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The Comparison of Six-month and Four-month Regimens of Chemotherapy in the Treatment of Smear Positive Pulmonary Tuberculosis

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The aim of this study was to determine the relapse rate and failure rate in the regimen of less than 6-months and this regimen was compared with the 6 month regimen. This study was an experimental clinical trial on one hundred of patients with pulmonary tuberculosis at Zahedan (a city in Southeast of Iran) in a time period of 5 years from August 1996. The study patients were adults with newly diagnosed, sputum smear positive pulmonary tuberculosis, who had no cavitation and no abnormality in more than one lobe on plain chest X-ray. Eligible patients were randomly allocated to one of the following regimens: (A) Isoniazid, Rifampicin, Pyrazinamide and Ethambutol daily for 2 months, followed by Isoniazid and Rifampicin daily for 2 months: (B) Isoniazid, Rifampicin, Pyrazinamide and Ethambutol daily for 2 months, followed by Isoniazide and Rifampicin daily for 4 months. The patients were assessed clinically and bacteriologically every month during treatment and every two months after treatment. Follow up was continued for 5 years. The results up to 5 years after treatment are presented here. Thirty three cases were treated with the 4- month regimen and 67 cases treated with the 6 month regimen. Then the relapse and failure rate was compared together for the two regimens. Over a follow-up period of 5 years, among the patients who were entered into the 4 month regimen (A), the relapse rate was 9.09% (3 cases) and the failure rate was zero. The relapse and failure rates in the 6- month regimen (B) were 8.95% (6 cases) and 4.48% (3 cases), respectively. This results showed that, there was no significant difference between two regimens in the relapse rate and the failure rate ($p>0.05$). Regimen of 4 months duration can achieve a high cure rate and low 5 years relapse rate in newly diagnosed patients with smear positive pulmonary tuberculosis where, there is not any report of drug resistance. Larger studies are needed to confirm these results.

Key words: Tuberculosis, chemotherapy, relapse rate, failure rate, Zahedan

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INTRODUCTION

Pulmonary tuberculosis is the most common manifestation of tuberculosis in human. When effective drugs were not available, 50% of patients with active pulmonary tuberculosis died within 2 years^[1]. During the past decade, several treatment trials for tuberculosis have been reported^[1-3]. One of the long-term goals in tuberculosis control has been to shorten the period of treatment while maintaining high rate of cure with low rate of relapse. The current, widely used 6-month regimen which is highly effective in the clinical setting, yet it is cumbersome to implement under control programme conditions^[1,2,4,5]. It is for note that the rates of non-adherence to treatment and patient default remained high despite the still shorter regimens used in a carefully selected patient population: more than 20% of the patients in all the regimens did not complete the recommended number of doses^[5]. The southeast region of Iran is an endemic area for tuberculosis. The annual incidence rate for all types of tuberculosis disease and smear-positive pulmonary tuberculosis in Zahedan (a city in southeast of Iran) has been about 70.7 and 41.6 per 100000 population, respectively^[6]. It has been defined that even 30% of well educated tuberculous patients do not complete their treatment because of long term treatment in this area^[7]. With regard to this fact, Although, the regimens of less than 6-months (3-month regimen of daily Isoniazid, Rifampicin, Streptomycin and Pyrazinamide), in the previous randomized clinical trial, in patients with smear and culture negative pulmonary tuberculosis, resulted in a nearly 100% favourable outcome at the end of treatment^[1,5,8]. We conducted a randomized, controlled clinical trial to assess the efficacy of regimens of less than 6-months for the treatment of smear-positive pulmonary tuberculosis.

MATERIALS AND METHODS

This study was an experimental trial that was conducted at Zahedan health center in August 1996. A total of 100 cases were enrolled in our study. The subjects were adult patients, at least 18 years old who had newly diagnosed smear positive pulmonary tuberculosis and they had minimal abnormality on plain chest X-ray (no cavity, no abnormality in more than one lobe). For admission to the study, the patients were required to consent to undergo all the investigations and also attend daily the health center for supervised outpatient treatment and allow home visit by health center staff. Those with concomitant hypertension, diabetes mellitus, epilepsy,

Table 1: Characteristics of 100 smear positive pulmonary tuberculosis patients according to drug regimen allocated

Characteristics	Regimen				Total
	Group A (n = 33)		Group B (n = 67)		
	Male	Female	Male	Female	
Sex	19	14	28	39	100
Age (Year)	<40	>40	<40	>40	100
	10	23	15	52	
Nationality	Iranian		Afghan		100
	87		13		

immunodeficiency, or serious form of extrapulmonary tuberculosis were not eligible. All patients were HIV sero-negative. Eligible patients who had at least two sputum smear positive for acid-fast bacilli were randomly allocated to one of the following two regimens by using random number table;

A-Isoniazid 300 mg (5 mg kg⁻¹), Rifampicin 600 mg (10 mg kg⁻¹), Pyrazinamide 1500 or 2000 mg (30 mg kg⁻¹) and Ethambutol 1200 or 1500 mg (20 mg kg⁻¹) daily for 2 months, followed by Isoniazid, Rifampicin daily for 2 months.

B-Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as above daily for 2 months, followed by Isoniazid and Rifampicin daily for 4 months (Table 1).

All drugs were administered under supervision as a single dose. Patients who missed clinical visit were visited at home and strongly encouraged to attend the clinic for treatment. A physician examined the patients every month and recorded adherence to treatment and the clinical response. Sputum specimens were examined every month by microscopy (not culture according to national tuberculosis guidelines, Iran) during the treatment phase and every two months during the follow-up phase for 2/years then every 3/months for 3/years.

The definition of failure in group A was: a positive sputum smear at the end of 4 months of treatment and in Group B: a positive sputum smear at the end of 5/months of treatment .

The definition of relapse was a positive sputum smear during the follow-up period (5/years). The patients who had criteria for relapse or failure were treated with the 8/month regimen (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin daily for 3 month, followed by Isoniazid, Rifampicin and Ethambutol daily for 5/months).

RESULTS AND DISCUSSION

According to sputum smear and using Chi-square test, there was no significant difference between two groups on relapse rate and failure rate (p>0.05). From the 33 patients who were treated with the 4-month regimen (Group A), only 3 patients had relapse (9.09%) and failure

Table 2: Outcome in 100 patients, failure and relapse during 5 years follow-up

Regimen	Total Patients	Relapse		Failure	
		(n)	%	(n)	%
A	33	3	9.09	0	0
B	67	6	8.95	3	4.48

Table 3: Numbering of relapse and failure according to nationality

	Number of relapse	Number of failure
Iranian	8	0
Afghanian	1	3

rate was zero. From the 67 cases who were treated with the 6 months regimen (Group B) 6 cases (8.95%) had relapse and 3 cases (4.48%) had failure (Table 2). Out of the 9 relapses 8 occurred within 2/years after completing of chemotherapy and the remaining one (Group A) occurred between 2 and 5 years. Out of the 9 patients with the relapse only one patient was Afghan. All of the patients with the failure (3 cases in two groups) were from Afghan patients. Among the patients with relapse, 2 patients aged less than 40 years. Analysis between nationality and the relapse rate and failure was not possible due to the limited numbers (Table 3).

Previous clinical trials of 3-or 4 month regimens for the treatment of smear and culture negative pulmonary tuberculosis had been successful^[1,5]. A 3-month regimen of daily Streptomycin, Isoniazid, Rifampicin and Pyrazinamide in the treatment of smear positive pulmonary tuberculosis in south India achieved high rate of culture conversion, but had relapse rate of 20% in the 21 months after treatment completion^[9]. Eule *et al.*^[10], studying the same regimen, also reported a relapse rate of 20% among 61 patients. For the 4/month regimen (Isoniasid, Rifampicin, Pyrazinamide for 8/weeks, followed by Isoniaside, Rifampicin for 8/weeks), he reported relapse rate was 13% in an East African study^[11] and 10% in Singapore^[12]. Present study showed that in the 4 month regimen the relapse rate was 9.09% and the failure rate was Zero. In the patients who were treated with the 6 month regimen in this study, the relapse rate was 8.95% and the failure rate was 4.48%. There has been no similar study in Iran. Previous studies had showed that patients who had smear positive pulmonary tuberculosis without cavitation on plain chest-Xray and had been treated with the 6 month regimen, the relapse rate was 5%^[1,13-17]. These studies suggest that a 3 or 4/month regimen with the traditional first-line anti tuberculosis drugs may be inadequate for the treatment of smear positive pulmonary tuberculosis. Other previous studies have tested relationship between the length of treatment and the risk of failure and relapse^[18-20]. Now a 6 month regimen is perfectly acceptable for the drug sensitive infection and the relapse rate in this regimen with no risk factor

(no cavitation, no positive culture after 2/months of treatment) is 2-3%^[1-3,21-26]. Although, it is defined that failure rate is high even in the well educated patients because of long term treatment^[5,7] but our study and other studies suggest that the 4/month regimen with the first-line anti tuberculosis drugs is inadequate for sterilizing the bacterial load because the relapse rate was more than 5%^[5,9-12]. But in our study, there was not significant difference between the relapse rates in two groups. Thus, for ultra-short regimens, we need more studies with the new drugs. Routinely, the regimen of less than 6 months is not recommended in the positive sputum smear pulmonary tuberculosis and this study was an initial trial. Although the current study showed that there was not significant difference on the relapse rate and failure rate in the 4 and 6/month regimens, but we do not advise this regimen especially when there is drug resistant infection. With regard to this fact, when Zahedan health center, reported 2 cases of drug resistant infection in this province (one in Chahbahar and other in Iranshahr, two cities in Sistan and Baluchestan province in Southeastern of Iran)) in the previous patients who were treated with the 6/month regimen (no in patients who were enrolled in this study), the 4/month regimen was stopped and this study that, at first was based on the two equal groups (50-50), was changed to 33 and 67 cases. Although, we did not observe significant difference between two regimens, but a regimen of less than 6 month is not recommended in these regions.

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REFERENCES

1. David, W.H., 2000 . Mycobacterium Tuberculosis. In: Principles and Practice of Infectious Diseases. 5th Edn., (Eds.) G.I. mandell, J.e. bennette, D. Raphael. Philadelphia: Chrchill Livingstone, pp: 2580-2592.
2. Anonymous, 2003. Treatment of Tuberculosis. Am. Thoracic. Soc. CDC Infect. Dis. Soc. MMWR., 52: 1-17.
3. Michael, D.I., 2000. Tuberculosis Chemotherapy. In: A Clinicians, Guide to Tb., pp: 211-220.
4. Fridman, L.N., 2001. TB Current Concept and Treatment. 2nd Edn., pp: 208-211
5. Narayanan, P.R., 2002. A randomised clinical trial for treatment of smear positive pulmonary tuberculosis with regimens using ofloxacin in the intensive phase. Ind. J. Tub., 49: 27-38.

6. Moghtaderi, A. and R. Alavi-Naini., 2003. Tuberculous radiculomyelitis; Review and presentation of 5 cases. *Intl. J. Tub. Lung Dis.*, 7: 1186-1190.
7. Sharifi-Mood, B., M. Metanat and M.R. Metanat, 1996. A comparative study on relapse rate and failure rate in 6 and 9/months regimens in pulmonary tuberculosis in Zabol. *Intl Bull Zahedan Health Center, Iran*, pp: 31-39.
8. Anonymous, 1989. A controlled treatment of 3-4-6 month regimens of chemotherapy for sputum smear negative and culture negative pulmonary TB result 5 years. Hong-Kong chest service tuberculosis Madras-britain research center. *Am. Rev. Res. Dis.*, 134: 871-877.
9. Anonymous, 1986. A controlled clinical trial of 3 and 5 month regimens in the treatment of sputum –smear positive pulmonary tuberculosis in South India. Tuberculosis Research Center, Madras. National Tuberculosis Institute. *Am. Rev. Res. Dis.*, 134: 27.
10. Eule, H., H. Beck and H. Evers, 1982. Daily and intermittent short –course chemotherapy using 4 drugs in recently detected bacillary pulmonary tuberculosis. *Bull. Intl. Union Tub.*, 57: 63.
11. Anonymous, 1982. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. East African/British medical Research Council Study. *Am. Rev. Res. Dis.*, 123: 165.
12. Anonymous, 1981. Clinical Trial of six month and four month regimens of chemotherapy in the treatment of pulmonary tuberculosis. The result up to 24 months. Singapore Tuberculosis Service/British Medical Research Council, *Tubercle*, 62: 95.
13. Anonymous, 1994. Treatment of tuberculosis infection in adult and children. *Am. J. Res. Crit. Care Med.*, 149: 1359-1374.
14. Davidson, V. and Le-Ho, 1992. Drug treatment of TB *Drugs*, 43: 651-657
15. Anonymous, 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am. J. Res. Crit. Care Med.*, 161: 221.
16. Anonymous, 2003. Treatment of tuberculosis. Centers for Diseases Control and Prevention. *Am. J. Res. Crit. Care Med.*, 167: 603
17. Burman, W.G. and B.E. Jones, 2002. Treatment of HIV associated tuberculosis in the era of effective antiretroviral therapy. *Am. J. Res. Crit. Care Med.*, 164: 7.
18. Anonymous, 2003. Treatment of Tuberculosis, A guidelines for national programmes. Geneva. WHO, pp: 321-327.
19. Young, D.B., 2003. Ten years of research progress and what's to come. *Tuberculosis*, 83: 77
20. Anonymous, 2003. Treatment of tuberculosis. *MMWR.*, 52: 1-77
21. Chadha, S.L. and R.P. Bhagi, 2001. Treatment outcome in tuberculosis patients under directly observed treatment Short course (DOTs) a short study. *Ind. J. Tub.*, 47: 155-8
22. Santha, T., O. Nazareth and M.S. Krishnamurty, 1989. Treatment of pulmonary tuberculosis patients treated with short course chemotherapy regimen in South India 5 year follow-up. *Tub. J.*, 70: 229-234
23. Dutt, A.K., D.Mores., W.W. Stead, 1984. Short course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampicin 7-years experiences with mainly outpatients. *Am. J. Med.*, 77: 232-242
24. Davidson, P.T. and H.Q. Le, 1992. Drug treatment of tuberculosis. *Drugs*, 43: 651-673
25. Cohn, D.L., B.L. Catlin and K.I. Peterson, 1990. A 62-dose, 6/months therapy for pulmonary and extrapulmonary tuberculosis; A twice weekly directly observed and cost effective regimen. *Am. Intl. Med.*, 112: 407-415
26. Perez Stable, E.J. and P.C. Hopewell, 1989. Current tuberculosis treatment regimens; Choosing the right one for young patients. *Clin. Chest Med.*, 10: 323-339