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Screening for Latent Tuberculosis Infection in Patients with Autoimmune Diseases Before Initiating TNF-α Inhibitors Therapy

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ABSTRACT

Introduction: QFT-GIT is more sensitive than TST in patients under immunosuppressive therapy, but TST detects more cases of LTBI. TST remains an inexpensive test worldwide, which does not need laboratory equipment. **Material and Methods:** Overall, 457 patients having autoimmune diseases were referred. Of those referred, 158 patients were screened with QFT-GIT and TST. No patient in the present study was known to be HIV positive, or had a history of tuberculosis contact the last year. Additionally, neither of the two methods distinguish latent from active TB, and neither one is better at recognizing patients with autoimmune diseases who could avail from preventive chemoprophylaxis. **Results:** QFT-GIT is more sensitive than TST in patients under immunosuppressive therapy, but TST detects more cases of LTBI. TST remains an inexpensive test worldwide, which does not need laboratory equipment. **Conclusion:** Since the literature for the economic evaluation of LTBI screening has not clearly defined which test is ultimately more cost-effective, low income countries like Greece should continue using TST as the primary method for diagnosis of LTBI.

Keywords: LTBI, autoimmune disease, TNF.

1. INTRODUCTION

Mycobacterium Tuberculosis (MTB) is the causative agent of tuberculosis. According to WHO, one-third of the global population is infected with MTB but doesn't transmit the disease (1). People with latent tuberculosis infection (LTBI) represent a large population with the potential for disease reactivation. The key point to controlling TB is systematic testing and treatment, thus targeted strategies for the protection of public health involves identifying people with latent infection, especially those at high risk of developing TB, such as patients with inflammatory autoimmune diseases (1).

Tumor necrosis factor TNFα is a pro-inflammatory cytokine which plays an important role in pathogenesis of several autoimmune disorders, and the immune response of MTB infection (2).

The introduction of TNFα inhibitor treatment of autoimmune diseases improved the everyday routines of patients. However, an increased risk of developing serious infections, including tuberculosis, was revealed (3). Screening for the diagnosis of suspected LTB or TB infection should include detailed medical history of exposure to MTB (previous history or close contact to active TB within the last year). Screening typically consists of Tuberculin Skin Test (TST) administration and evaluation after 48-72 hours and/or blood sampling for Quantiferon Tb Gold In-Tube (QFT-GIT), chest x-ray, (4, 5) and clinical history of active TB symptoms. TST has poor specificity in particular population groups, including BCG vaccinated and those who have been exposed to *NonTuberculosis Mycobacteria* (NTM). Moreover TST may show a false negative result in patients under immunosuppressive treatment (5).

In the last 15 years a new, in-vitro diagnostic method has been developed. QFT-GIT [Cellestis Limited, Carnegie Australia] which measures the interferon-γ (INF–γ) in peripheral blood after affection of specific proteins ESAT-6, CFP-10 and TB7.7 in stimulated T-cells. This method has been shown to be more specific for the detection of MTB than TST, as it's not affected by BCG vaccination or other environmental mycobacterium (6, 7).

2. AIM

The study aim was to compare the usefulness of the two tests in diagnosis of LTBI, in patients with autoimmune diseases considering initiation of therapy with TNF-α inhibitors.

3. SUBJECTS AND METHODS

The study was conducted at an Outpatient Tuberculosis Department of the General Pulmonary Disease Hospital of Athens "SOTIRIA" between 01/01/2008 and 31/12/2011. All patients included in the study received a medical referral to the outpatient clinic from a Rheumatologist, Dermatologist or Gastroenterologist. Demographic information, medical history, etiology for visiting the clinic, history of TB infection or exposure to MTB, therapy for LTB or TB infection in the past and immunosuppressive treatment were recorded from the medical patient's file. Overall, 457 patients having autoimmune diseases were referred. Of those referred, 158 patients were screened with QFT-GIT and TST. No patient in the present study was known to be HIV positive, or had a history of tuberculosis contact the last year.

Tuberculin Skin Test: Mantoux tests were evaluated after 48-72 hours by trained health care professionals. A negative result was defined as a TST with a diameter ≤ 5mm of transverse induration (8).

QuantiFERON-TB Gold In-Tube: QFT-GIT tests were reported as positive when identifying the antigens ESAT-6, CFP-10, (> =35 IU/ml, and > 25% of Nil), as negative, if non discovery of antigens (< 0.35 OR ≥ 0.35 and < 25% of Nil) and indeterminate (< 0.35 OR ≥ 0.35 and < 25% of Nil) (9). QFT-GIT was performed simultaneously with TST.

Chest x-ray: A chest x-ray was given to all patients requesting pulmonary evaluation of previous inactive TB (calcified or noncalcified nodules or fibrotic lesions) according to published guidelines (10). The presence of LTBI was established by having TST(+) and/or QFT-GIT(+), and abnormal findings in the chest x-ray suggestive old TB.

Therapies: Chemoprophylaxis for LTBI with isoniazid for 9 months or isoniazid for 6 months and isoniazid plus rifampicin for 3-4 months was administered to patients with TST(+) or QFT-GIT(+) in conjunction with findings on chest x-ray suggestive of previously treated TB (11). Drug therapies for autoimmune diseases were classified into corticosteroids, Disease Modifying Anti-Rheumatic Drugs (DMARDs) including methotrexate, azathioprine, and TNF α inhibitors (infliximab, etanercept or adalimumab). The study protocol was approved by the committee of School of Medicine of the University of Thessaly.

Statistical analysis

Quantitative variables were expressed as mean values with standard deviation (SD), while qualitative variables were expressed as absolute and relative frequencies. For the comparison of proportions chi-square and Fisher's exact tests were used. Logistic regression analysis in a stepwise method (p for entry 0.05, p for removal 0.10) was used in order to find independent factors associated with TST(+), QFT-GIT tests and abnormal x-ray. Adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated from the results of the logistic regression analyses. All reported p-values are two-tailed. Statistical significance was set at $p<0.05$.

Analyses were conducted using SPSS statistical software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Kappa values (κ) were calculated to assess the agreement between TST and QFT-GIT results. Kappa values were defined as: values ≤ 0 indicate no agreement, 0.01-0.20 none to slight, 0.21-0.40 fair, 0.41- 0.60 moderate, 0.61-0.80 substantial, and 0.81-1.00 almost perfect agreement.

4. RESULTS

The study group characteristics are summarized in Table 1. 158 patients underwent both TST and QFT-GIT. 94.9% (n=150) were born in Greece, 52.5% (n=83) were male, mean

	N (%)
Total	158 (100.0)
Sex	
Males	83 (52.5)
Females	75 (47.5)
Age (years) mean (SD)	49.4 (15.8)
Diagnosis	
Rheumatoid arthritis	58 (36.7)
Psoriasis / psoriasis arthritis	67 (42.4)
Spondylitis arthritis	19 (12.0)
Inflammatory bowel diseases (Crohn disease, colitis)	7 (4.4)
Other autoimmune diseases[1]	7 (4.4)
Nationality	
Greek	150 (94.9)
Non Greek	8 (5.1)
Immunosuppressive therapy in the past	
Corticosteroids	41 (25.9)
DMARDs[2]	44 (27.8)
TNF-α inhibitors	20 (12.7)
Other[3]	17 (10.8)
Duration of immunosuppressive therapy	
≤ 6 months	19 (16.2)
› 6 months	26 (22.2)
No therapy	72 (61.5)
Suggestion for preventive treatment for LTBI[4]	
Yes	83 (61.5)
No	52 (38.5)
Other [5]	23(14.6)
Kind of medication	
Isoniazid	72 (86.7)
Isoniazid + Rifampicin	5 (6.0)
Rifampicin	2 (2.4)
Other[6]	4 (4.8)
Comorbidity	
Yes	66 (41.8)
No	92 (58.2)
Tuberculosis infection in the past	(6.3)

Table 1. Sample characteristics. 1)Other autoimmune disease=Sjögren's syndrome, systemic lupus erythematosus, vasculitis, sclerosis; 2)DMARDs = Disease Modifying Anti-rheumatic Drugs; 3)Other= Nonsteroidal Anti-inflammatory Drugs (NSAIDs),vitamins, antibiotics; 4)LTBI= latent tuberculosis infection; 5)Other: Didn't appear to the appointment (n=11, 7.0%) ; Didn't seek for medical advice (n=12, 7.6%); 6) Other = Isoniazid+Rifampicin+Ethabutole, Ethamboutol+Quinolone

	N (%)	Results		
		Positive/ Abnormal	Negative/ Normal	Unknown
		N (%)	N (%)	N (%)
TST[1]	432 (94.5)	305 (70.6)	116 (26.8)	11 (2.6)
QFT-GIT[2]	175 (38.3)	53 (30.3)	112 (64.0)	10 (5.7)
Chest x-ray	285 (62.4)	65 (22.8)	206 (72.3)	14 (4.9)
BCG[3] vaccination	157 (34.4)	-	-	-
TST + QFT-GIT	158 (36.8)			
TST + Chest x-ray	271 (59.3)			
TST + BCG	153 (37.9)			

Table 2. TST, QFT-GIT and chest x-ray results of 457 patients. 1) Tuberculin Skin Test; 2) QuantiFERON®-TB Gold In-Tube Test; 3) Bacillus Calmette–Guérin Vaccin

	QFT-GIT			
	Negative	Positive	Indeterminate	
	N (%)	N (%)	N (%)	P
BCG				
No	25 (31.6)	6 (25.0)	1 (33.3)	0.001
Yes	54 (68.4)	18 (75.0)	2 (66.7)	
TST				
Negative	37 (35,2)	4 (8,2)	3 (75.0)	‹0.001
6-10mm	25 (23,8)	11 (22,4)	0 (.0)	
11-15mm	14 (13,3)	9 (18,4)	1 (25.0)	
›15mm	29 (27.6)	25 (51,0)	0 (.0)	

Table 3. QFT-GIT results associated with TST and BCG status. Pearson's chi-square test

age 49.4 years (±15.8 years). The leading cause of reference was psoriasis and psoriatic arthritis (42.4%, n=67). 41.8% of patients (n=66) had other health issues for which they were receiving therapy and 10 patients (6.6%) declared that they had been infected of TB in the past, but not during last year.

Table 2 presents the rate of the tests (TST, QFT-GIT, chest x-ray) and the BCG vaccination status of 457 patients. In table 3, the proportion of QFT-GIT(+) screening was higher in patients with TST >15 mm (51.0%) and significantly higher in comparison to groups with TST of 6-10 mm (22.4%), 11-15 mm (18.4%) and negative (8.2%) diameter (p<0.001). Also, the proportion of QFT-GIT(-) was higher in BCG vaccinated patients compared to those who did not receive vaccination in childhood (p=0.001). In table 4, TST(+) was found significantly more frequently in patients who did not receive corticosteroids (78.6 %, p=0.002), those recommended preventive treatment for LTBI (86.7%, p<0.001) and those with QFT-GIT(+) (91.8%, p<0.001). Among patients with QFT-GIT(+) 45.1% were over 49 (p<0.001). QFT-GIT(-) results were more frequent in TST(-)(90.9%, p<0.001). Most patients with BCG vaccination had QFT-GIT(-) results (84.8%, p=0.001). QFT-GIT(+)/TST(-) discordance was shown in 4 cases (9.1%), while QFT-GIT(-) /TST(+) was shown in 69 cases (60.5%). Normal chest x-ray correlated with younger age (92.3%, p=0.024) and QFT-GIT (-) results (89.0%, p=0.041). Regarding gender, underlying autoimmune disease, therapy with DMARDs and/or TNF-α inhibitors, duration of the immunosuppressive therapy, no significant associations were revealed for the three tests (Table 4).

Multivariate logistic regression results are presented in Table 5. Patients recommended chemoprophylaxis for LTBI had 5.35 times greater probability of having TST(+) versus patients who were not recommended (95% CI 2.13-13.46), p<0.001. Patients treated with corticosteroids had 79% lower probability of TST (+) (95% CI 0.08-0.55), p=0.002. TST(+) patients had 6.58 greater probability of QFT-GIT(+) test (95% CI 1.91- 2.73), p=0.003. QFT-GIT (+) patients had 33.3 times greater probability of being TST(+) versus QFT-GIT(-) patients QFT-GIT(-) (95% CI 3.85-288.06), p=0.001. Patients over 49 had 5.18 times greater QFT-GIT(+) (95% CI 1.77-15.14) p=0.003. Patients vaccinated with BCG had 76% lower probability of QFT-GIT(+) (95% CI 0.08-0.70) p=0.009. Patients over 49 had 3.71 times greater probability of having abnormal chest x-ray results (95% CI 1.13-12.27) p=0.031 (Table 5).

Agreement between TST and QFT-GIT was "moderate" with Kappa value (κ) equal to 0.43 (95% CI 0.18, 0.68) in cases of corticosteroids therapy. There was "slight" agreement in patients with rheumatoid arthritis [κ 0.20 (95% CI 0.01, 0.39)] and psoriasis [κ 0.18 (95% CI 0.07, 0.29)] and in BCG vaccinated [κ 0.04 (95% CI -0.04, 0.12)]. No agreement between the two tests was shown in patients who received TNT-a therapy [κ -0.07, (95% CI-0.39, 0.24)] (Table 6).

5. DISCUSSION

A high rate of patients (66.7%) had LTBI on the basis of TST(+) and the absence of BCG immunization, and (31.0%) QFT-GIT(+). The high rate of positive results may be due to age, since the mean age of the study population was 49.4, and older participants had potentially been exposed to the tuberculosis mycobacterium during childhood. The prevalence of disease in Greece was very high (30 to 60/100,000) until the 1980s (12). TB incidence in Greece declined by 40% from 1980 to 2000 and continues to decline (13).

In regard to TST(+), another possible explanation is that BCG immunization was performed when children entered school (4-7 years old), according to the Greek National Vaccination Program. This would agree with the findings of Farhat et al. (14) and Wang et al. (15) showing that BCG vaccination in latter childhood has a much higher effect on TST results than vaccination performed during infancy. However, the effect of vaccination wanes after 10 years and TST's reaction is usually moderate (14). Furthermore, when the study population is divided into 4 groups according to TST induration; negative, 6-10mm, 11-15mm and >15mm, we observed a high rate of QFT-GIT(-) results in TST(-) subgroup. Also a high rate of TST diameter >15mm had QFT-GIT(+) results, agreeing with Altet et al., (15,16) and suggesting that increased TST diameter >15 mm could indicate true LTBI (15). 45 cases were both (QFT-GIT(+) and TST(+) and were strongly associated in multiple logistic regression. In 73 cases, four QFT-GIT(+)/TST(-) and 69 QFT-GIT(-)/TST(+), results were discordant. This large difference in QFT-GIT(-) /TST(+) discordance shows that TST detected more cases of LTBI, although it is uncertain how many may have been false negatives or positives. The small number of QFT-GIT(+)/TST(-) cases suggests that TST was able to detect LTBI almost as well as QFT-GIT. Regarding the four TST(-)/ QFT-GIT(+) discordant results, three had rheumatoid arthritis, one had Spondylitis arthritis mean age 75 had other health issues and agrees with Weinfurter et al. study (17). Furthermore

	Positive TST		P*	Positive QFT-GIT		P*	Abnormal Chest x-ray		P*
	No (N=44)	Yes (N=114)		No (N=109)	Yes (N=49)		No (N=90)	Yes (N=17)	
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Age									
≤49.4	16 (21.1)	60 (78.9)	0.067	64 (84.2)	12 (15.8)	<0.001	48 (92.3)	4 (7.7)	0.024
>49.4	28 (34.1)	54 (65.9)		45 (54.9)	37 (45.1)		42 (76.4)	13 (23.6)	
Sex									
Females	26 (34.7)	49 (65.3)	0.069	54 (72)	21 (28)	0.436	41 (85.4)	7 (14.6)	0.739
Males	18 (21.7)	65 (78.3)		55 (66.3)	28 (33.7)		49 (83.1)	10 (16.9)	
Diagnosis									
Rheumatoid arthritis	20 (34.5)	38 (65.5)	0.125**	40 (69)	18 (31)	0.562**	35 (85.4)	6 (14.6)	0.089**
Spondyitis arthritis	6 (31.6)	13 (68.4)		14 (73.7)	5 (26.3)		12 (92.3)	1 (7.7)	
Psoriasis / psoriatic arthritis	12 (17.9)	55 (82.1)		46 (68.7)	21 (31.3)		38 (84.4)	7 (15.6)	
Inflammatory bowel diseases	3 (42.9)	4 (57.1)		6 (85.7)	1 (14.3)		5 (83.3)	1 (16.7)	
Other autoimmune diseases	3 (42.9)	4 (57.1)		3 (42.9)	4 (57.1)		0 (0)	2 (100)	
Tb infection in the past									
No	41 (27.7)	107 (72.3)	1.000**	105 (70.9)	43 (29.1)	0.071**	85 (85)	15 (15)	0.308**
Yes	3 (30.0)	7 (70.0)		4 (40.0)	6 (60.0)		5 (71.4)	2 (28.6)	
Corticosteroids									
No	25 (21.4)	92 (78.6)	0.002	82 (70.1)	35 (29.9)	0.614	66 (85.7)	11 (14.3)	0.557**
Yes	19 (46.3)	22 (53.7)		27 (65.9)	14 (34.1)		24 (80)	6 (20)	
DMARDs									
No	32 (28.1)	82 (71.9)	0.920	76 (66.7)	38 (33.3)	0.310	62 (82.7)	13 (17.3)	0.531
Yes	12 (27.3)	32 (72.7)		33 (75)	11 (25)		28 (87.5)	4 (12.5)	
TNF-a inhibitors									
No	40 (29)	98 (71)	0.402	97 (70.3)	41 (29.7)	0.352	75 (81.5)	17 (18.5)	0.122**
Yes	4 (20)	16 (80)		12 (60)	8 (40)		15 (100)	0 (0)	
Suggestion for preventive treatment for LTBI									
No	24 (46.2)	28 (53.8)	<0.001	39 (75)	13 (25)	0.058	35 (79.5)	9 (20.5)	0.299
Yes	11 (13.3)	72 (86.7)		49 (59)	34 (41)		48 (87.3)	7 (12.7)	
Positive TST									
No	44 (100.0)	0 (0.0)	-+	40 (90.9)	4 (9.1)	<0.001	20 (74.1)	7 (25.9)	0.128**
Yes	0 (0.0)	114 (100.0)		69 (60.5)	45 (39.5)		70 (87.5)	10 (12.5)	
Positive QFT-GIT									
No	40 (36.7)	69 (63.3)	<0.001	109 (100.0)	0 (0.0)	-+	65 (89.0)	8 (11.0)	0.041
Yes	4 (8.2)	45 (91.8)		0 (0.0)	49 (100.0)		25 (73.5)	9 (26.5)	
BCG									
No	15 (33.3)	30 (66.7)	0.104	26 (57.8)	19 (42.2)	0.001	24 (88.9)	3 (11.1)	0.705**
Yes	13 (19.7)	53 (80.3)		56 (84.8)	10 (15.2)		42 (91.3)	4 (8.7)	
Duration of immunosuppressive therapy									
No therapy	17 (23.6)	55 (76.4)	0.402	47 (65.3)	25 (34.7)	0.988	38 (84.4)	7 (15.6)	0.915**
<12 months	11 (36.7)	19 (63.3)		20 (66.7)	10 (33.3)		17 (81.0)	4 (19.0)	
>12 months	4 (26.7)	11 (73.3)		10 (66.7)	5 (33.3)		11 (84.6)	2 (15.4)	

Table 4. Association of medical history, medical examination and use of immunosuppressive therapy with TST, QFT-GIT and Chest x-ray.. *Pearson's chi-square test **Fisher's exact test +Not computed due to no distribution

		OR (95% CI) ‡	P
Positive TST			
Suggestion for preventive treatment for LTBI	No	1.00*	
	Yes	5.35 (2.13 – 13.46)	<0.001
Corticosteroids	No	1.00	
	Yes	0.21 (0.08 – 0.55)	0.002
Positive QFT-GIT	No	1.00	
	Yes	6.58 (1.91 – 22.73)	0.003
Positive QFT-GIT			
Age	≤49	1.00	
	>49	5.18 (1.77 – 15.14)	0.003
Positive TST	No	1.00	
	Yes	33.30 (3.85 – 288.06)	0.001
BCG	No	1.00	
	Yes	0.24 (0.08 – 0.70)	0.009
Abnormal chest x-ray			
Age	≤49	1.00	
	>49	3.71 (1.13 – 12.27)	0.031

Table 5. Results of multiple logistic regression to investigate factors associated with positive TST, positive QFT-GIT and chest x-ray. *indicates reference category ‡Odds Ratio (95% Confidence Interval)

	QFT-GIT(-)	QFT-GIT(+)	TOTAL	κ* (95% CI)
Patient with Rheumatoid arthritis				
TST (-)	17	3	20	0.20 (0.01, 0.39)
TST (+)	23	15	38	
Patient with Psoriasis				
TST (-)	12	0	12	0.18 (0.07, 0.29)
TST (+)	34	21	55	
Use of Corticosteroids in the past				
TST (-)	17	2	19	0.43 (0.18, 0.68)
TST (+)	10	12	22	
Use of TNF-α in the past				
TST (-)	2	2	4	-0.07 (-0.39, 0.24)
TST (+)	10	6	16	
BCG				
TST (-)	12	1	13	0.04 (-0.04, 0.12)
TST (+)	44	9	53	

Table 6. Agreement between TST and QFT-GIT results. *Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41- 0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect agreement

two patients had abnormal chest x-ray and three had received corticosteroids in combination with DMARDs and/or TNF-α therapy in the past for at least 6 months. These findings could be TST false negative due to inhibition of the immune cells relating to the level of immunosuppression (18). Among the 69 TST(+)/QFT-GIT(-) cases of discordance, TST's potential positive results could in part be explained by a younger age (mean age of 69 cases 42 years old) and cross reaction with BCG vaccine strains (n=44) in a country with a previously high rate of infection (14, 17). Moreover, Nienhaus and colleague (18) connected TST(+) results with receiving BCG vaccination after infancy and birthplace in a country with high TB incidence. Further the observed QFT-GIT (-) results could be false negative due to the use of immunosuppressive drugs which directly reduce the production of cytokines such as INF-γ and TNF-a from T cells (19). QFT-GIT vs. TST agreement was slight between the two screenings in patients with psoriasis and rheumatoid arthritis (k=0.18 and k=0.20). Lee et al. (20), from South Korea, an intermediate level TB country, found a poor agreement between the two tests in RA patients and healthy controls, basing their conclusions on differences in the individuals' immune status and the status of TB incidence in South Korea. Furthermore other studies have shown poor agreement between the two tests regardless of the TB status of the country (21, 22). In Greece TB incidence rates are low compared to other European Union countries, but this could be due in part to under reporting. According to the ECDC and WHO surveillance data, there were 665 new TB cases in 2008, declining to 490 cases in 2010 (23).

Four indeterminate QFT-GIT results were detected among positive and TST(-) results. One (4.1%), TST(+) with 11-15mm diameter and three (6.8%), TST(-). All patients were over 49. One TST(+) patient declared that he had TB when he was young and had received corticosteroids in combination with Nonsteroid Anti-inflammatory Drugs (NSAIDs). Our results are in accordance with Kobashi el al. (24) who concluded that indeterminate results were associated with older age and immunosuppressive therapy. On the contrary researchers from Italy (25), a low TB endemic country with a low BCG immunization rate, performed the two tests in 398 patients with autoimmune diseases and found a smaller rate of indeterminate results (1.2%) supporting that their findings confirms the accuracy of QFT-GIT in autoimmune patients who have been under immunosuppressive therapy in the past.

Age was found to be an aggravating factor for the QFT-GIT(+) and abnormal chest x-ray results, and correlated positively in the multiple logistic regression, in accordance with other studies (26). When considering LTBI, early detection and proper treatment are the priorities to control the disease and reduce the risk of progression to active disease in patients with autoimmune diseases. Strategies for the investigation of LTBI have small differences between USA, European countries and Australia, (10,27-29) but still it is unclear which is best. Taking into account at least one risk factor for LTBI such as TST(+) with cut-off point ≥ 5 mm (n=114, 72.1%), or QFT-GIT(+) (n=49, 31.0%) and chest x-ray findings of prior TB (n=17, 15.9 %,), only TST(+) patients are recommended chemoprophylaxis for LTBI. However if we identify latency by confirmed TST(+) and QFT-GIT(+) (n=45) then fewer patients would have been administrated chemoprophylaxis. However, because TB will develop among patients who have been infected with MTB, and because currently there isn't a gold standard method to distinguish the latent from active infection, the clinician should consider offering preventive chemoprophylaxis in patients with autoimmune diseases testing positive on either of the two tests (30).

Limitations: In any setting where records are reviewed retrospectively, it is not always possible to collect the same data for every patient. Items such as "dose" and "duration of use" were not available in every chart, neither was there information regarding patient compliance with previous treatment of autoimmune disease. While these would have been interesting, and allowed for a more in-depth look into the topic, it

was felt that the level of information available in the patient charts was enough to provide useful, representative data.

6. CONCLUSION

QFT-GIT is more sensitive than TST in patients under immunosuppressive therapy, but TST detects more cases of LTBI. TST remains an inexpensive test worldwide, which does not need laboratory equipment. Additionally, neither of the two methods distinguish latent from active TB, and neither one is better at recognizing patients with autoimmune diseases who could avail from preventive chemoprophylaxis. Since the literature for the economic evaluation of LTBI screening has not clearly defined which test is ultimately more cost-effective, low income countries like Greece should continue using TST as the primary method for diagnosis of LTBI.

- **Conflict of interest: none declared.**
- **Authors contribution:** DP contributed the conception and design of the study, collected data and carried out statistical analysis, prepared the manuscript, approved the paper to be submitted; DZ contributed the conception and design of the study, critically revised the paper, approved the paper to be submitted; PE contributed the conception and design of the study, critically revised the paper, approved the paper to be submitted; KK contributed the conception and design of the study, approved the paper to be submitted; GK critically revised the paper, final approval of the version to be submitted.

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