Original Article

IS IT WORTH TREATING CATEGORY I FAILURE PATIENTS WITH CATEGORY II REGIMEN?

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Summary
Background: Very little information is available on the drug susceptibility profile among patients who are treated with standardized short-course chemotherapy regimens under programme conditions.
Methods: Sputum samples were collected from new sputum smear-positive patients declared 'failure' after treatment with Category I regimen under tuberculosis control programme using DOTS strategy from a rural area of Tamil Nadu.
Results: Of 1463 patients started on Category I regimen between May1999 and December 2002, 74 cases were declared as 'failures' (smear positive at 5/6 months of treatment). We collected sputum samples from 60 (81%) of 74 'failures' and 27% (16 of 60) of them were culture-negative for *M tuberculosis* and 17% (10 of 60) had organisms resistant to Isoniazid and Rifampicin (MDR TB).
Conclusion: Based on the drug susceptibility profile at the time of 'failure', treating Category I 'failures' with Category II regimen with close monitoring appears to be justified.   [*Indian J Tuberc 2005; 52:203-206*]

INTRODUCTION

According to WHO's DOTS strategy, newly diagnosed sputum smear positive (NSS) patients with pulmonary tuberculosis who remain sputum smear positive after 5-months of treatment with Category I regimen consisting of $2H_3R_3Z_3E_3/4 H_3R_3$ are declared as 'failures'. They are treated with Category II regimen[1] consisting of $2S_3H_3R_3Z_3E_3/ 1H_3R_3 Z_3E_3/ 5H_3R_3E_3$.

An earlier report from the same area from our Centre had reported the significant risk factors for failure among Cat I patients to be non-conversion of sputum smear at the end of intensive phase, initial resistance to H and/or R, and smoking[2].

Recently, concerns have been expressed that treatment with Category II regimen may not be effective for such re-treatment cases. It has been suggested that they may be treated with a stronger regimen since such cases are likely to harbour drug-resistant organisms[3-5]. We examined the drug susceptibility profile of category I failure cases in a DOTS programme in rural Tamil Nadu to examine if these concerns had any basis.

MATERIAL AND METHODS

The study was conducted in a sub-district population of 580,000 in Tamil Nadu. Under the DOTS programme, tuberculosis (TB) cases were detected at 17 primary- and secondary-level governmental health facilities by screening 'chest symptomatics' using the diagnostic algorithm of Revised National Tuberculosis Control Programme (RNTCP) [6]. NSS cases were treated with Category I regimen, consisting of Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z) given three-times-a week during the intensive phase of 2-months and R and H three-times-a-week during the continuation phase of 4-months. Treatment outcomes were defined according to international guidelines [1].

The study population consisted of all NSS

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pulmonary TB patients who registered for DOTS treatment during May 1999 to December 2002 and were treated with the Category I regimen[6]. Additional sputum samples were collected from study subjects in sterile containers with Cetyl Pyridinium Chloride by the laboratory technicians of the respective centres at two time points, namely, on starting treatment and at 5/6 months after starting treatment, if sputum smear was positive. Sputum samples were cultured for *M. tuberculosis* on Lowenstein Jensen (L-J) medium[7]. The positive cultures were subjected to drug susceptibility for Isoniazid (H) and Rifampicin (R) by minimal inhibitory concentration (MIC) method[8]. Resistance was defined as an MIC of 5mg or more for Isoniazid and 128mg for Rifampicin[8].

The data were computerized and analysed using Epi- Info version 6.04d (Centres for Disease Control, Atlanta, GA). Independent risk factors and adjusted odds ratios (AOR) were obtained by stepwise logistic regression analysis using SPSS/PC+, version 13.0. The criterion for inclusion of variables in logistic regression was set at $P<0.1$ and 95% confidence intervals were calculated.

RESULTS

In all, 1463 study patients were registered between May 1999 and December 2002. Sputum was collected from 1395 (95%) and drug susceptibility profile was available for 1226 patients, 158 were negative on culture and 11 were contaminated. Of the 1226, 1094 (89%) had organisms susceptible to H and R, 111 (9%) resistant to H, 16 (1.3%) to H and R (Multi-Drug Resistant) and 5 (0.4%) to R alone.

Treatment outcome of the 1463 patients was as follows: 1117 (76%) had a successful treatment outcome, 212 (14.5%) had defaulted, 58 (4%) died, 74(5%) were declared to have failed while two were transferred out. Risk factors identified for failure were non-conversion of sputum smear at the end of intensive phase (AOR 2.6; 95% CI=1.5-4.5), initial resistance to H and/or R (AOR 11.2; 95% CI=6.4-19.6), and smoking (AOR 1.9; 95% CI=1.1-3.3) (data not tabulated).

Of the 74 failure cases, sputum samples were collected from 60 (81%) patients at the time of failure. Pre-treatment characteristics like age, sex, and initial smear grading, drug regularity and sputum conversion were similar among patients from whom sputum was not collected to those from whom sputum was collected (data not tabulated). Of the 60 cases from whom sputum was collected, 16 (27%) were negative on culture, 10 (17%, 95% CI:

Table: Drug susceptibility profile pre-treatment and at the time of failure among patients treated with Category I regimen

Sensitivity pattern (pre-treatment)	Total patients	Failure No. %		Sputum collected	Culture status and sensitivity pattern at failure			
						Resistant to		
					Sens.	H	H and R	S+C-
Sensitive	1094	34	3	26	14	1	-	11
Resistant to								
H	111	23	21	20	-	16	3	1
R	5	1	20	0	-	-	-	-
HR	16	7	44	7	-	-	6	1
S+C-**	158	5	3	4	2	1	-	1
Not available	79*	4	5	3	-	-	1	2
Total	1463	74	5	60 (81%)	16 (27%)	18 (30%)	10 (17%)	16 (27%)

* 11 with culture contamination and 68 with no sputum collection
** Smear positive Culture Negative

7-26) had MDR TB {of these, 6 had MDR TB at the time of starting treatment (Table 1)}. Further, 18 (30%) had H resistant organisms (16 had initial H resistance).

DISCUSSION

Under programme conditions, patients are declared 'failed' on Cat I regimen if smears become positive at 5-month or more after starting treatment. In our series, of the 74 patients declared to have 'failed', MDR TB (organisms resistant to H and R) was seen among 17% justifying the use of Cat II regimen for failures of Cat I treatment for the remaining 83% of patients. Thus, all failures do not have MDR TB.

A study from Vietnam[3] had reported 80% of Category I failure cases to have MDR TB. The regimen, 2SHRZ/6HE used for treatment in Vietnam differed from the $2REHZ_3/HR_3$ used in this programme. In the study from Vietnam, emergence of drug resistance was considered only for patients who had RFLP matching cultures at pre-treatment and at the time of failure. A programme-based study from Malawi [9] had reported that none of the failures to first line treatment with 6HE in the continuation phase following an intensive phase of either 2SHRZ or $2HRZE_3$ had MDR TB.

In controlled clinical trial using standardized short-course regimens for treating NSS patients[10], 81% of 320 patients with H resistance, had favourable treatment outcome and 13% had bacteriological relapse, respectively, during a 24-month period of follow up. Thus, 18 patients with resistance to H at the time of failure also are likely to respond to treatment with Cat II regimen. Another 27% were negative by culture and there is no cause for concern in treating these patients with Category II regimen.

Our finding that non-conversion at the end of intensive phase to be a significant risk factor for failure suggests that patients who remain smear-positive at the end of intensive phase need to be interrogated for prior anti-tuberculosis treatment. If such a history is forthcoming, treatment may be changed to Cat II regimen.

A change in the present policy to use 'stronger regimens' for these patients will have other implications. Although the proportion of failures is small, in a high burden country such as India, the absolute number of failures is high. For example, in 2002, of 358,496 NSS patients treated, there were around 9500 failures (Central TB Division, India: Personal communication). Providing culture and drug susceptibility testing for such a large number of patients across the country is logistically and economically non-feasible in low-income countries. Hence, in high burden countries without access to culture and drug susceptibility testing, all these patients will have to be treated with second line drugs.

In conclusion, our finding that nearly 80% of the 'failures' (as declared in the programme, based on smear results), have organisms susceptible to R, justifies the use of the currently recommended category II regimen for failures of category I treatment. Close monitoring of these patients will be required to identify failures early and if necessary, change of treatment can be considered for those patients who do not show any response to treatment with Cat II regimen at 3-months.
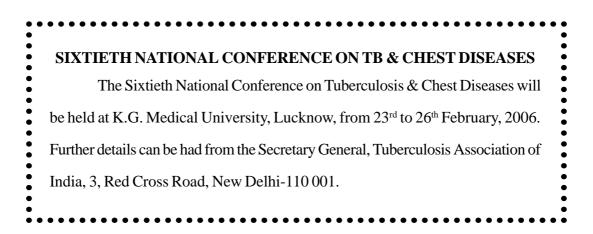
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