BİYOLOJİK AJAN KULLANIMI ÖNCESİ ENFEKSİYON HASTALIKLARI KONSÜLTASYONU

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD

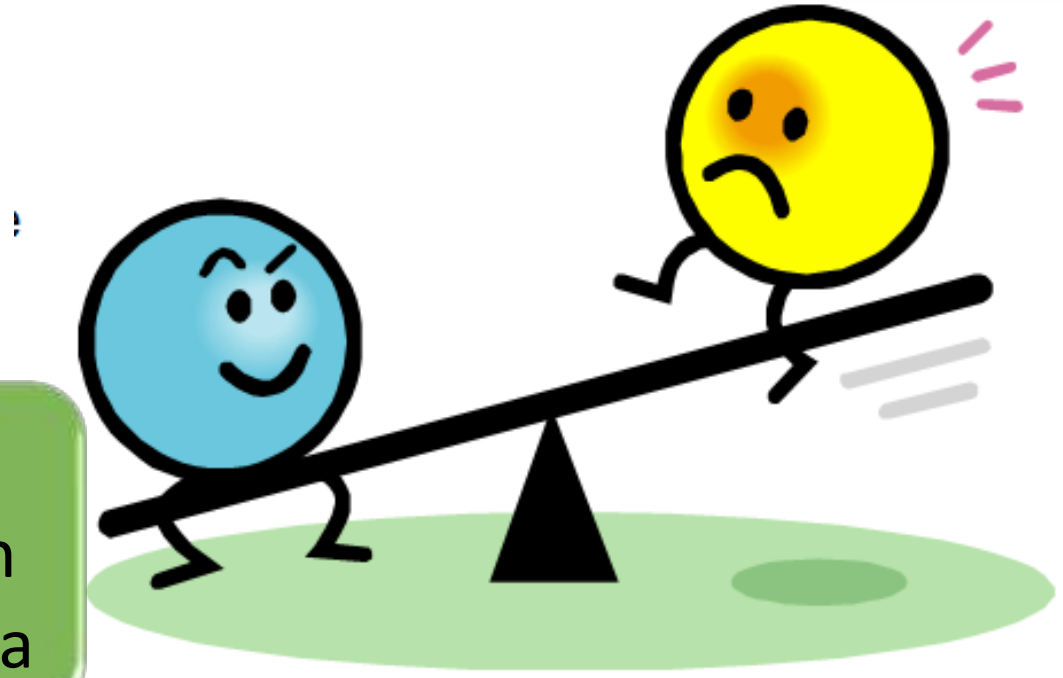
EKMUD Ankara Günleri
21 Mart 2018

Biyolojik ajanlar

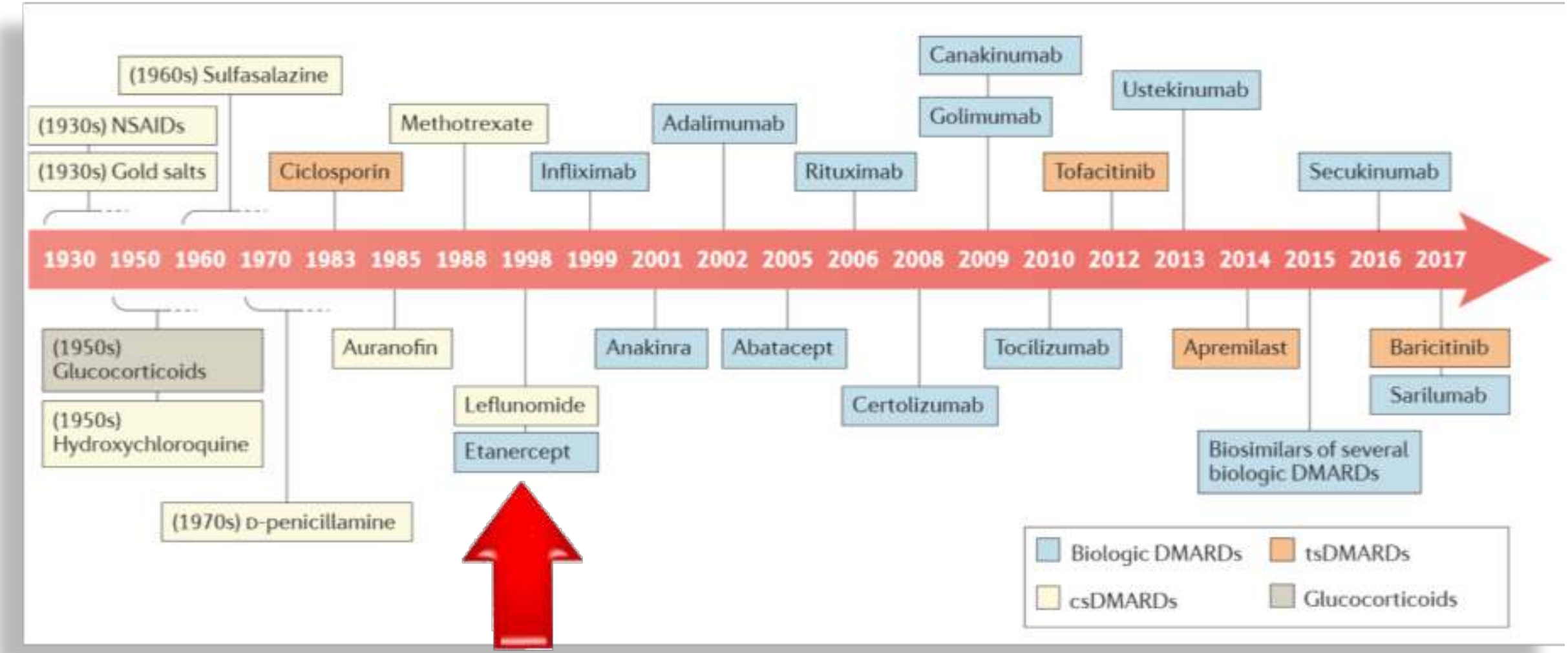
Hastalık gelişimi sürecinde rol alan immün veya genetik mediyatörlerden birini spesifik olarak hedef alan ilaçlar

Biyolojik yanıt düzenleyiciler
Gen terapileri
Hedefe yönelik tedaviler

Latent tüberküloz reaktivasyonu
Fungal, bakteriyel ve viral hastalıklar



Hastalık aktivitesini etkin şekilde baskılama



Nat Rev Rheumatol. 2017 Jul;13(7):443-448.

Kullanım alanları

- Romatolojik hastalıklar
- Maligniteler
- İnflamatuar barsak / göz hastalıkları
- Psöriazis
- Organ transplantasyonu
- Multiple skleroz
- Şiddetli astım
- ……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▼ **İLAÇ GÜVENLİK İZLEM FORMU***

SERİ NUMARASI

Hastanın adı, soyadı:
Hastanın yaşı ve cinsiyeti:
Hastane adı ve hastanın dosya numarası:
Hastanın tanısı ve tanı tarihi:
Bu tedavi öncesinde ilgili tanı ve endikasyon için kullanılan ilaçlar:
…… tedavisini endike kılan durum:
Başlangıçta tüberküloz değerlendirmesi PPD:…….. Akciğer grafisi:…….. INH profilaksisi yapılacaksa başlangıç ve bitim tarihi:…….. Malign veya pre-malign hastalık öyküsü:……

TÜRKİYE İLAÇ VE TIBBİ CİHAZ KURUMU (TİTCK)

ANASAYFA KURUMSAL MEVZUAT DUYURULAR İLAÇ TIBBİ CİHAZ KOZMETİK LABORATUVAR DENETİM İLETİŞİM

			İZLEM FORMU	FORMU	
Orencia	Abatasept	02.03.2018	PDF	PDF	PDF
Humira	Adalimumab	02.03.2018	PDF	PDF	PDF
Enbrel	Etanersept	02.03.2018	PDF	PDF	PDF
Simponi	Golimumab	02.03.2018	PDF	PDF	PDF
Remicade	İnfliksimab	02.03.2018	PDF	PDF	PDF
Remsima	İnfliksimab	02.03.2018	PDF	PDF	PDF
İlaris	Kanakinumab	02.03.2018	PDF	PDF	PDF
İbecta	Kanakinumab	02.03.2018	PDF	PDF	PDF
Verxant	Sekukinumab	02.03.2018	PDF	PDF	PDF
Cimzia	Sertolizumab	02.03.2018	PDF	PDF	PDF
Actemra	Tosilizumab	02.03.2018	PDF	PDF	PDF
Stelara	Ustekinumab	02.03.2018	PDF	PDF	PDF
Mabthera (kanser tanısı hariç)	Rituksimab	26.10.2017	PDF	PDF	PDF
Benlysta	Belimumab	26.10.2017	PDF	PDF	PDF
Xeljanz	Tofasitinib	26.10.2017	PDF	PDF	PDF
Entyvio	Vedolizumab	26.10.2017	PDF	PDF	PDF
Humira (orta üveit endikasyonu için)	Adalimumab	02.03.2018	PDF	PDF	PDF
Gazyva	Obinituzumab	26.10.2017	PDF	PDF	PDF

Neyin altına imza atıyoruz???

- Hastada halen klinik olarak aktif tüberküloz veya malignite bulunmamaktadır.
- Hasta, fungal enfeksiyon gelişimi riski yönünden değerlendirilmiştir.
- Hasta, ilacın tüberküloz, lenfoma ve malignite dahil riskleri konusunda uyarılmıştır.
- Bu formda yer alan ilaçların uygulanması için uygun aşıların yapılması önerilmiştir.
- Tosilizumab tedavisi alacak hastalar, komplike divertikülit belirtisi olabilecek karın ağrısı gibi semptomlar açısından uyarılmıştır.
- ..... tedavisi almasında medikal sakınca yoktur.

.....	.....	.....
İmza Adı Soyadı (Kaşe) Reçete Eden Hekim	İmza Adı Soyadı (Kaşe) İç Hastalıkları Uzmanı veya Çocuk Hastalıkları Uzmanı	İmza Adı Soyadı (Kaşe) Göğüs Hastalıkları Uzmanı veya Enfeksiyon Hastalıkları Uzmanı

* Bu form etanersept, infliksimab, adalimumab, abatasept, kanakinumab, ustekinumab, golimumab, tosilizumab, sertolizumab ve sekukinumab içeren ilaçlar için kullanılmaktadır.
* Bu form, tedavi süresince üç ayda bir doldurulmalıdır.
* Hasta başlangıçta ve ilaç kullanıldığı sürece tüberküloz, fungal enfeksiyon, lenfoma ve malign hastalıkların gelişimi yönünden reçete eden hekimler ile göğüs hastalıkları (veya enfeksiyon hastalıkları) ve iç hastalıkları (çocuklar için çocuk hastalıkları) uzmanlarınca yakından izlenmelidir.

T.C.
SAĞLIK BAKANLIĞI
Türkiye Halk Sağlığı Kurumu

T.C. Sağlık Bakanlığı
Türkiye Halk Sağlığı
Kurumu

Anti-TNF Kullanan Hastalarda

Tüberküloz Rehberi

2016

Gastroenterology 2015;148:215–219

AGA SECTION

American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy

K. Rajender Reddy,[1] Kimberly L. Beavers,[2] Sarah P. Hammond,[3] Joseph K. Lim,[4] and Yngve T. Falck-Ytter[5]

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RAED dergisi

Kılavuz / Guidelines

RAED Dergisi 2015;4(1):28-32. © 2015 RAED
doi:10.7599/raed.15.40085

Geliş tarihi / Received: Haziran / June 1, 2015
Kabul tarihi / Accepted: Eylül / September 5, 2015

Romatolojik hastalarda biyolojik ilaç kullanımı öncesi (viral) hepatit tarama kılavuzu

Guideline of the viral hepatitis screening before biologic agents use in patients with rheumatic diseases

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Yaşasın ESCMID rehber çıkarmış!

- Enfeksiyon hastalıkları uzmanları, hematologlar, onkologlar, romatologlar ve daha birçok branş hekiminin dahil olduğu
- Her grup/ilaç için
  - Etki mekanizması
  - Onaylı kullanımı, endikasyon dışı kullanımı
  - Konakta immünite üzerine beklenen etkileri
  - Klinik veriler
  - Öneriler

Accepted Manuscript

CMI
CLINICAL MICROBIOLOGY AND INFECTION

ARTICLE IN PRESS

Accepted Manuscript

ESCMID Study Group for Infections in Compr
Document on the safety of targeted and biolo
perspective (Immune checkpoint inhibitors, ce
phosphate receptor modulators and proteaso

Gil Redelman-Sidi, Olivier Michielin, Carlos C
Aguado, Mario Fernández-Ruiz, Oriol Manuel

PII: S1198-743X(18)30148-4
DOI: 10.1016/j.cmi.2018.01.030
Reference: CMI 1200

To appear in: *Clinical Microbiology and Infection*

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Accepted Date: 11 February 2018

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[6] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Table 2
Targeted and biological agents reviewed ESGICH Consensus Document

Section of document (study)	Targeted molecule	Agents reviewed
2 [1]	TNF-α	Infliximab, adalimumab, golimumab, certolizumab pegol, etanercept
3 [2]	IL-1	Canakinumab, anakinra, rilonacept, gevokizumab
	IL-5	Mepolizumab, reslizumab
	IL-6	Tocilizumab, siltuximab
	IL-12/23 common p40 subunit	Ustekinumab
	IL-17	Secukinumab, ixekizumab, brodalumab
	IgE	Omalizumab
	Complement factor C5	Eculizumab
4 [3]	VEGF	Bevacizumab, aflibercept
	VEFGR	Sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib, ramucirumab
	EGFR	Cetuximab, panitumumab
	ErbB2/HER2	Trastuzumab, pertuzumab
	ErbB receptor tyrosine kinases	Erlotinib, gefitinib, afatinib, osimertinib, lapatinib, neratinib
5 [4]	BCR-ABL tyrosine kinase	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
	BRAF/MEK kinases	Vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, encorafenib
	Bruton tyrosine kinase	Ibrutinib, acalabrutinib
	PI3K	Idelalisib, buparlisib, rigosertib, duvelisib
	Bcl-2	venetoclax
	Janus kinases	Ruxolitinib, tofacitinib, baricitinib
	mTOR	Everolimus, temsirolimus
6 [5]	CD19	Blinatumomab, inebilizumab, combotox
	CD20	Rituximab, ^{90}Y-ibritumomab tiuxetan, ofatumumab, ocrelizumab, veltuzumab, ^{131}I-tositumomab, obinutuzumab, ocaratuzumab, ublituximab
	CD52	Alemtuzumab
7 [6]	CD22	Epratuzumab, inotuzumab ozogamicin, moxetumomab pasedotox, combotox
	CD30	Brentuximab vedotin
	CD33	Gemtuzumab ozogamicin
	CD38	Daratumumab, isatuxumab
	CD40	Dacetuzumab, lucatumumab
	CD319 (SLAMF7)	Elotuzumab
	CCR4	Mogamulizumab
8 [7]	CTLA-4	Ipilimumab, tremelimumab
	PD-1 and PD1L	Nivolumab, pembrolizumab, atezolizumab
	LFA-3	Alefacept
	α4-Integrins, LFA-1	Natalizumab, vedolizumab, efalizumab
	Sphingosine 1–phosphate receptor	Fingolimod
	Proteosome	Bortezomib, carfilzomib, ixazomib

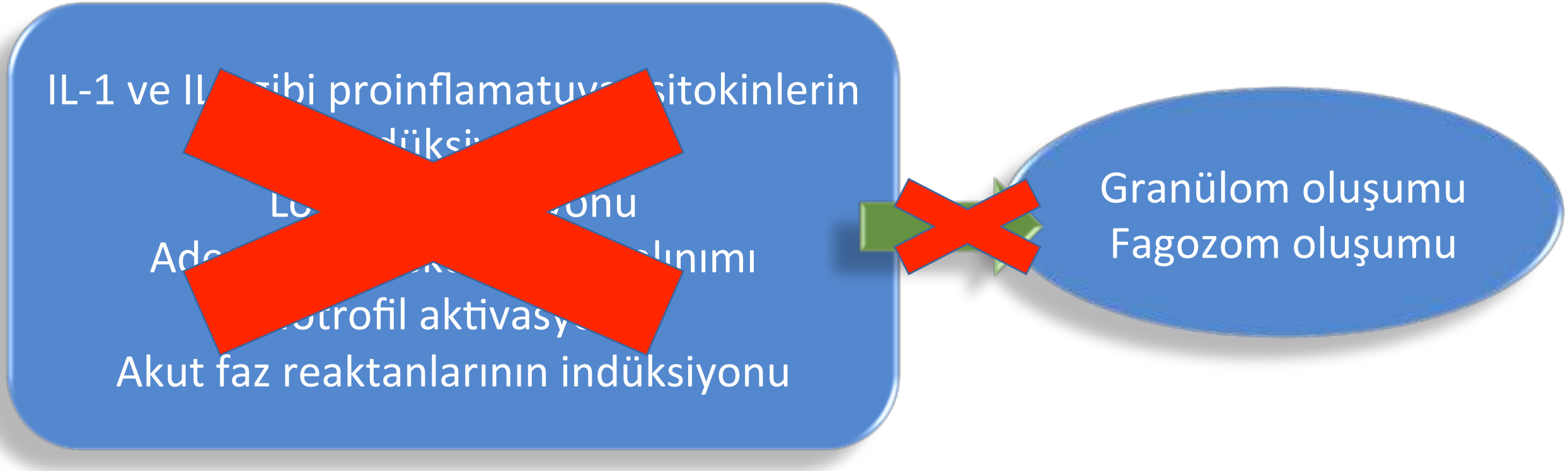
Bcl-2, B-cell lymphoma 2; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ESGICH, European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IgE, immunoglobulin E; IL, interleukin; LFA, lymphocyte function-associated antigen; mTOR, mammalian target of rapamycin; PD, programed death; PI3K, phosphatidylinositol-3-kinase; SLAMF7, signaling lymphocytic activation molecule F7; TNF, tumour necrosis factor; VEGF, vascular endothelium growth factor; VEGFR, VEGF receptor.

Çalışmaları karşılaştırmak zor

Çoğunluğu ilaç etkinliğini karşılaştırmak üzere planlanmış

- Altta yatan hastalıklar
- Riskler farklı
- Coğrafi farklılıklar
- Endemisite Koruma stratejileri

TNF alfa inhibitörleri



- Tbc gibi granülomatoz enfeksiyonlar
- Hücre içi patojenler (listeria, salmonella)
- Virüsler (HBV, VZV, JCV)
- İnvaziv fungal enfeksiyonlar (nötropeni)

Ali T et al. Clinical use of anti- TNF therapy and increased risk of infections. Drug Healthc Patient Saf 2013;5:79e99.

- TNF alfa tedavisi alan LTBE hastalarda reaktivasyon riski normal popülasyona göre 4 kat fazla

- Tedavi öncesi LTBE tanısı için optimal yaklaşım net değil.
- IGRA (QuantiFERON-TB, T-SPOT®.TB) TDT'ne göre artan spesifitesi nedeniyle daha sık kullanılmakta

Baddley JW, et al., 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-tumour necrosis factor-a agents), Clinical Microbiology and Infection (2018)

TBC açısından nasıl takip edelim?


EK-1

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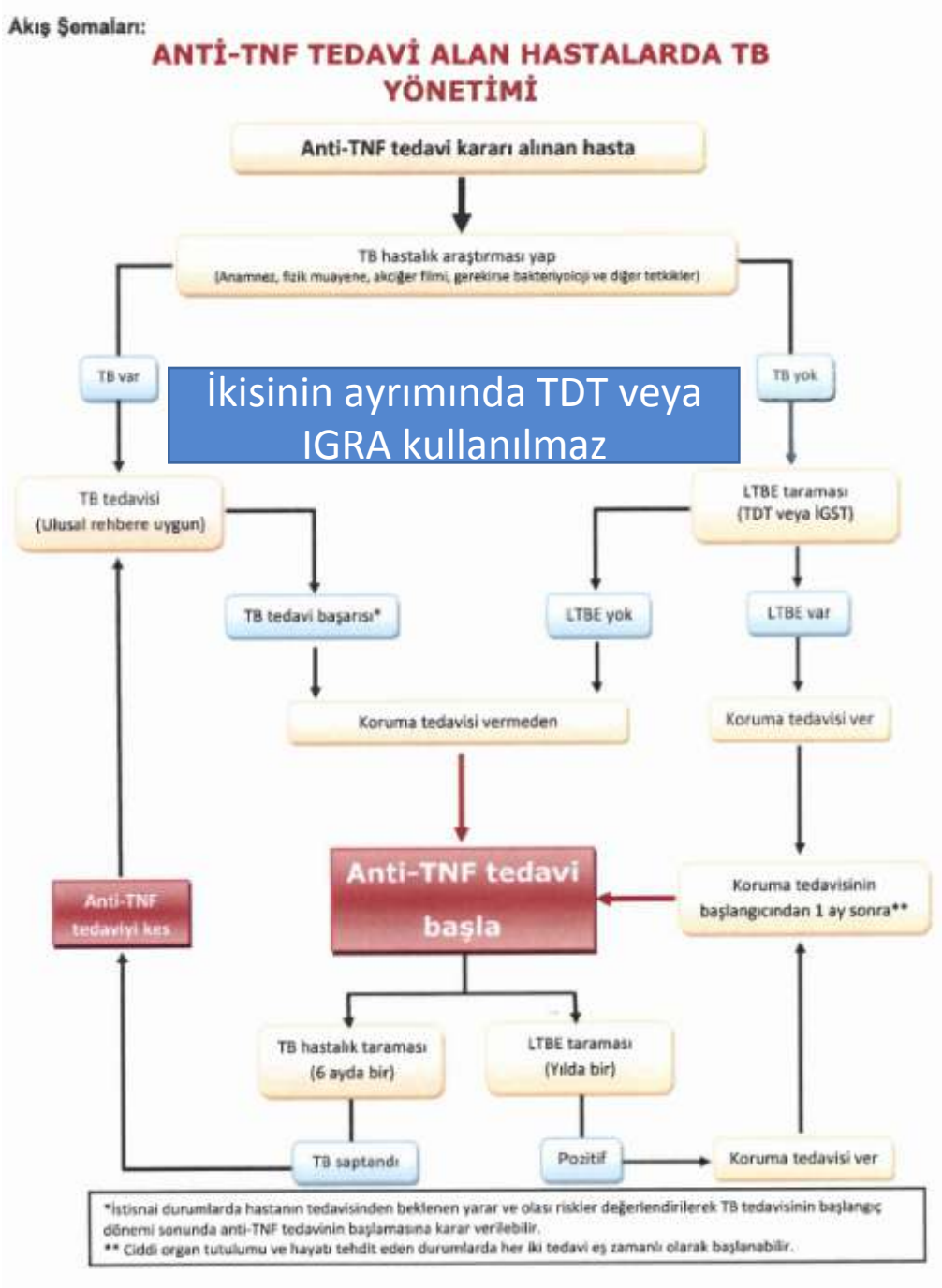
Kurumu

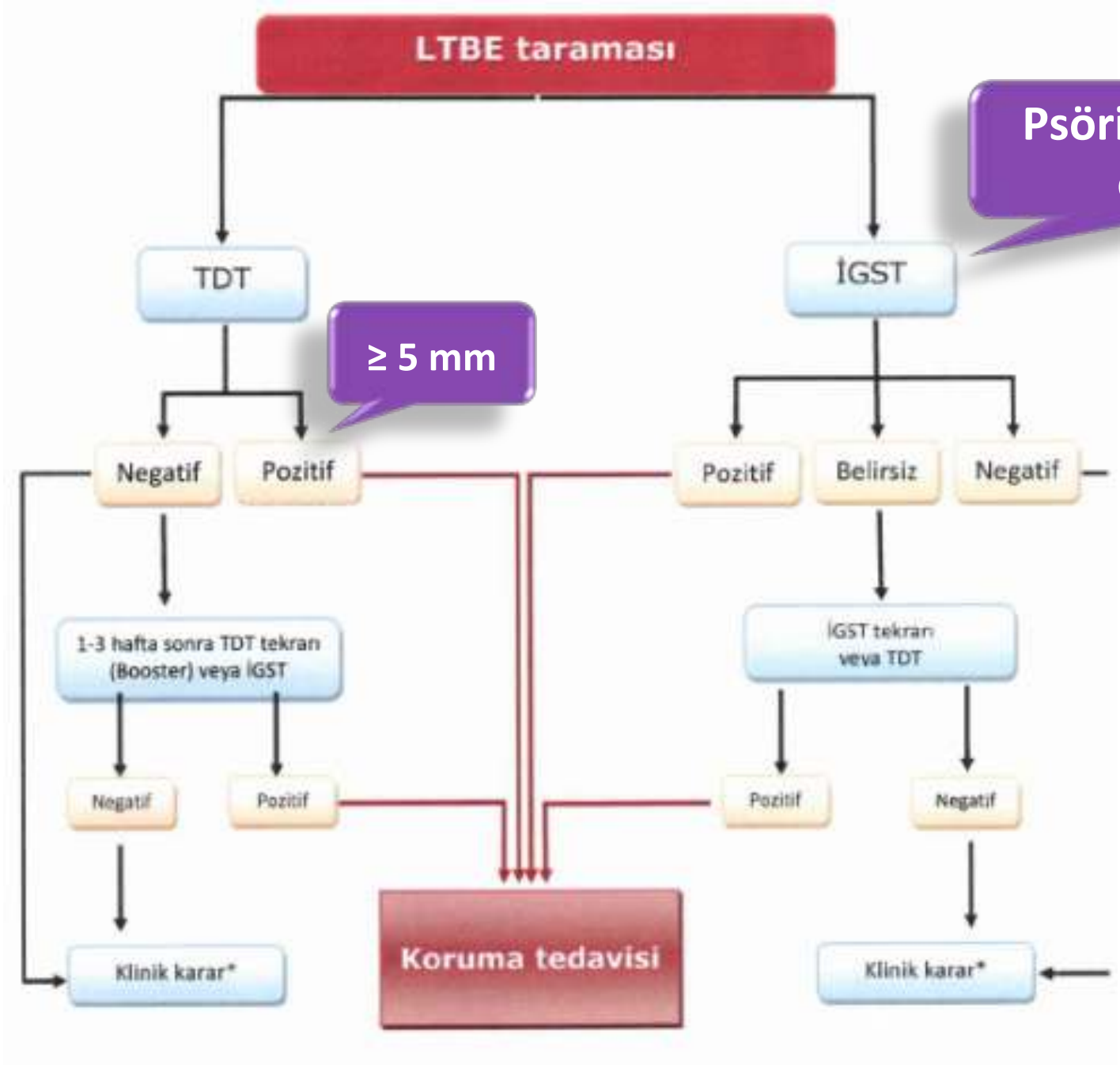
Anti-TNF Kullanan Hastalarda

Tüberküloz Rehberi
2016

- ✓ Aktif TBC varlığında anti-TNF tedavisi kontrendike, bu nedenle hastalar tedavi öncesi araştırılmalıdır.
- ✓ Anti-TNF tedavisi kesildikten sonra da TBC riski devam edebilir, en az 6 ay takip
- ✓ TBC tanısı konulan hastalarda tedavi tamamlanmadan anti-TNF tedavi başlanmamalıdır (Kar-zarar hesabı yapılarak istisnai durumlar hariç)
- ✓ Anti-TNF başlanan hastalar asemptomatik olsalar bile TBC açısından (anamnez, FM, radyoloji) 6 ayda bir kontrol edilmelidir.



- ✓ LTBE test sonuçları negatif olan hastalarda uzman hekim hastanın risk durumunu göz önüne alarak koruma tedavisi verebilir.


LTBE taraması
TDT
İGST
Psöriaziste tercih edilmeli
≥ 5 mm
Negatif
Pozitif
Pozitif
Belirsiz
Negatif
1-3 hafta sonra TDT tekran (Booster) veya İGST
İGST tekran veya TDT
Negatif
Pozitif
Pozitif
Negatif
Klinik karar*
Koruma tedavisi
Klinik karar*

Koruma tedavisi	• 9 ay INH • 4 ay RİF
Koruma tedavisi başlandıktan sonra anti-TNF kesildi	• Tedaviyi tamamla
Geçirilmiş TBC varlığında testler anlamsız	• TB hastalığı saptanırsa tedavi • Aktif hastalık yok ama şüphe/re-enf açısından risk varsa koruma tedavisi verilebilir

2011

- Anti-TNF ajanlar arasında sadece certolizumab TBC dışı ciddi enfeksiyonlar açısından artmış riske sahip

2013

- Sadece certolizumab için değil adalimumab ve infliximab için de aynı risk söz konusu

2015

- Hepsi için geçerli

Singh JA et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011
Michaud TL et al. The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a metaanalysis update of 44 trials. Am J Med 2014
Singh JA et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015

Anti-TNF vs TBC dışı ciddi enfeksiyonlar

Pnömoni
Cilt-yumuşak doku enfeksiyonları

→ En sık

Listeriozis
Granülomatöz enfeksiyonlar

Doran MF et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287e93.

Anti-TNF vs Viral enfeksiyonlar

- CMV ve EBV reaktivasyonu bildirilmiş fakat sayı az
- Herpes Zoster ile ilgili farklı çalışmalarda çelişen sonuçlar mevcut (30binden fazla hastanın dahil olduğu en geniş ABD vaka serisinde risk artışı bildirilmezken, Avrupa kayıtları HZ riskinde 2 kat artış bildirmiş)
- HCV reaktivasyonu nadir de olsa bildirilmiş.

Winthrop KL et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. JAMA 2013
Vassilopoulos D, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. Nat Rev Rheumatol 2012
Galloway JB et al. Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2013
Burton MJ et al. Safety of biologic and nonbiologic disease-modifying antirheumatic drug therapy in veterans with rheumatoid arthritis and hepatitis C virus infection. J Rheumatol 2017:565e70.

Anti TNF - Genel öneriler

- Ciddi enfeksiyon durumunda tedavi kısa süreli de olsa kesilmeli. En azından klinik yanıt gözlenmeden başlanmamalı

- Antibakteriyel, antifungal, antiPCP proflaksinin faydası gösterilmemiş.

EASL 2017 ne diyor?

- KT veya İS alacak tüm hastalar tedavi öncesi HBsAg, anti-HBs and anti-HBc ile taranmalı
- Seronegatifler aşılanmalı.
- Risk kategorisine göre yaklaşım
- Kronik hepatit B takibi, tedavisi, tedavi kesme kararı immünkompetan hasta grubu ile aynı şekilde

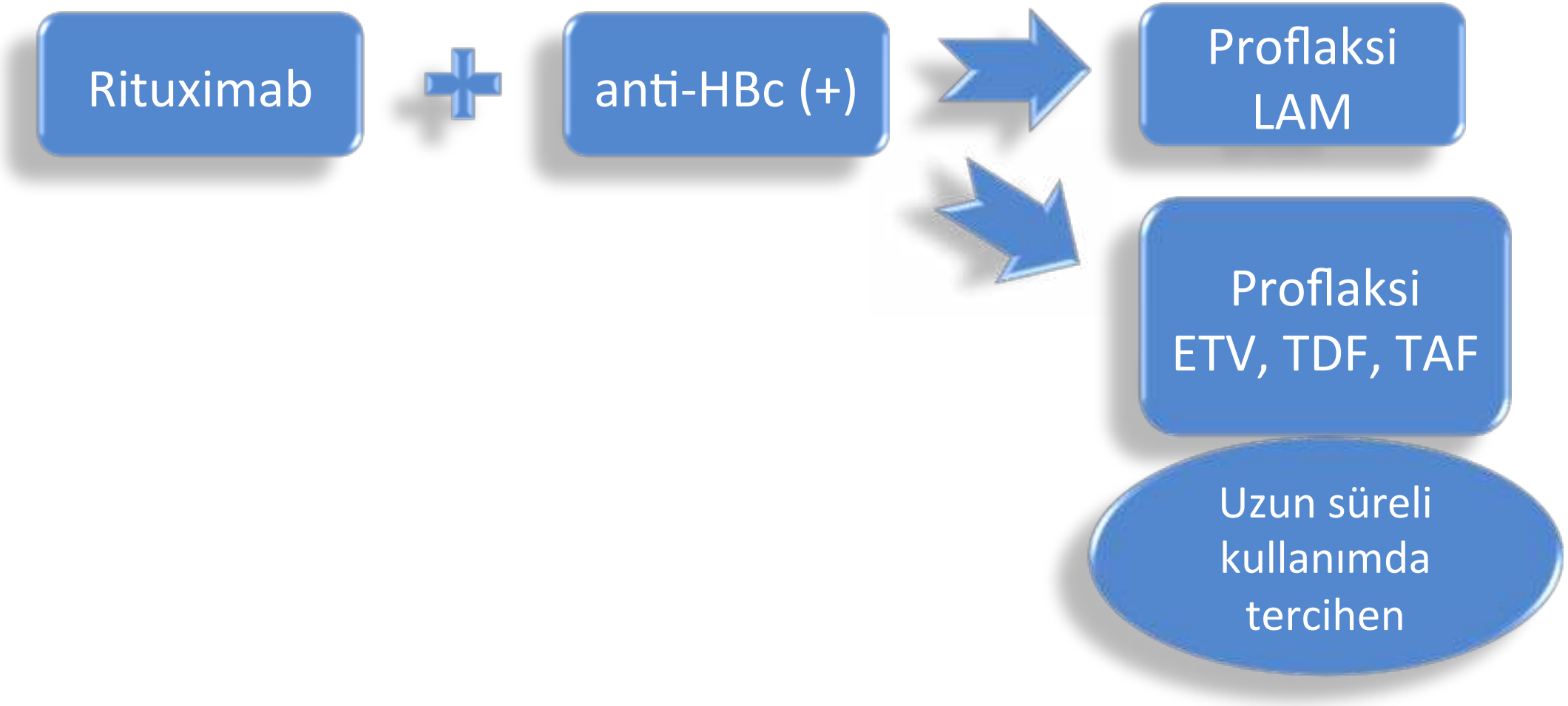
EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology 2017

EASL 2017

- Proflaksi immünsupresif kesildikten sonra en az 12 ay (Rituximab için 18 ay)
- Proflaksi süresince ve kesildikten 12 ay sonrasına kadar 3-6 ayda bir karaciğer fonksiyon testleri ve HBV DNA

Risk derecesi	HBsAg + Anti-HBc+	HBsAg – Anti-HBc+	Tedavi
Yüksek Risk >%10	B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab) Antrasiklin deriveleri (doxorubicin, epirubicin) Orta (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta	B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab)	Profilaksi
Orta Risk %1-10	TNF-alfa tedavisi (etanercept, adalimumab, certolizumab, infliximab) Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab) Tirozin kinaz inhibitörleri (imatinib, nilotinib) Düşük doz steroid (<10 mg/gün prednisone), 4 haftalık tedavi	TNF-alfa tedavisi (etanercept, adalimumab, certolizumab, infliximab) Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab) Tirozin kinaz inhibitörleri (imatinib, nilotinib) Orta doz (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta antrasiklin deriveleri (doxorubicin, epirubicin)	Profilaksi veya Pre-emptif
Düşük Risk <%1	İmmunsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate) İntra-artiküler kortikosteroidler 1 hafta süreli herhangi bir dozda oral steroid tedavisi	İmmunsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate) İntra-artiküler kortikosteroidler 1 hafta süreli herhangi bir dozda oral steroid tedavisi Düşük doz 4 haftalık steroid (<10 mg prednison)	Profilaksiye gerek yok

EASL 2017


Rituximab
anti-HBc (+)
Proflaksi
LAM
Proflaksi
ETV, TDF, TAF
Uzun süreli
kullanımda
tercihen

IL, IG ve kompleman faktörleri üzerine etkili ajanlar

IL-1 ailesi immün sistemin anahtar komponenti

Antagonistlerinin kısa süreli kullanımı ile ciddi enfeksiyöz komplikasyon riskinde anlamlı artış gözlenmemiş.

Accepted Manuscript

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)

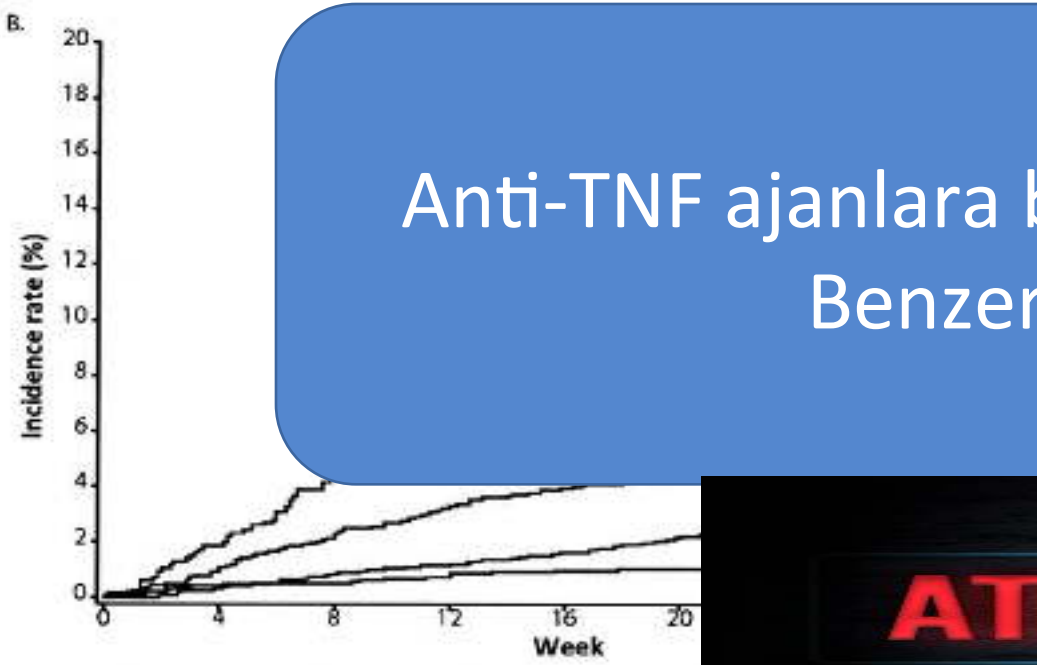
Kevin L. Winthrop, Xavier Mariette, Jose T. Silva, Esther Benamu, Leonard H. Calabrese, Alexandre Dumusc, Josef S. Smolen, José María Aguado, Mario Fernández-Ruiz

IL-1 antagonistleri: Anakinra, canakinumab, gevokizumab, rilonacept

- VZV, HBV reaktivasyon riski yok
- Komorbiditesi olan, ileri yaş hastalarda ciddi enfeksiyon riskinde belirgin artış
- LTBE açısından tedavi öncesi tarama

IL-6 antagonistleri: tocilizumab ve siltuximab

Anti-TNF ajanlara benzer artmış enfeksiyon riski
Benzer koruma stratejisi



	0 Risk factors	1 Risk factor		
Patients (n)	1975	2931		
Cumulative incidence at week 28 (%)	1.18	2.98	5.24	11.15

Log-rank test	χ^2	df	p Value
1 risk factor vs 0 risk factors	15.3133	1	<0.001
2 risk factors vs 0 risk factors	49.9071	1	<0.001
2 risk factors vs 1 risk factor	17.0593	1	<0.001
≥3 risk factors vs 0 risk factors	139.6476	1	<0.001
≥3 risk factors vs 1 risk factor	94.1461	1	<0.001

Koike T et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 2014;41:15-23.

Table 3. Summary of infection risks and suggested recommendations and management strategies.

Agents	Increased risk of overall infection	Risk of VZV / HBV infection	Risk of active TB	Observations and recommendations
Secukinumab, ixekizumab, brodalumab **IL-17 antagonisti**	Minor	No / no	Probably low (theoretical risk of progression of LTBI)	• Minor increase in the risk of mild to moderate infection • Increased risk of mild to moderate mucocutaneous candidiasis (slightly higher for brodalumab and ixekizumab than secukinumab) • Screening for LTBI before starting treatment (followed by appropriate therapy if needed)
Omalizumab **IgE antagonisti**	Minor	No / no	No	• Increased risk of mild to moderate parasitic infection (mainly due to geohelminths) • Screening for geohelminths before starting therapy in high-risk patients (migrants from endemic areas and residents of non-endemic areas with long-term stay in endemic areas), followed by specific therapy if needed • Alternatively, empirical broad-spectrum anthelmintic drugs (albendazole plus ivermectin) for migrants from endemic areas • Repeated screening for geohelminths during the course of therapy in patients at continuous high risk due to ongoing exposure (long-term residents in endemic areas)

Kompleman komponent C5 antagonisti eculizumab

Eculizumab

Sağlıklı kişilere oranla meningokok enfeksiyonu riski 10000 kat artmı

Uygun aşılanan kişilerde de dissemine meningokok veya gonokoksemi bildirilmiş

- Meningok
- FDA,EMA black
- FDA,EMA ve A ent konjuge aşı MenAC B)
- Kemoproflaksi (pen in veya ciprofloksasin)

Accepted Manuscript

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)

Małgorzata Mikulska, Simone Lanini, Carlota Gudiol, Lubos Drgona, Giuseppe Ippolito, Mario Fernández-Ruiz, Bernd Salzberger

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg- anti-HBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD19-targeted agents	Blinatumomab	No		es	Yes / yes	ND	Immunoglobulin replacement therapy if severe HGG
	Inebilizumab	ND	ND (probably in hematological malignancies)	ND	Probably yes / yes	ND	Immunoglobulin replacement therapy if severe HGG
CD20-targeted agents	Rituximab	Yes	ND (consider in hematological malignancies depending and concomitant therapy)	Possible (consider if concomitant corticosteroid therapy)	Yes / yes	ND, symptom-based approach in hematological malignancies	PML, HCV, enteroviral infections
	Obinutuzumab	Potentially yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	ND, probably yes / yes	ND, symptom-based approach in hematological malignancies	Enteroviral infections
	Ofatumumab	Yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	Yes / yes	ND, symptom-based approach in hematological malignancies	
	Veltuzumab	Potentially yes	ND (consider if hematological malignancies depending and concomitant therapy)	ND, possibly as rituximab	ND, probably yes / yes	ND, symptom-based approach in hematological malignancies	

4 haftalık iv sürekli infüzyona bağlı riskler

CD 20 antagonistleri: Rituximab, 90Y-ibritumomab, Ofatumumab, Obinutuzumab, Ocrelizumab

- HBV reaktivasyonuna dikkat 
- Rituximab içeren rejimlerde reaktivasyon riski yaklaşık 6 kat fazla

Mozessohn L et al. Hepatitis B reactivation in HBsAg-negative/HBcAbpositive patients receiving rituximab for lymphoma: a meta analysis. J Viral Hepat 2015

Ziakas PD, Karsaliakos P, Mylonakis E. Effect of prophylactic lamivudine for chemotherapyassociated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance. Haematologica 2009

HBsAg (-) / anti-HBc (+)

Aylık HBV DNA takibi

HBV DNA +

Preemptif antiviral tedavi

Daha pahalı
Uyum problemi

Mikulska M et al. 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), *Clinical Microbiology and Infection* (2018)

Rituximab vs PCP riski

- KT'ye eklendiğinde tek başına eklendiğinde artmış yok.
- Prednizolon (≥ 20 mg/gün en az 4 hafta) ile kombine edildiğinde PCP proflaksisi önerilmekte
- ECİL-5'de de alemtuzumab, rituximab başta olmak üzere birçok DMARD için önerilmekte

Mikulska M et al. 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), *Clinical Microbiology and Infection* (2018)

Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, et al. ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother 2016

CD 20 Antagonistleri vs HBV

HBsAg +

- ✓ ETV, TDF, TAF
- ✓ Tedavi bitiminden en az 12-18 hafta sonrasına kadar

HBsAg (-)
anti-HBc (+)

- ✓ LAM
- ✓ Tedavi bitiminden en az 12-18 hafta sonrasına kadar

Mikulska M et al. 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), *Clinical Microbiology and Infection* (2018)

CD52 antagonistleri: Alemtuzumab

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAg+ / HBsAg- anti-HBc+)	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD52-targeted agents	Alemtuzumab (MabCampath®)	Yes	Yes	Yes	Yes / prophylaxis or monitoring	Yes	IFI, BK and JC polyomaviruses reactivation
	Alemtuzumab (Lemtrada®)	No	Yes	No (lower dose, no need of additional immunosuppression)	Probably yes / prophylaxis or monitoring	No	HPV, TB, listeriosis, candidiasis

T hücre deplesyonu yapan diğer ilaçlara benzer immün supresyon
Ciddi enfeksiyon riski (HIV benzeri)

PCP proflaksisi
Antiherpes virüs proflaksisi (HSV, VZV, EBV)

CD52 antagonisti: Alemtuzumab

- HBV yaklaşımı CD20 antagonistleri ile benzer
- HCV reaktivasyonu açısından dikkat
- Latent TB zaten hepsinde bakmalıyız
- HPV açısından yıllık tarama
- Hijyenik ve güvenli gıda (listeriozis, toxoplazmozis vs)

Hücre içi sinyal yolları üzerine etkili ajanlar: Tirozin kinaz inhibitörleri, mTOR inhibitörleri

Agents	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib **BCR-ABL tirozin kinaz inhibtörleri**	Modest	IFI, HZ, tuberculosis, CMV (particularly with dasatinib)	No	Yes	• Higher risk of infection with dasatinib (particularly after HSCT) • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • No expected benefit from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib selumetinib, **BRAF ve MEK kinaz inhibitötleri**	None	No	No	No	• No apparent increase in the risk of infection • Some of the most common drug-related adverse effects (pyrexia, fatigue, arthralgia and skin rash) may mimicry an ongoing infection
Ibrutinib, acalabrutinib **Bruton's tirozin kinaz inhibitörleri**	Modest	PCP, IFI, PML	Yes (particularly in presence of additional risk factors)	No	• Modest increase in the risk of infection (contributing role of prior or concurrent therapies or inherent immune defects) • No expected benefit from the universal use of antibacterial or antifungal prophylaxis • Anti-*Pneumocystis* prophylaxis for CLL patients with additional risk factors (e.g., purine analogues or high-dose corticosteroids) • PML occasionally associated with the use of ibrutinib

Reinwald M et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), *Clinical Microbiology and Infection* (2018)

Agents	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Idelalisib, buparlisib, rigosertib, duvelisib **Ras/PI3K/Akt/ mTOR inhibitörleri**	Major	IFI, PCP, CMV	Yes	No	• Increased risk of OIs and life-threatening adverse events (hepatotoxicity, colitis and pneumonitis). • Anti-*Pneumocystis* prophylaxis during the course of therapy and for 2-6 month after its discontinuation • Monitoring for CMV infection during the course of therapy in CMV-seropositive patients or in presence of suspected CMV disease • Discontinuation of therapy in presence of suspected pneumonitis or grade 3-4 aminotransferase elevation or diarrhoea/colitis
Ruxolitinib, tofacitinib, baricitinib **JAK/STAT inhibitörleri**	Major	PCP, HZ, tuberculosis, CMV, EBV, PML	Yes (particularly in presence of additional risk factors)	Yes	• Increased risk of overall infection and OIs • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) • Anti-*Pneumocystis* prophylaxis in patients with additional risk factors (e.g., high-dose corticosteroids)
Sirolimus, everolimus temsirolimus, **mTOR inhibitörleri**	Major	HZ, tuberculosis	No	Yes	• Increased risk of infection in cancer patients, especially in those with additional risk factors (i.e., RCC, prior or concomitant cancer therapies, delay in wound healing or aphthous stomatitis). • Screening for chronic HBV infection and LTBI before starting therapy (followed by appropriate therapy if needed) • No expected benefit from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis

Reinwald M et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors), *Clinical Microbiology and Infection* (2018)

Accepted Manuscript

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)

Gil Redelman-Sidi, Olivier Michielin, Carlos Cervera, Camillo Ribi, José María Aguado, Mario Fernández-Ruiz, Oriol Manuel

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Reference: CMI 1200

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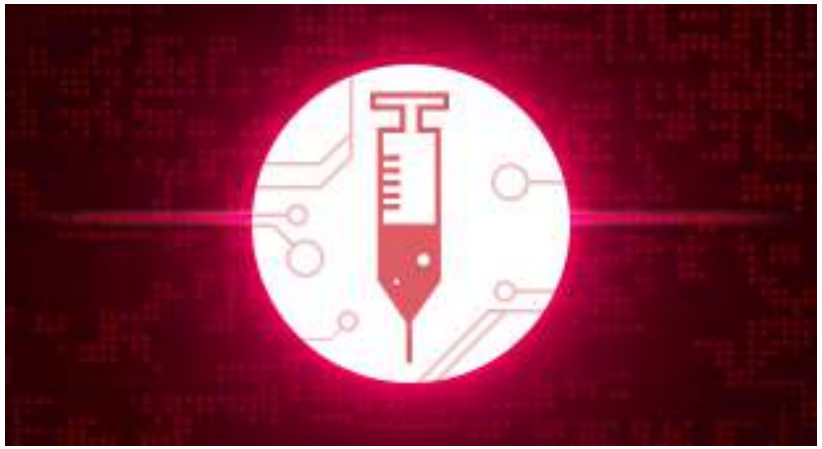
Immune checkpoint inhibitörleri
Adezyon inhibitörleri
Sphingosine-1 fosfat reseptör modülatörleri
Proteasome inhibitörleri

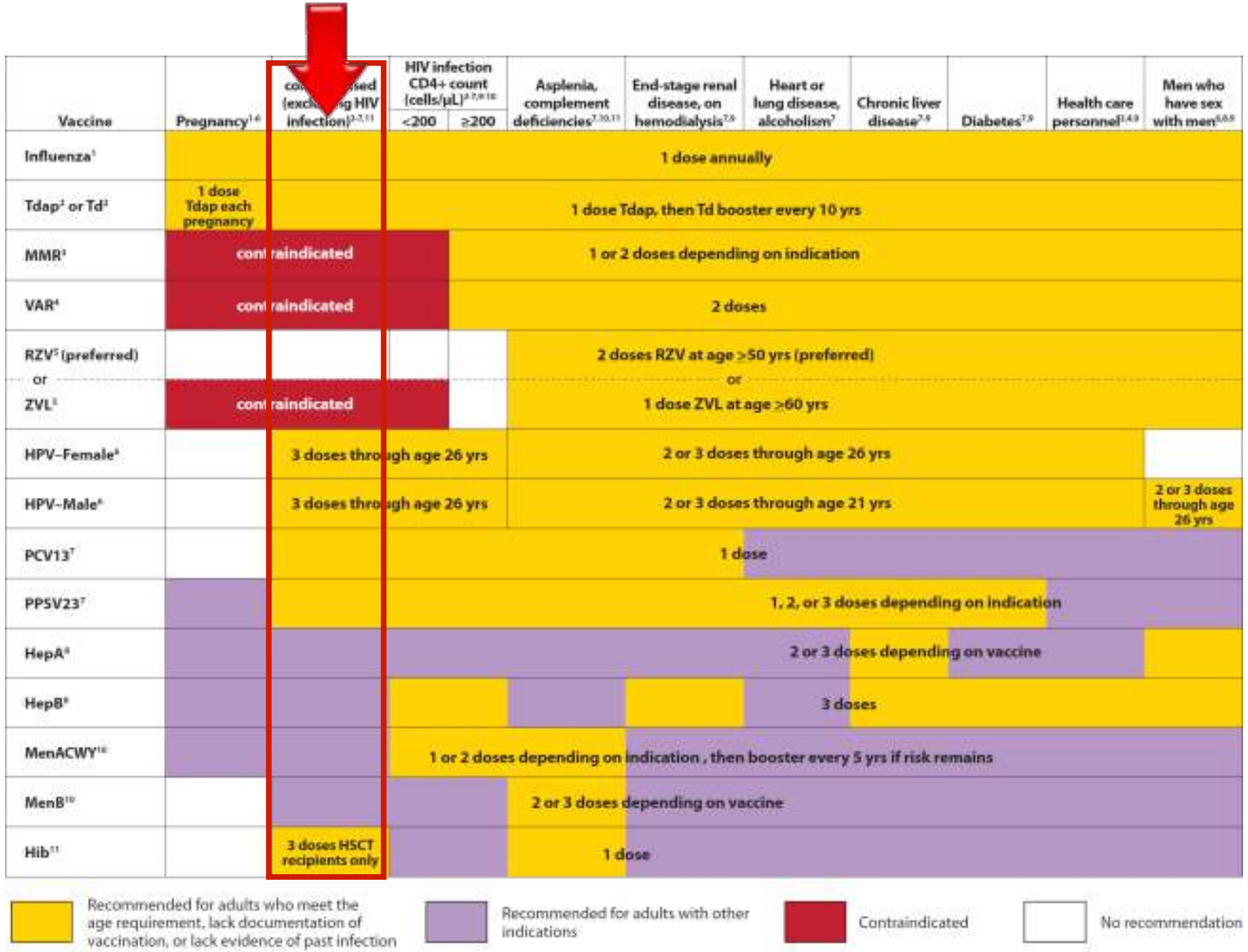
Redelman-Sidi G et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors), *Clinical Microbiology and Infection* (2018),

Agents	Pathway affected	Current indications	Increased risk of infection	Observations
Ipilimumab, tremelimumab	CTLA-4	Melanoma	Variable	• No intrinsic increase in the risk of infection • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e., corticosteroids and/or TNF-α-targeted agents)
Nivolumab, pembrolizumab, atezolizumab	PD-1 or PD-L1	Melanoma, NSCLC, HNSCC, Hodgkin lymphoma, urothelial carcinoma, bladder carcinoma, metastatic RCC, tumor with microsatellite instability	Variable	• No intrinsic increase in the risk of infection • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e., corticosteroids and/or TNF-α-targeted agents)
Alefacept	LFA-3/CD2 interaction	Plaque psoriasis (currently withdrawn)	Minor	• No apparent increase in the risk of infection (currently halted for economic reasons, not safety issues) • Transient peripheral blood CD4+ T-cell lymphopenia
Natalizumab, vedolizumab, efalizumab	α4β1, α4β7 and αLβ2 (CD11a subunit) integrins	MS, Crohn's disease, plaque psoriasis (currently withdrawn)	Major	• Increased risk of PML associated with the use of natalizumab and efalizumab (no cases described so far with vedolizumab) • Risk factors for natalizumab-induced PML include pre-treatment JCV serostatus, anti-JCV IgG antibody index, prior immunosuppression, and duration of treatment
Fingolimod	Sphingosine-1-phosphate receptor	Relapsing-remitting MS	Mild	• Increase in the risk of opportunistic infections, mainly due to herpesviruses (VZV) • Sustained, albeit reversible, peripheral blood lymphopenia (mostly affecting *naïve* and central memory CD4+ and CD8+ T-cell subsets)
Bortezomib, carfilzomib, ixazomib	Ubiquitin proteasome pathway	MM, relapsed or refractory mantle cell lymphoma	Major	• Increased risk of HZ and respiratory tract infections (including pneumonia) • Likely increased risk of influenza-related complications

Aşılama

Yanıt düşük
VZV, KKK gibi canlı aşılardan kaçınmalı
Pnömokok için yaşa uygun şekilde aşılama
İnaktif virüs aşıları (influenza vs)




Vaccine
Pregnancy[1,6]
HIV infection CD4+ count (cells/μL)[2,7,9,10]
<200
≥200
Asplenia, complement deficiencies[7,10,11]
End-stage renal disease, on hemodialysis[7,9]
Heart or lung disease, alcoholism[7]
Chronic liver disease[7,9]
Diabetes[7,9]
Health care personnel[1,4,9]
Men who have sex with men[5,6,9]
Influenza[1]
1 dose annually
Tdap[2] or Td[2]
1 dose Tdap each pregnancy
1 dose Tdap, then Td booster every 10 yrs
MMR[3]
1 or 2 doses depending on indication
VAR[4]
2 doses
RZV[5] (preferred)
or
ZVL[5]
2 doses RZV at age ≥50 yrs (preferred)
or
1 dose ZVL at age ≥60 yrs
HPV–Female[6]
3 doses through age 26 yrs
2 or 3 doses through age 26 yrs
HPV–Male[6]
2 or 3 doses through age 21 yrs
2 or 3 doses through age 26 yrs
PCV13[7]
1 dose
PPSV23[7]
1, 2, or 3 doses depending on indication
HepA[8]
2 or 3 doses depending on vaccine
HepB[8]
3 doses
MenACWY[10]
1 or 2 doses depending on indication , then booster every 5 yrs if risk remains
MenB[10]
2 or 3 doses depending on vaccine
Hib[11]
3 doses HSCT recipients only
1 dose
Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
Recommended for adults with other indications
Contraindicated
No recommendation

ACİP 2018

Sonuç olarak nelere dikkat?

- Sadece HBV ve TBC değil
- Etken ve hastalık spektrumu çok geniş
- Her başvuruda ayrıntılı anamnez, FM çok önemli
- Hastayı bilgilendirmek çok önemli

Bunlar henüz bildiklerimiz. Bakalım yıllar neler getirecek...


Teşekkürler...