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Sputum conversion at the end of intensive phase of Category-1 regimen in the treatment of pulmonary tuberculosis patients with diabetes mellitus or HIV infection: An analysis of risk factors

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***Background & objectives*: New smear-positive pulmonary tuberculosis (PTB) patients in the Revised National Tuberculosis Control Programme (RNTCP) are treated with a 6-month short-course chemotherapy (SCC) regimen irrespective of co-morbid conditions. We undertook this retrospective analysis to compare sputum conversion rates (smear, culture) at the end of intensive phase (IP) of Category-1 regimen among patients admitted to concurrent controlled clinical trials: pulmonary tuberculosis alone (PTB) or with type 2 diabetes mellitus (DM-TB) or HIV infection (HIV-TB), and to identify the risk factors influencing sputum conversion.**

***Methods*: In this retrospective analysis sputum conversion rates at the end of intensive phase (IP) in three concurrent studies undertaken among PTB, DM-TB and HIV-TB patients, during 1998 – 2002 at the Tuberculosis Research Centre (TRC), Chennai, were compared. Sputum smears were examined by fluorescent microscopy. HIV infected patients did not receive anti-retroviral treatment (ART). Patients with DM were treated with oral hypoglycaemic drugs or insulin (sc).**

***Results*: The study population included 98, 92 and 88 patients in the PTB, DM-TB and HIV-TB studies. At the end of IP the smear conversion (58, 61, and 62%) and culture conversion (86, 88 and 92%) rates were similar in the three groups respectively. The variables associated with lack of sputum smear or culture conversion were age >45 yr, higher pre-treatment smear and culture grading, and extent of the radiographic involvement.**

***Interpretation & conclusions*: Our findings confirm that the current policy of the control programme to treat all pulmonary TB patients with or with out co-morbid conditions with Category-I regimen appears to be appropriate**.

Key words Category-1 - diabetes mellitus - HIV - pulmonary tuberculosis - RNTCP - smear conversion

The Government of India's Revised National Tuberculosis Control Programme (RNTCP), based on the DOTS strategy, began as a pilot in 1993 for effective control of tuberculosis. By March 2006, it has expanded to cover the entire population of India[1]. In the RNTCP, new smear positive pulmonary TB patients are treated with a 6 month short-course chemotherapy (Category-1) regimen, which has an intensive phase of 2 months duration with 4 drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) and a continuation phase of 4 months with 2 drugs (isoniazid and rifampicin). The drugs are given three times a week throughout the treatment period. All new pulmonary TB patients are treated with this regimen irrespective of associated co-morbid conditions such as diabetes mellitus (DM) or HIV. However, treatment of TB in diabetes may pose problems as it has been reported that diabetic patients have some degree of impaired gastrointestinal (GI) drug absorption even in the absence of clinical gastroparesis[2]. Moreover the hyperglycaemic state may additionally interfere with achieving adequate tissue levels of the medications, or with alveolar macrophage/CD4+ cell function[3].

For patients receiving Category-1 regimen in the RNTCP, smear conversion at the end of the intensive phase (IP) of treatment is emphasized as an important early predictor of treatment success[4-7].The sputum conversion results are used both for management of patients and for monitoring programme performance. If the smear is positive, the intensive phase is extended by one more month for that patient. It also indirectly helps to verify whether DOT (Directly observed treatment) is being carried out and thus serves as an important evaluation indicator of programme performance. Therefore it assumes importance in the context of RNTCP as there are implications in terms of treatment decisions that could be made mid-course.

In this background, it is essential to evaluate risk factors such as age, smear grading, weight and associated co-morbid conditions like HIV infection and diabetes mellitus among TB patients that are likely to influence smear conversion. Although risk factors which influence smear conversion have been studied widely[8-10], there are few studies on smear conversion in HIV co-infected individuals[11] but none with associated diabetes mellitus.

We report here a retrospective analysis on comparison of smear and culture conversion at the end of the intensive phase of treatment in the three groups of patients, namely pulmonary tuberculosis (PTB), PTB with type 2 DM, and PTB with HIV infection and the risk factors that influence sputum smear and culture conversion in these patients. All these patients were treated with RNTCP Category-1 regimen.

Material & Methods

Study design: This is a retrospective analysis of three concurrent studies. The first study was a randomized controlled clinical trial with an objective to evaluate the efficacy of a 4 month regimen containing ofloxacin in PTB patients, where Category-1 RNTCP regimen was given to patients in the control arm. In the second study the efficacy of Category-1 RNTCP regimen was assessed in pulmonary TB patients with concomitant type 2 diabetes mellitus (NIDDM) (DM-TB). The third study was a randomized controlled clinical trial where the efficacy of a 9-month regimen with an extended continuation phase of 3 months was compared with the Category-1 RNTCP regimen (control regimen) in PTB patients with HIV co-infection (HIV-TB). These studies were conducted at the Chennai and Madurai divisions of Tuberculosis Research Centre (TRC), during 1998-2002.

Eligibility criteria: In all these studies only new smear positive pulmonary TB patients were enrolled. For the DM-TB study, the eligibility criteria were as follows: concomitant type 2 diabetes mellitus with plasma creatinine level of < 2 mg/dl, absence of acetone in urine and non-reactive for HIV. For the PTB study the patients were eligible if aged > 18 yr, weight was >30 kg and were HIV seronegative. For the HIV-TB study, HIV seropositive patients aged > 15 yr were eligible for enrollment. Patients in moribund state or with major systemic illnesses or with abnormal biochemical profile were not eligible for admission to any of these studies.

Pre-treatment assessment including investigations: Prior to enrolment into the respective studies, informed consent was obtained from all patients. All the studies have been approved by our Institutional Ethics Committee. A detailed history including previous anti-tuberculosis therapy was elicited. Sociological assessment including information on socio-demographic profile was done. A general clinical examination was performed and the patient's weight was recorded. Baseline investigations included chest X-ray, and examination of four sputa by smear and culture. X-rays were read by a panel of doctors to evaluate (*i*) the extent of X-ray involvement which was documented as unilateral or bilateral, (*ii*) the number

of zones involved (minimum1zone - maximum 6 zones, and (*iii*) presence or absence of cavitation[12]. HIV screening was performed after pre-test counselling using the Tridot Rapid (J. Mitra, India) test; all positive results were confirmed using Comb Aids Rapid (Span diagnostics, India) test and also by ELISA (J.Mitra, India). Routine laboratory investigations including estimation of Haemoglobin, total and differential leucocyte cell count, blood sugar, blood urea, serum creatinine, serum uric acid and liver functions were performed.

In addition, for DM-TB patients estimation of fasting blood sugar, lipid profile and glycosylated HbA_1c was done. In HIV-TB patients CD4, CD8 cell counts and CD4/CD8 ratio were undertaken using flowcytometer (Simultest-IMK Lymphocyte kit) and tuberculin testing with 1TU of PPD RT 23.

Bacteriology: Sputum smears were examined for acid fast bacilli (AFB) by fluorescence microscopy[13] and the specimens were processed by modified Petroff's method[14] and cultured on the Lowenstein-Jensen (LJ) medium. The sputum smears were graded according to the number of bacilli visualized per high power field (HPF) as follows: less than 6 bacilli per HPF (1+), 6-100 bacilli per HPF (2+) and more than 100 bacilli per HPF or large clumps (3+)[13]. The cultures were graded based on the type of growth in the LJ medium as follows: 20-100 colonies growth (1+), >100 colonies (2+) and confluent growth (3+)[15]. 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[14,15]. Drug resistance was defined as minimal inhibitory concentration (MIC) of 1mg or more for isoniazid and 128 mg for rifampicin[16].

Treatment regimen and follow up: The patients who fulfilled the eligibility criteria received Category-1 RNTCP regimen: $2\ E_3H_3R_3Z_3 / 4\ R_3H_3$. The dosage used for all these patients was as follows: ethambutol (E) 1200 mg, isoniazid (H) 600 mg, rifampicin (R) 450 mg (600 mg > 60 kg) and pyrazinamide (Z) 1500 mg. As recommended in the RNTCP extension of the intensive phase for patients producing positive smears at 2 months was not done for any of the patients. Treatment was completely supervised for the entire 6 months. If the patients failed to attend, home visits by the health visitor, social worker and doctor were made to retrieve the patients. For all patients, sputum smear and culture examinations were undertaken at monthly intervals for monitoring of progress. Patients were motivated for regular treatment at every attendance.

A diabetologist from the Government General Hospital (GH), Chennai monitored the diabetic status of patients with a fasting blood sugar estimation every month. Based on the blood sugar levels, they were either treated with oral hypoglycaemic drugs, which was collected from the department of diabetology at the GH every month, or insulin for which arrangements were made at our centre.

HIV infected patients received co-trimoxazole regularly if their CD_4 counts were < 250 cells/cu.mm. However, none of the HIV infected patients received anti-retroviral therapy (ART) as anti-retroviral treatment was not available in the Government hospitals during the period of this study.

Statistical analysis: SPSS version 13.0 Inc., Chicago, II, USA was used for all statistical analysis. Trend Chi-square test with Yates correction was used to compare the proportions, Fisher's exact test was used when the expected value of a cell was less than 5. A backward logistic regression was used to identify the independent risk factors for bacteriological conversion at 2 months after adjusting the effect of other factors. $P<0.05$ were considered significant.

Results

Study population and baseline characteristics: A total of 278 smear-positive patients were enrolled into the study: 98 patients in the PTB group, 92 in the DM-TB group and 88 in the HIV-TB group. In both HIV TB and PTB studies there were no exclusions. While 100 patients were enrolled in the DM-TB group, 6 were excluded as they had missed more than 25 per cent of the scheduled treatment and 2 patients had defaulted after initial 5 doses of treatment. Males were 73, 78 and 82 per cent in the PTB, DM-TB and HIV-TB group respectively. While the median age of the patients in the cohort was 38 yr (range 17-70 yr), the median age of DM-TB patients was 48 yr as compared to 31 yr in the PTB and 34 yr in the HIV-TB group. The median weight was 44 kg, however it was lowest in the HIV-TB group (42.6 kg) and was highest in the PTB group (45 kg). The initial smear and culture grading was highest (3+) in the PTB group and lowest in HIV-TB group (Table I).

Only those patients who had received >75 per cent of drug doses were considered for efficacy analysis.

Smear and culture conversion: At the end of intensive phase, among 278 patients, smear negativity was

Table I. Characteristics of the study population (n = 278)

		PTB (n=98)	DM-TB (n=92)	HIV-TB (n=88)	All (n=278)
Sex	Males	72(73)	72(78)	72(82)	216(78)
Age (yr)	Median	31.0	48.0	34.0	38.0
	Range	18-65	32-70	17-63	17-70
Weight (kg)	Median	45.0	44.3	42.6	44.0
	Range	29.0-74.7	31.5-74.0	18.5-70.0	18.5-74.7
Lung zones involved	>2 zones	68(69)	58(63)	53(60)	179(64)
Extent of the disease	Bilateral	64(65)	47(51)	59(67)	170(61)
Initial	1+	28(29)	43(47)	50(57)	121(44)
smear	2+	49(50)	38(41)	34(39)	121(44)
grading	3+	21(21)	11(12)	4(4)	36(13)
Intitial	≤ 1+	4(4)	12(13)	26(29)	42(15)
culture	2+	19(19)	23(25)	28(32)	70(25)
grading	3+	75(77)	57(62)	34(39)	166(60)

Figures in parentheses are percentages

Table II. Factors related to smear and culture conversion at the end of intensive phase

Parameters		Total (278)	Smear negative (168)		*P* value	Culture negative (246)		*P* value
			n	(%)		n	(%)	
Age (yr)	< 45	192	126	(66)	0.01	179	(93)	<0.001
	≥ 45	86	42	(49)		67	(78)	
Weight (kg)	< 40	81	47	(58)	NS	71	(88)	NS
	40-59.9	182	111	(61)		161	(88)	
	≥ 60	15	10	(67)		14	(93)	
Sex	Male	216	122	(56)	0.02	188	(87)	NS
	Female	62	46	(74)		58	(94)	
Pre-treatment	1 +	121	93	(77)				
smear grading	2 +	121	64	(53)	< 0.001			
	3 +	36	11	(31)				
Pre-treatment	≤1 +	42				41	(98)	<0.001
culture grading	2 +	70				68	(97)	
	3 +	160				137	(83)	
X-ray chest Extent	Bilateral	170	93	(55)	0.02	145	(85)	NS
of disease	Unilateral	108	75	(69)		101	(93)	
No. of zones involved	> 2	179	94	(53)		152	(85)	0.02
	≤ 2	99	74	(75)	<0.001	94	(95)	
Cavitation	Yes	55	30	(55)		49	(89)	
	No	223	138	(62)	NS	197	(88)	NS
Pre-treatment	Sensitive	260	158	(61)	NS	233	(90)	0.04
susceptibility	Resistant	18	10	(56)		13	(72)	
	H	16	9	(56)		11	(69)	
	R	2	1	(50)		2	(100)	

observed in 168 (60%) patients. The end of intensive phase culture conversion was observed in 246 (88%) patients. The smear and culture conversion in the three groups were as follows: PTB group (58, 86%), DM-TB group (61, 88%) and HIV-TB group (62, 92%) (Fig.). As there was no difference in the 3 groups with reference to smear and culture conversion, the 3 groups were amalgamated for further analysis.

Factors influencing smear conversion: The variables associated with lack of sputum smear conversion at the end of intensive phase among those analyzed were age > 45 yr (P=0.01), being males (P=0.02), higher pre-treatment smear grading (P<0.001), bilateral lung involvement (P=0.02) and involvement of more than 2 radiographic zones (P<0.001) in chest X-ray (Table II). On the other hand, presence of cavitation in the chest

X-ray and pre-treatment drug resistance were not associated with lack of sputum smear conversion.

Factors influencing culture conversion: The variables associated with lack of culture conversion were age >45 yr (P<0.001), higher pre-treatment culture grading (P<0.001), involvement of more than 2 radiographic zones in the X-ray chest (P=0.02) and presence of pre-treatment drug resistance (P=0.04) (Table II).

Logistic regression analysis showed that lack of smear conversion at the end of intensive phase were associated with age >45 yr (P=0.03), chest X-ray involvement of more than 2 zones (P=0.01) and higher pre-treatment smear grading (P<0.001), and lack of culture conversion were associated with age >45 yr (P=0.01), higher pre-treatment culture grading (P =0.01) and radiographic involvement of more than 2 zones (P=0.03) (Table III).

Discussion

The findings showed that smear and culture conversion at the end of intensive phase of Category-1 regimen was similar in PTB patients with or without associated diabetes mellitus or HIV co-infection. These were in conformity with the earlier studies[8,10,11]. The likely reason could be that HIV patients have been found to have a lower bacillary load in sputum compared to HIV negative persons though the difference was not statistically significant. We have also observed that there was no difference in smear and culture conversion between diabetics and non-diabetics. Hence the uniform policy of treating all new smear-positive PTB patients with Category-1 regimen irrespective of co-morbid conditions is acceptable.

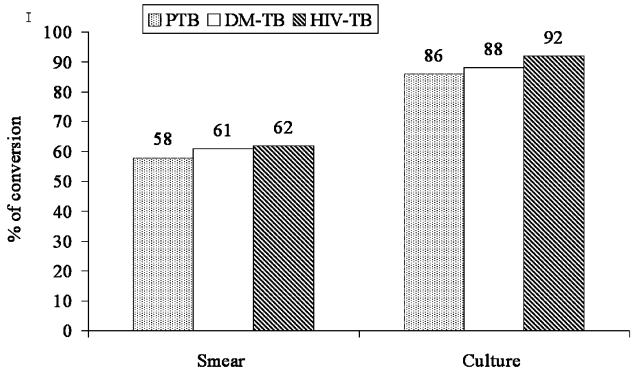

Fig. Smear and culture conversion at the end of 2 months of intensive phase among PTB, DM-TB and HIV-TB.

The low smear conversion rates observed in these studies when compared with the national average is likely to be due to the use of the fluorescent auramine rhodamine stain which is known to be more sensitive than the Ziehl-Neelsen stain in sputum smear reading for acid fast bacilli[17,18].

Factors such as age more than 45 yr, being males, higher pre-treatment smear grading and bilateral radiographic involvement with lesions in more than 2 zones were associated with lack of smear conversion. Earlier studies have shown that higher the age, higher is the lack of sputum smear conversion.[8,9] The reason might be that with advancing age there might be physical disability resulting in increased delay in clearing the bacilli probably due to decreasing immunity and also delay in seeking care and diagnosis which might lead to progression of the disease[19,20]. We have also observed lack of smear conversion in males. This might be due to associated habits like smoking and alcoholism although these were not studied.

Patients with higher smear grading (2+ and 3+) prior to treatment were less likely to convert compared to patients with 1+ smear. Similar findings have been reported earlier[8-10]. We have also observed that with higher culture grading, a longer time is taken for culture

Table III. Logistic regression results for variables significantly associated with delayed sputum smear and culture conversion at the end of Intensive phase

Dependent variable	Independent variable	Coefficient (B)	SE	Exp.(B)	95 % C I	*P* value
Smear conversion	Age	0.586	0.288	1.80	1.02 - 3.16	0.03
	No. of zones involved in chest X-ray	0.268	0.095	1.31	1.09 - 1.57	0.01
	Pre-treatment smear grading	0.97	0.207	2.64	1.76 - 3.96	<0.001
Culture conversion	Age	1.253	0.411	3.50	1.56 - 7.84	0.01
	No. of zones involved in chest X-ray	0.342	0.153	1.41	1.04 - 1.90	0.03
	Pre-treatment culture grading	1.263	0.491	3.54	1.35 - 9.26	0.01

conversion. Sputum smear and culture conversion appeared to be good in patients with advanced radiological disease, who were regular with Category-1 regimen treatment.

Severity of the disease as assessed radiographically showed that bilateral lesions and involvement of more than 2 zones were associated with lack of sputum smear and culture conversion. However, contrary to previous studies, we observed that radiologically assessed cavitation status was not related to sputum smear conversion[8-10].

In our series, the presence of pre-treatment isoniazid or rifampicin resistance did not influence smear conversion, as reported in earlier studies[11,21]. However, lack of culture conversion was observed among patients harbouring drug resistant bacilli. Although this observation was based on 18 patients with resistant organisms, it underscores the fact that if a patient remains culture positive at 2 months, it would be wise to undertake drug susceptibility tests eventhough drug susceptibility testing is not possible at present under the current programme conditions.

The limitation of this study was that this information was based on selected patients enrolled into controlled clinical trials who were chosen following rigid selection criteria. It may not reflect the patterns in the community in general. Moreover, they were treated with 2 months of intensive phase with no extension even if sputum was positive at the end of second month, which is not in conformity with the RNTCP guidelines. Sputum smear and culture conversion is likely to be multifactorial in DM-TB and HIV-TB patients who may have different risk factors for non-conversion at 2 months.

In conclusion, this study has shown that in sputum-positive pulmonary TB patients treated with Category-1 regimen, HIV co-infection or diabetes mellitus did not affect smear and culture conversion. Therefore the programme's recommendation of treating all smear positive pulmonary tuberculosis patients with Category-1 regimen irrespective of associated co-morbid conditions is appropriate as shown by examination of this intermediate outcome of 2-month sputum smear and culture conversion. However, these co-existing conditions have to be given due consideration in order to motivate patients regarding control of diabetes and co-trimoxaole prophylaxis with recommended ART regimens in HIV co-infected patients. The information on risk factors identified in this study may be crucial for policy makers to develop special guidelines for close monitoring of these patients as prolonged infectiousness may increase the transmission of disease in the community, which might impede the impact of the TB control programme. Programme managers should develop special packages to monitor persons aged 45 yr or more and facilitate early diagnosis of the disease.

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