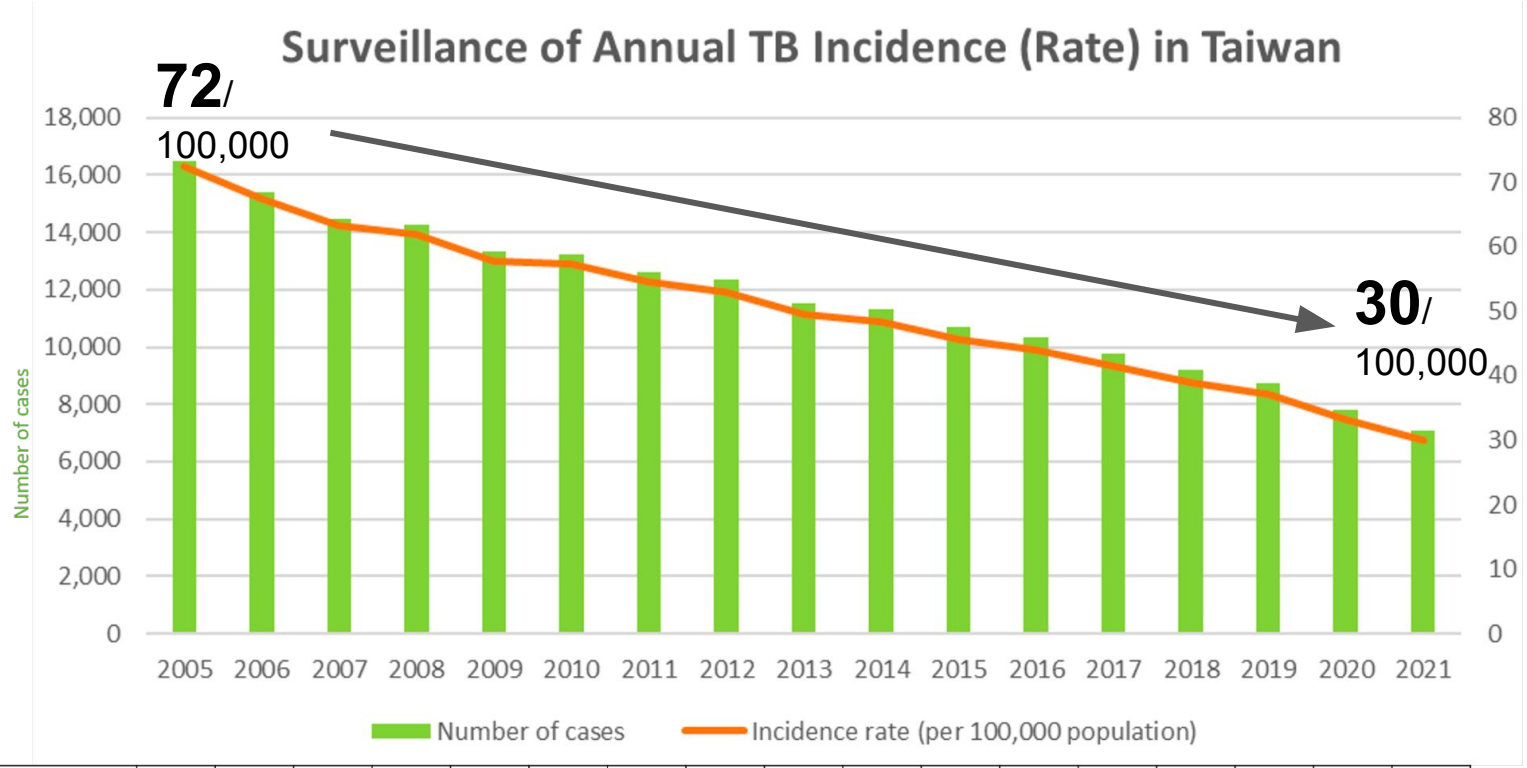
使用生物製劑之於TB的風險

2023-07-13

新竹台大 風濕免疫科 藍鼎淵



Indicator \ Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Number of cases	16,472	15,378	14,480	14,265	13,336	13,237	12,634	12,338	11,528	11,326	10,711	10,328	9,759	9,179	8,732	7,823	7062
Incidence rate (per 100,000 population)	72.5	67.4	63.2	62	57.8	57.2	54.5	53	49.4	48.4	45.7	43.9	41.4	38.9	37	33.2	30.1

Taiwan CDC report

Biologics/small molecules target for **autoimmune** disease

RA	PsA/PsO	IBD	SLE	Allergic disease / AD
TNF	TNF	TNF	CD20	IgE
IL-6 (1)	IL-12/23 (1)	IL-12/23 (1)	BAFF	IL4/13
CLTA4-Ag (1)	IL-17 (3)	Intergrin (1)	IFN	IL5
	IL-23 (2)			
JAKi	JAKi	JAKi		JAKi

Outline

- Screening for latent TB
- Efficacy of latent TB treatment
- Issues:
  - IGRA monitoring after LTBI treatment?
  - IGRA positive conversion
  - TB development in IGRA negative patients

Risk of latent TB reactivation: Lessons from TNF inhibitors (TNFi)

ORIGINAL ARTICLE

Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent

Joseph Keane, M.D., Sharon Gershon, Pharm.D., Robert P. Wise, M.D., M.P.H., Elizabeth Mirabile-Levens, M.D., John Kasznica, M.D., William D. Schwieterman, M.D., Jeffrey N. Siegel, M.D., and M. Miles Braun, M.D., M.P.H.

2001

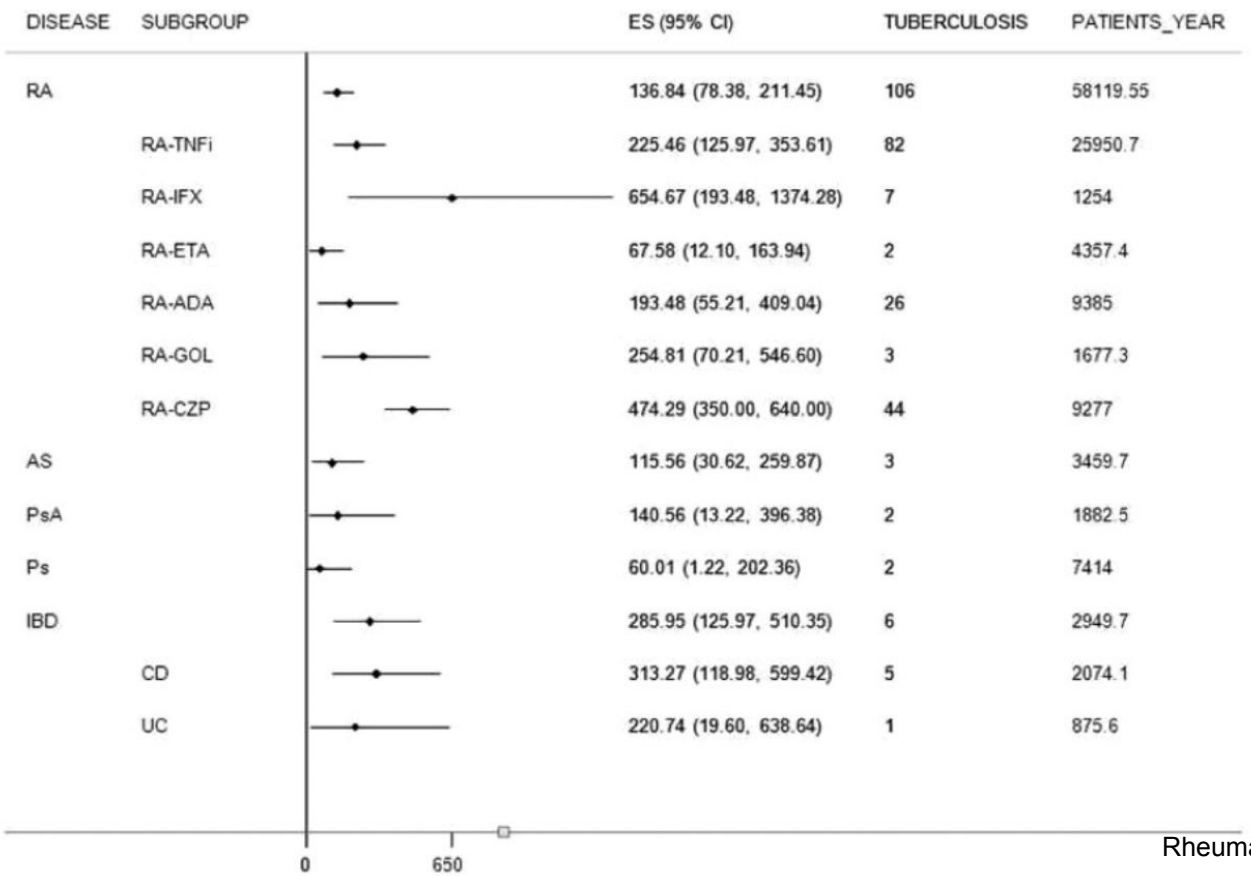
October 11, 2001
N Engl J Med 2001; 345:1098-1104
DOI: 10.1056/NEJMoa011110

- FDA MedWatch spontaneous reporting system
- **70** reported cases of tuberculosis after treatment with infliximab for a **median of 12 weeks** (70/147,000 = **47**/100,000)
- In 48 patients, tuberculosis developed **after three or fewer infusions.**
- **40%** patients had **extrapulmonary** disease
- Of the 70 reports, 64 were from countries with **a low incidence of tuberculosis**

N Engl J Med 2001; 345:1098-1104

RIsk of TB, noted from long-term extension study (LTE)

FIG. 4 Meta-analysis of incidence rates by disease of long-term extension studies



TB incidence rate: (/100,000)

RA: 136
- RA (TNFi): 225
- RA (IFX): 654

AS: 115

PsA: 140

PsO: 60

IBD: 285

Rheumatology (Oxford) . 2014 Oct;53(10):1872-85.

RIsk of TB, noted from real-world experience

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

	TB cases N°/Patient N°							
Source/Year/Ref.	Overall TB CaseN°/Patient N°	IFX	ETN	ADA	GOL	CZP	Anti-TNF TB incidence N°/100,000/year	Country TB incidence N°/100,000/year
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.

Expert Rev Anti Infect Ther . 2018 Jun;16(6):501-512.

TNFα maintains the granuloma integrity

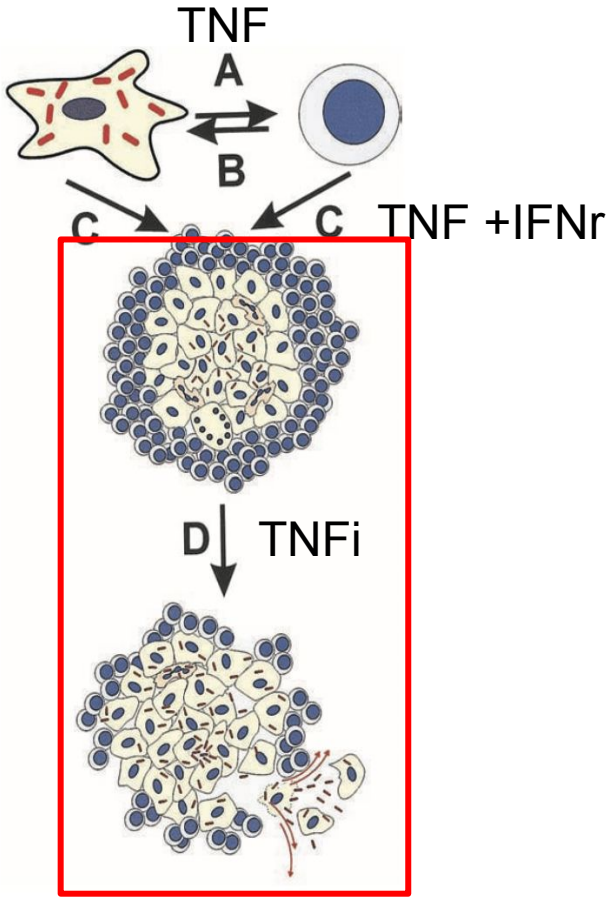


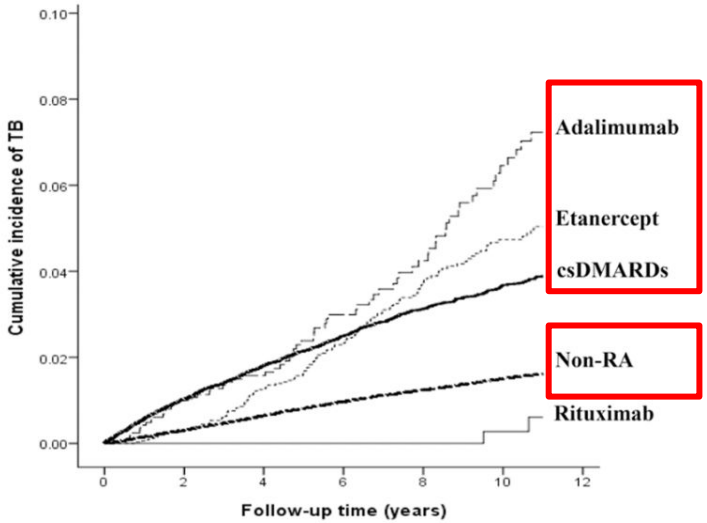
Figure 1. Multiple steps of action of TNF in antibacterial and inflammatory responses to *Mycobacterium tuberculosis* infection. *A,* Macrophage-derived TNF acts as a costimulus for T cells. *B,* T cell–derived TNF primes macrophages for mycobactericidal activity. *C,* Macrophage- and T cell–derived TNF, together with IFN-γ and chemokines, induces recruitment and organized accumulation of mononuclear cells into highly structured granulomas. TNF and IFN-γ also regulate excessive inflammation by inducing apoptosis of T cells. *D,* Anti-TNF therapy results in granuloma breakdown and dissemination of mycobacteria.

- More extrapulmonary TB
- More disseminated TB

Clin Infect Dis . 2005 Aug 1;41 Suppl 3:S199-203.

Taiwan NHI database (2000-2011)

- RA 42,180 patients, 1:4 matched with non-RA pateints
- TNFi ~ **5000** (ETN~3500, ADA~1500), RTX 700



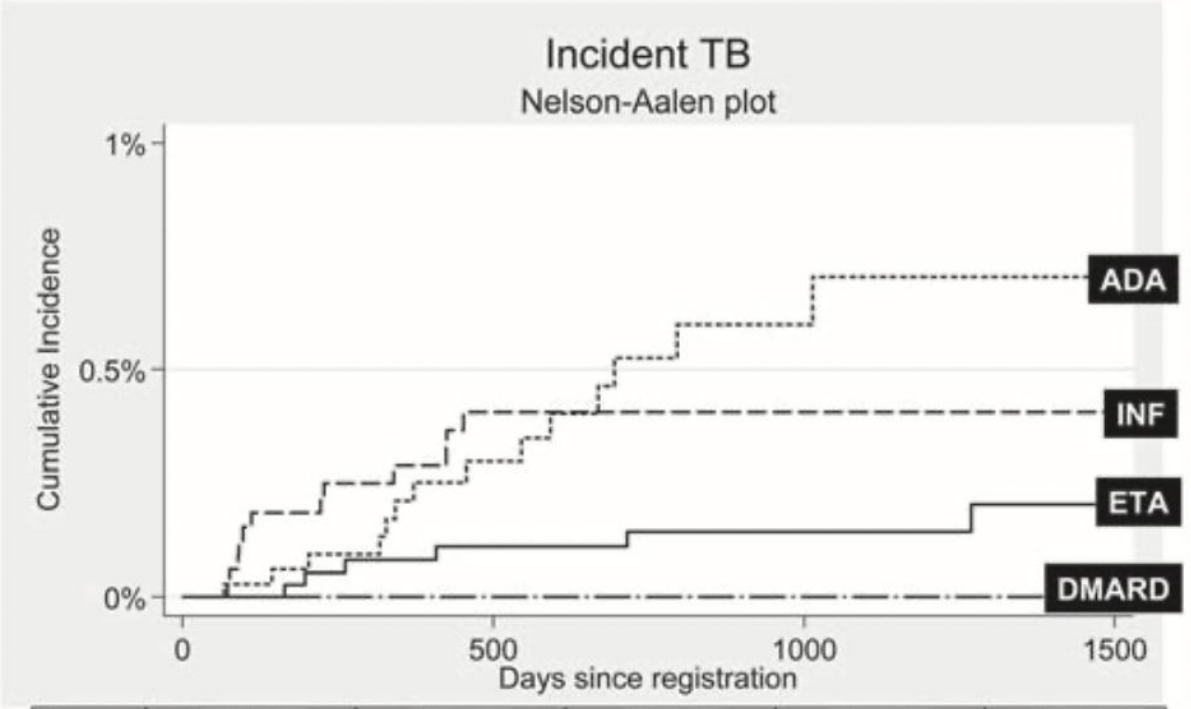
RA

Variable	Follow-up time (year)					
	0	2	4	6	8	10
Non-RA						
At risk	166,653	162,215	157,927	153,552	149,036	73,332
TB event	516	543	516	422	401	155
RA with csDMARDs						
At risk	33,278	27,405	22,056	17,049	12,332	5,016
TB event	344	213	158	110	69	19
RA with etanercept						
At risk	3,469	3,130	2,662	2,162	1,645	700
TB event	10	30	29	31	17	4
RA with adalimumab						
At risk	1,586	1,335	1,043	789	606	261
TB event	16	8	15	10	14	4
RA with rituximab						
At risk	756	702	598	488	387	169
TB event	-	-	-	-	1	1

- Adjusted HR of TB incidence, compared to csDMARD:
  - ETN1.16 (0.95-1.41)
  - ADA **1.52 (1.18-1.96)**

PLoS One. 2016; 11(4): e0153217.

Etanercept (ETN) has relative lower risk of TB

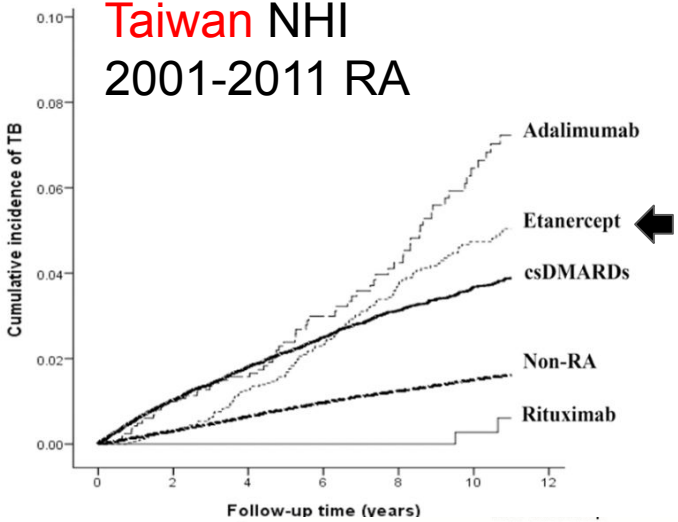


UK RA biologics cohort 2001-2008

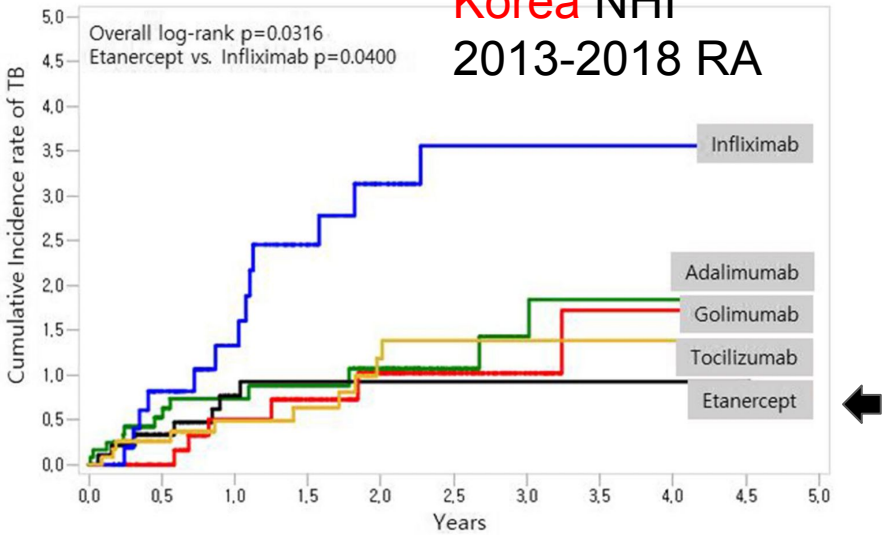
Drug	Registration (entry to study)	1 year (365 days)	2 years (730 days)	3 years (1095 days)	4 years (1460 days)
DMARD	3232	2652	1839	742	213
ETA	3913	3474	3051	2363	1020
INF	3295	2694	1918	1392	918
ADA	3504	2457	1531	729	247

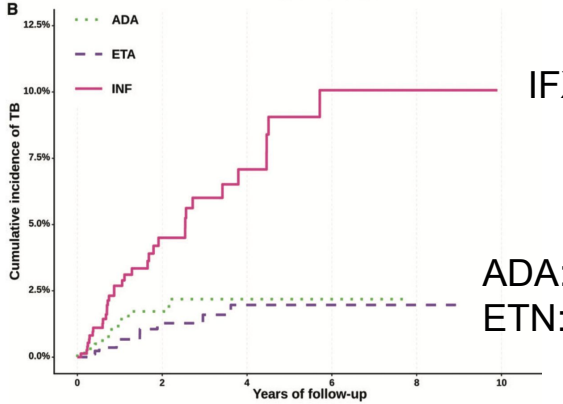
Etanercept (ETN) has relative lower risk of TB

Taiwan NHI
2001-2011 RA



Korea NHI
2013-2018 RA





IFX: 1855/100,000

ADA: 760/100,000
ETN: 435/100,000

Hong Kong NHI
2006-2015
RA, AS, IBD, PsO

PLoS One. 2016; 11(4): e0153217.
Rheumatology (Oxford). 2019 May 1;58(5):803-810
Arthritis Res Ther . 2022 Jun 27;24(1):157.

Other risk factors: comorbidity, age, TB exposure…

Table 1
Host-and traditional DMARD-related TB risk reactivation.

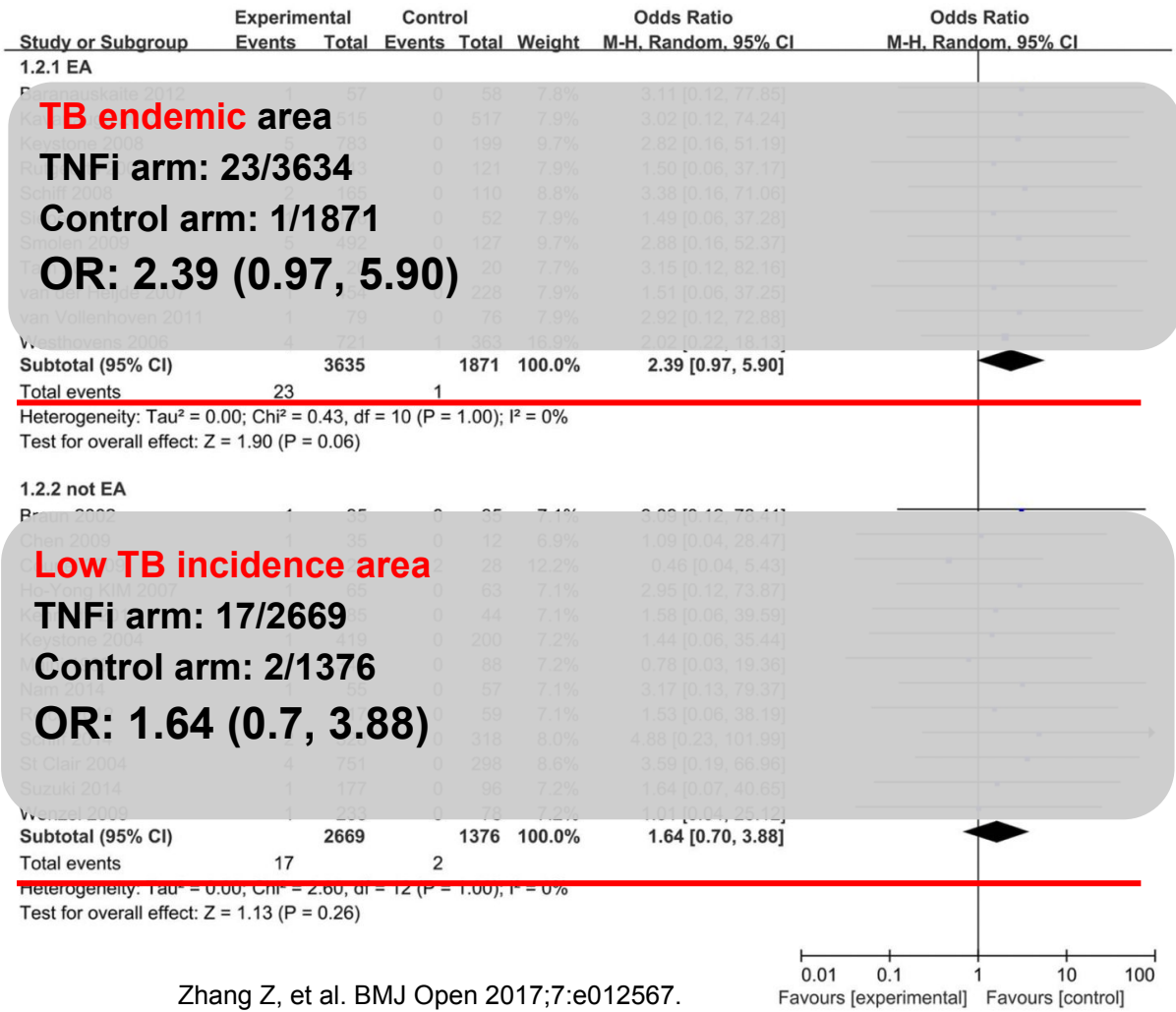
Host-related		Traditional DMARD-related	
Demographic characteristic and comorbidity	Estimated RR	Drug	Estimated RR
Age <50 years	2	Corticosteroids	2.4
Family history of TB	2.38	Methotrexate	3.4
Recent TB infection (<2 years)	15	Leflunomide	11.7
Former TB disease	2.69		
Exposure to active TB subjects	10.1	Cyclosporine	3.8
Cigarette smoker	2	Other (sulphasalazine, azathioprine, hydroxychloroquine)	1.6
Alcohol abuse	1.84		
Drug abuse	2.83		
Malnutrition, low body weight (BMI ≤ 20)	2		
Pso/PsA [24]	3.1		
Diabetes	3.11		
RA [21]	3.68		
AS [25]	3.9		
Silicosis	30		
Severe kidney disease	25		
Abnormal chest x-ray—with upper lobe fibronodular disease typical of healed TB infection	19		

Except where otherwise indicated, data are quoted from the reference number [20].
Abbreviations. DMARD: disease modifying anti-rheumatic drug; RR: relative risk; TB: tuberculosis; Pso: psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis.

Autoimmun Rev . 2015 Jun;14(6):503-9.

Background TB incidence should also be considred

Systemic review of **TNFi RCTs** (including extension periods)



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

Other risk factors: concomitant immunosuppressants

Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials

Roberto Lorenzetti[1], Angelo Zullo[1], Lorenzo Ridola[1], Andrea Picchianti Diamanti[2], Bruno Laganà[2], Luigi Gatta

	Case/total	OR	OR	OR
TNFi + MTX/AZA	24/4241	54 (5.3-88)	13.3 (3.7-100)	-
TNFi alone	2/5769	-	1	4 (0.2-15.7)
DMARDs	0/4673	1	-	1

Biologics/small molecules target for **autoimmune** disease

RA	PsA/PsO	IBD	SLE	Allergic disease / AD
TNF	TNF	TNF	CD20	IgE
IL-6 (1)	IL-12/23 (1)	IL-12/23 (1)	BAFF	IL4/13
CLTA4-Ag (1)	IL-17 (3)	Intergrin (1)	IFN	IL5
	IL-23 (2)	low risk		
JAKi	JAKi	JAKi		JAKi

Anti-IL17: Secukinumab

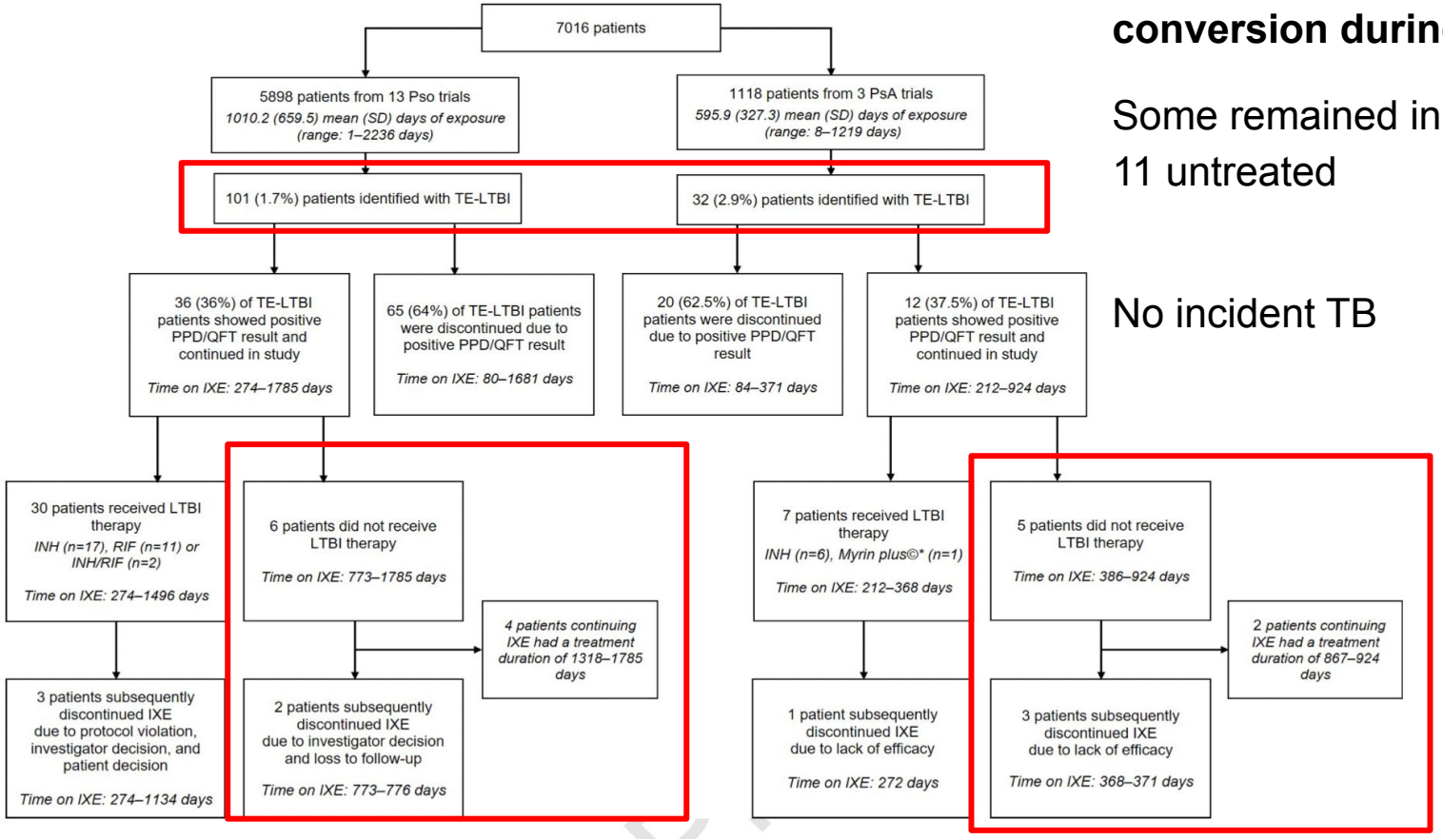
107 LTBI

12 untreated

No incident TB

1.1 Secukinumab (Cosentyx®)	Data from 10 phase 2 (A2211, A2211E1, A2220, and A2212) and phase 3 (ERASURE, FIXTURE, FEATURE, JUNCTURE, SCULPTURE, and STATURE) clinical trials[37,38] Patients received anti-tuberculosis treatment when LTBI was present[37,38]	3430	2725.0	0
	An analysis of the safety data from[39]: -21 phase 3 and phase 4 clinical trials (2PRECISE, AJP01 CARIMA, CLEAR, ERASURE, FEATURE, FIXTURE, GAIN, GESTURE, JUNCTURE, PRIME, PSORITUS, SCALP, SCULPTURE, TRANSFIGURE, FUTURE 1–3, MEASURE 1–3); -Postmarketing surveillance. Patients with LTBI had to receive tuberculosis chemoprophylaxis before being treated with secukinumab[39]	7355	Clinical trials: 16 226.9 Postmarketing surveillance: 96 054.0	0 (Five cases of 'de novo' active tuberculosis in postmarketing surveillance data)
	A more detailed analysis of the safety data from 5 phase 3 (ERASURE, FIXTURE, FEATURE, JUNCTURE and SCULPTURE) of those 21 clinical trials[40] Patients that tested positive for LTBI at screening received chemoprophylaxis[40]	132 with medical history of tuberculosis/LTBI -107 had a positive test -25 had a negative test	NA	0
	Patients with psoriasis that were found to have LTBI at screening and received secukinumab without previous chemoprophylaxis[42] **Follow-up period of 52 weeks[42]**	**12**	NA	0

Anti-IL17: Ixekizumab



133 IGRA positive conversion during treatment

Some remained in the trial

11 untreated

No incident TB

J Am Acad Dermatol. 2020 Nov;83(5):1436-1439.

Anti-IL17: Brodalumab

Drug	Study information	Number of patients	Exposure (patient-years)	Number of cases of tuberculosis reactivation
1.3 Brodalumab (Siliq® in US, Kyntheum® in Europe, Lumicef® in Japan)	Data from several distinct clinical trials with patients receiving brodalumab[51] Patients had to have a negative test at screening to be included in trials[51] All the patients who converted to a positive test during the follow-up period had to be discontinued from the study[51]	4464	NA	0
	Data from a 108-week extension study with Japanese patients.[52] Patients that were at risk of developing/ suspected to have tuberculosis were excluded from this study[52]	129	NA	0

No incident TB during RCT and extension studies

Anti-IL23: Guselkumab

2.1) Guselkumab (Tremfya®)	Data from 5 phase 1, phase 2 and phase 3 clinical trials (including VOYAGE 1, VOYAGE 2 and NAVIGATE) with patients with psoriasis receiving guselkumab[59]	105 patients tested positive at screening	NA	0
	Patients who tested positive at screening, received tuberculosis chemoprophylaxis[59]			
	A more detailed analysis of VOYAGE 1 and VOYAGE 2 safety data trough week 100 was developed[61]	1721 randomized in both studies	NA	0
	Patients with a positive test at screening received anti-tuberculosis treatment[61]	- 69 assigned to guselkumab with a positive test at screening		
	A group of patients assigned to receive guselkumab initiated tuberculosis chemoprophylaxis on the first dose day of the drug or after that day[61]	**(7 initiated chemoprophylaxis on the first dose day, 5 started after that day)**		
	Data from patients assigned to receive guselkumab in phase 3 clinical trial ECLIPSE[60]	534	NA	0

9/69 LTBI not having treatment, no incident TB

Biologics/small molecules target for **autoimmune** disease

RA	PsA/PsO	IBD	SLE	Allergic disease / AD
TNF	TNF	TNF	CD20	IgE
IL-6 (1)	IL-12/23 (1)	IL-12/23 (1)	BAFF	IL4/13
CLTA4-Ag (1)	IL-17 (3)	Intergrin (1)	IFN	IL5
	IL-23 (2)		Presumably low risk	
JAKi	JAKi	JAKi		JAKi

Biologics/small molecules target for **autoimmune** disease

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TNF	TNF	TNF	CD20	IgE
IL-6 (1)	IL-12/23 (1)	IL-12/23 (1)	BAFF	IL4/13
CLTA4-Ag (1)	IL-17 (3)	Intergrin (1)	IFN	IL5
	IL-23 (2)			
JAKi	JAKi	JAKi		JAKi

Risk of tocilizumab?

- **Low risk in previous literature**

Table 2: Non-anti-TNF-targeted biologics: reported TB cases from national registries and postmarketing surveillance.

Biologic	Country; patient N°	TB cases	IR	Expected IR/100/year (WHO)	Reference
Tocilizumab	Japan; 3881	4	0.22	15–100	[116]
	Japan; 302	0	0	15–100	[115]
	France; 1303	0	0	10–24	[142]
	Germany; 370	0	0	10–24	[143]
Rituximab	Germany; 2484	1	0.12	10–24	[145]
	Greece; 234	0	0	10–24	[144]
	Taiwan; 763	2	0.38	15–100	[140]
Abatacept	France; 682	0	0	10–24	[171]
	Japan; 231	0	0	15–100	[172]
Ustekinumab	Worldwide; 3474	0	0	NA	[180]
Secukinumab	Unavailable data	NA	NA	NA	NA

WHO: World Health Organization-estimated incidence of TB, 2016; NA: not applicable.

Mediators Inflamm . 2017;2017:8909834.

Risk of tocilizumab? however…

- **Korea** NHI, 2013-2018 RA
- Similar risk between tocilizumab and TNFi

Table 2 Risk of tuberculosis in patients with rheumatoid arthritis treated with biologic therapy

			Anti-TNF			
	All (*n* = 4736)	**ETA (*n* = 934)**	**INF (*n* = 561)**	**ADA (*n* = 1,218)**	**GOL (*n* = 858)**	**TOC (*n* = 1165)**
Duration of follow-up (days), median (IQR)	569 (230–1075)	640 (256–1225)	642 (222–1174)	510 (216–931)	475 (204–984)	612 (281–1061)
Person-years	8650.8	1879.7	1087.1	2050.9	1447.5	2185.6
Case of TB, *n*	48	7	13	12	6	10
Rate/100,000 person-years (95% CI)	554.9 (412.3–727.0)	372.4 (160.0–720.1)	1195.8 (657.8–1968.5)	585.1 (313.3–981.2)	414.5 (164.7–839.9)	457.5 (229.3–802.4)
Adjusted IRR[a]		1.00 (ref)	3.06 (1.22–7.69)	1.69 (0.66–4.33)	1.22 (0.41–3.67)	1.25 (0.47–3.31)

TNF tumor necrosis factor, *ETA* etanercept, *INF* infliximab, *ADA* adalimumab, *GOL* golimumab, *TOC* tocilizumab, *IQR* interquartile range, *TB* tuberculosis, *CI* confidence interval, *IRR* incidence rate ratio

[a] The IRR was adjusted for age, sex, and entry year

Risk of tocilizumab? however…

- **Hong Kong** NHI, 2006-2015, RA/SpA/PsO/IBD
- Non-negligible IR of tocilizumab users

Biologic	Patients, *n*	Obseved TB[a], *n*	Total PY	IR of TB/10^5 PY	SIR (95% CI)
TNF inhibitor[b]	2840	57	5962	956.1	13.37 (9.90–16.84)
Infliximab	760	34	1833	1855.4	25.95 (17.23–34.67)
Adalimumab	646	9	1184	760.1	10.63 (3.68–17.57)
Certolizumab	38	0	14	0.0	–
Etanercept	959	10	2299	435.0	6.08 (2.31–9.86)
Golimumab	437	4	632	632.8	8.85 (0.18–17.52)
Non-TNF biologic[c]	742	6	959	625.7	8.75 (1.75–15.75)
Abatacept	147	0	156	0.0	–
Rituximab	167	2	142	1404.5	19.64 (0–46.86)
Tocilizumab	371	4	631	633.8	8.86 (0.18–17.55)

Biologics/small molecules target for **autoimmune** disease

RA	PsA/PsO	IBD	SLE	Allergic disease / AD
TNF	TNF	TNF	CD20	IgE
IL-6 (1)	IL-12/23 (1)	IL-12/23 (1)	BAFF	IL4/13
CLTA4-Ag (1)	IL-17 (3)	Intergrin (1)	IFN	IL5
	IL-23 (2)			
JAKi	JAKi	JAKi		JAKi

Tofacitinib:
up to 750/100,000 in endemic area (>50/100,000)

Table 2 TB IRs for tofacitinib patients by background country IRs* (phase II, III and LTE studies)

	TB cases with tofacitinib (n)	Tofacitinib exposure (patient-years)	Crude TB IR † (95% CI)
Low‡ (0.01)	1	4852.3	0.02 (0.003 to 0.15)
Medium§ (≥0.01 and <0.05)	4	5020.5	0.08 (0.03 to 0.21)
High¶ (>0.05)	21	2791.1	0.75 (0.49 to 1.15)

- All LTBI treated
- 20/26 TB cases had **negative** IGRA initially

Baricitinib RCT progam:

Overall incidence rate = 11/7860 = 100 (/100,000)

Table 1 Overview of treatment-emergent infections, serious infection, TB, HZ, opportunistic infection and infection leading to death

	Placebo-controlled (to Week 24)*			2–4 mg-extended†		All-bari-RA
	Placebo N=1070 PYE=393.8‡	Bari 2 mg§ N=479 PYE=185.8‡	Bari 4 mg N=997 PYE=409.4‡	Bari 2 mg N=479 PYE=604.9‡	Bari 4 mg N=479 PYE=645.9‡	All-bari-RA N=3492¶ PYE=7860.3‡
TE infections, n (EAIR)	299 (75.9)	156 (84.0)	362 (88.4)***	230 (38.0)	266 (41.2)	2114 (26.9)
Led to temporary interruption of study drug	52 (13.4)	34 (18.3)	67 (16.6)	63 (10.4)	73 (11.3)	623 (8.0)
Led to permanent discontinuation from study drug	8 (2.0)	7 (3.8)	22 (5.2)**	11 (1.8)	22 (3.3)	139 (1.7)
Serious infection, n (IR)	17 (4.2)	8 (4.2)	16 (3.8)	20 (3.3)	31 (4.8)	231 (3.0)
Tuberculosis, n (IR)	0	0	1 (0.2)	0	6 (0.5)	11 (0.1)
HZ, n (IR)	4 (1.0)	6 (3.1)	18 (4.3)**	17 (2.8)	25 (3.9)	258 (3.3)

- 7-12% had LTBI
- 11 had TB; all in **4mg group**
  - 9/11 in **extension period**
  - **7/11 IGRA-**, 2/11 had LTBI treatment developed TB

Table S5. Tuberculosis rates and events by endemic region: general population and baricitinib RA program

Country	Published TB IR in General Population[a] per 100 People/Year[b]		Reports of TB in Patients Receiving Bari IR (n/N)	
Argentina	0.024		0.09 (1/424)	
Taiwan	0.039[c]	**39/** 100,000	1.26 (3/92)	**1260/** 100,000
Russian Federation	0.066		0.29 (1/130)	
South Korea	0.077		0.48 (1/84)	
India	0.211		1.00 (2/131)	
South Africa	0.781		1.99 (3/65)	

Screening for latent TB

Screening for LTBI: TST or IGRA?

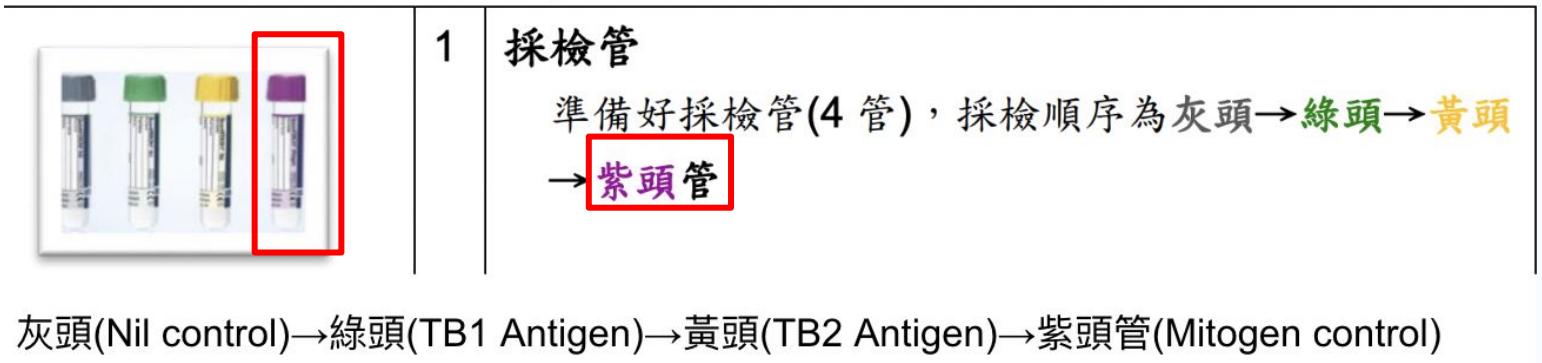
- Demonstration of “Mtb-specific **T-cell-mediated immune response**”
  - Tuberculin skin test (TST)
  - IFN-r release assays (IGRAs)

- IGRAs
  - Antigen peptides:
    - CFP-10, ESAT-6, TB7.7 (from **r**egion of **d**ifference [**RD1**])
    - RD1: deleted in BCG vaccines
  - ELISA: **QuantiFERON-TB** (**QFT**, Qiagen)
    - QFT-GIT (**G**old **I**n **T**ube)
    - QFT-Plus (Gold **Plus**)
  - ELISpot: **T-Spot TB** (Oxford Immnotec)

J Clin Microbiol . 2020 Aug 24;58(9):e01950-19.

QFT-Gold Plus (**QFT-Plus**): 4th generation of QFT

- Compared to **QFT-GIT** (**3rd generation**):
  - Addition of **TB2 antigen**
    - Shorter peptides from CFP-10 and ESAS-6
    - To detect both CD4 and **CD8 response**
  - Remove of TB7.7 antigen from antigen pool
  - Antigen formulation: spray vs resin-coated



J Clin Microbiol . 2020 Aug 24;58(9):e01950-19.

QFT-Gold Plus (**QFT-Plus**): 4th generation of QFT

- Questions to be answered:
  - TB2 - TB1:
    Representing CD8 response?
  - TB2 - TB1 > 0.6 IU/mL
    Threshold for CD8 response?

J Clin Microbiol . 2020 Aug 24;58(9):e01950-19.

Interpretation of IGRA results: **indeterminate** result

Nil (IU/ml)	TB Antigen minus Nil (IU/ml)	Mitogen minus Nil (IU/ml)*	QFT result	Report/Interpretation
≤8.0	< 0.35	≥ 0.5	Negative	*M. tuberculosis* infection NOT likely
	≥ 0.35 and < 25% of Nil value	≥ 0.5	Negative	*M. tuberculosis* infection NOT likely
	≥ 0.35 and ≥ 25% of Nil value	Any	Positive†	*M. tuberculosis* infection likely
	< 0.35	< 0.5	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness
	≥ 0.35 and < 25% of Nil value	< 0.5	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness
> 8.0§	Any	Any	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness

Over-react

Inadequate mitogen response

Efficacy of
latent TB screening and treatment
before biologics initiation

TB risk reduced by **preventive** latent TB treatment: Reduce up to 80% risk in **Spanish** biologics registry

Table 2. Rate of active TB in the BIOBADASER cohort before and after the specific recommendations, and risk ratio for the incidence of active TB compared with the risk in the background Spanish population and in the EMECAR patients*

	Patient-years of exposure to TNF antagonists	No. of active TB cases	Active TB rate per 100,000 (95% CI)	IRR versus background (95% CI)	IRR versus EMECAR (95% CI)†
All TB cases					
Pre-OR	6,126	32	522 (369–738)	20.9 (12.0–36.8)	–
Post-OR	1,699	2	117 (29–470)	4.7 (0.5–18.9)	–
$IRR_{recommendations}$‡	–	–	0.22 (0.03–0.88)	–	–
TB cases with RA only					
Pre-OR	4,780	27	564 (387–823)	22.6 (12.6–40.6)	6.2 (2.6–16.9)
Post-OR	1,049	1	95 (13–676)	3.8 (0.1–23.3)	1.0 (0.02–8.2)
$IRR_{recommendations}$‡			0.17 (0.004–1.02)	–	–

* TB = tuberculosis; IRR = incidence risk ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† EMECAR patients were patients with rheumatoid arthritis (RA) who were not treated with TNF antagonists and were followed up for 5 years in the Morbidity and Clinical Expression of Rheumatoid Arthritis study.
‡ $IRR_{recommendations}$ = IRR after the implementation of the specific recommendations for the management of latent TB infection.

- Spanish Biologics cohort
- After implanting latent TB screening/treatment guideline: TB incidence **522** > **117**/100,000 (IRR **0.22**)

Arthritis Rheum . 2005 Jun;52(6):1766-72.

TB risk reduced by **preventive** latent TB treatment: Reduce up to 80% risk in **Spanish** biologics registry

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$IRR_{recommendations}$‡			0.17 (0.004–1.02)	–	–

- After implanting latent TB screening/treatment guideline:
  - IRR **20.9** → **4.7** compared to **general population**
  - IRR **6.2** → **1.0** compared to **RA non-TNFi users**

Arthritis Rheum . 2005 Jun;52(6):1766-72.

TB risk reduced by **preventive** latent TB treatment: Reduce up to 50% risk in **Taiwan** NHI database

Table 3. Incidence rates (IRs) and hazard ratios (HRs) of tuberculosis (TB) disease by biologic exposure with csDMARDs-exposed patients as reference group, and by isoniazid prophylaxis therapy (INHP) with the absence of INHP as reference group.

	TB cases/py	Crude IR per100000 py	Crude HR(95%CI)	Adjusted HR (95% CI)
csDMARDs-exposed	913/231,759	394	1.00 (reference)	1.00 (reference)
INHP (-)(n = 36,148)#	913/231,697	394	1.00 (reference)	1.00 (reference)
INHP (+) (n = 14)	0/62	0	NA	NA
Adalimumab-exposed	67/11,171	600	1.52(1.19–1.95)**	1.52(1.18–1.96)*
INHP (-) (n = 1,615)#	66/10,713	616	1.00 (reference)	1.00 (reference)
INHP (+) (n = 63)	1/459	218	0.35(0.05–2.50)	0.45(0.06–3.24)
Etanercept-exposed	121/27,367	442	1.14(0.94–1.37)	1.16(0.95–1.41)
INHP (-) (n = 3,508)#	121/26,880	450	1.00 (reference)	1.00 (reference)
INHP (+) (n = 69)	0/487	0	NA	NA
Rituximab-exposed	2/6,179	32	0.08(0.02–0.34)**	0.08(0.02–0.31)**
INHP (-) (n = 755)#	2/6,119	33	1.00 (reference)	1.00 (reference)
INHP (+) (n = 8)	0/60	0	NA	NA

- 2000-2011 Taiwan HIRA database, 5000+ RA TNFi users
- ADA: IR **616**/100,000 > **218**/100,000 (LTBI treatment) (**IRR 0.45**)
- ETN: IR **450**/100,000 > No TB cases (LTBI treatment)

Ann Am Thorac Soc . 2017 May;14(5):690-697.

TB risk reduced by **preventive** latent TB treatment: Reduce up to 70% risk in **Korean** NHI database

Table 4. Incidence rates of tuberculosis development among patients treated for latent tuberculosis infection versus those not treated

	Number with TB Development	Person-Years	Incidence Rate per 1,000 Person-Years (95% CI)	Incidence Rate Ratio (95% CI)
Overall	113	10,801	10.46 (8.53–12.39)	
Treated for LTBI (at least once)	10	2,455	4.07 (1.55–6.60)	0.33 (0.17–0.63)
Not treated	103	8,346	12.34 (9.96–14.72)	1 (Reference)
Treated for LTBI (≥25% of recommended duration per regimen)	9	2,338	3.85 (1.33–6.37)	0.31 (0.16–0.62)
Not treated	104	8,463	12.29 (9.93–14.65)	1 (Reference)
Treated for LTBI (≥50% of recommended duration per regimen)	7	2,171	3.22 (0.84–5.61)	0.26 (0.12–0.56)
Not treated	106	8,630	12.28 (9.94–14.62)	1 (Reference)
Treated for LTBI (≥75% of recommended duration per regimen)	5	1,938	2.58 (0.32–4.84)	0.21 (0.09–0.52)
Not treated	108	8,863	12.19 (9.89–14.48)	1 (Reference)
Treated for LTBI* (≥100% of recommended duration per regimen)	2	1,566*	1.28 (−0.49 to −3.05)	0.11 (0.03–0.43)
Not treated	111	9,235	12.02 (9.78–14.26)	1 (Reference)

- 2011-2013 Korea HIRA database, 10863 TNFi users (RA, SpA, IBD)
- 23% had latent TB treatment
- IR **1046**/100,000 > **407**/100,000 (LTBI treatment) (**IRR 0.33**)

Ann Am Thorac Soc . 2017 May;14(5):690-697.

Endorsing LTBI screening and treatment, **decrease the TB incidence gap between LTBI and non-LTBI patients**

- South Korean NHI database

	Patient population	Biologcis	TB incidence (/100,000)	
			Patients **without** LTBI treatment	Patients **with** LTBI treatment
2011-2013	RA, SpA, BID	TNFi	**1046**	407
2013-2018	RA	TNFi, Tocilizumab	530	628

Ann Am Thorac Soc . 2017 May;14(5):690-697.

Note: LTBI treatment compliance important!

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Not treated	111	9,235	12.02 (9.78–14.26)	1 (Reference)

- **LTBI treatment duration** assocaited with TB incidence reduction (IRR 0.31 > 0.26 > 0.21 > 0.11)
  > complete LTBI treatment is important

Ann Am Thorac Soc . 2017 May;14(5):690-697.

Note: LTBI treatment compliance important!
3HP better than **9H** / 4R

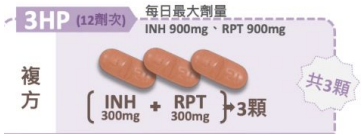
Table 3. Choice of latent tuberculosis treatment regimens and observed treatment duration in tumor necrosis factor antagonist users

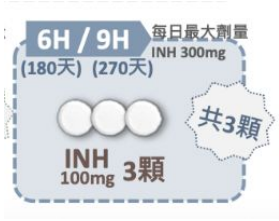
	Total	INH Monotherapy	RIF Monotherapy	Combination Therapy (INH + RIF)
Recommended duration of treatment	—	36 wk	16 wk	12 wk
Patients,* n (%)	2,461	1,846 (75.0)	204 (8.3)	411 (16.7)
Treatment completion,* n (%)	1,488	1,064 (57.6)	115 (56.4)	309 (75.2)
Observed treatment duration per regimen,* wk, median (IQR)	32.0 (15.0–40.4)	38.0 (26.9–41.7)	16.9 (9.0–18.6)	13.0 (12.0–14.0)

Definition of abbreviations: INH = isoniazid; IQR = interquartile range; RIF = rifampicin.
*For a total of 106 patients (4.3%) whose drug regimen for latent tuberculosis infection changed during their treatment course, we classified them according to their initial choice of regimen and counted treatment duration of the initial regimen only to calculate treatment completion rates.

50-60% (9H or 4R) vs
75% (3HP)

Ann Am Thorac Soc . 2017 May;14(5):690-697.





（雙面列印）

潛伏結核感染治療處方一覽表

112年印製

處方	處方藥品		總劑數與療程頻率	劑量 每日最大劑量	劑量 兒童	劑量 成人	常見副作用	使用限制	都治(DOPT)	推薦順序(接觸者除指標抗藥或使用限制外)
1HP[a]	複方	Isoniazid(INH) 300mg+ Rifapentine (RPT) 300mg	28天 (1個月) 每日服用	300mg	固定1顆		皮疹(蕁麻疹)為主、肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ <13歲兒童 ◆ 孕婦[c]	必須	推薦處方
		Rifapentine (RPT) 150mg		300mg	◆ 35-45 kg 1顆 ◆ >45 kg 2顆					
	單方	Isoniazid (INH) 300mg	28天 (1個月) 每日服用	300mg	300 mg					
		Rifapentine (RPT) 150mg		600mg	◆ <35 kg 300 mg ◆ 35-45 kg 450mg ◆ >45 kg 600 mg					
3HP[a]	複方	Isoniazid(INH) 300mg+ Rifapentine (RPT) 300mg	12個劑量 (3個月) 每週服用	900 mg	體重50kg以上 固定劑量3顆		皮疹、類流感症狀、過敏反應、(少數)肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ 孕婦[c]	必須	推薦處方
	單方	Isoniazid (INH) 300mg	12個劑量 (3個月) 每週服用	900 mg	◆ 2-11 歲 25mg/kg ◆ 12 歲(含)以上15mg/kg		皮疹、類流感症狀、過敏反應、(少數)肝毒性	◆ 指標個案INH或RMP抗藥之接觸者 ◆ <2歲兒童 ◆ 孕婦[c]	必須	推薦處方
		Rifapentine (RPT) 150mg		900 mg	◆ 10.0–14.0 kg 300 mg ◆ 14.1–25.0 kg 450 mg ◆ 25.1–32.0 kg 600 mg ◆ 32.1–49.9 kg 750 mg ◆ ≥50.0 kg 900 mg					
4R	Rifampin (RMP) 300mg		120天 (4個月) 每日服用	600 mg	15 (10-20)mg/kg	10 mg/kg	皮疹、腸胃不適/腸胃障礙、(少數)肝毒性	指標個案RMP抗藥之接觸者	必須	推薦處方
3HR[b]	Isoniazid (INH) 100mg		90天 (3個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	過敏反應、(少數)肝毒性	指標個案INH或RMP抗藥之接觸者	必須	推薦處方
	Rifampin (RMP) 300mg			600 mg	15 (10-20)mg/kg	10 mg/kg				
6H /9H	soniazid(INH) 100mg		180天(6個月) /270天(9個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	皮疹、周邊神經病變、肝毒性	指標個案INH抗藥之接觸者	建議	替代處方

a：1HP及3HP處方使用之INH300mg及HP複方為專案進口藥品，須簽署藥品使用同意書　c：目前尚未有足夠之孕婦臨床安全性相關試驗數據

b：3HR可依體重使用INH+RMP之二合一劑型

參考資料：WHO operational handbook on tuberculosis (Module 1 – Prevention): Tuberculosis preventive treatment. (2020)及疾病管制署結核病診治診引

CDC website

Note: Latent TB treatment **not eradicate** all TB risks

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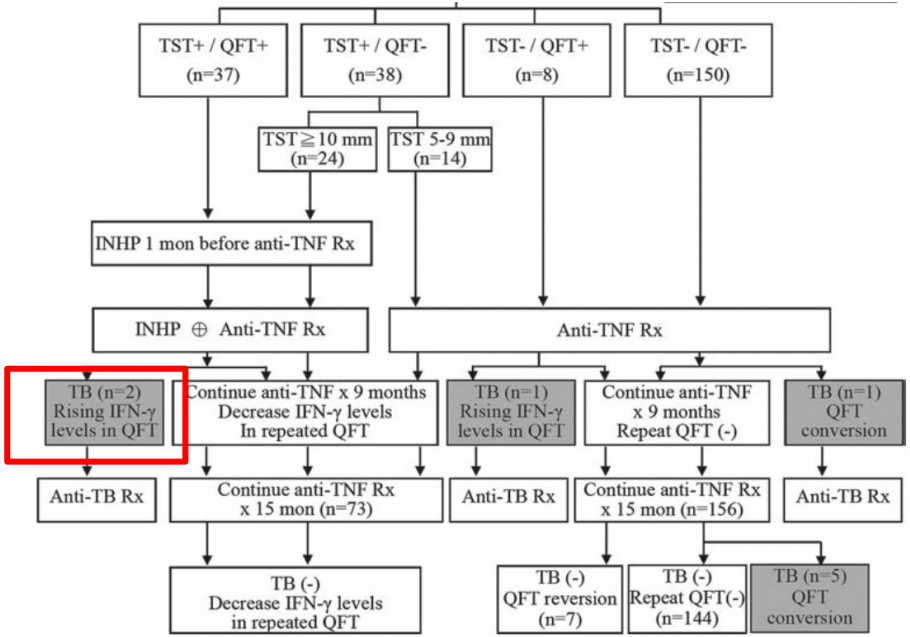


Ann Rheum Dis. 2012 Feb;71(2):231-7.
Ann Am Thorac Soc . 2017 May;14(5):690-697.

Issues:
IGRA monitoring
after LTBI treatment?
(IGRA reversion)

IGRA result flaucatuation after LTBI treatment

in health care workers, contacts, immigrants

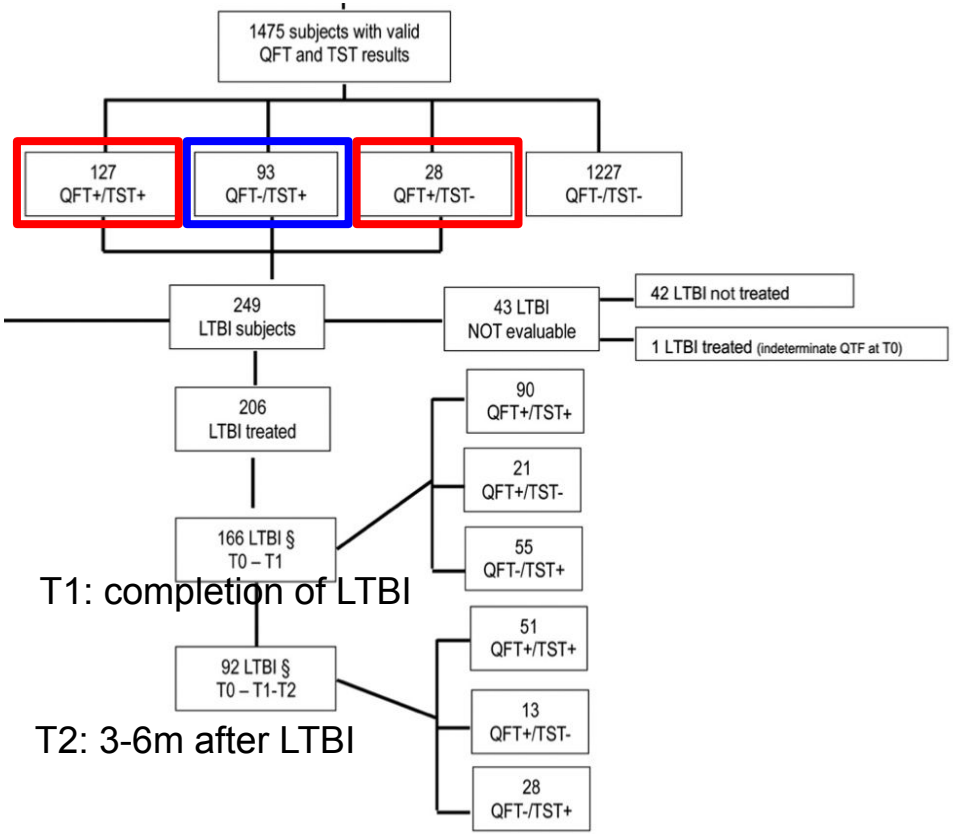
3.6-42% had reversion (+ → -)

Table 7 IGRA trends in LTBI treated subjects who scored IGRA-positive at baseline.

First author	Country	IGRA	Studied population	Number of subjects who scored IGRA-positive at baseline	LTBI therapy	Trends of IGRA	Trends of IGRA	Reversion at T1	Factors associated with reversion or decreasing trend
						Short term	T1	% (95%CI)	
Pai, 2006	India	QFT-GIT	Health care workers	10 IGRA positive	INH 6 months	na[a]	Decrease[c]	10 (2.5–44.5)	na[a]
Ewer, 2006	UK	ELISpot	Contacts	38 IGRA positive 25 controls	RIF+INH 3 months	Increase	Decrease	8 (1.7–21.4)	na[a]
Wilkinson, 2006	UK	ELISpot	Immigrants	16 IGRA positive 8 controls	RIF+INH 3 months	Increase	Decrease[c]	[b]	na[a]
Chee, 2007	Singapore	T-SPOT.*TB*	Close contacts	226 IGRA positive	INH 6 months	na[a]	Decrease	38 (31.3–44.3)	Younger age
Goletti, 2007	Italy	QFT-G	Contacts	28 IGRA positive 11 controls	INH 6 months	na[a]	Decrease	3.6 (0.1–18.3)	No past MTB exposure
Higuchi, 2008	Japan	QFT-G	Contacts	28 IGRA positive 5 controls	INH 6 months	na[a]	Decrease	25 (10.7–45)	na[a]
Herrmann, 2009	France	QFT-GIT	Children contacts	25 IGRA positive	RIF+INH 3 months	Increase	Decrease	[b]	na[a]
Lee, 2010	South Korea	QFT-GIT	Contacts	74 IGRA positive	RIF 4 months	na[a]	Decrease	42 (30.5–54)	Smaller TST size, lower IFN-γ value
Dyrhol-Riise, 2010	Norway	QFT-GIT	Contacts, immigrants and others	40 IGRA positive	RIF+INH 3 months	na[a]	No change	12,5	Low IFN-γ values at baseline

J Infect . 2013 Apr;66(4):346-56.

AIR patients receiving TNFi



- Italian cohort, 2006-2011
- AIIRD: RA, AS, PsA, PsO
- 10% had BCG vaccines

- TST and IGRA (QFT-GIT) screening before TNFi

J Infect . 2013 Apr;66(4):346-56.

~ **20%** (27/111) achived **reversion** (IGRA became negative)

Table 3 QFT-IT reversion and conversion in 166 LTBI subjects at the end of therapy (T1) using two different cut-off criteria for interpreting QFT-IT results.

QFT at T0	QFT at T1	
	Positive — *N* (%)	Negative — *N* (%)
Standard definition[a]		
Negative (<0.35 IU/ml) (55 subjects)	10 (18)	45 (82)
Positive (≥0.35 IU/ml) (111 subjects)	84 (76)	27 (24)
"Uncertainty zone" definition[b]		
Negative (<0.20 IU/ml) (47 subjects)	6(13)	39 (83)
Positive (>0.50 IU/ml) (102 subjects)	78 (76)	17 (17)

[a] No significant difference between the likelihood of reversion and conversion (OR 0.80, $p = 0.370$).
[b] No significant difference between the likelihood of reversion and conversion (OR 0.46, $p = 0.496$).

Table 5 Rate of reversion at the end of therapy (T1) by baseline IFN-γ value among the 111 subjects who scored QFT-IT-positive at baseline (T0), considering two different QFT-IT-positive scoring definitions.

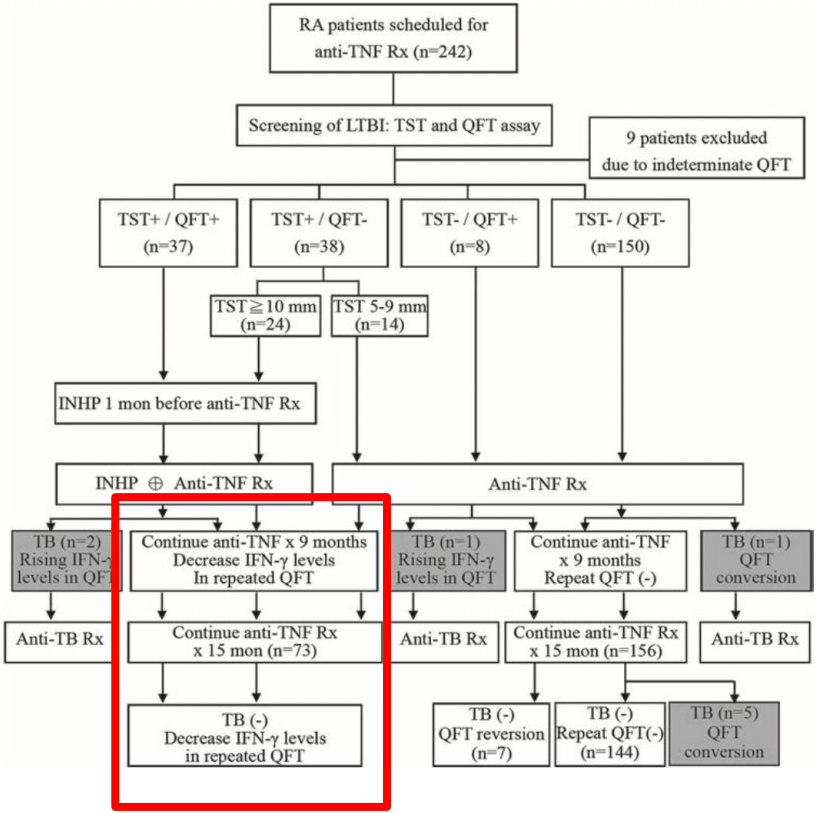
Standard definition				"Uncertainty zone" definition			
Baseline IFN-γ response (IU/ml)	No. of subjects	T1 QFT-IT reversion *N* (%, C.I.)	TST+ at T0 *N* (%, C.I.)	Baseline IFN-γ response (IU/ml)	No. of subjects	T1 QFT-IT (IFN-γ >0.50 UI/ml) *N* (%, C.I.)	T1 QFT-IT "true" reversion *N* (%, C.I.)
0.35—1.0	29	16 (55, 36—74)	23 (79, 63—92)	0.5—1.0	20	8 (40, 19—64)	8 (40, 19—64)
1.01—3.0	27	4 (15, 4—34)	21 (78, 58—91)	1.01—3.0	27	22 (81, 62—94)	3 (11, 2—29)
>3	55	7 (13, 5—25)	46 (84, 71—92)	>3	55	48 (87, 76—95)	6 (11, 4—22)
Total	111	27 (24, 17—33)	90 (81, 73—88)	Total	102	78 (76, 67—84)	17 (17, 10—25)

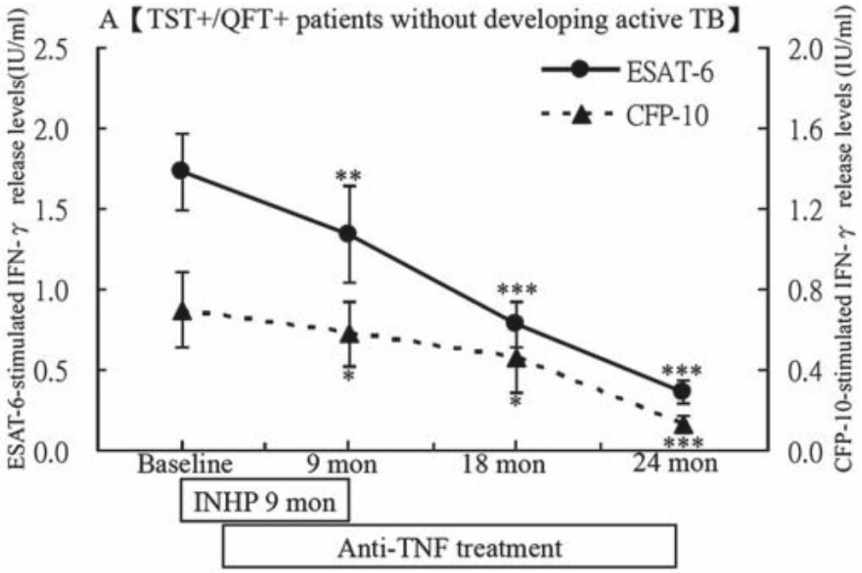
Definition of abbreviations: TST: tuberculin skin test; QFT-IT: QuantiFERON-TB Gold in-tube; IFN: interferon; CI: 95% confidence intervals.

No patient developed **active TB** after median f/u **33 months** (weather revert or not)

J Infect . 2013 Apr;66(4):346-56.

Decreased IFNγ response after latent TB treatment





Ann Rheum Dis . 2012 Feb;71(2):231-7.

Points to consider for
“IGRA monitoring after LTBI treatment”

- Possible cause for IGRA reversion (negative conversion):
  - Decreased viral burden (decreased stimulus)
  - Immune suppresion

- No evidence currently for incident TB developing in patient with persistent IGRA positivity

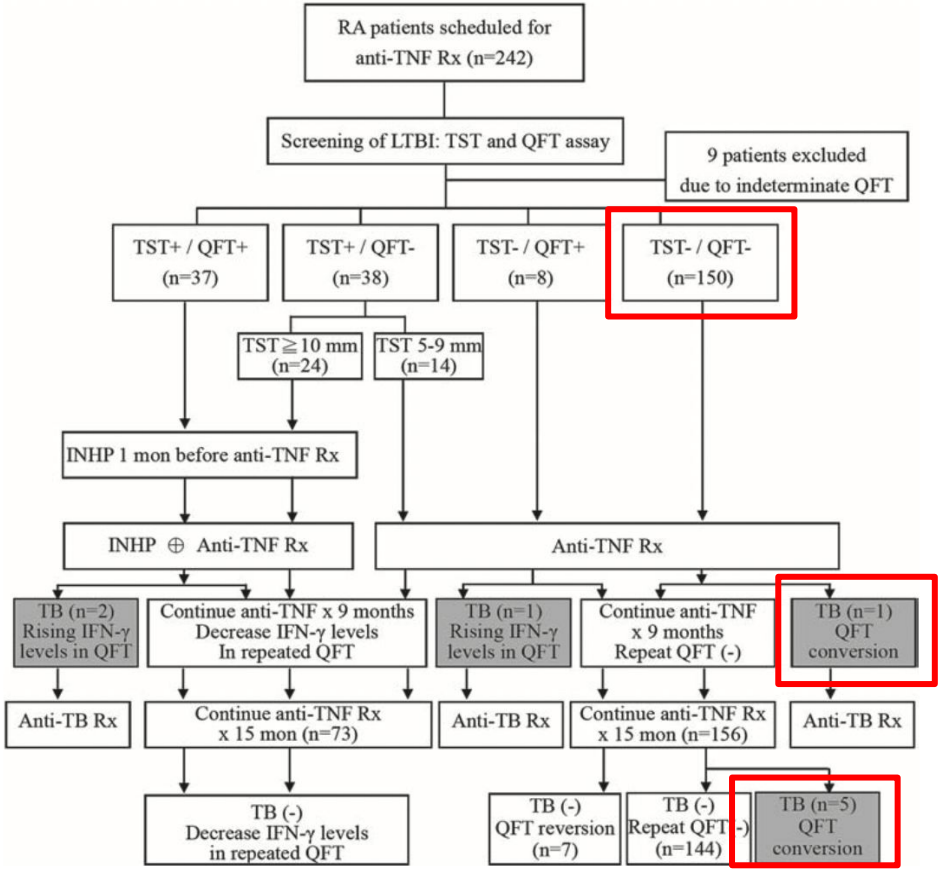
Issues:
TB development
in IGRA-negative patients

TB development in IGRA-negative patients

- VGH-Taichung (database): Etanercept / adalimumab: **4%** (6/150)
- Golimumab RCT progam (screen both IGRA/TST): **0.2%** (4/1893)
- Korean TNFi users (database): **1.2%** (103/8402)

VGH-Tachchung cohort

TB development in **IGRA(-)** patients:4% (6/150)



	Time to TB	TB sites
Adalim.	3	Pleura (Lt)
Etaner.	20	Miliary
Etaner.	22	Pulmonary
Adalim.	23	Pleura (Lt)
Etaner.	23	Joint (5th MTP)
Adalim.	24	Pulmonary

Ann Rheum Dis . 2012 Feb;71(2):231-7.

Cause: new exposure at endemic area?

Table 2 Demographic data and clinical characteristics of active tuberculosis in nine patients with RA undergoing anti-TNFα therapy

	Age/sex	Duration of RA (years)	Baseline TST/QFT	INHP	Used TNFα inhibitors	Duration of anti-TNF before tuberculosis (months)	Concomitant medications	Location of active tuberculosis	Anti-tuberculosis drug sensitivity
1	66/F	8.5	TST+/QFT+	+	Adalim.	2	MTX 15 mg/week PSL 5 mg/day	Pulmonary	INH-R RIF-S
2	54/F	10.6	TST+/QFT+	+	Adalim.	3	MTX 12.5 mg/week PSL 7.5 mg/day	Pulmonary	INH-S
3	62/F	10.2	TST−/QFT+	−	Adalim.	3	MTX 15 mg/week PSL 7.5 mg/day	Miliary	INH-S
4	72/F	8.5	TST−/QFT−	−	Adalim.	3	MTX 10 mg/week PSL 5 mg/day	Pleura (Lt)	INH-S
5	68/F	8.3	TST−/QFT−	−	Etaner.	20	MTX 15 mg/week PSL 5 mg/day	Miliary	INH-S
6	44/F	9.2	TST−/QFT−	−	Etaner.	22	MTX 12.5 mg/week PSL 5 mg/day	Pulmonary	INH-S
7	55/M	8.4	TST−/QFT−	−	Adalim.	23	MTX 15 mg/week PSL 7.5 mg/day	Pleura (Lt)	INH-S
8	40/F	12.2	TST−/QFT−	−	Etaner.	23	MTX 15 mg/week PSL 5 mg/day	Joint (5th MTP)	NA
9	61/F	10.8	TST−/QFT−	−	Adalim.	24	MTX 15 mg/week PSL 5 mg/day	Pulmonary	INH-S

Adalim, adalimumab; Etaner, etanercept; F, female; INHP, isoniazid prophylaxis; INH-R, resistant to isoniazid; INH-S, sensitive to isoniazid; Lt, left side; M, male; MTP, metatarsophalangeal joint; MTX, methotrexate; NA, not applicable; PSL, prednisolone; QFT, QuantiFERON-G assay; RA, rheumatoid arthritis; RIF-S, sensitive to rifampicin; TNFα, tumour necrosis factor alpha; TST, tuberculin skin test.

Ann Rheum Dis . 2012 Feb;71(2):231-7.

Cause: **false-negative** IGRA screening may occur in patients with **rheumatic** disease

Table 3: Results of TSPOT.TB assays by patient and drug grouping

TSPOT.TB result	Biologics				Not on biologics n tests (% of patients not on biologics)	Total n tests (%)
	Green n tests (%)	Amber n tests (%)	Red n tests (%)	Total on biologics n tests (% of all patients on biologics)		
Positive	104 (6.4)	32 (4.6)	94 (5.3)	230 *(5.6)*	3387 *(12.5)*	3617 (11.6)
Negative	1187 (73.6)	562 (80.2)	1387 (78.7)	3136 *(77.0)*	18726 *(69.0)*	21862 (70.0)
Borderline	42 (2.6)	13 (1.9)	43 (2.4)	98 *(2.4)*	860 *(3.2)*	958 (3.1)
Indeterminate	147 (9.1)	63 (9.0)	138 (7.8)	348 *(8.5)*	1781 *(6.6)*	2129 (6.8)
Other	133 (8.2)	30 (4.3)	100 (5.7)	263 *(6.5)*	2387 *(8.8)*	2650 (8.5)
Subtotals	1613	700	1762	4075	27141	31216

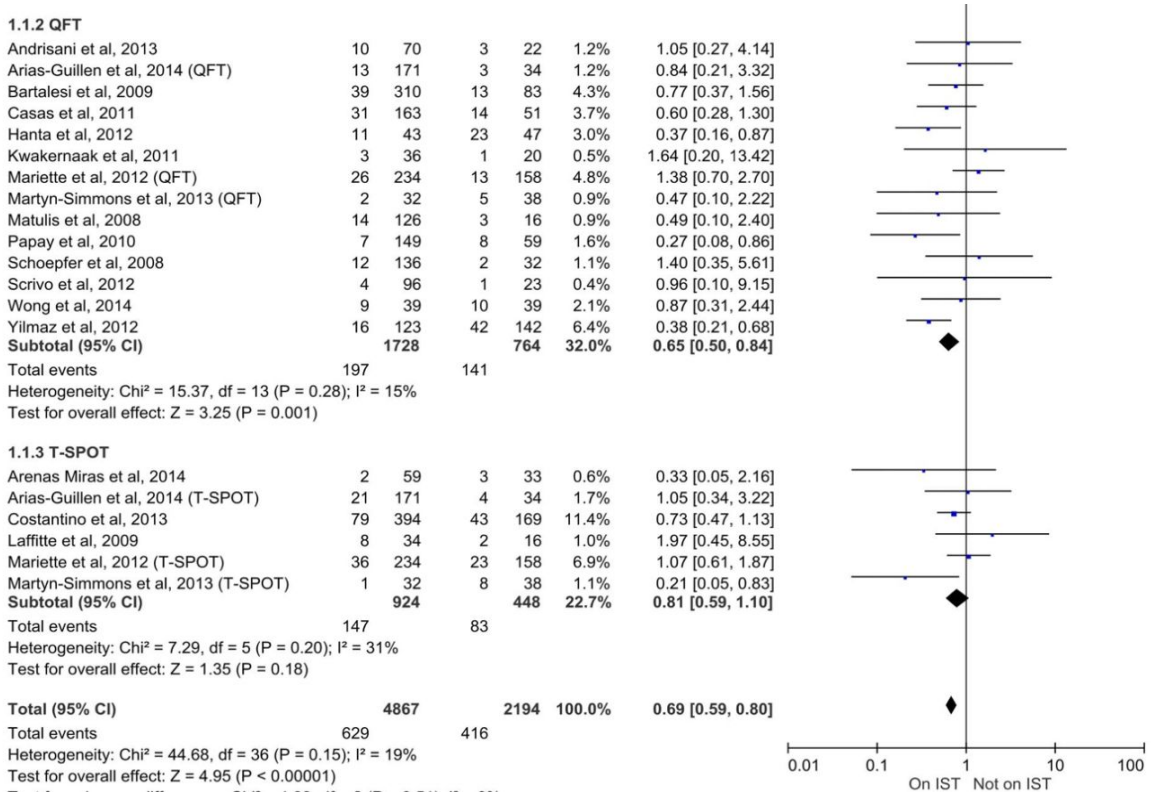
- UK Northen London biologics database and IGRA testing database
- Comapred to non-biologic users, biologics users have less positive results (5.6 vs 12.5%) and more indeterminate results (8.5 vs 6.6%)

ERJ Open Res . 2022 Nov 28;8(4):00193-2022.

Cause: **false-negative** IGRA screening may occur in patients with **rheumatic** disease

QFT
OR 0.65

T-SPOT
OR 0.81

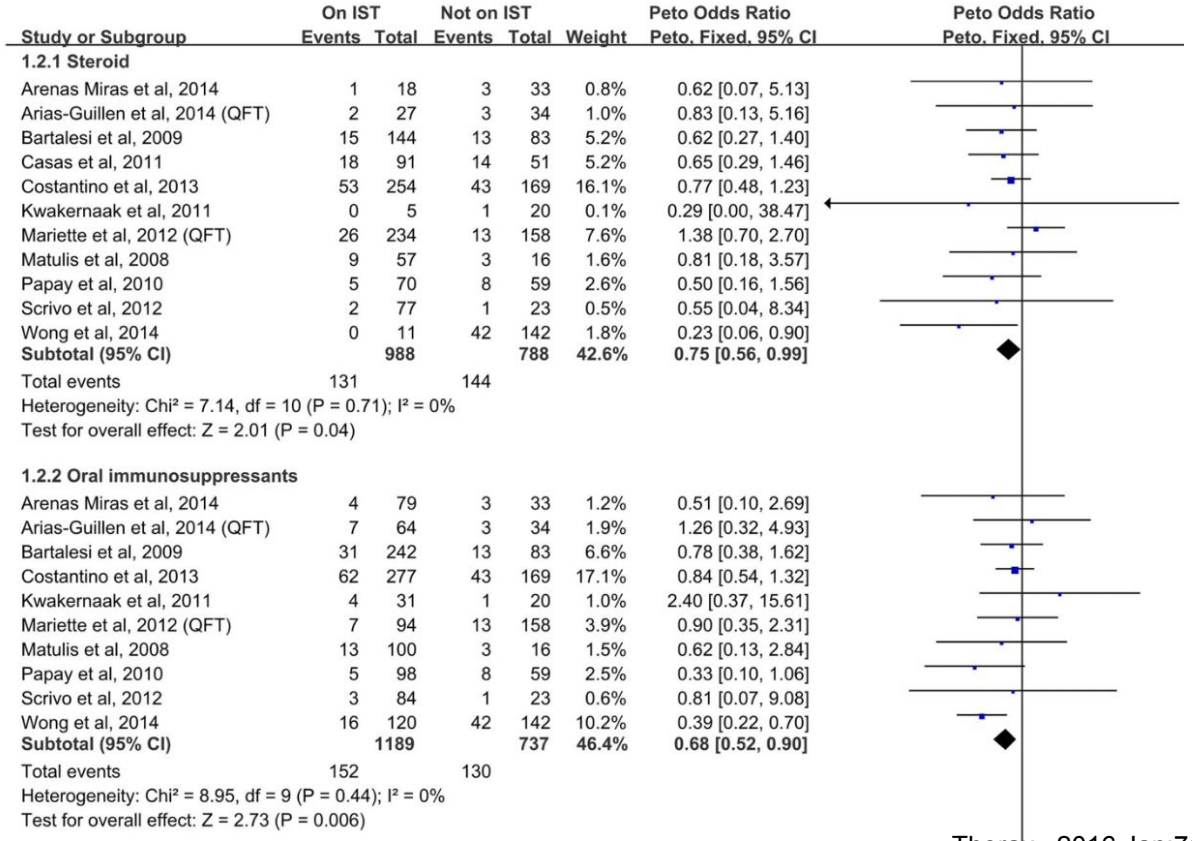


Thorax . 2016 Jan;71(1):64-72.

Cause: **false-negative** IGRA screening may occur in patients with **rheumatic** disease

Steroid
OR 0.75

Oral DMRAD
0.68



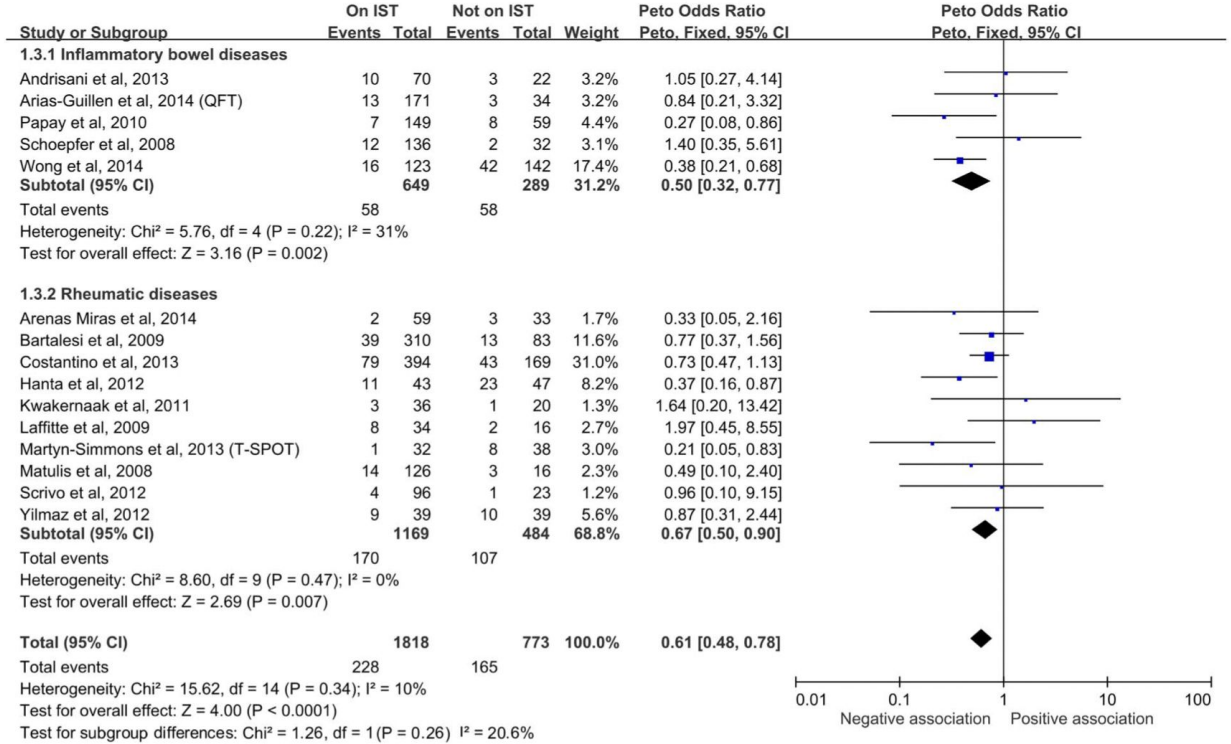
Study or Subgroup	On IST Events	On IST Total	Not on IST Events	Not on IST Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Steroid						
Arenas Miras et al, 2014	1	18	3	33	0.8%	0.62 [0.07, 5.13]
Arias-Guillen et al, 2014 (QFT)	2	27	3	34	1.0%	0.83 [0.13, 5.16]
Bartalesi et al, 2009	15	144	13	83	5.2%	0.62 [0.27, 1.40]
Casas et al, 2011	18	91	14	51	5.2%	0.65 [0.29, 1.46]
Costantino et al, 2013	53	254	43	169	16.1%	0.77 [0.48, 1.23]
Kwakernaak et al, 2011	0	5	1	20	0.1%	0.29 [0.00, 38.47]
Mariette et al, 2012 (QFT)	26	234	13	158	7.6%	1.38 [0.70, 2.70]
Matulis et al, 2008	9	57	3	16	1.6%	0.81 [0.18, 3.57]
Papay et al, 2010	5	70	8	59	2.6%	0.50 [0.16, 1.56]
Scrivo et al, 2012	2	77	1	23	0.5%	0.55 [0.04, 8.34]
Wong et al, 2014	0	11	42	142	1.8%	0.23 [0.06, 0.90]
Subtotal (95% CI)		**988**		**788**	**42.6%**	**0.75 [0.56, 0.99]**
Total events	131		144			
Heterogeneity: Chi² = 7.14, df = 10 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
1.2.2 Oral immunosuppressants						
Arenas Miras et al, 2014	4	79	3	33	1.2%	0.51 [0.10, 2.69]
Arias-Guillen et al, 2014 (QFT)	7	64	3	34	1.9%	1.26 [0.32, 4.93]
Bartalesi et al, 2009	31	242	13	83	6.6%	0.78 [0.38, 1.62]
Costantino et al, 2013	62	277	43	169	17.1%	0.84 [0.54, 1.32]
Kwakernaak et al, 2011	4	31	1	20	1.0%	2.40 [0.37, 15.61]
Mariette et al, 2012 (QFT)	7	94	13	158	3.9%	0.90 [0.35, 2.31]
Matulis et al, 2008	13	100	3	16	1.5%	0.62 [0.13, 2.84]
Papay et al, 2010	5	98	8	59	2.5%	0.33 [0.10, 1.06]
Scrivo et al, 2012	3	84	1	23	0.6%	0.81 [0.07, 9.08]
Wong et al, 2014	16	120	42	142	10.2%	0.39 [0.22, 0.70]
Subtotal (95% CI)		**1189**		**737**	**46.4%**	**0.68 [0.52, 0.90]**
Total events	152		130			
Heterogeneity: Chi² = 8.95, df = 9 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						

Thorax . 2016 Jan;71(1):64-72.

Cause: **false-negative** IGRA screening may occur in patients with **rheumatic** disease

IBD
OR 0.50

Rheuma
0.67



Study or Subgroup	On IST Events	On IST Total	Not on IST Events	Not on IST Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Inflammatory bowel diseases						
Andrisani et al, 2013	10	70	3	22	3.2%	1.05 [0.27, 4.14]
Arias-Guillen et al, 2014 (QFT)	13	171	3	34	3.2%	0.84 [0.21, 3.32]
Papay et al, 2010	7	149	8	59	4.4%	0.27 [0.08, 0.86]
Schoepfer et al, 2008	12	136	2	32	3.1%	1.40 [0.35, 5.61]
Wong et al, 2014	16	123	42	142	17.4%	0.38 [0.21, 0.68]
Subtotal (95% CI)		**649**		**289**	**31.2%**	**0.50 [0.32, 0.77]**
Total events	58		58			
Heterogeneity: Chi² = 5.76, df = 4 (P = 0.22); I² = 31%						
Test for overall effect: Z = 3.16 (P = 0.002)						
1.3.2 Rheumatic diseases						
Arenas Miras et al, 2014	2	59	3	33	1.7%	0.33 [0.05, 2.16]
Bartalesi et al, 2009	39	310	13	83	11.6%	0.77 [0.37, 1.56]
Costantino et al, 2013	79	394	43	169	31.0%	0.73 [0.47, 1.13]
Hanta et al, 2012	11	43	23	47	8.2%	0.37 [0.16, 0.87]
Kwakernaak et al, 2011	3	36	1	20	1.3%	1.64 [0.20, 13.42]
Laffitte et al, 2009	8	34	2	16	2.7%	1.97 [0.45, 8.55]
Martyn-Simmons et al, 2013 (T-SPOT)	1	32	8	38	3.0%	0.21 [0.05, 0.83]
Matulis et al, 2008	14	126	3	16	2.3%	0.49 [0.10, 2.40]
Scrivo et al, 2012	4	96	1	23	1.2%	0.96 [0.10, 9.15]
Yilmaz et al, 2012	9	39	10	39	5.6%	0.87 [0.31, 2.44]
Subtotal (95% CI)		**1169**		**484**	**68.8%**	**0.67 [0.50, 0.90]**
Total events	170		107			
Heterogeneity: Chi² = 8.60, df = 9 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Total (95% CI)		**1818**		**773**	**100.0%**	**0.61 [0.48, 0.78]**
Total events	228		165			
Heterogeneity: Chi² = 15.62, df = 14 (P = 0.34); I² = 10%						
Test for overall effect: Z = 4.00 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26) I² = 20.6%						

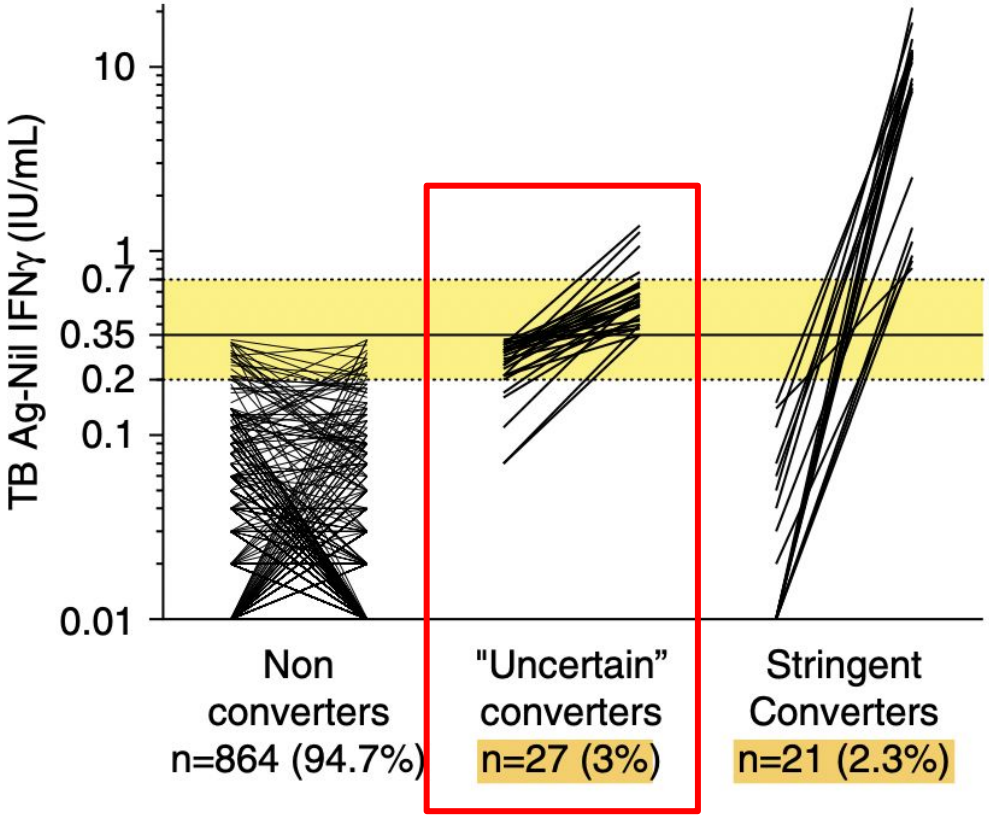
Thorax . 2016 Jan;71(1):64-72.

Points to consider for “IGRA screening negative patients”

- TB case may still occurs in endemic areas
- Cause
  - New exposure / contact
  - Initial false negative results

Issues:
IGRA positive conversions during follow-up?

“Uncertain” converter not uncommon



- South Africa adlolescent
- IGRA retesed after 3 months
- 5% converters
  - ~50% stringent
  - **~50% uncertain (0.2 ~ 0.7)**
- **No** incident TB occurred

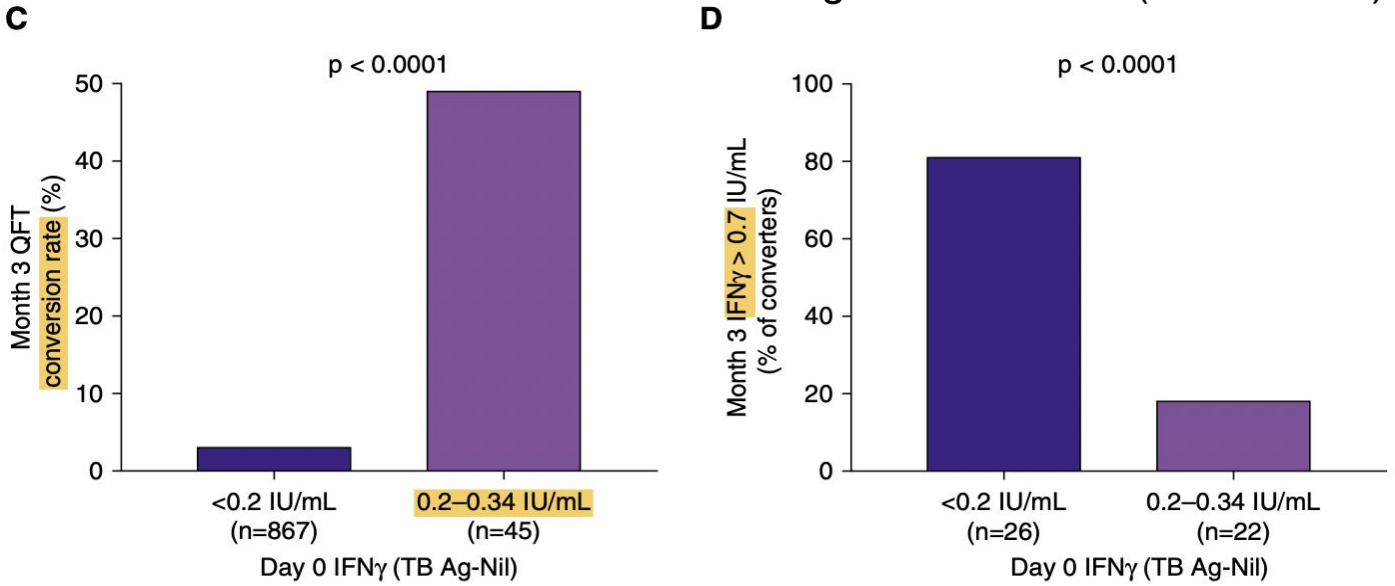
Am J Respir Crit Care Med Vol 196, Iss 5, pp 638–648, Sep 1, 2017

“Uncertain” converter not uncommon

IGRA values in most converters in “uncertain zone” (0.2 - 0.7 IU/mL)

~50% convertors had initial uncertain zone values

<20% with initial uncertain zone values had stringent conversion (> 0.7 IU/mL)



Am J Respir Crit Care Med Vol 196, Iss 5, pp 638–648, Sep 1, 2017

More “**stringent**” definition may help to identify patients at risk of active TB development?

Table 2. QuantiFERON-TB Gold In-Tube Conversion and Prospective Risk of Tuberculosis

QFT Class	TB Cases	n	Observation Years	Incidence (Cases/100 Person-Years)	95% Confidence Interval	*P* Value	IRR	95% Confidence Interval
Stringent nonconverters*	2	648	1,289.79	0.16	(0.02–0.56)	Reference	Reference	Reference
Stringent persistent positives†	19	989	1,953.07	0.97	(0.59–1.52)	0.005	6.27	(1.51–55.55)
Stringent converters‡	14	485	874.3	1.60	(0.88–2.69)	0.0003	10.33	(2.37–93.62)
“Uncertain” converters§	3	310	453.3	0.66	(0.14–1.95)	0.229	4.27	(0.49–51.10)

Definition of abbreviations: IRR = incidence rate ratio; QFT = QuantiFERON-TB Gold In-Tube; TB = tuberculosis.

- **Uncertain** convertes: <= 0.35 IU/mL ➡ > 0.35 IU/mL
- **Stringent** converters: <= 0.2 IU/mL ➡ > 0.7 IU/mL

- Adopt strigent defitinion: IR 160 ➡ 1600 (IRR **10.3**)

Am J Respir Crit Care Med Vol 196, Iss 5, pp 638–648, Sep 1, 2017

For AIR patients

- 4.6% (7/150 RA) [VGH-Taichung]
- 7% (5/70 Inflammatory arthritis) [Greek]
  - 40% had INH
  - **No** incdent TB during follow-up (27 +/- 12 months)

Ann Rheum Dis. 2012 Feb;71(2):231-7.
Ann Rheum Dis. 2015 Oct;74(10):1848-53.

Points to consider for “IGRA conversion during follow-up”

- Cause?
  - TB development
  - Contact / exposure to TB case
  - IGRA test variability
  - Immune reconstitution

- IGRA test variability
  - Different cut-off value may help? (e.g, <0.2 ➡ >0.7)

Summary

- In addition to **TNFi**, there were also reports of increased TB incidence regarding **IL6 inhibitor (tocilizumab)** and some **JAK inhibitors**
  - Concomitant risk (e.g, other immunosuppressant use) should also be considered for TB risk assessement
- **LTBI screening and treatment** decrease the TB incidence rate
  - 3HP regimen had better treatment completion rate

- No evidence for follow-up IGRA after LTBI treatment currently
- TB development not uncommon in **initial IGRA negative** patients
- No consensus regarding the management of **IGRA conversion** during biologics treatment