CONSIDERATION OF IMPROVEMENT MEASURES FROM LIMITATIONS OF IMMUNOLOGICAL TESTS—INCLUDING INTERFERON-γ RELEASE AND ANTIBODY-BASED DETECTION ASSAYS—FOR MYCOBACTERIUM TUBERCULOSIS INFECTION

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Abstract [Purpose] Mycobacterium tuberculosis (MTB) infection should be detected in all patients before progressing to active tuberculosis (TB); however, interferon-γ release assays (IGRAs) and serological assays cannot accurately detect TB infection in all patients. Therefore, we conducted a prospective study to determine whether TB infections in patients with active pulmonary TB could be reliably detected by combined use of both tests. [Methods] We consecutively enrolled 186 patients suspected of having pulmonary TB referred to our institute between October 2008 and March 2010 in this study. All patients underwent IGRA and serological assays at first visit and subjected for differential diagnoses. [Results] MTB infections could be detected in 49 of 50 patients with active pulmonary TB using tests of humoral and cellular immune responses. However, false-positive serological tests and IGRAs using TB-specific antigens were observed in patients with nontuberculous Mycobacterium (NTM), old TB, or other respiratory diseases. [Conclusion] MTB infections were detected in nearly all patients with active pulmonary TB using tests of humoral and cellular immune responses. However, these assays need to be improved in order to differentiate the active MTB infection from latent MTB infection or NTM infection using combined other separate antigens.

Key words: Mycobacterium tuberculosis infection, Interferon-γ release assay, Serological assay, Tuberculous glycolipid, Lipoarabinomannan polysaccharide

INTRODUCTION

The gold standard method to diagnose active Mycobacterium tuberculosis (MTB) disease is either culture-based isolation or the detection of MTB-specific nucleic acids by molecular methods[1,2]. Active tuberculosis (TB) disease develops in about 10% of infections, mostly within 1–2 years after exposure[3]. Remaining individuals enter into a state of latency (latent TB infection [LTBI]). Active TB developed as a result of MTB infection; therefore, MTB infection should be detected in all patients before progressing to active TB. Generally, the immunological method of detection for MTB infection can be grouped into two categories: serological (antibody detection) assays based on humoral immune responses and tests of cellular immune response (tuberculin skin tests and in vitro interferon [IFN]-γ release assays [IGRAs]). However, MTB infections cannot be detected using individual serological assays and IGRAs in all patients with pulmonary TB[4]. Commercial serological tests are not recommended for use in the diagnosis of pulmonary TB, and the use of IGRAs is discouraged for active pulmonary TB diagnosis in low- and middle-income countries.

We previously reported that the combined use of serological tests with three separate antigens, i.e., tuberculous glycolipid (TBGL) antigen, lipoarabinomannan polysaccharide (LAM) antigen, and antigen 60, which was prepared from purified protein derivatives, maximizes the effectiveness of serodiagnosis for pulmonary TB[5]. The sensitivity increased to 91.5% in patients with active pulmonary TB and to 86.0% in smear- and culture-negative patients, and the specificity was 87.5% in the healthy control groups. However, the combined use of IGRAs and serological tests with separate antigens has not been evaluated to determine its effectiveness and limitation for diagnosis of pulmonary TB. So, we conducted a prospective study to determine whether MTB infections in patients with active pulmonary TB could be reliably detected by both serological tests and IGRAs in clinical practice. We also discussed the limitations and improvement measures of

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