Biyolojik Ajan Kullanımı ve Bağışıklama

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Koç Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

08.09.2023

Neler konuşulacak?

- Biyolojik ajanlar
- Biyolojik ajanları kullananlarda infeksiyon riski ve yönetim
- Bağışıklama stratejileri ve Aşılar
- Soru & Katkı

biologic agents

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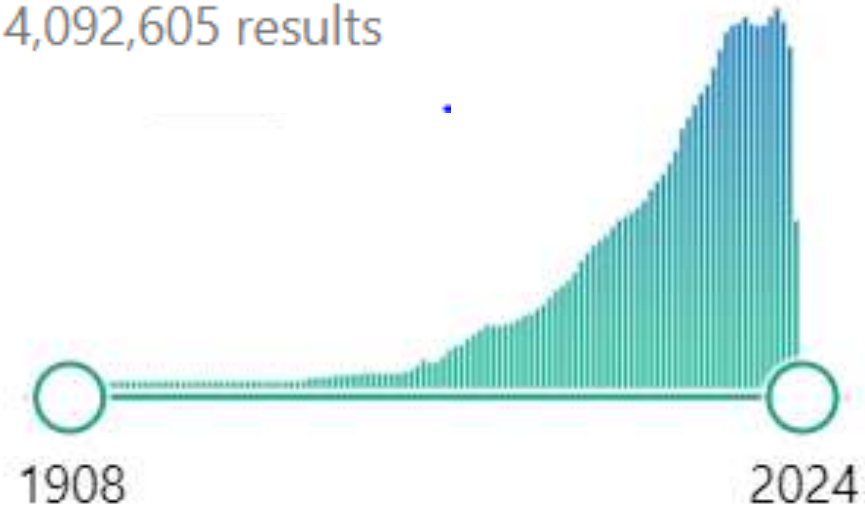
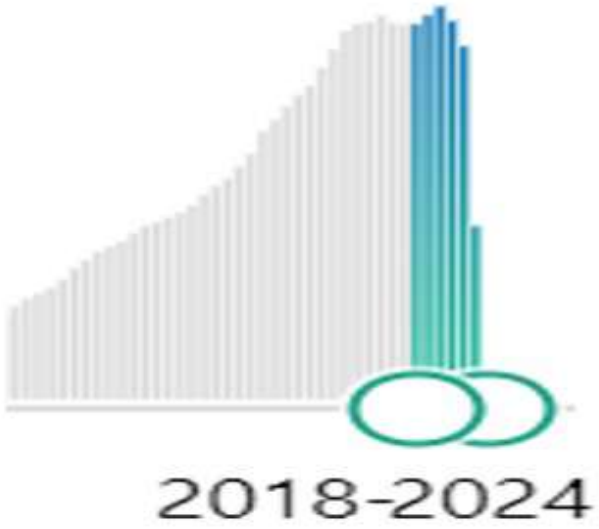
RESULTS BY YEAR

4,092,605 results

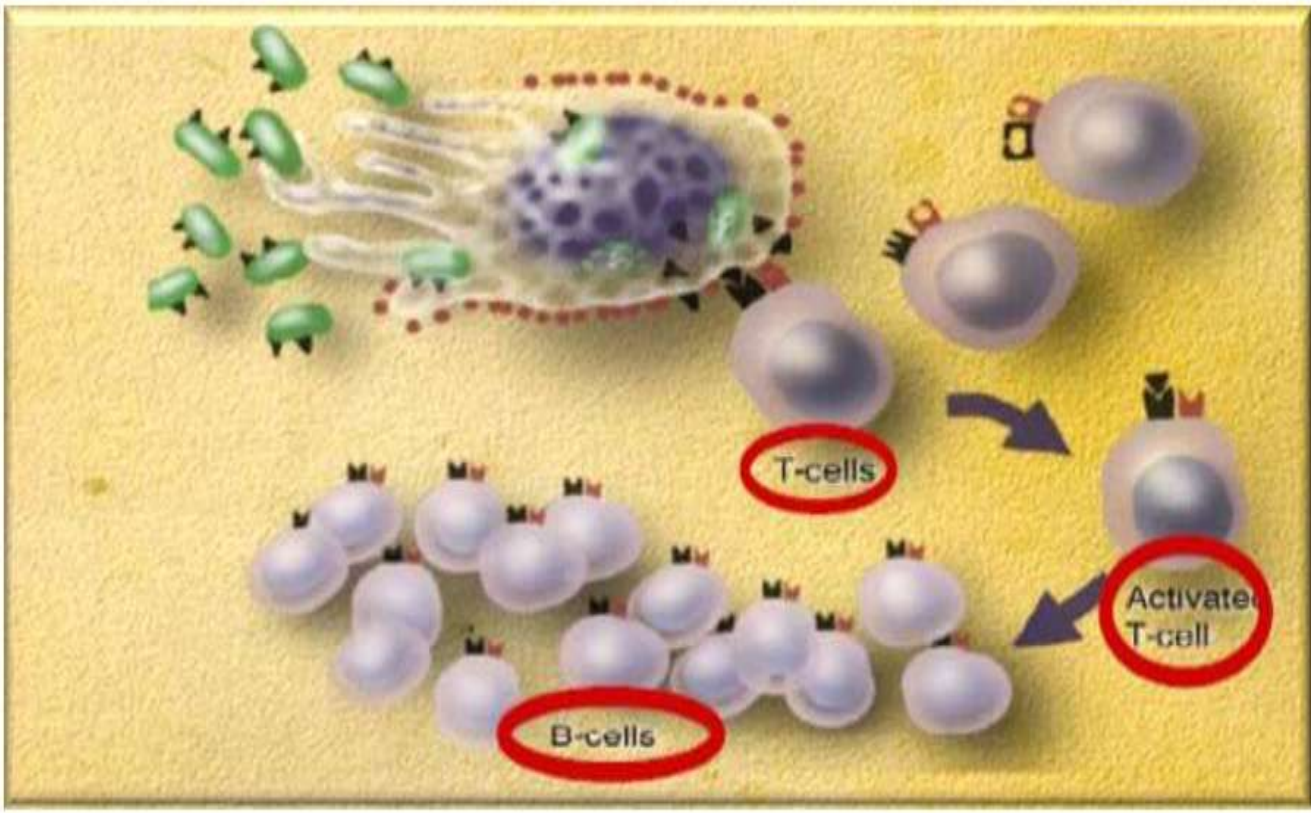


649,985 results



Biyolojik Ajan

- **Biyolojik tedaviler**; Hastalık gelişim sürecinde rol alan **immün** veya **genetik** mediyatörlerden birini **özgün olarak hedef alan ilaçlardır** =>“**Nokta atış**”
- İmmün sistemin **biyolojik yanıtını etkiler,** inflamasyonun özgün yollarını ve sinyallerini **bloke ederler**



Biyolojik Ajanlar

Biyolojik ajan:

rDNA teknolojisi ile canlı oluşumlar (*E.coli* and Chinese hamster ovary (CHO) cells veya dokular) içinde veya **doğal kaynaklardan** üretim (+)

Kullanılan kısaltmalar;

- -**cept**; Reseptör füzyon proteinleri
- -**mab**; Monoklonal antikorlar (mAB)
- -**ximab**; Şimerik monoklonal antikorlar
- -**(z)umab**; İnsan monoklonal antikorları
- -**inib**; inhibitörler

- ✓ Romatolojik hastalıklar
- ✓ Maligniteler => NHL, KML, ALL, vb.
- ✓ İnflamatuar barsak / göz hastalıkları
- ✓ Dermatoloji (Psöriazis vb.)
- ✓ Organ transplantasyonu
- ✓ Multiple skleroz
- ✓ Şiddetli astım
- ✓ .....
- ✓ **İnfeksiyon!!! (COVID-19)**

Biosimilar Insulins – What a Clinician Needs to Know?

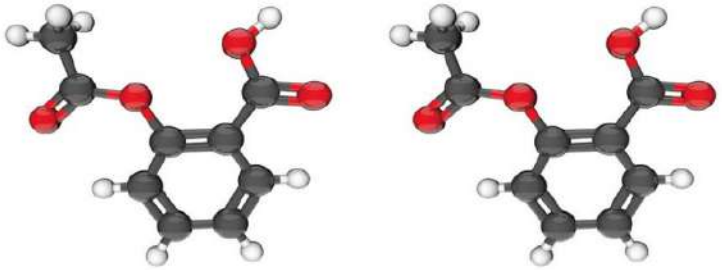
Sujoy Ghosh, Saptarshi Bose[1], Sandeep Gowda[2], Pradip Mukhopadhyay

- **Büyük**
- **Protein**
- **İmmünojen**

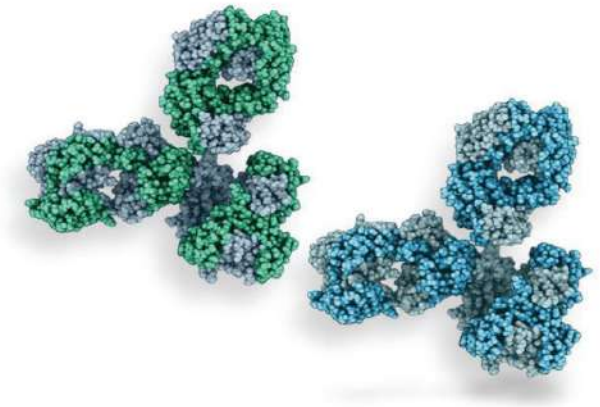
How to cite this article: Ghosh S, Bose S, Gowda S, Mukhopadhyay P. Biosimilar insulins – What a clinician needs to know? Indian J Endocr Metab 2019;23:400-6.

Practical Considerations for Integrating Biosimilars Into Clinical Practice

MEGAN B. MAY,[1] PharmD, BCOP, KATE DEEN TAUCHER,[2] PharmD, MHA, BCOP, and

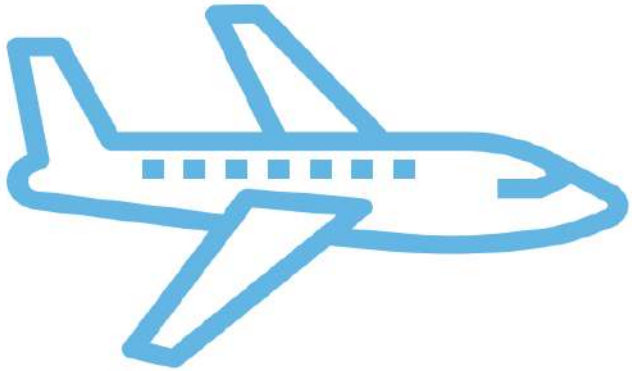


Aspirin (21 atoms)



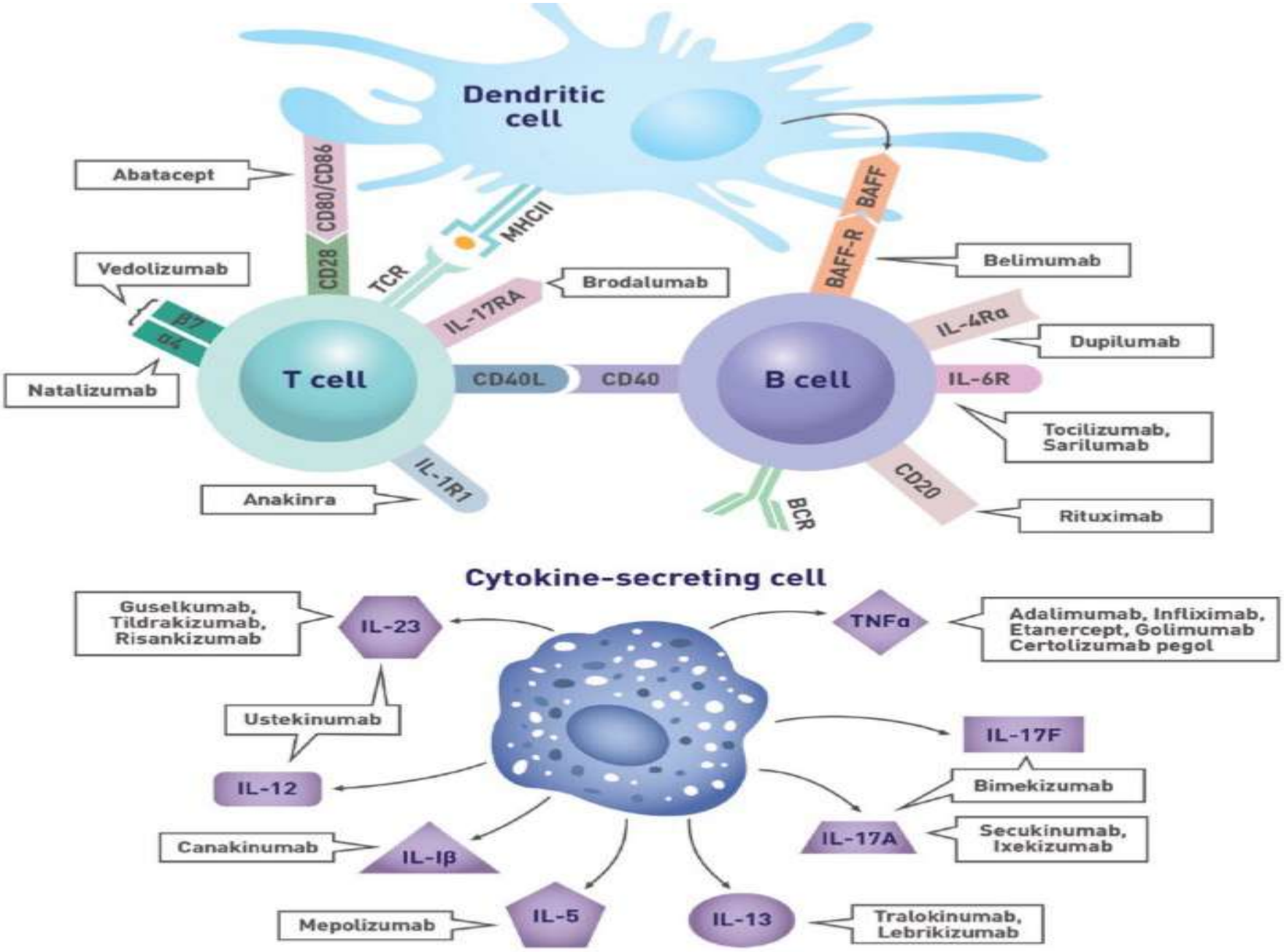
Biosimilar (25,000 atoms)

Bike (150 parts)



Airplane (6,000,000 parts)

J Adv Pract Oncol. 2021;12(4): 431–8.



J Cutaneous Med Surg. 2019; 23: 50-74.

Biyolojik tedavi ajanları etkilerini nasıl gösterirler?

1. Hastalığın patogenezinde yeri olan **sitokinin** etkisini bloke edenler

- ✓ Anti-**TNF** ajanlar
- ✓ **IL-1β** inhibitörleri (Anakinra)
- ✓ **IL-6R** inhibitörü (Tosilizumab)

2. B lenfositleri hedef alarak immün yanıtı baskılayanlar

B hücre **delesyonu** yapanlar (Rituksimab)

3. T lenfositlerde delesyona neden olmaksızın, T lenfosit aktivasyonunda görevli ko-stimülasyonu hedef alarak T hücre aktivasyonuyla **uygunsuz immün** yanıt baskılayanlar

T hücre ko-stimülasyon inhibitörleri (Abatasept)

Rheumatology. 5th ed. Philadelphia; 2015: 468–71.

TNF- α İnhibitörleri

TNF-α etkileri

- ✓ Adezyon moleküllerinin sunumu
- ✓ Diğer proinflamatuar sitokinlerin sentezi **(IL-1**, **IL-6**, **GM-CSF**)
- ✓ **T** hücresi, **B** hücresi ve makrofajların uyarılması
- ✓ Apoptoz indüksiyonu
- ✓ Anti-viral ve anti-tümör etkiler
- ✓ Regülatuar T hücre inhibisyonu
- ✓ TNF-α **granülom** oluşumunda ve idamesinde vazgeçilmez bir sitokin

Tablo 2. TNF inhibitörü ajanlarla gözlenen yan etkiler.

Sık görülenler

- Enjeksiyon yeri reaksiyonları
- İnfüzyon reaksiyonları
- Üst solunum yolu enfeksiyonları

Daha az görülen yan etkiler

- Ciddi enfeksiyonlar
- Mikobakteriyel enfeksiyonlar
- Fungal enfeksiyonlar
- Fırsatçı enfeksiyonlar
- Viral enfeksiyonlar (herpes zoster, hepatit B)

- ➢ TB, MAC gibi atipik mikobakteriler
- ➢ PCP, histoplazmoz, aspergilloz gibi funguslar
- ➢ Listeriyoz
- ➢ CMV, HSV, HBV

- Astım
- Erişkin respiratuvar distres sendromu
- Granülomatöz akciğer hastalığı
- Kolon perforasyonu

Comparative Risk of Serious Infections With Biologic and/or Immunosuppressive Therapy in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

Siddharth Singh,[*,‡] Antonio Facciorusso,[§] Parambir S. Dulai,[*] Vipul Jairath,[‖,¶] and William J. Sandborn[*]

Clin Gastroenterol&Hepatol. 2020;18:69–81

In a systematic search of publications, through March 18, 2018

Combination therapies for IBD that include **TNF antagonists**, especially with **corticosteroids**, are associated with a **higher risk of serious infection**, whereas monotherapy with an immunsuppressive agent is associated with a lower risk, **compared with monotherapy** with a TNF antagonist.

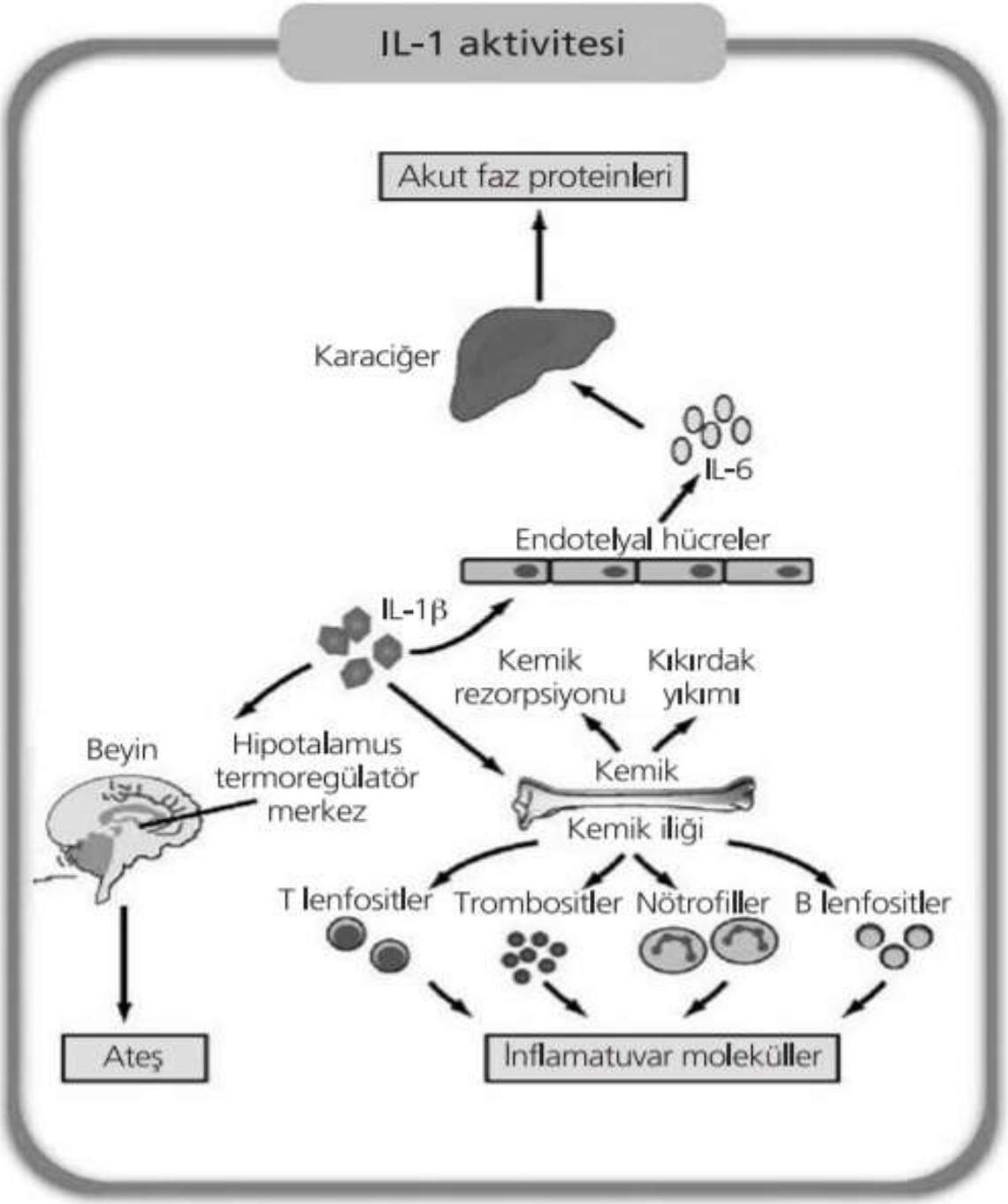
IL-1β sistemik etkileri

IL İnhibitörleri;
Göreceli güvenli

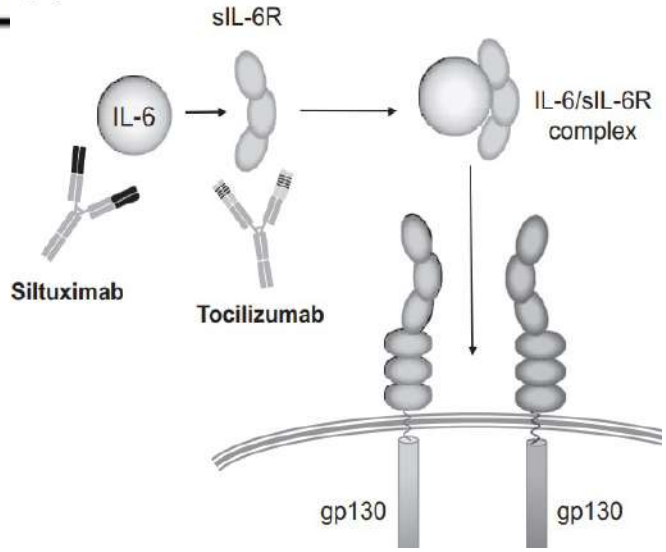
Yan etkiler;

- ✓ ÜSYİ başta
- ✓ **İnfeksiyon**lara yatkınlık

İnjeksiyon yeri **alerji**



Agents	Targeted molecule or pathway
Tocilizumab, siltuxumab	IL-6



Fare kökenli, humanize edilmiş, insan **IL-6R**'ye karşı oluşturulmuş monoklonal antikordur

- ✓ **VZV/HBV** riskini **artırıyor**
- ✓ Tedavi öncesi **HBV** taraması **(**HBsAg, **Anti-HBc** total, Anti-HBs)

  HBsAg pozitif => antiviral profilaksi

  Anti-HBc total pozitif => **HBV DNA** bakılmalı
- ✓ **Aktif TB** riskini **artırıyor**
- ✓ **LTBI** açısından dikkat, tedavi öncesi **TB** taranmalı
- ✓ Yaşa uygun **aşılamaları** yapılmalı

KL Winthrop, *Clin Microbiol Infect*. 2018;24:S21

2. B lenfositleri hedef alanlar

2. B lenfositleri hedef alanlar

- **B hücreleri** yok edici tedaviler ilk B hücre malignitelerinin için geliştirildi
- B hücre **deplesyon**u için günümüzde en yaygın B hücre yüzeyindeki **CD20** molekülünü hedef alanlar
- **B hücreleri** tüm lenfositlerin yaklaşık **%20'si**
- CD20 başlanması üzerinden işleyen tedavilerde plazma hücreleri etkilenmediği için **Ig** üretimi sürer

Rituksimab (RTX)

CD20 monoklonal antikoru olan bir füzyon proteini

REFLEX çalışması; RTX grubunda 100 hasta yılı infeksiyon **5.2** vs **3.7**

Fırsatçı infeksiyon riski de artar

TB ise pek beklenmez

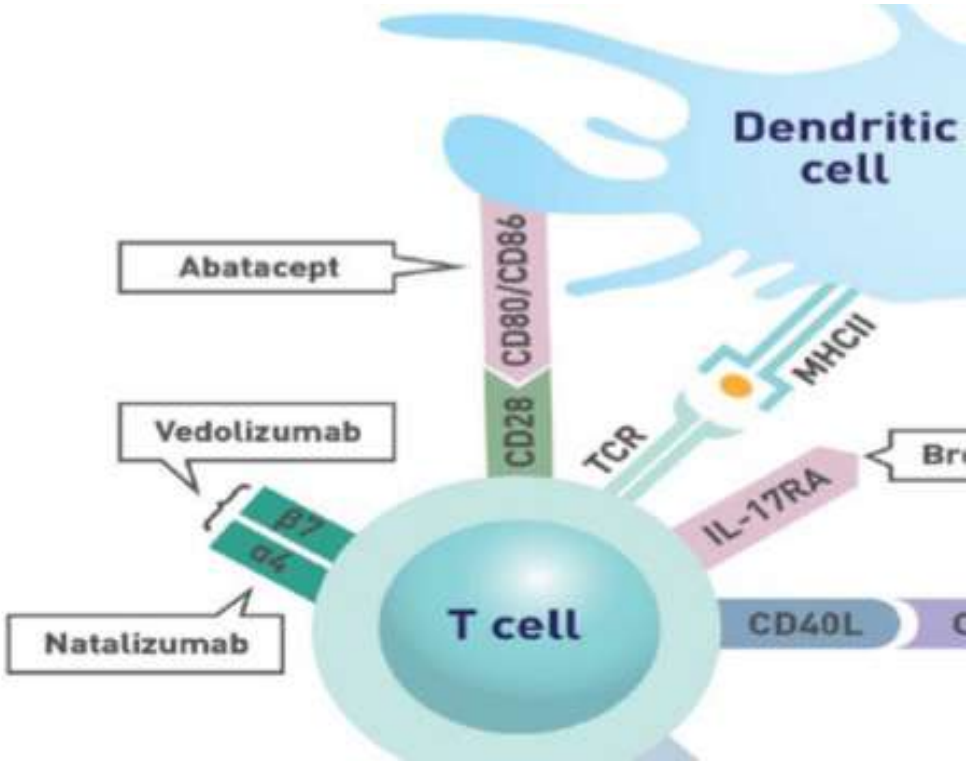
Rheumatology. 5th ed. Philadelphia; 2015: 472–8.

3. T Hücre Aracılı Biyolojik Tedavi Yaklaşımları

T hücreleri tüm lenfositlerin **%80** kadarını oluşturur

CD4, **CD8** ve **Treg** gibi alt grupları var

T hücre delesyonu üzerinden yapılacak tedaviler oldukça risklidir



Abatasept

APC yüzeyindeki **CD80/CD86** kompleksine bağlanır

T hücresine ko-stimülatuvar uyarılmasını önleyerek **T hücrenin** uyarılmasını inhibe eder

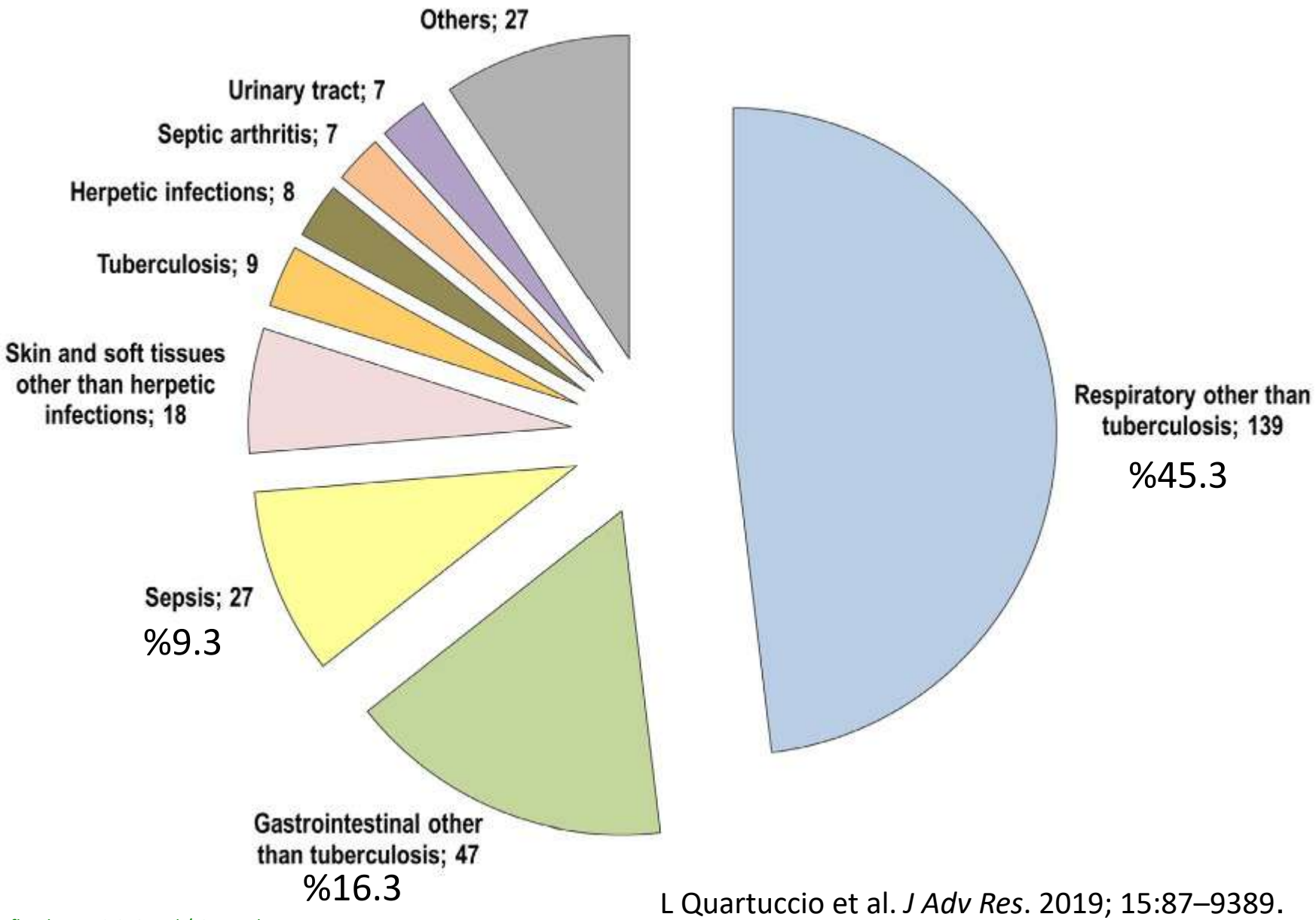
Ciddi infeksiyon sıklığı,

- ✓ %**2.6**
- ✓ Sadece **DMARD** grubunda **%1.7** bulunmuş

Clin Ther. 2010; 32:1855–70

Biyolojik ajanlar infeksiyon riskini artırır mı?

İtalya, **2006-2017** arasında **6801** hasta; RA, psoriazis ve ankilozan spondilit



L Quartuccio et al. *J Adv Res*. 2019; 15:87–9389.

Meta-analysis: hepatitis B reactivation in patients receiving biological therapy

Aim: To determine the prevalence of **HBVr with TNF alpha inhibitors**, **ustekinumab** and **vedolizumab**

The studies includ **rriers** with various rheumatological,

Results: We includ BV.

Sonuçlar: Klinik uygulama kılavuzlarının aksine, yüksek riskli gruplarda profilaktik antiviral tedavinin alımı düşüktü.

The prevalence of **HBVr** in **chronic carriers of HBV** / **occult HBV infection** was

- ✓ Adalimumab **17.1** / **5.0**%,
- ✓ Etanercept, **16.6** / **2.6**%
- ✓ Infliximab **40.5** / **4.4**%
- ✓ Ustekinumab **19.1** / **6.4**%

There were **39 HBVr** (26 in chronic HBV and 13 in the occult group) **without** any hepatic failure or death.

In the chronic HBVr group, only three of **24 patients received antiviral prophylaxis**.

El Jamaly H, *Aliment Pharmacol Ther*. 2022 ;56(7):1104-8.

Table 1
List of biologics and their infection risk

Biologic	Brand Name	Mechanism of Action	Approved Uses	Infection Risk
Certolizumab	Cimzia	TNF-α inhibitor; binds to human TNF-α with a K_D of 90 pM	Crohn disease, RA, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	Increased risk of opportunistic infections. Cases of reactive TB or new TB have occurred. Most common adverse reactions >7% (upper respiratory tract infection, rash, and urinary tract infection). New infection risk 0.91 per patient-year in RA patients.[48]
Adalimumab	Humira	TNF-α inhibitor; binds to human TNF-α	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Increased risk of serious infection. Cases of reactive TB or new TB have occurred.[49]
Infliximab	Remicade	TNF-α inhibitor; chimeric human and mouse peptide sequence monoclonal antibody	RA, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis	Most common adverse reactions (>10%), infections. Treated serious infections reported in 36% patients. Most common, sinusitis, pharyngitis, bronchitis, and urinary tract infections. Serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Cases of reactivation of TB or new TB infections have been observed.[50]
Golimumab	Simponi	TNF-α inhibitor	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Serious infections have been reported in 1.4% of treated patients. Serious infections include sepsis, pneumonia, cellulitis, abscess, TB, invasive fungal infections, and hepatitis B infection. Cases of reactivation of TB or new TB infections have been observed.[51]
Rituximab	Rituxan	B cell inhibitor	RA, Wegener's granulomatosis, pemphigus vulgaris, non-Hodgkin lymphoma, chronic lymphocytic leukemia	Serious infections have been reported in patients with prolonged hypogammaglobulinemia. Most common infections, nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.[52]

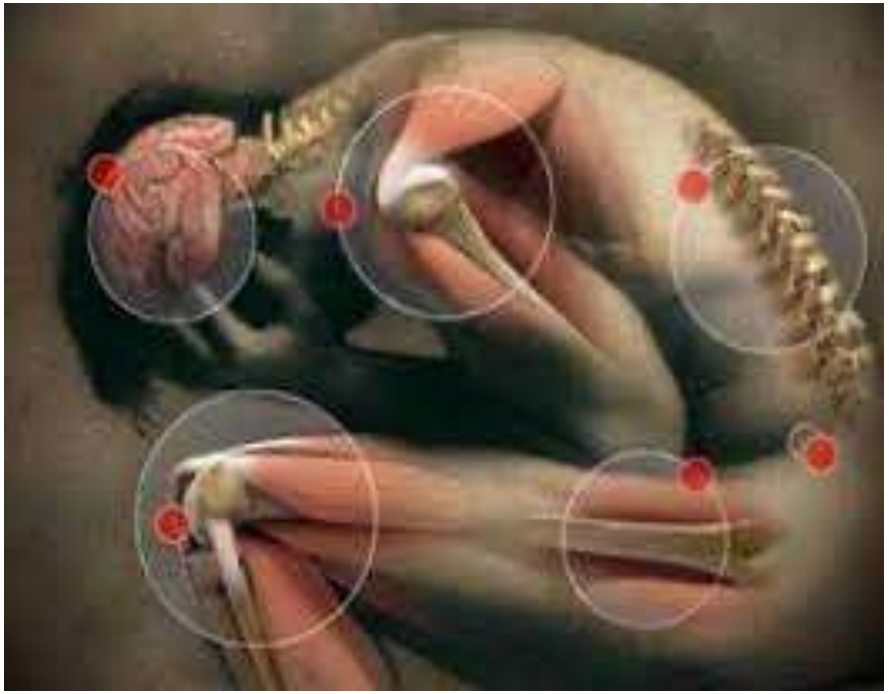
Immunol Allergy Clin N Am. 2021; 41: 639-52.

Table 1
(continued)

Biologic	Brand Name	Mechanism of Action	Approved Uses	Infection Risk
Anakinra	Kineret	IL-1 Inhibitor	RA	Incidence of infection was 40% in Kineret-treated patients, vs 35% in placebo-treated patients. Incidence of serious infections, 1.8% in Kineret-treated patients vs 0.6% in placebo. Most common infections, cellulitis, pneumonia, and bone and joint infections. Patients with asthma were at higher risk of developing infection (5%) vs placebo (<1%).[53]
Sarilumab	Kevzara	IL-6 inhibitor	RA	Serious infections have been reported. Most frequent pneumonia and cellulitis. Rate of overall infection 0.6%–0.8% in the treatment group compared with 0.5% in the placebo group. Rate of serious infection in events per 100 patient-years was 3.0 (150 mg) and 4.3 (200 mg) in the Kevzara treatment groups compared with 3.1 in the placebo group. Cases of TB have been reported.[54]
Tocilizumab	Actemra	IL-6 Inhibitor	RA, giant cell arteritis, polyarticular JIA, systemic JIA, cytokine release syndrome	Rate of overall infections, 119 events per 100 patient-years, similar to the MTX group. Serious infections, 3.6 per 100 patient-years, 1.5 per patient-years in the MTX group. Most common infections, upper respiratory tract infections and nasopharyngitis. Most common serious infections, pneumonia, urinary tract infection (UTI), cellulitis, herpes zoster. Cases of TB have been reported.[55]
Abatacept	Orencia	CTLA4 co-stimulator inhibitor	RA	Infections reported in 54% patients in the treatment group, 48% in the placebo group. Most common infections, upper respiratory tract infections, nasopharyngitis, sinusitis, UTI, influenza, bronchitis. Serious infections, 3% in the treatment group, 1.9% patients in the placebo group.[40]

Immunol Allergy Clin N Am. 2021; 41: 639-52.

Biyolojik ajanlar kullanımında infeksiyon yönetimi



ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents)

J.W. Baddley [1,*], F. Cantini [2], D. Goletti [3], J.J. Gómez-Reino [4], E. Mylonakis [5], R. San-Juan [6,8], M. Fernández-Ruiz [6,8], J. Torre-Cisneros [7,8]

Anti- TNF-α İnfeksiyon Gelişimini Önleyici Öneriler

✓**Aktif TB** ve diğer **granülamatöz hastalık** riskini **artırıyor**

✓**Fırsatçı bakteri, virus** infeksiyon risklerini **artırırlar.**

➢İnfeksiyon varlığında **doz azaltılmalı** ya da tedavi **kesilmeli**

➢**LTBI** açısından dikkat, tedavi öncesi **TB** taranmalı;

Tarama **ikili** yapılmalı hem **TST** hem de **ELISA- ELISpot**-based **IGRA**

Yüksek endemik yerlerde aralarda **tekrar** (Süre??)

Test pozitifliğinde **LTBI tedavi** verilmeli

➢Tedavi öncesi **HBV** taraması

Eksik/mevsimsel **aşılamaları** yapılmalı

JW Baddley, *Clin Microbiol Infect.* 2018;24:S10

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

K.L. Winthrop [1,*], X. Mariette [2], J.T. Silva [3], E. Benamu [4], L.H. Calabrese [5], A. Dumusc [6], J.S. Smolen [7], J.M. Aguado [8,9], M. Fernández-Ruiz [8,9]

Agents	Targeted molecule or pathway
Anakinra, cabakinumab, gevokizumab, rilonacept	Interleukin-1α (IL-1α) and/or IL-1β

- ✓ **VZV/HBV** riskini **artırmıyor**
- ✓ **LTBI** açısından dikkat, tedavi öncesi **TB** taranmalı
- ✓ Çocuk/erişkinde hafif/orta infeksiyonları **orta düzeyde** artırır
- ✓ Ciddi seyirli ve **ko-morbiditesi** olanlarda şiddetlendirir
- ✓ Altta yatan hastalığa göre **tedavi dozu** ve **süresi** yönet, gereğinde kesilebilir
- ✓ Yaşa uygun **aşılamaları** yapılmalı

KL Winthrop, *Clin Microbiol Infect*. 2018;24:S21

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52)

M. Mikulska [1,*], S. Lanini [2], C. Gudiol [3], L. Drgona [4], G. Ippolito [2], M. Fernández-Ruiz [5,6], B. Salzberger [7]

Agent	Mechanism of action	Specific infections reported in the literature
Rituksimab Anti-CD20 monoklonal Ab		Respiratory tract infection, fatal reactivation of chronic or occult HBV, HCV or HEV exacerbation, enteroviral infection, PCP, PML

L Drgona, *Clin Microbiol Infect.* 2018;24:S83.

Agents	Targeted molecule or pathway
Eculizumab	Complement component C5

Neisseria spp. infeksiyonu açısından **yüksek risk**;

- Meningokok aşıları (**MenACWY** ile **MenB**) tedavi başlanmadan en geç **2-4 hafta önce** yapılmalı
- Tedavi devam ederse **5 yıl** sonra yeniden rapel
- Meningokok profilaksisi (penisilin V veya siprofloksasin) en az 4 hafta aşıdan sonra veya antikor oluşumuna dek
- Yoğun immünosüpresyon varsa tedavi bitiminden **4 h sonrasına** dek devam

✓**Pnömokok** ve **Hib aşılamaları** yapılmalı

KL Winthrop, *Clin Microbiol Infect*. 2018;24:S21

Clin Microbiol Infect. 2018 June ; 24(Suppl 2): S95–S107. doi:10.1016/j.cmi.2018.01.030.

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors)

- **Proteasome inhibitors:**

Bortezomib, carfilzomib and ixazomib

Patients with **MM** are at higher **risk** of specific infectious **pneumococcal invasive** infection, **HZ** and **influenza**

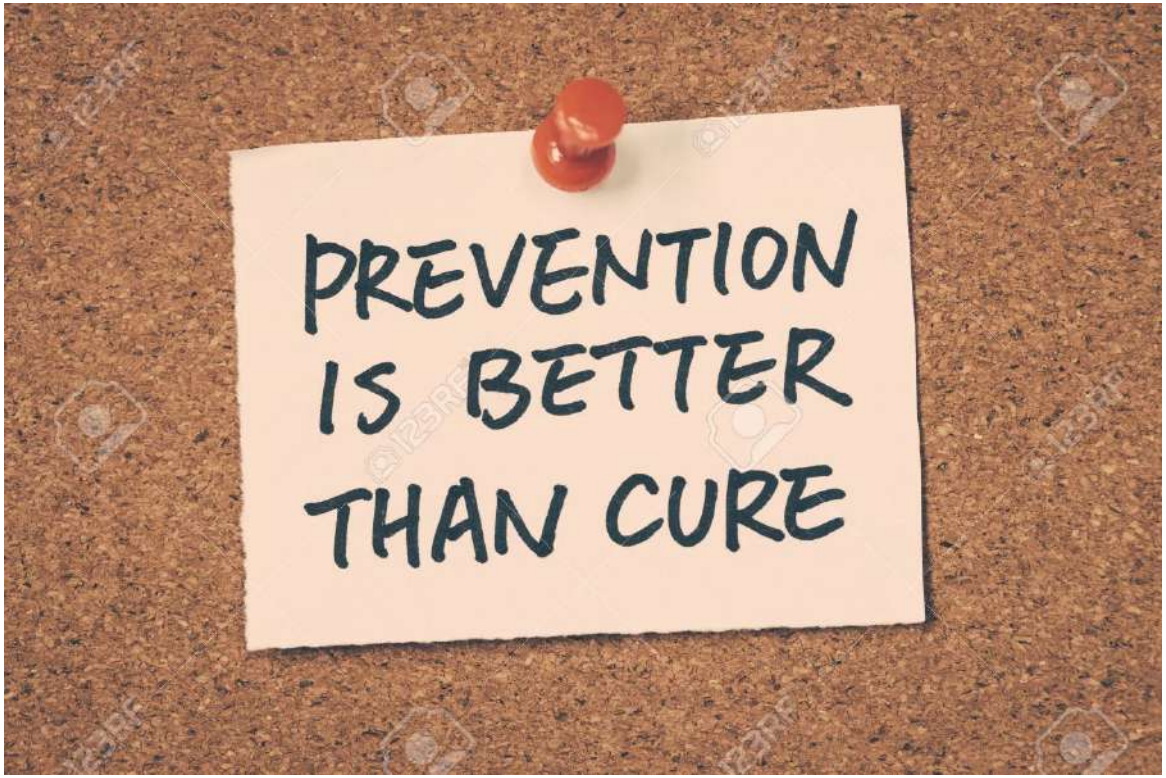
Antiviral prophylaxis

Acyclovir or valacyclovir

- Pneumococcal
- Influenza vaccination

❖ İnfeksiyon hastalıklarından korunma, ölüm ve sekellerinin azaltılmasında en önemli **iki yöntem**;

- **Sanitasyon**
- **İmmünizasyon**



Dutch philosopher Desiderius Erasmus

...vaccination rates in patients with immune-mediated diseases treated with immunosuppressants remain suboptimal, **primarily** due to **the absence of physician recommendations.**

Assala M, et al. *Joint Bone Spine*. 2017; 84:365-6.
Hua C, et al. *Rheumatology (Oxford)*. 2015; 54:748-50.

Aşı ‘’aşığı’’ Dr. Fikret KURT’un izniyle...

Biyolojik Ajan Kullanımında Aşı Önerileri

- ✓ Aşılar güvenli mi?
- ✓ Hangi aşılar?
- ✓ Ne zaman?
- ✓ Aşı etkinliği nasıl?
- ✓ Aşılar hastalığı etkiler mi?

Biyolojik Ajan Kullanan Hastalarda Aşıların Etkinliği ve Güvenirliği

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Inactivated and subunit vaccines				
Cholera (oral)	Vedolizumab	Healthy individuals	No significant difference in seroconversion rates but diminished the magnitude of antibody titre increase[131]	Well tolerated[131]
Hepatitis A	TNFi (pooled)	RA	Diminished humoral response compared to healthy individuals, but 86% of patients achieved seroprotection with 2 vaccine doses[132]	Well tolerated and did not result in exacerbation of disease activity[132]
		IBD	Diminished humoral response to the vaccine[28]	NA
Hepatitis B	Infliximab	IBD	Reduced humoral response to the vaccine[133]	NA
Influenza	Abatacept	RA	Results are variable but may reduce humoral response to the vaccine[136,137]	Well tolerated[136,137]
	Adalimumab	RA	No significant effect[138]	Well tolerated[138]
	Belimumab	SLE	Lower fold-increase in titres for some influenza strains compared with controls[139]	NA
Live attenuated vaccines				
Herpes zoster	TNFi (pooled)	RA, PsA, PsO, AS, IBD	Vaccination effectively protected patients from disease[74]	Vaccination was not associated with short-term increase in herpes zoster risk[74]
Measles, mumps, rubella	Etanercept	JIA	No significant effect on humoral response to vaccination; insignificant trend toward lower cellular response[80]	Well tolerated and did not cause disease exacerbation[80]
	Vedolizumab	IBD	Single case report of a patient achieving a positive measles antibody index following revaccination[158]	No adverse effect observed[158]
Yellow fever	Infliximab	RA	Similar response rates following revaccination in infliximab-treated patients with RA and controls; trend toward lower titres in patients, but analysis limited by small study numbers[81]	No adverse effect observed[81]

Hastalarda Aşı Önerileri
Başlangıç

- **Aşı öyküsü** alınmalı
- Aşı kaydı yoksa / öykü güvenilir değilse **serolojik testler** yapılmalı;
  - KKK
  - Suçiçeği
  - TB tarama
  - Viral hepatitler (HAV, HBV, HCV)
  - HIV

HBsAg, **Anti HBc** total,
Anti HBs

Aşılar Ne Zaman Verilmeli?

- ✓ Mümkünse aşılar planlanan immünosüpresif ilaçlardan **önce** başlanmalı (Güçlü-Orta öneri).
- ✓ **İnaktive** aşılar immünosüpresif **tedaviden ≥2 hafta önce** başlanmalı (Güçlü-Orta öneri)

To optimize the immunogenicity of **inactivated vaccines** in treatment-naive patients with immunemediated conditions, we suggest that immunization be performed **at least 2 weeks prior** to initiation of immunosuppressive therapy, whenever possible.
GRADE: Conditional recommendation; moderate-level evidence
*Vote: **71.4% strongly** agree, 28.6% agree*

J Cutaneous Med Surg. 2019; 23: 50 -74.

Aşılar Ne Zaman Verilmeli?

- ✓ Mümkünse aşılar planlanan immünosüpresif ilaçlardan **önce** başlanmalı
- ✓ **İnaktive** aşılar immünosüpresif **tedavide**
- ✓ **Canlı aşılar** immünosüpresif **tedaviden ≥**
  tedavi başlandıktan **sonra ilk iki hafta** için
  Düşük öneri)

vaccinated with **live attenuated vaccines**, we recommend that the **duration of viremia** following immunization be considered

- ❖ To optimize the immunogenicity of the **live attenuated herpes zoster vaccine** in treatment-naive patients with immunemediated conditions, we suggest immunization be performed **at least 2 to 4 weeks prior** to initiation of immunosuppressive therapy.
- ✓ Conditional recommendation; moderate-level evidence.

J Cutaneous Med Surg. 2019; 23: 50 -74.

Canlı Atenüe Aşılardan Sonra Oluşan Viremi Süresi

Vaccine	Length of Viremia
Varicella (Oka strain)	The vaccine strain could not be isolated up to 14 days postvaccination in children,[225] but 1 study detected the vaccine strain by PCR up to 5 weeks after immunization in 5 of 166 (3%) asymptomatic children given the varicella vaccine.[226]
Herpes zoster (Oka strain)	Varicella zoster virus DNA can be detected by PCR analysis in 16% (11/67) of individuals 2 weeks postvaccination[227] and up to 4 weeks in 6% (2/36) of individuals >60 years old.[71]
Yellow fever	Viremia after primary immunization wanes within 7 days postimmunization[228] and is generally cleared within 2 weeks of vaccination.[229]
Measles	The vaccine strain has not been isolated from human blood after immunization of healthy children,[230] but a study on macaques has shown the persistence of the Schwarz vaccine strain 7 to 9 days postvaccination.[231]
Mumps	There is a low risk of viremia with the mumps vaccine strains; however, the incidence of aseptic meningitis occurring 2 to 3 weeks after vaccination suggests that the potential is maintained in some vaccine strains. The frequency of vaccine-associated aseptic meningitis varies from approximately 1 in 1.8 million doses for the Jeryl Lynn strain to as high as 1 in 336 for the Urabe AM9 strain.[232]
Rubella	Viremia was documented 7 to 21 days postvaccination in some adults receiving the primary vaccination but not in children.[233]
Live polio (type 2 Sabin)	In adults, free virus is present in the serum between 2 and 5 days after vaccine administration, with antibody-bound virus being present up to 8 days after vaccination.[234] In children aged ≤17 months, free virus can be detected up to 8 days after vaccination.[235]

Genel Yaklaşım

- İmmünosüpresif tedavi alanlarda **canlı virus aşıları yapılmaz**
- Biyolojik ajandan en az **bir ay önce** uygulanmalı
- Düşük düzey immünosüpresyonda yapılabilir (zayıf öneri)

Düşük düzey immünosüpresyon

- ✓ Günlük prednizon dozu < 20 mg (veya eşdeğeri)
- ✓ Methotreksat ≤ 0,4 mg/kg haftalık
- ✓ Azathioprin ≤ 3 mg/kg gün
- ✓ 6-merkaptopurin <1,5 mg/kg gün

****KKK, varisella** aşıları istisna**/ Hasta temelli!**

Ev halkı aşılaması

- Risk azaltılması için önemli
- **Oral polio** aşısı uygulanmamalıdır
- **Rotavirus aşısı** olan bebeklerin bezlerini değiştirmemeli (**4 hafta**)

Live attenuated vaccines under immunosuppressive agents or biological agents: survey and clinical data from Japan

Koichi Kamei[1] · Isao Miyairi[2] · Kensuke Shoji[2] · Katsuhiro Arai[3] · Toshinao Kawai[4] · Masao Ogura[1] · Kenji Ishikura[1,5] · Mayumi Sako[6] · Hidefumi Nakamura[7]

European Journal of Pediatrics (2021) 180:1847–1854
https://doi.org/10.1007/s00431-021-03927-1

Pediatri merkezlerine anketler gönderilmiş. Ankette immünosüpresif veya biyolojik ajanlar içeren hastalara zayıflatılmış canlı aşılar önerilmiş.

In the patient research, data for **781 patients** were collected.

- **Vaccine-associated infections** were observed in only **two** patients (**0.3%**), both of whom had **varicella**, although they recovered promptly.
- **No life-threatening adverse events** were noted.

Sonuç:

✓Pediatri merkezlerinde immünosüpresif ilaç kullanan hastalarda canlı zayıflatılmış aşılara talep artmaktadır.

✓Çoğu hekim aşılanmaları gerektiğini düşünmektedir.

✓Canlı zayıflatılmış aşılarla aşılamanın hastalarda **güvenli** olduğu görüldü

İmmunosupresif Tedavi Sonrası Aşılama

Table 2

Treatment-free intervals required before and after immunization in patients on glucocorticoid or DMARD therapy, according to French and international recommendations.

Vaccine	Treatment	Glucocorticoid therapy		DMARDs			
		Oral ≥ 10 mg/d ≥ 2 weeks	Bolus	Methotrexate	Leflunomide	Hydroxy-chloroquine	Sulfasalazine
Live attenuated vaccines	Discontinuation	1 month	3 months	0[a] to 3 months	3 to 6 months[b]	No treatment-free interval	
	Resumption	2 to 4 weeks	2 to 4 weeks	2 to 4 weeks	2 to 4 weeks		
Inactivated vaccines	No treatment-free interval						

[a] According to US recommendations (American College of Rheumatology, Advisory Committee on Immunization Practices), the live attenuated vaccine against the VZV can be given during treatment with methotrexate (dosage ≤ 0.4 mg/kg/week).

[b] According to Canadian recommendations, the long half-life of leflunomide warrants a 6-month treatment-free interval before vaccination.

Biyolojik Ajanlarla Tedavi Sonrası Aşılama

- ✓ Hastalığı modifiye eden anti-romatizmal ilaçlar (**DMARDs**), glukokortikoidler ve/veya TNF α blokerlerinin kullanımı esnasında **aşılara yanıt olduğu** gösterilmiş.
- ✓ **B hücre inhibitörü** ajan kullanımında öncesinde ya da **başlangıçtan 6 ay sonra**, diğer kürden **4 hafta önce** uygulanmalı

Table 3
Treatment-free i

Vaccine		Belimumab
Live attenuated vaccines		3 months
Inactivated vaccines		1 month 6 months[b]
		1 month

[a] Issued by the French public health authority and the Inflammatory Rheumatism Group (CRI) of the French Society for Rheumatology (and based on drug half-life values)
[b] Immunization can be performed within 6 months after rituximab but, in this situation, the risk of a blunted vaccine response is high.

Biyolojik Ajanların Yarılanma Ömürleri

Family	Biologic	Isotype	Target	Half-Life
TNF inhibitors	Adalimumab	human IgG1	TNFα	10-20 days[184]
	Etanercept	IgG1 Fc domain + TNF receptor extracellular ligand-binding domain	TNFα, LTα (TNFβ)	4.2 days[185]
	Certolizumab	Humanized Fab′ conjugated to	TNFα	14 days[186]
Interleukin inhibitors	Dupilumab	Human IgG4	IL-4Rα	NA[189,a]
	Mepolizumab	Humanized IgG1κ	IL-5	16-22 days[190]
	Tocilizumab	Humanized IgG1κ	IL-6R	11-13 days[191]
	Sarilumab	Human IgG1	sIL-6Rα, mIL-6Rα	Initial: 8-10 days Terminal: 2-4 days[192]
	Anakinra	IL-1 receptor antagonist	IL-1R1	4-6 hours[193]
B-cell inhibitor	Rituximab	Chimeric IgG1κ	CD20	20.8 days[59]
	Belimumab	Human IgG1λ	BAFF (BLyS)	12.5-19.4 days[206]

Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2023

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 percentage and count		Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease; alcoholism[a]	Chronic liver disease	Diabetes	Health care personnel[b]	Men who have sex with men
			<15% or <200 mm³	≥15% and ≥200 mm³							
COVID-19			See Notes								
IIV4 or RIV4			1 dose annually								
or											
LAIV4		Co traindicated					Precaution			1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy		1 dose Tdap, then Td or Tdap booster every 10 years								
MMR	Contraindicated*	Contrainc cated		1 or 2 doses depending on indication							
VAR	Contraindicated*	Contrainc cated			2 doses						
RZV		2 dose at age ≥19 years			2 doses at age ≥50 years						
HPV	Not Recommended*	3 doses th rough age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
Pneumococcal (PCV15, PCV20, PPSV23)		1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)									
HepA					2, 3, or 4 doses depending on vaccine						
HepB	3 doses (see notes)	2, 3, or 4 doses depending on vaccine or condition									
MenACWY		1 or 2 doses depending on indication, see notes for booster recommendations									
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT[c] recipients only			1 dose						

Recommended vaccination for adults who meet age requirement, lack

ecommended vac nation for adults with an additional risk factor or another

Recommended vaccination based on shared clinical decision-making

Precaution–vaccination might be indicated if benefit of protection

Contraindicated or not recommended–vaccine should not be administered.

No recommendation/ Not appli

Veri Sınıflandırma Tipi: Genel / General

Vaccinations for adults with autoimmune inflammatory rheumatic conditions[1-5]

Nonlive (inactivated, killed, subunit, or recombinant)	Pneumococcus PCV15 followed by PPSV23 OR PCV20	All patients who have not previously received a conjugate pneumococcal vaccine*.
	Seasonal influenza virus	Annually for all patients¶.
	Hepatitis A virus	At-risk patients who have not been previously vaccinated.
	Hepatitis B virus	All patients 19 to 59 years old and at-risk patients ≥60 years old (eg, those with occupational or lifestyle risk factors) who have not been previously vaccinated; antibody titers should be checked following completion of vaccine series to ensure response.
		ıot been previously vaccinated, including those treated with eculizumab and those with
		ıot been previously vaccinated, including those with impaired splenic function.
		ars old[Δ] who have not been previously vaccinated.
		for healthy adults (eg, single dose of Tdap followed by Td booster every 10 years).
	Recombinant zoster vaccine (RZV; Shingrix)	Recommended prior to immunosuppression and for those on immunosuppression.
	COVID-19 vaccines◊	All patients per guidelines for immunocompromised adults◊.

- **Immunocompromising conditions (including persons with HIV regardless of CD4 count)**:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon).

https://www.uptodate.com/contents/immunizations-in-autoimmune-inflammatory-rheumatic-disease-in-adults/print#H2033453670

Eculizumab Complement component C5

(e.g., eculizumab, ravulizumab) use: 2-dose series MenACWY-D (Menactra, Menveo, or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains

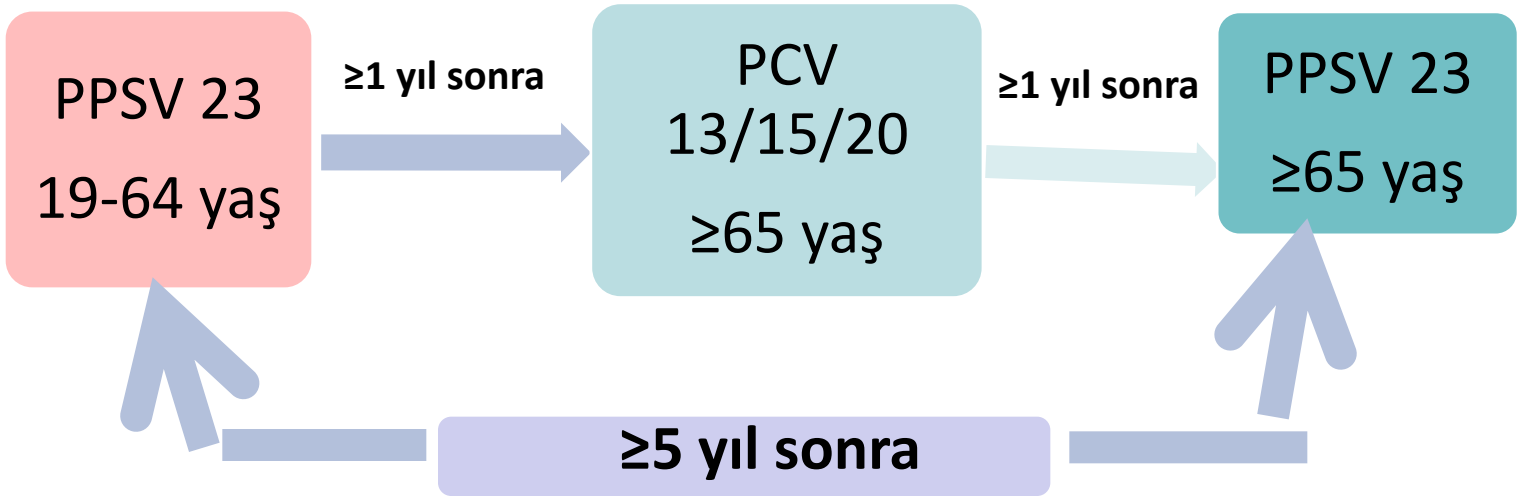
deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use, or microbiologists routinely exposed to *Neisseria meningitidis*: 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, 1–2, 6 months

Note: MenB vaccines may be administered simultaneously with MenACWY vaccines if indicated, but at a different anatomic site, if feasible.

Recommended Adult Immunization Schedule, USA, 2023

İmmünosüpresyonda pnömokok aşı seması

Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown: 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose.



Anatomik veya fonksiyonel aspleni, BOS kaçağı, kohlear implant hastalarında **en az 8 hafta**

Recommended Adult Immunization Schedule, USA, 2023

Vaccinations for adults with autoimmune inflammatory rheumatic conditions[1-5]

Live, attenuated[§]	Zoster vaccine, live (ZVL; Zostavax)[¥]	Can be given prior to immunosuppression and for those on low-dose immunosuppression if RZV is not available. **Contraindicated for those receiving moderately to highly immunosuppressive medications.**
	Measles, mumps, rubella	Patients who have not been previously vaccinated and/or lack evidence of measles immunity (measles IgG seronegative) or who may have potential for measles exposure (eg, through work or travel) when the vaccine can be given prior to immunosuppression. **Contraindicated for immunosuppressed patients.**
	Varicella	Patients who have not been previously vaccinated and/or lack evidence of varicella immunity (varicella IgG seronegative) or who may have potential for varicella exposure (eg, through work or family) when the vaccine can be given prior to immunosuppression. **Contraindicated for immunosuppressed patients.**
	Yellow fever	Patients residing in or traveling to endemic areas prior to immunosuppression. **Contraindicated for immunosuppressed patients.**

https://www.uptodate.com/contents/immunizations-in-autoimmune-inflammatory-rheumatic-disease-in-adults/print#H2033453670

İmmünosüpresif ajanın Bağışıklamaya Etkisi

Çoğu hastada bazı aşılara karşı **bağışıklık tepkisi körelmiş** olsa da, **aşıların yeterli koruma sağlaması beklenir**.

Bu ilaçlarla bağışıklık tepkisi; bağışıklık baskılayıcı **ilaç rejimine**, kullanılan **aşılara** ve **konak faktörlerine** bağlı olarak değişir.

	Methotrexate	TNF-alpha inhibitors	Anti-CD20 antibodies (eg, rituximab)	CTLA-4 inhibitors (eg, abatacept)	Janus kinase inhibitors (eg, tofacitinib)	Anti-IL-6 antibodies (eg, tocilizumab)
Pneumococcal vaccine	Decrease	Minimal effect	Substantial decrease	Decrease	Decrease	Minimal effect
Seasonal influenza vaccine	Probable decrease	Minimal effect	Substantial decrease	Decrease	Minimal effect	Minimal effect
Hepatitis B virus vaccine	Unknown	Decrease	Unknown	Unknown	Unknown	Unknown

https://www.uptodate.com/contents/immunizations-in-autoimmune-inflammatory-rheumatic-disease-in-adults/print#H2033453670

Sonuç olarak

*Biyolojik tedaviler **dinamik** bir alan

***Hastaların** durumu ve **yeni tedaviler** yakından izlenmeli

*Tedaviler başlanmadan önce **hastalığın kendisi**, **konak** risk faktörleri, **infeksiyona yatkınlığı** artıran durumlar multidisipliner irdelenmeli

*Her **vizit** profilaksi-aşı-korunma açısından **bir fırsattır**

Tedavi ve takip ekip işidir.

Teşekkürler...