Correspondence

Direct Observation Therapy–Plus Can Prevent Acquired Resistance to Fluoroquinolones Among Patients With Multidrug-Resistant Tuberculosis in Taiwan

To the Editor—Recently, Ershova et al investigated the risk factors associated with acquired resistance to injectable second-line drugs and fluoroquinolones among persons with tuberculosis in the United States [1]. They found that the only predictor of acquired resistance to fluoroquinolones was multidrug resistance (MDR) at the initiation of treatment and, therefore, suggested that providers strictly follow supervised treatment in this subgroup to avoid the development of resistance to second-line drugs and fluoroquinolones [1]. In May 2007, the direct observation therapy–plus (DOT-plus) program was implemented by the Taiwan Multidrug-resistant Tuberculosis Consortium to manage and care for patients with MDR tuberculosis. Based on the protocol, all patients with MDR tuberculosis need to continue medication for 18 months after conversion of sputum cultures from positive to negative, and need to be monitored twice a day for drug adherence and adverse events during the course of treatment. However, it is not clear whether the DOT-plus program prevents the development of acquired resistance to fluoroquinolones in patients with MDR tuberculosis in Taiwan. Therefore, in this study, we tried to elucidate the association between the rate of coverage of the DOT-plus program and the rate of acquired resistance to fluoroquinolones among MDR tuberculosis isolates during the period 2005–2011.

This study was conducted at the Chest Hospital, a 102-bed tuberculosis referral center located in southern Taiwan. All of the clinical isolates of *Mycobacterium tuberculosis* were identified to the species level using conventional biochemical methods and the indirect proportion method was used for susceptibility testing [2]. MDR isolates were defined as isolates that were resistant to at least isoniazid (0.2 mg/L) and rifampin (1 mg/L), fluoroquinolone-resistant isolates were defined as isolates that were resistant to any fluoroquinolone (ofloxacin 2 mg/L, levofloxacin 1.0 mg/L, or moxifloxacin 1.0 mg/L), and extensively drug-resistant (XDR) isolates were defined as isolates that were resistant to at least isoniazid and rifampin, as well as being resistant to any fluoroquinolone and any injectable second-line drug (capreomycin 10 mg/L and kanamycin 6 mg/L) [2]. Primary resistance was considered when a patient was infected with an isolate of *M. tuberculosis* that was already resistant to any fluoroquinolone at the initiation of treatment for MDR tuberculosis. Acquired resistance was considered when a patient was infected with a fluoroquinolone-susceptible *M. tuberculosis* isolate that became resistant to fluoroquinolones during treatment for MDR tuberculosis [1]. The trend in drug resistance over time was analyzed using the Cochran-Armitage trend test. Pearson correlation was used to evaluate the association

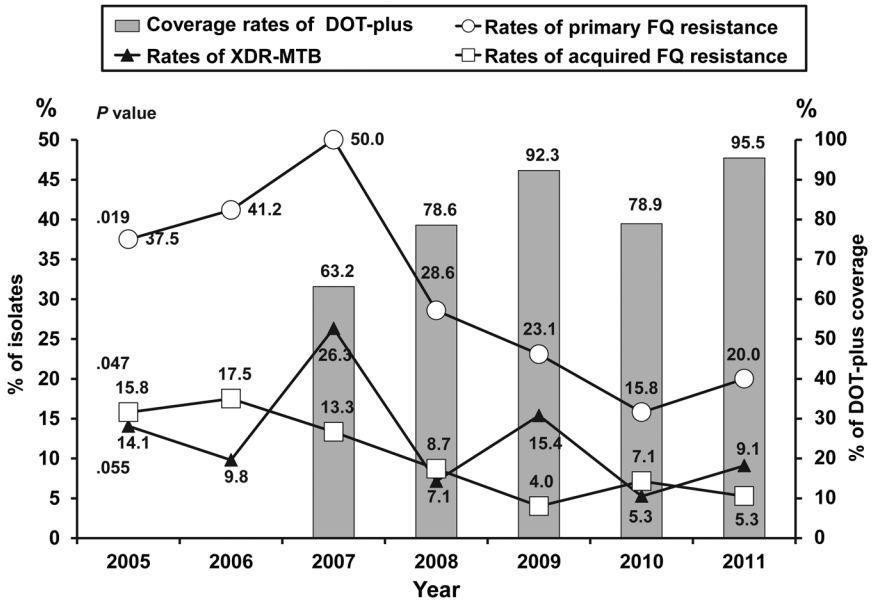

Figure 1. Coverage of direct observation therapy–plus and rate of primary resistance and acquired resistance to fluoroquinolones and extensively drug-resistant *Mycobacterium tuberculosis* isolates among patients with multidrug-resistant tuberculosis from 2005 through 2011. Abbreviations: DOT-plus, direct observation therapy–plus; FQ, fluoroquinolone; XDR-MTB, extensively drug-resistant *Mycobacterium tuberculosis*.

between the coverage rates of the DOT-plus program and the rate of acquired resistance to fluoroquinolones among *M. tuberculosis* isolates.

From January 2005 to December 2011, a total of 248 patients with culture-confirmed MDR tuberculosis were treated at our hospital. Of these patients, 70 (28.2%) were new patients and 178 (71.8%) had previously received antituberculosis treatment. A total of 85 (34.3%) patients had MDR isolates with primary resistance to fluoroquinolones (ofloxacin [n = 82], levofloxacin [n = 82], and moxifloxacin [n = 60]) at the initiation of MDR tuberculosis treatment, and 28 (11.3%) patients had isolates with acquired resistance to fluoroquinolones (ofloxacin [n = 17], levofloxacin [n = 18], and moxifloxacin [n = 20]) during MDR tuberculosis treatment. Results of the trend analysis revealed that after the DOT-plus program was implemented in 2007, the rates of primary resistance to fluoroquinolones ($P = .019$) as well as acquired resistance to fluoroquinolones ($P = .047$) and XDR tuberculosis ($P = .055$) decreased (Figure 1). There was a significant negative correlation between coverage rates of the DOT-plus program and rates of acquired resistance to fluoroquinolones ($r = -0.96$, $P = .01$) and a borderline negative correlation between rates of primary fluoroquinolone resistance ($r = -0.78$, $P = .12$) and XDR tuberculosis ($r = -0.54$, $P = .35$).

There are several significant findings in this study. First, the resistance rates to fluoroquinolones, including ofloxacin, moxifloxacin, and levofloxacin, among the MDR tuberculosis isolates significantly decreased in Taiwan after implementation of the DOT-plus program for MDR tuberculosis patients. Moreover, we found a significant negative association between the coverage rates of DOT-plus and the rates of acquired resistance to fluoroquinolones. These findings indicate that the implementation of the DOT-plus program significantly decreased the rates of acquired resistance to fluoroquinolones among MDR tuberculosis patients. Moreover, the program prevents the development of infections with XDR tuberculosis, which are associated with poor treatment outcome and a high mortality rate [3].

In conclusion, we found that the DOT-plus program significantly decreased the rate of acquired resistance to fluoroquinolones among MDR tuberculosis patients. This finding suggests that the DOT-plus program is useful in the management of patients with MTR tuberculosis, especially in areas that are endemic for MDR tuberculosis.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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