Olgularla Romatolojide Aşılama Yönetimi

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EBÇG

Romatolojik Hastalıklar

İnflamatuar romatolojik hastalıklar

Dejeneratif eklem hastalıkları

Romatolojik sorunla birlikte olan metabolik ve endokrin hastalıklar

Eklem dışı hastalıklar

İnfeksiyöz etkenlerle ilişkili romatolojik sendromlar

Kemik, kıkırdak hastalıkları

Diğer

Romatolojik hastalıklarda infeksiyon hastalıkları riski artar:

Romatoloji Hastalarında

- Aşı ile önlenebilir hastalıklarda artış
- Daha ağır seyir

Romatoloji Hastalarında

- İnfeksiyon hastalığı
- İnfeksiyon hastalığına bağlı olarak ilaçların azaltılması, kesilmesi

- Hastalığın aktivasyonuna yol açabilir

Romatolojik Hastalıklarda Aşı Önerileri

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

Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

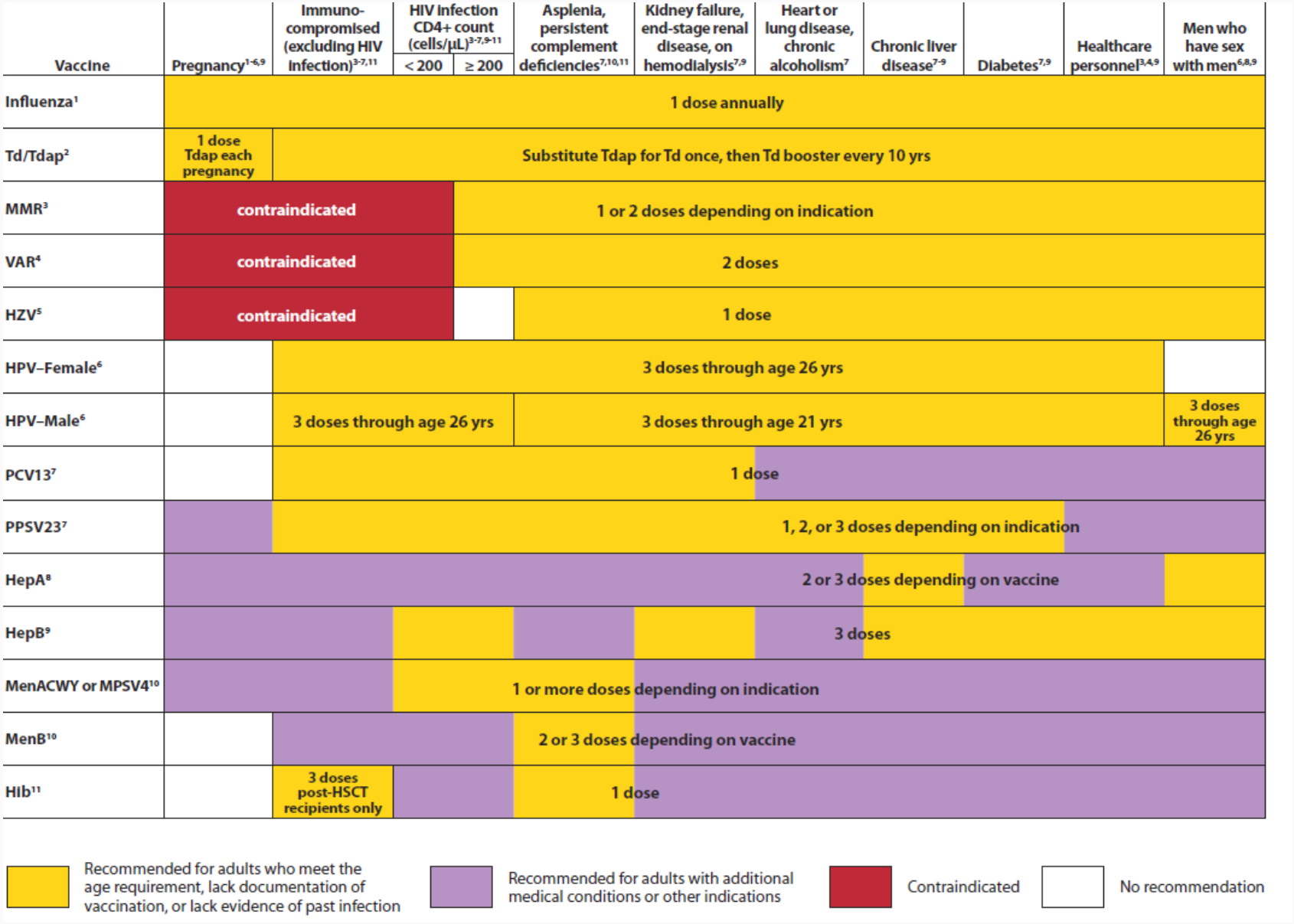
Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza[1]	1 dose annually				
Td/Tdap[2]	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR[3]	1 or 2 doses depending on indication				
VAR[4]	2 doses				
HZV[5]				1 dose	
HPV–Female[6]	3 doses				
HPV–Male[6]	3 doses				
PCV13[7]	1 dose				
PPSV23[7]	1 or 2 doses depending on indication				1 dose
HepA[8]	2 or 3 doses depending on vaccine				
HepB[9]	3 doses				
MenACWY or MPSV4[10]	1 or more doses depending on indication				
MenB[10]	2 or 3 doses depending on vaccine				
Hib[11]	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with additional medical conditions or other indications

No recommendation



Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017

Romatoloji Hastalarında Kullanılan İmmunosupresif Ajanlar

- Glukokortikoidler
- Hastalığı modifiye edici anti-romatolojik ajanlar
  - methotreksat, leflunomid, azathioprin, siklosporin, siklofosfamid, mikofenolat
- Hastalığı modifiye edici biyolojik ajanlar

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 Germano[1†], Maria Sofia Cattaruzza[2†], John Osborn[2], Aurora Tarantino[1,3], Roberta Di Rosa[1], Simonetta Salemi[1] and Raffaele D'Amelio[1*]

Results: Three hundred and thirtyone infections [318 (96.1%) non-serious and 13 (3.9%) serious] have been registered among 176 of the 341 patients (52%). The IR/100 patient-years of all infections was 36.3 ranging from 12.4 (DMARDs + CS) to 62.7 (anti-TNFα + CS). The most frequent infection site was respiratory 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.

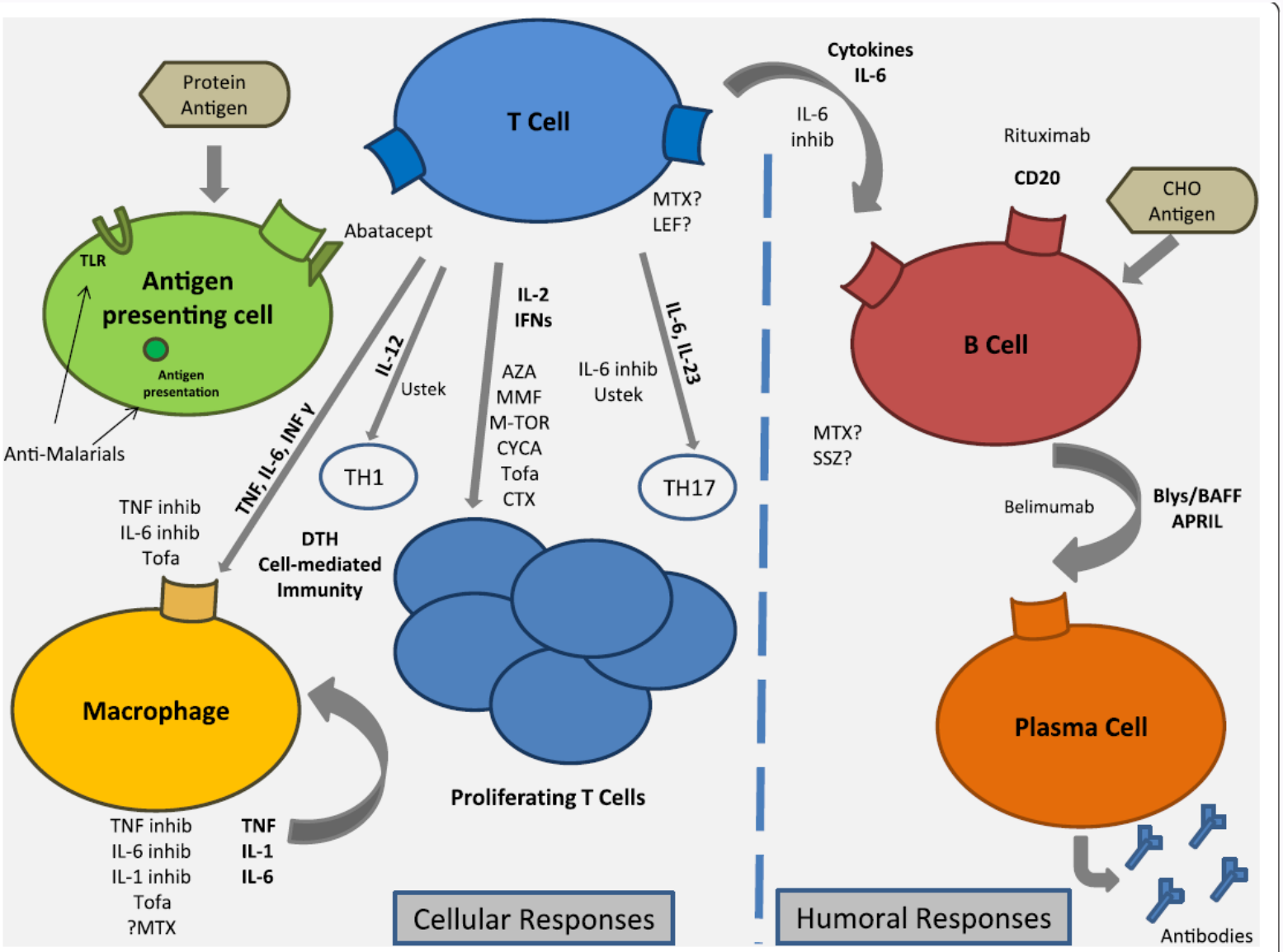
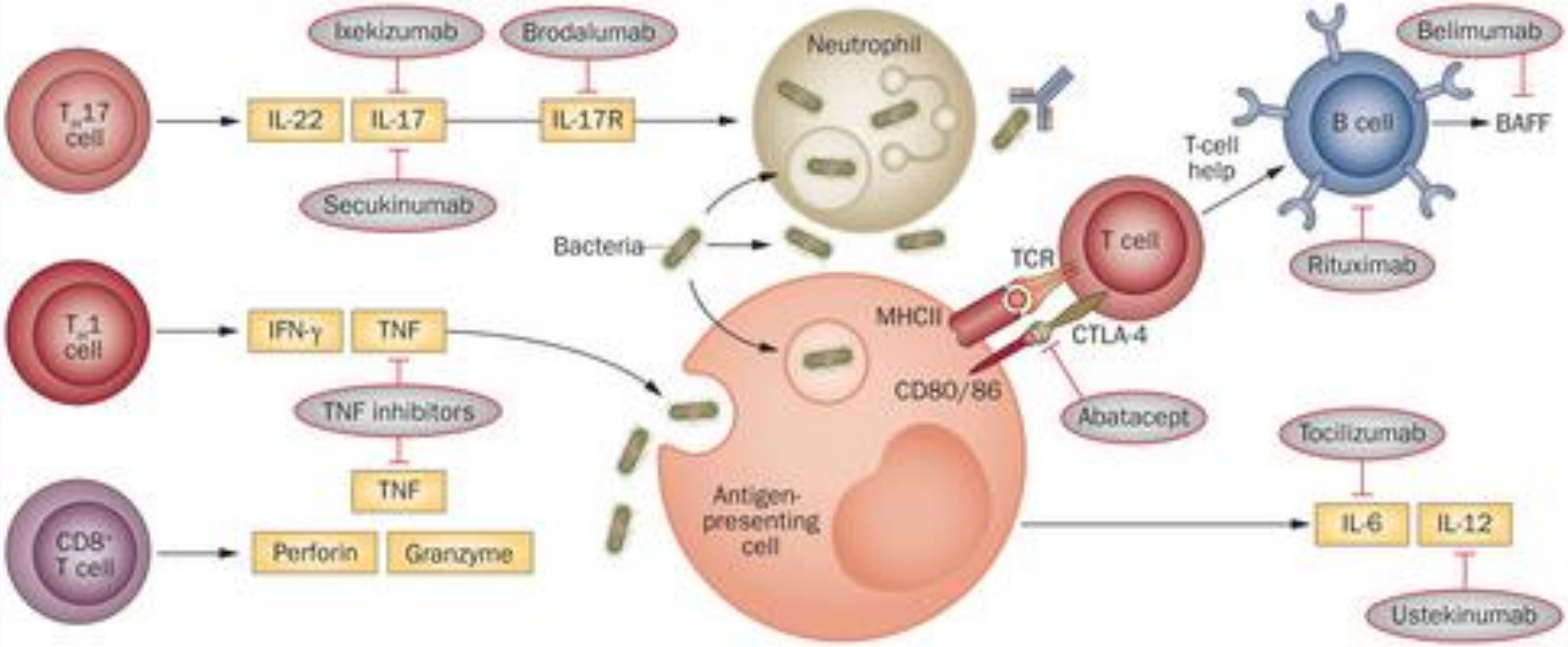


Figure 1 Immunomodulatory therapies. AZA, azathioprine; BAFF, B-cell activating factor; Blys, B lymphocyte stimulator; CHO, carbohydrate; CTX, cyclophosphamide; CYCA, cyclosporine A; DTH, delayed type hypersensitivity; INF, interferon; inhib, inhibitor; LEF, leflunomide; MMF, mycophenolate mofetil; M-TOR, mammalian target of rapamycin; MTX, methotrexate; SSZ, sulfasalazine; TLR, toll-like receptor; Tofa, tofacitinib; Ustek, ustekinumab.

Biyolojik Ajanların Etki Mekanizmaları



NATURE REVIEWS | RHEUMATOLOGY,2014

Olgu-1

- 53 yaşında, K, Romatoid artrit tanısı var (5 yıl)
- Rituksimab tedavisi önerilmiş
- Tedavi öncesi kontrol için gelmiş

- Hangi testler?
- Hangi aşılar?
- Ne zaman tedavi alabilir?

Romatolojik Hastalarda Aşı Önerileri-Başlangıç

- Her bir vizit aşılama için bir fırsat
- Aşı öyküsü alınmalı
- Aşı kaydı yoksa öykü güvenilir değilse serolojik testler yapılmalı
- Aşılama immunosupresif veya biyolojik ajanlar başlanmadan önce yapılmalı

Hangi Aşılar?

- İnfluenza
- Td/Tdap
- MMR
- Suçiçeği-zoster
- HPV (yaşa göre)
- Pnömokok
- Riske göre diğer aşılar

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

	Planned Immunosuppression		Low-level Immunosuppression[a]		High-level Immunosuppression[a]	
Vaccine	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

Table 1. Vaccination scheme in adults with rheumatic diseases

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	

Individuals who do not have immunity and contraindications

Individuals who have risk factors and don't have contraindications

[1]It is recommended to comply with the schedule for the polysaccharide and conjugate pneumococcal vaccines (recommendations with regards to risk groups are summarized in Table 2).

[2]In cases of asplenia (including elective splenectomy and persistent complement deficiencies).

[3]Scheme in persons who have completed the primary immunization for tetanus vaccine.

Tanrıover M, et al.

Eur J Rheumatol 2016; 3: 29-35

Aşılar Ne Zaman Verilmeli

Mümkünse aşılar planlanan immunosupresif ilaçlardan önce başlanmalı (güçlü-orta öneri).

Canlı aşılar immunsupresif tedaviden ≥4 hafta önce başlanmalı ve tedavi başlandıktan sonra ilk iki hafta içinde verilmemeli (güçlü-düşük öneri)

İnaktive aşılar immunospresif tedaviden ≥2 hafta önce başlanmalı (güçlü-orta öneri)

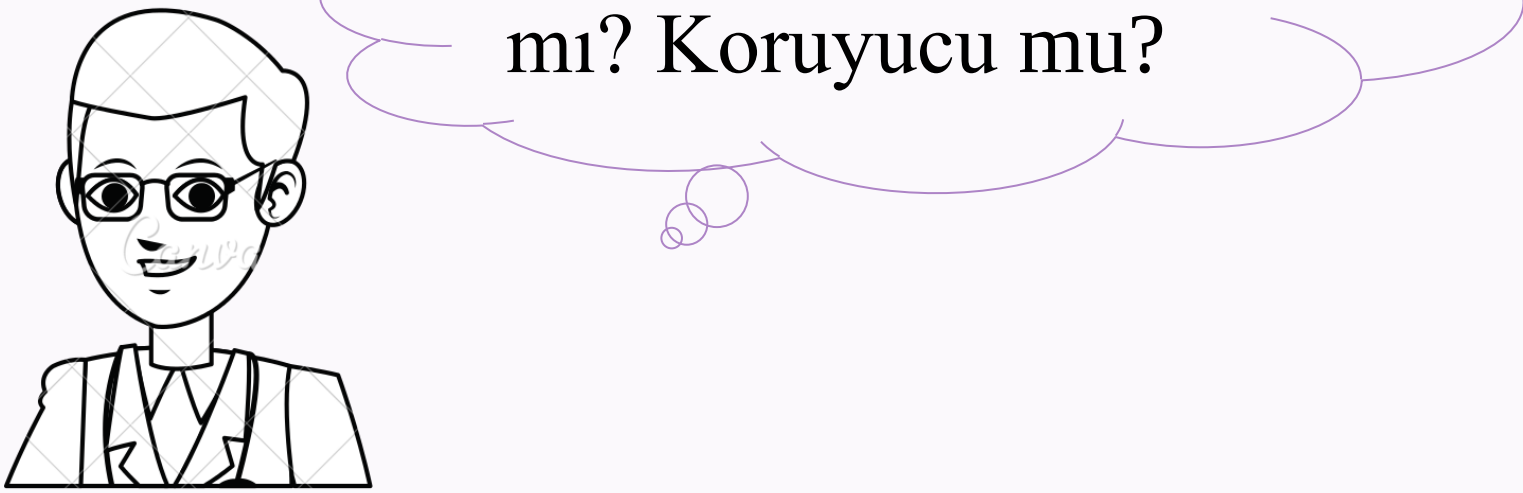
Acil tedavi gerekiyorsa, tedaviyi engellememeli!

Singh et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research,2015

Olgu 2- Ekim ayı

https://turkagram.com/profil/emelak

- 63 Y, K, doktor annesi
- Romatoid artrit tanısı 15 yıldır
- Son altı aydır abatacept kullanıyor



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

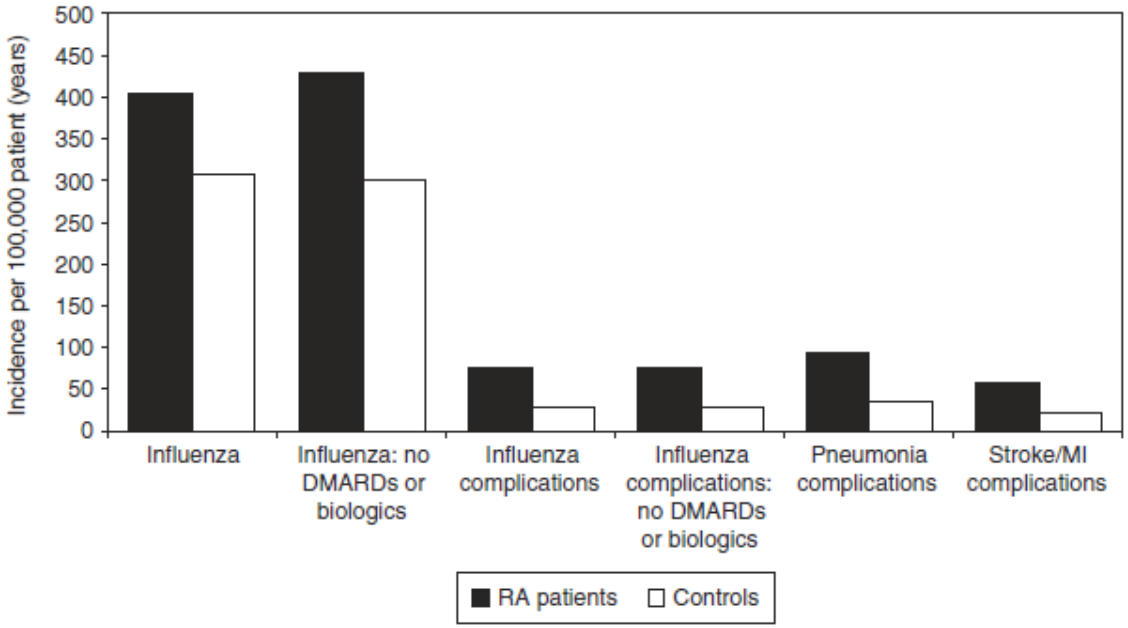


Figure 1 Incidence of influenza and complications in RA patients and controls recruited from the MarketScan database.

Blumentals *et al. BMC Musculoskeletal Disorders* 2012, **13**:158
http://www.biomedcentral.com/1471-2474/13/158

Table 1
Excerpt from the tabulated specific immunization recommendations for adults treated with immunosuppressants, glucocorticoids, and/or biotherapies.

	Contraindicated vaccines: live attenuated vaccines	Strongly recommended vaccines	Inactivated vaccines recommended in the general population
Patients with autoimmune disease treated with glucocorticoids and/or immunosuppressants and/or biotherapies	BCG Yellow fever Influenza (nasal attenuated) MMR Varicella/herpes zoster[a]	Seasonal influenza (inactivated vaccine) Pneumococcus	Diphtheria, tetanus, polio, and pertussis Hepatitis B Meningococcus Papillomavirus

[a] According to US recommendations (Advisory Committee on Immunization Practices), the live attenuated vaccine against varicella and herpes zoster can be given during treatment with methotrexate (dosage $\leq$ 0.4 mg/kg/week) or azathioprine ($\leq$ 3.0 mg/kg/day).

ACR RA Treatment Recommendations

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	*✓(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	*✓(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

Singh et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research,2015

İmmunomodülatör Tedavilerde Aşı Etkinliği

Table 3 Summary of data for vaccine efficacy and safety with immunomodulatory therapies

Drug	Protein vaccines	Carbohydrate vaccines	DTH/cellular immunity	Neoantigen	Live virus
Non-biologic immunomodulators					
Corticosteroids	--/↓	--	ND	ND	Zoster OK with CCS <20 mg/day
Methotrexate	↓↓	↓	--	--	Zoster OK with MTX <0.4 mg/kg/week
Anti-malarials	--	--	ND	ND	Probably safe, possible ↓ response
Sulfasalazine	--/↓	ND	ND	ND	Probably safe, not formally studied
Leflunomide	--	ND	ND	ND	ND
Azathioprine	--	--/↓	ND	ND	Zoster OK <3 mg/kg/day
Mycophenolate	↓↓	↓↓	↓	↓	Avoid
Calcineurin Inhibitors	--/↓	ND	↓	ND	Avoid
Biologicals and targeted immunomodulators					
TNF inhibitors	--/↓	--/↓	--	ND	Avoid
Abatacept (CTLA4-Ig)	↓	↓	ND	↓	Avoid
Rituximab (anti-CD20)	--/↓	↓↓	↓	↓↓	Avoid
Tocilizumab (anti-IL6)	--	--	ND	ND	Avoid
Ustekinumab (anti-IL-12/23)	--	--	ND	ND	Avoid
IL-1 inhibitors (anakinra, Rilonacept, canakinumab)	ND	ND	ND	ND	Avoid
Belimumab (anti-BLyS)	ND	ND	ND	ND	Avoid
Tofacitinib (Jak1/3)	--/↓	↓	ND	ND	Avoid

↓ decreased, ↓↓ markedly decreased, -- no effect. BLyS, B lymphocyte stimulator; CCS, corticosteroids; DTH, delayed type hypersensitivity; MTX, methotrexate; ND, not determined; TNF, tumor necrosis factor.

McMahan and Bingham III *Arthritis Research & Therapy* 2014, **16**:506

Romatoid Artrit Tedavilerinin Aşı Yanıtına Etkileri ve Aşı Endikasyonları

	MTX	TNF inhibitors	Rituximab	Abatacept	Tofacitinib	Tocilizumab	Indications
Influenza	±	OK	↓↓	↓[b]	OK	OK	All patients regardless of immunosuppression, ideally before biologics or MTX, yearly
Pneumococcus*	↓	OK	↓↓	↓	↓	OK	All patients regardless of immunosuppression, ideally before biologics or MTX
Hepatitis B	?	↓	?	?	?	?	All at-risk patients regardless of immunosuppression
Human papilloma virus	?	?	?	?	?	?	All patients age ≤26, regardless of immunosuppression
Herpes zoster	?	?	?	?	?	?	All patients ≥50 not on biologics or high-dose corticosteroids. Should be given ≥2 weeks before starting biologics or ≥4 weeks after stopping biologics
Yellow fever	?	?	?	?	?	?	Contraindicated for patients using immunosuppressives

İmmunosupresif tedaviden bağımsız olarak tüm RA hastaları **yıllık grip aşısı** olmalı

Friedman and Winthrop. Curr Opin Rheumatol 2016, 28:330–336

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 res

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

Olgu 3- Poliklinik

- 38 Y, K, evli, iki çocuklu
- Eşine kronik HBV infeksiyonu tanısı konulmuş
- Tarama testleri istendi
  - ✓HBsAg negatif
  - ✓Anti-HBs negatif
  - ✓Anti-HBc-total negatif
  - ✓Hepatit B aşısı önerisi

Olgu-3

- SLE tanısı var.
- Hidroksiklorokin alıyor

Hepatit B aşısı hastalığını alevlendirir mi?

Aşı-Otoimmünite İlişkisi?

Otoimmün hastalıklarda grip aşısına hastalıkta geçici alevlenme bazı olgu raporlarında var.

Prospektif çalışmalarda neden-sonuç ilişkisi gösterilememiş

Olursa da hafif

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

MMR aşısı jüvenil idiopatik artritli hastalarda klinik veya laboratuar olarak ölçülen bir kötüleşmeye yol açmamış

Multipl sklerozlu hastalarda sarı humma aşısı ile az sayıda hastada relaps rapor edilmiş.

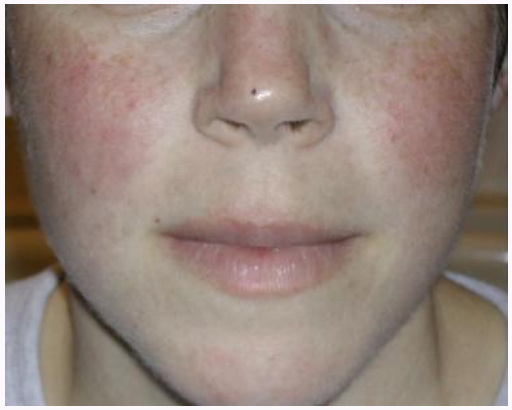
Liao Z, et al.(2016. PLoS ONE 11(2): e0147856

Hepatit B Aşısı Önerisi

- Tüm immunosupresif tedavi alacak hastalar HBV infeksiyonu, HCV infeksiyonu yönünden taranmalı
- Risk grubunda olan tüm hastalara hepatit B aşısı yapılmalı.

Mori S, Fujiyama S. Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. World J Gastroenterol 2015; 21:10274–10289.

Olgu-4: Konsültasyon



- 28 Y, K, ev hanımı, iki çocuğu var
- Yeğenine suçiçeği tanısı konulmuş
  - İki gün önce misafir gelmiş

- SLE hastalığı var
- İmuran(5 mg/kg) + düşük doz steroid kullanıyor

Olgu-4

- VZV IgG antikorları negatif
- Yakın temaslılara aşı uygulanmış

- Profilaksi?

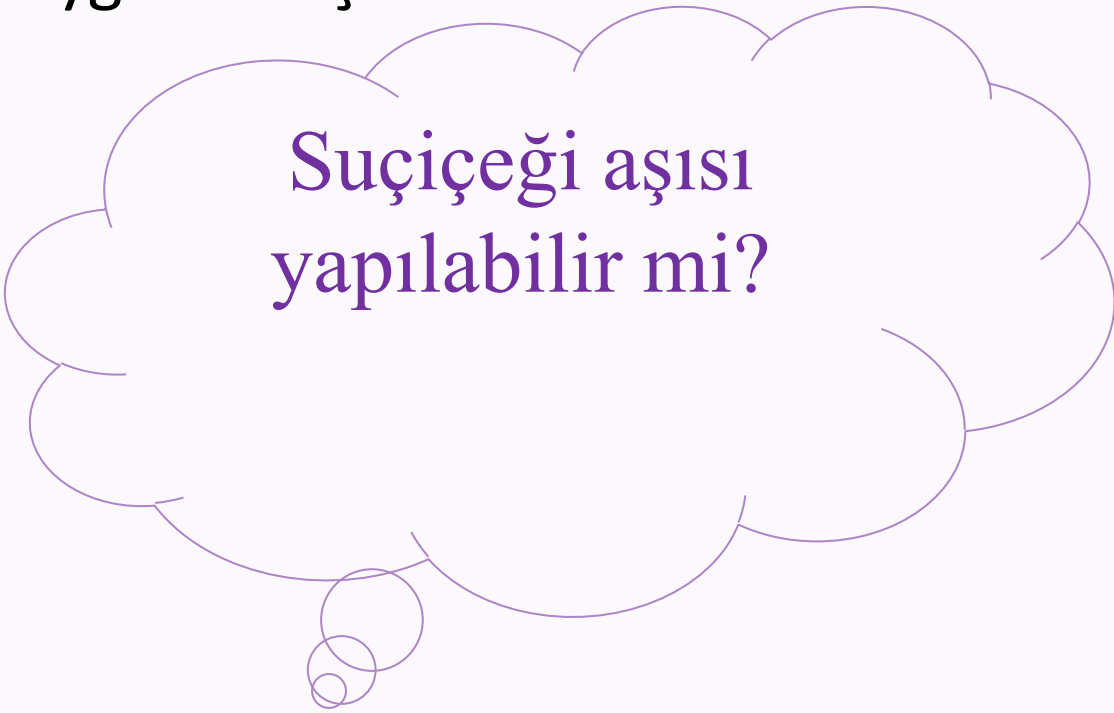


Table 1. Isolated case reports of varicella with pulmonary involvement in IBD patients.

Author, year	Age/sex	IBD	Therapy	Presentation	Pulmonary Xray/CT scan	Therapy	Evolution	Outcome
Deutsh, 1995	15/M	CD	6-MP [6 weeks after stopping prednisolone]	3 day of symptoms, rhinorrhoea, dry cough, wheezing, cutaneous rash, progressive respiratory distress	Diffuse interstitial infiltrates	Acyclovir intravenous	Intensive care, mechanical ventilation on D3	Died D27 of admission. Autopsy: ARDS and DIC
Vergara, 2001	27/M	CD	Azathioprine	Fever 40°C, cutaneous disseminated rash, hypoxaemia, renal and hepatic insufficiency	Diffuse interstitial infiltrate	Acyclovir intravenous	Intensive care admission, multi-organ dysfunction	Died in a few hours
Bernal, 2003	40/F	CD	Azathioprine	Fever 38°C, rash	Diffuse interstitial infiltrate	Acyclovir intravenous, 14 days	Favourable	Normal Xray at week 6, resumed azathioprine
Lemyze, 2003	18/F	CD	Azathioprine [for 9 months]	3 day of symptoms, thoraco-abdominal pain, fever [40°C], cutaneous disseminated rash, dyspnoea, no cough	Diffuse interstitial infiltrate. CT scan: micronodular opacities	Acyclovir intravenous, 10 days	Favourable	Recovered
Leung, 2004	26/M	CD	6-MP + infliximab [9 days after first dose], prednisolone	Fever 38.4°C, chills, nausea, vomiting, abdominal pain, rash	Unknown	Acyclovir intravenous on D2	Respiratory failure on the subsequent days; intubation, mechanical ventilation; hepatic, cardiac, renal failure; DIC	Died D4
Tougeron, 2006	33/M	CD	Azathioprine, infliximab, prednisolone 10 mg/day	2 day of symptoms, thoraco-abdominal pain, fever [38.2°C], cutaneous disseminated rash, hepatitis	Interstitial infiltrate on medium lobe, then diffuse	Acyclovir intravenous, 10 days	Hepatitis, severe cytolysis; dyspnoea and hypoxaemia D2 after admission; favourable after that	Recovered
Springfeld, 2009	25/M	CD	Azathioprine	3 days of symptoms, rash on the back, trunk, and arms, abdominal pain, hepatitis	Unknown	D1: prednisolone 75 mg/day, D2: imipnem, D3:acyclovir intravenous, D5: added foscarnet	Fulminant hepatitis, disseminated rash; dyspnoea; intensive care admission; D3 mechanically ventilated; D5 shock, severe ARDS	Died D6 [multi-organ failure: liver, lung, renal]
Monaghan, 2010	65/M	CD	Azathioprine [1 week of treatment], prednisolone 35 mg/day	Fever, headache, shortness of breath, nausea, vomiting, abdominal discomfort, hypotension, tachypnoea, vesiculopustular rash on forehead and trunk	Unknown	Antibiotics, antifungals, acyclovir, activated protein C, steroids	Hepatic failure and shock; intensive care admission; D3 mechanical ventilation	Recovered
Wuber, 2010	?	?	Infliximab	Pneumonia				Died

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Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients

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Results: We have identified 217 patients with IBD under infliximab who were vaccinated for hepatitis B, 172 (79%) with Crohn's Disease and the remaining with ulcerative colitis; 114 patients (53%) were male and mean age was 33 ± 11 years. Overall, HBV vaccine was successful in 164 (76%) patients. Only 14 patients were vaccinated after infliximab was initiated, and only two of them had antibody levels above 10 IU/L. Among the patients that received vaccination before the beginning of infliximab, 88% of those who were vaccinated before starting azathioprine developed antibodies in contrast to 55% who already were under azathioprine. In multivariable analysis, treatment with infliximab (adjusted OR [95% CI]: 17.642 [8.514–33.937]) and with azathioprine (adjusted OR [95% CI]: 3.344 [1.653–9.145]) were the only factors associated with weaker response to HBV vaccination.

Conclusion: The response rate to the standard HBV vaccination in IBD patients is low mainly in those treated with infliximab and/or azathioprine.

Genel Yaklaşım

- İmmunosupresif tedavi alanlarda ya da immunosupresyonda canlı virüs aşıları yapılmaz
- Tüm hastalarda suçiçeği immünite durumu belirlenmeli
- En az bir ay önce uygulanmalı
  - Özel durumlar hariç
- Düşük düzey immunosupresyonda yapılabilir (zayıf öneri)

Immunization of patients with autoimmune inflammatory rheumatic diseases

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Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016; 68:1–26.

Düşük düzey immunosupresyon

- 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

Vaccination of Immunocompromised Host. CID 2014:58 .

Pileggi GS, de Souza CB, Ferriani VP: Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken) 2010, 62:1034–1039.

Ev halkı aşılaması

- Risk azaltılması için önemli
    - Oral polio aşısı
    - Canlı grip aşısı önerilmez
- Rotavirüs aşısı olan bebeklerin bezlerini değiştirmemeli (4 hafta)

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	
	Resumption	2 to 4 weeks	2 to 4 weeks	2 to 4 weeks	2 to 4 weeks	interval	
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.

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Biyolojik Ajanlarla Tedavi Sonrası Aşılama

Table 3
Treatment-free intervals before and after vaccine administration in patients treated with biological agents, according to French recommendations[a] and summaries of product characteristics.

Vaccine	Biotherapy	TNFα antagonists					Abatacept	Tocilizumab	Ustekinumab	Anti-IL-1		Rituximab	Belimumab
		Etanercept	Adalimumab	Golimumab	Certolizumab	Infliximab				Anakinra	Canakinumab		
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.

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Özet

Romatolojik hastalıklarda aşılama çok önemli

Hastalığa, risk durumu, daha önceki aşılanma-hastalığı geçirme, bellek yanıt ve ilaca, doza, süresine göre aşılar belirlenmeli

- Her bir aşı
- Her bir kişide

Kontrendikasyonlar iyi belirlenmeli

Her vizit aşı-korunma açıından bir fırsat g

Sonuç olarak

Romatolojik hastalıklarda aşı uygulaması karmaşık bir süreç

Sürekli güncellenen rehberlere gereksinim var

Çoğu öneri için kanıt düzeyi yetersiz

Birçok aşının birçok ilaçla kullanımında etkinliği değerlendirilmemiş durumda

Aşıların etkinliğini değerlendirme sorunu var

Her hasta yakın izlenmeli

Hastalar bilgilendirilmeli ve eğitimi sağlanmalı

Erişkinde aşılama ile ilgili engeller tanımlanmalı ve stratejiler geliştirilmeli

Multidisipliner yaklaşım çok önemli

Kurtin et al. Ruffing. Rheum Dis Clin N Am 43 (2017) 15–26

Katılımınız için teşekkürler..