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Association between tuberculosis recurrence and interferon-γ response during treatment

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KEYWORDS
Tuberculosis;

Summary *Objectives:* We investigated the relationship between tuberculosis recurrence and *Mycobacterium tuberculosis* antigen-stimulated interferon-gamma (IFN-γ) responses during

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Recurrence;
Interferon-γ release assay;
Cellular response

treatment.
Methods: Plasma IFN-γ levels in active pulmonary tuberculosis patients ($n = 407$) were analyzed using QuantiFERON-TB Gold In-Tube™ (QFT-IT) at 0, 2, and 7 months of the 8-month treatment received from 2007 to 2009 and the patients were followed up for another 16 months after treatment. Risk factors for recurrence were assessed using the log-rank test and Cox proportional hazard models. Random coefficient models were used to compare longitudinal patterns of IFN-γ levels between groups.
Results: QFT-IT showed positive results in 95.6%, 86.2%, and 83.5% at 0, 2, and 7 months, respectively. The antigen-stimulated IFN-γ responses varied significantly during the treatment course ($P < 0.0001$). Unexpectedly, positive-to-negative conversion of QFT-IT results between 0 and 2 months was significantly associated with earlier recurrence (adjusted hazard ratio, 5.57; 95% confidence interval, 2.28−13.57). Time-dependent changes in IFN-γ levels were significantly different between the recurrence and nonrecurrence groups ($P < 0.0001$).
Conclusions: Although the IGRA response varies individually, early response during the treatment course may provide an insight into host immune responses underlying tuberculosis recurrence.

Introduction

Tuberculosis (TB) remains a major global health problem, resulting in 8.7 million new cases and 1.4 million deaths annually, and multidrug-resistant TB occurs in approximately 3.7% new cases and 20% previously treated cases.[1] Recurrence is thus a major risk factor for multidrug-resistant TB cases[2] and increases the TB burden.[3−5] TB recurrence is defined as a second episode of active disease as a result of relapse (endogenous reactivation) or exogenous reinfection after completion of previous treatment.[6] Biomarkers are necessary for the assessment of treatment effectiveness including early recurrence.[7]

The interferon-gamma (IFN-γ) release assay (IGRA) is an immunological diagnostic test designed to detect TB infection. In this assay, IFN-γ levels produced by primed blood lymphocytes after stimulation with *Mycobacterium tuberculosis* (MTB)-specific antigens in vitro are measured. According to the assay's principle and research findings obtained from animal models, the IGRA response may be attenuated proportional to decreased bacterial antigen load as a result of successful anti-TB treatment.[8,9] However, clinical researchers argue that little correlation exists between the commercial IGRA response and bacillary burden,[10] on the basis of various tests including grade of sputum smear or presence of cavities on chest X-rays (CXRs).[11]

Although many studies have demonstrated a decrease in IFN-γ values during treatment,[12−16] others have shown inconsistent changes and increases have also been reported occasionally.[17−20] Thus, most clinicians believe that monitoring changes in the IGRA response during anti-TB treatment may have limited use in evaluating the effectiveness of treatment[21]; however studies on the relationship of the IGRA response to subsequent episodes of TB recurrence are lacking. In this study, we investigated whether longitudinal patterns of the IGRA response during the treatment period are associated with TB recurrence.

Materials and methods

Ethics statement

A written consent was obtained from each participant. In the case of minors, the parents provided the written consent. The study was approved by the ethical committees of the Ministry of Health, Vietnam and National Center for Global Health and Medicine, Japan.

Study population

In total, 506 unrelated patients aged ≥16 years with smear- and culture-positive pulmonary TB and without history of TB treatment, were consecutively recruited from July 2007 to March 2009 in Hanoi, Vietnam. The MTB culture test was performed using Löwenstein−Jensen media. MTB isolates were subjected to niacin and drug susceptibility tests for streptomycin (SM), isoniazid (INH), ethambutol, and rifampicin. Peripheral blood samples were obtained at diagnosis before initiation of anti-TB treatment (0 months, baseline) for analyzing total blood count, human immunodeficiency virus (HIV) status, and IGRA. IGRA test was repeated at 2 months immediately after the intensive treatment period and at 7 months at the final stage of the maintenance treatment period of the standard 8-month regimen of 2SHRZ/6HE, which was commonly administered during the study period in Vietnam. CXRs were obtained at the baseline and results were interpreted by two unbiased readers blinded to the IGRA results. In the present analysis, patients with multidrug-resistant TB as well as HIV coinfection were excluded.