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Prevalence of Latent Tuberculosis Infection in Patients who are Candidates for Biological Therapy

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Original Article

Abstract

Background: *Tuberculosis remains one of the biggest global human killer's accountings for 9.4 million new cases of active tuberculosis and 3 million tuberculosis -related deaths with an incidence of 140/100,000 inhabitants. More than 90% (up to 8 million) of total TB Tuberculosis cases occurring in developing countries and more than half of all deaths (2 million) occurring in Asia.*

Objective: *To assess the burden of latent TB in patient's candidate for biological therapy.*

Patients and method: *A descriptive cross-sectional study conducted at Baghdad teaching hospital during the period from the 1st of April 2020 to the end of March 2021. A consecutive sampling included 150 respondent's candidates for biological therapy were included in this study.*

Results: *The mean age of patients was 38.9±11.4 years. TST was positive in 23.3% of studied patients. Significant association between positive TST findings and middle age group (p=0.05). A significant association was observed between positive TST results and gender (p=0.001). Also, significant association between prolonged duration of the disease, and positive TST.*

Conclusions: *The TST were positive in about only one quarter of patients with chronic immunomodulated diseases who are candidate for biological therapy, and significant associations were found between age group, and TST positive.*

Keywords: *Latent tuberculosis infection, biological therapy, Active tuberculosis*

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1. INTRODUCTION

Latent tuberculosis infection (LTBI) Latent tuberculosis infection is a positive TST in the absence of clinical, radiological and laboratory evidence of tuberculosis disease. The WHO recommends effective TB control, but diagnosis and control are dependent on early detection and identification of LTBI individuals at high risk of reactivation and progression to active TB disease (1). Identification of a primary source or suspicions of LTBI or active TB disease face difficulties Introduction pg. 4 due to the absence of any gold standard diagnostic tests. Areas highly endemic for TB disease suffer from negative consequences of the disease, for example economic costs related directly or indirectly to TB (2). Difference between LTBI and active TB disease Latent tuberculosis infection occurs when the number and activity of tuberculosis bacterial germs becomes enough to cause symptoms in normal healthy-looking individuals. Active TB cases are commonly presented with suspect symptoms such as a chronic cough for more than 3 weeks, fever with hemoptysis or weight loss, and/or fatigue and night sweats (3). Diagnostic methods for LTBI. The Tuberculin skin test (TST) was historically the sole method of determining LTBI for epidemiological studies as well as for informing treatment decisions. TST relies on delayed hypersensitivity to an intradermal injection of purified protein derivative (PPD) of mycobacterium bovis, an antigen found in both mycobacterium tuberculosis and other nontuberculous mycobacteria (NTM) (4). Given that there is no gold standard for diagnosing LTBI, determining the sensitivity and specificity of the TST is very difficult. One review reports sensitivity and specificity of 89% and 85% respectively for TST (5) when culture confirmed TB is used as the gold standard, although the TST has no role in diagnosing active TB. There are several limitations and confounding factors of the TST with varying importance and clinical effect depending on the source of the study reviewed. First, TST quality is an operator dependent test, and requires trained and skilled healthcare professionals to correctly place and read the test. Even among trained healthcare workers, measurement of the TST induration is a qualitative measurement subjective to inter-observer measurement bias (6). Second, the TST requires two visits, one for placement and one for reading, which among certain populations results in decreased adherence and unread tests. Third, there is a concern for false positive TST arising from three main sources: booster effect from frequent TST, cross reaction with Bacillus Calmette–Guérin (BCG) vaccine, and cross reactivity with NTM. The true effect of BCG vaccine on TST results remains elusive, as a wide body of literature exists with conflicting Introduction pg. 6 conclusions. If given in

infancy only, it is believed that BCG does not markedly affect TST results in adults, and contributes to 1 false positive per 100 tests ten years after receiving the vaccine (4). However, when BCG is given after 1 year of life, the number of false positives is higher, and the BCG effect lasts for longer, although it decreases with age. False positive TST results due to NTM are very uncommon, and are not thought to be clinically significant in high prevalence areas. If this is a concern in a specific population, there are intradermal tests that use tuberculosis specific antigens. Lastly, the TST is dependent on a functioning immune system, and its sensitivity declines with HIV infection due to inability to mount an immune response, termed energy. There is no quantitative measure of CD4 count at which point an immune response will no longer manifest, however it has been shown that more HIV-infected people have a positive TST with CD4>200 compared to those with CD4 (7).

Biological therapy and latent tuberculosis:

The advent of biological therapies has greatly improved the treatment and management of immune-mediated diseases such as Crohn's disease, psoriasis, rheumatoid arthritis, ankylosing spondylitis and multiple sclerosis and many types of cancer (Kidney cancer, Kaposi's sarcoma, Melanoma, Certain types of leukemia and lymphoma) (8-10), allowing for a better quality of life for these patients (11). Biologic drugs are now a staple in the clinical approach to severe forms of these diseases. However, they require careful management given their suppressive effect on the patient's immune system (12). Introduction pg. 8 Screening for latent tuberculosis infection (LTBI) is mandatory in patients with who are candidates for biological therapy and it is recommended by European and American guidelines. Indeed, the risk of developing active tuberculosis in patients treated with tumour necrosis factor (TNF) –inhibitors is five times more likely compared with subjects not exposed to biological therapies. It has been estimated that in 20–50% of subjects exposed to Mycobacterium tuberculosis, the bacilli resist the innate immune response, and actively multiply within the macrophages with the infection spreading to nearby cells. The cell-mediated immune response leads to the formation of a granulomatous reaction, which does not effectively clear M. tuberculosis infection, but it inhibits bacterial multiplication leading to LTBI in about 90% of cases. (13, 14) LTBI is a condition in which viable bacteria are metabolically active but contained within macro-phages and granulomas. Although carriers do not have tuberculosis symptoms and cannot spread the infection to others, it is estimated that around 10% of carriers are potentially at risk of developing an active infection, which is both symptomatic and contagious. This can occur during

a change in the immunological status of the patient, such as reduced immunity caused by immunosuppressive therapies including TNF-a inhibitors (15).

2. PATIENTS and METHODS

Study design, setting and timing: A descriptive cross-sectional study conducted at Baghdad teaching hospital during the period from the 1st of April 2020 to the end of March 2021. Sampling and patient A consecutive sampling included 150 patient's candidates for biological therapy were included in this study (i.e. those with contraindication and/or intolerance and/or non-responsive to conventional systemic treatment including methotrexate, cyclosporine, salazopyrin and/or corticosteroids)

Data collection: data were collected by using a specially designed questionnaire form. These forms included information about sociodemographic characteristics (Name, date of birth, gender, smoking history, occupation, history of previous lung diseases, history of Tb contact, BCG status, past medical history, type of disease treated with biological treatment (duration, current therapy and its dose), investigations (tuberculin skin test, chest radiograph).

Exclusion criteria:

1. Patients with active TB
2. Patients with history of previous TB infection
3. Patients who refused to do TST Method: The TST was performed before starting biological therapy.

The patients interviewed at out-patient clinic. The Mantoux technique was used and 5units of Purified Protein derivative, at Chest and respiratory disease Patients and method pg. 10 institute were applied by an intradermal injection in the middle third of the inner forearm. Skin reaction was quantified 48 to 72 hours after the injection. The largest transverse diameter of indurations was measured in millimeters. Patients who did not complete the test were excluded from the study. All patients were sent for chest radiography.

Positive TST results were dependent on: Criteria for a positive tuberculin skin test (16):

1- >=5 in: Immunosuppressed patients, steroid dependents, close contacts of persons with active TB, persons with chest radiograph consistent with old TB, HIV infected persons.

2- >=10 in: immigrants from countries endemic in TB, injection drug users, low income and

homeless persons, healthcare workers, persons with recent tuberculin test conversion.

3- >=15 in: any person without a defined risk factor for tuberculosis.

Statistical analysis:

• Data were analyzed by using SPSS IBM program version 23.

• Data are presented as means ± variance compared using an unpaired t-test.

• Chi-square or Fisher s exact ’tests compared means and percentages when appropriate.

Probability values < 0.05 were considered statistically significant in all analyses.

3. RESULTS

A total of 150 patients were included in this study with mean age of 38.9±11.4 years; 3.3% less than 20 years age, 15.3% 20-29 years, 31.3% 30-39 years, 30.7% of them were in age group 40-49 years and 19.4% 50 years of age and more. Male patients were more than females with male to female ratio as 1.5:1. Diseases were commonly Ankylosing Spondylitis (47.3% ,71 patients), Rheumatoid arthritis (34.7% ,52 patients), psoriasis (8% ,12 patients), Behcet disease (5.3% ,8 patients), AS and RA (2.7% ,4 patients), Crohns disease (1.3% ,2 patients) and Juvenile Arthritis (0.7% ,1 patients) as illustrated in (**Figure 1**). The mean duration of disease was 7.2±6.1 years; 28.7% of patients had duration of less than 5 years, 22.7% 5-9 years and 48.6% 10 years and more. All these data were illustrated in (**Table 1**). The TST was positive in 23.3% of studied patients. All these data were illustrated in (**Figure 2**). There was a significant association between positive TST results and patients in middle age group (p=0.05). A significant association was observed between male gender and positive TST results (p=0.001). All these data were illustrated in (**Table 2**). Although the frequency of workers with negative TST is much higher than those with positive TST, but a significant association was observed between worker patients and positive TST findings (p=0.009) (34.1% of worker patients had positive TST ,80% of all positive TST results were among worker patients). There was a significant association between smoking status and TST findings (p=0.001) (31.8% of current smokers had positive TST, 42.3% of all positive TST patients are among current smokers). All these data were illustrated in (**Table 3**). There is no significant association was observed between the type of immunomodulated disease and positive TST results (p=0.1) (32.4% of all AS patients had positive TST ,while 65.7% of all positive TST patients had AS). But significant association between prolonged duration of disease and positive TST findings (p=0.04). All these data were illustrated in (**Table 4**).

Table 1. duration of the diseases

Duration of disease (year)	No.	%
<5	43	28.7
5-9	34	22.7
≥10	73	48.6
Total	150	100.0
Mean duration ± SD (7.2±6.1 years)		

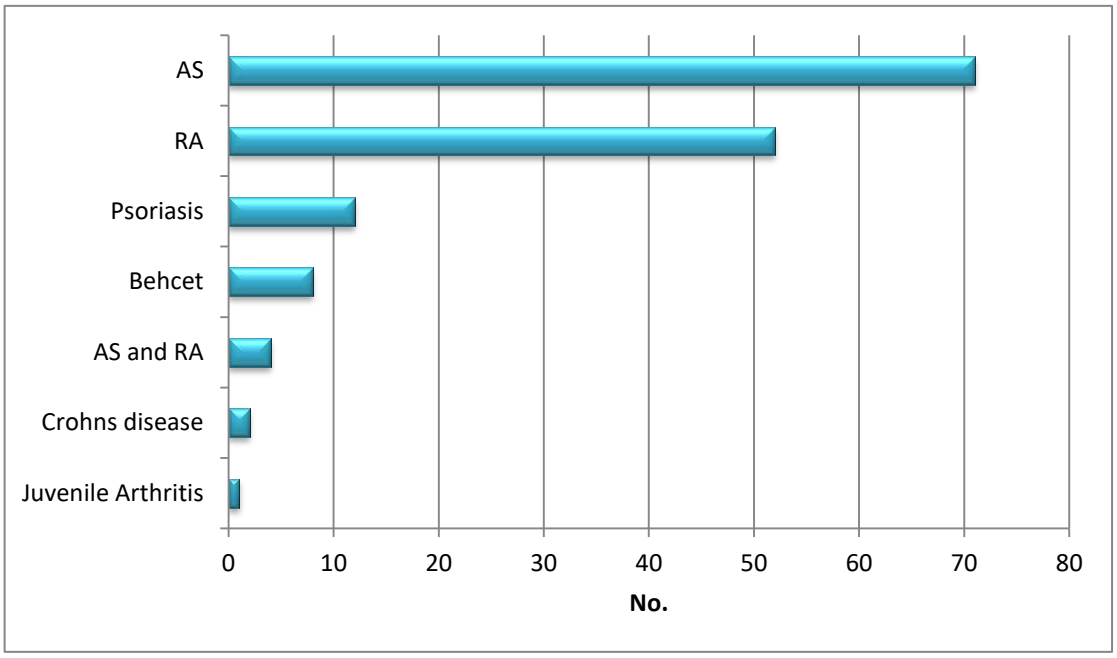

Figure 1. Types of Diseases, (*AS: Ankylosing spondylitis, RA; Rheumatoid arthritis*).

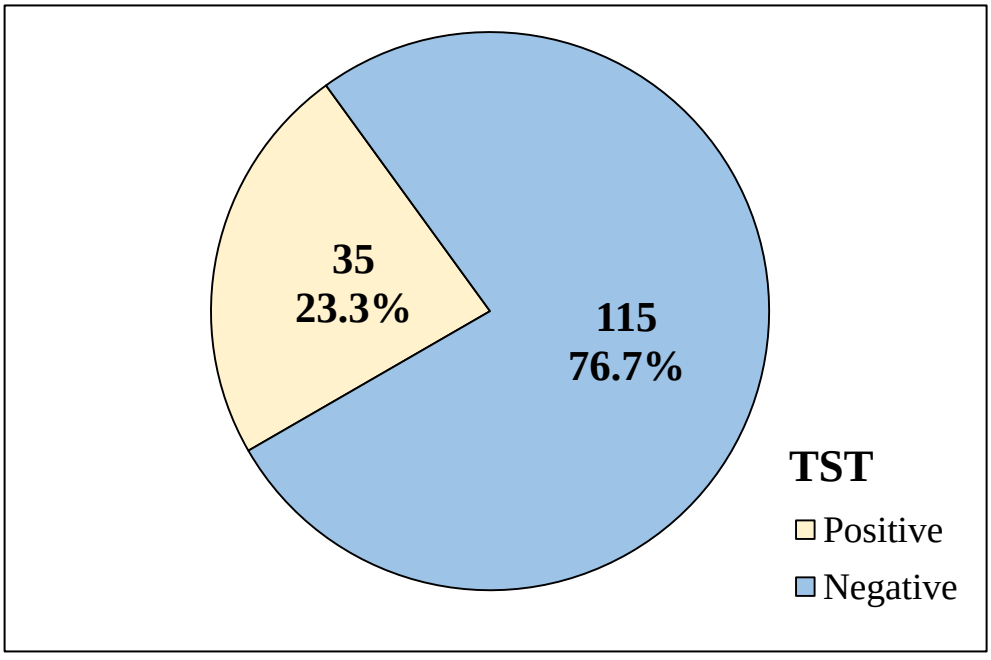

Figure 2. TST finding of patients (TST: Tuberculin Skin Test)

Table 2. Distribution of demographic characteristics according to TST results.

Variable		Positive TST		Negative TST		P-Value
		No.	%	No.	%	
Age (year)	<20	0	-	5	4.3	0.05
	20-29	6	17.1	17	14.8	
	30-39	12	34.2	35	30.4	
	40-49	16	45.8	30	26.1	
	≥50	1	2.9	28	24.4	
Gender	Male	29	82.9	62	54	0.001
	Female	6	17.1	53	46	

**Fishers exact test, ** Fishers exact t-test, S=Significant.*

Table 3. Distribution of social characteristics according to TST results.

Variable		Positive TST		Negative TST		Total	P
		No.	%	No.	%	No.	
Occupation	Workers	28	34.1	54	65.9	82	0.009*s
	Student	6	30.0	14	70.0	20	
	Housewife	1	2.3	42	97.7	43	
	Retired	0	0.0	5	100.0	5	
Smoking	Current smoker	14	31.8	30	68.2	44	0.001**s
	Non smoker	13	13.4	84	86.6	97	
	Ex-smoker	8	88.9	1	11.1	9	

* Fishers exact test, ** Chi-square test, S=Significant. TST: Tuberculin Skin Test

Table 4. Distribution of patients according to the type and duration of disease

Variable		Positive TST		Negative TST		Total	P-Value
		No.	%	No.	%	(no.)	
Type of disease	AS	23	32.4	48	67.6	71	0.1* NS
	RA	10	19.2	42	80.8	52	
	Behcet disease	2	25.0	6	75.0	8	
	Psoriasis	0	0.0	12	100.0	12	
	AS and RA	0	0.0	4	100.0	4	
	Crohn's	0	0.0	2	100.0	2	
	Juvenile Arthritis	0	0.0	1	100.0	1	
Duration	<5 years	5	11.6	38	88.4	43	0.04** S
	5-9 years	11	32.4	23	67.6	34	
	≥10 years	19	26.0	54	74.0	73	

* Fishers exact test, ** Chi-square test, S=Significant.RA: Rheumatoid Arthritis, AS: Ankylosing Spondylitis.

4. DISCUSSION

Screening for latent TB in patients with chronic inflammatory diseases as inflammatory arthritis who will be candidates for biological therapy is important to prevent complications of TB-reactivation. However, currently there is no 'gold standard' for the diagnosis of latent TB (17). The main age group in our study was 40-49 years. Male patients were more than females with male to female ratio as 1.5:1. This is in agreement with that mentioned by WHO 2011, when male were more than female and it occur in age group between 15-50 years old (18). In the present study the commonest diseases reffered for biological therapy were Ankylosing Spondylitis, Rheumatoid arthritis, psoriasis subsequently, while in Garziera G et al, (19) study the underlying diseases were rheumatoid arthritis (RA) in 50.6% (N = 89), ankylosing spondylitis (AS) in 27.8% (N = 49), and psoriatic arthritis (PsA) in 17.6% (N = 31). This may be due to difference in sample size collection at the time of the study regarding the disease incidence and prevalence. The current study revealed that about one quarter of cases were TST positive and the majorities were negative TST. This prevalence is relatively near that mentioned in Garziera G et al (19), 29.5%, in previous studies conducted in Brazil (27.0%) (20) and Peru (29.0%) (21) . Lower prevalence of positive TST was described by other studies conducted in Brazil (13.4%) (22) and in India (20.4%) (23). On the other hand, high prevalence were revealed in Renata M et al, (24) found that TBI screening was positive in (43.6%) patients and in studies conducted in France it was 47.2% of patients, were TST-positive (25). These divergent results among studies could be explained by differences in patient's characteristics like immunosuppression ,HIV infection, concomitant diseases or medications, the age of BCG vaccine administration. Discussion pg. 20 Regarding to the age, it was found that TST positive in the present study significantly associated with middle age group. This is not in agreement with Li et al, 2014 study when reported that prevalence of TST positivity significantly increased with age (26) . Furthermore, according to the reports of Pareek et al. and Shanaube et al., the result TST was associated with increasing age (27, 28) . It is uncertain whether increased age is the risk factor of contracting TBI or whether increased cumulative exposure to Mycobacterium tuberculosis and/or NTM as people grow older increases positivity of both tests. This difference with current study may be attributed to that the majority of our

patients sample were in middle age group and this may be due to that the age presentation of immune mediated diseases is usually in middle and young age group (29) . As for the relation between gender and positive TST, the current study revealed a significant association with gender the positive TST were more common in male than female, which is in accordance to Ting WY et al, (30) 2014. Furthermore similar to Lee SJ et al, (31) 2014 found that male were more than female regarding the TST positive. Sex disparities in active TB are widely reported globally, several possible causes are proposed to explain the observations. The gender inequalities in cultural and social aspects are enormous in some developing countries that are also TB endemic areas. These inequalities affect the help-seeking behaviors and reduce the access of women to health care services. The under notification of active TB cases in females may be due to the gender bias in these areas, especially in a passive case-finding setting (32-34) . Moreover, men may have more social contact than women and thus lead to an increased risk of exposure to contagious cases (35) . Discussion pg. 21 Regarding to the relation between employment and TST in this study, it was revealed that employed patients is the main group than others with significant association with positive TST than other groups this may be due to this group is more contact with population than other group. The smoker patients (smoker + Ex-smoker) are more common than that not smoking with significant association between Ex-smoker and positive TST. Garziera G et al, (19) revealed that there is no significant association were found between TST results and smoking status. Arnson Y, et al, (36) the cigarette smoking affects both the innate and adaptive immune arms. Cigarette smoke was shown to augment the production of numerous pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8 GM-CSF and to decrease the levels of anti-inflammatory cytokines such as IL-10. Tobacco smoke via multiple mechanisms leads to elevated IgE concentrations and to the subsequent development of atopic diseases and asthma. Cigarette smoke has also been shown to induce macrophages and dendritic cells activity. Also there was a significant association between long time duration (≥10 years) of the immunomodulated diseases and positive TST results. This may be due to prolonged use of immunosuppressives and depressed immunity with the progression of the disease.

5. CONCLUSIONS

The TST were positive in about only one quarter of patients with chronic immunomodulated diseases who are candidate for biological therapy, and significant associations were found between age group, and TST positive.

Ethical Clearance:

Ethical issues were taken from the research ethics committee. Informed consent was obtained from each participant. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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