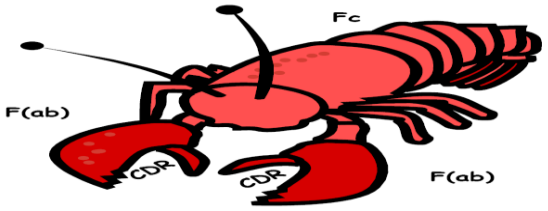
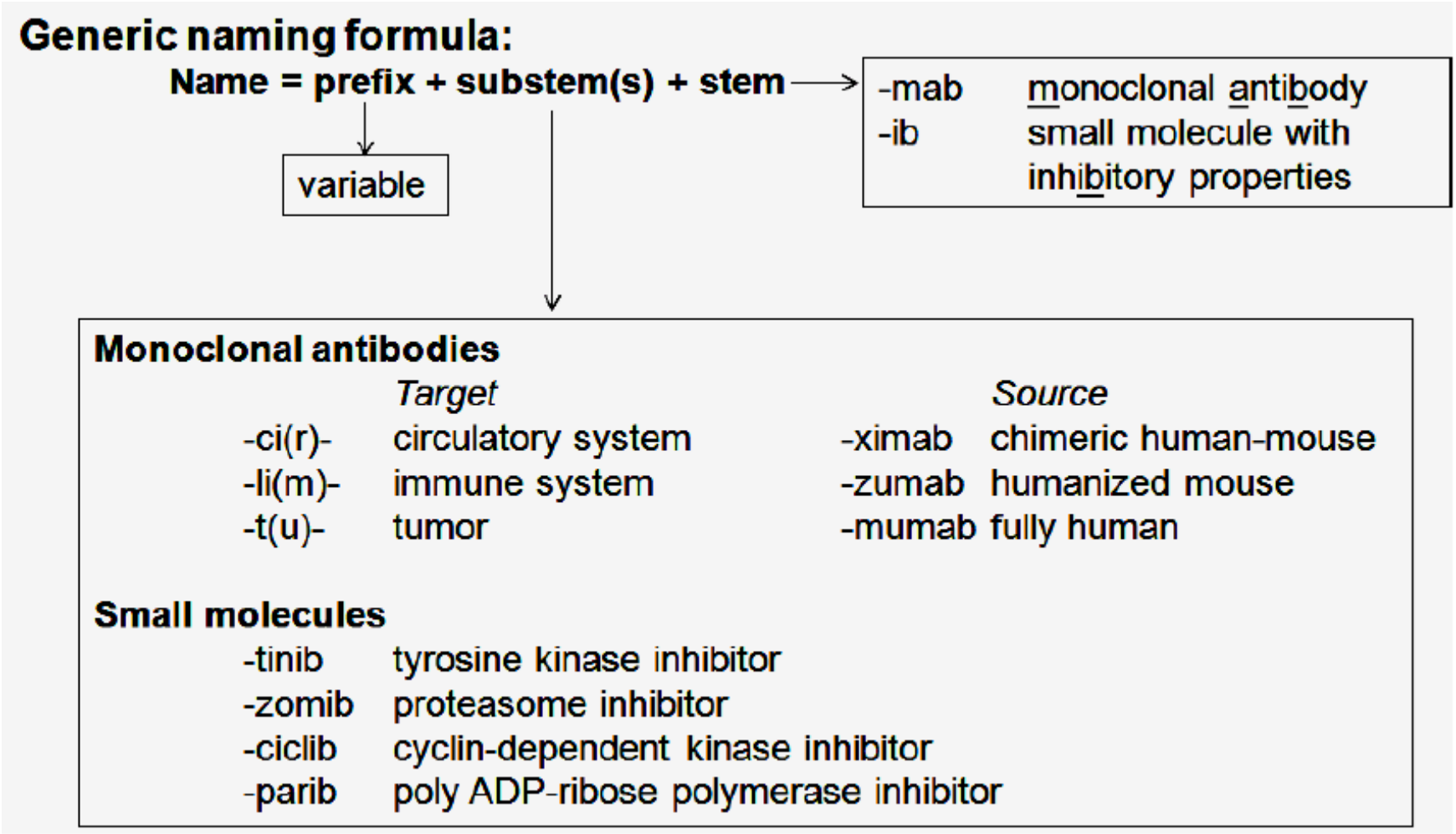
“Yeni” İmmünosüpresif Ajanlar ve İnfeksiyonlar



İnfeksiyon Yönetimi: Korunma, Tanı ve Tedavi

Yrd. Doç. Dr. Tümer GÜVEN
Yıldırım Beyazıt Üniversitesi

YENİ MOLEKÜLLER NASIL OKUNUR?



Yeni immünosüpresif ajanlar - 1

Jenerik isim	Hedef	Hastalıklar
Bevacizumab	VEGF	Çok sayıda kanser
Cetuximab	EGFR1	Kolon, Baş-boyun
Panitumumab	EGFR1	Kolon
Trastuzumab	HER-2	Meme
Brentuximab	CD30	Hodgkin Hastalığı
Gemtuzumab	CD33	AML
Visilizumab	CD3 antikoru	Ülseratif kolit, Crohn Hastalığı
Daclizumab	IL-2 reseptör antikoru	Transplant hastaları, Multipl skleroz
Basiliximab	IL-2 reseptör antikoru	Renal Transplant hastaları
Anakinra	IL-1 reseptör antikoru	Romatoid artrit, Otoimmün hastalıklar
Tocilizumab	IL-6 reseptör antikoru	Romatoid Artrit Juvenil idiopatik artrit
Abatacept	T-cell co-stimulatory pathways (CD80 veya CD86)	Romatoid Artrit
Alemtuzumab	CD52	KLL, Lenfoma

Yeni immünosüpresif ajanlar - 2

Jenerik isim	Hedef	Hastalıklar
Rituximab	CD20	Lenfoma Romatoid artrit
İnfliximab	TNF	Romatoid artrit Ankilozan spondilit Spondiloartropati Ülseratif kolit Crohn hastalığı Psöriazis
Etanercept	TNF/LTα	
Adalimumab	TNF	
Sertolizumab	TNF	
Golimumab	TNF	

Table 1
The prebiologic era: frequency of infections among patients with RA and healthy controls from a Minnesota cohort

Infection Type	Incidence per 100 Patient-Years RA	Incidence per 100 Patient-Years Non-RA	Relative Risk (95% Confidence Interval)
Pneumonia	4.0	2.4	1.7 (1.5–1.9)
Skin	3.0	0.9	3.3 (2.7–4.1)
Sepsis	0.78	0.51	1.5 (1.1–2.1)
Septic joint	0.40	0.02	14.9 (6.1–73.7)
Intra-abdominal	0.22	0.08	2.8 (1.4–6.2)
Osteomyelitis	0.17	0.01	10.6 (3.4–126.8)

Doran MF, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46(9):2287–93.

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

Table 2
Dose-dependent increase in hospitalized infection observed with glucocorticoid use, from the SABER study

Exposures	Events, Number	Person-Years, Number	Rate, per 100 Person-Years	Hazard Ratio (95% CI) for Propensity Score-Matched Cohorts	Adjusted Hazard Ratios (95% CI)
RA Nonbiologic regimens	326	4192	7.78	Ref.[1]	Ref.[1]
Tumor necrosis factor α antagonists	497	6089	8.16	1.05 (0.91–1.21)	1.05 (0.91–1.21)
Baseline glucocorticoid use, prednisone equivalents					
None					Ref.[1]
>0–<5 mg/d					1.32 (1.10–1.58)
5–10 mg/d					1.78 (1.47–2.15)
>10 mg/d					2.95 (2.41–3.61)

Data from Grijalva CG, Chen L, Delzell, E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA 2011;306:2331–9.

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

Table 3
The biologic era: rates and RRs of serious infections in patients with RA using anti-TNF therapy from European and North American observational cohort studies

Country, Year	Crude Incidence per 100 Patient-Years Anti-TNF Treated	Crude Incidence per 100 Patient-Years Nonbiologic Comparator	Adjusted RR[a] (95% CI)
Germany,[37] 2005	6.4, ETN 6.2, INF	2.3	2.2 (0.9–5.4) ETN 2.1 (0.8–5.5) INF
United Kingdom,[34] 2007	5.5	3.9	1.3 (0.9–1.8)[c] 4.6 (1.8–11.9)[b]
United States,[8] 2007	2.9[d]	1.4[d]	4.2 (2.0–8.8)[d] 1.9 (1.3–2.8)
Sweden,[32] 2007	4.7	NR	1.4 (1.2–1.7)[e]
United States,[7] 2007	4.9	3.8	1.3 (0.8–2.1)
United States,[35] 2011	8.2	7.8	1.05 (0.9–1.2)
Germany,[10] 2011	4.8	2.3	1.8 (1.2–2.7)[f]
Japan,[91] 2011	6.4	2.6	2.4 (1.1–5.05)[g]

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

Table 4

The biologic era: rates and RRs of opportunistic infections in patients with RA using anti-TNF therapy from European and North American observational cohort studies

Country, Year	Outcome Studied	Crude Incidence per 100,000 Patient-Years Anti-TNF Treated	Crude Incidence per 100,000 Patient-Years Nonbiologic Comparator	Adjusted RR[b] (95% CI)
United Kingdom,[33] 2006	OI	192[b,c]	0[b]	NR
France,[92] 2006	OI[d]	152[a]	NR	NR
United States,[93] 2010	OI	3000[b]	1600[b]	1.7 (0.95–2.9)

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

Table 5
The biologic era: rates and RRs of specific opportunistic infections in patients with RA using anti-TNF therapy from European and North American observational cohort studies

Country, Year	Outcome Studied	Crude Incidence per 100,000 Patient-Years Anti-TNF Treated	Crude Incidence per 100,000 Patient-Years Nonbiologic Comparator	Adjusted RR[b] (95% CI)
United Kingdom,[39] 2010	TB	95[b]	0[b]	UNDEF
France,[92] 2011	TB	117[a]	NR	NR
United States,[94] 2011	TB	56[b]	9[b]	NR
United States,[82] 2011	NTM	105[b]	19[b]	NR
France,[92] 2006	*Legionella* pneumonia	37.5[c]	NR	NR
United States,[95] 2009	Zoster	1060	1118	NR
Germany,[10] 2011	Zoster	980[b]	560[b]	1.63
United Kingdom,[36] 2011	Zoster	1600	800	1.7

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

“Yeni” İmmünosüpresif Ajanlar ve İnfeksiyonlar

- Bakteriyel infeksiyonlar
- Fungal infeksiyonlar
- Tüberküloz (Akciğer ve AC dışı)
- Atipik mikobakteriler
- Diğer infeksiyonlar
- Viral infeksiyonlar
  - Genel
  - VZV, HBV, HCV
- İnfeksiyon Yönetimi ve tedavi öncesi testler?
- Aşılama

"Yeni" İmmünosüpresif Ajanlar ve İnfeksiyonlar

RİTUXİMAB

- Kanser tedavisinde (kombinasyon içinde)
  - Lenfoma
  - KLL
- Romatoid Artrit
  - MTX ile kombinasyon halinde
  - TNF inhibitörüne yanıt alınamayan
  - TNF inhibitörü başlanması uygun olmayan

RİTUXİMAB / ALEMTUZUMAB…

İnfeksiyon ne kadar sık?

- **Meta-analiz:**
- Opportunistik enfeksiyonlar
- 1996-2004
- 17 makale
- 992 hasta
    - 535 Rituximab
    - 409 Alemtuzumab
    - 48 her ikisi

Cornely OA, et al. Opportunistic infections (OI) following monoclonal antibody treatment . Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No 16S (June 1 Supplement), 2005: 2562**. Meta-analiz**.

RİTUXİMAB / ALEMTUZUMAB…

İnfeksiyon ne kadar sık?

- **Opportunistik enfeksiyon sıklığı:**

	299 hasta	**% 30.1**
• Nedeni gösterilemeyen :	109 hasta	(% 36.5)
• Viral re-aktivasyon:	100 hasta	(%33.4)
• Bakteriyel enfeksiyon:	44 hasta	(%14.7)
• Fungal enfeksiyon:	26 hasta	(%8.7)
• Protozoal enfeksiyon:	11 hasta	(%3.7)
• Viral enfeksiyon:	9 hasta	(%3.0)

Cornely OA, et al. Opportunistic infections (OI) following monoclonal antibody treatment . Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No 16S (June 1 Supplement), 2005: 2562**. Meta-analiz**.

RİTUXİMAB / ALEMTUZUMAB…

İnfeksiyon ne kadar sık?

- **Viral re-aktivasyon:**
  - CMV: 58 hasta (%19.4)
  - Herpes simpleks : 30 hasta (%10)
  - Varicella zoster: 11 hasta (%3,7)
  - EBV: 1 hasta (%0.3)

- **PCP:** 11 hasta (%3,7)

Cornely OA, et al. Opportunistic infections (OI) following monoclonal antibody treatment . Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings.Vol 23, No 16S (June 1 Supplement), 2005: 2562. **Meta-analiz.**

RİTUXİMAB / ALEMTUZUMAB…

İnfeksiyon ne kadar sık?

İNFEKSİYONLARA BAĞLI ÖLÜM

20 HASTA!

Cornely OA. Opportunistic infections (OI) following monoclonal antibody treatment . Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings.Vol 23, No 16S (June 1 Supplement), 2005: 2562. Meta-analiz.

Biyolojik ajanlar ve İnfeksiyon sıklığı

Table 1 Serious infections in clinical trials of biologic therapies

Study (location)	Design	Disease	Agent	Number of patients	Risk ratio (95% CI)
Bongartz *et al.*[3] (international)	Meta-analysis	RA	Infliximab, adalimumab	5,014	OR = 2.1 (1.31–3.1)
Salliot *et al.*[16] (international)	Meta-analysis	RA	Abatacept Rituximab Anakinra	1,960 745 2,062	OR = 1.35 (0.78–2.32) OR = 1.45 (0.56–3.73) OR = 2.75 (0.90–8.35)
Hoshi *et al.*[21] (Japan)	Clinical trial, registry control	RA	Tocilizumab	601	Adjusted SIR = 2.41 (1.68–3.34)
Singh *et al.*[4] (international)	Meta-analysis	All indications	All biologics Adalimumab Etanercept Certolizumab pegol Golimumab Infliximab Abatacept Anakinra Rituximab Tocilizumab	41,036 7,018 7,334 1,929 2,895 6,242 3,543 3,821 4,485 3,769	OR = 1.19 (0.94–1.52) OR = 1.12 (0.73–1.70) OR = 1.06 (0.74–1.51) OR = 3.51 (1.59–7.79) OR = 1.29 (0.71–2.35) OR = 1.45 (0.99–2.13) OR = 0.57 (0.30–1.08) OR = 1.08 (0.47–2.50) OR = 0.97 (0.64–1.48) OR = 1.58 (0.85–2.94)

Abbreviations: RA, rheumatoid arthritis; SIR, standard incidence ratio.

Woodrick RS & Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. Nat Rev Rheumatol 2011;7;639–652.**Review**.

OPEN ACCESS

EXTENDED REPORT

Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients

Ronald F van Vollenhoven,[1] Paul Emery,[2] Clifton O Bingham III,[3] Edward C Keystone,[4] Roy M Fleischmann,[5] Daniel E Furst,[6] Nicola Tyson,[7] Neil Collinson,[7] Patricia B Lehane[7]

Handling editor Tore K Kvien

► Additional data are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2012-201956).

[1]Unit for Clinical Therapy

ABSTRACT

Objectives Evaluation of long-term safety of rituximab in rheumatoid arthritis (RA).

Methods Pooled observed case analysis of data from patients with moderate-to-severe, active RA treated with rituximab in a global clinical trial programme.

Results As of September 2010, 3194 patients had received up to 17 rituximab courses over 9.5 years

B cell-targeted therapy using the anti-CD20 monoclonal antibody rituximab is an effective treatment for RA. In combination with methotrexate (MTX), rituximab improves the signs and symptoms of RA and slows joint damage progression.[8–15] Data from eight randomised, placebo-controlled trials in patients with moderately to severely active RA demonstrated that the overall

Ann Rheum Dis 2013;**72**:1496–1502. doi:10.1136/annrheumdis-2012-201956

Table 1 Patient characteristics at baseline*

	Rituximab + MTX All Exposure (n=3194)	Rituximab + MTX >5 years (n=627)	Placebo + MTX (n=818)

Table 2 Summary of adverse events/100 pt-years

	Rituximab+MTX All Exposure (n=3194)	Rituximab+MTX >5 years (n=627)	Placebo+MTX (n=818)
Exposure (pt-years)	11 962	4418	1107
AEs/100 pt-years (95% CI)	263.10 (260.21 to 266.02)	254.12 (249.46 to 258.86)	315.43 (305.14 to 326.06)
SAEs/100 pt-years (95% CI)	14.40 (13.73 to 15.09)	14.30 (13.23 to 15.46)	13.82 (11.79 to 16.19)
Infections/100 pt-years (95% CI)	81.64 (80.04 to 83.27)	75.41 (72.89 to 78.02)	90.39 (84.96 to 96.17)
SIEs/100 pt-years (95% CI)	3.94 (3.60 to 4.31)	3.26 (2.77 to 3.84)	3.79 (2.80 to 5.13)

AE, adverse event; MTX, methotrexate; pt-year, patient-year; SAE, serious adverse event; SIE, serious infection event.

81,64 x 119,62 = 9765 infeksiyon

3,94 x 119,62 = 471 Ciddi infeksiyon

van Vollenhoven RF, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72(9):1496-502.

- En sık görülen infeksiyonlar (>%5)
  - ÜSYE
  - Nazofarenjit
  - Üriner sistem enfeksiyonları
  - Bronşit
  - Sinüzit
  - Gastroenterit
  - İnfluenza
  - Alt solunum yolu enfeksiyonları

van Vollenhoven RF, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72(9):1496-502.

- **Ciddi opportunistik infeksiyonlar nadir;**
- **9 vaka**
  - Atipik pnömoni (2)
  - Kandidemi (1)
  - Farengeal abse (1)
  - Scedosporium AC enfeksiyonu (1)
  - *Pneumocystis jirovecii* (1)
  - Progresif Multifokal Lökoensefalopati (1)
  - Akciğer Tüberkülozu (2)

van Vollenhoven RF, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72(9):1496-502.

MTX ve TNF Antagonistleri

- Meta-analiz
- 7971 Romatoid artrit hastası
  - MTX : 4206
  - TNF antagonistleri : 1804
  - MTX + TNF antagonistleri : 2855
  - DMARDs : 1274

Greenberg JD, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 February ; 69(2): 380–386**. META-ANALİZ**

Risk of infection stratified by current treatment of rheumatoid arthritis

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Number of infections	1714	890	1514	447
Person years of follow-up	5141	2130	4031	1663
Unadjusted rate/100 person-years	33.3	41.8	37.6	26.9
Adjusted rate*/100 person-years	30.9 (29.2 to 32.7)	40.1 (37.0 to 43.4)	37.1 (34.9 to 39.3)	24.5 (21.8 to 27.5)

* Adjusted rates are per 100 person-years estimated with 95% CI in parentheses. Rates were adjusted for age, gender, race, education, duration of rheumatoid arthritis, modified Health Assessment Questionnaire, functional class, physician global, patient global, patient pain, swollen and tender joint counts, body mass index, disability status, liver disorder, lung disease, diabetes, ischaemic heart disease, alcohol use, smoking and prednisone use.

Greenberg JD, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 February ; 69(2): 380–386. **META-ANALİZ**

Rate of specific types of infection by treatment group

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Site of infection				
URI	660 (12.8)	303 (14.2)	522 (13.0)	148 (9.0)
Sinusitis	370 (7.2)	166 (7.8)	331 (8.2)	71 (4.3)
Urinary tract	157 (3.1)	81 (3.8)	111 (2.8)	32 (2.0)
Cellulitis	59 (1.3)	49 (2.3)	71 (1.8)	18 (1.1)
Non-pyogenic pneumonia	51 (1.0)	40 (1.9)	61 (1.5)	16 (1.0)
Pyogenic pneumonia	49 (1.0)	22 (1.0)	46 (1.1)	22 (1.3)
Bursitis	9 (0.2)	5 (0.2)	7 (0.2)	3 (0.2)
Infectious arthritis	9 (0.2)	5 (0.2)	5 (0.1)	2 (0.2)
Septicaemia	8 (0.2)	8 (0.4)	10 (0.3)	4 (0.2)
Other	342 (7.0)	211 (9.9)	350 (8.7)	131 (7.9)
Type of infectious organism				
Opportunistic	84 (1.6)	63 (3.0)	101 (2.5)	28 (1.7)
Non-opportunistic	1436 (27.9)	734 (34.5)	1245 (30.9)	378 (22.7)
All types of infection	1714 (33.3)	890 (41.8)	1514 (37.6)	447 (26.9)

Frequencies listed with crude rates per 100 person-years in parentheses. Totals differ as there were individual visits and intervals in which multiple infections were reported.

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumour necrosis factor; URI, upper respiratory infection.

Greenberg JD, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 February ; 69(2): 380–386. **META-ANALİZ**

Adjusted risk of infection in patients with rheumatoid arthritis (RA

	Adjusted IRR (95% CI)	p Value
Current RA treatments		
TNF antagonists	1.52 (1.30 to 1.78)	<0.001
MTX	1.30 (1.12 to 1.50)	<0.001
Prednisone	1.05 (0.97 to 1.15)	0.251
Other DMARDs	Reference	–
Clinical variables		
Smoking (ever)	1.52 (1.38 to 1.67)	<0.001
Chronic lung disease	1.31 (1.15 to 1.50)	<0.001
Diabetes mellitus	1.33 (1.15 to 1.52)	0.001
Tender joint count	1.01 (1.00 to 1.02)	0.009
ACR functional class	1.23 (1.12 to 1.34)	<0.001
Body mass index	1.01 (1.00 to 1.02)	0.002

Greenberg JD, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 February ; 69(2): 380–386**. META-ANALİZ**

Opportunistik enfeksiyonlar

	MTX	TNF Ant.	MTX + TNF Ant.	DMARDs
	n=4206	n=1804	n=2855	n=1274
Varicella zoster virüs	32	26	56	7
PCP	3	4	3	3
Tüberküloz	3	1	1	-

Greenberg JD, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 February ; 69(2): 380–386. **META-ANALİZ**

ARTHRITIS & RHEUMATISM
Vol. 54, No. 8, August 2006, pp 2368–2376
DOI 10.1002/art.21978

Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti–Tumor Necrosis Factor Therapy

Results From the British Society for Rheumatology Biologics Register

W. G. Dixon, K. Watson, M. Lunt, K. L. Hyrich, British Society for Rheumatology Biologics Register Control Centre Consortium, A. J. Silman, and D. P. M. Symmons, on behalf of the British Society for Rheumatology Biologics Register

Objective. **To determine whether the rate of serious infection is higher in anti–tumor necrosis factor (anti-TNF)–treated rheumatoid arthritis (RA) patients**

soft tissue infections was increased in anti-TNF–treated patients, with an adjusted IRR of 4.28 (95% confidence interval 1.06–17.17). There was no difference in infec-

- TNF Antagonisti 7664 hasta
- DMARDs 1354 hasta

Table 4. Rates of all serious infections, by drug*

	DMARD (n = 1,354)	Etanercept (n = 3,596)	Infliximab (n = 2,878)	Adalimumab (n = 1,190)
Person-years	1,352	4,075	4,618	1,175
No. of infections	56	209	255	61
Rate of infections/1,000 person-years (95% CI)	41.4 (31.4–53.5)	51.3 (44.7–58.5)	55.2 (48.8–62.2)	51.9 (39.9–66.2)
Adjusted IRR†	Referent	0.97 (0.63–1.50)	1.04 (0.68–1.61)	1.07 (0.67–1.72)

* DMARD = disease-modifying antirheumatic drug; 95% CI = 95% confidence interval; IRR = incidence rate ratio.

† Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking.

Dixon WG et al. Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti–Tumor Necrosis Factor Therapy ARTHRITIS & RHEUMATISM. 2006: 54;2368–2376.

Table 5. Rates of site-specific infections*

	DMARD		Anti-TNF		
	No.	Incidence rate/ 1,000 person-years	No.	Incidence rate/ 1,000 person-years	Adjusted IRR (95% CI)†
Lower respiratory tract	36	26.6 (18.7–36.7)	203	20.6 (17.9–23.6)	0.77 (0.46–1.31)
Skin and soft tissue	4	3.0 (0.8–7.6)	118	12.0 (9.9–14.3)	4.28 (1.06–17.17)
Bone and joint	4	3.0 (0.8–7.6)	68	6.9 (5.4–8.7)	1.12 (0.32–3.88)
Urinary tract	3	2.2 (0.5–6.5)	45	4.6 (3.3–6.1)	1.70 (0.32–9.03)

* Anti-TNF = anti–tumor necrosis factor (see Table 4 for other definitions).
† Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking.

Dixon WG et al. Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti–Tumor Necrosis Factor Therapy ARTHRITIS & RHEUMATISM. 2006: 54;2368–2376.

Table 6. Details of bacterial intracellular infections

Patient age/sex	Ethnicity	Organism	Site of infection	Treatment	Months from treatment start date
59/F	Caucasian	*Mycobacterium tuberculosis* (probable)	Cervical lymph node	Infliximab	7
74/F	Caucasian	*Mycobacterium tuberculosis*	Colon	Infliximab	3
47/M	Caucasian	*Mycobacterium tuberculosis*	Omentum	Infliximab	2
47/M	Caucasian	*Mycobacterium tuberculosis* (presumed)	Pleura	Infliximab	3
66/F	Caucasian	*Mycobacterium tuberculosis*	Lower respiratory tract	Infliximab	16
77/F	Caucasian	*Mycobacterium tuberculosis*	Posterior pharangeal wall	Adalimumab	11
50/F	Pakistani	*Mycobacterium tuberculosis*	Cervical lymph node	Infliximab	4
71/M	Caucasian	*Mycobacterium tuberculosis* (presumed)	Meninges	Etanercept	2
66/F	African Caribbean	*Mycobacterium tuberculosis*	Lower respiratory tract	Etanercept	9
63/F	Not known	*Mycobacterium tuberculosis* (probable)	Meninges	Infliximab	3
59/M	Caucasian	*Legionella pneumophila*	Lower respiratory tract	Infliximab	32
49/M	Caucasian	*Legionella pneumophila*	Lower respiratory tract	Infliximab	4
47/M	Caucasian	*Listeria monocytogenes*	Meninges	Infliximab	2
67/M	Caucasian	*Listeria monocytogenes*	Joint	Etanercept	0
60/F	Caucasian	*Listeria monocytogenes*	Joint	Adalimumab	14
63/F	Caucasian	*Mycobacterium fortuitum*	Lower respiratory tract	Etanercept	4
80/F	Caucasian	*Salmonella* sp.	Bowel and joint	Etanercept	9
57/F	Caucasian	*Salmonella* sp.	Joint	Infliximab	27
54/F	Caucasian	*Salmonella* sp.	Bowel	Etanercept	2

Dixon WG et al. Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti–Tumor Necrosis Factor Therapy ARTHRITIS & RHEUMATISM. 2006: 54;2368–2376.

“Yeni” İmmünosüpresif Ajanlar
ve
MANTAR İNFEKSİYONLARI

Mantar İnfeksiyonları

REVIEW

- 1966-2007 yılları arası
- İnvaziv fungal enfeksiyon
- İnfliximab, Etanercept, Adalizumab
  - **281 İFİ**
    - İnfliximab: 226 (%80)
    - Etanercept: 44 (%16)
    - Adalimumab: 11 (%4)

Sotirios Tsiodras, et al. Fungal Infections Complicating Tumor Necrosis Factor α Blockade Therapy. Mayo Clin Proc. 2008;83(2):181-194**. Review.**

Mantar İnfeksiyonları

HASTA GRUBU

- Romatoid artrit ve diğer inflamatuvar artritler: 54
- İnflamatuvar barsak hastalığı: 16
- GVHD (allojenik KİT sonrası): 31
- Psöriazis: 2
- Bilinmeyen: 178
- Toplam: 281

Sotirios Tsiodras, et al. Fungal Infections Complicating Tumor Necrosis Factor α Blockade Therapy. Mayo Clin Proc. 2008;83(2):181-194. Review.

Mantar İnfeksiyonları

- **Fungal enfeksiyon görülme zamanı**
  - İnfliximab: 55 gün (15-140 gün)
  - Etanercept: 144 gün (46-240 gün)
- **En az 1 diğer immünosüpresif ajan kullanımı**
  - 104 hastayla ilgili veriye ulaşılabilmiş
  - 102 hastada pozitif (%98)
  - Genellikle kortikosteroid

Sotirios Tsiodras, et al. Fungal Infections Complicating Tumor Necrosis Factor α Blockade Therapy. Mayo Clin Proc. 2008;83(2):181-194. Review.

TABLE 2. **Fungal Infections Associated With Anti–Tumor Necrosis Factor α Therapy**[a]

Infectious agents	Infliximab	Etanercept	Adalimumab
Aspergillus species (n=64)	48	14	2
Zygomycetes (n=4)	3	NC	1
Candida species (n=64)	54	9	1
Cryptococcus species (n=28)	17	10	1
Blastomyces species (n=2)	ND	ND	ND
Coccidioides species (n=29)	27	2	NC
Histoplasma species (n=84)	72	8	4
Sporothrix species (n=1)	1 [b]	NC	NC
Prototheca species (n=1)	1	NC	NC
Tinea or pityriasis versicolor (n=6)	3	1	2
Total	226	44	11

[a] ND = no data available; NC = no cases identified.
[b] In this case etanercept was used as well, but symptoms worsened while the patient received infliximab.

Sotirios Tsiodras, et al. Fungal Infections Complicating Tumor Necrosis Factor α Blockade Therapy. Mayo Clin Proc. 2008;83(2):181-194. Review.

Mantar İnfeksiyonları

- **İFİ dağılımı**
  - Histoplazmozis: 84 (%30)
  - Kandidiyazis: 64 (%23)
  - Aspergilloz: 64 (%23)
- Genellikle **PNÖMONİ**
- 90 hastanın tedavi sonucuna ulaşılabilmiş
  - **29 ölüm**

Sotirios Tsiodras. Fungal Infections Complicating Tumor Necrosis Factor α Blockade Therapy. Mayo Clin Proc. 2008;83(2):181-194. Review.

“Yeni” İmmünosüpresif Ajanlar
ve
TÜBERKÜLOZ

Tuberculosis Infection in Patients With Rheumatoid Arthritis and the Effect of Infliximab Therapy

Frederick Wolfe,[1] Kaleb Michaud,[2] Janice Anderson,[2] anc

ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 372–379
DOI 10.1002/art.20009

- CDC verilerine göre 1999-2000 yıllarında Amerika'da Tüberküloz insidansı
  - 6,4 ve 5,8 / 100.000
- İnfliximab tedavisi alan RA hastalarında Tüberküloz insidansı
  - 52,5 / 100.000
- **Tüberküloz insidansında 8-9 kat artış!**

Tuberculosis Infection in Patients With Rheumatoid Arthritis and the Effect of Infliximab Therapy

Frederick Wolfe,[1] Kaleb Michaud,[2] Janice Anderson,[2] and

ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 372–379
DOI 10.1002/art.20009

Table 5. Characteristics of individual RA patients who developed TB*

Age/sex	Ethnic origin	Treatment duration, months			Date TB reported	PPD†		TB site
		Infliximab	Prednisone	MTX		2001	2002	
66.9/F	White	1	0	1	8/1/2001	0	0	Extrapulmonary
65.9/F	White	7	0	0	2/6/2002	0	0	PIP joint
69.7/F	Hispanic	12	0	0	6/19/2002	0	0	Cervical node
78.2/F	White	3	1	0	8/6/2002	0	0	Pulmonary

* MTX = methotrexate; PPD = purified protein derivative; PIP = proximal interphalangeal (see Table 2 for other definitions).
† Refers to PPD in 2001 or 2002 prior to development of TB.

TCT yapılmamış ve profilaksi de almamışlar!

Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR)

Ann Rheum Dis 2010;69:522–528.

W G Dixon,[1] K L Hyrich,[1] K D Watson,[1] M Lunt,[1]
B S R B R Control Centre Consortium, D P M Symmons,[1] on behalf of the BSR Biologics Register

- TNF Antagonisti 10712 hasta
  - Etanercept (ETA) 3913 hasta
  - İnfliximab (INF) 3295 hasta
  - Adalimumab (ADA) 3504 hasta
- 2008 yılına kadar 40 Tüberküloz vakası bildirilmiş

Table 4 Classification and sites of TB infection, by drug

	ETA n = 8 {5}	INF n = 12 {11}	ADA n = 20 {11}	All anti-TNF n = 40 {27}
Pulmonary, n = 15 (38% total)				
Lower respiratory tract	4 {2}	2 {2}	6 {3}	12 {7}
Pleural	–	2 {2}	1 {1}	3 {3}
Total pulmonary	4 {2}	4 {4}	7 {4}	15 {10}
Extra-pulmonary (including disseminated), n = 25 (62% total)				
Bone and joint	1 {1}	–	–	1 {1}
Gastrointestinal	–	3 {3}	–	3 {3}
Lymph node	2 {2}	2 {2}	2 {2}	6 {6}
Central nervous system	–	1 {1}	2 {1}	3 {2}
Pharyngeal wall	–	–	1 {1}	1 {1}
Disseminated	1 {0}	2 {1}	8 {3}	11 {4}
Total extrapulmonary	4 {3}	8 {7}	13 {7}	25 {17}

Numbers represent number of cases attributable to most recent drug {number of cases while "on drug"}.
ADA, adalimumab; ETA, etanercept; INF, infliximab; TB, tuberculosis; TNF, tumour necrosis factor.

Dixon WG et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522–528

Tüberküloz görülme oranları

- Adalimumab 144 / 100.000
- İnfliximab 136 / 100.000
- Etanercept 39 / 100.000

Tüberküloz görülme zamanı

- İnfliximab 5,5 ay
- Etanercept 13,4 ay
- Adalimumab 18,5 ay

Dixon WG et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522–528

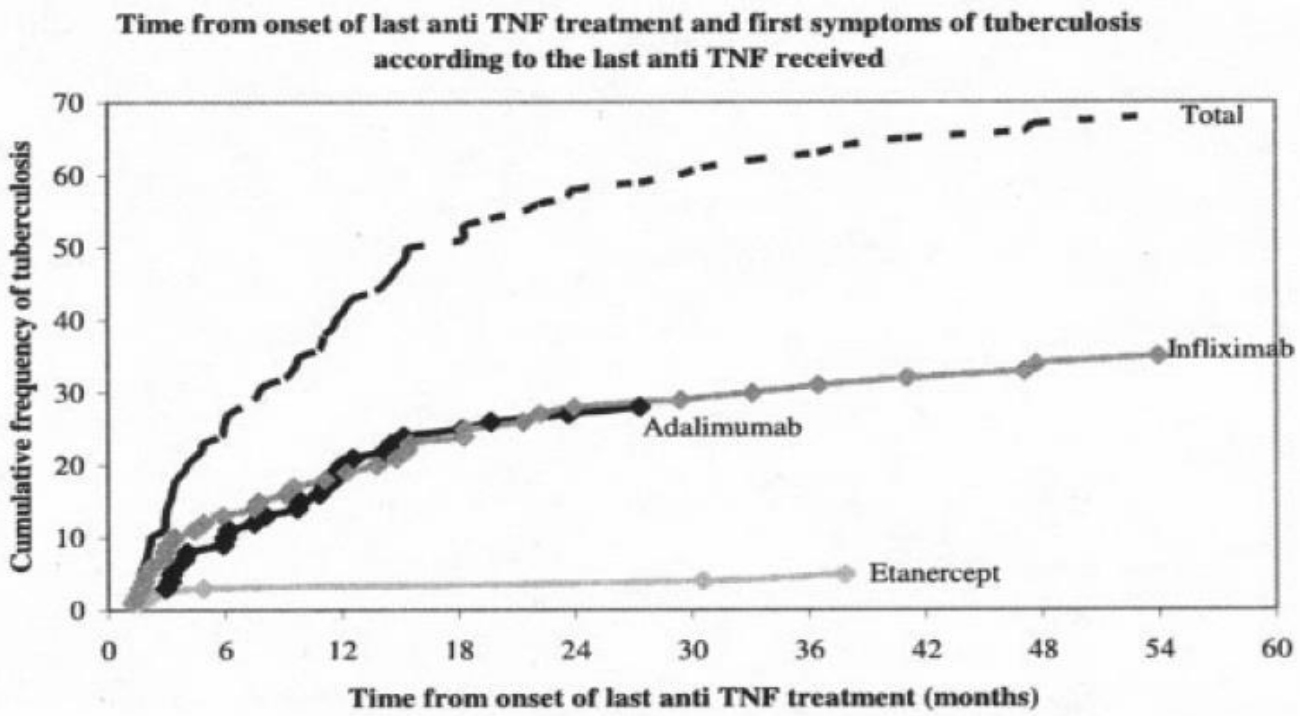


Figure 1. Cumulative incidence of tuberculosis as a function of the duration of anti–tumor necrosis factor (anti-TNF) treatment, in total and for individual anti-TNF agents.

Fransa'dan bir çalışma, 69 tüberküloz olgusu, Hiçbir hasta doğru profilaksi almamış!

- İnfliximab 36 vaka
- Adalimumab 28 vaka
- Etanercept 5 vaka

Tubach F et al. Risk of Tuberculosis Is Higher With Anti–Tumor Necrosis Factor Monoclonal Antibody Therapy Than With Soluble Tumor Necrosis Factor Receptor Therapy. ARTHRITIS & RHEUMATISM . Vol. 60, No. 7, July 2009, pp 1884–1894.

Türkiye'den bir çalışma

- 2005 – 2008
- TNF Antagonisti tedavisi alan 702 hasta

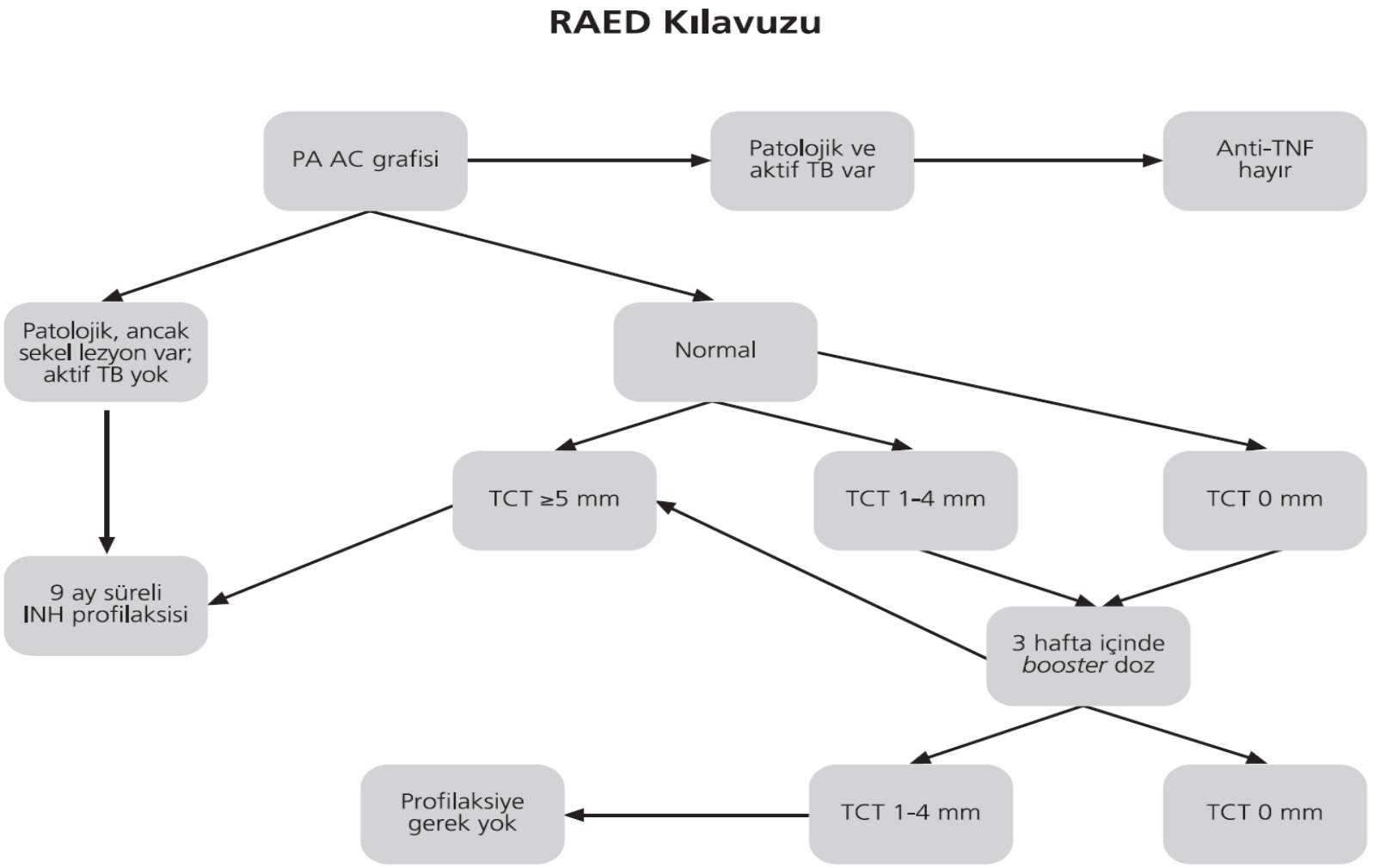
- Tüm hastalara PA AC grafisi ve TCT
- PA AC grafisinde fibrotik lezyonu olan veya TCT ≥ 5mm olan tüm hastalara INH profilaksisi başlanmış (9ay)

Çağatay T. et al. Follow-up results of 702 patients receiving tumor necrosis factor-alpha antagonists and evaluation of risk of tuberculosis. Rheumatology International. 2010;30;1459-1463.

Türkiye'den bir çalışma

- TCT ≥ 5mm 434 hasta (%61.8)
- Profilaksi alan hasta sayısı 583 (%83)
- Takipler sırasında 6 hastada aktif tüberküloz gelişmiş
  - 4 Pulmoner
  - 2 Extra-pulmoner
- Bu hastalar profilaksi önerilen grupta ancak 4 tanesi uygun profilaksi almış

Çağatay T. et al. Follow-up results of 702 patients receiving tumor necrosis factor-alpha antagonists and evaluation of risk of tuberculosis. Rheumatology International. 2010;30;1459-1463.



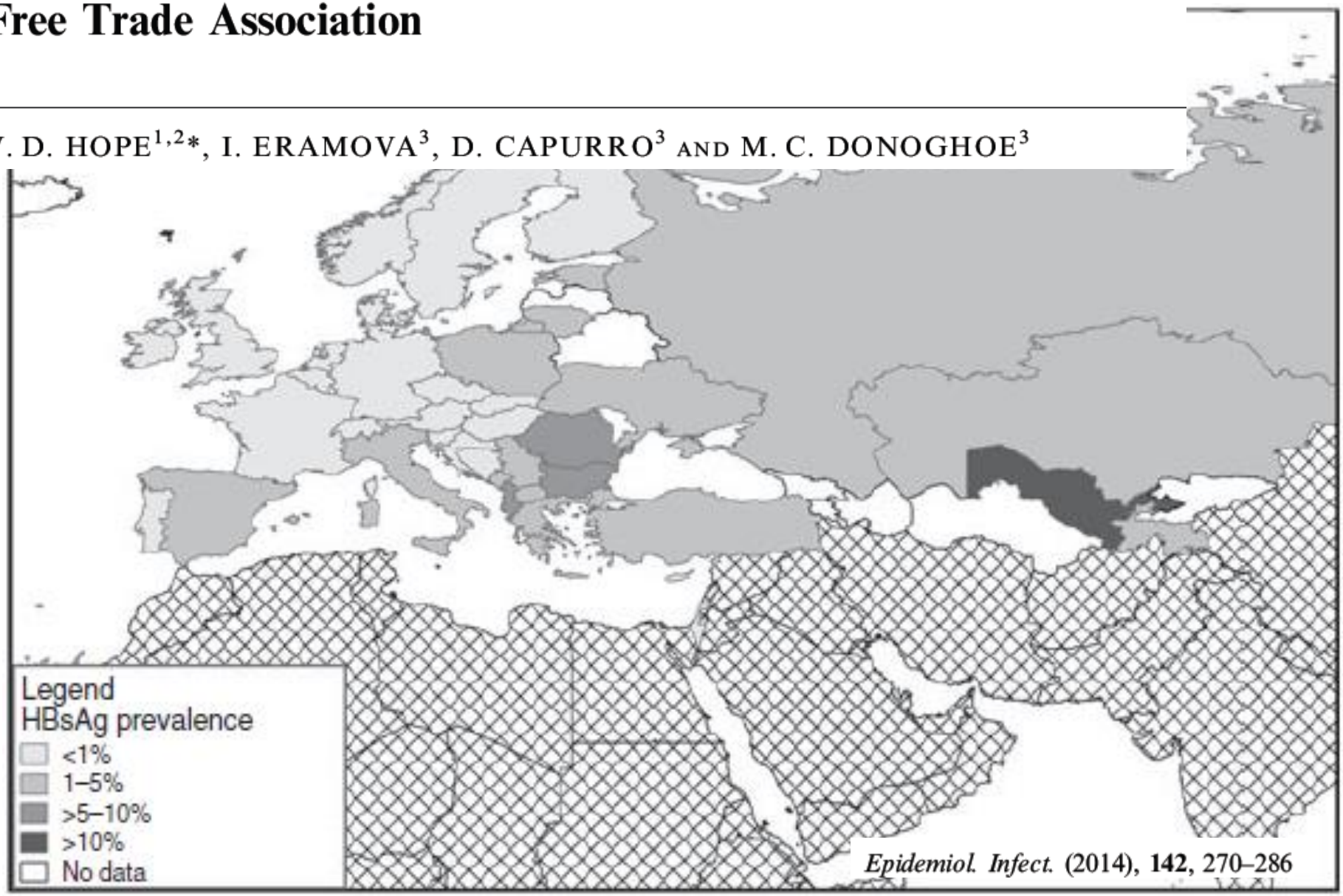
Şekil 1. Romatoloji Araştırma ve Eğitim Derneği (RAED) tarafından anti-TNF tedavi verilmesi planlanan olgularda tüberküloz için geliştirilmiş tarama ve algoritm görülmektedir. **INH:** İzoniyazid, **PA AC:** Postero anterior akciğer grafisi; **TB:** Tüberküloz; **TCT:** Tüberkülin deri testi

Melike Kalfa, Kenan Aksu. Anti-tümör nekrozis faktör-α tedavisi ve enfeksiyon. RAED Dergisi 2011;3:49-56.

“Yeni” İmmünosüpresif Ajanlar ve HEPATİT

Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association

V. D. HOPE[1,2]*, I. ERAMOVA[3], D. CAPURRO[3] AND M. C. DONOGHOE[3]



Epidemiol. Infect. (2014), **142**, 270–286

Lenfomalı Hastalarda HBV Reaktivasyonuna Sebep olan Ajanlar

Sınıf	Ajanlar
Kortikosteroidler	Dekzametazon, metilprednizolon, prednizolon
Antitümor antibiyotikler	Aktinomisin D, bleomisin, daunorubisin, doksorubisin, epirubisin, mitomisin-C
Plant alkaloidler	Vinblastin, vinkristin
Alkilleyici ajanlar	Karboplatin, klorambusil, sisplatin, siklofosfamid, ifosfamid
Antimetabolitler	Azauridin, sitarabin, fluourasil, gemsitabin, merkaptopurin, methotreksat, tioguanin
Monoklonal antikorlar	Alemtuzumab, rituksimab
Diğer	Colaspase, docetaxel, etoposide, fludarabine, folinic acid, interferon, procarbazine

Yeo W, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergo ing anticancer therapy with or without rituximab. J Clin Oncol. 2009 Feb 1;27(4):605-11.

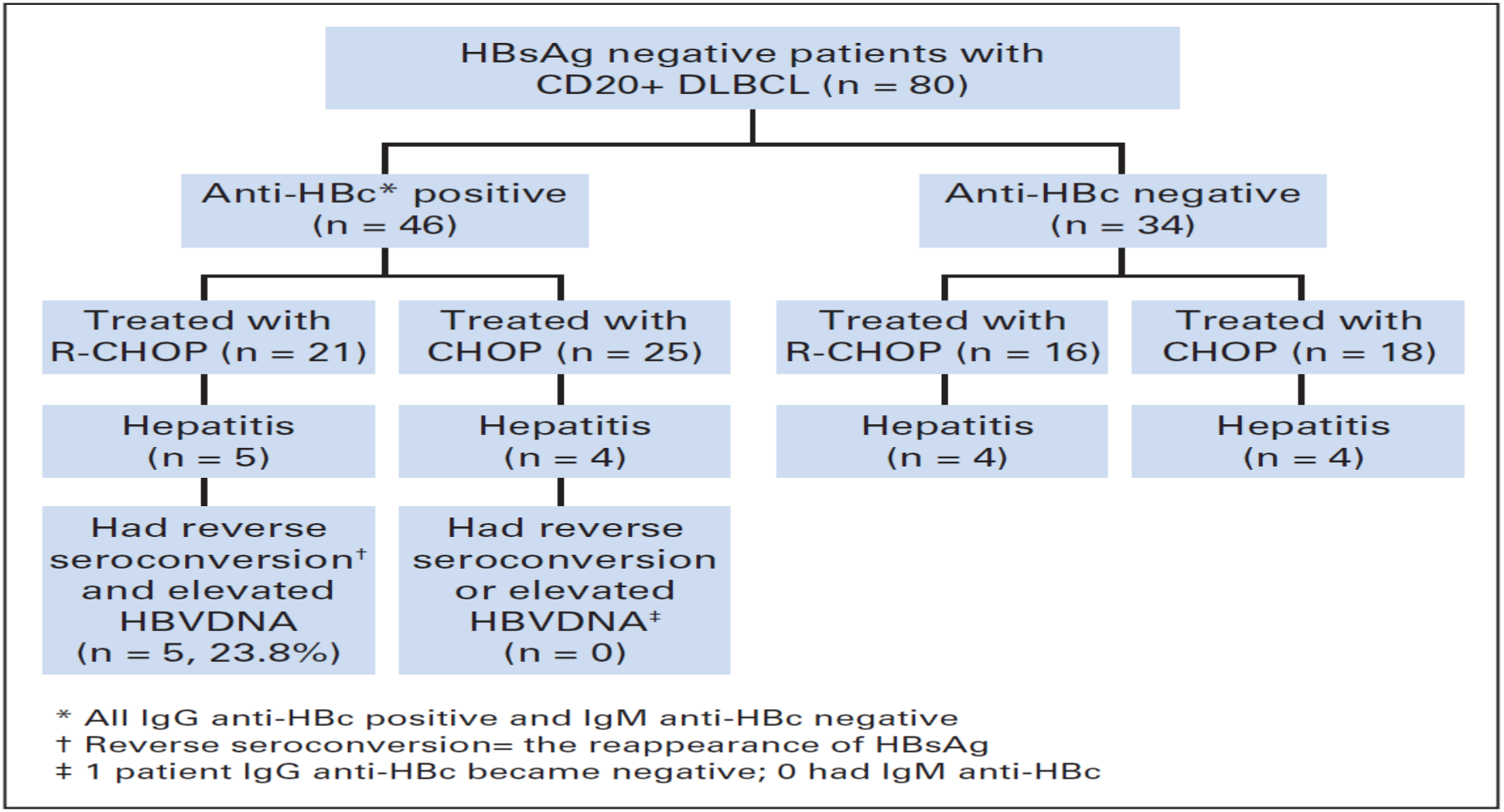


Fig 2. Hepatitis outcomes of 80 hepatitis B surface antigen (HBsAg)–negative patients studied. DLBCL, diffuse large B-cell lymphoma; anti-HBc, antibody to hepatitis B core antigen; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

Yeo W, et al. Hepatitis B Virus Reactivation in Lymphoma Patients With Prior Resolved Hepatitis B Undergoing Anticancer Therapy With or Without Rituximab. Journal of Clinical Oncology 2009; 27.

VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hepatitis B Virus Reactivation in Lymphoma Patients With Prior Resolved Hepatitis B Undergoing Anticancer Therapy With or Without Rituximab

Winnie Yeo, Tung C. Chan, Nancy W.Y. Leung, Wai Y. Lam, Frankie K.F. Mo, Miu Ting Chu, Henry L.Y. Chan, Edwin P. Hui, Kenny I.K. Lei, Tony S.K. Mok, and Paul K.S. Chan

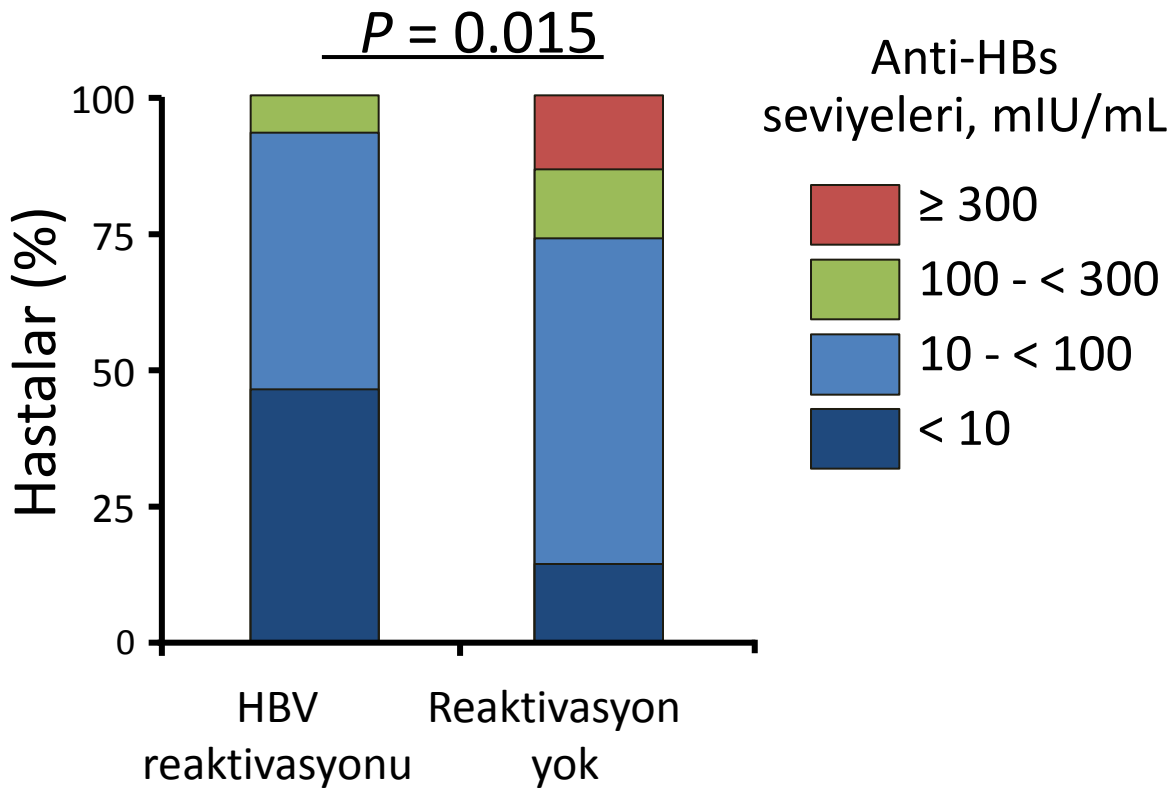
Table 1. Details and Outcome of the Five CD20$^+$ DLBCL Patients Who Were HBsAg Negative/Anti-HBc Positive and Who Developed HBV Reactivation After R-CHOP

				Baseline			At Diagnosis of HBV Reactivation						
Patient No.	Age (years)	Sex	Stage of Lymphoma	Anti-HBs	HBV DNA (copies/μL)	ALT (U/L)	No. of Cycles of R-CHOP Received Before Reactivation	No. of Days Between Last R-CHOP and Reactivation	HBV DNA (copies/μL)	Peak ALT (U/L)	Peak Total Bilirubin (μmol/L)	Treatment With Lamivudine	Outcome
1	77	M	II	—	0	21	6	85	71,118.4	2,110	249	Yes	Died of HBV reactivation
2	58	M	III	—	0	27	5	19	4,840	362	65	Yes	Alive and well
3	60	M	IV	—	0	35	8	110	111,726.4	3,499	192	No	Alive with lymphoma
4	63	M	I	—	0	24	6	78	66,267.1	649	19	Yes	Alive and well
5	46	M	II	—	0	13	6	170	231,597.6	809	29	Yes	Died of lymphoma

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; HBV, hepatitis B virus; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; anti-HBs, antibody to hepatitis B surface antigen; M, male.

HBV Reaktivasyonu ve Rituximab

Anti-HBs seviyesi ne kadar düşük ise reaktivasyon daha sık (P = 0.015)

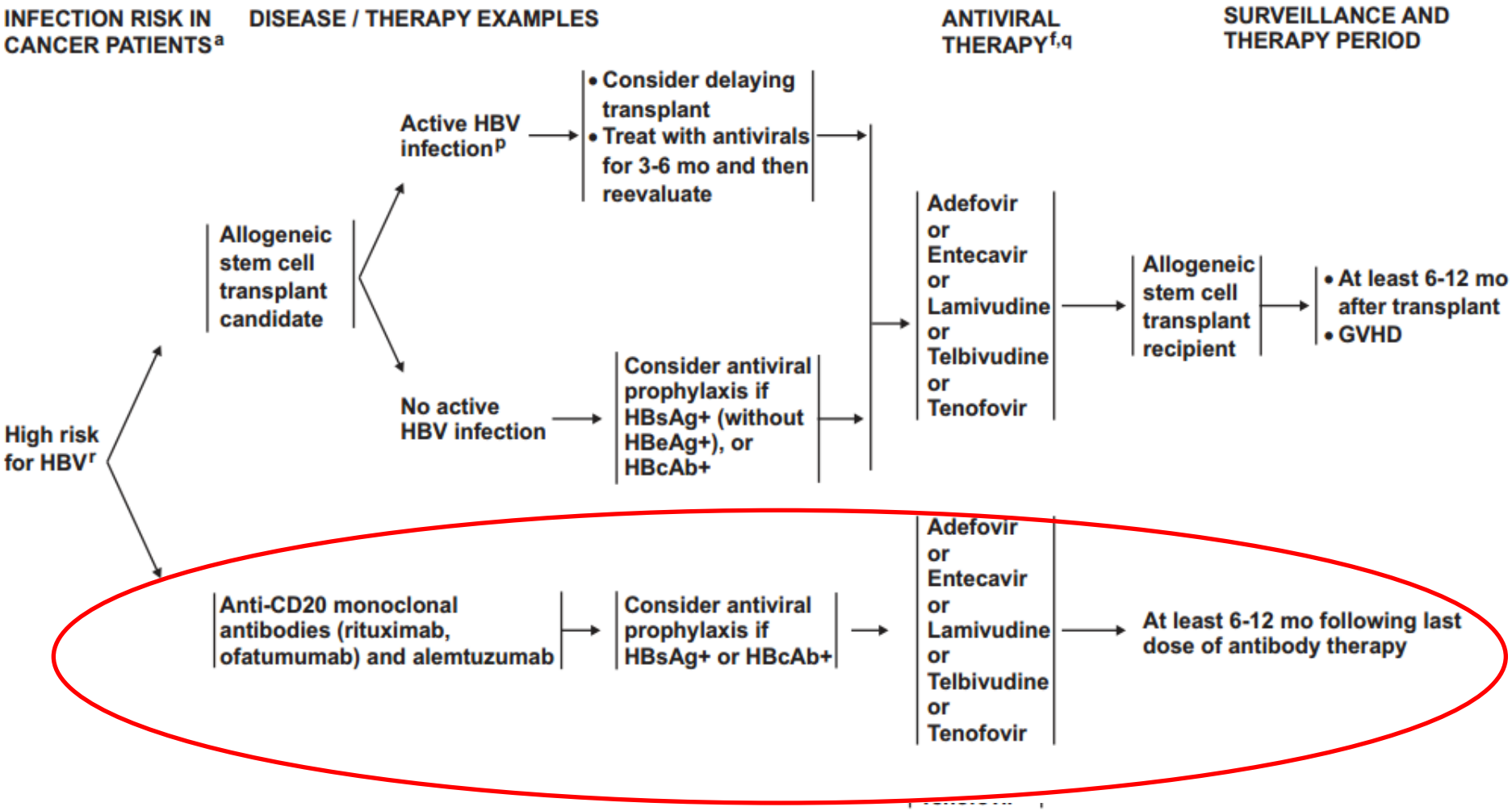


Seto W, et al. AASLD 2013; Abstract 34

Rituximab Alan Anti-HBc Pozitif Hastaların Yönetimi

- Konsensus yok, sınırlı bilgi var
- Seçenekler
  - KT den önce antiviral başla
  - KT sırasında sıkı HBV DNA izlemi yap... HBV DNA pozitifleşirse tedaviye başla
  - KT sırasında sıkı HBsAg izlemi yap... Pozitifleşirse tedaviye başla
  - HBsAg ve HBV DNA'yı birlikte izle

PREVENTION OF HEPATITIS B VIRUS (HBV) REACTIVATION OR DISEASE



[f] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions

[p] Chronic hepatitis based on biopsy or active viral replication (ie, high levels of HBsAg+ and/or HBeAg+). Biopsy should be performed if clinical suspicion of disease. In case of cirrhosis reconsider decision for transplant.

[q] Order of listed agents is alphabetical and does not reflect preference.

[r] Defined as patients with HBsAg+ serology or with prior resolved HBV infection (HBsAg-, HBsAb+, HBcAb+ serology) planned for allogeneic HSCT or anti-CD20, antiCD52 monoclonal antibody therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis

M Esteve, C Saro, F González-Huix, F Suarez, M Forné, J M Viver

Gut 2004;**53**:1363–1365. doi: 10.1136/gut.2004.040675

İspanya'dan bir çalışma

- 80 Crohn hastası
  - 3 hasta HBsAg (+)
  - 3 hasta Anti-HBc IgG (+) ve Anti-HBs (+)
  - 1 hasta Anti-HCV (+) ve HCV-RNA (-)
- İnfliximab tedavisi başlanıyor!
- SONUÇ:
  - 3 HBsAg (+) hastanın 2'sinde aktivasyon
  - 1 Hasta KC Yetmezliği ölüm
    - Tedavi öncesi HBsAg (+), HBV-DNA (-)

Hepatitis B Virus (HBV) Reactivation in Patients Receiving Tumor Necrosis Factor (TNF)-Targeted Therapy

Analysis of 257 Cases

*Roberto Pérez-Alvarez, MD, Cándido Díaz-Lagares, MD, Francisco García-Hernández, MD, Leopoldo Lopez-Roses, MD, PhD, Pilar Brito-Zerón, MD, PhD, Marta Pérez-de-Lis, MD, PhD, Soledad Retamozo, MD, Albert Bové, MD, PhD, Xavier Bosch, MD, PhD, Jose-Maria Sanchez-Tapias, MD, PhD, Xavier Forns, MD, PhD, Manuel Ramos-Casals, MD, PhD, and the BIOGEAS Study Group**

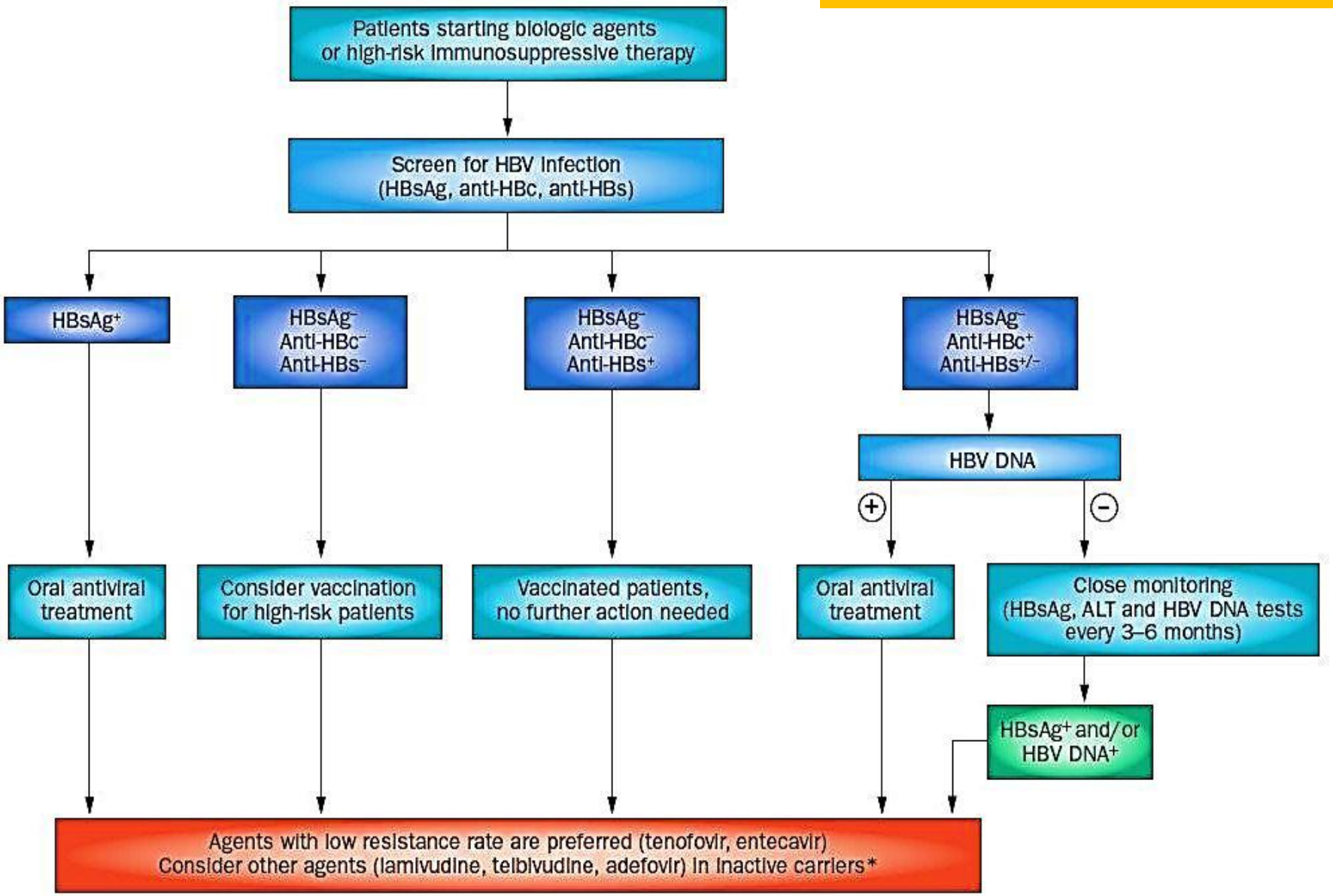
- HBV markerları pozitif 257 hasta
- 89 hasta HBsAg (+) taşıyıcı
- 168 Anti-HBcIgG (+)
- HBV re-aktivasyonu
  - 35 HBsAg (+) taşıyıcıda (39%)
  - Daha önce immünosüpresif ajan kullananlarda re-aktivasyon daha sık
  - Anti-viral profilaksi alanlarda daha düşük
    - %23 vs. %62

Hepatitis B Virus (HBV) Reactivation in Patients Receiving Tumor Necrosis Factor (TNF)-Targeted Therapy

Analysis of 257 Cases

*Roberto Pérez-Alvarez, MD, Cándido Díaz-Lagares, MD, Francisco García-Hernández, MD, Leopoldo Lopez-Roses, MD, PhD, Pilar Brito-Zerón, MD, PhD, Marta Pérez-de-Lis, MD, PhD, Soledad Retamozo, MD, Albert Bové, MD, PhD, Xavier Bosch, MD, PhD, Jose-Maria Sanchez-Tapias, MD, PhD, Xavier Forns, MD, PhD, Manuel Ramos-Casals, MD, PhD, and the BIOGEAS Study Group**

- 5 hastada Akut KC yetmezliği
  - 4 ölüm
- Anti-HBcIgG (+) hastalarda reaktivasyon 9 hasta (5%)
- 1 hastada fulminan KC yetmezliği ve ölüm



Dimitrios Vassilopoulos & Leonard H. Calabrese. Management of rheumatic disease with comorbid HBV or HCV infection Nature Reviews Rheumatology 8, 348-357 (June 2012). **REVIEW**

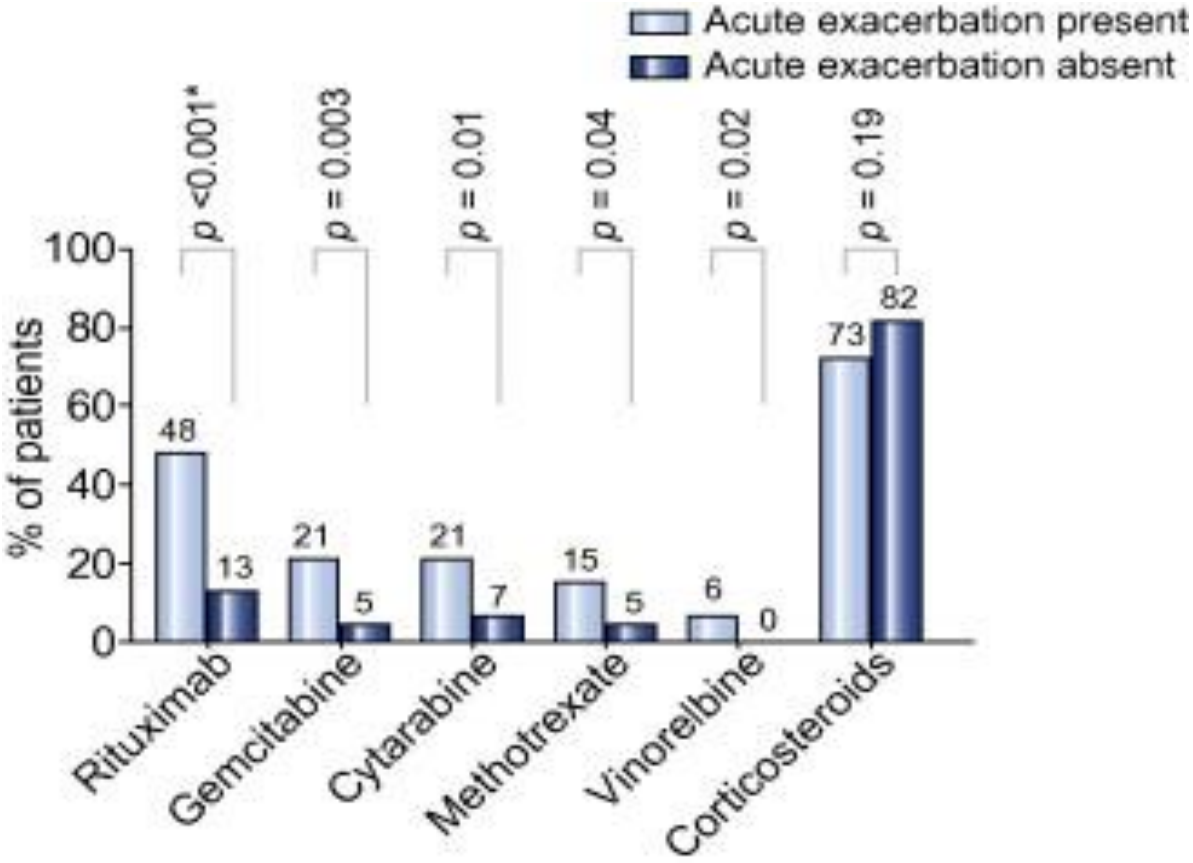
Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients

Parag Mahale[1], Dimitrios P. Kontoyiannis[1], Roy F. Chemaly[1], Ying Jiang[1], Jessica P. Hwang[2], Marta Davila[3], Harrys A. Torres[1,*]

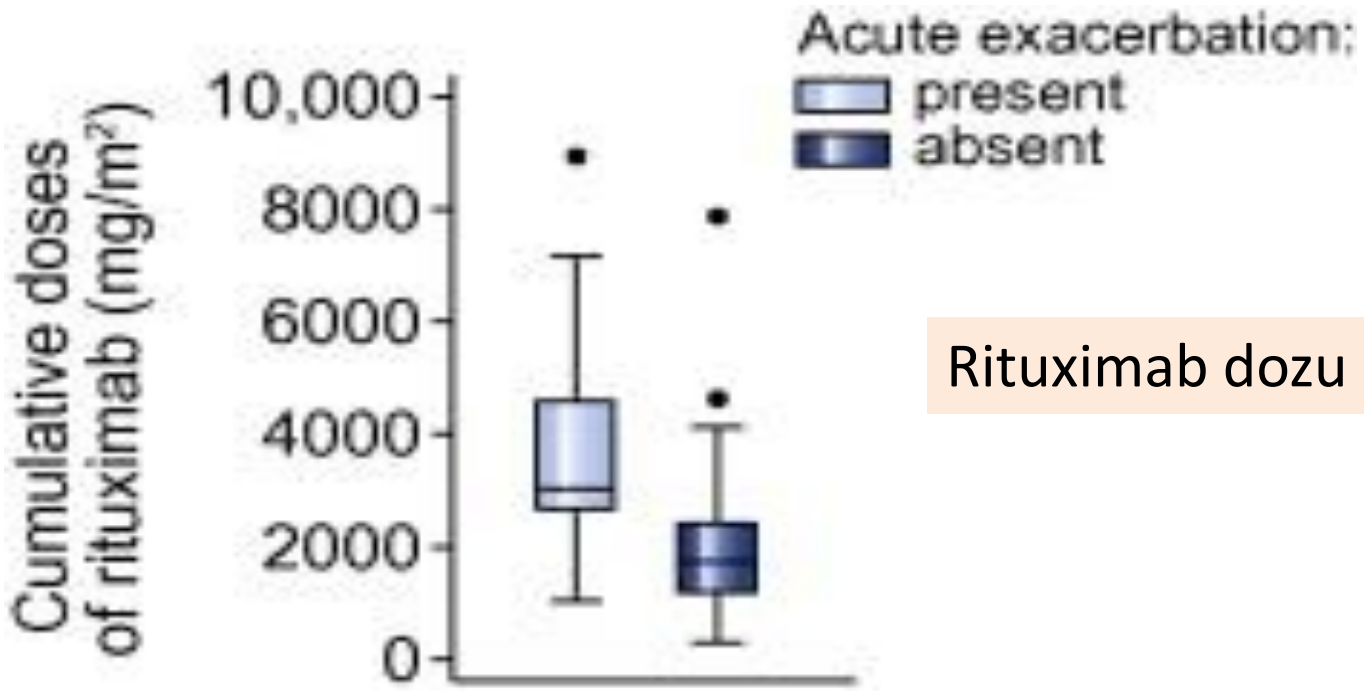
- 308 kanser hastası
  - Akut alevlenme %11
    - %79'u erkek
    - Ortalama yaş; 55



J Hepatology 2012

Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients

Parag Mahale[1], Dimitrios P. Kontoyiannis[1], Roy F. Chemaly[1], Ying Jiang[1], Jessica P. Hwang[2], Marta Davila[3], Harrys A. Torres[1,*]



Rituximab dozu önemli

Journal of Hepatology, 2012, 1177–1185

Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review

Rheumatology 2011;50:1700–1711

Alexandra M. G. Brunasso[1,2], Matteo P[illegible], Andrea Gulia[illegible] and Cesare Massone[5]

TABLE 1 Numbers of patients treated with anti-TNF-α agents in the setting of HCV infection

Baseline pathology in association with HCV infection	Patients treated with etanercept	Patients treated with infliximab	Patients treated with adalimumab	Patients treated with infliximab or etanercept	Mean duration of anti-TNF-α therapy	References
RA	59	23	8	5	13.15 months	[22–34]
PsA	6	1	1	NA	9.8 months	[21, 30, 35–37]
Psoriasis	8	NA	NA	NA	12 months	[38–42, 55, 56]
PsA and psoriasis	8	NA	NA	NA	14.5 months	[39–41, 55, 57]
CD	NA	6	NA	NA	15.3 weeks	[46–50]
AS	NA	1	NA	NA	13 months	[37]
Cryoglobulinaemia	NA	1	NA	NA	NA	[50]
Vasculitis	NA	2	NA	NA	4 weeks	[51]
None	19	NA	NA	NA	24 weeks	[52]
HCV-related oligo- and polyarthritis	9	NA	NA	NA	3 months	[53]
PM	1	NA	NA	NA	14 months	[30]

NA: not available.

Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review

Rheumatology 2011;50:1700–1711

Alexandra M. G. Brunasso[1,2], Matteo Puntoni[3], Andrea Gulia[4] and Cesare Massone[5]

- 95 RA hastası
- Etanercept 59
- İnfliximab 23
- Adalimumab 8
- Etanercept+İnfliximab 5

Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review

Rheumatology 2011;50:1700–1711

Alexandra M. G. Brunasso[1,2], Matteo Puntoni[3], Andrea Gulia[4] and Cesare Massone[5]

- Transaminazlarda yükselme
  - Etanercept 1 hasta (HCV viral yük artışı yok)
- HCV viral yük artışı
  - Etanercept 4 hasta
    - 1 hastada viral yük 12 kat, transaminazlar 3 kat artmış
  - İnfliximab 3 hasta

TNF-Alfa Antagonistleri ve Aşılar

- TNF-alfa antagonistleri kullanan hastalar aşılandığında oluşan bağışıklama biraz azalmış olabilir ama genellikle koruma için yeterlidir.

- Yıllık influenza aşısı kullandığı ilaçlardan bağımsız olarak tüm RA hastalarına önerilir.

- Pnömokok aşısının MTX ve TNF-alfa antagonisti uygulanan hastalarda kullanımı ile ilgili öneriler olmamasına rağmen, bu hastalara pnömokok aşısı yaptırmak ve bunu mümkünse tedavi başlamadan yapmak doğru bir strateji gibi görünmektedir.

- Bu hastalarda canlı aşılar kontrendikedir.

Sonuç

- TNF-alfa antagonistleri ile tedavi edilecek hastalara influenza ve pnömokok aşısı yaptırmaları önerilir.

- Tedavi başlamadan önce tüm hastalar Hepatit B ve C virüsü açısından taranmalı, pozitif olan hastalar uygun profilaktik tedaviyi almalıdır.

- Bu ilaçlar ile tedavi başlanmadan önce hastalar anamnez, fizik muayene, TCT ve AC grafisi ile latent tbc açısından taranmalı, pozitif olan hastalar uygun şekilde tedavi edilmelidir.

Teşekkürler…