

Anti-TNF α and tuberculosis

A rheumatologist point of view



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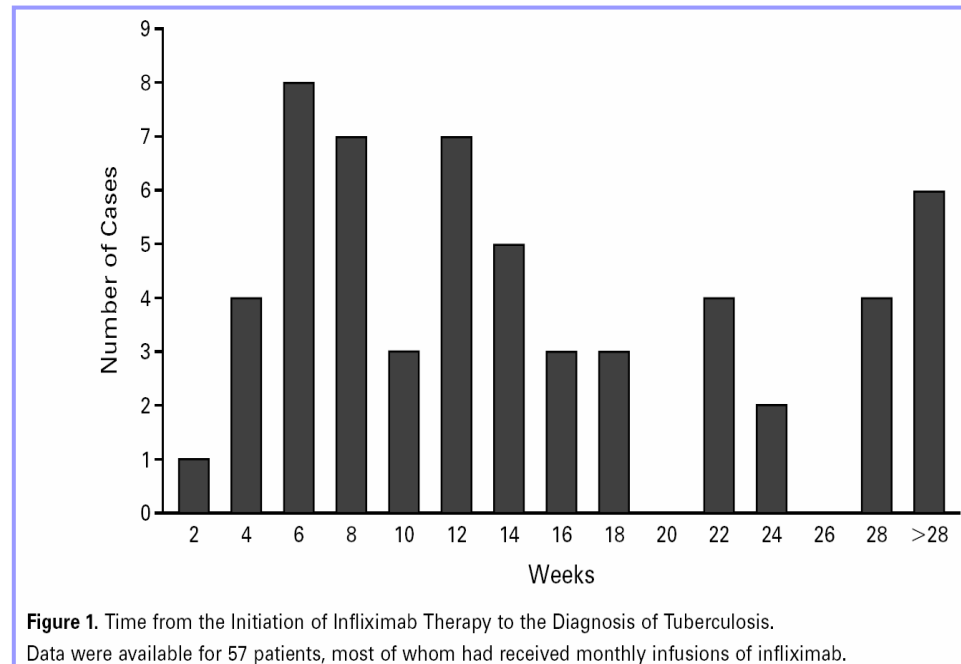
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Risk of active tuberculosis

Anti-TNF therapy has been linked to an increase risk of active tuberculosis

- ◆ 13 cases during 4870 patient years of clinical trials with Adalimumab, 8 occurring phase I and II with higher doses, 5 occurred during Phase III



Risk of active tuberculosis

A small but definite risk, higher than in background population

◆ Post-Approval

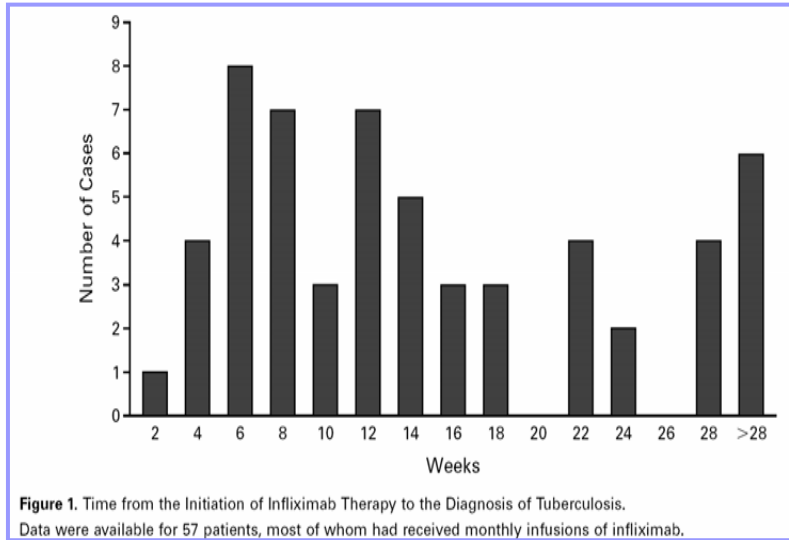
- ❖ 295 cases of Infliximab associated tuberculosis reported to FDA (8/02) for an estimated rate of 37cases/100,000 US and 150 cases/100,000 EU
 - ❖ background rate of tuberculosis in RA patients 6.2 cases/100,000 US and 20 cases/100,000 EU
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Risk of active tuberculosis

Relatively short delay between start of treatment and disease diagnosis

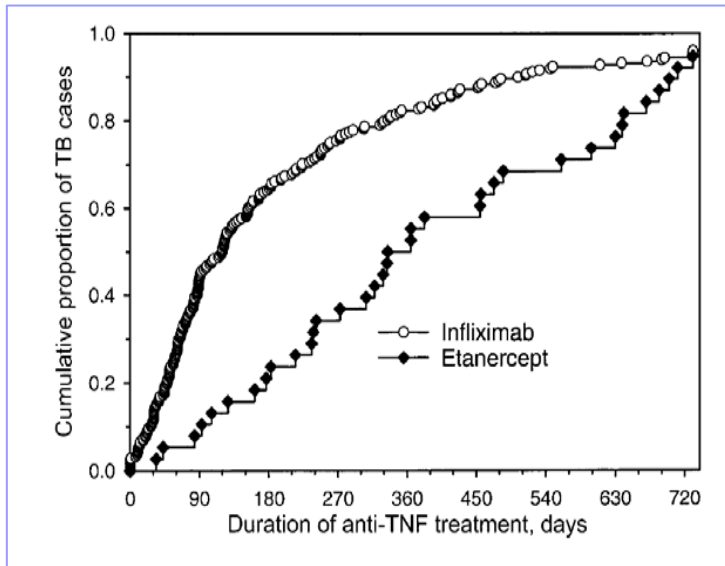
Most cases appear to be reactivation of latent tuberculosis

- ◆ Median Rx duration 12 wks with infliximab
- ◆ 91% of cases occurred low incidence countries - both suggest reactivation



Risk of active tuberculosis

Risk appears to vary with the agent used, but described and present with all agents



- ◆ No cases of tuberculosis in etanercept clinical trials. (N=3280 US and EU)
- ◆ 25 cases tuberculosis associated with etanercept reported to FDA MedWatch program as of 2002
- ◆ Median etanercept treatment duration 11.5 month

Table 1. Absolute numbers and rates of granulomatous infections per 100,000 among US patients treated with infliximab or etanercept, as reported to the Food and Drug Administration Adverse Event Reporting System, from January 1998 through September 2002.

Infection	Infliximab (n = 197,000)	Etanercept (n = 113,000)	RR	P
Aspergillosis	17 (8.63)	7 (6.19)	1.39	.243
Candidiasis	20 (10.15)	6 (5.31)	1.91	.061
Bartonellosis	1 (0.51)	0 (0)563
Coccidioidomycosis	11 (5.58)	1 (0.88)	6.31	.013
Cryptococcosis	10 (5.08)	8 (7.08)	0.72	.179
Histoplasmosis	37 (18.78)	3 (2.65)	7.07	<.0001
Legionellosis	1 (0.51)	0 (0)563
Leprosy	1 (0.51)	0 (0)563
Listeriosis	17 (8.63)	1 (0.88)	9.75	.0006
Nontuberculous mycobacterioses	22 (11.17)	7 (6.19)	1.80	.066
Nocardiosis	7 (3.55)	1 (0.88)	4.02	.090
Pneumocystosis	1 (0.51)	0 (0)563
Salmonellosis	0 (0)	2 (1.77)	0.00	.031
Toxoplasmosis	4 (2.03)	0 (0)101
Tuberculosis	106 (53.81)	32 (28.32)	1.90	<.0001
Total	255 (129.44)	68 (60.18)	2.15	<.0001

NOTE. Data are no. of infections (no. of infections/100,000 treated patients), except where noted. P values were determined by use of Poisson analysis. RR, risk ratio (infliximab:etanercept). Data are from Wallis et al. [11].

Risk of active tuberculosis

*More than 50% extrapulmonary
Concomitant immunosuppressives common*

- ◆ Infliximab: in a subgroup of 70, 56% extrapulmonary
- ◆ Etanercept: 52% extrapulmonary
- ◆ 79% concurrent immunosuppressives (corticosteroids alone or with MTX)

TABLE 2. CHARACTERISTICS OF 70 PATIENTS WITH TUBERCULOSIS AFTER INFLIXIMAB THERAPY.

CHARACTERISTIC	VALUE
Age — yr	
Range	18–83
25th percentile	39
Median	57
75th percentile	67
Indication — no. (%)	
Crohn's disease	18 (26)
Rheumatoid arthritis	47 (67)
Juvenile rheumatoid arthritis	2 (3)
Ankylosing spondylitis	2 (3)
Behçet's disease	1 (1)
Recent immunosuppressant use — no. (%)	55 (79)
Methotrexate alone	6 (9)
Methotrexate plus corticosteroids	28 (40)
Corticosteroids alone	14 (20)
Azathioprine plus corticosteroids	3 (4)
Other individual or combined immunosuppressants	4 (6)
Not reported	15 (21)
Interval between first dose and diagnosis — wk*	
Range	1–52
25th percentile	8
Median	12
75th percentile	22
No. of doses*	
Range	1–9
25th percentile	2
Median	3
75th percentile	3

Chemoprophylaxis for latent TB

Chemoprophylaxis treatment appears efficient at preventing active tuberculosis in this setting

Most “resistant” cases appear to be link to poor compliance with recommendations

Data from the national spanish registry (BIOBADASER)
Screening recommandations issued in March 2002 (5'198 patients with 15 cases of TB)
7x increased risk when recommendations were not followed

Table 1. Evolution of the incidence rate (IR) of active tuberculosis (ATB) per 100,000 patient-years in treatments started before and after the issue of the recommendations*

Treatment started	Patient-years	Cases	IR (95% CI)	IRR vs. general population (95% CI)†	IRR vs. RA not exposed to TNF blockers (95% CI)‡
Before March 2002	8,671	41	472 (384–642)	19 (11–32)	5.8 (2.5–15.4)
After March 2002-January 2006	8,717	15	172 (103–285)	7 (3–13)	2.4 (0.8–7.2)
100% compliance	4,546	2§	43 (11–175)	1.8 (0.28–7.1)	Undetermined¶
<100% compliance	4,170	13	311 (181–536)	13 (6–25)	4.8 (1.04–44.3)

The need for screening recommendations

The impossible "no risk" strategy

- ◆ All patients are ideally treated with chemoprophylactic treatment before any anti-TNF therapy. However,..
 - ❖ Chemoprophylaxis is not devoid of adverse effects
 - ❖ Chemoprophylaxis is cumbersome for patients (adherence)
 - ❖ Anti-TNF treatment is delayed for a least one month
 - ◆ Thus, chemoprophylaxis should be reserved to specific patient with a significant risk of developing anti-TNF induced active TB
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Chemoprophylaxis guidelines

Guidelines are intended to optimize the risk evaluation in the various populations

- ◆ Based on the evaluation of
 - ❖ Patient history of past TB or contage
 - ❖ Standard chest X-ray evaluation for signs of previous TB infection
 - ❖ Tuberculin skin-test
 - ❖ Country of birth and ethnic group

Table 1 National guidelines

LTBI screening and TNF blocker use national guidelines	Risk assessment, examination, and chest radiograph	TST	TST details	Positive TST	First-line LTBI treatment	Reference
UK	All patients	Patients on immunosuppressive therapy excluded	One step	5 mm in unvaccinated, 15 mm in vaccinated,	6 months INH	BTS [20]
USA	All patients (chest radiograph if TST positive)	All patients	One step	5 mm, ignore BCG	9 months INH	MMWR [21]
Spain	All patients	All patients	Two step	5 mm	9 months INH	Gómez-Reino <i>et al.</i> [22]
France	All patients	All patients	One step	10 mm	2 months RIF/PZA	Mariette and Salmon [23]
Ireland	All patients	All patients	One step	5 mm, ignore BCG	9 months INH	Kavanagh <i>et al.</i> [24]
Switzerland	All patients	IGRA recommended	IGRA preferred	TST not recommended	9 months INH	Beglinger <i>et al.</i> [25]

BCG, bacillus Calmette–Guérin; BTS, British Thoracic Society; IGRA, interferon gamma release assay; INH, isoniazid; LTBI, latent tuberculosis infection; MMWR, Morbidity and Mortality Weekly Report; PZA, pyrazinamide; RIF, rifampicin; TNF, tumor necrosis factor; TST, tuberculin skin test.

A rheumatologist point of view on guidelines

- ◆ stringency is increasing with time (IDR <5mm), increasing the number of patients to treat with chemoprophylaxis
 - ◆ sometimes disconnected from practice (assumption HIV or hepatitis patients will not be treated with anti-TNF as contraindicated according to the manufacturers)
 - ◆ not always easy to assess, in particular for the non-specialist and the number of patients make referral unpractical
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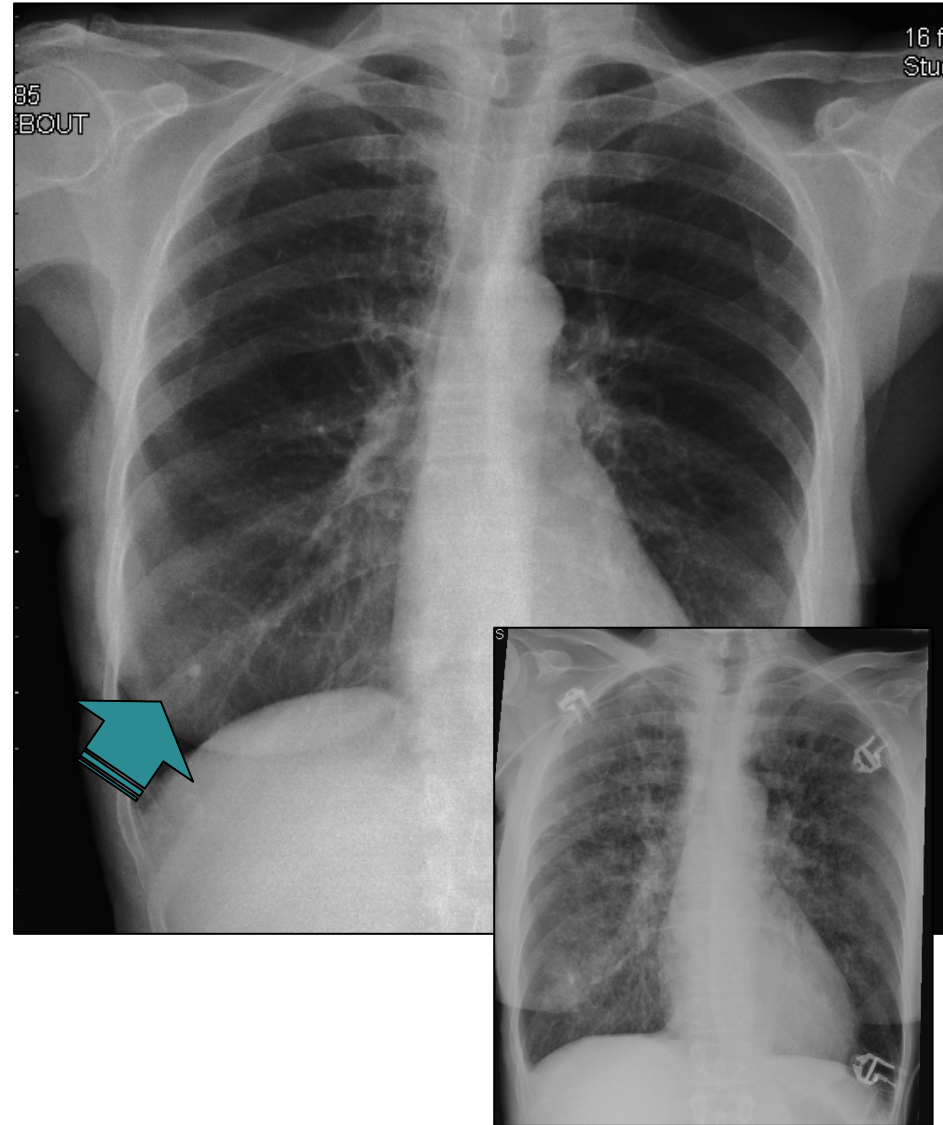
Guidelines limitations – some examples

◆ History:

- ❖ Difficult, in particular in the migrant
- ❖ What is a migrant from a risk point of view ?
- ❖ What is a « significant » contage ?

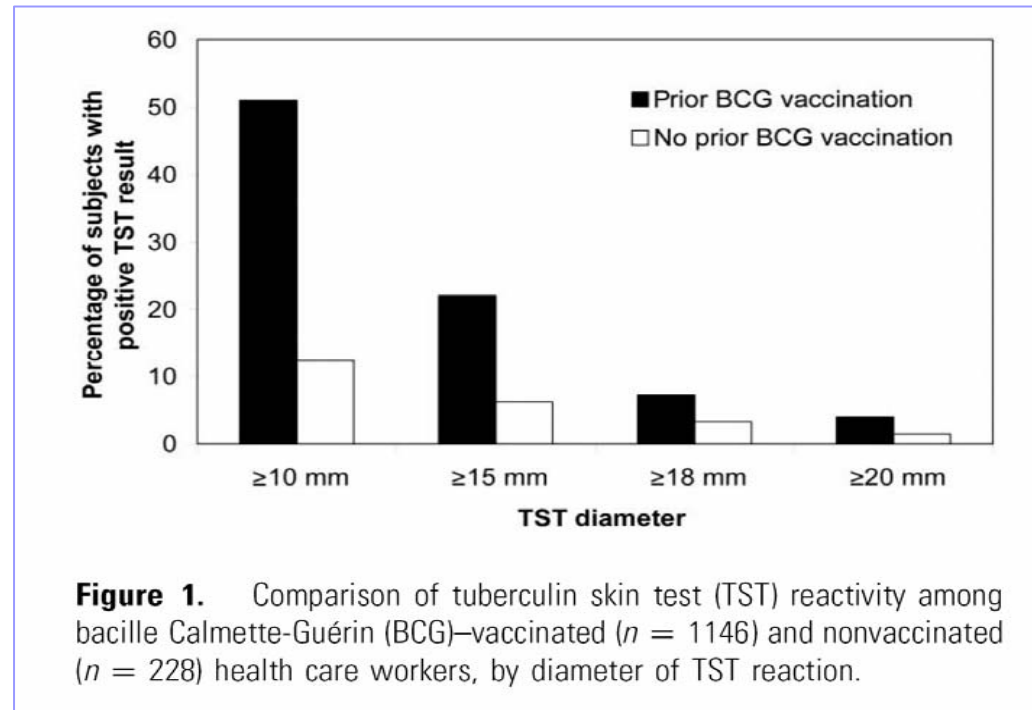
◆ Chest x-ray

- ❖ Quality of the x-ray
- ❖ Quality of the interpretation
- ❖ Specificity of the observed lesions



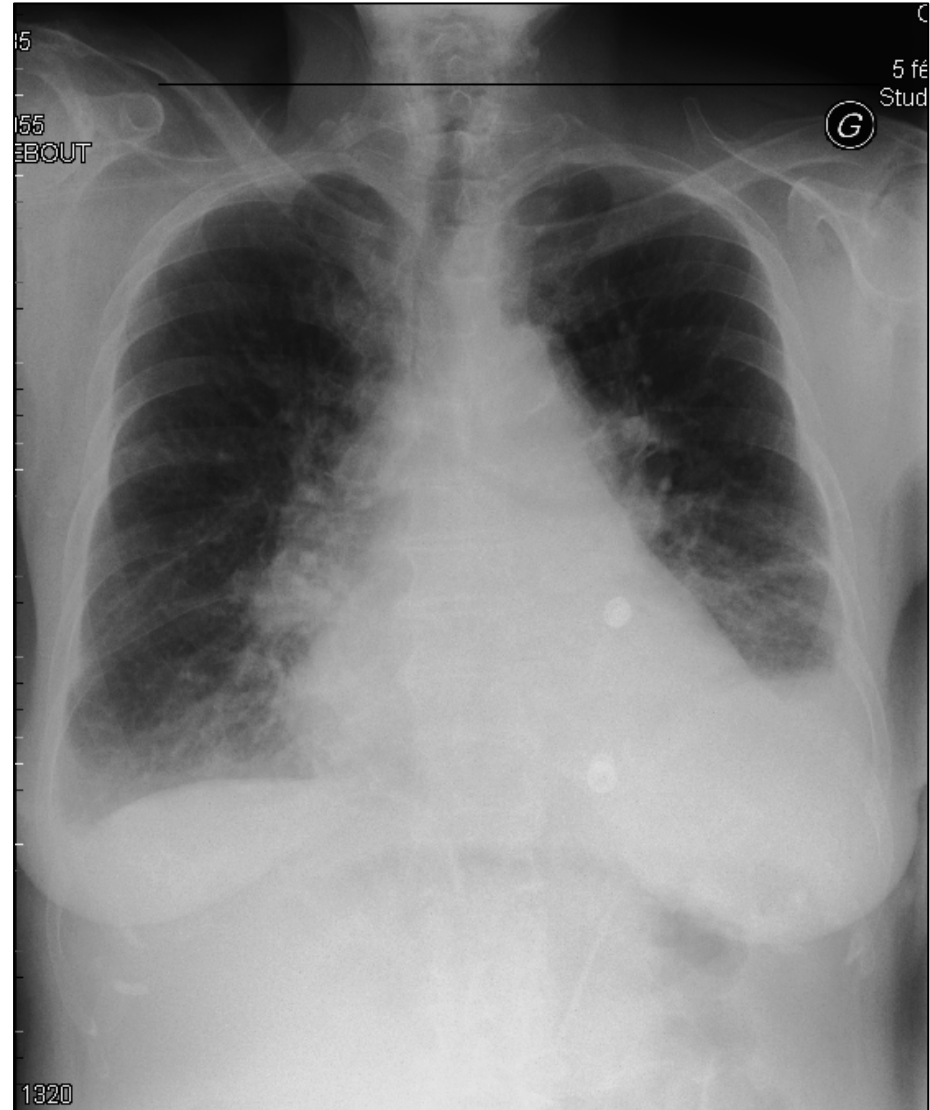
IDR – again the rheumatologist point of view

- ◆ 48 hours delay for read - out and 2 clinic visits
- ◆ Wide variation in interpretation
- ◆ Technically demanding (practical realization)
- ◆ Interpretation in patient previously immunized with BCG
- ◆ Interpretation in patient under immunosuppressive therapy



T-SPOT TB® PROJECT – the case alpha

- ◆ Mrs J, born in 1922
 - ❖ Severe RA, resistant to conventional DMARDs
 - ❖ Chronic corticotherapy
- ◆ Pulmonary tuberculosis and scrofula at age 16
- ◆ 2 years in a sanatorium (Leysin)
- ◆ Never ever received any specific treatment
- ◆ T-spot TB® negative



Practical experience in Lausanne - T-Spot TB®

◆ Hypothesis:

- ❖ T-Spot TB® or another IGRA test will adequately identify all patients at risk of tuberculosis reactivation under anti-TNF treatment
- ❖ T-Spot TB® will demonstrated better specificity than traditional guidelines resulting in a reduced use of chemoprophylaxis

◆ Methods:

- ❖ Single center, prospective observational study in a real-life setting (no exclusion criteria)
 - ❖ All candidate for anti-TNF therapy are assess
 - For traditional risks as recommended in guidelines (past history, tuberculin skin test, recent chest X-ray and country of provenance)
 - By T-Spot TB® (negative versus positive)
 - ❖ Chemoprophylaxis is prescribed only to patient with positive T-spot TB® regardless of traditional risk assessment
 - ❖ Patients are prospectively followed for signs and symptoms of tuberculosis, in particular all patients with positive traditional risk assessment and negative T-Spot TB®
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Population demographic

First 70 patients			
Diagnostics		Concomitant immunosuppressive therapy	
Rheumatoid arthritis	30 (43%)	none	27 (39%)
Ankylosing spondylitis	23 (33%)	corticosteroids	16 (23%)
Psoriatic arthritis	11 (16%)	methotrexate	23 (33%)
others	6 (8%)	others	21 (30%)
Age (average)	43 years	Sexe	39 female: 31 male

Phase I results - preliminary

Number of patients - 70			
Traditional risk factors		T-spot TB®	
Positive tuberculin skin test (>10mm)	18 (26%)	Positive	5 (7%)
Positive chest x-ray	5 (7%)	Needed to be repeated	2 (3%)
Positive history	8 (11%)	Undetermined	1 (1.4%)
other	10 (14%)		
<i>Prophylaxis required</i>	<i>25 (36%)</i>		<i>6 (8.5%)</i>
Comparaison of traditional versus T-Spot TB®			
Both evaluation positive			4
Traditional evaluation positive with negative T-Spot TB®			15 (skin only) / 25 (all)
Traditional evaluation negative with positive T-Spot TB®			1

Phase II – current practice

- ◆ We have applied this strategy since the first patient in all anti-TNF treated patients in our clinic since 200
 - ◆ Average of 5 to 10 new patients per months
 - ◆ 2 cases of TB reactivation
 - ❖ both were positive for both recommendation sets
 - ❖ Both had received chemoprophylaxis (9 and 6 months INH)
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Conclusions

- ◆ Within the limits of our observation, it appears that the use of an IGRAs is adequately efficient and non inferior to current recommendations to detect high risk patients for TB reactivation
 - ◆ It should replace any IDR evaluation which has too many false positive reactions, thus preventing the unnecessary use of chemoprophylaxis
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Thank you for your attention
