The Deviation from Standardized Treatment Regimen in 108 Randomly Selected Smear-positive Tuberculosis Patients

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Abstract

Purpose: To better understand the anti-tuberculosis regimen and dosage prescribed to smear-positive tuberculosis (TB) patients and to compare the regimen to standardized[0] treatment specified in the second edition of Taiwan Guideline on TB Diagnosis and Treatment.

Materials and methods: All patients newly diagnosed with smear-positive TB in Taiwan during April 1 to May 31, 2007 were enrolled. Patients were randomly sampled with a ratio of one to ten. TB case management cards and prescription from yellow booklet were reviewed by physicians.

Results: A total of 125 cases of smear-positive TB patients were analyzed. Because TB was later ruled out for 14 cases and information could not be accessed for three, they were excluded from analysis. Of the 108 cases

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analyzed, 14.8% (16) received non-standardized regimen, 4.6% (5) were prescribed divided doses for once daily drugs, and 28.7% (31) were given non-standardized dosage of one of the anti-TB medications.

Conclusions: The evaluation of prescription to patients revealed that some regimens were not standardized from the initiation of treatment without specific reasons. All providers who treat patients with TB must have knowledge to prescribe standard treatment and the means to assess the adherence to the regimen according to WHO and International Standard of TB Care.

Key words: anti-tuberculosis regimen, smear positive, tuberculosis

Introduction

Directly observed treatment short course (DOTS) program was officially launched in Taiwan on 1 April, 2006. The goal of this program was to enroll every tuberculosis (TB) patients who are smear-positive in DOTS. The program expanded gradually and then expanded to TB patients who were culture positive and at high risk of poor compliance since the latter part of 2007. One year after the program was launched, the coverage rate of DOTS of smear-positive TB patients has risen to over 85% [1]. For smear-positive TB patients covered by DOTS program, the 12-month treatment success rate for the cohort enrolled between 1 April and 30 June, 2006 was 71.5%; meanwhile, the treatment success rate for non-DOTS patients was 51.6% ($p< 0.001$) [1]. However, the DOTS treatment success was still below 85%, the goal set by World Health Organization (WHO) [2]. There are several factors which can influence treatment success, including the severity of the disease, the quality of TB diagnosis and proper medication, the compliance of TB patients, and the quality of TB control. With the implementation of DOTS program, it can

improve the compliance, increase treatment success, and decrease relapse and drug resistance [3]. Understanding the anti-TB regimen and dosage prescribed to smear-positive TB patients [4]and comparing the regimen to standardized[0] treatment specified in the second edition of Taiwan Guideline on TB Diagnosis and Treatment is needed [5].

Materials and methods

Data collection

All patients newly diagnosed with smear-positive TB in Taiwan during April 1 to May 31, 2007 were enrolled. Patients were randomly sampled with a ratio of one to ten. In Taiwan, the Communicable Disease control Acts required suspected or confirmed TB cases reported to the public health system within 7 days. Therefore, TB case management cards and prescription from yellow booklet were reviewed by nine medical officers in Centers for Disease Control three months after diagnosis of TB was confirmed. Insufficient data or clinical information was acquired through personal communication with public health nurses, diagnosing physicians or by reviewing medical charts.

Dosage and regimen combinations for standard short-course anti-TB treatment

The recommended dosage in the second edition of Taiwan Guideline on TB Diagnosis and Treatment [5] was revised according to Treatment of Tuberculosis written by the American Thoracic Society, the United States Centers for Disease Control and Prevention, and Infectious Diseases Society of America [6]. The standard short-course regimen is a 6-month regimen containing rifampicin throughout and pyrazinamide in the intensive phase [4]. Retreatment regimen, for relapsed patients, comprised of four anti-TB medications plus streptomycin; this

recommendation in the second edition of Taiwan Guideline on TB Diagnosis and Treatment was revised according to the WHO guideline [7]. Second-line anti-TB drugs were defined according to WHO definition [8].

Results

A total of 125 cases of smear-positive TB patients were analyzed. Because TB was later ruled out for 14 cases and information could not be accessed for three, they were excluded from analysis. Five cases were relapsed cases, and 103 were new cases. Of the 108 cases analyzed, 14.8% (16) received non-standardized regimen, 4.6% (5) were prescribed divided doses for once daily drugs, and 28.7% (31) were given non-standardized dosage of one of the anti-TB medications.

Among the 16 cases receiving non-standardized regimen, there were 20 problems identified. Thirty percent of the cases were placed on fluoroquinolones, but they did not meet the criteria for second line drug use. Twenty-five percent of the cases were placed streptomycin, but they did not meet the criteria. Twenty percent of the cases did not receive pyrazinamide in their intensive phase of treatment without specific reason. Four relapsed cases did not receive re-treatment regimen as they should have.

As to drug frequency errors, 4.6% (5) of the cases were placed on divided doses of once daily drugs. Divided doses were given to these cases for weeks with no proper reason. As to the dosage, there were 31 (28.7%) cases who received regimens with improper dose of at least one of the anti-TB medications. A total of 38 problems were identified in these 31 cases. The leading three problems were as following: 28.9% had Rifater under-dose in 28.9%; rifampicin under-dose in 13.2%; pyrazinamide under-dose in 13.2%,

ethambutol under-dose in 13.2%; isoniazid overdose in 10.5%; and ethambutol overdose in 10.5%.

During the evaluation of the regimens prescribed, we also evaluated the quality of case management cards recorded by public health nurses. Of the 108 cases analyzed, 11.1% lacked patient weight, and 27.8% lacked proper documentation of medication; for example, check box of the medication was checked but there was no dosage.

Discussion

In Taiwan, the majority of TB regimens are prescribed by physicians in clinics and hospitals paid by Nation Health Insurance. Funding for DOTS program, launched on April 1st, 2006, was provided by public health authority to incorporate TB care from both private and public sectors. To achieve the goal of halving TB within 10 years by 2015, Taiwan government launched and increased the coverage of DOTS program [1, 9]. To enhance the benefit of this strategy, the first priority is to ensure the regimen is internationally-accepted, and the dosage conforms to international recommendations [10].

This study showed that some non-standardized regimens were used, and no specific reasons were given. Through this general survey, we showed that use of incorrect prescription was common. All providers who treat TB patients must have the knowledge to prescribe standardized treatment and the means to assess the adherence to the regimen according to WHO and International Standard of TB Care [4]. Therefore, public health authorities should strengthen and encourage continuing education programs of anti-TB medication prescriptions, to remind and regulate every provider to give proper care for their TB patients.

Look into those prescription errors, some frequently encountered problems should be further explored to find the solution. Fluoroquinolones are safe and easily tolerated. These features lead to abuse in TB patients in several countries and increased drug resistance in *Mycobacterium tuberculosis* [11, 12]. With further transmission, it may lead to treatment failure in multidrug-resistant TB cases. Physicians can apply for fluoroquinolones use in TB patients who have indications through Taiwan Centers for Disease Control branch offices. This way, TB patients are ensured to receive free second line drugs, including fluoroquinolones. National Health Insurance Bureau started to regulate fluoroquinolone use in TB patients with no indication in September, 2007 and the impact of this policy should be closely monitored. So far, despite widespread use of fluoroquinolones for treatment of common bacterial infections, resistance among clinical isolates of *M. tuberculosis* remains rare, occurring primarily among multidrug-resistant strains [13-15].

Some uncertainties exist for physicians and keep them from adhering to the published TB care guideline. Some physicians use standard four drug regimen plus streptomycin when the TB case has cavitations. They believe the use of streptomycin accelerates sputum conversion, but rifampicin-containing regimens, without streptomycin, already allow effective short-course treatment even of patients with smear-positive cavitary disease [16]. Some physicians omit pyrazinamide usage in the intensive phase of treatment, simply because the patient has history of gout. At currently recommended doses, pyrazinamide rarely causes serious toxicity. Joint pain is common, but can be successfully managed with acetylsalicylic acid or other analgesics, anti-inflammatory agents, and does not require withdrawal of the drug. Classic gout is rarely seen; if it develops, gout

can be treated with colchicine. Serum concentration of uric acid are often elevated but asymptomatic increase does not require any treatment [17]. Pyrazinamide given in the initial intensive phase allows a reduction in treatment duration from 9 to 6 months so that the resource of DOTS program can be better utilized [7]. The two key drugs, isoniazid and rifampicin should not be given in divided doses because achieving a high peak serum concentration for these drugs is more important than having a continuous inhibitory level [18, 19]. Therefore, once daily regimen for standard short-course treatment is recommended. Some physicians under-dose anti-TB medications or refuse to use pyrazinamide, because they believe omitting pyrazinamide or under-dosing of rifampicin, isoniazid and pyrazinamide may decrease the possibility of hepatic toxicity, even when the patient has not encountered any liver problems. A balance between toxicity and maximum therapeutic range has been done for all first-line anti-TB drugs and is the basis for the current dosage recommendations. Physicians should provide regimen sufficient to achieve minimum bactericidal concentration [20].

In conclusions, the evaluation of prescription given to smear-positive TB patients revealed that some regimens were non-standardized from initiation of treatment without specific reasons. All providers who treat patients with TB must have the knowledge to prescribe standard treatment and the means to assess the adherence to the regimen according to WHO and International Standard of TB Care. To achieve the goal of halving TB within 10 years by 2015, Taiwan government launched and increased the coverage of DOTS program, however, to enhance the benefit of this strategy, the first priority is to ensure the regimen is internationally-accepted, and the dosage conforms to international recommendations.

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