Latent Tuberculosis Infection - Diagnosis and Treatment

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Abstract

INTRODUCTION: Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active tuberculosis (TB). Diagnosis and treatment for LTBI are important for TB, especially in high-risk populations. Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are used to diagnose LTBI.

AIM: The study aims to present the first results with IGRA test compared with TST in the screening of LTBI and the treatment results in the cases with LTBI in Macedonia.

MATERIAL AND METHODS: In this study 73 cases diagnosed and treated with LTBI in 2016 were included. For diagnosis of LTBI, we used TST RT -23 5T.U. and commercial IGRA test such as QuantiFERON-TB Gold In-Tube (QFT-IT).

RESULTS: Out of 73 cases with LTBI, 61.64% were men, and 38.36% were women. Among all age groups, the most frequent were cases between 5 and 14 years old (54.79%). Among the evaluated risk groups for LTBI, the most frequent were children household contacts with pulmonary TB cases (61-83.65%), followed by people living with HIV (9-12.33%) and only 3 cases with other medical reasons. Positive TST had 34 cases (46.57%) and positive IGRA test 25 cases (34.25%). Regarding the treatment regimes, we use two regimes: 50 cases (68.44%) received 6 months daily regime with Isoniazid, and 23 cases (31.51%) received 3 months daily regime with Isoniazid and Rifampicin. Treatment outcomes showed that the most patients completed treatment regimes: 55 (75.34%) and only 10 (13.09%) interrupted the treatment.

CONCLUSION: Despite the progress made in the last few years, several challenges remain to be addressed for better management of LTBI which will contribute to strength TB control in the country.

Introduction

Tuberculosis is one of the most prevalent infections of human beings and a formidable public health challenge that shows little sign of abating [1]. Primary infection with *M. tuberculosis* leads to clinical disease in only ~ 10% of individuals. In the remaining cases, the ensuing immune response arrests the further growth of *M. tuberculosis*. However, the pathogen is completely eradicated in only ~ 10% people, while the immune response in the remaining ~ 90% individuals only succeeds in the containment of infection as some bacilli escape killing by blunting the microbicide mechanisms of immune cells and remain in no replicating (dormant or latent) state in old lesions. The process is termed as latent tuberculosis infection (LTBI) and is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB [2].

Persons with LTBI do not have active tuberculosis and do not feel sick but may develop it in the near or remote future, a process called TB reactivation [3]. The lifetime risk of reactivation TB for a person with documented LTBI is estimated to be 5 - 10%, with the majority developing TB disease within the first five years after initial infection and lifetime risk, is ~ 50% in HIV coinfected individuals [4][5]. However, the risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the

host. Finding LTBI provides an opportunity to treat and prevent reactivation of the latent infection that leads to active disease, especially in people with compromised immune systems.

Systematic diagnosis and treatment of LTBI is part of the new End TB strategy by World Health Organization (WHO) and achieving ≥ 90% LTBI treatment coverage among people living with HIV (PLHIV), and child contacts of TB cases are one of the global priority targets [6].

Available tests to demonstrate prior tuberculosis infection include the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) [7].

In the Republic of Macedonia, the systematic screening for LTBI and treating people who have risk factors for developing active TB is part of the National tuberculosis program (NTP). The Macedonian national guideline for LTBI updated in 2016, recommends three main groups with risk factors for management of LTBI: children as household contacts of pulmonary TB cases, PLHIV and patients initiating anti-TNF treatment or receiving immunosuppressive therapy.

The study aims to present our first results with IGRA test compared with TST in the screening of LTBI and the treatment results in the cases with LTBI.

Material and Methods

A retrospective cohort study was undertaken, based on data systematically collected on all persons undergoing the TST-based and the IGRA-based LTBI screening programme and treatment programme during 2016. All data were obtained from the Central unit for registration of TB and LTBI in the Republic of Macedonia, at the Institute for Lung Diseases and TB. In this study 73 cases diagnosed and treated with LTBI were included. For diagnosis of LTBI, we used TST RT-23 5T.U. and induration ≥ 5 mm was considered as positive results. The other test was commercial IGRA such as QuantiFERON-TB Gold In-Tube (QFT-IT), and it was performed by measuring interferon-γ (IFN-γ) with Enzyme-Linked Immunosorbent Assay (ELISA). In the most cases, diagnosis of LTBI was obtained with both tests: with the exception that TST and IGRA test was not performed in 11 (15.07%) and 36 (49.1%) cases respectively. According to our national guidelines for treatment of LTBI, there are two used therapeutic regimes: the daily regime of Isoniazid (H) for 6 months or daily regime of Isoniazid and Rifampicin (R) for 3 months. All cases with LTBI were followed during the treatment period, and the treatment outcomes were presented.

The differences of category variables were present with the distribution of the frequencies. For comparison of the differences of the data Fischer-exact test was used. A statistical difference was considered to be significant when the p-value was < 0.05.

Results

Of 73 cases with LTBI, 61.64% were men, and 38.36% were women. According to the age, 61 (83.56%) were children, and 12 (16.43) were adults. Among all age groups, the most frequent were cases between 5and 14 years old (54.79%), Table 1.

Table 1: Distribution of cases with LTBI according to the gender and age groups

Gender	n (%)
Men	45 (61.64)
Women	28 (38.36)
Total	73 (100.00)
Age groups	n (%)
0 – 4	21 (28.77)
5 – 14	40 (54.79)
15 – 24	2 (2.74)
25 – 34	4 (5.48)
35 – 44	0 (0.%)
45 – 54	5 (6.85)
55 – 64	1 (1.37)
Total	73 (100.00)

In this study three groups of cases with risk factors were screened for LTBI and the most frequent were children household contacts with pulmonary TB cases (61-83.65%), followed by PLHIV (9-12.33%) and only 3 cases with other medical reasons: 1 case that initiated anti TNF therapy and 2 that received immunosuppressive therapy, named as others (Table 2). According to the data from our NTP, in 2016 among 360 TB contacts examined, 15 were TB cases (4.16%), and 61 were with LTBI (16.9%).

Table 2: Different groups with risk factors for the screening of LTBI

Risk groups	n (%)
Contact with TB cases	61 (83.56)
PLHIV	9 (12.33)
Others	3 (4.11)
Total	73 (100.00)

In Table 3 and Table 4 the results obtain with TST, and IGRA test was separately presented. In Table 5 the combination of both tests was presented, and it is obvious that in all cases included in the study one or both tests were performed.

Table 3: Results of TST at the time of screening for LTBI

TST test	n (%)
Negative	28 (38.36)
Positive :5 – 14mm	11 (15.07)
Positive :15 – 20mm	18 (24.66)
Positive : 20 – 34mm	5 (6.85)
Not done	11 (15.07)
Total	73 (100.00)

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Even we used to perform both tests in each case; there were 11 cases without TST and 36 without IGRA test. TST confirmed 34 positive cases (46.57%), IGRA test 25 positive cases (34.25%) and both tests were positive in 11 cases (15.06%) and both negative in 6 cases (8.21%).

Table 4: Results of IGRA test at the time of screening of LTBI

IGRA test	n (%)
Negative	12 (16.44)
Positive	25 (34.25)
Not done	36 (49.31)
Total	73 (100.00)

There were 17 cases in which only TST was performed and 1case in which only IGRA was performed, and the results were negative. Those 18 and those 6 cases were both tests confirmed to be negative, were without laboratory confirmation for LTBI (Total 24).

Table 5: Combination of TST and IGRA

Test	IGRA pos	IGRA neg	IGRA not done	Total
TST pos	10	5	19	34
TST neg	5	6	17	28
TST not done	10	1	/	11
Total	25	12	36	73

In Macedonia, there is obligatory Bacillus Calmette–Guerin (BCG) vaccine for all newborn. Besides this, the results showed that nearly one-third of evaluated cases were with the negative status of BCG vaccination (Table 6).

Table 6: BCG status of cases with LTBI

BCG status	n (%)
Positive	51 (69.86)
Negative	21 (28.77)
Unknown	1 (1.37)
Total	73 (100.00)

Regarding different treatment regime for LTBI, 50 cases received daily regime with H for 6 months and 23 cases received daily regime of H/R for 3 months (Table 7).

Table 7: Different treatment regime for LTBI

Treatment regimes	n (%)
6 months Isoniazid	50 (68.49)
3 months Isoniazid and Rifampicin	23 (31.51)
Total	73 (100.00)

Treatment outcomes showed that 75.34% of treated cases with LTBI completed treatment, and only 13.69% did not finish the whole regime (table 8).

Table 8: Treatment outcomes in 73 cases with LTBI

Treatment outcomes	n (%)
Completed treatment	55 (75.34)
Interrupted treatment	10 (13.69)
Interrupted treatment due to negative control TST	8 (10.96)
Total	73 (100.00)

In an aim to evaluate if there were some factors that influenced the treatment outcome, the correlation test was performed between the gender, age groups, different risk groups for detecting LTBI, different therapeutic regimes and the treatment outcomes, and we did not find any statistically significant correlation (Table 9).

Table 9: Correlation of gender, age groups, risk groups and treatment regimes of cases with LTBI and treatment outcomes

		Treatment outcome		
	N	Interrupted	Completed	Interrupted due to negative control TST
Gender				
Men	45 (61.64)	7 (70)	33 (60)	5 (62.5)
Women	28 (38.36)	3 (30)	22 (40)	3 (37.5)
		Fisher exact, two-tailed p = 0.9		
Age groups				
0 – 4	21 (28.77)	2 (20)	16 (29.09)	3 (37.5)
5 – 14	40 (54.79)	6 (60)	29 (52.73)	5 (62.5)
15 – 24	2 (2.74)	1 (10)	1 (1.82)	0
25 – 34	4 (5.48)	0	4 (7.27)	0
45 – 54	5 (6.85)	1 (10)	4 (7.27)	0
55 – 64	1 (1.37)	0	1 (1.82)	0
		Fisher exact, two-tailed p = 0.875		
Risk groups				
Contact with TB	61 (83.56)	8 (80)	45 (81.81)	8 (100.0)
PLHIV	9 (12.33)	2 (20)	7 (12.73)	0
Others	3 (4.11)	0	3 (5.45)	0
		Fisher exact, two-tailed p = 0.54		
Treatment regime				
6 months H	50 (68.49)	7 (70)	38 (69.09)	5 (62.5)
3 months H/R	23 (31.51)	3 (30)	17 (30.91)	3 (37.5)
		Fisher exact, two-tailed p = 0.54		

Discussion

The presented study shows our results of using two tests (TST and IGRA) for detecting the LTBI in the Republic of Macedonia and treatment outcomes: in 2016 there were 73 cases diagnosed with LTBI that received preventive therapy. In Macedonia, for many years ago, only TST was used for screening the LTBI mostly among children household contacts of pulmonary TB cases; we did not use this test for screening LTBI among the adults even they were contacts with TB cases. All these adult contacts according to our NTP were screened only for active TB. Because BCG vaccination is obligatory for all newborns in Macedonia, it was difficult to interpret TST positive results: whether they are due to the cross-reaction with BCG vaccination, or to the infection with Mycobacterium tuberculosis. In 2013, IGRA test with high specificity was introduced for screening LTBI in our NTP which meant to reduce false positivity due to BCG vaccination or nontuberculous mycobacteria (NTM) infection. In the beginning its indication was limited only to children contacts with TB cases and PLHIV, and after this first period we expanded the indication according to the recommendation from Guidelines on the management of latent tuberculosis infection [5] to the patients initiating anti-tumor necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or hematologic transplantation, and patients

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with silicosis, but its implementation was going very slowly. There is a modification in the Macedonian Guidelines for LTBI in 2016, from the 2008 Guidelines. In 2016 there were only 9 cases with PLHIV and 3 cases with other medical risk factors screened and treated of LTBI.

All cases with LTBI in this study were not screened with both tests: according to our practice for many years ago, TST was performed in all children - 61 and only in1 adults (62-84.93%). IGRA was performed in half of the cases (37-50.68%): 12 adults and 25 children.

According to the data from the literature, there is no ideal test for detecting Mycobacterium tuberculosis infection even both tests are moderately sensitive and highly specific [7]. The disadvantages of TST include the need for two visits (to place the TST and to read it 48-72 hours later), inter-reader variability in measuring millimetres of induration, diminished response caused by immunosuppression, boosting on repeat testing, and potential cross-reaction with nontuberculous mycobacteria and *M. bovis* BCG vaccine [8]. The introduction of the IGRA was an advance in diagnostic technology. IGRA detect LTBI by measuring IFN-gamma release in response to antigens present in Mycobacterium tuberculosis, but not BCG vaccine and most nontuberculous mycobacteria.

The evidence base for these tests has expanded rapidly and now, the result of some systematic reviews indicate that in comparison to TST, IGRAs can detect LTBI with a higher specificity, negative (NPV) and positive (PPV) predictive values, as they are not confounded by previous BCG vaccination [9] [10] [11].

Regarding the treatment regimes we use two regimes: 50 cases (68.44%) received 6months daily regime with H, and 23 cases (31.51%) received 3months daily regime with HR. We have to comment that according to our results there were 24 cases without laboratory confirmation of LTBI, but besides that, they were treated with preventive therapy for LTBI. This was because they were children at 5 or under the age of 5 with very close household contact with pulmonary TB. It is according recommendations by WHO and other association that people living with HIV and children under the age of 5 years who are close household or close contact with people with TB and who have negative TST or IGRA results (with normal chest radiograph) should be treated for LTBI and another TST or IGRA performed 8-10 weeks after contact has ended. If a repeat TST or IGRA result is positive, treatment should be continued. If it is negative, treatment can usually be discontinued [5] [12] [13].

According to the Guidelines from WHO and the Centers for Disease Control and Prevention (CDC) there are four treatment regimes for LTBI: 9 or 6 months of daily self-administered H, 4 months of

daily self-administered R, 3 months of daily self - administered H/R, and the newest 3 months of once-weekly directly observed isoniazid-rifapentine [5][14]. WHO recommends either 6 or 9 months of daily 9H as the standard for treatment of LTBI [5]. For people living with HIV infection, 9 months of therapy is recommended. The benefits of preventive therapy to individuals with LTBI have been demonstrated in some randomised clinical trials [15] [16].

The results from this study showed that most patients completed treatment regimes: 55 (75.34%) and only 10 (13.09%) interrupted the treatment. 8 (10.96%) of them interrupted treatment because of negative control TST after 8 weeks of the window period. We did not find that some factors such as gender, age groups, different risk groups or treatment regimes correlated with the treatment outcomes. In our study cases, we did not register some serious adverse effects from therapy. In the study of Denholm et al. even adverse effects were frequently identified among the cases with LTBI, there were also, high levels of treatment adherence and completion [17]. The analysis from some studies identified the following determinants as detrimental to treatment completion: adverse drug reactions, longer duration of treatment, immigrant status, long distance from a health facility, the presence of stigma, alcohol and drug use, unemployment and time lag between diagnosis and treatment [5]. One randomised trial showed a significant increase in completion rate in the 3-month weekly rifapentine plus isoniazid regimen compared to the 9-month isoniazid regimen [18].

Analysis of this study presented the program for diagnosis and treatment of LTBI in Macedonia and compared the findings with the actual recommendations. When the IGRA's has been introduced in our program, big progress was made in the widening the indication for detecting LTBI. Detecting and treating cases who are at risk to develop active TB, will contribute to better control of TB in Macedonia. Using IGRA tests among household contacts with pulmonary TB will help for better selection of cases that need preventive therapy. Despite the progress, several challenges remain to be addressed: further strengthening in the optimum use of both tests, to assess the ability of these tests to predict tuberculosis disease, their reproducibility over serial tests, and discordance between tests. Regarding the treatment as soon as possible we should provide the use of 3 months of once-weekly directly observed isoniazid-rifapentine regime.

References

1. Global TB report. World Health Organization. Geneva, Switzerland: WHO, 2015.

2. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et

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al and TBNET. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009; 33:956–73. https://doi.org/10.1183/09031936.00120908 PMid:19407047

3. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974; 99:131–8. https://doi.org/10.1093/oxfordjournals.aje.a121593 PMid:4810628

4. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis—the perfect storm. Journal of Infectious Diseases. 2007; 196(1):S86–S107. https://doi.org/10.1086/518665 PMid:17624830

5. Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: WHO, 2015.

6. End TB Strategy, WHO, 2015.

7. Person AK, Pettit AC, and Sterling AT. Diagnosis and treatment of latent tuberculosis infection: an update. Curr Respir Care Rep. 2013; 2(4):199-207. https://doi.org/10.1007/s13665-013-0064-y PMid:25298921 PMCid:PMC4185413

8. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection-United States, 2010. MMWR Recomm Rep. 2010:1–25. PMid:20577159

9. Lalvani A, Pareek M. Interferon gamma release assays: principles and practice. Enferm Infecc Microbiol Clin. 2010 Apr; 28(4):245-52. https://doi.org/10.1016/j.eimc.2009.05.012 PMid:19783328

10. Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-γ release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. European Respiratory Journal. 2011; 37(1):88–99. https://doi.org/10.1183/09031936.00115110 PMid:21030451

11. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Annals of internal medicine. 2007; 146 (5):340–54. https://doi.org/10.7326/0003-4819-146-5-200703060-00006 PMid:17339619

12. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000; 161 (4 pt 2):S221-S247. PMid:10764341

13. Centers for Disease Control and Prevention CDC. Latent tuberculosis infection: A guide for primary health care providers. MMWR, 2013.

14. Centers for Disease Control and Prevention CDC. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2011; 60:1650–3. PMid:22157884

15. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, Goldberg SV. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA pediatrics. 2015; 169(3):247-55. https://doi.org/10.1001/jamapediatrics.2014.3158 PMid:25580725

16. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, Memish Z, Khan K, Gardam M, Hoeppner V, Benedetti A. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Annals of internal medicine. 2008; 149(10):689-97. https://doi.org/10.7326/0003-4819-149-10-200811180-00003 PMid:19017587

17. Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C and Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. Drug Healthc Patient Saf. 2014; 6:145–149. https://doi.org/10.2147/DHPS.S68837 PMid:25364275 PMCid:PMC4211866

18. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011; 365:2155–66. https://doi.org/10.1056/NEJMoa1104875 PMid:22150035