Letter to the Editor

Cost-effectiveness Analysis of Two Therapeutic Regimens for Newly Diagnosed Smear-negative Pulmonary Tuberculosis*

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Tuberculosis (TB) has a severe effect on human health and causes a huge economic burden[1]. Previous studies have demonstrated that patients with smear-negative pulmonary TB accounted for approximately 60%-70% of the total pulmonary TB cases[2]. Therefore, it is extremely important to formulate safe, effective, and economic therapeutic regimens for patients with smear-negative pulmonary TB[3].

The current study shows that TB induces a pathological immune response that may involve modulation of the immune response toward a more Th-2-like response, a unique survival strategy. Similarly, another study[4] showed that inhibiting the biological synthesis of lipopolysaccharides increased the survival rate of mice infected with *Acinetobacter baumannii*, and rats fed with TB-infected meat were protected against infection after a later challenge with TB. These studies provide experimental evidence for the potential benefits of immunotherapy to treat TB.

In this study, we carried out a cost-effectiveness analysis to compare a 4-month combined immunotherapy with antituberculosis drugs (Group A) and a 6-month standard pharmacotherapy of only antituberculosis drugs (Group B) for patients with newly diagnosed smear-negative pulmonary TB. The results are expected to provide a reference for the selection of economically viable and effective clinical therapeutic regimens.

This study included patients with smear-negative pulmonary TB who were diagnosed and received medical treatment at the Baiyun Center for Chronic Disease Control, Institute for Tuberculosis Control of Jiangmen, Guangdong Province. Inclusion criteria were (1) patients aged 18-70 years, (2) patients who met the diagnostic criteria of smear-negative pulmonary TB, i.e., negative microscopic results of at least three sputum smear samples stained for the observation of acid-fast bacilli, (3) patients with chest X-ray manifestations of active pulmonary TB or without any clinical symptoms of TB, and (4) patients with smear-negative pulmonary TB who never used anti-TB treatment before or received treatment for less than 1 month of irregular treatment.

Using the chronological order of enrollment to assign each patient to either Group A or Group B, a total of 105 patients were randomly classified into Group A, and another 96 patients were assigned to Group B. In Group A, a combined immunotherapy with a *Mycobacterium vaccae* strain was used based on the current standard chemotherapy regimen for smear-negative pulmonary TB, with a total treatment course of 4 months. In Group B, a 6-month standard chemotherapy regimen was used. Both therapeutic regimens included two phases of treatment; the first phase was a reinforcement period (2 months) for both groups, and the second phase was a consolidation period of 2 months for Group A as well as 4 months for Group B, as shown in Supplementary Table S1 (available in www.besjournal.com).

The effective rates of the treatment at the end of the two therapeutic regimens were adopted as benchmarks of effectiveness. The following four evaluation criteria were used for determining whether a therapeutic regimen was effective: (1) whether the patient has completed the therapy, (2) whether the sputum smear was negative by

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microscopy at the end of the therapy, (3) whether the clinical symptoms have disappeared, and (4) whether the focus has been absorbed. If any of the four criteria is not met, the therapeutic regimen was defined as ineffective.

Effective rate = number of cases with effective therapy / total number of treated participants in the group × 100%.

In the study of pharmaceutical economics, cost includes direct cost (direct medical cost and direct non-medical cost), indirect cost, and hidden cost[5]. The cost was quantified in monetary units, and the effective rate was adopted to represent the therapeutic effect of pulmonary TB treatment. Since hidden cost is generally not manifested by consumption of tangible resources and is difficult to measure in currency, we did not include hidden cost in this study.

The subjects enrolled were patients with newly diagnosed smear-negative pulmonary TB. The total cost of therapy = direct cost of therapy (including anti-TB drug cost, supplementary drug cost, physical examination fee, and auxiliary examination fee) + the actual treatment costs imposed by medical institutions and charged to patients + direct non-medical costs (transport expenses and boarding and lodging expenses incurred by patients and their family members during the medical treatment process, based on the price that patients have actually paid) + indirect cost [loss of production due to medical treatment by patients and their family members, which is equal to loss of working time (hours) × 18.3 yuan/h].

Based on the total cost and the effectiveness of the therapy, we calculated the cost-effectiveness ratio (CER) and the incremental cost-effectiveness ratio (ICER) to determine the additional treatment cost that achieved an increase of 1% therapeutic effect for each therapeutic regimen. According to the evaluation criteria proposed by the World Health Organization, the threshold in this study was the per capita GDP of Guangdong Province in 2015, which was 67,503.00 yuan. We examined the effects of changes in key variables (± 10%) on the reliability of the results for both therapeutic regimens and explored the reliability of the cost-effectiveness analysis by conducting sensitivity analysis.

The SPSS 18.0 software was used for performing the statistical analysis. Quantitative data (e.g., evaluation of therapeutic effectiveness) were analyzed using the *t*-test and the Chi-square test. $P < 0.05$ indicated a statistically significant difference.

This study was approved by the Institutional Ethics Review Committee of the two study areas. In this study, Group A included 60.95% of males and 67.62% of married patients, while Group B recruited 72.92% of males and 66.67% of married patients. No statistically significant difference was observed in terms of age, gender, and marital status between Group A and Group B ($P > 0.05$) (Supplementary Table S2, available in www.besjournal.com).

In Group A, eight patients had adverse gastrointestinal tract reactions such as nausea and diarrhea. Two of them suffered slightly adverse reactions that gradually disappeared after observation and treatment; six of them received a short-term symptomatic treatment while they continued their regimen A treatment.

In Group B, 14 patients had similar adverse reactions as those observed in Group A patients. Eight of them suffered slightly adverse reactions that disappeared very soon after they received short-term symptomatic treatment without drug withdrawal. Six of them suffered adverse reactions that did not disappear within a short period of time; to ensure the safety of these patients, drug withdrawal was carried out.

The incidence rates of adverse reactions in Group A and Group B patients were 7.62% and 14.58%, respectively, without a statistically significant difference ($P > 0.05$). The effective rate of therapy was 93.33% (98/105) for Group A and 93.75% (90/96) for Group B, with no statistically significant difference ($P > 0.05$) observed, as shown in Table 1.

The total costs in Group A and Group B were (5,143.44 ± 1,763.46) and (5,732.74 ± 1,799.36) RMB, respectively. The average total cost, direct medical cost, and indirect cost in Group A were lower than their corresponding values in Group B, whereas the average direct non-medical cost in Group A was slightly higher than that in Group B. In terms of total cost, patients treated using regimen A saved 589.74 RMB on average when compared with patients treated using regimen B. There were statistically significant differences in total cost and direct medical cost between regimen A and regimen B ($P < 0.05$), as shown in Table 2.

The CER values of total cost for Group A and Group B were 55.11% and 61.15%, respectively, indicating that patients in Group A and Group B needed to spend 55.11 and 61.15 RMB more for every 1% increase in therapeutic effect, respectively. Therefore, compared with Group B, Group A was found to be more economically cost-effective.

Except for direct non-medical cost, the CER values of all other costs, including direct medical cost, indirect medical cost, and total cost, for regimen A were smaller than those of regimen B, as shown in Table 3. The ICER for regimen A was 1,403.10 (0 < ICER < per capita GDP), suggesting that regimen A has a relatively higher cost-effectiveness value and therefore should be chosen as a priority therapeutic regimen for patients with newly diagnosed smear-negative pulmonary TB (Table 3).

In this study, we used changes in total cost to represent the effects of changes in medical cost on the cost-effectiveness analysis. Under the condition of a 10% increase in total cost, no statistically significant change was observed in the value of ΔC/ΔE , suggesting that total cost had little impact on the results of the cost-effectiveness analysis, as shown in Table 4.

No statistically significant difference was observed in adverse reactions or effective rate between the therapeutic regimens ($P > 0.05$). Based on the results of the cost-effectiveness analysis, Group A entailed a shorter treatment duration period, which could increase the compliance and reduce the chances of drug resistance due to irregular treatment or treatment interruption[6-7].

Currently, the drug cost is the major expenditure for patients with newly diagnosed smear-negative pulmonary TB[8], with the direct medical cost accounting for 98% of the total cost. Group A imposed a shorter treatment course than Group B, and the average cost was 5,143.44 RMB. From the perspective of direct medical cost, Group A had a lower cost than Group B during the medical treatment process and helped save 582.93 RMB on average per patient, which relieved the burden of medical costs. A previous study[9] showed that the per capita expenditure for patients with smear-negative pulmonary TB was 4,205 RMB, accounting for 45% of the total expenditure of the household[10].

Table 1. Comparison of Effective Rate of Two Therapeutic Regimens

Effectiveness Indicator	Regimen A, *n* (%)	Regimen B, *n* (%)	χ^2	*P*
Effective			0.014	0.905
Yes	98 (93.33)	90 (993.75)		
No	7 (96.67)	6 (96.25)		

Table 2. Comparison of Costs of Two Therapeutic Regimens ($\overline{x} \pm s$, RMB)

Type of Costs	Regimen A	Regimen B	*t*	*P*
Direct medical cost (RMB)	5,075.15 ± 1,759.12	5,658.08 ± 1,747.76	**-2.354**	**0.020**
Direct non-medical cost (RMB)	9.82 ± 16.86	9.78 ± 17.64	0.016	0.988
Indirect cost (RMB)	58.03 ± 52.88	64.88 ± 49.83	-0.942	0.347
Total cost (RMB)	5,143.44 ± 1,763.46	5,732.74 ± 1,799.36	**-2.158**	**0.032**

Table 3. Comparison of Cost-effectiveness Analysis between Two Therapeutic Regimens

Type of Cost/Therapeutic Effect		Cost-effectiveness Ratio (CER)		Incremental Cost-effectiveness Ratio (ICER)
		Group A	Group B	
Treatment costs	Direct medical cost (RMB)	54.38	60.35	1,387.93
	Direct non-medical cost (RMB)	0.11	0.10	-0.10
	Indirect cost (RMB)	0.62	0.69	16.31
	Total cost (RMB)	55.11	61.15	1,403.10

Table 4. Sensitivity Analysis of Two Therapeutic Regimens After 10% Increase in Total Cost

Regimens	Cost Increase 10%	Effect (E)%	C/E	ICER (ΔC/ΔE)*
Group A	5,657.78	93.33	60.62	1,421.38
Group B	6,306.01	93.75	67.26	-

Note. *ΔC/ΔE= (total cost of Group A - total cost of Group B)/(effect of Group A - effect of Group B).

Therefore, the promotion of a shorter regimen can relieve the financial burden of patients to a certain extent. In addition, no statistically significant differences were observed in the effective rate and the adverse reaction rate between the two groups. Since Group A was found to be more economically favorable than Group B, Group A should be regarded as a priority regimen. Notably, the sensitivity analysis results suggested that changes in drug prices had little impact on the analysis results.

In summary, Group A exhibits the characteristics of safety, effectiveness, and economy and can be more affordable than Group B for the treatment of patients with newly diagnosed smear-negative pulmonary TB. Our study provides a valuable reference for selecting clinical therapeutic regimens in a rational manner, which can increase the effectiveness of TB treatments while controlling the costs, for the eventual control of TB worldwide.

The authors declare that they have no competing interests.

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Supplemented Table S1. Comparison of Two Therapeutic Regimens

Time	Group A		Group B	
	Injection	Drugs	Injection	Drugs
15 days (2 weeks)	immune stimulant	HRZE* quadruple FDC drugs	placebo	HRZE quadruple FDC drugs
30 days (1 month)	immune stimulant		placebo	
45 days (1 and a half months)	immune stimulant		placebo	
60 days (2 months)	immune stimulant		placebo	
75 days (2 and a half months)	immune stimulant	HR# bigeminy drugs	placebo	HR bigeminy drugs
90 days (3 months)	immune stimulant		placebo	
120 days (4 months)	/		/	
180 days (6 month)	/	drug withdrawal	/	

Note. *HRZE = Isoniazid (H) and Rifampicin (R) and Pyrazinamide (Z) and Ethambutol (E). HR# = Isoniazid (H) and Rifampicin (R).

Supplemented Table S2. Demographic Characteristics of Patients Using Two Therapeutic Regimens

Basic Information	Group A, *n* (%)	Group B, *n* (%)	χ^2	*P*
Age	36.7 (13.89)	36.7 (13.31)	*t*-test	1
Gender				
Male	64.0 (60.95)	70.0 (72.92)	3.23	0.072
Female	41.0 (39.05)	26.0 (27.08)		
Marriage				
Married	71.0 (67.62)	64.0 (67.62)	0.61	0.895