Letter to the Editor

The Impact of Directly Observed Therapy on Preventive Treatment for Latent Tuberculosis Infection among Students in Dalian, China

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Preventive treatment has an essential effect on latent tuberculosis infection (LTBI) [purified protein derivative (PPD) induration ≥15 mm]. Between 2010 and 2013, there were 6 tuberculosis (TB) outbreaks in the universities in Dalian, China. So far, in Dalian, the directly observed therapy (DOT) and full course management (FCM) were widely used in the preventive treatment of LTBI. However, it is yet to be determined which one of them has better efficacy. Therefore, the purpose of our study was to explore the performance of these two strategies for LTBI preventive treatment. The chi-square test and exact test were used to perform statistical analysis. In total, 794 LTBI patients were enrolled in this study, of which 443 were included in the DOT group and 351 in the FCM group. In 287 students who said ditto to take prophylactic treatment (DOT 149 and FCM 79), the compliance rate for the DOT group was 90.3% (149/165), while that for the FCM group was 64.8% (79/122). This difference between the two groups was statistically significant (χ^2=28.03, *P*=1.19E-07). The DOT group showed an effective intervention rate of 81.5%, while that for the FCM group was 28.5%. Again, this difference was significant (χ^2=56.17, *P*=6.63E-14). Further, in 228 students who truly started taking treatment, 26 cases exhibited various adverse reactions (11.4%, 26/228), the most frequent one being elevated liver enzyme levels (6.6%, 15/228). In addition, the major reason for the treatment interruption was adverse reactions in the DOT group, and 6 (28.6%) LTBI patients discontinued treatment due to the adverse reactions of the anti-TB drugs. We also performed a one-year follow-up after the completion of the 3-month treatment. Out of the 794 close contacts, a total of 9 cases (1.1%) developed active TB. These results show that DOT is an effective preventive treatment for LTBI and would play an irreplaceable role in improving preventive treatment adherence and treatment outcomes.

China is one of the 22 tuberculosis (TB) high-burden countries, globally[1]. The fifth national TB survey conducted in 2010 showed that the prevalence of active TB was 459/100,000, when compared with the prevalence of 466/10,000 in 2000[2]. Despite of the slow decline in the prevalence has been majorly due to the high rate of TB infection in China. It is estimated that 44.5% of China's population were infected with TB. This high proportion of infected TB patients is still a serious public health issue in China[2].

Students are at high risk for TB infection in China[3]. Many TB outbreaks have been reported in schools in several provinces of China[3]. The students, especially resident students, live in a crowded environment and experience irregular life in school. Consequently, once a TB patient emerges in school, numerous close contact students tend to be infected with TB. Additionally, university managers regardless of their health management and sanitation facilities have not been perfect, still expanding enrollment, this conflicting situation eventually led students to tuberculosis immunity in general downward trend. This poor health situation may cause latent TB to develop into active TB cases. Hence, the current status highlights the urgent need for actions to prevent the incidence of TB among latent TB students.

The directly observed therapy short-course (DOTS) is the main strategy for the management of TB patients, worldwide[4]. Numerous studies have demonstrated that the implementation of the DOT strategy can significantly improve the cure rate of TB

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by increasing patient compliance to anti-TB treatment[5]. Treatment of latent TB infection (LTBI) is strongly recommend as an effective method for preventing TB in people who show positive tuberculin skin tests and who are at risk for reactivated TB[6]. Unfortunately, ensuring the completion of treatment among LTBI is quite difficulty because patients are asymptomatic. Thus, the completion rates of treatment among LTBI patients ranges from 43% to 90%[7-8]. The poor compliance of the LTBI patients may further result in the occurrence of drug-resistant TB. In China, the full course management (FCM) strategy, rather than the DOTS strategy, is used for managing TB infection. Considering infrequent follow ups by clinicians, unsatisfactory compliance can be anticipated among the LTBI patients during anti-TB treatment.

Dalian, located in Liaoning Province, has 30 colleges and universities, a total of 309,000 students. There were several TB outbreaks in the schools in Dalian. To our best knowledge, there is no clinical study on the effectiveness of DOTS in the management of LTBI. Therefore, we conducted the present study, to explore the effectiveness of the DOT strategy for the preventive treatment of LTBI.

In a TB outbreak, LTBI is defined as the case in which no abnormalities are revealed on chest radiography, while the purified protein derivative (PPD) test shows an induration of ≥15 mm[9]. In the present study, the LTBI in the FCM group was supervised as follows: the clinicians from the local TB dispensary performed follow-ups thrice, to supervise medication in the first, second, and third month after treatment, respectively. In addition, the LTBI in the DOT group was supervised daily by clinicians, guardians, or volunteers. The treatment regimen for LTBI included isoniazid 0.3 g, once/d, and rifapentine 0.6 g, twice/week, as suggested in previous studies[10]. The rifapentine was adjusted to 0.45 g if the patient's body weight was less than 50 kg[10].

The compliance of LTBI treatment was evaluated based on 4 indicators: ① the medication compliance rate=the number of student with LTBI who chose to receive the treatment/the total number of LTBI patients; ② regular treatment rate per month= counted as completed treatment for the whole month, including whose missing medication during the regimen was less than 3 times during treatment; ③ systematic management rate=number of completed regimens during the whole treatment/total number of students who took medication, means medication leakage less than 9 times in the treatment duration of 90 days of preventive treatment; and ④ effective intervention rate of LTBI=treatment compliance rate×regular treatment rate.

We collected 794 close contacts from the 6 TB outbreaks in the universities during 2010 and 2013. To ensure comparability between the two groups included in the study, TB outbreak criteria were specified as follows: ① TB outbreak, mainly homologous, which excluded the special type of hybrid dissemination; ② the schools harboring the TB outbreaks had to be boarding schools; and ③ all LTBI patients were roughly in the same age group, ranging between 18-21 years.

A chi-square test was used to compare the different groups, and the difference was considered statistically significant if $P<0.05$. Due to the small number of subjects in each group, an exact test was used to evaluate the reasons for discontinuing treatment, and the close contacts secondary cases in the follow-up period. SPSS 14.0 was used to perform the statistical analysis.

The study was approved by the Dalian Tuberculosis Hospital Ethical Committee. Written informed consent was obtained from the students prior to participation in the investigation.

As shown in Table 1, a total of 794 LTBI patients were enrolled in this study, including 443 in the DOT group and 351 in the FCM group. Statistical analysis revealed that there was no significant difference in the following characteristics between the DOT and FCM groups: sex, age, clusters of secondary cases and TST ≥15 mm, all *P* values were more than 0.05 separately.

The compliance rate of the DOT group was 90.0%, that of the FCM group was 67.0%, and the difference between the two groups was statistically significant (χ^2=28.03, *P*=1.19E-07). When we compared the rate of regular medication at four weeks, eight weeks, and twelve weeks, the two groups showed significant differences in all the regular medication rates (χ^2 values were 60.33, 69.32, and 66.17 respectively, while *P* values were 8.01E-15, 8.36E-17, and 4.13E-16, respectively) (Table 2). Regarding the rate of effectiveness of the intervention for LTBI, the DOT group showed a rate of 81.5%, while the FCM group showed a rate of 28.5%, thus showing a significant difference (χ^2=56.17, *P*=6.63E-14).

In this study, 228 students chose prophylactic treatment (DOT 149, FCM 79), 26 cases (11.4%,

26/228) exhibited various adverse reactions, the most frequent one being abnormal liver function (6.6%, 15/228). In addition, most of the adverse reactions (8.7%) were mild and tolerable, and there was no need to adjust the anti-TB regimen, while serious adverse reactions were observed in 6 LTBI cases, accounting for 2.6% of all LTBI students. Moreover, 3 students (1.3%) had serious digestive symptoms including nausea, vomiting, and diarrhea. Only 1 student (0.4%, 1/228) showed psychiatric symptoms (Table 3).

In all, 64 LTBI cases discontinued the treatment, including 21 cases from the DOT group and 43 students from the FCM group. The major reason for treatment interruption was adverse reaction in the DOT group, and 6 (28.6%) patients discontinued treatment because of the adverse reaction of the anti-TB drugs. For the FCM group, inadequate attention (17/43, 39.5) was the most frequent reason for treatment interruption, the proportion of which was significantly higher in the FCM group as compared to that in the DOT group. In contrast, there were no significant differences between the DOT and FCM groups in terms of the other reasons (Table 4).

We further performed a one-year follow-up after the completion of the 3-month treatment. Out of the 794 close contacts, 9 (1.1%) patients developed into active TB. The rate of incidence of TB in the PPD≥15 mm irregular or the refused medication groups was 2.5% (3/122), while none from the PPD≥15 mm regular medication group progressed to active TB. Due to the small sample size of active patients, the difference between these two groups was not significant. Surprisingly, 6 (1.2%, 6/507) close contact students from the PPD <15 mm group developed pulmonary TB in the next year (Table 5).

Table 1. Study Population Distribution in the Experimental and Control Groups

Item	DOT Group (*n*=443) *n*(%)	FCM Group (*n*=351) *n*(%)	χ^2 (t)	*P*
Male	3169 (71.3)	253 (72.1)	0.05	0.82
Female	127 (28.7)	98 (27.9)		
Average age ($\bar{x}\pm s$)	19.9±0.09	18.8±0.73	1.67	0.09
Clusters of secondary cases	15 (3.4)	16 (4.6)	0.72	0.40
TST ≥15 mm	165 (37.2)	122 (34.8)	0.525	0.47

Table 2. Regular Medication and Systematical Management Investigation among LTBI Students

Item	DOT Group (*n*=165) *n* (%)	FCM Group (*n*=122) *n* (%)	χ^2	*P*
Choose prophylactic treatment	149 (90.3)	79 (64.8)	28.03	1.19E-07
Regular medication of 4 weeks	138 (92.6)	48 (60.8)	60.33	8.01E-15
Regular medication of 8 weeks	132 (88.6)	38 (46.8)	69.32	8.36E-17
Regular medication of 12 weeks	128 (85.9)	36 (45.6)	66.17	4.13E-16

Table 3. Adverse Drug Reaction

Item		DOT Group	FCM Group	Total
Liver function abnormal	Mild	8	3	11
	DILI	2	2	4
Digestive symptoms	Mild	2	4	6
	Intolerance	1	0	1
Psychiatric symptoms	Mild	1	1	2
	Intolerance	1	0	1
Rash	Mile	0	1	1
	Intolerance	0	0	0

Table 4. Interruption Causes of LTBI Preventive Treatment

Item	DOT Group (*n*=21) *n* (%)	FCM Group (*n*=43) *n* (%)	χ^2	*P*
Adverse drug reaction	6 (28.6)	9 (20.9)	0.459	0.50
Fear of medication	5 (23.8)	6 (14.0)	0.963	0.33
Parents intervention	5 (23.8)	11 (25.6)	0.024	0.88
Subjective neglect	3 (14.3)	17 (39.5)	4.187	0.04
Other	2 (9.5)	0 (0)	0.257	0.10

Table 5. The Secondary TB Cases in Three Groups of Close Contact with One-Year Follow-up

Group*	Students Number	Secondary TB Case *n* (%)
PPD <15 mm	507	6 (1.2)
PPD ≥15 mm regular medication	165	0 (0)
PPD ≥15 mm irregular or refuse	122	3 (2.5)

Note. Irregular or non medication group included close contact who were confirmed LTBI and PPD ≥15 mm, but did agreed to carry the preventive treatment. *, χ^2=1.38, *P*=0.15.

Internationally, DOTS is recommended as a control strategy for TB[11]. Our results demonstrate that DOT could improve the compliance of prevention treatment, which in turn leads to low TB incidence in the follow-ups. Although it is not possible to treat all LTBI cases with direct observation, because of the large number of LTBI cases in China, efforts should be made to provide DOT to LTBI patients who are at high risk for developing active TB, including those with an HIV infection, as well as close contacts in TB outbreaks[12-13]. An adverse reaction serves as the most frequent reason responsible for treatment interruption. In addition, influence of parents, which misleads students, also caused interruption, which cannot be ignored.

In this study, we also found that 6 students with PPD <15 mm developed active pulmonary TB. An induration of PPD >5 mm is an indication for preventive treatment of latent TB, as reported by several studies[14]. However, the standard level of PPD induration for LTBI has been defined as 15 mm rather than 5 mm, because of the routine BCG vaccination that is administered to newborns. The high TB incidence in the PPD <15 mm group indicates that the current standard of the PPD induration to diagnose LTBI may lead to a misdiagnosis, indicating a lower incidence of LTBI. Additionally, considering the high prevalence of TB in China, these patients may be infected by other TB patients, rather than the TB outbreak itself. Thus, further molecular genotyping analyses will help us understand the potential mechanism involved in these 6 cases of secondary TB.

In conclusion, this study revealed that DOT is a very effective strategy for LTBI preventive treatment, and would play an irreplaceable role in improving preventive treatment adherence and treatment outcomes.

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