KLiMiK 2024

24. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

Olgularla Biyolojik Ajanlar ile İlişkili İnfeksiyonlara Yaklaşım

Pneumocystis jirovecii Pnömonisi

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Sunum Akışı…

- Olgu
- Biyolojik ajanlar
- PCP risk faktörleri
- Hangi biyolojik ajanlar ile PCP
- Profilaksi hangi durumda

Olgu

- 64 yaş kadın
- 8 yıl seronegatif RA
- Kuru öksürük, halsizlik, ateş, nefes darlığı (4 gün)
- Dış merkez azitro ve levo tedavisi
- Klinik değişiklik yok

Olgu

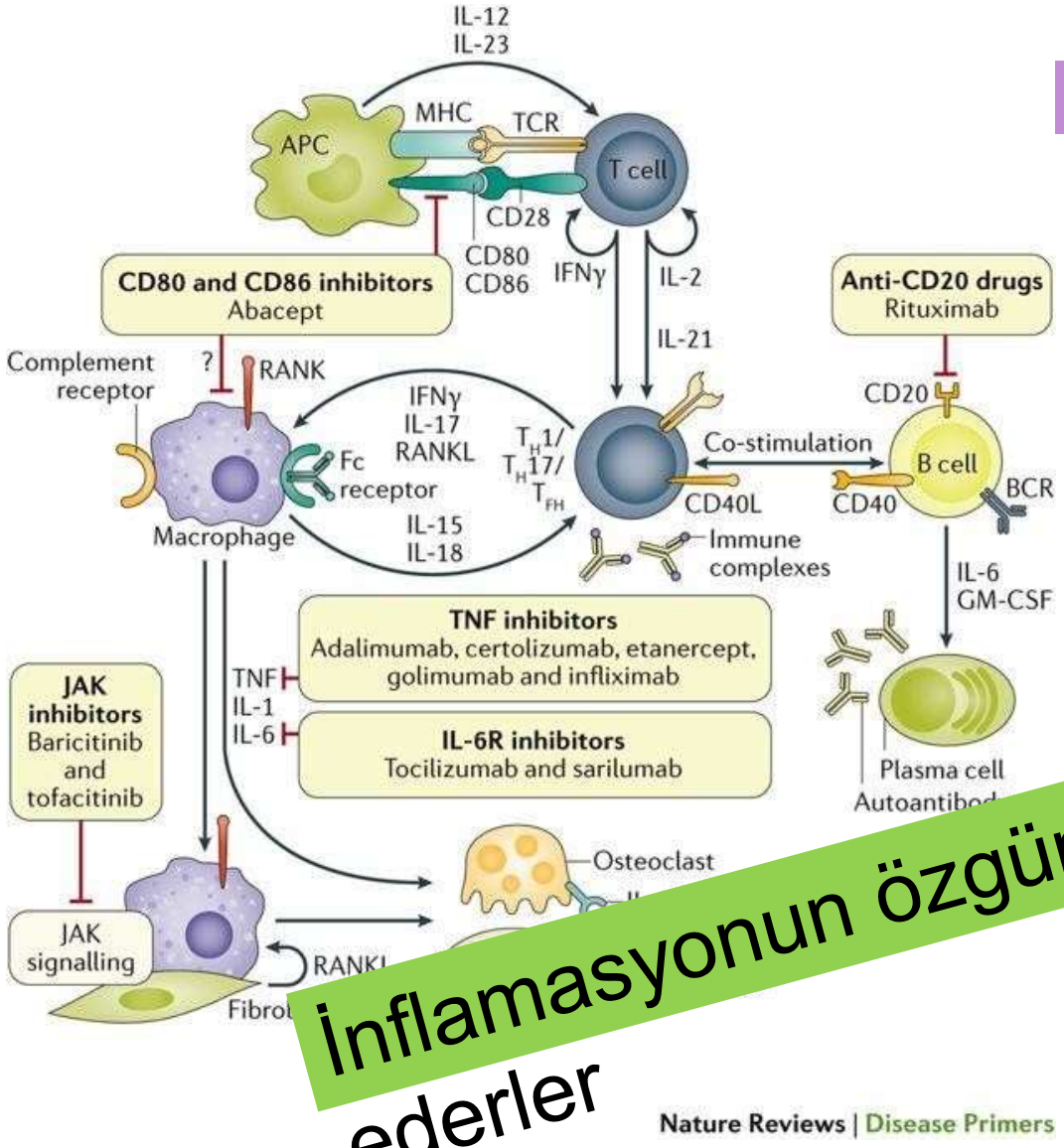
- Özgeçmiş: 8 yıl sero(-) RA→ Sülfasalazin, MTX, prednisolon
- Tedavi dirençli→ Adalimumab 40 mg (2 hft ara ile) 7 ay
- Parsiyel yanıt tedavi stop
- Abatacept + MTX→ şikayetler gerilemiş
- FM:
  - SS: 34, Nbz: 110, ateş 38.1, TA: 118/74mmHg.

Biyolojik ajan

- Romatolojik/otoimmun hastalıklar→
  - Patogenezde sorumlu hücre veya protein blokajı
  - Sistemik enflamasyon ve hastalık aktivitesinde baskılama

- Biyolojik ajanlar→
  - Antikorlar, interlökinler ve aşılar

Biyolojik ajan

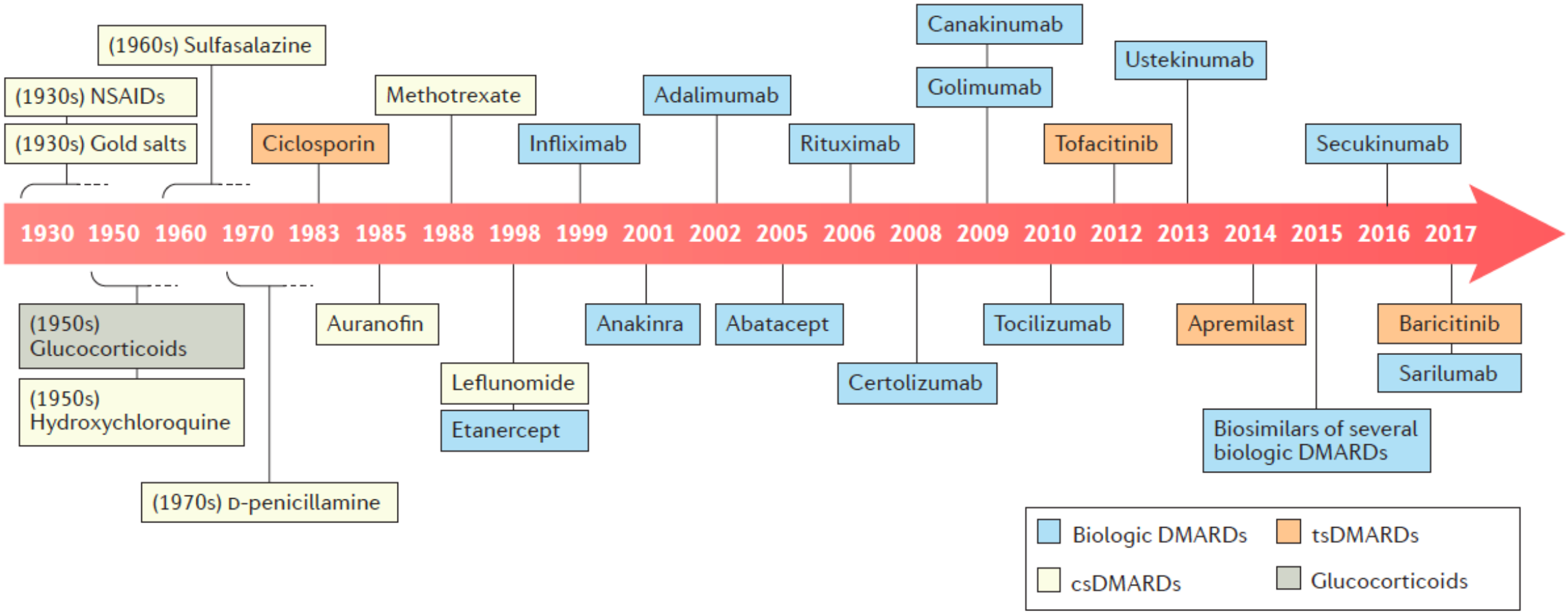


T hücre aktivasyonu için gerekli olan sinyalleri bloke ederek

Sitokin fonksiyonlarını bozarak

B hücrelerin düzeylerini azaltarak

İnflamasyonun özgün yollarını ve sinyallerini bloke ederler


(1960s) Sulfasalazine
(1930s) NSAIDs
(1930s) Gold salts
Methotrexate
Ciclosporin
Infliximab
Adalimumab
Canakinumab
Golimumab
Ustekinumab
Rituximab
Tofacitinib
Secukinumab
1930 1950 1960 1970 1983 1985 1988 1998 1999 2001 2002 2005 2006 2008 2009 2010 2012 2013 2014 2015 2016 2017
(1950s) Glucocorticoids
(1950s) Hydroxychloroquine
(1970s) D-penicillamine
Auranofin
Leflunomide
Etanercept
Anakinra
Abatacept
Certolizumab
Tocilizumab
Apremilast
Biosimilars of several biologic DMARDs
Baricitinib
Sarilumab
Biologic DMARDs
tsDMARDs
csDMARDs
Glucocorticoids

Hastalık Modifiye Edici Antiromatizmal İlaçlar (DMARD)

Sentetik DMARD'lar (sDMARD'lar)

- Konvansiyonel Sentetik (cs DMARD)
- Hedefe Yönelik Sentetik (tsDMARD)

Biyolojik DMARD'lar (bDMARD'lar)

- Orijinal Biyolojik (bo DMARD)
- Biyobenzer (bs DMARD)

Smolen JS, et al. Ann Rheum Dis 2014;73:3-5.

DMARD

RHEUMATOLOGY
Guidelines
British Society for Rheumatology
Rheumatology 2019;58:220–226
doi:10.1093/rheumatology/key207
Advance Access publication 21 August 2018

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—Executive summary

csDMARDs	boDMARDs	tsDMARDs
Methotrexate (MTX)	TNF Inhibitors	JAK Inhibitors
Hydroxychloroquine (HCQ)	• Etanercept	• Tofacitinib
Sulfasalazine (SSZ)	• Adalimumab	• Baricitinib
Leflunomide (LEF)	• Certolizumab	
	• Golimumab	
	• Infliximab	
	Abatacept	
	Rituximab	
	IL-6 Receptor Inhibitors	
	• Tocilizumab	
	• Sarilumab	

Biyolojik ajanlar

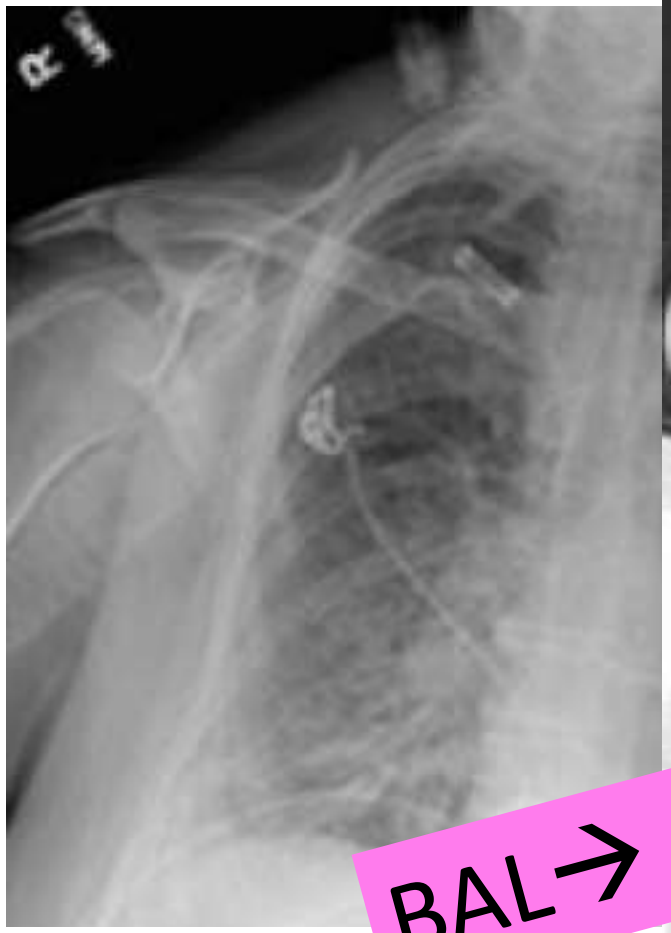
İnfeksiyon Riski

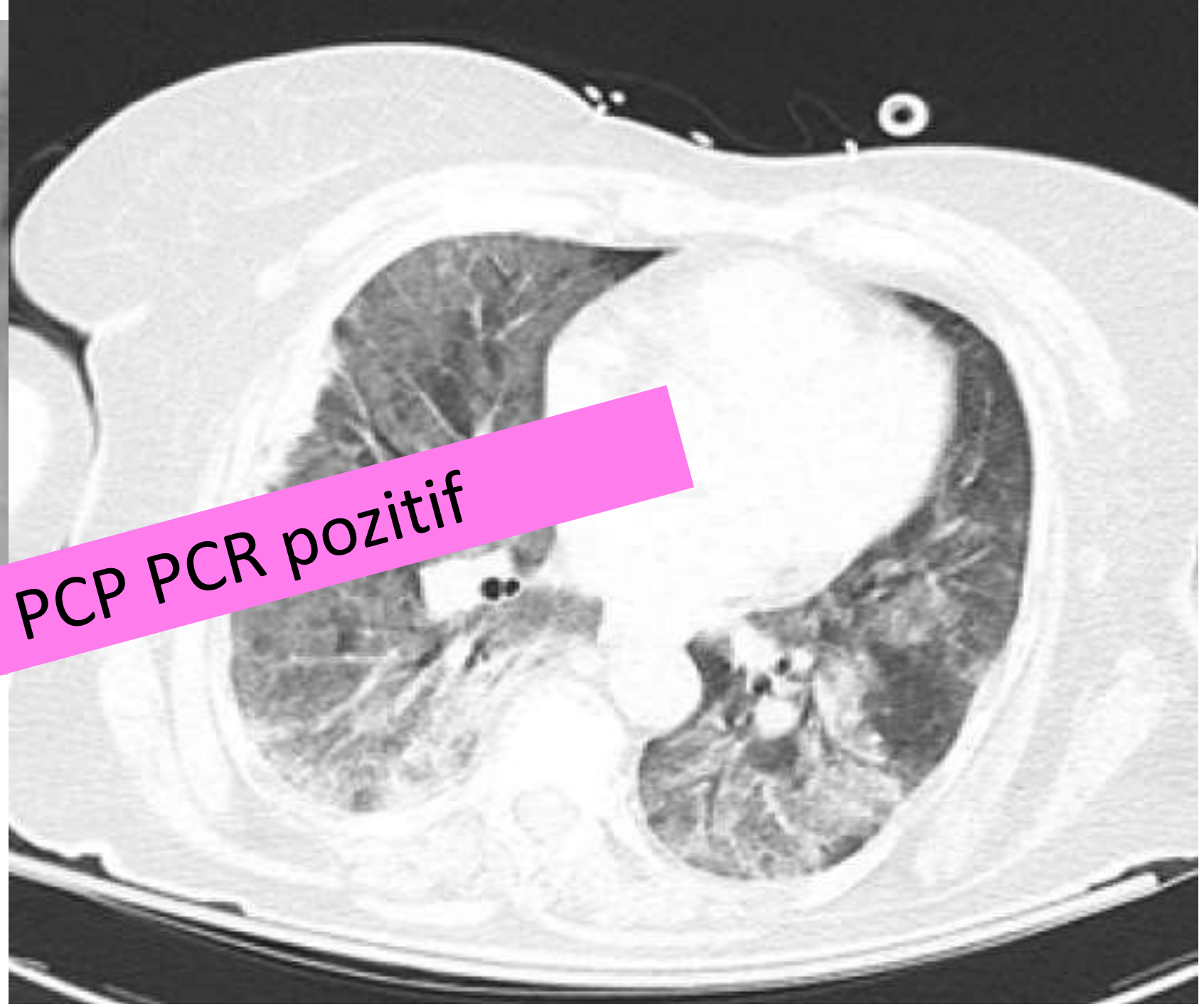
Doktorlar

İnfeksiyon kontrolü

Olgu

- WBC 7.790/μ L lenfopeni yok
- LDH **417** (135-214) U/L
- PaO2: 80, CRP: 112 mg/dL, sedim: 89 mm/sa
- Toraks BT→Diffüz retiküler intertisiyel infiltrasyon, buzlu cam





BAL→ PCP PCR pozitif

Olgu

- YBU takip→ NIV
- Ampirik ab
- Trimethoprim/sulfamethoxazol ve prednisolon
- AB stop
- 21 gün TMP/SXT ve steroid
- Servis izlemi

PCP risk faktörleri ve prognoz

- HIV (+)→ CD4<200
- Organ transplantasyon
- KİT
- Prematür infant
- T lenfosit fonk bozukluğu
- KT, immunsupresif ilaç
- HIV→ profilaksi ile %70-80→ %6-7

- Mortalite
  - Tedavisiz → %100
  - Tedavi ile→ %5-40
- HIV (-) bireylerde mortalite →%40-60
- HIV(+)→ %6-7

Chest. 2000;118(3):704–11.

Incidence of *Pneumocystis jiroveci* Pneumonia among Groups at Risk

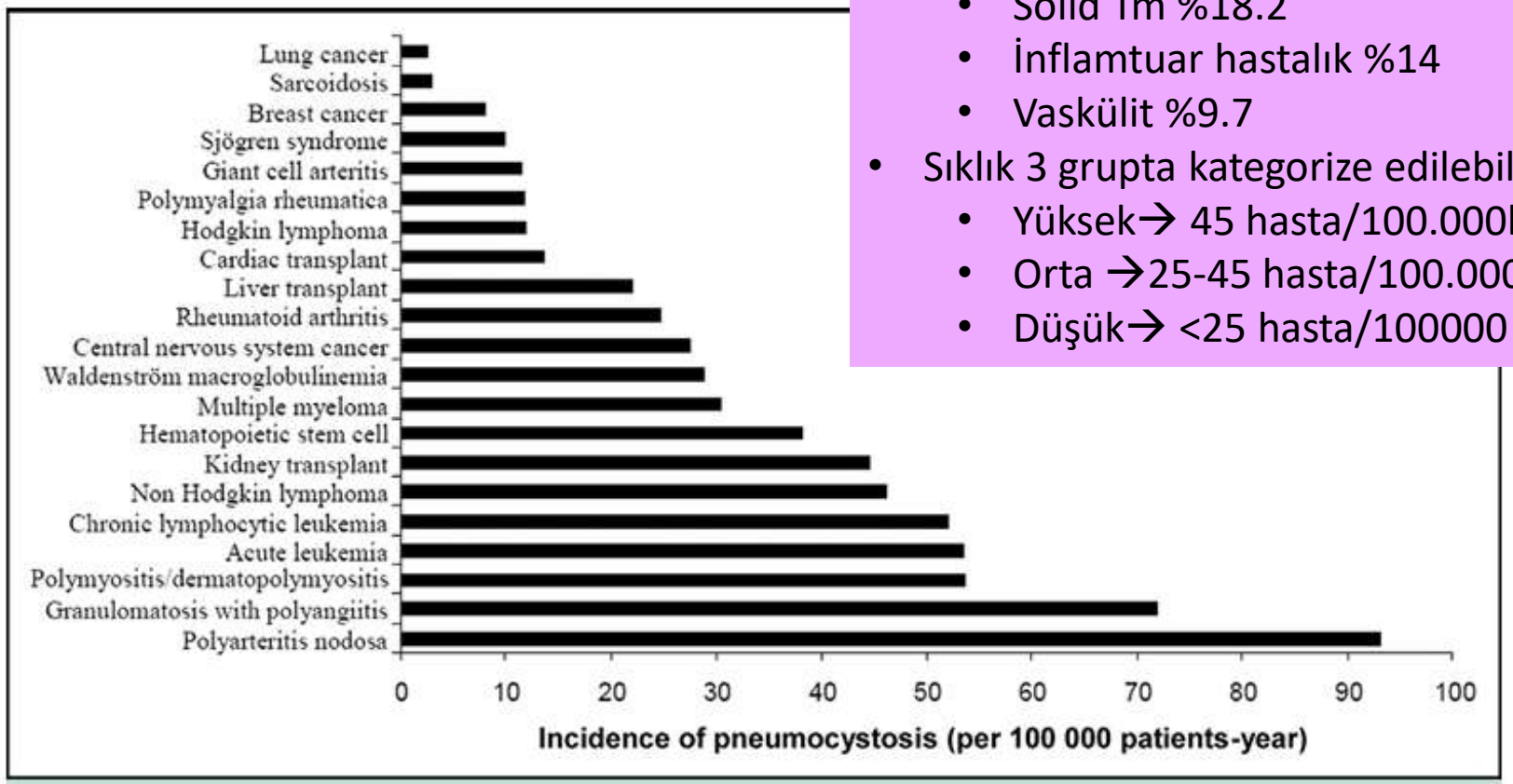


Figure 2 Estimated incidence of *Pneumocystis jiroveci* pneumonia among groups at risk.

- 1990-2010
- En sık altta yatan hastalık→
  - hematolojik malignite %32
  - Solid Tm %18.2
  - İnflamtuar hastalık %14
  - Vaskülit %9.7
- Sıklık 3 grupta kategorize edilebilir;
  - Yüksek→ 45 hasta/100.000hasta yılı: PAN, GPA, PM, DM, akut lösemi
  - Orta →25-45 hasta/100.000 hasta yılı: Waldenström,MM, SSS kanser
  - Düşük→ <25 hasta/100000 hasta yılı :Diğer tm

Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014

L. Cooley,[1] C. Dendle,[2,3] J. Wolf,[4,5] B. W. Teh,[6] S. C. Chen,[7,8,9] C. Boutlis[10,11]

INTERNAL MEDICINE JOURNAL

Table 2 Indications for *Pneumocystis jirovecii* chemoprophylaxis in patients (adults and children) with malignancy and recommended agent

Haematological malignancy (grade of recommendation)

Note: Patients may have multiple or cumulative risk factors; consider underlying disease, disease status and treatment-related immunosuppression.

Known indications:

- Allogeneic HSCT (all) (C)
- ALL (all) (A)
- AML or lymphoma regardless of treatment protocol (children only) (C)
- Autologous HSCT (all children and selected high-risk adults) (C)
- Regimens: R-CHOP14, high-dose methotrexate (C)
- Lymphocyte-depleting agents (e.g. alemtuzumab) or patients whose CD4 count <200 cells/uL before commencing chemotherapy (C)
- Corticosteroids: where 16–25 mg prednisolone or ≥4 mg dexamethasone for ≥4 weeks is planned (C)
- Regimens: FCR, ABVD, gemcitabine (single centre reports of higher risk for these regimens; consider prophylaxis) (D)

Solid tumours (grade of recommendation)

Regimens where 16–25 mg prednisolone or ≥4 mg dexamethasone for ≥4 weeks is planned (C)

Brain tumours, particularly if temozolomide or craniospinal irradiation is planned (B)

Other solid tumours undergoing myelosuppressive chemotherapy (children only) (C)

First-line prophylactic agent should be trimethoprim-sulfamethoxazole, unless:

(i) Previous allergy or hypersensitivity to sulfa-drugs
Recommend: trimethoprim-sulfamethoxazole desensitisation (unless previous anaphylaxis)

(ii) Planned methotrexate chemotherapy in adults
Recommend: second-line prophylactic agent

A second-line prophylactic agent should be used if trimethoprim-sulfamethoxazole is contraindicated:

(i) Dapsone, OR

(ii) Pentamidine (nebulised, monthly), OR

(iii) Atovaquone

Prophylaxis should continue for at least 6 weeks after steroid cessation. A longer period of prophylaxis may be required if ongoing chemotherapy (e.g. cytarabine, cyclophosphamide, fludarabine, fluorouracil, methotrexate) is planned. Life-long prophylaxis should be considered if the patient has had a previous episode of PJP and persisting immunosuppression.

Curr Rheumatol Rep (2017) 19: 35
DOI 10.1007/s11926-017-0664-6

Pneumocystis Pneumonia and the Rhe
Which Patients Are At Risk and How

Table 1 Risk factors for the development of PCP in patients with CTD

Established	Suspected[a]	Possible
Low CD4+ count	Glucocorticoids	Younger age[b]
Lymphopenia	Cyclophosphamide	Male[b]
	Rituximab	Hispanic decent[b]
	Methotrexate	Asian decent[b]
	Anti-TNF inhibitors	Private medical insurance[b]
	Azathioprine	Interstitial pulmonary fibrosis[c]
		Caucasian decent[d]
		Australian autumnal season[d]

Table 3 Authors' recommendations for PCP prophylaxis in CTD

Disease	Prophylaxis?	To whom?	Conditional factors[b]	NNT [5••]
GPA	Yes	All patients undergoing induction therapy		32
SLE	Conditional[a]	High dose GC	Lymphopenia Low CD4+ count Immunosuppressive regimen	110
PM/DM	Conditional[a]	High-dose GC	Lymphopenia Low CD4+ count More severe disease	73
PAN, AAV	Conditional[a]	During induction therapy and/or high dose GC	Lymphopenia Low CD4+ count	110
RA	No	–	–	1099
GCA	No	–	–	–
Scleroderma	No	–	–	110

GPA granulomatosis with polyangiitis, *SLE* systemic lupus erythematosus, *DM* dermatomyositis, *PM* polymyositis, *PAN* polyarteritis nodosa, *AAV* ANCA-associated vasculitis, *RA* rheumatoid arthritis, *GCA* giant cell arteritis

[a] Conditional recommendation means there is not enough evidence to support wide spread use but consider on a case-by-case basis taking into account the above specific factors

[b] Specific numerical values for these items are not evidence-based. Given the lower risk of PCP in these populations, lower values would be less likely capture patients who do not need prophylaxis (minimizing harm). Could consider <500 cells/mm^3 for lymphopenia and <200 cells/mm^3 for CD4+ count. Lower threshold levels of lymphopenia in SLE may be indicated given common disease-related lymphopenia (<350 cells/mm^3 [25])

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Q: Do patients on biologic drugs for rheumatic disease need PCP prophylaxis?

Risk factors for *Pneumocystis jirovecii* pneumonia in patients on biologic therapy for rheumatic disease

Clinical risk factors
Age > 65[5,21,22]
Preexisting pulmonary disease[9,21,22]
Granulomatosis with polyangiitis[4,19]
Microscopic polyangiitis[4]
Polyarteritis nodosa[19]
Inflammatory myopathy[19]
Systemic lupus erythematosus[19]

Laboratory testing indicators
Lymphopenia (< 500 cells/mm^3)[5,18]
Low CD4 count (< 200 cells/mm^3)[5,18]
Low immunoglobulin G level[9]

Pharmacologic risk factors
Concomitant chronic glucocorticoid therapy[3–6,9,17,21,28] (≥ 15 mg/day of prednisone for 4 weeks or longer)[4,5]
Concomitant therapy with nonbiologic disease-modifying antirheumatic drug or cytotoxic agent[5,7,9,22]

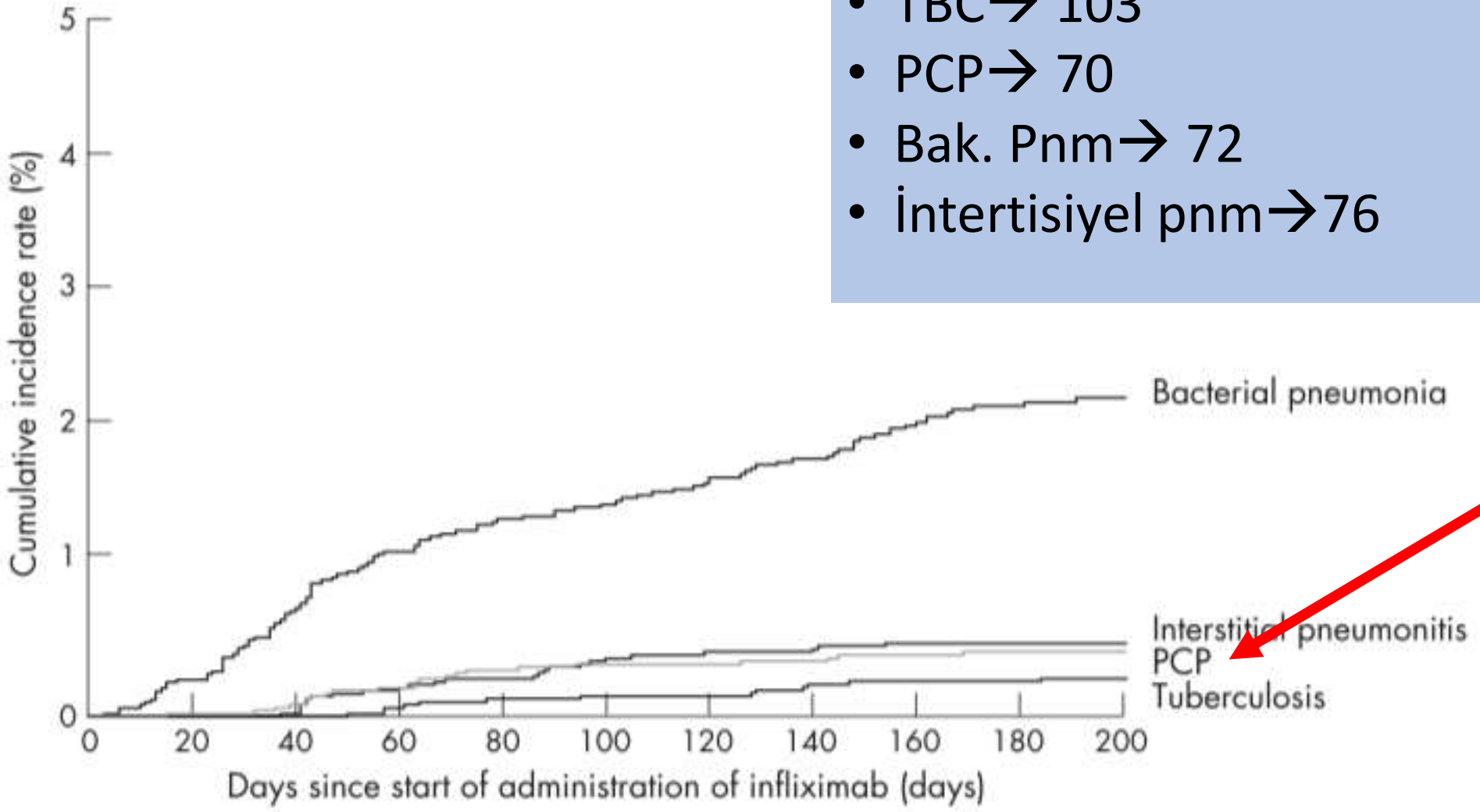
Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis

Reg. No.	1–5000	1–1000	1001–2000	2001–3000	3001–4000	4001–5000
Investigated cases	5000	1000	1000	1000	1000	1000
Important ADRs						
Bacterial pneumonia	108 (2.2%)	30	14	22	12	30
(Suspected) *P jirovecii* pneumonia	22 (0.4%)	6	1	3	6	6
Tuberculosis	14 (0.3%)	6	5	0	2	1
Interstitial pneumonitis	25 (0.5%)	4	5	8	2	6
Infusion reactions	484 (9.7%)	105	119	99	80	81
Serious infusion reaction	24 (0.5%)	7	8	3	3	3

Ann Rheum Dis 2008;**67**:189–194.

Ortalam gün sayısı

- TBC→ 103
- PCP→ 70
- Bak. Pnm→ 72
- İntertisiyel pnm→76



www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 35), pp: 59729-59739

Meta-Analysis

Risk factors for mortality from pneumocystis carinii pneumonia (PCP) in non-HIV patients: a meta-analysis

- Mortalite %30.6
- Risk fakt→ İleri yaş, kadın, sol. Yetm. LDH yüksekliği
- Komorbidite→
  - Hematolojik malignite %30
  - Otoimmun hastalık %20
  - KİT/SOT %14
  - Solid tm %6

RHEUMATOLOGY

Rheumatology 2018;57:997–1001
doi:10.1093/rheumatology/key023
Advance Access publication 26 February 2018

Concise report

Opportunistic infections in rheumatoid arthritis patients exposed to biologic therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

- 19 282 hasta izlenmiş
- TB dışı fırsatçı enf→ 134 vaka/100.000 py
- Farklı ilaç grupları arasında fırsatçı enf. açısından fark yok
- Rituximab ile PCP sıklığı anti-TNF'ye göre daha yüksek(HR= 3.2)

Narrative review

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)

- Anti-Pneumocystis profilaksi→
  - KT ve steroid
- Alemtuzumab (anti-CD52) özellikle lösemi ve SOT alıcılarında PCP riskini artırır.
- Profilaksi bu hasta grubuna da uygun
- EORTC→Rituximab ile steroid (20 mg/gün >4 hft) birlikteliğinde

Clinical Microbiology and Infection 24 (2018) S71–S82

Narrative review

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

- Anti-TNF-a →İnfliximab, adalimumab, golimumab, certolizumab ve etanercept
  - 2X4 kat TB riski
  - Etanercept için bu risk diğerlerine göre daha az
  - PCP profilaksisi rutin önerimez

Clinical Microbiology and Infection 24 (2018) S10–S20

ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients

Journal of Antimicrobial Chemotherapy

- PCP profilaksisi→
  - ALL
  - Allo KİT
  - Alemtuzumab, fludarabine/cyclophosphamide/rituximab ve KS 4 hft

J Antimicrob Chemother 2016; **71**: 2397–2404
doi:10.1093/jac/dkw157 Advance Access publication 12 May 2016

RHEUMATOLOGY

Rheumatology 2012;51:2120–2130
doi:10.1093/rheumatology/kes244
Advance Access publication 22 September 2012

Review

Pneumocystis jirovecii infection: an emerging threat to patients with rheumatoid arthritis

TABLE 1 Incidence and mortality rate of *P. jirovecii* pneumonia in RA patients during immunosuppressive therapy in Japan

Anti-RA agents	PCP incidence, *n* (%)[a]	Mortality, *n* (%)[a]
MTX	236	28 (11.9)
Tacrolimus	14	4 (28.6)
Infliximab	188 (0.3)	19 (10.1)
Etanercept	81 (0.1)	15 (18.5)
Adalimumab	54 (0.3)	10 (18.5)
Golimumab	1 (0.03)	0
Tocilizumab	14 (0.2)	2 (14.3)
Abatacept	9 (0.1)	2 (22.2)

Pneumocystis jirovecii Pneumonia in Rheumatoid Arthritis Patients: Risks and Prophylaxis Recommendations

Libertas Academica
FREEDOM TO RESEARCH

Table 1. Prevalence of *Pneumocystis jirovecii* pneumonia in RA patients during biological antirheumatic therapy in Japan.

DRUGS	MECHANISMS OF ACTION	PCP PREVALENCE NUMBER (%)	MORTALITY NUMBER (%)
Infliximab	TNFα inhibitor (anti-TNFα antibody)	188 (0.3)	19 (10.1)
Etanercept	TNFα inhibitor (soluble TNF receptor)	81 (0.1)	15 (18.5)
Adalimumab	TNFα inhibitor (anti-TNFα antibody)	54 (0.3)	10 (18.5)
Tocilizumab	Anti–IL-6 receptor antibody	14 (0.2)	2 (14.3)
Abatacept	T-cell signaling inhibitor	9 (0.1)	2 (22.2)

- PubMed ve EMBASE→
  - RA hastalarında biyolojik ajan cinsine göre fark yok

BMC Infectious Diseases

BioMed Central

Debate

Open Access

Autoimmune inflammatory disorders, systemic corticosteroids and pneumocystis pneumonia: A strategy for prevention

- 1 ay sonrasında immunsupresif hasta CD4
  - steroid doz >15 mg prednisolone /gün
  - >3 ay lenfosit sayısı <600 cells/mm3
- CD4< 200 ise profilaksi
- PCP öyküsü varsa immunsupresif tedavi verilen her hasta

Hangi biyolojik ajanlar ile PCP gelişebilir?

TNF Inhibitors	Treatment with TNF inhibitors should be started at least one month after initiation of the anti-TB regimen (isoniazid, rifampin, or the combination of isoniazid and rifampin). TNF inhibitors should be discontinued if active tuberculosis occurs.[13]
	Tenofovir or Entecavir is recommended for infected HBs Ag-positive patients at least two weeks before the initiation of TNF inhibitors. Antiviral agents should be continued for at least six months after the withdrawal of TNF inhibitors.[13,85] Antiviral prophylaxis is not recommended in HBs-Ag negative and anti-HBc-positive patients treated with TNF inhibitors.[13] Tenofovir or Entecavir is recommended in the case of HBV reactivation. TNF inhibitors are not recommended in the acute phase of hepatitis B, chronic untreated hepatitis B, and HBV infected patients with Child-Pugh B and C.[86]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under TNF inhibitors who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
IL-1-targeted agents	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months is recommended.[8]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under IL-1 targeted agents who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]

Hangi biyolojik ajanlar ile PCP gelişebilir?

CD30-targeted agent	Both HBs Ag positive and HBs Ag negative anti-HBc positive patients should receive antiviral prophylaxis before the administration of brentuximab vedotin.[12]
	HSV prophylaxis is recommended in patients on brentuximab vedotin.[12]
	PCP prophylaxis is recommended in patients on brentuximab vedotin.[12]
	Secondary CMV prophylaxis is recommended in patients with a history of CMV disease who are candidates for brentuximab vedotin rechallenge.[12]
CD38-targeted agents	Antiviral treatment could be considered in HBS-Ag positive patients who are candidates for CD-38 targeted agents.[12] Monitoring of HBV viral load is recommended in HBS-Ag negative and HBV-Ab positive patients.[12]
	HSV prophylaxis is recommended in VZV seropositive patients at least one week before the administration of daratumumab and continued for 12 weeks after discontinuation[12]
	PCP prophylaxis is recommended in patients receiving concomitant glucocorticoids, and CD-38 targeted agents.[12]
CD40-targeted agents	PCP prophylaxis should be considered in patients on CD-40 targeted agents.[12]
	Regular monitoring of CMV PCR and signs, as well as symptoms of CMV disease, are recommended in patients on CD-40 targeted agents.[12]

CD319-targeted agents	HSV prophylaxis is recommended in VZV seropositive patients.[12]
	PCP prophylaxis is recommended in patients receiving concomitant glucocorticoids and elotuzumab.[12]
CCR4-targeted agent	PCP prophylaxis is recommended in patients on mogamulizumab.[12]
	HSV prophylaxis is recommended in patients on mogamulizumab.[12]
Anti-CD20 monoclonal antibodies	HBs Ag-positive patients should receive antiviral prophylaxis (preferably tenofovir or entecavir) before the administration of anti-CD20 monoclonal antibodies. HBs Ag-negative/anti-HBc-positive patients should receive antiviral prophylaxis (could be lamivudine) before administration of anti-CD20 monoclonal antibodies. Antiviral agents should be continued for at least 12–18 months after the completion of anti-CD20 monoclonal antibody treatment and if viral load remains undetectable.[10,14] HBV viral load should be monitored for 12 months after discontinuation of antiviral prophylaxis.[10] Anti-CD20 monoclonal antibodies should be discontinued if reactivation of hepatitis B occurs. ECIL and ESCMID guidelines recommend PCP prophylaxis in patients receiving anti-CD20 monoclonal antibodies and corticosteroids equivalent to ≥ 20 mg prednisolone for more than four weeks.[10,26] ECIL and NCCN guidelines recommend PCP prophylaxis in CLL patients treated with Rituximab/Ofatumumab/ Obinutuzumab, and purine analogs/high dose methylprednisolone; Fludarabine-Cyclophosphamide-Rituximab (FCR) and Pentostatin-Cyclophosphamide-Rituximab (PCR) regimens for ≥ six months after completion of treatment.[14,26] Some experts consider PCP prophylaxis for granulomatosis polyangiitis patients on rituximab and patients with rheumatologic diseases who have underlying pulmonary diseases.[39] PCP prophylaxis is optional for patients undergoing R-CHOP 14 regimen.[26]

Anti-CD52 monoclonal antibody	PCP prophylaxis is recommended in patients treated with alemtuzumab for hematologic malignancies and indications other than multiple sclerosis for at least 2–6 months and should be continued until $CD_4^+ \geq 200$ cells/μL.[26] PCP infection associated with alemtuzumab used in multiple sclerosis is extremely rare, and prophylaxis is not routinely recommended.[64] If alemtuzumab is administered for solid organ transplantation induction, the American Society of Transplant recommends PCP prophylaxis for at least 6–12 months after induction. Life long duration of PCP prophylaxis may be considered for lung and small bowel transplant or patients with chronic CMV infection or prior history of PCP infection.[17] If alemtuzumab is administered for conditioning of allogeneic hematopoietic stem cell transplantation, PCP prophylaxis is recommended for at least six months.[14]
T-Cell Co-stimulation Blocker	Antiviral treatment is recommended in HBs Ag- positive patients who are candidates for abatacept therapy.[30] Monitoring of HBV viral load is recommended in HBsAg-negative and anti-HBc- positive patients.[30]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under abatacept who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
Agent targeting B-cell activating factor	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under abatacept who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]

IL-5-targeted agents	Some experts recommend PCP prophylaxis in Eosinophilic Granulomatosis with Polyangiitis (EGPA) patients on IL-5 targeted agents.[39]
IL-12 and IL-23-targeted agent	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[8]
	Antiviral treatment is recommended in HBS-Ag positive patients who are candidates for ustekinumab therapy.[8] Monitoring of HBV viral load is recommended in HBS-Ag negative and HBV-Ab positive patients.[8]
	Some experts consider PCP prophylaxis in rheumatologic disease patients on ustekinumab who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
IL-17-targeted agents	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[8]
	Some experts consider PCP prophylaxis in rheumatologic disease patients on secukinumab who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
Proteasome inhibitors	HSV/VZV prophylaxis is recommended in VZV seropositive patients at least four weeks after discontinuation of therapy.[11]
	PCP prophylaxis could be considered in multiple myeloma patients treated with high dose corticosteroids.[11]


Doğru yerde
profilaksi

Teşekkürler.....