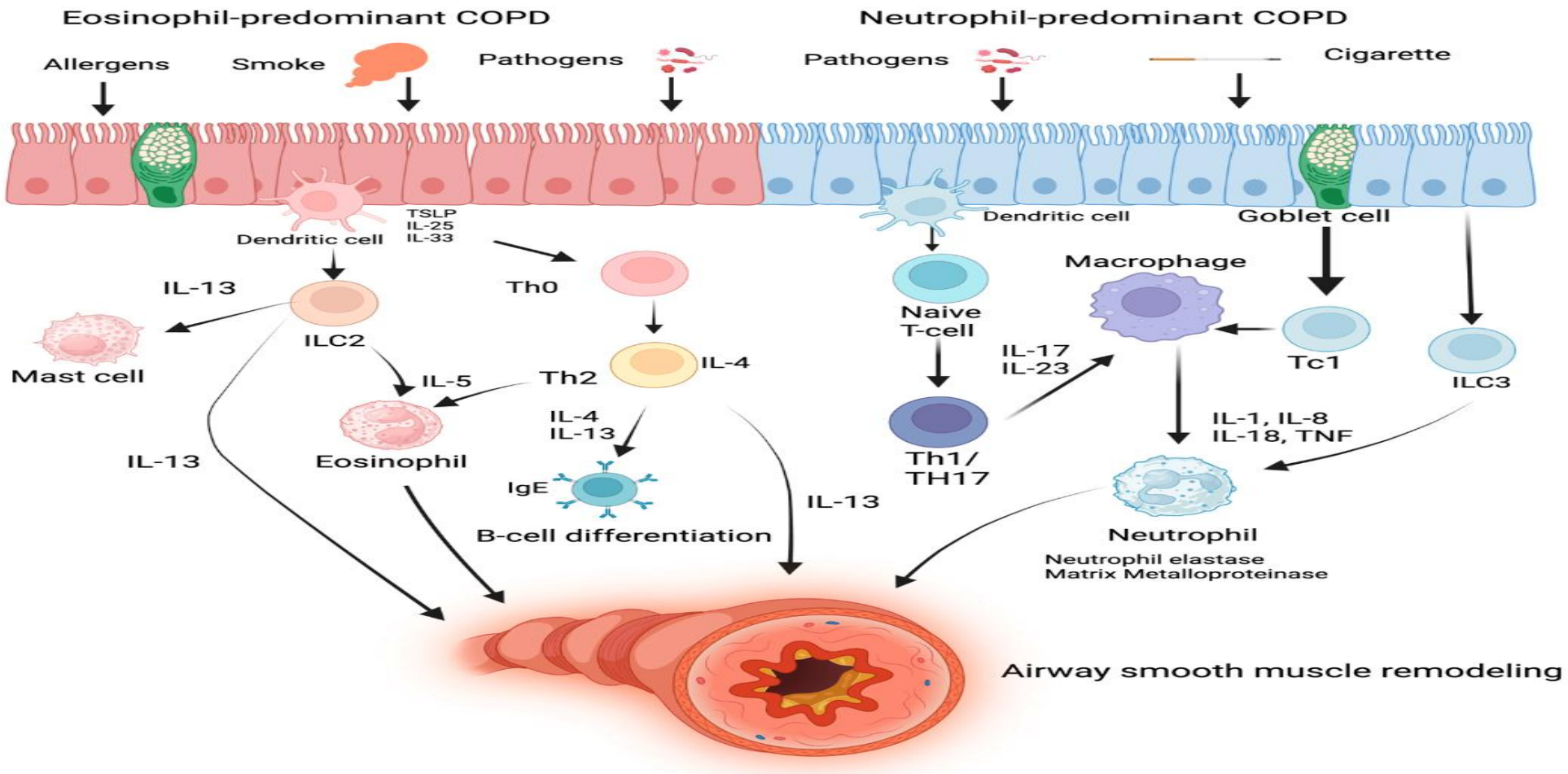


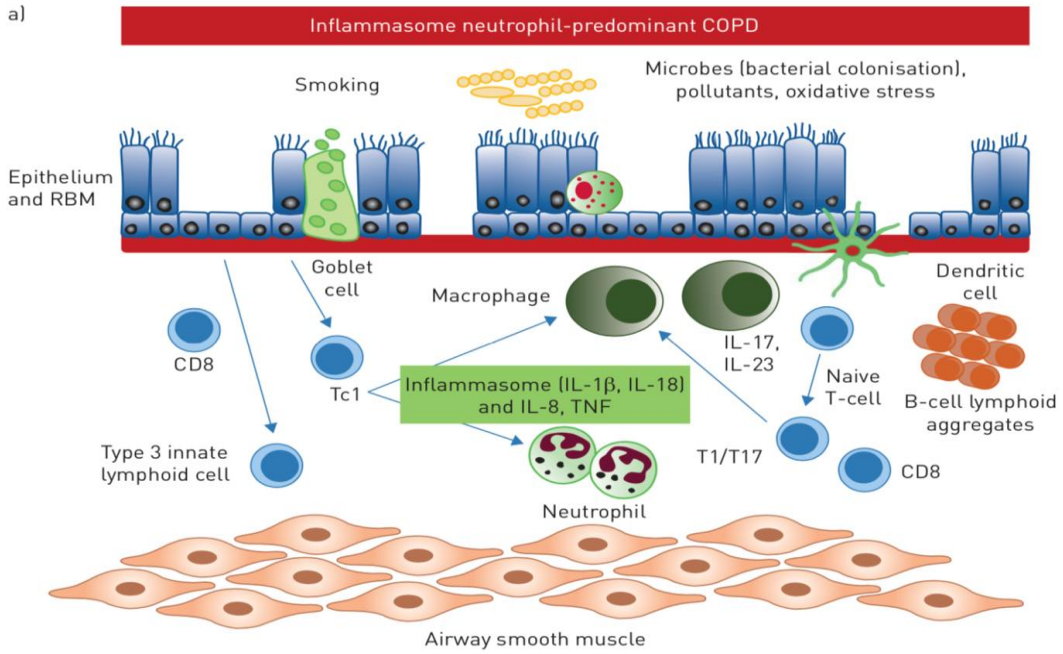
Figure 1. Inflammatory pathways in COPD.

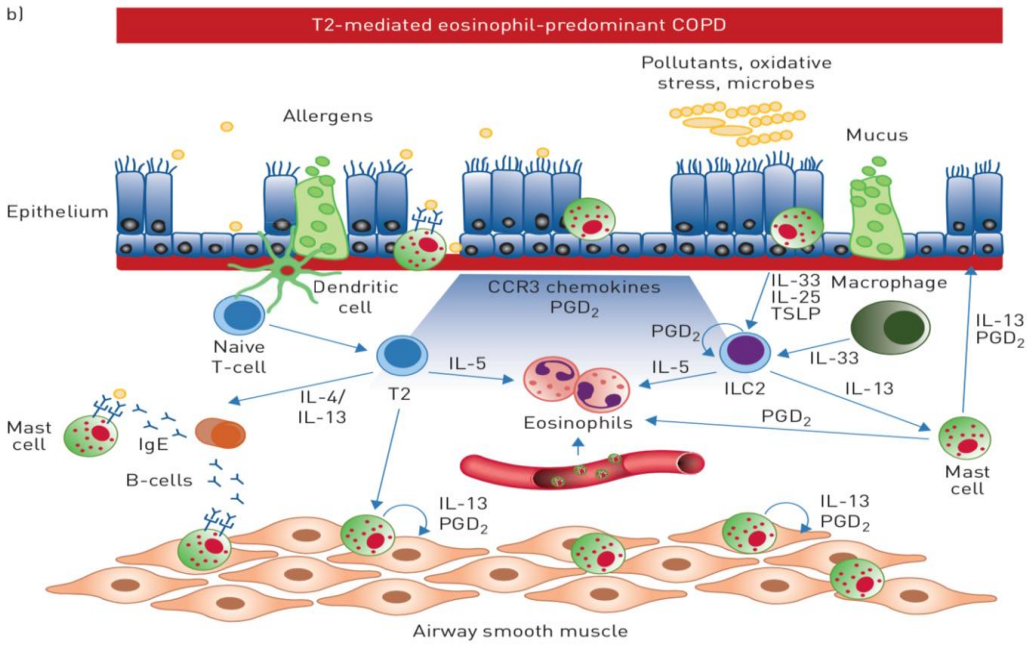
J. Clin. Med. **2024**, *13*, 6339. https://doi.org/10.3390/jcm13216339

CrossMark

Airway inflammation in COPD: progress to precision medicine

KOAH'ta Havayolu İnflamasyonu:Tedavide gelişmeler





<u>Nötrofilik inflamasyon (T1 ve T17 aktivasyonu ile):</u>
İnflamazom =>Bakteriyel kolonizasyon ve Disbiyoz

<u>Eozinofilik İnflamasyon (T2 aracılı) (%10-40)</u>

FIGURE 3 Cytokine networks in a) neutrophil-associated inflammasome-mediated chronic obstructive pulmonary disease (COPD) and b) eosinophil-associated T2-mediated COPD, illustrating immunological responses to multiple environmental stimuli. RBM: reticular basement membrane; IL: interleukin; TNF: tumour necrosis factor; PGD: prostaglandin D; TSLP: thymic stromal lymphopoietin

Eur Respir J 2019; 54: 1900651

TABLE 2 Randomised placebo-controlled trials of anti-neutrophil, tumour necrosis factor (TNF)- and inflammasome-targeted therapies in chronic obstructive pulmonary disease (COPD)

Drug/target (study) [reference]	Subjects n	Dosage, duration	Primary outcome	Secondary outcome
Anti-IL-8; IL-8 (NCT00035828) [62]	109	800 mg loading dose, 400 mg per month for 3 months, 5-month follow-up	↓ Severity of dyspnoea as measured by TDI	↔ Health status, lung function, 6MWT, rescue use of albuterol
Anti-CXCR2 [63]		50 mg twice daily or 80 mg twice daily, 4 weeks	Safety and tolerability	↓ Blood neutrophil counts
Anti-CXCR2 [64]		10 mg, 30 mg or 50 mg, 6 months	↑ FEV_1 at 6 months	↔ Time to first exacerbation ↓ Absolute and percentage sputum neutrophil counts ↔ SGRQ score ↑ Rate of respiratory infection ★
Infliximab; anti-TNF (NCT00244192) [65]	22	5 $mg \cdot kg^{-1}$, 8 weeks	↔ Sputum inflammatory cells	↔ FEV_1, SGRQ
Etanercept; anti-TNF (NCT 00789997) [66]	81	50 mg, 90 days	↔ FEV_1 over 14 days from exacerbation onset	↔ 90-day treatment failure, dyspnoea, health status
Infliximab; TNF (NCT00056264) [67]	157	3 $mg \cdot kg^{-1}$ or 5 $mg \cdot kg^{-1}$, 44 weeks	↔ CRQ	↔ FEV_1, 6MWT, TDI ↑ Malignancy, pneumonia ★
CNTO 6785(61); anti-IL-17 (NCT01966549) [68]	186	6 $mg \cdot kg^{-1}$ every 2 weeks for 4 weeks, then every 4 weeks for remaining 8 weeks	↔ Pre-bronchodilator FEV_1 % predicted	↔ Post-bronchodilator FEV_1 % predicted ↔ SGRQ-C ↔ Frequency of AECOPD ↔ Weekly usage of rescue medication
MEDI 8968; anti-IL-1 (NCT01448850) [69]	160	300 mg every 4 weeks, 52 weeks	↔ Moderate-to-severe exacerbations	↔ SGRQ-C
Canakinumab/IL-1 (NCT00581945) [70]		1×1 $mg \cdot kg^{-1}$, 2×3 $mg \cdot kg^{-1}$, 42×6 $mg \cdot kg^{-1}$, 45 weeks	Changes from baseline in FEV_1, FVC No statistical analysis provided for changes in FEV_1, FVC from baseline	Serious adverse events No statistical analysis provided

IL: interleukin; TDI: transition dyspnoea index; 6MWT: 6-min walk test; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire; SGRQ-C: SGRQ for COPD patients; AECOPD: acute exacerbation of COPD; FVC: forced vital capacity; ↑: increase; ↓: decrease; ↔: no change.

<u>Randomize plasebo kontrollü Anti-nötrofilik, TNF ve inflamazom hedefli çalışmalar;</u>

Anti-IL-8 => Dispnede(TDI) iyileşme göstermiş. Sonraki çalışmalarda alevlenmeleri azaltmadığı görülmüş.

Diğer çalışmalar (anti-nötrofilik, TNF, IL-17, IL-1) => pr sonlanım (-), hatta anti-TNF(İnfliximab)'da malignite ve pnömoni riskinde ↑

Eur Respir J 2019; 54: 1900651

Table 1. *Cont.*

Author	Trial Name	Drug Studied	Targeted Molecule	Year	Sample Size and Population	Primary Endpoint	Findings
Calverley, P [45]	NCT01448850	MEDI8968	IL-1 receptor 1 inhibitor	2017	N = 324, aged 45–75 years with ≥2 exacerbations in the past year	Moderate/severe acute exacerbations of COPD at week 56	No difference in exacerbation rate, lung function, or quality of life Incidence of treatment-emergent adverse events similar
Rennard, SI [46]		Infliximab	TNF-α	2007	N = 234, aged 40 years and older with moderate to severe COPD	Change from baseline in CRQ total score at week 24	No difference in CRQ Numerical increase in cancer and pneumonia
Rennard, SI [47]	REMICADE NCT00056264	Infliximab	TNF-α	2012	N = 234, who received ≥1 dose of infliximab for COPD	Number of patients with a malignancy and number of patients who died throughout the 5-year follow-up period	Cumulative incidence of malignancy over time was similar across all treatment groups Distribution of deaths across all groups was similar across groups
Lazaar, A [48]	NCT03034967	Danirixin	CXCR2 antagonist	2020	N = 614, aged 40–80 years with mild to moderate COPD	Incidence and severity of respiratory symptoms measured by E-RS: COPD scores	No difference in E-RS: COPD, SGRQ-C, or CAT scores Increased incidence of exacerbations and pneumonia in danirixin-treated groups

Abbreviations: BEC, blood eosinophil count; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Disease Questionnaire; E-RS: COPD, Evaluating Respiratory Symptoms in COPD; FEF 25–75, forced expiratory flow at 25 and 75% of the pulmonary volume; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; N, number; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients.

European Journal of Internal Medicine 125 (2024) 28–31

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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Clinical Insights

Towards precision medicine in COPD: Targeting type 2 cytokines and alarmins

Gilda Varricchi [a,b,c,d,*], Remo Poto [a,c]

KOAH'da Tip 2 inflamasyonu hedef alan Tedaviler

European Journal of Internal Medicine 125 (2024) 28–31

KOAH’da Tip 2 inflamasyonu hedef alan Tedaviler

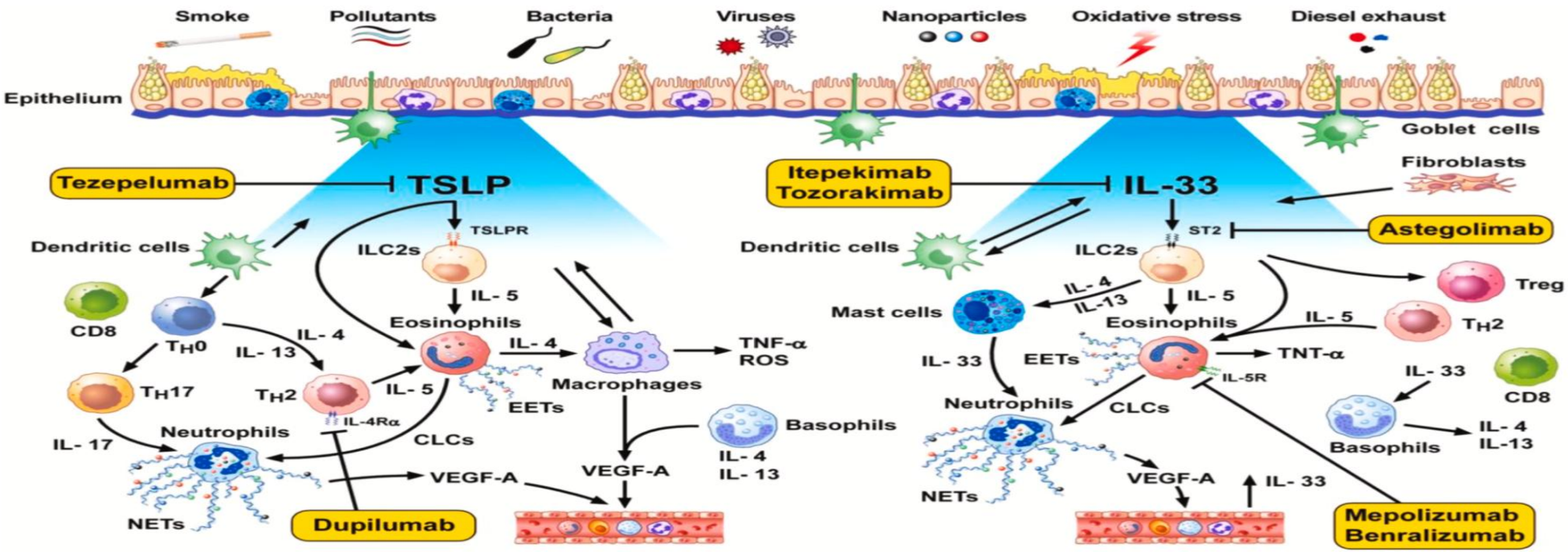

Fig. 1. Legend: Schematic representation of the role of type 2 inflammatory pathways and epithelial-derived alarmins in COPD. In response to insults to the airway epithelium, TSLP and IL-33 are released from damaged epithelial cells. TSLP promotes airway inflammation through binding to its TSLP receptor (TSLPR), which is present on several immune cells including type 2 innate lymphoid cells (ILC2s), dendritic cells, Th2 and Treg cells, eosinophils, and macrophages. IL-33 binds to its ST2 receptor expressed on ILC2s, dendritic cells, eosinophils, mast cells, macrophages, Th2 and Treg cells, and basophils. The activation of these cells results in the production of several cytokines which in turn activate a plethora of other immune cells, contributing to the pathobiology of COPD. Mepolizumab (anti-IL-5), benralizumab (anti-IL-5Rα), and dupilumab (anti-IL-4Rα) inhibit type 2 inflammatory cytokines. Tezepelumab (anti-TSLP), astegolimab (anti-ST2) and itepekimab (anti-IL-33) block epithelium-derived alarmins or their receptors on target immune cells. Tozorakimab is an anti-IL-33 monoclonal antibody (mAb) that inhibits IL-33 signaling *via* ST2 on target immune cells and RAGE/EGFR on epithelial cells to reduce inflammation and epithelial dysfunction, respectively [11].

KOAH’da T2 inlamasyon ve Tedavi Yolakları

TSLP ve IL-33 ; sigara dumanı, virüsler gibi saldırılar ile havayolu epitelinin hasarlamması sonucu salınan alarminlerdir. Mast h, Eozinofil ve tip 2 Lenfoid hücrelerinin aktivasyonunda rol oynarlar. Hem astımda hem KOAH’ta hem T2 yüksek, hem de T2 düşük inflamasyonda rol alırlar.

European Journal of Internal Medicine 125 (2024) 28–31

Table 1
Biologics targeting type 2 cytokines or alarmins under development for chronic obstructive pulmonary disease (COPD) treatment.

Biologic	Target	Clinical Trial/Reference	Results
Mepolizumab	IL-5	NCT02105961 (METREO—Completed) NCT02105948 (METREX-Completed) [26]	Mepolizumab reduces exacerbations in patients with eosinophil-associated COPD Blood eosinophil counts allow for identification of COPD patients who experience exacerbations while treated with maximal ICS-based triple maintenance therapy who are likely to benefit from mepolizumab
		NCT05320939	Phase II ongoing study
		NCT05138250 (SUMMER)	Phase III ongoing study
		NCT04075331 (COPD-HELP)	Phase II - Phase III ongoing study
		NCT04133909 (MATINEE)	Phase III ongoing study
Benralizumab	IL-5Rα	NCT02138916 (GALATHEA-Completed) NCT02155660 (TERRANOVA-Completed) [27]	Benralizumab was not associated with a lower annualized rate of exacerbations than placebo among patients with COPD and a blood eosinophil count of ≥ 220 cells/μl
		NCT04053634 (RESOLUTE- Recruiting)	Phase III ongoing study
		NCT05273359 (Not yet Recruiting)	Phase II scheduled study
Dupilumab	IL-4Rα	NCT03930732 (BOREAS-Completed)	Dupilumab treatment resulted in 30 % reduction in annualized rate of exacerbations, improved lung function (evidenced by an increased FEV_1 of 160 mL at 12 weeks), and quality of life.
		NCT04456673 (NOTUS-Active, Not recruiting)	Phase III ongoing study

- **Mepolizumab (IL-5):** METREO ve METREX çalışmaları (52 hf, 100-300 mg/4hf, sc)=> Eoz. KOAH'ta alevlenmeleri azaltmış

-**Benralizumab (IL-5Ra):** GALATHEA ve TERRANOVA çalışmaları (10-30-100 mg/8 hf, sc)=> alevlenmelerde azalma Ø
(IL-5; IgA ve B h farklılaşmasında da önemli rolü+)(Post-hoc analizde alev↓ (100 mg doz, ≥3 alav öyküsü olan Eoz >220 KOAH))

- **Dupilumab (IL-4Ra):** BOREAS ve NOTUS çalışmaları (52 hf, 300 mg/2hf, sc)=> Eoz KOAH'ta alevlenmeleri azalttığı gösterilmiş, FEV1'de anlamlı artış.

* Bu çalışmalarda dahil edilen hastaların Eozinofil cut-off sayıları farklı !
* KOAH'ta alevlenmeleri azaltmada Astıma göre daha yüksek Eozinofil sayısı gerekli.

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Table 1. Targeted therapies in COPD.

Author	Trial Name	Drug Studied	Targeted Molecule	Year	Sample Size and Population	Primary Endpoint	Findings
Pavord, ID [35]	METREX NCT02105948	Mepolizumab	IL-5	2017	N = 837 with COPD and moderate to severe exacerbations while on triple therapy BEC ≥ 150 cells/μL at screening or ≥300 cells/μL during the past year	Annual rate of moderate or severe exacerbations	↓ rate of exacerbation 1.40 (rate ratio 0.82, 95% CI 0.68–0.98, $p = 0.04$) ↑ time to first moderate or severe exacerbation Safety profile similar to placebo
Pavord, ID [35]	METREO NCT02105961	Mepolizumab	IL-5	2017	N = 675, COPD and moderate to severe exacerbations while on triple therapy and BEC ≥ 150 cells/μL at screening or ≥300 cells/μL during the past year	Annual rate of moderate or severe exacerbations	↓ mean rate of exacerbation in treatment groups but not statistically significant No difference in rate of exacerbations between treatment groups (100 mg vs. 300 mg) Safety profile similar to placebo
Criner, GJ [38]	GALATHEA NCT02138916	Benralizumab	IL-5Rα	2019	N = 1120 with moderate to very severe COPD, COPD symptoms and ≥2 moderate or 1 severe exacerbation in the past year and with BEC ≥ 220 cells/μL	Annualized COPD exacerbation rate ratio at 56 weeks	Numerical but nonsignificant reduction in rate of annualized exacerbation Safety profile similar to placebo
Criner, GJ [38]	TERRANOVA NCT02155660	Benralizumab	IL-5Rα	2019	N = 1545 with moderate to very severe COPD, COPD symptoms and ≥2 moderate or 1 severe exacerbation in the past year and with BEC ≥ 220 cells/μL	Annualized COPD exacerbation rate ratio at 56 weeks	Numerical but nonsignificant reduction in rate of annualized exacerbation Safety profile similar to placebo
Bhatt, SP [39]	BOREAS NCT03930732	Dupilumab	IL-4Rα	2023	N = 939 COPD with BEC ≥300 cells/μL, FEV1/FVC <0.70, FEV1 30–70%, and on triple therapy with high risk of exacerbation	Annualized rate of moderate or severe COPD exacerbation	↓ rate of exacerbation 0.78 (95% CI 0.64–0.93) ↑ prebronchodilator FEV1 Adverse events similar to placebo
Bhatt, SP [40]	NOTUS NCT04456673	Dupilumab	IL-4Rα	2024	N = 935 with BEC ≥300 cells/μL, FEV1/FVC < 0.70, FEV1 30–70%, and on triple therapy with high risk of exacerbation	Annualized rate of moderate or severe exacerbation	↓ rate of exacerbation 0.86 (95% CI 0.70–1.06), rate ratio 0.66 (95% CI 0.54–0.82, $p < 0.001$) ↑ prebronchodilator FEV1 Adverse events similar to placebo

Tablo 2. KOAH tedavisinde biyolojik ajanlar.

İsim	Hedef	Kullanımı	Faydası	Yan Etkiler
Tip 2 inflamasyonu hedef alanlar				
Dupilumab	IL-4Ra (IL4/IL13)	İki haftada bir, subkütan 300 mg	• Yıllık orta/ağır alevlenme oranında azalma (%30) • Solunum fonksiyonunda ve semptomlarda iyileşme • Yaşam kalitesinde iyileşme	• Enjeksiyon bölgesinde reaksiyon • Geçici eozinofili • Hipereozinofili (ateş, eklem ağrıları, döküntüler..) • Nadiren HES, eozinofilik vaskülitler
Mepolizumab	IL-5	Dört haftada bir, subkütan 100 mg	• Yıllık orta/ağır alevlenme oranında azalma (%20) • Alevlenmelere kadar geçen sürede uzama	• Aşırı duyarlılık reaksiyonları • Herpes zoster enfeksiyonu (< %1)
Benralizumab	IL-5Ra	Sekiz haftada bir, subkütan 100 mg	• Alevlenmeleri azaltmada anlamlı fark saptanmamış olup, faz 3 devam eden çalışmaları mevcut. • Post-hoc analizde Eoz > 220/uL ve yılda ³ 3 alevlenme öyküsü olan, sekiz hafta ara ile 100 mg Benralizumab alan grupta alevlenmelerde azalma olduğu görülmüş.	• Enjeksiyon bölgesi reaksiyonları

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Hangi Tedavi?
Nasıl?

KOAH Tedavisinde Biyolojiklerin Kullanımını Destekleyen Kanıtlar

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Molecule/RCT*	Key inclusion criteria[a]	Annualized rate of moderate/severe exacerbations	Lung function improvement (pre-BD FEV1)[d]	Quality of life improvement (SGRQ)
Dupilumab (300 mg/2 weeks)				
BOREAS[1] (n=939)	FEV1 post-BD 30-70% chronic bronchitis[b] eos ≥ 300 (screen)	RR 0.70; P < 0.001	83mL; P < 0.001	-3.4; P = 0.002
NOTUS[2] (n=935)	FEV1 post-BD 30-70% chronic bronchitis[b] eos ≥ 300 (screen)	RR 0.66; P < 0.001	62mL; P = 0.02	-3.4[e]
Mepolizumab (100 mg/4 weeks)				
MATINEE[3] (n=804)	FEV1 post-BD 20-80% eos ≥ 300 (screen) and eos ≥ 150 (previous year)	RR 0.79; P = 0.01	NS	NS
METREX[4] (n=836)	FEV1 post-BD 20-80% eos ≥ 150 (screen) or eos ≥ 300 (previous year)[c]	RR 0.82; P = 0.04	NS	NS
METREO[4] (n=674)	FEV1 post-BD 20-80% eos ≥ 150 (screen) or eos ≥ 300 (previous year)	RR 0.80; P = 0.07	NS	NS

*Molecules are listed in order of approval in the US.

These results cannot be directly compared across trials as there were different patient populations included.

a: all studies recruited patients with exacerbations in the previous year while receiving inhaled triple therapy
b: patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes
c: pre-defined eosinophilic population
d: at 52 weeks
e: significance not tested according to hierarchical testing procedure

NS: not statistically significant; eos: blood eosinophils (cells/µL); SGRQ: St George's Respiratory Questionnaire; BD: bronchodilator; RR: relative risk.

References: [1]Bhatt et al. N Engl J Med 2023;389:205-214; [2]Bhatt et al. N Engl J Med 2024;390:2274-2283; [3]Sciurba et al. N Engl J Med 2025;392:1710-1720; [4]Pavord et al. N Engl J Med 2017;377:1613-1629.

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KOAH Tedavisinde Biyolojiklerin Kullanımını Destekleyen Kanıtlar

2026
Teaching Slide Set

Molecule/RCT*	Key inclusion criteria[a]	Annualized rate of moderate/severe exacerbations	Lung function improvement (pre-BD FEV1)[d]	Quality of life improvement (SGRQ)
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Mepolizumab (100 mg/4 weeks)				
MATINEE[3] (n=804)	FEV1 post-BD 20-80% eos ≥ 300 (screen) and eos ≥ 150 (previous year)	RR 0.79; P = 0.01	NS	NS
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METREO[4] (n=674)	FEV1 post-BD 20-80% eos ≥ 150 (screen) or eos ≥ 300 (previous year)	RR 0.80; P = 0.07	NS	NS

*Molecules are listed in order of approval in the US.

These results cannot be directly compared across trials as there were different patient populations included.

a: all studies recruited patients with exacerbations in the previous year while receiving inhaled triple therapy
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c: pre-defined eosinophilic population
d: at 52 weeks
e: significance not tested according to hierarchical testing procedure

NS: not statistically significant; eos: blood eosinophils (cells/µL); SGRQ: St George's Respiratory Questionnaire; BD: bronchodilator; RR: relative risk.

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Son bir yıl içinde ≥1 Hospitalizasyon gereken veya ≥2 sistemik steroid-antibiyotik kullanımı gereken sık alevlenmeleri olan hastalarda;
- KOAH tanısını yeniden değerlendir
- Sigara ve çevresel maruriziyetleri sorgula
-İnhaler tedaviyi optimize et, tedavi uyumu, inhaler teknik, yan etki, dozu kontrol et
-Komorbiditeleri değerlendir

↓

Periferik kan Eozinofilleri **≥300 /uL mi?**

↓

Periferik kan Eozinofilleri ≥ 300 /uL;

1. Dupilumab: 300 mg/2hf, subkutan

   veya

2. Mepolizumab: 100 mg/4hf, subkutan

↓

Periferik kan Eozinofilleri < 300 /uL;

1. Azitromisin (250 mg 1x1 hergün oral veya 500mg 1x1 haftada 3 gün, oral)
2. Roflumilast (500 mg, 1x1, oral)
3. Ensifentrin (3mg, 2x1, nebülize)

↓

Hastaları yan etkiler ve alevlenmeler üzerine etkileri açısından takip et!

(Eğer iyi tolere edilir ise, bu tedaviler ile çalışma süreleri bir yıl)

Şekil 2. Sık alevlenme öyküsü olan KOAH hastalarında tedavi algoritması.

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İnflamasyonu Hedefleyen Gelecek Tedaviler

Table 1. *Cont.*

Author	Trial Name	Drug Studied	Targeted Molecule	Year	Sample Size and Population	Primary Endpoint	Findings
Yousuf, AJ [41]	COPD-ST2OP NCT03615040	Astegolimab	ST2 blocker	2022	N = 97 with moderate to very severe COPD and ≥2 exacerbations in the past year	Exacerbation rate with a negative binomial count model in the intention-to-treat population	No significant difference in exacerbation rate at 48 weeks ↑ patient reported SGRQ-C −3.3 (95% CI −6.4 to −0.2, $p = 0.039$) Treatment-emergent adverse events were similar between groups
Rabe, KF [42]	NCT03546907	Itepekimab	IL-33	2021	N = 343, aged 40–75 years, current or previous ≥10 pack year smoking history, diagnosis of COPD for at least 1 year	Annualized rate of moderate to severe exacerbation of COPD during 24–52-week treatment period	No significant change in annualized rate of exacerbation RR 0.81 (95%CI 0.61–1.07, $p = 0.13$) ↑ prebronchodilator FEV1 LSMD 0.06 (95% CI 0.01–0.10, $p = 0.024$) Treatment-emergent adverse events were similar between groups Nasopharyngitis (28 [16%] in the itepekimab group vs. 29 [17%] in the placebo group) Bronchitis (18 [10%] in itepekimab vs. 14 [8%] in placebo)
Singh, D [43]	NCT04039113	Tezepelumab	TSLP	2024	N = 333, patients aged 40–80 years, moderate to severe COPD	Annualized rate of moderate to severe exacerbation of COPD over 52 weeks	No statistically significant change in overall rate of moderate to severe exacerbation (17% relative reduction, $p = 0.1042$) Greater reduction observed in patients with blood eosinophils ≥ 300 cells/μL (37% reduction [95% CI 7, 57]) Adverse events and serious adverse events similar
NOVARTIS [44]	NCT00581945	Canakinumab	IL-1β	2010	N = 147 with COPD and FEV1 ≤ 50% and one exacerbation in the past 2 years	Change in FEV1, FVC, SVC, and FEF 25–75%	Numerical but nonsignificant reduction in exacerbation rate

Tezepelumab	TSLP	NCT04039113 (COURSE-Completed)	Phase IIa completed study
		NCT05507242 (UPSTREAM-COPD-Recruiting)	Phase II ongoing study
Astegolimab	ST2	NCT03615040 (COPD-ST2OP) Completed) [28]	In patients with moderate-to-very severe COPD, Astegolimab did not reduce exacerbation rate, but did improve health status compared with placebo.
		NCT05878769 (Recruiting)	Phase III ongoing study
		NCT05037929 (Recruiting)	Phase IIb ongoing study
Tozorakimab	IL-33	NCT04631016 (FRONTIER-4- Completed)	Phase II ongoing study
		NCT05158387 (TITANIA-Recruiting)	Phase III ongoing study
		NCT05166889 (OBERON-Recruiting)	Phase III ongoing study
Itepekimab	IL-33	NCT04701983 (AERIFY-1-Recruiting)	Phase III ongoing study
		NCT04751487 (AERIFY-2, Recruiting)	Phase III ongoing study
		NCT05326412 (AERIFY-3-Recruiting)	Phase II ongoing study

- **Tezepelumab (TSLP)**: Faz2 çalışmada alevlenmelerde azalma => Faz3 çalışması devam ediyor

- **Astegolimab (ST2):** KOAH'ta alevlenme oranlarını azaltmamış (Faz2b anlamlı çıkmış ancak Faz 3'de anlamsız)

- **Tozorakimab (IL-33): Faz3 çalışması devam ediyor**

- **Itepekimab (IL-33): Ex**-smoker'da alevlenme oranında %42 anlamalı↓ , Faz3 çalışmaları (AERIFY-1/2) devam ediyor. (AERIFY-1 anlamlı alev↓, AERIFY-2 anlamsız, AERIFY-4 devam ediyor)

(Aktif sigara kullanmanın nötrofilik inflamasyonu baskın hale getirerek T2 inflamatuar yanıtı gölgeleyebileceğine vurgu yapılmış)

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Tablo 2. KOAH tedavisinde biyolojik ajanlar.

İsim	Hedef	Kullanımı	Faydası	Yan Etkiler
Epitelyal Alarmin sitokinleri hedef alanlar				
Tezepelumab	TSLP	Sekiz haftada bir 420 mg, sc	Faz 3 çalışmaları devam ediyor	• Enjeksiyon bölgesi reaksiyonları
Astegolimab	ST2	İki haftada bir 476 mg	Alevlenmeleri azaltmada faz 2b çalışmasında anlamlılık saptanmış iken, faz 3 çalışmasında saptanmamıştır.	• Enjeksiyon bölgesi reaksiyonları
Tozorakimab	IL-33	-	Faz 3 çalışması devam ediyor	• Enjeksiyon bölgesi reaksiyonları
İtepekimab	IL-33	-	Ex-smoker'da alevlenme oranında azalma görülmüş olup, faz 3 çalışmaları AERIFY-1'de alevlenmelerde azalma anlamlı, AERIFY-2'de alevlenmelerde azalma anlamsız olup, AERIFY-4 devam etmektedir.	• Enjeksiyon bölgesi reaksiyonları (hafif-orta)

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Endotip-Fenotipe göre Tedavi Yaklaşımı

1) Eozinofilik: IKS, anti-IL4R, anti-IL5
2) Nötrofilik(enfeksiyon baskın, IKS yanıtı düşük): Azitromisin (ex-smoker)
3) Sık alevlenen: LABA/LAMA/IKS, exsmoker->Azitromisin, kr Bronşit->Roflumilast
4) Kronik bronşit: Roflumilast, Mukoregülatuarlar, Azitro,
5) Amfizem baskın: Pulmoner Rehabilitasyon, Endobronşiyal valüm azaltıcı işlemler
6) Alfa-1 AT eks.:Replasman tedavisi
7) ACO: IKS (LABA/LAMA/IKS)

Sonuç

- Eozinofilik (kan Eozinofil sayısı ≥300/uL, Triple tedavi almasına rağmen alevlenme öyküsü olan hastalarda;

Dupilumab kr bronşiti olan hastalarda alevlenmeleri azaltır, akciğer fonksiyonu ve yaşam kalitesini iyileştirir (**Kanıt A)**

Mepolizumab (kr bronşit olsun veya olmasın) alevlenmeleri azaltır (**Kanıt A)**

-Astegolumab ve İtepekimab… ile ilgili umut verici ön bulgular saptanmış ancak ek kanıtlara ihtiyaç var

- Non-eozinofilik (non-T2) grupta hedefleyici tedaviler => !!! (biyobelirteçler => Roflumilast(kr bronşit) / Azitromisin (bakteriyel kolonizasyon, ex-smoker) / Mukoregülatuar

Teşekkürler

Astım ve KOAH Yönetiminde

Güncel Yaklaşımlar

7 Şubat 2026

Point Hotel Taksim, İstanbul