Original Article

ASSESSMENT OF LONG TERM STATUS OF SPUTUM POSITIVE PULMONARY TB PATIENTS SUCCESSFULLY TREATED WITH SHORT COURSE CHEMOTHERAPY

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Summary

Background: Long term status of pulmonary tuberculosis (PTB) patients treated with short course chemotherapy (SCC) regimens remains unknown.

Objective: To assess the clinical, bacteriological, radiological status and health related quality of life (HRQoL) of PTB patients 14 -18 years after successful treatment with SCC.

Methodology: In a cross-sectional study, cured PTB patients treated during 1986 – 1990 at the Tuberculosis Research Centre (TRC) were investigated for their current health status including pulmonary function tests (PFT). The St Georges respiratory questionnaire (SGRQ) was used to assess the HRQoL

Results: The mean period after treatment completion for the 363 eligible participants was 16.5yrs (range 14-18 yrs, 84% coverage) ; 25 (7 %) had been re-treated and 52 (14%) died. Among the investigated, 58 (29%) had persistent respiratory symptoms; 170(86%) had radiological sequelae but none had active disease. Abnormal PFT was observed in 96 (65%) with predominantly restrictive type of disease in 66(45%). The SGRQ scores for activity and impact were high implying impairment in HRQoL.

Conclusion: Assessment of long term status of cured PTB patients showed an impairment of lung functions and HRQoL highlighting the need to address these issues in the management of TB that may provide added value to patient care.

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INTRODUCTION

Standardised and directly observed six month regimen is currently recommended for the treatment of Pulmonary Tuberculosis (PTB). The main objective of treatment in PTB is to achieve high bacteriological cure rates. Though the patients are cured of the disease, the information on the long term status of the patients successfully treated with short course chemotherapy (SCC) regimens remains largely unknown. Studies have documented that about 1/3rd of the cured PTB patients do have respiratory complaints at the end of treatment seeking medical care[1,2]. The morbidity in PTB patients while on treatment or at the end of treatment has been reported using subjective (quality of life) as well as objective (pulmonary function tests) measurements[1-7]. However, the long term status of cured PTB patients has not been studied. This information is essential to quantify the impact of disease for appropriate early interventions in the management of patients with PTB. Hence the Tuberculosis Research Centre (TRC) undertook a study to assess the clinical, bacteriological and radiological status of PTB patients14 -18 years after successful completion of treatment with SCC .The aim of the present communication is to analyze the morbidity in these patients.

METHODOLOGY

Setting

TRC has been undertaking randomized controlled clinical trials in the treatment of pulmonary and extra-pulmonary forms of TB since 1956 with the objective of evolving suitable chemotherapeutic regimens in patients suffering from TB. The patients enrolled in the trial are followed up bacteriologically and radiologically for a maximum period of five years.

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Study population

This cross-sectional study was conducted at TRC, Chennai, during August 2004 – 2005. The study population included patients enrolled during 1986-1990 and had bacteriological quiescence (ie. culture negative) at the 60th month of follow-up. These were new PTB patients (≤ 1 month of previous anti-tuberculosis drugs) who were treated with first line anti-tuberculosis drugs namely isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in one of the following SCC regimens which included six month intermittent (2EHRZ$_2$/4EHR$_2$, 2HRZ$_2$/4RH$_2$) or nine month daily (2EHRZ/ 6EH) regimens.

All efforts were made to interview the patients during home visits or over the telephone. In case of reported death of the patient, a doctor's visit was made to probe the reasons for death (verbal autopsy)

When the patient attended the centre, a detailed history which included re-treatment during the follow-up period was elicited, after obtaining informed consent. Information was also obtained on habits which included smoking and alcoholism, respiratory symptoms and co-morbid conditions like diabetes, hypertension, bronchial asthma and cardiac problem. The blood pressure, weight and height were recorded and a general and systemic examination was performed. Other investigations included postero-anterior chest radiography, two sputum examination by smear and culture for tubercle bacilli, 12 lead Electrocardiogram (ECG) and Pulmonary function test (PFT) by Spirometry. The quality of life was assessed by a trained social worker using the St. Georges respiratory questionnaire (SGRQ).

Bacteriology: Sputum smears were examined for AFB by fluorescence microscopy.[8] and the specimens were processed by modified Petroff's method and cultured on the LJ medium.[9] All positive cultures were subjected to identification tests for *Mycobacterium tuberculosis* and to drug susceptibility tests using the minimal inhibitory concentration method for isoniazid and rifampicin[10,11].

Radiology: The chest x-rays were read by a panel of three doctors. The following observations were recorded namely a) the extent of lung involvement which was documented as unilateral or bilateral, b) the number of zones involved (minimum one-zone to maximum six -zones and c) presence or absence of cavitation[12].

Electrocardiogam (ECG): A 12 lead ECG was recorded for the patients and independently read by the cardiologist. The criteria laid down by WHO (1961) were used for the ECG based diagnosis of cor-pulmonale[13].

Pulmonary function testing (PFT) – PFT was performed according to the techniques mentioned in the operating manual of the spirometry (sensormedix) with special reference to American Thoracic society of Standardization of spirometry.[14] The parameters measured in spirometry include Forced Vital Capacity (FVC), Forced expiratory volume in 1 second (FEV$_1$), ratio of FEV$_1$ to FVC (FEV$_1$%). For assessing chronic changes, the observed values of FVC, FEV$_1$, and FEV$_1$% were expressed as a percentage of the predicted values by using the regression equation developed by Vijayan[15]. Lung function impairments were classified according to the above mentioned parameters as normal/restrictive disease/obstructive disease/combined disease[14] .

St Georges respiratory questionnaire (SGRQ): In the present study. SGRQ, a standardized, airways disease specific respiratory questionnaire, was used to measure health related quality of life (HRQoL)[16,17] This health status instrument consisting of 50 items is grouped under three components namely symptoms (8 items) which measures respiratory symptoms, activity (16 items) which measures impairment of mobility or physical activity and impact (26 items) which measures the psychosocial impact of disease). This tool has been validated for use in chronic pulmonary diseases including TB in many countries including India[18-23]. SGRQ scores were calculated using score calculation algorithms and missing data imputation recommended by its developer (P.W. Jones, St Georges Hospital Medical School, London, UK) Scores ranging from 0 to

100 are calculated for each component, as well as a total score which summarizes the responses to all items. Higher scores correspond to worse health-related quality of life.

Analysis

The data were analyzed using a statistical software package (SPSS, version 13 for Windows; Inc; Chicago IL). The SGRQ was scored with the scoring calculator (Excel-based) provided with the instrument. For each SGRQ scale, distribution characteristics, the percentage of patients with missing information and reliability estimates were

calculated. Analysis of variance and t-test were used to compare SGRQ scores between groups defined by functional characteristics.

RESULTS

There were 455 patients who were treated between 1986-1990 and for the present study 92 were excluded since 63 were re-treated for relapse, seven had defaulted, 20 died of non-tuberculous cause and in two patients treatment was changed. Hence 363 were eligible for the present study (Figure). This included 163 and 200 patients who were treated with daily and intermittent regimens of
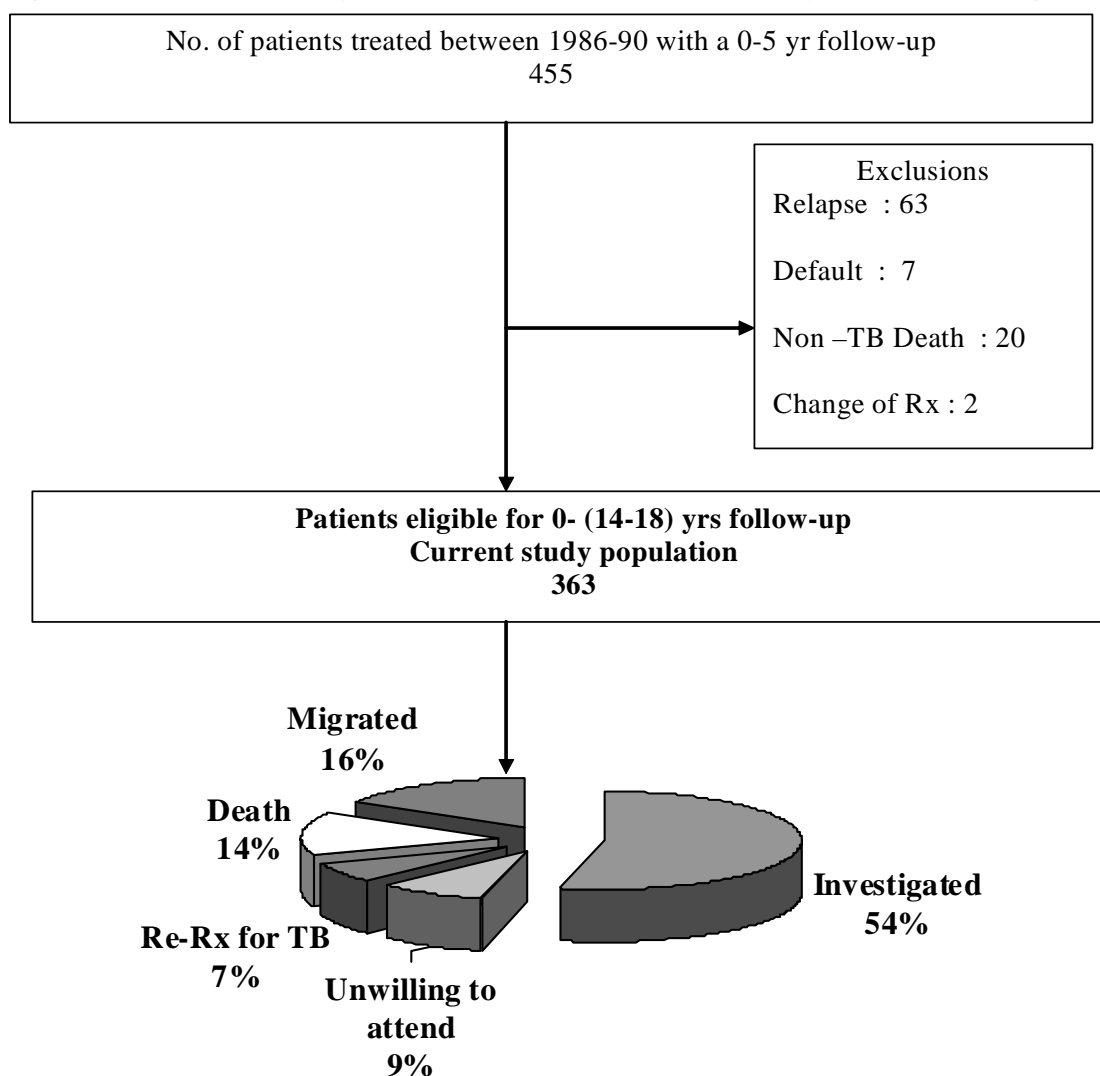
Figure: Status of pulmonary TB patients treated with SCC after a period of 14-18 years (n = 363)

SCC respectively. The mean period after treatment completion for the 363 eligible participants was 16.5yrs (range 14-18 years).There were 59 (16%) patients who had migrated and information is available for the remaining, giving a coverage of 84%. There were 25 (7%) who had been re-treated and 52 (14%) patients who had died. Among the 227 patients who were available, 198 (87%) attended our centre for investigations to assess the current health status.

Re-treatment: Among the 25 (7%) patients who were retreated, two were re-treated for extra-pulmonary TB (Brain tuberculoma, TB lymphadenitis).

Mortality: A verbal autopsy of the 52 (14%) patients who expired including five females revealed no deaths due to active TB. The mean age of these patients at the time of death was 50yrs. The cause of death could be attributed to respiratory pathology in 15 (29%) patients as the history of events preceding death were repeated attacks of cough and breathlessness necessitating frequent hospitalization or medications.

Profile of patients who were investigated: The mean age of the 198 patients who were investigated was 46yrs (range 27-73years). Majority 124 (63%) were males among whom 50% were smokers. (Table-1).

Clinical: Respiratory complaints were reported by 58 (29%) of the patients, mainly of frequent cough and/or breathlessness.

Bacteriology: Sputum smear and culture negativity was seen in 193 (97%) of the study participants.

Table 1. Characteristics of the patients who were investigated (n= 198)

Parameters		n	%
Sex	Male	124	63
Habits	Smoking	62	50
	Alcohol	47	38
Respiratory symptoms free		140	71
Bacteriology	AFB smear negative	193	97
	M.tb culture negative	196	99
Chest X-ray	Normal	28	14
	Abnormal	170	86
	Fibrosis	62	36
	Calcification	41	24
	Fibrosis & Calcification	59	35
	Others	8	5
	Zones ≤ 2	71	42
	>2	99	58
ECG			
	Normal	160	81
	Cor-pulmonale	21	11
	Others	13	6
	Un co-operative	4	2

Table 2: Types of abnormality in lung function in 148 investigated patients treated 14-18 years ago with SCC

Type of disease	Males		Females		Total	
	n	%	n	%	n	%
Normal	37	38	15	30	52	35
Restrictive disease	34	35	32	64	66	45
Obstructive disease	7	7	0	0	7	5
Combined disease	20	20	3	6	23	16
Total	98	100	50	100	148	100

Among the five patients who had positive smears, three patients were culture negative while two patients' cultures grew *Mycobacterium kansasii*.

Radiology: There were 28 (14%) patients with normal chest radiography while others had abnormality predominantly of fibrosis and or calcification.

Spirometry: The pulmonary function tests were performed in 148 (75%) patients who were willing to participate which included 98 males and 50 females (Table-2). The spirometry was normal for 52 (35%) of the participants. The predominant lung function impairment was restrictive type of disease in 66 (45%) patients and this was observed more in females - 32 (64%). Obstructive and combined type of lung function impairments were predominant in males. The difference in lung function impairments between the smokers and non-smokers was not statistically significant.

Electrocardiogram (ECG): Features suggestive of cor-pulmonale was observed in 21(11%) of the patients. The abnormal ECG changes observed in the remaining 14(7%) patients were that of left ventricular hypertrophy or heart rate disturbances like sinus bradycardia or tachycardia.

SGRQ: Tables 3 and 4 describe mean SGRQ scale scores in study population according to sex, smoking behaviour, ECG, chest X-ray and FEV_1% predicted.

Table 3: Distribution characteristics and reliability estimates SGRQ scales in the study population weighted sample (n=198)

	Symptoms	Activity	Impact	Overall
Mean Normal values*	12	9	2	6
Mean observed values	16.46	28.95	14.11	19.60
SD	18.63	23.19	23.96	20.65
Observed range	0-79.53	0-100	0-92.5	0-83.65
% with missing data	1.5	3.1	4.6	5.1

* Reference No: 26

Table 4: Mean SGRQ scale scores by demographical and clinical characteristics of the study population.

		Symptom	Activity	Impact	Overall
Mean Normal values*		12	9	2	6
Sex	Male	15.10	24.55	10.95	16.43
	Female	18.78	36.27	19.24	24.72
	p value	NS	0.001	0.03	0.01
Male	Smoker	19.63	30.37	14.56	21.00
	Non-smoker	11.45	19.98	8.07	12.85
	p value	0.02	0.02	NS	0.03
Chest	Abnormal	17.46	28.72	15.05	20.23
Radiography	Normal	10.58	30.29	8.79	16.12
	p value	0.01	NS	NS	NS
No. of zones involved ≤ 2		15.07	29.34	12.76	19.03
Chest radiography >2		17.90	28.56	15.46	20.17
	p value	NS	NS	NS	NS
ECG	Abnormal	20.85	36.36	21.08	26.17
	Normal	15.31	27.34	12.19	17.89
	p value	NS	0.03	NS	NS
PFT (n= 148)					
FEV_1 % $\leq 80\%$		19.35	28.98	14.10	19.97
predicted >80%		15.06	28.15	13.28	18.57
	p value	NS	NS	NS	NS

* Reference No: 26

The mean SGRQ scores for symptom, activity and impact including overall scores were high (increased impairment) among this group of patients as compared to that of general population. The overall scores were significantly higher for females (p=0.01) and smokers (p=0.03). However, abnormal chest X-ray, ECG and FEV_1% predicted did not correlate significantly with high SGRQ scores.

The above mentioned clinical, bacteriological, radiological, spirometry and ECG findings were not different from those who were treated with daily or intermittent SCC regimens.

DISCUSSION

To our knowledge, this study is the first of its kind to assess the long term status of PTB patients, 14-18 years after treatment with SCC regimens. There were 58 (29%) participants who had persistent respiratory symptoms and 170 (86%) with radiological sequelae. Lung functions impairments were present in 96 (65%) while ECG showed evidence of cor-pulmonale in 21(11%). Thus majority of the cured PTB patients had significant morbidity as evidenced by impairment in pulmonary functions and high SGRQ scores. This

study highlights the presence of respiratory system related morbidity among the microbiologically cured PTB patients.

Persistent respiratory symptoms observed in approximately 1/3rd of the patients in the present study is an important cause of concern. Studies have documented that cured PTB patients continue to have respiratory symptoms (30-47%) at the end of treatment, (40%) after one year of treatment and (15.9%) after two and a half years after treatment[1,2,5,24] In another study 14% of treated PTB patients continued to attend the out-patient department for more than five years for respiratory complaints.[25] Since all the investigated patients in the present study were culture negative for *Mycobacterium tuberculosis*, there is a need to educate the patients that persistence of symptoms is not synonymous with reactivation of the disease.

The respiratory disease specific SGRQ scores were higher in this cohort of patients which implies an impairment in the quality of life which is in conformity with other studies done among PTB patients[18,19]. As data pertaining to SGRQ scores in general population in India is not available, the normative values for a general population studied in Spain recommended in SGRQ manual is used for comparison. The symptom, activity and impact scores observed in our study after a mean period of 16.5 years after successful treatment for TB were 16, 28 and 14 respectively as compared to general population scores of 12, nine and two on a scale of 100[26]. These findings suggest that the scores of the treated PTB patients were high (indicating worse status) when compared to the general population. Similar to earlier SGRQ studies in PTB patients, the score for impact was lower than that of symptom and activity[18,19] The scores were less when compared to patients with other respiratory diseases like interstitial lung disease, COPD or bronchiectasis[20,21,22]. These findings suggest that HRQoL among treated PTB patients was suboptimal when compared to the general population, but better when compared to other respiratory diseases.

Generally the observed SGRQ scores are higher for females[27]. In this cohort the female participants had a significantly higher scores in SGRQ suggestive of impairment of HRQoL with reference to activity and impact of disease as compared to males. An earlier study done on PTB patients while on treatment showed no gender differences in the SGRQ scores[18]. Among the males, in smokers SGRQ showed significant impairment of quality of life emphasizing the need to create an awareness about smoking cessation among treated TB patients.

Lung function impairments after TB is an unrecognized cause of chronic lung disease worldwide[7]. In the present study PFT was done in 75% of the patients. The predominant lung function patterns observed in these patients were restrictive and combined type similar to other published studies[6,7]. Our findings, similar to a previous reports have shown that females had more restrictive type of disease compared to males[3]. A previous study among treated PTB patients from our centre showed that the main ventilatory type of abnormality was restrictive in nature where as a study from Pretoria concluded that equal number of patients had restrictive/ obstructive type of disease[6,28]. However, a study from South Africa which was done at an average of 16 years after TB treatment showed that 68% of the patients had chronic obstructive lung disease[29]. Impairments in lung function in the present study were not significantly high among smokers. The published studies on smoking and lung function impairments in PTB patients are varied[19,30]. The patients with a FEV_1% Pred. of $\leq$80% had high SGRQ scores implying poor quality of life though it did not attain statistical significance

We observed a mortality of 14% in this cohort of patients. A study done among PTB patients irrespective of being treated has shown a mortality rate of 24% and lung function impairment as the probable cause of death in 15% after a duration of 10 years[30]. Although 15 patients in our study had frequent respiratory complaints or hospitalization among those who expired, it was not possible to conclude that TB sequelae was the probable cause of death.

The high coverage observed in our study could be attributed to the stringent efforts in screening for domiciliary stability for enrollment of patients to our controlled clinical trials. We observed no difference in the profile of patients treated with daily or intermittent anti-tuberculosis therapy. This highlights the fact that intermittent chemotherapy is as effective as daily pertaining to the long term impact of pulmonary TB.

The major limitation of this study is that the observations made need not be confined to TB sequelae alone and could be due to the aging and or health related factors of the study population. The lack of concurrent age-sex matched controls coupled with the lack of baseline investigations for pulmonary functions and assessment of quality of life is also another major limitation.

Despite the above mentioned limitations, this study has shown that treated and cured PTB patients do suffer from long term morbidity. India is a high burden country for TB and there is an active and well structured Revised National TB Control Programme (RNTCP) operating successfully covering the entire population since March 2006. The RNTCP has treated more than 8.1 million patients, and thereby prevented almost 1.46 million TB deaths.[31] As the programme matures, its level of sophistication will undoubtedly increase.[1] **From the findings of this study it appears that the providers and programme managers have a responsibility to recognize and address the long term impact of TB even after patients are cured. Addressing issues relevant to the quality of life and considering measures for pulmonary rehabilitation will provide added value to the programme.**

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