

Conversion of QuantiFERON-TB Gold Plus following Isoniazid Prophylaxis among Latent Tuberculosis Patients

Sawang Saenghirunvattana, MD ; Chitchamai Siangproh, BSc ; Natsuda Wongkhot, BSc ; Chonticha Noomcharoen, RN ; Paulet Barro Ortiz, RN



Sawang Saenghirunvattana, MD

Chest Center, Bangkok Hospital Headquarters,
Bangkok, Thailand

* Address Correspondence to author:
Sawang Saenghirunvattana, MD
Chest Center, Bangkok Hospital Headquarters
2 Soi Soonvijai 7, New Petchburi Rd.,
Bangkok 10310, Thailand.
email: sawang.sa@bangkokhospital.com

Received: April 26, 2019
Revision received: June 02, 2019
Accepted after revision: July 10, 2019
BKK Med J 2019;15(2): 145-148.
DOI: 10.31524/bkkmedj.2019.09.003
www.bangkokmedjournal.com

Abstract

OBJECTIVES: To evaluate the conversion of QuantiFERON-TB Gold plus (QFT-Plus) following Isoniazid prophylaxis among latent tuberculosis (LTB) patient.

MATERIAL AND METHODS: We conducted a case series starting in December 2016 up to the present March 2019. Twenty asymptomatic cases were identified to have had exposure to active tuberculosis (TB) infection, undergone chest x-ray and QFT-Plus test. Those with positive test QFT-Plus results with negative chest x-ray reports were prescribed with Isoniazid 300mg tablet once daily for nine months. Post prophylaxis, chest x-ray and QFT-Plus were repeated to determine the conversion results.

RESULT: All 20 participants were QFT-Plus test positive and chest x-ray negative. The average age was 47 ± 5.7 years and there were eighteen females and two males. Two had underlying conditions: valvular heart disease and peripheral neuropathy. All took the nine-month Isoniazid prophylaxis and repeated the QFT-Plus test and chest x-ray. Chest x-ray results again were all negative. Eighteen cases revealed persistence of positive QFT-Plus and two cases were negative. The initial conversion rate of QFT-Plus post treatment (2017) was ten percent. In the succeeding years (2018 and 2019), another ten percent conversion was reported and sixteen cases maintained their positive baseline score.

CONCLUSION: To our knowledge this clinical series is the first to report 20% conversion rate of QFT-Plus among LTB participants prescribed with a nine-month Isoniazid prophylaxis. This study only evaluated the conversion of QFT-Plus with LTB participants being treated with 9-month Isoniazid. As there is no gold standard on the definition and distinction of conversion and reversion, further studies are warranted to optimize the correlation between the efficacy of varied latent tuberculosis infection (LTBI) and TB treatment regimen and conversion of QFT-Plus results.

Keywords: quantiferon-tuberculosis gold plus, QFT-Plus

Globally, Tuberculosis is one of the top 10 causes of mortality and the primary cause from a single infectious agent over and above HIV/AIDS. In 2017, ten million people were infected with it. Furthermore, in Thailand the World Health Organization (WHO) conducted a TB survey in 2017; where there were 80,160 cases documented compare to the recorded 62,135 in 2015 both new and relapsed cases.¹ This disease causes suffering socioeconomically to impoverished countries thus affecting people's quality of life.² A study done by Zenner et al³ stated the importance of early screening and detection of LTBI to effectively eradicate TB. Additionally, the increasing rate of latent TB poses a challenge to both organizations and stakeholders committed to end TB. Hence, to efficiently reduce the high rate of unidentified LTB cases that might lead to active TB in the future; a unified, well implemented, and advanced approach is crucial.⁴ Tuberculin skin test (TST) remains the most accessible diagnostic tool for the detection of TB but it has its disadvantages. One of which is the tendency for its result to be misinterpreted.⁵ The necessity Of creating a refined and convenient diagnostic test in detecting TB particularly LTB had led to the innovation of blood test based diagnostic test.⁶ QuantiFERON-TB Gold Plus (QFT-Plus), a new generation interferon-gamma (IFN- γ) release assay (IGRA) is a modern alternative to the traditional TST or Mantoux test appears to be of higher specificity and provides better detection of LTBI alongside with other diagnostic tests.^{7,8} Isoniazid is the treatment regimen for this study. According to Kim HW et al, isoniazid is effective in treating LTBI.⁹ While most studies

focus on the efficacy of QuantiFERON test, there have not been many evaluations of the conversion rate on the positive results of QFT-Plus. To our knowledge, this is the first study that specifically evaluated QFT-Plus conversion to individuals with latent TB, treated with nine-month Isoniazid.

Materials and Methods

A retrospective approach was used to collect data from the potential participants. The data taken was as follows: age, gender and previous medical history, all were reviewed and verified. In this clinical series which ran from December 2016 till March 2019, prospective subjects were carefully identified and verified based on the results of recorded diagnostic testing (X-ray and QFT-Plus). Twenty asymptomatic cases were eligible for the study. The average age of the 20-member group was 47 ± 5.7 years, eighteen females and two males. Two patients had underlying conditions namely valvular heart disease and peripheral neuropathy. In addition, eligible participants for the study were known to have been previously exposed to active TB infection, undergone chest x-ray with negative results, and at baseline a positive score of QFT-Plus test. The criteria of exclusion for this study were participants' non-compliance with the treatment regimen and participants whose treatment regimen had been changed.

Intervention

All the qualified participants were prescribed with Isoniazid 300mg tablet once a day for nine months. And for the two participants that exhibited adverse reaction to isoniazid; rifampicin 600mg 1 tablet per day to complete nine-month treatment was prescribed. The initiated time of treatment was also taken into

consideration, therefore it was done at the same time point to avoid inconsistency. According to the manufacturer of QuantiFERON (Qiagen, Germany) "its intended use is in conjunction with risk assessment, radiology and other medical and diagnostic assessment" therefore at the initial diagnostic test we include x-ray test aside from QFT-Plus test to ensure the consistency of our evaluation with our participants.

Measurement of Safety during Treatment

Isoniazid has long been considered a hepatotoxic drug⁹; therefore, a mandatory monthly liver function test was performed for each of the qualified participants. Moreover, clinical symptoms like nausea, vomiting and drug rash were routinely assessed and noted.

Results

The participants' completion and adherence to the nine months treatment regimen was satisfactory. Post prophylaxis, follow up chest x-rays from all participants were taken and revealed negative results. Subsequently, the QFT-Plus test was also obtained and showed a substantial number of patients (18) remained positive and two patients had negative results. From the clinical findings of the 20 participants, two cases were noted to have an allergic reaction (skin rash and itchiness) to Isoniazid, thus, the treatment plan was changed to Rifampicin 600mg 1 tablet per day to complete the nine month of prophylaxis. The recent 2018 and 2019 QFT-Plus follow up test revealed a progressive decline on the positive QFT-Plus results, as evident with the additional two patients with negative test, respectively. We have chosen a bar graph to easily illustrate the progress and results of the QFT-Plus test.

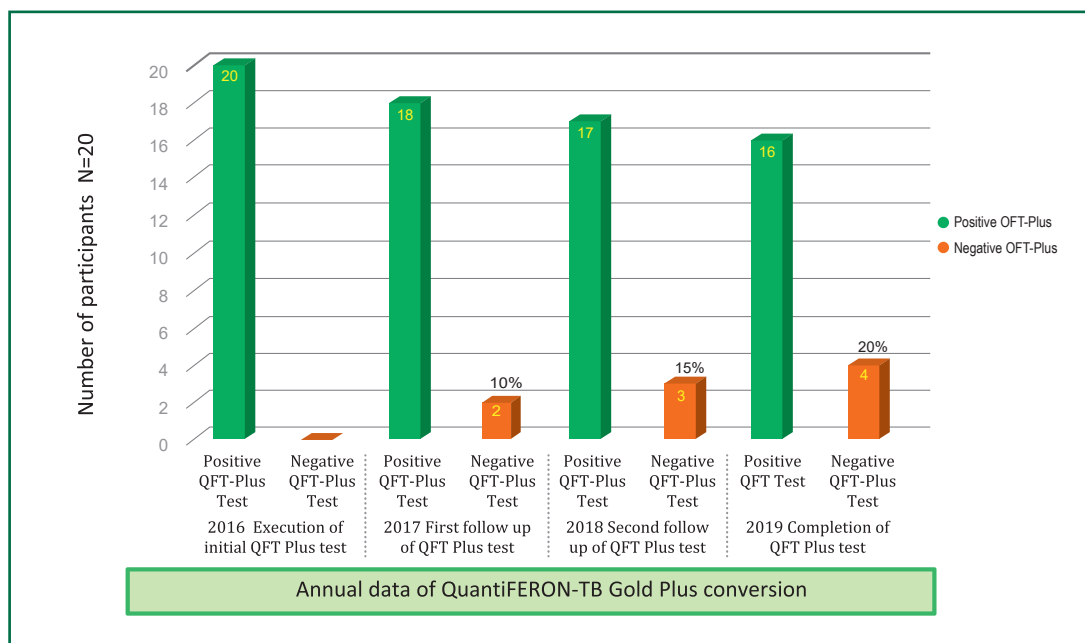


Figure 1: The bar graph above shows the total number of converter (positive result followed by a negative result) from the initial QuantiFERON-TB Gold Plus test to the final QFT-Plus test. The data presented in percentage as follows 20 = 100% and 1 = 5%.

Discussion

Interferon (IFN γ) Release Assay test has been widely accepted as a blood test in diagnosing LTBI as mentioned by Leutkemeyer et al.¹⁰ QuantiFERON test not only is useful in detecting TB or LTBI but is used as a supplemental tool to aid a varied medical approach in detecting and managing pulmonary diseases.¹¹ Therefore, in this clinical series QFT-Plus an Interferon (IFN)- γ release assays has been utilized due to its effectiveness as a reliable tool in diagnosing TB particularly LTB. LTB hinders progress in ending TB; hence, prompt identification of LTB cases along with an effective treatment regimen could help eliminate LTB.⁷ In support with the aforementioned effort, we particularly choose latent TB patient as our cohort for this study. We evaluated the conversion of positive QFT-Plus post nine-month of isoniazid treatment. Andrews JR et al.¹² posited that the conversion of QFT-Plus is apparent when the positive baseline score follows a negative result. In our study, among the twenty participants who had undergone QFT-Plus test, four participants showed conversion, as evident in the succeeding follow up QFT-Plus test, and sixteen participants remained positive. Post treatment in 2017, to determine conversion among participants whose QFT-Plus test was taken, 2 (10%) participants showed a conversion on their results. In 2018 and 2019, another follow-up QFT-Plus test was carried out and 2 patients showed conversion results respectively. TB prophylaxis prescribed to the LTB participants had less apparent effect on the conversion rate of QFT-Plus in relation to base line results of the participants. Our study has concordance with Johnson et al.¹³ in which their study suggested that the efficacy of isoniazid is unsatisfactory. The seemingly unremarkable result of our study might be attributed the limited number of participants thus making this a limitation of our study.

Hepatotoxic Event

This clinical series utilized Isoniazid (INH) as the prophylactic drug. Isoniazid (INH) remained the time-tested drug and recommended choice of drug in combating TB Infection.¹⁴

One of the author's research study about the efficacy of Isoniazid treatment to TB cases among HIV patients, revealed how isoniazid halted the progression of asymptomatic TB into active TB.¹⁵ However, along with the profound significance of this drug comes its feasible tendency to induce liver damage,¹⁶ therefore, a monthly liver function test was required and performed for all of the qualified patients. Fortunately, none of the 20 qualified participants developed a hepatotoxic reaction towards the treatment regimen.

Correlation with other studies

A QuantiFERON related study done by Japanese authors Komiya et al evaluated the reversion rates of QuantiFERON-TB Gold (QFT-Gold). The authors stated that "reversion rates of negative QFT-Gold correlates to magnitude of IFN- γ response prior to the treatment and increasing age."¹⁷ The Japanese researchers use QFT-Gold whereas we utilized QFT-Plus. This may be of a different generation but according to a study done by Petruccioli et al.,¹⁸ "QFT-Plus and QFT-Gold in tube assays showed a substantial agreement and similar accuracy in the detection of active TB as well as LTBI." The above mentioned reversion and conversion might be perplexing, as there is no stringent definition of conversion and reversion. Currently, the available determinant of conversion and reversion is provided by the QuantiFERON manufacturer (Qiagen, Germany).

Conclusion

To our knowledge this clinical series is the first to report 20% conversion of QFT-Plus among LTB participants prescribed with a nine-month Isoniazid prophylaxis. This study only evaluated the conversion of QFT-Plus with LTB participants being treated with 9-month Isoniazid. As there is no gold standard in the definition of conversion and reversion, further studies are needed to optimize the correlation between the efficacy of varied LTBI and TB treatment regimen and conversion of QFT-Plus results.

References

- 1 World Health Organization. Global Tuberculosis Report 2018. Executive Summary. Geneva. Switzerland. 2018
- 2 Rajeswari R, Balasubramanian R, Muniyandi M, et al. Socio-economic impact of tuberculosis on patients and family in India. *Int J Tuberc Lung Dis* 1919;3(10):869-77.
- 3 Zenner D, Loutet MG, Harris R, et al. Evaluation of 17 years of LTBI screening in North West England: A retrospective cohort study of reactivation. *Eur Respir J* 2017;50:1602505.
- 4 Houben RMGJ, Dodd PJ, The Global Burden of Latent Tuberculosis Infection: A Re- estimation using mathematical modeling. *PloS Med* 2016;13(10):e1002152.
- 5 Rissel NL, Belcher BW, Bushyhead JB et al. The Accuracy of Tuberculin Skin Test: Self-Assessment by Adult Outpatients. *Public Health Rep.* July- August 1985; 100(4): 439-445
- 6 Lee E, Holzman RS. Evolution and Current Use of the Tuberculin Test. *Clin Infect Dis* 2002;34:365-70
- 7 Yi L, Sasaki Y, Nagai H, et al. Evaluation of QuantiFERON-TB Gold Plus for detection of Mycobacterium tuberculosis infection in Japan. *Sci Rep* 2016;6:30617.
- 8 Azghay M, Bouchaud O, Mechai F et al. Utility of QuantiFERON-TB Gold In-Tube assay in adult, pulmonary and extrapulmonary, active tuberculosis diagnosis. *Int J Infect Dis* 2016;44:25-30.
- 9 Kim HW, Kim JS. Treatment of Latent Tuberculosis Infection and Its Clinical Efficacy. *Tuberc Respir Dis (Seoul)* 2018;81(1):6-12.
- 10 Luetkemeyer AF, Charlebois ED, Flores LL et al. Comparison of an interferon- γ Release Assay with Tuberculin Skin Testing in HIV- infected individuals. *AM J Respir Crit Care Med* 2007;175:737-42.

- 11 Saenghirunvattana S. Useful of Quantiferon G in managing solitary pulmonary nodule of less than 3cm. *Eur Respir J* 2011;38:2659.
- 12 Andrews JR, Hatherill M, Mahomed H, et al. The dynamics of QuantiFERON-TB Gold IN-TUBE Conversion and Reversion in a Cohort of South African Adolescents. *Am J Respir Crit Care Med* 2015;191(5):584-91.
- 13 Johnson JL MD, Geldenhuys H, Thiel B et al. Effects of Isoniazid Therapy for Latent TB Infection on QuantiFERON-TB Gold In-Tube responses in adults with positive Tuberculin Skin Test Results in a High Incidence Area. *Chest* 2014;145(3):612-7.
- 14 World Health Organization. Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programs 2008. Geneva. Switzerland.
- 15 Saenghirunvattana S. Effect of Isoniazid prophylaxis on incidence of active tuberculosis among Thai HIV-infected individuals, *J Med Assoc Thai* 1996;79(5):285-7.
- 16 Centers for Disease Prevention. Severe Isoniazid Associated Liver Injuries among persons being treated for Latent Tuberculosis Infection-United States-2004-2008. *MMWR Morb Mortal Rep* 2010;59(08):224-9.
- 17 Komiya K, Ariga H, Kurashima A, et al. Reversion rates of QuantiFERON-TB Gold are related to pretreatment IFN-gamma levels, *J Infect* 2011;63(1):48-53
- 18 Pettruccioli E, Vanini V, Chiacchio T et al. Analytical evaluation of Quantiferon-Plus and Quantiferon-Gold In-Tube assays in subjects with or without tuberculosis. *Tuberculosis* 2017;106:38-43.