ORIGINAL ARTICLE

Multidrug-resistant tuberculosis outbreak in an Italian prison: tolerance of pyrazinamide plus levofloxacin prophylaxis and serial interferon gamma release assays

A. Bedini[1], E. Garlassi[6], C. Stentarelli[2], S. Petrella[2], M. Meacci[3], B. Meccugni[3], M. Meschiari[1], E. Franceschini[1], S. Cerri[4], A. Brasacchio[1], F. Rumpianesi[3], L. Richeldi[7] and C. Mussini[5]

1) *Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria, Policlinico of Modena,* 2) *Medical Department, Sant'Anna Penitentiary,* 3) *Service of Microbiology, Azienda Ospedaliero-Universitaria, Policlinico of Modena,* 4) *Clinic of Lung Diseases, University of Modena,* 5) *Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena,* 6) *Department of Infectious Diseases, Ospedale Santa Maria Nuova, Reggio Emilia, Italy and* 7) *University of Southampton, Southampton, UK*

Abstract

The optimal treatment for latent tuberculosis infection (LTBI) in subjects exposed to multidrug-resistant (MDR) tuberculosis (TB) remains unclear, and the change in response of the QuantiFERON-TB Gold In-Tube (QTB-IT) test during and after treatment is unknown. Between May 2010 and August 2010, 39 prisoners at the 'Casa Circondariale' of Modena, Italy, were exposed to a patient with active pulmonary MDR TB. All contacts were tested with the tuberculin skin test and QTB-IT. Upon exclusion of active TB, subjects positive to both tests were offered 6 months' treatment with pyrazinamide (PZA) and levofloxacin (LVX). QTB-IT testing was repeated at 3 and 6 months after initial testing in all subjects who were offered LTBI treatment. Seventeen (43.5%) of 39 subjects tested positive to both tuberculin skin test and QTB-IT test, and 12 (70.5%) agreed to receive therapy with PZA and LVX at standard doses. Only five (41.6%) of 12 subjects completed 6 months' treatment. Reasons for discontinuation were asymptomatic hepatitis, gastritis and diarrhoea. The QTB-IT values decreased in all subjects who completed the treatment, in two (33%) of six of those who received treatment for less than 3 months and in one (50%) of two patients who discontinued therapy after 3 months. The QTB-IT test results never turned negative. Despite the small number of subjects, the study confirmed that PZA plus LVX is a poorly tolerated option for MDR LTBI treatment. We observed a large degree of variation in the results of the QTB-IT test results among participants. The study confirmed that the interferon gamma release assay is not a reliable tool for monitoring the treatment of MDR LTBI in clinical practice.

Keywords: Hepatotoxicity, latent tuberculosis infection, levofloxacin, multidrug-resistant tuberculosis, pyrazinamide, QuantiFERON-TB Gold In-Tube
Original Submission: 1 December 2015; **Revised Submission:** 16 March 2016; **Accepted:** 23 March 2016
Article published online: 7 April 2016

Corresponding author: A. Bedini, Infectious Diseases Department, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Via del pozzo 71, 41125 Modena, Italy
E-mail: andreabedini@yahoo.com

Introduction

Multidrug-resistant (MDR) tuberculosis (TB) is defined as *Mycobacterium tuberculosis* that is resistant at least to isoniazid (INI) and rifampicin (RIF). Extensively drug-resistant (XDR) TB is defined as *M. tuberculosis* resistant to INI, RIF, any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin) [1]. As the number of people with MDR TB or XDR TB increases, so does the number of their contacts, and it is precisely these contacts who need to be identified and properly managed. The management of contacts of MDR and XDR TB patients is particularly challenging, as the evidence for the best intervention is limited. In drug-susceptible TB, preventive therapy in individuals with latent TB infection (LTBI) has been shown to be

http://dx.doi.org/10.1016/j.nmni.2016.03.010

effective in reducing the future risk of developing TB disease [2]. The concept is also valid for MDR and XDR TB but is limited by the current lack of availability of effective drugs against MDR and XDR TB infections, with an unacceptable adverse event (AE) profiles in otherwise healthy individuals. During the past decades, the treatment recommended for LTBI in contacts exposed to MDR TB was pyrazinamide (PZA) combined with either ethambutol (ETB) or a fluoroquinolone [3]. These recommendations were supported by expert opinion but not by controlled trials [4]. Some reports have highlighted the potential hepatotoxicity of combined treatments of PZA plus ETB and PZA plus levofloxacin (LVX) for MDR LTBI [5,6], inducing the World Health Organization and the international community to change the approach to the contacts of MDR TB cases, preferring a careful clinical follow-up of 2 years rather than antibiotic treatment [7].

Interferon gamma (IFN-γ) release assays (IGRAs) are important tools for LTBI diagnosis and surveillance for new TB infection [8–10]. IGRAs are *in vitro* assays based on the detection of IFN-γ production in response to early-secreted antigenic target 6 kDa protein (ESAT-6) and culture filtrate protein 10 (CFP-10). These antigens are specific to *M. tuberculosis* and are absent from all bacillus Calmette-Guérin vaccine strains and most environmental mycobacteria [11,12]. The QuantiFERON-TB Gold In-Tube (QTB-IT; Cellestis, Valencia, CA, USA) test contains a third *M. tuberculosis*–specific antigen (TB7.7) and uses an enzyme-linked immunosorbent assay for detection of IFN-γ responses. The US Centers for Disease Control and Prevention have recommended the use of the QTB-IT test as an appropriate substitute for the tuberculin skin test (TST) in contact investigations [13]. Interpretation of serial IGRAs is challenging because of nonspecific variation, conversions and reversions. Previous studies have proposed that conversions, reversions and nonspecific variations occur with both serial IGRAs and TST [14–19]. In addition, previous TST results may boost the subsequent IGRA responses, rendering the interpretation of serial IGRA results more difficult [20]. Until now, in LTBI subjects, most serial IGRAs were performed after INI or rifampin preventive treatment [21–23]. However, to our knowledge, there are no reports evaluating serial IGRAs after treatment for MDR LTBI with PZA plus LVX.

The aim of the present study was to evaluate the tolerance of the MDR LTBI treatment and the kinetics of QTB-IT in three groups of patients: those who concluded 6 months' treatment with PZA and LVX, those who received less than 6 months' treatment and those who refused treatment.

Patients and Methods

One inmate of 'Casa Circondariale S. Anna' penitentiary (Modena, Northern Italy) was diagnosed with active pulmonary TB in August 2010. The case was diagnosed with bacteriologically confirmed pulmonary TB, and susceptibility testing of the *M. tuberculosis* strain showed resistance to RIF and INI as well as reduced susceptibility to ETB (resistance to 5.00 μg/mL, susceptibility to 7.50 μg/mL). The investigation of the outbreak was initiated by performing TST and QTB-IT tests in all individuals who had contact with the index case during the 2 months before the diagnosis. To exclude other cases of active TB, all the individuals who had positive results for both the TST and QTB-IT test underwent chest X-ray and a high-resolution computed tomographic (HRCT) scan of the chest. All patients who tested positive by TST and QTB-IT with a normal chest HRCT result were considered for 6 months' directly observed LTBI treatment regimen including PZA and LVX. Acceptance of LTBI treatment required written informed consent. The prophylactic regimen was administrated by directly observed therapy. HIV, hepatitis C virus and hepatitis B virus serology were performed before treatment; liver function testing (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) was performed at baseline, 2 weeks after the beginning of treatment and then monthly. LTBI treatment was discontinued if the increase in ALT or AST was greater than four times the upper limit of normal (ALT, 42 IU/L; AST, 42 IU/L) or if the patient experienced drug-related AEs.

The QTB-IT test was repeated after 3 and 6 months in all subjects.

Tuberculin skin test

TST was administered using the Mantoux method with 2TU PPD RT23 (Statens Serum Institute, Copenhagen, Denmark) [3]. The induration size was measured after 48 to 72 hours by a trained medical doctor, and a 10 mm induration size was set as the cutoff value.

QTB-IT test

All participants were tested by QTB-IT as per the manufacturer's instructions (http://www.quantiferon.com/irm/content/quantiferon-tb-gold1.aspx?RID=300). An IFN-γ response to the ESAT-6/CFP-10/TB7.7 mixture $\geq$0.35 IU/mL above the nil control value (and $\geq$25% of the nil control) was considered a positive result for the QTB-IT test. If a response to *M. tuberculosis*–specific antigens (corrected for the nil control) was <0.35 IU/mL and the response to the positive control was >0.5 IU/mL, then the response was considered negative. Indeterminate results were classified as nil-corrected IFN-γ responses <0.35 IU/mL and positive control responses <0.5 IU/mL. QTB-IT test reversion was arbitrarily defined as a change from a positive ($\geq$0.35 IU/mL) to a negative (<0.35 IU/mL) result.

When the QTB-IT antigen-specific value was >10.0 IU/mL, we performed a 1:10 dilution of the plasma samples and we repeated the IGRA determination; finally, the QTB-IT value was multiplied by 10.