Original Article

INFLUENCE OF DRUG SUSCEPTIBILITY ON TREATMENT OUTCOME AND SUSCEPTIBILITY PROFILE OF 'FAILURES' TO CATEGORY II REGIMEN

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Summary

***Objective*:** To assess the influence of drug resistance on treatment outcome among patients treated with Category-II regimen and document drug susceptibility pattern of "Failures" to this regimen.

***Design*:** A retrospective analysis of patients registered from May 1999 through December 2004.

***Results*:** Treatment success was 42% among 572 patients and was similar among patients with fully susceptible or resistant but non-MDR organisms (41% of 254 and 40% of 128 patients, respectively). Among 49 MDR-TB patients, 27% had successful treatment outcome. The failure rates among patients with fully susceptible, resistant but non-MDR and MDR bacilli, were 6%, 12% and 27% respectively. Default was significantly higher among males (53% *vs*. 34%: p<0.01) smokers (57% *vs*. 36%: p <0.001), alcoholics (58% vs. 39%: p <0.001) and patients with higher initial smear grading (2+ or 3+, 56% vs. scanty or 1+, 44%: p <0.01). DST results were available for 60% (31 of 52) of failures and 10 had MDR-TB.

Conclusion*:** The low success rate to the re-treatment regimen was mainly due to non-compliance. Failure was observed among 9% of patients and MDR-TB was 32% among Category II failures. The currently recommended Category II regimen appears to be adequate for majority of re-treatment cases. ***[Indian J Tuberc 2006; 53:141-148]

***Key words*:** Treatment outcome, Category II regimen, failure, RNTCP, MDR-TB

BACKGROUND

The Revised National Tuberculosis Control Programme (RNTCP) based on the globally recommended Directly Observed Treatment-Short-course (DOTS) strategy was implemented in India in a phased manner since 1993. Treatment outcome among new smear-positive pulmonary tuberculosis (PTB) patients to category-I regimen has been reported to be good with a success rate of 83% or higher at national level [1, 2]. For previously treated patients, the success rate to the re-treatment regimen (CAT-II) was low (71%). Among patients typed as 'failure' and treated with re-treatment regimen, risk of subsequent failure was higher, compared to other types[1, 2].

There is concern regarding the effectiveness of category-II (CAT-II) regimen for re-treatment cases especially for 'Failures'[3,4]. Whether or not this re-treatment regimen is appropriate depends on the prevalence of drug resistance among these cases and treatment adherence. In India, it is reported that, 1-3.4% of new patients have had multi-drug resistant TB (MDR TB)[5]. Studies on acquired resistance have shown rates of resistance to Isoniazid ranging from 34.5-67%, for Streptomycin around 25% and for Rifampicin from 2.8-37.3%[6].

Tuberculosis Research Centre (TRC) has been monitoring the DOTS programme in one Tuberculosis Unit (TU), Tiruvallur district, Tamil Nadu. This paper describes the treatment outcome among different types of patients admitted to the re-treatment regimen, the influence of drug resistance on treatment outcome and the drug susceptibility pattern among patients who failed to this regimen.

METHODOLOGY

Tuberculosis Research Centre (TRC) is undertaking a series of epidemiological surveys (Disease and tuberculin surveys to estimate prevalence of TB and infection) in an area of Tiruvallur district since 1999. RNTCP was implemented by Government of Tamil Nadu in this

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area and TRC was monitoring the same up to 2004 December. Monitoring and follow up were done according to RNTCP guidelines[7]. Definitions recommended under RNTCP were followed to define treatment outcomes. As an operational study, we have been conducting Drug Resistance Surveillance (DRS) of patients treated under RNTCP in this area. Drug sensitivity testing (DST) was done for all patients at the initiation of treatment and whenever they produced a positive smear during the treatment period. HIV screening was not done since it is not recommended under RNTCP. This paper gives the findings of a retrospective analysis of patients registered under category II regimen of RNTCP.

Study area and population

The study area has a population of 580,000 spread over 209 villages and 9 urban clusters, situated about 45 kilometres from Chennai. The area has 17 governmental health care facilities, including 7 designated microscopy centres. Smear positive patients, with history of previous anti-tuberculosis treatment for more than one month, comprising cases of 'Failure', Treatment after Default ('TAD'), and 'Relapse' started on the CAT-II regimen from 1999 to 2004, constituted the study population. For outcome of treatment, we have included patients registered up to December 2003 since TRC was monitoring the programme only up to December 2004.

Setting

Patients attending any of the health facilities with a history of cough for 3-weeks or more, were screened for tuberculosis by sputum smear microscopy (Ziehl-Neelsen method). Diagnosis, treatment and monitoring were done according to RNTCP guidelines[7,8]. The standard re-treatment regimen of RNTCP in India consists of 3 months of Isoniazid (H), Rifampicin(R), Pyrazinamide(Z), and Ethambutol(E), with addition of Streptomycin (S) in the initial two months, followed by 5 months of R, H and E ($2SHRZE_3/1EHRZ_3/5HRE_3$) given three times a week, throughout the 8 months period . Patients whose sputum smears remained positive at the end of intensive phase of three months, treatment with R, H, Z and E was extended for one more month.

Drug sensitivity testing

Two additional sputum specimens were collected for drug sensitivity tests (DST) within one week of starting treatment and whenever they produced a positive sputum by smear microscopy, during treatment. The sputum samples were processed for culture for *M. tuberculosis* on Lowenstein - Jensen medium[9]. Cultures positive for *M.tuberculosis* were subjected to indirect sensitivity test for H, R, E and S. The resistance to H and R was determined by absolute concentration method (MIC) and to S by Resistance Ratio (RR) methods[10,11]. An MIC of 5mg/L or more, 8mg/L or more and an MIC of 128mg/L or more were defined as resistance for H, E and R respectively and an RR of 8 or more was considered as resistance to streptomycin..

Statistical analysis

The data were scrutinized for completeness and all the records were keyed in twice. Chi-square test of significance was performed to test the difference between different proportions. Yates corrected two-tailed P values ≤ 0.05 were considered as significant. The potential risk factors for default were studied by univariate analysis using Epi Info version 6.04 d (Centers for Disease Control, Atlanta, GA, 2001).

RESULTS

From May 1999 through December 2004, a total of 697 smear-positive patients were started on re-treatment with CAT-II regimen. The proportion of smear-positive re-treatment cases to the total smear-positive cases ranged from 24.5% in 1999 to 22.8% in 2004. The 697 patients included - 32% cases of 'Relapse', 20% 'Failure' and 47% 'TAD' cases.

Treatment outcome according to 'type' of cases

Of the 697 smear-positive patients registered

Table 1: Treatment outcome of 572 re-treatment cases registered to CAT II regimen.

Type of Cases	No.	Treatment Outcome									
		Success		Failure		Defaulted		Died		T- out	
		No.	%	No.	%	No.	%	No.	%	No.	%
Relapse	187	96	51	15	8	66	35	9	5	1	1
Failure	111	36	32	15	14	51	46	9	8	0	0
TAD	274	106	39	22	8	123	45	23	8	0	0
Total	572	238	42	52	9	240	42	41	7	1	0.002

to CAT-II regimen, 575 patients whose treatment outcome was available by December 2004 are included in the analysis (Table 1). (Three cases belonging to the type "others" were excluded from analysis, since the number was very few and they could not be combined with any other group for analysis.). Of the total 572 cases, 238 (42%) had a successful treatment outcome (cure-41%, treatment completed-1%) and 240 (42%) defaulted. 'Relapse' cases had a significantly higher cure rate (51%) compared to 'Failure' and TAD cases ($p < 0.01$). Fifty-two (9%) patients failed to the re-treatment regimen; 14% (15 of 111) among 'Failures', 8% (15 of 187) among 'Relapses', and 8% (22 of 274) among 'TAD' cases. However the difference was not statistically significant. The time at which patients defaulted were available for 219 out of the total 240 from the treatment cards and 49% defaulted within the first 3 months of treatment. The rate and time of default were almost similar in all types of patients. Forty-one (7%) patients died during the course of the treatment. Of the 37 patients for whom information is available, 70% died within 3 months of starting treatment.

Response to treatment according to drug susceptibility pattern

Of the 572 cases included in this analysis, even though it was planned to collect sputum specimens from all patients, specimens could not be collected from 50 (9%) patients within one week of treatment initiation due to operational reasons. Among 431 patients who produced positive cultures, 254 (59%) harboured sensitive bacilli, 128 (30%) resistant but non-MDR bacilli, and 49 (11%) had MDR-TB (Table 2). There was no growth in the culture for 91 (17%) patients. Among 254 patients harbouring sensitive bacilli and 128 with resistant but non-MDR bacilli, the cure rates (41%, 40%) were almost similar. Among 49 patients with MDR-TB, 13 (27%) had a favourable outcome. The failure rates were 6%, 12% and 27% among patients with fully susceptible, resistant but non-MDR and MDR bacilli, respectively. The failure rate was highest among patients with MDR-TB ($p<0.05$). The default rate was high and almost similar in all groups (46%, 38%, and 39%), irrespective of the drug susceptibility profile. The MDR-TB observed was 9% (20 of 226), 22% (14 of 63), and 11% (15 of 142) among TAD, 'Failures', and 'Relapses' respectively (Table 2). The MDR-TB observed among 'Failures' was significantly higher (22%) compared to that observed in the other two types of patients ($p<0.05$).

Among the 91 (17%) patients who produced no growth in the culture, 56% had a successful treatment outcome, 35% defaulted, 3% died and 5% failed. Of the 111 'Failure' cases registered to the CAT-II regimen, sputum specimens were collected from 94 cases. Thirty-one of the 94 (33%) 'Failure' cases did not show any growth in the culture. Considering all 94 'Failure' cases for whom sputum specimens were collected, MDR-TB could be documented in 14 (15%) of the cases, compared to 22% considering only patients with growth in culture. The culture negativity among TAD and Relapse cases was 12% (30/256) and 17% (30/172) respectively.

Table 2: Treatment outcome related to drug sensitivity pattern (n=431)

Drug sensitivity results	Success		Default		Died		Failed		Total	
	No.	%	No.	%	No	%	No.	%	N	%*
TAD										
Sensitive	55	38	68	47	11	8	10	7	144	64
Resistant (non-MDR)	24	39	23	37	7	11	8	13	62	27
HR resistant	6	(30)	8	(40)	2	(10)	4	(20)	20	9
Total	**85**	**38**	**99**	**44**	**20**	**9**	**22**	**9**	**226**	
Failure										
Sensitive	4	(21)	12	(63)	2	(11)	1	(5)	19	30
Resistant (non-MDR)	11	37	12	40	4	13	3	10	30	48
HR resistant	1	(7)	6	(43)	2	(14)	5	(36)	14	22
Total	**16**	**25**	**30**	**48**	**8**	**13**	**9**	**14**	**63**	
Relapse										
Sensitive	46	51	37	41	5	5	3	3	91	64
Resistant (non-MDR)	16	42	13	36	3	8	4	11	36	25
HR resistant	6	(40)	5	(33)	0	(0)	4	(27)	15	11
Total	**68**	**48**	**55**	**39**	**8**	**6**	**11**	**8**	**142**	
Grand Total										
Sensitive to H&R	105	41	117	46	18	7	14	6	254	59
Resistant but non-MDR	51	40	48	38	14	11	15	12	128	30
HR resistant	13	27	19	39	4	8	13	27	49	11
Total	**169**	**39**	**184**	**43**	**36**	**8**	**42**	**10**	**431**	

*Percentage to the column total
Figures in parenthesis indicate the denominator <25

We analysed risk factors for default for 42% of patients who had defaulted. In univariate analysis, of treatment success *vs* default, a higher default was significantly associated with sex {66% (47 of 71) among females *vs* 47% (193 of 410) among males: P<0.01}, smoking {64% (106 of 166) among non-smokers *vs* 43% (83 of 195) among smokers: P<0.001}, alcoholism {56% (112 of 199) among non-users *vs* 42% (68 of 162) among users, P<0.001} and initial smear grading {56% (112 of 216) with scanty or 1+ smears *vs* 44% (118 of 265) with 2+ or 3+ smears, P<0.01}.

Sputum smear-positivity at the end of 3 or 4 months of treatment

Of the 572 re-treatment patients, sputum smear results at the end of three months were not available for 153 (27%) patients (126 defaulted and 27 died during the intensive period). One hundred (17%) remained sputum smear-positive at the end

Table 3. Sputum smear-positivity at the end of 3 or 4 months of treatment

Type of patients	Sputum smear results after starting treatment									Total
	End of 3 months						End of 4 months			
	Negative		Positive		N.A.		Negative	Positive	N A	
	No	%	No	%	No	%	No	No	No	No.
TAD	143	52	45	16	86	31	15	13	17	274
Failure	51	46	34	31	26	23	8	15	11	111
Relapse	125	67	21	11	41	22	8	6	7	187
Total	319	56	100	17	153	27	31	34	35	572

of three months of treatment (Table 3) and intensive phase of treatment was extended for one more month. Of these 100 patients, 34 patients remained sputum smear positive at the end of four months of treatment. A higher proportion (31%) of' 'Failure' cases remained sputum smear positive at the end of 3 months of treatment compared to other types of patients (16% for TAD, 11% for Relapses). Of the 100 patients who remained sputum smear-positive at the end of 3 months of treatment, 26% were cured, 25% failed, 6% died and 43% defaulted.

Drug susceptibility profile among patients with positive smear during treatment

Of the 100 patients who remained sputum smear positive at the end of three months of treatment, 26% (24 of 91 patients) had MDR-TB at the time of starting treatment. At the end of third month of treatment, of the 53 cases for whom sputum was collected, 12 (23%) had MDR-TB and 17 (32%) had no growth on the culture (Table 4). At the end of 4 months of treatment, 34 (6%) patients

Table 4: Drug susceptibility profile of patients who produced positive sputum at 3 months, 4 months and at the time of failure

Sensitivity pattern	Positive at 3-m (N=100)		Positive at 4-m (N=34)		Failed (N=52)	
	Initial	At 3-m	Initial	At 4-m	Initial	At Failure
Sp. not collected	8	45	3	11	5	18
Cul. Contaminated	1	2	1	1	0	3
Total	**9**	**47**	**4**	**12**	**5**	**21**
	No. %	No. %	No. %	No. %	No. %	No. %
Cul Neg.	12 13	17 32	2 7	2 9	5 11	4 13
H & R – Sensitive	28 31	12 23	6 20	3 14	15 32	9 29
Resistant but Non-MDR	27 30	12 23	12 40	8 36	14 30	8 26
RH resistant	**24 26**	**12 23**	**10 33**	9* 41	13 28	10* 32
Total	**91**	**53**	**30**	**22**	**47**	**31**

Figure in parenthesis indicates the denominator <25
*Including one patient in each who was initially non-MDR (both H resistant)

remained sputum smear positive. The drug sensitivity results showed that, 33% of 30 cases (sputum not collected from four cases) had MDR-TB initially and at fourth month, of the 22 cases for whom DST results were available, 9 (41%) had MDR-TB including one who was initially non-MDR, and 9% had negative culture.

Fifty-two patients who remained smear positive at the end of fifth month or later during treatment were declared 'failed' to the CAT-II regimen. Drug susceptibility profile at the initiation of re-treatment is available for 47 and 13 (28%) had MDR-TB. At the time of failure, of the 31 cases for whom sputum specimens were collected, 10 (32%) had MDR-TB (including one who was initially non-MDR). Of these 52 'Failures', 27 patients had converted to sputum smear negativity at the end of intensive phase.

DISCUSSION

The proportion of smear-positive re-treatment cases in this DOTS implemented area, over a period of 5 years, from 1999 through 2004, did not show any significant changes and it ranged from 24.5% in 1999 to 22.9% in 2004. Among the re-treatment TB patients, nearly 50% constituted patients who came for re-treatment after defaulting to the previous regimen.

The low success rate (42%) to the CAT-11 regimen was mainly due to the high default (42%) during treatment. If all these defaulted patients (240) also had been regular for treatment, the treatment success would have been 72%. Another important finding revealed in this analysis is that the prevalence of drug resistance (non-MDR as well as MDR) was almost similar initially and at the time of failure. Development of resistance to Rifampicin among patients who failed to CAT II regimen was low (2 patients with initial resistance to H emerged resistance to R.)

The favourable outcome to the re-treatment regimen was similar among patients with TB due to susceptible and resistant but non-MDR bacilli. The failure rates were 6%, 15% and 27% among patients with fully susceptible, resistant but non-MDR and MDR bacilli, respectively, suggesting the re-treatment regimen had been effective in a majority of patients. However, it may not be adequate for patients with multi-drug resistant TB. Similarly in a retrospective cohort study of patients enrolled into the WHO / IUATLD global project on drug resistance surveillance in 6 countries, Espinal et al[12] has reported that of the 876 re-treatment cases, 44.5% were drug resistant, including 19% of MDR-TB. Among them, 57% had a successful outcome, 6% died, and 14% failed. And failure rates among re-treatment cases were higher in those with multi-drug resistant TB and with any Isoniazid resistance other than multi-drug resistance.

High default rate (42%) was the major reason for the low cure rate in this area. Default rate was similar in all groups of patients, irrespective of the type of patients or their drug resistance pattern. The success rate (42%) for the re-treatment cases in this report is significantly low compared to the national average of around 70%[1,2]. However, our findings are comparable to that reported by Sophia Vijay et al[13] from Bangalore (resistance to any drug 40%, MDR-TB 12.8%, cure rate 39.8%, default rate 43.8%).

There is concern regarding the efficacy of CAT-II regimen for re-treatment of TB patients especially for 'Failure' cases, since a high proportion of them may be having MDR-TB. The prevalence of multi-drug resistant TB in re-treatment patients in this area was 11% and it was higher (22%) among 'Failure' cases. Few studies have reported very high rates of MDR-TB in patients who fail to CAT-I regimen. A case-control study from Peru,[14] reported a cure rate of 93% to CAT-I ($2EHRZ/4R_2H_2$), and nearly 75% MDR-TB among failures to this regimen. Treatment failure in urban Lima has been identified as a strong predictor of MDR-TB. Quy et al[15] from Vietnam has reported that of the 40 failure cases to CAT-I regimen (2SHRZ/6EH), 80% had MDR-TB. Among 39 relapse cases, 8% had MDR-TB. Cure rate among relapse cases was 82.5%, while among 119 failure cases, the cure rate was 47% with 39% of patients failing to the regimen. A report from Malawi[16] has reported a treatment outcome of 65% for patients with recurrent TB, 81% of CAT-II

patients had susceptible organisms and MDR-TB was observed only in 4% of cases. In a retrospective study Gninafon et al[17], from Cotonou, Benin, has reported satisfactory and comparable success rates among re-treatment patients (78%) and new cases (82%). The success rate was similar among relapses (80%) and failures (85%). The failure rate for all re-treatment patients was low (3%). The reasons attributed for the excellent results by the authors were the low rate of both primary (0.3%) and secondary (11%) multi-drug-resistance and Rifampicin was given only under strict supervision. Response to the WHO-recommended re-treatment regimen varies great deal between countries, depending on the prevalence of drug resistance among these patients and the quality of TB control.

Treatment compliance is the most crucial factor for the successful outcome of any effective regimen. Default was significantly more among male patients, alcoholics and smokers. These groups of patients need to be targeted with additional health education and intensive counselling and supervision.

In TB cases with MDR-TB the standard retreatment regimen result in unacceptably high failure rates[12] and for all other drug resistant forms of TB, Rifampicin-based short course chemotherapy gives satisfactory results[18]. **This study also shows that the RNTCP policy in India of treating all re-treatment cases with the WHO recommended re-treatment regimen may be adequate except for the MDR-TB patients. DST should be done for patients who remain sputum smear positive during the re-treatment period and appropriate regimens should be started as early as possible for better treatment outcome and to reduce transmission of drug resistant TB.** Of the patients who remained sputum smear-positive at the end of 3 and 4 months of treatment, 23% and 41% respectively had MDR-TB. Among the patients who failed to CAT-II regimen, 32% had MDR-TB. The limitations of this report are high default rate and DST could not be done for a significant number of cases who remained smear positive during treatment. However, the initial drug susceptibility profile was similar among patients for whom sputum was not collected to those from whom sputum was collected. The results are from a localized area and need to be confirmed from other areas as well.

CONCLUSION

The low success rate to the CAT-II regimen was mainly due to the high default during treatment. If treatment compliance can be ensured for all patients majority of patients registered to CAT-II regimen can have a successful treatment outcome. Development of resistance to Rifampicin observed among failures to CAT II regimen was low. A high proportion of patients who failed to CAT-II regimen had either susceptible or resistant but non-MDR bacilli. The high default rate observed in the study area suggests the need for enhanced counselling and supervision with targeted health education.

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