Comparative evaluation of three and six month therapeutic regimens for smear negative pulmonary tuberculosis

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Abstract
Both smears positive and negative Pulmonary Tuberculosis (PTB) patients are routinely treated by six month therapeutic regimen. The aim of this study was to compare three and six month regimens chemotherapy for smear negative PTB among tuberculosis patients. Fifty-two patients with smear negative PTB randomly divided into two groups took part in this comparative clinical trial study. The patients in first group were treated with our recommended regimen (rifampicin, isoniazide, and ofloxacin) and another group with standard regimen according directly observed treatment short course strategy. Cure rates in first and second group were 96.5% and 100% respectively. There was no difference between two groups in responding to anti tuberculosis chemotherapy (p>0.05). This study showed that three month therapeutic regimen is as effective as six month therapeutic regimen and may be considered effective treatment for adult patients with unprogressive smear negative PTB.

Introduction

Pulmonary tuberculosis is an endemic and relatively a common infectious disease in Iran [1-3]. The goals of anti tuberculosis therapy are prevention of spread of infection or disease [4-7], preventing relapses [8,9], overcoming drug resistance [10-12], minimizing drug toxicities [13], and maximizing patient acceptance [13,14]. In recent years, new agents have been available, and field trials have demonstrated that certain combination and strategies are effective when given for short periods [15,16].

Directly Observed Treatment Short Course (DOTS) strategy was employed for National Program of Tuberculosis control (NPT) [15]. DOTS has been employed in Iran for NPT since 1997 [2]. Both smear positive and smear negative pulmonary tuberculosis (SPPTB, SNPTB) patients are routinely treated by six month therapeutic regimen according to NPT [2]. Subsiding the initial signs and symptoms SNPTB and conversion sputum from positive acid-fast bacillus (AFB) to negative (SPPTB) are the criteria for improvement. No change or worsen the clinical findings or conversion the sputum from negative to positive reflects the failure to treatment. Although six month therapeutic regimen is a treatment of choice for smear positive patients [13-16], but for various reasons, for example, economic (expensively of drugs), drug toxicity, patient

compliance, and availability of drugs, shorter and fewer drug combination can be employed, when resistance is not a concern for anti tuberculosis therapy such as smear negative pulmonary tuberculosis [4,8,10]. In this study three and six month chemotherapy regimens in two groups of SNPTB patients were compared.

Patients and methods

This is a comparative clinical trial study, which was done from Dec 2002 to Dec 2004 in Ahvaz (SW of Iran). Three hundred and ten patients with pulmonary tuberculosis were referred to our private clinic or infectious ward in Razi hospital, Ahvaz, Iran. The age range of patients was 20-50 years old, with mean range 35 years. Sixty-two patients, 28 (45.1%) females and 34 (54.9%) males with smear negative results in sputum examination and mild to moderate illness (general appearance and without evidence of overwhelming TB in chest radiography) randomly selected for study.

After explaining the purpose of the study and taking written consent, they took part in the study. They were randomly divided in two groups; the patients with odd numbers as group I (31 patients) and patients with even numbers as group II (31 patients). The criteria for SNPTB [2] are shown in table 1. Exclusion criteria were conversion the sputum exam for AFB from negative to positive, other pulmonary disease diagnosed during study period, drug discontinuation, or death. The patients in group I were treated with our recommended therapeutic regimen, and patients in group II with standard therapeutic regimen according DOTS strategy (Table 2).

Table1: Criteria for diagnosing patients as smear negative pulmonary tuberculosis

Symptoms	Cough (with duration two weeks or more) with or without fever, Sweating, anorexia and weight loss.
Signs	Sputum with or without blood, dyspnea, body temperature 38°C or more
Lab findings	High ESR, positive CRP
Chest radiography	Radiographic changes suggestive tuberculosis
Sputum exam for AFB	Negative in three samples (three consecutive days)
Response to two weeks antibiotic therapy (not for TB)	No responses (clinical, paraclinical)

ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; AFB, Acid Fast Bacillus; TB, Tuberculosis

Table 2: Oral anti- tuberculosis chemotherapy regimens

Groups	Regimens	Drugs	Duration
I	three month regimen	Rifampicin + isoniazide + ofloxacin	three months
II	six month regimen		
	Attack phase	Isoniazide + rifampicin + ethambutol + pyrazineamide	Two months
	Continuing phase	Isoniazide +rifampicin	Four months

Rifampicin (10mg/kg), isoniazide (5mg/kg), ofloxacin (200-400mg), ethambutol (15mg/kg), pyrazineamide (30mg/kg)

The patients in two groups were followed up for clinical improvement such as subsiding (fever, cough and anorexia) and weight gain, bacteriologic changes (conversion sputum exam from negative to positive results), chest radiographic changes (resolving

abnormal finding) and drug toxicity after three and six months in group I and group II respectively. Patient was considered cured if initial signs and symptoms were subsided and with evidence of radiographic improvement, and was considered as failure if there was no change or worsen the clinical findings or conversion the sputum from negative to positive. Follow up investigation was done for nine months after finishing treatment in group I and six months in group II, two times monthly (every two weeks) for three first visits and once monthly for remaining visits. Data were analyzed in SPSS 11.5 (SPSS Inc., Chicago) by using descriptive statistics and the chi square test.

Results

Two patients in group I were excluded from this study. The first as smear positive pulmonary, because conversion her sputum from negative to positive (AFB were seen in two samples of her sputum exam) at the end of first two months therapy. The second patient diagnosed as lung cancer during treatment (referred to lung oncologist). Three patients in group II were excluded.

One patient due to drug discontinuation, the second died due to car accident and the third, because of sputum conversion (negative to positive).

Finally, fifty seven patients included in this study. Clinical and radiographic improvement was observed in 28 of 29 patients in group I (cure rate of 96.5%) and in 28 of 28 patients in group II (cure rate of 100%) (Table 3). There was no significant difference between two groups in responses to anti tuberculosis chemotherapy (p>0.05). There was no serious drug toxicity in this study except in one patient (3.5%) in group II (laboratory based hepatitis) who improved after stopping the drugs for two weeks and then starting without any difficulty. Minor side effects such as abdominal pain in one patient (3.4%) in group I and in two (7.1%) in group II were seen. In addition, mild nausea in two (6.8%) patients in group I and in one (3.5%) in group II was seen. Five-fold increases in liver transaminase were also detected in one patient (3.5%) in group II. There was also no significant difference between two groups for serious drug toxicity (p>0.05).

Table 3: The results of anti-tuberculosis therapy after three and six months in group I and II

Groups	Clinical improvement	Radiographic improvement	Lab. response	Total response
I, n=29	28	28	29	28 (96.5%)
II, n=28	28	28	28	28 (100%)

Discussion

Standard anti-tuberculosis therapy (six month therapeutic regimen) is a treatment of choice for smear SPPTB [2,4,13-15] because the risk of *Mycobacterium tuberculosis* resistance and emerging multi-drug resistance tuberculosis (MDR-TB). In patients with few mycobacterium in their pulmonary lesions, the risk of resistance and emerging MDR-TB is very low [4,6,10], and from economic views (expensive drugs, numerous drugs), drug toxicity (hepatitis) and unnecessary use of drugs [10,11], so it is believed that shorter duration and fewer drug

combination can be employed in anti-TB chemotherapy for SNPTB [4].

There are few reports on short chemoprophylaxis but not on chemotherapy, so it is impossible to compare the results of this study with other studies. This study showed that three month therapeutic regimen containing daily rifampicin 600mg and isoniazide 300mg and ofloxacin 400mg are as effective as standard six month therapeutic regimen in treating of mild to moderate smear negative pulmonary tuberculosis. We believe that this three month therapeutic regimen for adult patients

(particularly in aged old patients) should be considered an appropriate anti TB therapeutic regimen, because of less duration, better patient compliance, good effectiveness, low expenses and low drug toxicity.

In conclusion three month therapeutic regimen containing rifampicin (600mg/day), isoniazide (300mg/day) and ofloxacin (400mg/day) may be considered as an effective treatment for adult patients with unprogressive smear negative pulmonary tuberculosis.

Acknowledgment

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