ORIGINAL ARTICLE
https://doi.org/10.4046/trd.2020.0038
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2020;83:283-288

trd
Tuberculosis & Respiratory Diseases

Evolution of Interferon-Gamma Release Assay Results and Submillisievert Chest CT Findings among Close Contacts of Active Pulmonary Tuberculosis Patients

Soonho Yoon, M.D., Ph.D.[1], Do-CiC Mihn, M.D., Ph.D.[2], Jin-Wha Song, M.D.[3], Sung A Kim, R.N.[4] and Jae-Joon Yim, M.D.[4]

[1]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, [2]Seegene Medical Foundation, Seoul, [3]Department of Internal Medicine, Veterans Health Service Medical Center, Seoul, [4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

Background: Latent tuberculosis (TB) infection among TB contacts is diagnosed using plain chest radiography and interferon-gamma release assays (IGRAs). However, plain chest radiographs often miss active TB, and the results of IGRA could fluctuate over time. The purpose of this study was to elucidate changes in the results of the serial IGRAs and in the findings of the serial submillisievert chest computed tomography (CT) scans among the close contacts of active pulmonary TB patients.

Methods: Patients age 20 or older with active pulmonary TB and their close contacts were invited to participate in this study. Two types of IGRA (QuantiFERON-TB Gold In-Tube assay [QFT-GIT] and the T-SPOT.*TB* test [T-SPOT]) and submillisievert chest CT scanning were performed at baseline and at 3 and 12 months after enrollment.

Results: In total, 19 close contacts participated in this study. One was diagnosed with active pulmonary TB and was excluded from further analysis. At baseline, four of 18 contacts (22.2%) showed positive results for QFT-GIT and T-SPOT; there were no discordant results. During the follow-up, transient and permanent positive or negative conversions and discordant results between the two types of IGRAs were observed in some patients. Among the 17 contacts who underwent submillisievert chest CT scanning, calcified nodules were identified in seven (41.2%), noncalcified nodules in 14 (82.4%), and bronchiectasis in four (23.5%). Some nodules disappeared over time.

Conclusion: The results of the QFT-GIT and T-SPOT assays and the CT images may change during 1 year of observation of close contacts of the active TB patients.

Keywords: Latent Tuberculosis; Tomography, Spiral Computed; Interferon-Gamma Release Tests

Address for correspondence: Jae-Joon Yim, M.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Phone: 82-2-2072-2059, **Fax:** 82-2-762-9662, **E-mail:** yimjj@snu.ac.kr
Received: Apr. 15, 2020, **Revised:** Jun. 9, 2020, **Accepted:** Jul. 7, 2020, **Published online:** Jul. 9, 2020

Introduction

Tuberculosis (TB) has a great impact on human health. Globally, an estimated 10.0 million (range, 9.0–11.1 million) people fell ill with TB in 2018, a number that has been relatively stable in recent years. In 2018, there were an estimated 1.2 million TB deaths among human immunodeficiency virus (HIV)–negative people and an additional 251,000 deaths among HIV-positive people[1].

To eradicate TB, the diagnosis of latent TB infection and the prevention of active TB through treatment is crucial. The recent contacts of patients with active pulmonary TB constitute a high-risk group for progression to active TB[2]. Korean TB guidelines recommend plain chest radiographs and acid-fast staining with mycobacterial culture of sputum for the close contacts of patients with active pulmonary TB. If there is no evidence of active pulmonary TB, the tuberculin skin test or an interferon-gamma release assay (IGRA) should be performed to diagnose latent TB infection[3].

However, plain chest radiographs often miss active TB. According to a previous study, 18 of 87 close TB contacts were diagnosed as having active pulmonary TB. Nine of the 18 had normal chest radiograph images, but had lesions that were suggestive of active TB on chest computed tomography (CT) scans[4]. Meanwhile, the results of IGRAs fluctuated over time in some individuals[5].

The aim of this study was to elucidate changes in the serial results of two types of IGRAs and in the findings of serial submillisievert chest CT scans among close contacts of active pulmonary TB patients.

Materials and Methods

1. Participants

Patients aged 20 years or more with active pulmonary TB who were diagnosed at Seoul National University Hospital between October 1, 2017, and November 30, 2018, and their close contacts were invited to participate in this study. A diagnosis of active pulmonary TB was made if (1) a culture of *Mycobacterium tuberculosis* was positive or (2) polymerase chain reaction results indicated *M. tuberculosis* in sputum or bronchoscopic specimens. Close contacts were defined as those living in the same house or who shared the same room for 4 weeks or longer. All participants gave written informed consent, and the protocol of this study was reviewed and approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. H-1704-157-849).

2. Follow-up of close contacts

At the time of enrollment, we interviewed and examined the participants. We performed two types of IGRA tests (QuantiFERON-TB Gold In-Tube assay [QFT-GIT, Qiagen, Hilden, Germany] and the T-SPOT.*TB* test [T-SPOT, Oxford Immunotec, Oxford, UK]) and submillisievert chest CT scanning at baseline and at 3 and 12 months after enrollment.

The QFT-GIT assay was performed in two stages, according to the instructions of the manufacturer[6]. The cutoff value for a positive result was (antigen–nil) ≥0.35 IU/mL of interferon-γ and ≥25% of the nil sample. The T-SPOT test was also done according to the instructions of the manufacturer[7]. Test wells were scored as positive if (the number of spots in panel A [ESAT-6]–nil) and/or (the number of spots in panel B [CFP-10]–nil) ≥8.

3. Submillisievert chest CT scanning

All chest CT scans were obtained using a dual-source, 192-channel, multidetector CT scanner (Somatom Force; Siemens Healthineers, Forchheim, Germany) without intravenous administration of contrast medium. The CT parameters were as follows: a peak kilo-voltage of 100 kV with spectral shaping by tin (Sn) filtration, a reference tube current of 40 mA·sec, a tube rotation time of 0.25 milliseconds, a detector collimation of 0.6×1.92 mm, and a reconstruction kernel of Br59-3. Patients were scanned in the supine position at full inspiration in the craniocaudal direction from the lung apex to the lung base. CT images were reconstructed by 3-mm and 1-mm slice thicknesses in the transverse plane and 3-mm slice thickness in the coronal plane. The mean dose–length product and effective dose per CT scan were 8.9±2.7 mGy·cm and 0.13±0.03 mSv, respectively[8].

4. Statistical analysis

Categorical variables were summarized as numbers with percentages, and continuous variables are presented as the median and the interquartile range (IQR). All statistical analyses were performed using Stata, version 13.0 (Stata Corp., College Station, TX, USA).

Results

1. Demographic and clinical characteristics of index patients with active pulmonary TB

In total, 19 patients with active pulmonary TB participated in this study (15 [78.9%] were men; median age, 70 years [IQR, 61–80]). One patient (5.3%) was a current smoker and 10 (52.6%) were ex-smokers. Two (10.5%) had a history of TB, five (26.3%) had diabetes, and two (10.5%) were taking immune suppressants. The most common symptoms were cough (9 patients, 47.4%) and sputum (9 patients, 47.4%). Of the 19 pa-

tients, 18 (94.7%) were diagnosed based on *M. tuberculosis*-positive culture from sputum. Two (10.5%) were diagnosed as having multidrug-resistant TB (Table 1).

2. Demographic and clinical characteristics of close contacts

In total, 19 close contacts participated in this study. One was diagnosed as having active pulmonary TB and was excluded from further analysis. The median age of the remaining 18 close contacts was 64 years (IQR, 52–72), and four (22.2%) were male. The median BMI of the 18 close contacts was 24.1 kg/m^2 (IQR, 22.8–26.4). None of the close contacts had a history of TB, but four (22.2%) had diabetes. Among the close contacts, 17 (94.4%) were family members of index patients and one was a full-time care giver (Table 2).

Table 1. Clinical characteristics of 19 index patients with active pulmonary TB

Characteristic	Value
Total	19 (100)
Male sex	15 (78.9)
Age, yr	70 (61–80)
Smoking	
Current	1 (5.3)
Ex-smoker	10 (52.6)
History of TB	2 (10.5)
Diabetes	5 (26.3)
Immune suppressant use	2 (10.5)
Symptoms	
Cough	9 (47.4)
Sputum	9 (47.4)
Weight loss	4 (21.1)
Hemoptysis	2 (10.5)
Diagnosis	
Sputum AFB smear positive	12 (63.2)
Sputum mycobacterial culture positive	18 (94.7)
Sputum MTB-PCR positive	13 (68.4)
Sputum Xpert assay positive	13 (68.4)
Bronchial washing AFB smear positive*	3 (15.8)
Bronchial washing mycobacterial culture positive*	5 (26.3)
Bronchial washing Xpert assay positive*	6 (31.6)
Drug resistance	
MDR	2 (10.5)
Resistance, but not MDR	0 (0)
Radiography	
Cavity	5 (26.3)
Bilateral involvement	13 (68.4)

Values are presented as number (%) or median (interquartile range).
*Bronchial washing was performed in six patients.
TB: tuberculosis; AFB: acid-fast baclli; MTB-PCR: *Mycobacterium tuberculosis* polymerase chain reaction; MDR: multidrug resistant.

3. Results of serial QFT-GIT and T-SPOT assays

At baseline, QFT-GIT and T-SPOT assays were performed in 18 close contacts. Four (22.2%) showed positive results for both QFT-GIT and T-SPOT, and there were no discordant results. At 3 months, both tests were repeated in 15 close contacts. Only one (6.7%) showed positive results in both tests, five (33.3%) showed positive QFT-GIT/negative T-SPOT results, and one (6.7%) showed negative QFT-GIT/positive T-SPOT results. At 12 months, both tests were performed in 15 close contacts. Two (13.3%) showed positive results in both tests and another two (13.3%) showed positive QFT-GIT/negative T-SPOT results, but none showed negative QFT-GIT but positive T-SPOT results (Table 3).

One contact (participant 7) showed positive conversion in QFT-GIT assay results at 3 months and at 12 months from negative results at baseline. The levels of interferon-γ (TB antigen-minus null) at baseline, 3 months, and 12 months were

Table 2. Baseline characteristics of 18 close contacts

Characteristic	Value
Total	18 (100)
Male sex	4 (22.2)
Age, yr	64 (52–72)
BMI (kg/m^2)	24.1 (22.8–26.4)
History of TB	0 (0)
Diabetes	4 (22.2)
Immune suppressant use	1 (5.6)
Type of contacts	
Family	17 (94.4)
Care giver	1 (5.6)
Submillisievert chest CT (n=17)	
No abnormality	1 (5.9)
Presence of bronchiectasis	4 (23.5)
Presence of nodules	16 (94.1)
Micronodule only	3 (17.6)
With calcified nodules	7 (41.2)
Decrease in the number of nodules over time	2 (11.8)

Values are presented as number (%) or median (interquartile range).
BMI: body mass index; TB: tuberculosis; CT: computed tomography.

Table 3. Serial changes of QFT and T-SPOT results in 18 close contacts

Participant No.	Index patient		Baseline		3 Months		12 Months	
	AFB smear positive	Presence of cavity	QFT	T-SPOT	QFT	T-SPOT	QFT	T-SPOT
1	Yes	Yes	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
2	Yes	Yes	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
3	Yes	No	Pos.	Pos.	Pos.*	Neg.*	Pos.	Pos.
4	Yes	Yes	Neg.	Neg.	Neg.*	Pos.*	Neg.	Neg.
5	Yes	No	Neg.	Neg.				
6	Yes	No	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
7	Yes	No	Neg.	Neg.	Pos.*	Neg.*	Pos.*	Neg.*
8	Yes	No	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.
9	Yes	No	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
10	No	No	Neg.	Neg.	Pos.*	Neg.*	Neg.	Neg.
11	Yes	Yes	Pos.	Pos.	Pos.*	Neg.*	Pos.*	Neg.*
12	No	Yes	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
13	No	No	Neg.	Neg.			Neg.	Neg.
14	No	No	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
15	No	No	Pos.	Pos.	Pos.*	Neg.*		
16	Yes	No	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
17	No	No	Neg.	Neg.				
18	No	No	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

*Indicates discordant results between QFT and T-SPOT.
QFT: QuantiFERON-TB Gold In-Tube assay; T-SPOT: T-SPOT.*TB* test; AFB: acid-fast baclli; Neg: negative; Pos: positive.

0.18, 1.12, and 1.23 IU/mL, respectively. However, the T-SPOT was consistently negative. Another contact (participant 10) showed positive conversion at 3 months in the QFT-GIT result but had reconverted to negative at 12 months. In this contact, the levels of interferon-γ at baseline, 3 months, and 12 months were 0.00, 0.37, and 0.17 IU/mL, respectively. Others showed consistent QFT-GIT results through the serial tests (Supplementary Table S1). In terms of the T-SPOT assay, one contact (participant 4) showed positive conversion at 3 months, but had reconverted to negative at 12 months. Another contact (participant 11) showed consistent negative conversion at 3 and 12 months (Table 3, Supplementary Table S2).

4. Results of submillisievert chest CT scanning

At baseline, submillisievert chest CT scanning was performed in 17 close contacts. Calcified nodules were identified in seven (41.2%), noncalcified nodules in 14 (82.4%), and bronchiectasis in four (23.5%). Two of seven contacts with calcified nodule(s) had positive IGRA results at baseline. In addition, two of 14 contacts with noncalcified nodules had positive IGRA results at baseline. Changes in serial CT findings were detected in two close contacts (participants 2 and 9) in whom some of the noncalcified nodules disappeared (Table 4). For these two contacts, both QFT-GIT and T-SPOT assays were negative at baseline, 3 months, and 12 months.

Discussion

We investigated the consistency over time of the results of two IGRAs (the QFT-GIT and T-SPOT assays) and the findings of submillisievert chest CT scans performed serially for 1 year among the close contacts of patients with active pulmonary TB. We observed persistent or transient conversions of IGRAs among the contacts. Furthermore, we showed that most of the close contacts had nodules (mainly noncalcified) on submillisievert chest CT, and some of these nodules regressed over time.

At baseline, four of the 18 close contacts showed positive results for both QFT-GIT and T-SPOT, and there were no discordant results. However, the evolution of the results over time was diverse. Participants 7 showed negative results of both QFT-GIT and T-SPOT at enrollment. However, at 3 and 12 months, QFT-GIT had converted to positive, but the T-SPOT results remained negative throughout the 1-year observation

Table 4. Radiographic lesions and their changes on submillisievert chest CT scans in 18 close contacts

Participant No.	Calcified nodule	Noncalcified nodule	Bronchiectasis	Temporal change
1	No	Yes	Yes	No
2	No	Yes	No	Yes
3	Yes	No	No	No
4	No	Yes	No	No
5	Yes	Yes	Yes	No
6	Yes	No	No	No
7	No	Yes	No	No
8	No	No	No	No
9	No	Yes	No	Yes
10	Yes	Yes	No	No
11	No	Yes	No	No
12	No	Yes	No	No
13	Yes	Yes	No	No
14	Yes	Yes	Yes	No
15	Yes	Yes	No	No
16	No	Yes	Yes	No
17	Not performed			
18	No	Yes	No	No

CT: computed tomography.

period. These mismatches could be explained by possible false-positive QFT-GIT results or false-negative T-SPOT results. It is noteworthy that discordant results between QFT-GIT and T-SPOT assays have been reported[9-11]. One difference between the current study and these previous studies is that they reported that T-SPOT was more sensitive than QFT-GIT. In other words, the previous studies more frequently found negative QFT-GIT/positive T-SPOT results[9-11]. The reason why we more frequently observed positive QFT-GIT/negative T-SPOT results is not clear.

In participant 4, the T-SPOT result converted positive at 3 months but returned to negative at 12 months. Given that QFT-GIT was consistently negative in that contact, this transient conversion of T-SPOT could be understood as the intrinsic poor reproducibility of IGRAs in serial testing[5,12].

The importance of chest CT in the diagnosis of latent TB infection has been noted. Previously, our group reported that 9 of 18 patients who were diagnosed with active pulmonary TB in the investigation of an outbreak had normal chest radiographs but had lesions suggesting active pulmonary TB on chest CT scans[4]. Using submillisievert chest CT among six close contacts, we detected the development of multidrug-resistant TB at an early stage in one contact[13]. Furthermore, chest CT can be useful in the detection of latent TB infection. One study group reported that five of 10 patients in whom active pulmonary TB developed after liver transplantation had normal chest radiographs but had lesions suggesting healed TB on chest CT at evaluation for transplantation[14]. In the current study, we used submillisievert chest CT (for which radiation exposure is as low as plain chest postero-anterior and lateral radiographs) and detected one active pulmonary TB patient whose chest radiograph was normal. Furthermore, we identified calcified/noncalcified nodules or bronchiectasis in the majority of our close contact participants. Change of radiographic lesions during one year-observation was identified in only two contacts. In both of them, some of the noncalcified nodules disappeared and no clinical or bacteriological evidence of active pulmonary TB had been confirmed during study period. Although we could not precisely understand the significance of these small lesions, studies involving larger numbers of TB contacts and observation over a longer period could elucidate the clinical meaning of these findings.

To correctly interpret the results of our study, its limitations should be recognized. First, the number of participants was small. Because of this limitation, we could not provide fully generalizable information. However, our study provides some pointers as a preliminary investigation of this topic. Second, the participants were relatively old, with a median age of 64 years. Consequently, we could not be sure that the lung parenchymal abnormalities identified on submillisievert chest CT developed from the current episode of exposure. Studies involving larger numbers of close contacts with a wider range

of ages could confirm and explain the meaning of the findings of the current study.

In conclusion, the results of QFT-GIT and T-SPOT assays and the extent of CT lesions may change during 1 year's observation of the close contacts of active TB patients. The clinical meaning of these findings should be elucidated in large-scale studies in the future.

Authors' Contributions

Conceptualization: Yim JJ. Methodology: Yoon S, Mihn DC. Formal analysis: Yoon S, Mihn DC, Yim JJ. Data curation: Song JW, Kim SA, Yim JJ. Writing - original draft preparation: Yim JJ. Writing - review and editing: Song JW, Yoon S, Mihn DC. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by the Seoul National University College of Medicine Research Fund (grant 03-2017-0010).

Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Serial values of QuantiFERON-TB Gold In-Tube assay in 18 close contacts.

Supplementary Table S2. Serial values of QuantiFERON-TB Gold In-Tube ass T-SPOT.*TB* test in 18 close contacts.

References

1. World Health Organization. Global tuberculosis report 2019. WHO/CDS/TB/2019.15 [Internet]. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf.
2. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. N Engl J Med 2015;372:2127-35.
3. Joint Committee for the Revision of Korean Guidelines for Tuberculosis, Korea Centers for Disease Control and Prevention. Korean guidelines for tuberculosis. 3rd ed. Seoul: Korean Academy of Tuberculosis and Respiratory Diseases; 2017.
4. Lee SW, Jang YS, Park CM, Kang HY, Koh WJ, Yim JJ, et al. The role of chest CT scanning in TB outbreak investigation. Chest 2010;137:1057-64.
5. Park JS, Lee JS, Kim MY, Lee CH, Yoon HI, Lee SM, et al. Monthly follow-ups of interferon-gamma release assays among health-care workers in contact with patients with TB. Chest 2012;142:1461-8.
6. QuantiFERON-TB Gold In Tube test. ELISA package insert. Hilden: Qiagen; 2016.
7. T-SPOT.TB, blood test package insert. Oxford: Oxford Immunotec; 2017.
8. Deak PD, Smal Y, Kalender WA. Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product. Radiology 2010;257:158-66.
9. Arend SM, Thijsen SF, Leyten EM, Bouwman JJ, Franken WP, Koster BF, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. Am J Respir Crit Care Med 2007;175:618-27.
10. Lee JY, Choi HJ, Park IN, Hong SB, Oh YM, Lim CM, et al. Comparison of two commercial interferon-gamma assays for diagnosing *Mycobacterium tuberculosis* infection. Eur Respir J 2006;28:24-30.
11. Bae W, Park KU, Song EY, Kim SJ, Lee YJ, Park JS, et al. Comparison of the sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB according to patient age. PLoS One 2016;11:e0156917.
12. Joshi M, Monson TP, Joshi A, Woods GL. IFN-gamma release assay conversions and reversions: challenges with serial testing in U.S. health care workers. Ann Am Thorac Soc 2014;11:296-302.
13. Lee SC, Yoon SH, Goo JM, Yim JJ, Kim CK. Submillisievert computed tomography of the chest in contact investigation for drug-resistant tuberculosis. J Korean Med Sci 2017;32:1779-83.
14. Lyu J, Lee SG, Hwang S, Lee SO, Cho OH, Chae EJ, et al. Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates. Liver Transpl 2011;17:963-8.