Original Article

Four-month Chemotherapy in the Treatment of Smear-negative Pulmonary Tuberculosis: Results at 30 to 60 Months

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Abstract

***Introduction**: Most patients with active pulmonary tuberculosis (PTB) are treated with a 6-month short course regimen. The purpose of the present study was to assess the efficacy of using 4 months of chemotherapy to treat patients with smear-negative PTB. **Methods**: A total of 314 patients were randomised to a daily or combined (daily and intermittent) regimen as follows: (1) 2HRZ/2HR—2 months of isoniazid (H), rifampicin (R) and pyrazinamide (Z), followed by 2 months of H and R or (2) 2HRZ/2H_3R_3—2 months of HRZ as in regimen 1, followed by H and R given 3 times weekly for 2 months or 4 months if initial sputum specimens were culture positive. **Results**: One hundred and fifty-eight patients were assigned to the daily regimen and 156 to the combined regimen. Of the 158 patients, 99 had negative cultures and 59 had positive cultures. There was no relapse among 96 culture-negative patients assessed at 30 months and 68 patients at 60 months. However, 6 patients had no radiological response while 1 was considered on review to have non-tuberculous disease. There was no relapse among 57 culture-positive patients assessed at 30 months and 41 at 60 months. In the combined regimen group, 102 had negative cultures and 54 had positive cultures. There was 1 relapse in the culture-negative group of 100 patients assessed at 30 months and 74 at 60 months. There was no radiological response in 5 patients. One patient in the culture-positive group failed therapy but there were no relapses during follow-up to 60 months. **Conclusion**: A 4-month daily or combined regimen appears to be highly effective in the treatment of non-immunocompromised patients with smear- and culture-negative PTB.*

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Key words: Four-month chemotherapy, Pulmonary tuberculosis, Smear negative

Introduction

Patients with active pulmonary tuberculosis (PTB) are usually treated with a 6-month regimen in which chemotherapy is administered daily, intermittently or as a combined (daily and intermittent) regimen. However, patients with smear-negative PTB who have small lesions in the lung may not require the full duration of chemotherapy. Indeed, previous studies have shown that 4 months of chemotherapy is highly effective for the treatment of smear-negative PTB,[1,2] but chemotherapy for 2 or 3 months is inadequate.[3] The regimens investigated differed from those used in Singapore. The aim of the present study was to assess the efficacy of shortening chemotherapy from 6 to 4 months, using regimens which are given routinely in Singapore. The results of treatment and follow-up over a period from 30 to 60 months are presented in this report.

Materials and Methods

Patients aged 15 years and above were assessed for admission to the study. The admission criteria included patients who had respiratory symptoms and chest X-ray abnormality compatible with a diagnosis of PTB (e.g. upper zone infiltrates) but with negative sputum smear examination for acid-fast bacilli (AFB) on 4 consecutive occasions. Most of the patients were referred by the primary health care clinics and private practitioners after having failed to improve following a course of antibiotics. Simple blood tests and relevant laboratory investigations were carried out to exclude non-tuberculous disease. When malignancy was suspected, patients were referred to the Medical Departments at Tan Tock Seng Hospital (TTSH) for further diagnostic evaluation. Patients were excluded if they had a recent or past history of treatment for PTB, a

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history of mental disorder, alcohol or drug abuse and pregnancy. All patients gave informed consent. The study was approved by the tuberculosis (TB) research committee in TTSH.

Regimens Studied

All patients were assessed by physicians at the Department of Tuberculosis Control (DTBC). Two regimens were used in the study:

1) a daily regimen of isoniazid (H), rifampicin (R) and pyrazinamide (Z) for 2 months followed by H and R for 2 months;
2) the same combination of drugs as (1) for the first 2 months, followed by H and R 3 times a week for 2 months.

Selected patients were randomised to 1 of the 2 regimens by opening consecutively numbered sealed envelopes. In a previous study,[4] the 2 regimens were found to be equally effective for the treatment of smear-positive PTB in Singapore, when given for a total duration of 6 months. In the present study, chemotherapy was given for a total of 4 months for patients allocated to the daily regimen regardless of the culture results. However, for patients allocated to the combined regimen, the 3-times weekly phase of therapy was prolonged to 4 months (total duration of 6 months) for patients with culture-positive disease. A longer duration of treatment was given because of concern that a 4-month combined regimen might not be adequate for patients with cavitary disease.

Drug Dosages

In the initial 2-month phase of therapy, the following drug dosages were given as a single dose: isoniazid 300 mg, rifampicin 450 mg or 600 mg, pyrazinamide 1.5 g or 2 g. The higher dosages were given for those weighing >50 kg. In the subsequent phase of therapy, the same dosages of isoniazid and rifampicin were continued for a further 2 months for patients on the daily regimen, while those treated with a combined regimen were given a higher dosage of isoniazid (15 mg/kg) and a fixed dosage of 600 mg rifampicin thrice weekly for 2 or 4 months.

Assessment and Follow-up of Patients

All patients were assessed at the Department of Tuberculosis Control. A chest X-ray was done at entry to the study and at 4 months (for those on the 4-month regimen) and 6 months (for those on the 6-month regimen); in both the daily and combined regimens, chest X-ray was done at 12 months and thereafter annually up to 60 months. The chest radiograph was read independently by a radiologist (TKK) at the TTSH, who was blinded to the regimen given. The extent of lung disease was classified as minimal, moderate and far advanced.[5] Four sputum specimens were examined pretreatment by direct smear and culture for *Mycobacterium tuberculosis* and thereafter 1 specimen was examined monthly to 12 months, every 3 months from 12 to 30 months and every 6 months from 30 to 60 months. Positive cultures were tested for drug sensitivity to streptomycin, isoniazid and rifampicin. When a sputum smear or culture became positive, 3 additional sputum specimens were collected at monthly intervals for bacteriological examination. Assessment of relapse was made independently by a physician who had no knowledge of the treatment given. Treatment was given under direct observation for all patients at the polyclinics nearest to their home or place of work.

Population Studied

A total of 322 patients were found eligible for the study over a period from 10 September 1990 to 12 March 1996. Eight patients opted out of the study before randomisation. The remaining 314 patients were randomised to 2 treatment regimens (Fig. 1). The patient characteristics are shown in Table I. There were 158 patients in the daily regimen group and 156 in the combined regimen. Four patients died after they had defaulted, 3 on the daily regimen (at months 12, 32 and 48) and 1 on the 4-month combined regimen (month 39). The deaths were due to non-tuberculous causes. Our original intention to follow-up all patients for 60 months could not be achieved because of slow enrolment of patients to the study. The study was terminated on 12 August 1998 when almost all patients had completed 30 months of follow-up and 70% had completed 60 months. The number and proportion of patients on follow-up from 30 to 60 months in the 2 treatment groups are shown in Table II.

Extent of Disease

The radiological extent of lung disease are shown in

TABLE I: BASELINE CHARACTERISTICS OF PATIENTS

Characteristic	Daily regimen n = 158	Combined regimen n = 156
Mean age (range) [y]	33.5 (15-64)	31.5 (15-66)
Age group [y]		
15-34	95 (60%)	98 (63%)
35-54	44 (28%)	49 (31%)
≥55	19 (12%)	9 (6%)
Mean weight [kg]	54.8	53.3
Male — no. (%)	121 (73%)	114 (77%)
Disease extent		
Minimal	143 (90%)	144 (92%)
Moderate	15 (10%)	12 (8%)
Far advanced	0 (0%)	0 (0%)
Cavitation	4 (2.5%)	6 (3.8%)
Diabetes	5 (3.1%)	3 (1.9%)

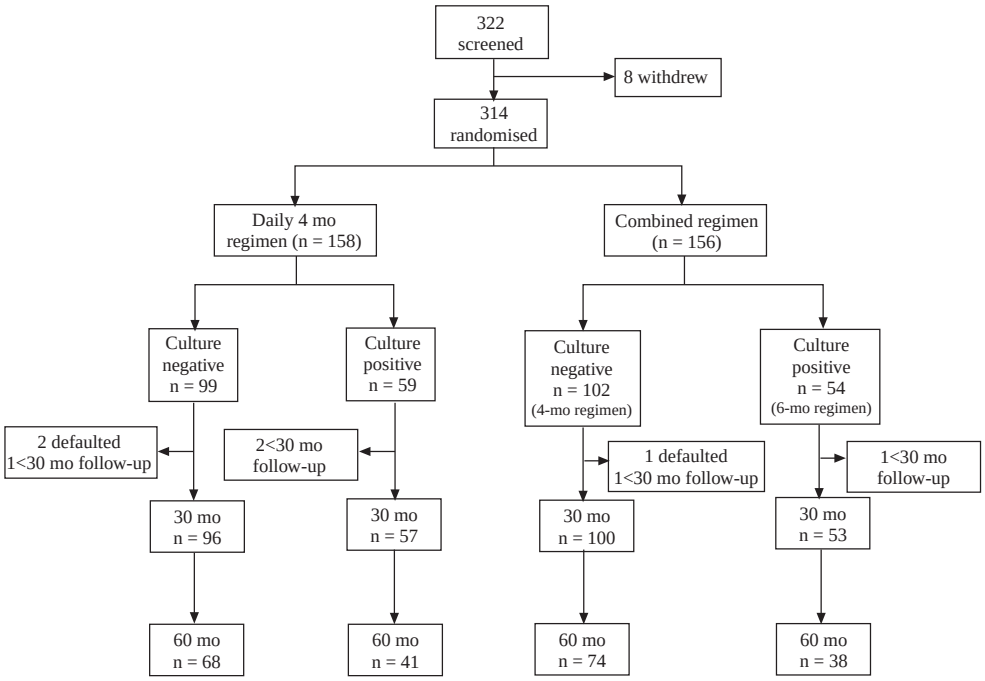

Fig. 1. Profile of study.

TABLE II: PATIENT FOLLOW-UP AND TREATMENT OUTCOME (30 TO 60 MONTHS)

Regimen	Month of follow-up No. and (%)†					Adverse outcome
	EOC	30 mo	36 mo	48 mo	60 mo	
2HRZ/2HR (C–)*	99	96 (97)	89 (90)	77 (78)	68 (69)	Nil
2HRZ/2HR (C+)*	59	57 (97)	56 (95)	50 (85)	41 (69)	Nil
2HRZ/2H_3R_3(C–)*	102	100 (98)	96 (94)	81 (79)	74 (72)	1 relapse
2HRZ/4H_3R_3(C+)*	54	53 (98)	53 (98)	46 (85)	38 (70)	1 failure

H: isoniazid; R: rifampicin; Z: pyrazinamide; (C–): culture-negative group; (C+): culture-positive group; EOC: end of chemotherapy

* The number in front of the abbreviations indicates duration of chemotherapy in months; the number in subscript indicates frequency of drug administration per week.

† (%) = No. of patients at each follow-up period/No. of patients at end of chemotherapy.

Table I. Most of the patients had minimal disease (90% to 92%) with cavitation being present in 2.5% to 4% of patients.

Analysis

The main outcome of interest was therapeutic efficacy which was assessed by the occurrence of treatment failure and relapse. Analysis was based on the intention to treat principle. Failure was defined as clinical and radiologic deterioration at the end of 4 or 6 months of treatment in patients with culture-negative disease and failure of sputum culture conversion towards the end of therapy in patients with culture-positive disease. Relapse was defined as clinical and radiological deterioration following therapy with or without bacteriological confirmation. Bacteriological relapse was defined as the presence of a positive sputum culture with 5 or more colonies in at least 2 of 3 specimens during a 3-month period. The radiological response to chemotherapy was classified as follows: (i) no change, (ii) <50% clearing of opacities, (iii) >50% clearing and (iv) complete clearing and (v) deterioration. The radiological status at 30 months is shown in Table III.

Results

Four-month Daily Regimen

Culture-negative cases

There were 99 patients on the daily 4-month regimen; 96 were assessable at 30 months after excluding 2 defaulters who later passed away and 1 who had not completed 30 months of follow-up. There was no change in the chest

TABLE III: RADIOLOGICAL STATUS AT 30 MONTHS

Radiological status	Daily regimen				Combined regimen			
	2HRZ/2HR(C–)*		2HRZ/2HR(C+)*		2HRZ/2H_3R_3 (C–)*		2HRZ/4H_3R_3 (C+)*	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No change	6	6.3	0	0	5	5	0	0
<50% clearing	0	0	0	0	2	2†	0	0
>50% clearing	81	84.4	52	91	84	84	52‡	98
Complete clearing	9	9.3	5	9	9	9	1	2
Total	96	100	57	100	100	100	53	100

H: isoniazid; R: rifampicin; Z: pyrazinamide; (C–): culture-negative group; (C+): culture-positive group

* The number in front of the abbreviations indicates duration of chemotherapy in months; the number in subscript indicates frequency of drug administration per week.

† One patient relapsed at 13 months with positive cultures.

‡ One patient failed therapy with positive cultures at 5, 6 and 7 months.

TABLE IV: ADVERSE REACTIONS REQUIRING SIGNIFICANT CHANGE IN THERAPY

Reaction	Regimen	Patients (n)	Month of onset
Jaundice	2HRZ/2HR, (C–)*	2	2nd,3rd
	2HRZ/2HR (C+)*	3	1st, 3rd, 3rd
	2HRZ/2H_3R_3 (C–)*	3	<1st, 1st, 2nd
Rash +/- pruritus	2HRZ/2HRm (C–)*	1	1st
	2HRZ/2HR, (C+)*	2	<1st, <1st
	2HRZ/2H_3R_3 (C–)*	2	<1st, 1st
Fever	2HRZ/2H_3R_3 (C+)*	1	2nd
Total		14	

H: isoniazid; R: rifampicin; Z: pyrazinamide; (C–): culture-negative group; (C+): culture-positive group

* The number in front of the abbreviations indicates duration of chemotherapy in months; the number in subscript indicates frequency of drug administration per week.

radiograph in 6 patients, partial clearing was seen in 81 patients and complete clearing in 9 patients (Table III). One patient was considered to have pyogenic lung infection on review after the end of therapy. There was no relapse on follow-up to 30 months and 60 months when 68 patients were assessable. One patient died at month 48 from heart failure. Exclusion of the 6 patients with no radiological improvement (assuming that these were probably inactive disease) and 1 with non-tuberculous disease would reduce the number of patients assessed at 30 and 60 months to 89 and 61, respectively.

Culture-positive cases

Fifty-nine patients on the daily 4-month regimen had culture-positive disease. All had sputum culture conversion at the end of 2 months. There were no cases of drug resistance. Of the 59 patients with culture-positive disease, 57 were assessable at 30 months and 2 patients had not completed follow-up. Fifty-two showed partial radiological clearing and 5 complete clearing. There was no relapse in this group over a period from 30 to 60 months, at the end of which 41 patients were assessable.

Combined Regimen

Four-month regimen

Of the 102 patients with culture-negative PTB allocated to the 4-month intermittent regimen, 100 patients were assessable at 30 months and 74 patients at 60 months. One had not completed follow-up while 1 defaulted at 24 months and was later reported to have died at 39 months. There was no change in chest radiograph in 5 patients, 86 showed partial clearing and 9 showed complete clearing (Table III). One patient had chest X-ray deterioration associated with bacteriological relapse at 13 months from the start of therapy. Treatment for this patient was interrupted for 1 month during month 2 because of drug-induced fever. There were no further relapses subsequently. If patients with no radiological change were excluded (assuming that they had no active disease), the adjusted number of patients assessed at 30 and 60 months would be 95 and 69, respectively.

Six-month intermittent regimen

Of the 54 patients given 6 months of therapy with the combined regimen, 53 were assessable at 30 months. One patient had not completed follow-up. Fifty-two showed partial clearing and 1 showed complete clearing. One patient failed treatment with cultures becoming positive from month 5 to month 7. He missed a total of 13 days of therapy. There were no relapses during follow-up to 60 months, at which time 38 patients were assessable.

Adverse Reaction

There were 14 patients (Table IV) with adverse reaction requiring major modification of treatment. Eight patients

(5 in the 4-month daily regimen and 3 in the combined regimen) developed clinical jaundice, 5 within the first 2 months of starting treatment and 3 in the third month. Five patients (3 in the daily 4-month regimen and 2 in the combined regimen) had drug-induced rash and 1 patient ($2HRZ/2H_3R_3$) developed fever and headache in the second month. Twenty patients (11 in the daily regimen and 9 in the combined regimen) had minor reactions with interruption of therapy for 2 to 5 days. The reactions were mainly fever, rash, or a combination of both, headache and body ache.

Discussion

The accurate diagnosis of active PTB is a problem in any study on patients with smear-negative PTB. Diagnosis can only be confirmed when the initial sputum cultures were positive for *Mycobacterium tuberculosis* complex or subsequently when bacteriological relapse occurs during follow-up. Diagnostic accuracy can only be assessed if patients with suspected active PTB are not given treatment initially until there is more definite evidence of disease activity during follow-up, e.g. radiological deterioration with or without bacteriological confirmation. A study in Hong Kong[3] of smear-negative PTB included a control group of untreated patients. It showed that 74% of patients had bacteriologic or radiographic evidence of active disease over a period of 5 years and a further 15% had evidence of unstable lung lesions indicated by changes in the chest radiograph during follow-up. Thus in this study, the diagnosis of active PTB was correct in a high proportion of patients.

In the present study, we did not include a control group because we believed that postponement of treatment would not be acceptable to most of our patients. Nevertheless, the proportion (36%) of smear-negative patients with initial positive cultures is similar to the results (35%) in Hong Kong[1] including the high proportion of young patients and the predominance of patients with small lung lesions. In the same study,[1] the authors reported on the high percentage (89%) of patients with culture-negative disease who were judged to have probably active lung disease by radiological assessment, while the rest were considered to have doubtfully active, probably inactive or doubtful tuberculosis disease. In the present study, 94% of patients were assessed to have active PTB, based on radiological improvement following treatment. However, it is recognised that the diagnosis of active PTB based on the chest radiograph is not very reliable and there is always the possibility of including patients with inactive or non-tuberculous disease. Nevertheless, we have tried to minimise the risk of over-diagnosis by selecting patients with typical radiographic changes.

Long-term follow-up is important to detect early as well as late relapse, which is more likely to occur in patients with smear-negative disease. This is attributed to the higher proportion of dormant and semidormant bacilli in small tuberculous lesions.[6] A retrospective study[7] of patients in Hong Kong who adhered strictly to a 4-month course of treatment given under programme conditions revealed 10 relapses, of whom 9 occurred within 18 months of starting treatment. However, in a 5-year prospective study in Hong Kong of smear- and culture-negative patients treated with a 4-month regimen,[1] 58% (7 of 12) of patients in the culture-negative group relapsed within 24 months after the end of chemotherapy and the remainder in subsequent months. In the culture-positive group, 71% (5 of 7) of patients relapsed within 24 months. In the present study, almost 100% of patients had completed 30 months of follow-up and approximately 70% for 60 months.

The present study showed no relapses at 30 months (relapse rate, 0%; 95% CI, 0-4.1) among 89 patients with culture-negative PTB and 57 with culture-positive disease treated with a daily 4-month regimen. In the group treated with a combined regimen, there was 1 relapse at 13 months (relapse rate, 1%; 95% CI, 0.2-5.7) among 95 patients treated with a 4-month regimen. In this patient, therapy was discontinued for 1 month in the initial phase because of drug reaction. One patient on the 6-month regimen failed treatment, with cultures becoming positive from month 5 to 7. This patient missed a total of 13 days of therapy. In both the daily and combined regimens, there were no further relapses during 60 months of follow-up. As the patient characteristics were similar in both treatment groups, combining the treatment results for culture-negative patients gave 1 relapse among 184 patients (relapse rate, 0.5%; 95% CI, 0.1-3) at 30 months and 130 patients (relapse rate, 0.8%; 95% CI, 0.1-4) at 60 months. Exclusion of patients who developed significant drug reaction requiring modification or interruption of treatment for >1 week would reduce the number of patients assessed at 30 and 60 months to 176 and 122, respectively, and the single patient who relapsed would not be included. The very small number of relapse suggests that a 4-month daily or combined regimen is highly effective in the treatment of smear- and culture-negative PTB. However, the 4-month regimen cannot be given for patients with smear-positive PTB or patients with extensive disease because of the high relapse rate (13% to 14%) during 5 to 8 years of follow-up.[8]

Two previous studies in Hong Kong[1] and Arkansas[2] had shown low relapse rates with a 4-month regimen. However, different drug regimens were used in both countries. In Arkansas, patients with smear- and culture-negative PTB were treated with 1 month of daily isoniazid and rifampicin, followed by the same drugs given twice weekly for 3

months. There was a relapse rate of 1.2% (5/414) over a median follow-up period of 44 months. Most of the patients were in the older age group (mean age 60 years) and only 28% showed clinical or radiographic evidence of response to treatment. Nevertheless, it was estimated that 4 months of chemotherapy prevented a larger number of expected relapses (n = 60 to 65), based on a 5% reactivation of disease per annum for the first 5 years of follow-up. The relapse rate in Hong Kong was 4% (12/325) for patients with smear- and culture-negative PTB treated with a 4-drug, thrice weekly regimen of isoniazid, rifampicin, pyrazinamide and streptomycin. When the same combination of drugs was given daily or 3 times weekly to patients with smear-negative and culture-positive disease, the respective relapse rates were 3% and 2% during 60 months of follow-up.

In Singapore, resistance to isoniazid alone or in combination with other primary drugs was 3.8% in 1990[9] at the commencement of the study. The resistance rate has remained low from 1990 to 1998.[10] Hence, a 3-drug regimen initially, followed by 2 drugs in the maintenance phase, would be effective for most patients locally where the prevalence of HIV infection is low. However, in countries where there is a high prevalence of HIV infection and a greater risk of drug resistance, a 3-drug regimen or a 4-month duration of chemotherapy would not be appropriate for the treatment of smear-negative PTB.[11]

It has been estimated that approximately 50% of patients in many countries have small radiographic lesions associated with smear-negative disease.[12] In 1990 when patients were admitted to the present study, about 63% of patients had bacillary-positive PTB and this proportion increased to 69% in 1998. Thus, about 31% to 37% of patients had bacillary-negative PTB. The percentage would increase if smear-negative but culture-positive TB patients were also included. Most of the patients with bacillary-negative PTB were found to have minimal disease which accounted for 39% of all newly diagnosed cases in 1998. A reduction of chemotherapy to 4 months would benefit this group of patients by improving patient compliance and reducing the risk of drug toxicity. A 4-month regimen, especially the combined regimen, would be very suitable for directly observed therapy (DOT) which has been shown to improve treatment completion rates and outcomes.[13,14]

Conclusion

A limitation of this study is the small number of patients, especially those treated with the 4-month combined regimen. Nevertheless, the results indicated that a 4-month short course regimen of isoniazid and rifampicin, with pyrazinamide given during the first 2 months, is highly effective in the treatment of non-immunocompromised patients with smear- and culture-negative PTB in Singapore. The daily 4-month regimen is also effective for culture-positive patients but the evidence is less conclusive because of the smaller number of patients. The efficacy of the 4-month combined regimen for culture-positive patients is not known as it was not investigated in this study. The 4-month regimens used in the present study are not new but are the shortened versions of highly effective 6-month regimens which have been used successfully in Singapore for many years. The daily 4-month regimen was considered acceptable by the American Thoracic Society[15] for the treatment of smear- and culture-negative PTB provided that there was little possibility of drug resistance.

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