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A Comparative study between the two interferon gamma releasing assays in the diagnosis of pulmonary tuberculosis

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Abstract:

Objectives: To examine and compare the diagnostic value of Interferon gamma releasing assay (IGRAs) (T-SPOT TB and Qunati FERON Gold in Tube) in the diagnosis of pulmonary tuberculosis.

Materials and methods: The study included 40 patients with active pulmonary tuberculosis. They were attendance of Respiratory Health Care Centers in Mosul City for the period from March to December 2013. From each patient a sputum sample was collected and processed for culture on Löwenstein-Jensen (L-J media). Twelve milliliters (ml) of blood from each patients was collected (10 ml collected in heparinised tube for T SPOT TB and 2 ml in QFT-GIT special tubes)

Results: From the total 40 patients with positive AFB staining 37 (92.5%) were culture positive. The specificity of both IGRAs were 100% . The sensitivity of T- SPOT TB test was 91.89%, while the QFT-GIT sensitivity was 86.49%. The positive predictive value of both IGRAs was 100%. The negative predictive value of T SPOT TB was 50 %, while that of QFT-GIT was 37.5 %. There was a moderate degree of agreement between the T -SPOT TB and QFT–GIT in (82.5%, k=0.54, 95%CI). The results of the two IGRAs are not affected by BCG vaccination status of TB patients.

Conclusions: The IGRAs could provide a supplementary information as part of diagnostic work-up for tuberculosis diagnosis but it is important to note that a negative IGRA does not rule out active TB . Moreover, and of the two IGRAs, QFT GIT is more convenient to adopted for diagnostic use.

Key words: Tuberculosis, T-SPOT TB, Quanti FERON Gold in tube.

Introduction

With approximately 9 million patients annually, tuberculosis (TB) contributes significantly to world-wide mortality and morbidity, specially in low-income countries. Despite lower TB mortality rates in high income countries, diagnosis and subsequent treatment of TB remains a health priority in order to prevent spread of disease and reduce the economic cost associated with patient care (1). However, TB control still relies on tests such as culture, smear microscopy and chest radiographs, despite their known limitations. Culture, the reference standard for active TB, is time consuming and often not available in resource poor settings. Smear microscopy, the most rapid and widely used TB test, is highly specific but has poor sensitivity (2, 3). More recently, two quantitative T-cell interferon- γ release assays (IGRAs), namely Quanti FERON-TB Gold In-tube (QFT-GIT; Cellestis, Carnegie, VIC, Australia) and T-SPOT TB test (Oxford Immunotec, Abingdon, United Kingdom), have been developed. These assays represent a long-awaited advancement in the field of TB diagnostics and are widely anticipated to replace the century-old tuberculin skin test (4). The IGRAs are based on the principle that upon exposure to *Mycobacterium tuberculosis* (MTB) *in vitro*, antigen specific T- cells present in the blood become activated and secret INF - γ (3 ,5, 6). The tests involve stimulation of blood T cells with the MTB antigen overnight and measurement of subsequent INF-γ and the detection of INF - γ indicates TB infection (7). To avoid cross reactivity these tests use the antigen encoded in the region of determination 1 (RD1) (6,8). These antigens include the ESAT6 (early secreted antigen target -6) and CFP10 (culture filtrate protein -10) along with TB 7.7 antigen (9, 10).

Since IGRAs cannot distinguish between latent TB infection and active TB, their use for the diagnosis of active disease has been extensively debated (4). The current work is aimed to examine and compare the diagnostic value of both commercially available IGRAs in the diagnosis of active pulmonary tuberculosis.

Subject, materials and methods

Forty patients apparently suffering from active pulmonary tuberculosis with positive sputum smear for acid fast bacilli were enrolled in this study. They were attendance of the Respiratory Health Care Centers in Mosul City. The collection of samples was carried out from March 2013 up to December 2013. A Questionnaire Form included information related to the patients and their diseases was completed.

Sample collection and processing

An expectorated sputum sample was collected in sterile 50 ml container from each patient have positive direct smear for AFB. The smears stained using Ziehl Neelsen staining, the stains and procedure of staining were used as directed by Winn *et al*., 2006 (11). The patients were taught how to collect the sputum sample by coughing up the sputum deep from the lungs in a well ventilated areas. The sputum sample was processed by homogenization, decontamination and concentration for culture on Löwenstein-Jensen (L-J) medium. Twelve ml of venous blood was drawn from each patient. Ten ml were obtained and transported in a heparinised tubes and used for T- SPOT TB test. Two ml were collected for QFT-GIT assay in special tubes provided by Cellestis, Australia, QIAGEN Company.

The T-SPOT TB assay (Oxford, Immunotec, United Kingdom) is a simplified variant of the ELISPOT assay technique. The peripheral blood mononuclear cells (PBMCs) are separated from a whole blood sample and washed to remove any sources of background interfering signal. The PBMCs are then counted to achieve a standardized cell number is which was (250,000+ 50,000 PBMCs per well). The T -SPOT TB assay require 4 wells to be used for each sample. A nil control to identify non-specific cell activation using cell culture media incubated with the PBMCs, TB-specific antigens including Panel A (ESAT6) and Panel B (CFP10), and a positive control containing phytohaemagglutinin to confirm PBMCs functionality.

The T-SPOT was performed according to the manufactures training**.** The results for T -SPOT TB were interpreted by subtracting the spot count in the nil control well from the spot count in each of the two panels according to the following algorithms :

1. The test result is positive if the spots in Panel A minus spot in Nil and/or spots in Panel B minus Nil ≥6.
2. The test result is negative if both (spots Panel A minus spots in Nil) &(spots Panel B minus spots Nil) ≤5.
3. The test results considered borderline where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5,6 or 7 spots.

The QFT-GIT test is performed in two stages according to the manufacturer's guiding instruction . First, whole blood was collected into each of the QFT –GIT blood collection tubes, the tubes were incubated at 37 Celsius as soon as possible, and within 16 hours of collection. Following a 16 to 24 hour incubation period, the tubes were centrifuged, the plasma is removed and stored at -20 Celsius in small aliquot tubes. The amount of IFN-γ (IU/ml) measured by ELISA, the test was considered positive when IFN-γ response to the TB Antigen tube was ≥0.35 IU/ml.

Statistical analysis

The data were analyzed statistically according to Dunn and Clack, 2009(12) . The degree of agreement between T-SPOT TB test and QFT-GIT was calculated using Kappa test (k). Sensitivity, specificity, positive predictive value(PPV) and negative predictive value (NPV) were also calculated.

Results

The 40 patients included in the present study had an active pulmonary tuberculosis since they were all AFB –positive. Their age ranged between 13 to 65 years with mean ± SD of 35.9± 13.65, of whom 24 (60%) were males and 16 (40%) were females. The medical history of these patients revealed all the 40 patients had a history of cough for more than one month and 38 (95%) had fever. Thirty three (82.5%) patients had history of night sweating, while 15(37.5%) had haemoptysis. Only 10 (25%) patients complained of loss of weight (Figure 1). The culture of the 40 AFB positive sputum samples showed that 37 (92.5%) had growth on L-J media and 3(7.5%) samples revealed no growth (culture negative).

The T -SPOT TB test gave positive result in 35 (87.5%) patients and all the T-SPOT TB positive patients were culture positive. A negative T-SPOT TB test was found in 5 (12.5%) patients. Two out of the 5 were culture positive and the other 3 were culture negative (Table1). There was a high statistical difference in the results of culture and T-SPOT TB test at *p*-value of < 0.001. The specificity of T-SPOT TB was 100%, while its sensitivity was 91.89 %. The PPV of this test was 100% and its NPV reached to 50 % (Table 1).

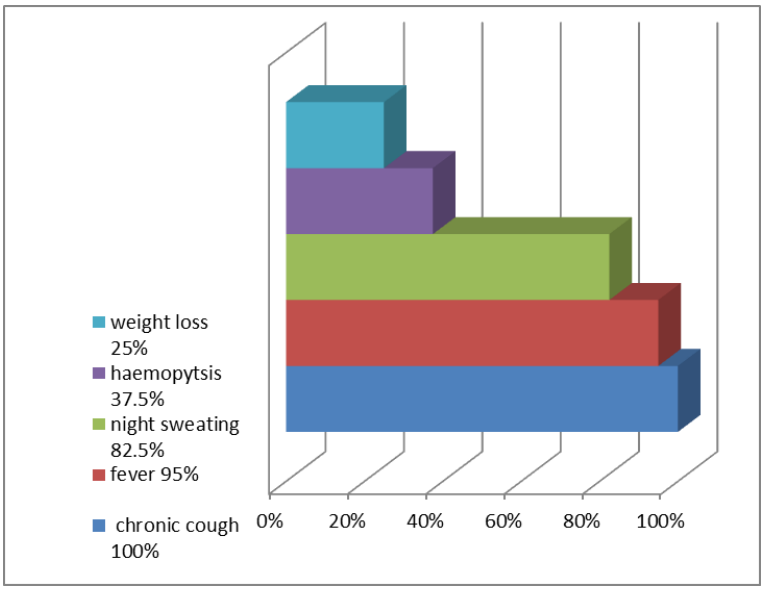

Figure 1: Clinical history in patients with tuberculosis

The QFT-GIT immunoassay was positive in 32 (80%) and negative in 8(20%) patients. All the QFT-GIT positive patients were culture positive while, 5 out of the 8 patients with negative QFT-GIT were culture positive. The remaining 3 patients with negative QFT-GIT were culture negative (Table 5). There was a high statistical difference between the results of mycobacterial culture and QFT-GIT at *p*-value <0.001. The specificity of QFT-GIT was 100%, while its sensitivity reached to 86.49%, and the test gave 100% PPV and 37.5% NPV(Table2).

Table 1: T-SPOT TB test and culture in tuberculosis patients

TB patients	Culture positive n(37)	Culture negative n(3)	Total
T-SPOT TB positive	35	0	35
T-SPOT TB negative	2	3	5
Total	37	3	40
p-value	<0.001		
Specificity %	100		
Sensitivity%	91.89		
PPV %	100		
NPV %	50		

Table 2: QFT-GIT and culture results in patients with tuberculosis.

TB patients	Culture positive n(37)	Culture negative n(3)	Total
QFT-GIT positive	32	0	32
QFT-GIT negative	5	3	8
Total	37	3	40
p-value	<0.001		
Specificity %	100		
Sensitivity%	86.49		
PPV%	100		
NPV%	37.5		

The T-SPOT TB and QFT-GIT gave four patterns of concordance and discordance. The two concordance were the positive (T-SPOT TB +/QFT-GIT +) and the negative (T-SPOT TB -/QFT-GIT-). The two discordant types were T-SPOT TB +/ QFT-GIT- and T-SPOT TB-/QFT-GIT+.

The first pattern of concordance T-SPOT TB+/QFT-GIT+ was found in 31(77.5%) of patients. The other type of concordance T-SPOT TB-/QFT- GIT- was observed in 4 (10%)patients. The discordant T- SPOT TB+/QFT- GIT- was detected in 4 (10%) patients, while the discordant pattern of T-SPOT TB-/QFT-GIT+ was found in only one patient (2.5%) ,Table 3. There was a moderate degree of agreement between T-SPOT TB and QFT- GIT as Cohens Kappa coefficient revealed a value of k=0.54 with agreement of 82.5 %.

Table 3 : The concordance between T- Spot TB and QFT-GIT in patients with tuberculosis

TB patients	QFT- GIT positive no.(%)	QFT -GIT negative no. (%)	Total
T-SPOT TB positive	31 (77.5)	4 (10%)	35
T-SPOT TB negative	1 (2.5)	4 (10)	5
Total	32	8	40
Degree of agreement =82.5% Kappa = 0.54 (moderate agreement)			

The history of BCG vaccination in the patients included in the study was positive in14 (35%) and was negative in 26 (65%) patients. In the 35 positive T-SPOT TB patients, 11(31.43%) were BCG vaccinated and 24 (68.57%) were not vaccinated while, in the 5 T- SPOT TB negative 3 (60%) vaccinated and 2 (40%) patients were non-vaccinated. There was no statistical difference between the state of BCG vaccination and the out- come of T-SPOT TB test results (Table 4).

Table 4: T- SPOT TB test and BCG vaccination in patients with tuberculosis

Vaccination status	T-SPOT TB positive no.(%)	T-SPOT TB negative no.(%)	Total
BCG positive	11(31.43)	3(60)	14
BCG negative	24 (68.57)	2(40)	26
Total	35	5	40
X^2 = 1.569 *p*- value 0.1 (Not significant)			

In the 32 positive QFT-GIT, 10 (31.25%) gave positive history for BCG vaccination and 22 (68.75%) were non-vaccinated. The QFT-GIT negative patients were divided equally into BCG vaccinated and BCG non-vaccinated, 4 (50%) patients for each group. There was also, no statistical difference (p=0.25) between the results of QFT-GIT and BCG vaccination status in TB patients (Table 5).

Table 5: QFT-GIT and BCG vaccination status in patients with tuberculosis

Vaccination status	QFT-GIT positive	QFT-GIT negative	Total
BCG positive	10(31.25%)	4(50%)	14
BCG negative	22 (68.75%)	4 (50%)	26
Total	32	8	40
X^2 = 0.8 *p* -value 0.25 (Not significant)			

Discussion

Several studies have tested the performance of the two IGRAs as diagnostic aid in mycobacterial diseases (13). The 100% specificity of T-SPOT TB test in detection of MTB denoted in the current study is in agreement with other studies (14, 15,16). The latter studies reported a specificity of T-SPOT TB test ranging from 98% to 100%. However, other works done by Simsek *et al*., 2010 (17) and Sester *et al*., 2011(18) reported lower specificity of 79% and 82% respectively. Furthermore, the sensitivity of T-SPOT TB test in the present study is 91.89%, which is slightly lower than that reported by Abdel Samea *et al*., 2013 (16), who recorded 100% sensitivity. Another study done by Simsek and Colleagues 2010 (17) reported a sensitivity of T- SPOT TB test of 51.4% which is lower than that of the current work. However, the sensitivity of T-SPOT TB in the present study is in agreement with the result of Biachi *et al*., 2009 (19).

The specificity of the QFT-GIT in the current study is 100%, which is reported also by several other studies done (15,16, 20,21). However, a lower specificity of 62.5 % has been recorded by Simsek *et al*., 2010 (17). On the other hand, the sensitivity QFT-GIT in this study was 86.49% which is consistent with the results of Eddin and Monem, 2011(22). The discrepancies in the specificity and sensitivity of the IGRAs between different studies may be explained on the basis of the stages of TB disease (complicated or not), high versus low burden TB diseases areas and host factors, such as age, nutritional status, immunosupression and other co-morbid conditions (e.g. diabetes mellitus).

In the current study, the two IGRAs have the same specificity but T-SPOT TB versus QFT-GIT is more sensitive in detecting MTB infection. This was demonstrated by the higher positive results revealed by T-SPOT TB than QFT-GIT in patients with pulmonary TB. Whether such an increase in sensitivity could make this test clinically useful in the evaluation of active tuberculosis remains to be determined.

Furthermore, the T-SPOT TB test and QFT-GIT had a high PPV of 100%, which goes with the results of other studies (16, 20, 21). These studies reported a PPV that range from 85% to 100%. On the other hand, these studies also reported a high NPV from 80 % to100 % which disagrees with the results of the current study where the NPV was low for both T-SPOT TB test and QFT-GIT.

The concordance between T-SPOT TB test and QFT-GIT in this study revealed a moderate degree of agreement (k = 0.54) which goes with results demonstrated by Lee *et al*., 2006 and Arend *et al*., 2007 (22,24). In contrast to the present study, other studies ((19, 25) compared the T-SPOT TB test and QFT-GIT in active TB patients obtained a high inter assay agreement of (83.2 % k =0.66) rather than a moderate one.

The discrepancies between the results of the two test may be explained on the basis that the more sensitive test can detect the patients with affected immune system due to various immunosuppressive factors (disease, drug or old age). The immunosuppressive factors affect the CD4 memory T cells in reducing their ability to produce different cytokines including the INF- γ (26). Although, there is discrepancies in both tests but both are specific and sensitive enough to detect TB infection.

The two commercialized IGRAs are similar in terms of the antigens used (ESAT 6 and CFP10) and the

incubation time (overnight or 16–24 h). The main differences between the two assays that QFT-GIT use a 3rd antigen (TB 7.7), the technique of IFN- γ detection is ELISA versus ELISPOT, and the specimens used are whole blood versus mononuclear cells. Of the two assays, QFT-GIT seems to be more convenient than T- SPOT, as it utilizes whole blood instead of mononuclear cells, beside ELISA is being more commonly used and simpler to perform than ELISPOT. In addition, the ELISPOT assay requires an expensive ELISPOT reader for accuracy, but is sensitive enough to detect single IFN- γ producing cells.

The evaluation of the results of BCG vaccination status and results of both T-SPOT TB test and QFT-GIT in the current study revealed that there is no statistical association between the two parameters in both TB patients . These results are consistent with several other studies done on active TB patients (17, 25, 27, 28). These results showed enough evidence that both IGRAs are not affected by the BCG vaccination which is reflected by high specificity of the two assays as they utilize specific antigens (ESAT 6 and CFP 10). The use of these two antigens provide a great improvement in the diagnosis of active TB as well as in the discrimination between MTB infection and former BCG vaccination. Therefore, the utilization of IGRAs could reduce the false diagnosis of MTB infection in particular BCG vaccinated and in non -MTB infected subjects.

In conclusion, IGRAs provide a supportive and complementary information as a part of the diagnostic work tools for tuberculosis. It is also important to note that a positive result confirms diagnosis of tuberculosis, but a negative IGRA does not rule it out . Of the two IGRAs QFT GIT is more convenient to be used.

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المقارنة بين فحصي أطلاق الانترفيرون جاما في تشخيص التدرن الرئوي

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الملخص

الأهداف: اختبار ومقارنة المقدرة التشخيصية لفحصي اطلاق الانترفيرون جاما (T SPOT TB and FERON Gold in Tube) في تشخيص التدرن الرئوي.

المواد وطريقة الدراسة: شملت الدراسة على 40 مريضا مصابا بالتدرن الرئوي النشط الذين كانوا يراجعون مراكز الرعاية الصحية التنفسية في مدينة الموصل للفترة من شهر آذار إلى شهر كانون الأول لعام 2013. تم جمع عينة قشع من كل مريض وزراعتها على الوسط الزرعي Löwenstein-Jensen (L-J). أيضا تم جمع 12 مل من الدم من كل مريض, 10 مل وضعت في أنابيب اختبار تحوي على الهيبارين لغرض اجراء فحص T-SPOT TB و 2 مل في أنابيب مخصصة لفحص QuantiFERON.

النتائج: من أصل 40 مريض ايجابي للصبغة المقاومة للحموضة 37(92.5%) كانت نتيجة الاستنبات ايجابية. وبالنسبة لدرجة خصوصية فحصي إطلاق الانترفيرون جاما وصلت إلى 100% وقدرت حساسية T-SPOT TB ب 91.89%. في حين بلغت حساسية QFT-GIT 86.4%. كانت القيمة التنبؤية الايجابية للفحصين 100%. اما القيمة التنبؤية السلبية لفحص T SPOT TB كانت50% بينما لفحص QFT-GIT كانت 37.5% كما أن درجة الاتفاق بين فحصي اطلاق الانترفيرون جاما كانت متوسطة(k=0.45,% 82.5) في حالة التدرن. كما اثبت أن نتيجة فحصي إطلاق الانترفيرون جاما لا تتأثر بلقاح BCG في مرضى التدرن.

الاستنتاجات: يمكن استخدام فحصي اطلاق الانترفيرون جاما كجزء من العملية التكميلية لتشخيص التدرن لكن من المهم ملاحظة ان النتيجة السالبة للفحصين لا يستبعدان الإصابة بمرض التدرن و أن من بين الفحصين, فحص QFT-GIT أكثر ملائمة للاستخدام.