The diagnostic performance of TB-IGRA on HIV infected patients with active tuberculosis is associated with CD4+ T-cell counts

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Abstract

Objective: To investigate the factors associated with the diagnostic performance of interferon-gamma release assay (IGRA) in HIV infected patients with active tuberculosis (TB).

Methods: We retrospectively analyzed the data of HIV infected patients with active tuberculosis patients from 2016-2019 who conformed with the inclusion criteria and the exclusion criteria. All patients included were performed with TB-IGRA. For evaluating the diagnostic performance of TB-IGRA, patients were divided into positive TB-IGRA and negative TB-IGRA groups. And all statistical analysis was performed using SPSS

Results: Performed by logistic regression analysis, we found that CD4 cell counts is independent risk factor for false negative of TB-IGRA ($P < 0.001$). Additionally, false negative of TB-IGRA were 68.75%, 24.29% and 14.63%, respectively, in the three groups whose CD4+ T cell counts were $< 20/\mu\text{L}$, $20-100/\mu\text{L}$ and $> 100/\mu\text{L}$, with the highest frequency in subjects with CD4+ T cell counts $< 20/\mu\text{L}$ ($P < 0.001$). And false negative of TB-IGRA were 68.75%, 27.77%, 20.58% and 14.63%, respectively, in the four groups $< 20/\mu\text{L}$ ($n = 32$), $20-50/\mu\text{L}$ ($n = 36$), $51-100/\mu\text{L}$ ($n = 34$) and $> 100/\mu\text{L}$ ($n = 82$). The group of CD4+ T cell counts $< 20/\mu\text{L}$ had the highest false negative ($P < 0.001$). There was no significant difference in the groups of $20-50/\mu\text{L}$, $51-100/\mu\text{L}$ and $> 100/\mu\text{L}$ ($P = 0.483$, $P = 0.623$, respectively).

Conclusion: The low level of CD4+ T-cell counts increase false negative TB-IGRA in HIV infected patients with active tuberculosis. These data suggest IGRA assays may have unreliable diagnostic performance results among patients with advanced HIV especially CD4+ T cell counts were $< 20/\mu\text{L}$.

Introduction

Global data in 2017 showed that tuberculosis (TB) caused 10.0 million cases and 1.3 million deaths, and 60% of notified TB patients had a documented human immunodeficiency virus (HIV) test result. Number of 464 633 TB cases among HIV-positive people were reported; of these, 84% were on antiretroviral therapy (ART) [1]. Advanced immunodeficiency of HIV-infected persons had a greater risk of active TB [2]. Moreover, tuberculosis is one of the most common diseases resulting in morbidity and mortality in the world [1, 3].

The immunodiagnosis for *Mycobacterium tuberculosis* (MTB) infection diagnosis was a new adjuvant method, and the interferon-gamma release assay (IGRA) was one of the most important advances of immunodiagnosis which has been widely applied and accepted in the clinic [4, 5]. Enzyme-linked immunosorbent spot (ELISPOT) assay and enzyme-linked immunosorbent assay (ELISA) to detect IFN- γ released into culture supernatants are two forms of the IGRAs, which using the immunogenic and specific MTB antigens including early secreted antigenic target (ESAT-6) and culture filtrate protein 10kDa (CFP-10) for immunodiagnosis [6, 7].

A certain false negative rate had been found in IGRA among patients with tuberculosis especially in HIV infected individuals[8]. In addition, older age, non-Hispanic white race/ethnicity, being tested with T-SPOT.TB, albumin-globulin ratio, CD4+ and CD8+ had been think as the factors for TB-IGRA diagnosis in previous studies[8, 9]. In HIV infected patients without active TB, TB-IGRA assay with MTB specific antigens were negatively correlated to numbers of circulating CD4+ T-cells, and was influenced by the degree of immunodeficiency[10]. However, the in-depth studies of the IGRA diagnosis in HIV infected patients with active tuberculosis has not been found.

The determined diagnosis in HIV infected patients with active tuberculosis is important, and further research is needed. The objectives of this study were to investigate the factors associated with the diagnostic performance of IGRA in HIV infected patients with active tuberculosis. And to determine the impact that different hierarchy CD4+ T-cell counts towards the performance of the IGRA assay among active tuberculosis patients.

Methods

Study population

All patients (>16 years of age) diagnosed as HIV infected patients with naïve active tuberculosis in the infectious department of Xixi Hospital of Hangzhou in China, who were enrolled from January 1, 2016 to September 1, 2019, were retrospectively included into the study. HIV infection was confirmed in accordance with Centers for Disease Control and Prevention (CDC) definitions. History of AIDS diagnosis was determined according to the AIDS management guidelines[11].

The patients diagnosed with active TB was based on laboratory data (sputum smear microscopy and/or identification of *M. tuberculosis* in sputum/blood culture and/or GeneXpert for bronchial lavage). And the diagnosis of pulmonary TB with culture, smear and GeneXpert negativity was based on the combination of signs, symptoms, computed tomography (CT), good response to against TB treatment and the clinician's opinion. In addition, the diagnosis of extra pulmonary TB with clinically suspected but negative sputum results and normal CT was based on Fine Needle Aspiration Cytology and Pathology. All patients received anti-tuberculosis treatment and had written informed consent.

The exclusion criteria were as follows: (1) patients who did not undergo TB-IGRA examination; (2) history of administration of agents with activity against TB treatment; (3) evidence of nontuberculous mycobacteria infection; (4) patients with combined cirrhosis; (6) patients with other immune deficiencies (including malignancy, congenital immunodeficiency and treated with immunosuppressants); and (7) patients with immune reconstitution inflammatory syndrome (IRIS).

Clinical biochemical parameters and TB-IGRA assay

Laboratory data including white blood cell (WBC), neutrophil counts, lymphocyte counts, red blood cell counts (RBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin (ALB), CD4+cell counts, CD8 cell counts, CD4+ to CD8+ ratio, platelet counts(PLT), platelet distribution width(PDW), alanine transaminase (ALT) and aspartate transaminase (AST) were examined in a central laboratory in our hospital within 12 hours of patient admission.

Mycobacterium tuberculosis IFN- γ release assay according to the manufacturer's instructions using the Wantai quantitative diagnostic kit (WT-IGRA, Beijing Wantai Biological Pharmacy Corporation Ltd). First, BD (American BD company) heparin lithium anticoagulation blood collection tubes were used to extract more than 5 ml of venous blood, anticoagulant dissolved by immediately gently inverting and mixing more than 3 times. Whole blood was collected and dispensed into 3 different culture tubes. "T" was a test culture tube to which tuberculosis specific antigens ESAT-6 and CFP-10 are added; "N" was a bottom control culture tube; "P" was a positive control culture tube with non-specific stimulating antigen phytohemagglutinin (PHA). 1 ml of venous blood was dispensed to each culture tube and mixed it upside down for more than 3 times before dispensing. After the dispensing, the culture tube was gently inverted 5 times, and immediately cultured in a 37 ° C incubator (22 $\pm$ 2) h. After standing culture (22 $\pm$ 2) h, it was taken out, and the supernatant was collected by centrifugation. Secondly, the content of IFN-7 in the supernatant was quantitatively detected by double antibody sandwich method. Whether or not the positive of M. tuberculosis infection was determined based on the amount of IFN-7 specifically raised in the stimulation culture system. In theory, each subject can respond to the non-specific stimulating antigen PHA.

Statistical analysis

Discrete data were presented as counts (percentage), and continuous data were presented as the mean $\pm$ standard deviation for normally distributed, medians and interquartile ranges for non-normally distributed. The differences between continuous data were tested using the Mann-Whitney U-test (nonparametric) or the Student t test (normally distributed). The differences between categorical data were evaluated using the χ^2 test with Continuity correction. P values were evaluated by Bonferroni correction. For predicting false negative rates, we performed univariate and multivariate analyses by logistic regression analysis. Receiver operating characteristic curve (ROC) analysis was conducted to present a varying cut-off values of CD4+ T cell counts for positive TB-IGRA and negative TB-IGRA. All statistical analysis was performed using SPSS, version 19 (SPSS, Armonk, NY, USA), and P < 0.05 was considered statistically significant.

Results

Clinical data pertaining to HIV-infected patients with active TB between positive TB-IGRA and negative TB-IGRA

184 patients were divided into positive TB-IGRA (n = 133) and negative TB-IGRA (N = 51) groups. The sensitivity of the TB-IGRA was 72.28% among the 184 patients. And clinical characteristics and baseline demographics of the 184 patients between positive TB-IGRA and negative TB-IGRA groups are shown in Table 1. Analysis of positive and negative TB-IGRA performance results, we found that significant difference in CD4+ T-cell counts, CD8 cell counts, CD4+ to CD8+ ratio, ALB, ESR, Lymphocyte count and AST. ($P \leq 0.001$; $P = 0.001$; $P \leq 0.001$; $P = 0.005$; $P = 0.047$; $P = 0.001$; $P = 0.004$, respectively).

Univariate and multivariate analyses of the diagnostic performance of TB-IGRA on HIV infected patients with active tuberculosis

Performed by logistic regression analysis, we determined the value of CD4+ T-cell counts for the diagnostic performance of TB-IGRA. In univariate analysis, CD4 cell counts, CD8 cell counts, CD4+ to CD8+ ratio, ALB, ESR, Lymphocyte count and AST were found to be independent risk factors for false negative of TB-IGRA. In multivariate analysis, we analyzed the CD4 cell counts, CD8 cell counts, CD4+ to CD8+ ratio, ALB, ESR, Lymphocyte count and AST, we found that CD4 cell counts were independent risk factors for false negative of TB-IGRA (Table 2, $P = 0.001$).

Hierarchy low CD4+ T-cell counts in HIV infected patients with active tuberculosis is associated with false negative of TB-IGRA

We found the level of CD4+ T-cell counts was significantly lower in negative TB-IGRA group (Fig 1A, $P < 0.001$). Additionally, we obtained an optimal cut-off value (28.5cells/mm³) of CD4+ T-cell counts after ROC analysis. For examining whether hierarchy declines of CD4+ T cells were associated with the diagnostic performance of TB-IGRA on HIV infected patients with active tuberculosis, we divided levels of CD4+ T-cell counts into three groups based on: $<20/\mu\text{L}$ (n = 32), 20–100/ μL (n = 70) and $>100/\mu\text{L}$ (n = 82). And false negative of TB-IGRA were 68.75%, 24.29% and 14.63%, respectively, in the three groups whose CD4+ T cell counts $<20/\mu\text{L}$ had the highest false negative (Fig 1B, $P < 0.001$). And we divided levels of CD4+ T-cell counts into two groups based on: $\leq 50/\mu\text{L}$ (n = 68) and $>50/\mu\text{L}$ (n = 116). False negative of TB-IGRA were 47.05% and 16.38%, (Fig 1C, $P < 0.001$). In addition, we divided levels of CD4+ T-cell counts into four groups based on: $<20/\mu\text{L}$ (n = 32), 20–50/ μL (n = 36), 51–100/ μL (n = 34) and $>100/\mu\text{L}$ (n = 82). And false negative of TB-IGRA were 68.75%, 27.77%, 20.58% and 14.63%, respectively, in the four groups whose CD4+ T cell counts $<20/\mu\text{L}$ had the highest false negative (Fig 1D, $P < 0.001$). There was no significant difference in the groups of 20–50/ μL , 51–100/ μL and $>100/\mu\text{L}$ ($P = 0.483$, $P = 0.623$, respectively).

Discussion

Tuberculosis is the leading cause of death among patients co-infected with HIV. And due to a high frequency of smear-negative and high rates of extrapulmonary TB in HIV co-infected people, it is difficult for diagnosis of TB[12]. In the past two decades, the immune diagnosis of Mycobacterium tuberculosis

infection provided rapid and accurate results than traditional laboratory techniques in the fight against TB. However, the diagnostic performance of TB-IGRA on HIV infected patients with active tuberculosis was not clear enough.

In this study, the sensitivity of the TB-IGRA assay was 72.28% in HIV infected patients with active TB. The sensitivity of the TB-IGRA test in HIV-1 infected persons with active TB was higher than the reported in the studies of Prabhavathi et al[13], Sauzullo et al[14] and Takwoingi et al[15] (54.55%;66%; 67.3%, respectively), and lower than the reported in the studies of Danel et al[16] and Aichelburg et al[17] (88.0%; 90.9%, respectively). And we evaluate the sensitivity of IGRA test in HIV infected patients with active TB is approximately 60%–90% in studies using a large number of samples; it may be different in studies with a small number of samples.

A similar results of the TB-IGRA was reported by Yu et al that TB-IGRA test were affected by the level of low CD4(+) cell counts[18]. However, hierarchy of CD4+ T-cell counts was not used for further explanation. In our study, CD4+ T-cell counts were divided into three groups of $<20/\mu\text{L}$, $20-100/\mu\text{L}$ and $>100/\mu\text{L}$. And we found that the groups of CD4+ T-cell counts $<20/\mu\text{L}$ in HIV infected patients with active tuberculosis had a high false negative 68.75% of TB-IGRA. And there were significant differences compared with the groups whose CD4+ T cell counts were $20-100/\mu\text{L}$ and $>100/\mu\text{L}$; $20-50/\mu\text{L}$, $51-100/\mu\text{L}$ and $>100/\mu\text{L}$. Moreover, there were no significant differences in groups of $20-100/\mu\text{L}$ and $>100/\mu\text{L}$; $20-50/\mu\text{L}$, $51-100/\mu\text{L}$ and $>100/\mu\text{L}$. These data suggest that IGRA may have unreliable diagnostic performance results among advanced HIV patients with active tuberculosis whose CD4+ T cell counts were $<20/\mu\text{L}$. But IGRA may had the value of assisted diagnosis with advanced HIV patients with active tuberculosis whose CD4+ T cell counts were $>20/\mu\text{L}$.

Dheda et al, Cattamanchi et al and Cai et al suggested that IGRA B positive rates was not affected by CD4+ T-cell depletion in HIV infection and active TB [19–21]. But they used an ELISPOT-based IGRA that was not same as our methods. The study of Ahamed et al suggested that no significant difference in CD4 count between QFT-G positive and negative subjects but they also suggested that the sensitivity of the assay was impaired when CD4 count <200 cells/ μL in HIV patients with active TB [22]. Our results strongly support Leidl et al that showed QuantiFERON-TB Gold In-Tube (QFT-G-IT) positive rates are correlated with T-cell stratification in patients with HIV-infection and active TB whose CD4+ T-cells counts of >250 , $100-250$ and $<100/\mu\text{L}$ [10]. And we made more detailed in T-cell stratification.

There are some limitations in our study. The diagnosis of active TB in patients including smear and culture negative results, was made only by clinical and radiology. However, the positive rate of smear and culture is low for diagnosis of active TB and we found good response to anti-TB treatment from enrolled patients by following up. Another limitation of our study is it did not report the specificity of TB-IGRA since we did not get the subjects of HIV positive TB negative individuals in our population.

Conclusions

The low level of CD4+ T-cell counts increase false negative TB-IGRA in HIV infected patients with active tuberculosis. These data suggest IGRA assays may have unreliable diagnostic performance results among advanced HIV patients with active TB whose CD4+ T cell counts were $<20/\mu\text{L}$.

List Of Abbreviations

IGRA, interferon-gamma release assay; TB, tuberculosis; HIV, human immunodeficiency virus; ART, antiretroviral therapy; MTB, Mycobacterium tuberculosis; WBC, white blood cell; RBC, red blood cell counts; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ALB, albumin; PLT, platelet counts; PDW, platelet distribution width; ALT, alanine transaminase; AST, aspartate transaminase.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the first author on reasonable request.

Authors' contributions

M. Y. W. designed research; performed research; analysed data and wrote the manuscript. J. T. C. collected the data and modified the manuscript. X. T. D. cleaned and analysed the data. Z. D. Z. and J. H. Y. contributed to project conception, data analysis interpretation, and manuscript preparation. J. C. S. and J. Y. contributed to data analysis interpretation and manuscript preparation.

Ethics approval and consent to participate

All patients provided written informed consent and this study was approved by Ethics Committee of Xixi Hospital of Hangzhou in China. All procedures and methods were performed in accordance with the relevant international guidelines and regulations in order to reduce physical discomfort of the subjects.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Clinical data analyses in HIV-infected patients with active TB between positive TB-IGRA and negative TB-IGRA.

	Positive TB-IGRA	Negative TB-IGRA	<i>p</i> -value
Subjects (<i>n</i>)	133	51	NA
Male/female	119/14	45/6	0.809
Median Age, year	41(16-86)	39(23-74)	0.548
Median CD4+ T cell counts, / μ L	108(0-797)	25(0-700)	<0.001
Median CD8+ T cell counts, / μ L	541(40-2078)	354(74-1805)	0.001
CD4+ to CD8+ ratio	0.33(0-3.92)	0.05(0-0.67)	<0.001
CRP, mg/dl	46.00(0.40-209.80)	35.00(0.39-203.00)	0.532
ALB, g/l	31.6(14.8-50.5)	27.5(16.3-49.4)	0.005
ESR, mm/h	62.90 $\pm$ 31.26	74.73 $\pm$ 35.91	0.047
WBC, 10^9 /L	5.54(0-12.21)	5.66(1.80-33.00)	0.894
Neutrophil counts, 10^9 /L	3.81(0.35-61.20)	4.07(1.12-29.60)	0.233
Lymphocyte counts, 10^9 /L	1.02(0-2.99)	0.68(0.07-3.94)	0.001
RBC, 10^{12} /L	3.65 $\pm$ 0.82	3.54 $\pm$ 0.79	0.391
PLT, 10^9 /L	242.50(7.90-266.00)	255.00(3.50-477.00)	0.628
PDW, fl	11.10(7.60-106.00)	11.10(7.20-21.60)	0.936
ALT, U/L	21(4-667)	22(7-190)	0.326
AST, U/L	27(8-542)	40(10-139)	0.004
Patients on HARRT, n (%)	62	22	0.671
HIV-1 viral load, copies/mL			
≥ 100 copies/mL	82	27	
<100 copies/mL	51	24	0.282
TB disease			
Pulmonary	72	25	0.104
Extrapulmonary	15	12	
Pulmonary and extrapulmonary	46	14	
Acid-fast staining method(n)	38	13	0.840
Pathology(n)	11	2	0.520

Table 2. Univariate and multivariate analyses of the diagnostic performance of TB-IGRA on HIV infected patients with active tuberculosis.

	Odds ratio	95% CI	<i>P</i> value
Univariate analysis			
CD4 cell count, / μ L	1.006	1.003-1.010	0.001
CD8 cell count, / μ L	1.002	1.001-1.003	0.004
CD4+ to CD8+ ratio	40.189	3.925-411.482	0.002
ALB, g/l	1.070	1.018-1.124	0.008
ESR, mm/h	0.989	0.979-0.999	0.031
Lymphocyte count, $10^9/L$	2.379	1.271-4.452	0.007
AST, U/L	0.999	0.994-1.004	0.671
Multivariate analysis			
CD4 cell count, / μ L	1.006	1.003-1.010	0.001

Figures

Figure 1