BİYOLOJİK AJAN KULLANIMINDA

AŞILAMA

Dr. Süda TEKİN

Koç Üniversitesi Hastanesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Neler Konuşulacak?

- Biyolojik ajanlar
- Biyolojik ajanları kullananlarda infeksiyon riski
- Tedavi öncesi hastanın değerlendirilmesi
- Aşılamanın yönetimi
- Sonuç ve beklentiler

1893: metastatik sarkomalı hastada, streptokok enf gelişimi kanser yapısında gerilemeye neden oldu

BCG: immun yanıtı değiştirici olarak kullanılmaya başlandı

1957: interferon keşfi

1970: moleküler biyoloji bilimi temelleri

1975: monoklonal antikorların keşfi

1980: rekombinant teknolojinin gelişimi

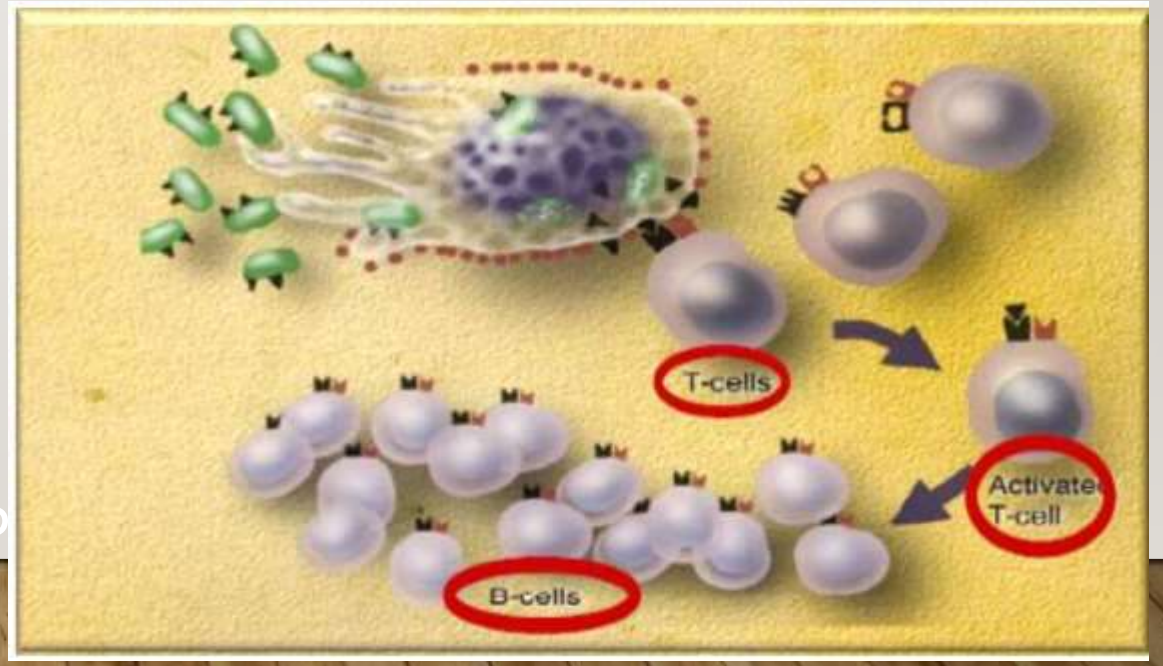
Biyolojik tedavi

Biyolojik Ajan

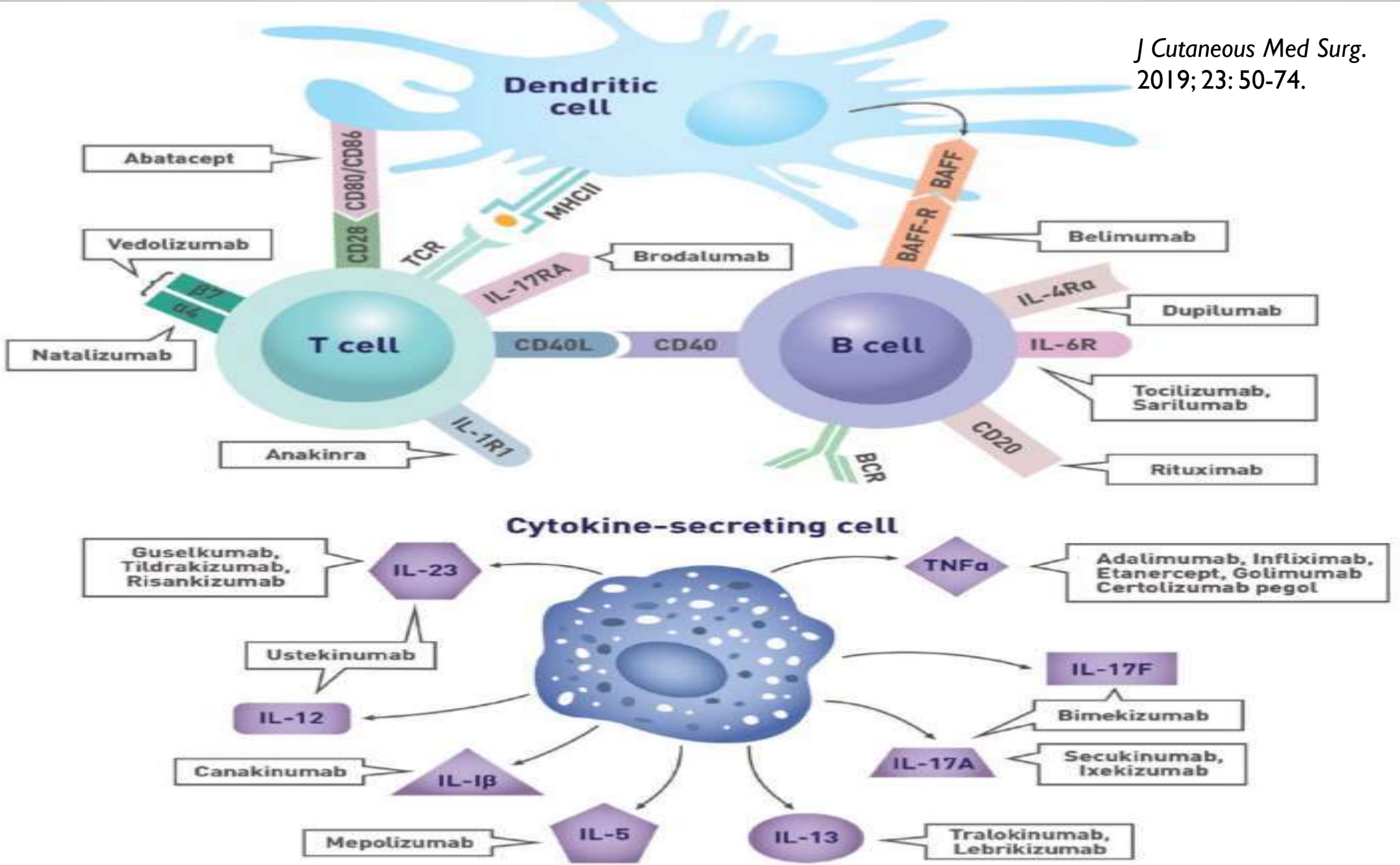
- **Biyolojik tedaviler**; hastalık gelişim sürecinde rol alan **immün** veya **genetik** mediyatörlerden birini **özgün olarak hedef alan ilaçlardır** =>"**Nokta atış**"
- İmmün sistemin **biyolojik yanıtını etkiler,** inflamasyonun özgün yollarını ve sinyallerini **bloke ederler**
- Kullanıma **1998**'de girmiş yeni ilaçlar

Biyolojik ajanlar;

- ✓ Anti-**TNF** ajanlar
- ✓ **IL-1β** inhibitörleri
- ✓ **IL-6R** inhibitörü (tosilizumab)
- ✓ **B** hücre delesyonu yapanlar (rituksimab)
- ✓ **T** hücre ko-stimülasyon inhibitörleri (abatasep



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



Biyolojik Ajanların Endikasyonları

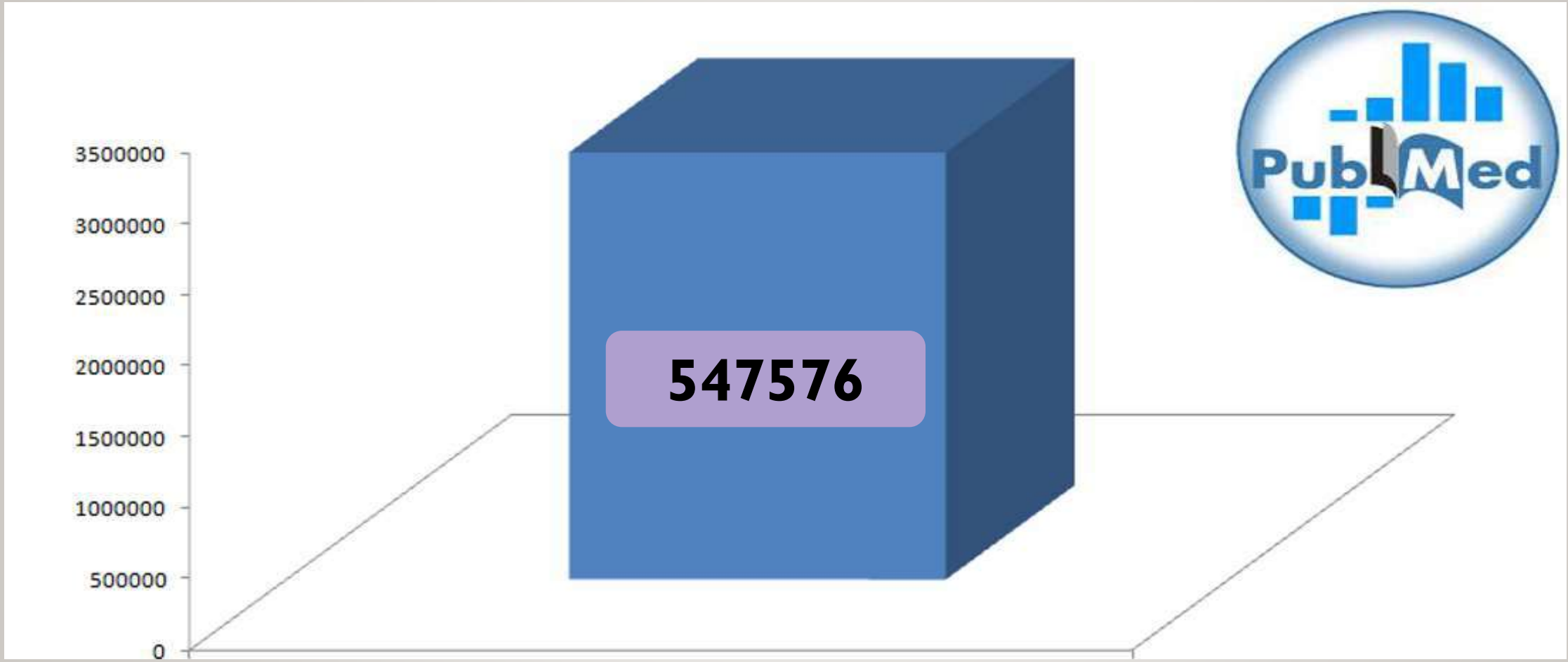
- ✓ Romatolojik hastalıklar
- ✓ Maligniteler => NHL, KML, ALL, kolorektal kanser
- ✓ İnflamatuar barsak / göz hastalıkları
- ✓ Psöriazis
- ✓ Organ transplantasyonu
- ✓ Multiple skleroz
- ✓ Şiddetli astım
- ✓ .....

Kullanılan kısaltmalar;

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

Son 5 yılda…

PubMed.gov | PubMed ▾ | biologic agents



Biyolojik Ajanlar İnfeksiyon Riskini Artırır mı?

Germano et al. Journal of Translational Medicine 2014, 12:77
http://www.translational-medicine.com/content/12/1/77

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Infection risk in Rheumatoid Arthritis and Spondyloarthropathy patients under treatment with DMARDs, Corticosteroids and TNF-α antagonists

Valentina Germ
Simonetta Sale

İnfeksiyonun en çok görülme zamanı;

- İlk **3-6** ay
- **anti-TNF** kullanımı sırasında ciddi infeksiyon riskinin en çok arttığı zaman dilimi (IRR **4.6**)

Results: Three hu serious] have been registered among as 36.3 ranging from 12.4 (DMARDs + C tract, and bacteria were responsible for three quarters of all infections. In the multivariate analysis, adding anti-TNFα to DMARDs doubled the IRR compared to DMARDs alone, anti-TNFα + CS significantly tripled it, whereas anti-TNFα + CS + DMARDs only increased the risk 2.5 times. The degree of disease activity was strongly and significantly associated with the infection risk (severe or moderate versus mild, IRR = 4). Female sex was significantly associated with increased infection risk, while duration of disease and anti-influenza vaccination were protective, the latter even for cutaneous/soft-tissue (mainly herpetic) infections.

Conclusion: The combination anti-TNFα with CS was found to be the most pro-infective treatment, whereas DMARDs alone were relatively safe. Physicians, therefore, should be aware that there may be an increased risk of infection when using anti-TNFα and CS therapy together. Anti-influenza vaccination appears to provide broad protection, adding evidence to support its use in these patients, and deserves further study.

Review

Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs

P.L. Meroni[1], D. Zavaglia[2], C. Girmenia[3]

Clin Exp Rheumatol. 2018; 36: 317-28.

RA & RA olmayanlara

- İnfeksiyon nedeniyle hastaneye yatma/ölüm riski **1.5-2kat yüksek**
- Özellikle **ASYİ, deri-YDİ, ÜSİ**

Drug	SI incidence rate, patients with events per 100 pt-years (N. of trials considered)	Risk ratio/difference of SI *versus* placebo (N. of trials considered)
Abatacept	3.04 (11)	1.18/0.40 (4)
Rituximab	3.72 (8)	0.99/-0.02 (5)
Tocilizumab	5.45 (13)	1.82/1.51 (9)
Infliximab	6.11 (11)	0.83/-0.52 (3)
Etanercept	4.06 (17)	1.00/0 (1)

Clinical Gastroenterology and Hepatology 2016;14:1385–1397

SYSTEMATIC REVIEWS AND META-ANALYSES

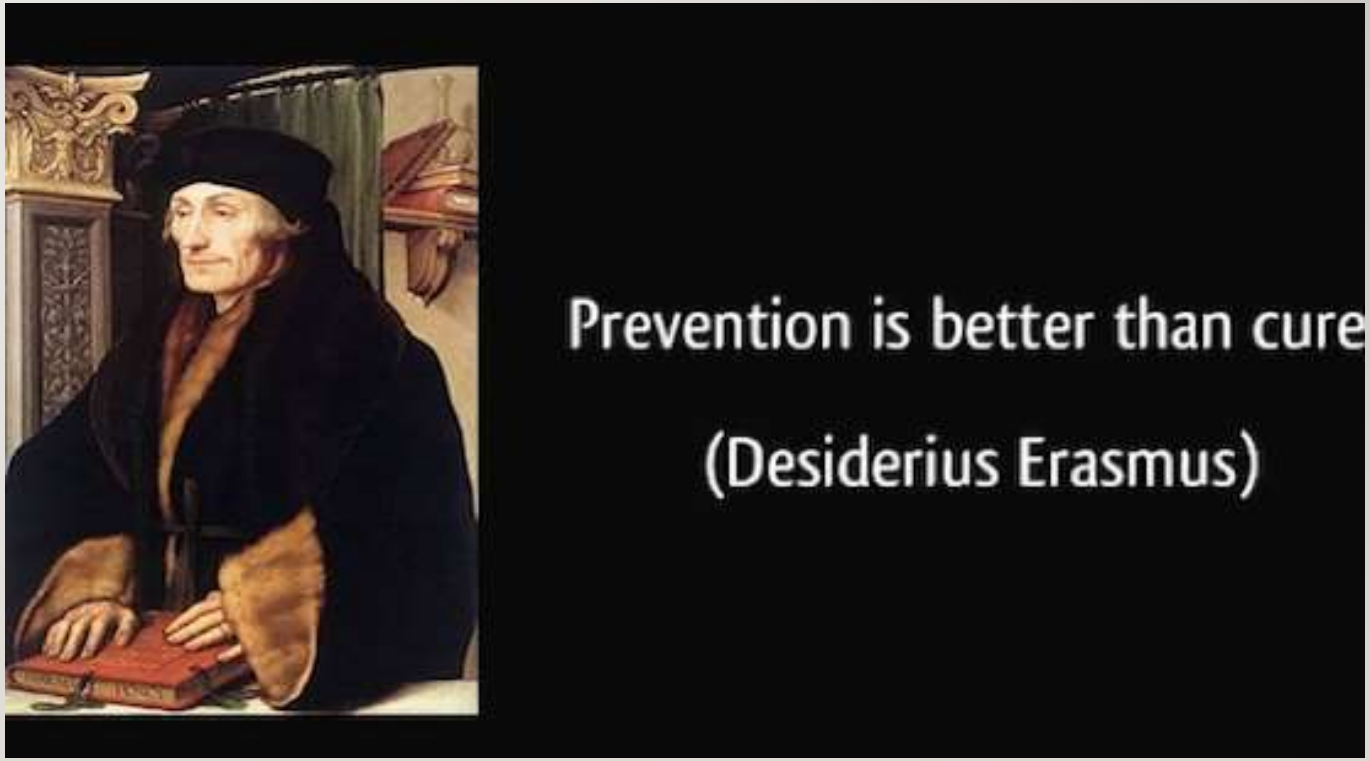
Fasiha Kanwal, Section Editor

Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis

Stefanos Bonovas,* Gionata Fiorino,* Mariangela Allocca,* Theodore Lytras,‡,§,‖ Georgios K. Nikolopoulos,‖ Laurent Peyrin-Biroulet,¶ and Silvio Danese#

- Farklı arama motorları
- Toplam 49 randomize plasebo-kontrollü çalışma
- 14 590 katılımcı
  - ✓ 24 çalışmadan 8832 katılımcı
  - ✓ Fırsatçı infeksiyon tedavi grubu&plasebo => **%1.10 & 0.58**
  - ✓ İnfeksiyon **riski artmış** (OR, 1.90; 95% CI, **1.21–3.01**)

- İnfeksiyon hastalıklarından korunma, ölüm ve sekellerinin azaltılmasında en önemli **iki yöntem**;
  - **Sanitasyon**
  - **İmmünizasyon**



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

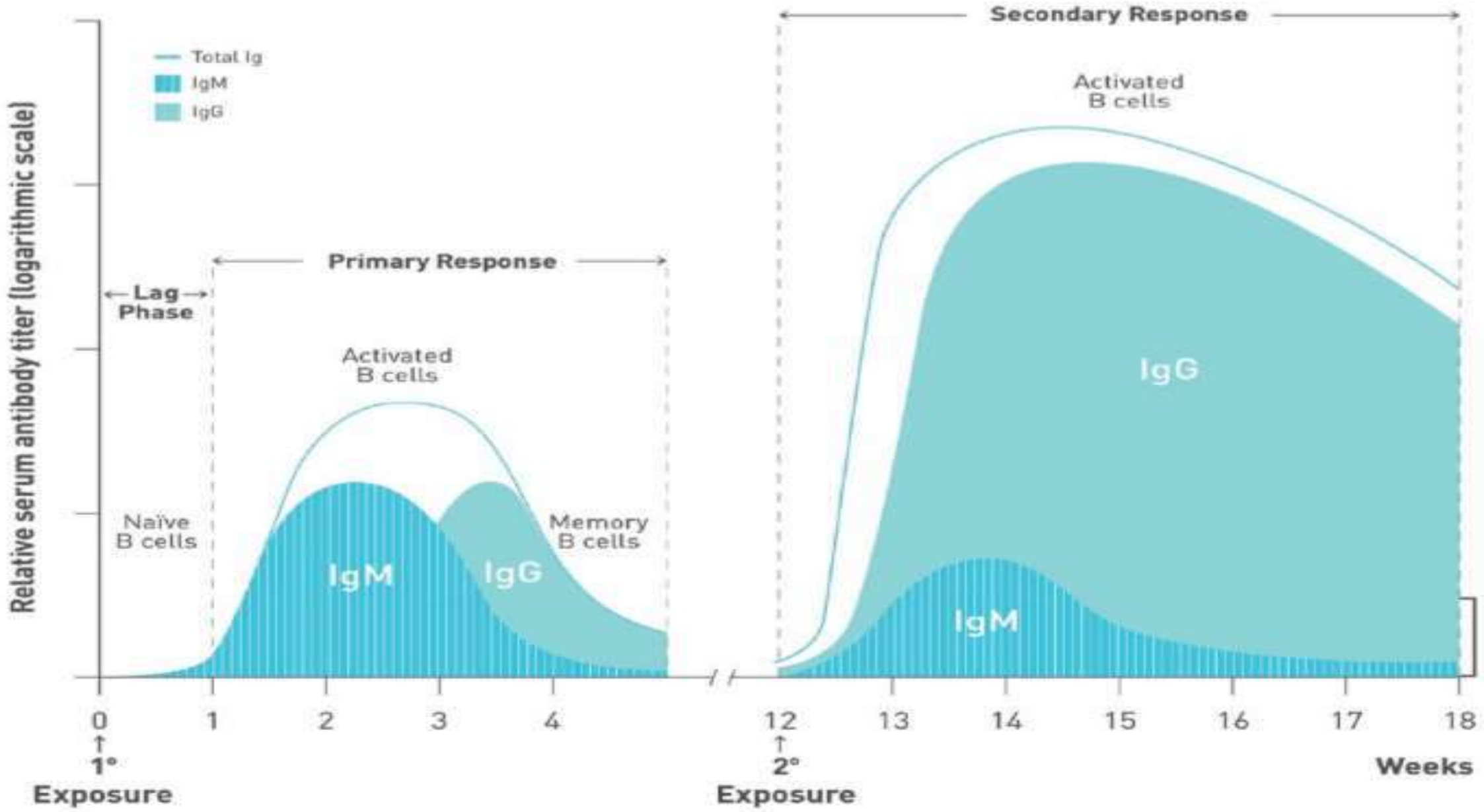
Assala M, et al. *Joint Bone Spine*. 2017; 84:365-6.
Hua C, et al. *Rheumatology (Oxford)*. 2015; 54:748-50.

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

Biyolojik Ajan Kullanımında Aşı Önerileri

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

İmmünizasyonu Takiben Oluşan Antikor Kinetikleri



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

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

Recommendations	Grade of the evidence
The vaccination status should be assessed in the initial work-up of patients with AIIRD	no grade of evidence possible; strength of recommendation D;
Vaccination in patients with AIIRD should ideally be administered during stable disease	no grade of evidence possible; strength of recommendation D
Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD	grade of evidence IV; strength of recommendation D
Vaccination in patients with AIIRD can be administered during the use of disease-modifying anti-rheumatic drugs and tumour necrosis factor α blocking agents but should ideally be administered before starting B cell depleting biological therapy	grade of evidence IIa; strength of recommendation B
Inactivated influenza vaccination should be strongly considered for patients with AIIRD	grade of evidence Ib–III; strength of recommendation B–C
23-valent polysaccharide pneumococcal vaccination (23-PPV) should be strongly considered for patients with AIIRD	grade of evidence Ib–III; strength of recommendation B–C
Patients with AIIRD should receive tetanus toxoid vaccination in accordance to recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulins should be administered	grade of evidence II; strength of recommendation B–D
Herpes zoster vaccination may be considered in patients with AIIRD	grade of evidence III–IV; strength of recommendation C–D
Human papillomavirus vaccination should be considered in selected patients with AIIRD	grade of evidence III; strength of recommendation C–D
In hyposplenic/asplenic patients with AIIRD influenza, pneumococcal, *Haemophilus infl uenzae* b and meningococcal C vaccinations are recommended	grade of evidence IV; strength of recommendation D
Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk	grade of evidence II–III; strength of recommendation B–D
Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD	no grade of evidence; strength of recommendation D
BCG vaccination is not recommended in patients with AIIRD	grade of evidence III; strength of recommendation C–D;

EULAR recommendations. *Ann Rheum Dis* 2011;70:414-22

Table 1. Vaccination scheme in adults with rheumatic diseases

Eur J Rheumatol. 2016; 3: 29-35.

Vaccine	18–64 years	≥65 years
Influenza	1 dose annually	
[1,2]Pneumococcal (polysaccharide/conjugate)	1–2 doses	1–2 doses
[3]Tetanus, diphtheria (Td)	A booster dose of vaccine every 10 years	
Hepatitis B	3 doses (0, 1, and 6 months) [May need to be applied as high-dose vaccine (0, 1, 2, and 6 Months) and double doses of vaccine in high risk patients who are going to receive biological agents or medium to high dose corticosteroids depending on the serological status)	
Hepatitis A	2 doses of vaccine (0 and 6 months)	
[4]Varicella/Herpes zoster	Contraindicated in persons with immunosuppression: can be administered in consultation with a specialist in specific cases	
[4]Measles, mumps, rubella (MMR)	Contraindicated in persons with immunosuppression: can be administered in consultation with a specialist in specific cases	
[2]Meningococcal (quadrivalent conjugate meningococcal vaccine)	2 doses of vaccine at least 2 months apart Can be repeated every 5 years if at continued risk	
[2]Haemophilus influenzae type B	1 dose	
[5]Human papillomavirus (HPV)	2 or 3 doses	

Table 6. Vaccination of Persons With Chronic Inflammatory Diseases on Immunosuppressive Medications

IDSA 2014

Vaccine	Planned Immunosuppression		Low-level Immunosuppression[a]		High-level Immunosuppression[a]	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis A	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis B	U	Strong, moderate	U	Strong, low	U	Strong, low
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U	Strong, low	U	Strong, low
Human papillomavirus	U: 11–26 y	Strong, moderate	U: 11–26 y	Strong, low	U: 11–26 y	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U[b]	Strong, moderate	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–varicella–live	U[b]	Strong, low	X	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Pneumococcal conjugate (PCV13)	R[c]	Strong, moderate	U: <6 y R: ≥6 y[c]	Strong, low strong, very low	U: <6 y R: ≥6 y[c]	Strong, low strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, very low
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Rotavirus–live	U	Strong, moderate	X	Weak, very low	X	Weak, very low
Varicella–live	U[b]	Strong, moderate	X[d]	Weak, very low	X	Strong, moderate
Zoster–live	R: age 50–59 y[e] U: age ≥60 y	Weak, low strong, low	R: age 50–59 y[e] U: age ≥60 y	Weak, very low Strong, very low	X	Weak, very low

IDSA. Vaccination of Immunocompromised Host. *CID*. 2014;58:e44-100

Review

Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs

P.L. Meroni[1], D. Zavaglia[2], C. Girmenia[3]

Clin Exp Rheumatol. 2018; 36: 317-28.

Table III. 2015 recommendations regarding the use of vaccines in patients with rheumatoid arthritis of the American College of Rheumatology (ACR) (7).

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal [1]	Influenza [2]	Hepatitis B [3]	Human papilloma	Herpes zoster
Before initiating therapy					
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended	Recommended [4]
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended	Recommended [4]
While already taking therapy					
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended	Not recommended
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended	Not recommended

Singh JA, *Arthritis Rheumatol.* 2016; 68: 1-26

Vaccination Guidelines for Patients With Immune-Mediated Disorders on Immunosuppressive Therapies

Journal of Cutaneous Medicine and Surgery
2019, Vol. 23(1) 50–74

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1203475418811335
journals.sagepub.com/home/jcms

Canadian Dermatology Association

Association canadienne de dermatologie

CME

Kim A. Papp[1,2], Boulos Haraoui[3], Deepali Kumar[4,5], John K. Marshall[6], Robert Bissonnette[7], Alain Bitton[8], Brian Bressler[9,10], Melinda Gooderham[2,11], Vincent Ho[9], Shahin Jamal[12], Janet E. Pope[13,14], A. Hillary Steinhart[5,15], Donald C. Vinh[8,16], and John Wade[9,17]

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

- ✓ İmmünosüpresif **tedavi alan hastalara uygulanan aşıların etkinliği ve güvenliğiyle ilgili çalışmalar/literatür 2009-2017** yılları arasında araştırılmış.
- ✓ Kurul; Aşı alanında uzman **infeksiyon** HU, **gastroenterolog**, **dermatolog**, **romatolog**

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]

J Cutaneous Med Surg. 2019; 23(1) 50 –74.

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.

Singh *et al. Arthritis Care & Research*, 2015

Aşılar Ne Zaman Verilmeli?

- ✓ Mümkünse aşılar planlanan immünosüpresif ilaçla
- ✓ **İnaktive** aşılar immünosüpresif **tedaviden ≥2 h**
- ✓ **Canlı aşılar** immünosüpresif **tedaviden ≥4 ha**

  tedavi başlandıktan **sonra ilk iki hafta** içinde **verilm** (Güçlü-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(1) 50 –74.

Singh *et al. Arthritis Care & Research*, 2015

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]

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

Genel Yaklaşım

- İmmünosüpresif tedavi alanlarda **canlı virus aşıları yapılmaz**
- Tüm hastalarda **suçiçeği** immünite durumu belirlenmeli
- En az bir ay önce uygulanmalı
- Özel durumlar hariç
- Düşük düzey immünosüpresyonda yapılabilir (zayıf öneri)

**KKK, varisella ve Herpes zoster aşıları istisna/ Hasta temelli!

Düşük düzey immünosüpresyon

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

Ev halkı aşılaması

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

Vaccination of Immunocompromised Host. *CID* 2014:58

Aşılar Ne Zaman Verilmeli?

- ✓ Mümkünse aşılar planlanan immünosüpresif ilaçlardan **önce** başlanmalı
- ✓ **İnaktive** aşılar immünosüpresif **tedaviden ≥2 hafta önce** başlanmalı
- ✓ **Canlı** aşılar immünosüpresif **tedaviden ≥4 hafta önce** başlanmalı ve tedavi başlandıktan **sonra ilk iki hafta** içinde **verilmemeli**
- ✓ Acil tedavi gerekiyorsa, tedaviyi **engellememeli!**

- ❖ In patients with immune-mediated diseases treated with **rituximab** who require optimal vaccine immunogenicity, we recommend that **immunization be deferred to ⩾5 months after** the **last dose** and **at least 4 weeks prior** to the subsequent dose of **rituximab**.
- ✓ GRADE: Strong recommendation; low-level evidence
- ✓ Vote: 14.3% strongly agree, **78.6% agree**, 7.1% disagree

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

Singh *et al. Arthritis Care & Research*, 2015

Aşılar İmmünosüpresif Tedaviden Sonra Ne Zaman Uygulanmalı

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]

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

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.

Joint Bone Spine. 2016; 83:135-41

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
Treatm

Vacci												Rituximab	Belimumab
Live attenuated vaccines	Stop	2 to 12 weeks	10 to 12 weeks	8 to 12 weeks	10 to 12 weeks	6 to 12 weeks	10 to 12 weeks	10 to 12 weeks	12 to 15[a] weeks	2 days to 3 months	3 months	6 months	3 months
	Re-start	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	2 weeks[a]	3 weeks	3 weeks	1 month	1 month
Inactivated vaccines	Stop	No treatment interruption										6 months[b]	6 months[b]
	Re-start											1 month	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.

Joint Bone Spine. 2016; 83:135-41

Aşı-Otoimmünite İlişkisi?

- ✓ Otoimmün hastalıklarda **grip** aşısına hastalıkta geçici alevlenme (olgu raporları)
- ✓ Prospektif çalışmalarda **neden-sonuç** ilişkisi **gösterilememiş**
- ✓ SLE ve RA'li hastalarda infeksiyondan daha fazla aktiviteye **yol açmaz**.

✓ **HBV** aşısı SLE ve RA'li hastalarda hastalık aktivitesi üzerinde **etkisi yok**

✓ **Pnömokok** aşısının etkisi yok

✓ KKK aşısı jüvenil idiopatik artritli hastalarda klinik veya laboratuvar olarak ölçülen bir kötüleşmeye yol açmamış

Liao Z, et al. 2016. *PLoS ONE* 11: e014785

Low rate of influenza and pneumococcal vaccine coverage in rheumatoid arthritis: Data from the international COMORA cohort

Ihsane Hmamouchi[a,b,*], Kevin Winthrop[c], Odile Launay[d], Maxime Dougados[a]

[a] Paris Descartes University, APHP Cochin Hospital, Rheumatology Department, Paris, France
[b] Mohammed V University, Faculty of Medicine, Laboratory of Biostatistics, Clinical Research and Epidemiology, El Ayachi Hospital, Rheumatology Department, Rabat, Morocco
[c] Division of Infectious Diseases, Public Health and Preventive Medicine, Oregon Health and Science University, Portland, OR, USA
[d] Paris Descartes University, AP-HP Cochin Hospital, CIC Cochin Pasteur, Inserm, CIC 1417, Paris, France

Background: Rheumatoid Arthritis (RA) patients are at increased risk of suffering from respiratory infections than the general public. Vaccinations against *Streptococcus pneumococcus* and influenza are recommended, but not often used in RA. Our objectives were: (1) to describe pneumococcal and influenza vaccine coverage in RA patients across various countries and (2) to identify factors associated with their usage.

Methods: Using data from the COMORA cohort, 3920 RA patients were enrolled across 17 countries. We collected patient demographic and disease characteristics, and reported vaccine use over a six month time period. We used logistic regression to evaluate factors related to pneumococcal and influenza vaccine coverage.

Results: Overall vaccination coverage within the recommendations was low with huge disparities between countries: 17.2% (95%CI: 16.0–18.4) for pneumococcal vaccination (from 0% in Morocco to 56.5% in France) and 25.3% (95%CI: 23.8–26.5) for influenza vaccination (less than 1% in Morocco and Egypt to 66.2% in Japan). In countries where immunization was more frequent, we found that predictive factors of vaccination were older age, lower disease activity, higher educational level, use of biotherapy, absence of corticosteroid therapy, and presence of comorbidities.

ABD'de RA'li hastaların %28,5'u pnömokok aşısı, %45,8'i grip aşısı yaptırmakta. Yaş, eğitim seviyesi, eşlik eden hastalıklar, biyolojik ajan kullanımı , hastalık aktivitesi, aşılamayı etkileyen faktörler,.

Vaccine 33 (2015) 1446–1452

Alten et al. BMC Musculoskeletal Disorders (2016) 17:231
DOI 10.1186/s12891-016-1082-z

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept

Rieke Alten[1,7*], Clifton O. Bingham III[2], Stanley B. Cohen[3], Jeffrey R. Curtis[4], Sheila Kelly[5], Dennis Wong[5] and Mark C. Genovese[6]

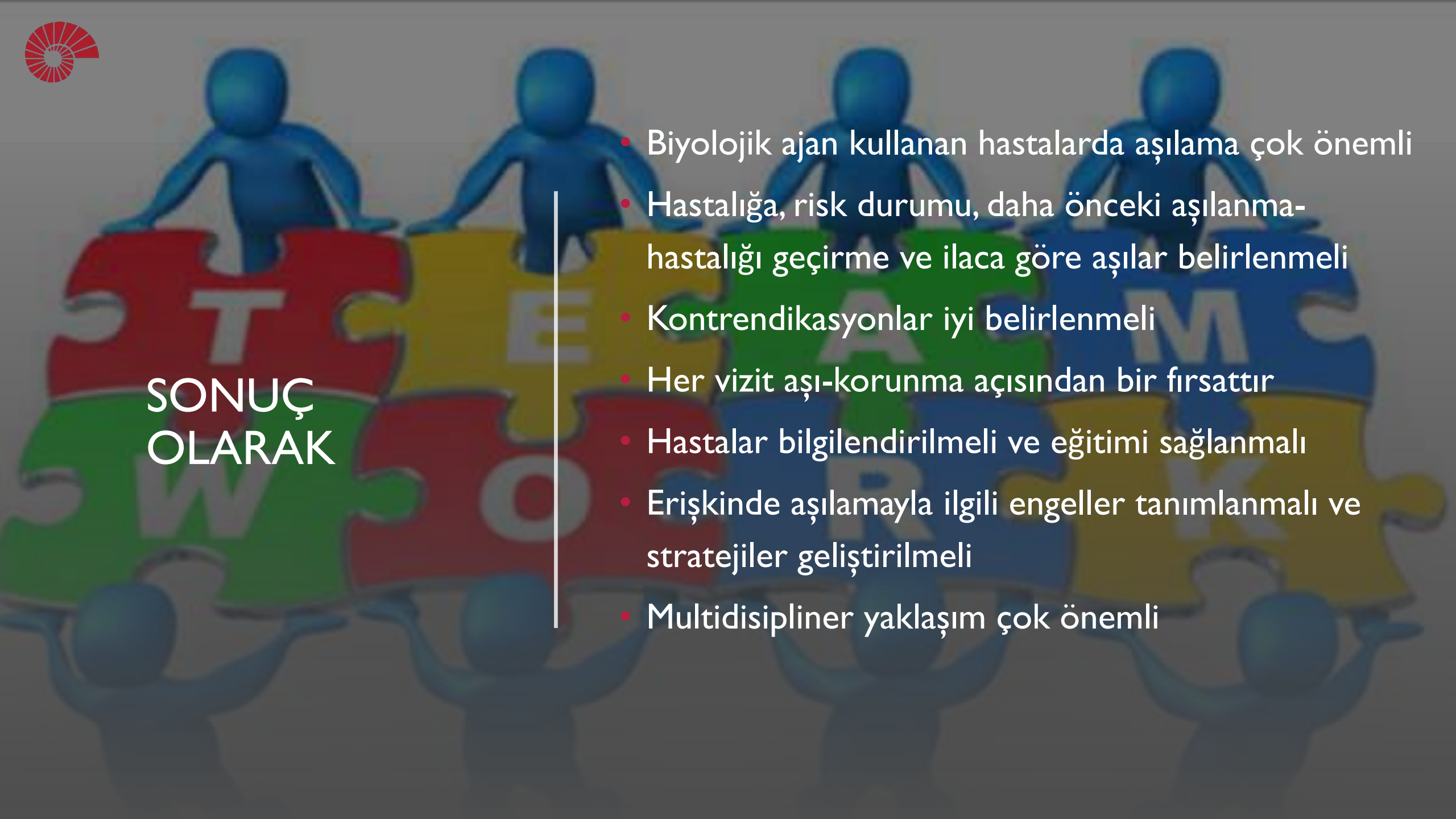
Methods: Two multicenter, open-label sub-studies enrolled patients from the ACQUIRE (pneumococcal and influenza) and ATTUNE (pneumococcal) studies at any point during their SC abatacept treatment cycle following completion of ≥3 months' SC abatacept. All patients received fixed-dose abatacept 125 mg/week with background DMARDs. A pre-vaccination blood sample was taken, and after 28 ± 3 days a final post-vaccination sample was collected. The primary endpoint was the proportion of patients achieving an immunologic response to the vaccine at Day 28 among patients without a protective antibody level to the vaccine antigens at baseline (pneumococcal: defined as ≥2-fold increase in post-vaccination titers to ≥3 of 5 antigens and protective antibody level of ≥1.6 μg/mL to ≥3 of 5 antigens; influenza: defined as ≥4-fold increase in post-vaccination titers to ≥2 of 3 antigens and protective antibody level of ≥1:40 to ≥2 of 3 antigens). Safety and tolerability were evaluated throughout the sub-studies.

Results: Pre- and post-vaccination titers were available for 113/125 and 186/191 enrolled patients receiving the PPSV23 and influenza vaccine, respectively. Among vaccinated patients, 47/113 pneumococcal and 121/186 influenza patients were without protective antibody levels at baseline. Among patients with available data, 73.9 % (34/46) and 61.3 % (73/119) met the primary endpoint and achieved an immunologic response to PPSV23 or influenza vaccine, respectively. In patients with pre- and post-vaccination data available, 83.9 % in the pneumococcal study demonstrated protective antibody levels with PPSV23 (titer ≥1.6 μg/mL to ≥3 of 5 antigens), and 81.2 % in the influenza study achieved protective antibody levels (titer ≥1:40 to ≥2 of 3 antigens) at Day 28 post-vaccination. Vaccines were well tolerated with SC abatacept with background DMARDs.

Conclusions: In these sub-studies, patient
able to mount an appropriate immune re

Trial registration: NCT00559585 (register

Abatacept alan hastaların çoğunluğunda pnömokok (%89) ve grip aşısı (%81) ile primer ya da pekiştirme dozu olarak yeterli yanıt elde edilmiş.
Her iki aşı da güvenli bulunmuş.
Tedaviden önce aşı yapılması tercih edilmeli



SONUÇ OLARAK

- Biyolojik ajan kullanan hastalarda aşılama çok önemli
- Hastalığa, risk durumu, daha önceki aşılanma-hastalığı geçirme ve ilaca göre aşılar belirlenmeli
- Kontrendikasyonlar iyi belirlenmeli
- Her vizit aşı-korunma açısından bir fırsattır
- Hastalar bilgilendirilmeli ve eğitimi sağlanmalı
- Erişkinde aşılamayla ilgili engeller tanımlanmalı ve stratejiler geliştirilmeli
- Multidisipliner yaklaşım çok önemli

İnsanlığın sebep olduğu doğal veya kültürel atıklara son!!!!

Sağlıklı çevre sağlıklı yaşam