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Original Article

Evaluation of Treatment Indications, Tuberculin Skin Test, and Bacillus Calmette-Guerin Vaccination Scars in the Cases of Latent Tuberculosis Infection Treatment

Beyhan Çakar

Ankara Tuberculosis Control Dispensary, Ankara, Turkey

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Abstract

OBJECTIVES: The aim of our study was to evaluate the latent tuberculosis infection (LTBI) treatment application and to investigate if there is change between tuberculin skin test (TST) results according to bacillus Calmette-Guerin (BCG) scar numbers after LTBI treatment with isoniazid (INH).

MATERIAL AND METHODS: Data were collected from the LTBI treatment files from the dispensary of 2006. The results were statistically evaluated.

RESULTS: Latent tuberculosis infection was administered to 253 cases in 2006. The male/female case rate was 51/49. The age of most patients was under 15 years out of 14 cases. The mean age was 8.92±6.87 years (range, 0-84 years). One case had liver function test abnormality and INH was stopped in the first month of treatment. The completion rate of LTBI treatment was 95%. BCG vaccination rate was 93%. Active tuberculosis did not develop during the LTBI treatment in our study. Of all the cases, 221 scar numbers and TST were full. Of all cases 221 the scar numbers and TST value were full.TST of the 221 cases according to BCG vaccine scar numbers and indications were compared pre- and post-treatment with INH. Indications for LTBI treatment in these cases were close contact with smear-positive active pulmonary tuberculosis cases (n=77, 35%), TST-positive children aged <15 years (n=138, 62%), and the other (n=6, 3%) immunosuppressed patient cases. After treatment with INH, TST values decreased in the TST-positive children aged <15 years with one and 2 scars, with a statistically significant this result were found statistically significant ($p<0.05$).

CONCLUSION: The age of patients in most cases with LTBI treatment was under 15 years. The treatment completion rate and BCG vaccination rate were high. One case had liver function test abnormality. Active tuberculosis did not develop during the LTBI treatment. In the group with TST-positive children aged <15 years with one and 2 BCG vaccine scars, the decrease between pre- and post-treatment TST results showed a statistically significant difference.

KEYWORDS: Tuberculin skin test, bacillus Calmette-Guerin vaccine, isoniazid, latent tuberculosis infection treatment

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INTRODUCTION

Tuberculosis is an air-bone infectious disease and can affect all the organs by the lymphohematogenous route; however, it is rarely transmitted via the skin and gastrointestinal tract. *Mycobacterium tuberculosis* (MTB) is transmitted from individuals with active pulmonary tuberculosis through aerosols released during coughing, sneezing, or speaking When a person with active pulmonary tuberculosis coughs, sneezes, or speaks, then some individuals are infected with transmitted through *Mycobacterium tuberculosis*-contained aerosol droplets. Latent tuberculosis infection (LTBI) is the presence of MTB *Mycobacterium tuberculosis* in an individual without any clinical, imaging, or microbiologic evidence of the active disease. According to the World Health Organization (WHO), 30% of the global population is infected with MTB. LTBI is an important source of future tuberculosis cases. Progression to an active tuberculosis disease in LTBI can be prevented. Five percent of cases with LTBI develop active tuberculosis within the first 2 years after infection. In another 5% of LTBI, the immune system effectively controls the dormancy of the bacteria and reactivates it at a later time point. The immune system effectively renders the bacteria dormant and reactivates it at a later time point. The remaining 90% of LTBI do not develop tuberculosis. Children are more likely to develop active tuberculosis after infection (around 30%) compared to adults [1-3]. According to the global tuberculosis 2016 report of WHO, the incidence of tuberculosis cases has decreased by 1.5% from 2014 to 2015 worldwide; however, tuberculosis is still one of the major causes of mortality (1.8 million tuberculosis deaths). The tuberculosis detection rate is 58%, and 10.4 million new tuberculosis cases are reported [4].

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Address for Correspondence: Beyhan Çakar, Ankara Tuberculosis Control Dispensary, Ankara, Turkey
E-mail: becakar@yahoo.com

The most effective method for tuberculosis control is early identification of active cases, isolation, and contact investigations of index tuberculosis cases. LTBI treatment and bacillus Calmette-Guerin (BCG) vaccination are important prophylactic measures against tuberculosis. The diseases that weaken the immune system (blood and lymph system cancers and human immune deficiency virus [HIV] infection) or immunosuppressive therapies (tumor necrosis factor [TNF]-α blockers or corticosteroids), jejunoileal bypass, organ transplantations, low weight, diabetes mellitus, malnutrition, homelessness, and alcoholism are significant risk factors for activation of LTBI. BCG vaccination can prevent miliary and meningeal tuberculosis but cannot eliminate tuberculosis infection. BCG vaccination is advised for tuberculosis control, particularly in developing countries with high incidences of tuberculosis [5-7].

The aim of this study was to evaluate the application of LTBI treatment (indications, demographic data, BCG vaccine scar, tuberculin skin test (TST) values, adverse effects, and therapy results) and to investigate if there is change between TST results according to BCG scar numbers after LTBI treatment with isoniazid (INH).

MATERIAL AND METHODS

Study Population

Data were collected and evaluated from the cases that received LTBI treatment at the Ankara Tuberculosis Control Dispensary No. 7 (Ankara, Turkey) in 2006. Data were collected from the LTBI treatment files from the Ankara Tuberculosis Control Dispensary No. 7 (Ankara, Turkey) in 2006. The results were statistically evaluated.

According to the national guidelines, LTBI treatment indications; children aged <15 years showing a positive TST response; cases of TST conversion (increase of least 6 mm over the past 2 years without BCG vaccination); patients aged <35 years who have come in close contact with active pulmonary tuberculosis cases, patients aged <35 years who have sequela lesions similar to tuberculosis but without active tuberculosis patients aged <35 years who have sequela without active tuberculosis in the chest x ray [8]. Other risk factors for activation of LTBI include HIV infection, patients using TNF-α inhibitors or corticosteroids, silicosis, apical fibrotic lesions, low weight, diabetes mellitus, blood and lymph system cancers, jejunoileal bypass, and organ transplantations.

Tuberculin skin test was performed by intra-dermal injection on the two-third up dorsal face of the left forearm in accordance with the Mantoux technique. Tuberculin consists of 5 units of 0.1 mL of purified protein derivative (PPD; RT23). The transverse diameter (long axis of the forearm) of induration at the site of the injection and not redness was measured 72 hours after the application of tests. It was read using the palpable and pen methods and recorded in millimeters. The application of tests, reading, and presence and number of BCG scars were evaluated by the same trained nurses in our dispensary. There was no ambiguity between smallpox and BCG vaccination scars since smallpox vaccination was not implemented in Turkey. There was no ambiguity between smallpox and BCG vaccination scars. Because smallpox vaccination was not applıed in Turkey. It was assessed according to our national guidelines. For BCG-vaccinated cases, an induration size of ≤5 mm was defined as negative, 6-14 mm was considered previous vaccination BCG or non-tuberculous mycobacteria (NTM) exposure, and an induration of >15 mm was considered positive (tuberculosis infection or NTM exposure). For non-vaccinated subjects, an induration of 6-9 mm was regarded as negative, while >10 mm was considered positive. A chest X-ray was performed before the LTBI treatment. If the cases did not report active tuberculosis, LTBI treatment was administered. The Control Society of the Turkish Ministry of Health recommends the treatment with INH for 6 months at 10 mg/kg/day in children and 5 mg/kg/day in adults (maximum 300 mg/day). The duration of the treatment is 9 months for HIV positive patients or those with immunosuppression. If patients could not receive INH or were resistant to INH, rifampicin 10 mg/kg/day can be given for 4 months (maximum 600 mg/day) [8]. Before 2007, 2- or 3 time BCG vaccinations (revaccination) according to TST result have been applied in the national vaccination program. Second BCG vaccinations (revaccination) according to TST result have been applied in the national vaccination program. If TST result negative sometimes two or three BCG vaccinations were applied. Currently, for 2-3-month-old healthy babies, one dose BCG vaccination is recommended, unless any contraindications exist. After the first 3 months, BCG vaccination is applied according to the TST reaction, If the result of TST is 0-5 mm, BCG vaccination is applied; for 5-9 mm TST result, BCG is applied again 1 week later (booster effect), if the result 5-9 mm, BCG vaccination is applied, if the result is >10 mm, the child was considered LTBI. It was investigated tuberculosis diseases in child and its close contact. We investigated whether or not child and the close contacts have tuberculosis diseases. BCG vaccination is not administered after 6 years of age [8].

This study was approved by the Department of Tuberculosis Control at the Ministry of Health (dated: July 06, 2015; number: 518 Ankara, Turkey). The patients were informed and the consent was provided by the patients or relatives.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) program version 15. Descriptive statistics are presented as mean±standard deviation (SD) for variables with normal distribution, as median (minimum-maximum) for variables with non-normal distribution, and as number of events (%) for nominal variables. Wilcoxon test and paired t test were used to compare pretreatment and post-treatment TST values according to BCG vaccine scar numbers. $P<0.05$ was considered statistically significant for all results.

RESULTS

In our dispensary, 91 tuberculosis cases were recorded in 2006. Among them, there were 56 (62%) pulmonary tuberculosis (53 of 56 cases sputum acid-fast bacilli (AFB) smear-positive), 23 (25%) non-pulmonary tuberculosis, and 12 (13%) pulmonary tuberculosis plus non-pulmonary tuber-

Table 1. Total numbers of cases that used LTBI treatment and mean age, SD, age range of evaluated (TST and scar) cases according to groups (close contact with a smear-positive active pulmonary tuberculosis cases, TST- positive cases, and others)

	Total cases, n (%)	Evaluated cases, n (%)	Age of evaluated cases, mean±SD (range), years
TST-positive cases	150(59)	138 (62)	8.27±2.19 (1-15)
Smear-positive tuberculosis contact	96(38)	77 (35)	7.56±3.76 (1-17)
Others	7(3)	6 (3)	38.83±28.07 (6-84)
Total	253	221	8.85±7.13 (1-84)

LTBI: latent tuberculosis infection; SD: standard deviation; tuberculosis: Tuberculosis; TST: tuberculin skin test

Table 2. Distribution of evaluated TST cases according to age group

Age groups, years	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65+	Total
Numbers	21	190	7	0	1	1	0	1	221
%	10	86	3	0	1	0	0	0	100

TST: tuberculin skin test

culosis cases. LTBI treatment was administered to 253 cases during 2006. The male/female case rate was 51/49. The mean age was 8.92±6.87 years (range, 0-84 years); the age of 14 cases were >15 years. The number of cases with BCG scars was as follows: one scar in 171 (68%) cases, 2 scars in 59 (23%) cases, and 3 scars in 6 (2%) cases. Seventeen cases (7%) were without BCG scars. A TST reaction of ≥15 mm was detected in 74% of cases. Pre-treatment TST results were 0-4 mm in 14 (7%) cases, 5-14 mm in 49 (19%) cases, and ≥15 mm in 188 (74%) cases. TST results of 2 (1%) cases were unavailable. Indications for LTBI treatment included 96 (38%) smear-positive cases, 150 (59%) TST positive (111 of them were found in primary school TST screening before second BCG vaccine application), and 7 (3%) cases of immunosuppression (2 cases TNF-α inhibitors and 4 cases of steroid treatment, with 1 case of renal transplantation). LTBI treatment was not administered to cases with TST conversion and sequela lesions in our study. INH treatment (10 mg/kg, maximum 300 mg/day) was given 6 months for TST-positive cases and 9 months (only 7 cases) for immunosuppressed patients. In total, 240 (95%) patients completed the therapy; in 5 of them LTBI treatment ended with BCG vaccination; one case (13-year-old adolescent) had liver function test abnormality and INH was discontinued in the first month. Others cases (n=7) discontinued LTBI treatment because of doctor's advice or the patients did not want to use the drug. The cases were followed up with the 4 chest radiographies between 3 and 12 months for early identification of active tuberculosis. If the cases had the symptoms of fever, night sweats, weight loss, prolonged cough-producing sputum, and chest pain, a dispensary visit was recommended and tuberculosis disease was investigated.

Bacillus Calmette-Guerin vaccination scar numbers, pre-treatment and post-treatment TST of 221 cases were full. TST values according to BCG vaccine scar numbers were compared pre- and post-treatment. In this study, 221 cases included close contact with smear-positive active pulmonary tuberculosis cases (n=77, 35%), TST-positive children aged <15 years (n=138, 62%), and the other (n=6, 3%) patients with immunosuppression. Table 1 shows the mean age±SD and age range for the cases according to groups. Of the cases, 86% were between 5 and 14 years (Table 2). TST values of the indication groups according to BCG vaccine scar numbers were compared. Table 3 shows TST values of the indication groups according pre-treatment and post-treatment, mean ± standard deviation, and minimum and maximum values of TST according to scar numbers and groups. The difference between TST before and after LTBI treatment was evaluated statistically. The difference between TST results were statistically significant (p=0.00) in TST-positive children aged <15 years with one and 2 BCG vaccine scars. The decreased difference in smear-positive active pulmonary tuberculosis cases and other groups was not statistically significant (Table 3).

DISCUSSION

The most effective methods for preventing tuberculosis infection are early identification of active pulmonary tuberculosis cases and isolation. The closeness and duration with active pulmonary tuberculosis cases increases the risk of LTBI. The replication and proliferation capability of MTB may persist for years. This leads to sensitization of monocytes in the peripheral blood. The presence of these sensitized monocytes can be measured with a TST or the interferon-γ release assays (IGRA). Both tests are based on the cell-mediated immune response to MTB antigens. The IGRA is an immune response to merely 2 or 3 tuberculosis antigens but the TST is immune response to 200 tuberculosis antigens [2,3,5]. From positive TST to negative TST is known reversion. If MTB is successfully eliminated (transient infection) or if there is minimal MTB activity in the primary complex, it indicates that T-cells are no longer sensitized. A conversion is known to occur if negative TST becomes positive indicating a new MTB infection [6].

Tuberculin skin test, introduced in 1910 by Mantoux and also known as the PPD test, is used in the diagnosis of tuberculosis and evaluation of latent tuberculosis cases. It is a convenient and inexpensive test. The disadvantages include 2 visits, inter-reader variability in measuring induration, and cross-reaction with non-tuberculous mycobacteria and *M.*

Table 3. Pre- and post-treatment TST values, mean±SD, minimum and maximum TST values, BCG scar numbers according to groups (close contact with smear-positive active pulmonary tuberculosis cases, TST positive cases, and others) and p values.

BCG vaccine scar (n)	Groups	TST	Case numbers	Mean TST	SD	Minimum-maximum	p
Scar 0	TST-positive	First TST	5	16.40	0.89	15-17	0.06
		Last TST	5	14.20	2.68	10-17	
	Smear-positive	First TST	10	8.70	6.30	0-17	0.35
	tuberculosis contact	Last TST	10	7.10	6.59	0-16	
	others	First TST	1	6.0		6-6	
		Last TST	1	17.00		17-17	
Scar 1	TST-positive	First TST	99	17.98	2.53	15-25	0.00**
		Last TST	99	14.76	3.46	0-25	
	Smear-positive	First TST	51	11.84	5.98	0-22	0.61
	tuberculosis contact	Last TST	51	12.06	5.49	0-24	
	others	First TST	3	15.00	3.60	11-18	0.10
		Last TST	3	9.00	8.54	0-17	
Scar 2	TST-positive	First TST	31	18.35	2.82	15-26	0.00**
		Last TST	31	14.39	3.13	8-21	
	Smear-positive	First TST	14	13.71	5.12	5-24	0.85
	contact	Last TST	14	13.86	5.34	1-25	
	others	First TST	2	18.00	2.82	16-20	0.31
		Last TST	2	21.50	2.12	20-23	
Scar 3	TST positive	First TST	3	17.67	1.52	16-19	0.10
		Last TST	3	13.00	5.19	7-16	
	Smear-positive	First TST	2	18.00	2.82	16-20	0.65
	tuberculosis contact	Last TST	2	14.50	4.95	11-18	

BCG: bacillus Calmette-Guerin; SD: standard deviation; TST: tuberculin skin test
** significant at the 0.05 level

bovis. TST test with indurations of >15 mm is more likely to be the result of tuberculosis infection than of BCG vaccination. TST is a delayed-type hypersensitivity reaction. A negative test does not always mean that a person is free of tuberculosis. People who have been infected with tuberculosis and are HIV positive or have undergone cancer chemotherapy or steroid therapy, have viral infection, or poor nutrition may not have a positive skin test possibly due to a poor immune function [3,6,9].

Bacillus Calmette-Guerin vaccination is important for tuberculosis control program, particularly for high tuberculosis incidence in developing countries. The protective efficacy of BCG vaccine is most appropriate for infants. Post-vaccination tuberculin reactivity is not an indicator of protective efficacy of BCG vaccination. The tuberculin reactivity of BCG vaccine is effective against miliary and meningeal tuberculosis but cannot prevent or eliminate tuberculosis infection. The patient age, tuberculosis localization, the geographic area, previous sensitization to mycobacteria, and the patient's immune status are crucial in the efficiency of the vaccine. The efficacy of BCG vaccine against tuberculosis can reach up to 80% in children and 50% in adults. Previous exposure to environmental mycobacteria may be an important limiting factor for the BCG vaccine [10-12]. The history of BCG vaccination may be ignored when TST is interpreted in adults. [12-15]. Gibbs et al. [16] suggested that BCG vaccination gives approximately 60% protection, particularly against tuberculous meningitis and disseminated tuberculosis.

The ideal BCG vaccine would produce a scar at the site of injection [12]. A study has shown that infants vaccinated in child health clinics indicated that less than 60%-80% had a detectable scar 3-4 years after vaccination. The incidence of scar formation has also been reported to be lower with the multi-puncture method compared to the intra-dermal method [17]. In our study, 93% of our cases had a detectable scar.

Isoniazid is used in both treatment of active tuberculosis and in LTBI. INH can cause hepatotoxicity that related with age and frequently occurs within the first 3 months of treatment [18]. The incidence of INH hepatotoxicity was reported between 0.1% and 8% in different studies. Devrim et al. [19] showed INH hepatotoxicity the effect of age in children during a 7-year period and tuberculosis or latent infection were included in this study showed INH hepatotoxicity the effect of children tuberculosis or latent infection during a 7-year study period. Hepatotoxicity was observed in 12 (1.7%) of 695 patients, and 4 patients (0.57%) had moderate-to-severe hepatotoxicity. Kunst et al. [20] found that the rate of hepatotoxicity was 1.8%. The rates were higher among those aged

≥35 years than those aged <35 years. Wu et al. [21] studied 84 centers performing pediatric liver transplants during a 10-year period; 20 cases of INH-related liver failure were found, and the estimated incidence of liver failure was up to 3.2/100,000 for children on prophylactic INH. The mean age was 9.8 years (range, 1.3-17). The mean length of INH therapy was 3.3 months (range, 0.5-9). According to Smieja et al. [22], INH was associated with hepatotoxicity in 0.36% of patients on 6 months of treatment and in 0.52% of patients treated for 12 months. In our study, one of 253 cases (0.4%) had liver function test abnormality and INH was stopped in the first month of treatment.

The therapy in TST-positive patients can reduce the risk of disease reactivation and development of active tuberculosis. The effectiveness of INH treatment measured varied between 25% and 92% in the studies [22,23]. In our study, in TST-positive children aged <15 years with one and 2 BCG vaccine scars, the decrease difference between pre and post-treatment TST results were statistically significant (59%; 130/221).

Kwara et al. [24] performed a retrospective analysis wherein of 845 patients with LTBI, 690 (81.6%) initiated INH therapy, of whom 426 (61.7%) completed the therapy.

Shieh et al. [25] showed that of 217 patients, 90% were of foreign origin, and 28.6% of these completed the therapy under a usual clinic. A prospective study showed that only 53% of patients completed the therapy [26]. Erkens et al. [27] showed that of 1,049 children with LTBI started on LTBI treatment in 2005-2012, and 90% completed the treatment. In our study, the LTBI treatment completion rate was 95%. Patients, household contacts, and their families were educated about LTBI and LTBI treatment drugs before the treatment was administered. Education follow up and good communication are important factors in the treatment. It was high according other studies.

In our study, the age of the cases with LTBI treatment were under 15 years out of 14 case. One case had liver function test abnormality and INH was stopped in the first month of treatment. BCG vaccination and LTBI treatment completion rates were high. When we investigated if there is change in the difference between pre- and post-treatment TST results according to BCG scar numbers after LTBI treatment with INH, it was found that in TST-positive children aged <15 years with one and 2 BCG vaccine scars, the difference was statistically significant. These results again emphasized that LTBI treatment and BCG vaccination are the most effective preventive methods for tuberculosis control program similar other studies.

Ethics Committee Approval: This study was approved by the Department of Tuberculosis Control at the Ministry of Health (Decision Date: 6.7.2015/Decision Number: 518).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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