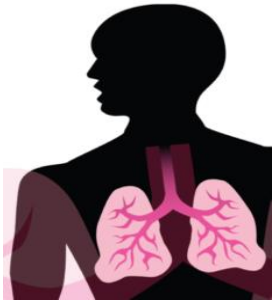


TB screening for medical specialties – an update

Onn Min Kon

NIHR HPRU in Respiratory Infections

NHS National Institute for Health Research

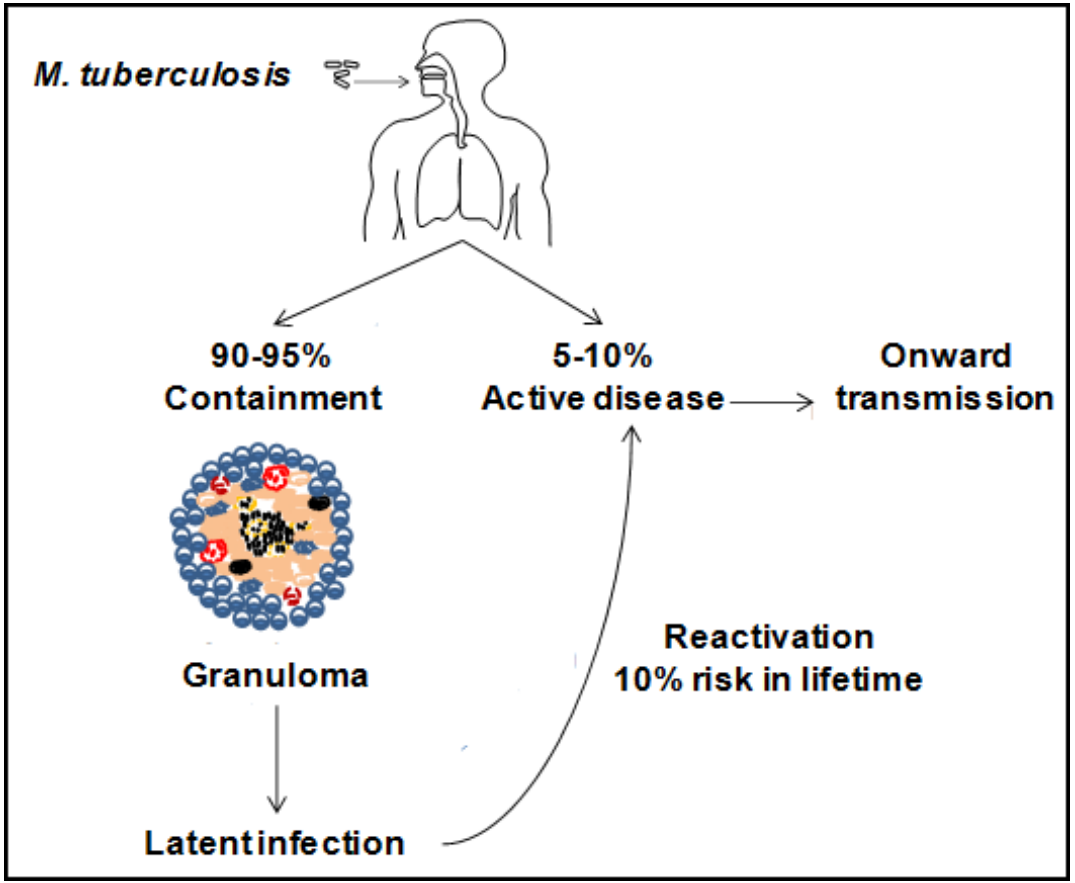
Imperial College London

Public Health England

Imperial College Healthcare NHS Trust

Declarations

-I organise and chair a global TB summit annually for Qiagen (non remunerated)
-Prior non restricted grant from Cepheid
-Prior consultancy for Otsuka

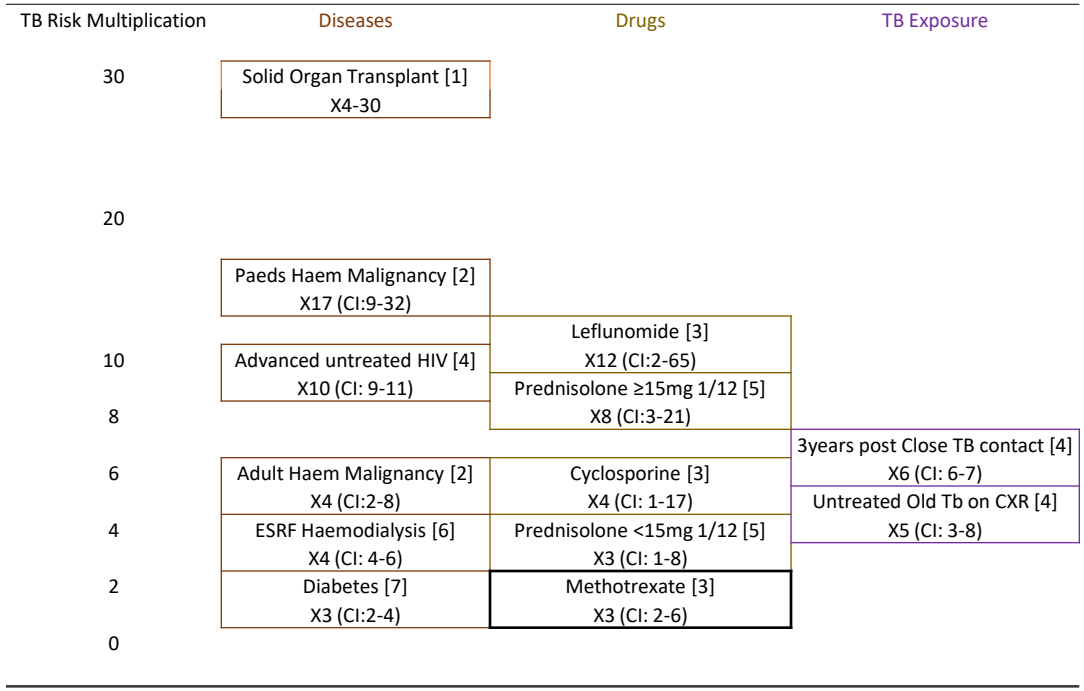

M. tuberculosis
90-95%
Containment
5-10%
Active disease
Onward
transmission
Granuloma
Reactivation
10% risk in lifetime
Latent infection

‘Biological’ and ‘Targeted’ Therapy - an expanding use/portfolio

- Rheumatology
- Gastroenterology
- Haematology
- Dermatology
- Neurology
- Oncology
- Renal
- Respiratory

Agent	Mechanism
Abatacept	CTLA-4
Adalimumab	Anti-TNF α
Certolizumab pegol	Anti-TNF α
Etanercept	Anti-TNF α
Golimumab	Anti-TNF α
Infliximab	Anti-TNF α
Rituximab	Anti-CD20
Tocilizumab	Anti-IL-6 receptor
Tofacitinib	JAK1 and JAK3 inhibitor
Ustekinumab	Anti-IL-12/IL-23
Vedolizumab	α4β7 integrin

Latent TB Reactivation Risk without Biologics is Variable



[1] *Subramanian et al (2019) Mycobacterium tuberculosis Infections in Solid Organ Transplantation: Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation.*

[2] *Dobler CC et al. (2017) Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis. Eur Respir J*

[3] *Brassard P et al.(2009) Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum*

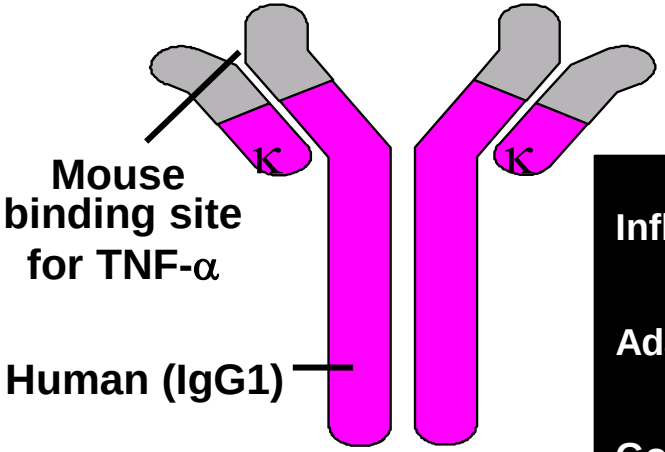
[4] *Horsburgh CR et al. (2011) Latent Tuberculosis Infection in the United States. N Engl J Med*

[5] *Jick SS et al. (2006) Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Care Res*

[6] *Min J et al. (2018) End-stage Renal Disease and Risk of Active Tuberculosis: a Nationwide Population-Based Cohort Study. J Korean Med Sci.*

[7] *Jeon CY et al (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med*

Anti-TNF-α therapies



Infliximab (Remicade) -

chimaeric MoAB

Adalimumab (Humira) -

fully human MoAB

Golimumab (Simponi) -

human IgG1 κ MoAB

Certolizumab pegol (Cimzia) -

PEGylated Fab' fragment of a humanized TNF inhibitor MoAB

Enbrel (Etanercept) :

soluble TNF-receptor
dimeric p75 TNFR
bound to Fc of IgG1

Infliximab and TB

- 70 reported cases from 147,000 given infliximab ***worldwide*** between 1998-2001
- 40 (56%) ***extra-pulmonary*** TB (US rate 18%)
- 17 (24%) ***disseminated TB*** (US rate < 2%))
- Most within 3 treatment cycles (median 12 wks)
- No granuloma in lung biopsy in one patient
- Probable reactivation
- 64/70 patients from areas of low incidence (< 20 per 100,000)

Conclusions Active tuberculosis may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent tuberculosis infection or disease.
(N Engl J Med 2001;345:1098-104.)

The New England Journal of Medicine

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.

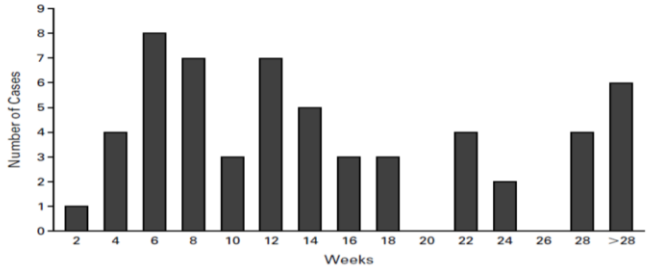


Figure 1. Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.
Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

Different risks associated with specific agents

British Society for Rheumatology Biologics Registry (*Dixon 2012*)

- Adalimumab (144 events/100 000 pyrs)
- Infliximab (136 events/100 000 pyrs)
- Etanercept (39 events/100 000 pyrs)

IRR compared with etanercept-treated patients

- Infliximab was 3.1 (95% CI 1.0, 9.5)
- Adalimumab 4.2 (95% CI 1.4, 12.4)

French registry (*Tubach et al Arthritis Rheum 2009)*

Standardised incidence ratios of TB:

Infliximab	18.6 (13.4-25.8)
Adalimumab	29.3 (20.3 – 42.4)
Etanercept	1.8 (0.7 -4.3)

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)

W G Dixon,[1] K L Hyrich,[1] K D Watson,[1] M Lunt,[1] J Galloway,[1] A Ustianowski,[2] B S R B R Control Centre Consortium, D P M Symmons,[1] on behalf of the BSR Biologics Register

Pattern

- 15/40 cases (38%) pulmonary
- 25/40 (62%) extrapulmonary
- 11/40 (28%) disseminated

Median time to TB diagnosis

- ETA - 13.4 months
- INF- 5.5 months
- ADA -18.5 months

Extrapulmonary

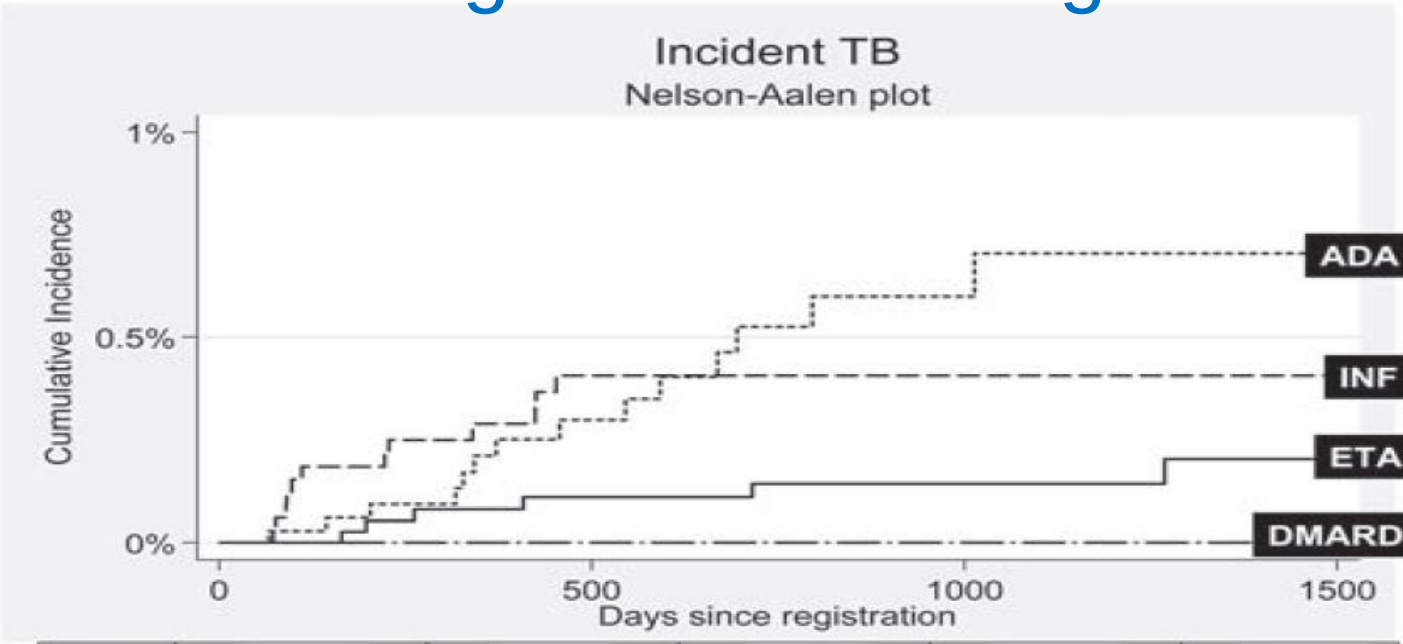
- ETA – 50%
- INF - 67%
- ADA - 65%

Disseminated

- ADA 8/20 (40%) cases
- INF 2/12 (17%)
- ETA 1/8 (13%)

Dixon et al. Ann Rheum Dis 2010;69:522–528.

Differing time-lines in agents



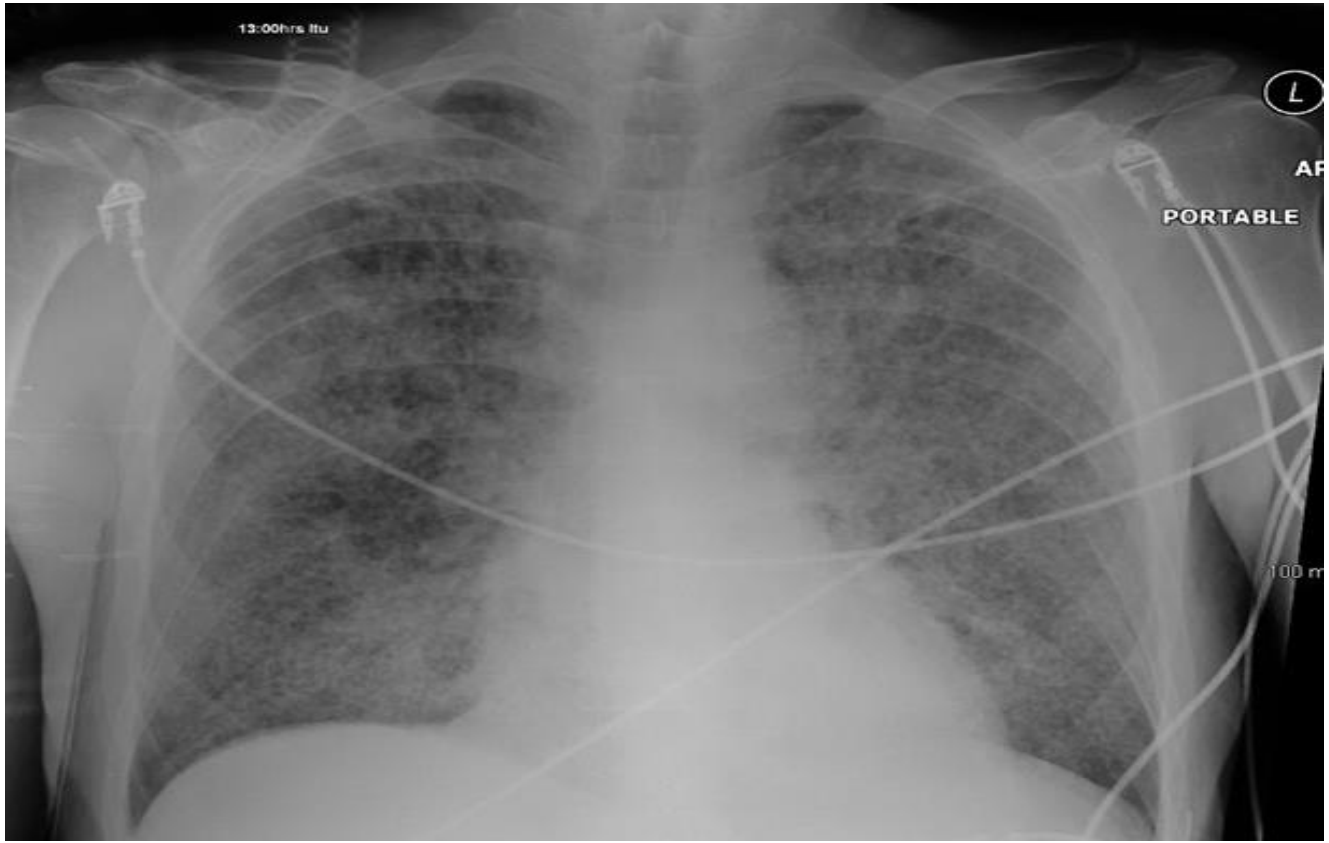
Drug	Registration (entry to study)	1 year (365 days)	2 years (730 days)	3 years (1095 days)	4 years (1460 days)
DMARD	3232	2652	1839	742	213
ETA	3913	3474	3051	2363	1020
INF	3295	2694	1918	1392	918
ADA	3504	2457	1531	729	247

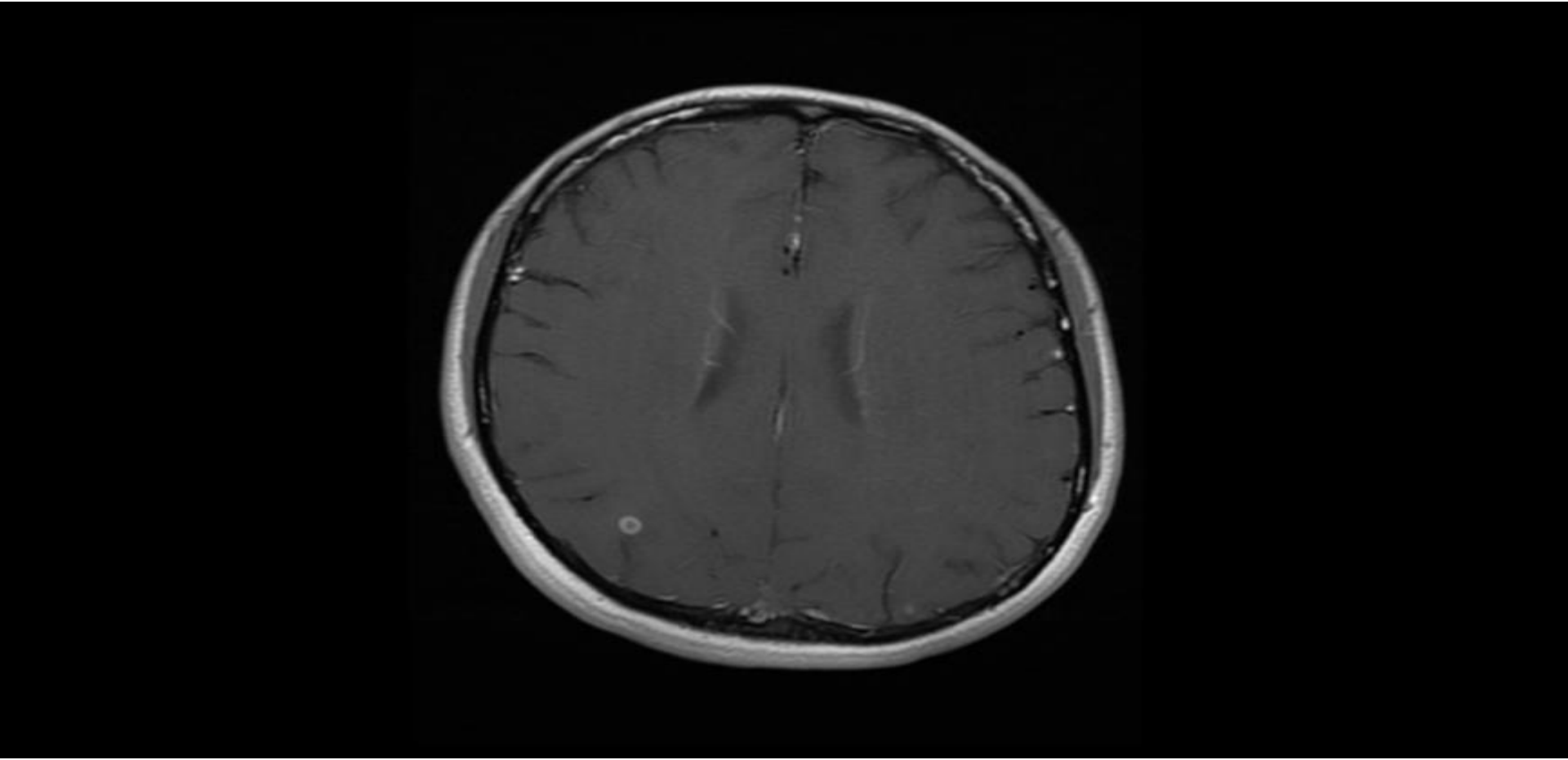
Dixon et al. Ann Rheum Dis 2010;69:522–528.

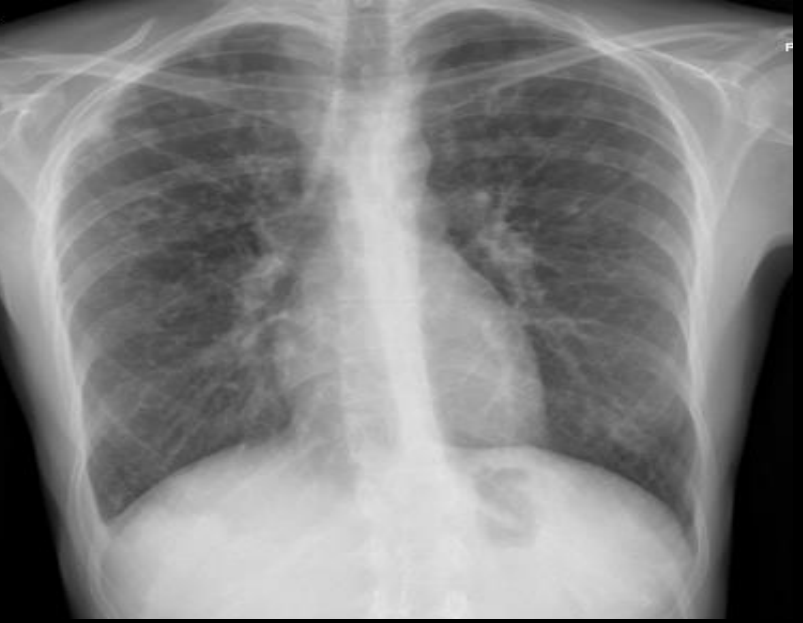
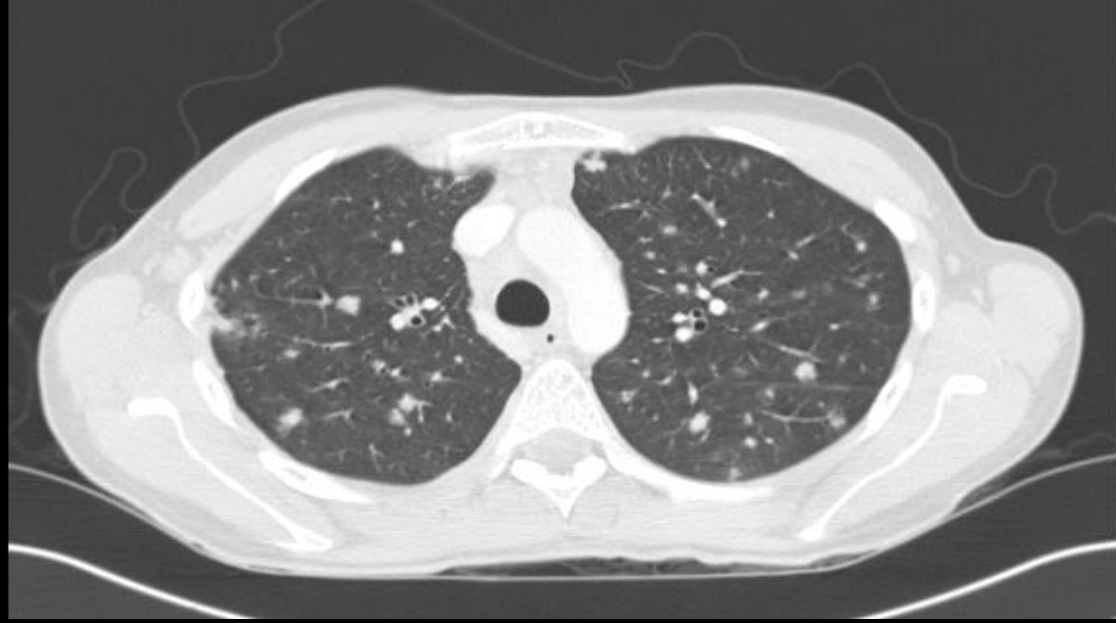
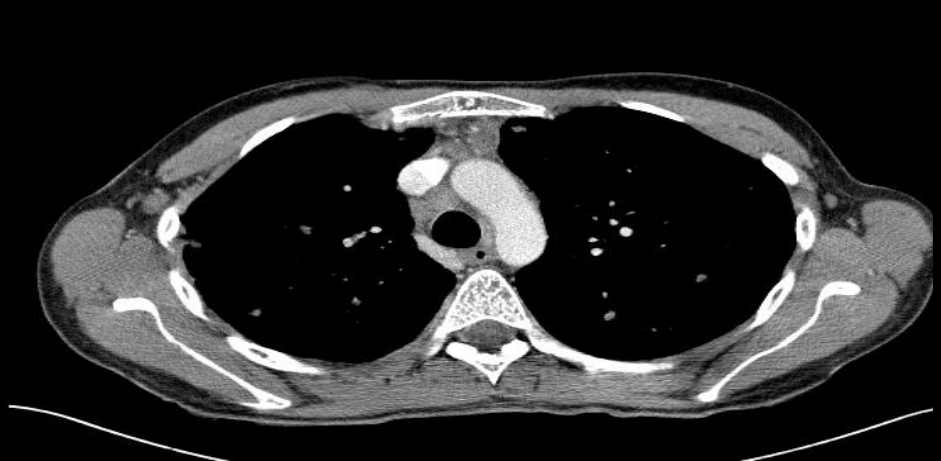
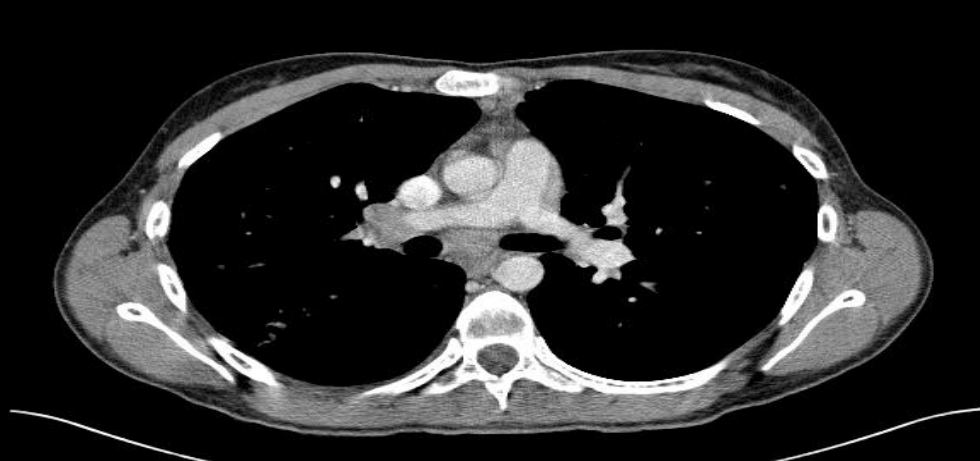
61 year old caucasian retired male with Crohn's disease

- Infliximab therapy 3 months

- Weight loss of about 15kg and 1 month history of feeling unwell





TNF α inhibitors
infliximab, adalimumab (humira), golimumab, certolizumab pegol, etanercept

- **Rheumatoid Arthritis confers TB risk without biologics**
  - X 4.2; (95% CI 2.7 to 6.7) [1]
- **Meta-analysis of RCTs & Registry/Cohort Studies (for RA)** [2]
  - TNF-α inhibitors in RA x 4.0 (95% CI 2.4-6.9)
- **Meta-analysis of RCTs & Long Term Extension Studies** [3]
  - RA rates higher than PS, UC, Crohns
  - Lower rates in etanercept than infliximab/adalimumab

[1] Arkema et al. Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? *Annals of the Rheumatic Diseases* 2015;

[2]Jin Wen et al The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies J Rheumatol 2015

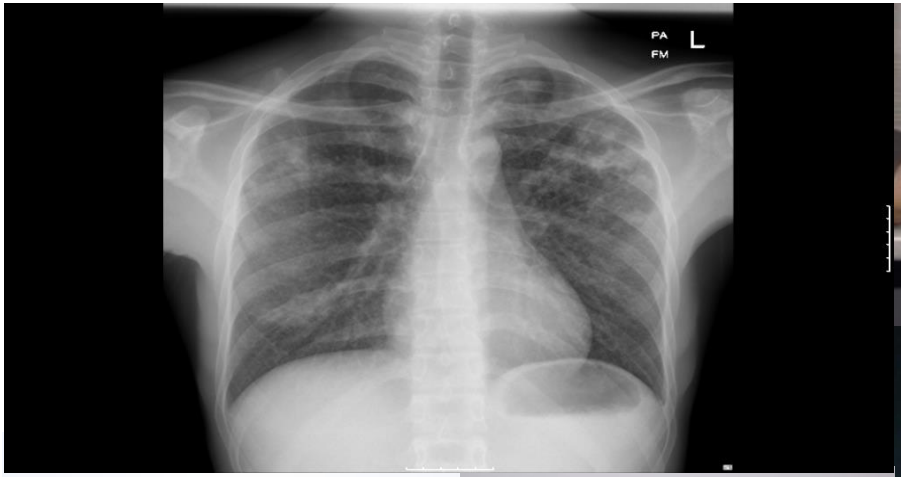
[3] Souto Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib; Rheumatology 2014

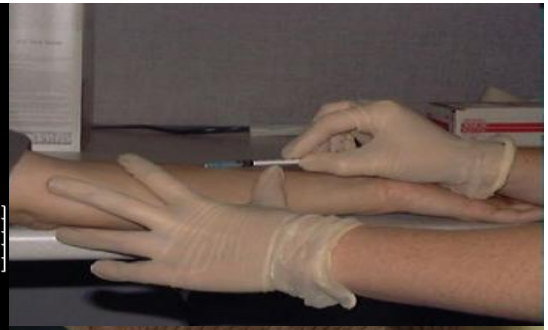
KL Winthrop et al
Clinical Microbiology and Infection (2018)

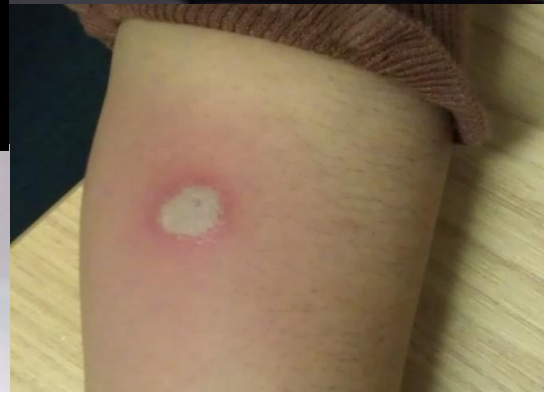
- IL-1 antagonists: anakinra, canakinumab or rilonacept: theoretical risk – screen *though risk low*
- Anti IL-5 - no theoretical nor clinical data – No screening
- Interleukin-6-targeted agents: tocilizumab and siltuximab – screen
- Interleukin-12/23 p40-targeted agents: ustekinumab: screen
- Interleukin-17-targeted agents: secukinumab, ixekizumab and brodalumab: screen - *risk of progression to active TB low*
- IgE-targeted agents: omalizumab: no theoretical nor clinical data – No screening
- Complement component 5-targeted agents: eculizumab - no theoretical nor clinical data – No screening

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

‘Immunological’ tests







Role of plain chest radiology

- Retrospective review data - RA, AS, PsA LTBI screening for biologics Jan 2013 - April 2014
- 238 rheumatic patients underwent LTBI screening
- 46 (19.3%) had positive IGRA tests, 178 (74.8%) had negative results, and 14 (5.9%) had indeterminate results.
- Healed tuberculosis in 18.1% of all patients
  - 23.9% in the IGRA -positive patients vs 16.9% in the IGRA-negative patients (OR 1.55 95% CI: 0.71–3.39, p = 0.27).
- IGRA-non-positive patients with old TB-suggestive CXR comprised 13.4% (32/238)
  - one of them developed pulmonary tuberculosis within one year after screening.
- *'IGRA-non-positive patients with old TB-suggestive CXR comprise a significant portion in rheumatic patients and merit cautious follow-up by rheumatologists, tuberculosis specialists, and pulmonologists'*

Wang et al. BMC Pulmonary Medicine (2020) 20:232

TST is attenuated in RA

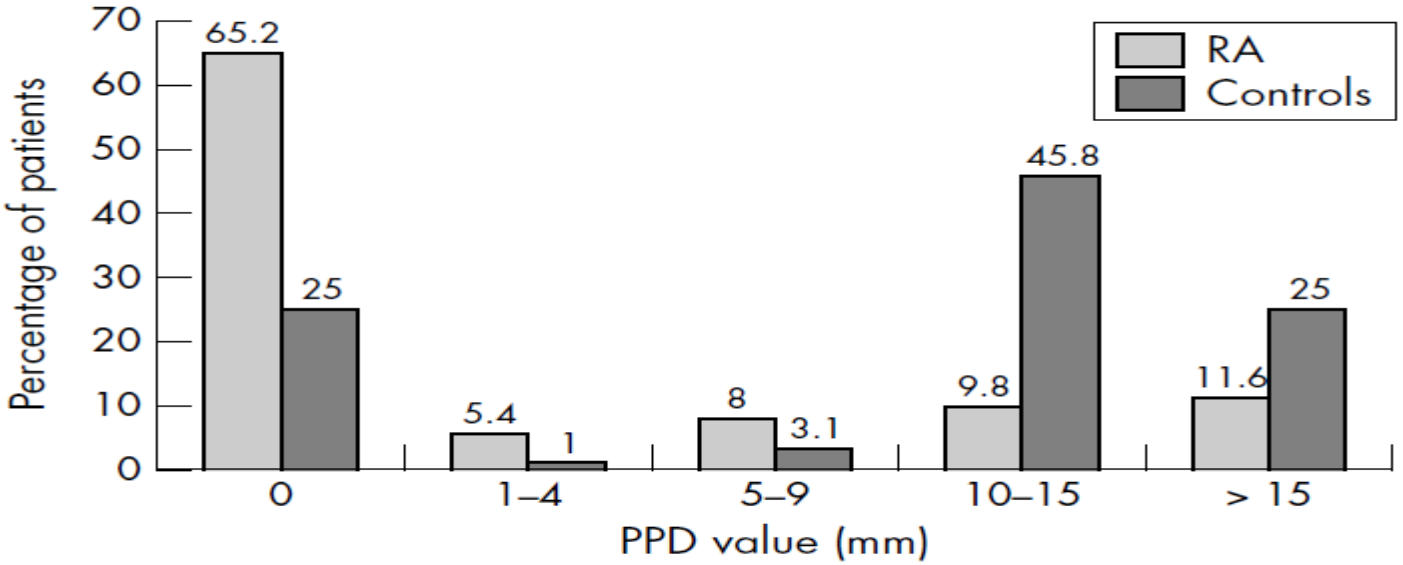


Figure 1 Induration sizes to tuberculin skin testing in patients with RA and controls.

CONCISE REPORT

Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis

D Ponce de León, E Acevedo-Vásquez, A Sánchez-Torres, M Cucho, J Alfaro, R Perich, C Pastor, J Harrison, C Sánchez-Schwartz

Ann Rheum Dis 2005;**64**:1360–1361. doi: 10.1136/ard.2004.029041

Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population.

Lima Peru

101 RA patients and 93 controls
5mm cutoff on RA/ 10mm in controls

- QFT comparable between RA and controls (44.6% vs 59.1% NS)
- TST significantly less in RA (26.7%) than controls (65.6%)

Ponce de Leon et al
J Rheumatol. 2008 May;35(5):776-81.

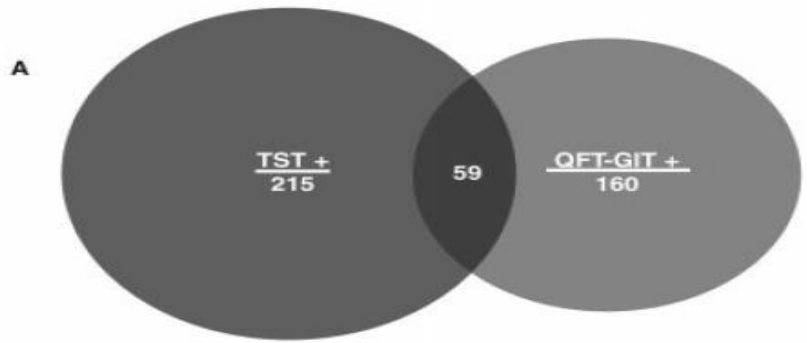
Screening for latent tuberculosis infection: performance of tuberculin skin test and interferon-γ release assays under real-life conditions

S Kleinert,[1] H-P Tony,[1] K Krueger,[2] J Detert,[3] F Mielke,[4] K Rockwitz,[5] R Schwenke,[6] G R Burmester,[3] R Diel,[7] M Feuchtenberger,[1] C Kneitz[8]

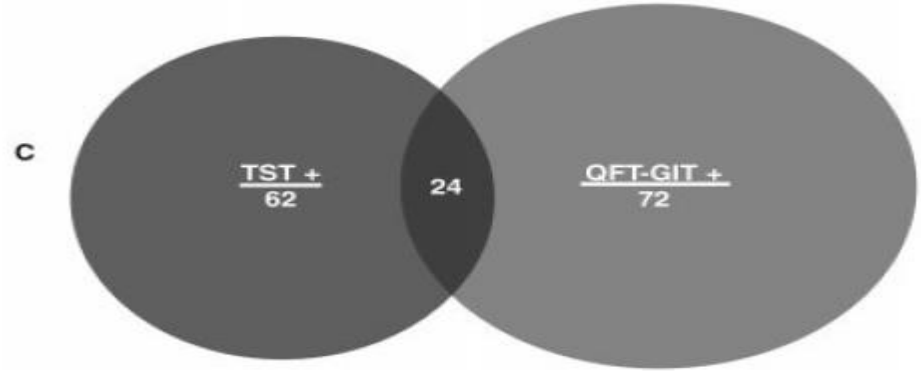
Ann Rheum Dis 2012;**71**:1791–1795.

- Patients in 62 German rheumatology centres - screened TST and IGRA (TSPOT or QFT)
- 1529 - TST, 844 - TSPOT and 685 - QFT
- **'LTBI'**
  - **8.0% - positive TST *and* no previous BCG**
  - **7.9% - positive IGRA**
  - **11.1% Combination**
- Clinical risk factors (CRF) for LTBI in 122 patients
  - TST influenced by CRF (OR 6.2; CI 4.08 to 9.44, p<0.001) and BCG vaccination status (OR 2.9; CI 2.00 to 4.35, p<0.001)
  - QFT and TSPOT ***only*** influenced by CRF (QFT: OR 2.6; CI 1.15 to 5.98, p=0.021; TSPOT: OR 8.7; CI 4.83 to 15.82, p<0.001)
- **'In patient populations with low rates of TB incidence and BCG vaccination, the use of both TST and IGRA may maximise sensitivity in detecting LTBI but may also reduce specificity'**

RA/ psoriatic arthritis/ankylosing spondylitis
phase III trials of golimumab
- QuantiFERON-TB Gold In-Tube
- TST RT23 – 5mm cutoff



All

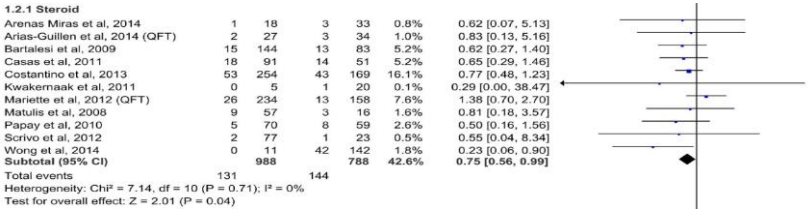


BCG naive

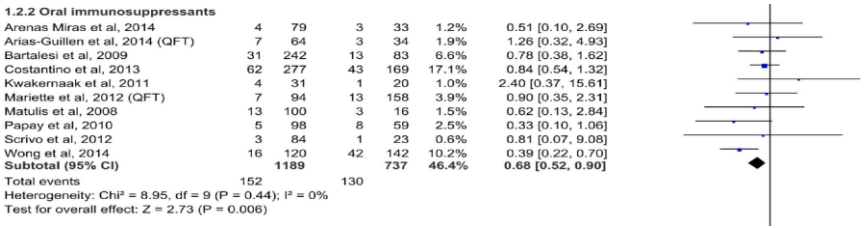
BCG

ARTHRITIS & RHEUMATISM
Vol. 64, No. 7, July 2012, pp 2068–2077

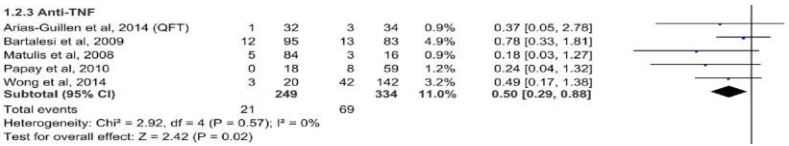
Hsia et al.



Steroids/ immunosuppressants/ anti TNF attenuate IGRA performance



Steroids/ **immunosuppressants**/ anti TNF attenuate IGRA performance



Steroids/ immunosuppressants/ **anti TNF** attenuate IGRA performance

Wong SH, et al. Thorax 2016;71:64–72.

Epidemiology versus risk* of treatment

- ‘Individual’ risk
  - Prior LTBI/ TB - never treated
  - Close contact
  - Positive IGRA/TST
  - Imaging evidence

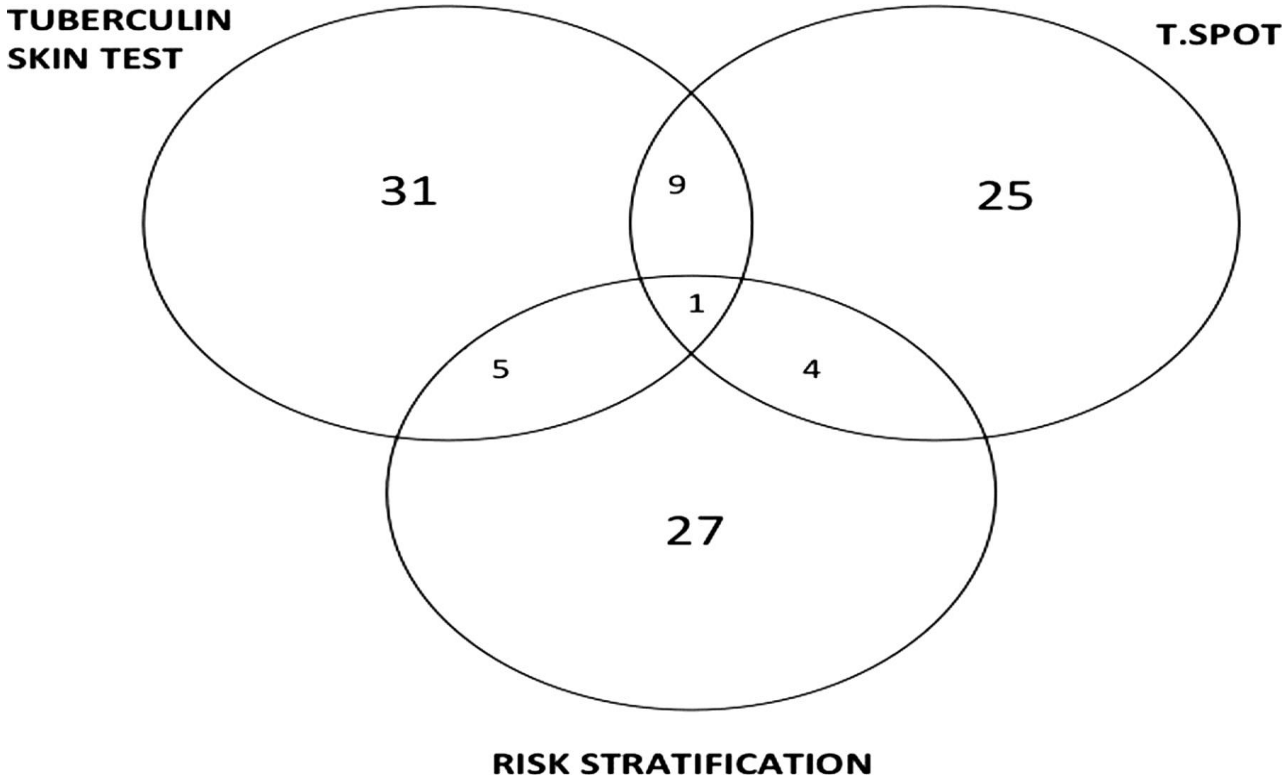
- ‘Population’ risk
  - Ethnicity
  - Country of birth
  - Where one lives

‘Individual’ risk > ‘Population’ risk

Adjust if on DMARDS/steroids

**** Of progression from latent to active TB***

Overlapping yield for tests when positive



Singanayagam A et al. Thorax 2013;68:955-961

Treatment of TST positive RA cases post implementation of screening reduced TB incidence

INH 9 months given if:

1) history of untreated or partially treated TB, or exposure to an active TB case
2) CXR showing residual changes indicative of prior TB infection
3) reaction of 5 mm in diameter TST or 2-step TST (359 patients - 28%)

risk ratio for the incidence of active TB, compared with the background population, before March 2002 was 25.15 (95% CI 14.05–45.17) and dropped 74% to 6.72 (95% CI 0.16–41.07) following the official recommendations date

Effectiveness of Recommendations to Prevent Reactivation of Latent Tuberculosis Infection in Patients Treated With Tumor Necrosis Factor Antagonists

Loreto Carmona,[1] Juan J. Gómez-Reino,[1] Vicente Rodríguez-Valverde,[2] Dolores Montero,[3] Eliseo Pascual-Gómez,[4] Emilio Martin Mola,[5] Luis Carreño,[6] and Manuel Figueroa,[7] on behalf of the BIOBADASER Group

ARTHRITIS & RHEUMATISM
Vol. 52, No. 6, June 2005, pp 1766–1772

In moderate incidence setting – LTBI therapy efficacious

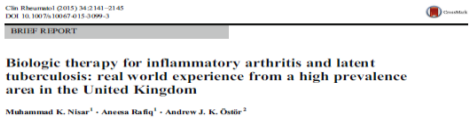
- 10,863 patients commenced on anti-TNF therapy between 2011 and 2013
- South Korea TB incidence 86/100,000
- Conducted after introduction national guidelines for TB screening pre TNF agents
  - IGRA or TST with 10-mm cut-off
  - Chest radiograph
- Incidence active TB
  significantly lower in the 22.7% who received any preventive therapy (0.4%) compared with those who did not (1.2%) (4.07/1,000 person-years vs. 12.34/1,000 person-years; incidence rate ratio = 0.33)
- Risk reduction greatest in those who completed a full course of preventive therapy (ie adherence)

NOTES:

- **Significant percentage of those in the untreated, presumed IGRA-negative group developed active TB**
- Moderate TB burden settings such as South Korea, screening for LTBI may not adequately predict the risk for TB
- ?treating all future TNF antagonist recipients for LTBI - number to treat is still high at 123

Lee J, Kim E, Jang EJ, Lee CH, Lee EY, Im JP, Han SK, Yim JJ. Efficacy of treatment for latent tuberculosis in patients undergoing treatment with a tumor necrosis factor antagonist. Ann Am Thorac Soc 2017; 14:690–697.

When to start/restart biological therapy?


Clin Rheumatol (2015) 34:2141–2145
DOI 10.1007/s10067-015-3099-3

BRIEF REPORT

Biologic therapy for inflammatory arthritis and latent tuberculosis: real world experience from a high prevalence area in the United Kingdom

Muhammad K. Nisar[1] · Aneesa Rafiq[1] · Andrew J. K. Östör[2]

- Guidance
  - TB Net 2010 ERJ – 4 weeks of LTBI/ ACTIVE complete first
  - BTS 2005 – ACTIVE ideally 2 months / or complete
  - BTS 2005 – LTBI ideally complete first

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis 2019

Latent and reactivated TB

- Patients should be treated with prophylactic anti-TB treatment prior to commencing a biologic (grade 1B, SOA 99%); ***therapy may be commenced after completing at least 1 month of anti-TB treatment*** and patients should be monitored every 3 months (grade 2C, SOA 91%).
- Patients who have had previous inadequate treatment for active TB should be investigated for active TB. In these individuals even when active disease has been excluded, the annual risk of TB (reactivation) is much higher than the general population rate, so the risk–benefit analysis favours chemoprophylaxis (grade 1C, SOA 98%).
- As TB reactivation risk is higher with anti-TNF mAb drugs (notably ADA and IFX) than for ETN, consider ETN in preference for those who require anti-TNF therapy and are at high risk of TB reactivation (grade 1B, SOA 99%).

Active TB

- Patients with evidence of active TB should be treated before starting a biologic (grade 1C, SOA 99%); ***therapy may be commenced after completing at least 3 months of anti-TB treatment, and there is evidence that the patient is improving with evidence of culture negativity*** (grade 2C, SOA 91%).

GUIDELINES

BJD
British Journal of Dermatology

British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update*

C.H. Smith,[1] Z.Z.N. Yiu,[2] T. Bale,[3] A.D. Burden,[4] L.C. Coates,[5,6] W. Edwards,[7] E. MacMahon,[8] S.K. Mahil,[1] A. McGuire,[9] R. Murphy,[10,11,12] C. Nelson-Piercy,[13] C.M. Owen,[14] R. Parslew,[15] O.A. Uthman,[16] R.T. Woolf,[1] L. Manounah,[17] M.C. Ezejimofor,[17] L.S. Exton,[17] and M.F. Mohd Mustapa[17] on behalf of the British Association of Dermatologists' Clinical Standards Unit

- ***Consider screening for latent tuberculosis (TB) with an interferon-gamma release assay (IGRA) alone, or with an IGRA and concurrent Mantoux test; be aware of the individual's risk factors for TB when interpreting results.***
- Apply local policy on the use of a plain chest radiograph for screening for TB to rule out abnormalities at base line including granulomas indicative of prior infection and other confounding lung diseases. If positive, assess for active TB and/or management of latent TB in consultation with a TB specialist (see NICE tuberculosis guideline).
- In people who require treatment for latent TB [3 months of isoniazid (with pyridoxine) and rifampicin, or 6 months of isoniazid (with pyridoxine)], aim to complete 2 months of treatment before commencing biologic therapy.
- Any symptoms or signs suggestive of TB, new exposure to TB or prolonged residence in a high-incidence setting should prompt further clinical assessment and investigation, including a repeat IGRA. Be aware that active TB on TNF antagonist therapy is often disseminated and extrapulmonary; symptoms may include unexplained weight loss, night sweats, nonresolving cough, haemoptysis and lymphadenopathy.
- Inform people that they should seek medical advice if symptoms of TB develop during or after treatment with a biologic therapy and issue a patient alert card in line with Medicines and Healthcare products Regulatory Agency guidance.

Other biologics Lower Risk Agents
Non TNF α inhibitors

Biologic	Country; patient N°	TB cases	IR	Expected IR/100/year (WHO)	
Tocilizumab	Japan; 3881	4	0.22	15–100	Post marketing surveillance
	Japan; 302	0	0	15–100	Disease registry
	France; 1303	0	0	10–24	
	Germany; 370	0	0	10–24	
Rituximab	Germany; 2484	1	0.12	10–24	
	Greece; 234	0	0	10–24	
	Taiwan; 763	2	0.38	15–100	
Abatacept	France; 682	0	0	10–24	
	Japan; 231	0	0	15–100	
Ustekinumab	Worldwide; 3474	0	0	NA	Disease registry
Secukinumab	Unavailable data	NA	NA	NA	

IL6

CD20

CD28

IL12/23
IL17

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

Drug target site

Cantini et al.Risk of Tuberculosis Reactivation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Receiving Non-Anti-TNF-Targeted Biologics. Mediators Inflamm 2017

Risk for latent tuberculosis infection reactivation among patients with psoriasis on biologics treatment: A meta-analysis

X. Zhu, X. Pan, M. Da et al. Journal of Infection 89 (2024) 106226

Table 1
Subgroup analysis of LTBI reactivation rates based on characteristics of included studies.

Characteristic	No. of studies	LTBI reactivation	95% CI	Heterogeneity (I^2), %	*p* value
Prophylaxis					
Receive treatment	17	0.0000	0.0000-0.0009	10.10	0.336
Did not receive treatment	12	0.0000	0.0000-0.0040	0.00	0.975
Types of biologics					
IL-17 inhibitors	10	0.0000	0.0000-0.0000	0.00	0.997
IL-23 inhibitors	4	0.0000	0.0000-0.0038	0.00	0.935
TNF-α inhibitors	5	0.0127	0.0000-0.0579	40.57	0.151
Study design					
Retrospective	17	0.0000	0.0000-0.0005	3.32	0.415
Prospective	3	0.0087	0.0000-0.0350	NA	NA
Geographic region					
Europe	8	0.0000	0.0000-0.0074	16.42	0.301
Asia	6	0.0011	0.0000-0.0128	0.00	0.722
South America	2	0.0162	0.0162-0.0474	NA	NA

IL-17, interleukin-17; IL-23, interleukin-23; TNF-α, tumor necrosis factor-α; NA, not available.

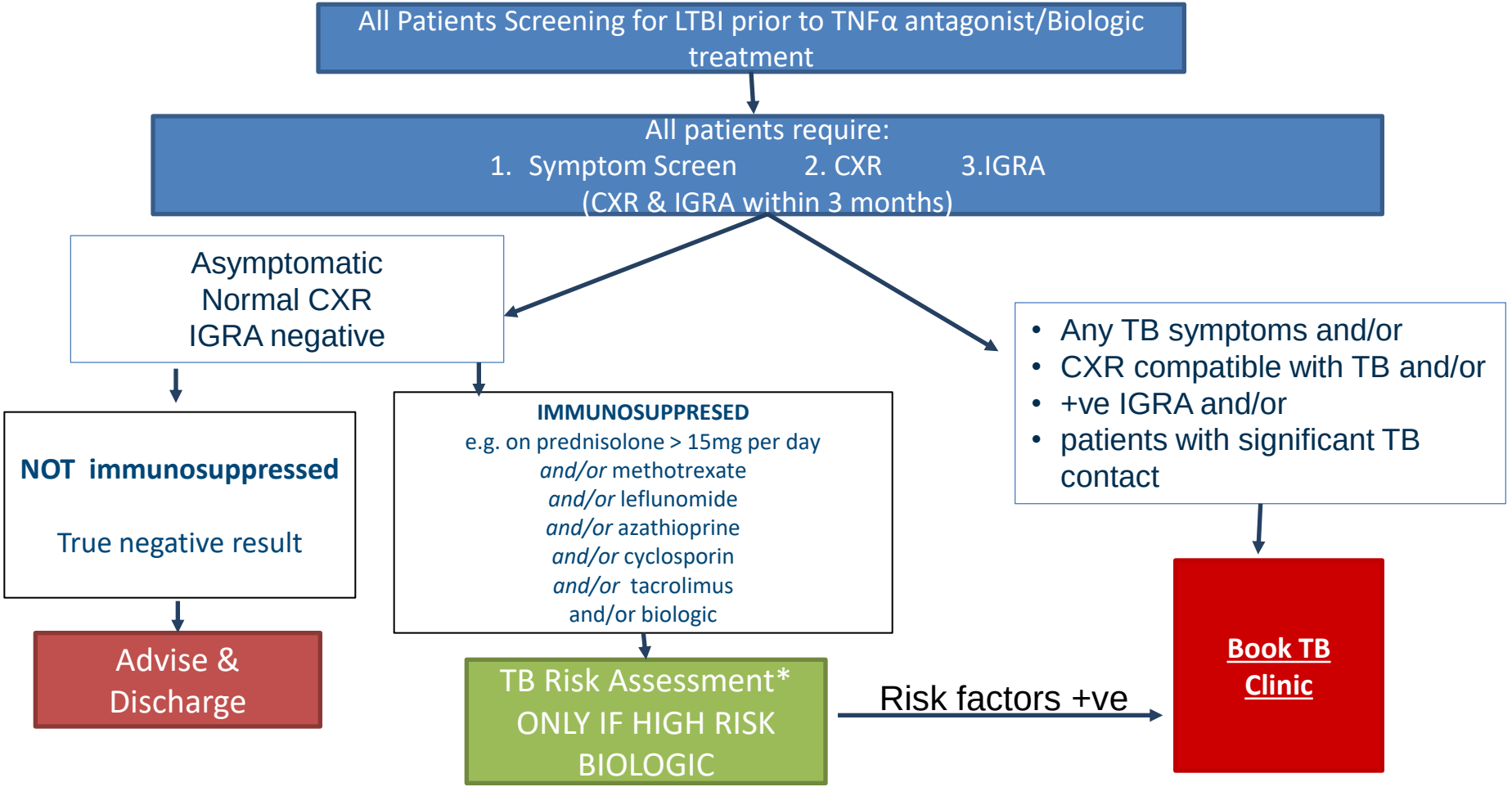
Traffic Light Drug List

- All patients who are prescribed a '**GREEN**' biologic drug DO NOT require a TB screen
- All patient who are prescribed a '**RED**' or '**AMBER**' biologic drug DO require a TB screen.
- '**AMBER**' drugs represent a lower risk of TB reactivation than '**RED**' drugs and these should be selected in preference to '**RED**' drugs if patients are considered to have a high risk of TB reactivation after discussion with the TB team

Appendix A: The Targeted and Biologic Drug Traffic Light Drug List for TB Risk. September 2020

Targeted molecule	Named drug examples	ESGIGH Consensus Document: Is LTBI testing recommended?	Summary Product Characteristics. Is LTBI testing recommended?	Notes
TNFα (monoclonal antibody)	adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	yes	yes	
TNFα (soluble receptor)	Etanercept	yes	yes	Likely lowest TB risk in anti TNFα group
IL-1	anakinra, canakinumab	Yes	yes	Theoretical increased TB risk only
IL-4	dupilumab	N/A	no	
IL-5	mepolizumab, reslizumab	no	no	
IL-6	tocilizumab, sarilumab	yes	yes	Rate of TB Cases lower than background TB risk*
IL-12/23 common p40 subunit	ustekinumab, guselkuman tildrakizumab, risankizumab	yes	yes	No TB cases associated with ustekinumab and secukinumab **
IL-17	secukinumab, ixekizumab, brodalumab	yes	yes	
IgE	omalizumab	no	no	
Complement factor C5	eculizumab	no	no	
VEGF	aflibercept, bevacizumab,	no	no	
VEFGR	axitinib,cabozantinib, pazopanib,	no	no	
EGFR	cetuximab, panitumumab	no	no	
ErbB2/HER2	pertuzumab, trastuzumab,	no	no	
ErbB receptor tyrosine kinases	afatinib, erlotinib, gefitinib, lapatinib,	no	no	
BCR-ABL tyrosine kinase	bosutinib, dasatininib, imatinib, nilotiinib,	no	no	
BRAF/MEK kinases	cobimetinib, dabrafenib, trametinib,	no	no	
Bruton tyrosine kinase	ibrutinib,	no	no	
PI3K	Idelalisib	no	no	
Bcl-2	venetoclax	no	no	
Janus kinases	baricitnib, ruxolitinib, tofacitnib	yes	yes	
mTOR	everolimus, sirolimus, temsirolimus	'may be advisable'	no	Evidence unclear. TB assessment if additional
CD19	Blinatumomab	no	no	
CD20	rituximab, ofatumumab, ocrelizumab,	no	no	
CD52	Alemtuzumab	yes	yes	
CD22	epratuzumab, inotuzumab, ozogamicin	no	no	
CD28	abatacept	not reviewed	yes	
CD30	brentuximab vedotin	no	no	
CD33	gemtuzumab ozogamicin	no	no	
CD38	daratumumab,	no	no	
CD319 (SLAMF7)	elotuzumab	no	no	
CTLA-4	ipilimumab	If additional I/suppression	no	Evidence unclear. TB assessment if additional
PD-1 and PD1L	atezolizumab, nivolumab,	If additional I/suppression	no	Evidence unclear. TB assessment if additional
a4-Integrins, LFA-1	natalizumab	no	no	
a4-Integrins, LFA-1	vedolizumab	no	yes	Likely safe in terms of TB risk, but more data
Sphingosine 1ephosphate receptor	fingolimod	no	no	In Multiple Sclerosis [Error! Reference source n
Proteosome	bortezomib, carfilzomib, ixazomib	no	no	

Key: red is proven higher risk for TB reactivation, green relatively low risk and amber uncertain [2,3] ESGIGCH=*European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts.* *In rheumatoid arthritis ** In Psoriatic arthritis and Ankylosing spondylitis meta-analysis [4]. ***Evidence unclear, consider testing in additional TB risk factors. I/suppression=Immunosuppression


All Patients Screening for LTBI prior to TNFα antagonist/Biologic treatment
All patients require:
1. Symptom Screen 2. CXR 3.IGRA
(CXR & IGRA within 3 months)
Asymptomatic
Normal CXR
IGRA negative
• Any TB symptoms and/or
• CXR compatible with TB and/or
• +ve IGRA and/or
• patients with significant TB contact
NOT immunosuppressed
True negative result
IMMUNOSUPPRESED
e.g. on prednisolone > 15mg per day
and/or methotrexate
and/or leflunomide
and/or azathioprine
and/or cyclosporin
and/or tacrolimus
and/or biologic
Advise & Discharge
TB Risk Assessment*
ONLY IF HIGH RISK BIOLOGIC
Risk factors +ve
Book TB Clinic

Triage tool

Results

NO	YES	Any TB Symptoms
NO	YES	Chest Radiograph abnormalities
NO	YES	IGRA positive or indeterminate
NO	YES	Immunosuppressed* already AND Resident (>3 months) in a high incidence TB country within 5 years
NO	YES	Contact with known TB
NO	YES	Previous TB disease
Extra info		

** 'Immunosuppressed' is defined as being prescribed the following medications:*

prednisolone > 15mg per day> 1 month	*azathioprine*
methotrexate	*cyclosporine*
leflunomide	*tacrolimus*

Or with end stage renal failure i.e. dialysis or transplant

Patients who are immunosuppressed may have false negative IGRA results

If answer 'NO' to all above: does not require TB service referral
Any 'YES' responses: require a TB team referral

Negative predictive value IGRA

- T-SPOT.TB NPV was 99.20%

- dropped to 99.17% when simulated where borderline IGRA results regarded as negative

- Patients on biologics more likely to have a negative IGRA result than patients not on
- No statistically significant change in conversion or reversion rates between groups
- 19 of 9263 patients on biologics developed active TB after starting biologics

- at an incidence rate of 55.1 per 100 000 patient-years

- ***despite screening in half of the 16 patients***

- Most drugs implicated were known to be high risk

- although rituximab (5) and natalizumab (1) cases

Cafferkey J et al. ERJ Open Res 2022 Nov 28;8(4):00193-2022

CASE BASED DISCUSSIONS

Tuberculosis during TNF-α inhibitor therapy, despite screening

Regina W Hofland,[1] Steven F T Thijsen,[2] Marc A M T Verhagen,[3] Yolande Schenk,[4] Ailko W J Bossink[1]

Case 1

48 year old woman (?ethnicity) with IBD

TST negative / Tspot indeterminate

No prophylaxis – stopped Infliximab

Three months later

- Travelled in country incidence 101 per 100 000

Returned - TB meningitis 5 weeks later and died 2 weeks later

Case 2

41 year old Moroccan man with Ankylosing Spondylitis

TST/Tspot negative - Infliximab

Travelled to Morocco (approximately 82 per 100,000) 6 weeks

Returned 3 months later EPTB - M.bovis

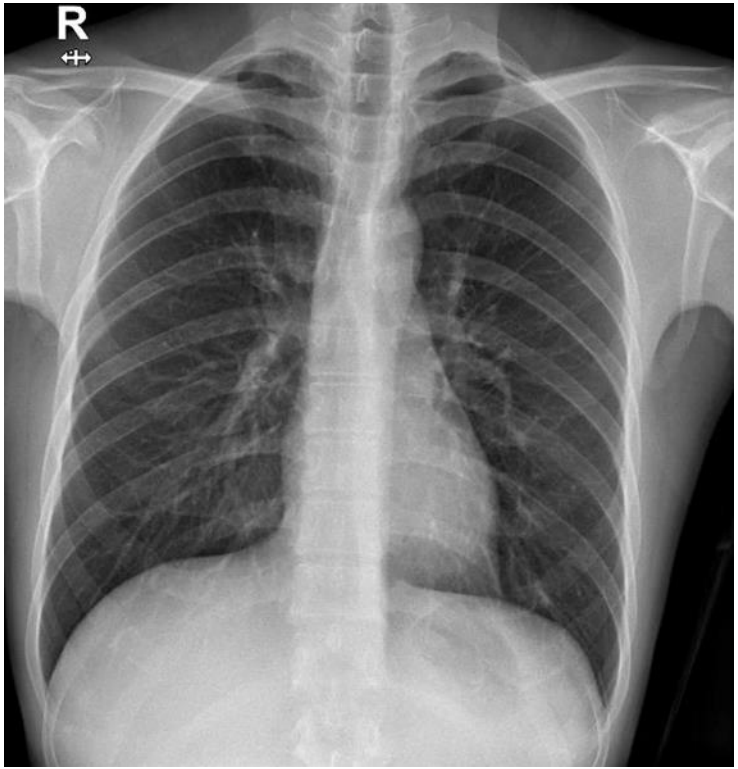
Thorax 2013 68: 1079-1080

36 year old Filipino male

- Crohn’s Disease
- Infliximab candidate
- Philippines – UK 2009
- Works in finance
- No contacts
- Last travel 2017

Screened July 2020

- Non reactive T Spot
- CXR normal
- Infliximab August 2020



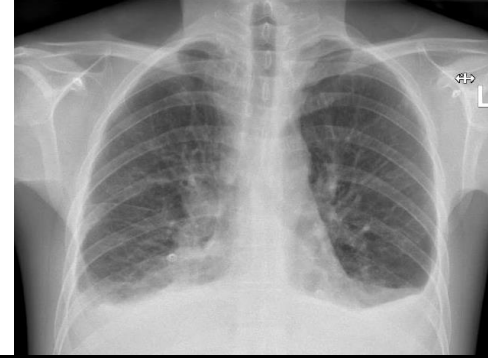
Feb 2021

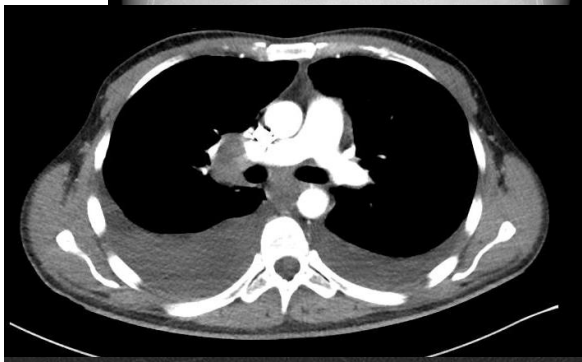
- 6 week history
  - Non productive cough
  - Fever
  - Lethargy
  - SOB
  - Then night sweats
- Bilateral pleural effusions CXR
- CT – 5mm nodules/ bilateral effusions

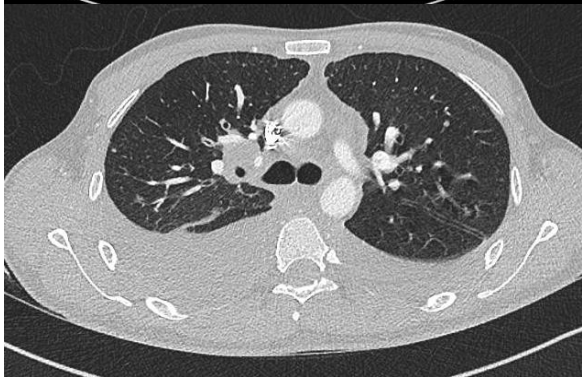
/ hilar nodes/ splenic lesions

Sputum scanty pos/ culture +ve/ fully sensitive TB

Pleural effusions smear neg/ culture pos







Emerging TB Risk Agents? Immune Checkpoint Inhibiotors

nivolumab and pembrolizumab (PD-1),
atezolizumab, avelumab, and durvalumab (PD-L1),
ipilimumab (CTLA-4)

FDA Adverse events reporting:

a.2015-2020 >73K adverse affects. [1]

72 TB were due to PD-1/PD-L1 inhibitors. OR 1.79 (CI 1.42-2.26)

45 cases (62.5%) due to nivolumab, 18 (25%) due to pembrolizumab, 5 (7%) due to atezolizumab and 4 (5.5%) due to durvalumab.

Median Time to diagnosis 6.3months (CI 1-24 months)

b. 2011-2021 [2]

74 cases pTB reported OR 3.16 (95%CI 2.2-4.)

Lung Ca (75%), Melanoma (12%)

Systematic Review & Meta-analysis.

27 Studies met inclusion criteria. 35 TB cases, rate 2,000 per 100, 000 [3]

[1] Anand et al Mycobacterial infections due to PD-1 and PD-L1 checkpoint inhibitors ESMO open 2020
[2] Zhu et al, Pulmonary tuberculosis associated with immune checkpoint inhibitors: a pharmacovigilance study *Brief communication* Thorax 2022
[3] Liu et al Increased Tuberculosis Incidence Due to Immunotherapy Based on PD-1 and PD-L1 Blockade: A Systematic Review and Meta-Analysis Front Immunol 2022 May

Rescreening

- BTS 2005 - NO guidance
- NICE 2016 - NO guidance
- British Society Rheumatology 2018 – NO guidance
- American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis 2015 - rescreen annually high risk
- Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics - 2019 – rescreen annually high risk
- WHO 2020 – NO guidance
- 2020 British Association of Dermatologists - NO guidance

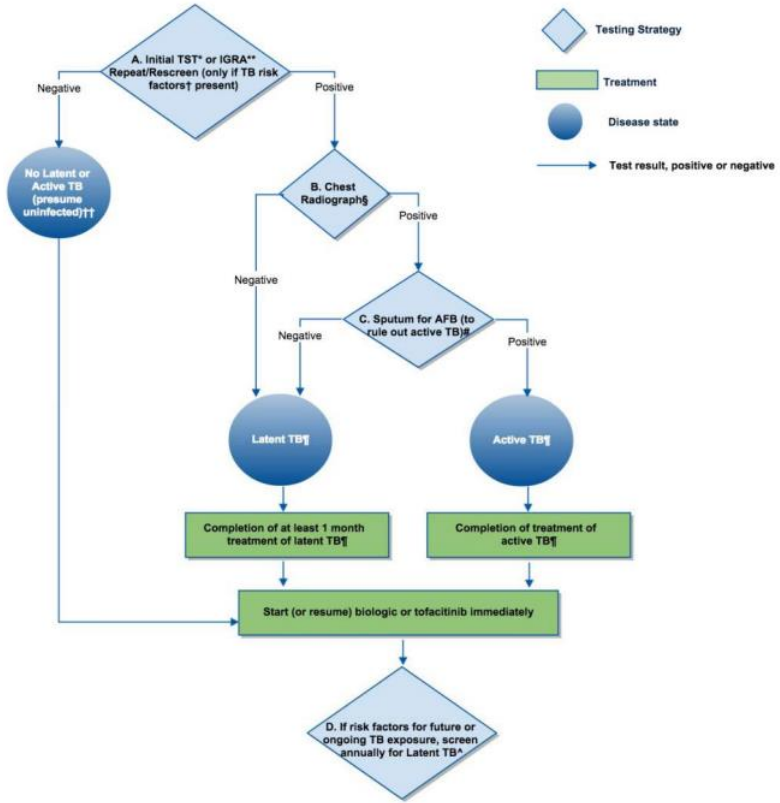
- *British Journal of Dermatology (2020) 183, pp628–637*

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Annual screening if any risk factors

Risk factors defined based on Centers for Disease Control

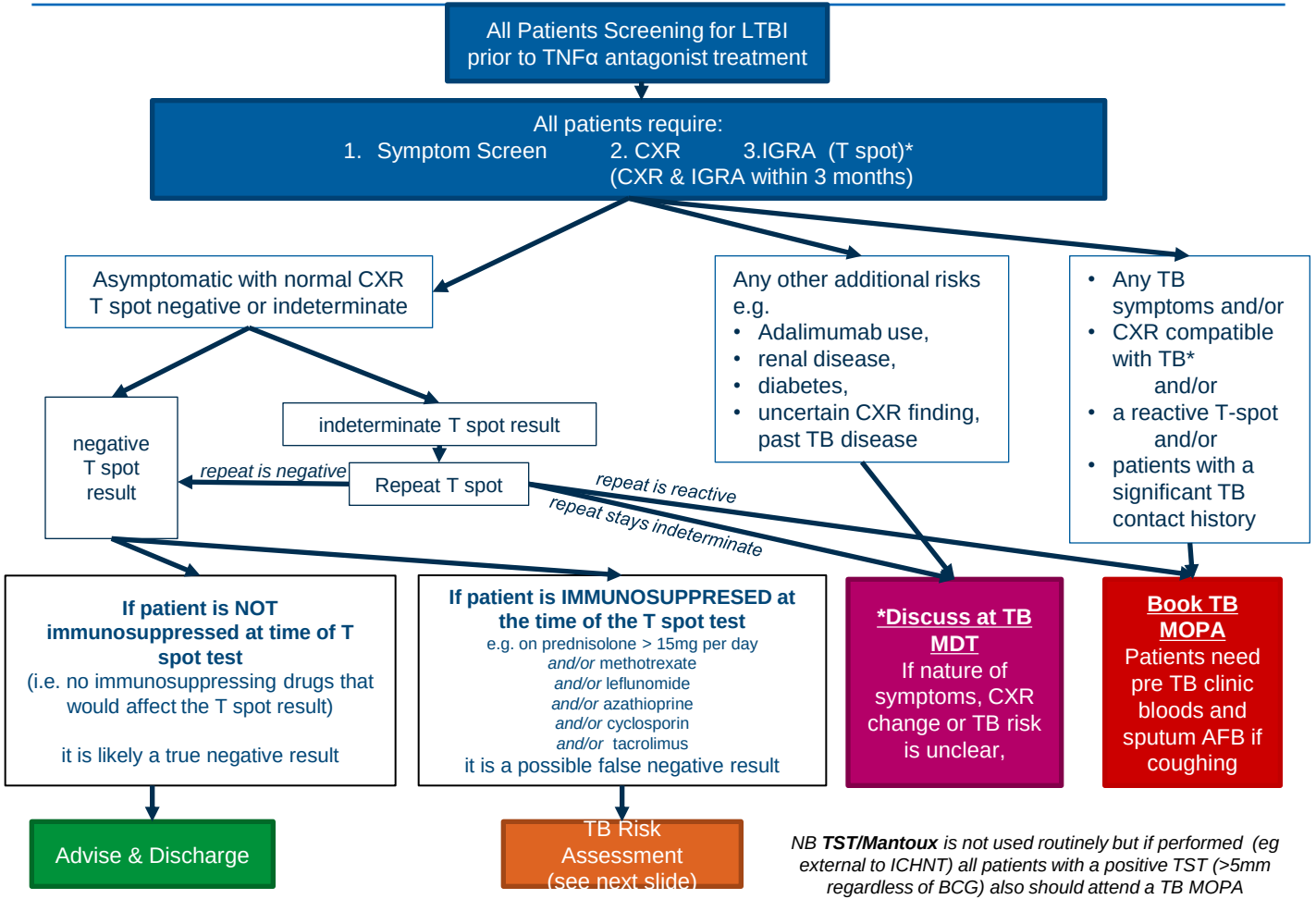
- close contacts active TB
- foreign-born high incidence TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
- persons who visit areas with a high prevalence of active TB, especially if visits are frequent or prolonged
- residents and employees of congregate settings whose clients are at increased risk for active TB (e.g., correctional facilities, long-term care facilities, and homeless shelters)
- health care workers who serve clients who are at increased risk for active



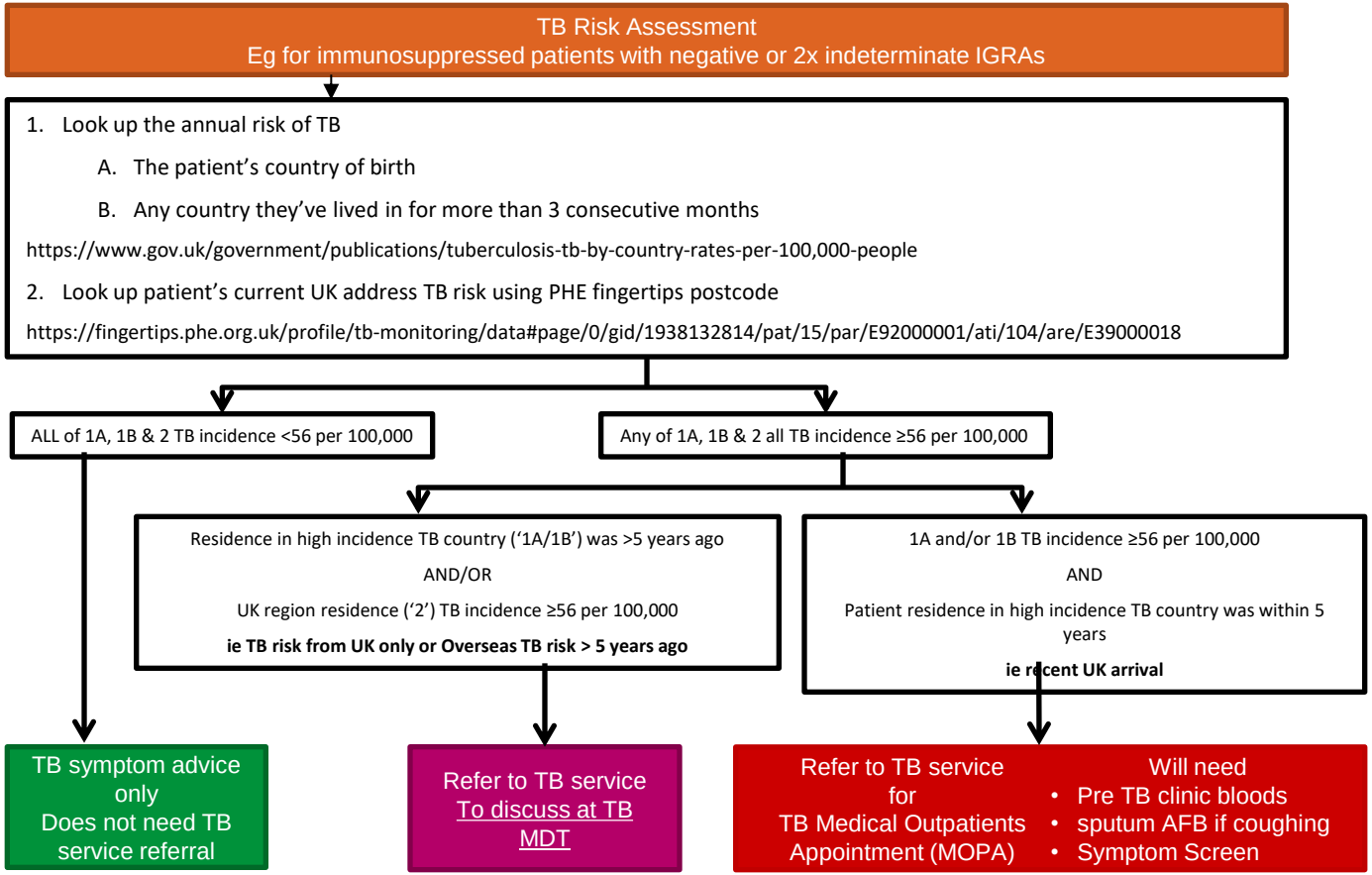
Arthritis Care & Research DOI 10.1002/acr.22783 VC 2015, American College of Rheumatology

IGRA Conversion

- IGRA conversion 14 of 119 patients (11.8%) – South Korea
  - Kim HW et al. Rheumatology International (2020) 40:471–479
- Conversion rate TST (n=11, 22% or 3.47/100 patient-years) versus T-SPOT.TB (n=4, 8% or 1.74/100 patient-years) - Athens
  - Thomas K et al. Pathogens and Immunity - Vol 5, No 1: 2020



*NB **TST/Mantoux** is not used routinely but if performed (eg external to ICHNT) all patients with a positive TST (>5mm regardless of BCG) also should attend a TB MOPA*



*56 per 100,000 cut off is derived from an approximate 5X risk of TB on TNFa antag vs the incidence of hepatitis estimate 278 per 100,000 ie risk of TB outweighs Risk of TB 5X56= 280> Risk of drug induced Hepatitis 278.

Biological Treatment - Summary points

- Anti-TNF therapy
  - extrapulmonary and disseminated pattern
  - disease activation characteristics are agent dependent
- Ongoing stratification of more agents
- Screen for LTBI/TB **before** initiating steroids/immunosuppressive treatment/anti-TNF
- Effect of steroids/anti-TNF and DMARDs on tests
- Most ‘sensitive’ approach is tri-modality (**TST/IGRA/CXR**) – no single test is ‘perfect’/ gold standard
- Risk/ epidemiology useful once on steroids/ immunosuppressants (*but only on high risk treatments)*
- Pathway and screening locally derived
- Rifampicin/Isoniazid 3 months OR Isoniazid 6 months if drug interactions important
- Rescreen only if new/ ongoing exposure or travel - ? Change if high incidence setting
- Vigilance/advise even in ‘screen negatives’