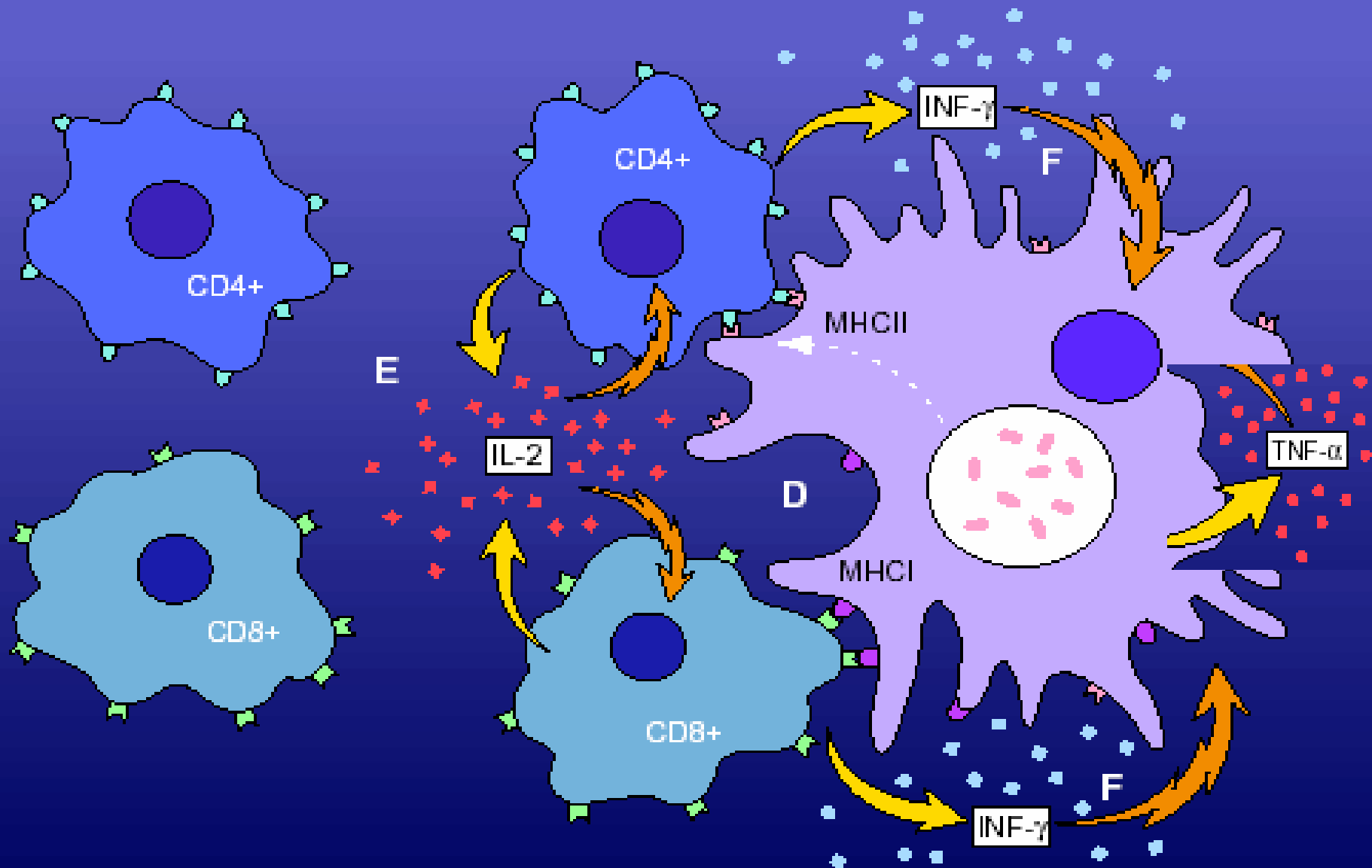


Performance of an IFN-gamma assay for the diagnosis of LTBI in immunosuppressed rheumatologic outpatients: prospective study

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Immune response to *M. tuberculosis*



TNF- α is a important cytokine in TB infection:

effective granuloma formation (studies with TNF-alpha knock-out mice)

NOS2 induction in macrophages

TNF- α plays a central role in Rheumatoid arthritis (RA) and Crohn's disease:

induction of IL-1, IL-6

upregulation of chemokines and their receptors

Tuberculosis and TNF- α inhibitors

- Cases of Tuberculosis have been seen in Infliximab clinical trials
- 295 cases of Infliximab associated TB reported to FDA (1998-2002)
- Estimated rate of 37 cases/100,000 US and 150 cases/100,000 EU
- Background rate tuberculosis in RA patients 6.2 cases/100,000 US and 20 cases/100,000 EU

**TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB,
A TUMOR NECROSIS FACTOR α -NEUTRALIZING AGENT**

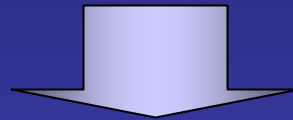
JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

- 70 patients developed TB, 56% extrapulmonary, 79% concurrent immunosuppressives (Corticosteroids alone or with Methotrexate)
- Median duration of treatment 12 wks, 91% of cases occurred in low incidence countries - both suggest reactivation

Treatment of Rheumatoid Arthritis With Tumor Necrosis Factor Inhibitors May Predispose to Significant Increase in Tuberculosis Risk

A Multicenter Active-Surveillance Report

Juan J. Gómez-Reino,¹ Loreto Carmona,² Vicente Rodríguez Valverde,³ Emilio Martín Mola,⁴
and Maria Dolores Montero,⁵ on behalf of the BIOBADASER Group



**1.3% of infliximab treated patients developed
active TB**

Number of patients:	1357
Mean age:	51±15
Disseminated:	5/17
TST:	pos: 1/17
	neg: 5/17
	not done... 11/17

Objective of our study

To assess the performance of an IFN-gamma based assay (QFT Gold in Tube, QFT-GIT) in rheumatic patients treated with immunosuppressive drugs, including TNF-alpha inhibitors

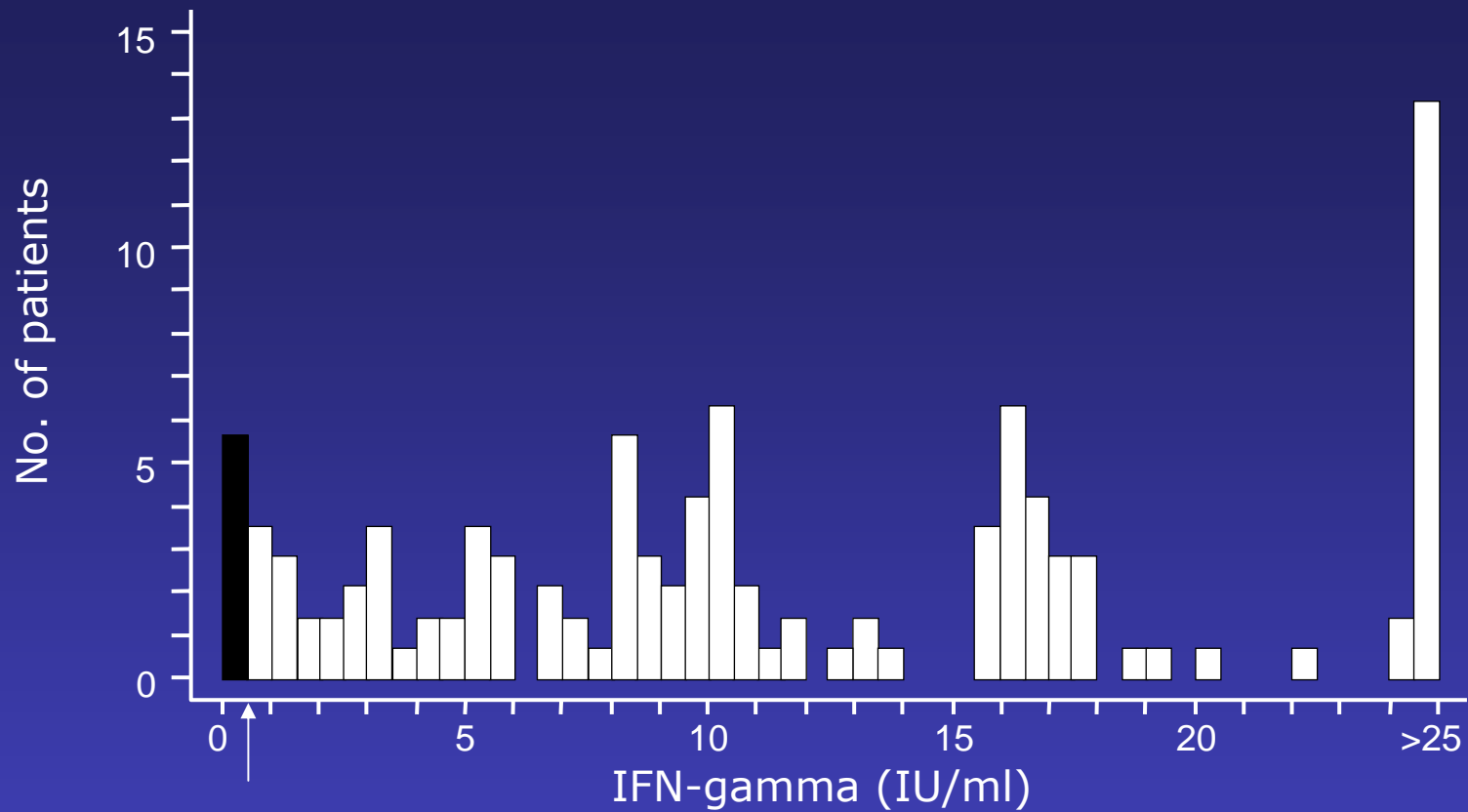
Design, Methods, Statistics

- Prospective study
- Consecutive, unselected patients admitted to the clinic of rheumatology
- BCG history: scar inspection, vaccination cards
- TST: performed as part of routine clinical procedures
- Uni- and multivariable logistic regression models to explore:
 - the association of QFT-GIT and TST results with the risk factors for LTBI and BCG vaccination status
 - influence of treatment regimen on the mitogen induced IFN-gamma secretion

Results

Characteristic	All patients (n=142)	IFN-g pos. (n=17)	TST pos. (n=46)
Age (years [SD])	47.9 (13.2)	51.8 (11.0)	45.6 (10.6)
Women (n [%])	71 (50%)	11 (65%)	18 (39%)
BCG vaccinated (n [%])	118 (83%)	12 (71%)	42 (91%)
Risk factors for latent tuberculosis (n [%])	44 (31%)	15 (88%)	20 (43%)
Born or resident in high-prevalence country	28 (20%)	7 (41%)	11 (24%)
History of household contact	10 (7%)	3 (18%)	6 (13%)
Chest X-ray suggestive of tuberculosis	10 (7%)	6 (35%)	2 (4%)
History of active tuberculosis	2 (1%)	2 (12%)	1 (2%)
Treatment regimen (n [%])			
TNF-α inhibitors, DMARDs and corticosteroids	20 (14%)	2 (12%)	2 (4%)
TNF-α inhibitors and DMARDs	44 (31%)	3 (18%)	12 (26%)
TNF-α inhibitors and corticosteroids	5 (4%)	0 (0%)	2 (4%)
TNF-α inhibitors only	15 (11%)	0 (0%)	6 (13%)
DMARDs and corticosteroids	26 (18%)	6 (35%)	12 (26%)
DMARDs only	10 (7%)	2 (12%)	4 (9%)
Corticosteroids only	6 (4%)	1 (6%)	0 (0%)
No TNF-α inhibitors, DMARDs, or corticosteroids	16 (11%)	3 (18%)	8 (17%)

Table 1. Patients' characteristics



Cutpoint for response to mitogen stimulation, IFN-g \geq 0.5 IU/ml

Figure 1. Response to mitogen stimulation, non-responders (n=8, 6%)

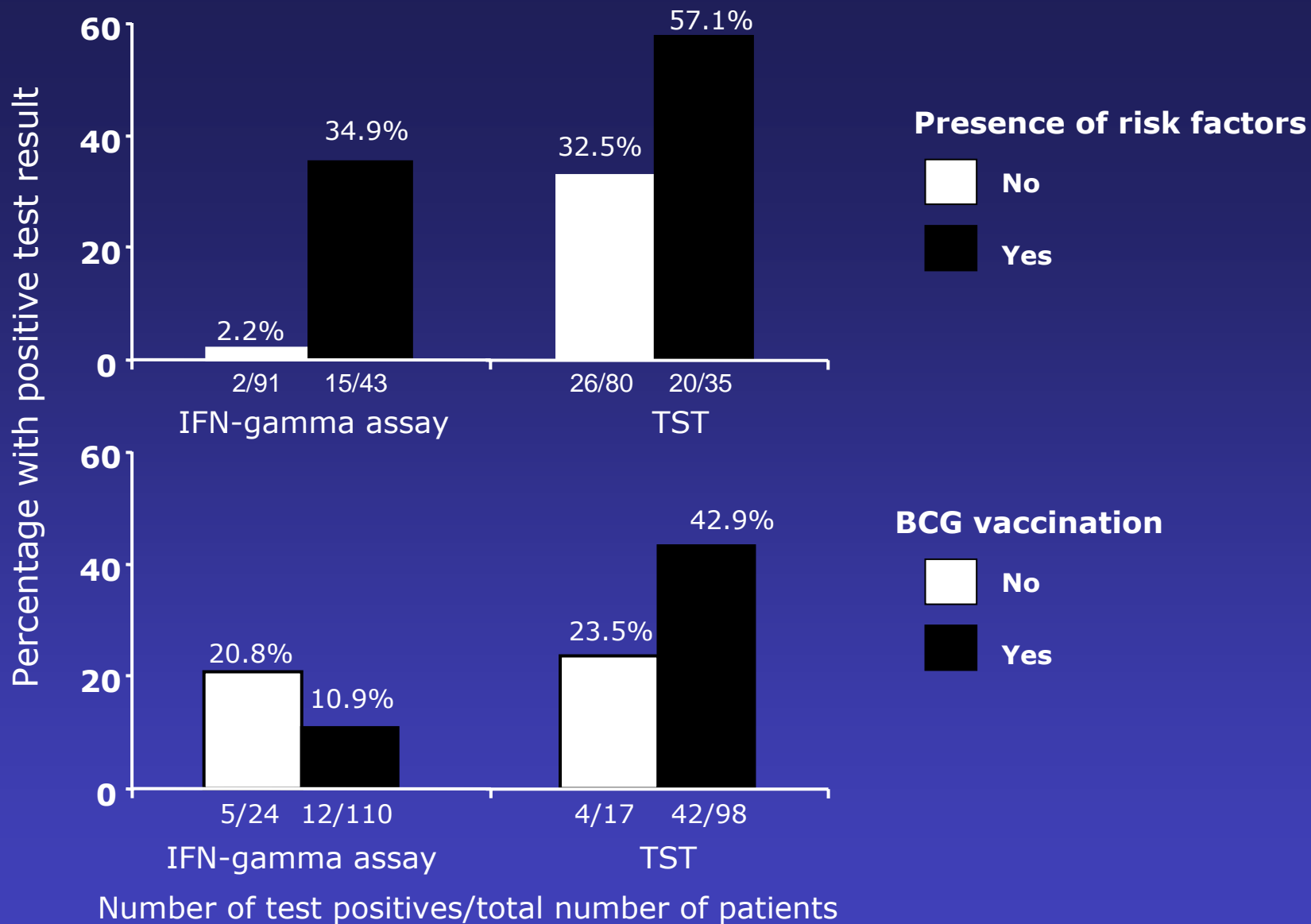


Figure 2. Results of IFN-gamma assay and TST according to the presence or absence of risk factors for latent tuberculosis (top) and BCG vaccination (bottom).

Characteristic	IFN-g assay (n=134)		TST (n=115)		p-value for IFN-g vs TST
	OR (95%-CI)	p-value	OR (95%-CI)	p-value	
Univariable analysis					
Risk factor	23.8 (5-110)	<0.001	2.77 (1.22-6.27)	0.015	0.009
BCG vaccination	0.47 (0.15-1.47)	0.20	2.44 (0.74-8.01)	0.14	0.025
Multivariable analysis					
Risk factor	29.2 (5.91-144)	<0.001	4.81 (1.8-12.8)	0.002	0.041
BCG vaccination	1.79 (0.49-6.5)	0.37	5.83(1.46-23.3)	0.013	0.2

Table 2. Association between the presence of any risk factor for LTBI or BCG vaccination status and results of IFN-gamma assay and tuberculin skin test

Characteristic	Univariable		Multivariable	
	Odds ratio (95%-CI)	p-value	Odds ratio (95%-CI)	p-value
Presence of risk factor	23.8 (5.14 - 111)	<0.001	30.5 (5.76 - 162)	<0.001
BCG vaccination	0.47 (0.15 - 1.47)	0.20	2.46 (0.59 - 10.2)	0.22
Corticosteroids	1.94 (0.70 - 5.39)	0.21	1.11 (0.30 - 4.14)	0.87
DMARDs	1.50 (0.46 - 4.92)	0.50	2.34 (0.52 - 10.6)	0.27
TNF-a inhibitors	0.21 (0.07 - 0.63)	0.006	0.19 (0.05 - 0.76)	0.019

Table 3. Association between the presence of any risk factor for LTBI, BCG vaccination status or drug regimen and results of IFN-gamma assay

Conclusions

Immunosuppressed patients can detectably respond to mitogen stimulation in a ESAT-6/CFP-10 IFN-gamma assay.

TNF- α inhibitors attenuate mitogen and ESAT-6/CFP-10 induced IFN-gamma response of leukocytes *in vivo*.

IFN-gamma assay was superior compared to the TST for detection of LTBI in patients receiving immunosuppressive therapy.

Antigen specific IFN-gamma assays such as the ELISA employed in our study can therefore be used in addition to or instead of the TST for diagnostic screening of LTBI in immunosuppressed rheumatic patients.



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