BİYOLOJİK AJAN TEDAVİSİ
ve
TÜBERKÜLOZ

Dr. M. Sezai Taşbakan

E.Ü.T.F. Göğüs Hastalıkları

Anabilim Dalı

Biyolojik Ajanlar

TNF-? antagonistleri	İnfliximab Etanercept Adalimumab Golimumab Certolizumab
B hücre inhibitörleri	Rituximab
IL inhibitörleri	Anakinra (IL-1) Tocilizumab (IL-6)
Selektif kostimülasyon inhibitörü	Abatacept

TNF-α Antagonistleri

1. Monoklonal antikorlar:
   a. Şimerik monoklonal antikorlar: İnfliksimab
   b. Tam insan yapısında monoklonal antikorlar: Adalimumab, Golimumab
   c. Pegile humanize antikorlar (Fab Parçası): Sertolizumab pegol

2. Reseptör füzyon proteinleri:
   a. TNFR1 Ig füzyon proteini: Etanersept

Biyolojik Ajanların Endikasyonları

Table 1 – Currently available biological agents in patients with immune-mediated inflammatory disease and the indications in Japan.

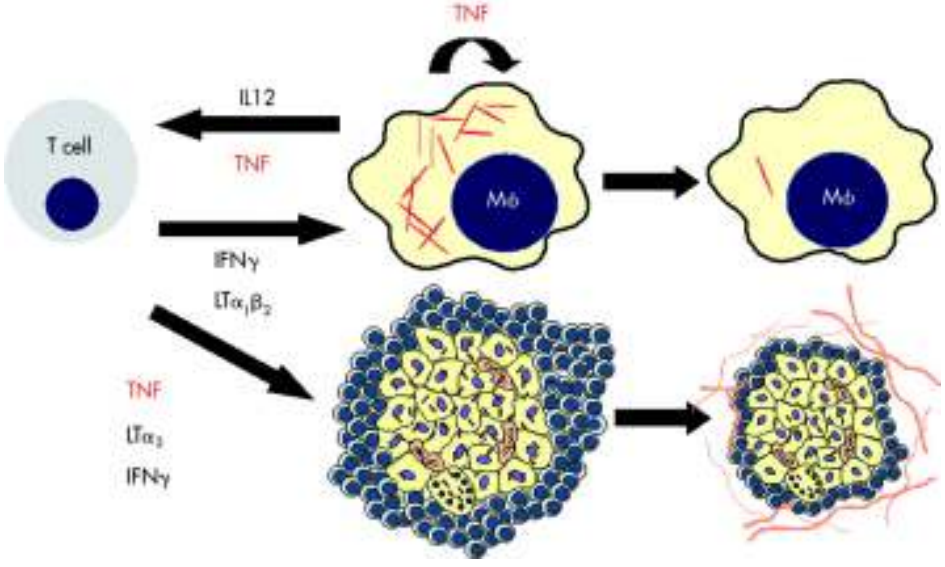
	IFX	ADA	GLM	CZP	ETN	TCZ	ABA	RTX	UTK
Rheumatoid arthritis	○	○	○	○	○	○	○	×	×
Juvenile idiopathic arthritis	×	○	×	×	○	○	×	×	×
Psoriasis	○	○	×	×	×	×	×	×	○
Psoriatic arthritis	○	○	×	×	×	×	×	×	×
Spondyloarthritis	○	○	×	×	×	×	×	×	×
Crohn's disease	○	○	×	×	×	×	×	×	×
Ulcerative colitis	○	○	×	×	×	×	×	×	×
Behçet's disease	○	○	×	×	×	×	×	×	×
Castleman's disease	×	×	×	×	×	○	×	×	×
Granulomatosis with polyangiitis and microscopic polyangiitis	×	×	×	×	×	×	×	○	×

○ with approval to use; × without approval to use.

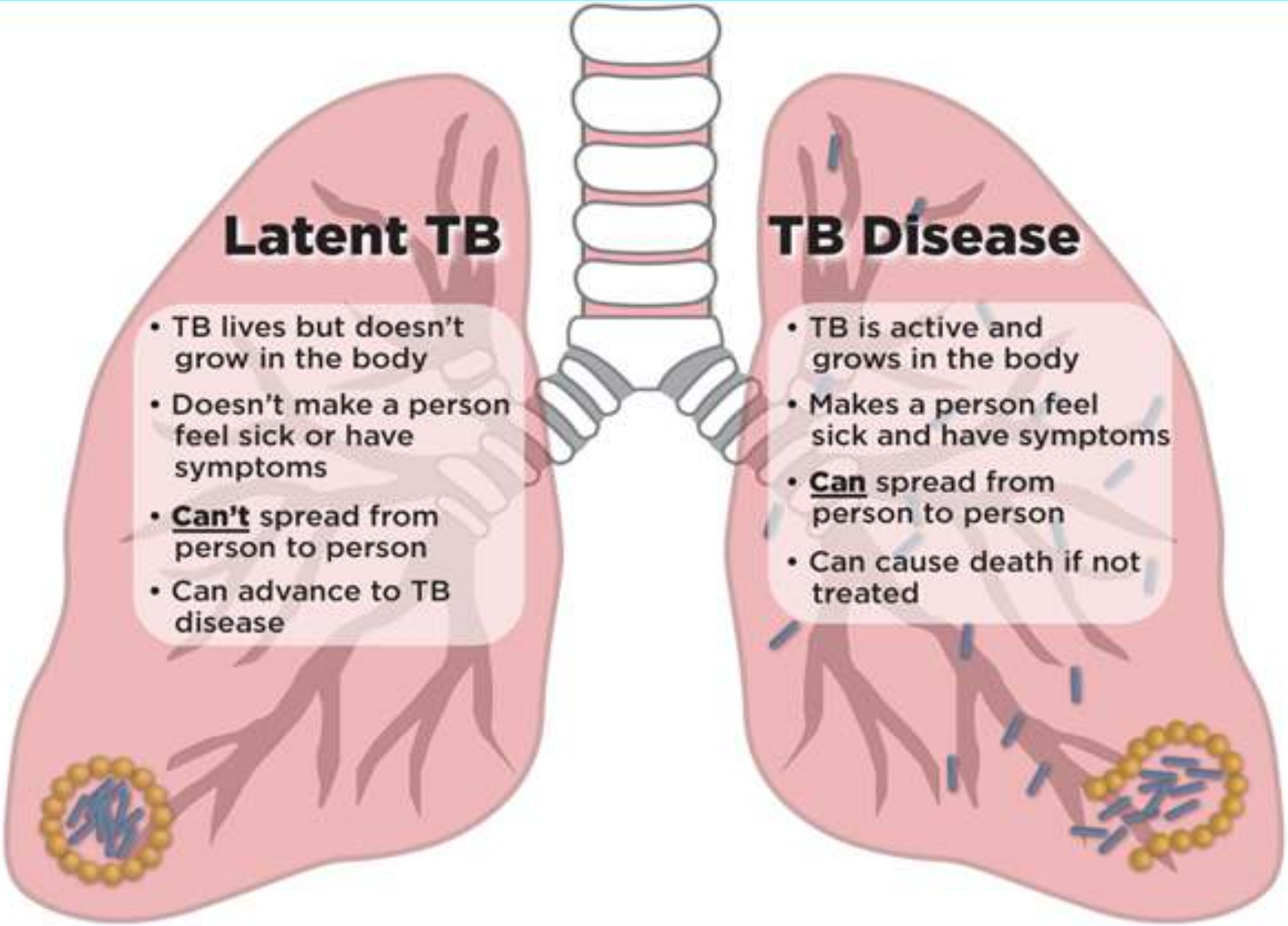
IFX: infliximab, ADA: adalimumab, GLM: golimumab, CZP: certolizumab pegol, ETN: etanercept, TCZ: tocilizumab, ABA: abatacept, RTX: rituximab, UTK: ustekinumab.

TNF ve Enfeksiyonlar

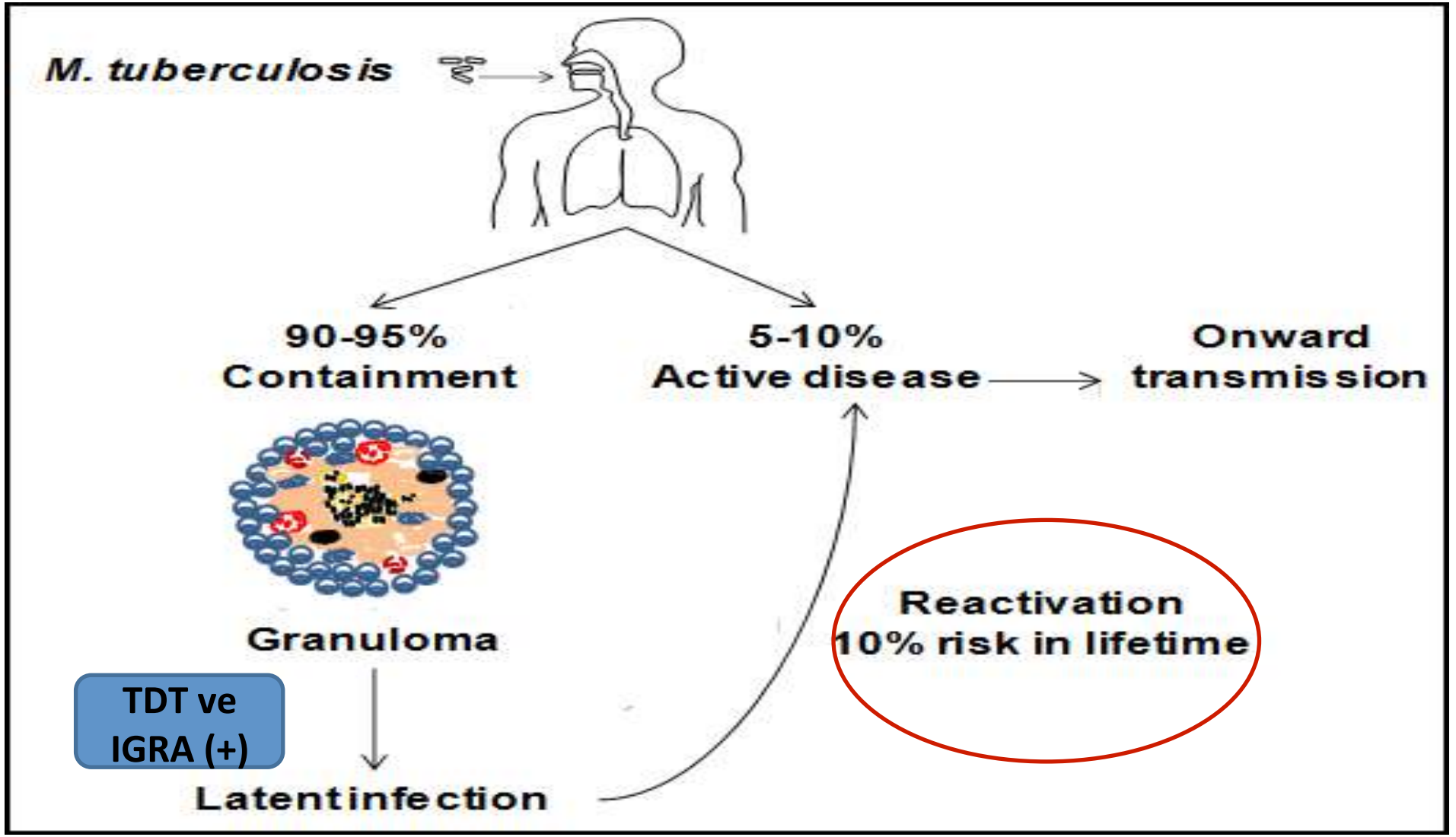
- TNF bakteriyel ve viral enfeksiyonlara karşı konak yanıtında önemli
- Makrofaj aktivasyonu
- Enfeksiyon alanındaki immun yanıtın başlamasında etkili
- İntrasellüler patojenlere karşı
  - TB
  - Legionella
  - P. jirovecii
  - Nokardia



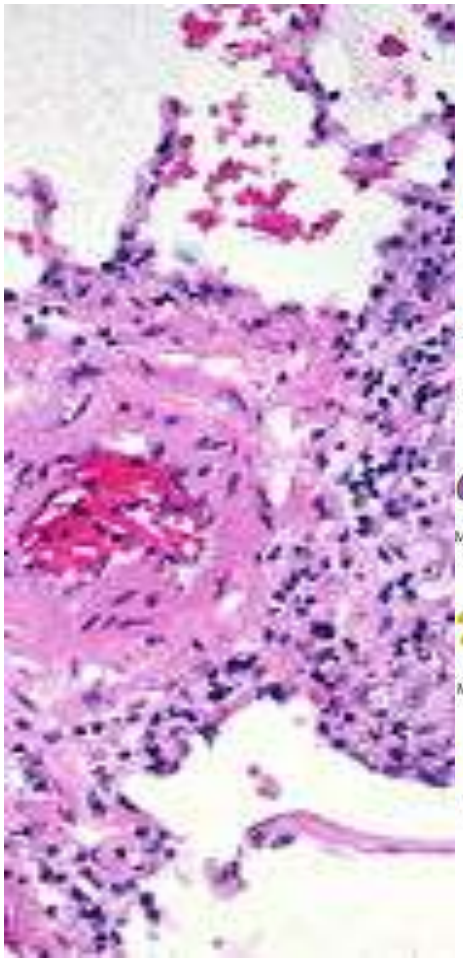
Tüberküloz

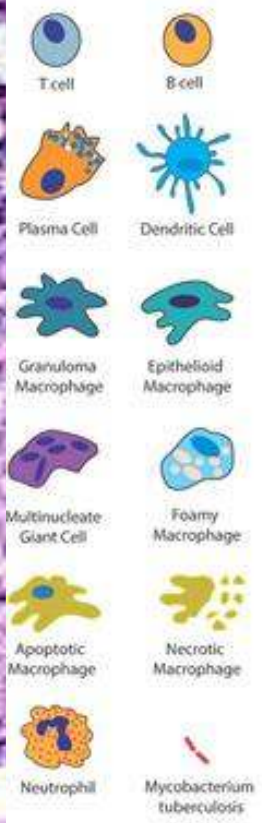

Latent TB
• TB lives but doesn't grow in the body
• Doesn't make a person feel sick or have symptoms
• Can't spread from person to person
• Can advance to TB disease
TB Disease
• TB is active and grows in the body
• Makes a person feel sick and have symptoms
• Can spread from person to person
• Can cause death if not treated

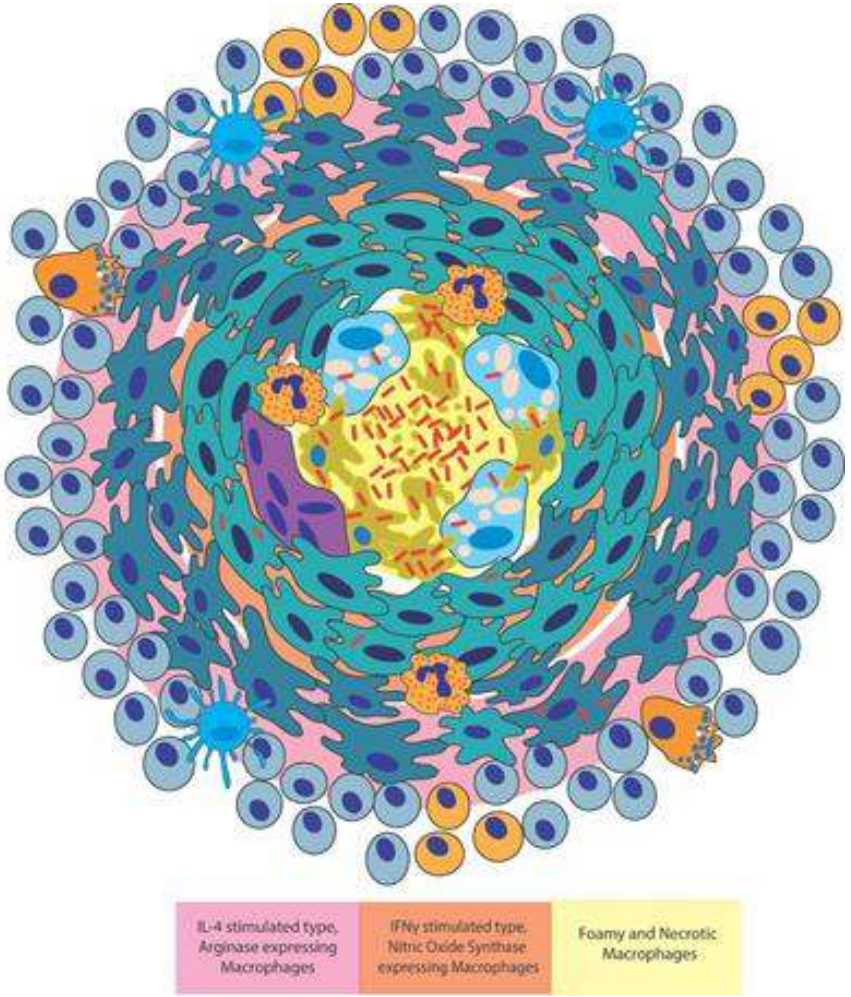
Latent Tüberküloz Enfeksiyonu



Latent Tüberküloz Enfeksiyonu







Biyolojik Ajan ve LTBI

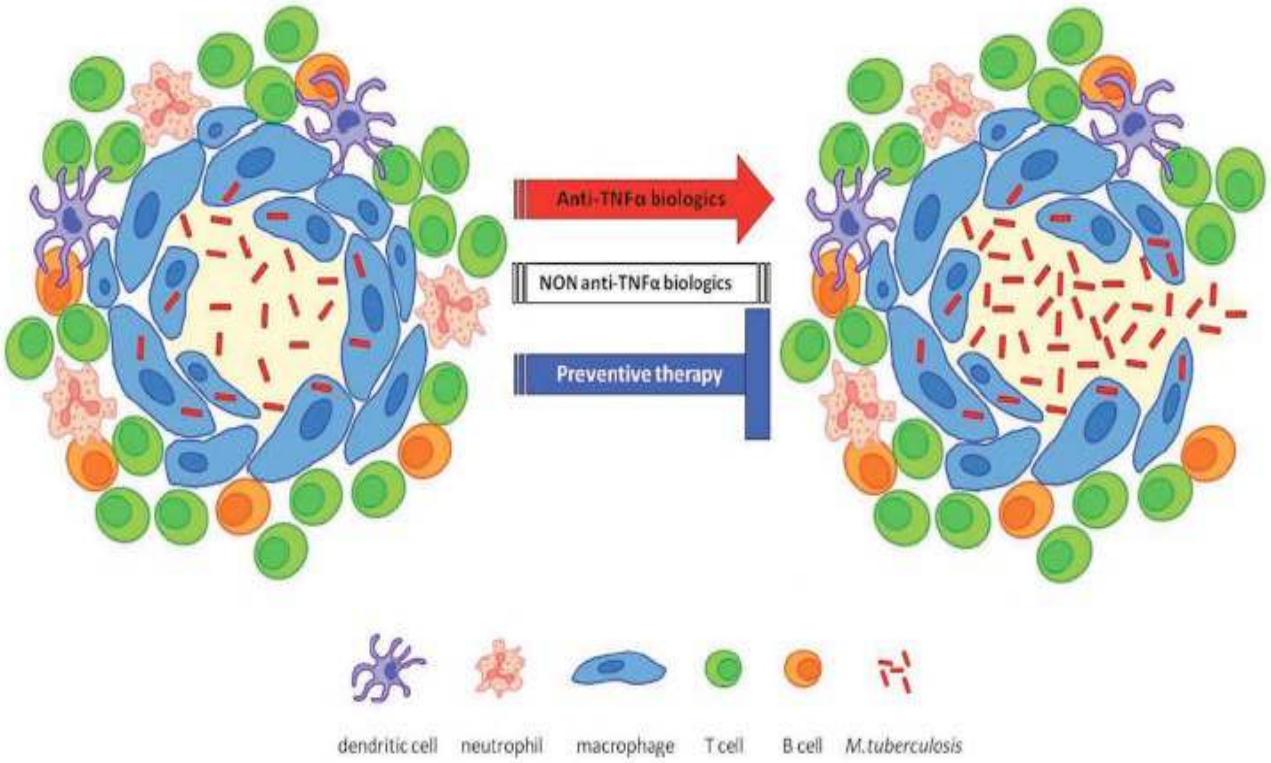


Figure 2. Modulation of the granuloma integrity by preventive treatment for tuberculosis and biologic therapy.
The granuloma is a complex and well organized cellular structure in which M. tuberculosis is contained within a necrotic region surrounded by epithelioid macrophages and a rim of B and T lymphocytes. The TNF-α has been recognized as a key factor for the maintenance of this structure. Indeed, changes in its levels, as induced by anti-TNF biologics may disrupt the granuloma integrity -losing the bacterial containment- and may contribute to active TB reactivation. By contrast, based on the available data, the non anti-TNF biologics, inhibiting CD20, CD28, IL-1, IL-6, IL-12, IL-23, or IL-17, have a negligible or absent effect on TB granuloma integrity. Preventing therapy with isoniazid or rifamycins is supposed to reduce mycobacteria load leading to a decrease of the risk to develop active TB.

Tüberküloz

TLAR 1947

Turk J Rheumatol 2013;28(3):149-162
doi: 10.5606/tjr.2013.3052

Original Article

The Reported Adverse Effects Related to Biological Agents Used for the Treatment of Rheumatic Diseases in Turkey

Romatizmal Hastalıkların Tedavisinde Biyolojik Ajanların Kullanımına Bağlı Türkiye'de Bildirilmiş Yan Etkiler

Erkan KILIÇ,[1] Gamze KILIÇ,[1] Özgür AKGÜL,[1] Gürkan AKGÖL,[2] Salih ÖZGÖÇMEN[1]

[1]*Department of Physical Medicine and Rehabilitation, Medical Faculty of Erciyes University, Division of Rheumatology, Kayseri, Turkey*
[2]*Department of Physical Medicine and Rehabilitation, Bingöl State Hospital, Bingöl, Turkey*

Objectives: This study aims to review the reported adverse events related to the use of biological agents used for the treatment of rheumatic diseases in Turkey.

Patients and methods: Between January 2000 and January 2012, the literature was searched in English and Turkish for case reports and case series using the MedLine, Web of Science, and Scopus databases reporting adverse effects related to the use of biological agents including infliximab, etanercept, adalimumab, anakinra, rituximab which were used for the treatment of rheumatic diseases.

Results: A total of 53 patients (21 males, 32 females) with rheumatic disease who suffered from adverse effects related to the use of biological agents were reported in Turkey in the literature. The mean age was 39.0±15.6 years, while the mean disease duration was 10.6±8.2 years. The mean time from the initiation of the biological agents to the onset of the adverse events was 8.8±9.2 months. The most frequently seen biological agent-related adverse effects were observed in patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA). Tuberculosis (TB) was the most commonly reported adverse effect with in 14 patients (26.4%). Other adverse events included psoriasis (15.1%), solid tumors (7.6%), lymphoma (5.7%), drug-induced lupus (3.8%), and menstrual bleeding (3.8%). A total of 77.4% patients who

Amaç: Bu çalışmada Türkiye'de romatizmal hastalıkların tedavisinde kullanılan biyolojik ajanlara bağlı gelişen bildirilmiş yan etkiler derlendi.

Hastalar ve yöntemler: Ocak 2000 ile Ocak 2012 tarihleri arasında romatizmal hastalıkların tedavisinde kullanılan infliksimab, etanersept, adalimumab, anakinra, rituksimab dahil olmak üzere biyolojik ajanlara bağlı gelişen yan etkileri bildiren olgu ve olgu serileri MedLine, Web of Science ve Scopus veri tabanları kullanılarak İngilizce ve Türkçe dillerinde tarandı.

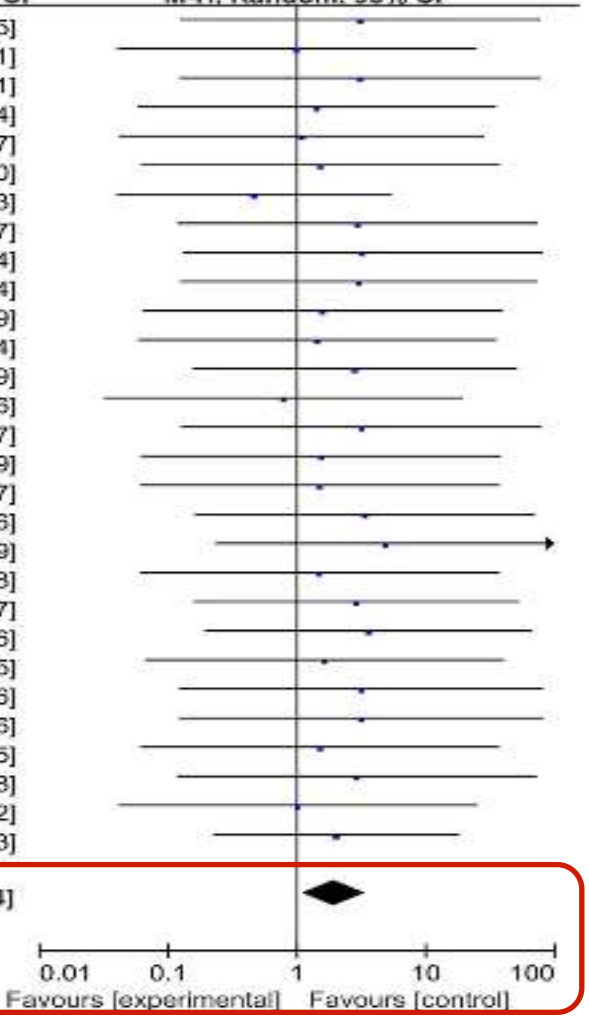
Bulgular: Literatürde Türkiye'den biyolojik ajana bağlı yan etki görülen romatizmal hastalıklı toplam 53 olgu (21 erkek, 32 kadın) bildirilmiştir. Yaş ortalaması 39.0±15.6 yıl ve ortalama hastalık süresi 10.6±8.2 yıl idi. Biyolojik ajanlara başlanması ile yan etkinin ortaya çıkması arasındaki geçen süre ortalama 8.8±9.2 aydı. Biyolojik ajan kullanımına bağlı olarak en sık görülen yan etki ankilozan spondilit (AS) ve romatoid artrit (RA) hastalarında gözlendi. En sık bildirilen yan etki 14 hastada (%26.4) tüberküloz idi. Diğer yan etkiler psöriyazis (%15.1), solid tümör (%7.6), lenfoma (%5.7), ilaca bağlı lupus (%3.8) ve menstrüel kanama (%3.8) idi. Yan etki gelişen olguların toplam %77.4'ünde biyolojik

BMJ Open Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Baranauskaite 2012	1	57	0	58	3.1%	3.11 [0.12, 77.85]
Barker 2011	1	653	0	215	3.2%	0.99 [0.04, 24.41]
Braun 2002	1	35	0	35	3.1%	3.09 [0.12, 78.41]
Breedveld 2006	1	542	0	257	3.2%	1.43 [0.06, 35.14]
Chen 2009	1	35	0	12	3.1%	1.09 [0.04, 28.47]
Colombel 2010	1	338	0	170	3.2%	1.52 [0.06, 37.40]
Couriel 2009	1	29	2	28	5.4%	0.46 [0.04, 5.43]
Ho-Yong KIM 2007	1	65	0	63	3.1%	2.95 [0.12, 73.87]
Judson 2014	1	55	0	58	3.1%	3.22 [0.13, 80.74]
Kavanaugh 2013	1	515	0	517	3.2%	3.02 [0.12, 74.24]
Kennedy 2014	1	85	0	44	3.1%	1.58 [0.06, 39.59]
Keystone 2004	1	419	0	200	3.2%	1.44 [0.06, 35.44]
Keystone 2008	5	783	0	199	3.9%	2.82 [0.16, 51.19]
Maini 1999	1	340	0	88	3.2%	0.78 [0.03, 19.36]
Nam 2014	1	55	0	57	3.1%	3.17 [0.13, 79.37]
Reich 2012	1	117	0	59	3.2%	1.53 [0.06, 38.19]
Rutgeerts 2005	1	243	0	121	3.2%	1.50 [0.06, 37.17]
Schiff 2008	2	165	0	110	3.5%	3.38 [0.16, 71.06]
Schiff 2014	2	328	0	318	3.5%	4.88 [0.23, 101.99]
Sieper 2014	1	106	0	52	3.2%	1.49 [0.06, 37.28]
Smolen 2009	5	492	0	127	3.9%	2.88 [0.16, 52.37]
St Clair 2004	4	751	0	298	3.8%	3.59 [0.19, 66.96]
Suzuki 2014	1	177	0	96	3.2%	1.64 [0.07, 40.65]
Tam 2012	1	20	0	20	3.1%	3.15 [0.12, 82.16]
Van Den Bosch 2002	1	20	0	20	3.1%	3.15 [0.12, 82.16]
van der Heijde 2007	1	454	0	228	3.2%	1.51 [0.06, 37.25]
van Vollenhoven 2011	1	79	0	76	3.2%	2.92 [0.12, 72.88]
Wenzel 2009	1	233	0	78	3.2%	1.01 [0.04, 25.12]
Westhovens 2006	4	721	1	363	6.8%	2.02 [0.22, 18.13]
Total (95% CI)		**7912**		**3967**	**100.0%**	**1.94 [1.10, 3.44]**
Total events	45		3			

Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 28 (P = 1.00); I² = 0%

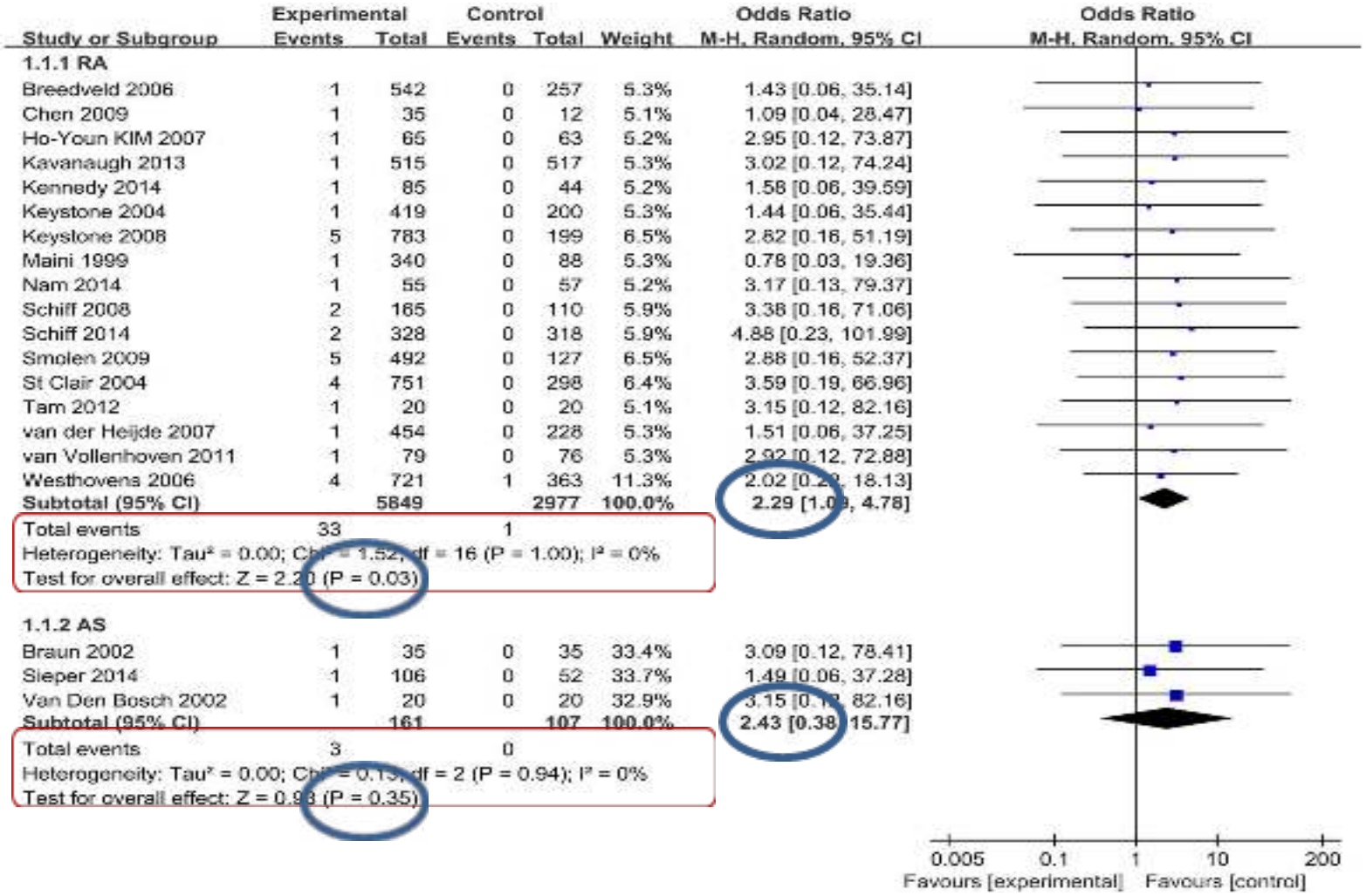
Test for overall effect: Z = 2.28 (P = 0.02)



Zhang Z, et al. BMJ Open 2017;7:e012567

BMJ Open

Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials



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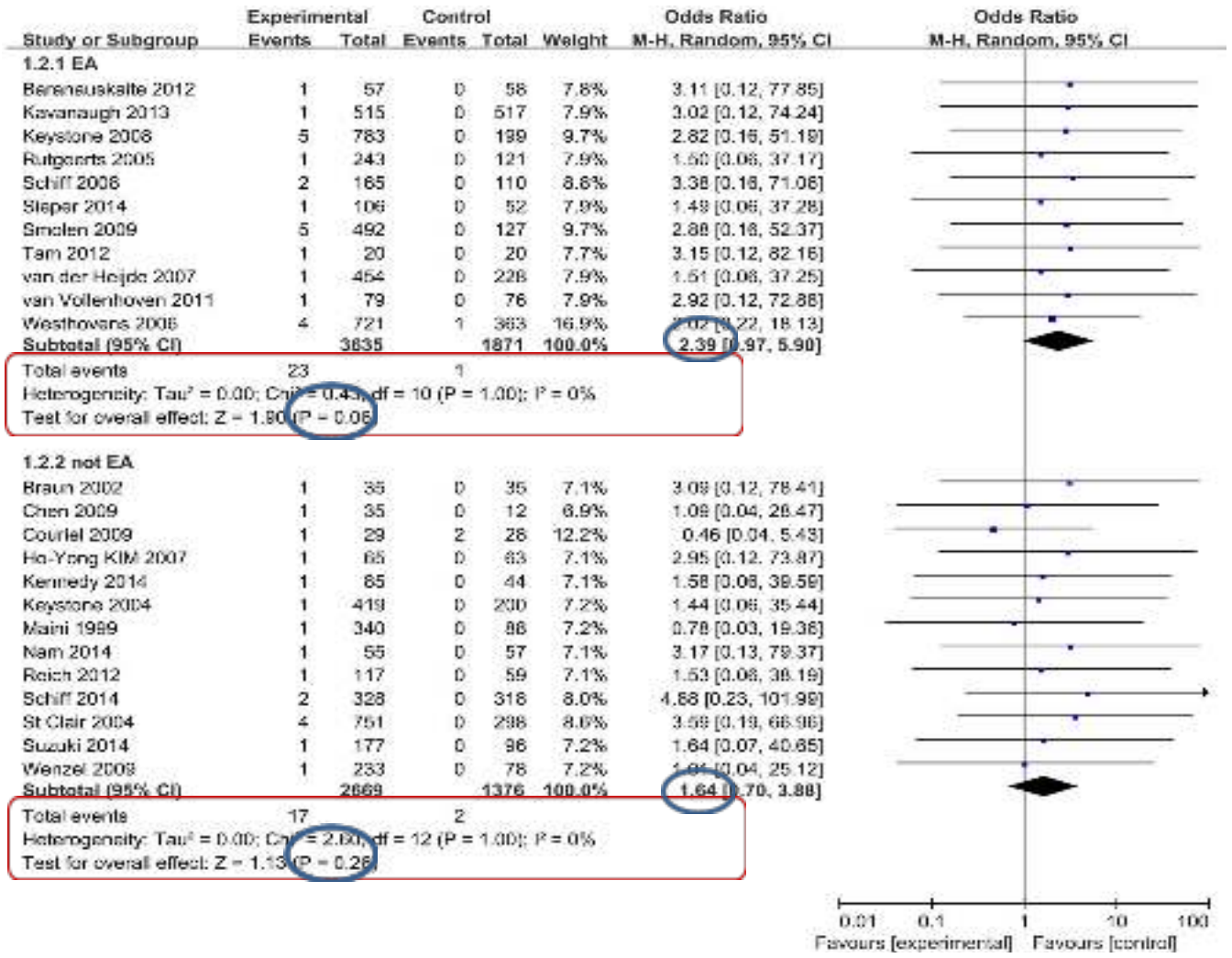

Zhang Z, et al. BMJ Open 2017;7:e012567

Table 2. Anti-TNF and TB risk: data from post-marketing surveillance and National Registries.

Source/Year/Ref.	TB cases N°/Patient N°						Anti-TNF TB incidence N°/100,000/year	Country TB incidence N°/100,000/year
	Overall TB CaseN°/Patient N°	IFX	ETN	ADA	GOL	CZP		
BIOBADASER, Spain 2003 [109]	17/1324/	17/1138	0/186	0*	0*	0*	95	21
ARTIS, Sweden 2005 [84]	17/1565	11/NA	6/NA	0*	0*	0*	118	6.3
RABBIT, Germany 2005 [108]	1/858	1/346	0/512	0*	0*	0*	116	8
Pharmetrics, Canada 2006 [85]	51/4558	19/1074	32/3484	0*	0*	0*	257	5
BIOBADASER, Spain 2007 [86]	8/3088	5/1137	2/1336	1/625	0*	0*	172	21
Japan 2008 [111]	14/5000	14/5000	NA	NA	0*	0*	280	28
LOHREN, Italy 2009 [87]	5/1064	3/519	1/242	1/303	0*	0*	246	8
RATIO, France 2009 [88]	NA	41/NA	5/NA	23/NA	0*	0*	116	8.7
Japan 2009 [113]	10/7091	NA	10/7091	NA	0*	0*	141	28
BSRBR, UK 2010 [110]	40/14,096	12/3718	8/5521	20/4857	0*	0*	95	14
South Korea, 2011 [89]	3/354	2/78	0/210	1/66	0*	0*	561	69.8
BIOBADAMEX, Mexico 2011 [90]	8/1590	§/525	§/679	§/386	0*	0*	125	23
GISEA, Italy 2012 [91]	9/2769	6/837	1/1130	2/802	0*	0*	32	8
Northern California, USA 2013 [119]	23/10,429	8/2778	8/5320	7/2331	NA	0*	17	5
Jordan 2014 [92]	3/140	1/53	0/26	2/61	NA	0*	714	5.5
Japan 2016 [66]	22/7755	NA	NA	22/7755	NA	NA	94	16
BIOBADABRASIL, Brasil 2017 [112]	5/942	1/293	1/283	3/366	0*	NA	286	42
Taiwan 2017 [118]	35/835	NA	24/443	11/332	0/60	NA	279	44
CORRONA, USA 2018 [93]	2/6023	§/1205	§/1442	§/1769	§/632	0/975	33	5

TB: tuberculosis; TNF: Tumor Necrosis Factor; IFX: infliximab; ADA: adalimumab; GOL: golimumab, CZP: certolizumab pegol, ETN: etanercept; 0*: not yet licensed; §: not reported 2 active TB cases without specify the anti-TNF therapy; NA: not analyzed.

Zhang Z, et al. BMJ Open 2017;7:e012567

Biyolojik Ajanlar ve Tüberküloz Epidemiyoloji

- **İspanya çalışması:**
  - Genel popülasyon x 1
  - RA x 7
  - RA+ anti-TNF x 20
- LTBI tarama/ profilaksi sonrası;
  - Genel popülasyon x 1
  - RA x 1
  - RA+ anti-TNF x 4

Arthritis Rheum. 2003 Aug;48(8):2122-7

Clin Rheumatol (2009) 28:421–426
DOI 10.1007/s10067-008-1067-x

ORIGINAL ARTICLE

Increased risk of tuberculosis in patients treated with antitumor necrosis factor alpha

Osman Elbek · Meral Uyar · Neriman Aydın · Şermin Börekçi · Nazan Bayram · Hasan Bayram · Öner Dikensoy

- 240 olgu, anti-TNF
  - Etanercept (%50) ve İnfliximab (%50)
- 184 (%77.6) BCG skarı
- 185 (%77.1) INH profilaksisi
- 2 aktif TB (her ikisi de INH almış) (832/100000)

Anti TNF-Alfa Kullanan Hastalarda Tüberküloz Sıklığı

Tuberculosis Frequency in Patients Taking TNF-alpha Blokers

Coşkun Doğan, Nesrin Kıral, Sevda Şener Cömert, Ali Fidan, Benan Çağlayan, Banu Salepçi
Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Türkiye

Turk Toraks Derg 2012; 13: 93-8

- 179 olgu, anti-TNF
  - İnfiliximab, n=52 (%29.1)
  - Adalimumab, n=59 (%33)
  - Etanercept, n=68 (%38)
- %67 BCG skarı
- %70.9 INH profilaksisi
- 2 aktif TB
  - INH profilaksisi 1 hasta
  - 1 miliyer, 1 plevra TB (1116/100000)

ANTİ-TNF-ALFA TEDAVİSİ VERİLEN OLGULARDA LATENT TÜBERKÜLOZ İNFEKSİYONU AÇISINDAN İZLEM SONUÇLARIMIZ

Pınar Mutlu,[1] Can Sevinç,[2] Oğuz Kılınç,[2] Eyüp Sabri Uçan[2]

[1] Artvin Devlet Hastanesi, Göğüs Hastalıkları Bölümü, Artvin

[2] Dokuz Eylül Üniversitesi, Tıp Fakültesi, Göğüs Hastalıkları AD, İzmir

Nobel Med 2014; 10(1): 47-52

- 196 olgu, anti-TNF
  - İnfliksimab 98 olgu (%50),
  - Etanercept 66 olgu (%33,7) ve
  - Adalimumab 32 olgu (%16,3)
- %91.4 BCG skarı
- %82.1 INH profilaksisi
- 1 plevra TB (INH profilaksisi almış) (510/100000)

Clinical Investigations

Respiration

Respiration 2015;90:101–108
DOI: 10.1159/000434684

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Factors Affecting the Tuberculosis Risk in Patients Receiving Anti-Tumor Necrosis Factor-α Treatment

Sermin Borekci[a] Ersan Atahan[a] Deniz Demir Yilmaz[a] Nejdiye Mazıcan[a]
Berna Duman[a] Yesim Ozguler[b] Benan Musellim[a] Vedat Hamuryudan[b]
Gul Ongen[a]

- 1964 olgu, anti-TNF
  - Etanercept, n=760 (%38.7)
  - Infliximab, n=684 (%34.8)
  - Adalimumab, n=520 (%26.5)
- 16 aktif TB (814/100000)
  - INH profilaksisi 9 hasta
  - 5 pulmoner, **11 ekstrapulmoner**

✓ **Behçet hastalığı yüksek TB riski, TDT≥10 mm düşük TB riski**

Biyolojik Ajanlar ve Tüberküloz Epidemiyoloji

- Anti-TNF tedavi ile risk yaklaşık **10-20 kat** artıyor
- Ekstrapulmoner TB daha sık (>%50)

Biyolojik Ajanlar ve TB

- **Hangi ilaçlarda risk fazla?**
- Anti-TNF- alfa monoklonal antikorlar **(adalimumab ve infliximab)**, soluble TNF-alfa reseptör tedavi ajanlarına **(etanercept)** göre daha yüksek TB riskine sahiptir
- Diğer ajanlarda belirgin risk artışı yok

Biyolojik Ajanlar ve TB

Biologic	FDA-approved indications (as of 1 November 2016)[a]	RR of TB compared to that in the general population
Adalimumab	AS, JIA, RA, Ps, PsA, Crohn's, UC	29.3 (95% CI, 20.3–42.4) (3) based on SIR (standardized for age and sex)
Infliximab	AS, RA, Ps, PsA, Crohn's, UC	18.6 (95% CI, 13.4–25.8) (3) based on SIR (standardized for age and sex)
Etanercept	AS, JIA, RA, Ps, PsA	1.8 (95% CI, 0.7–4.3) (3) based on SIR (standardized for age and sex) 3.5
Certolizumab pegol	AS, RA, PsA, Crohn's	No definite increase in RR in pooled data from RCTs (4)
Golimumab	AS, RA, PsA, UC	No definite increase in RR in pooled data from RCTs (5)
Rituximab	Chronic lymphocytic leukemia, non-Hodgkin lymphomas, granulomatosis with polyangiitis, microscopic polyangiitis, RA	No definite increase in RR in pooled data from RCTs (6)
Tocilizumab	JIA, RA	No definite increase in RR in pooled data from RCTs (7)
Vedolizumab	UC, Crohn's	No definite increase in RR from drug safety data (8)
Ustekinumab	Ps, PsA, Crohn's	No definite increase in RR from drug safety data (9) First choice in patients with PsA at high infection and TB risk (10)
Abatacept	JIA, RA	No definite increase in RR in pooled data from RCTs (6)

[a]AS, ankylosing spondylitis; Crohn's, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, plaque psoriasis; PsA, psoriatric arthritis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; UC, ulcerative colitis.

Biyolojik Ajanlar ve TB

- **Hangi hastalarda risk fazla?**
  - **RA**, AS, Psoriatik artrit, Behçet
  - Methotrexate, azothiopirine ek kullananlar
  - TB insidansı yüksek bölgelerde yaşayanlar
  - LTBI tedavisi almayan veya tamamlamayanlar

Table 3. Frequency of tuberculosis (TB) according to rheumatologic condition.

Diseases	TB/Control Group, n/N	%
Ankylosing spondylitis	38/3898	0.97
Rheumatoid arthritis	25/2808	0.89
Psoriatic arthritis	4/457	0.87
Behçet disease	5/124	4
Other disease	1/408	0.24

J Rheumatol. 2016 Mar;43(3):524-9

Biyolojik Ajan Kullanan Hastalarda LTBI Taraması ve Koruyucu Tedavisi

Biyolojik Ajanlar ve LTBI

Table 1. Recommended indications for diagnosis and treatment of LTBI according to WHO guidelines.

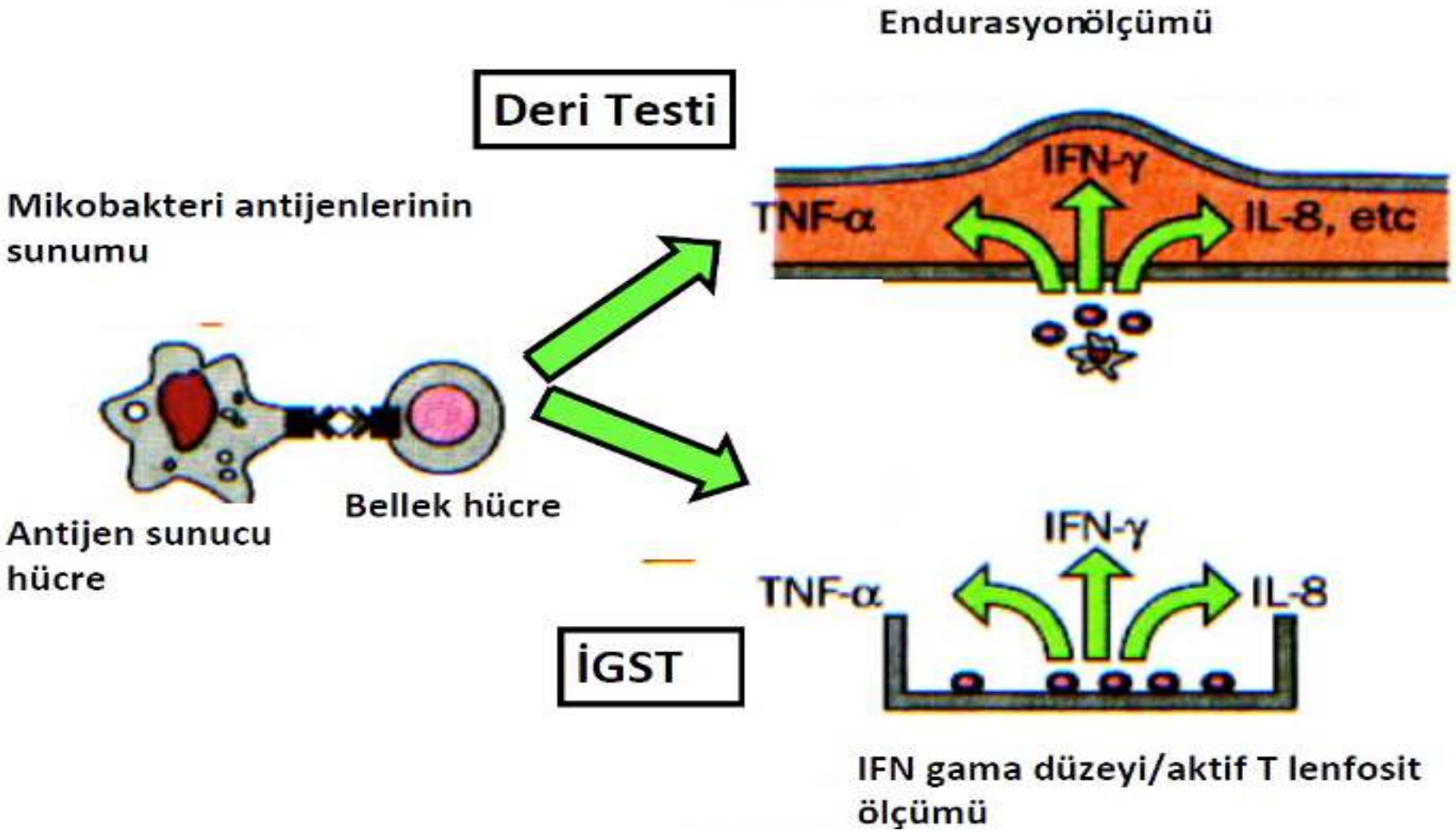
	Risk of developing TB disease compared to those without risk factors	References
Contacts of pulmonary TB patients	16–46	[5]
People with HIV	80–110	[6]
Patients initiating ant-TNF therapy	10	[7,119]
Patients receiving dialysis	8	[8]
Patients preparing for organ transplantation	70–300	[9–11]
Patients with silicosis	1.4–2.5	[12,13]
Healthcare workers	2.4	[14–16]
Residents and employees of high-risk congregate settings (correctional facilities, nursing homes, homeless shelters)		[17]
Immigrants from high TB burden countries	15	[18,19]
Illicit drug users	3	[20]

TB: tuberculosis; HIV: human immunodeficiency virus; TNF: tumor necrosis factor; WHO: World Health Organization.

Biyolojik Ajanlar ve LTBI

- Dünya nüfusunun 1/3'ü enfekte
- Tüm biyolojik ajan kullananlarda LTBI taraması önerilir
- Biyolojik ajan başlamadan önce;
  - TB risk faktörü öyküsü
  - PA akc gr, HRCT
  - IGST ya da TDT ile LTBI taraması

Biyolojik Ajan ve LTBI
Hangi test?



Biyolojik Ajan ve LTBI
Hangi test?

PPD ve Yeni Tanı Testleri Özellikleri	PPD	IFN'a dayalı testler
BCG	Etkilenir	Etkilenmez
Nontüberküloz mikobakteri (NTM)	Etkilenir	Etkilenmez
Duyarlılık	%75-90	%80-95
Özgüllük	%70-95	%95-100
BCG'li Özgüllük	%53	%89
Test Pozitif TB gelişme ilişkisi	Orta	Güçlü
Booster Etki	Var	Yok
TB Hast. Şiddeti	Etkilenme Az	Etkilenmeyebilir
TB Temas İlişkisi	Var	Var
İmmünsupresyon	Etkiler	Etkilenme Az
Ağır deri lezyonları	Etkilenebilir	Etkilenmez
Aktif TB Öngörü	Var	Daha Güçlü
Test Süresi	2-3 gün	1-2 Gün
Maliyet	Ucuz	Pahalı
Personel İhtiyacı	Var	Var
Cihaz Gereksinim	Yok	Var

PPD sonucu hem immünsüpresyondan hem deri lezyonlarından etkilenir ve latent TB'un profilaksisi için yanlış karar verdirebilir.

Biyolojik Ajan ve LTBI

TABLE 2 Recommendations for LTBI screening and treatment in different countries[a]

Agency and/or country or region, year	LTBI screening tests	LTBI treatment regimen (duration in months, medication)	Anti-TNF-α starting delay	Repeat testing
Centers for Disease Control and Prevention, United States, 2004 and 2010 (update) (54, 55)	TST or IGRA, combined use of TST and IGRA supported Positive TST: ≥5 mm	9H	No definite recommendation, completion of LTBI treatment before anti-TNF-α therapy, if possible	Only in individuals at increased risk for TB infection
American College of Rheumatology, United States (56)	TST or IGRA	Not specified	1 mo	Annually in individuals with risk factor for future or ongoing TB exposure
Canada, 2013 (57)	TST or IGRA, combined (sequential) use of TST and IGRA supported	9H	No recommendation	Only in individuals at increased risk for TB infection
British Thoracic Society, United Kingdom, 2005 (58)	Use of risk stratification tables (and chest X ray) for patients on IST. TST performed only in patients not on IST (positive TST is ≥15 mm in BCG-vaccinated patients and ≥5 mm in non-BCG-vaccinated patients)	6H 3RH	≥2 mo Delay until completed LTBI treatment if abnormal chest X ray, history of TB	Not specified
France, 2003 (59, 60)	TST only Positive TST: ≥10 mm	2RZ 3RH 9H	≥3 wks	Not specified
Switzerland, 2007 (61)	IGRA only	9H 4R	1 mo	Not specified
TBNET International consensus, Europe (23)	TST or IGRA. TST performed only in patients without BCG. Positive TST: ≥10 mm	9–12H 3RH	4 wks	Not specified

[a]R, rifampin; H, isoniazid; Z, pyrazinamide; IST, immunosuppressive therapy.

Biyolojik Ajan ve LTBI Tedavisi

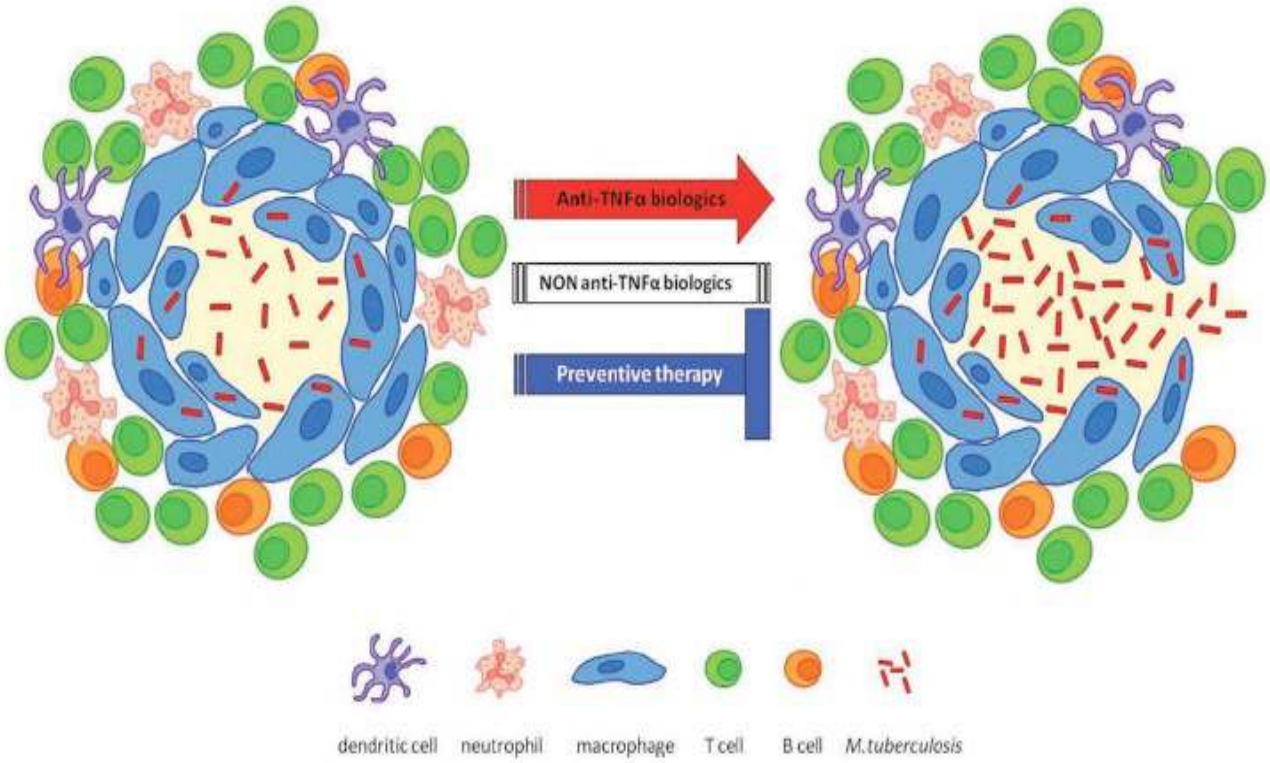


Figure 2. Modulation of the granuloma integrity by preventive treatment for tuberculosis and biologic therapy.
The granuloma is a complex and well organized cellular structure in which M. tuberculosis is contained within a necrotic region surrounded by epithelioid macrophages and a rim of B and T lymphocytes. The TNF-α has been recognized as a key factor for the maintenance of this structure. Indeed, changes in its levels, as induced by anti-TNF biologics may disrupt the granuloma integrity -losing the bacterial containment- and may contribute to active TB reactivation. By contrast, based on the available data, the non anti-TNF biologics, inhibiting CD20, CD28, IL-1, IL-6, IL-12, IL-23, or IL-17, have a negligible or absent effect on TB granuloma integrity. Preventing therapy with isoniazid or rifamycins is supposed to reduce mycobacteria load leading to a decrease of the risk to develop active TB.

Biyolojik Ajan ve LTBI Tedavisi

- İspanya, 2005
- Aktif TB gelişimini %78 azaltıyor

- TB risk faktörü varsa
- PA akciğer grafisinde TB skarı varsa
- IGRA ya da TDT pozitifse
  - Kemoprofilaksi (9 ay INH ya da 4 ay RIF)

- Kemoprofilaksiden 3-4 hafta sonra biyolojik ajan başlanabilir

Biyolojik Ajan Kullanan Hastaların İzlemi

- Biyolojik ajan tedavisi bittikten sonra en az 6 ay daha izlem
- Tedavi süresince 3 ayda bir akciğer grafisi
- LTBI(-) olan hastaların izlem taraması
  - Riskli hastalarda (endemik bölgeye seyahat vb) yılda bir (CDC/The American College of Rheumatology)

Biyolojik Ajan Kullanan Hastaların İzlemi

- İzlemde LTBI saptanma oranı
  - TDT ile %13
  - QFT ile %7
  - T-SPOT.TB ile %10

- Ann Rheum Dis 2015, 74:1848–1853

Biyolojik Ajan Kullananlarda Aktif TB

- Ekstrapulmoner!!! ve dissemine TB daha sık
- Biyolojik ajan kesilip TB tedavisi başlanır
- Biyolojik ajan ne zaman tekrar başlanacak tartışmalı

- **Öneri;**
- TB tedavisinin 3 ayı tamamlandığında biyolojik ajan tedavisi tekrar başlanabilir (TB menenjit hariç)
  - Direnç sonuçları
  - Klinik değerlendirme

Biyolojik Ajan Kullananlarda Aktif TB

- **<u>IRIS (Immune Reconstitution Inflammatory Syndrome)</u>**
- Anti-TNF kullanan, TB saptanan hastalarda
- %7-12
- Ortalama 1.5 ay sonra
- Tedavi
  - KS
  - Anti-TNF tedavinin tekrar başlaması (düşük doz)

Biz ne yapalım?

Romatoloji Araştırma ve Eğitim Derneği ve Türk Toraks Derneği'nin Hazırladığı Ortak Uzlaşı Raporu; 2005, 2009

- TDT ve IGST testleri negatif olan, akciğer grafisinde fibrotik/kalsifik lezyonu bulunmayan ve son 1 yıl içinde aktif TB hastalığı olan birisi ile yakın temas içinde bulunmamış olan kişilerde latent TB infeksiyonu olmadığı ve tedavi ihtiyacının bulunmadığı düşünülür

- Aşağıdaki koşullarda, 9 ay INH ya da 4 ay RIF ile latent TB infeksiyonu tedavisi önerilir:
  - Akciğer grafisi normal olmasına karşın, TDT (≥5 mm) ve/veya IGST pozitif olan hastalar
  - Akciğer grafisinde kuşkulu fibrotik/kalsifik lezyonlar, ve/veya TDT ve/veya IGST pozitifliği olan, ancak aktif TB hastalığı dışlanmış olan hastalar
  - Son 1 yıl içerisinde aktif TB hastalığı olan biriyle yakın temas içinde bulunanlar
  - TB açısından yüksek riskli sağlık personeli olanlar

S.B. Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi 2011-2019

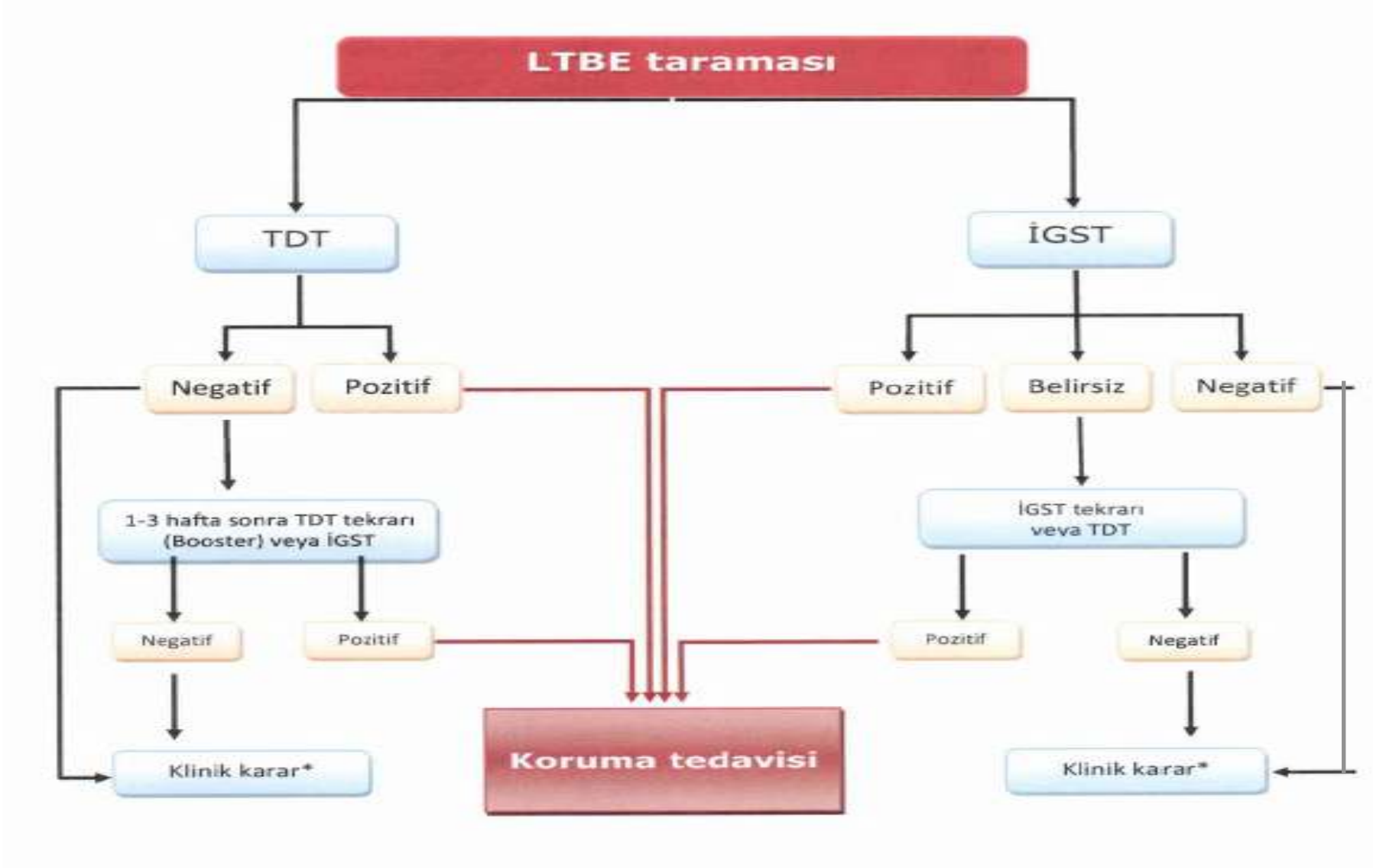
S.B. Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi 2019

- Türkiyede TB insidansı 100000'de 16
- Anti-TNF alanlarda TB riski;
  - Türkiye'de **10-20** kat daha fazla

S.B. Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi 2019

- Anti-TNF alacak hastaların LTBI taraması yapılır
- TDT≥5 ya da IGST (+)→ LTBI
- LTBI saptananlarda tedavi edilir, anti-TNF tedavi 1 ay ertelenir
- Anti-TNF tedavi başladıktan sonra 6 ayda bir izlem
- LTBI saptanmayanlarda yıllık LTBI taraması önerilir

S.B. Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi 2019



S.B. Anti-TNF Kullanan Hastalarda Tüberküloz Rehberi 2019

Anti-TNF kullanımı anında TB gelişmesi

- Anti-TNF kesilip anti-TB tedavi başlanır
- Aktif TB'da anti-TNF ilaç tedavi bitimine kadar verilmez
- İstisnai durumlarda başlangıç tedavisi sonrası anti-TNF başlanabilir

Teşekkürler…