Tuberculosis and treatment with biologics

Judith Bruchfeld
MD, Associate professor, Senior consultant
TB centre, Karolinska, Sweden

No conflicts of interest

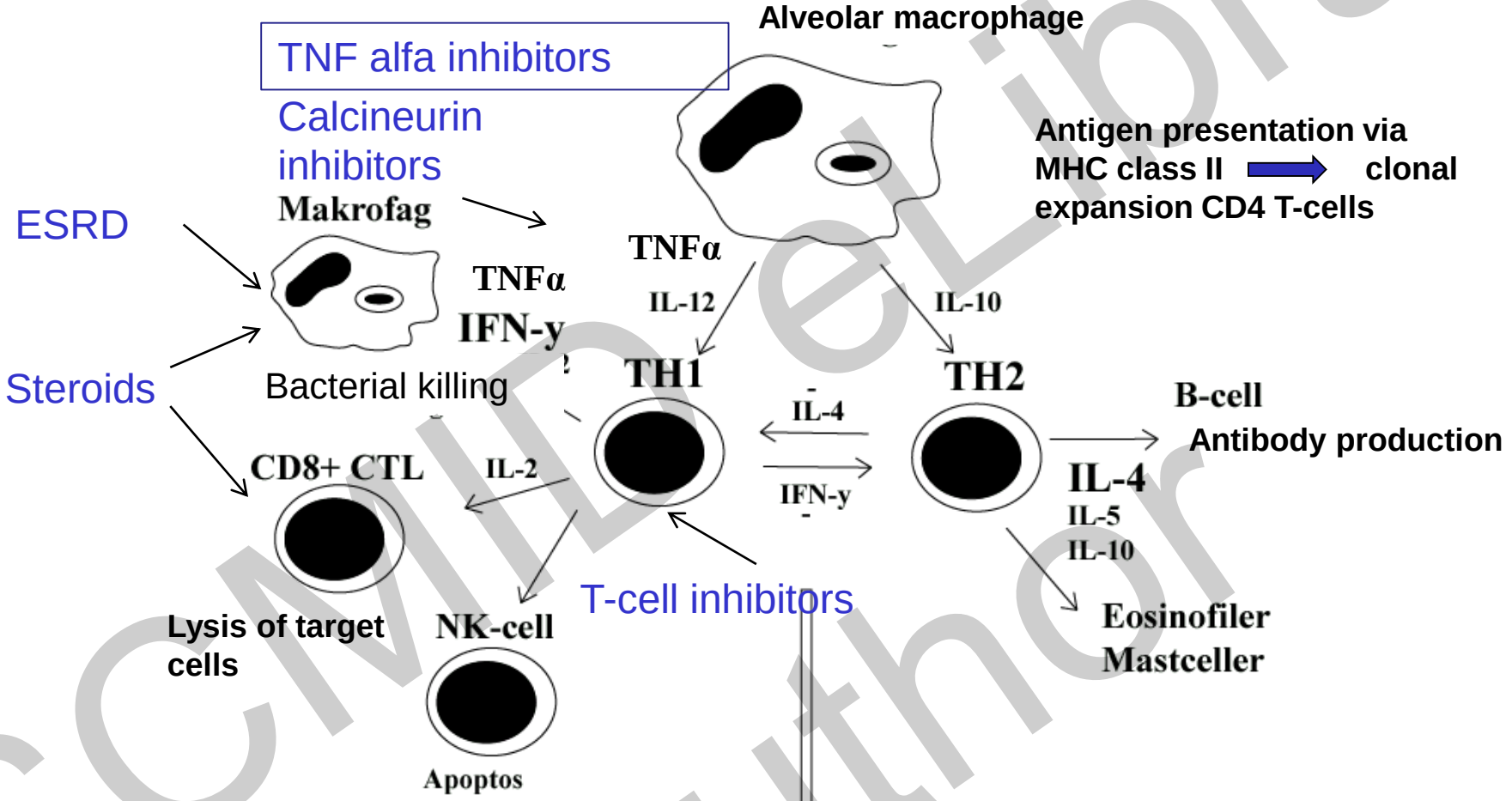
Overview

- Different infections and the immune-system
- Different groups of biologics and specific infections
- TB screening and treatment
- Case presentation

Case

- 27 year old male patient with ankylosing spondylitis. Candidate for biologic treatment.
- Adalumimab (Humira) planned.
- Screening prior to treatment with QFT and CXR. QFT negative in borderline zone 0.20-0.34 IU/ml. CXR normal.
- Action taken?

The immune response and *M tuberculosis*



Cellmediated immunity
Viral infections
Intracellular bacteria

Humoral immunity
Extracellular bacteria
Helminth infections

Pathogenesis

- Immune response mounted by the host primarily through the macrophage and lymphocyte cell lines

vigorous cellular activation involving cell-mediated immunity and tissue hypersensitivity mechanisms

Granuloma formation, solid tubercle
Bacterial proliferation halted
Primary lesion and metastic foci involute= **latency (85-90%)**

Resolution of infection in ? %

Positive immune reactive test (3-8-10 weeks)

Insufficient immune response

Primary progressive pulmonary or extrapulmonary disease

Endogenous reactivation (post-primary tuberculosis)

10-15% with immuncompetence
5-10% within 2-(5) yrs
5% later

Exogenous reinfection

Specific infections with TNF alfa blockers (infliximab, adalumimab, etanercept)

- Increased risk of serious infections (life-threatening or requiring admission or hospital care)
- In particular risk for intracellular or opportunistic infections such as tuberculosis, Legionella, Listeria, Salmonella, herpes, Pneumocystis jiroveci
- In endemic areas (e.g. USA) also increased risk for certain fungal infections (Histoplasma, Coccidiodes immitis)
- Risk for less serious infections (eg UTI, URI) not well studied

Specific infections with TNF alfa blockers

- In meta-analysis significantly increased risk of mycobacterial and viral infections (hepatitis B activation, HSV, CMV, EBV)

- If TB often early onset (within 6 months) after initiation of TNF alfablockers and increased proportion of extrapulmonary or disseminated TB

Salliot et al ARD, BMJ 2008

Kourbeti et al CID 2014;58(12):1649-57

Are patients with RA still at an increased risk of tuberculosis and what is the role of biological treatments? (Ann Rheum Dis. 2015;74(6):1212-7)

Elizabeth Arkema, ScD
Jerker Jonsson, MD
Eva Baecklund, MD, PhD
Judith Bruchfeld, MD, PhD
Nils Feltelius, MD, PhD
Johan Askling, MD, PhD
on behalf of the ARTIS Study Group

Karolinska Institute
Swedish Institute for Infectious Disease Control
Medical Products Agency
Uppsala University

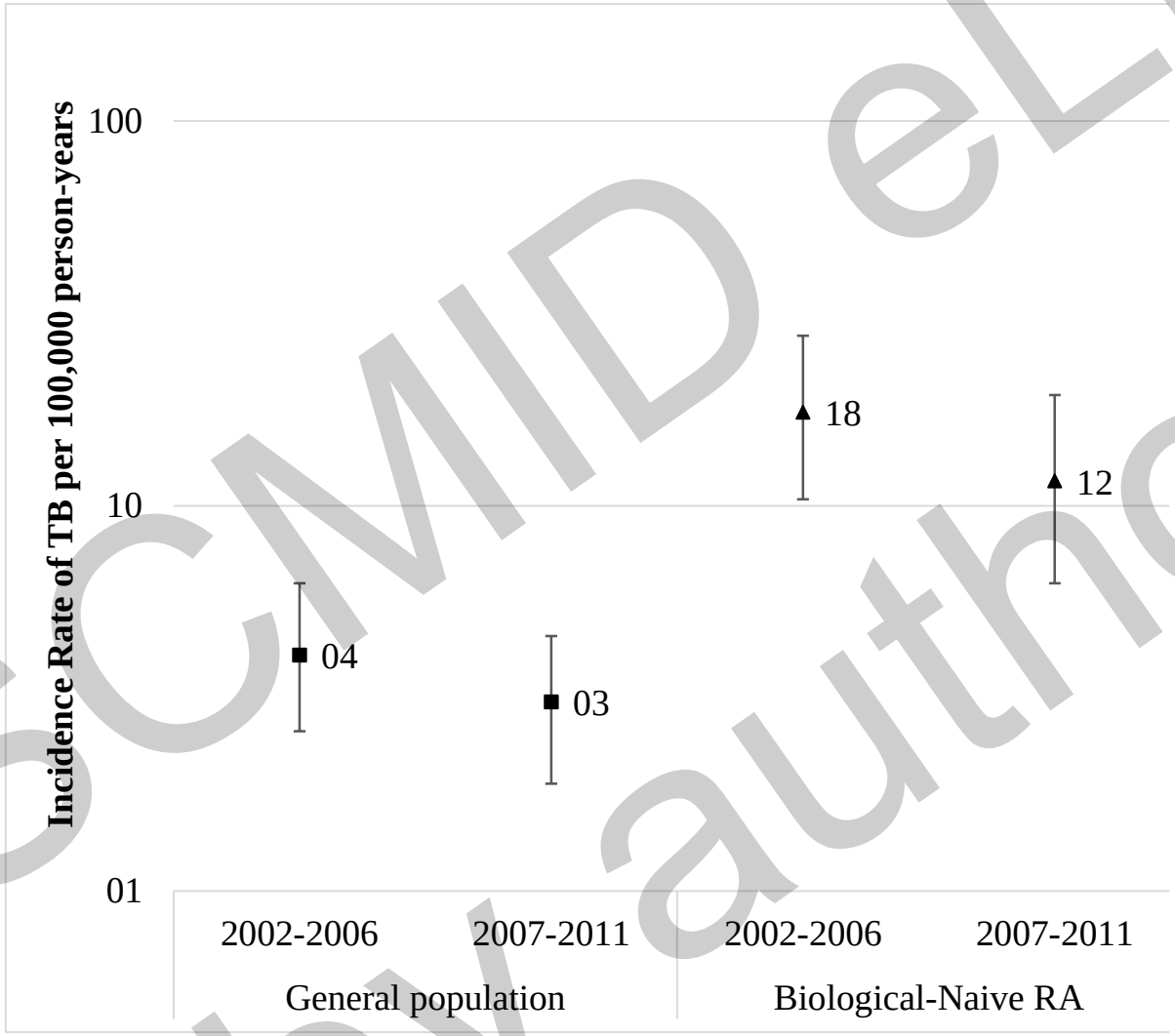
Objectives

1. To estimate the risk of TB in patients with RA compared to the general population

2. To estimate the risk of TB in patients who were exposed to biological therapy in an era of introducing TB screening 2002-2011

3. To compare the risks between biological exposures

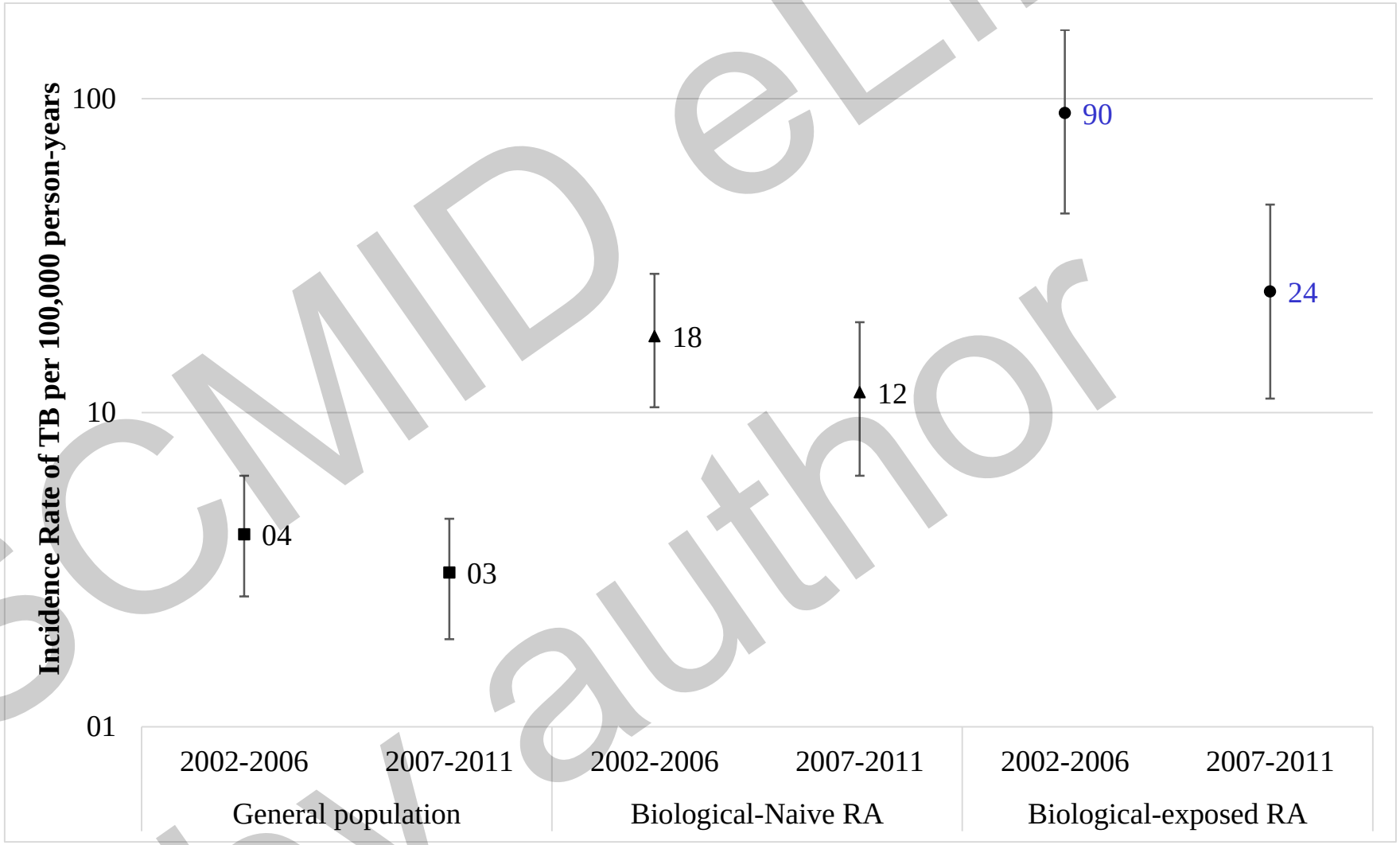
Incidence rates of TB in the general population and biological-naive RA population by calendar period



2002-2006
HR = 4.3 (95%CI 2.3, 8.2)

2007-2011
HR = 3.9 (95%CI 2.0, 7.8)

Incidence rates of TB in each population by calendar period



Hazard Ratio of Tuberculosis

Biological-exposed compared to biological-naive RA

	Biological-naive RA		Biological-exposed RA		
	No. of TB cases	**Person-years**	**No. of TB cases**	**Person-years**	**Hazard Ratio (95% CI)**
Overall	32	223,661	18	48,228	**4.4 (2.3, 8.5)**
Follow-up time					
<5 y	22	151,929	17	37,948	**7.8 (3.7, 16.4)**
≥5 y	10	71,754	1	10,280	**1.2 (0.2, 6.2)**
Calendar period					
2002-2006	18	102,845	10	11,126	**8.0 (3.4, 18.9)**
2007-2011	14	120,816	8	37,102	**2.4 (0.9, 6.2)**

Hazard Ratio and 95% confidence interval (CI) estimated from Cox proportional hazard models using calendar time as the time scale comparing biological-exposed to biological-naïve adjusted for age, sex, country of origin, education, history of COPD, diabetes and cancer. Exposed person time defined as starting at 1st exposure to biological until first of death, emigration, tuberculosis or December 31, 2011.

Screening details in biological-exposed TB cases

	Number (%) Total = 18
Screening	
Complete	3 (17%)
Only chest x-ray	4 (22%)
No data	7 (39%)
Not done	4 (22%)
Risk factor (> 1 possible)	
Born before 1950	13 (72%)
Family history of TB	4 (22%)
Work-related risk	3 (17%)
Born in a high incidence country	1 (6%)
Born in a non-Nordic country	5 (28%)

Hazard Ratios of TB

Individual biologicals compared to etanercept

	TB Cases	Person-years	Crude IR (95%CI) per 100,000 py	Hazard Ratio (95%CI)
Etanercept	2	16,778	11.9 (1.4 to 43.1)	**1.0 (ref)**
Infliximab	5	9,889	50.6 (16.4, 118.0)	**2.4 (0.4, 13.7)**
Adalimumab	6	9,635	62.3 (22.9, 135.5)	**4.7 (1.0, 23.5)**
Golimumab	0	243	0 (0, 1232.8)	-
Certolizumab Pegol	0	204	0 (0, 1468.5)	-
Rituximab	1	3,204	31.2 (0.8, 173.9)	**1.4 (0.1, 21.0)**
Abatacept	0	789	0 (0, 379.7)	-
Tocilizumab	0	582	0 (0, 514.7)	-
Anakinra	0	376	0 (0, 796.7))	-

Conclusions

- Biological-naive RA population had a 4-fold increased risk of TB compared to the general population
- Biological-exposed RA patients have a 4.4-fold increased risk of TB compared to biological-naive RA
- Risk has decreased since 2002 but increased awareness and screening has not completely removed this risk
- Of the main anti-TNFs, etanercept-exposure was associated with the lowest risk.
- Many cases of TB in RA also occurred in biological-naive patients, underscoring the need to be vigilant about TB risk in biological-naive RA as well.

Specific infections: abatacept (Orencia)

- Modulates CD80/CD86 mediated CD28 co-stimulating signal which is required for full T-cell activation and reduces antigen specific TNF alfa, interferon gamma and IL2 production

- Serious infections such as sinusitis, pneumonia and soft tissue infections have been reported but not significantly more compared to placebo. No herpes and pneumocystis infections reported.

- No increased frequency of TB in clinical placebo-controlled studies comparing abatacept with infliximab or in post-marketing súrveillance

  ATTEST study, Schiff et al. ARD/BMJ 2007 and in meta-analysis by Salliot et al, ARD/BMJ 2008

Specific infections: rituximab (Mabthera)

- B-cell depletion by anti-CD20 monoclonal antibody
- Meta-analysis does not show increased risk for serious infections compared to placebo (Salliot et al ARD/BMJ 2008)
- Reported infections in rituximab group consisted of bronchopneumonia, septic arthritis, pyelonephritis, gastroenteritis, epiglottitis, cellulitis and acute hepatitis B.
- No increased risk for active TB.
- Pneumocystis pneumonia reported in several publications, linked to concomitant steroid and chemotherapy

Specific infections: ustekinumab (Stelara)

- Human monoclonal antibody binding to the shared p40 subunit of IL 12 and 23 thus blocking signaling to the respective receptors.
- Genetic defect of IL12/IL23 P40 genes or the IL12 receptor linked to immune deficiency and disseminated forms of environmental mycobacterioses, salmonellosis and BCG infections.
- Controlled phase 2 and phase 3 studies (PHOENIX 1 and 2, ACCEPT) in TB low endemic countries with 3 year follow-up showed no increased risk of severe infections compared to placebo.
- All participants were screened for LTBI and treated if positive prior to administration of study drug.
- One patient in PHOENIX 1 study developed a disseminated herpes zoster infection.

Specific infections: ustekinumab (Stelara)

- Active TB described in 65 year old man from Taiwan after 2 doses of ustekinumab in clinical trial in Taiwan and Korea.

- CXR showed fibronodular apical infiltration. TST and Quantiferon negative. Did not receive treatment for LTBI prior to treatment with Stelara.

- Referenser: Papp K et al, Lancet 2008;271:1675-1684
  Leonardo C et al, Lancet 2008; 371: 1665-1674
  Griffiths CEM et al, NEJM 2010;362(2):118-128

TB risk with other immunomodulating treatment

- Interleukin-6 inhibitor (Roactemra) and apremilast (Otezla)- no increased TB risk described.

- Steroids- increased TB risk with doses of ≥15 mg prednisolon daily for more than a month

- Metotrexate and azathioprin (Imurel) at doses given in systemic diseases show no increased TB risk

Crowley et al J Am Acad Derm 2017

Kavanaugh et al BMJ 2014

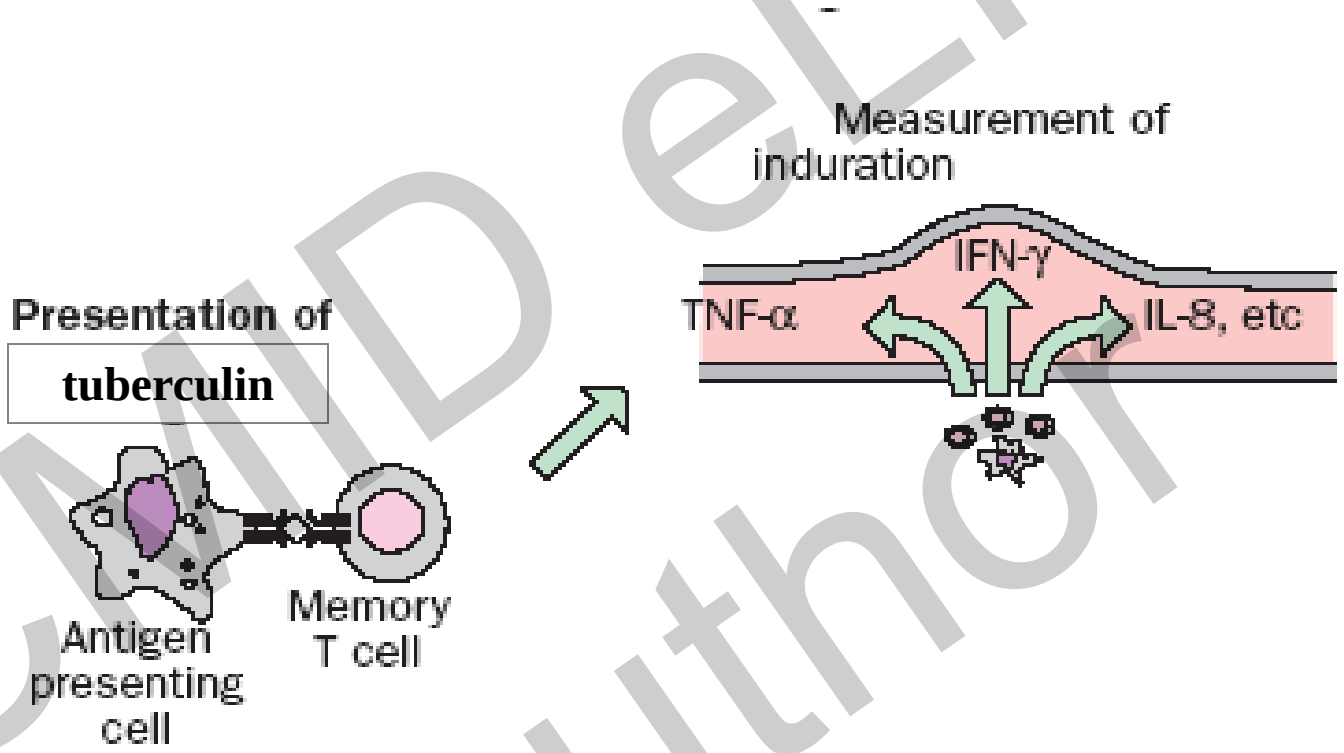
Diagnosis of active and latent TB

- Active TB-go for the bug!

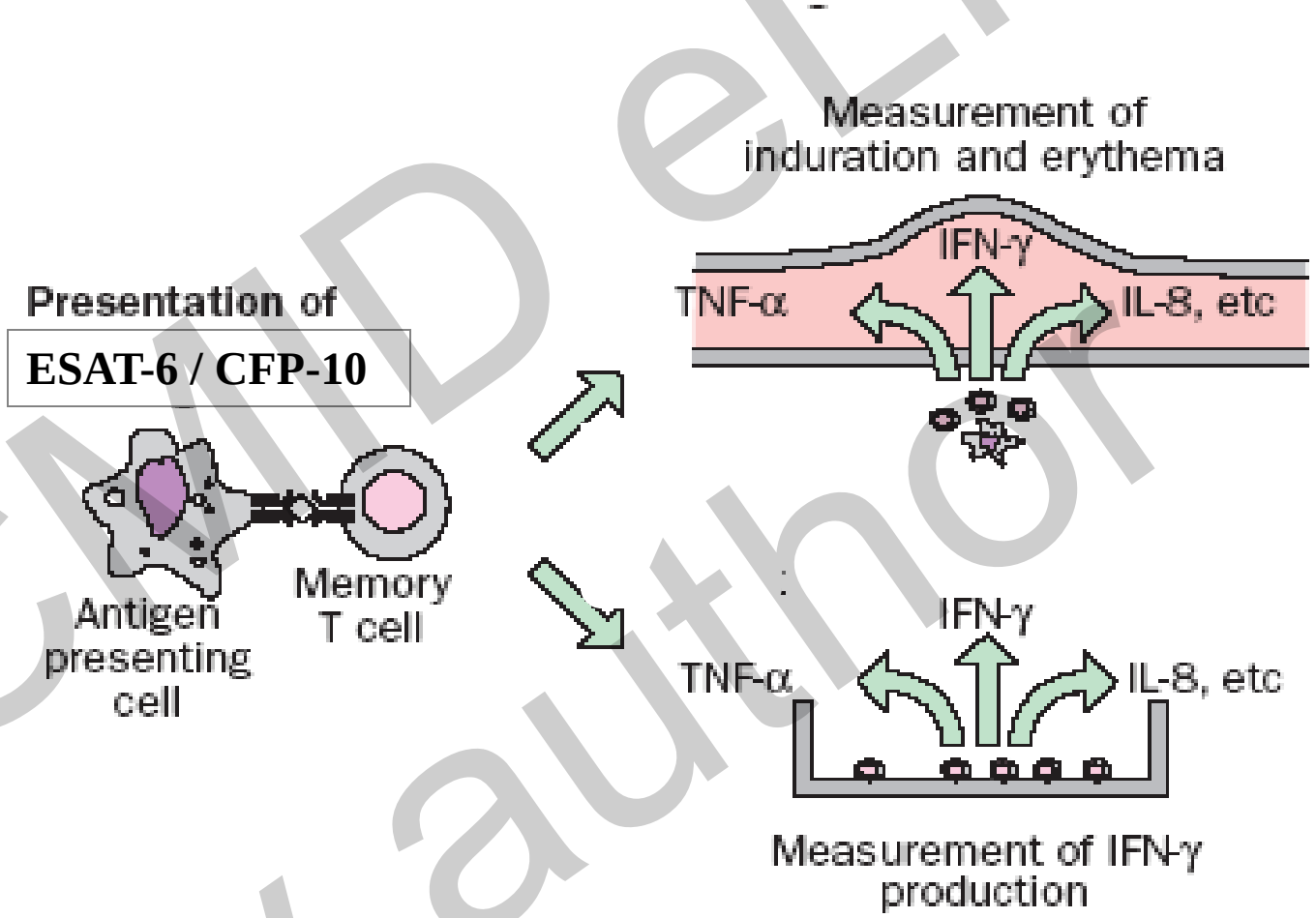
- Latent TB - lack of golden standard.

Therefore combined assessment of thorough patient history (epidemiology), immune-reactive testing (TST and IGRAs) and CXR.

Tuberculin skin test (PPD) for TB reactivity



Laboratory tests for TB-reactivity



IGRA = Interferon-Gamma Release Assay

Two commercially available tests:

Quantiferon TB Plus
ELISA-test Qiagen

T-SPOT.TB
Elispot-test Oxford Immunotec, Oxford

Tuberculin antigens present in

Tuberculosis complex

M *tuberculosis*
M *africanum*
M *bovis*

BCG vaccine-strains

M *bovis* danish substrain
M *bovis* glaxo substrain
M *bovis* gothenburg substrain
M *bovis* montreal substrain
M *bovis* moreau substrain
M *bovis* pasteur substrain
M *bovis* tice substrain
M *bovis* tokyo substrain

Enviromental strains (NTM)

M *abcessus*
M *avium*
M *branderi*
M *celatum*
M *chelonae*
M *fortuitum*
M *gordonii*
M *intracellulare*
M *malmoense*
M *oenavense*
M *scrofulaceum*
M *smegmatis*
M *terrae*
M *vaccae*
M *xenopi*
M *kansasii*
M *marinum*
M *szulgai*

Tuberculin

ESAT-6 and CFP-10 antigens present in

Tuberculosis complex

M *tuberculosis*
M *africanum*
M *bovis*

BCG vaccine-strains

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ESAT-6
CFP-10

Tests for TB immune reactivity

As TST a positive IGRA indicates that an immune response to TB antigens is present, but can not

1. indicate if a true infection with *M. tuberculosis* is present
2. if this infection is recent or remote (of importance for risk of activation in immunocompetence).
3. can not differentiate between active disease or LTBI
4. sensitivity of immune-reactive tests for diagnosis of LTBI unknown

Advantage IGRA vs TST: absence of reactivity in positive control indicates failure to respond immunologically

TB screening principles prior to biologics

- Prior to treatment all patients should be investigated with regard to active and latent TB
- History: Epidemiology regarding risk of TB-exposure and previous TB disease (standardized questionnaire)
- Clinical examination: TB-suspected findings?
- TST (>= 5 mm in the US, 10 mm according to European guidelines if BCG vaccinated, ≥6 mm in HIV infection). IGRAs.
- CXR with specific questions regarding TB suspected changes (preferably 3 months prior to screening)

Performance of immune-reactive tests in immunosuppression

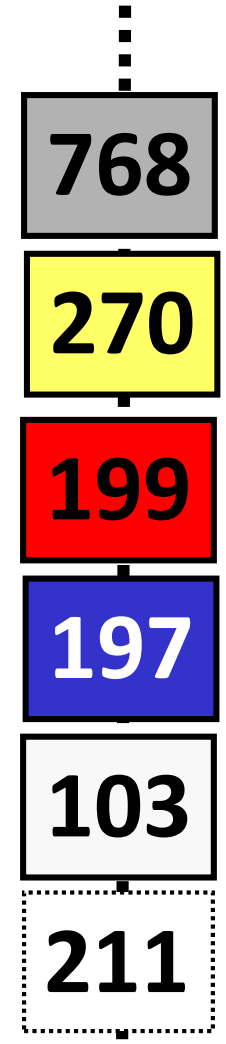
- European multicenter study (TB-NET) where TST and both IGRAs were compared head to head in patients with various immunosuppressive conditions.

- Test results were correlated to clinical data
  - TB risk factors
  - Level of immunosuppression

Sester, M., van Leth, F., Bruchfeld, J., Bumbacea, D., Cirillo, D.M., Gorek Dilektasli et al, **Risk assessment of tuberculosis in immunocompromized patients - A TBNET study.** *Am J Respir Crit Care Med* 2014;

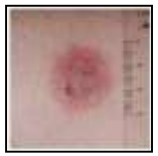
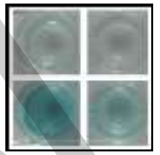
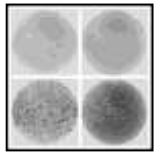
Patients

- HIV infection
  - high/low CD4 counts
- End-stage renal disease
- Rheumatoid arthritis
- Solid organ transplantation
  - kidney, kidney-pancreas, lung, liver
- Stem cell transplantation
- Immunocompetent low-risk controls



17 centers from 11 countries

Association with TB exposure

	OR	95% CI	OR	95% CI	OR	95% CI
HIV moderate	1.8	0.7-4.4	1.6	0.9-3.1	2.0	1.2-3.4
CRF none	1.2	0.6-2.6	1.2	0.6-2.4	1.5	0.7-2.9
RA strong	2.7	1.4-5.1	4.4	2.1-9.4	4.9	2.4-10.2
SOT moderate	1.6	0.4-6.8	2.2	1.0-4.6	1.6	0.4-6.7
SCT none	n.a.	n.a.	1.4	0.2-8.8	0.9	0.1-8.0

Active TB cases on follow-up

Median onset 21.4 months

	TST (mm)	ELISPOT (SFC)	ELISA (U/ml)	chemoprevention		HIV CDC	HAART	HIV load	CD4 T cells/µl
				offered	done				
HIV	positive (20)	positive (18)	positive (2.7)	no	no	C2	no	25285	492
HIV	positive (12)	positive (16)	positive (0.39)	no	no	C3	yes	83176	245
HIV	positive (5)	positive (125)	negative (0.15)	yes	no	A3	no	38700	22
HIV	negative (0)	negative (0)	negative (0)	no	no	A2	no	15900	371
HIV	negative (0)	negative (1)	indeterminate (0.13)	yes	no	C3	yes	120000	50
HIV	negative (0)	negative (4)	indeterminate (0)	yes	no	A1	no	38200	333
SOT	negative (0)	negative (0)	indeterminate (0)	no	no	n.a.	n.a.	n.a.	unknown
HIV	negative (0)	negative (1)	negative (0.09)	no	no	A2	no	<50	369
HIV	negative (0)	negative (0)	negative (0.12)	no	no	C3	yes	60	271
HIV	positive (10)	indeterminate (49)*	positive (0.7)	no	no	A2	no	10071	263
HIV	negative (0)	positive (9)	negative (0.09)	no	no	A3	yes	90	354

Immune-reactive testing recommendations in Sweden

- If history of previous active or latent TB no indication for immunologic testing. Evaluate if previous TB treatment is sufficient.

- In remaining cases, TST initially and IGRA if negative TST at reading to optimize sensitivity.

- TST and IGRA can be taken simultaneously if deemed more practical.

- Difficulties in interpretation of IGRAs: conversion/reversion over time, borderline zone with suspicion of non-specificity identified (0.20-0.7/99 IU/ml, cutoff 0.35 IU/ml)

Jonsson J, Westman A, **Bruchfeld J**, Sturegård E, Gaines H, Schön T. A borderline range for Quantiferon Gold In-Tube test results. PLoS One. 2017 Nov 2;12(11):e0187313. doi: 10.1371/journal.pone.0187313. eCollection 201.

Interpretation of immune-reactive testing

- Important to consider that neither negative TST nor IGRA excludes LTBI. **Test results must always be interpreted together with patient history, clinical and laboratory data**.

- Screening and treatment of LTBI should be performed by physician/unit with TB experience or by TB specialist

- Non-specialized centers should refer to TB specialist if
  - suspicion of active TB
  - borderline TST (6–9 mm) and negative IGRA without TB risk factors,
  - TB epidemiology difficult to assess previously
  - treated or untreated active or latent TB

Treatment of LTBI

- A generous attitude towards treatment of LTBI should be the rule. Better to be safe than sorry!

- Drug of choice: isoniazid (INH) 9 months with vitamin B6 (pyridoxin) substitution or rifampicin 4 months if intolerance to INH. Other alternatives RPT/INH 12 weeks, FQ 6 months.

- If radiologic changes and/ or history of previous TB/inadequate previous TB treatment individual assessment and investigation.

- Liver values at least once a month during treatment. Hepatotoxicity more common > 35 years but excellent adherence (Kan B, Kalin M, Wedren S, **Bruchfeld J**, Completing treatment of latent tuberculosis: patient´s background matters Int J Tuberc Lung Dis. 2013; 17:597-602).

- Treatment with biologics usually initiated one month after initiation of LTBI treatment. If urgent given simultaneously.

Strategy if active TB during anti-TNF

- Discontinuation of anti-TNF until stable TB situation, usually at least after 2 months intensive phase TB treatment, drug sensitive *Mtb* strain and clinical response

Case

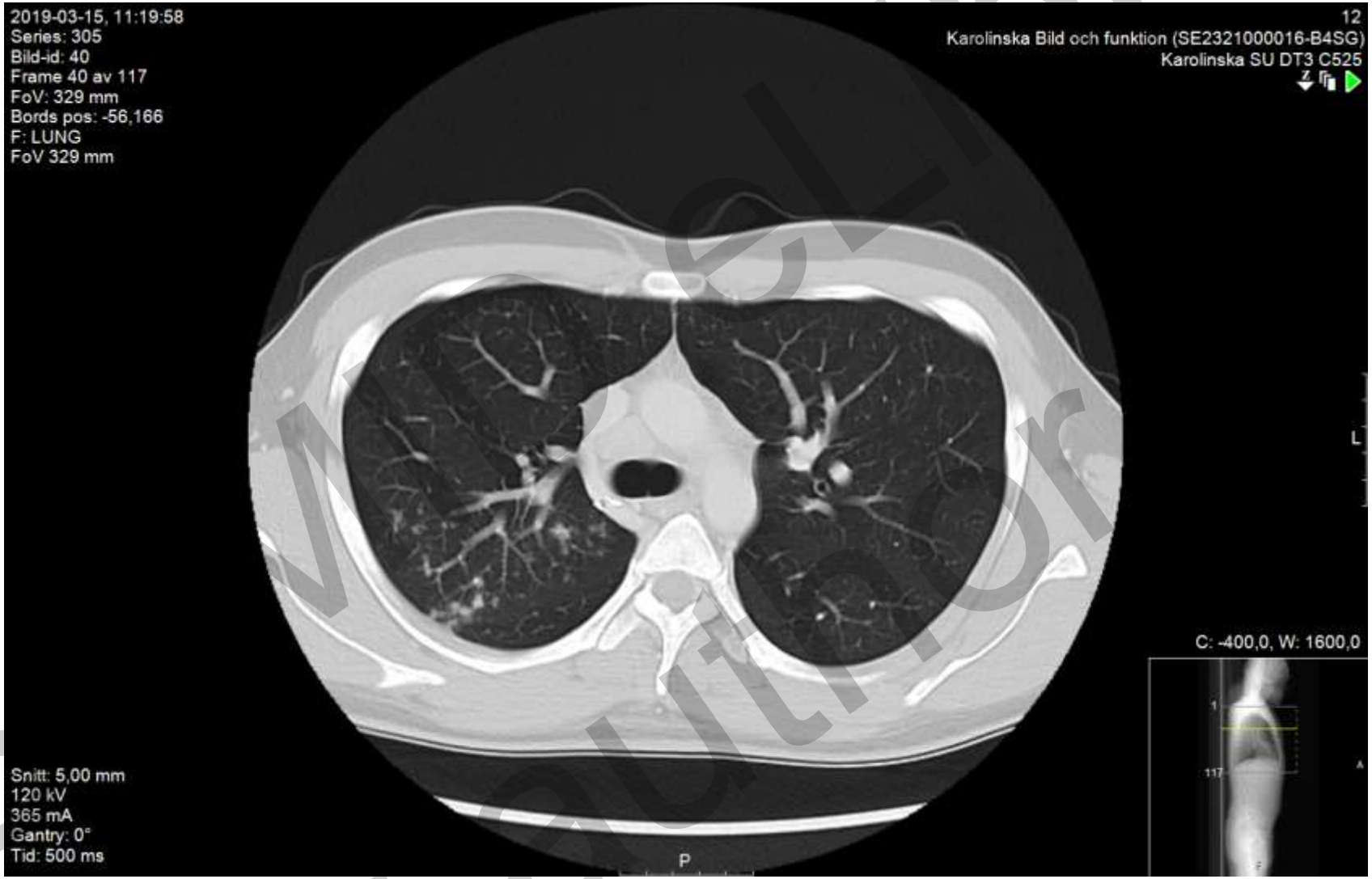
- 27 year old male patient with ankylosing spondylitis. Candidate for biologic RX.
- Adalumimab (Humira) planned.
- Screening prior to treatment with QFT and CXR October 2018. QFT negative but in borderline zone (0.2-0.34). CXR negative.
- Additional information? Screening complete?

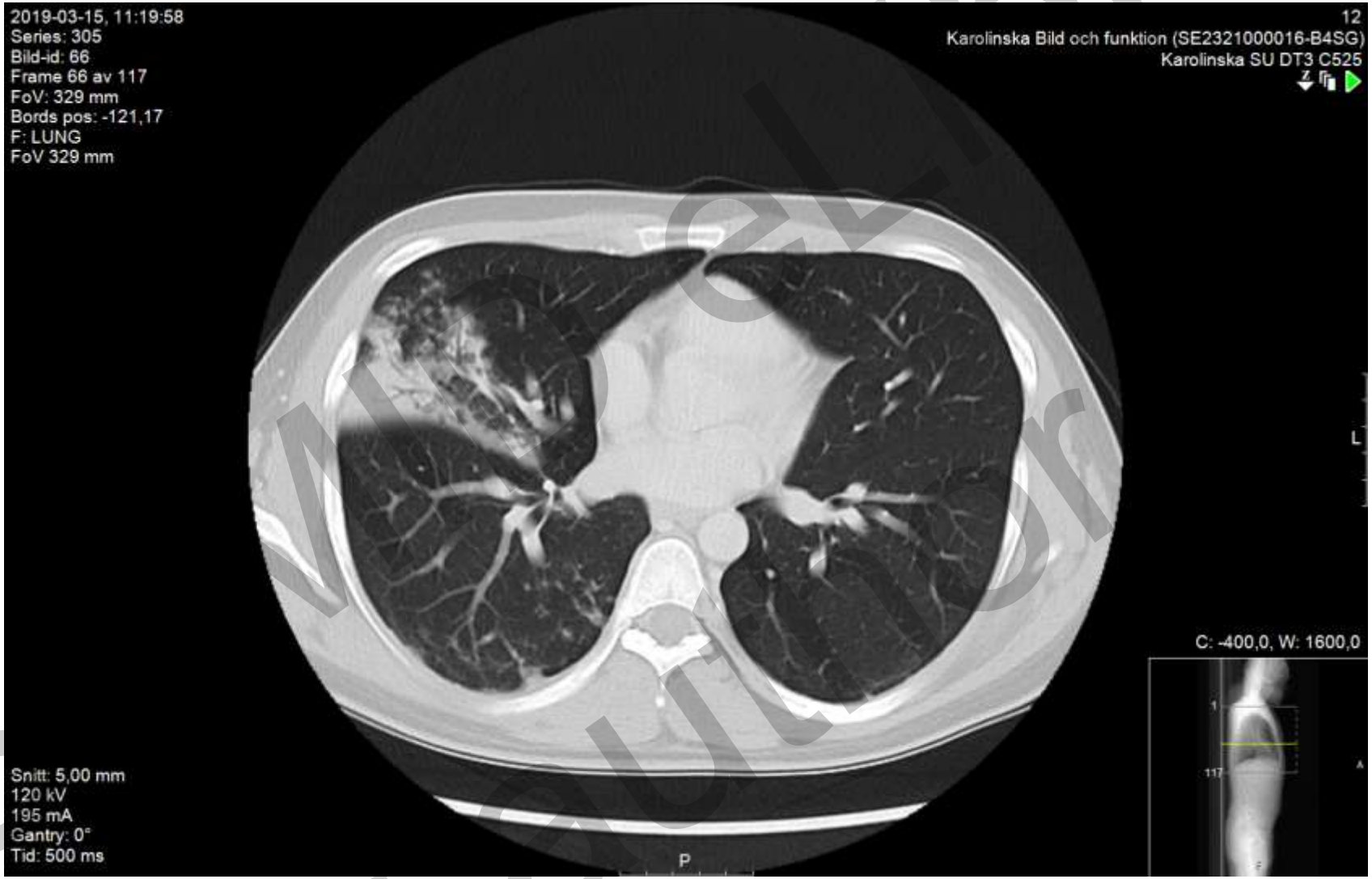
Case

- Immigrated from India 2017. Not TB screened upon arrival.
- Started on Humira Oct 2018.
- Humira monitoring visit Febr 6 at Reumatology dept, reports fever 39-40 C° since 2 weeks, night sweats, weight loss 5 kg. No cough.
- CXR negative. Referred to TB centre for new TB screening.
- TST 20 mm, QFT positive >1 IU/ml TB ag 1 and 2.
- Continued fever, weight loss 10 kg. ESR 82 mm compared to 32 mm before Humira. CT thorax/abdomen shows intrathoracic and neck lymphadenopathy.

Case

- Admitted for investigation.
- Bronchoscopy and transbronchial biopsy of enlarged lymphnode. Histopathological report not conclusive. Microscopy and PCR neg for Mtb complex. Dismissed with follow-up at the OPD TB centre. ESR 109 mm. Anemia. Trombocytosis.
- At follow-up patient reports productive cough which started after bronchoscopy. Continued spiking fever in the afternoon/evenings and night sweats.
- New CT performed, readmitted. ESR 117. CRP 50. Hb 114.

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Case

- Sputum x 3 negative in microscopy and PCR. Planned for new bronchoscopy. Meanwhile TB laboratory reports growth of Mtb complex in lymphnode material.
- Drug sensitive strain to PZA, RIF, INH and EMB.
- Started on standard treatment.
- What could have been done differently?

Thank you!

- de Vries M, Arkema EV, Jonsson J, **Bruchfeld J,** Jacobsson LTH, Askling J on behalf of the ARTIS Study Group. Tuberculosis risk in ankylosing spondylitis, other spondyloarthritis and psoriatic arthritis in Sweden**.** Arthritis Care Res (Hoboken). 2017 Dec 1. doi: 10.1002/acr.2348

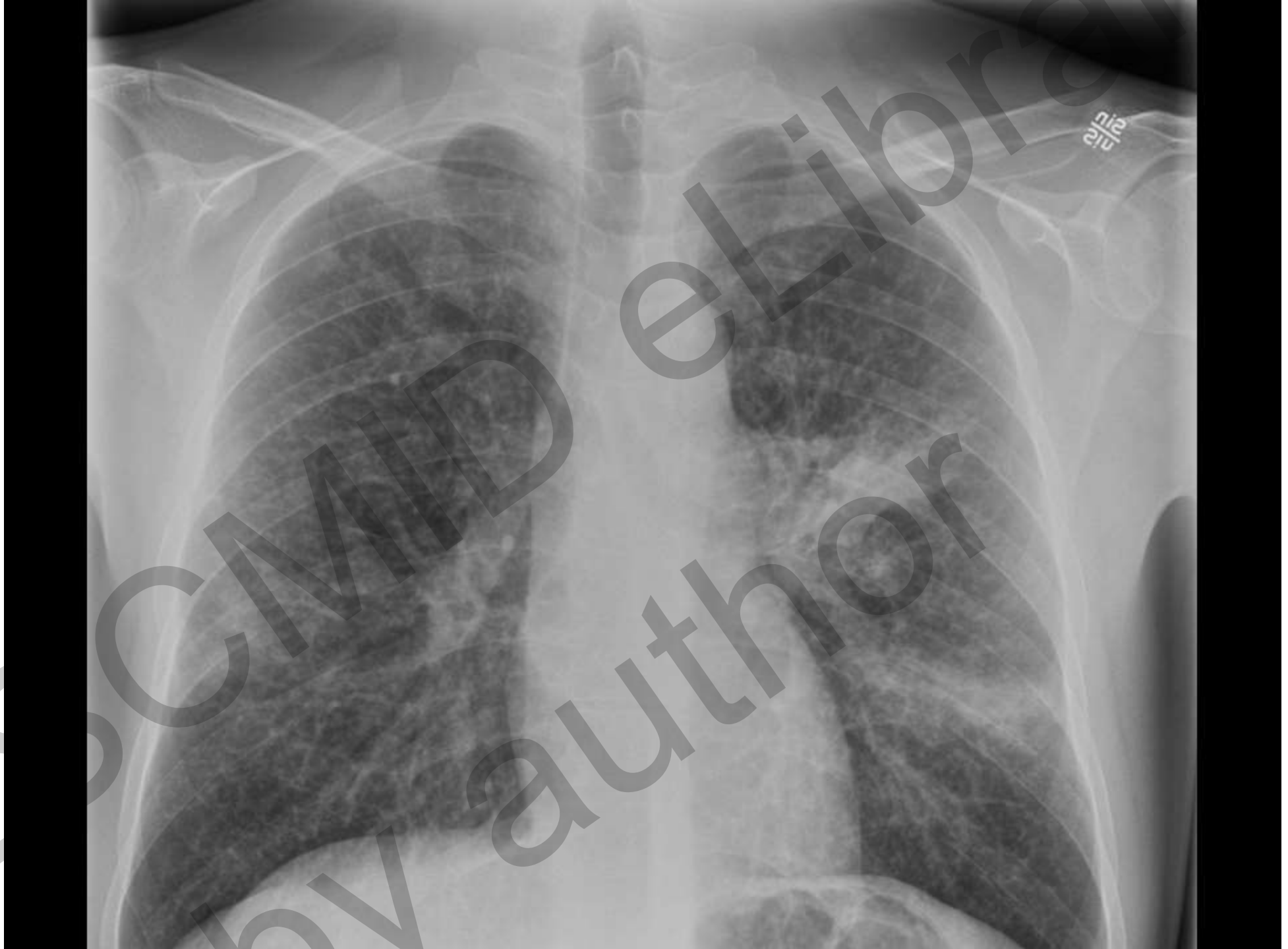
Case

- 41-year old male with well controlled Mb Crohn, on medication with Remicade and Pentasa. Married, 2 childern born 2009 and 2011.

- Referred from GP 150330 due to fever and cough since Christmas. In Januari CXR showed left perihilar infiltrate.

- Treated with PcV x 2 without improvement, therafter, Doxycyklin x 2 and somewhat better but since beginning of March worsening of cough and high fever. Night sweats sicne a longer time priod. Probably no weight loss.

- CXR March 2015 shows progression.



Case

- Additional information?

Case

- No travels to TB endemic countries. No risk occupation. No previous TB exposure. No prior BCG vaccination.

- TB screening prior to Remicade negative regarding TST/ IGRA/ CXR

- Further investigation?

Case

- Sputum x 3 for *Mtb* negative in microscopy and PCR.
- Bronchoscopy 150401.
- Started on standard TB treatment.
- PCR positive for *Mtb* in bronchial secretion, later growth of DS strain.
- Way of transmission?

Case

- Patient firmly denies risk factors for TB exposure.
- On a direct question for TB nurse ”have you met somebody with chronic cough who comes form countries where TB is common?”
- the patient answers that their cleaning lady, a woman from Mongolia who cleans the house every second week has been coughing for at least 6 months. Mostly when the family is not at home but the patient has met the cleaning lady twice.
- ”28/1 vi urged X to seek hospital care and then we never saw her again”
- X admitted 28/1 at the Clinic of Infectious Diseases and diagnosed with smear-positive TB, DS Mtb.